AO 120 (Rev. 08/10)

TO:	REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK
Mail Stop 8 Director of the U.S. Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313-1450	

In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been filed in the U.S. District Court for the District of Delaware on the following

☐ Trademarks or ☑ Patents. (☐ the patent action involves 35 U.S.C. § 292.):

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
	7/11/2014	for the District of Delaware

PLAINTIFF	DEFENDANT
CUBIST PHARMACEUTICALS, INC.	FRESENIUS KABI USA, LLC

	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1	6,468,967	10/22/2002	Cubist Pharmaceuticals, Inc.
2	6,852,689	2/8/2005	Cubist Pharmaceuticals, Inc.
3	8,058,238	11/15/2011	Cubist Pharmaceuticals, Inc.
4	8,129,342	3/6/2012	Cubist Pharmaceuticals, Inc.
5			

In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY ☐ Amendment ☐ Answer ☐ Cross Bill ☐ Other Pleading	
PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1		
2		
3		
4		
5		

In the above—entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT

CLERK	(BY) DEPUTY CLERK	DATE

Copy 1—Upon initiation of action, mail this copy to Director **Copy 3—Upon termination of action, mail this copy to Director**
Copy 2—Upon filing document adding patent(s), mail this copy to Director **Copy 4—Case file copy**

AO 120 (Rev. 08/10)

TO:	**Mail Stop 8 Director of the U.S. Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313–1450**	**REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK**

In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been filed in the **U.S. District Court for the District of New Jersey** on the following:
____ Trademarks or **X** Patents. (____ the patent action involves 35 U.S.C. § 292.)

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
3:13–cv–06016–MAS–DEA	06/10/2013	TRENTON, NJ

PLAINTIFF	DEFENDANT
CUBIST PHARMACEUTICALS, INC.	STRIDES, INC.

PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1 6,468,967	10/22/2002	CUBIST PHARMACEUTICALS, INC
2 6,852,689B2	2/8/2005	CUBIST PHARMACEUTICALS, INC
3 8,058,238	11/15/2011	CUBIST PHARMACEUTICALS, INC
4 8,129,342B2	3/6/2012	CUBIST PHARMACEUTICALS, INC
5		

In the above––entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY ___ Amendment ___ Answer ___ Cross Bill ___ Other Pleading	
PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1		
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3		
4		
5		

In the above––entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT

CLERK	(BY) DEPUTY CLERK	DATE
William T. Walsh	s/ KIM STILLMAN	10/10/2013

Copy 1––Upon initiation of action, mail this copy to Director Copy 3––Upon termination of action, mail this copy to Director
Copy 2––Upon filing document adding patent(s), mail this copy to Director Copy 4––Case file copy

AO 120 (Rev. 08/10)

TO:	REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK
Mail Stop 8 Director of the U.S. Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313-1450	

In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been filed in the U.S. District Court for the District of Delaware on the following

☐ Trademarks or ☑ Patents. (☐ the patent action involves 35 U.S.C. § 292.):

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
	10/9/2013	for the District of Delaware

PLAINTIFF	DEFENDANT
CUBIST PHARMACEUTICALS, INC.	STRIDES, INC. and AGILA SPECIALTIES PRIVATE LIMITED

	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1	6,468,967 B1	10/22/2002	Cubist Pharmaceuticals, Inc.
2	6,852,689 B2	2/8/2005	Cubist Pharmaceuticals, Inc.
3	8,058,238 B2	11/15/2011	Cubist Pharmaceuticals, Inc.
4	8,129,342 B2	3/6/2012	Cubist Pharmaceuticals, Inc.
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In the above—entitled case, the following patent(s)/ trademark(s) have been included:

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PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
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3:13–cv–06016–MAS–DEA	10/10/2013	TRENTON, NJ

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CUBIST PHARMACEUTICALS, INC.	STRIDES, INC.

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Copy 2—Upon filing document adding patent(s), mail this copy to Director Copy 4—Case file copy

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 8,058,238 B2
APPLICATION NO. : 11/739180
DATED : November 15, 2011
INVENTOR(S) : Thomas Kelleher et al.

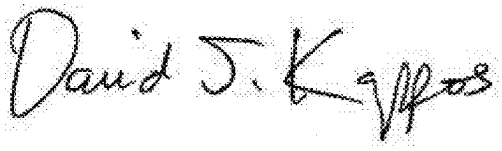
It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

IN THE CLAIMS:

In Column 45, line 38, Claim 139, replace "claim 48" with -- claim 49 --.

In Column 47, lines 57 and 58, Claim 176, replace "greater than or 93%" with -- greater than or about 93% --.

Signed and Sealed this
Twenty-fourth Day of January, 2012



David J. Kappos
Director of the United States Patent and Trademark Office

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appl. No. : 11/739,180 Confirmation No.: 8837

Patent No. : 8,058,238 B2

Applicant : Thomas Kelleher et al.

Filed : April 24, 2007

Issued : November 15, 2011

TC/A.U. : 1656

Examiner : Chih Min Kam

Docket No. : C062-02/03 US

Customer No. : 34103

REQUEST FOR CERTIFICATE OF CORRECTION UNDER 37 C.F.R. § 1.322

Applicants hereby request that a Certificate of Correction be issued in the patent identified above. The errors to be corrected are of a minor, typographical nature and are described in detail on the enclosed PTO/SB/44 form.

The errors occurred through the fault of the office; therefore, no fee is believed due at this time. Please charge deposit account no. 50-1986 if any fees are believed due at this time.

Respectfully submitted,

Dated: December 28, 2011

/Nicholas M. Boivin/
Nicholas M. Boivin, Reg. No. 45,650
Attorney for Applicants

Cubist Pharmaceuticals, Inc.
65 Hayden Avenue
Lexington, Massachusetts 02421
Tel: (781) 860-8660
Fax: (781) 860-1407

PTO/SB/44 (09-07)
Approved for use through 08/31/2013. OMB 0651-0033
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.
(Also Form PTO-1050)

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 8,058,238 B2

APPLICATION NO.: 11/739,180

ISSUE DATE : November 15, 2011

INVENTOR(S) : Thomas Kelleher et al.

It is certified that an error appears or errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In Column 45, line 38, replace "claim 48" with -- claim 49 --.

In Column 47, lines 57 and 58, replace "greater than or 93%" with -- greater than or about 93% --.

MAILING ADDRESS OF SENDER (Please do not use customer number below):

Nicholas Boivin, Cubist Pharmaceuticals, Inc.
65 Hayden Avenue
Lexington, MA 02421

Electronic Acknowledgement Receipt

EFS ID:	11717005
Application Number:	11739180
International Application Number:	
Confirmation Number:	8837
Title of Invention:	HIGH PURITY LIPOPEPTIDES
First Named Inventor/Applicant Name:	Thomas Kelleher
Customer Number:	34103
Filer:	Nicholas M.C. Boivin
Filer Authorized By:	
Attorney Docket Number:	C062-02/03 US
Receipt Date:	28-DEC-2011
Filing Date:	24-APR-2007
Time Stamp:	14:21:51
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Request for Certificate of Correction	C062_02_03_US_20111228_Cert_of_Cor.pdf	658909 8c4bfebf445df90149f66e4a65fb01bd5f185909	no	2

Warnings:

Information:

Total Files Size (in bytes):	658909

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/739,180	11/15/2011	8058238	C062-02/03 US	8837

34103 7590 10/26/2011

Intellectual Property Department
Cubist Pharmaceuticals, Inc.
65 Hayden Avenue
Lexington, MA 02421

ISSUE NOTIFICATION

The projected patent number and issue date are specified above.

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment is 0 day(s). Any patent to issue from the above-identified application will include an indication of the adjustment on the front page.

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Application Assistance Unit (AAU) of the Office of Data Management (ODM) at (571)-272-4200.

APPLICANT(s) (Please see PAIR WEB site http://pair.uspto.gov for additional applicants):

Thomas Kelleher, Weston, MA;
Jan-Ji Lai, Westborough, MA;
Joseph P. DeCourcey, Charlestown, MA;
Paul Lynch, Arlington, MA;
Maurizio Zenoni, Milan, ITALY;
Auro Tagliani, Pavia, ITALY;

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

Bib Data Sheet

CONFIRMATION NO. 8837

SERIAL NUMBER	FILING OR 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
11/739,180	04/24/2007 RULE	514	1656	C062-02/03 US

APPLICANTS

Thomas Kelleher, Weston, MA;
Jan-Ji Lai, Westborough, MA;
Joseph P. DeCourcey, Charlestown, MA;
Paul Lynch, Arlington, MA;
Maurizio Zenoni, Milan, ITALY;
Auro Tagliani, Pavia, ITALY;

**** CONTINUING DATA ***************************

This application is a CON of 10/747,485 12/29/2003 ABN which is a DIV of 09/735,191 11/28/2000 PAT 6,696,412
which claims benefit of 60/177,170 01/20/2000

**** FOREIGN APPLICATIONS *********************

IF REQUIRED, FOREIGN FILING LICENSE GRANTED
** 05/08/2007

Foreign Priority claimed	STATE OR COUNTRY	SHEETS DRAWING	TOTAL CLAIMS	INDEPENDENT CLAIMS
☐ yes ☐ no	MA	11	53	1
35 USC 119 (a-d) conditions met ☐ yes ☐ no ☐ Met after Allowance				
Verified and Acknowledged Examiner's Signature Initials				

ADDRESS
34103

TITLE

HIGH PURITY LIPOPEPTIDES

FILING FEE RECEIVED	FEES: Authority has been given in Paper No. _____ to charge/credit DEPOSIT ACCOUNT No. _____ for following:
8591	☐ All Fees ☐ 1.16 Fees (Filing) ☐ 1.17 Fees (Processing Ext. of time) ☐ 1.18 Fees (Issue) ☐ Other _____ ☐ Credit

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
11/739,180	04/24/2007	Thomas Kelleher	C062-02/03 US

CONFIRMATION NO. 8837

34103
Intellectual Property Department
Cubist Pharmaceuticals, Inc.
65 Hayden Avenue
Lexington, MA 02421

POA ACCEPTANCE LETTER

OC000000050087820

Date Mailed: 09/29/2011

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 09/08/2011.

The Power of Attorney in this application is accepted. Correspondence in this application will be mailed to the above address as provided by 37 CFR 1.33.

/cbowen/

Office of Data Management, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

54103 7590 09/07/2011

Intellectual Property Department
Cubist Pharmaceuticals, Inc.
65 Hayden Avenue
Lexington, MA 02421

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/739,180	04/24/2007	Thomas Kelleher	C062-02703 US	8837

TITLE OF INVENTION: HIGH PURITY LIPOPEPTIDES

APPLN. TYPE	SMALL ENTITY	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	YES	$755	$300	$0	$1055	12/07/2011

EXAMINER	ART UNIT	CLASS-SUBCLASS
KAM, CHIH MIN	1656	514-009000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

☐ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) the names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) the name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 Cubist Pharmaceuticals, Inc.
2
3

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THIS PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE: Cubist Pharmaceuticals, Inc.
65 Hayden Avenue

(B) RESIDENCE: (CITY and STATE OR COUNTRY) Lexington, MA 02421

Please check the appropriate assignee category or categories (will not be printed on the patent): ☐ Individual ☒ Corporation or other private group entity ☐ Government

4a. The following fee(s) are submitted:
☒ Issue Fee
☒ Publication Fee (No small entity discount permitted)
☐ Advance Order - # of Copies

4b. Payment of Fee(s): **(Please first reapply any previously paid issue fee shown above)**
☐ A check is enclosed.
☐ Payment by credit card. Form PTO-2038 is attached.
☒ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment, to Deposit Account Number 50-1266 (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)
☐ a. Applicant claims SMALL ENTITY status. See 37 CFR 1.27. ☒ b. Applicant is no longer claiming SMALL ENTITY status. See 37 CFR 1.27(g)(2).

NOTE: The Issue Fee and Publication Fee (if required) will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the United States Patent and Trademark Office.

Authorized Signature [signature] Date September 26, 2011

Typed or printed name Nicholas M. Boivin Registration No. 45,650

This collection of information is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Electronic Patent Application Fee Transmittal

Application Number:	11739180
Filing Date:	24-Apr-2007
Title of Invention:	HIGH PURITY LIPOPEPTIDES
First Named Inventor/Applicant Name:	Thomas Kelleher
Filer:	Nicholas M.C. Boivin
Attorney Docket Number:	C062-02/03 US

Filed as Large Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Utility Appl issue fee	1501	1	1740	1740
Publ. Fee- early, voluntary, or normal	1504	1	300	300

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	**2040**

Electronic Acknowledgement Receipt

EFS ID:	10975756
Application Number:	11739180
International Application Number:	
Confirmation Number:	8837
Title of Invention:	HIGH PURITY LIPOPEPTIDES
First Named Inventor/Applicant Name:	Thomas Kelleher
Customer Number:	34103
Filer:	Nicholas M.C. Boivin
Filer Authorized By:	
Attorney Docket Number:	C062-02/03 US
Receipt Date:	26-SEP-2011
Filing Date:	24-APR-2007
Time Stamp:	16:41:04
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$2040
RAM confirmation Number	3032
Deposit Account	501986
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Issue Fee Payment (PTO-85B)	C062_02_03_US_20110926_Issue_Fee_Payment.pdf	793331 9f96613824221fde88ff9ff95de976d778442620	no	1
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	32100 02ec42818e2457b177166fa36aec92a9e267f450	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	825431		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

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New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/SB/81 (01-09)
Approved for use through 11/30/2011. OMB 0651-0035
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

POWER OF ATTORNEY OR REVOCATION OF POWER OF ATTORNEY WITH A NEW POWER OF ATTORNEY AND CHANGE OF CORRESPONDENCE ADDRESS

Application Number	11/739,180
Filing Date	April 24, 2007
First Named Inventor	Thomas Kelleher
Title	High Purity Lipopeptides
Art Unit	1656
Examiner Name	Chih-Min Kam
Attorney Docket Number	C062-02/03 US

I hereby revoke all previous powers of attorney given in the above-identified application.

☐ A Power of Attorney is submitted herewith.

OR

☒ I hereby appoint Practitioner(s) associated with the following Customer Number as my/our attorney(s) or agent(s) to prosecute the application identified above, and to transact all business in the United States Patent and Trademark Office connected therewith.

34103

OR

☐ I hereby appoint Practitioner(s) named below as my/our attorney(s) or agent(s) to prosecute the application identified above, and to transact all business in the United States Patent and Trademark Office connected therewith:

Practitioner(s) Name	Registration Number

Please recognize or change the correspondence address for the above-identified application to:

☒ The address associated with the above-mentioned Customer Number.

OR

☐ The address associated with Customer Number:

OR

☐ Firm or Individual Name					
Address					
City		State		Zip	
Country					
Telephone		Email			

I am the:

☐ Applicant/Inventor.

OR

☒ Assignee of record of the entire interest. See 37 CFR 3.71.
Statement under 37 CFR 3.73(b) (Form PTO/SB/96) submitted herewith or filed on _____

SIGNATURE of Applicant or Assignee of Record

Signature	/Nicholas M. Boivin/	Date	September 8, 2011
Name	Nicholas M. Boivin	Telephone	(781) 860-8660
Title and Company	Intellectual Property Counsel, Cubist Pharmaceuticals, Inc.		

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.

☒ *Total of 1 forms are submitted.

PTO/SB/96 (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

STATEMENT UNDER 37 CFR 3.73(b)

Applicant/Patent Owner: Cubist Pharmaceuticals, Inc.

Application No./Patent No.: 11/739,180 Filed/Issue Date: April 24, 2007

Titled:

Cubist Pharmaceuticals, INc. (Name of Assignee), a Corporation (Type of Assignee, e.g., corporation, partnership, university, government agency, etc.)

states that it is:

1. [X] the assignee of the entire right, title, and interest in;

2. [ ] an assignee of less than the entire right, title, and interest in
(The extent (by percentage) of its ownership interest is _____ %); or

3. [ ] the assignee of an undivided interest in the entirety of (a complete assignment from one of the joint inventors was made)

the patent application/patent identified above, by virtue of either:

A. [ ] An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the United States Patent and Trademark Office at Reel _____, Frame _____, or for which a copy therefore is attached.

OR

B. [X] A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as follows:

1. From: Inventor Paul D. Lynch To: Perseptive Biosystems, Inc

The document was recorded in the United States Patent and Trademark Office at
Reel 024070, Frame 0280, or for which a copy thereof is attached.

2. From: Perseptive Biosystems, Inc. To: Cubist Pharmaceuticals, Inc.

The document was recorded in the United States Patent and Trademark Office at
Reel 019202, Frame 0011, or for which a copy thereof is attached.

3. From: Inventors To: Cubist Pharmaceuticals, Inc.

The document was recorded in the United States Patent and Trademark Office at
Reel 019201, Frame 0897, or for which a copy thereof is attached.

[ ] Additional documents in the chain of title are listed on a supplemental sheet(s).

[ ] As required by 37 CFR 3.73(b)(1)(i), the documentary evidence of the chain of title from the original owner to the assignee was, or concurrently is being, submitted for recordation pursuant to 37 CFR 3.11.

[NOTE: A separate copy (*i.e.*, a true copy of the original assignment document(s)) must be submitted to Assignment Division in accordance with 37 CFR Part 3, to record the assignment in the records of the USPTO. See MPEP 302.08]

The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

/Nicholas M. Boivin/ — Signature
09/08/2011 — Date
Nicholas M. Boivin — Printed or Typed Name
IP Counsel — Title

UNITED STATES PATENT AND TRADEMARK OFFICE

UNDER SECRETARY OF COMMERCE FOR INTELLECTUAL PROPERTY AND
DIRECTOR OF THE UNITED STATES PATENT AND TRADEMARK OFFICE

501117205A

MARCH 12, 2010

PTAS

CUBIST PHARMACEUTICALS, INC.
65 HAYDEN AVENUE
INTELLECTUAL PROPERTY DEPARTMENT
LEXINGTON, MA 02421

UNITED STATES PATENT AND TRADEMARK OFFICE
NOTICE OF RECORDATION OF ASSIGNMENT DOCUMENT

THE ENCLOSED DOCUMENT HAS BEEN RECORDED BY THE ASSIGNMENT DIVISION OF THE U.S. PATENT AND TRADEMARK OFFICE. A COMPLETE MICROFILM COPY IS AVAILABLE AT THE ASSIGNMENT SEARCH ROOM ON THE REEL AND FRAME NUMBER REFERENCED BELOW.

PLEASE REVIEW ALL INFORMATION CONTAINED ON THIS NOTICE. THE INFORMATION CONTAINED ON THIS RECORDATION NOTICE REFLECTS THE DATA PRESENT IN THE PATENT AND TRADEMARK ASSIGNMENT SYSTEM. IF YOU SHOULD FIND ANY ERRORS OR HAVE QUESTIONS CONCERNING THIS NOTICE, YOU MAY CONTACT THE EMPLOYEE WHOSE NAME APPEARS ON THIS NOTICE AT 571-272-3350. PLEASE SEND REQUEST FOR CORRECTION TO: U.S. PATENT AND TRADEMARK OFFICE, MAIL STOP: ASSIGNMENT SERVICES BRANCH, P.O. BOX 1450, ALEXANDRIA, VA 22313.

RECORDATION DATE: 03/12/2010 REEL/FRAME: 024070/0280
NUMBER OF PAGES: 5

BRIEF: CORRECTIVE ASSIGNMENT TO CORRECT THE RECEIVING PARTY DATA PREVIOUSLY RECORDED ON REEL 019201 FRAME 0966. ASSIGNOR(S) HEREBY CONFIRMS THE CORRECTIVE ASSIGNMENT TO CORRECT ONE RECORDED AT 019201/0966 TO CHANGE ASSIGNEE TO PERSEPTIVE BIOSYSTEMS, INCORPORATED.
DOCKET NUMBER: C062-02/03 US

ASSIGNOR:
LYNCH, PAUL D DOC DATE: 02/13/2001

ASSIGNEE:
PERSEPTIVE BIOSYSTEMS,
INCORPORATED
500 OLD CONNECTICUT PATH
FRAMINGHAM, MASSACHUSETTS 01701

SERIAL NUMBER: 11/739180 FILING DATE: 04/24/2007
PATENT NUMBER: ISSUE DATE:
TITLE: HIGH PURITY LIPOPEPTIDES

JEEVON JONES, EXAMINER
ASSIGNMENT SERVICES BRANCH
PUBLIC RECORDS DIVISION

ASSIGNMENT

I/We,

(1) Paul D. Lynch,

residing at

(1) 29 Cypress Road
Arlington, MA 02474,

for good and valuable consideration, receipt of which is hereby acknowledged, have assigned, sold and transferred to and do hereby assign, sell and transfer to PERSEPTIVE BIOSYSTEMS, INCORPORATED a corporation organized and existing under the laws of the STATE OF DELAWARE and having an office and a place of business at 500 OLD CONNECTICUT PATH, FRAMINGHAM, MASSACHUSETTS 01701 its successors and assigns: (1) ~~the~~ entire right, title and interest in the United States and in all countries throughout the world in and to any and all my/our inventions and discoveries disclosed in the application for Letters Patent in the United States entitled: HIGH PURITY LIPOPEPTIDES, LIPOPEPTIDES MICELLES AND PROCESSES FOR PREPARING SAME, and filed in the United States Patent and Trademark Office on NOVEMBER 28, 2000, under Serial Number 09/735,191, including any renewals, revivals, reissues, reexaminations, extensions, continuations and divisions thereof, and any substitute applications therefor; (2) the full and complete right to file patent applications in the name of PERSEPTIVE BIOSYSTEMS, INCORPORATED its designee, or in my/our names at PERSEPTIVE BIOSYSTEMS, INCORPORATED or its designee's election, on the aforesaid inventions, discoveries and applications in all countries of the world; (3) ~~the~~ entire right, title and interest in and to any Letters Patent

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which may issue thereon in the United States or in any other country of the world and any renewals, revivals, reissues, reexaminations and extensions of the same; and (4) the entire right, title and interest in all Convention and Treaty Rights of all kinds thereon, including without limitation all rights of priority in any country of the world, in and to the above inventions, discoveries and applications.

I/We hereby authorize and request the competent authorities to grant and to issue any and all such Letters Patent in the United States and throughout the world to PERSEPTIVE BIOSYSTEMS, INCORPORATED as the assignee of the entire right, title and interest therein, as fully and entirely as the same would have been held and enjoyed by me/us had this assignment, sale and transfer not been made.

I/We agree, at any time, upon the request of PERSEPTIVE BIOSYSTEMS, INCORPORATED to execute and to deliver to PERSEPTIVE BIOSYSTEMS, INCORPORATED any additional applications for patents for said inventions and discoveries, or any part or parts thereof, and any applications for patents of confirmation, registration and importation based on any Letters Patent issuing on said inventions, discoveries or applications, and divisions, continuations, renewals, revivals, reissues, reexaminations and extensions thereof.

I/We further agree at any time to execute and to deliver upon request of PERSEPTIVE BIOSYSTEMS, INCORPORATED such additional documents, if any, as are necessary or desirable to secure patent protection on said inventions, discoveries and applications throughout all countries of the world, and otherwise to do the necessary to give full effect to and to perfect the rights of PERSEPTIVE BIOSYSTEMS, INCORPORATED under this Assignment, including the execution, delivery and procurement of any and all

further documents evidencing this assignment, transfer and sale as may be necessary or desirable.

ASSIGNORS:

Paul Lynch 2/13/11
PAUL D. LYNCH

On this 13th day of February, 2011, PAUL D. LYNCH (1) personally appeared before me, a Notary Public in and for The Commonwealth of Pennsylvania, and executed the foregoing Assignment and duly acknowledged to me that such Assignment was executed for the uses and purposes therein expressed.

Notary Public

ASSIGN.2
2/6/1

UNITED STATES PATENT AND TRADEMARK OFFICE

UNDER SECRETARY OF COMMERCE FOR INTELLECTUAL PROPERTY AND
DIRECTOR OF THE UNITED STATES PATENT AND TRADEMARK OFFICE

APRIL 27, 2007

PTAS

500264041A

CUBIST PHARMACEUTICALS, INC.
65 HAYDEN AVENUE
INTELLECTUAL PROPERTY
LEXINGTON, MA 02421

UNITED STATES PATENT AND TRADEMARK OFFICE
NOTICE OF RECORDATION OF ASSIGNMENT DOCUMENT

THE ENCLOSED DOCUMENT HAS BEEN RECORDED BY THE ASSIGNMENT DIVISION OF THE U.S. PATENT AND TRADEMARK OFFICE. A COMPLETE MICROFILM COPY IS AVAILABLE AT THE ASSIGNMENT SEARCH ROOM ON THE REEL AND FRAME NUMBER REFERENCED BELOW.

PLEASE REVIEW ALL INFORMATION CONTAINED ON THIS NOTICE. THE INFORMATION CONTAINED ON THIS RECORDATION NOTICE REFLECTS THE DATA PRESENT IN THE PATENT AND TRADEMARK ASSIGNMENT SYSTEM. IF YOU SHOULD FIND ANY ERRORS OR HAVE QUESTIONS CONCERNING THIS NOTICE, YOU MAY CONTACT THE EMPLOYEE WHOSE NAME APPEARS ON THIS NOTICE AT 571-272-3350. PLEASE SEND REQUEST FOR CORRECTION TO: U.S. PATENT AND TRADEMARK OFFICE, MAIL STOP: ASSIGNMENT SERVICES BRANCH, P.O. BOX 1450, ALEXANDRIA, VA 22313.

RECORDATION DATE: 04/24/2007

REEL/FRAME: 019202/0011
NUMBER OF PAGES: 4

BRIEF: ASSIGNMENT OF ASSIGNOR'S INTEREST (SEE DOCUMENT FOR DETAILS).
DOCKET NUMBER: C062-02/03 US

ASSIGNOR:
PERSEPTIVE BIOSYSTEMS, INC.

DOC DATE: 02/13/2001

ASSIGNEE:
CUBIST PHARMACEUTICALS, INC.
65 HAYDEN AVENUE
LEXINGTON, MASSACHUSETTS 02421

SERIAL NUMBER: 11739180
PATENT NUMBER:
TITLE: HIGH PURITY LIPOPEPTIDES

FILING DATE:
ISSUE DATE:

ASSIGNMENT SERVICES BRANCH
PUBLIC RECORDS DIVISION

ASSIGNMENT

WHEREAS, the undersigned, PERSEPTIVE BIOSYSTEMS, INCORPORATED, a corporation organized and existing under the laws of the STATE OF DELAWARE and having an office and a place of business at 500 OLD CONNECTICUT PATH, FRAMINGHAM, MASSACHUSETTS 01701, has full right to convey the entire interest in the invention entitled: HIGH PURITY LIPOPEPTIDES, LIPOPEPTIDES MICELLES AND PROCESSES FOR PREPARING SAME, and filed in the United States Patent and Trademark Office on NOVEMBER 28, 2000, under Serial Number 09/735,191; and

WHEREAS, CUBIST PHARMACEUTICALS, INCORPORATED, a corporation organized and existing under the laws of the STATE OF DELAWARE and having an office and a place of business at 24 EMILY STREET, CAMBRIDGE, MASSACHUSETTS 02139, is desirous of acquiring the entire interest in said invention, in said United States patent application and in any Letters Patent which may issue thereon;

NOW, THEREFORE, be it known that for good and valuable consideration, the receipt and sufficiency of which is hereby acknowledged, the undersigned has sold, assigned and transferred to and does hereby sell, assign, and transfer to CUBIST PHARMACEUTICALS, INCORPORATED, its successors, assigns and legal representatives: (1) ~~the~~ its entire right, title and interest in the United States and in all countries throughout the world in and to any and all inventions and discoveries disclosed in said patent application, including any renewals, revivals, reissues, reexaminations, extensions, continuations and divisions thereof, and any substitute applications therefor; (2) the full and complete right to file patent applications in the name of CUBIST PHARMACEUTICALS, INCORPORATED its designee or its designee's election, on the aforesaid

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inventions, discoveries and applications in all countries of the world; (3) the entire right, title and interest in and to any Letters Patent which may issue thereon in the United States or in any other country of the world and any renewals, revivals, reissues, reexaminations and extensions of the same; and (4) the entire right, title and interest in all Convention and Treaty Rights of all kinds thereon, including without limitation all rights of priority in any country of the world, in and to the above inventions, discoveries and applications.

PERSEPTIVE BIOSYSTEMS, INCORPORATED hereby authorizes and requests the competent authorities to grant and to issue any and all such Letters Patent in the United States and throughout the world to CUBIST PHARMACEUTICALS, INCORPORATED as the assignee of the entire right, title and interest therein, as fully and entirely as the same would have been held and enjoyed by PERSEPTIVE BIOSYSTEMS, INCORPORATED had this assignment, sale and transfer not been made.

PERSEPTIVE BIOSYSTEMS, INCORPORATED agrees, at any time, upon the request of CUBIST PHARMACEUTICALS, INCORPORATED to execute and to deliver to CUBIST PHARMACEUTICALS, INCORPORATED any additional applications for patents for said inventions and discoveries, or any part or parts thereof, and any applications for patents of confirmation, registration and importation based on any Letters Patent issuing on said inventions, discoveries or applications, and divisions, continuations, renewals, revivals, reissues, reexaminations and extensions thereof.

PERSEPTIVE BIOSYSTEMS, INCORPORATED further agrees at any time to execute and to deliver upon request of CUBIST PHARMACEUTICALS, INCORPORATED such additional documents, if any, as are necessary or desirable to secure patent protection on said inventions, discoveries

and applications throughout all countries of the world, and otherwise to do the necessary to give full effect to and to perfect the rights of CUBIST PHARMACEUTICALS, INCORPORATED under this Assignment, including the execution, delivery and procurement of any and all further documents evidencing this assignment, transfer and sale as may be necessary or desirable.

ASSIGNOR:

PERSEPTIVE BIOSYSTEMS, INCORPORATED
Joseph E. Malandrakis
President
PerSeptive Biosystems, Inc.

On this 13th day of February, 2001, Joseph E. Malandrakis personally appeared before me, a Notary Public in and for Framingham, Massachusetts, and executed the foregoing Assignment and duly acknowledged to me that such Assignment was executed for the uses and purposes therein expressed.

Notary Public

ASSIGN.2
2/6/1

UNITED STATES PATENT AND TRADEMARK OFFICE

UNDER SECRETARY OF COMMERCE FOR INTELLECTUAL PROPERTY AND
DIRECTOR OF THE UNITED STATES PATENT AND TRADEMARK OFFICE

APRIL 24, 2007

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CUBIST PHARMACEUTICALS, INC.
65 HAYDEN AVENUE
INTELLECTUAL PROPERTY
LEXINGTON, MA 02421

UNITED STATES PATENT AND TRADEMARK OFFICE
NOTICE OF RECORDATION OF ASSIGNMENT DOCUMENT

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PLEASE REVIEW ALL INFORMATION CONTAINED ON THIS NOTICE. THE INFORMATION CONTAINED ON THIS RECORDATION NOTICE REFLECTS THE DATA PRESENT IN THE PATENT AND TRADEMARK ASSIGNMENT SYSTEM. IF YOU SHOULD FIND ANY ERRORS OR HAVE QUESTIONS CONCERNING THIS NOTICE, YOU MAY CONTACT THE EMPLOYEE WHOSE NAME APPEARS ON THIS NOTICE AT 571-272-3350. PLEASE SEND REQUEST FOR CORRECTION TO: U.S. PATENT AND TRADEMARK OFFICE, MAIL STOP: ASSIGNMENT SERVICES BRANCH, P.O. BOX 1450, ALEXANDRIA, VA 22313.

RECORDATION DATE: 04/24/2007

REEL/FRAME: 019201/0897
NUMBER OF PAGES: 9

BRIEF: ASSIGNMENT OF ASSIGNOR'S INTEREST (SEE DOCUMENT FOR DETAILS).
DOCKET NUMBER: C062-02/03 US

ASSIGNOR:
KELLEHER, THOMAS J. DOC DATE: 01/12/2001

ASSIGNOR:
LAI, JAN-JI DOC DATE: 01/12/2001

ASSIGNOR:
DECOURCEY, JOSEPH P. DOC DATE: 02/01/2001

ASSIGNOR:
ZENONI, MAURIZIO DOC DATE: 01/19/2001

ASSIGNOR:
TAGLIANI, AURO R. DOC DATE: 01/19/2001

ASSIGNEE:
CUBIST PHARMACEUTICALS, INC.
65 HAYDEN AVENUE
LEXINGTON, MASSACHUSETTS 02421

SERIAL NUMBER: 11739180
PATENT NUMBER:
TITLE: HIGH PURITY LIPOPEPTIDES

FILING DATE:
ISSUE DATE:

ASSIGNMENT SERVICES BRANCH
PUBLIC RECORDS DIVISION

ASSIGNMENT

I/We,

(1) Thomas J. Kelleher,
(2) Jan-Ji Lai,
(3) Joseph P. DeCourcey,
(4) Paul D. Lynch,
(5) Maurizio Zenoni, and
(6) Auro R. Tagliani,

residing, respectively, at

(1) 36 Laxfield Street
Weston, MA 02493,
(2) 5 Roy Street
Westborough, MA 01581,
(3) 3 Auburn Street
Charlestown, MA 02129,
(4) 29 Cypress Road
Arlington, MA 02474,
(5) Via Fleming #7
Paullo, Milan 20067
Italy, and
(6) Via Marangoni #1
Pavia, Italy 27100,

for good and valuable consideration, receipt of which is hereby acknowledged, have assigned, sold and transferred to and do hereby assign, sell and transfer to CUBIST PHARMACEUTICALS, INCORPORATED a corporation organized and existing under the laws of the STATE OF DELAWARE and having an office and a place of business at 24 EMILY STREET, CAMBRIDGE, MASSACHUSETTS 02139 its successors and assigns: (1) the entire right, title and interest in the United States and in all countries throughout the world in

ASSIGN.2
1/9/1

and to any and all my/our inventions and discoveries disclosed in the application for Letters Patent in the United States entitled: HIGH PURITY LIPOPEPTIDES, LIPOPEPTIDES MICELLES AND PROCESSES FOR PREPARING SAME, and filed in the United States Patent and Trademark Office on NOVEMBER 28, 2000, under Serial Number 09/735,191, including any renewals, revivals, reissues, reexaminations, extensions, continuations and divisions thereof, and any substitute applications therefor; (2) the full and complete right to file patent applications in the name of CUBIST PHARMACEUTICALS, INCORPORATED its designee, or in my/our names at CUBIST PHARMACEUTICALS, INCORPORATED or its designee's election, on the aforesaid inventions, discoveries and applications in all countries of the world; (3) the entire right, title and interest in and to any Letters Patent which may issue thereon in the United States or in any other country of the world and any renewals, revivals, reissues, reexaminations and extensions of the same; and (4) the entire right, title and interest in all Convention and Treaty Rights of all kinds thereon, including without limitation all rights of priority in any country of the world, in and to the above inventions, discoveries and applications.

I/We hereby authorize and request the competent authorities to grant and to issue any and all such Letters Patent in the United States and throughout the world to CUBIST PHARMACEUTICALS, INCORPORATED as the assignee of the entire right, title and interest therein, as fully and entirely as the same would have been held and enjoyed by me/us had this assignment, sale and transfer not been made.

I/We agree, at any time, upon the request of CUBIST PHARMACEUTICALS, INCORPORATED to execute and to deliver to CUBIST PHARMACEUTICALS, INCORPORATED any additional applications for patents for said inventions and discoveries, or any part or parts thereof, and any

applications for patents of confirmation, registration and importation based on any Letters Patent issuing on said inventions, discoveries or applications, and divisions, continuations, renewals, revivals, reissues, reexaminations and extensions thereof.

I/We further agree at any time to execute and to deliver upon request of CUBIST PHARMACEUTICALS, INCORPORATED such additional documents, if any, as are necessary or desirable to secure patent protection on said inventions, discoveries and applications throughout all countries of the world, and otherwise to do the necessary to give full effect to and to perfect the rights of CUBIST PHARMACEUTICALS, INCORPORATED under this Assignment, including the execution, delivery and procurement of any and all further documents evidencing this assignment, transfer and sale as may be necessary or desirable.

ASSIGNORS:

Thomas J Kelleher 1-12-01 (1)
THOMAS J. KELLEHER

On this 12th day of January, 2001, THOMAS J. KELLEHER (1) personally appeared before me, a Notary Public in and for The county of Middlesex, Massachusetts, and executed the foregoing Assignment and duly acknowledged to me that such Assignment was executed for the uses and purposes therein expressed.

Julia A. Vaughan
Notary Public

ASSIGN.2
1/9/1

(2)

JAN-JI LAI

On this 12th day of January, 2001, JAN-JI LAI (2) personally appeared before me, a Notary Public in and for the county of Middlesex, Massachusetts, and executed the foregoing Assignment and duly acknowledged to me that such Assignment was executed for the uses and purposes therein expressed.

Notary Public

(3)

JOSEPH P. DeCOURCEY

Witnessed:

Signature: _____

Name: _____

Signature: _____

Name: _____

ASSIGN.2
1/9/1

(2)

JAN-JI LAI

On this _____ day of _____, _____, JAN-JI LAI (2) personally appeared before me, a Notary Public in and for _____, and executed the foregoing Assignment and duly acknowledged to me that such Assignment was executed for the uses and purposes therein expressed.

_____

Notary Public

(3)

JOSEPH P. DeCOURCEY

Witnessed:

Signature: Rosa Leone

Name: ROSA LEONE

Signature: Carlo Marian

Name: CARLO MARIANI

ASSIGN.2
1/9/1

(4)

PAUL D. LYNCH

On this _____ day of _____, _____, PAUL D. LYNCH (4) personally appeared before me, a Notary Public in and for _____, and executed the foregoing Assignment and duly acknowledged to me that such Assignment was executed for the uses and purposes therein expressed.

_____
Notary Public

(5)
MAURIZIO ZENONI

Witnessed:

Signature: _____

Name: ALESSANDRO DONADELLI

Signature: _____

Name: IVAN CARBONI

(6)
AURO R. TAGLIANI

Witnessed:

Signature: _____

Name: ALESSANDRO DONADELLI

Signature: _____

Name: IVAN CARBONI

ASSIGN.2
1/9/1

ACKNOWLEDGEMENT OF ASSIGNEE:

CUBIST PHARMACEUTICALS, INCORPORATED

By: _____
Alan D. Watson
Senior Vice President,
Corporate Development

On this 17th day of January, 2001, Alan D. Watson personally appeared before me, a Notary Public in and for the County of Middlesex, Massachusetts, and duly acknowledged the executed Assignment on behalf of the Assignee.

_____
Notary Public

ASSIGN.2
1/9/1

Electronic Acknowledgement Receipt

EFS ID:	10904336
Application Number:	11739180
International Application Number:	
Confirmation Number:	8837
Title of Invention:	HIGH PURITY LIPOPEPTIDES
First Named Inventor/Applicant Name:	Thomas Kelleher
Customer Number:	34103
Filer:	Nicholas M.C. Boivin
Filer Authorized By:	
Attorney Docket Number:	C062-02/03 US
Receipt Date:	08-SEP-2011
Filing Date:	24-APR-2007
Time Stamp:	16:47:55
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Power of Attorney	C062_02_03_POA_SB_81_Form.pdf	636098 99c2706371e19691ece4ce68b9b02a4f59b6ec42	no	1

Warnings:

Information:

2	Assignee showing of ownership per 37 CFR 3.73(b).	C062_02_03_US_Statement_Under_3_73_SB_96_Form.pdf	6917443 3d5ba37bf5acac49f8e1b744a067ba312a1bcb01	no	20

Warnings:	
Information:	
Total Files Size (in bytes):	7553541

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

NOTICE OF ALLOWANCE AND FEE(S) DUE

34103 7590 09/07/2011

Intellectual Property Department
Cubist Pharmaceuticals, Inc.
65 Hayden Avenue
Lexington, MA 02421

EXAMINER
KAM, CHIH MIN

ART UNIT	PAPER NUMBER
1656	

DATE MAILED: 09/07/2011

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/739,180	04/24/2007	Thomas Kelleher	C062-02/03 US	8837

TITLE OF INVENTION: HIGH PURITY LIPOPEPTIDES

APPLN. TYPE	SMALL ENTITY	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	YES	$755	$300	$0	$1055	12/07/2011

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the SMALL ENTITY status shown above.

If the SMALL ENTITY is shown as YES, verify your current SMALL ENTITY status:

A. If the status is the same, pay the TOTAL FEE(S) DUE shown above.

B. If the status above is to be removed, check box 5b on Part B - Fee(s) Transmittal and pay the PUBLICATION FEE (if required) and twice the amount of the ISSUE FEE shown above, or

If the SMALL ENTITY is shown as NO:

A. Pay TOTAL FEE(S) DUE shown above, or

B. If applicant claimed SMALL ENTITY status before, or is now claiming SMALL ENTITY status, check box 5a on Part B - Fee(s) Transmittal and pay the PUBLICATION FEE (if required) and 1/2 the ISSUE FEE shown above.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

34103 7590 09/07/2011

Intellectual Property Department
Cubist Pharmaceuticals, Inc.
65 Hayden Avenue
Lexington, MA 02421

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/739,180	04/24/2007	Thomas Kelleher	C062-02/03 US	8837

TITLE OF INVENTION: HIGH PURITY LIPOPEPTIDES

APPLN. TYPE	SMALL ENTITY	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	YES	$755	$300	$0	$1055	12/07/2011

EXAMINER	ART UNIT	CLASS-SUBCLASS
KAM, CHIH MIN	1656	514-009000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

❑ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

❑ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list

(1) the names of up to 3 registered patent attorneys or agents OR, alternatively,

(2) the name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 _____

2 _____

3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. The following fee(s) are submitted:

❑ Issue Fee

❑ Publication Fee (No small entity discount permitted)

❑ Advance Order - # of Copies _____

4b. Payment of Fee(s): **(Please first reapply any previously paid issue fee shown above)**

❑ A check is enclosed.

❑ Payment by credit card. Form PTO-2038 is attached.

❑ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)

❑ a. Applicant claims SMALL ENTITY status. See 37 CFR 1.27.

❑ b. Applicant is no longer claiming SMALL ENTITY status. See 37 CFR 1.27(g)(2).

NOTE: The Issue Fee and Publication Fee (if required) will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the United States Patent and Trademark Office.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

This collection of information is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/739,180	04/24/2007	Thomas Kelleher	C062-02/03 US	8837

34103 7590 09/07/2011

Intellectual Property Department
Cubist Pharmaceuticals, Inc.
65 Hayden Avenue
Lexington, MA 02421

EXAMINER	
KAM, CHIH MIN	

ART UNIT	PAPER NUMBER
1656	

DATE MAILED: 09/07/2011

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment to date is 0 day(s). If the issue fee is paid on the date that is three months after the mailing date of this notice and the patent issues on the Tuesday before the date that is 28 weeks (six and a half months) after the mailing date of this notice, the Patent Term Adjustment will be 0 day(s).

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Notice of Allowability	Application No.	Applicant(s)
	11/739,180	KELLEHER ET AL.
	Examiner	Art Unit
	CHIH-MIN KAM	1656

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *5/27/2011*.
2. ☒ The allowed claim(s) is/are *2-29,31-36,38-44,47-52,54-56,58-86 and 88-200*.
3. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
   a) ☐ All b) ☐ Some* c) ☐ None of the:
      1. ☐ Certified copies of the priority documents have been received.
      2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
      3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

4. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.
5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
      1) ☐ hereto or 2) ☐ to Paper No./Mail Date _____.
   (b) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).
6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)	5. ☐ Notice of Informal Patent Application
2. ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)	6. ☐ Interview Summary (PTO-413), Paper No./Mail Date _____ .
3. ☐ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date _____	7. ☒ Examiner's Amendment/Comment
4. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material	8. ☒ Examiner's Statement of Reasons for Allowance
	9. ☐ Other _____.
/Chih-Min Kam/ Primary Examiner, Art Unit 1656	

DETAILED ACTION

Status of the Claims

1. Claims 2-29, 31-36, 38-44, 47-52, 54-56 and 58-200 are pending.

Applicants' amendment filed May 27, 2011 is acknowledged. Claims 2-4, 6, 7, 10, 54, 55, 58, 62, 76, 82, 83, 85, 87-92, 94, 95, 108, 109 and 115 have been amended, claim 1 has been cancelled, and new claims 161-200 have been added. Therefore, claims 2-29, 31-36, 38-44, 47-52, 54-56 and 58-200 are examined.

Withdrawn Claim Rejections - 35 USC § 112

2. The previous rejection of claim 8-29, 31-36, 38-44, 47-52, 55-56, 58-114 and 116-160 under 35 U.S.C.112, second paragraph, is withdrawn in view of applicants' amendment of the claims and applicants' response at page 35 in the amendment filed May 27, 2011.

Withdrawn Claim Rejections - 35 USC § 102

3. The previous rejection of claims 1 and 54 under U.S.C. 102(e) as being as anticipated by Baker *et al.* (US RE39,071 E) is withdrawn in view of applicants' amendment to the claims, applicants' cancellation of the claims, and applicants' response at page 34 in the amendment filed May 27, 2011.

Withdrawn Claim Rejections - Obviousness Type Double Patenting

4. The previous rejection of claims 1 and 54 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 18-20, 26, 28 and 29 of U.S. Patent RE39,071 E is withdrawn in view of applicants' amendment to the claims, applicants' cancellation of the claims, and applicants' response at page 34 in the amendment filed May 27, 2011.

Specification

5. Applicants' amendment to the specification regarding "CROSS-REFERENCE TO RELATED APPLICATIONS" at page 1 lines 5-9 is acknowledged. Applicants' petition filed May 27, 2011 under 37 CFR 1.78(a)(3),(6) to accept an unintentionally delayed priority claim has been granted.

Examiner's Amendment

An **Examiner's Amendment** to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment was given in a telephone interview with Nicholas M. Boivin on August 16, 2011.

Examiner's Amendment to the Claims:

Cancel claim 87.

Claims 2-4, 6, 54-56, 58, 60, 62-76, 80, 89, 94-96, 98, 116-127, 129, 133, 142, 149-160, 162, 171-179, 184, 189, 191-194 and 196-200 have been amended as follows:

2. (Currently Amended) A composition comprising essentially pure daptomycin purified by a process comprising the steps of:

(a) subjecting daptomycin to conditions forming a daptomycin aggregate; and

(b) obtaining ~~at least a portion of~~ the essentially pure daptomycin from the daptomycin aggregate.

3. (Currently Amended) A composition comprising daptomycin that is substantially free of anhydro-daptomycin and substantially free of β-isomer of daptomycin, the daptomycin being purified by a process comprising the steps of:

(a) subjecting daptomycin to conditions forming a daptomycin aggregate; and

(b) obtaining ~~at least a portion of~~ the daptomycin that is substantially free of anhydro-daptomycin ~~and~~ or substantially free of β-isomer of daptomycin from the daptomycin aggregate.

4. (Currently Amended) The composition according to claim 3 that is essentially free of anhydro-daptomycin, wherein the step of obtaining the daptomycin that is essentially free of anhydro-daptomycin from the daptomycin aggregate further comprises the steps of:

(c) subjecting the daptomycin aggregate to conditions to form monomeric daptomycin; and

(d) obtaining ~~at least a portion of~~ the daptomycin that is essentially free of anhydro-daptomycin from the monomeric daptomycin.

6. (Currently Amended) A composition comprising purified daptomycin that is substantially free of each of impurities 1 to 14 defined by peaks 1-14 shown in FIG. 12, the purified daptomycin being obtained by a process comprising the steps of:

(a) subjecting daptomycin to conditions forming a daptomycin aggregate;

(b) subjecting the daptomycin aggregate to conditions forming monomeric daptomycin; and

(c) obtaining ~~at least a portion of~~ the daptomycin from the monomeric daptomycin, the daptomycin aggregate or a combination thereof.

54 (Currently amended) A ~~purified daptomycin~~ pharmaceutical composition comprising essentially pure daptomycin purified by a process comprising the steps of:

(a) forming micelles comprising daptomycin;

(b) converting the micelles to a non-micellar daptomycin composition comprising daptomycin in a non-micellar state; and

(c) obtaining ~~at least a portion of~~ the purified daptomycin from the micelles, the non-micellar daptomycin composition, or a combination thereof.

55. (Currently Amended) The pharmaceutical composition of claim 54 comprising daptomycin of at least ~~about~~ 98% purity measured relative to daptomycin impurities 1-14 defined by peaks 1-14 shown in FIG. 12.

56. (Currently Amended) The ~~method~~ pharmaceutical composition of claim 54 wherein the ~~composition is~~ daptomycin ~~of~~ is at least ~~about~~ 99% ~~purity~~ pure.

58. (Currently Amended) A ~~new~~ composition comprising daptomycin of greater than or about 93% purity relative to daptomycin impurities that arise in fermentation or purification of daptomycin, and wherein the daptomycin impurities comprise impurities 1-14 defined by peaks 1-14 shown in FIG. 12, and the daptomycin is obtained by a process comprising the step of forming a micelle comprising daptomycin.

60. (Currently Amended) The composition of claim 58, wherein the purity of daptomycin is at least ~~95%~~ 93%.

62. (Currently Amended) A purified daptomycin composition comprising daptomycin of greater than or about 93% purity relative to impurities 1-14 defined by peaks 1-14 shown in FIG. 12, the daptomycin being obtained by a process comprising the step of forming an aggregate comprising daptomycin.

63. (Currently Amended) The ~~daptomycin~~ composition of claim 62, wherein the purity of daptomycin is at least ~~95%~~ 93%.

64. (Currently Amended) The composition of claim 58 wherein impurity 1 is present in an amount no more than ~~about~~ 1%.

65. (Currently Amended) The composition of claim 58 wherein impurity 2 is present in an amount no more than ~~about~~ 0.5%.

66. (Currently Amended) The composition of claim 58 wherein impurity 3 is present in an amount no more than ~~about~~ 1%.

67. (Currently Amended) The composition of claim 58 wherein impurity 4 is present in an amount no more than ~~about~~ 0.5%.

68. (Currently Amended) The composition of claim 58 wherein impurity 5 is present in an amount no more than ~~about~~ 0.5%.

69. (Currently Amended) The composition of claim 58 wherein impurity 6 is present in an amount no more than ~~about~~ 1%.

70. (Currently Amended) The composition of claim 58 wherein impurity 7 is present in an amount no more than ~~about~~ 1%.

71. (Currently Amended) The composition of claim 58 wherein impurity ~~9~~ 8 is present in an amount no more than ~~about 0.5%~~ 4%.

72. (Currently Amended) The composition of claim ~~58~~ 64 wherein impurity ~~10~~ 8 is present in an amount no more than ~~about 0.5%~~ 1%.

73. (Currently Amended) The composition of claim ~~58~~ 71 wherein impurity ~~11~~ 8 is present in an amount no more than ~~about 0.5%~~ 1%.

74. (Currently Amended) The composition of claim 58 wherein impurity 12 is present in an amount no more than ~~about~~ 0.5%.

75. (Currently Amended) The composition of claim 58 wherein impurity 14 is present in an amount no more than ~~about~~ 0.1%.

76. (Currently Amended) The composition of claim 62, wherein the daptomycin is obtained by a process comprising:

a) subjecting a daptomycin solution to conditions forming a daptomycin aggregate;

b) separating the daptomycin aggregate from low molecular weight contaminants; and

c) subjecting the daptomycin aggregate to conditions in which the daptomycin aggregate dissociates into daptomycin monomers.

80. (Currently Amended) The composition of claim 79, wherein the daptomycin monomers ~~of~~ are separated from the high molecular weight contaminants by a size selection technique.

89. (Currently Amended) The composition of claim 82, wherein the ~~aggregate is a~~ micelle ~~consisting~~ consists of daptomycin.

94. (Currently Amended) The composition of claim 93, wherein the ~~micelle comprising~~ daptomycin preparation of step a) that comprises micelle ~~is at~~ has a pH of 2.5 to 4.7, and the preparation further comprises 300 to 500 mM NaC1 and is at a temperature of 2-15 degrees C.

95. (Currently Amended) The composition of claim 62, wherein the daptomycin is obtained by a process further comprising:

~~a) subjecting a daptomycin solution to conditions forming [[a]]the daptomycin aggregate;~~

~~b)~~ a) separating the daptomycin aggregate from low molecular weight contaminants; and

~~c)~~ b) subjecting the daptomycin aggregate to conditions in which the daptomycin aggregate dissociates into daptomycin monomers.

96. (Currently Amended) The composition of claim 95, wherein the daptomycin aggregate of step ~~b)~~ a) is separated from the low molecular weight contaminants by a size selection technique.

98. (Currently Amended) The composition of claim 97 further comprising separating the daptomycin monomers obtained from step ~~c)~~ b) from high molecular weight contaminants.

116. (Currently Amended) The composition of claim 62 wherein impurity 1 is present in an amount no more than ~~about~~ 1%.

117. (Currently Amended) The composition of claim 62 wherein impurity 2 is present in an amount no more than ~~about~~ 0.5%.

118. (Currently Amended) The composition of claim 62 wherein impurity 3 is present in an amount no more than ~~about~~ 1%.

119. (Currently Amended) The composition of claim 62 wherein impurity 4 is present in an amount no more than ~~about~~ 0.5%.

120. (Currently Amended) The composition of claim 62 wherein impurity 5 is present in an amount no more than ~~about~~ 0.5%.

121. (Currently Amended) The composition of claim 62 wherein impurity 6 is present in an amount no more than ~~about~~ 1%.

122. (Currently Amended) The composition of claim 62 wherein impurity 7 is present in an amount no more than ~~about~~ 1%.

123. (Currently Amended) The composition of claim 62 wherein impurity ~~9~~ 8 is present in an amount no more than ~~about 0.5%~~ 4%.

124. (Currently Amended) The composition of claim ~~62~~ 116 wherein impurity ~~10~~ 8 is present in an amount no more than ~~about 0.5%~~ 1%.

125. (Currently Amended) The composition of claim ~~62~~ 123 wherein impurity ~~11~~ 8 is present in an amount no more than ~~about 0.5%~~ 1%.

126. (Currently Amended) The composition of claim 62 wherein impurity 12 is present in an amount no more than ~~about~~ 0.5%.

127. (Currently Amended) The composition of claim 62 wherein impurity 14 is present in an amount no more than ~~about~~ 0.1%.

129. (Currently Amended) The composition of claim 63, wherein the daptomycin is obtained by a process comprising:

a) subjecting a daptomycin solution to conditions forming a daptomycin aggregate;

b) separating the daptomycin aggregate from low molecular weight contaminants; and

c) subjecting the daptomycin aggregate to conditions in which the daptomycin aggregate dissociates into daptomycin monomers.

133. (Currently Amended) The composition of claim 132, wherein the daptomycin monomers ~~of~~ are separated from the high molecular weight contaminants by a size selection technique.

142. (Currently Amended) The composition of claim ~~135~~ 141, wherein the aggregate is a micelle.

149. (Currently Amended) The composition of claim 63 wherein impurity 1 is present in an amount no more than ~~about~~ 1%.

150. (Currently Amended) The composition of claim 63 wherein impurity 2 is present in an amount no more than ~~about~~ 0.5%.

151. (Currently Amended) The composition of claim 63 wherein impurity 3 is present in an amount no more than ~~about~~ 1%.

152. (Currently Amended) The composition of claim 63 wherein impurity 4 is present in an amount no more than ~~about~~ 0.5%.

153. (Currently Amended) The composition of claim 63 wherein impurity 5 is present in an amount no more than ~~about~~ 0.5%.

154. (Currently Amended) The composition of claim 63 wherein impurity 6 is present in an amount no more than ~~about~~ 1%.

155. (Currently Amended) The composition of claim 63 wherein impurity 7 is present in an amount no more than ~~about~~ 1%.

156. (Currently Amended) The composition of claim 63 wherein impurity ~~9~~ 8 is present in an amount no more than ~~about 0.5%~~ 4%.

157. (Currently Amended) The composition of claim ~~63~~ 149 wherein impurity ~~10~~ 8 is present in an amount no more than ~~about 0.5%~~ 1%.

158. (Currently Amended) The composition of claim ~~63~~ 156 wherein impurity ~~11~~ 8 is present in an amount no more than ~~about 0.5%~~ 1%.

159. (Currently Amended) The composition of claim 63 wherein impurity 12 is present in an amount no more than ~~about~~ 0.5%.

160. (Currently Amended) The composition of claim 63 wherein impurity 14 is present in an amount no more than ~~about~~ 0.1%.

162. (Currently Amended) The composition of claim 161, wherein the daptomycin is purified by a process comprising the steps of:

(a) subjecting a daptomycin solution to conditions forming the daptomycin aggregate;

(b) separating the daptomycin aggregate from low molecular weight contaminants; and

(c) subjecting the daptomycin aggregate to conditions in which the daptomycin micelle dissociates into daptomycin monomers.

171. (Currently Amended) A purified daptomycin composition of greater than or about 93% purity relative to impurities 1-14 defined by peaks 1-14 shown in FIG. 12, the purified daptomycin composition obtained by a process comprising the steps of:

(a) subjecting daptomycin to conditions forming daptomycin micelles and

(b) obtaining ~~at least a portion of~~ the purified daptomycin from the daptomycin micelles.

172. (Currently Amended) The purified daptomycin composition of claim 171, wherein the step of obtaining the purified daptomycin from the daptomycin micelles further comprises the steps of:

(c) subjecting the daptomycin micelles to conditions forming monomeric daptomycin from the daptomycin micelles; and

(d) obtaining ~~at least a portion of~~ the purified daptomycin from the monomeric daptomycin.

173. (Currently Amended) The purified daptomycin composition of claim 172, wherein the step of subjecting the daptomycin micelles to conditions to form monomeric daptomycin from the daptomycin micelles includes one or more of the following steps:

(a) raising the pH of the daptomycin ~~aggregate~~ micelles to about 6.0 or higher;

(b) adjusting the daptomycin concentration to below the critical micelle concentration;

(c) contacting the daptomycin ~~aggregate~~ micelles with an organic solvent; and

(d) raising the temperature of the daptomycin ~~aggregate~~ micelles above or about 15 degrees C.

174. (Currently Amended) The purified daptomycin composition of claim 171, wherein the step of obtaining the daptomycin from the daptomycin micelles further comprises the steps of:

(c) filtering the daptomycin micelles under conditions in which the daptomycin micelles are retained on the filter;

(d) collecting the daptomycin aggregate;

(e) subjecting the daptomycin micelles to conditions to form monomeric daptomycin from the daptomycin micelles; and

(f) obtaining ~~at least a portion of~~ the purified daptomycin from the monomeric daptomycin.

175. (Currently Amended) A purified daptomycin composition of greater than or about 93% purity relative to impurities 1-14 defined by peaks 1-14 shown in FIG. 12, the purified daptomycin composition obtained by a process comprising the steps of:

(a) subjecting an aqueous solution comprising daptomycin at or above the critical daptomycin micelle concentration to a pH of 3.0 to 4.8 at a temperature of about 2-15 degrees C to form a daptomycin preparation; and

(b) obtaining the purified daptomycin from the daptomycin preparation obtained in step (a).

176. (Currently Amended) The composition of claim 175, wherein the daptomycin preparation comprises daptomycin aggregates, and wherein the process further comprises:

(a) ~~the process further comprises~~ filtering the daptomycin preparation ~~is filtered~~ to obtain a filtered daptomycin material comprising the daptomycin aggregates; and

(b) ~~the purified daptomycin is obtained from the filtered daptomycin material by a process comprising the step of~~ contacting the filtered daptomycin material with an organic solvent or a solvent having a pH of at least or about 6.0.

177. (Currently Amended) The composition of claim 176, wherein the purified daptomycin is obtained by contacting the filtered daptomycin material with a hydrophobic interaction chromatography (HIC) resin and eluted with ~~an organic~~ a solvent at a pH of about 6.0-7.5.

178. (Currently Amended) A purified daptomycin composition of greater than or about 93% purity relative to impurities 1-14 defined by peaks 1-14 shown in FIG. 12, wherein the ~~%~~

percent purity is measured by HPLC analysis ~~according to the resolution method in Table 2~~, and the purified daptomycin composition is obtained from a lipopeptide aggregate comprising daptomycin.

179. (Currently Amended) A purified daptomycin composition of greater than or about 93% purity relative to impurities 1-14 defined by peaks 1-14 shown in FIG. 12, wherein the ~~%~~ percent purity is measured by HPLC analysis ~~according to the resolution method in Table 2~~, and the purified daptomycin composition is obtained by a process comprising the steps of:

(a) fermenting a culture of ~~*S.*~~ *Streptomyces roseosporus* to produce daptomycin;

(b) contacting the daptomycin from step (a) with an anion exchange resin;

(c) eluting the daptomycin from the anion exchange resin in step (b) with a solvent having a pH of about 6.0-6.5 to obtain a daptomycin solution;

(d) adjusting the pH of the daptomycin solution from step (c) to about 3.0 to 4.8 and a temperature ~~of the solution from step (c)~~ to about 2-15 degrees C to obtain a daptomycin aggregate solution comprising [[a]] daptomycin aggregates; and

(e) filtering the daptomycin aggregate solution to separate daptomycin aggregates from the daptomycin aggregate solution; and

(f) obtaining the purified daptomycin from the daptomycin aggregates.

184. (Currently Amended) The composition of claim 183, wherein ~~the step of converting~~ the daptomycin micelles collected in step (ii) are converted to the non-micellar daptomycin in step (b).

189. (Currently Amended) The composition of claim ~~185~~ 183, wherein the ~~aggregate comprises~~ daptomycin micelles are formed by a process comprising one or more steps selected from the group consisting of: adjusting the pH of a daptomycin preparation to a

pH of about 2.5 to 5.0, combining daptomycin with 300 to 500 mM NaC1 in an aqueous solution; and providing a daptomycin preparation at a temperature of 2-15 degrees C.

191. (Currently Amended) The composition of claim 178, wherein the daptomycin composition is at least or about 95% pure.

192. (Currently Amended) The composition of claim 178, wherein the daptomycin composition is at least or about 97% pure.

193. (Currently Amended) The composition of claim 178, wherein the daptomycin composition is at least or about 98% pure.

194. (Currently Amended) The composition of claim 178, wherein the daptomycin composition is at least ~~about 99%~~ 93% pure.

196. (Currently Amended) The composition of claim 2, wherein the daptomycin has greater than ~~about 93%~~ 98% purity measured by HPLC analysis ~~according to the resolution method in Table 2, and the purified daptomycin composition is obtained from a lipopeptide aggregate comprising daptomycin~~.

197. (Currently Amended) The composition of claim 3, wherein the daptomycin has greater than or about 93% purity measured by HPLC analysis ~~according to the resolution method in Table 2, and the purified daptomycin composition is obtained from a lipopeptide aggregate comprising daptomycin~~.

198. (Currently Amended) The composition of claim 4, wherein the daptomycin has greater than or about 93% purity measured by HPLC analysis ~~according to the resolution method in Table 2, and the purified daptomycin composition is obtained from a lipopeptide aggregate comprising daptomycin~~.

199. (Currently Amended) The composition of claim ~~6~~ 62, wherein the daptomycin has
greater than ~~about~~ 93% purity measured by HPLC analysis ~~according to the resolution method in~~

~~Table 2, and the purified daptomycin composition is obtained from a lipopeptide~~ the daptomycin ~~aggregate comprising daptomycin~~.

200. (Currently Amended) The composition of claim 115, wherein the daptomycin has greater than or about 93% purity measured by HPLC analysis ~~according to the resolution method in Table 2, and the purified daptomycin composition is obtained from a lipopeptide aggregate comprising daptomycin~~.

The following is an Examiner's Statement of Reasons for Allowance: The following reference is the closest art to the claimed invention. Baker *et al.* (US RE39,071 E, reissue of U.S. Patent 5,912,226) teach an antibacterial composition comprising daptomycin (LY146032) obtained in substantially pure form, which refers to daptomycin that contains less than 2.5% of a combined total of anhydro-daptomycin and beta-isomer of daptomycin (column 8, lines 50-60; Examples 4 and 5), where daptomycin is purified by a procedure using Diaion HP-20 resin column, followed by HPLC and another HP-20 resin column (Examples 1-5). Baker *et al.* also teach the preparation of a pharmaceutical formulation comprising the purified daptomycin (LY146032) with pharmaceutical carriers or excipients (column 9, lines 47-59), and an antibiotic composition comprised of a combination of a compound of formula 1 (i.e., anhydro-A21978C; column 1, lines 14-21), a compound of formula 2 (isomer of A21978C) and a compound of formula 3 (the parent cyclic peptide of A21978C; LY146032) or pharmaceutically acceptable salts. However, Baker *et al.* do not disclose a composition comprising purified daptomycin selected from the group consisting of: (a) essentially pure daptomycin, (b) daptomycin that is substantially free of anhydro-daptomycin and substantially free of β-isomer of daptomycin, (c) daptomycin that is essentially free of anhydro-daptomycin and substantially free of β-isomer of daptomycin, (d) daptomycin that is free of anhydro-daptomycin and substantially free of β-isomer of daptomycin, (e) daptomycin that is substantially free of each of impurities 1 to 14 defined by peaks 1-14 shown in FIG. 12, and (f) daptomycin that is essentially free of each of impurities 1 to 14 defined by peaks 1-14 shown in FIG. 12. Therefore, the claims are allowable over the art of record.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chih-Min Kam whose telephone number is (571) 272-0948. The examiner can normally be reached on 8.00-4:30, Mon-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath Rao can be reached at 571-272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Chih-Min Kam/
Primary Examiner, Art Unit 1656

CMK
August 16, 2011

Search Notes	Application No.	Applicant(s)	
	11/739,180	KELLEHER ET AL.	
	Examiner	Art Unit	
	CHIH-MIN KAM	1656	

SEARCHED			
Class	Subclass	Date	Examiner
514	9, 11, 2, 14	7/25/2011	CMK
530	317, 322	7/25/2011	CMK
530	344	7/25/2011	CMK
435	886	7/25/2011	CMK

INTERFERENCE SEARCHED			
Class	Subclass	Date	Examiner
514	**9,11,2,14**	**7/25/2011**	**CMK**
530	317,322	7/25/2011	CMK
530	344	7/25/2011	CMK
435/866		7/25/2011	CMK

SEARCH NOTES (INCLUDING SEARCH STRATEGY)		
	DATE	EXMR
EAST Search on USPAT, USPGPUB, DERWENT, EPO, JPO; STN search on MEDLINE, BIOSIS, EMBASE, SCISEARCH, AGRICOLA.	2/13/2008	CMK
Search strategy enclosed, Inventor name search, Parent applications 60/177,170 and 09/735,191, 10/747,48 have been reviewed.	2/13/2008	CMK
Update the search	10/28/2008	CMK
Update the search	8/5/2009	CMK
Update the search	2/3/2010	CMK
Update the search	11/11/2010	CMK
Update the search	**7/25/2011**	**CMK**

=> d his

(FILE 'HOME' ENTERED AT 18:19:13 ON 25 JUL 2011)

FILE 'MEDLINE, CAPLUS, BIOSIS, EMBASE, SCISEARCH, AGRICOLA' ENTERED AT 18:19:33 ON 25 JUL 2011

L1 8447 S DAPTOMYCIN

L2 2964 S SUBSTANTIALLY PURE

L3 2390 S ESSENTIALLY PURE

L4 0 S L1 (P) (L2 OR L3)

L5 2 S L1 (P) IMPURITIES

L6 2 DUPLICATE REMOVE L5 (0 DUPLICATES REMOVED)

L7 5 S ANHYDRO-DAPTOMYCIN OR BETA-DAPTOMYCIN

L8 5 DUPLICATE REMOVE L7 (0 DUPLICATES REMOVED)

L9 5 S L8 NOT L6

L10 119012 S ANION EXCHANGE

L11 11444 S HYDROPHOBIC INTERACTION CHROMATOGRAPHY

L12 2 S L1 (P) L10 (P) L11

L13 1 S L12 NOT (L6 OR L9)

L14 415 S (LY 146032) OR A-21978C OR A54145 OR A-21978

L15 1 S L14 (P) (L2 OR L3)

L16 1 S L15 NOT (L6 OR L9 OR L13)

L17 223 S KELLEHER T?/AU

L18 12875 S LAI J?/AU

L19 13 S DECOURCEY J?/AU

L20 4027 S LYNCH P?/AU

L21 88 S ZENONI M?/AU

L22 144 S TAGLIANI A?/AU

L23 17357 S L17 OR L18 OR L19 OR L20 OR L21 OR L22

L24 20 S L23 AND L1

L25 8 DUPLICATE REMOVE L24 (12 DUPLICATES REMOVED)

L26 7 S L25 NOT (L5 OR L9 OR L16)

=> log y

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	1176	daptomycin	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2011/08/17 07:27
L2	61083	substantially adj pure	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2011/08/17 07:27
L3	15607	essentially adj pure	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2011/08/17 07:27
L4	9	L1 same (L2 or L3)	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2011/08/17 07:27
L5	15	impurities same L1	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2011/08/17 07:27
L6	14	anhydro-daptomycin or beta-daptomycin	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2011/08/17 07:28
L7	56873	anion adj exchange	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2011/08/17 07:28
L8	14726	hydrophobic adj interaction adj chromatography	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2011/08/17 07:28
L9	7	L1 same L7 same L8	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2011/08/17 07:28
L10	108	(Ly adj "146032") or A-21978C or A54145 or A-21978	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2011/08/17 07:28
L11	2	L10 same (L2 or L3)	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2011/08/17 07:28
L12	20	kelleher adj thomas.in.	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2011/08/17 07:29
L13	11	lai adj jan-ji.in.	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2011/08/17 07:29
L14	3	decourcey adj joseph.in.	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2011/08/17 07:29
L15	30	lynch adj paul.in.	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2011/08/17 07:29
L16	78	zenoni adj maurizio.in.	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2011/08/17 07:29
L17	7	tagliani adj auro.in.	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2011/08/17 07:29
L18	132	L12 or L13 or L14 or L15 or L16 or L17	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2011/08/17 07:29
L19	9	L18 and L1	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2011/08/17 07:29

8/ 17/ 2011 7:29:41 AM
C:\ Users\ ckam\ Documents\ EAST\ Workspaces\ % daptomycin-1.wsp

Issue Classification	Application/Control No.	Applicant(s)/Patent under Reexamination	
	11/739,180	KELLEHER ET AL.	
	Examiner	Art Unit	
	CHIH-MIN KAM	1656	

ISSUE CLASSIFICATION

ORIGINAL						CROSS REFERENCE(S)							
CLASS				SUBCLASS	CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)							
514				9	514	11	2	14					
INTERNATIONAL CLASSIFICATION					530	317	322	344					
C	0	7	K	7/50	435	886							
C	0	7	K	7/00									
				/									
				/									
				/									

(Assistant Examiner) (Date)

(Legal Instruments Examiner) (Date)

/Chih-Min Kam/ 8/16/2011

(Primary Examiner) (Date)

Total Claims Allowed: 192

O.G. Print Claim(s)	O.G. Print Fig.
1	NONE

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original
	1	54	31	24	61	44	91	157	121	116	151	13	181
1	2	55	32	49	62	45	92	158	122	117	152	14	182
3	3	56	33	92	63	46	93	159	123	118	153	15	183
4	4	57	34	25	64	47	94	152	124	119	154	16	184
6	5	58	35	27	65	132	95	160	125	120	155	17	185
8	6	59	36	28	66	133	96	161	126	121	156	18	186
9	7		37	29	67	134	97	162	127	114	157	19	187
51	8	85	38	30	68	135	98	163	128	122	158	184	188
52	9	86	39	31	69	136	99	93	129	123	159	20	189
53	10	87	40	32	70	137	100	94	130	124	160	185	190
66	11	88	41	33	71	139	101	95	131	165	161	186	191
67	12	89	42	26	72	140	102	96	132	166	162	187	192
68	13	90	43	34	73	141	103	97	133	167	163	188	193
69	14	91	44	35	74	142	104	98	134	169	164	189	194
70	15		45	36	75	138	105	100	135	170	165	190	195
71	16		46	125	76	143	106	101	136	171	166	2	196
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74	19	62	49	128	79	146	109	99	139	173	169	164	199
75	20	63	50	129	80	147	110	104	140	174	170	175	200
76	21	64	51	130	81	148	111	105	141	176	171		201
77	22	65	52	37	82	149	112	106	142	177	172		202
78	23		53	38	83	150	113	107	143	178	173		203
79	24	10	54	39	84	48	114	108	144	179	174		204
80	25	11	55	40	85	50	115	109	145	180	175		205
81	26	12	56	131	86	151	116	110	146	181	176		206
82	27		57		87	153	117	111	147	182	177		207
83	28	21	58	42	88	154	118	112	148	183	178		208
84	29	22	59	41	89	155	119	113	149	191	179		209
	30	23	60	43	90	156	120	115	150	192	180		210

SPE RESPONSE FOR CERTIFICATE OF CORRECTION

DATE : **08/11/11**

TO SPE OF : ART UNIT: **3769 Attn: YAO SAMCHUAN (SAM) C (SPE)**

SUBJECT : Request for Certificate of Correction for Appl. No.: **11/583434** Patent No.: **7967016**

CofC mailroom date: 08/01/11

Please respond to this request for a certificate of correction within 7 days.

FOR IFW FILES:

Please review the requested changes/corrections as shown in the **COCIN** document(s) in the IFW application image. No new matter should be introduced, nor should the scope or meaning of the claims be changed.

Please complete the response (see below) and forward the completed response to scanning using document code **COCX**.

FOR PAPER FILES:

Please review the requested changes/corrections as shown in the attached certificate of correction. Please complete this form (see below) and forward it with the file to:

Certificates of Correction Branch (CofC)
Randolph Square – 9D10-A
Palm Location 7580

Note: Please check Related U.S. Application Data & Cross-Reference to Related Application

Tasneem Siddiqui
Certificates of Correction Branch
703-756-1814 & 703-756-1593

Thank You For Your Assistance

The request for issuing the above-identified correction(s) is hereby:
Note your decision on the appropriate box.

- ☐ **Approved** — **All** changes apply.
- ☐ **Approved in Part** — Specify below which changes **do not** apply.
- ☐ **Denied** — State the reasons for denial below.

Comments: _____

_____

_____

_____ _____
SPE **Art Unit**

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JUN 14 2011

OFFICE OF PETITIONS

Intellectual Property Department
Cubist Pharmaceuticals, Inc.
65 Hayden Avenue
Lexington MA 02421

In re Application of	:	
KELLEHER et al.	:	
Application No. 11/739,180	:	DECISION ON PETITIONS
Filed: April 24, 2007	:	UNDER 37 CFR 1.78(a)(3) AND (a)(6)
Attorney Docket No. C062-02/03 US	:	

This is a decision on the petitions under 37 CFR §§ 1.78(a)(3) and 1.78(a)(6), filed May 27, 2011, to accept an unintentionally delayed claim under 35 U.S.C. §§120 and 119(e) for the benefit of the prior-filed applications as set forth in the currently filed Application Data Sheet.

The petitions are **GRANTED.**

A petition for acceptance of a claim for late priority under 37 CFR §§ 1.78(a)(3) and 1.78(a)(6) is only applicable to those applications filed on or after November 29, 2000. Further, the petition is appropriate only after the expiration of the period specified in 37 CFR §§ 1.78(a)(2)(ii) and 1.78(a)(5)(ii). In addition, the petition under 37 CFR §§ 1.78(a)(3) and 1.78(a)(6) must be accompanied by:

(1) the reference required by 35 U.S.C. §§ 120 and 119(e) and 37 CFR §§ 1.78(a)(2)(i) and 1.78(a)(5)(i) of the prior-filed application, unless previously submitted;

(2) the surcharge set forth in § 1.17(t); and

(3) a statement that the entire delay between the date the claim was due under 37 CFR §§ 1.78(a)(2)(ii) and 1.78(a)(5)(ii) and the date the claim was filed was unintentional. The Director may require additional information where there is a question whether the delay was unintentional.

Additionally, the instant nonprovisional application must be pending at the time of filing of the reference to the prior-filed provisional application as required by 37 CFR 1.78(a)(5)(ii). Further, the nonprovisional application claiming the benefit of the prior-filed provisional application must have been filed within twelve months of the filing date of the prior-filed provisional application.

All the above requirements having been satisfied, the late claim for benefit of priority under 35 U.S.C. §§ 120 and 119(e) is accepted as being unintentionally delayed.

The granting of the petition to accept the delayed benefit claim to the prior-filed applications under 37 CFR §§ 1.78(a)(3) and 1.78(a)(6) should not be construed as meaning that this application is entitled to the benefit of the filing date of the prior-filed applications. In order for this application to be entitled to the benefit of the prior-filed applications, all other requirements under 35 U.S.C. §§120 and 1.78(a)(1) and (a)(2) and under 35 U.S.C. §119(e) and 37 CFR 1.78(a)(4) and (a)(5) must be met. Similarly, the fact that the corrected Filing Receipt accompanying this decision on petition includes the prior-filed applications should not be construed as meaning that applicant is entitled to the claim for benefit of priority to the prior-filed applications noted thereon. Accordingly, the examiner will, in due course, consider this benefit claim and determine whether the application is entitled to the benefit of the earlier filing date.

A corrected Filing Receipt, which includes the priority claim to the prior-filed applications, accompanies this decision on petition.

Any questions concerning this matter may be directed to Jose' G Dees at (571) 272-1569. All other inquiries concerning either the examination procedures or status of the application should be directed to the Technology Center.

This application is being forwarded to Technology Center Art Unit 1656 for consideration by the examiner of the claim under 35 U.S.C. § §120 and 119(e) of the prior-filed nonprovisional and provisional applications.

David Bucci
Petitions Examiner
Office of Petitions

ATTACHMENT : Corrected Filing Receipt

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
11/739,180	04/24/2007	1656	8291	C062-02/03 US	53	1

CONFIRMATION NO. 8837

34103
Intellectual Property Department
Cubist Pharmaceuticals, Inc.
65 Hayden Avenue
Lexington, MA 02421

CORRECTED FILING RECEIPT

Date Mailed: 06/13/2011

Receipt is acknowledged of this non-provisional patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

Applicant(s)

Thomas Kelleher, Weston, MA;
Jan-Ji Lai, Westborough, MA;
Joseph P. DeCourcey, Charlestown, MA;
Paul Lynch, Arlington, MA;
Maurizio Zenoni, Milan, ITALY;
Auro Tagliani, Pavia, ITALY;

Power of Attorney: None

Domestic Priority data as claimed by applicant

This application is a CON of 10/747,485 12/29/2003 ABN
which is a DIV of 09/735,191 11/28/2000 PAT 6,696,412
which claims benefit of 60/177,170 01/20/2000

Foreign Applications (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.)

If Required, Foreign Filing License Granted: 05/08/2007

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 11/739,180**

Projected Publication Date: Not Applicable

Non-Publication Request: No

Early Publication Request: No
**** SMALL ENTITY ****

Title

High Purity Lipopeptides

Preliminary Class

514

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4158).

LICENSE FOR FOREIGN FILING UNDER

Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

GRANTED

The applicant has been granted a license under 35 U.S.C. 184, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" followed by a date appears on this form. Such licenses are issued in all applications where the conditions for issuance of a license have been met, regardless of whether or not a license may be required as

set forth in 37 CFR 5.15. The scope and limitations of this license are set forth in 37 CFR 5.15(a) unless an earlier license has been issued under 37 CFR 5.15(b). The license is subject to revocation upon written notification. The date indicated is the effective date of the license, unless an earlier license of similar scope has been granted under 37 CFR 5.13 or 5.14.

This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Bureau of Industry and Security, Department of Commerce (15 CFR parts 730-774); the Office of Foreign AssetsControl, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

NOT GRANTED

No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Appln. of:	Thomas Kelleher et al.	
Appln. No.:	11/739,180	Examiner: Chih Min Kam
Filed:	April 24, 2007	Art Unit: 1656
For:	HIGH PURITY LIPOPEPTIDES	Conf. No.: 8837
Attorney Docket No: C062-02/03 US		

PETITION UNDER 37 CFR § 1.78(a)(3),(6) TO ACCEPT AN UNINTENTIALLY DELAYED PRIORITY CLAIM

Mail Stop Petitions
Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Applicants hereby petition under 37 CFR § 1.78(a)(3),(6) for acceptance and recognition of the following priority claim:

"The present application is a continuation of ~~claims priority to~~ United States Patent Application No. 10/747,485, filed December 29, 2003 and now abandoned, which is a divisional of ~~claims priority to~~ United States Patent No. 09/735,191 filed November 28, 2000 (now U.S. Patent No. 6,696,412)~~January 20, 2001~~, which claims the benefit of United States Provisional application No. 60/177,170, filed January 20, 2000, all of which are incorporated by reference herein in their entireties."

In the Reply submitted herewith, Applicants amend the specification to contain the foregoing priority claim in the first sentence following the title.

The entire delay between the date the foregoing priority claim was due under 37 CFR § 1.78(a)(2)(ii),(5)(ii) and the present was unintentional. At the time of filing, Applicants intended to claim priority in accordance with the foregoing priority claim, as evidenced by the cross-reference contained in the first sentence of the specification as filed. Applicants now recognize that the original cross-reference did not indicate the relationships between the present application, United States Patent Application No. 10/747,485, and United States Patent Application No. 09/735,191, as required by 37

CFR § 1.78(a)(2)(i). Accordingly, Applicants now provide the foregoing cross-reference, which specifies that the present application is a continuation of United States Patent Application No. 10/747,485, which is a divisional of United States Patent Application No. 09/735,191.

Applicants request that the surcharge set forth in 37 CFR § 1.17(t) be charged to the Deposit Account No. 23-1925.

Applicants respectfully request that this petition be granted and that the foregoing priority claim be accepted and recognized in this application.

Respectfully submitted,

Date: May 27, 2011

/Nicholas M. Boivin/
Nicholas M. Boivin, Reg. No. 45,650
Attorney for Applicant

Cubist Pharmaceuticals, Inc.
65 Hayden Avenue
Lexington, Massachusetts 02421
Tel.: (781) 860-8660
Fax: (781) 860-1407

UNITED STATES PATENT & TRADEMARK OFFICE
Washington, D.C. 20231

REQUEST FOR PATENT FEE REFUND

1 Date of Request: 06/09/11

2 Serial/Patent # 11/739,180

3 Please refund the following fee(s):		4 PAPER NUMBER	5 DATE FILED	6 AMOUNT
	Filing			$
	Amendment			$
	Extension of Time			$
	Notice of Appeal/Appeal			$
	Petition		05/27/11	$ 1,410.00
	Issue			$
	Cert of Correction/Terminal Disc.			$
	Maintenance			$
	Assignment			$
	Other			$

7 TOTAL AMOUNT OF REFUND: $ 1,410.00

8 TO BE REFUNDED BY:

	Treasury Check
X	Credit Deposit A/C #:

9 5 0 -- 1 9 8 6

10 REASON:

X	Overpayment
	Duplicate Payment
	No Fee Due (Explanation):

Petition was not treated on the merits

11 REFUND REQUESTED BY:

TYPED/PRINTED NAME: Jose Dees TITLE: Petitions Examiner

SIGNATURE: PHONE: 272-6692 1569

OFFICE: Office of Petitions

****

THIS SPACE RESERVED FOR FINANCE USE ONLY:

APPROVED: DATE: 6/13/11

Instructions for completion of this form appear on the back. After completion, attach white and yellow copies to the official file and mail or hand-carry to:

Office of Finance
Refund Branch
Crystal Park One, Room 802B

FORM PTO 1577
(01/90)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Appln. of:	Thomas Kelleher et al.	
Appln. No.:	11/739,180	Examiner: Chih Min Kam
Filed:	April 24, 2007	Art Unit: 1656
For:	HIGH PURITY LIPOPEPTIDES	Conf. No.: 8837
Attorney Docket No: C062-02/03 US		

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Mail Stop Petitions
Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

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CFR § 1.78(a)(2)(i). Accordingly, Applicants now provide the foregoing cross-reference, which specifies that the present application is a continuation of United States Patent Application No. 10/747,485, which is a divisional of United States Patent Application No. 09/735,191.

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Date: May 27, 2011

/Nicholas M. Boivin/
Nicholas M. Boivin, Reg. No. 45,650
Attorney for Applicant

Cubist Pharmaceuticals, Inc.
65 Hayden Avenue
Lexington, Massachusetts 02421
Tel.: (781) 860-8660
Fax: (781) 860-1407

Electronic Patent Application Fee Transmittal

Application Number:	11739180
Filing Date:	24-Apr-2007
Title of Invention:	High Purity Lipopeptides
First Named Inventor/Applicant Name:	Thomas Kelleher
Filer:	Nicholas M.C. Boivin
Attorney Docket Number:	C062-02/03 US

Filed as Large Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Claims in excess of 20	1202	40	52	2080
Independent claims in excess of 3	1201	3	220	660
Miscellaneous-Filing:				
Petition:				
Priority accept. unintent. delayed claim	1454	1	1410	1410
Patent-Appeals-and-Interference:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Extension - 3 months with $0 paid	1253	1	1110	1110
Miscellaneous:				
		Total in USD ($)		**5260**

Electronic Acknowledgement Receipt

EFS ID:	10183660
Application Number:	11739180
International Application Number:	
Confirmation Number:	8837
Title of Invention:	High Purity Lipopeptides
First Named Inventor/Applicant Name:	Thomas Kelleher
Customer Number:	34103
Filer:	Nicholas M.C. Boivin
Filer Authorized By:	
Attorney Docket Number:	C062-02/03 US
Receipt Date:	27-MAY-2011
Filing Date:	24-APR-2007
Time Stamp:	15:09:48
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$5260
RAM confirmation Number	1701
Deposit Account	501986
Authorized User	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)

1	Extension of Time	C062-02-03_US_20110527_Petition_Ext.pdf	331527 97efdb4f6d51d9564ab3110a4b7e28a574edf19f	no	2
Warnings:					
Information:					
2	Amendment/Req. Reconsideration-After Non-Final Reject	C062-02-03_US_20110527_Resp.pdf	115827 b77cd8c372d2243d3d5c30f6af4c9c3bf3c9704f	no	35
Warnings:					
Information:					
3	Petition for review by the Office of Petitions.	C062-02-03_US_20110527_Petition_To_Accept_Unintentional_Delayed_Priority_Claim.pdf	18265 dec1040b41df512eaa6d869c9408d47e9fc38827	no	2
Warnings:					
Information:					
4	Fee Worksheet (PTO-875)	fee-info.pdf	36977 41323bfa2c5a16b727682dbd13be882ec871129f	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	502596		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

<u>New Applications Under 35 U.S.C. 111</u>
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

<u>National Stage of an International Application under 35 U.S.C. 371</u>
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

<u>New International Application Filed with the USPTO as a Receiving Office</u>
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/SB/22 (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARMENT OF COMMERCE

PETITION FOR EXTENSION OF TIME UNDER 37 CFR 1.136(a) **FY 2009** (*Fees pursuant to the Consolidated Appropriations Act, 2005 (H.R. 4818).*)	Docket Number (Optional) C062-02/03 US
Application Number 11/739,180	Filed April 24, 2007
For HIGH PURITY LIPOPEPTIDES	
Art Unit 1656	Examiner Chih-Min Kam

This is a request under the provisions of 37 CFR 1.136(a) to extend the period for filing a reply in the above identified application.

The requested extension and fee are as follows (check time period desired and enter the appropriate fee below):

		Fee	Small Entity Fee	
☐	One month (37 CFR 1.17(a)(1))	$130	$65	$
☐	Two months (37 CFR 1.17(a)(2))	$490	$245	$
☑	Three months (37 CFR 1.17(a)(3))	$1110	$555	$ 555.00
☐	Four months (37 CFR 1.17(a)(4))	$1730	$865	$
☐	Five months (37 CFR 1.17(a)(5))	$2350	$1175	$

☐ Applicant claims small entity status. See 37 CFR 1.27.

☐ A check in the amount of the fee is enclosed.

☐ Payment by credit card. Form PTO-2038 is attached.

☑ The Director has already been authorized to charge fees in this application to a Deposit Account.

☐ The Director is hereby authorized to charge any fees which may be required, or credit any overpayment, to Deposit Account Number _____.

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

I am the

☐ applicant/inventor.

☐ assignee of record of the entire interest. See 37 CFR 3.71.
Statement under 37 CFR 3.73(b) is enclosed (Form PTO/SB/96).

☐ attorney or agent of record. Registration Number _____

☑ attorney or agent under 37 CFR 1.34.
Registration number if acting under 37 CFR 1.34 45,650

/Nicholas M. Boivin/ — Signature

May 27, 2011 — Date

Nicholas M. Boivin — Typed or printed name

781-860-8631 — Telephone Number

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below.

☑ Total of 1 forms are submitted.

This collection of information is required by 37 CFR 1.136(a). The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 6 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appl. No.	:	11/739,180	Confirmation No.	8837
Applicant	:	Thomas Kelleher		
Filed	:	April 24, 2007		
TC/A.U.	:	1656		
Examiner	:	Chih-Min Kam		
Docket No.	:	C062-02/03 US		
Customer No.	:	34103		

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

RESPONSE AND AMENDMENT

This Amendment is responsive to the Office Action mailed November 30, 2010 (hereafter "the Office Action") in the above-identified application. A Petition for a Three (3) Month Extension of Time is enclosed. In the absence of such a petition, Applicant requests that this paper be considered as a Petition for a Three (3) Month Extension of Time. Please deduct the petition fee and apply any other charges or credits required for entry of this paper to Deposit Account No. 50-1986, referencing attorney docket number C062-02/03 US.

Kindly amend the application as follows:

AMENDMENT TO THE SPECIFICATION

Please replace the paragraph captioned "CROSS-REFERENCE TO RELATED APPLICATIONS" at page 1, lines 5-9 in its entirety with the following amended paragraph:

-- The present application is a continuation of United States Patent Application No. 10/747,485, filed December 29, 2003 and now abandoned, which is a divisional of United Stated Patent Application No. 09/735,191, filed November 28, 2000 (now U.S. Patent No. 6,696,412), which claims the benefit of United States Provisional application No. 60/177,170, filed January 20, 2000, all of which are incorporated by reference herein in their entireties. --

Differences between the original text at page 1, lines 5-9 differs and the amended paragraph above in the manner indicated below.

The present application is a continuation of ~~claims priority to~~ United States Patent Application No. 10/747,485, filed December 29, 2003 and now abandoned, which is a divisional of ~~claims priority to~~ United States Patent No. 09/735,191 filed November 28, 2000 (now U.S. Patent No. 6,696,412)~~January 20, 2001~~, which claims the benefit of United States Provisional application No. 60/177,170, filed January 20, 2000, all of which are incorporated by reference herein in their entireties.

AMENDMENT TO THE CLAIMS

Please amend the claims as indicated below. This listing of the claims will replace all previous claim listings.

1. (Cancelled).

2. (Currently Amended) A composition comprising essentially pure daptomycin purified by a process comprising the steps of

(a) subjecting daptomycin to conditions forming a daptomycin aggregate and

(b) obtaining at least a portion of the essentially pure daptomycin from the daptomycin aggregate.

3. (Currently Amended) A composition comprising daptomycin that is substantially free of anhydro-daptomycin and substantially free of β-isomer of daptomycin, the daptomycin being purified by a process comprising the steps of

(a) subjecting daptomycin to conditions forming a daptomycin aggregate and

(b) obtaining at least a portion of the daptomycin that is substantially free of anhydro-daptomycin and substantially free of β-isomer of daptomycin from the daptomycin aggregate.

4. (Currently Amended) The composition according to claim 3 that is essentially free of anhydro-daptomycin, wherein the step of obtaining the daptomycin that is essentially free of anhydro-daptomycin from the daptomycin aggregate further comprises the steps of:

(c) subjecting the daptomycin aggregate to conditions to form monomeric daptomycin and

(d) obtaining at least a portion of the daptomycin that is essentially free of anhydro-daptomycin from the monomeric daptomycin.

5. (Original) The composition according to claim 3 that is free of anhydro-daptomycin.

6. (Currently Amended) A composition comprising purified daptomycin that is substantially free of each of impurities 1 to 14 defined by peaks 1-14 shown in FIG. 12, the purified daptomycin being obtained by a process comprising the steps of

(a) subjecting daptomycin to conditions forming a daptomycin aggregate;

(b) subjecting the daptomycin aggregate to conditions forming monomeric daptomycin; and

(c) obtaining at least a portion of the daptomycin from the monomeric daptomycin, the daptomycin aggregate or a combination thereof.

7. (Currently Amended) The composition according to claim 6, wherein the purified daptomycin ~~that~~ is essentially free of each of impurities 1 to 14 defined by peaks 1-14 shown in FIG. 12.

8. (Previously Presented) The composition of claim 62, wherein daptomycin purity is measured by HPLC.

9. (Previously Presented) The composition of claim 62 further comprising a pharmaceutically acceptable carrier or excipient.

10. (Currently Amended) The[[A]] pharmaceutical composition according to claim 9, further comprising one or more antibiotics, one or more antifungal agents, or both an antibiotic and an antifungal agent.

11. (Previously Presented) The composition according to claim 62 or 115 wherein the daptomycin is purified by a process comprising the steps of:

a) supplying a fermentation broth;

b) fermenting *Streptomyces roseosporus* with a feed of n-decanoic acid to produce daptomycin in the fermentation broth;

c) clarifying the fermentation broth to obtain a clarified solution;

d) subjecting the clarified solution to anion exchange chromatography to obtain an enriched daptomycin preparation;

e) subjecting the enriched daptomycin preparation to hydrophobic interaction chromatography to obtain a semi-purified daptomycin preparation; and

f) subjecting the semi-purified daptomycin preparation to anion exchange chromatography to obtain the composition.

12. (Original) The composition according to claim 11, wherein the feed of n-decanoic acid is regulated to achieve a residual concentration of n-decanoic acid of no more than 50 parts per million (ppm) during fermentation.

13. (Original) The composition according to claim 11, wherein said clarifying comprises filtration or centrifugation and depth filtration.

14. (Original) The composition according to claim 11, wherein the anion exchange chromatography in d) is performed using a resin comprising a copolymer of 2-methacrylic acid and ethyleneglycol dimethacrylate (EDGM).

15. (Original) The composition according to claim 11, wherein the hydrophobic interaction chromatography is performed using a resin comprising a co-polymer of cross-linked divinylbenzene/stryene.

16. (Original) The composition according to claim 15, wherein the hydrophobic interaction chromatography is performed at neutral pH and a solvent concentration that is reduced compared to the solvent concentration used when performing the hydrophobic interaction chromatography at acidic pH.

17. (Original) The composition according to claim 16, wherein the resin is recycled by loading the column at an acidic pH and eluting the column at a neutral pH.

18. (Original) The composition according to claim 11, wherein the anion exchange chromatography in f) is performed using a resin comprising a copolymer of 2-methacrylic acid and ethyleneglycol dimethacrylate (EDGM).

19. (Original) The composition according to claim 11, wherein the anion exchange chromatography is used to reduce the level of solvent in the clarified solution.

20. (Original) The composition according to claim 11, wherein the anion exchange chromatography is performed via continuous flow chromatography.

21. (Original) The composition according to claim 11, wherein the process further comprises the step of filtering daptomycin.

22. (Original) The composition according to claim 11, wherein the process further comprises the step of depyrogenating daptomycin using ultrafiltration.

23. (Currently Amended) The composition according to claim 22, wherein said depyrogenating comprises the steps of:

i) providing a daptomycin solution under conditions in which the daptomycin is in a monomeric and nonmicellar state;

ii) filtering the daptomycin solution under conditions in which the daptomycin passes through the filter but pyrogens do not pass through the filter;

iii) subjecting the daptomycin solution to conditions forming a daptomycin aggregate;

iv) filtering the daptomycin aggregate under conditions in which the daptomycin aggregate is retained on the filter; and

v) collecting the daptomycin aggregate.

24. (Original) The composition according to claim 22, wherein the process further comprises the step of lyophilizing daptomycin.

25. (Original) The composition according to claim 22, wherein the anion exchange chromatography is performed via radial flow chromatography.

26. (Original) The composition according claim 11, wherein said clarifying comprises microfiltration or centrifugation.

27. (Original) The composition according to claim 11, wherein the process further comprises the steps of filtering and concentrating daptomycin.

28. (Original) The composition according to claim 11, wherein the process further comprises the step of separating the enriched daptomycin from low molecular weight material by ultrafiltration.

29. (Original) The composition according to claim 28, wherein the process further comprises the step of depyrogenating the daptomycin.

30. (Canceled).

31. (Original) The pharmaceutical composition of claim 9 comprising essentially pure daptomycin.

32. (Original) The pharmaceutical composition of claim 9 comprising daptomycin that is substantially free of anhydro-daptomycin and substantially free of β-isomer of daptomycin.

33. (Original) The pharmaceutical composition of claim 9 comprising daptomycin that is essentially free of anhydro-daptomycin and substantially free of β-isomer of daptomycin.

34. (Original) The pharmaceutical composition of claim 9 comprising daptomycin that is free of anhydro-daptomycin and substantially free of β-isomer of daptomycin.

35. (Original) The pharmaceutical composition of claim 9 comprising daptomycin that is substantially free of each of impurities 1 to 14 defined by peaks 1-14 shown in FIG. 12.

36. (Original) The pharmaceutical composition of claim 9 comprising daptomycin that is essentially free of each of impurities 1 to 14 defined by peaks 1-14 shown in FIG. 12.

37. (Canceled).

38. (Previously Presented) A method for preparing a pharmaceutical composition comprising combining the composition of claim 62 with a pharmaceutically acceptable carrier or excipient.

39. (Original) The method of claim 38 wherein the composition is essentially pure daptomycin.

40. (Original) The method of claim 38 wherein the composition is daptomycin that is substantially free of anhydro-daptomycin and substantially free of β-isomer of daptomycin.

41. (Original) The method of claim 38 wherein the composition is daptomycin that is essentially free of anhydro-daptomycin and substantially free of β-isomer of daptomycin.

42. (Original) The method of claim 38 wherein the composition is daptomycin that is free of anhydro-daptomycin and substantially free of β-isomer of daptomycin.

43. (Original) The method of claim 38 wherein the composition is daptomycin that is substantially free of each of impurities 1 to 14 defined by peaks 1-14 shown in FIG. 12.

44. (Original) The method of claim 38 wherein the composition is daptomycin that is essentially free of each of impurities 1 to 14 defined by peaks 1-14

shown in FIG. 12.

45. (Canceled).

46. (Canceled).

47. (Previously Presented) The pharmaceutical composition of claim 9 wherein the composition is essentially pure daptomycin.

48. (Previously Presented) The pharmaceutical composition of claim 9 wherein the composition is daptomycin that is substantially free of anhydro-daptomycin and substantially free of β-isomer of daptomycin.

49. (Previously Presented) The pharmaceutical composition of claim 9 wherein the composition is daptomycin that is essentially free of anhydro-daptomycin and substantially free of β-isomer of daptomycin.

50. (Previously Presented) The pharmaceutical composition of claim 9 wherein the composition is daptomycin that is free of anhydro-daptomycin and substantially free of β-isomer of daptomycin.

51. (Previously Presented) The pharmaceutical composition of claim 9 wherein the composition is daptomycin that is substantially free of each of impurities 1 to 14 defined by peaks 1-14 shown in FIG. 12.

52. (Previously Presented) The pharmaceutical composition of claim 9 wherein the composition is daptomycin that is essentially free of each of impurities 1 to 14 defined by peaks 1-14 shown in FIG. 12.

53. (Canceled).

54. (Currently Amended) A purified daptomycin ~~The~~ composition ~~of claim~~

~~1~~ comprising ~~substantially~~ essentially pure daptomycin purified by a process comprising the steps of

(a) forming micelles comprising daptomycin;

(b) converting the micelles to a non-micellar daptomycin composition comprising daptomycin in a non-micellar state; and

(c) obtaining at least a portion of the purified daptomycin from the micelles, the non-micellar daptomycin composition, or a combination thereof.

55. (Currently Amended) The pharmaceutical composition of claim [[9]]54 comprising ~~substantially pure~~ daptomycin of at least about 98% purity measured relative to daptomycin impurities 1-14 defined by peaks 1-14 shown in FIG. 12.

56. (Currently Amended) The method of claim [[38]]54 wherein the composition is ~~substantially pure~~ daptomycin of at least about 99% purity.

57. (Canceled).

58. (Currently Amended) A new composition comprising daptomycin of greater than about 93% purity~~, wherein the purity of the daptomycin is~~ relative to daptomycin impurities that arise in fermentation or purification of daptomycin, and wherein the daptomycin impurities comprise impurities 1-14 defined by peaks 1-14 shown in FIG. 12, and the daptomycin is obtained by a process comprising the step of forming a micelle comprising daptomycin.

59. (Previously Presented) The composition of claim 58, wherein the daptomycin impurities arise in fermentation.

60. (Previously presented) The composition of claim 58, wherein the purity is at least 95%.

61. (Previously Presented) The composition of claim 60, wherein the daptomycin impurities arise in fermentation.

62. (Currently Amended) A purified daptomycin composition comprising daptomycin ~~Daptomycin~~ of greater than about 93% purity relative to impurities 1-14 defined by peaks 1-14 shown in FIG. 12, the daptomycin being obtained by a process comprising the step of forming an aggregate comprising daptomycin.

63. (Previously presented) The daptomycin of claim 62, wherein the purity is at least 95%.

64. (Previously Presented) The composition of claim 58 wherein impurity 1 is present in an amount no more than about 1%.

65. (Previously Presented) The composition of claim 58 wherein impurity 2 is present in an amount no more than about 0.5%.

66. (Previously Presented) The composition of claim 58 wherein impurity 3 is present in an amount no more than about 1%.

67. (Previously Presented) The composition of claim 58 wherein impurity 4 is present in an amount no more than about 0.5%.

68. (Previously Presented) The composition of claim 58 wherein impurity 5 is present in an amount no more than about 0.5%.

69. (Previously Presented) The composition of claim 58 wherein impurity 6 is present in an amount no more than about 1%.

70. (Previously Presented) The composition of claim 58 wherein impurity

7 is present in an amount no more than about 1%.

71. (Previously Presented) The composition of claim 58 wherein impurity 9 is present in an amount no more than about 0.5%.

72. (Previously Presented) The composition of claim 58 wherein impurity 10 is present in an amount no more than about 0.5%.

73. (Previously Presented) The composition of claim 58 wherein impurity 11 is present in an amount no more than about 0.5%.

74. (Previously Presented) The composition of claim 58 wherein impurity 12 is present in an amount no more than about 0.5%.

75. (Previously Presented) The composition of claim 58 wherein impurity 14 is present in an amount no more than about 0.1%.

76. (Currently Amended) The composition of claim [[58]]62, wherein the daptomycin is obtained by a process comprising

a) subjecting a daptomycin solution to conditions forming a daptomycin aggregate;

b) separating the daptomycin aggregate from low molecular weight contaminants;

c) subjecting the daptomycin aggregate to conditions in which the daptomycin aggregate dissociate into daptomycin monomers.

77. (Previously Presented) The composition of claim 76, wherein the daptomycin aggregate of step b) is separated from the low molecular weight contaminants by a size selection technique.

78. (Previously Presented) The composition of claim 77, wherein the size selection technique is ultrafiltration or size exclusion chromatography.

79. (Previously Presented) The composition of claim 78 further comprising separating the daptomycin monomers obtained from step c) from high molecular weight contaminants.

80. (Previously Presented) The composition of claim 79, wherein the daptomycin monomers of are separated from the high molecular weight contaminants by a size selection technique.

81. (Previously Presented) The composition of claim 80, wherein the size selection technique is ultrafiltration or size exclusion chromatography.

82. (Currently Amended) The composition of claim 58, wherein the daptomycin is obtained by a process comprising

a) separating daptomycin from high molecular weight contaminants;

b) subjecting the daptomycin of step a) to conditions forming [[a]]the micelle comprising daptomycin ~~aggregate~~; and

c) separating the micelle comprising daptomycin ~~aggregate~~ from low molecular weight contaminants.

83. (Currently Amended) The composition of claim 82, wherein the micelle comprising daptomycin ~~aggregate~~ of step c) is separated from the low molecular weight contaminants by a size selection technique.

84. (Previously Presented) The composition of claim 83, wherein the size selection technique is ultrafiltration or size exclusion chromatography.

85. (Currently Amended) The composition of claim 84, further comprising

subjecting the micelle comprising daptomycin ~~aggregate~~ of step c) to conditions in which the micelle comprising daptomycin ~~aggregate~~ dissociates into daptomycin monomers.

86. (Previously Presented)The composition of claim 76, wherein the aggregate is a micelle.

87. (Currently Amended)The composition of claim 82, wherein the aggregate is a daptomycin micelle.

88. (Currently Amended) The composition of claim 58, wherein the daptomycin is obtained by a process comprising

a) subjecting a daptomycin solution to conditions forming a daptomycin micelle~~aggregate~~;

b) filtering the daptomycin micelle~~aggregate~~ under conditions in which the daptomycin micelle~~aggregate~~ is retained on the filter; and

c) collecting the daptomycin micelle~~aggregate~~.

89. (Currently Amended) The composition of claim 82, wherein the aggregate is a micelle consisting of daptomycin.

90. (Currently Amended) The composition of claim 58, wherein the daptomycin is obtained by subjecting a daptomycin solution to conditions effective to ~~forming~~ form daptomycin micelles.

91. (Currently Amended) The composition of claim 58, wherein the micelle comprising daptomycin is obtained by adjusting any one or more of temperature, salt concentration, daptomycin concentration, and pH of the solution to cause a concentration of the daptomycin in the solution to be above a critical micelle concentration.

92. (Currently Amended) The composition of claim 58, wherein the micelle comprising daptomycin is obtained by subjecting a daptomycin solution to a pH of 2.5 to 5.0.

93. (Previously Presented) The composition of claim 58, wherein the daptomycin is obtained by a process comprising:

a) adjusting the pH of a daptomycin preparation to a pH of 2.5 to 5.0;

b) filtering the daptomycin preparation of step a) on an ultrafiltration membrane;

c) adjusting the pH of the daptomycin preparation of step b) to a pH of 6.5.

94. (Currently Amended) The composition of claim 93, wherein the micelle comprising daptomycin preparation of step a) is at a pH of 2.5 to 4.7, and the preparation further comprises 300 to 500 mM NaCl and is at a temperature of 2-15 degrees C.

95. (Currently Amended) The[[A]] composition of claim 62, wherein the daptomycin is obtained by a process further comprising

a) subjecting a daptomycin solution to conditions forming [[a]]the daptomycin aggregate;

b) separating the daptomycin aggregate from low molecular weight contaminants;

c) subjecting the daptomycin aggregate to conditions in which the daptomycin aggregate dissociate into daptomycin monomers.

96. (Previously Presented) The composition of claim 95, wherein the daptomycin aggregate of step b) is separated from the low molecular weight contaminants by a size selection technique.

97. (Previously Presented) The composition of claim 96, wherein the size

selection technique is ultrafiltration or size exclusion chromatography.

98. (Previously Presented) The composition of claim 97 further comprising separating the daptomycin monomers obtained from step c) from high molecular weight contaminants.

99. (Previously Presented) The composition of claim 98, wherein the daptomycin monomers are separated from the high molecular weight contaminants by a size selection technique.

100. (Previously Presented) The composition of claim 99, wherein the size selection technique is ultrafiltration or size exclusion chromatography.

101. (Previously Presented) The composition of claim 62, wherein the daptomycin is obtained by a process comprising

a) separating daptomycin from high molecular weight contaminants.

b) subjecting the daptomycin of step a) to conditions forming a daptomycin aggregate; and

c) separating the daptomycin aggregate from low molecular weight contaminants.

102. (Previously Presented) The composition of claim 101, wherein the daptomycin aggregate of step c) is separated from the low molecular weight contaminants by a size selection technique.

103. (Previously Presented) The composition of claim 102, wherein the size selection technique is ultrafiltration or size exclusion chromatography.

104. (Previously Presented) The composition of claim 103, further comprising subjecting the daptomycin aggregate of step c) to conditions in which the

daptomycin aggregate dissociates into daptomycin monomers.

105. (Previously Presented) The composition of claim 95, wherein the aggregate is a micelle.

106. (Previously Presented) The composition of claim 101, wherein the aggregate is a micelle.

107. (Previously Presented) The composition of claim 62, wherein the daptomycin is obtained by a process comprising

a) subjecting a daptomycin solution to conditions forming a daptomycin aggregate;

b) filtering the daptomycin aggregate under conditions in which the daptomycin aggregate is retained on the filter; and

c) collecting the daptomycin aggregate.

108. (Currently Amended) The composition of claim [[101]]107, wherein the daptomycin aggregate is a micelle comprising daptomycin.

109. (Currently Amended) The composition of claim 62, wherein the daptomycin is obtained by subjecting a daptomycin solution to conditions effective to formforming the aggregate comprising daptomycin micelles.

110. (Previously Presented) The composition of claim 62, wherein the daptomycin is obtained by adjusting any one or more of temperature, salt concentration, daptomycin concentration, and pH of the solution to cause a concentration of the daptomycin in the solution to be above a critical micelle concentration.

111. (Previously Presented) The composition of claim 62, wherein the daptomycin is obtained by subjecting a daptomycin solution to a pH of 2.5 to 5.0.

112. (Previously Presented) The composition of claim 62, wherein the daptomycin is obtained by a process comprising:

a) adjusting the pH of a daptomycin preparation to a pH of 2.5 to 5.0;

b) filtering the daptomycin preparation of step a) on an ultrafiltration membrane;

c) adjusting the pH of the daptomycin preparation of step b) to a pH of 6.5.

113. (Previously Presented) The composition of claim 112, wherein the daptomycin preparation of step a) is at a pH of 2.5 to 4.7, and the preparation further comprises 300 to 500 mM NaCl and is at a temperature of 2-15 degrees C.

114. (Previously Presented) The composition of claim 58 wherein the daptomycin is obtained by a process comprising:

a) subjecting a solution of daptomycin to anion exchange chromatography to obtain an enriched daptomycin preparation;

b) subjecting the enriched daptomycin preparation to hydrophobic interaction chromatography to obtain a semi-purified daptomycin preparation; and

c) subjecting the semi-purified daptomycin preparation to anion exchange chromatography.

115. (Currently Amended) A composition comprising <u>purified daptomycin obtained from a daptomycin aggregate, the purified daptomycin selected from the group consisting of:</u>

(a) essentially pure daptomycin,

(b) daptomycin that is substantially free of anhydro-daptomycin and substantially free of β-isomer of daptomycin,

(c) daptomycin that is essentially free of anhydro-daptomycin and substantially free of β-isomer of daptomycin,

(d) daptomycin that is free of anhydro-daptomycin and substantially free of β-isomer of daptomycin,

(e) daptomycin that is substantially free of each of impurities 1 to 14 defined by peaks 1-14 shown in FIG. 12, [[or]]and

(f) daptomycin that is essentially free of each of impurities 1 to 14 defined by peaks 1-14 shown in FIG. 12.

116. (Previously Presented) The composition of claim 62 wherein impurity 1 is present in an amount no more than about 1%.

117. (Previously Presented) The composition of claim 62 wherein impurity 2 is present in an amount no more than about 0.5%.

118. (Previously Presented) The composition of claim 62 wherein impurity 3 is present in an amount no more than about 1%.

119. (Previously Presented) The composition of claim 62 wherein impurity 4 is present in an amount no more than about 0.5%.

120. (Previously Presented) The composition of claim 62 wherein impurity 5 is present in an amount no more than about 0.5%.

121. (Previously Presented) The composition of claim 62 wherein impurity 6 is present in an amount no more than about 1%.

122. (Previously Presented) The composition of claim 62 wherein impurity 7 is present in an amount no more than about 1%.

123. (Previously Presented) The composition of claim 62 wherein impurity 9 is present in an amount no more than about 0.5%.

124. (Previously Presented) The composition of claim 62 wherein impurity 10 is present in an amount no more than about 0.5%.

125. (Previously Presented) The composition of claim 62 wherein impurity 11 is present in an amount no more than about 0.5%.

126. (Previously Presented) The composition of claim 62 wherein impurity 12 is present in an amount no more than about 0.5%.

127. (Previously Presented) The composition of claim 62 wherein impurity 14 is present in an amount no more than about 0.1%.

128. (Previously Presented) The composition of claim 62 wherein the daptomycin is obtained by a process comprising:

a) subjecting a solution of daptomycin to anion exchange chromatography to obtain an enriched daptomycin preparation;

b) subjecting the enriched daptomycin preparation to hydrophobic interaction chromatography to obtain a semi-purified daptomycin preparation; and

c) subjecting the semi-purified daptomycin preparation to anion exchange chromatography.

129. (Previously Presented) The composition of claim 63, wherein the daptomycin is obtained by a process comprising

a) subjecting a daptomycin solution to conditions forming a daptomycin aggregate;

b)separating the daptomycin aggregate from low molecular weight contaminants;

c) subjecting the daptomycin aggregate to conditions in which the daptomycin aggregate dissociate into daptomycin monomers.

130. (Previously Presented) The composition of claim 129, wherein the daptomycin aggregate of step b) is separated from the low molecular weight contaminants by a size selection technique.

131. (Previously Presented) The composition of claim 130, wherein the size selection technique is ultrafiltration or size exclusion chromatography.

132. (Previously Presented) The composition of claim 131 further comprising separating the daptomycin monomers obtained from step c) from high molecular weight contaminants.

133. (Previously Presented) The composition of claim 132, wherein the daptomycin monomers of are separated from the high molecular weight contaminants by a size selection technique.

134. (Previously Presented) The composition of claim 133, wherein the size selection technique is ultrafiltration or size exclusion chromatography.

135. (Previously Presented) The composition of claim 63, wherein the daptomycin is obtained by a process comprising

a) separating daptomycin from high molecular weight contaminants.

b) subjecting the daptomycin of step a) to conditions forming a daptomycin aggregate; and

c)separating the daptomycin aggregate from low molecular weight contaminants.

136. (Previously Presented) The composition of claim 135, wherein the daptomycin aggregate of step c) is separated from the low molecular weight contaminants by a size selection technique.

137. (Previously Presented) The composition of claim 136, wherein the size selection technique is ultrafiltration or size exclusion chromatography.

138. (Previously Presented) The composition of claim 137, further comprising subjecting the daptomycin aggregate of step c) to conditions in which the daptomycin aggregate dissociates into daptomycin monomers.

139. (Previously Presented) The composition of claim 129, wherein the aggregate is a micelle.

140. (Previously Presented) The composition of claim 135, wherein the aggregate is a micelle.

141. (Previously Presented) The composition of claim 63, wherein the daptomycin is obtained by a process comprising

a) subjecting a daptomycin solution to conditions forming a daptomycin aggregate;

b) filtering the daptomycin aggregate under conditions in which the daptomycin aggregate is retained on the filter; and

c) collecting the daptomycin aggregate.

142. (Previously Presented) The composition of claim 135, wherein the aggregate is a micelle.

143 (Previously Presented) The composition of claim 63, wherein the daptomycin is obtained by subjecting a daptomycin solution to conditions effective to forming micelles.

144. (Previously Presented) The composition of claim 63, wherein the daptomycin is obtained by adjusting any one or more of temperature, salt concentration, daptomycin concentration, and pH of the solution to cause a concentration of the daptomycin in the solution to be above a critical micelle concentration.

145. (Previously Presented) The composition of claim 63, wherein the daptomycin is obtained by subjecting a daptomycin solution to a pH of 2.5 to 5.0.

146. (Previously Presented) The composition of claim 63, wherein the daptomycin is obtained by a process comprising:

a) adjusting the pH of a daptomycin preparation to a pH of 2.5 to 5.0;

b) filtering the daptomycin preparation of step a) on an ultrafiltration membrane;

c) adjusting the pH of the daptomycin preparation of step b) to a pH of 6.5.

147. (Previously Presented) The composition of claim 146, wherein the daptomycin preparation of step a) is at a pH of 2.5 to 4.7, and the preparation further comprises 300 to 500 mM NaCl and is at a temperature of 2-15 degrees C.

148. (Previously Presented) The composition of claim 63 wherein the daptomycin is obtained by a process comprising:

a) subjecting a solution of daptomycin to anion exchange chromatography to obtain an enriched daptomycin preparation;

b) subjecting the enriched daptomycin preparation to hydrophobic interaction chromatography to obtain a semi-purified daptomycin preparation; and

c) subjecting the semi-purified daptomycin preparation to anion exchange chromatography.

149. (Previously Presented) The composition of claim 63 wherein impurity 1 is present in an amount no more than about 1%.

150. (Previously Presented) The composition of claim 63 wherein impurity 2 is present in an amount no more than about 0.5%.

151. (Previously Presented) The composition of claim 63 wherein impurity 3 is present in an amount no more than about 1%.

152. (Previously Presented) The composition of claim 63 wherein impurity 4 is present in an amount no more than about 0.5%.

153. (Previously Presented) The composition of claim 63 wherein impurity 5 is present in an amount no more than about 0.5%.

154. (Previously Presented) The composition of claim 63 wherein impurity 6 is present in an amount no more than about 1%.

155. (Previously Presented) The composition of claim 63 wherein impurity 7 is present in an amount no more than about 1%.

156. (Previously Presented) The composition of claim 63 wherein impurity 9 is present in an amount no more than about 0.5%.

157. (Previously Presented) The composition of claim 63 wherein impurity 10 is present in an amount no more than about 0.5%.

158. (Previously Presented) The composition of claim 63 wherein impurity 11 is present in an amount no more than about 0.5%.

159. (Previously Presented) The composition of claim 63 wherein impurity 12 is present in an amount no more than about 0.5%.

160. (Previously Presented) The composition of claim 63 wherein impurity 14 is present in an amount no more than about 0.1%.

Please enter the following new claims:

161. (New) The composition of claim 115, wherein the daptomycin aggregate comprises a daptomycin micelle.

162. (New) The composition of claim 161, wherein the is purified by a process comprising the steps of:

(a) subjecting a daptomycin solution to conditions forming the daptomycin aggregate;

(b) separating the daptomycin aggregate from low molecular weight contaminants;

c) subjecting the daptomycin aggregate to conditions in which the daptomycin micelle dissociates into daptomycin monomers.

163. (New) The composition of claim 162, wherein the daptomycin aggregate consists of daptomycin micelles.

164. (New) The composition of claim 162, wherein the step of subjecting the daptomycin solution to conditions forming a daptomycin aggregate includes adjusting one or more of temperature, salt concentration, daptomycin concentration, and pH of the daptomycin solution to form the daptomycin aggregate.

165. (New) The composition of claim 164, wherein the daptomycin aggregate comprises daptomycin micelles.

166. (New) The composition of claim 162, wherein the step of subjecting the daptomycin solution to conditions forming the daptomycin aggregate results in a concentration of the daptomycin in the daptomycin solution at or above the critical micelle concentration.

167. (New) The composition of claim 163, wherein the step of

subjecting a daptomycin solution to conditions forming daptomycin micelles includes subjecting the daptomycin solution to a pH of about 3.0 to 4.8 and a temperature of about 2-15 degrees C.

168. (New) The composition of claim 162, wherein the step of subjecting a daptomycin solution to conditions forming a daptomycin aggregate includes one or more of the following:

(a) the daptomycin solution having a pH of about 2.5 to 5.0,

(b) the daptomycin solution having a temperature of about 2-15 degrees C, and

(c) the daptomycin solution having a daptomycin concentration at or above the critical micelle concentration.

169. (New) The composition of claim 162, wherein the step of subjecting the daptomycin aggregate to conditions in which the daptomycin aggregate dissociate into daptomycin monomers includes one or more of the following:

(a) raising the pH of the daptomycin aggregate to about 6.0 or higher;

(b) adjusting the daptomycin concentration to below the critical micelle concentration;

(c) contacting the daptomycin aggregate with an organic solvent; and

(d) raising the temperature of the daptomycin aggregate above about 15 degrees C.

170. (New) The composition of claim 169, wherein the organic solvent is selected from the group consisting of: n-butanol, isopropyl alcohol, acetonitrile, and a combination thereof.

171. (New) A purified daptomycin composition of greater than about 93% purity relative to impurities 1-14 defined by peaks 1-14 shown in FIG. 12, the purified daptomycin composition obtained by a process comprising the steps of

(a) subjecting daptomycin to conditions forming daptomycin micelles and

(b) obtaining at least a portion of the purified daptomycin from the daptomycin micelles.

172. (New) The purified daptomycin composition of claim 171, wherein the step of obtaining the purified daptomycin from the daptomycin micelles further comprises the steps of:

(c) subjecting the daptomycin micelles to conditions forming monomeric daptomycin from the daptomycin micelles; and

(d) obtaining at least a portion of the purified daptomycin from the monomeric daptomycin.

173. (New) The purified daptomycin composition of claim 172, wherein the step of subjecting the daptomycin micelles to conditions to form monomeric daptomycin from the daptomycin micelles includes one or more of the following:

(a) raising the pH of the daptomycin aggregate to about 6.0 or higher;

(b) adjusting the daptomycin concentration to below the critical micelle concentration;

(c) contacting the daptomycin aggregate with an organic solvent; and

(d) raising the temperature of the daptomycin aggregate above about 15 degrees C.

174. (New) The purified daptomycin composition of claim 171, wherein the step of obtaining the daptomycin from the daptomycin micelles further comprises the steps of:

(c) filtering the daptomycin micelles under conditions in which the daptomycin micelles are retained on the filter;

(d) collecting the daptomycin aggregate;

(e) subjecting the daptomycin micelles to conditions to form monomeric daptomycin from the daptomycin micelles; and

(f) obtaining at least a portion of the purified daptomycin from the monomeric daptomycin.

175. (New) A purified daptomycin composition of greater than about 93% purity relative to impurities 1-14 defined by peaks 1-14 shown in FIG. 12, the purified daptomycin composition obtained by a process comprising the steps of

(a) subjecting an aqueous solution comprising daptomycin at or above the critical daptomycin micelle concentration to a pH of 3.0 to 4.8 at a temperature of about 2-15 degrees C to form a daptomycin preparation; and

(b) obtaining the purified daptomycin from the daptomycin preparation obtained in step (a).

176. (New) The composition of claim 175, wherein the daptomycin preparation comprises daptomycin aggregates, and wherein:

(a) the process further comprises filtering the daptomycin preparation is filtered to obtain a filtered daptomycin material comprising the daptomycin aggregates; and

(b) the purified daptomycin is obtained from the filtered daptomycin material by a process comprising the step of contacting the filtered daptomycin material with an organic solvent or a solvent having a pH of at least about 6.0.

177. (New) The composition of claim 176, wherein the purified daptomycin is obtained by contacting the filtered daptomycin material with a HIC resin and eluted with an organic solvent at a pH of about 6.0-7.5

178. (New) A purified daptomycin composition of greater than about 93% purity relative to impurities 1-14 defined by peaks 1-14 shown in FIG. 12, wherein the % purity is measured by HPLC analysis according to the resolution method in Table 2, and the purified daptomycin composition is obtained from a lipopeptide aggregate comprising daptomycin.

179. (New) A purified daptomycin composition of greater than about 93% purity relative to impurities 1-14 defined by peaks 1-14 shown in FIG. 12, wherein the %

purity is measured by HPLC analysis according to the resolution method in Table 2, and the purified daptomycin composition is obtained by a process comprising the steps of

(a) fermenting a culture of *S. roseosporus* to produce daptomycin;

(b) contacting the daptomycin from step (a) with an anion exchange resin;

(c) eluting the daptomycin from the anion exchange resin in step (b) with a solvent having a pH of about 6.0-6.5 to obtain a daptomycin solution;

(d) adjusting the pH of the daptomycin solution from step (c) to about 3.0 to 4.8 and a temperature of the solution from step (c) to about 2-15 degrees C to obtain a daptomycin aggregate solution comprising a daptomycin aggregates; and

(e) filtering the daptomycin aggregate solution to separate daptomycin aggregates from the daptomycin aggregate solution; and

(f) obtaining the purified daptomycin from the daptomycin aggregates.

180. (New) The composition of claim 179, wherein the daptomycin aggregates comprise daptomycin micelles.

181. (New) The composition of claim 54, wherein the purified daptomycin is obtained from the non-micellar daptomycin.

182. (New) The composition of claim 54, wherein the daptomycin micelles are converted to the non-micellar state by altering one or more of: temperature, pH, electrolyte concentration and daptomycin concentration.

183. (New) The composition of claim 54, wherein the daptomycin is purified by a process further comprising the steps of:

i) filtering the daptomycin micelles under conditions in which the daptomycin micelles are retained on the filter; and

ii) collecting the daptomycin micelles.

184. (New) The composition of claim 183, wherein the step of

converting the daptomycin micelles collected in step (ii) are converted to the non-micellar daptomycin in step (b).

185. (New) The composition of claim 184, wherein the purified daptomycin is obtained from the non-micellar daptomycin in step (c).

186. (New) The composition of claim 185, wherein the purified daptomycin is obtained by a process further comprising the step of lyophilizing the purified daptomycin.

187. (New) The composition of claim 186, wherein the purified daptomycin is substantially free of each of impurities 1 to 14 defined by peaks 1-14 shown in FIG. 12.

188. (New) The composition of claim 178, wherein the daptomycin is obtained by adjusting any one or more of temperature, salt concentration, daptomycin concentration, and pH of a daptomycin solution to cause a concentration of the daptomycin in the solution to be above a daptomycin critical micelle concentration.

189. (New) The composition of claim 185, wherein the aggregate comprises daptomycin micelles formed by a process comprising one or more steps selected from the group consisting of: adjusting the pH of a daptomycin preparation to a pH of about 2.5 to 5.0, combining daptomycin with 300 to 500 mM NaCl in an aqueous solution; and providing a daptomycin preparation at a temperature of 2-15 degrees C.

190. (New) The composition of claim 178, wherein the aggregate comprises daptomycin micelles formed by a process further comprising subjecting daptomycin micelles, daptomycin in a non-micellar state, or a combination thereof to anion exchange chromatography.

191. (New) The composition of claim 178, wherein the daptomycin composition is at least about 95% pure.

192. (New) The composition of claim 178, wherein the daptomycin composition is at least about 97% pure.

193. (New) The composition of claim 178, wherein the daptomycin composition is at least about 98% pure.

194. (New) The composition of claim 178, wherein the daptomycin composition is at least about 99% pure.

195. (New) The composition of claim 178, wherein the daptomycin composition is essentially free of anhydro daptomycin.

196. (New) The composition of claim 2, wherein the daptomycin has greater than about 93% purity measured by HPLC analysis according to the resolution method in Table 2, and the purified daptomycin composition is obtained from a lipopeptide aggregate comprising daptomycin.

197. (New) The composition of claim 3, wherein the daptomycin has greater than about 93% purity measured by HPLC analysis according to the resolution method in Table 2, and the purified daptomycin composition is obtained from a lipopeptide aggregate comprising daptomycin.

198. (New) The composition of claim 4, wherein the daptomycin has greater than about 93% purity measured by HPLC analysis according to the resolution method in Table 2, and the purified daptomycin composition is obtained from a lipopeptide aggregate comprising daptomycin.

199. (New) The composition of claim 6, wherein the daptomycin has greater than about 93% purity measured by HPLC analysis according to the resolution method in Table 2, and the purified daptomycin composition is obtained from a lipopeptide aggregate comprising daptomycin.

200. (New) The composition of claim 115, wherein the daptomycin has greater than about 93% purity measured by HPLC analysis according to the resolution method in Table 2, and the purified daptomycin composition is obtained from a lipopeptide aggregate comprising daptomycin.

REMARKS

Amendments to the Specification

The specification has been amended to contain the references required by 37 CFR § 1.78(a)(2),(5) to establish a claim of priority under 35 USC §§ 119(e) and 120. More specifically, the CROSS-REFERENCE TO RELATED APPLICATIONS has been amended to recite the relationships between the present application, United States Patent Application No. 10/747,485, and United States Patent Application No. 09/735,191. Applicants submit, along with this Response and Amendment, a Petition under 37 CFR 1.78(a)(3),(6) to Accept an Unintentionally Delayed Priority Claim. Applicants have also submitted a similar Petition in United States Patent Application No. 10/747,485, the parent of the present application, in order to comply with the requirement of MPEP 201.11(III)(C) that appropriate reference be made in each intermediate application in the chain of prior applications.. Each Petition includes (1) the reference required by 37 CFR § 1.78(a)(2),(5); (2) the surcharge set forth in 37 CFR § 1.17(t); and (3) a statement that the entire delay between the date that the priority claim was due under 37 CFR § 1.78(a)(2)(ii),(5)(ii) and the present was unintentional. In view of the foregoing amendments and Petitions, Applicants respectfully request recognition of the recited priority claim

Amendments to the Claims

Claims 1-29, 31-36, 38-44, 46-52, 54-56, and 58-160 were pending in the present application. Applicant has canceled claim 1, and amended claims 2-4, 6-7, 10, 54- 56, 58, 62, 76, 82-83, 85, 87-95, 108-109 and 115 and added new claims 161-200. Support for the claim amendments and new claims 161-200 can be found throughout the specification as filed. No new matter is added. Accordingly, upon entry of the instant amendments, claims 2-29, 31-36, 38-44, 46-52, 54-56, and 58-200 are pending in this application.

Allowed Claims

Claims 2-7 and 115 have been allowed (Office Action at page 1).

Claim Rejections under 35 USC §102

The Office Action rejects claims 1 and 54 under 35 USC § 102(e) as being anticipated by RE39,071 ("Baker") (Office Action at pages 4-6).

Applicants respectfully disagree. However, without acquiescing to the Examiner's rejection, Applicants submit that with the cancellation of claim 1 this rejection is now rendered moot regarding claim 1. With respect to claim 54, this rejection has been obviated by amending the claim to recite "essentially pure" daptomycin (as set forth in allowed claim 2). Applicants reserve the right to pursue embodiments described in canceled subject matter in one or more subsequent continuation patent applications.

Notwithstanding, Applicant respectfully disagrees and traverses this rejection based on arguments presented below and previously made of record. Applicant's previous remarks in earlier Office Action Responses are incorporated herein by reference.

Claim Rejections under Obviousness-Type Double Patenting

The Office Action rejects claims 1 and 54 over claims 18-20, 26, 28 and 29 of Baker based on the judicially-created doctrine of non-statutory obviousness-type double patenting. The Office Action states that claims 1 and 54 disclose a composition comprising substantially pure daptomycin, and maintains that "[t]his is an obvious variation in view of claims 18-20, 26 and 28 of [Baker]…" (Office Action at page 7). Applicant has elected to cancel claim 1 and amend claim 54 to cover certain preferred embodiments of the invention. Applicant respectfully submits that the claim amendments herein obviate the basis for this rejection. Applicant reserves the right to pursue embodiments described in canceled subject matter in one or more subsequent continuation patent applications. Applicant respectfully requests reconsideration and withdrawal of this rejection.

Claim Rejections Under 35 USC § 112, ¶2

The Office Action rejects claims 8-29, 31-36, 38-44, 47-52, 55-56, 58-114 and 116-160 under 35 USC §112, second paragraph as being indefinite (Office Action at page 3). Specifically, the Office Action maintains that the recitation of "impurities 1-14" renders the rejected claims indefinite because "it is not clear what these impurities are, and how they are defined" (Office Action at page 3). Applicant has elected to amend independent claims 58, 62, and 115 from which the rejected claims depend to focus on certain preferred embodiments of the invention. Applicant respectfully submits that the claim amendments herein obviate the basis for this rejection. Applicant reserves the right to pursue embodiments described in canceled subject matter in one or more subsequent continuation patent applications. Applicant respectfully requests reconsideration and withdrawal of this rejection.

CONCLUSION

For the reasons presented above, Applicant respectfully requests reconsideration and prompt allowance of all pending claims.

Respectfully submitted,

Date: May 27, 2011
/Nicholas M. Boivin/
Nicholas M. Boivin, Reg. No. 45,650
Attorney for Applicant

Cubist Pharmaceuticals, Inc.
65 Hayden Avenue
Lexington, Massachusetts 02421
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C062-02-03 20110530 US Resp to 20101130 OA

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Total Pages - 2

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Re: U.S. Patent Application Serial No. 11/739,180
Our Ref.: C062-02/03 US

Dear Sir:

Attached is a Credit Card Payment Form for any additional fees that may become due for the filing of the following documents in the Response/Petition for extension of time/ Petition under 37 C.F.R. § 1.78(a)(3),(6) to accept an unintentionally delayed priority claim (11/739,180)/Petition under 37 C.F.R. § 1.78(a)(3);(6) to accept an unintentionally delayed priority claim (10/747,485). Please credit Deposit Account 50-1986 for the payment amount indicated in the enclosed Credit Card Payment Form (PTO-2038).

Very truly yours,

Nicholas M. Boivin
Intellectual Property Counsel

NMB/jld
Attachment

cc: Jodi Doherty, Senior Intellectual Property Paralegal (w/o encl.)

65 Hayden Avenue, Lexington, MA 02421 P 781.860.8660 F 781.860.1407 www.cubist.com

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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 11/739,180	Filing Date 04/24/2007	☐ To be Mailed

APPLICATION AS FILED – PART I

	(Column 1)	(Column 2)	SMALL ENTITY ☒		OR	OTHER THAN SMALL ENTITY	
FOR	NUMBER FILED	NUMBER EXTRA	RATE ($)	FEE ($)		RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =		OR	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =			X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	

APPLICATION AS AMENDED – PART II

		(Column 1)		(Column 2)	(Column 3)	SMALL ENTITY		OR	OTHER THAN SMALL ENTITY	
	05/27/2011	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)		RATE ($)	ADDITIONAL FEE ($)
AMENDMENT	Total (37 CFR 1.16(i))	* 194	Minus	** 194	= 0	X $26 =	0	OR	X $ =	
	Independent (37 CFR 1.16(h))	* 7	Minus	***7	= 0	X $110 =	0	OR	X $ =	
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE	0	OR	TOTAL ADD'L FEE	

		(Column 1)		(Column 2)	(Column 3)					
		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)		RATE ($)	ADDITIONAL FEE ($)
AMENDMENT	Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =		OR	X $ =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =		OR	X $ =	
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

Legal Instrument Examiner:
/KENDALL JONES/

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/739,180	04/24/2007	Thomas Kelleher	C062-02/03 US	8837

34103 7590 11/30/2010

Intellectual Property Department
Cubist Pharmaceuticals, Inc.
65 Hayden Avenue
Lexington, MA 02421

EXAMINER	
KAM, CHIH MIN	

ART UNIT	PAPER NUMBER
1656	

MAIL DATE	DELIVERY MODE
11/30/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	11/739,180	KELLEHER ET AL.	
	Examiner	Art Unit	
	CHIH-MIN KAM	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 September 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-29,31-36,38-44,47-52,54-56 and 58-160* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *2-7 and 115* is/are allowed.

6)☒ Claim(s) *1,8-29,31-36,38-44,47-52,54-56,58-114 and 116-160* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *24 April 2007* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/22/10*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

1. Claims 1-29, 31-36, 38-44, 47-52, 54-56 and 58-160 are pending.

Applicants' amendment filed September 22, 2010 is acknowledged. Claims 2, 3, 6, 8, 9, 11, 38, 47-52, 58, 59 and 61 have been amended, claims 46 and 57 have been cancelled, and new claims 64-160 have been added. Therefore, claims 1-29, 31-36, 38-44, 47-52, 54-56 and 58-160 are examined.

Withdrawn Claim Objections

2. The previous objection to claims 2-7, 31-36, 39-44, 47-52, 59 and 61-63 is withdrawn in view of applicants' amendment to the claims in the amendment filed September 22, 2010.

Withdrawn Claim Rejections - 35 USC § 102

3. The previous rejection of claims 8-29, 38, 46, 55-56, 58 and 60 under 35 U.S.C. 102(e) as being as anticipated by Baker *et al.* (US RE39,071 E) is withdrawn in view of applicants' amendment to the claims, applicants' cancellation of the claims, and applicants' response at pages 23-24 in the amendment filed September 22, 2010.

Withdrawn Claim Rejections - Obviousness Type Double Patenting

4. The previous rejection of claims 8-9, 46, 55, 57, 58 and 60 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 18-20, 26, 28 and 29 of U.S. Patent RE39,071 E is withdrawn in view of applicants' amendment to the claims, and applicants' cancellation of the claims in the amendment filed September 22, 2010.

New Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 8-29, 31-36, 38-44, 47-52, 55-56, 58-114 and 116-160 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 8-29, 31-36, 38-44, 47-52, 55-56, 58-114 and 116-160 are indefinite because of the use of the term "impurities 1-14". The term cited renders the claim indefinite, it is not clear what these impurities are, and how they are defined. Claims 8-29, 31-36, 38-44, 47-52, 55-56, 59-61, 63-114 and 116-160 are included in this rejection for being dependent on a rejected claim and not correcting the deficiency of the claims from which they depend.

7. Claims 8-29, 31-36, 38-44, 47-52, 55-56, 95-113 and 116-160 are indefinite because of the use of the term "The composition" or "the composition", while the independent claim (i.e., claim 62) recites the term "Daptomycin", not "A composition".

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the

reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

8. Claims 1 and 54 are rejected under 35 U.S.C. 102(e) as anticipated by Baker *et al.* (US RE39,071 E, reissue of U.S. Patent 5,912,226, filed December 16, 1991).

Baker *et al.* teach an antibacterial composition comprising daptomycin (LY146032) obtained in substantially pure form, which refers to daptomycin that contains less than 2.5% of a combined total of anhydro-daptomycin and beta-isomer of daptomycin (column 8, lines 50-60; Examples 4 and 5; claim 1(g), 54), where daptomycin is purified by a procedure using Diaion HP-20 resin column, followed by HPLC and another HP-20 resin column (Examples 1-5). Baker *et al.* also teach the preparation of a pharmaceutical formulation comprising the purified daptomycin (LY146032) with pharmaceutical carriers or excipients (column 9, lines 47-59), and an antibiotic composition comprised of a combination of a compound of formula 1 (i.e., anhydro-A21978C; column 1, lines 14-21), a compound of formula 2 (isomer of A21978C) and a compound of formula 3 (the parent cyclic peptide of A21978C; LY146032) or pharmaceutically acceptable salts (Reissue: claim 18).

Response to Arguments

Applicants indicate that the purity of daptomycin in Baker can only be interpreted as defined by Baker, thus Baker can be interpreted to read that there is 97.5% of daptomycin over a daptomycin plus anhydro-daptomycin ("A") plus beta isomer daptomycin ("B") composition. The present application describes daptomycin purity relative to daptomycin plus anhydro-daptomycin (impurity No. 13) plus beta isomer daptomycin (impurity No. 8) plus 12 other impurities (impurities 1-7, 9-12 and 14) as described in Table 3 of the specification. Thus, Baker

uses a different purity and does not teach purity over the 14 daptomycin impurities. Applicants also indicate that Baker methods yield at best about 93% pure daptomycin measured under the current application while it yields 97.5% purity under its own teachings. Applicants further assert that evidence of inherency and/or notice of facts to support the inherency of the present claims have not been provided. Regarding product-by process claims, claims 11-29 have been amended to depend on claim 62 or claim 115, thus the basis for rejection is overcome. Therefore, Baker does not anticipate claims 1 and 54, the rejection under 35 U.S.C. 102 (e) should be withdrawn (pages 21-24 of the response).

Applicants' response has been fully considered. Regarding claim 1(g) and claim 54, the arguments are not found persuasive because of the following reasons. Baker *et al.* teach an antibacterial composition comprising daptomycin (LY146032) obtained in substantially pure form, which refers to daptomycin that contains less than 2.5% of a combined total of anhydro-daptomycin and beta-isomer of daptomycin (column 8, lines 50-60; Examples 4 and 5). Since Baker *et al.* do not indicate other impurities besides anhydro-daptomycin and beta-isomer of daptomycin are contained in the daptomycin (LY146032) in substantially pure form, it reads that the daptomycin has more than 97.5% purity. While Baker implies that other degradants are present, but are not predominant in the pH range that optimizes the transpeptidation reactions, the reference does not indicate other degradants are present after the purification procedure (column 8, lines 45-49). While Baker's later work (U.S. Patent 4,874,843) shows undetermined impurities at least as great as 7%, and daptomycin has at best 93% purity, the '843 patent only use a single HP-20 resin column to purify daptomycin with a yield of 50-60% (Example 1-2), which is different from the purification procedure (i.e., Diaion HP-20 resin column, followed by

HPLC and another HP-20 resin column) used by Baker *et al.* in the US RE39,071 E (e.g., with a very low yield in Example 3). Thus, even Baker (U.S. Patent 4,874,843) shows undetermined impurities at least as great as 7%, and daptomycin has at best 93% purity, it does not mean that the daptomycin purified by Baker *et al.* in the US RE39,071 E has at best 93% purity since the purification procedures used by two patents are different. As shown in Example 2 of the present application, the purity level of the daptomycin was 91% using the purification method from the '843 patent, and the daptomycin sample was further confirmed to contain fourteen impurities (Example 10), which does not mean the daptomycin purified by Baker *et al.* in the US RE39,071 E would have at best 93% purity when a different purification procedure is used. The daptomycin purified by Baker *et al.* in the US RE39,071 E is obtained in substantially pure form that contains less than 2.5% of a combined total of anhydro-daptomycin and beta-isomer of daptomycin as taught by Baker *et al.* is not different from the claimed composition as indicated in claims 1(g) and 54 because the claimed substantially pure daptomycin has also >97% purity without indicating the existence of other 14 impuritites. Therefore, the rejection of claim 1(g) and claim 54 are maintained.

Claim Rejections-Obviousness Type Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

9. Claims 1 and 54 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 18-20, 26 and 28 of U.S. Patent RE39,071 E. Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 1 and 54 in the instant application disclose a composition comprising substantially pure daptomycin (i.e., >97% purity daptomycin). This is obvious variation in view of claims 18-20, 26 and 28 of the patent which disclose an antibiotic composition comprised of a combination of a compound of formula 1 (i.e., anhydro-daptomycin), a compound of formula 2 (i.e., beta-isomer of daptomycin) and a compound of formula 3 (i.e., daptomycin, A21978C), or pharmaceutically acceptable salts thereof, wherein the total amount of the compound of formula 1 and the compound of formula 2 or salts thereof, in the combination is less than 6 weight percent; or a pharmaceutical formulation comprising a combination of a compound of formula 1 (i.e., anhydro-daptomycin), a compound of formula 2 (i.e., beta-isomer of daptomycin) and a compound of formula 3 (i.e., daptomycin, A21978C), or pharmaceutically acceptable salts thereof, wherein the total amount of the compound of formula 1 and the compound of formula 2 or salts thereof, in the combination is less than 6 weight percent. Both claims of instant application and the patent are directed to a composition comprising substantially pure daptomycin (i.e., >97% purity daptomycin); or a pharmaceutical composition comprising the composition and a pharmaceutically acceptable carrier or excipient. Thus, claims 1 and 54 in present application and claims 18-20, 26 and 28 of the patent are obvious variations of a composition comprising substantially pure daptomycin (i.e., >97% purity daptomycin).

Response to Arguments

Applicants indicate that they reserve their right to file a terminal disclaimer upon an indication of allowance of these claims over Baker under 35 U.S.C. § 102(e) as requested above or to cancel such claims in a further amendment (page 24 of the response).

Applicants' response has been considered and the rejection is maintained.

Conclusion

10. Claims 1, 8-29, 31-36, 38-44, 47-52, 54-56, 58-114 and 116-160 are rejected; and claims 2-7 and 115 are free of art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chih-Min Kam whose telephone number is (571) 272-0948. The examiner can normally be reached on 8.00-4:30, Mon-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath Rao can be reached at 571-272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Chih-Min Kam/
Primary Examiner, Art Unit 1656

CMK

November 27, 2010

Search Notes	Application No.	Applicant(s)	
	11/739,180	KELLEHER ET AL.	
	Examiner	Art Unit	
	CHIH-MIN KAM	1656	

SEARCHED			
Class	Subclass	Date	Examiner
514	9, 11, 2, 14		
530	317, 322		
530	344		
435	886		

INTERFERENCE SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES (INCLUDING SEARCH STRATEGY)		
	DATE	EXMR
EAST Search on USPAT, USPGPUB, DERWENT, EPO, JPO; STN search on MEDLINE, BIOSIS, EMBASE, SCISEARCH, AGRICOLA.	2/13/2008	CMK
Search strategy enclosed, Inventor name search, Parent applications 60/177,170 and 09/735,191, 10/747,48 have been reviewed.	2/13/2008	CMK
Update the search	10/28/2008	CMK
Update the search	8/5/2009	CMK
Update the search	2/3/2010	CMK
Update the search	11/11/2010	CMK

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	979	daptomycin	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2010/11/11 14:39
L2	57288	substantially adj pure	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2010/11/11 14:39
L3	14746	essentially adj pure	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2010/11/11 14:39
L4	9	L1 same (L2 or L3)	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2010/11/11 14:39
L5	11	impurities same L1	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2010/11/11 14:39
L6	11	anhydro-daptomycin or beta-daptomycin	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2010/11/11 14:39
L7	53568	anion adj exchange	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2010/11/11 14:42
L8	13724	hydrophobic adj interaction adj chromatography	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2010/11/11 14:42
L9	7	L1 same L7 same L8	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2010/11/11 14:42
L10	107	(Ly adj "146032") or A-21978C or A54145 or A-21978	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2010/11/11 14:42
L11	2	L10 same (L2 or L3)	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2010/11/11 14:42
L12	20	kelleher adj thomas.in.	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2010/11/11 14:43
L13	10	lai adj jan-ji.in.	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2010/11/11 14:43

L14	3	decourcey adj joseph.in.	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2010/11/11 14:43
L15	28	lynch adj paul.in.	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2010/11/11 14:43
L16	70	zenoni adj maurizio.in.	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2010/11/11 14:43
L17	6	tagliani adj auro.in.	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2010/11/11 14:43
L18	120	L12 or L13 or L14 or L15 or L16 or L17	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2010/11/11 14:43
L19	8	L18 and L1	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2010/11/11 14:43

11/11/2010 2:48:20 PM
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PTO/SB/08b (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 1

Complete if Known	
Application Number	11739180
Filing Date	2007-04-24
First Named Inventor	Kelleher, Thomas J.
Art Unit	1656
Examiner Name	Chih-Min Kam
Attorney Docket Number	C062-02/03 US

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
/CMK./		Molloy, M. et al., Abstract, "Structure & Anhydro-Daptomycin and Iso-Daptomycin," ACS 200th Meeting, 1990.	
/CMK./		Molloy, M. et al., Poster, "Structure & Anhydro-Daptomycin and Iso-Daptomycin," ACS 200th Meeting, 1990.	

Examiner Signature	/Chih Min Kam/	Date Considered	11/27/2010

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

1 Applicant's unique citation designation number (optional). 2 Applicant is to place a check mark here if English language Translation is attached.

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(FILE 'HOME' ENTERED AT 14:50:16 ON 11 NOV 2010)

FILE 'MEDLINE, CAPLUS, BIOSIS, EMBASE, SCISEARCH, AGRICOLA' ENTERED AT
14:50:54 ON 11 NOV 2010
L1 7611 S DAPTOMYCIN
L2 2905 S SUBSTANTIALLY PURE
L3 2355 S ESSENTIALLY PURE
L4 0 S L1 (P) (L2 OR L3)
L5 0 S L1 AND (L2 OR L3)
L6 2 S L1 (P) IMPURITIES
L7 4 S ANHYDRO-DAPTOMYCIN OR BETA-DAPTOMYCIN
L8 6 S L6 OR L7
L9 6 DUPLICATE REMOVE L8 (0 DUPLICATES REMOVED)
L10 115464 S ANION EXCHANGE
L11 11064 S HYDROPHOBIC INTERACTION CHROMATOGRAPHY
L12 2 S L1 (P) L10 (P) L11
L13 1 S L12 NOT (L9)
L14 554 S (LY146032) OR A-21978C OR A54145 OR A-21978
L15 1 S L14 (P) (L2 OR L3)
L16 1 S L15 NOT (L9 OR L13)
L17 207 S KELLEHER T?/AU
L18 12081 S LAI J?/AU
L19 13 S DECOURCEY J?/AU
L20 3918 S LYNCH P?/AU
L21 83 S ZENONI M?/AU
L22 144 S TAGLIANI A?/AU
L23 16433 S L17 OR L18 OR L19 OR L20 OR L21 OR L22
L24 20 S L23 AND L1
L25 8 DUPLICATE REMOVE L24 (12 DUPLICATES REMOVED)
L26 0 S L25 AND (L2 OR L3)
L27 0 S L25 AND L7
L28 7 S L25 NOT (L9 OR L16)

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appl. No.	:	11/739,180	Confirmation No.	8837
Applicant	:	Thomas Kelleher		
Filed	:	April 24, 2007		
TC/A.U.	:	1656		
Examiner	:	Chih-Min Kam		
Docket No.	:	C062-02/03 US		
Customer No.	:	34103		

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

RESPONSE AND AMENDMENT

This Amendment is responsive to the Office Action mailed March 22, 2010 (hereafter "the Office Action") in the above-identified application.

Kindly amend the application as follows:

Certificate of Transmission/Mailing

I hereby certify that this correspondence (Preliminary Amendment) is being deposited with the United States Postal Service with sufficient postage as First Class Mail and is addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 or is being facsimile transmitted to the USPTO on the date shown below.

_____ _____
Date

AMENDMENT TO THE CLAIMS

1. (Previously presented) A composition comprising

(a) essentially pure daptomycin,

(b) daptomycin that is substantially free of anhydro-daptomycin and substantially free of β-isomer of daptomycin,

(c) daptomycin that is essentially free of anhydro-daptomycin and substantially free of β-isomer of daptomycin,

(d) daptomycin that is free of anhydro-daptomycin and substantially free of β-isomer of daptomycin,

(e) daptomycin that is substantially free of each of impurities 1 to 14 defined by peaks 1-14 shown in FIG. 12, or

(f) daptomycin that is essentially free of each of impurities 1 to 14 defined by peaks 1-14 shown in FIG. 12 or

(g) substantially pure daptomycin.

2. (Currently amended) ~~The composition of claim 1~~ A composition comprising essentially pure daptomycin.

3. (Currently amended) ~~The composition of claim 1~~ A composition compromising daptomycin that is substantially free of anhydro-daptomycin and substantially free of β-isomer of daptomycin.

4. (Original) The composition according to claim 3 that is essentially free of anhydro-daptomycin.

5. (Original) The composition according to claim 3 that is free of anhydro-daptomycin.

6. (Currently amended) ~~The composition of claim 1~~ A composition comprising daptomycin that is substantially free of each of impurities 1 to 14 defined by peaks 1-14 shown in FIG. 12.

7. (Original) The composition according to claim 6 that is essentially free of each of impurities 1 to 14 defined by peaks 1-14 shown in FIG. 12.

8. (Currently amended) The composition of claim ~~1~~ 62, wherein daptomycin purity is measured by HPLC.

9. (Currently amended) The composition of claim ~~1~~ 62 further comprising a pharmaceutically acceptable carrier or excipient.

10. (Original) A pharmaceutical composition according to claim 9, further comprising one or more antibiotics, one or more antifungal agents, or both an antibiotic and an antifungal agent.

11. (Currently amended) The composition according to claim ~~1~~ 62 or 115 wherein the daptomycin is purified by a process comprising the steps of:

a) supplying a fermentation broth;

b) fermenting *Streptomyces roseosporus* with a feed of n-decanoic acid to produce daptomycin in the fermentation broth;

c) clarifying the fermentation broth to obtain a clarified solution;

d) subjecting the clarified solution to anion exchange chromatography to obtain an enriched daptomycin preparation;

e) subjecting the enriched daptomycin preparation to hydrophobic interaction chromatography to obtain a semi-purified daptomycin preparation; and

f) subjecting the semi-purified daptomycin preparation to anion exchange chromatography to obtain the composition ~~of claim 1~~.

12. (Original) The composition according to claim 11, wherein the feed of n-decanoic acid is regulated to achieve a residual concentration of n-decanoic acid of no more than 50 parts per million (ppm) during fermentation.

13. (Original) The composition according to claim 11, wherein said clarifying comprises filtration or centrifugation and depth filtration.

14. (Original) The composition according to claim 11, wherein the anion exchange chromatography in d) is performed using a resin comprising a copolymer of 2-methacrylic acid and ethyleneglycol dimethacrylate (EDGM).

15. (Original) The composition according to claim 11, wherein the hydrophobic interaction chromatography is performed using a resin comprising a co-polymer of cross-linked divinylbenzene/stryene.

16. (Original) The composition according to claim 15, wherein the hydrophobic interaction chromatography is performed at neutral pH and a solvent

concentration that is reduced compared to the solvent concentration used when performing the hydrophobic interaction chromatography at acidic pH.

17. (Original) The composition according to claim 16, wherein the resin is recycled by loading the column at an acidic pH and eluting the column at a neutral pH.

18. (Original) The composition according to claim 11, wherein the anion exchange chromatography in f) is performed using a resin comprising a copolymer of 2-methacrylic acid and ethyleneglycol dimethacrylate (EDGM).

19. (Original) The composition according to claim 11, wherein the anion exchange chromatography is used to reduce the level of solvent in the clarified solution.

20. (Original) The composition according to claim 11, wherein the anion exchange chromatography is performed via continuous flow chromatography.

21. (Original) The composition according to claim 11, wherein the process further comprises the step of filtering daptomycin.

22. (Original) The composition according to claim 11, wherein the process further comprises the step of depyrogenating daptomycin using ultrafiltration.

23. (Original) The composition according to claim 22 wherein said depyrogenating comprises the steps of:

i) providing a daptomycin solution under conditions in which the daptomycin is in a monomeric and nonmicellar state;

ii) filtering the daptomycin solution under conditions in which the daptomycin passes through the filter but pyrogens do not pass through the filter;

iii) subjecting the daptomycin solution to conditions forming a daptomycin aggregate;

iv) filtering the daptomycin aggregate under conditions in which the daptomycin aggregate is retained on the filter; and

v) collecting the daptomycin aggregate.

24. (Original) The composition according to claim 22, wherein the process further comprises the step of lyophilizing daptomycin.

25. (Original) The composition according to claim 22, wherein the anion exchange chromatography is performed via radial flow chromatography.

26. (Original) The composition according claim 11, wherein said clarifying comprises microfiltration or centrifugation.

27. (Original) The composition according to claim 11, wherein the process further comprises the steps of filtering and concentrating daptomycin.

28. (Original) The composition according to claim 11, wherein the process further comprises the step of separating the enriched daptomycin from low molecular weight material by ultrafiltration.

29. (Original) The composition according to claim 28, wherein the process further comprises the step of depyrogenating the daptomycin.

30. Canceled

31. (Original) The pharmaceutical composition of claim 9 comprising essentially pure daptomycin.

32. (Original) The pharmaceutical composition of claim 9 comprising daptomycin that is substantially free of anhydro-daptomycin and substantially free of β-isomer of daptomycin.

33. (Original) The pharmaceutical composition of claim 9 comprising daptomycin that is essentially free of anhydro-daptomycin and substantially free of β-isomer of daptomycin.

34. (Original) The pharmaceutical composition of claim 9 comprising daptomycin that is free of anhydro-daptomycin and substantially free of β-isomer of daptomycin.

35. (Original) The pharmaceutical composition of claim 9 comprising daptomycin that is substantially free of each of impurities 1 to 14 defined by peaks 1-14 shown in FIG. 12.

36. (Original) The pharmaceutical composition of claim 9 comprising daptomycin that is essentially free of each of impurities 1 to 14 defined by peaks 1-14 shown in FIG. 12.

37. Canceled

38. (Currently amended) A method for preparing a pharmaceutical composition comprising combining the composition of claim ~~1~~ 62 with a

pharmaceutically acceptable carrier or excipient.

39. (Original) The method of claim 38 wherein the composition is essentially pure daptomycin.

40. (Original) The method of claim 38 wherein the composition is daptomycin that is substantially free of anhydro-daptomycin and substantially free of β-isomer of daptomycin.

41. (Original) The method of claim 38 wherein the composition is daptomycin that is essentially free of anhydro-daptomycin and substantially free of β-isomer of daptomycin.

42. (Original) The method of claim 38 wherein the composition is daptomycin that is free of anhydro-daptomycin and substantially free of β-isomer of daptomycin.

43. (Original) The method of claim 38 wherein the composition is daptomycin that is substantially free of each of impurities 1 to 14 defined by peaks 1-14 shown in FIG. 12.

44. (Original) The method of claim 38 wherein the composition is daptomycin that is essentially free of each of impurities 1 to 14 defined by peaks 1-14 shown in FIG. 12.

45. Canceled

46. Canceled

47. (Currently amended) The pharmaceutical composition of claim ~~46~~ 9 wherein the composition is essentially pure daptomycin.

48. (Currently amended) The pharmaceutical composition of claim ~~46~~ 9 wherein the composition is daptomycin that is substantially free of anhydro-daptomycin and substantially free of β-isomer of daptomycin.

49. (Currently amended) The pharmaceutical composition of claim ~~46~~ 9 wherein the composition is daptomycin that is essentially free of anhydro-daptomycin and substantially free of β-isomer of daptomycin.

50. (Currently amended) The pharmaceutical composition of claim ~~46~~ 9 wherein the composition is daptomycin that is free of anhydro-daptomycin and

substantially free of β-isomer of daptomycin.

51. (Currently amended) The pharmaceutical composition of claim ~~46~~ 9 wherein the composition is daptomycin that is substantially free of each of impurities 1 to 14 defined by peaks 1-14 shown in FIG. 12.

52. (Currently amended) The pharmaceutical composition of claim ~~46~~ 9 wherein the composition is daptomycin that is essentially free of each of impurities 1 to 14 defined by peaks 1-14 shown in FIG. 12.

53. Canceled

54. (Previously presented) The composition of claim 1 comprising substantially pure daptomycin.

55. (Previously presented) The pharmaceutical composition of claim 9 comprising substantially pure daptomycin.

56. (Previously presented) The method of claim 38 wherein the composition is substantially pure daptomycin.

57. Canceled

58. (Currently amended) A new composition comprising daptomycin of greater than about 93% purity, wherein the purity of the daptomycin is relative to daptomycin impurities that arise in fermentation or purification of daptomycin and wherein the daptomycin impurities comprise impurities 1-14.

59. (Currently amended) The composition of claim 58, wherein the daptomycin impurities ~~comprise impurities 1-14~~ arise in fermentation.

60. (Previously presented) The composition of claim 58, wherein the purity is at least 95%.

61. (Currently amended) The composition of claim 60, wherein the daptomycin impurities ~~comprise impurities 1-14~~ arise in fermentation.

62. (Previously presented) Daptomycin of greater than about 93% purity relative to impurities 1-14.

63. (Previously presented) The daptomycin of claim 62, wherein the purity is at least 95%.

Please enter the following new claims.

64. (New) The composition of claim 58 wherein impurity 1 is present in an amount no more than about 1%.

65. (New) The composition of claim 58 wherein impurity 2 is present in an amount no more than about 0.5%.

66. (New) The composition of claim 58 wherein impurity 3 is present in an amount no more than about 1%.

67. (New) The composition of claim 58 wherein impurity 4 is present in an amount no more than about 0.5%.

68. (New) The composition of claim 58 wherein impurity 5 is present in an amount no more than about 0.5%.

69. (New) The composition of claim 58 wherein impurity 6 is present in an amount no more than about 1%.

70. (New) The composition of claim 58 wherein impurity 7 is present in an amount no more than about 1%.

71. (New) The composition of claim 58 wherein impurity 9 is present in an amount no more than about 0.5%.

72. (New) The composition of claim 58 wherein impurity 10 is present in an amount no more than about 0.5%.

73. (New) The composition of claim 58 wherein impurity 11 is present in an amount no more than about 0.5%.

74. (New) The composition of claim 58 wherein impurity 12 is present in an amount no more than about 0.5%.

75. (New) The composition of claim 58 wherein impurity 14 is present in an amount no more than about 0.1%.

76. (New) The composition of claim 58, wherein the daptomycin is obtained by a process comprising

a) subjecting a daptomycin solution to conditions forming a daptomycin aggregate;

b)separating the daptomycin aggregate from low molecular weight

contaminants;

c) subjecting the daptomycin aggregate to conditions in which the daptomycin aggregate dissociate into daptomycin monomers.

77. (New) The composition of claim 76, wherein the daptomycin aggregate of step b) is separated from the low molecular weight contaminants by a size selection technique.

78. (New) The composition of claim 77, wherein the size selection technique is ultrafiltration or size exclusion chromatography.

79. (New) The composition of claim 78 further comprising separating the daptomycin monomers obtained from step c) from high molecular weight contaminants.

80. (New) The composition of claim 79, wherein the daptomycin monomers of are separated from the high molecular weight contaminants by a size selection technique.

81. (New) The composition of claim 80, wherein the size selection technique is ultrafiltration or size exclusion chromatography.

82 (New) The composition of claim 58, wherein the daptomycin is obtained by a process comprising

a) separating daptomycin from high molecular weight contaminants;

b) subjecting the daptomycin of step a) to conditions forming a daptomycin aggregate; and

c) separating the daptomycin aggregate from low molecular weight contaminants.

83. (New) The composition of claim 82, wherein the daptomycin aggregate of step c) is separated from the low molecular weight contaminants by a size selection technique.

84. (New) The composition of claim 83, wherein the size selection technique is ultrafiltration or size exclusion chromatography.

85 (New) The composition of claim 84, further comprising subjecting the daptomycin aggregate of step c) to conditions in which the daptomycin aggregate dissociates into daptomycin monomers.

86. (New)The composition of claim 76, wherein the aggregate is a micelle.

87. (New)The composition of claim 82, wherein the aggregate is a micelle.

88. (New) The composition of claim 58, wherein the daptomycin is obtained by a process comprising

a) subjecting a daptomycin solution to conditions forming a daptomycin aggregate;

b) filtering the daptomycin aggregate under conditions in which the daptomycin aggregate is retained on the filter; and

c) collecting the daptomycin aggregate.

89. (New) The composition of claim 82, wherein the aggregate is a micelle.

90 (New) The composition of claim 58, wherein the daptomycin is obtained by subjecting a daptomycin solution to conditions effective to forming micelles.

91. (New) The composition of claim 58, wherein the daptomycin is obtained by adjusting any one or more of temperature, salt concentration, daptomycin concentration, and pH of the solution to cause a concentration of the daptomycin in the solution to be above a critical micelle concentration.

92. (New) The composition of claim 58, wherein the daptomycin is obtained by subjecting a daptomycin solution to a pH of 2.5 to 5.0.

93. (New) The composition of claim 58, wherein the daptomycin is obtained by a process comprising:

a) adjusting the pH of a daptomycin preparation to a pH of 2.5 to 5.0;

b) filtering the daptomycin preparation of step a) on an ultrafiltration membrane;

c) adjusting the pH of the daptomycin preparation of step b) to a pH of 6.5.

94.(New) The composition of claim 93, wherein the daptomycin preparation of step a) is at a pH of 2.5 to 4.7, and the preparation further comprises 300 to 500 mM NaCl and is at a temperature of 2-15 degrees C.

95 (New) A composition of claim 62, wherein the daptomycin is obtained by a process comprising

a) subjecting a daptomycin solution to conditions forming a daptomycin aggregate;

b) separating the daptomycin aggregate from low molecular weight contaminants;

c) subjecting the daptomycin aggregate to conditions in which the daptomycin aggregate dissociate into daptomycin monomers.

96. (New) The composition of claim 95, wherein the daptomycin aggregate of step b) is separated from the low molecular weight contaminants by a size selection technique.

97. (New) The composition of claim 96, wherein the size selection technique is ultrafiltration or size exclusion chromatography.

98. (New) The composition of claim 97 further comprising separating the daptomycin monomers obtained from step c) from high molecular weight contaminants.

99. (New) The composition of claim 98, wherein the daptomycin monomers are separated from the high molecular weight contaminants by a size selection technique.

100. (New) The composition of claim 99, wherein the size selection technique is ultrafiltration or size exclusion chromatography.

101 (New) The composition of claim 62, wherein the daptomycin is obtained by a process comprising

a) separating daptomycin from high molecular weight contaminants.

b) subjecting the daptomycin of step a) to conditions forming a daptomycin aggregate; and

c) separating the daptomycin aggregate from low molecular weight contaminants.

102. (New) The composition of claim 101, wherein the daptomycin aggregate of step c) is separated from the low molecular weight contaminants by a size selection technique.

103. (New) The composition of claim 102, wherein the size selection technique is ultrafiltration or size exclusion chromatography.

104. (New) The composition of claim 103, further comprising subjecting the daptomycin aggregate of step c) to conditions in which the daptomycin aggregate dissociates into daptomycin monomers.

105. (New) The composition of claim 95, wherein the aggregate is a micelle.

106. (New) The composition of claim 101, wherein the aggregate is a micelle.

107. (New) The composition of claim 62, wherein the daptomycin is obtained by a process comprising

a) subjecting a daptomycin solution to conditions forming a daptomycin aggregate;

b) filtering the daptomycin aggregate under conditions in which the daptomycin aggregate is retained on the filter; and

c) collecting the daptomycin aggregate.

108. (New) The composition of claim 101, wherein the aggregate is a micelle.

109. (New) The composition of claim 62, wherein the daptomycin is obtained by subjecting a daptomycin solution to conditions effective to forming micelles.

110. (New) The composition of claim 62, wherein the daptomycin is obtained by adjusting any one or more of temperature, salt concentration, daptomycin concentration, and pH of the solution to cause a concentration of the daptomycin in the solution to be above a critical micelle concentration.

111. (New) The composition of claim 62, wherein the daptomycin is obtained by subjecting a daptomycin solution to a pH of 2.5 to 5.0.

112. (New) The composition of claim 62, wherein the daptomycin is obtained by a process comprising:

a) adjusting the pH of a daptomycin preparation to a pH of 2.5 to 5.0;

b) filtering the daptomycin preparation of step a) on an ultrafiltration membrane;

c) adjusting the pH of the daptomycin preparation of step b) to a pH of 6.5.

113. (New) The composition of claim 112, wherein the daptomycin preparation of step a) is at a pH of 2.5 to 4.7, and the preparation further comprises 300 to 500 mM NaCl and is at a temperature of 2-15 degrees C.

114. (New) The composition of claim 58 wherein the daptomycin is obtained by a process comprising:

a) subjecting a solution of daptomycin to anion exchange chromatography to obtain an enriched daptomycin preparation;

b) subjecting the enriched daptomycin preparation to hydrophobic interaction chromatography to obtain a semi-purified daptomycin preparation; and

c) subjecting the semi-purified daptomycin preparation to anion exchange chromatography.

115. (New) A composition comprising

(a) essentially pure daptomycin,

(b) daptomycin that is substantially free of anhydro-daptomycin and substantially free of β-isomer of daptomycin,

(c) daptomycin that is essentially free of anhydro-daptomycin and substantially free of β-isomer of daptomycin,

(d) daptomycin that is free of anhydro-daptomycin and substantially free of β-isomer of daptomycin,

(e) daptomycin that is substantially free of each of impurities 1 to 14 defined by peaks 1-14 shown in FIG. 12, or

(f) daptomycin that is essentially free of each of impurities 1 to 14 defined by peaks 1-14 shown in FIG. 12.

116. (New) The composition of claim 62 wherein impurity 1 is present in an amount no more than about 1%.

117. (New) The composition of claim 62 wherein impurity 2 is present in an amount no more than about 0.5%.

118. (New) The composition of claim 62 wherein impurity 3 is present in an amount no more than about 1%.

119. (New) The composition of claim 62 wherein impurity 4 is present in

an amount no more than about 0.5%.

120. (New) The composition of claim 62 wherein impurity 5 is present in an amount no more than about 0.5%.

121. (New) The composition of claim 62 wherein impurity 6 is present in an amount no more than about 1%.

122. (New) The composition of claim 62 wherein impurity 7 is present in an amount no more than about 1%.

123. (New) The composition of claim 62 wherein impurity 9 is present in an amount no more than about 0.5%.

124. (New) The composition of claim 62 wherein impurity 10 is present in an amount no more than about 0.5%.

125. (New) The composition of claim 62 wherein impurity 11 is present in an amount no more than about 0.5%.

126. (New) The composition of claim 62 wherein impurity 12 is present in an amount no more than about 0.5%.

127. (New) The composition of claim 62 wherein impurity 14 is present in an amount no more than about 0.1%.

128. (New) The composition of claim 62 wherein the daptomycin is obtained by a process comprising:

a) subjecting a solution of daptomycin to anion exchange chromatography to obtain an enriched daptomycin preparation;

b) subjecting the enriched daptomycin preparation to hydrophobic interaction chromatography to obtain a semi-purified daptomycin preparation; and

c) subjecting the semi-purified daptomycin preparation to anion exchange chromatography.

129. (New) The composition of claim 63, wherein the daptomycin is obtained by a process comprising

a) subjecting a daptomycin solution to conditions forming a daptomycin aggregate;

b)separating the daptomycin aggregate from low molecular weight

contaminants;

c) subjecting the daptomycin aggregate to conditions in which the daptomycin aggregate dissociate into daptomycin monomers.

130. (New) The composition of claim 129, wherein the daptomycin aggregate of step b) is separated from the low molecular weight contaminants by a size selection technique.

131. (New) The composition of claim 130, wherein the size selection technique is ultrafiltration or size exclusion chromatography.

132. (New) The composition of claim 131 further comprising separating the daptomycin monomers obtained from step c) from high molecular weight contaminants.

133. (New) The composition of claim 132, wherein the daptomycin monomers of are separated from the high molecular weight contaminants by a size selection technique.

134. (New) The composition of claim 133, wherein the size selection technique is ultrafiltration or size exclusion chromatography.

135. (New) The composition of claim 63, wherein the daptomycin is obtained by a process comprising

a) separating daptomycin from high molecular weight contaminants.

b) subjecting the daptomycin of step a) to conditions forming a daptomycin aggregate; and

c)separating the daptomycin aggregate from low molecular weight contaminants.

136. (New) The composition of claim 135, wherein the daptomycin aggregate of step c) is separated from the low molecular weight contaminants by a size selection technique.

137. (New) The composition of claim 136, wherein the size selection technique is ultrafiltration or size exclusion chromatography.

138 (New) The composition of claim 137, further comprising subjecting the daptomycin aggregate of step c) to conditions in which the daptomycin aggregate

dissociates into daptomycin monomers.

139. (New) The composition of claim 129, wherein the aggregate is a micelle.

140. (New) The composition of claim 135, wherein the aggregate is a micelle.

141. (New) The composition of claim 63, wherein the daptomycin is obtained by a process comprising

a) subjecting a daptomycin solution to conditions forming a daptomycin aggregate;

b) filtering the daptomycin aggregate under conditions in which the daptomycin aggregate is retained on the filter; and

c) collecting the daptomycin aggregate.

142. (New) The composition of claim 135, wherein the aggregate is a micelle.

143 (New) The composition of claim 63, wherein the daptomycin is obtained by subjecting a daptomycin solution to conditions effective to forming micelles.

144. (New) The composition of claim 63, wherein the daptomycin is obtained by adjusting any one or more of temperature, salt concentration, daptomycin concentration, and pH of the solution to cause a concentration of the daptomycin in the solution to be above a critical micelle concentration.

145. (New) The composition of claim 63, wherein the daptomycin is obtained by subjecting a daptomycin solution to a pH of 2.5 to 5.0.

146. (New) The composition of claim 63, wherein the daptomycin is obtained by a process comprising:

a) adjusting the pH of a daptomycin preparation to a pH of 2.5 to 5.0;

b) filtering the daptomycin preparation of step a) on an ultrafiltration membrane;

c) adjusting the pH of the daptomycin preparation of step b) to a pH of 6.5.

147. (New) The composition of claim 146, wherein the daptomycin preparation of step a) is at a pH of 2.5 to 4.7, and the preparation further comprises 300 to

500 mM NaCl and is at a temperature of 2-15 degrees C.

148. (New) The composition of claim 63 wherein the daptomycin is obtained by a process comprising:

a) subjecting a solution of daptomycin to anion exchange chromatography to obtain an enriched daptomycin preparation;

b) subjecting the enriched daptomycin preparation to hydrophobic interaction chromatography to obtain a semi-purified daptomycin preparation; and

c) subjecting the semi-purified daptomycin preparation to anion exchange chromatography.

149. (New) The composition of claim 63 wherein impurity 1 is present in an amount no more than about 1%.

150. (New) The composition of claim 63 wherein impurity 2 is present in an amount no more than about 0.5%.

151. (New) The composition of claim 63 wherein impurity 3 is present in an amount no more than about 1%.

152. (New) The composition of claim 63 wherein impurity 4 is present in an amount no more than about 0.5%.

153. (New) The composition of claim 63 wherein impurity 5 is present in an amount no more than about 0.5%.

154. (New) The composition of claim 63 wherein impurity 6 is present in an amount no more than about 1%.

155. (New) The composition of claim 63 wherein impurity 7 is present in an amount no more than about 1%.

156. (New) The composition of claim 63 wherein impurity 9 is present in an amount no more than about 0.5%.

157. (New) The composition of claim 63 wherein impurity 10 is present in an amount no more than about 0.5%.

158. (New) The composition of claim 63 wherein impurity 11 is present in an amount no more than about 0.5%.

159. (New) The composition of claim 63 wherein impurity 12 is present in

an amount no more than about 0.5%.

160. (New) The composition of claim 63 wherein impurity 14 is present in an amount no more than about 0.1%.

REMARKS

Amendments to the Claims

Claims 1-29, 31-36, 38-44, 46-52, 54-57, and 58-63 were pending in the present application. Applicants have added new claims 64-160. Support for claims 64-160 can be found throughout the specification. For example, support for claims 64-75, 116-127, and 149-160 can be found in Table 3, paragraph 179 and support for claims 76-113 and 129-147 can be found in paragraphs 99-128.

Applicants have amended claims 2, 3, 6, 8, 9, 11, 47-52, 58, 59, and 61. Support for these amended claims can be found throughout the specification.

Applicants have canceled claims 46 and 57 without prejudice or disclaimer to Applicants' rights to pursue the same or similar subject matter in the future.

No new matter is introduced by the claim amendments.

Accordingly, upon entry of the instant amendments, claims 1-29, 31-36, 38-44, 47-52, 54-56, 58-160 will be pending in this application.

The Pending Claims are Allowable

Applicants have elected to amend the claims to cover subject matter the Office Action indicates to be allowable. In particular, the Office Action at page 8 reads:

> Claims 2-7, 31-36, 39-44, 47-52, 59, and 61-63 are objected to because the claims are dependent from a rejected claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

In response, claims 2, 3, and 6 have been rewritten in independent form to place them in condition for allowance. Therefore, claims 2, 3, 6 - along with the dependent claims 4, 5 and 7 – are in condition for allowance.

Claim 62 is written in independent form, and is not rejected in the Office Action. Dependent claims 9 and 38 are amended to depend from independent claim 62. As amended, dependent claims 31-36, 39-44, and 47-52 now depend from either amended claim 9 or amended claim 38, Applicants respectfully request allowance of claims 62, 9, 38, 31-36, 39-44, and 47-52.

Claim 58 is amended to cover subject matter indicated as allowable in the Office Aciton. Claims 60-61 depend on amended claim 58. Accordingly, Applicants request allowance of claims 58-61.

Notwithstanding, Applicants traverse rejections of the claims. Claims 1, 8-29, 38, 46, 54-58 and 60 stand rejected under 35 U.S.C. § 102(e) as anticipated by Baker *et al.* (US RE39,071 E, hereafter Baker), and claims 1, 8-9, 46, 54-55, 57, 58 and 60 stand rejected under the doctrine of obviousness-type double patenting over claims 18-20, 26, 28 and 29 of Baker. Claims 2-7, 31-36, 39-44, 47-52, 59 and 61-63 are objected to. Notwithstanding the amendments herein, Applicants respectfully overcome and traverse the rejections for the reasons set forth below.

I. Acknowledgement of Withdrawal of Rejection under 35 U.S.C.§ 103(a)

Applicants acknowledge with thanks the withdrawal of the rejection of the claims under 35 U.S.C. § 103(a).

II. Baker Does Not Anticipate Under 35 U.S.C § 102(e)

The Office Action reads: "the rejection of claim 1(g) and its dependent claims are maintained" and cites Example 3 of Baker as the grounds for rejection.

"In order to render a determination of anticipation under 35 U.S.C. 102, the reference must teach every aspect of the claimed invention either explicitly or impliedly. Any feature not directly taught must be inherently present." MPEP 706.02 V. "To serve as an anticipation when the reference is silent about the asserted inherent characteristic [i.e. one not directly taught], such gap in the reference may be filled with recourse to extrinsic evidence. Such evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill." *Continental Can Co. USA v. Monsanto Co.,* 948 F.2d 1264, 1268, 20 USPQ2d 1746, 1749 (Fed. Cir. 1991).

A. Baker Does Not Expressly Or Inherently Include All of the Limitations of the Present Claims

1. Baker Uses a Different Daptomycin Purity Than the Present Application

Although the Office Action posits that the substantially pure daptomycin in Baker "reads that the daptomycin has more than 97.5% purity," the purity of daptomycin in Baker can only be interpreted as defined by Baker. In Baker, "substantially pure form means that LY146032 contains less than 2.5 percent of a combined total of anhydro-LY146032 and isomer-LY146032." Col. 8, ll. 55-57. Baker can be interpreted to read that there is 97.5% of daptomycin over a daptomycin plus anhydro-daptomycin ("A") plus beta isomer daptomycin ("B") composition.

The present application describes daptomycin purity relative to daptomycin plus anhydro daptomycin (impurity No. 13) plus beta-isomer (impurity No. 8) **plus 12 other impurities** (impurities 1-7, 9-12 and 14) (the fourteen daptomycin impurities) as described in Table 3 of the specification**.** Therefore, it is consistent to say that, as described in detail below in II.A.2, the Baker methods yield at best about 93% pure daptomycin measured under the current application while it yields 97.5% purity under its own teachings.

Accordingly, Baker uses a different purity and does not teach purity over the fourteen daptomycin impurities.

2. Evidence of Inherency and/or Official Notice of Facts To Support The Inherency of the Present Claims Have Not Been Provided

"In relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." Ex parte Levy, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990) (emphasis in original). Any suggestion that the daptomycin purity of Baker inherently anticipates the purity presently claimed requires a citation to some extrinsic evidence from which the suggestion necessarily follows. No citation has been made to any extrinsic support for

any purity different from that explained above.

If the Examiner were to rely upon facts relating to the purity of the daptomycin compositions taught in Baker without documentary evidence, such official notice is not appropriate as a basis for asserting that Baker inherently discloses the claimed daptomycin compositions:

> [o]fficial notice without documentary evidence to support an examiner's conclusion is permissible only in some circumstances....Official notice unsupported by documentary evidence should only be taken by the examiner where the facts asserted to be well-known, or to be common knowledge in the art are capable of instant and unquestionable demonstration as being well-known (MPEP 2144.03).

Applicants submit that the inherent characteristics of the teachings of Baker, particularly vis-à-vis the twelve other daptomycin impurities, are not well known or common knowledge capable for instant and unquestionable demonstration.

A. The Present Claims, When Properly Interpreted, Are Not Anticipated by Baker

The Office Action reads:

> Baker et al discloses a composition or pharmaceutical composition comprising substantially pure daptomycin, which meets the criteria of claim 1(a)-1(d) and 1(g), and its dependent claims because the term "comprising" indicates the composition can contain something else besides substantially or essentially pure daptomycin (Office Action at pages 3-4, emphasis in original).

While "comprising" is open-ended, it is not so open as to vitiate the claim limitation of the daptomycin. In particular, the "something else" that the Office Action asserts is within claimed inventions using "comprising" cannot alter the claimed daptomycin to not have the daptomycin purity of the claim. A proper use of comprising would maintain the existing purity limitations to the extent claimed and not attempt to read the limitation out of the claim. By adding "something else," the claims were interpreted in a manner inconsistent with both the specification and their plain meaning. This interpretation is not permitted:

> Indeed, the rules of the PTO require that application claims must "conform to the invention as set forth in the remainder of the specification and the terms

> and phrases used in the claims must find clear support or antecedent basis in the description so that the meaning of the terms in the claims may be ascertainable by reference to the description." 37 CFR 1.75(d)(1)... The words of a claim must be given their "plain meaning"... (MPEP 2111, 2111.01).

Based on the plain meaning of the claims, the daptomycin within the composition -- not necessarily the entire composition itself -- must be interpreted to retain the claimed characteristics. Therefore, Baker does not meet the criteria of claim 1(a)-1(d) and 1(g), and its dependent claims because the term "comprising" cannot eliminate the claimed purity.

B. Request for Reconsideration and Withdrawal Of Rejection Under 35 U.S.C. § 102(e)

Baker does not anticipate claims 1 and 54 under 35 U.S.C § 102(e) when the claims are properly interpreted primarily because: (1) Baker teaches a different measurement of purity which does not consider the fourteen daptomycin impurities and (2) Baker had at best about 93% pure daptomycin when including the twelve additional daptomycin impurities. Therefore the rejection is traversed. Accordingly, Applicant respectfully requests withdrawal of the rejection under 35 U.S.C. § 102(e) and reconsideration and allowance of all pending claims.

C. New Claims 64-160 Depend from Objected to Claims

New claims 64-160 depend from claims directed to subject matter merely objected to solely for depending from an otherwise rejected claim and thus should be allowed.

III. Product-by-Process Claim Interpretation

The Office Action reads that claims 11-29 are not patentable because the product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself, and the patentability of a product does not depend on its method of production. As this basis for rejection is overcome in the present claims, Applicants reserve the right to later challenge the different interpretations applied

to product-by-process claims.

IV. Obviousness-Type Double Patenting

The Office Action reads that claims 1, 8-9, 46, 54-55, 57, 58 and 60 are rejected over claims 18-20, 26, 28 and 29 of Baker. Applicants reserve their right to file a terminal disclaimer upon an indication of allowance of these claims over Baker under 35 U.S.C. § 102(e) as requested above or to cancel such claims in a further amendment.

CONCLUSION

For the reasons presented above, Applicant respectfully requests reconsideration and prompt allowance of all pending claims. A Petition for Extension of Time is enclosed. In the absence of such a petition, Applicants request that this paper be considered to include such a Petition for a Three (3) Month Extension of Time. Please deduct the petition fee and apply any other charges or credits required for entry of this amendment to Deposit Account No.50-1986, referencing attorney docket number C062-02/03 US. No authorization is given to deduct the issue fee at this time.

Respectfully submitted,

Date:September 22, 2010
/William D. DeVaul/
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C062-02-03 US 20100922 Resp to 20100322 OA.doc

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appl. No.	:	11/739,180	Confirmation No.	8837
Applicant	:	Thomas J. Kelleher		
Filed	:	April 24, 2007		
TC/A.U.	:	1656		
Examiner	:	Chih-Min Kam		
Docket No.	:	C062-02/03 US		
Customer No.	:	34103		

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313

SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT

Pursuant to 37 C.F.R. §§ 1.56, 1.97(c) and 1.98, applicants make of record the following documents which are listed on the enclosed Form PTO/SB/08a. Copies of the following document(s) are enclosed herewith:

Molloy, M. et al., Abstract,"Structure & Anhydro-Daptomycin and Iso-Daptomycin," ACS 200th Meeting, 1990.

Molloy, M. et al., Poster, "Structure & Anhydro-Daptomycin and Iso-Daptomycin," ACS 200th Meeting, 1990.

REMARKS

Applicants have submitted an abstract and a poster.

Applicants request that the cited documents be fully considered by the Examiner during the course of examination of this application and that a copy of Form PTO/SB/08a, as considered, initialed, and signed by the Examiner, be returned with the next communication.

No fee is believed to be due in connection with this filing, however, please apply any other charges or credits to Deposit Account No. 50-1986, referencing attorney docket number C062-02/03 US.

Respectfully submitted,

Dated: September 22, 2010
Customer No.: 34103
Cubist Pharmaceuticals, Inc.
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C062-02-03 US 20100115 Suppl IDS letter

/William D. DeVaul/
William D. DeVaul, Reg. No. 42,483
Attorney for Applicants

PTO/SB/08b (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 1

Complete if Known	
Application Number	11739180
Filing Date	2007-04-24
First Named Inventor	Kelleher, Thomas J.
Art Unit	1656
Examiner Name	Chih-Min Kam
Attorney Docket Number	C062-02/03 US

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
		Molloy, M. et al., Abstract, "Structure & Anhydro-Daptomycin and Iso-Daptomycin," ACS 200th Meeting, 1990.	
		Molloy, M. et al., Poster, "Structure & Anhydro-Daptomycin and Iso-Daptomycin," ACS 200th Meeting, 1990.	

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

1 Applicant's unique citation designation number (optional). 2 Applicant is to place a check mark here if English language Translation is attached.

Privacy Act Statement

The **Privacy Act of 1974 (P.L. 93-579)** requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (*i.e.*, GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Doc Code: TRAN.LET

Document Description: Transmittal Letter

PTO/SB/21 (07-09)
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TRANSMITTAL FORM

(to be used for all correspondence after initial filing)

Total Number of Pages in This Submission	36

Application Number	11739180
Filing Date	2007-04-24
First Named Inventor	Kelleher, Thomas J.
Art Unit	1656
Examiner Name	Chih-Min Kam
Attorney Docket Number	C062-02/03 US

ENCLOSURES (*Check all that apply*)

- ☑ Fee Transmittal Form
  - ☐ Fee Attached
- ☑ Amendment/Reply
  - ☐ After Final
  - ☐ Affidavits/declaration(s)
- ☑ Extension of Time Request
- ☐ Express Abandonment Request
- ☑ Information Disclosure Statement
- ☐ Certified Copy of Priority Document(s)
- ☐ Reply to Missing Parts/ Incomplete Application
  - ☐ Reply to Missing Parts under 37 CFR 1.52 or 1.53
- ☐ Drawing(s)
- ☐ Licensing-related Papers
- ☐ Petition
- ☐ Petition to Convert to a Provisional Application
- ☐ Power of Attorney, Revocation Change of Correspondence Address
- ☐ Terminal Disclaimer
- ☐ Request for Refund
- ☐ CD, Number of CD(s) _____
  - ☐ Landscape Table on CD
- ☐ After Allowance Communication to TC
- ☐ Appeal Communication to Board of Appeals and Interferences
- ☐ Appeal Communication to TC **(Appeal Notice, Brief, Reply Brief)**
- ☐ Proprietary Information
- ☐ Status Letter
- ☐ Other Enclosure(s) (please Identify below):

Remarks

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm Name	Cubist Pharmaceuticals, Inc.		
Signature	/William D. DeVaul/		
Printed name	William D. DeVaul		
Date	September 22, 2010	Reg. No.	42,483

CERTIFICATE OF TRANSMISSION/MAILING

I hereby certify that this correspondence is being facsimile transmitted to the USPTO or deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on the date shown below:

Signature			
Typed or printed name		Date	

Privacy Act Statement

The **Privacy Act of 1974 (P.L. 93-579)** requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

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2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
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6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (*i.e.*, GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
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9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Electronic Patent Application Fee Transmittal

Application Number:	11739180
Filing Date:	24-Apr-2007
Title of Invention:	High Purity Lipopeptides
First Named Inventor/Applicant Name:	Thomas Kelleher
Filer:	William D. DeVaul
Attorney Docket Number:	C062-02/03 US

Filed as Small Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Claims in excess of 20	2202	135	26	3510
Independent claims in excess of 3	2201	4	110	440
Multiple dependent claims	2203	1	195	195
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Extension - 3 months with $0 paid	2253	1	555	555
Miscellaneous:				
		Total in USD ($)		**4700**

Electronic Acknowledgement Receipt

EFS ID:	8478370
Application Number:	11739180
International Application Number:	
Confirmation Number:	8837
Title of Invention:	High Purity Lipopeptides
First Named Inventor/Applicant Name:	Thomas Kelleher
Customer Number:	34103
Filer:	William D. DeVaul
Filer Authorized By:	
Attorney Docket Number:	C062-02/03 US
Receipt Date:	22-SEP-2010
Filing Date:	24-APR-2007
Time Stamp:	21:35:01
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$4700
RAM confirmation Number	7645
Deposit Account	501986
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

Charge any Additional Fees required under 37 C.F.R. Section 1.17 (Patent application and reexamination processing fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Extension of Time	C062-02-03_US_20100922_Petition_Ext.pdf	331536 d406943cde79d4a9a50de895a52e5dc59be047d3	no	2
Warnings:					
Information:					
2	Amendment/Req. Reconsideration-After Non-Final Reject	C062-02-03_US_20100922_Response.pdf	94774 1c8320110c98fe2e0a4cb5e0b805df08c05b9bc2	no	25
Warnings:					
Information:					
3	Transmittal Letter	C062-02-03_US_2010922_Supp l_IDS_Ltr.pdf	16160 ee73ac7fe4fed3a95da6886092dc6c6d07428741	no	2
Warnings:					
Information:					
4	Information Disclosure Statement (IDS) Filed (SB/08)	C062-02-03_US_20100922_IDS.pdf	338885 25e2d77cb29229fe553c3d29b23fe9ffec37b062	no	2
Warnings:					
Information:					
This is not an USPTO supplied IDS fillable form					
5	NPL Documents	Molloy_Abstract.pdf	227387 7ceb2c2b4777618649e781f7efad4fb629f54651	no	2
Warnings:					
Information:					
6	NPL Documents	Debono_Poster_2.pdf	270775 fa251b7ca61f3fc4a755dc18f439f3b5f19a7cd4	no	3
Warnings:					
Information:					
7	Miscellaneous Incoming Letter	C062-02-03_US_20100922_Transm.pdf	68443 311303503d6aa9a0f6e6061d5a69c33010214de8	no	2
Warnings:					
Information:					
8	Fee Worksheet (PTO-875)	fee-info.pdf	36799 19a6dc29da6841ba08ca8f11e302d43738d5f357	no	2
Warnings:					
Information:					

Total Files Size (in bytes):	1384759

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/SB/22 (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARMENT OF COMMERCE

PETITION FOR EXTENSION OF TIME UNDER 37 CFR 1.136(a) **FY 2009** (*Fees pursuant to the Consolidated Appropriations Act, 2005 (H.R. 4818).*)	Docket Number (Optional) C062-02/03 US
Application Number 11/739,180	Filed April 24, 2007
For HIGH PURITY LIPOPEPTIDES	
Art Unit 1656	Examiner Chih-Min Kam

This is a request under the provisions of 37 CFR 1.136(a) to extend the period for filing a reply in the above identified application.

The requested extension and fee are as follows (check time period desired and enter the appropriate fee below):

	Fee	Small Entity Fee	
☐ One month (37 CFR 1.17(a)(1))	$130	$65	$
☐ Two months (37 CFR 1.17(a)(2))	$490	$245	$
☑ Three months (37 CFR 1.17(a)(3))	$1110	$555	$ 555.00
☐ Four months (37 CFR 1.17(a)(4))	$1730	$865	$
☐ Five months (37 CFR 1.17(a)(5))	$2350	$1175	$

☐ Applicant claims small entity status. See 37 CFR 1.27.

☐ A check in the amount of the fee is enclosed.

☐ Payment by credit card. Form PTO-2038 is attached.

☑ The Director has already been authorized to charge fees in this application to a Deposit Account.

☐ The Director is hereby authorized to charge any fees which may be required, or credit any overpayment, to Deposit Account Number _____.

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

I am the

☐ applicant/inventor.

☐ assignee of record of the entire interest. See 37 CFR 3.71.
Statement under 37 CFR 3.73(b) is enclosed (Form PTO/SB/96).

☐ attorney or agent of record. Registration Number _____

☑ attorney or agent under 37 CFR 1.34.
Registration number if acting under 37 CFR 1.34 42,483

/William D. DeVaul/ — Signature

September 22, 2010 — Date

William D. DeVaul — Typed or printed name

781-860-8559 — Telephone Number

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below.

☑ Total of 1 forms are submitted.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

PTO/SB/06 (07-06)
Approved for use through 1/31/2007. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number	Filing Date	☐ To be Mailed
11/739,180	04/24/2007	

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY ☒ RATE ($)	SMALL ENTITY ☒ FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =		OR	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =			X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT	09/22/2010	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE ($)	SMALL ENTITY ADDITIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 194	Minus	** 59	= 135	X $26 =	3510	OR	X $ =	
	Independent (37 CFR 1.16(h))	* 7	Minus	***3	= 4	X $110 =	440	OR	X $ =	
	☐ Application Size Fee (37 CFR 1.16(s))									
	☒ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						195	OR		
						TOTAL ADD'L FEE	4145	OR	TOTAL ADD'L FEE	

AMENDMENT		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =		OR	X $ =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =		OR	X $ =	
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

Legal Instrument Examiner:
/DORIS M. KING/

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/739,180	04/24/2007	Thomas Kelleher	C062-02/03 US	8837

34103 7590 03/22/2010

Intellectual Property Department
Cubist Pharmaceuticals, Inc.
65 Hayden Avenue
Lexington, MA 02421

EXAMINER	
KAM, CHIH MIN	

ART UNIT	PAPER NUMBER
1656	

MAIL DATE	DELIVERY MODE
03/22/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	11/739,180	KELLEHER ET AL.	
	Examiner	Art Unit	
	CHIH-MIN KAM	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 November 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-29,31-36,38-44,46-52 and 54-63* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,8-29,38,46,54-58 and 60* is/are rejected.

7)☒ Claim(s) *2-7,31-36,39-44,47-52,59 and 61-63* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *24 April 2007* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/13/09, 1/15/10*.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. *20100222* .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Interview Summary	Application No.	Applicant(s)	
	11/739,180	KELLEHER ET AL.	
	Examiner	Art Unit	
	CHIH-MIN KAM	1656	

All participants (applicant, applicant's representative, PTO personnel):

(1) *CHIH-MIN KAM*.

(2) *Jill M. Mandelblatt*.

(3)*William D DeVaul*.

(4)_____.

Date of Interview: *07 January 2010*.

Type: a)☒ Telephonic b)☐ Video Conference
c)☐ Personal [copy given to: 1)☐ applicant 2)☐ applicant's representative]

Exhibit shown or demonstration conducted: d)☐ Yes e)☒ No.
If Yes, brief description: _____.

Claim(s) discussed: *pending claims*.

Identification of prior art discussed: *US RE39,071 E*.

Agreement with respect to the claims f)☐ was reached. g)☒ was not reached. h)☐ N/A.

Substance of Interview including description of the general nature of what was agreed to if an agreement was reached, or any other comments: *Discussing the rejection under 35 USC 102(e)/103(a), the statement that was added to the specification regarding a joint research agreement and amendment to the claims applicants will file part of joint research agreement and assignment* .

(A fuller description, if necessary, and a copy of the amendments which the examiner agreed would render the claims allowable, if available, must be attached. Also, where no copy of the amendments that would render the claims allowable is available, a summary thereof must be attached.)

THE FORMAL WRITTEN REPLY TO THE LAST OFFICE ACTION MUST INCLUDE THE SUBSTANCE OF THE INTERVIEW. (See MPEP Section 713.04). If a reply to the last Office action has already been filed, APPLICANT IS GIVEN A NON-EXTENDABLE PERIOD OF THE LONGER OF ONE MONTH OR THIRTY DAYS FROM THIS INTERVIEW DATE, OR THE MAILING DATE OF THIS INTERVIEW SUMMARY FORM, WHICHEVER IS LATER, TO FILE A STATEMENT OF THE SUBSTANCE OF THE INTERVIEW. See Summary of Record of Interview requirements on reverse side or on attached sheet.

Summary of Record of Interview Requirements

Manual of Patent Examining Procedure (MPEP), Section 713.04, Substance of Interview Must be Made of Record
A complete written statement as to the substance of any face-to-face, video conference, or telephone interview with regard to an application must be made of record in the application whether or not an agreement with the examiner was reached at the interview.

Title 37 Code of Federal Regulations (CFR) § 1.133 Interviews
Paragraph (b)

In every instance where reconsideration is requested in view of an interview with an examiner, a complete written statement of the reasons presented at the interview as warranting favorable action must be filed by the applicant. An interview does not remove the necessity for reply to Office action as specified in §§ 1.111, 1.135. (35 U.S.C. 132)

37 CFR §1.2 Business to be transacted in writing.
All business with the Patent or Trademark Office should be transacted in writing. The personal attendance of applicants or their attorneys or agents at the Patent and Trademark Office is unnecessary. The action of the Patent and Trademark Office will be based exclusively on the written record in the Office. No attention will be paid to any alleged oral promise, stipulation, or understanding in relation to which there is disagreement or doubt.

The action of the Patent and Trademark Office cannot be based exclusively on the written record in the Office if that record is itself incomplete through the failure to record the substance of interviews.

It is the responsibility of the applicant or the attorney or agent to make the substance of an interview of record in the application file, unless the examiner indicates he or she will do so. It is the examiner's responsibility to see that such a record is made and to correct material inaccuracies which bear directly on the question of patentability.

Examiners must complete an Interview Summary Form for each interview held where a matter of substance has been discussed during the interview by checking the appropriate boxes and filling in the blanks. Discussions regarding only procedural matters, directed solely to restriction requirements for which interview recordation is otherwise provided for in Section 812.01 of the Manual of Patent Examining Procedure, or pointing out typographical errors or unreadable script in Office actions or the like, are excluded from the interview recordation procedures below. Where the substance of an interview is completely recorded in an Examiners Amendment, no separate Interview Summary Record is required.

The Interview Summary Form shall be given an appropriate Paper No., placed in the right hand portion of the file, and listed on the "Contents" section of the file wrapper. In a personal interview, a duplicate of the Form is given to the applicant (or attorney or agent) at the conclusion of the interview. In the case of a telephone or video-conference interview, the copy is mailed to the applicant's correspondence address either with or prior to the next official communication. If additional correspondence from the examiner is not likely before an allowance or if other circumstances dictate, the Form should be mailed promptly after the interview rather than with the next official communication.

The Form provides for recordation of the following information:

- Application Number (Series Code and Serial Number)
- Name of applicant
- Name of examiner
- Date of interview
- Type of interview (telephonic, video-conference, or personal)
- Name of participant(s) (applicant, attorney or agent, examiner, other PTO personnel, etc.)
- An indication whether or not an exhibit was shown or a demonstration conducted
- An identification of the specific prior art discussed
- An indication whether an agreement was reached and if so, a description of the general nature of the agreement (may be by attachment of a copy of amendments or claims agreed as being allowable). Note: Agreement as to allowability is tentative and does not restrict further action by the examiner to the contrary.
- The signature of the examiner who conducted the interview (if Form is not an attachment to a signed Office action)

It is desirable that the examiner orally remind the applicant of his or her obligation to record the substance of the interview of each case. It should be noted, however, that the Interview Summary Form will not normally be considered a complete and proper recordation of the interview unless it includes, or is supplemented by the applicant or the examiner to include, all of the applicable items required below concerning the substance of the interview.

A complete and proper recordation of the substance of any interview should include at least the following applicable items:

1) A brief description of the nature of any exhibit shown or any demonstration conducted,
2) an identification of the claims discussed,
3) an identification of the specific prior art discussed,
4) an identification of the principal proposed amendments of a substantive nature discussed, unless these are already described on the Interview Summary Form completed by the Examiner,
5) a brief identification of the general thrust of the principal arguments presented to the examiner,
   (The identification of arguments need not be lengthy or elaborate. A verbatim or highly detailed description of the arguments is not required. The identification of the arguments is sufficient if the general nature or thrust of the principal arguments made to the examiner can be understood in the context of the application file. Of course, the applicant may desire to emphasize and fully describe those arguments which he or she feels were or might be persuasive to the examiner.)
6) a general indication of any other pertinent matters discussed, and
7) if appropriate, the general results or outcome of the interview unless already described in the Interview Summary Form completed by the examiner.

Examiners are expected to carefully review the applicant's record of the substance of an interview. If the record is not complete and accurate, the examiner will give the applicant an extendable one month time period to correct the record.

Examiner to Check for Accuracy

If the claims are allowable for other reasons of record, the examiner should send a letter setting forth the examiner's version of the statement attributed to him or her. If the record is complete and accurate, the examiner should place the indication, "Interview Record OK" on the paper recording the substance of the interview along with the date and the examiner's initials.

DETAILED ACTION

1. The Request for Continued Examination (RCE) filed on November 13, 2009 under 37 CFR 1.114 is acknowledged. An action on the RCE follows.

Status of the Claims

2. Claims 1-29, 31-36, 38-44, 46-52 and 54-63 are pending.

Applicants' amendment filed November 13, 2009 is acknowledged. New claims 58-63 have been added. Therefore, claims 1-29, 31-36, 38-44, 46-52 and 54-63 are examined.

Withdrawn Claim Rejections - 35 USC § 103

3. The previous rejection of claims 2-5, 31-34, 39-42 and 47-50 under 35 U.S.C. 103(a) as being unpatentable over Baker *et al.* (US RE39,071 E) is withdrawn in view of applicants' statement added to the specification regarding a joint research agreement, and applicant's response at pages 9-10 in the amendment filed November 13, 2009.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

4. Claims 1, 8-29, 38, 46, 54-58 and 60 are rejected under 35 U.S.C. 102(e) as anticipated by Baker *et al.* (US RE39,071 E, reissue of U.S. Patent 5,912,226, filed December 16, 1991).

Baker *et al.* teach an antibacterial composition comprising daptomycin (LY146032) obtained in substantially pure form, which refers to daptomycin that contains less than 2.5% of a combined total of anhydro-daptomycin and beta-isomer of daptomycin (column 8, lines 50-60; Examples 4 and 5; claim 1(g), 54, 58 and 60), where daptomycin is purified by a procedure using Diaion HP-20 resin column, followed by HPLC and another HP-20 resin column (Examples 1-5, claim 8). Baker *et al.* also teach the preparation of a pharmaceutical formulation comprising the purified daptomycin (LY146032) with pharmaceutical carriers or excipients (column 9, lines 47-59; claims 9, 38, 46 and 55-57). Baker *et al.* indicate the daptomycin (LY146032) is in substantially pure form and contains less than 2.5% of a combined total of anhydro-daptomycin and beta-isomer of daptomycin, thus claims 11-29 are not patentable because the product by process claims are limited by and defined by the process, determination of patentability is based on the product itself, and the patentability of a product does not depend on its method of production (see MPEP 2113). In the instant case, the composition comprising daptomycin (LY146032) that is in substantially pure form and contains less than 2.5% of a combined total of anhydro-daptomycin and beta-isomer of daptomycin as indicated in the patent is not different from the claimed composition comprising substantially pure daptomycin (>97% daptomycin), even though the daptomycin of reference is purified by a different process. Baker *et al.* also disclose an antibiotic composition comprised of a combination of a compound of formula 1 (i.e., anhydro-A21978C; column 1, lines 14-21), a compound of formula 2 (isomer of A21978C) and a

compound of formula 3 (the parent cyclic peptide of A21978C; LY146032) or pharmaceutically acceptable salts (Reissue: claim 18; claim 10 of instant application).

Response to Arguments

Applicants indicate that the purity of daptomycin in Baker can only be interpreted as defined by Baker, thus Baker can be interpreted to read that there is 97.5% of daptomycin over a daptomycin plus anhydro-daptomycin ("A") plus beta isomer daptomycin ("B") composition. The present application describes daptomycin purity relative to daptomycin plus anhydro-daptomycin (impurity No. 13) plus beta isomer daptomycin (impurity No. 8) plus 12 other impurities (impurities 1-7, 9-12 and 14) as described in Table 3 of the specification. Thus, Baker uses a different purity and does not teach purity over the 14 daptomycin impurities. Applicants also indicate that Baker had at best about 93% purity against the 14 daptomycin impurities, while comparing Baker's later work in US 4,874,843 with Baker's RE39,071, which use similar purification procedure. Applicants further assert that evidence of inherency and/or notice of facts to support the inherency of the present claims have not been provided. Furthermore, Baker does not specifically describe the following limitations:

1. essentially pure daptomycin (i.e. at least 98% daptomycin in the present application),

2. daptomycin substantially free of anhydro-daptomycin and substantially free of β-isomer of daptomycin (each no more than 1%),

3. daptomycin essentially free of anhydro-daptomycin (no more than 0.5%) and substantially free of β-isomer of daptomycin (no more than 1%),

4. daptomycin free of anhydro-daptomycin (no more than 0.1%) and substantially free of β-isomer of daptomycin (no more than 1%), and

5. daptomycin that substantially or essentially free of each of impurities 1 to 14 defined by peaks 1-14 of FIG. 12,

6. at least 95% pure daptomycin, and

7. greater than about 93% pure daptomycin.

Therefore, Baker did not anticipate claims 1-5, 8-29, 31-34, 38-42, 46-50 and 54-57, the rejection under 35 U.S.C. 102 (e) should be withdrawn (pages 10-17 of the response).

Applicants' response has been fully considered. Regarding claims 1(a)-1(f), 2-5, 31-34, 39-42 and 47-50, the arguments are found persuasive and the rejection is withdrawn. However, regarding claim 1(g) and its dependent claims, the arguments are not found persuasive because of the following reasons. Baker *et al.* teach an antibacterial composition comprising daptomycin (LY146032) obtained in substantially pure form, which refers to daptomycin that contains less than 2.5% of a combined total of anhydro-daptomycin and beta-isomer of daptomycin (column 8, lines 50-60; Examples 4 and 5). Since Baker *et al.* do not indicate other impurities besides anhydro-daptomycin and beta-isomer of daptomycin are contained in the daptomycin (LY146032) in substantially pure form, it reads that the daptomycin has more than 97.5% purity. While Baker implies that other degradants are present, but are not predominant in the pH range that optimizes the transpeptidation reactions, the reference does not indicate other degradants are present after the purification procedure (column 8, lines 45-49). While Baker's later work (U.S. Patent 4,874,843) shows undetermined impurities at least as great as 7%, and daptomycin has at

best 93% purity, the '843 patent only use a single HP-20 resin column to purify daptomycin with a yield of 50-60% (Example 1-2), which is different from the purification procedure (i.e., Diaion HP-20 resin column, followed by HPLC and another HP-20 resin column) used by Baker *et al.* in the US RE39,071 E (e.g., with a very low yield in Example 3). Thus, even Baker (U.S. Patent 4,874,843) shows undetermined impurities at least as great as 7%, and daptomycin has at best 93% purity, it does not mean that the daptomycin purified by Baker *et al.* in the US RE39,071 E has at best 93% purity since the purification procedures used by two patents are different. As shown in Example 2 of the present application, the purity level of the daptomycin was 91% using the purification method from the '843 patent, and the daptomycin sample was further confirmed to contain fourteen impurities (Example 10), which does not mean the daptomycin purified by Baker *et al.* in the US RE39,071 E would have at best 93% purity when a different purification procedure is used. The daptomycin purified by Baker *et al.* in the US RE39,071 E is obtained in substantially pure form that contains less than 2.5% of a combined total of anhydro-daptomycin and beta-isomer of daptomycin as taught by Baker *et al.* is not different from the claimed composition as indicated in claim 1(g) because the claimed substantially pure daptomycin has also >97% purity without indicating the existence of other 14 impuritites. Therefore, the rejection of claim 1(g) and its dependent claims are maintained.

Claim Rejections-Obviousness Type Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

5. Claims 1, 8-9, 46, 54-55, 57, 58 and 60 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 18-20, 26, 28 and 29 of U.S. Patent RE39,071 E. Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 1, 8-9, 46, 54-55, 57, 58 and 60 in the instant application disclose a composition comprising substantially pure daptomycin (i.e., >97% purity daptomycin); or a pharmaceutical composition comprising the composition and a pharmaceutically acceptable carrier or excipient. This is obvious variation in view of claims 18-20, 26, 28 and 29 of the patent which disclose an antibiotic composition comprised of a combination of a compound of formula 1 (i.e., anhydro-daptomycin), a compound of formula 2 (i.e., beta-isomer of daptomycin) and a compound of formula 3 (i.e., daptomycin, A21978C), or pharmaceutically acceptable salts thereof, wherein the total amount of the compound of formula 1 and the compound of formula 2 or salts thereof, in the combination is less than 6 weight percent; or a pharmaceutical formulation comprising a combination of a compound of formula 1 (i.e., anhydro-daptomycin), a compound of formula 2 (i.e., beta-isomer of daptomycin) and a compound of formula 3 (i.e., daptomycin, A21978C), or pharmaceutically acceptable salts thereof, wherein the total amount of the compound of formula 1 and the compound of formula 2 or salts thereof, in the combination is less than 6 weight percent and the pharmaceutical formulation further comprises from about 0.1 to about 90 weight percent of the A21978C. Both

claims of instant application and the patent are directed to a composition comprising substantially pure daptomycin (i.e., >97% purity daptomycin); or a pharmaceutical composition comprising the composition and a pharmaceutically acceptable carrier or excipient. Thus, claims 1, 8-9, 46, 54-55, 57, 58 and 60 in present application and claims 18-20, 26, 28 and 29 of the patent are obvious variations of a composition comprising substantially pure daptomycin (i.e., >97% purity daptomycin); or a pharmaceutical composition comprising the composition and a pharmaceutically acceptable carrier or excipient.

Claim Objections

6. Claims 2-7, 31-36, 39-44, 47-52, 59 and 61-63 are objected to because the claims are dependent from a rejected claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

7. Claims 1, 8-29, 38, 46, 54-58 and 60 are rejected; and claims 2-7, 31-36, 39-44, 47-52, 59 and 61-63 are objected to.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chih-Min Kam whose telephone number is (571) 272-0948. The examiner can normally be reached on 8.00-4:30, Mon-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath Rao can be reached at 571-272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Chih-Min Kam/
Primary Examiner, Art Unit 1656

CMK
February 22, 2010

Search Notes	Application No.	Applicant(s)	
	11/739,180	KELLEHER ET AL.	
	Examiner	Art Unit	
	CHIH-MIN KAM	1656	

SEARCHED			
Class	Subclass	Date	Examiner
514	9, 11, 2, 14		
530	317, 322		
530	344		
435	886		

INTERFERENCE SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES (INCLUDING SEARCH STRATEGY)		
	DATE	EXMR
EAST Search on USPAT, USPGPUB, DERWENT, EPO, JPO; STN search on MEDLINE, BIOSIS, EMBASE, SCISEARCH, AGRICOLA.	2/13/2008	CMK
Search strategy enclosed, Inventor name search, Parent applications 60/177,170 and 09/735,191, 10/747,48 have been reviewed.	2/13/2008	CMK
Update the search	10/28/2008	CMK
Update the search	8/5/2009	CMK
Update the search	2/3/2010	CMK

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(FILE 'HOME' ENTERED AT 17:15:46 ON 03 FEB 2010)

FILE 'MEDLINE, CAPLUS, BIOSIS, EMBASE, SCISEARCH, AGRICOLA' ENTERED AT
17:16:13 ON 03 FEB 2010
L1 6384 S DAPTOMYCIN
L2 2833 S SUBSTANTIALLY PURE
L3 2231 S ESSENTIALLY PURE
L4 0 S L1 (P) (L2 OR L3)
L5 2 S L1 (P) IMPURITY
L6 2 DUPLICATE REMOVE L5 (0 DUPLICATES REMOVED)
L7 4 S ANHYDRO-DAPTOMYCIN OR BETA-DAPTOMYCIN
L8 4 S L7 NOT L6
L9 108122 S ANION EXCHANGE
L10 10235 S HYDROPHOBIC INTERACTION CHROMATOGRAPHY
L11 2 S L1 (P) L9 (P) L10
L12 1 S L11 NOT (L6 OR L8)
L13 385 S (LY 146032) OR A-21978C OR A54145 OR A-21978
L14 1 S L13 (P) (L2 OR L3)
L15 1 S L14 NOT (L12 OR L8 OR L6)
L16 195 S KELLEHER T?/AU
L17 10832 S LAI J?/AU
L18 12 S DECOURCEY J?/AU
L19 3483 S LYNCH P?/AU
L20 74 S ZENONI M?/AU
L21 130 S TAGLIANI A?/AU
L22 14713 S L16 OR L17 OR L18 OR L19 OR L20 OR L21
L23 20 S L22 AND L1
L24 0 S L23 AND (L2 OR L3)

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PTO/SB/08a (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	11739180
Filing Date	2007-04-24
First Named Inventor	Thomas Kelleher
Art Unit	1656
Examiner Name	Chih-Min Kam
Attorney Docket Number	C062-02/03 US

U.S.PATENTS

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	Art Unit	1656
	Examiner Name	Chih-Min Kam
	Attorney Docket Number	C062-02/03 US

/CMK./	1	United States Application No. 07/060,148, filed June 10, 1987, Baker et al.	☐

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EXAMINER SIGNATURE

Examiner Signature	/Chih Min Kam/	Date Considered	03/16/2010

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EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	795	daptomycin	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2010/02/03 17:09
L2	53524	substantially adj pure	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2010/02/03 17:09
L3	13946	essentially adj pure	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2010/02/03 17:09
L4	8	L1 same (L2 or L3)	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2010/02/03 17:09
L5	9	impurities same L1	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2010/02/03 17:10
L6	9	anhydro-daptomycin or beta-daptomycin	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2010/02/03 17:10
L7	50318	anion adj exchange	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2010/02/03 17:11
L8	12738	hydrophobic adj interaction adj chromatography	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2010/02/03 17:11
L9	6	L1 same L7 same L8	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2010/02/03 17:11
L10	104	(Ly adj "146032") or A-21978C or A54145 or A-21978	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2010/02/03 17:11
L11	2	L10 same (L2 or L3)	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2010/02/03 17:11
L12	20	kelleher adj thomas.in.	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2010/02/03 17:12
L13	9	lai adj jan-ji.in.	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2010/02/03 17:12

L14	3	decourcey adj joseph.in.	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2010/02/03 17:12
L15	28	lynch adj paul.in.	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2010/02/03 17:12
L16	66	zenoni adj maurizio.in.	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2010/02/03 17:12
L17	6	tagliani adj auro.in.	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2010/02/03 17:12
L18	115	L12 or L13 or L14 or L15 or L16 or L17	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2010/02/03 17:12
L19	7	L18 and L1	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2010/02/03 17:12

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First Named Inventor	Thomas J. Kelleher
Art Unit	1656
Examiner Name	Chih-Min Kam
Attorney Docket Number	C062-02/03 US

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/CMK./	2	Agreement between Cubist Pharmaceuticals, Inc. and Eli Lilly and Company dated October 6, 2000. (Redacted form from SEC Edgar).	☐
/CMK./	3	Assignment of US RE 39,071 from Eli Lilly and Company to Cubist Pharmaceuticals, Inc. recorded on April 23, 2007. Reel/Frame: 019181/0916.	☐
/CMK./	4	MAIO, ET AL., "Daptomycin biosynthesis in Streptomyces roseosporus: cloning and analysis of the gene cluster and revision of peptide sterochemistry," Microbiology, (Vol 151), (P. 1507-1523), (2005).	☐

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	3	Assignment of US RE 39,071 from Eli Lilly and Company to Cubist Pharmaceuticals, Inc. recorded on April 23, 2007. Reel/Frame: 019181/0916.	☐
	4	MAIO, ET AL., "Daptomycin biosynthesis in Streptomyces roseosporus: cloning and analysis of the gene cluster and revision of peptide sterochemistry," Microbiology, (Vol 151), (P. 1507-1523), (2005).	☐

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Examiner Name	Chih-Min Kam
Attorney Docket Number	C062-02/03 US

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☒ See attached certification statement.

☐ Fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ None

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Jill M. N. Mandleblatt/	Date (YYYY-MM-DD)	2010-01-15
Name/Print	Jill M. N. Mandelblatt	Registration Number	37,878

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Electronic Acknowledgement Receipt

EFS ID:	6822511
Application Number:	11739180
International Application Number:	
Confirmation Number:	8837
Title of Invention:	High Purity Lipopeptides
First Named Inventor/Applicant Name:	Thomas Kelleher
Customer Number:	34103
Filer:	Jill Michel-Netka Mandelblatt/Jodi Doherty
Filer Authorized By:	Jill Michel-Netka Mandelblatt
Attorney Docket Number:	C062-02/03 US
Receipt Date:	15-JAN-2010
Filing Date:	24-APR-2007
Time Stamp:	16:15:54
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Miscellaneous Incoming Letter	C062-02_03_US_Transmittal.pdf	57875 61293412d2fb72474608a99b8202a89100c75930	no	1

Warnings:	
Information:	

2	Miscellaneous Incoming Letter	C062-02_03_US_20100115_IDS_letter.pdf	16708 26e108123330bd1f51309dac0d795a6ebc043ed3	no	2
Warnings:					
Information:					
3	NPL Documents	Lilly_Ex_1.pdf	3527490 b9b6972d6d3add41192107afbdbdba3ce09f96e6	no	23
Warnings:					
Information:					
4	NPL Documents	Lilly_Ex_2.pdf	3567645 264cca51dd450e6bdcec648fa0386e441b74b0c3	no	21
Warnings:					
Information:					
5	NPL Documents	Assignmrnt_Doc.pdf	357038 e2e7abac1a681ab2e98de5aad90b5a06253213bd	no	3
Warnings:					
Information:					
6	NPL Documents	Miao_Art.pdf	4072699 75ba3491f56e194db30731a61e363b741c78586b	no	17
Warnings:					
Information:					
7	Information Disclosure Statement (IDS) Filed (SB/08)	C062-02_03_US_IDS.pdf	391845 e176beddfbeb0afe1602740d2ba0501263ae9561	no	3
Warnings:					
Information:					
This is not an USPTO supplied IDS fillable form					
		Total Files Size (in bytes):	11991300		

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New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Doc Code: TRAN.LET

Document Description: Transmittal Letter

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TRANSMITTAL FORM

(to be used for all correspondence after initial filing)

Total Number of Pages in This Submission	70

Application Number	11/739,180
Filing Date	April 24, 2007
First Named Inventor	Thomas Kelleher
Art Unit	1656
Examiner Name	Chih-Min Kam
Attorney Docket Number	C062-02/03 US

ENCLOSURES (*Check all that apply*)

- ☐ Fee Transmittal Form
  - ☐ Fee Attached
- ☐ Amendment/Reply
  - ☐ After Final
  - ☐ Affidavits/declaration(s)
- ☐ Extension of Time Request
- ☐ Express Abandonment Request
- ☒ Information Disclosure Statement
- ☐ Certified Copy of Priority Document(s)
- ☐ Reply to Missing Parts/ Incomplete Application
  - ☐ Reply to Missing Parts under 37 CFR 1.52 or 1.53
- ☐ Drawing(s)
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- ☐ Petition
- ☐ Petition to Convert to a Provisional Application
- ☐ Power of Attorney, Revocation Change of Correspondence Address
- ☐ Terminal Disclaimer
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  - ☐ Landscape Table on CD
- ☐ After Allowance Communication to TC
- ☐ Appeal Communication to Board of Appeals and Interferences
- ☐ Appeal Communication to TC **(Appeal Notice, Brief, Reply Brief)**
- ☐ Proprietary Information
- ☐ Status Letter
- ☒ Other Enclosure(s) (please Identify below):

4 Cited References

Remarks

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm Name	Cubist Pharmaceuticals, Inc.		
Signature	/Jill M.N. Mandleblatt/		
Printed name	Jill M. N. Mandelblatt		
Date	January 15, 2010	Reg. No.	37,878

CERTIFICATE OF TRANSMISSION/MAILING

I hereby certify that this correspondence is being facsimile transmitted to the USPTO or deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on the date shown below:

Signature			
Typed or printed name		Date	

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appl. No.	:	11/739,180	Confirmation No.	8837
Applicant	:	Thomas J. Kelleher		
Filed	:	April 24, 2007		
TC/A.U.	:	1656		
Examiner	:	Chih-Min Kam		
Docket No.	:	C062-02/03 US		
Customer No.	:	34103		

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313

SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT

Pursuant to 37 C.F.R. §§ 1.56, 1.97(c) and 1.98, applicants make of record the following documents which are listed on the enclosed Form PTO/SB/08a. Copies of the following documents are enclosed herewith:

Agreement between Cubist Pharmaceuticals, Inc. and Eli Lilly and Company dated November 7, 1997 (redacted form from SEC Edgar);

Agreement between Cubist Pharmaceuticals Inc. and Eli Lilly and Company dated October 6, 2000 (redacted form from SEC Edgar);

Assignment of US RE 39, 071 from Eli Lilly and Company to Cubist Pharmaceuticals, Inc. recorded on April 23, 2007. Reel/Frame: 019181/0916; and

MAIO, et al, "Daptomycin biosynthesis in Streptomyces roseosporus: cloning and analysis of the gene cluster and revision of peptide sterochemistry," Micobiology, 151, 1507-1523 (2005).

REMARKS

Applicants have submitted the two Agreements and the Assignment document upon request of the Examiner.

Applicants request that the cited documents be fully considered by the Examiner during the course of examination of this application and that a copy of Form PTO/SB/08a, as considered, initialed, and signed by the Examiner, be returned with the next communication.

No fee is believed to be due in connection with this filing, however, please apply any other charges or credits to Deposit Account No. 50-1986, referencing attorney docket number C062-02/03 US.

Respectfully submitted,

Dated: January 15, 2010

Customer No.: 34103
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Lexington, Massachusetts 02421
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C062-02-03 US 20100115 IDS letter

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Jill M.N. Mandelblatt, Reg. No. 37,878
Patent Agent for Applicants

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appl. No.	:	11/739,180	Confirmation No.	8837
Applicant	:	Thomas Kelleher		
Filed	:	April 24, 2007		
TC/A.U.	:	1656		
Examiner	:	Chih-Min Kam		
Docket No.	:	C062-02/03 US		
Customer No.	:	34103		

Mail Stop **RCE**
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313

REQUEST FOR CONTINUED EXAMINATION (RCE) AND RESPONSE AND AMENDMENT

Applicants submit the following amendments in connection with a Request for Continued Examination filed herewith pursuant to 37 CFR §1.114. This Preliminary Amendment is responsive to the Final Office Action mailed August 11, 2009 (hereafter "the Office Action") in the above-identified application.

Kindly amend the application as follows:

Certificate of Transmission/Mailing

I hereby certify that this correspondence (Preliminary Amendment) is being deposited with the United States Postal Service with sufficient postage as First Class Mail and is addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 or is being facsimile transmitted to the USPTO on the date shown below.

_____ _____
Date

AMENDMENT TO THE SPECIFICATION

Replace the first paragraph of the specification at page 1, lines 5-9 with the following paragraph

The present application claims priority to United States Patent Application No. 10/747,485, filed December 29, 2003, which claims priority to United States Patent Application No. 09/735,191 filed ~~January 20, 2001~~ November 28, 2000, now US Patent No. 6,696,412, which claims the benefit of United States Provisional ~~application~~ Application No. 60/177,170, filed January 20, 2000, all of which are incorporated by reference herein in their entireties.

On page 1, line 10, please insert the following Paragraph:

The present invention was the subject of a joint research agreement within the meaning of 35 U.S.C § 103(c)(3), between Cubist Pharmaceuticals, Inc. and Eli Lilly and Company, and said agreement was in effect on or before the date the claimed invention was made.

AMENDMENT TO THE CLAIMS

1. (Previously presented) A composition comprising

(a) essentially pure daptomycin,

(b) daptomycin that is substantially free of anhydro-daptomycin and substantially free of β-isomer of daptomycin,

(c) daptomycin that is essentially free of anhydro-daptomycin and substantially free of β-isomer of daptomycin,

(d) daptomycin that is free of anhydro-daptomycin and substantially free of β-isomer of daptomycin,

(e) daptomycin that is substantially free of each of impurities 1 to 14 defined by peaks 1-14 shown in FIG. 12, or

(f) daptomycin that is essentially free of each of impurities 1 to 14 defined by peaks 1-14 shown in FIG. 12 or

(g) substantially pure daptomycin.

2. (Original) The composition of claim 1 comprising essentially pure daptomycin.

3. (Original) The composition of claim 1 compromising daptomycin that is substantially free of anhydro-daptomycin and substantially free of β-isomer of daptomycin.

4. (Original) The composition according to claim 3 that is essentially free of anhydro-daptomycin.

5. (Original) The composition according to claim 3 that is free of anhydro-daptomycin.

6. (Original) The composition of claim 1 that is substantially free of each of impurities 1 to 14 defined by peaks 1-14 shown in FIG. 12.

7. (Original) The composition according to claim 6 that is essentially free of each of impurities 1 to 14 defined by peaks 1-14 shown in FIG. 12.

8. (Original) The composition of claim 1, wherein daptomycin purity is measured by HPLC.

9. (Original) The composition of claim 1 further comprising a pharmaceutically acceptable carrier or excipient.

10. (Original) A pharmaceutical composition according to claim 9, further comprising one or more antibiotics, one or more antifungal agents, or both an antibiotic and an antifungal agent.

11. (Original) The composition according to claim 1 wherein the daptomycin is purified by a process comprising the steps of:

a) supplying a fermentation broth;

b) fermenting *Streptomyces roseosporus* with a feed of n-decanoic acid to produce daptomycin in the fermentation broth;

c) clarifying the fermentation broth to obtain a clarified solution;

d) subjecting the clarified solution to anion exchange chromatography to obtain an enriched daptomycin preparation;

e) subjecting the enriched daptomycin preparation to hydrophobic interaction chromatography to obtain a semi-purified daptomycin preparation; and

f) subjecting the semi-purified daptomycin preparation to anion exchange chromatography to obtain the composition of claim 1.

12. (Original) The composition according to claim 11, wherein the feed of n-decanoic acid is regulated to achieve a residual concentration of n-decanoic acid of no more than 50 parts per million (ppm) during fermentation.

13. (Original) The composition according to claim 11, wherein said clarifying comprises filtration or centrifugation and depth filtration.

14. (Original) The composition according to claim 11, wherein the anion exchange chromatography in d) is performed using a resin comprising a copolymer of 2-methacrylic acid and ethyleneglycol dimethacrylate (EDGM).

15. (Original) The composition according to claim 11, wherein the hydrophobic interaction chromatography is performed using a resin comprising a co-polymer of cross-linked divinylbenzene/stryene.

16. (Original) The composition according to claim 15, wherein the hydrophobic interaction chromatography is performed at neutral pH and a solvent

concentration that is reduced compared to the solvent concentration used when performing the hydrophobic interaction chromatography at acidic pH.

17. (Original) The composition according to claim 16, wherein the resin is recycled by loading the column at an acidic pH and eluting the column at a neutral pH.

18. (Original) The composition according to claim 11, wherein the anion exchange chromatography in f) is performed using a resin comprising a copolymer of 2-methacrylic acid and ethyleneglycol dimethacrylate (EDGM).

19. (Original) The composition according to claim 11, wherein the anion exchange chromatography is used to reduce the level of solvent in the clarified solution.

20. (Original) The composition according to claim 11, wherein the anion exchange chromatography is performed via continuous flow chromatography.

21. (Original) The composition according to claim 11, wherein the process further comprises the step of filtering daptomycin.

22. (Original) The composition according to claim 11, wherein the process further comprises the step of depyrogenating daptomycin using ultrafiltration.

23. (Original) The composition according to claim 22 wherein said depyrogenating comprises the steps of:

i) providing a daptomycin solution under conditions in which the daptomycin is in a monomeric and nonmicellar state;

ii) filtering the daptomycin solution under conditions in which the daptomycin passes through the filter but pyrogens do not pass through the filter;

iii) subjecting the daptomycin solution to conditions forming a daptomycin aggregate;

iv) filtering the daptomycin aggregate under conditions in which the daptomycin aggregate is retained on the filter; and

v) collecting the daptomycin aggregate.

24. (Original) The composition according to claim 22, wherein the process further comprises the step of lyophilizing daptomycin.

25. (Original) The composition according to claim 22, wherein the anion exchange chromatography is performed via radial flow chromatography.

26. (Original) The composition according claim 11, wherein said clarifying comprises microfiltration or centrifugation.

27. (Original) The composition according to claim 11, wherein the process further comprises the steps of filtering and concentrating daptomycin.

28. (Original) The composition according to claim 11, wherein the process further comprises the step of separating the enriched daptomycin from low molecular weight material by ultrafiltration.

29. (Original) The composition according to claim 28, wherein the process further comprises the step of depyrogenating the daptomycin.

30. Canceled

31. (Original) The pharmaceutical composition of claim 9 comprising essentially pure daptomycin.

32. (Original) The pharmaceutical composition of claim 9 comprising daptomycin that is substantially free of anhydro-daptomycin and substantially free of β-isomer of daptomycin.

33. (Original) The pharmaceutical composition of claim 9 comprising daptomycin that is essentially free of anhydro-daptomycin and substantially free of β-isomer of daptomycin.

34. (Original) The pharmaceutical composition of claim 9 comprising daptomycin that is free of anhydro-daptomycin and substantially free of β-isomer of daptomycin.

35. (Original) The pharmaceutical composition of claim 9 comprising daptomycin that is substantially free of each of impurities 1 to 14 defined by peaks 1-14 shown in FIG. 12.

36. (Original) The pharmaceutical composition of claim 9 comprising daptomycin that is essentially free of each of impurities 1 to 14 defined by peaks 1-14 shown in FIG. 12.

37. Canceled

38. (Original) A method for preparing a pharmaceutical composition comprising combining the composition of claim 1 with a pharmaceutically acceptable

carrier or excipient.

39. (Original) The method of claim 38 wherein the composition is essentially pure daptomycin.

40. (Original) The method of claim 38 wherein the composition is daptomycin that is substantially free of anhydro-daptomycin and substantially free of β-isomer of daptomycin.

41. (Original) The method of claim 38 wherein the composition is daptomycin that is essentially free of anhydro-daptomycin and substantially free of β-isomer of daptomycin.

42. (Original) The method of claim 38 wherein the composition is daptomycin that is free of anhydro-daptomycin and substantially free of β-isomer of daptomycin.

43. (Original) The method of claim 38 wherein the composition is daptomycin that is substantially free of each of impurities 1 to 14 defined by peaks 1-14 shown in FIG. 12.

44. (Original) The method of claim 38 wherein the composition is daptomycin that is essentially free of each of impurities 1 to 14 defined by peaks 1-14 shown in FIG. 12.

45. Canceled

46. (Original) A pharmaceutical composition prepared by the method of claim 38.

47. (Original) The pharmaceutical composition of claim 46 wherein the composition is essentially pure daptomycin.

48. (Original) The pharmaceutical composition of claim 46 wherein the composition is daptomycin that is substantially free of anhydro-daptomycin and substantially free of β-isomer of daptomycin.

49. (Original) The pharmaceutical composition of claim 46 wherein the composition is daptomycin that is essentially free of anhydro-daptomycin and substantially free of β-isomer of daptomycin.

50. (Original) The pharmaceutical composition of claim 46 wherein the

composition is daptomycin that is free of anhydro-daptomycin and substantially free of β-isomer of daptomycin.

51. (Original) The pharmaceutical composition of claim 46 wherein the composition is daptomycin that is substantially free of each of impurities 1 to 14 defined by peaks 1-14 shown in FIG. 12.

52. (Original) The pharmaceutical composition of claim 46 wherein the composition is daptomycin that is essentially free of each of impurities 1 to 14 defined by peaks 1-14 shown in FIG. 12.

53. Canceled

54. (Previously presented) The composition of claim 1 comprising substantially pure daptomycin.

55. (Previously presented) The pharmaceutical composition of claim 9 comprising substantially pure daptomycin.

56. (Previously presented) The method of claim 38 wherein the composition is substantially pure daptomycin.

57. (Previously presented) The pharmaceutical composition of claim 46 wherein the composition is substantially pure daptomycin.

58. (New) A composition comprising daptomycin of greater than about 93% purity, wherein the purity of the daptomycin is relative to daptomycin impurities that arise in fermentation or purification of daptomycin.

59. (New) The composition of claim 58, wherein the daptomycin impurities comprise impurities 1-14.

60. (New) The composition of claim 58, wherein the purity is at least 95%.

61. (New) The composition of claim 60, wherein the daptomycin impurities comprise impurities 1-14.

62. (New) Daptomycin of greater than about 93% purity relative to impurities 1-14.

63. (New) The daptomycin of claim 62, wherein the purity is at least 95%.

REMARKS

Amendments to the Specification

Applicants have amended the first paragraph of the specification to provide the filing date of the 10/747,485 application and the patent number for the patent that issued from United States Patent Application No. 09/735,191. In addition, Applicants have corrected the filing date of United States Patent Application No. 09/735,191.

Applicants have amended the specification to comply with 35 U.S.C. § 103(c)(2)(C)) and 37 C.F.R. §1.71 (g)(1). No new matter is introduced by these amendments to the specification.

Amendments to the Claims

Claims 1-29, 31-36, 38-44, 46-52 and 54-57 were pending in the present application. Applicants have added new claims 58-63. Support for claims 58-63 can be found throughout the specification, for example, on page 5, lines 12-19; page 7, lines 23-25; page 9, lines 16-19; page 11, lines 19-20; page 12, lines 12-16; and Example 10. No new matter is introduced by these amendments to the claims.

Accordingly, upon entry of the instant amendments, claims 1-29, 31-36, 38-44, 46-52 and 54-63 will be pending in this application.

The Claim Rejections Over Baker Are Overcome and Traversed

Claims 1-5, 8-29, 31-34, 38-42, 46-50 and 54-57 stand rejected under 35 U.S.C.§ 102(e) as anticipated by or, in the alternative under U.S.C. § 103(a) as unpatentable over Baker *et al.* (US RE39,071 E, hereafter Baker). Claims 6-7, 35-36, 43-44 and 51-52 are objected to. Applicants respectfully overcome and traverse the rejection for the reasons set forth below.

I. The Subject Matter of Baker Cannot Preclude Patentability Under 35 U.S.C § 103

The present invention was made by or on the behalf of parties to a joint research agreement, within the meaning of 35 U.S.C § 103(c)(3) and 37 C.F.R §1.104 (c)(4)(ii), that was in effect on or before the date the claimed invention was made and the claimed

invention was made as a result of activities undertaken within the scope of the joint research agreement. The present application claims the benefit of a January 20, 2000 filing date, and, at the time the claimed invention was made, the subject matter of Baker was "owned by the same person or subject to an obligation of assignment to the same person" within the meaning further described by 35 U.S.C. § 103(c)(2)-(3) as amended by the Cooperative Research and Technology Enhancement Act of 2004 (CREATE Act).

By the statement made above and the corresponding amendment to the Specification, Applicants have satisfied 35 U.S.C § 103(c). Accordingly, under 35 U.S.C § 103(c), the subject matter of Baker cited under § 102(e) shall not preclude patentability under 35 U.S.C. § 103. Applicants request that the rejection of the claims under 35 U.S.C. § 103(a) be withdrawn.

II. Baker Does Not Anticipate Claims 1-5, 8-29, 31-34, 38-42, 46-50 and 54-57 Under 35 U.S.C § 102(e)

The Office Action reads: "Baker discloses a composition or pharmaceutical composition comprising substantially pure daptomycin which meets the criteria of claim 1(a)-1(d) and 1(g), and its dependent claims because the term 'comprising' indicates the composition can contain something else besides substantially pure daptomycin or essentially pure daptomycin." According to the Office Action, it is obvious that a composition as taught by Baker, encompasses the embodiments of claim 1(a)-1(d) and 1(g) of the present invention because claim 1(a)-1(d) and 1(g) "merely recites substantially or essentially pure daptomycin that may contain slight amount of anhydro-daptomycin and beta-isomer of daptomycin."

Applicants overcome and traverse the rejection. To the extent the rejection is based on obviousness under 35 U.S.C. § 103(a), the rejection was overcome based on the amendment to the specification. To the extent the rejection is maintained under 35 U.S.C. § 102(e), Applicants traverse because, even with the open-ended "comprising" claim language, the claimed limitations have not been met expressly or inherently for reasons set forth below.

"In order to render a determination of anticipation under 35 U.S.C. 102, the reference **must teach every aspect of the claimed invention either explicitly or impliedly**. Any feature not directly taught must be inherently present." MPEP 706.02 V. "To serve as an anticipation when the reference is silent about the asserted inherent characteristic [i.e. one not directly taught], such gap in the reference may be filled with recourse to extrinsic evidence. **Such evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference**, and that it would be so recognized by persons of ordinary skill." *Continental Can Co. USA v. Monsanto Co.*, 948 F.2d 1264, 1268, 20 USPQ2d 1746, 1749 (Fed. Cir. 1991).

The following limitations were acknowledged in the August 11, 2009 Office Action (page 3) as not specifically described in Baker:

1. essentially pure daptomycin (i.e. at least 98% daptomycin in the present application),
2. daptomycin substantially free of anhydro-daptomycin and substantially free of β-isomer of daptomycin (each no more than 1%),
3. daptomycin essentially free of anhydro-daptomycin (no more than 0.5%) and substantially free of β-isomer of daptomycin (no more than 1%),
4. daptomycin free of anhydro-daptomycin (no more than 0.1%) and substantially free of β-isomer of daptomycin (no more than 1%), and
5. daptomycin that substantially or essentially free of each of impurities 1 to 14 defined by peaks 1-14 of FIG. 12 (acknowledged by mere objection to certain claims).

In addition, the following limitations as presented in the new claims added above are not described by Baker:

6. at least 95% pure daptomycin, and
7. greater than about 93% pure daptomycin.

A. Baker Does Not Expressly Or Inherently Include All of the Limitations of the Present Claims

1. Baker Uses a Different Daptomycin Purity Than the Present Application

Although the Office Action posits that the substantially pure daptomycin in Baker "reads that the daptomycin has more than 97.5% purity," the purity of daptomycin in Baker can only be interpreted as defined by Baker. In Baker, "substantially pure form means that LY146032 contains less than 2.5 percent of a combined total of anhydro-LY146032 and isomer-LY146032." Col. 8, ll. 55-57. Baker can be interpreted to read that there is 97.5% of daptomycin over a daptomycin plus anhydro-daptomycin ("A") plus beta isomer daptomycin ("B") composition.

The present application describes daptomycin purity relative to daptomycin plus anhydro daptomycin (impurity No. 13) plus beta-isomer (impurity No. 8) **plus 12 other impurities** (impurities 1-7, 9-12 and 14) (the fourteen daptomycin impurities) as described in Table 3 of the specification. Therefore, it is consistent to say that, as described in detail below in II.A.2, the Baker methods yield at best about 93% pure daptomycin measured under the current application while it yields 97.5% purity under its own teachings.

Accordingly, Baker uses a different purity and does not teach purity over the fourteen daptomycin impurities.

2. Baker Had At Best About 93% Purity Against The Fourteen Daptomycin Impurities

Although the Examiner has written that Baker (previously described as denoting US Patent RE39,071) could have better purity than the Baker's later work in the US Patent 4,874,843 (the '843 patent), i.e. "when a different purification procedure is used," the '843 patent and Baker use the same procedure. Those procedures whether followed under the '843 patent or Baker yield 93% pure daptomycin against the fourteen daptomycin impurities.

Baker claims priority to U.S. Serial No. 07/060,148 ("the '148 application," now abandoned) and the experimental details of Baker are identical to the '148 application. The '843 patent reads: "The novel process of this invention was previously disclosed, but not claimed in U.S. patent application No. 07/060,148, filed June 10, 1987, for use in purifying the β-isomer of LY146032." See the '843 patent, col. 1, ll. 41-44. Thus, the '843 patent (by reference back) and Baker (by identical disclosure) use the same purification procedures as those in the '148 patent application. A copy of the '148 application is being furnished to the Examiner under an Information Disclosure Statement filed with this Preliminary Amendment.

In addition, the '843 patent's and Baker's use of similar methods is further confirmed by direct comparison of the two references in the following table:

Method of Producing Daptomycin in the '843 Patent	Method of Producing Daptomycin in Baker Example 3 (comprehensive process description)
Semipure LY146032 is dissolved in an acetonitrile-methanol-sodium acetate buffer solvent and passes through a column containing HP20ss resin. The column is developed with the same solvent (Col. 1, line 67 to Col 2, line 3)	Intermediate quality LY146032 solution is applied to a HP20ss column that had been equilibrated with the developing solvent acetonitrile-methanol sodium acetate buffer (Col. 11, line 65 to Col. 12, line 9)
Purified fractions containing LY146032 are combined, diluted with water and loaded on a column containing HP20 resin. The column is washed with water to remove salt, eluted with acetonitrile-water (60:40) and the LY146032 (Col. 2, line 4-7)	Fractions containing isomer LY146032 were pooled and desalted using Dianion HP20 resin as washed with deionized water then isomer LY146032 was eluted with 60:40 acetonitrile-water to give an enriched desalted preparation of isomer-LY146032 (Col. 12, ll. 14-27)
final resolution and separation from structurally similar compounds is impeded by the presence of impurities which were not identifiable by uv of the fermentation broth. attempts to remove these impurities by various chromatographic methods, including reverse-phase chromatography over silica gel/C18, normal phase chromatography over silica gel and ion-exchange chromatography failed to significantly improve the purity of ly146032 over the HP20 as described above. All of these methods were plagued by low capacity, poor resolution and low recovery of LY146032. (Col. 3, ll. 11-14	Preparation was further purified using reverse phase C18 column followed by a Dianion HP 20 resin column in reverse mode (Col. 12, ll. 28-30)

and ll. 22-30)	

As pointed out in earlier communications, the instant application provides comparative testing of the compositions disclosed in Baker that definitively establishes that Baker does not inherently disclose the presently claimed compositions. Baker provides daptomycin no more pure than the '843 patent since the purification process for the Baker and '843 patent were the same, and, as noted in the '843 patent, final resolution and separation of daptomycin (LY146032) from structurally similar compounds was impeded by the presence of impurities that were not identifiable by ultraviolet analysis of the fermentation broth. The '843 patent describes that despite a variety of additional purification attempts, **the highest yields obtained were about 93%,** i.e. 93% daptomycin versus the fourteen daptomycin impurities, not just anhydro daptomycin and beta isomer. See page 3, line 12 through page 4, line 2 of the present specification. Thus, the reasonable implication for Baker upon a close read of the '843 patent is that the material in Baker was at best only about 93% pure daptomycin under the present application.

3. Evidence of Inherency and/or Official Notice of Facts To Support The Inherency of the Present Claims Have Not Been Provided

"In relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." Ex parte Levy, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990) (emphasis in original). Any suggestion that the daptomycin purity of Baker inherently anticipates the purity presently claimed requires a citation to some extrinsic evidence from which the suggestion necessarily follows. No citation has been made to any extrinsic support for any purity different from that explained above.

If the Examiner were to rely upon facts relating to the purity of the daptomycin compositions taught in Baker without documentary evidence, such official notice is not appropriate as a basis for asserting that Baker inherently discloses the claimed daptomycin compositions:

> [o]fficial notice without documentary evidence to support an examiner's conclusion is permissible only in some circumstances....Official notice unsupported by documentary evidence should only be taken by the examiner where the facts asserted to be well-known, or to be common knowledge in the art are capable of instant and unquestionable demonstration as being well-known (MPEP 2144.03).

Applicants submit that the inherent characteristics of the teachings of Baker, particularly vis-à-vis the twelve other daptomycin impurities, are not well known or common knowledge capable for instant and unquestionable demonstration.

B. The Present Claims, When Properly Interpreted, Are Not Anticipated by Baker

The Office Action reads:

> Baker et al discloses a composition or pharmaceutical composition comprising substantially pure daptomycin, which meets the criteria of claim 1(a)-1(d) and 1(g), and its dependent claims because the term "comprising" indicates the composition can contain something else besides substantially or essentially pure daptomycin (Office Action at pages 3-4, emphasis in original).

While "comprising" is open-ended, it is not so open as to vitiate the claim limitation of the daptomycin. In particular, the "something else" that the Office Action asserts is within claimed inventions using "comprising" cannot alter the claimed daptomycin to not have the daptomycin purity of the claim. A proper use of comprising would maintain the existing purity limitations to the extent claimed and not attempt to read the limitation out of the claim. By adding "something else," the claims were interpreted in a manner inconsistent with both the specification and their plain meaning. This interpretation is not permitted:

> Indeed, the rules of the PTO require that application claims must "conform to the invention as set forth in the remainder of the specification and the terms and phrases used in the claims must find clear support or antecedent basis in the description so that the meaning of the terms in the claims may be ascertainable by reference to the description." 37 CFR 1.75(d)(1)... The words of a claim must be given their "plain meaning"... (MPEP 2111, 2111.01).

Based on the plain meaning of the claims, the daptomycin within the composition -- not necessarily the entire composition itself -- must be interpreted to retain the claimed

characteristics. Therefore, Baker does not meet the criteria of claim 1(a)-1(d) and 1(g), and its dependent claims because the term "comprising" cannot eliminate the claimed purity.

C. Request for Reconsideration and Withdrawal Of Rejection Under 35 U.S.C. § 102(e)

As stated previously (*vide supra)*, Baker does not specifically described nor can it be interpreted to describe:

1. essentially pure daptomycin (i.e. at least 98% daptomycin in the present application),
2. daptomycin substantially free of anhydro-daptomycin and substantially free of β-isomer of daptomycin (each no more than 1%),
3. daptomycin essentially free of anhydro-daptomycin (no more than 0.5%) and substantially free of β-isomer of daptomycin (no more than 1%),
4. daptomycin free of anhydro-daptomycin (no more than 0.1%) and substantially free of β-isomer of daptomycin (no more than 1%), and
5. daptomycin that substantially or essentially free of each of impurities 1 to 14 defined by peaks 1-14 of FIG. 12 (acknowledged by mere objection to certain claims),
6. at least 95% pure daptomycin, and
7. greater than about 93% pure daptomycin.

Baker does not anticipate claims 1-5, 8-29, 31-34, 38-42, 46-50 and 54-57 under 35 U.S.C § 102(e) when the claims are properly interpreted primarily because: (1) Baker teaches a different measurement of purity which does not consider the fourteen daptomycin impurities and (2) Baker had at best about 93% pure daptomycin when including the twelve additional daptomycin impurities. Therefore the rejection is traversed. Accordingly, Applicant respectfully requests withdrawal of the rejection under 35 U.S.C. § 102(e) and reconsideration and allowance of all pending claims.

III. Product-by-Process Claim Interpretation

The Office Action reads that claim 11-29 are not patentable because the product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself, and the patentability of a product does not depend on its method of production. Although the above arguments under 35 U.S.C. §§ 102(e) and 103 render the statement of product-by-process patentability moot, the claims should be interpreted as broadly for infringement as they were to determine patentability.

CONCLUSION

For the reasons presented above, Applicant respectfully requests reconsideration and prompt allowance of all pending claims. A Petition for Extension of Time is enclosed. Please deduct the petition fee and apply any other charges or credits to Deposit Account No.50-1986, referencing attorney docket number C062-02/03 US.

Respectfully submitted,

Date:November 13, 2009

/Jill M. Mandelblatt/
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C062-02-03 US 20091113 resp to 20090811 OA

PTO/SB/08a (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	11739180
Filing Date	2007-04-24
First Named Inventor	Thomas Kelleher
Art Unit	1656
Examiner Name	Chih-Min Kam
Attorney Docket Number	C062-02/03 US

U.S.PATENTS

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1					

If you wish to add additional U.S. Patent citation information please click the Add button.

U.S.PATENT APPLICATION PUBLICATIONS

Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1					

If you wish to add additional U.S. Published Application citation information please click the Add button.

FOREIGN PATENT DOCUMENTS

Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] i	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1							☐

If you wish to add additional Foreign Patent Document citation information please click the Add button

NON-PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	11739180
	Filing Date	2007-04-24
	First Named Inventor	Thomas Kelleher
	Art Unit	1656
	Examiner Name	Chih-Min Kam
	Attorney Docket Number	C062-02/03 US

	1	United States Application No. 07/060,148, filed June 10, 1987, Baker et al.	☐

If you wish to add additional non-patent literature document citation information please click the Add button

EXAMINER SIGNATURE

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	11739180
	Filing Date	2007-04-24
	First Named Inventor	Thomas Kelleher
	Art Unit	1656
	Examiner Name	Chih-Min Kam
	Attorney Docket Number	C062-02/03 US

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☐ Fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☑ None

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Jill M. N. Mandelblatt/	Date (YYYY-MM-DD)	2009-11-13
Name/Print	Jill M. N. Mandelblatt	Registration Number	37,878

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

PTO/SB/22 (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARMENT OF COMMERCE

PETITION FOR EXTENSION OF TIME UNDER 37 CFR 1.136(a) **FY 2009** *(Fees pursuant to the Consolidated Appropriations Act, 2005 (H.R. 4818).)*	Docket Number (Optional) C062-02/03 US
Application Number 11/739,180	Filed April 24, 2007
For High Purity Lipopeptides	
Art Unit 1656	Examiner Chih-Min Kam

This is a request under the provisions of 37 CFR 1.136(a) to extend the period for filing a reply in the above identified application.

The requested extension and fee are as follows (check time period desired and enter the appropriate fee below):

		Fee	Small Entity Fee	
[X]	One month (37 CFR 1.17(a)(1))	$130	$65	$ 65.00
[ ]	Two months (37 CFR 1.17(a)(2))	$490	$245	$
[ ]	Three months (37 CFR 1.17(a)(3))	$1110	$555	$
[ ]	Four months (37 CFR 1.17(a)(4))	$1730	$865	$
[ ]	Five months (37 CFR 1.17(a)(5))	$2350	$1175	$

[X] Applicant claims small entity status. See 37 CFR 1.27.

[ ] A check in the amount of the fee is enclosed.

[ ] Payment by credit card. Form PTO-2038 is attached.

[ ] The Director has already been authorized to charge fees in this application to a Deposit Account.

[X] The Director is hereby authorized to charge any fees which may be required, or credit any overpayment, to Deposit Account Number 50-1986.

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

I am the

[ ] applicant/inventor.

[ ] assignee of record of the entire interest. See 37 CFR 3.71.
Statement under 37 CFR 3.73(b) is enclosed (Form PTO/SB/96).

[ ] attorney or agent of record. Registration Number _____

[X] attorney or agent under 37 CFR 1.34.
Registration number if acting under 37 CFR 1.34 37,878

/Jill M. N. Mandelblatt/ — Signature
November 13, 2009 — Date

Jill M. N. Mandelblatt — Typed or printed name
(781) 860-8660 — Telephone Number

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below.

[X] Total of 1 forms are submitted.

PTO/SB/17 (10-08)
Approved for use through 06/30/2010. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Effective on 12/08/2004.
Fees pursuant to the Consolidated Appropriations Act, 2005 (H.R. 4818).

FEE TRANSMITTAL
For FY 2009

☑ Applicant claims small entity status. See 37 CFR 1.27

TOTAL AMOUNT OF PAYMENT ($) 548.00

Complete if Known	
Application Number	11/739,180
Filing Date	April 24, 2007
First Named Inventor	Thomas Kelleher
Examiner Name	Chih-Min Kam
Art Unit	1656
Attorney Docket No.	C062-02/03 US

METHOD OF PAYMENT (check all that apply)

☐ Check ☐ Credit Card ☐ Money Order ☐ None ☐ Other (please identify): _____

☑ Deposit Account Deposit Account Number: 50-1986 Deposit Account Name: Cubist Pharmaceuticals, I

For the above-identified deposit account, the Director is hereby authorized to: (check all that apply)

☑ Charge fee(s) indicated below ☐ Charge fee(s) indicated below, **except for the filing fee**

☑ Charge any additional fee(s) or underpayments of fee(s) under 37 CFR 1.16 and 1.17 ☑ Credit any overpayments

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

FEE CALCULATION

1. BASIC FILING, SEARCH, AND EXAMINATION FEES

	FILING FEES		SEARCH FEES		EXAMINATION FEES		
		Small Entity		Small Entity		Small Entity	
Application Type	Fee ($)	Fee ($)	Fee ($)	Fee ($)	Fee ($)	Fee ($)	Fees Paid ($)
Utility	330	165	540	270	220	110	
Design	220	110	100	50	140	70	
Plant	220	110	330	165	170	85	
Reissue	330	165	540	270	650	325	
Provisional	220	110	0	0	0	0	

2. EXCESS CLAIM FEES

Fee Description	Fee ($)	Small Entity Fee ($)
Each claim over 20 (including Reissues)	52	26
Each independent claim over 3 (including Reissues)	220	110
Multiple dependent claims	390	195

Total Claims		Extra Claims		Fee ($)		Fee Paid ($)
59	- 20 or HP =	3	x	26.00	=	78.00

HP = highest number of total claims paid for, if greater than 20.

Indep. Claims		Extra Claims		Fee ($)		Fee Paid ($)
3	- 3 or HP =	0	x	110.00	=	0

HP = highest number of independent claims paid for, if greater than 3.

Multiple Dependent Claims	
Fee ($)	Fee Paid ($)

3. APPLICATION SIZE FEE

If the specification and drawings exceed 100 sheets of paper (excluding electronically filed sequence or computer listings under 37 CFR 1.52(e)), the application size fee due is $270 ($135 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).

Total Sheets		Extra Sheets		Number of each additional 50 or fraction thereof		Fee ($)		Fee Paid ($)
	- 100 =		/ 50 =		(round **up** to a whole number) x		=	

4. OTHER FEE(S)

	Fees Paid ($)
Non-English Specification, $130 fee (no small entity discount)	
Other (e.g., late filing surcharge):	

SUBMITTED BY

Signature	/Jill M. N. Mandelblatt/	Registration No. (Attorney/Agent) 37,878	Telephone 617-860-8660
Name (Print/Type)	Jill M. N. Mandelblatt		Date November 13, 2009

Electronic Patent Application Fee Transmittal

Application Number:	11739180
Filing Date:	24-Apr-2007
Title of Invention:	High Purity Lipopeptides
First Named Inventor/Applicant Name:	Thomas Kelleher
Filer:	Jill Michel-Netka Mandelblatt/Jodi Doherty
Attorney Docket Number:	C062-02/03 US

Filed as Small Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Claims in excess of 20	2202	3	26	78
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension - 1 month with $0 paid	2251	1	65	65
Miscellaneous:				
Request for continued examination	2801	1	405	405
		Total in USD ($)		**548**

Electronic Acknowledgement Receipt

EFS ID:	6454526
Application Number:	11739180
International Application Number:	
Confirmation Number:	8837
Title of Invention:	High Purity Lipopeptides
First Named Inventor/Applicant Name:	Thomas Kelleher
Customer Number:	34103
Filer:	Jill Michel-Netka Mandelblatt/Jodi Doherty
Filer Authorized By:	Jill Michel-Netka Mandelblatt
Attorney Docket Number:	C062-02/03 US
Receipt Date:	13-NOV-2009
Filing Date:	24-APR-2007
Time Stamp:	19:05:56
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$548
RAM confirmation Number	7698
Deposit Account	501986
Authorized User	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)

1		C062-02_03_20091113_RCE_Filing.pdf	2212876 c3d5f079e3b59e0f110ef165ec8b00ce1ab41b4c	yes	56

Multipart Description/PDF files in .zip description		
Document Description	**Start**	**End**
Miscellaneous Incoming Letter	1	1
Amendment Submitted/Entered with Filing of CPA/RCE	2	19
Information Disclosure Statement (IDS) Filed (SB/08)	20	22
NPL Documents	23	54
Extension of Time	55	55
Miscellaneous Incoming Letter	56	56

Warnings:

Information:

2	Fee Worksheet (PTO-875)	fee-info.pdf	33877 06cd77aa18e83dd8d9618a0ba2e1054d6d7d659c	no	2

Warnings:

Information:

Total Files Size (in bytes):	2246753

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/SB/30 (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Request for Continued Examination (RCE) Transmittal

Address to:
Mail Stop RCE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Application Number	11/739,180
Filing Date	April 24, 2007
First Named Inventor	Thomas Kelleher
Art Unit	1656
Examiner Name	Chih-Min Kam
Attorney Docket Number	C062-02/03 US

This is a Request for Continued Examination (RCE) under 37 CFR 1.114 of the above-identified application.
Request for Continued Examination (RCE) practice under 37 CFR 1.114 does not apply to any utility or plant application filed prior to June 8, 1995, or to any design application. See Instruction Sheet for RCEs (not to be submitted to the USPTO) on page 2.

1. Submission required under 37 CFR 1.114 Note: If the RCE is proper, any previously filed unentered amendments and amendments enclosed with the RCE will be entered in the order in which they were filed unless applicant instructs otherwise. If applicant does not wish to have any previously filed unentered amendment(s) entered, applicant must request non-entry of such amendment(s).

   a. ☐ Previously submitted. If a final Office action is outstanding, any amendments filed after the final Office action may be considered as a submission even if this box is not checked.

      i. ☐ Consider the arguments in the Appeal Brief or Reply Brief previously filed on _____

      ii. ☐ Other _____

   b. ☒ Enclosed

      i. ☒ Amendment/Reply

      ii. ☐ Affidavit(s)/ Declaration(s)

      iii. ☒ Information Disclosure Statement (IDS)

      iv. ☒ Other Pet. for Ext. of Time/Fee Transmittal
      Reference Cited

2. Miscellaneous

   a. ☐ Suspension of action on the above-identified application is requested under 37 CFR 1.103(c) for a period of _____ months. (Period of suspension shall not exceed 3 months; Fee under 37 CFR 1.17(i) required)

   b. ☐ Other _____

3. Fees The RCE fee under 37 CFR 1.17(e) is required by 37 CFR 1.114 when the RCE is filed.

   a. ☒ The Director is hereby authorized to charge the following fees, any underpayment of fees, or credit any overpayments, to Deposit Account No. 50-1986.

      i. ☒ RCE fee required under 37 CFR 1.17(e)

      ii. ☒ Extension of time fee (37 CFR 1.136 and 1.17)

      iii. ☐ Other _____

   b. ☐ Check in the amount of $ _____ enclosed

   c. ☐ Payment by credit card (Form PTO-2038 enclosed)

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT REQUIRED

Signature	/Jill M. N. Mandelblatt/	Date	November 13, 2009
Name (Print/Type)	Jill M. N. Mandelblatt	Registration No.	37,878

CERTIFICATE OF MAILING OR TRANSMISSION

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Mail Stop RCE, Commissioner for Patents, P. O. Box 1450, Alexandria, VA 22313-1450 or facsimile transmitted to the U.S. Patent and Trademark Office on the date shown below.

Signature			
Name (Print/Type)		Date	

This collection of information is required by 37 CFR 1.114. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Mail Stop RCE, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

PTO/SB/06 (07-06)
Approved for use through 1/31/2007. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number	Filing Date	☐ To be Mailed
11/739,180	04/24/2007	

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY ☒ RATE ($)	SMALL ENTITY ☒ FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =		OR	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =			X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT 11/13/2009	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE ($)	SMALL ENTITY ADDITIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	* 59	Minus	** 53	= 6	X $26 =	156	OR	X $ =	
Independent (37 CFR 1.16(h))	* 3	Minus	***3	= 0	X $110 =	0	OR	X $ =	
☐ Application Size Fee (37 CFR 1.16(s))									
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
					TOTAL ADD'L FEE	156	OR	TOTAL ADD'L FEE	

AMENDMENT	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)	OR	RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =		OR	X $ =	
Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =		OR	X $ =	
☐ Application Size Fee (37 CFR 1.16(s))									
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
					TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

Legal Instrument Examiner:
/Trina Steptoe/

Document code: WFEE

United States Patent and Trademark Office
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/739,180	04/24/2007	Thomas Kelleher	C062-02/03 US	8837

34103 7590 08/11/2009

Intellectual Property Department
Cubist Pharmaceuticals, Inc.
65 Hayden Avenue
Lexington, MA 02421

EXAMINER	
KAM, CHIH MIN	

ART UNIT	PAPER NUMBER
1656	

MAIL DATE	DELIVERY MODE
08/11/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	11/739,180	KELLEHER ET AL.	
	Examiner	Art Unit	
	CHIH-MIN KAM	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 May 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-29,31-36,38-44,46-52 and 54-57* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,8-29,31-34,38-42,46-50 and 54-57* is/are rejected.

7)☒ Claim(s) *6,7,35,36,43,44,51 and 52* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *24 April 2007* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. *20090808* .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Interview Summary	Application No.	Applicant(s)	
	11/739,180	KELLEHER ET AL.	
	Examiner	Art Unit	
	CHIH-MIN KAM	1656	

All participants (applicant, applicant's representative, PTO personnel):

(1) *CHIH-MIN KAM*.

(2) *Jill Mandelblatt*.

(3)*William DeVaul*.

(4)_____.

Date of Interview: *14 May 2009*.

Type: a)☒ Telephonic b)☐ Video Conference
c)☐ Personal [copy given to: 1)☐ applicant 2)☐ applicant's representative]

Exhibit shown or demonstration conducted: d)☐ Yes e)☐ No.
If Yes, brief description: _____.

Claim(s) discussed: *pending claims*.

Identification of prior art discussed: *Baker et al. (US RE39,071E)*.

Agreement with respect to the claims f)☐ was reached. g)☒ was not reached. h)☐ N/A.

Substance of Interview including description of the general nature of what was agreed to if an agreement was reached, or any other comments: *Discussing the Baker reference regarding the purity of daptomycin (LY 146032), applicants would present the arguments and evidence indicating the purity of LY146032 in Baker'sreference is best 93% in the coming amendment.*.

(A fuller description, if necessary, and a copy of the amendments which the examiner agreed would render the claims allowable, if available, must be attached. Also, where no copy of the amendments that would render the claims allowable is available, a summary thereof must be attached.)

THE FORMAL WRITTEN REPLY TO THE LAST OFFICE ACTION MUST INCLUDE THE SUBSTANCE OF THE INTERVIEW. (See MPEP Section 713.04). If a reply to the last Office action has already been filed, APPLICANT IS GIVEN A NON-EXTENDABLE PERIOD OF THE LONGER OF ONE MONTH OR THIRTY DAYS FROM THIS INTERVIEW DATE, OR THE MAILING DATE OF THIS INTERVIEW SUMMARY FORM, WHICHEVER IS LATER, TO FILE A STATEMENT OF THE SUBSTANCE OF THE INTERVIEW. See Summary of Record of Interview requirements on reverse side or on attached sheet.

DETAILED ACTION

Status of the Claims

1. Claims 1-29, 31-36, 38-44, 46-52 and 54-57 are pending.

Applicants' amendment filed May 15, 2009 is acknowledged. Claim 1 has been amended, and new claims 54-57 have been cancelled. Therefore, claims 1-29, 31-36, 38-44, 46-52 and 54-57 are examined.

Claim Rejections - 35 USC § 102/103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. Claims 1-5, 8-29, 31-34, 38-42, 46-50 and 54-57 are rejected under 35 U.S.C. 102(e) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as unpatentable over Baker *et al.* (US RE39,071 E, reissue of U.S. Patent 5,912,226, filed December 16, 1991).

Baker *et al.* teach an antibacterial composition comprising daptomycin (LY146032) obtained in substantially pure form, which refers to daptomycin that contains less than 2.5% of a combined total of anhydro-daptomycin and beta-isomer of daptomycin (column 8, lines 50-60; Examples 4 and 5; claim 1(g), 54), where daptomycin is purified by a procedure using Diaion HP-20 resin column, followed by HPLC and another HP-20 resin column (Examples 1-5, claim 8). Baker *et al.* also teach the preparation of a pharmaceutical formulation comprising the purified daptomycin (LY146032) with pharmaceutical carriers or excipients (column 9, lines 47-59; claims 9, 38, 46 and 55-57). Although Baker *et al.* do not specifically disclose the daptomycin (LY146032) that is essentially pure (i.e., at least 98% of a sample being daptomycin as defined at page 11, lines 23-26 of the instant specification); that is substantially free of anhydro-daptomycin (no more than 1%; page 11, lines 27-29) and substantially free of β-isomer of daptomycin (no more than 1%); that is essentially free of anhydro-daptomycin (no more than 0.5%; page 12, lines 1-3) and substantially free of β-isomer of daptomycin (no more than 1%); that is free of anhydro-daptomycin (no more than 0.1%; page 12, lines 4-6) and substantially free of β-isomer of daptomycin (no more than 1%), the reference does indicate the daptomycin (LY146032) is in substantially pure form and contains less than 2.5% of a combined total of anhydro-daptomycin and beta-isomer of daptomycin. Furthermore, Baker *et al.* discloses a composition or pharmaceutical composition comprising substantially pure daptomycin, which meets the criteria of claim 1(a)-1(d) and 1(g), and its dependent claims because the term

"comprising" indicates the composition can contain something else besides substantially or essentially pure daptomycin. Since claim 1(a)-1(d) and 1(g) merely recites substantially or essentially pure daptomycin that may contain slight amount of anhydro-daptomycin and beta-isomer of daptomycin, it is obvious that a composition comprising LY146032 that is substantially pure taught by Baker *et al.*, which encompass the embodiments of essentially pure daptomycin at least 98% pure (claims 1(a), 2, 31, 39, 47), the embodiments of substantially free of anhydro-daptomycin (no more than 1%) and substantially free of β-isomer of daptomycin (no more than 1%; claims 1(b), 3, 32, 40, 48), the embodiments of essentially free of anhydro-daptomycin (no more than 0.5%) and substantially free of β-isomer of daptomycin (no more than 1%; claims 1(c), 4, 33, 41, 49), and the embodiments of free of anhydro-daptomycin (no more than 0.1%) and substantially free of β-isomer of daptomycin (no more than 1%; claims 1(d), 5, 34, 42, 50). It is also obvious that claims 11-29 are not patentable because the product by process claims are limited by and defined by the process, determination of patentability is based on the product itself, and the patentability of a product does not depend on its method of production (see MPEP 2113). In the instant case, the composition comprising daptomycin that is substantially free of anhydro-daptomycin and beta-isomer of daptomycin (less than 2.5% impurity) as indicated in the patent is not different from the claimed composition comprising essentially or substantially pure daptomycin (>98% daptomycin), even though the daptomycin of reference is purified by a different process. Baker *et al.* also disclose an antibiotic composition comprised of a combination of a compound of formula 1 (i.e., anhydro-A21978C; column 1, lines 14-21), a compound of formula 2 (isomer of A21978C) and a compound of formula 3 (the

parent cyclic peptide of A21978C; LY146032) or pharmaceutically acceptable salts (Reissue: claim 18; claim 10 of instant application).

Response to Arguments

Applicants indicate that Baker did not provide LY146032 that is at least 97.5% pure because (A) other impurities are implied in Baker, (B) a dozen other impurities later discovered by Applicants were unappreciated in Baker and were at least 7% in Baker's later work, and (C) Baker's later work teaches at best 93% purity. Regarding item A, applicants argue that Baker did not discuss overall purity of daptomycin in the composition, and Baker does not disclose the purity level of daptomycin in the sample but discloses the level of anhydro-daptomycin and beta-isomer of daptomycin in relation to daptomycin. Baker implies that other degradants are present, but are not predominant in the pH range that optimizes the transpeptidation reactions. Regarding item B, applicants argue that Baker likely had less than 93% LY146032 because it did not recognize existence of other impurities and Baker's later work (U.S. Patent 4,874,843) shows undetermined impurities at least as great as 7%. Regarding item C, applicants argue that Baker's later work (U.S. Patent 4,874,843) describes at best 93% purity. Furthermore, the Applicants described the use of the purification method from the '843 patent in Example 2 of the present application (See page 52, lines 1-5), and the purity level of the composition was 91%. Moreover, Applicants' use of the HPLC method described in the present invention revealed that the daptomycin purified by the '843 patent's method in Example 2 of the present application contained fourteen impurities (anhydro daptomyein, beta-isomer of daptomycin and 12 additional impurities; see Example 10, page 57, line 10- page 60, line 8), It was Applicants' present discovery of the impurities and the resulting method to produce more pure forms of

daptomyein that are non-obvious over Baker. In view of the foregoing, the rejection should be withdrawn (pages 8-12 of the response).

Applicants' response has been fully considered. However, the arguments are not found persuasive because of the following reasons. Regarding item A, Baker *et al.* teach an antibacterial composition comprising daptomycin (LY146032) obtained in substantially pure form, which refers to daptomycin that contains less than 2.5% of a combined total of anhydro-daptomycin and beta-isomer of daptomycin (column 8, lines 50-60; Examples 4 and 5). Since Baker *et al.* do not indicate other impurities besides anhydro-daptomycin and beta-isomer of daptomycin are contained in the daptomycin (LY146032) in substantially pure form, it reads that the daptomycin has more than 97.5% purity. While Baker implies that other degradants are present, but are not predominant in the pH range that optimizes the transpeptidation reactions, the reference does not indicate other degradants are present after the purification procedure (column 8, lines 45-49). Regarding items B and C, while Baker's later work (U.S. Patent 4,874,843) shows undetermined impurities at least as great as 7%, and daptomycin has at best 93% purity, the '843 patent only use a single HP-20 resin column to purify daptomycin, which is different from the purification procedure (i.e., Diaion HP-20 resin column, followed by HPLC and another HP-20 resin column) used by Baker *et al.* in the US RE39,071 E. Thus, even Baker (U.S. Patent 4,874,843) shows undetermined impurities at least as great as 7%, and daptomycin has at best 93% purity, it does not mean that the daptomycin purified by Baker *et al.* in the US RE39,071 E has at best 93% purity since the purification procedures used by two patents are different. As shown in Example 2 of the present application, the purity level of the daptomycin was 91% using the purification method from the '843 patent, and the daptomycin sample was

further confirmed to contain fourteen impurities (Example 10), which does not mean the daptomycin purified by Baker *et al.* in the US RE39,071 E would have at best 93% purity when a different purification procedure is used. Even if the daptomycin purified by Baker *et al.* in the US RE39,071 E does not have 97.5% purity, the composition comprising daptomycin (LY146032) obtained in substantially pure form that contains less than 2.5% of a combined total of anhydro-daptomycin and beta-isomer of daptomycin as taught by Baker *et al.* is not different from the claimed composition as indicated in claim 1(a)-1(d) and 1(g) because the term "comprising" indicates the composition can contain something else besides substantially or essentially pure daptomycin in a composition comprising substantially or essentially pure daptomycin. Therefore, the rejection of claim 1(a)-1(d) and its dependent claims are maintained.

Claim Objections

3. Claims 6-7, 35-36, 43-44 and 51-52 are objected to because the claims are dependent from a rejected claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

4. Claims 1-5, 8-29, 31-34, 38-42, 46-50 and 54-57 are rejected; and claims 6-7, 35-36, 43-44 and 51-52 are objected to.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chih-Min Kam whose telephone number is (571) 272-0948. The examiner can normally be reached on 8.00-4:30, Mon-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber can be reached at 571-272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Chih-Min Kam/
Primary Examiner, Art Unit 1656

CMK
August 8, 2009

Search Notes	Application No.	Applicant(s)	
	11/739,180	KELLEHER ET AL.	
	Examiner	Art Unit	
	CHIH-MIN KAM	1656	

SEARCHED			
Class	Subclass	Date	Examiner
514	9, 11, 2, 14		
530	317, 322		
530	344		
435	886		

INTERFERENCE SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES (INCLUDING SEARCH STRATEGY)		
	DATE	EXMR
EAST Search on USPAT, USPGPUB, DERWENT, EPO, JPO; STN search on MEDLINE, BIOSIS, EMBASE, SCISEARCH, AGRICOLA.	2/13/2008	CMK
Search strategy enclosed, Inventor name search, Parent applications 60/177,170 and 09/735,191, 10/747,48 have been reviewed.	2/13/2008	CMK
Update the search	10/28/2008	CMK
Update the search	8/5/2009	CMK

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	721	daptomycin	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2009/08/05 08:52
L2	51311	substantially adj pure	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2009/08/05 08:52
L3	13508	essentially adj pure	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2009/08/05 08:52
L4	7	L1 same (L2 or L3)	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2009/08/05 08:52
L5	8	impurities same L1	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2009/08/05 08:53
L6	8	anhydro-daptomycin or beta-daptomycin	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2009/08/05 08:53
L7	48441	anion adj exchange	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2009/08/05 08:54
L8	12152	hydrophobic adj interaction adj chromatography	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2009/08/05 08:54
L9	5	L1 same L7 same L8	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2009/08/05 08:54
L10	102	(Ly adj "146032") or A-21978C or A54145 or A-21978	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2009/08/05 08:54
L11	2	L10 same (L2 or L3)	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2009/08/05 08:54
L12	20	kelleher adj thomas.in.	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2009/08/05 08:54
L13	8	lai adj jan-ji.in.	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2009/08/05 08:54

L14	3	decourcey adj joseph.in.	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2009/08/05 08:54
L15	27	lynch adj paul.in.	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2009/08/05 08:54
L16	64	zenoni adj maurizio.in.	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2009/08/05 08:54
L17	6	tagliani adj auro.in.	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2009/08/05 08:54
L18	111	L12 or L13 or L14 or L15 or L16 or L17	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2009/08/05 08:54
L19	6	L18 and L1	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2009/08/05 08:54

8/5/09 8:55:28 AM
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(FILE 'HOME' ENTERED AT 08:56:32 ON 05 AUG 2009)

FILE 'MEDLINE, CAPLUS, BIOSIS, EMBASE, SCISEARCH, AGRICOLA' ENTERED AT
08:56:56 ON 05 AUG 2009
L1 5773 S DAPTOMYCIN
L2 2767 S SUBSTANTIALLY PURE
L3 2193 S ESSENTIALLY PURE
L4 0 S L1 (P) (L2 OR L3)
L5 2 S L1 (P) IMPURITIES
L6 2 DUPLICATE REMOVE L5 (0 DUPLICATES REMOVED)
L7 4 S ANHYDRO-DAPTOMYCIN OR BETA-DAPTOMYCIN
L8 4 DUPLICATE REMOVE L7 (0 DUPLICATES REMOVED)
L9 4 S L8 NOT L5
L10 105954 S ANION EXCHANGE
L11 9991 S HYDROPHOBIC INTERACTION CHROMATOGRAPHY
L12 2 S L1 (P) (L10) (P) L11
L13 2 DUPLICATE REMOVE L12 (0 DUPLICATES REMOVED)
L14 1 S L13 NOT (L5 OR L7)
L15 384 S (LY 146032) OR A-21978C OR A54145 OR A-21978
L16 1 S L15 (P) (L2 OR L3)
L17 1 S L16 NOT (L5 OR L7 OR L14)
L18 189 S KELLEHER T?/AU
L19 10273 S LAI J?/AU
L20 12 S DECOURCEY J?/AU
L21 3444 S LYNCH P?/AU
L22 73 S ZENONI M?/AU
L23 125 S TAGLIANI A?/AU
L24 14103 S L18 OR L19 OR L20 OR L21 OR L22 OR L23
L25 20 S L24 AND L1
L26 0 S L25 AND (L2 OR L3)
L27 1 S L25 AND IMPURITIES
L28 0 S L27 NOT (L5 OR L7 OR L14)

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appl. No.	:	11/739,180	Confirmation No.	8837
Applicant	:	Thomas Kelleher et al.		
Filed	:	April 24, 2007		
TC/A.U.	:	1656		
Examiner	:	Chih Min Kam		
Docket No.	:	C062-02/03 US		
Customer No.	:	34103		

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
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AMENDMENT

This Amendment is filed in response to the Office Action mailed November 17, 2008 (hereafter "the Office Action") in the above-identified application.

Certificate of Transmission/Mailing

I hereby certify that this correspondence (Amendment) is being deposited with the United States Postal Service with sufficient postage as First Class Mail and is addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 or is being facsimile transmitted to the USPTO on the date shown below.

May 15, 2009 Jodi O'Herlihy

AMENDMENTS TO THE CLAIMS

1. (Currently amended) A composition comprising

(a) essentially pure daptomycin,

(b) daptomycin that is substantially free of anhydro-daptomycin and substantially free of β-isomer of daptomycin,

(c) daptomycin that is essentially free of anhydro-daptomycin and substantially free of β-isomer of daptomycin,

(d) daptomycin that is free of anhydro-daptomycin and substantially free of β-isomer of daptomycin,

(e) daptomycin that is substantially free of each of impurities 1 to 14 defined by peaks 1-14 shown in FIG. 12, or

(f) daptomycin that is essentially free of each of impurities 1 to 14 defined by peaks 1-14 shown in FIG. 12 or

(g) substantially pure daptomycin.

2. (Original) The composition of claim 1 comprising essentially pure daptomycin.

3. (Original) The composition of claim 1 compromising daptomycin that is substantially free of anhydro-daptomycin and substantially free of β-isomer of daptomycin.

4. (Original) The composition according to claim 3 that is essentially free of anhydro-daptomycin.

5. (Original) The composition according to claim 3 that is free of anhydro-daptomycin.

6. (Original) The composition of claim 1 that is substantially free of each of impurities 1 to 14 defined by peaks 1-14 shown in FIG. 12.

7. (Original) The composition according to claim 6 that is essentially free of each of impurities 1 to 14 defined by peaks 1-14 shown in FIG. 12.

8. (Original) The composition of claim 1, wherein daptomycin purity is measured by HPLC.

9. (Original) The composition of claim 1 further comprising a pharmaceutically acceptable carrier or excipient.

10. (Original) A pharmaceutical composition according to claim 9, further comprising one or more antibiotics, one or more antifungal agents, or both an antibiotic and an antifungal agent.

11. (Original) The composition according to claim 1 wherein the daptomycin is purified by a process comprising the steps of:

a) supplying a fermentation broth;

b) fermenting *Streptomyces roseosporus* with a feed of n-decanoic acid to produce daptomycin in the fermentation broth;

c) clarifying the fermentation broth to obtain a clarified solution;

d) subjecting the clarified solution to anion exchange chromatography to obtain an enriched daptomycin preparation;

e) subjecting the enriched daptomycin preparation to hydrophobic interaction chromatography to obtain a semi-purified daptomycin preparation; and

f) subjecting the semi-purified daptomycin preparation to anion exchange chromatography to obtain the composition of claim 1.

12. (Original) The composition according to claim 11, wherein the feed of n-decanoic acid is regulated to achieve a residual concentration of n-decanoic acid of no more than 50 parts per million (ppm) during fermentation.

13. (Original) The composition according to claim 11, wherein said clarifying comprises filtration or centrifugation and depth filtration.

14. (Original) The composition according to claim 11, wherein the anion exchange chromatography in d) is performed using a resin comprising a copolymer of 2-methacrylic acid and ethyleneglycol dimethacrylate (EDGM).

15. (Original) The composition according to claim 11, wherein the hydrophobic interaction chromatography is performed using a resin comprising a co-polymer of cross-linked divinylbenzene/stryene.

16. (Original) The composition according to claim 15, wherein the hydrophobic interaction chromatography is performed at neutral pH and a solvent

concentration that is reduced compared to the solvent concentration used when performing the hydrophobic interaction chromatography at acidic pH.

17. (Original) The composition according to claim 16, wherein the resin is recycled by loading the column at an acidic pH and eluting the column at a neutral pH.

18. (Original) The composition according to claim 11, wherein the anion exchange chromatography in f) is performed using a resin comprising a copolymer of 2-methacrylic acid and ethyleneglycol dimethacrylate (EDGM).

19. (Original) The composition according to claim 11, wherein the anion exchange chromatography is used to reduce the level of solvent in the clarified solution.

20. (Original) The composition according to claim 11, wherein the anion exchange chromatography is performed via continuous flow chromatography.

21. (Original) The composition according to claim 11, wherein the process further comprises the step of filtering daptomycin.

22. (Original) The composition according to claim 11, wherein the process further comprises the step of depyrogenating daptomycin using ultrafiltration.

23. (Original) The composition according to claim 22 wherein said depyrogenating comprises the steps of:

i) providing a daptomycin solution under conditions in which the daptomycin is in a monomeric and nonmicellar state;

ii) filtering the daptomycin solution under conditions in which the daptomycin passes through the filter but pyrogens do not pass through the filter;

iii) subjecting the daptomycin solution to conditions forming a daptomycin aggregate;

iv) filtering the daptomycin aggregate under conditions in which the daptomycin aggregate is retained on the filter; and

v) collecting the daptomycin aggregate.

24. (Original) The composition according to claim 22, wherein the process further comprises the step of lyophilizing daptomycin.

25. (Original) The composition according to claim 22, wherein the anion exchange chromatography is performed via radial flow chromatography.

26. (Original) The composition according claim 11, wherein said clarifying comprises microfiltration or centrifugation.

27. (Original) The composition according to claim 11, wherein the process further comprises the steps of filtering and concentrating daptomycin.

28. (Original) The composition according to claim 11, wherein the process further comprises the step of separating the enriched daptomycin from low molecular weight material by ultrafiltration.

29. (Original) The composition according to claim 28, wherein the process further comprises the step of depyrogenating the daptomycin.

30. Canceled

31. (Original) The pharmaceutical composition of claim 9 comprising essentially pure daptomycin.

32. (Original) The pharmaceutical composition of claim 9 comprising daptomycin that is substantially free of anhydro-daptomycin and substantially free of β-isomer of daptomycin.

33. (Original) The pharmaceutical composition of claim 9 comprising daptomycin that is essentially free of anhydro-daptomycin and substantially free of β-isomer of daptomycin.

34. (Original) The pharmaceutical composition of claim 9 comprising daptomycin that is free of anhydro-daptomycin and substantially free of β-isomer of daptomycin.

35. (Original) The pharmaceutical composition of claim 9 comprising daptomycin that is substantially free of each of impurities 1 to 14 defined by peaks 1-14 shown in FIG. 12.

36. (Original) The pharmaceutical composition of claim 9 comprising daptomycin that is essentially free of each of impurities 1 to 14 defined by peaks 1-14 shown in FIG. 12.

37. Canceled

38. (Original) A method for preparing a pharmaceutical composition comprising combining the composition of claim 1 with a pharmaceutically acceptable

carrier or excipient.

39. (Original) The method of claim 38 wherein the composition is essentially pure daptomycin.

40. (Original) The method of claim 38 wherein the composition is daptomycin that is substantially free of anhydro-daptomycin and substantially free of β-isomer of daptomycin.

41. (Original) The method of claim 38 wherein the composition is daptomycin that is essentially free of anhydro-daptomycin and substantially free of β-isomer of daptomycin.

42. (Original) The method of claim 38 wherein the composition is daptomycin that is free of anhydro-daptomycin and substantially free of β-isomer of daptomycin.

43. (Original) The method of claim 38 wherein the composition is daptomycin that is substantially free of each of impurities 1 to 14 defined by peaks 1-14 shown in FIG. 12.

44. (Original) The method of claim 38 wherein the composition is daptomycin that is essentially free of each of impurities 1 to 14 defined by peaks 1-14 shown in FIG. 12.

45. Canceled

46. (Original) A pharmaceutical composition prepared by the method of claim 38.

47. (Original) The pharmaceutical composition of claim 46 wherein the composition is essentially pure daptomycin.

48. (Original) The pharmaceutical composition of claim 46 wherein the composition is daptomycin that is substantially free of anhydro-daptomycin and substantially free of β-isomer of daptomycin.

49. (Original) The pharmaceutical composition of claim 46 wherein the composition is daptomycin that is essentially free of anhydro-daptomycin and substantially free of β-isomer of daptomycin.

50. (Original) The pharmaceutical composition of claim 46 wherein the

composition is daptomycin that is free of anhydro-daptomycin and substantially free of β-isomer of daptomycin.

51. (Original) The pharmaceutical composition of claim 46 wherein the composition is daptomycin that is substantially free of each of impurities 1 to 14 defined by peaks 1-14 shown in FIG. 12.

52. (Original) The pharmaceutical composition of claim 46 wherein the composition is daptomycin that is essentially free of each of impurities 1 to 14 defined by peaks 1-14 shown in FIG. 12.

53. Canceled

54. (New) The composition of claim 1 comprising substantially pure daptomycin.

55. (New)The pharmaceutical composition of claim 9 comprising substantially pure daptomycin.

56. (New)The method of claim 38 wherein the composition is substantially pure daptomycin.

57. (New)The pharmaceutical composition of claim 46 wherein the composition is substantially pure daptomycin.

REMARKS

Applicants undersigned agent thanks the Examiner for the telephone interview conducted on May 14, 2009. Although no further agreement was reached on the allowability of the claims, Applicants believe the interview provided a helpful explanation of the invention and the basis for the amendment to claim 1 herein and the introduction of claims 54-57. Applicants also acknowledge with thanks the Examiner's indication in the Office Action Summary that certain claims would be allowable if they were not dependent on unallowable claims.

The Claim Amendments

Claims 1-29, 31-36, 38-44 and 46-52 were pending in the present application. Applicants have amended claim 1. Applicants have added claims 54-57. Support for amended claim 1 can be found in claim 1 as originally filed. Support for added claim 54 can be found in originally filed claims 1 and 30. Support for new claim 55 can be found in original claim 37. Support for new claim 56 can be found in original claim 45. Support for claim 57 can be found in original claim 53. Accordingly, upon entry of the instant amendments, claims 1-29, 31-36, 38-44, 46-52 and 54-57 will be pending in this application.

Rejection under 35 U.S.C. §103(a)

Claims 1-5, 8-29, 31-34, 38-42 and 46-50 are rejected under 35 U.S.C. §103(a) as being unpatentable over Baker et al. (US RE39071 E, hereafter Baker). The Office Action states that Baker teaches antibacterial compositions comprising daptomycin in substantially pure form, which refers to daptomycin that contains less than 2.5% of a combined total of anhydro daptomycin and beta-isomer daptomycin where daptomycin is purified using Dianion HP-20 resin column and HPLC. The Office Action reads that Baker does not specifically disclose the daptomycin compositions of the present invention, but "the reference docs indicate that daptomycin (LY146032) contains less than 2.5% of a combined total of anhydro-daptomycin and β -isomer of daptomycin, thus it is obvious that LY146032 is at least 97.5% pure, which encompasses embodiments of at least 98% pure(claims 1(a), 2, 31, 39, 47), the embodiments of substantially free of anhydro-daptomycin (no more than 1%) and substantially free β-isomer of daptomycin

(no more than 1%; claims 3, 32, 40, 48), the embodiments of essentially free anhydro-daptomycin (no more than 0.5%) and substantially free of β-isomer of daptomycin (no more than 1%; claims 1(c) 4, 33, 41, 49), and the embodiments of free of anhydro-daptomycin (no more than 0.1%) and substantially free of β-isomer of daptomycin (no more than 1%; claims 1(d), 5, 32, 42, 50)"[emphasis added].

Applicants respectfully traverse because Baker did not provide LY146032 that is at least 97.5% pure because (A) other impurities are implied in Baker, (B) a dozen other impurities later discovered by Applicants were unappreciated in Baker and were at least 7% in Baker's later work, and (C) Baker's later work teaches at best 93% purity. As explained in detail below, it would not have been obvious how to make the claimed invention based on Baker.

(A) The statement in the Office action that "it is obvious that LY146032 [in Baker] is at least 97.5% pure..." is an unreasonable assumption. While Baker teaches compositions of daptomycin that contain less than 2.5% of a combined total of anhydro daptomycin and beta-isomer daptomycin, Baker does not discuss overall purity of daptomycin in the composition. Baker does not disclose the purity level of daptomycin in the sample but discloses the level of anhydro-daptomycin and beta isomer of daptomycin in relation to daptomycin. In fact, Baker implies that other degradants are present, but they are not predominant in the pH range that optimizes the transpeptidation reactions. See column 8, lines 47-48 ("In the preparation of formulation 1 and 2 compounds [anhydro form and beta-isomer], a pH range of 4-6 is optimum for the transpeptidation reactions. At pH levels below 4 and above 6, other degradation processes predominate.").

(B) Baker likely had less than 93% LY146032 because it did not recognize existence of other impurities and Baker's later work shows undetermined impurities at least as great as 7%. Baker does not indicate the levels of any other impurities present in the compositions prepared by Baker or suggest that the other twelve impurities described in the specification of the present application were appreciated. Applicants submit that although Baker did not disclose other impurities, other impurities were likely present in the Baker preparations as evidenced by Baker's later work disclosed in his '843 application and Applicants' own work in the present application. Baker likely contained

but did not disclose the 12 impurities of the present application and that Baker did not have even 93% purity as a "substantially pure form" as the term was used in Baker thus that phrase must have been used differently in Baker than in the present application.

(C) Baker's later filed work describes at best 93% purity. For example, Baker's later filed '843 patent, which is dealt with extensively in the present application, and the specification of the present application teaches, that prior to the Applicant's invention the highest LY146032 purity levels observed were 90-93%. See for example, page 4, line 29, through page 5, line 2 and the '843 Patent col. 2, ll. 40-44. United States Patent 4,874,843, (based on an application by filed by Baker December 3, 1987, i.e. after the June 10, 1987 priority of Baker's '226 patent) describes several daptomycin purification methods. The '843 patent states that final resolution and separation of daptomycin from structurally similar compounds was impeded by the presence of impurities that were not identifiable by ultraviolet analysis of the fermentation broth. In addition, the '843 patent also states that despite a variety of additional purification attempts, the highest yields obtained were about 93%. See page 3, line 12 through page 4, line 2 of the present specification. In addition, the Applicants described the use of the purification method from the '843 patent in Example 2 of the present application. See page 52, lines 1-5. After purification by the '843 patent's method as described in Example 2 of the present specification, Applicants noted that the purity level of the composition was 91%. It is therefore unreasonable to assume that Baker's preparation was 97.5% daptomycin because of the absence of the other later identified impurities and Baker's work described in the later filed application describing the best purity levels seen.

Applicants' use of the HPLC method described in the present invention revealed that the daptomycin purified by the '843 patent's method in Example 2 of the present application contained fourteen impurities (anhydro daptomycin, beta-isomer of daptomycin and 12 additional impurities). See Example 10, page 57, line 10, through page 60, line 8. It was Applicants' present discovery of the impurities and the resulting method to produce more pure forms of daptomycin that are non-obvious over Baker. The disclosure of '843 and Applicants work (example 2) teach that the highest purity of daptomycin prior to the Applicants invention is 91-93%. Therefore, one of skill in the

art, based on the disclosure of '843 would acknowledge that there is at best a total of 7% of impurities that exist in the composition. Baker accounts for at most only 2.5% of these impurities and is silent on the other 4.5 % of impurities that are inherent in the composition. In any event, Baker could not have had a daptomycin purity of greater than 93%. Based on this reasoning and Baker's acknowledgement that there are other degradants (*vide supra)*, it is incorrect to extrapolate that the LY146032 of Baker is 97.5% pure.

In In Re Rijckaert, 9 F.3d 1531, 1534 (Fed. Cir. 1993), the court acknowledged that "That which may be inherent is not necessarily known. Obviousness cannot be predicated on what is unknown." Based on the Applicant's arguments (*vide supra*), it is clear that other impurities were present in the Baker composition but unappreciated at the time. Applicants submit that these impurities were not known based on the disclosure by Baker nor by the disclosure of '843. The '843 patent does not identify the impurities present in the composition, nor does the '843 patent contemplate how to remove these impurities. Based on the disclosure of the '843 patent, more than routine experimentation would be required by one of ordinary skill in the art to achieve increased purity of daptomycin given the multitude of attempts made to increase the purity and the recognition that, at best, only 93% daptomycin was achievable. See column 1 line 55 through column 2, line 44 of the '843 patent. The '843 patent does not describe the isolation of any impurities. The '843 patent does not provide a means for separating and isolating the impurities, characterizing the impurities nor does the '843 patent suggest a method to remove the impurities. Prior to Applicant's invention one of skill in the art would not have believed higher purity of daptomycin was achievable because, without knowledge of what impurities were present in '843, no means existed for a method to remove said impurities. Even if one's goal was to achieve higher purity of daptomycin, '843 does not suggest how to accomplish this. The '843 patent does not teach what the impurities are, therefore there is no starting point for one of skill in the art to remove these impurities. In Abbott Laboratories v. Sandoz Inc., 544 F.3d 1341, 1352 (Fed. Cir. 2008), the court ruled that "knowledge of the goal does not render its achievement obvious." Thus, the desire for more purity would not render obvious how to achieve it.

In addition, Baker is silent on how to obtain anhydro-daptomycin and beta-isomer of daptomycin at the lower percentages described in the present invention. Baker is also silent with respect to the individual amounts of anhydro-daptomycin and beta-isomer of daptomycin disclosed in the present invention.

The Office Action states that claim 11-29 are not patentable because the product by process claims are limited by and defined by the process, determination of patentability is based on the product itself, and the patentability of the product does not depend on its method of production. Applicants have established (*vide supra*) that the composition is not obvious in light of Baker, therefore the rejection is overcome. For the reasons set forth above, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. § 103(a).

CONCLUSION

For the reasons presented above, Applicants respectfully request reconsideration and prompt allowance of all pending claims. A Petition for Extension of Time is enclosed. Please deduct the petition fee and apply any other charges or credits to Deposit Account No. 50-1986, referencing attorney docket number C062-02/03.

Respectfully submitted,

Date: May 15, 2009

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Patent Agent for Assignee

C062-02-03 US 20090515 response to 20081117OA

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MAY 15 2009

PETITION FOR EXTENSION OF TIME UNDER 37 CFR 1.136(a) FY 2009 *(Fees pursuant to the Consolidated Appropriations Act, 2005 (H.R. 4818).)*	Docket Number (Optional) C062-02/03 US
Application Number 11/739,180	Filed April 24, 2007
For High Purity Lipopeptides	
Art Unit 1656	Examiner Chih Min Kam

This is a request under the provisions of 37 CFR 1.136(a) to extend the period for filing a reply in the above identified application.

The requested extension and fee are as follows (check time period desired and enter the appropriate fee below):

	Fee	Small Entity Fee	
☐ One month (37 CFR 1.17(a)(1))	$130	$65	$
☐ Two months (37 CFR 1.17(a)(2))	$490	$245	$
☑ Three months (37 CFR 1.17(a)(3))	$1110	$555	$ 555.00
☐ Four months (37 CFR 1.17(a)(4))	$1730	$865	$
☐ Five months (37 CFR 1.17(a)(5))	$2350	$1175	$

☑ Applicant claims small entity status. See 37 CFR 1.27.

☐ A check in the amount of the fee is enclosed.

☐ Payment by credit card. Form PTO-2038 is attached.

☐ The Director has already been authorized to charge fees in this application to a Deposit Account.

☑ The Director is hereby authorized to charge any fees which may be required, or credit any overpayment, to Deposit Account Number 50-1986.

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I am the

☐ applicant/inventor.

☐ assignee of record of the entire interest. See 37 CFR 3.71. Statement under 37 CFR 3.73(b) is enclosed (Form PTO/SB/96).

☑ attorney or agent of record. Registration Number 37,878

☐ attorney or agent under 37 CFR 1.34. Registration number if acting under 37 CFR 1.34 _____

/Jill M.N. Mandelblatt/ — Signature

May 15, 2009 — Date

Jill M.N. Mandelblatt — Typed or printed name

781-860-8660 — Telephone Number

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below.

☑ Total of 1 forms are submitted.

This collection of information is required by 37 CFR 1.136(a). The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 6 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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MAY 15 2009

PTO/SB/21 (04-09)
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Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

TRANSMITTAL FORM

(to be used for all correspondence after initial filing)

Total Number of Pages in This Submission

Application Number	11/739,180
Filing Date	April 24, 2007
First Named Inventor	Thomas Kelleher
Art Unit	1656
Examiner Name	Chih Min Kam
Attorney Docket Number	C062-02/03 US

ENCLOSURES *(Check all that apply)*

- ☑ Fee Transmittal Form
  - ☐ Fee Attached
- ☑ Amendment/Reply
  - ☐ After Final
  - ☐ Affidavits/declaration(s)
- ☑ Extension of Time Request
- ☐ Express Abandonment Request
- ☐ Information Disclosure Statement
- ☐ Certified Copy of Priority Document(s)
- ☐ Reply to Missing Parts/ Incomplete Application
  - ☐ Reply to Missing Parts under 37 CFR 1.52 or 1.53
- ☐ Drawing(s)
- ☐ Licensing-related Papers
- ☐ Petition
- ☐ Petition to Convert to a Provisional Application
- ☐ Power of Attorney, Revocation Change of Correspondence Address
- ☐ Terminal Disclaimer
- ☐ Request for Refund
- ☐ CD, Number of CD(s) _____
  - ☐ Landscape Table on CD
- ☐ After Allowance Communication to TC
- ☐ Appeal Communication to Board of Appeals and Interferences
- ☐ Appeal Communication to TC (Appeal Notice, Brief, Reply Brief)
- ☐ Proprietary Information
- ☐ Status Letter
- ☐ Other Enclosure(s) (please identify below):

Remarks

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm Name	Cubist Pharmaceuticals, Inc.		
Signature	/Jill M.N. Mandelblatt/		
Printed name	Jill M.N. Mandelblatt		
Date	May 15, 2009	Reg. No.	37,878

CERTIFICATE OF TRANSMISSION/MAILING

I hereby certify that this correspondence is being facsimile transmitted to the USPTO or deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on the date shown below:

Signature	Jodi Doherty		
Typed or printed name	Jodi Doherty	Date	May 15, 2009

This collection of information is required by 37 CFR 1.5. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and1.14. This collection is estimated to 2 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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PTO/SB/17 (10-08)
Approved for use through 06/30/2010. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Effective on 12/08/2004.
Fees pursuant to the Consolidated Appropriations Act, 2005 (H.R. 4818).

FEE TRANSMITTAL
For FY 2009

☑ Applicant claims small entity status. See 37 CFR 1.27

TOTAL AMOUNT OF PAYMENT	($)	555.00

Complete if Known	
Application Number	11/739,180
Filing Date	April 24, 2007
First Named Inventor	Thomas Kelleher
Examiner Name	Chih Min Kam
Art Unit	1656
Attorney Docket No.	C062-02/03 US

METHOD OF PAYMENT (check all that apply)

☐ Check ☐ Credit Card ☐ Money Order ☐ None ☐ Other (please identify): _____

☑ Deposit Account Deposit Account Number: 50-1986 Deposit Account Name: Cubist Pharmaceuticals, I

For the above-identified deposit account, the Director is hereby authorized to: (check all that apply)

☑ Charge fee(s) indicated below ☐ Charge fee(s) indicated below, **except for the filing fee**

☑ Charge any additional fee(s) or underpayments of fee(s) under 37 CFR 1.16 and 1.17 ☑ Credit any overpayments

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FEE CALCULATION

1. BASIC FILING, SEARCH, AND EXAMINATION FEES

Application Type	FILING FEES Fee ($)	FILING FEES Small Entity Fee ($)	SEARCH FEES Fee ($)	SEARCH FEES Small Entity Fee ($)	EXAMINATION FEES Fee ($)	EXAMINATION FEES Small Entity Fee ($)	Fees Paid ($)
Utility	330	165	540	270	220	110	
Design	220	110	100	50	140	70	
Plant	220	110	330	165	170	85	
Reissue	330	165	540	270	650	325	
Provisional	220	110	0	0	0	0	

2. EXCESS CLAIM FEES

Fee Description	Fee ($)	Small Entity Fee ($)
Each claim over 20 (including Reissues)	52	26
Each independent claim over 3 (including Reissues)	220	110
Multiple dependent claims	390	195

Total Claims	Extra Claims	Fee ($)	Fee Paid ($)
53 - 20 or HP =		x	=

HP = highest number of total claims paid for, if greater than 20.

Indep. Claims	Extra Claims	Fee ($)	Fee Paid ($)
1 - 3 or HP =		x	=

HP = highest number of independent claims paid for, if greater than 3.

Multiple Dependent Claims Fee ($)	Fee Paid ($)

3. APPLICATION SIZE FEE

If the specification and drawings exceed 100 sheets of paper (excluding electronically filed sequence or computer listings under 37 CFR 1.52(c)), the application size fee due is $270 ($135 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).

Total Sheets	Extra Sheets	Number of each additional 50 or fraction thereof	Fee ($)	Fee Paid ($)
- 100 =	/ 50 =	(round up to a whole number) x		=

4. OTHER FEE(S)

	Fees Paid ($)
Non-English Specification, $130 fee (no small entity discount)	
Other (e.g., late filing surcharge): Petition for Extension of Time (Three Months)	555.00

SUBMITTED BY

Signature	/Jill M.N. Mandelblatt/	Registration No. (Attorney/Agent) 37,878	Telephone 781-860-8660
Name (Print/Type)	Jill M.N. Mandelblatt		Date May 15, 2009

PTO/SB/06 (07-06)
Approved for use through 1/31/2007. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number	Filing Date	☐ To be Mailed
11/739,180	04/24/2007	

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY ☒ RATE ($)	SMALL ENTITY ☒ FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =		OR	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =			X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT 05/15/2009	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE ($)	SMALL ENTITY ADDITIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	* 53	Minus	** 53	= 0	X $26 =	0	OR	X $ =	
Independent (37 CFR 1.16(h))	* 2	Minus	***3	= 0	X $110 =	0	OR	X $ =	
☐ Application Size Fee (37 CFR 1.16(s))									
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
					TOTAL ADD'L FEE	0	OR	TOTAL ADD'L FEE	

AMENDMENT	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)	OR	RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =		OR	X $ =	
Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =		OR	X $ =	
☐ Application Size Fee (37 CFR 1.16(s))									
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
					TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

Legal Instrument Examiner:
/DENISE t. LILES/

=> d his

(FILE 'HOME' ENTERED AT 15:57:07 ON 28 OCT 2008)

FILE 'MEDLINE, CAPLUS, BIOSIS, EMBASE, SCISEARCH, AGRICOLA' ENTERED AT
15:57:37 ON 28 OCT 2008
L1 4657 S DAPTOMYCIN
L2 2695 S SUBSTANTIALLY PURE
L3 2157 S ESSENTIALLY PURE
L4 0 S L1 (P) (L2 OR L3)
L5 2 S L1 (P) IMPURITIES
L6 2 DUPLICATE REMOVE L5 (0 DUPLICATES REMOVED)
L7 4 S ANHYDRO-DAPTOMYCIN OR BETA-DAPTOMYCIN
L8 4 DUPLICATE REMOVE L7 (0 DUPLICATES REMOVED)
L9 4 S L8 NOT L5
L10 102337 S ANION EXCHANGE
L11 9600 S HYDROPHOBIC INTERACTION CHROMATOGRAPHY
L12 2 S L1 (P) L10 (P) L11
L13 2 DUPLICATE REMOVE L12 (0 DUPLICATES REMOVED)
L14 1 S L13 NOT (L5 OR L9)
L15 373 S (LY 146032) OR A-21978C OR A54145 OR A-21978
L16 1 S L15 (P) (L2 OR L3)
L17 1 S L16 NOT (L5 OR L9 OR L14)
L18 189 S KELLEHER T?/AU
L19 9485 S LAI J?/AU
L20 9 S DECOURCEY J?/AU
L21 3383 S LYNCH P?/AU
L22 73 S ZENONI M?/AU
L23 116 S TAGLIANI A?/AU
L24 13242 S L18 OR L19 OR L20 OR L21 OR L22 OR L23
L25 20 S L24 AND L1
L26 8 DUPLICATE REMOVE L25 (12 DUPLICATES REMOVED)
L27 6 S L26 NOT (L5 OR L9 OR L14 OR L17)

=> log y

EAST Search History

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	599	daptomycin	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2008/10/28 14:36
L2	48078	substantially adj pure	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2008/10/28 14:36
L3	12793	essentially adj pure	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2008/10/28 14:36
L4	7	L1 same (L2 or L3)	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2008/10/28 14:36
L5	8	impurities same L1	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2008/10/28 15:51
L6	8	anhydro-daptomycin or beta-daptomycin	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2008/10/28 15:51
L7	45693	anion adj exchange	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2008/10/28 15:52
L8	11134	hydrophobic adj interaction adj chromatography	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2008/10/28 15:52
L9	5	L1 same L7 same L8	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2008/10/28 15:52
L10	97	(Ly adj "146032") or A-21978C or A54145 or A-21978	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2008/10/28 15:53
L11	2	10 same (2 or 3)	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2008/10/28 15:53
L12	20	kelleher adj thomas.in.	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2008/10/28 15:54
L13	7	lai adj jan-ji.in.	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2008/10/28 15:54
L14	3	decourcey adj joseph. in.	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2008/10/28 15:54

L15	27	lynch adj paul.in.	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2008/10/28 15:54
L16	62	zenoni adj maurizio.in.	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2008/10/28 15:54
L17	5	tagliani adj auro.in.	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2008/10/28 15:54
L18	107	L12 or L13 or L14 or L15 or L16 or L17	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2008/10/28 15:54
L19	5	L18 and L1	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2008/10/28 15:54

10/28/08 3:55:07 PM
C:\Documents and Settings\ckam\My Documents\EAST\Workspaces\%daptomycin-1.wsp

UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/739,180	04/24/2007	Thomas Kelleher	C062-02/03 US	8837

34103 7590 11/17/2008

Intellectual Property Department
Cubist Pharmaceuticals, Inc.
65 Hayden Avenue
Lexington, MA 02421

EXAMINER	
KAM, CHIH MIN	

ART UNIT	PAPER NUMBER
1656	

MAIL DATE	DELIVERY MODE
11/17/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	11/739,180	KELLEHER ET AL.	
	Examiner	Art Unit	
	CHIH-MIN KAM	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 August 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-29,31-36,38-44 and 46-52* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,8-29,31-34,38-42 and 46-50* is/are rejected.

7)☒ Claim(s) *6,7,35,36,43,44,51 and 52* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *24 April 2007* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

1. Claims 1-29, 31-36, 38-44 and 46-52 are pending.

Applicants' amendment filed August 18, 2008 is acknowledged. Claim 1 has been amended, and claims 30, 37, 45 and 53 have been cancelled. Therefore, claims 1-29, 31-36, 38-44 and 46-52 are examined.

Withdrawn Claim Objections

2. The previous objection to claims 2-7, 10, 31-34, 39-42 and 47-50 is withdrawn in view of a new ground of rejection made on these claims.

Withdrawn Claim Rejections - 35 USC § 102

3. The previous rejection of claims 1, 8, 9, 11-30, 37, 38, 45-46 and 53 under 35 U.S.C. 102(e) as being anticipated by Baker *et al.* (US RE39,071 E, reissue of U.S. Patent 5,912,226), is withdrawn in view of applicants' amendment to the claim, and applicant's response at pages 8-9 in the amendment filed August 18, 2008.

New Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 1-5, 8-29, 31-34, 38-42 and 46-50 are rejected under 35 U.S.C. 103(a) as being unpatentable over Baker *et al.* (US RE39,071 E, reissue of U.S. Patent 5,912,226, filed December 16, 1991).

Baker *et al.* teach an antibacterial composition comprising daptomycin (LY146032) in substantially pure form, which refers to daptomycin that contains less than 2.5% of a combined total of anhydro-daptomycin and beta-isomer of daptomycin (column 8, lines 50-60; Example 4), where daptomycin is purified by a procedure using Diaion HP-20 resin column and HPLC (Examples 1-3, claim 8). Baker *et al.* also teach a pharmaceutical formulation comprising the purified daptomycin (LY146032) with pharmaceutical carriers or excipients can also be prepared (column 9, lines 47-59; claims 9, 38, 46). Although Baker *et al.* do not specifically disclose the daptomycin (LY146032) that is essentially pure (i.e., at least 98% of a sample being daptomycin as defined at page 11, lines 23-26 of the instant specification); that is substantially free of anhydro-daptomycin (no more than 1%; page 11, lines 27-29) and substantially free of β-isomer of daptomycin (no more than 1%); that is essentially free of anhydro-daptomycin (no more than 0.5%; page 12, lines 1-3) and substantially free of β-isomer of daptomycin (no more than 1%); that is free of anhydro-daptomycin (no more than 0.1%; page 12, lines 4-6) and substantially free of β-isomer of daptomycin (no more than 1%), the reference does indicate the daptomycin (LY146032) contains less than 2.5% of a combined total of anhydro-daptomycin and beta-isomer of daptomycin, thus it is obvious that LY146032 is at least 97.5% pure, which encompass the embodiments at least 98% pure (claims 1(a), 2, 31, 39, 47), the embodiments of substantially free of anhydro-daptomycin (no more than 1%) and substantially free of β-isomer of daptomycin (no more than 1%; claims 1(b), 3, 32, 40, 48), the embodiments of essentially free of anhydro-

daptomycin (no more than 0.5%) and substantially free of β-isomer of daptomycin (no more than 1%; claims 1(c), 4, 33, 41, 49), and the embodiments of free of anhydro-daptomycin (no more than 0.1%) and substantially free of β-isomer of daptomycin (no more than 1%; claims 1(d), 5, 34, 42, 50). It is also obvious that claims 11-29 are not patentable because the product by process claims are limited by and defined by the process, determination of patentability is based on the product itself, and the patentability of a product does not depend on its method of production (see MPEP 2113). In the instant case, the composition comprising daptomycin that is substantially free of anhydro-daptomycin and beta-isomer of daptomycin (less than 2.5% impurity, or at least 97.5% pure) as indicated in the patent is the similar to the claimed composition comprising essentially pure daptomycin (>98% daptomycin), even though the daptomycin of reference is purified by a different process. Baker *et al.* also disclose an antibiotic composition comprised of a combination of a compound of formula 1 (i.e., anhydro-A21978C; column 1, lines 14-21), a compound of formula 2 (isomer of A21978C) and a compound of formula 3 (the parent cyclic peptide of A21978C; LY146032) or pharmaceutically acceptable salts (Reissue:claim 18; claim 10 of instant application).

Claim Objections

5. Claims 6-7, 35-36, 43-44 and 51-52 are objected to because the claims are dependent from a rejected claim.

Conclusion

6. Claims 1-5, 8-29, 31-34, 38-42 and 46-50 are rejected; and claims 6-7, 35-36, 43-44 and 51-52 are objected to.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chih-Min Kam whose telephone number is (571) 272-0948. The examiner can normally be reached on 8.00-4:30, Mon-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber can be reached at 571-272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Chih-Min Kam/
Primary Examiner, Art Unit 1656

CMK
November 12, 2008

Search Notes	Application No.	Applicant(s)	
	11/739,180	KELLEHER ET AL.	
	Examiner	Art Unit	
	CHIH-MIN KAM	1656	

SEARCHED			
Class	Subclass	Date	Examiner
514	9, 11, 2, 14		
530	317, 322		
530	344		
435	886		

INTERFERENCE SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES (INCLUDING SEARCH STRATEGY)		
	DATE	EXMR
EAST Search on USPAT, USPGPUB, DERWENT, EPO, JPO; STN search on MEDLINE, BIOSIS, EMBASE, SCISEARCH, AGRICOLA.	2/13/2008	CMK
Search strategy enclosed, Inventor name search, Parent applications 60/177,170 and 09/735,191, 10/747,48 have been reviewed.	2/13/2008	CMK
Update the search	10/28/2008	CMK

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appl. No.	:	11/739,180	Confirmation No.	8837
Applicant	:	Thomas Kelleher et al.		
Filed	:	April 24, 2007		
TC/A.U.	:	1656		
Examiner	:	Chih Min Kam		
Docket No.	:	C062-02/03 US		
Customer No.	:	34103		

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313

AMENDMENT

This Amendment is filed in response to the Office Action mailed February 19, 2008, (hereafter "the Office Action") in the above-identified application.

Certificate of Transmission/Mailing

I hereby certify that this correspondence (.) is being deposited with the United States Postal Service with sufficient postage as First Class Mail and is addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 or is being facsimile transmitted to the USPTO on the date shown below.

_____ _____
Date

AMENDMENTS TO THE CLAIMS

1. (Currently amended) A composition comprising

(a) essentially pure daptomycin,

(b) daptomycin that is substantially free of anhydro-daptomycin and substantially free of β-isomer of daptomycin,

(c) daptomycin that is essentially free of anhydro-daptomycin and substantially free of β-isomer of daptomycin,

(d) daptomycin that is free of anhydro-daptomycin and substantially free of β-isomer of daptomycin,

(e) daptomycin that is substantially free of each of impurities 1 to 14 defined by peaks 1-14 shown in FIG. 12, or

(f) daptomycin that is essentially free of each of impurities 1 to 14 defined by peaks 1-14 shown in FIG. 12~~, or~~

~~(g) substantially pure daptomycin.~~

2. (Original) The composition of claim 1 comprising essentially pure daptomycin.

3. (Original) The composition of claim 1 compromising daptomycin that is substantially free of anhydro-daptomycin and substantially free of β-isomer of daptomycin.

4. (Original) The composition according to claim 3 that is essentially free of anhydro-daptomycin.

5. (Original) The composition according to claim 3 that is free of anhydro-daptomycin.

6. (Original) The composition of claim 1 that is substantially free of each of impurities 1 to 14 defined by peaks 1-14 shown in FIG. 12.

7. (Original) The composition according to claim 6 that is essentially free of each of impurities 1 to 14 defined by peaks 1-14 shown in FIG. 12.

8. (Original) The composition of claim 1, wherein daptomycin purity is measured by HPLC.

9. (Original) The composition of claim 1 further comprising a pharmaceutically acceptable carrier or excipient.

10. (Original) A pharmaceutical composition according to claim 9, further comprising one or more antibiotics, one or more antifungal agents, or both an antibiotic and an antifungal agent.

11. (Original) The composition according to claim 1 wherein the daptomycin is purified by a process comprising the steps of:

a) supplying a fermentation broth;

b) fermenting *Streptomyces roseosporus* with a feed of n-decanoic acid to produce daptomycin in the fermentation broth;

c) clarifying the fermentation broth to obtain a clarified solution;

d) subjecting the clarified solution to anion exchange chromatography to obtain an enriched daptomycin preparation;

e) subjecting the enriched daptomycin preparation to hydrophobic interaction chromatography to obtain a semi-purified daptomycin preparation; and

f) subjecting the semi-purified daptomycin preparation to anion exchange chromatography to obtain the composition of claim 1.

12. (Original) The composition according to claim 11, wherein the feed of n-decanoic acid is regulated to achieve a residual concentration of n-decanoic acid of no more than 50 parts per million (ppm) during fermentation.

13. (Original) The composition according to claim 11, wherein said clarifying comprises filtration or centrifugation and depth filtration.

14. (Original) The composition according to claim 11, wherein the anion exchange chromatography in d) is performed using a resin comprising a copolymer of 2-methacrylic acid and ethyleneglycol dimethacrylate (EDGM).

15. (Original) The composition according to claim 11, wherein the hydrophobic interaction chromatography is performed using a resin comprising a co-polymer of cross-linked divinylbenzene/stryene.

16. (Original) The composition according to claim 15, wherein the hydrophobic interaction chromatography is performed at neutral pH and a solvent

concentration that is reduced compared to the solvent concentration used when performing the hydrophobic interaction chromatography at acidic pH.

17. (Original) The composition according to claim 16, wherein the resin is recycled by loading the column at an acidic pH and eluting the column at a neutral pH.

18. (Original) The composition according to claim 11, wherein the anion exchange chromatography in f) is performed using a resin comprising a copolymer of 2-methacrylic acid and ethyleneglycol dimethacrylate (EDGM).

19. (Original) The composition according to claim 11, wherein the anion exchange chromatography is used to reduce the level of solvent in the clarified solution.

20. (Original) The composition according to claim 11, wherein the anion exchange chromatography is performed via continuous flow chromatography.

21. (Original) The composition according to claim 11, wherein the process further comprises the step of filtering daptomycin.

22. (Original) The composition according to claim 11, wherein the process further comprises the step of depyrogenating daptomycin using ultrafiltration.

23. (Original) The composition according to claim 22 wherein said depyrogenating comprises the steps of:

i) providing a daptomycin solution under conditions in which the daptomycin is in a monomeric and nonmicellar state;

ii) filtering the daptomycin solution under conditions in which the daptomycin passes through the filter but pyrogens do not pass through the filter;

iii) subjecting the daptomycin solution to conditions forming a daptomycin aggregate;

iv) filtering the daptomycin aggregate under conditions in which the daptomycin aggregate is retained on the filter; and

v) collecting the daptomycin aggregate.

24. (Original) The composition according to claim 22, wherein the process further comprises the step of lyophilizing daptomycin.

25. (Original) The composition according to claim 22, wherein the anion exchange chromatography is performed via radial flow chromatography.

26. (Original) The composition according claim 11, wherein said clarifying comprises microfiltration or centrifugation.

27. (Original) The composition according to claim 11, wherein the process further comprises the steps of filtering and concentrating daptomycin.

28. (Original) The composition according to claim 11, wherein the process further comprises the step of separating the enriched daptomycin from low molecular weight material by ultrafiltration.

29. (Original) The composition according to claim 28, wherein the process further comprises the step of depyrogenating the daptomycin.

30. Canceled

31. (Original) The pharmaceutical composition of claim 9 comprising essentially pure daptomycin.

32. (Original) The pharmaceutical composition of claim 9 comprising daptomycin that is substantially free of anhydro-daptomycin and substantially free of β-isomer of daptomycin.

33. (Original) The pharmaceutical composition of claim 9 comprising daptomycin that is essentially free of anhydro-daptomycin and substantially free of β-isomer of daptomycin.

34. (Original) The pharmaceutical composition of claim 9 comprising daptomycin that is free of anhydro-daptomycin and substantially free of β-isomer of daptomycin.

35. (Original) The pharmaceutical composition of claim 9 comprising daptomycin that is substantially free of each of impurities 1 to 14 defined by peaks 1-14 shown in FIG. 12.

36. (Original) The pharmaceutical composition of claim 9 comprising daptomycin that is essentially free of each of impurities 1 to 14 defined by peaks 1-14 shown in FIG. 12.

37. Canceled

38. (Original) A method for preparing a pharmaceutical composition comprising combining the composition of claim 1 with a pharmaceutically acceptable

carrier or excipient.

39. (Original) The method of claim 38 wherein the composition is essentially pure daptomycin.

40. (Original) The method of claim 38 wherein the composition is daptomycin that is substantially free of anhydro-daptomycin and substantially free of β-isomer of daptomycin.

41. (Original) The method of claim 38 wherein the composition is daptomycin that is essentially free of anhydro-daptomycin and substantially free of β-isomer of daptomycin.

42. (Original) The method of claim 38 wherein the composition is daptomycin that is free of anhydro-daptomycin and substantially free of β-isomer of daptomycin.

43. (Original) The method of claim 38 wherein the composition is daptomycin that is substantially free of each of impurities 1 to 14 defined by peaks 1-14 shown in FIG. 12.

44. (Original) The method of claim 38 wherein the composition is daptomycin that is essentially free of each of impurities 1 to 14 defined by peaks 1-14 shown in FIG. 12.

45. Canceled

46. (Original) A pharmaceutical composition prepared by the method of claim 38.

47. (Original) The pharmaceutical composition of claim 46 wherein the composition is essentially pure daptomycin.

48. (Original) The pharmaceutical composition of claim 46 wherein the composition is daptomycin that is substantially free of anhydro-daptomycin and substantially free of β-isomer of daptomycin.

49. (Original) The pharmaceutical composition of claim 46 wherein the composition is daptomycin that is essentially free of anhydro-daptomycin and substantially free of β-isomer of daptomycin.

50. (Original) The pharmaceutical composition of claim 46 wherein the

composition is daptomycin that is free of anhydro-daptomycin and substantially free of β-isomer of daptomycin.

51. (Original) The pharmaceutical composition of claim 46 wherein the composition is daptomycin that is substantially free of each of impurities 1 to 14 defined by peaks 1-14 shown in FIG. 12.

52. (Original) The pharmaceutical composition of claim 46 wherein the composition is daptomycin that is essentially free of each of impurities 1 to 14 defined by peaks 1-14 shown in FIG. 12.

53. Canceled

REMARKS

The Claim Amendments

Applicants have amended claim 1 to further limit the claim. Support for amended claim 1 can be found in original claim 1. Claims 30, 37, 45 and 53 have been canceled.

Claims 1-29, 31-36, 38-44, and 46-52 are pending in this application.

No new matter has been added.

Rejections under 35 U.S.C. § 102(e)

Claims 1, 8, 9, 11-30, 37, 38, 45-46 and 53 stand rejected under 35 U.S.C. § 102(e) as anticipated by Baker *et al.* (US Patent 5,912,226, filed December 16, 1991, now RE 39,071). The Office Action states that the prior art date of the reference is determined under 35 U.S.C. § 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. § 102(e)). Applicants note however, that the Revised 35 U.S.C. § 102(e) as amended by the AIPA and as further amended by the Intellectual Property and High Technology Technical Amendment Act of 2002 should apply in this case.

According to the Manual of Patent Examining Procedures (MPEP) 706.02(a)IIB, the revised statutory provisions under 35 U.S.C. § 102(e) as amended by the AIPA and as further amended by the Intellectual Property and High Technology Technical Amendment Act of 2002 "...supersede all previous versions of 35 U.S.C. § 102(e) and 374, with only one exception, which is when the potential reference is based on an international application filed prior to November 29, 2000." Since '226 is not based on an international patent application filed before November 29, 2000, the revised 35 U.S.C. § 102(e) applies.

The Office Action reasons that claims 1(g), 8 and 30 are anticipated by '226. because, '226 teaches an antibacterial composition comprising daptomycin in substantially pure form, which refers to daptomycin that contains less than 2.5% of a combined total of anhydro-daptomycin and beta-isomer daptomycin. In addition, the Office Action states that claims 9, 37, 38 45-46 and 53 are also anticipated by '226 because '226 discloses that pharmaceutical compositions comprising purified daptomycin with pharmaceutical carriers or excipients can be prepared. The Office Action states that claims 11-29 are anticipated by '226 because "even though the product by process claims

are limited by and defined by the process, determination of patentability is based on the product itself, and the patentability of a product does not depend on its method of production (see MPEP 2113)."

In order to expedite prosecution, Applicants have amended claim 1 to remove "(g) substantially pure daptomycin" from the claim and canceled claims 30, 37, 45 and 53. Applicants make these amendments without prejudice and may pursue the deleted subject matter in a Continuation Application.

For the reasons stated above, '226 does not anticipate amended claim 1.

The arguments set forth above are applicable to the rejections of claims, 8-9, 11-29, 38, and 46, since all of these claims ultimately depends from amended Claim 1. Claims 30, 37, 45 and 53 have been canceled (*vida supra*)

The Office Action states that claims 9, 37, 38, 45-46 and 53 are anticipated by '226 because '226 discloses that purified daptomycin with pharmaceutical carriers and excipients can be prepared. The '226 patent does not disclose the level of purity of daptomycin that are in these preparations. As stated above, '226 does not anticipate claims 9, 8 and 46 because '226 does not satisfy all of the limitations of the present invention.

The Office Action states that claim 11-29 are anticipated by '226 because the product by process claims patentability is determined by the product itself and that the composition comprising daptomycin that is substantially free of anhydro-daptomycin and beta isomer of daptomycin is the same as the claimed composition even though the daptomycin of reference is purified by a different process. Applicants have now amended claim 1 from which claims 11-29 depend, and have removed the reference to substantially pure daptomycin. Thus, Applicants have established (*vide supra*) that the composition is not anticipated by '226, therefore the rejection is overcome. Additionally, although the above arguments render the Patent Office's statement of product by process patentability moot, Applicants do not acquiesce to the law as stated by the Examiner because claims should be interpreted the same way for patentability as for infringement.

For the reasons set forth above, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. § 102(e).

CONCLUSION

For the reasons presented above, Applicants respectfully request reconsideration and prompt allowance of all pending claims. A Petition for Extension of Time is enclosed. Please deduct the petition fee and apply any other charges or credits to Deposit Account No. 50-1986, referencing attorney docket number C062-02/03 US.

Respectfully submitted,

Date: August 18, 2008

Cubist Pharmaceuticals, Inc.
65 Hayden Avenue
Lexington, Massachusetts 02421
Tel.: (781) 860-8660
Fax: (781) 860-1407

/Jill M. N. Mandelblatt/

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Jill M.N. Mandelblatt, Reg. No. 37,878
Patent Agent for Assignee

C062-02-03 US 20080818 Resp to 20080219 OA.doc

PTO/SB/22 (08-08)
Approved for use through 08/31/2008. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARMENT OF COMMERCE

PETITION FOR EXTENSION OF TIME UNDER 37 CFR 1.136(a) **FY 2008** ***(Fees pursuant to the Consolidated Appropriations Act, 2005 (H.R. 4818).)***	Docket Number (Optional) C062-02/03 US
Application Number 11/739,180	Filed April 24, 2007
For High Purity Lipopeptides	
Art Unit 1656	Examiner Chih Min Kam

This is a request under the provisions of 37 CFR 1.136(a) to extend the period for filing a reply in the above identified application.

The requested extension and fee are as follows (check time period desired and enter the appropriate fee below):

		Fee	Small Entity Fee	
☐	One month (37 CFR 1.17(a)(1))	$120	$60	$
☐	Two months (37 CFR 1.17(a)(2))	$460	$230	$
☒	Three months (37 CFR 1.17(a)(3))	$1050	$525	$ 525.00
☐	Four months (37 CFR 1.17(a)(4))	$1640	$820	$
☐	Five months (37 CFR 1.17(a)(5))	$2230	$1115	$

☒ Applicant claims small entity status. See 37 CFR 1.27.

☐ A check in the amount of the fee is enclosed.

☐ Payment by credit card. Form PTO-2038 is attached.

☐ The Director has already been authorized to charge fees in this application to a Deposit Account.

☒ The Director is hereby authorized to charge any fees which may be required, or credit any overpayment, to Deposit Account Number 50-1986. I have enclosed a duplicate copy of this sheet.

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

I am the

☐ applicant/inventor.

☐ assignee of record of the entire interest. See 37 CFR 3.71.
Statement under 37 CFR 3.73(b) is enclosed (Form PTO/SB/96).

☐ attorney or agent of record. Registration Number _____

☒ attorney or agent under 37 CFR 1.34.
Registration number if acting under 37 CFR 1.34 37,878

/Jill M.N. Mandelblatt/ — Signature
August 18, 2008 — Date

Jill M.N. Mandelblatt — Typed or printed name
(781) 860-8660 — Telephone Number

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below.

☒ Total of 1 forms are submitted.

Electronic Patent Application Fee Transmittal

Application Number:	11739180
Filing Date:	24-Apr-2007
Title of Invention:	High Purity Lipopeptides
First Named Inventor/Applicant Name:	Thomas Kelleher
Filer:	Jill Michel-Netka Mandelblatt/Viana Daly
Attorney Docket Number:	C062-02/03 US

Filed as Small Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Extension - 3 months with $0 paid	2253	1	525	525

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
			Total in USD ($)	**525**

Electronic Acknowledgement Receipt

EFS ID:	3796720
Application Number:	11739180
International Application Number:	
Confirmation Number:	8837
Title of Invention:	High Purity Lipopeptides
First Named Inventor/Applicant Name:	Thomas Kelleher
Customer Number:	34103
Filer:	Jill Michel-Netka Mandelblatt/Viana Daly
Filer Authorized By:	Jill Michel-Netka Mandelblatt
Attorney Docket Number:	C062-02/03 US
Receipt Date:	18-AUG-2008
Filing Date:	24-APR-2007
Time Stamp:	15:24:35
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$525
RAM confirmation Number	672
Deposit Account	501986
Authorized User	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)

1		C062-02-03_US_20080814_Resp_to_20080219_OA.pdf	554549 355d98b2b81565 3edc4a79a59bf878c57852f89d	yes	13

Multipart Description/PDF files in .zip description		
Document Description	**Start**	**End**
Miscellaneous Incoming Letter	1	1
Miscellaneous Incoming Letter	2	2
Amendment - After Non-Final Rejection	3	12
Extension of Time	13	13

Warnings:

Information:

2	Fee Worksheet (PTO-06)	fee-info.pdf	30343 ca7a8291ec0f51f2289cb4181f5d7b64dfb1a0a6	no	2

Warnings:

Information:

Total Files Size (in bytes):	584892

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

<u>New Applications Under 35 U.S.C. 111</u>
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

<u>National Stage of an International Application under 35 U.S.C. 371</u>
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

<u>New International Application Filed with the USPTO as a Receiving Office</u>
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/SB/21 (08-08)
Approved for use through 08/31/2008. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

TRANSMITTAL FORM

(to be used for all correspondence after initial filing)

Application Number	11/739,180
Filing Date	April 24, 2007
First Named Inventor	Thomas Kelleher
Art Unit	1656
Examiner Name	Chih Min Kam
Total Number of Pages in This Submission: 13	Attorney Docket Number: C062-02/03 US

ENCLOSURES *(Check all that apply)*

- [X] Fee Transmittal Form
- [X] Fee Attached
- [X] Amendment/Reply
- [ ] After Final
- [ ] Affidavits/declaration(s)
- [X] Extension of Time Request
- [ ] Express Abandonment Request
- [ ] Information Disclosure Statement
- [ ] Certified Copy of Priority Document(s)
- [ ] Reply to Missing Parts/ Incomplete Application
- [ ] Reply to Missing Parts under 37 CFR 1.52 or 1.53
- [ ] Drawing(s)
- [ ] Licensing-related Papers
- [ ] Petition
- [ ] Petition to Convert to a Provisional Application
- [ ] Power of Attorney, Revocation Change of Correspondence Address
- [ ] Terminal Disclaimer
- [ ] Request for Refund
- [ ] CD, Number of CD(s) _____
- [ ] Landscape Table on CD
- [ ] After Allowance Communication to TC
- [ ] Appeal Communication to Board of Appeals and Interferences
- [ ] Appeal Communication to TC **(Appeal Notice, Brief, Reply Brief)**
- [ ] Proprietary Information
- [ ] Status Letter
- [ ] Other Enclosure(s) (please Identify below):

Remarks

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm Name	Cubist Pharmaceuticals, Inc.		
Signature	/Jill M.N. Mandelblatt/		
Printed name	Jill M.N. Mandelblatt		
Date	August 18, 2008	Reg. No.	37,878

CERTIFICATE OF TRANSMISSION/MAILING

I hereby certify that this correspondence is being facsimile transmitted to the USPTO or deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on the date shown below:

Signature			
Typed or printed name		Date	

This collection of information is required by 37 CFR 1.5. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and1.14. This collection is estimated to 2 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

PTO/SB/17 (10-07)
Approved for use through 06/30/2010. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Effective on 12/08/2004.
Fees pursuant to the Consolidated Appropriations Act, 2005 (H.R. 4818).

FEE TRANSMITTAL
For FY 2008

[X] Applicant claims small entity status. See 37 CFR 1.27

TOTAL AMOUNT OF PAYMENT ($) 525.00

Complete if Known	
Application Number	11/739,180
Filing Date	April 24, 2007
First Named Inventor	Thomas Kelleher
Examiner Name	Chih Min Kam
Art Unit	1656
Attorney Docket No.	C062-02/03 US

METHOD OF PAYMENT (check all that apply)

[ ] Check [ ] Credit Card [ ] Money Order [ ] None [ ] Other (please identify): _____

[X] Deposit Account Deposit Account Number: 50-1986 Deposit Account Name: Cubist Pharmaceuticals, Inc.

For the above-identified deposit account, the Director is hereby authorized to: (check all that apply)

[X] Charge fee(s) indicated below
[ ] Charge fee(s) indicated below, **except for the filing fee**
[X] Charge any additional fee(s) or underpayments of fee(s) under 37 CFR 1.16 and 1.17
[X] Credit any overpayments

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

FEE CALCULATION

1. BASIC FILING, SEARCH, AND EXAMINATION FEES

Application Type	FILING FEES Fee ($)	FILING FEES Small Entity Fee ($)	SEARCH FEES Fee ($)	SEARCH FEES Small Entity Fee ($)	EXAMINATION FEES Fee ($)	EXAMINATION FEES Small Entity Fee ($)	Fees Paid ($)
Utility	310	155	510	255	210	105	0.00
Design	210	105	100	50	130	65	
Plant	210	105	310	155	160	80	
Reissue	310	155	510	255	620	310	
Provisional	210	105	0	0	0	0	

2. EXCESS CLAIM FEES

Fee Description	Fee ($)	Small Entity Fee ($)
Each claim over 20 (including Reissues)	50	25
Each independent claim over 3 (including Reissues)	210	105
Multiple dependent claims	370	185

Total Claims	Extra Claims	Fee ($)	Fee Paid ($)
49 (53** XXXX) - 20 or HP =	-4	x _____ =	0.00

HP = highest number of total claims paid for, if greater than 20.

Indep. Claims	Extra Claims	Fee ($)	Fee Paid ($)
1 - 3 or HP =	-2	x _____ =	0.00

HP = highest number of independent claims paid for, if greater than 3.

Multiple Dependent Claims Fee ($)	Multiple Dependent Claims Fee Paid ($)

3. APPLICATION SIZE FEE

If the specification and drawings exceed 100 sheets of paper (excluding electronically filed sequence or computer listings under 37 CFR 1.52(e)), the application size fee due is $260 ($130 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).

Total Sheets	Extra Sheets	Number of each additional 50 or fraction thereof	Fee ($)	Fee Paid ($)
_____ - 100 =	_____	/ 50 = _____ (round **up** to a whole number)	x 130.00 =	0.00

4. OTHER FEE(S)

	Fees Paid ($)
Non-English Specification, $130 fee (no small entity discount)	
Other (e.g., late filing surcharge): Petition for three month extension of time	525.00

SUBMITTED BY

Signature	/Jill M.N. Mandelblatt/	Registration No. (Attorney/Agent) 37,878	Telephone 781-860-8660
Name (Print/Type)	Jill M.N. Mandelblatt		Date August 18, 2008

PTO/SB/06 (07-06)
Approved for use through 1/31/2007. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number	Filing Date	☐ To be Mailed
11/739,180	04/24/2007	

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY ☒ RATE ($)	SMALL ENTITY ☒ FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY FEE ($)
☒ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	75		N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =		OR	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =			X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	75		TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT 08/18/2008

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE ($)	SMALL ENTITY ADDITIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	* 49	Minus	** 53	= 0	X $25 =	0	OR	X $ =	
Independent (37 CFR 1.16(h))	* 1	Minus	***3	= 0	X $105 =	0	OR	X $ =	
☐ Application Size Fee (37 CFR 1.16(s))									
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
					TOTAL ADD'L FEE	0	OR	TOTAL ADD'L FEE	

AMENDMENT

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)		RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =		OR	X $ =	
Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =		OR	X $ =	
☐ Application Size Fee (37 CFR 1.16(s))									
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
					TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

Legal Instrument Examiner:
/GLORIA TRAMMELL/

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/739,180	04/24/2007	Thomas Kellcher	C062-02/03 US	8837

34103 7590 02/19/2008

Intellectual Property Department
Cubist Pharmaceuticals, Inc.
65 Hayden Avenue
Lexington, MA 02421

EXAMINER	
KAM, CHIH MIN	

ART UNIT	PAPER NUMBER
1656	

MAIL DATE	DELIVERY MODE
02/19/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	11/739,180	KELLEHER ET AL.	
	Examiner	Art Unit	
	CHIH-MIN KAM	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-53 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1,8,9,11-30,37,38,45,46 and 53 is/are rejected.

7)☒ Claim(s) 2-7,10,31-36,39-44 and 47-52 is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on 24 April 2007 is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date 8/14/07.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

1. Claims 1-53 are pending and examined.

Information Disclosure Statement (IDS)

2. The references on IDS filed August 14, 2007 have been considered and signed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

3. Claims 1, 8, 9, 11-30, 37, 38, 45-46 and 53 are rejected under 35 U.S.C. 102(e) as anticipated by Baker *et al.* (US RE39,071 E, reissue of U.S. Patent 5,912,226, filed December 16, 1991).

Baker *et al.* teach an antibacterial composition comprising daptomycin (LY146032) in substantially pure form, which refers to daptomycin that contains less than 2.5% of a combined total of anhydro-daptomycin and beta-isomer of daptomycin (column 8, lines 50-60; Example 4;

claims 1(g), 30), where daptomycin is purified by a procedure using Diaion HP-20 resin column and HPLC (Examples 1-3, claim 8). A pharmaceutical formulation comprising the purified daptomycin (LY146032) with pharmaceutical carriers or excipients can also be prepared (column 9, lines 47-59; claims 9, 37, 38, 45-46 and 53). The reference also anticipates claims 11-29 because although the product by process claims are limited by and defined by the process, determination of patentability is based on the product itself, and the patentability of a product does not depend on its method of production (see MPEP 2113). In the instant case, the composition comprising daptomycin that is substantially free of anhydro-daptomycin and beta-isomer of daptomycin (< 2.5%) as indicated in the patent is the same as the claimed composition comprising substantially pure daptomycin (>95% daptomycin), even though the daptomycin of reference is purified by a different process.

Claim Objections

4. Claims 2-7, 10, 31-36, 39-44 and 47-52 are objected to because the claims are dependent from a rejected claim.

Conclusion

5. Claims 1, 8, 9, 11-30, 37, 38, 45-46 and 53 are rejected; and claims 2-7, 10, 31-36, 39-44 and 47-52 are objected to.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chih-Min Kam whose telephone number is (571) 272-0948. The examiner can normally be reached on 8.00-4:30, Mon-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Bragdon can be reached at 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Chih-Min Kam, Ph. D.
Primary Patent Examiner

CHIH-MIN KAM
PRIMARY EXAMINER

CMK
February 14, 2008

PTO/SB/08a (05-07)
Approved for use through 09/30/2007. OMB 0651-0031
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	11739180
	Filing Date	2007-04-24
	First Named Inventor	Kelleher, Thomas J.
	Art Unit	1656
	Examiner Name	Chih Min Kam
	Attorney Docket Number	C062-02/03 US

U.S.PATENTS						
Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
/CMK/	1	4482487		1984-11-13	Abbott et al.	
	2	4524135		1985-06-18	Abbott et al.	
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/CMK/	9	5271935		1993-12-21	Franco et al.	
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	Art Unit	1656
	Examiner Name	Chih Min Kam
	Attorney Docket Number	C062-02/03 US

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U.S.PATENT APPLICATION PUBLICATIONS

Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
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Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] i	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
/CMK/	1	EP 0095295 A1	EP		1983-11-30	Eli Lilly Co		☐
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	3	EP 0294990 A2	EP		1988-12-14	Eli Lilly Co		☐
	4	EP 0337731 B1	EP		1989-10-18	Eli Lilly Co		☐
/CMK/	5	EP 0386951 A2	EP		1990-09-12	Eli Lilly Co		☐

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
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	Filing Date	2007-04-24
	First Named Inventor	Kelleher, Thomas J.
	Art Unit	1656
	Examiner Name	Chih Min Kam
	Attorney Docket Number	C062-02/03 US

	6	~~EP 0629630 A1~~	~~EP~~		~~1994-12-21~~	~~HOECHST AG~~		☐
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/CMK/	8	WO 00/18419	WO		2000-04-06	Cubist Pharmaceuticals, Inc.		☐
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	13	WO 99/27957	WO		1999-06-10	IMMUNE RESPONSE CORP INC		☐
/CMK/	14	WO 99/43700	WO		1999-09-02	HOECHST MARION ROUSSEL DE GMBH		☐
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	First Named Inventor	Kelleher, Thomas J.
	Art Unit	1656
	Examiner Name	Chih Min Kam
	Attorney Docket Number	C062-02/03 US

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T5
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	First Named Inventor	Kelleher, Thomas J.
	Art Unit	1656
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	Attorney Docket Number	C062-02/03 US

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Examiner Signature	/Chih-Min Kam/	Date Considered	02/13/2008

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CONFIRMATION NO. 8837

SERIAL NUMBER	FILING or 371(c) DATE RULE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
11/739,180	04/24/2007	514	1656	C062-02/03 US

APPLICANTS

Thomas Kelleher, Weston, MA;
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Paul Lynch, Arlington, MA;
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Auro Tagliani, Pavia, ITALY;

CMK

**** CONTINUING DATA ***************************

This application is a CON of 10/747,485 12/29/2003 ABN, which is a DIV of 09/735,191, 11/28/2000 PAT 6,696,412, which claims benefit of 60/177,170, 1/20/2000

**** FOREIGN APPLICATIONS *************************** none CMK

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05/08/2007

Foreign Priority claimed ☐ Yes ☒ No 35 USC 119(a-d) conditions met ☐ Yes ☒ No Verified and Acknowledged Examiner's Signature	☐ Met after Allowance Initials	STATE OR COUNTRY	SHEETS DRAWINGS	TOTAL CLAIMS	INDEPENDENT CLAIMS
		MA	11	53	1

ADDRESS

Intellectual Property Department
Cubist Pharmaceuticals, Inc.
65 Hayden Avenue
Lexington, MA 02421
UNITED STATES

TITLE

High Purity Lipopeptides

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BIB (Rev. 05/07).

Search Notes	Application No.	Applicant(s)	
	11/739,180	KELLEHER ET AL.	
	Examiner	Art Unit	
	CHIH-MIN KAM	1656	

SEARCHED			
Class	Subclass	Date	Examiner
514	9, 11, 2, 14	not searched	
530	317, 322		
530	344		
435	886		

INTERFERENCE SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES (INCLUDING SEARCH STRATEGY)		
	DATE	EXMR
EAST Search on USPAT, USPGPUB, DERWENT, EPO, JPO; STN search on MEDLINE, BIOSIS, EMBASE, SCISEARCH, AGRICOLA.	2/13/2008	CMK
Search strategy enclosed, Inventor name search, Parent applications 60/177,170 and 09/735,191, 10/747,48 have been reviewed.	2/13/2008	CMK

EAST Search History

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	533	daptomycin	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2008/02/13 17:37
L2	45422	substantially adj pure	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2008/02/13 17:37
L3	12220	essentially adj pure	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2008/02/13 17:37
L4	7	L1 same (L2 or L3)	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2008/02/13 17:37
L5	8	impurities same L1	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2008/02/13 17:43
L6	8	anhydro-daptomycin or beta-daptomycin	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2008/02/13 17:44
L7	43363	anion adj exchange	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2008/02/13 17:45
L8	10299	hydrophobic adj interaction adj chromatography	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2008/02/13 17:45
L9	5	L1 same L7 same L8	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2008/02/13 17:45
L10	17	Ly adj "146032"	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2008/02/13 17:45
L11	90	(Ly adj "146032") or A-21978C or A54145 or A-21978	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2008/02/13 17:45

EAST Search History

L12	2	(L10 or L11) same (L2 or L3)	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2008/02/13 17:45
L13	19	kelleher adj thomas.in.	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2008/02/13 17:47
L14	7	lai adj jan-ji.in.	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2008/02/13 17:47
L15	3	decourcey adj joseph.in.	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2008/02/13 17:47
L16	27	lynch adj paul.in.	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2008/02/13 17:47
L17	61	zenoni adj maurizio.in.	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2008/02/13 17:47
L18	5	tagliani adj auro.in.	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2008/02/13 17:47
L19	105	L13 or L14 or L15 or L16 or L17 or L18	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2008/02/13 17:47
L20	5	L19 and L1	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2008/02/13 17:47

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L2 2628 S SUBSTANTIALLY PURE
L3 2122 S ESSENTIALLY PURE
L4 0 S L1 (P) (L2 OR L3)
L5 2 S L1 (P) IMPURITIES
L6 2 DUPLICATE REMOVE L5 (0 DUPLICATES REMOVED)
L7 4 S ANHYDRO-DAPTOMYCIN OR BETA-DAPTOMYCIN
L8 4 DUPLICATE REMOVE L7 (0 DUPLICATES REMOVED)
L9 4 S L8 NOT L6
L10 99387 S ANION EXCHANGE
L11 9215 S HYDROPHOBIC INTERACTION CHROMATOGRAPHY
L12 2 S L1 (P) L10 (P) L11
L13 1 S L12 NOT (L5 OR L7)
L14 264 S LY (W) 146032
L15 8 S A-21978C IR A54145 OR A-21978
L16 1 S (L14 OR L15) (P) (L2 OR L3)
L17 1 S L16 NOT (L13 OR L5 OR L7)
L18 183 S KELLEHER T?/AU
L19 8860 S LAI J?/AU
L20 8 S DECOURCEY J?/AU
L21 3274 S LYNCH P?/AU
L22 107 S TAGLIANI A?/AU
L23 12424 S L18 OR L19 OR L20 OR L21 OR L22
L24 20 S L23 AND L1
L25 8 DUPLICATE REMOVE L24 (12 DUPLICATES REMOVED)
L26 6 S L25 NOT (L13 OR L5 OR L7 OR L17)

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APPLICATION NUMBER	FILING OR 371(c) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
11/739,180	04/24/2007	Thomas Kelleher	C062-02/03 US

CONFIRMATION NO. 8837

34103
CUBIST PHARMACEUTICALS, INC.
65 HAYDEN AVENUE
LEXINGTON, MA02421

Title: High Purity Lipopeptides

Publication No. US-2007-0191280-A1
Publication Date: 08/16/2007

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Application Number:	11739180
International Application Number:	
Confirmation Number:	8837
Title of Invention:	High Purity Lipopeptides
First Named Inventor/Applicant Name:	Thomas Kelleher
Customer Number:	34103
Filer:	Jill Michel-Netka Mandelblatt/Viana Daly
Filer Authorized By:	Jill Michel-Netka Mandelblatt
Attorney Docket Number:	C062-02/03 US
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Filing Date:	24-APR-2007
Time Stamp:	16:18:22
Application Type:	Utility under 35 USC 111(a)

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appl. No.	:	11/739,180	Confirmation No.	8837
Applicant	:	Thomas J. Kelleher		
Filed	:	April 24, 2007		
TC/A.U.	:	1656		
Examiner	:	Chih Min Kam		
Docket No.	:	C062-02/03 US		
Customer No.	:	34103		

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INFORMATION DISCLOSURE STATEMENT
TRANSMITTAL OF FORM PTO-1449 UNDER 37 C.F.R. §§1.97 AND 1.98

Pursuant to 37 C.F.R. §§1.97 and 1.98, the references listed on the attached PTO Form PTO/SB/08a/b(s) are cited for consideration by the Examiner.

Check applicable box(es):

☒ Copies of non-US patent document references cited on the attached form are:

☐ Enclosed.

☒ Not enclosed because the references were cited in the parent application, US Serial No. 09/735,191 filed November 28, 2000 (now US Patent No. 6,696,412 dated February 2, 2004) of which the present application is a divisional and/or were cited in the first divisional application, US Serial No. 10/747,485, filed on December 29, 2003, which is the divisional of the same parent application, US Serial No. 09/735,191. Copies of any of the

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Signer Name _____ Signature Date _____

cited references will be gladly furnished upon request.

United States Patent 5,912,226 reissued as patent No. RE 39,071 on April 19, 2006. A change in assignment of RE 39,071 to Cubist Pharmaceuticals, Inc. was made on April 23, 2007.

☒ No fees are believed due for this submission because:

☒ An Office Action has not yet been received.

☐ The application was filed less than 3 months ago.

☐ The reference(s) was (were) cited in a foreign search report not more than three months before the filing of this statement and was (were) not previously known by Applicant(s).

If any fees are deemed necessary, the Commissioner is authorized to charge Deposit Account No. 50-1986 referencing attorney docket number C062-02/03 US.

Respectfully submitted,

Dated: August 14, 2007

/Jill M.N. Mandelblatt/
Timothy J. Douros, Reg. No. 41,716
William D. DeVaul, Reg. No. 42,483
Attorneys for Assignee
Jill M.N. Mandelblatt, Reg. No. 37,878
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Fax: (781) 860-1407

C062-02-03 20070801 IDS letter

PTO/SB/08a (05-07)
Approved for use through 09/30/2007. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	11739180
	Filing Date	2007-04-24
	First Named Inventor	Kelleher, Thomas J.
	Art Unit	1656
	Examiner Name	Chih Min Kam
	Attorney Docket Number	C062-02/03 US

U.S.PATENTS						
Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	4482487		1984-11-13	Abbott et al.	
	2	4524135		1985-06-18	Abbott et al.	
	3	4537717		1985-08-27	Abbott et al.	
	4	4800157		1989-01-24	Eaton et al.	
	5	4874843		1989-10-17	Baker	
	6	4331594		1982-05-25	Hamill et al.	
	7	4882164		1989-11-21	Ferro et al.	
	8	4885243		1989-12-05	Huber et al.	

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	9	5271935		1993-12-21	Franco et al.	
	10	5387670		1995-02-07	Roy et al.	
	11	5573936		1996-11-12	Kreuzman et al.	
	12	5629288		1997-05-13	Lattrell et al.	
	13	5912226		1999-06-15	Baker et al.	
	14	5955509		1999-09-21	Webber et al.	
	15	6194383		2001-02-27	Hammann et al.	
	16	RE32310		1986-12-16	Debono	
	17	RE32311		1986-12-16	Debono	
	18	RE32333		1987-01-20	Hamill et al.	
	19	RE32455		1987-07-07	Hamill et al.	

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	20	RE39071		2006-04-19	Baker et al.	

If you wish to add additional U.S. Patent citation information please click the Add button.

U.S.PATENT APPLICATION PUBLICATIONS

Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1					

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FOREIGN PATENT DOCUMENTS

Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] i	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1	EP 0095295 A1	EP		1983-11-30	Eli Lilly Co		☐
	2	EP 0178152 A2	EP		1986-04-16	Eli Lilly Co		☐
	3	EP 0294990 A2	EP		1988-12-14	Eli Lilly Co		☐
	4	EP 0337731 B1	EP		1989-10-18	Eli Lilly Co		☐
	5	EP 0386951 A2	EP		1990-09-12	Eli Lilly Co		☐

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	Examiner Name	Chih Min Kam
	Attorney Docket Number	C062-02/03 US

	6	EP 0629636 A1	EP		1994-12-21	HOECHST AG		☐
	7	DE19807972 A1	DE		1999-08-26	HOECHST MARION ROUSSEL DE GMBH		☐
	8	WO 00/18419	WO		2000-04-06	Cubist Pharmaceuticals, Inc.		☐
	9	WO 01/44271	WO		2001-06-21	Cubist Pharmaceuticals, Inc.		☐
	10	WO 01/44272	WO		2001-06-21	Cubist Pharmaceuticals, Inc.		☐
	11	WO 01/44274	WO		2001-06-21	Cubist Pharmaceuticals, Inc.		☐
	12	WO 99/27954	WO		1999-06-10	INST NAT SANTE RECH MED (FR); CENTRE NAT RECH SCIE		☐
	13	WO 99/27957	WO		1999-06-10	IMMUNE RESPONSE CORP INC		☐
	14	WO 99/43700	WO		1999-09-02	HOECHST MARION ROUSSEL DE GMBH		☐
	15							☐

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NON-PATENT LITERATURE DOCUMENTS

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	11739180
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	Art Unit	1656
	Examiner Name	Chih Min Kam
	Attorney Docket Number	C062-02/03 US

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T5
	1	DEBONO, M. et al.; "Enzymatic and Chemical Modifications of Lipopeptide Antibiotic A21978C: The Synthesis and Evaluation of Daptomycin (LY146032)," J. Antibiotics; 41; 1988; pages 1093-1105	☐
	2	DESAI, J. D., et al.; "Microbial Production of Surfactants and Their Commercial Potential," Microbiology and Molecular Biology Review; Volume 61; Number 1; 1997; pages 47-64; American Society for Microbiology;	☐
	3	FOSTEL, Jennifer M., et al.; "Emerging Novel Antifungal Agents," DDT; Volume 5; Number 1; January 2000; pages 25-32; Elsevier Science Ltd.	☐
	4	HOROWITZ, Sarah, et al; "Isolation and Characterization of a Surfactant Produced by Bacillus Licheniformis 86," J. Industrial Microbiol.; 6; 1990; pages 243-248; Society for Industrial Microbiology;	☐
	5	KIRSCH, Lee E., et al.; "Kinetics of the Aspartyl Transporation of Daptomycin, a Novel Lipopeptide Antibiotic," Pharmaceutical Research; Volume 6; Number 5; 1989; pages 387-393; Plenum Publishing Corporation	☐
	6	LASIC, Dan D., et al.; "Novel Applications of Liposomes," Trends Biotechnology; Volume 16; July 1998; pages 307-321; Elsevier Science Ltd.	☐
	7	LASIC, Danilo D., et al.; "Mixed Micelles in Drug Delivery," Nature; Volume 355; Issue No. 6357; January 16, 1992; pages 279-280	☐
	8	LIN, S.-C. et al., "General Approach for the Development of High-Performance Liquid Chromatography Methods for Biosurfactant Analysis and Purification," J. Chromatography; 825; 1998; pages 149-159	☐
	9	LIN, S.-C. et al.; "Recovery and Purification of the Lipopeptide Biosurfactant of Bacillus Subtillis by Ultrafiltration," Biotechology Techniques; Volume 11; Number 6; June 1997; pages 413-416; Chapman Hall.	☐
	10	MULLIGAN, Catherine N., et al., "Recovery of Biosurfactants by Ultrafiltration," J. Chem. Tech. Biotechnology.; 47; 1990; pages 23-29; Society of Chemical Industry; Printed in Great Britian	☐

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	11	SCHOTT, H.; "Colloidal Dispersions," Remington: The Science and Practice of Pharmacy; Volume 1; 19th Edition; 1995; pages 252-277; Mack Publishing Company; Easton, Pennsylvania USA	☐
	12	SHAW, Duncan J.; "Liquid-Gas and Liquid-Liquid Interfaces," Introduction to Colloid and Surface Chemistry; 1989; pages 64-114; 4th Edition; Butterworth-Heinemann Ltd. Great Britian	☐
	13	STERLING, John; "Membrane-Based System Combines Selective Separation with High-Volume Throughput," Genetic Engineering News; Volume 19; Number 20; November 15, 1999; pages 1, 34	☐
	14	SUPERSAXO, Andreas et al.; "Mixed Micelles as Proliposomal, Lymphotropic Drug Carrier," Pharmaceutical Research; Volume 8; Number 10; 1991; pages 1286-1291; Plenum Publishing Corporation	☐
	15	SWEADNER, Kathleen J. et al., "Filter Removal of Endotoxin (Pyrogens) in Solution in Different States of Aggregation," Applied and Environmental Microbiology; Volume 34; Number 4; 1977; pages 382-385; American Society for Microbiology; Printed in the USA	☐
	16	TALLY, F.P., et al.; "Daptomycin: A Novel Agent for Gram Positive Infections," Exp. Opinion Invest. Drugs; 8; 1999; 1223-1238.	☐
	17	THIMON, L. et al., "Surface-Active Properties of Antifungal Lipopeptides Produced by Bacillus Substillis," J. Am. Oil Chem. Soc.; 69; 1992; pages 92-93	☐
	18	YAKIMOV, Michail M. et al.; "Characterization of a New Lipopeptide Surfactant Produced by Thermotolerant and Halotolerant Subsurface Bacillus Licheniformis BAS50," Applied and Environmental Microbiology; Volume 61; Number 5; 1995; pages 1706-1713; American Society for Microbiology;	☐

If you wish to add additional non-patent literature document citation information please click the Add button

EXAMINER SIGNATURE

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

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	Art Unit	1656
	Examiner Name	Chih Min Kam
	Attorney Docket Number	C062-02/03 US

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☒ See attached certification statement.

☐ Fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☐ None

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Jill M.N. Mandelblatt/	Date (YYYY-MM-DD)	2007-08-14
Name/Print	Jill M.N. Mandelblatt	Registration Number	37,878

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these record s.

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3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

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6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

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APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
11/739,180	04/24/2007	1646	1250	C062-02/03 US	53	1

CONFIRMATION NO. 8837

34103
CUBIST PHARMACEUTICALS, INC.
65 HAYDEN AVENUE
LEXINGTON, MA02421

FILING RECEIPT

Date Mailed: 05/08/2007

Receipt is acknowledged of this regular Patent Application. It will be considered in its order and you will be notified as to the results of the examination. Be sure to provide the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION when inquiring about this application. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please mail to the Commissioner for Patents P.O. Box 1450 Alexandria Va 22313-1450. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections (if appropriate).**

Applicant(s)

Thomas Kelleher, Weston, MA;
Jan-Ji Lai, Westborough, MA;
Joseph P. DeCourcey, Charlestown, MA;
Paul Lynch, Arlington, MA;
Maurizio Zenoni, Milan, ITALY;
Auro Tagliani, Pavia, ITALY;

Power of Attorney: None

Domestic Priority data as claimed by applicant

This application is a CON of 10/747,485 12/29/2003

Foreign Applications

If Required, Foreign Filing License Granted: 05/08/2007

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US11/739,180**

Projected Publication Date: 08/16/2007

Non-Publication Request: No

Early Publication Request: No

** SMALL ENTITY **

Title

High Purity Lipopeptides

Preliminary Class

514

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Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

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Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4158).

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PTO/SB/05 (04-07)
Approved for use through 04/30/2007. OMB 0651-0032
U.S. Patent and Trademark Office. U.S. DEPARTMENT OF COMMERCE

UTILITY PATENT APPLICATION TRANSMITTAL

(Only for new nonprovisional applications under 37 CFR 1.53(b))

Attorney Docket No.	C062-02/03 US
First Inventor	Thomas Kelleher
Title	High Purity Lipopeptides
Express Mail Label No.	

APPLICATION ELEMENTS

See MPEP chapter 600 concerning utility patent application contents.

1. [X] **Fee Transmittal Form** (e.g., PTO/SB/17)
   (Submit an original and a duplicate for fee processing)
2. [X] **Applicant claims small entity status.** See 37 CFR 1.27.
3. [X] **Specification** [*Total Pages* 71]
   Both the claims and abstract must start on a new page
   (For information on the preferred arrangement, see MPEP 608.01(a))
4. [X] **Drawing(s)** (*35 U.S.C. 113*) [*Total Sheets* 11]
5. **Oath or Declaration** [*Total Sheets* 7]
   a. [ ] Newly executed (original or copy)
   b. [X] A copy from a prior application (37 CFR 1.63(d))
   (for continuation/divisional with Box 18 completed)
   i. [ ] DELETION OF INVENTOR(S)
   Signed statement attached deleting inventor(s) name in the prior application, see 37 CFR 1.63(d)(2) and 1.33(b).
6. [ ] **Application Data Sheet.** See 37 CFR 1.76
7. [ ] **CD-ROM or CD-R** in duplicate, large table or Computer Program *(Appendix)*
   [ ] Landscape Table on CD
8. **Nucleotide and/or Amino Acid Sequence Submission**
   (if applicable, items a. – c. are required)
   a. [ ] Computer Readable Form (CRF)
   b. Specification Sequence Listing on:
      i. [ ] CD-ROM or CD-R (2 copies); or
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   c. [ ] Statements verifying identity of above copies

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ACCOMPANYING APPLICATION PARTS

9. [ ] **Assignment Papers** (cover sheet (PTO-1595) & document(s))
   Name of Assignee _____
10. [ ] **37 CFR 3.73(b) Statement** *(when there is an assignee)* [ ] **Power of Attorney**
11. [ ] **English Translation Document** *(if applicable)*
12. [ ] **Information Disclosure Statement** (PTO/SB/08 or PTO-1449)
    [ ] Copies of foreign patent documents, publications, & other information
13. [ ] **Preliminary Amendment**
14. [ ] **Return Receipt Postcard** (MPEP 503)
    (*Should be specifically itemized*)
15. [ ] **Certified Copy of Priority Document(s)**
    (if foreign priority is claimed)
16. [ ] **Nonpublication Request** under 35 U.S.C. 122(b)(2)(B)(i). Applicant must attach form PTO/SB/35 or equivalent.
17. [ ] Other: _____

18. If a CONTINUING APPLICATION, *check appropriate box, and supply the requisite information below and in the first sentence of the specification following the title, or in an Application Data Sheet under 37 CFR 1.76:*

[X] Continuation [ ] Divisional [ ] Continuation-in-part (CIP) of prior application No.: 10/747,485

Prior application information: *Examiner* Chih Min Kam *Art Unit:* 1656

19. CORRESPONDENCE ADDRESS

[X] The address associated with Customer Number: 34103 ***OR*** [ ] Correspondence address below

Name					
Address					
City		State		Zip Code	
Country		Telephone		Email	

Signature	/Jill M.N. Mandelblatt/	Date	April 24, 2007
Name (Print/Type)	Jill M. Mandelblatt	Registration No. (Attorney/Agent)	37,878

PTO/SB/17 (04-07)
Approved for use through 04/30/2007. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Effective on 12/08/2004.
Fees pursuant to the Consolidated Appropriations Act, 2005 (H.R. 4818).

FEE TRANSMITTAL
For FY 2007

☒ Applicant claims small entity status. See 37 CFR 1.27

TOTAL AMOUNT OF PAYMENT ($) 1,325.00

Complete if Known	
Application Number	
Filing Date	April 24, 2007
First Named Inventor	Thomas Kelleher
Examiner Name	
Art Unit	
Attorney Docket No.	C062-02/03 US

METHOD OF PAYMENT (check all that apply)

☐ Check ☐ Credit Card ☐ Money Order ☐ None ☐ Other (please identify): _____

☒ Deposit Account Deposit Account Number: 50-1986 Deposit Account Name: Cubist Pharmaceuticals, Inc.

For the above-identified deposit account, the Director is hereby authorized to: (check all that apply)

☒ Charge fee(s) indicated below ☐ Charge fee(s) indicated below, **except for the filing fee**

☒ Charge any additional fee(s) or underpayments of fee(s) under 37 CFR 1.16 and 1.17 ☒ Credit any overpayments

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FEE CALCULATION

1. BASIC FILING, SEARCH, AND EXAMINATION FEES

	FILING FEES		SEARCH FEES		EXAMINATION FEES		
		Small Entity		Small Entity		Small Entity	
Application Type	Fee ($)	Fee ($)	Fee ($)	Fee ($)	Fee ($)	Fee ($)	Fees Paid ($)
Utility	300	150	500	250	200	100	500.00
Design	200	100	100	50	130	65	
Plant	200	100	300	150	160	80	
Reissue	300	150	500	250	600	300	
Provisional	200	100	0	0	0	0	

2. EXCESS CLAIM FEES

Fee Description	Fee ($)	Small Entity Fee ($)
Each claim over 20 (including Reissues)	50	25
Each independent claim over 3 (including Reissues)	200	100
Multiple dependent claims	360	180

Total Claims		Extra Claims		Fee ($)		Fee Paid ($)
53	- 20 or HP =	33	x	25.00	=	825.00

HP = highest number of total claims paid for, if greater than 20.

Indep. Claims		Extra Claims		Fee ($)		Fee Paid ($)
1	- 3 or HP =	-2	x		=	0.00

HP = highest number of independent claims paid for, if greater than 3.

Multiple Dependent Claims	
Fee ($)	Fee Paid ($)

3. APPLICATION SIZE FEE

If the specification and drawings exceed 100 sheets of paper (excluding electronically filed sequence or computer listings under 37 CFR 1.52(e)), the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).

Total Sheets		Extra Sheets		Number of each additional 50 or fraction thereof		Fee ($)		Fee Paid ($)
82	- 100 =	-18	/ 50 =		(round up to a whole number) x	125.00	=	0.00

4. OTHER FEE(S)

	Fees Paid ($)
Non-English Specification, $130 fee (no small entity discount)	
Other (e.g., late filing surcharge):	

SUBMITTED BY

Signature	/Jill M.N. Mandelblatt/	Registration No. (Attorney/Agent)	37,878	Telephone	781-860-8660
Name (Print/Type)	Jill M.N. Mandelblatt			Date	April 24, 2007

PTO/SB/05 (04-07)
Approved for use through 04/30/2007. OMB 0651-0032
U.S. Patent and Trademark Office. U.S. DEPARTMENT OF COMMERCE

UTILITY PATENT APPLICATION TRANSMITTAL

(Only for new nonprovisional applications under 37 CFR 1.53(b))

Attorney Docket No.	C062-02/03 US
First Inventor	Thomas Kelleher
Title	High Purity Lipopeptides
Express Mail Label No.	

APPLICATION ELEMENTS

See MPEP chapter 600 concerning utility patent application contents.

1. [X] **Fee Transmittal Form** (e.g., PTO/SB/17)
   (Submit an original and a duplicate for fee processing)
2. [X] **Applicant claims small entity status.** See 37 CFR 1.27.
3. [X] **Specification** [*Total Pages* 71]
   Both the claims and abstract must start on a new page
   (For information on the preferred arrangement, see MPEP 608.01(a))
4. [X] **Drawing(s)** (*35 U.S.C. 113*) [*Total Sheets* 11]
5. **Oath or Declaration** [*Total Sheets* 7]
   a. [ ] Newly executed (original or copy)
   b. [X] A copy from a prior application (37 CFR 1.63(d))
   (for continuation/divisional with Box 18 completed)
   i. [ ] DELETION OF INVENTOR(S)
   Signed statement attached deleting inventor(s) name in the prior application, see 37 CFR 1.63(d)(2) and 1.33(b).
6. [ ] **Application Data Sheet.** See 37 CFR 1.76
7. [ ] **CD-ROM or CD-R** in duplicate, large table or Computer Program *(Appendix)*
   [ ] Landscape Table on CD
8. **Nucleotide and/or Amino Acid Sequence Submission**
   (if applicable, items a. – c. are required)
   a. [ ] Computer Readable Form (CRF)
   b. Specification Sequence Listing on:
      i. [ ] CD-ROM or CD-R (2 copies); or
      ii. [ ] Paper
   c. [ ] Statements verifying identity of above copies

ADDRESS TO: **Commissioner for Patents**
P.O. Box 1450
Alexandria VA 22313-1450

ACCOMPANYING APPLICATION PARTS

9. [ ] **Assignment Papers** (cover sheet (PTO-1595) & document(s))
   Name of Assignee _____
10. [ ] **37 CFR 3.73(b) Statement** *(when there is an assignee)* [ ] **Power of Attorney**
11. [ ] **English Translation Document** *(if applicable)*
12. [ ] **Information Disclosure Statement** (PTO/SB/08 or PTO-1449)
    [ ] Copies of foreign patent documents, publications, & other information
13. [ ] **Preliminary Amendment**
14. [ ] **Return Receipt Postcard** (MPEP 503)
    (*Should be specifically itemized*)
15. [ ] **Certified Copy of Priority Document(s)**
    (if foreign priority is claimed)
16. [ ] **Nonpublication Request** under 35 U.S.C. 122(b)(2)(B)(i). Applicant must attach form PTO/SB/35 or equivalent.
17. [ ] Other: _____

18. If a CONTINUING APPLICATION, *check appropriate box, and supply the requisite information below and in the first sentence of the specification following the title, or in an Application Data Sheet under 37 CFR 1.76:*

[X] Continuation [ ] Divisional [ ] Continuation-in-part (CIP) of prior application No.: 10/747,485

Prior application information: *Examiner* Chih Min Kam *Art Unit:* 1656

19. CORRESPONDENCE ADDRESS

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Name (Print/Type)	Jill M. Mandelblatt	Registration No. (Attorney/Agent)	37,878

PTO/SB/17 (04-07)
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Examiner Name	
Art Unit	
Attorney Docket No.	C062-02/03 US

METHOD OF PAYMENT (check all that apply)

☐ Check ☐ Credit Card ☐ Money Order ☐ None ☐ Other (please identify): _____

☒ Deposit Account Deposit Account Number: 50-1986 Deposit Account Name: Cubist Pharmaceuticals, Inc.

For the above-identified deposit account, the Director is hereby authorized to: (check all that apply)

☒ Charge fee(s) indicated below ☐ Charge fee(s) indicated below, **except for the filing fee**

☒ Charge any additional fee(s) or underpayments of fee(s) under 37 CFR 1.16 and 1.17 ☒ Credit any overpayments

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

FEE CALCULATION

1. BASIC FILING, SEARCH, AND EXAMINATION FEES

	FILING FEES		SEARCH FEES		EXAMINATION FEES		
		Small Entity		Small Entity		Small Entity	
Application Type	Fee ($)	Fee ($)	Fee ($)	Fee ($)	Fee ($)	Fee ($)	Fees Paid ($)
Utility	300	150	500	250	200	100	500.00
Design	200	100	100	50	130	65	
Plant	200	100	300	150	160	80	
Reissue	300	150	500	250	600	300	
Provisional	200	100	0	0	0	0	

2. EXCESS CLAIM FEES

Fee Description	Fee ($)	Small Entity Fee ($)
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Each independent claim over 3 (including Reissues)	200	100
Multiple dependent claims	360	180

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53	- 20 or HP =	33	x 25.00	=	825.00

HP = highest number of total claims paid for, if greater than 20.

Indep. Claims		Extra Claims	Fee ($)		Fee Paid ($)
1	- 3 or HP =	-2	x	=	0.00

HP = highest number of independent claims paid for, if greater than 3.

Multiple Dependent Claims	
Fee ($)	Fee Paid ($)

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Total Sheets		Extra Sheets		Number of each additional 50 or fraction thereof	Fee ($)		Fee Paid ($)
82	- 100 =	-18	/ 50 =	_____ (round up to a whole number)	x 125.00	=	0.00

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	Fees Paid ($)
Non-English Specification, $130 fee (no small entity discount)	
Other (e.g., late filing surcharge): _____	

SUBMITTED BY

Signature	/Jill M.N. Mandelblatt/	Registration No. (Attorney/Agent)	37,878	Telephone	781-860-8660
Name (Print/Type)	Jill M.N. Mandelblatt			Date	April 24, 2007

HIGH PURITY LIPOPEPTIDES

CROSS-REFERENCE TO RELATED APPLICATIONS

The present application claims priority to United States Patent Application No. 10/747,485 which claims priority to United States Patent No. 09/735,191 filed January 20, 2001, which claims the benefit of United States Provisional application No. 60/177,170, filed January 20, 2000, all of which are incorporated by reference herein in their entireties.

TECHNICAL FIELD OF THE INVENTION

The present invention relates to a highly purified form of lipopeptides, including daptomycin, a lipopeptide antibiotic with potent bactericidal activity against gram-positive bacteria, including strains that are resistant to conventional antibiotics. The present invention also relates to a process for preparing the highly purified form of the lipopeptide. The present invention further relates to micelles of lipopeptides. The present invention also relates to pharmaceutical compositions of the lipopeptide micelles and methods of using these compositions. The present invention also relates to methods of making lipopeptide micelles from non-associated monomers of the lipopeptides, and for converting lipopeptide micelles to non-associated monomers. The present invention also relates to a process for preparing lipopeptides using micelles that is easily scaled for commercial production.

BACKGROUND OF THE INVENTION

The rapid increase in the incidence of gram-positive infections—including those caused by antibiotic resistant bacteria—has sparked renewed interest in the development of novel classes of antibiotics. One such class is the lipopeptide antibiotics, which includes daptomycin. Daptomycin has potent bactericidal activity *in vitro* against clinically relevant gram-positive bacteria that cause serious and life-threatening diseases. These bacteria include resistant pathogens, such as vancomycin-resistant enterococci

(VRE), methicillin-resistant *Staphylococcus aureus* (MRSA), glycopeptide intermediary susceptible *Staphylococcus aureus* (GISA), coagulase-negative staphylococci (CNS), and penicillin-resistant *Streptococcus pneumoniae* (PRSP), for which there are very few therapeutic alternatives. See, *e.g.*, Tally et al., 1999, Exp. Opin. Invest. Drugs 8:1223-1238, hereafter "Tally". Daptomycin's inhibitory effect is a rapid, concentration-dependent bactericidal effect *in vitro* and *in vivo*, and a relatively prolonged concentration-dependent post-antibiotic effect *in vivo*.

Daptomycin is described by Baltz in Biotechnology of Antibiotics, 2nd Ed., ed. W.R. Strohl (New York: Marcel Dekker, Inc.), 1997, pp. 415-435, hereafter "Baltz." Daptomycin, also known as LY 146032, is a cyclic lipopeptide antibiotic that can be derived from the fermentation of *Streptomyces roseosporus*. Daptomycin is a member of the factor A-21978C_0 type antibiotics of *S. roseosporus* and is comprised of a decanoyl side chain linked to the N-terminal tryptophan of a cyclic 13–amino acid peptide (Fig. 1). Daptomycin has an excellent profile of activity because it is highly effective against most gram-positive bacteria; it is highly bactericidal and fast-acting; it has a low resistance rate and is effective against antibiotic-resistant organisms. The compound is currently being developed in a variety of formulations to treat serious infections caused by bacteria, including, but not limited to, methicillin resistant *Staphylococcus aureus* (MRSA) and vancomycin resistant enterococci (VRE).

A number of United States Patents describe A-21978C antibiotics and derivatives thereof including daptomycin (LY 146032) as well as methods of producing and isolating the A-21978C antibiotics and derivatives thereof.

United States Patent Re. 32,333, Re. 32,455 and 4,800,157 describe a method of synthesizing daptomycin by cultivating *Streptomyces roseosporus* NRL15998 under submerged aerobic fermentation conditions. United States Patent 4,885,243 describes an improved method of synthesizing daptomycin by feeding a fermentation culture a decanoic fatty acid or ester or salt thereof.

United States Patents Re. 32,310, Re. 32,311, 4,537,717, 4,482,487 and 4,524,135 describe methods of deacylating the A-21978C antibiotic and reacylating the

peptide nucleus and antibiotic derivatives made by this process. All of these patents describe a purified deacylated A-21978C antibiotic nucleus or a derivative thereof which was isolated from the fermentation broth by filtration and then purified by Diaion HP-20 chromatography and silica gel/C18 chromatography.

United States Patents Re. 32,333 and Re. 32,455 disclose a purification method in which a filtrate of whole fermentation broth was purified through a number of precipitation and extraction steps to obtain a crude A-21978C complex. The crude complex was further purified by ion exchange chromatography on IRA-68 and two rounds of silica gel chromatography. Individual A-21978C factors were separated by reverse-phase silica gel or silica gel/C18. United States Patents Re. 32,333 and Re. 32,455 also disclose that A-21978C may be purified by batch chromatography using Diaion HP-20 resin followed by silica-gel column chromatography.

United States Patent 4,874,843 describes a daptomycin purification method in which the fermentation broth was filtered and passed through a column containing HP-20 resin. After elution, the semipurified daptomycin was passed through a column containing HP-20ss, and then separated again on HP-20 resin. The '843 patent states that final resolution and separation of daptomycin from structurally similar compounds by this method is impeded by the presence of impurities that are not identifiable by ultraviolet analysis of the fermentation broth. The '843 patent further states that attempts to remove these impurities by reverse phase chromatography over silica gel, normal phase chromatography over silica gel or ion exchange chromatography also failed to significantly improve the purity of daptomycin. The '843 patent also discloses a "reverse method" for purification comprising the steps of contacting an aqueous solution of the fermentation product with a non-functional resin in aqueous phase, physically removing the water from the charged resin, rewetting the charged resin with a polar organic solvent, washing the resin with the organic solvent, eluting the fermentation product from the resin by increasing the polarity of the solvent and recovering the fermentation product. The '843 patent teaches that this method improves the final purity from about 80% to about 93% and increases the yield from about 5% to

about 35%; however, the '843 patent does not disclose the type of impurities present in the daptomycin preparation.

United States Patent 5,912,226 describes the identification and isolation of two impurities produced during the manufacture of daptomycin. Daptomycin, an α-aspartyl peptide, becomes transpeptidated to form a stable intermediate in which the aspartyl group becomes an anhydro-succinimido group (Fig. 3). The '226 patent teaches that the presence of this intermediate, designated anhydro-daptomycin, is more pronounced at pH 4-6. Rehydration of the anhydro-succinimido form produces a second degradation product that contains an β-aspartyl group and is designated the β-isomer form of daptomycin (Fig. 2).

The '226 patent discloses that the t-BOC derivative of anhydro-daptomycin may be isolated by chromatography over reverse phase silica gel/C-18 column, precipitated, and repurified by reverse phase silica gel/C-18 chromatography. The '226 patent also teaches that the β-isomer form of daptomycin may be purified by chromatography over a Diaion HP-20ss resin, desalted by chromatography over a Diaion HP-20 resin, and further purified using a reverse-phase C-18 column followed by a HP-20 resin column in reverse mode.

Kirsch et. al. (Pharmaceutical Research, 6:387-393, 1989, hereafter "Kirsch") stated that anhydro-daptomycin and the β-isomer were produced in the purification of daptomycin. Kirsch described methods to minimize the levels of anhydro-daptomycin and the β-isomer through manipulation of pH conditions and temperature conditions. However, Kirsch was unable to stabilize daptomycin and prevent the conversion of daptomycin to anhydro-daptomycin and its subsequent isomerization to β-isomer. Kirsch was also unable to prevent the degradation of daptomycin into other degradation products unrelated to anhydro-daptomycin and β-isomer.

The '226 patent states that daptomycin may be prepared using these procedures so that the daptomycin contains no more than 2.5% by weight of a combined total of anhydro-daptomycin and β-isomer, but gives no indication of the levels of other impurities. In the method taught in United States Patent 4,874,843 and in large-scale

preparations of daptomycin for clinical trials, the highest daptomycin purity levels observed has been about 90%-93%. There is a need for a commercially feasible method to produce more highly purified daptomycin and, if possible, to increase its yield after purification. Furthermore, it would be desirable to obtain purified daptomycin that contains little or none of anhydro-daptomycin and the β-isomer form of daptomycin. It would also be desirable to reduce the levels of a number of other impurities in daptomycin. However, there has been no method available in the art that has been shown to be able to further reduce the levels of anhydro-daptomycin, β-isomer form and other impurities in the daptomycin product.

SUMMARY OF THE INVENTION

The instant invention addresses these problems by providing commercially feasible methods to produce high levels of purified lipopeptides. In a preferred embodiment, the lipopeptide is daptomycin or a daptomycin-related lipopeptide. In one embodiment of the instant invention, commercially feasible methods are disclosed that results in daptomycin at a purity level of 95-97%. In another embodiment of the instant invention, a commercially feasible method is disclosed that almost completely eliminates the major impurities anhydro-daptomycin and β-isomer as well as other impurities in preparations of daptomycin. In another embodiment of the invention, commercially feasible methods are disclosed for purifying lipopeptides, including daptomycin or a daptomycin-related lipopeptide, comprising separating lipopeptide micelles from low molecular weight contaminants and separating non-associated lipopeptides from high molecular weight contaminants. The invention also provides high performance liquid chromatography (HPLC) methods of analyzing the purity of daptomycin and detecting and characterizing other impurities in daptomycin, some of which were previously unknown.

The invention also provides purified daptomycin that possesses a purity of at least 98% or that is substantially or essentially free of anhydro-daptomycin and β-isomer. The invention provides purified daptomycin that is free or essentially free of

anhydro-daptomycin and contains a much lower level of the β-isomer and of other contaminants than was previously possible to obtain in the prior art. The invention also provides lipopeptide micelles. In a preferred embodiment, the micelle comprises daptomycin or a daptomycin-related lipopeptide. The invention also provides pharmaceutical compositions comprising highly purified daptomycin or a daptomycin-related lipopeptide micelles and methods of using these compositions.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 shows the structure of daptomycin.

Fig. 2 shows the structure of impurity 8, CB-131010 (previously identified as the β-isomer, LY213846).

Fig. 3 shows the structure of impurity 13, CB-130952 (previously identified as anhydro-daptomycin, LY178480).

Fig. 4 shows the proposed structure of impurity 1, CB-131012 (previously identified as LY212218).

Fig. 5 shows the proposed structure of impurity 2, CB-131011.

Fig. 6 shows the proposed structure of impurity 3, CB-131008 (previously identified as LY213928).

Fig. 7 shows the proposed structure of impurity 4, CB-131006.

Fig. 8 shows the proposed structure of impurity 6, CB-130989 (previously identified as LY213827).

Fig. 9 shows the proposed structure of impurity 7, CB-131005.

Fig. 10 shows the proposed structure of impurity 12, CB-131009.

Fig. 11 shows the proposed structure of impurity 14, CB-131078 (previously identified as LY109208).

Fig. 12 shows an HPLC chromatogram for a bulk preparation of daptomycin, including impurities 1 to 14.

Fig. 13 shows an HPLC chromatogram for a preparation of daptomycin after purification on a Poros P150 resin.

Figs. 14A-14C show micellar structures. Fig. 14A shows a spherical micelle, in which the hydrophobic tails of amphipathic molecules are oriented toward the center of the sphere while the hydrophilic heads of the amphipathic molecules are oriented towards the outside of the sphere, in contact with the aqueous environment. Fig. 14A shows an example in which the hydrophilic heads are negatively charged. Fig. 14B shows a lipid bilayer structure in which two layers of amphipathic molecules assemble such that the hydrophobic tails of each layer are oriented towards each other while the hydrophilic heads on either side of the bilayer are in contact with the aqueous environment. Lipid bilayers may be either spherical or planar. Fig. 14C shows a liposome, in which a lipid bilayer, such as that shown in Fig. 14B, forms a spherical structure enclosing an aqueous interior. The hydrophilic heads of the liposome face the aqueous interior and the external aqueous environment.

Fig. 15 shows the results of an experiment to determine the critical micellar concentration (cmc) of daptomycin at pH 4.0.

Fig. 16 shows the size distribution of daptomycin micelles by light scatter. The daptomycin micelles have an average size of 5.4 nm (54 A).

DETAILED DESCRIPTION OF THE INVENTION

Objects of the Invention

One object of the present invention is to provide a method for purifying lipopeptides that is easily scaled for commercial production comprising a unique combination of anion exchange chromatography and hydrophobic interaction chromatography. In a preferred embodiment, the method is used to manufacture purified daptomycin that is greater than 95% pure and exhibits reduced levels of impurities compared to daptomycin prepared by prior art methods. In another preferred embodiment, the method is used to manufacture daptomycin using reduced levels of solvents compared to those used in prior art methods. In another preferred embodiment, the method is used to manufacture purified daptomycin-related lipopeptides that are greater than 95% pure.

Another object of the present invention is to provide a method for increasing the levels of a lipopeptide produced by a microorganism by feeding the fermentation culture a reduced level of a fatty acid. Using lower levels of decanoic acid than those proposed for daptomycin fermentation in United States Patent 4,885,243 results in improved economics in addition to producing a highly pure form of daptomycin or a daptomycin-related lipopeptide. In a preferred embodiment, the method is used to increase the concentration and amount of daptomycin produced by *Streptomyces roseosporus* while minimizing the production of related contaminants. Lower levels of contaminants in the fermentation broth results in a more efficient recovery and purification of daptomycin, which provides for a manufacturing process with a higher yield.

Another object of the present invention is to provide a method for purifying daptomycin or daptomycin related lipopeptides comprising the use of modified buffer enhanced anion exchange chromatography. In a preferred embodiment, the method is used to produce daptomycin that is at least 98% pure or that is substantially or essentially free of anhydro-daptomycin or β-isomer. In another preferred embodiment, the method is used to purify daptomycin-related lipopeptides to at least 98% purity.

Another object of the present invention is to provide a process chromatography method to purify a lipopeptide comprising a novel combination of anion exchange chromatography, hydrophobic interaction chromatography and modified buffer enhanced anion exchange chromatography. In a preferred embodiment, the process chromatography method is used to purify daptomycin or a daptomycin-related lipopeptide. The modified buffer unexpectedly permits a separation of anhydro-daptomycin from daptomycin not previously possible in prior chromatography methods.

Another object of the invention is to provide a method for purifying lipopeptides that is easily scaled for commercial production using lipopeptide micelles. In one embodiment, the method comprises converting a lipopeptide solution from a monomeric, nonmicellar state to a micellar state and back again during purification procedures. In a preferred embodiment, the method comprises subjecting the lipopeptides

to conditions in which micelles are formed, separating the lipopeptide micelles from low molecular weight contaminants by, e.g., a size separation technique. In another preferred embodiment, the method comprises subjecting the lipopeptides to conditions in which the lipopeptides are in monomeric form and separating the monomeric lipopeptide molecules from high molecular weight molecules or aggregates by, e.g., a size separation technique. In a more preferred embodiment, the method comprises both steps: subjecting the lipopeptides to conditions in which micelles are formed and separating the lipopeptide micelles from low molecular weight contaminants, and then subjecting the lipopeptide micelles to conditions in which the lipopeptides are in monomeric form and separating the lipopeptide monomers from high molecular weight molecules or aggregates. These two steps may be performed in either order. In an even more preferred embodiment, the size separation technique is ultrafiltration or size exclusion chromatography.

A further object of the present invention is to provide improved methods for measuring the purity of lipopeptides, including daptomycin, by high pressure liquid chromatography (HPLC).

Another object of the present invention is to provide purified lipopeptides, such as daptomycin or a daptomycin-related lipopeptide, and pharmaceutically acceptable salts or formulations thereof. In a preferred embodiment, the present invention provides daptomycin or a daptomycin-related lipopeptide purified by one of the methods described in the specification. The present invention also provides pharmaceutical compositions of a purified lipopeptide or its salts and methods of administering these compositions. In a preferred embodiment, the pharmaceutical composition comprises purified daptomycin.

Another object of the present invention is to provide lipopeptide micelles and pharmaceutically acceptable formulations thereof. In a preferred embodiment, the present invention provides daptomycin micelles or a daptomycin-related lipopeptide micelle and pharmaceutically acceptable formulations thereof. In another embodiment, the invention also provides methods of administering the lipopeptide micelles or pharmaceutical formulations thereof to patients in need thereof. In a preferred

embodiment, the lipopeptide micelles are administered intravenously, parenterally, intramuscularly or topically.

Definitions

Unless otherwise defined, all technical and scientific terms used herein have the meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. The practice of the present invention employs, unless otherwise indicated, conventional techniques of chemistry, biochemistry and microbiology and basic terminology used therein.

The term "isolated" refers to a compound or product that is refers to a compound which represents at least 10%, preferably at least 20% or 30%, more preferably at least 50%, 60% or 70%, and most preferably at least 80% or 90% of the compound present in the mixture.

The term "lipopeptide" refers to a molecule that comprises a lipid-like moiety covalently linked to a peptide moiety, as well as salts, esters, amides and ethers thereof. The term "lipopeptide" also encompasses protected forms of lipopeptides in which one or more amino, carboxylate or hydroxyl groups are protected. See, e.g., "Protective Groups in Organic Synthesis" by Theodora W. Greene, John Wiley and Sons, New York, 1981 for examples of protecting groups. In a preferred embodiment, the lipopeptide is an antibiotic. In another preferred embodiment, the lipopeptide is LY 303366, echinocandins, pneumocandins, aculeacins, surfactin, plipastatin B1, amphomycin or the lipopeptide derivative disclosed in United States Patent 5,629,288. These lipopeptides are known in the art. See, e.g., United States Patent 5,202,309 and International PCT Application WO 00/08197. In another preferred embodiment, the lipopeptide is a daptomycin-related molecule, including, *inter alia*, daptomycin, A54145, a daptomycin-related lipopeptide disclosed in United States Patent 4,537,717, 4,482,487, Re. 32,311, Re. 32,310, 5,912,226, currently in reissue as United States Serial No. 09/547,357, United States Provisional Applications Nos. 60/170,943, 60/170,946 or 60/170,945, filed December 15, 1999, United States Provisional Application No.

60/208,222, filed May 30, 2000, all of which are specifically incorporated herein by reference, or an A-21978 antibiotic in which the n-decanoyl fatty acid side chain of daptomycin is replaced by an n-octanoyl, n-nonanoyl, n-undecanoyl, n-dodecanoyl, n-tridecanoyl or n-tetradecanoyl fatty acid side chain. The daptomycin-related lipopeptides disclosed in 60/170,943, 60/170,946, 60/170,945, and 60/208,222 relate to synthetic and semisynthetic lipopeptides in which the ornithine or kynurine residues or the fatty acid side chain of daptomycin are modified. In a more preferred embodiment, the lipopeptide is daptomycin. The term daptomycin-related lipopeptide refers to compounds described above, and salts thereof.

The term "daptomycin" refers to the n-decanoyl derivative of the factor A-21978C_0 type antibiotic, or a pharmaceutical acceptable salt thereof. "Daptomycin" is synonymous with LY146032. See Fig. 1.

The term "anhydro-daptomycin" refers to the daptomycin derivative in which the α-aspartyl group of daptomycin is transpeptidated to an anhydro-succinimido group. See Fig. 3.

The term "β-isomer" or "β-isomer of daptomycin" refers to the daptomycin derivative that contains a β-aspartyl group instead of an α-aspartyl group. See Fig. 2.

Daptomycin or a daptomycin-related lipopeptide is "substantially pure" when at least 95% of a sample is daptomycin or daptomycin-related lipopeptide. Preferably, daptomycin or daptomycin-related lipopeptide is "substantially pure" when at least 97% of a sample is daptomycin or daptomycin-related lipopeptide.

Daptomycin or daptomycin-related lipopeptide is "essentially pure" when at least 98% of a sample is daptomycin or daptomycin-related lipopeptide. Preferably, daptomycin or daptomycin-related lipopeptide is "essentially pure" when at least 99% of a sample is daptomycin or daptomycin-related lipopeptide.

Daptomycin or daptomycin-related lipopeptide is "substantially free" of another compound when the other compound is present in an amount that is no more than 1% of the amount of the daptomycin or daptomycin-related lipopeptide preparation.

Daptomycin or daptomycin-related lipopeptide is "essentially free" of another compound when the other compound is present in an amount that is no more than 0.5% of the amount of the daptomycin or daptomycin-related lipopeptide preparation.

Daptomycin or daptomycin-related lipopeptide is "free" of another compound when the other compound is present in an amount that is no more than 0.1% of the amount of the daptomycin or daptomycin-related lipopeptide preparation. Alternatively, daptomycin or daptomycin-related lipopeptide is "free" of another compound when the compound cannot be detected by HPLC under conditions of maximum sensitivity in which a limit of detection is approximately 0.05% or less of the amount of the daptomycin or daptomycin-related lipopeptide preparation. Exemplary HPLC methods are described herein (Tables 1 and 2).

"Purified" daptomycin or daptomycin-related lipopeptide refers to substantially pure daptomycin or daptomycin-related lipopeptide, essentially pure daptomycin or daptomycin-related lipopeptide, or a salt thereof, or to daptomycin, daptomycin-related lipopeptide, or a salt thereof which is substantially free, essentially free, or free of another compound.

"Partially purified" daptomycin or daptomycin-related lipopeptide refers to daptomycin, daptomycin-related lipopeptide, or a salt thereof that is less than 90% pure.

The purity of daptomycin, daptomycin-related lipopeptide or of another lipopeptide refers to the lipopeptide prior to its formulation in a pharmaceutical composition. The purity may be measured by any means including nuclear magnetic resonance (NMR), gas chromatography/mass spectroscopy (GC/MS), liquid chromatography/mass spectroscopy (LC/MS) or microbiological assays. A preferred means for measuring the purity of daptomycin is by analytical high pressure liquid chromatography (HPLC).

The term "micelle" refers to aggregates of amphipathic molecules. In an aqueous media, the lipophilic domains of the molecules of the aggregate are oriented toward the interior of the micelle and the hydrophilic domains are in contact with the

medium. Micelle structures include, but are not limited to, spherical, laminar, cylindrical, ellipsoidal, vesicular (liposomal), lamellar and liquid crystal. See Fig. 14.

The term "mixed micelle" refers to a particular type of micelle in which the micelle contains more than a single type of amphipathic molecule. In the context of this invention, mixed micelles contain a lipopeptide and at least one other amphipathic molecule which may be another lipopeptide. Mixed micelles contain at least 10% of the lipopeptide by weight. In other embodiments, a mixed micelle contains at least 20%, 30%, 40%, 50%, 60%, 70%, 80% or 90% of the lipopeptide.

The term "micellar solution" refers to a solution in which more than 50% of the lipopeptide molecules in the solution are present in micelles, as measured by weight. Preferably, at least 60%, 70%, 80%, 90% or 95% of the molecules are present in micelles. A micellar solution is retained on a ultrafiltration membrane that has a 10,000 dalton nominal molecular weight (NMW) cutoff.

The term "critical micelle concentration" (cmc) refers to the particular concentration of molecules, which is dependent upon temperature, salt concentration and the nature and type of amphipathic molecule. Above the cmc, the unassociated monomers and micelles exist in equilibrium.

The term "monomer" refers to an amphipathic molecule that is not part of an aggregate but that exists as a single molecule. In the context of this invention, the term monomer refers to a non-associated lipopeptide.

The term "monomeric solution" refers to a solution in which more than 50% of the lipopeptide molecules are present as monomers as measured by weight. Preferably at least 60%, 70%, 80%, 90% or 95% are present as monomers. A monomeric solution is not retained on a ultrafiltration membrane that has a 10,000 dalton NMW cutoff but rather passes through the membrane.

The term "low ionic strength buffer" refers to a solution that has a salt concentration below 50mM; the term "medium ionic strength buffer" refers to a solution that has a salt concentration between 50-250mM; the term "high ionic strength buffer" refers to a solution that has a salt concentration greater than 250mM.

Methods for Manufacturing Purified Lipopeptides

One embodiment of the present invention is drawn to a process chromatography method that produces a purified lipopeptide in a commercially feasible manner. In a preferred embodiment, the lipopeptide is daptomycin or a daptomycin-related lipopeptide. The process chromatography method comprises sequentially using anion exchange chromatography, hydrophobic interaction chromatography (HIC) and anion exchange chromatography to purify a preparation containing a lipopeptide, such as daptomycin or a daptomycin-related lipopeptide.

In a preferred embodiment of the instant invention, the purification method further comprises altering the fermentation conditions in which the A21978C-containing crude product is produced by *Streptomyces roseosporus* in order to increase daptomycin production and decrease impurities and related contaminants produced by the *S. roseosporus* fermentation culture.

A preferred embodiment of the process chromatography method is described below:

Streptomyces roseosporus is fermented with a feed of n-decanoic acid, as disclosed in United States Patent 4,885,243, with the modification that the decanoic acid feed is kept at the lowest levels possible without diminishing the overall yield of the fermentation. In a preferred embodiment, the residual decanoic acid is maintained at less than 50 parts per million (ppm) during aerobic fermentation. In a more preferred embodiment, the residual decanoic acid is maintained between one and 20 ppm during aerobic fermentation. In an even more preferred embodiment, the residual decanoic acid is maintained at approximately ten ppm during aerobic fermentation. In a preferred embodiment, the concentration of residual decanoic acid is measured throughout fermentation and the feed level of decanoic acid is adjusted to continuously keep the residual decanoic acid levels within the preferred parameters. The prior art does not describe the *in situ* specific and low residual constant decanoic acid concentrations required to achieve optimal expression of daptomycin containing lower levels of impurities.

After fermentation, the extracellular solution is clarified by removing the mycelia from the fermentation broth. Removing the mycelia from the fermentation is performed by any standard separation technique, such as centrifugation or microfiltration. In a preferred embodiment, the fermentation broth is clarified by microfiltration, such as by using a Pall Sep™ membrane system. In a more preferred embodiment, the fermentation broth is clarified using an industrial centrifuge, such as a Westfalia™ centrifuge, followed by a finishing depth filter. Other devices, such as filter presses, rotary drum filters or disposable depth filters, may be used to remove mycelia from fermentation broth to produce a clarified broth suitable for large-scale column chromatography.

In another embodiment, daptomycin may be extracted from mycelial fermentation directly by using an organic solvent such as butanol prior to clarification on a solvent separating centrifuge or filter. Any alcohol with four carbons or more may be used in the extraction according to this embodiment. A preferred solvent is n-butanol. Using an organic solvent results in an initial additional purification of daptomycin compared to a purely aqueous separation of daptomycin. For example, daptomycin partitions into n-butanol when n-butanol is used in a concentration greater than 10% and when the process is conducted under conditions in which the n-butanol forms a separate phase, *e.g.*, at a pH value of 4-5, which is near the isoelectric point of daptomycin (see Example 4).

In another embodiment, daptomycin is produced in an immobilized reactor that uses preactivated mycelia for the non-fermentation production of daptomycin using an energy source, preferably a sugar, elemental components, such as amino acids and ammonia, and decanoic acid. Production of daptomycin in an immobilized enzyme reactor is then processed by methods described herein.

After clarification of the fermentation broth, the levels of daptomycin are enriched, (*i.e.* concentrated) in the clarified solution by anion exchange chromatography. The clarified solution is first contacted with an anion exchange resin under conditions in which most or all of daptomycin binds to the anion exchange resin. After binding, the

resin is washed with an appropriate ionic aqueous buffer to remove unbound material and some of the daptomycin impurities. Finally, the purified daptomycin bound to the resin is eluted under conditions in which daptomycin will dissociate from the resin.

The binding, washing and elution steps may be performed according to this invention using buffers and methods known in the art. For instance, elution may be performed by using a buffer containing an elevated salt concentration compared to the wash buffer, a buffer that has a lower pH compared to the wash buffer, or a buffer that has both a higher salt concentration and a lower pH than the wash buffer. In a preferred embodiment, daptomycin is bound to the anion exchange resin that has been equilibrated in a buffer containing no added salt or a low salt concentration at a pH that is neutral to basic. The loaded resin is washed with three column bed volumes of water and then three to six bed volumes of an intermediate salt buffer containing 30 to 60 mM NaCl. Daptomycin is eluted from the column with one to three column volumes of an elevated salt and/or lower pH buffer containing 300 to 500 mM NaCl. Higher concentrations of sodium chloride and alternative salts such as potassium chloride will also elute daptomycin from the resin. In a preferred embodiment, a high flow rate anionic exchange resin is used. In a more preferred embodiment, FP-DA 13 resin (Mitsubishi) is used.

The anion exchange chromatography may be performed by column chromatography or may be accomplished in batch mode. For commercial production, it may be preferred to use batch mode. The anion exchange resin may be washed and eluted with stepwise salt gradients or with a continuous salt gradient. A suitable stepwise or continuous salt gradient is any one that permits the separation of daptomycin from contaminants. In a preferred embodiment, a continuous salt gradient is one which ranges from 0 to 1000 mM NaCl. In a more preferred embodiment, a continuous salt gradient is one which ranges from 100 to 500 mM NaCl or from 0 to 400 mM NaCl. Radial flow chromatography may also be used, as described in United States Patents 5,756,680, 4,865,729, 4,840,730 or 4,708,782.

After anion exchange chromatography, the daptomycin preparation is further purified by hydrophobic interaction chromatography (HIC). One embodiment of

this step is described in United States Patent 4,874,843, herein incorporated by reference.

The eluted aqueous daptomycin preparation is contacted with a HIC resin under conditions in which most or all of daptomycin will bind to the resin. The water content of the daptomycin-loaded resin is reduced by contacting the resin with an increased concentration of a non-polar solvent. The resin is washed with an appropriate polar organic solvent under conditions in which impurities dissociate from the resin while daptomycin remains bound. Finally, the daptomycin preparation is eluted under conditions in which daptomycin dissociates from the resin. In general, daptomycin is eluted using a solvent-containing buffer with a lower polarity (higher polar solvent level) and/or higher pH than the wash buffer.

In a preferred embodiment, the non-functional resin for HIC is small particle HP-20ss (Mitsubishi). The bound daptomycin is specifically removed from the HP-20ss resin with an organic phase solvent, such as one containing isopropyl alcohol, acetonitrile, butanol or other suitable solvent. In a more preferred embodiment, daptomycin is bound to HP-20ss resin that has been equilibrated in an acetate buffer containing 10% acetonitrile or equivalent polar solvent, such as isopropyl alcohol. The daptomycin-loaded resin is washed with at least three column bed volumes of equilibration buffer. The daptomycin-loaded resin is further freed of additional impurities by washing with three to six bed volumes of an acetate wash buffer containing a non-eluting concentration of the polar solvent. In a preferred embodiment, the daptomycin-loaded resin is washed with 30% acetonitrile or 45% isopropyl alcohol. The daptomycin-loaded resin is eluted with one to three bed volumes of acetate buffer containing 35% or more acetonitrile or greater than 50% isopropyl alcohol. In a preferred embodiment, daptomycin is eluted with 35% acetonitrile at pH 4.0-5.0 or 55-60% isopropyl alcohol. In another embodiment, the daptomycin-loaded resin is eluted with one to three bed volumes of buffer at an increased pH. In this embodiment, the pH of the buffer is gradually increased to elute different compounds from the column at different rates due to charge differences. At elevated pH, *e.g.*, pH 6.0-7.0, the elution concentration of acetonitrile is reduced to 10-20%. Similarly, at elevated pH, *e.g.*, pH 6.0-7.0 the elution concentration

of isopropyl alcohol is reduced to 20-25%. Control of the temperature under which chromatography is performed also influences solvent concentration. Elution at lower temperatures, i.e., under refrigerated conditions, requires increased levels of solvent at all pH conditions.

After HIC, the organic solvent in the daptomycin preparation is reduced by anion exchange chromatography. In a preferred embodiment, FP-DA 13 is used as discussed *supra*.

After the second anion exchange chromatography, the purified daptomycin is depyrogenated, filtered and concentrated under refrigerated conditions. Filtering daptomycin may be performed by any method known in the art. In one embodiment, filtering and depyrogenating may be performed by:

i) providing a daptomycin solution under conditions in which the daptomycin is in a monomeric and nonmicellar state;

ii) filtering the daptomycin solution under conditions in which the daptomycin will pass through the filter but pyrogens will not pass through the filter, e.g., having the daptomycin solution at pH 6.0-8.0 and filtering the solution with an ultrafilter that is rated between 3,000 NMW and 30,000 NMW;

iii) altering the daptomycin solution that has passed through the filter such that the daptomycin aggregates, e.g., by changing the pH of the daptomycin solution to 2.5-4.5 such that daptomycin forms micelles;

iv) filtering the daptomycin solution under conditions in which the daptomycin will be retained on the filter, e.g., concentrating the daptomycin on an ultrafilter of 30,000 NMW or less, such as a reverse osmosis membrane; and

v) collecting the depyrogenated daptomycin.

In a preferred embodiment, daptomycin of step (ii) is filtered under pressure on a 10,000 dalton molecular weight cutoff (MWCO) ultra-filter at a pH of approximately 7-8. In a more preferred embodiment, daptomycin is at an initial concentration of less than 40 mg/ml, more preferably, at a concentration of approximately 31.25 mg/mL. Under these conditions, daptomycin passes through the filter but pyrogens

such as lipopolysaccharides (LPS) do not. After the initial ultra-filtration, the pH of the filtrate is lowered to pH 2.5 to 4.5 and the filtrate is concentrated on a 10,000 MWCO ultra-filter to approximately 120 mg/mL. Under these conditions, daptomycin is retained on the filter. In a preferred embodiment, the pH of the filtrate is pH 3.5. Subsequent to concentration, the concentration of daptomycin is adjusted to 105 mg/mL, checked for endotoxin levels, and used to fill vials under aseptic conditions.

In another embodiment, reverse osmosis nanofiltration is performed at pH 1.5-3.0. The low pH and refrigerated conditions are used to retard degradation of purified daptomycin. Daptomycin may be further filtered through a 0.2 μm filter to reduce bioburden and then lyophilized either in bulk or in vials.

As an alternative to the above ultra-filtration and concentration step, the eluted fractions containing daptomycin are mixed with butanol (either n-, iso- or t-butanol) at a pH of approximately 4.5, in a ratio of greater than one part butanol to nine parts daptomycin solution. In a preferred embodiment, one part butanol is mixed with four parts daptomycin solution to yield a 20% butanol solution. The butanol-daptomycin solution is allowed to separate into organic and aqueous phases. Daptomycin partitions into the organic phase, which is collected. The dehydration of daptomycin in the organic solvent may stabilize daptomycin and prevent the degradation of the purified daptomycin to anhydro-daptomycin and subsequent formation of β-isomer. Finally, daptomycin can be returned to the aqueous phase by adding buffer at pH 6.5-7.5 to the organic phase. After concentration or collection of daptomycin, daptomycin is lyophilized.

In another embodiment of the instant invention, the process chromatography method is used to purify lipopeptides other than daptomycin, such as A54145, LY303366, echinocandins, pneumocandins, aculeacin, surfactin, plipastatin B1, amphomycin or the lipopeptide derivative disclosed in United States Patent 5,629,288. In another embodiment, the process chromatography method is used to purify daptomycin-related lipopeptides, including A54145, or a lipopeptide disclosed in United States Patent 4,537,717, 4,482,487, Re. 32,311, Re. 32,310, 5,912,226, currently in reissue as United States Serial No. 09/547,357, United States Provisional Applications Nos. 60/170,943,

60/170,946 or 60/170,945, filed December 15, 1999, United States Provisional Application No. 60/208,222, filed May 30, 2000, or an A-21978 antibiotic in which the n-decanoyl fatty acid side chain of daptomycin is replaced by an n-octanoyl, n-nonanoyl, n-undecanoyl, –dodecanoyl, n-tridecanoyl or n-tetradecanoyl fatty acid side chain.

In another embodiment of the instant invention, a "Salt Cloud Method" [Genetic Engineering News, Vol. 19, No. 20, pages 1, 34 and 43, (November 15, 1999)] is used in the purification of daptomycin or other lipopeptides. The Salt Cloud Method is a membrane-based system that combines selective separations with high-volume throughput. The Salt Cloud Method can be used in conjunction with those process steps disclosed herein or separately to purify daptomycin or other lipopeptides.

Another embodiment of the instant invention is drawn to a chromatography method that produces a highly purified lipopeptide not achievable by prior art chromatography methods. The chromatography method comprises the use of modified buffer enhanced anion exchange chromatography to purify a preparation containing a lipopeptide. In a preferred embodiment, the method is used to produce highly purified daptomycin or a daptomycin-related lipopeptide. This method, when used with partially purified daptomycin, produces daptomycin that is at least 98% pure. The method also produces daptomycin that is free or essentially free of anhydro-daptomycin. The method comprises the following steps:

Partially purified daptomycin is prepared by any method known in the art or as described herein. The daptomycin preparation is then further purified by modified buffer enhanced anion exchange chromatography. Daptomycin is bound to anion exchange resin in the presence of an appropriate ionic modified buffer under conditions in which daptomycin binds to the resin ion in a monomeric and non-micellar state. The modified buffer comprises a buffering agent, such as, without limitation, acetate, phosphate, citrate and Tris-HCl, or any other buffering agent that buffers well at neutral pH. The modified buffer further comprises one or more chaotropic agents, including, without limitation, guanidine, ammonia, urea, a strong reducing agent, benzoate, ascorbate or another ionic enhancer capable of modifying the buffer so that daptomycin is

easily separated from impurities. The daptomycin-loaded resin is washed with an appropriate ionic modified buffer to elute impurities, including anhydro-daptomycin. Daptomycin is then eluted under conditions that permit the separation of daptomycin from impurities that remain bound to the resin, including the β-isomer.

In a preferred embodiment, the modified buffer is at a neutral pH (a pH of 6 to 8) and contains 2 to 6 M urea. In a further preferred embodiment, the anion exchange resin is Porous Resin P150 or Porous D50 (PE Biosystems). In a more preferred embodiment, the anion exchange resin is Porous P150. In a preferred embodiment, daptomycin is bound to the resin in a low ionic strength buffer, washed with a low to medium ionic strength buffer and eluted with a high ionic strength buffer. In one preferred embodiment, daptomycin is bound to the Porous P150 resin in a Tris buffer pH 7.0 containing 6 M urea. The daptomycin-loaded Porous P150 resin is washed with three bed volumes of Tris buffer or other suitable buffer containing a salt level that removes contaminants and anhydro-daptomycin without eluting daptomycin. Daptomycin is eluted from the Porous P150 resin with Tris buffer or other suitable buffer under elevated salt conditions that will leave additional impurities, including a significant portion of β-isomer, bound to the column. In another preferred embodiment, Poros P150 is used and daptomycin is bound to the resin in an acetate buffer pH 6.0 containing 2 M urea. The daptomycin-loaded Poros P150 resin is washed and eluted similar to the method above except that an acetate buffer pH 6.0 containing 2 M urea is used. Product fractionation may be measured by HPLC or by UV monitoring.

The modified buffer enhanced anion exchange chromatography may be performed by column chromatography or may be accomplished in batch mode. Radial flow chromatography may also be used, as described in United States Patents 5,756,680, 4,865,729, 4,840,730 or 4,708,782. The modified buffer enhanced anion exchange resin may be washed and eluted with stepwise salt gradients or with a continuous salt gradient. A suitable stepwise or continuous salt gradient is any one that permits the separation of daptomycin from impurities including, but not limited to, anhydro-daptomycin and β-isomer. In a preferred embodiment, a continuous salt gradient is 0 to 1000 mM NaCl. In

a more preferred embodiment, the salt gradient is 100 to 500 mM NaCl or 0 to 400 mM NaCl.

In another embodiment of the instant invention, modified buffer enhanced anion exchange chromatography is used to purify lipopeptide compounds other than daptomycin. These lipopeptide compounds include, without limitation, A54145, LY303366, echinocandins, pneumocandins, aculeacin, surfactin and plipastatin B1 (Tsuge et al., 1996, Arch. Microbiol. 165:243-51) and lipopeptide derivatives as shown in United States Patent 5,629,288. In another embodiment, modified buffer enhanced anion exchange chromatography is used to purify a daptomycin-related lipopeptide such as A54145, or a lipopeptide disclosed in United States Patent 4,537,717, 4,482,487, Re. 32,311, Re. 32,310, 5,912,226, currently in reissue as United States Serial No. 09/547,357, United States Provisional Applications Nos. 60/170,943, 60/170,946 or 60/170,945, filed December 15, 1999, United States Provisional Application No. 60/208,222, filed May 30, 2000, or an A-21978 antibiotic in which the n-decanoyl fatty acid side chain of daptomycin is replaced by an n-octanoyl, n-nonanoyl, n-undecanoyl, –dodecanoyl, n-tridecanoyl or n-tetradecanoyl fatty acid side chain.

In another embodiment of the instant invention, a novel combination of process chromatography steps is used to purify daptomycin or a daptomycin-related lipopeptide. The method comprises anion exchange chromatography, small particle reverse phase chromatography and modified buffer enhanced anion exchange chromatography. The purification method may further comprise altering the fermentation conditions in which the A21978C-containing crude product is produced by *Streptomyces roseosporus*. These methods produce daptomycin or a daptomycin-related lipopeptide that is at least 98% pure. In a preferred embodiment, the methods produce daptomycin or a daptomycin-related lipopeptide that is more than 99% pure.

A preferred embodiment of the process chromatography method is described below:

Streptomyces roseosporus is fermented with a feed of n-decanoic acid, as disclosed in United States Patent 4,885,243, with the modification that the decanoic acid

feed is kept at the lowest levels possible without diminishing the overall yield of the fermentation as described *supra*. In an alternative embodiment, a different feedstock may be used so long as it ultimately provides an n-decanoyl group for addition to the daptomycin nucleus. Examples of these feedstocks are, without limitation, decanoic amide, decanoic esters including butyl esters, crude sources of coconut or palm oil, animal source decanoic acid, various salts of decanoic acid, and petrochemical sources of decanoic acid. After fermentation, the extracellular solution is clarified as described *supra*. In an alternative embodiment, daptomycin may be extracted from mycelia using an organic solvent such as n-butanol prior to clarification on a solvent separating centrifuge or filter as described *supra*. After clarification of the fermentation broth, the level of daptomycin is enriched in the clarified solution first by anion exchange chromatography and then by HIC as described *supra*.

After completion of HIC, the organic solvent in the daptomycin preparation is reduced by any method known in the art. In a preferred embodiment, the organic solvent is reduced by anion exchange chromatography, as described *supra*. Daptomycin should be eluted from the column in a buffer compatible with the buffer required for the modified buffer enhanced chromatography. Alternatively, the elution buffer may be exchanged for the modified buffer by reverse osmosis or filtration on a 10,000 MWCO filter. In another preferred embodiment, the organic solvent is reduced by evaporation or dilution in buffer. In a third preferred embodiment, the reverse phase chromatography solvent and residual salt is removed using reverse osmosis at pH 1.5-4.0 or ultrafiltration at pH 2.5-4.5. The resultant product may be frozen for bulk storage or dried by lyophilization and then rehydrated in water or in the buffer used for the modified buffer enhanced anion exchange chromatography.

Daptomycin is further purified by modified buffer enhanced anion exchange chromatography as described *supra*.

After modified buffer enhanced anion exchange chromatography, the purified daptomycin is filtered and concentrated under refrigerated conditions. Filtering daptomycin may be performed by any method known in the art. In a preferred

embodiment, daptomycin is depyrogenated and concentrated as described *supra*. Alternatively, daptomycin may be concentrated by reverse osmosis under refrigerated conditions at a pH of 1.5 to 4. The low pH and refrigerated conditions are used to retard the degradation of purified daptomycin.

As an alternative or in addition to the above filtration and concentration step, the eluted fractions containing daptomycin from the modified buffer enhanced anion exchange chromatography may be mixed with butanol (either n-, iso- or *t*-butanol) at a pH of approximately 4.5, in a ratio of greater than one part butanol to nine parts daptomycin solution. In a preferred embodiment, one part butanol is mixed with four parts daptomycin solution to yield a 20% butanol solution. The butanol-daptomycin solution is allowed to separate into organic and aqueous phases. Daptomycin partitions into the organic phase, which is collected. The dehydration of daptomycin in the organic solvent may stabilize daptomycin and prevent the degradation of the purified daptomycin to anhydro-daptomycin and subsequent formation of β-isomer.

After concentration or collection of daptomycin, daptomycin is lyophilized.

In another embodiment of the instant invention, the process chromatography is used to purify lipopeptides other than daptomycin, such as those described *supra*.

Formation of Lipopeptide Micelles and Methods of Use Thereof

Another embodiment of the invention provides lipopeptide micelles, methods for forming lipopeptide micelles and methods of using the lipopeptide micelles for lipopeptide purification and pharmaceutical compositions. In a preferred embodiment, the lipopeptide is a daptomycin-related molecule, including, *inter alia*, daptomycin, A54145, a daptomycin-related lipopeptide disclosed in United States Patent 4,537,717, 4,482,487, Re. 32,311, Re. 32,310, 5,912,226, currently in reissue as United States Serial No. 09/547,357, United States Provisional Applications Nos. 60/170,943, 60/170,946 or 60/170,945, filed December 15, 1999, United States Provisional

Application No. 60/208,222, filed May 30, 2000, or an A-21978 antibiotic in which the n-decanoyl side chain of daptomycin is replaced by an n-octanoyl, n-nonanoyl, n-undecanoyl, n-dodecanoyl, –tridecanoyl or n-tetradecanoyl side chain. In a more preferred embodiment, the lipopeptide is daptomycin.

Micelles are aggregates of amphipathic molecules. In aqueous media, the lipophilic parts of the molecules are oriented toward the interior of the micelle and the hydrophilic parts of the molecules are in contact with the aqueous media. Micelles form spontaneously in a solution containing amphipathic molecules if the concentration of the molecules is high enough.

Micelle formation causes changes in several bulk physical properties of a solution including changes in osmotic pressure, turbidity, electrical conductance, surface tension, co-ion and counterion activities (in the case of ionic amphipathic molecules), refractive index, UV and NMR spectra, partial molar volume, viscosity, diffusion coefficient and dye solubilization. The cmc can be determined by measuring one or more of these micelle-dependent physical properties as a function of concentration of the amphipathic molecule. The size and shape of micelles can be determined by dynamic laser light scattering, ultracentrifugation, viscosity and/or low-angle X-ray scattering experiments. Micelles can also exist in liquid crystal phases.

Lipopeptides may be aggregated into micelles by providing a concentration of lipopeptide that is greater than the cmc of the lipopeptide. The cmc is dependent upon the nature of the lipopeptide and the temperature, salt concentration and pH of the aqueous solution comprising the lipopeptide. With respect to the nature of the lipopeptide, the cmc of a lipopeptide is reduced by the addition of CH_2 groups to the lipophilic carbon chains. Thus, given the cmc for daptomycin at a particular salt concentration, temperature and pH, then an A-21978 type antibiotic in which the n-decanoyl fatty acid side chain is replaced by n-octanoyl, or –nonanoyl fatty acid side chain will have a higher cmc, while an A-21978 antibiotic in which the n-decanoyl fatty acid side chain of daptomycin is replaced by an n-undecanoyl, n-dodecanoyl, –tridecanoyl or n-tetradecanoyl fatty acid side chain will have a lower cmc relative to daptomycin.

In one embodiment of the invention, the cmc of a lipopeptide may be manipulated by adding or subtracting a CH_2 group to the lipopeptide. In a preferred embodiment, the lipopeptide is A-21978, in which the n-decanoyl fatty acid side chain of daptomycin is replaced by an n-octanoyl, n-nonanoyl, n-undecanoyl, –dodecanoyl, n-tridecanoyl or n-tetradecanoyl fatty acid side chain. In another embodiment, one can calculate the approximate cmc of a lipopeptide following the teachings of the specification. Given the cmc for a lipopeptide such as daptomycin, one may calculate the approximate cmc of a related lipopeptide in which the n-decanoyl fatty acid side chain is replaced by an n-octanoyl, n-nonanoyl, n-undecanoyl, n-dodecanoyl, n-tridecanoyl or n-tetradecanoyl fatty acid side chain. The above may be carried out by methods known by one skilled in the art.

In another preferred embodiment, given the cmc for one lipopeptide, one can calculate the approximate cmc for a lipopeptide that contains a related peptide moiety. In a preferred embodiment, given the cmc for daptomycin and the teachings of the prior art, one may readily determine the cmc for a related lipopeptide such as A54145, a daptomycin-related lipopeptide disclosed in United States Patent 4,537,717, 4,482,487, Re. 32,311, Re. 32,310, 5,912,226, currently in reissue as United States Serial No. 09/547,357, United States Provisional Applications Nos. 60/170,943, 60/170,946 or 60/170,945, filed December 15, 1999, United States Provisional Application No. 60/208,222, filed May 30, 2000.

In another embodiment of the invention, the cmc of a lipopeptide is manipulated by changing the temperature of the solution comprising the lipopeptide. The cmc for a lipopeptide usually increases with increasing temperature of the solution. Thus, micelle formation is promoted by decreasing the temperature and is hindered by increasing the temperature. For instance, a solution comprising a lipopeptide may form micelles at 4°C because at that temperature the cmc is lowered and the lipopeptide concentration is above the cmc; however, the same lipopeptide solution may be monomeric at 20°C because the cmc has increased with the temperature and the lipopeptide concentration is now below the cmc. Thus, in a preferred embodiment, the

concentration of a lipopeptide is higher than the cmc at one temperature and is lower than the cmc at another, higher temperature. In a more preferred embodiment, the lipopeptide is daptomycin or a daptomycin-related molecule, such as those described *supra*. In an even more preferred embodiment, the lipopeptide is daptomycin.

In another preferred embodiment, the ability to manipulate the formation of micelles of a lipopeptide by using different temperatures to affect the cmc is used in the purification of the lipopeptide. In a more preferred embodiment, the lipopeptide is daptomycin or a related molecule, such as those described *supra*. In an even more preferred embodiment, the lipopeptide is daptomycin. In another preferred embodiment, the ability to manipulate lipopeptide micelle formation by altering the temperature is used to make pharmaceutical compositions that are micellar under certain temperature conditions and monomeric under other temperature conditions. In a preferred embodiment, the pharmaceutical compositions comprise daptomycin or a daptomycin-related lipopeptide, as described *supra*. In another preferred embodiment, the pharmaceutical compositions comprise daptomycin.

In a further embodiment of the invention, the addition of an electrolyte is used to decrease the cmc of an ionic lipopeptide. In a preferred embodiment, a salt, such as NaCl, is added to a solution comprising lipopeptide to reduce the repulsion between charged groups in a lipopeptide micelle. In a preferred embodiment, the lipopeptide is daptomycin or a daptomycin-related molecule, such as that described *supra*. For instance, the peptide moiety of daptomycin contains three aspartic acid residues and an L-threo-3-methylglutamic acid residues (3-MG), all of which would be charged at neutral pH. Thus, addition of an electrolyte, such as NaCl or an equivalent salt, will decrease the cmc of daptomycin. In a preferred embodiment, the salt concentration is at least 100 mM. In a more preferred embodiment, the salt concentration is 150 mM to 300 mM salt. In an even more preferred embodiment, the salt is NaCl.

A decrease in the cmc is also observed with addition of an electrolyte for other lipopeptides, such as molecules related to daptomycin that contain aspartic acid residues, 3-MG residues or other charged residues. Therefore, in a preferred

embodiment, a salt is added to a solution to decrease the cmc of a daptomycin-related lipopeptide, such as A54145, a daptomycin-related lipopeptide disclosed in United States Patent 4,537,717, 4,482,487, Re. 32,311, Re. 32,310, 5,912,226, currently in reissue as United States Serial No. 09/547,357, United States Provisional Applications Nos. 60/170,943, 60/170,946 or 60/170,945, filed December 15, 1999, United States Provisional Application No. 60/208,222, filed May 30, 2000, or an A-21978 antibiotic in which the n-decanoyl fatty acid side chain of daptomycin is replaced by an n-octanoyl, n-nonanoyl, n-undecanoyl, –dodecanoyl, n-tridecanoyl or n-tetradecanoyl fatty acid side chain. In another embodiment, the salt concentration is decreased in order to increase the cmc of an ionic lipopeptide. In a preferred embodiment, the ionic lipopeptide is daptomycin or a daptomycin-related lipopeptide, as described *supra*.

In another preferred embodiment, the ability to manipulate the formation of micelles of a lipopeptide by altering electrolyte concentration to affect the cmc is used in the purification of the lipopeptide. In a more preferred embodiment, the lipopeptide is daptomycin or a daptomycin-related molecule, such as those described *supra*. In an even more preferred embodiment, the lipopeptide is daptomycin. In another preferred embodiment, the ability to manipulate lipopeptide micelle formation by electrolyte concentration is used to make pharmaceutical compositions that are micellar at certain electrolyte concentrations and monomeric under other electrolyte concentrations. In a preferred embodiment, the pharmaceutical compositions comprise daptomycin or a daptomycin-related lipopeptide, as described *supra*. In another preferred embodiment, the pharmaceutical compositions comprise daptomycin.

In another embodiment of the invention, the pH of a solution comprising a lipopeptide is manipulated to influence the cmc of the lipopeptide. In a preferred embodiment, the lipopeptide is daptomycin or a daptomycin-related molecule, such as those described *supra*. In an even more preferred embodiment, the lipopeptide is daptomycin. In one embodiment, the pH is manipulated so that the concentration of a lipopeptide is higher than the cmc at one pH and is lower than the cmc at another pH. For instance, for daptomycin, the cmc at pH 4.0 in water at a temperature of 20-25°C was

much lower than at pH 6.0 or 7.5. At pH 4.0, the cmc is approximately 400 μg/mL under these conditions. See Fig. 15. Further, daptomycin is monomeric even at 150 mg/mL daptomycin at pH 6.5 (wherein the salt concentration is 150 mM to 300 mM NaCl and the temperature is 4°C). Thus, for daptomycin, the cmc at pH 4.0 is lower than in solutions of either higher pH or lower pH. The change in cmc at different pH levels may also be used for other charged lipopeptides, including lipopeptides that are related to daptomycin, as described *supra*.

In another preferred embodiment, the ability to manipulate the formation of micelles of a lipopeptide by altering the pH to affect the cmc is used in the purification of the lipopeptide. In a more preferred embodiment, the lipopeptide is daptomycin or a daptomycin-related molecule, such as those described *supra*. In an even more preferred embodiment, the lipopeptide is daptomycin. In another preferred embodiment, the ability to manipulate lipopeptide micelle formation by pH is used to make pharmaceutical compositions that are micellar at a particular pH and monomeric under another pH. In a preferred embodiment, the pharmaceutical compositions comprise daptomycin or a daptomycin-related lipopeptide, as described *supra*. In another preferred embodiment, the pharmaceutical compositions comprise daptomycin.

In another aspect of the invention, the lipopeptide may be part of a mixed micelle. A mixed micelle is one in which the lipopeptide forms a micelle with one or more other types of amphipathic molecules. Examples of such amphipathic molecules include, without limitation, medium and long chain fatty acids, phosphoglycerides (phospholipids), sphingomyelin, glycolipids and cholesterol. In one embodiment, medium chain-length alcohols can be incorporated into the micelle, where they reduce electrostatic repulsion and steric hindrance, thus lowering the cmc of the lipopeptide. In another embodiment, the addition of one or more types of amphipathic molecules can be used to alter the structure of the micelle from a spherical micelle (See Fig. 14, part a) to a lipid bilayer structure (See Fig. 14, part b) or to a liposome structure (See Fig. 14 part c). In general, mixed micelles comprising phospholipids and/or glycolipids will cause a

spherical micelle to convert to a lipid bilayer structure, which serve as permeability barriers to ions and most polar molecules.

In another embodiment, the mixed micelle can be formed from two or more different lipopeptides. For instance, the mixed micelle can be formed from daptomycin and another lipopeptide, such as A54145 or a daptomycin-related lipopeptide, as discussed *supra*. In another embodiment, the mixed micelle may comprise a lipopeptide along with one or more therapeutically useful amphipathic molecules, such as an antibiotic, an anti-inflammatory or an anti-fungal agent, which are known to those having ordinary skill in the art. In a preferred embodiment, the lipopeptide is daptomycin or a daptomycin-related lipopeptide such as A54145, the daptomycin-related lipopeptides disclosed *supra*, or an A-21978 antibiotic in which the n-decanoyl fatty acid side chain of daptomycin is replaced by an n-octanoyl, n-nonanoyl, n-undecanoyl, n-dodecanoyl, n-tridecanoyl or n-tetradecanoyl fatty acid side chain. In a more preferred embodiment, the lipopeptide is daptomycin.

In another embodiment of the invention, the micelle, whether mixed or comprising a single type of lipopeptide molecule, comprises a lipopeptide that is therapeutically useful. In a preferred embodiment, the lipopeptide is an antibiotic. In an even more preferred embodiment, the lipopeptide is daptomycin. Daptomycin forms micelles of approximately 5.4 nm (54 A) at a concentration of 1 mg/mL at pH of approximately 4.0 in water. See Fig. 16.

In another preferred embodiment, the micelles comprise one or more different types of therapeutic substances. In one embodiment, a therapeutic substance can be mixed with the lipopeptide in solution such that a micelle is formed from the lipopeptide and the therapeutic substance is trapped in the hydrophobic interior. In another embodiment, a therapeutic substance is mixed with a lipopeptide and one or more other amphipathic molecules such that a mixed micelle is formed from the lipopeptide and other amphipathic molecules and the therapeutic substance is found in the hydrophobic interior. In a preferred embodiment, the therapeutic substance is an antibiotic, an anti-inflammatory or an anti-fungal agent. In a more preferred embodiment,

the therapeutic substance is an antibiotic or antifungal agent disclosed *infra*. In another preferred embodiment, the therapeutic substance is soluble in a hydrophobic environment but is not soluble in an aqueous solution.

In another embodiment of the invention, the lipopeptides may be formed into liposomes, which are vesicular micelles in which a spherical lipid bilayer surrounds an aqueous interior. See Fig. 14, part c. Liposomes are advantageous for therapeutic uses because they easily fuse with a plasma membrane and can also be used to trap substances in their inner aqueous compartment. The substance can be one that is only soluble in aqueous solutions. In one embodiment, a solution comprising a lipopeptide and another amphipathic molecule can be sonicated to produce liposomes. In another embodiment, the lipopeptide alone can be sonicated to produce liposomes. In a preferred embodiment, the liposome comprises daptomycin or a daptomycin-related lipopeptide such as A54145, a lipopeptide disclosed in United States Patent 4,537,717, 4,482,487, Re. 32,311, Re. 32,310, 5,912,226, currently in reissue as United States Serial No. 09/547,357, United States Provisional Applications Nos. 60/170,943, 60/170,946 or 60/170,945, filed December 15, 1999, United States Provisional Application No. 60/208,222, filed May 30, 2000, or A-21978 antibiotic in which the n-decanoyl fatty acid side chain of daptomycin is replaced by an n-octanoyl, n-nonanoyl, n-undecanoyl, –dodecanoyl, n-tridecanoyl or n-tetradecanoyl fatty acid side chain. In a more preferred embodiment, the lipopeptide is daptomycin.

In another preferred embodiment, the liposomes comprise one or more therapeutic substances in their inner aqueous compartments. In a preferred embodiment, the therapeutic substance is an antibiotic, an anti-inflammatory or an anti-fungal agent. In a more preferred embodiment, the therapeutic substance is an antibiotic or antifungal agent disclosed *infra*. In another preferred embodiment, the therapeutic substance is soluble in aqueous solution. In another preferred embodiment, a pharmaceutical composition comprises the liposome.

In a preferred embodiment, a pharmaceutical composition comprises lipopeptide micelles or lipopeptide micelle containing a therapeutic substance. The

lipopeptide micelles may be spherical micelles, mixed micelles or liposomes. Pharmaceutical compositions comprising lipopeptide micelles may minimize local irritation upon injection or when administered intravenously. In one embodiment, the pharmaceutical composition comprises a salt, a buffer to maintain a particular pH and micelles. In a further embodiment, the pharmaceutical composition comprises one or more agents to stabilize the micelles and/or to stabilize the lipopeptide or other therapeutic substance. In one embodiment, the pharmaceutical composition also comprises one or more therapeutic substances. In a preferred embodiment, the therapeutic substance is an antibiotic, an anti-inflammatory or an antifungal agent. In a more preferred embodiment, the therapeutic substance is an antibiotic or antifungal agent disclosed *infra*. The therapeutic substance can be in addition to the therapeutic substance that is incorporated into the micelle, or can be the therapeutic agent that is incorporated into the micelle.

The pharmaceutical composition can be dried or lyophilized, in which case the micelles are formed when either an aqueous solution, such as water or a buffer is added to the pharmaceutical composition. In a preferred embodiment, the pharmaceutical composition is lyophilized and contains a physiological concentration of salt when reconstituted and a buffer that maintains a pH at which micelles spontaneously form at room temperature when sterile water or other buffer is added. In an even more preferred embodiment, the pharmaceutical composition comprises daptomycin or related lipopeptide, such as A54145, the daptomycin-related lipopeptides disclosed *supra*, or an A-21978 antibiotic in which the n-decanoyl fatty acid side chain of daptomycin is replaced by an n-octanoyl, n-nonanoyl, n-undecanoyl, n-dodecanoyl, n-tridecanoyl or n-tetradecanoyl fatty acid side chain. In an even more preferred embodiment, the lipopeptide is daptomycin. In another embodiment, the pharmaceutical composition is aqueous. This is preferred when liposomes are used. In a preferred embodiment, the pharmaceutical composition comprises a stabilizing agent for the liposomes.

In another aspect of the invention, the micellar solution is isolated and/or purified. In one embodiment, micelles are isolated from smaller substituents by

ultrafiltration. The choice of ultrafiltration membrane will be based upon the size of the micelle. In general, a 10,000 NMW or 30,000 NMW membrane will be sufficient to retain micelles while permitting smaller substituents, such as contaminants to flow through. In another embodiment, micelles can be isolated and/or purified by dialysis, density gradient centrifugation or size exclusion chromatography. These methods are well-known in the art. In one embodiment, the micelles are more than 30% pure, where purity is measured as the weight of the micelles compared to the weight of monomeric forms of the lipopeptide or of other molecules. In a preferred embodiment, the micelles are more than 50%, 60%, 70%, 80%, 90% or 95% pure.

In another aspect of the invention, the ability to form lipopeptide micelles and then to disassociate them by altering temperature, pH, electrolyte concentration and/or lipopeptide concentration provides a method for purifying lipopeptides. In one embodiment, the method comprises purifying lipopeptides from low molecular weight contaminants by subjecting lipopeptides to conditions in which the lipopeptides form micelles and then separating the micelles from the contaminants by a size selection technique, such as ultrafiltration or size exclusion chromatography. In another embodiment of the invention, the method comprises concentrating lipopeptides by subjecting lipopeptides to conditions in which the lipopeptides form micelles and then concentrating them by a size selection technique. In a more preferred embodiment, the method comprises both purification and concentration as a single step.

In another embodiment of the invention, the method comprises purifying a lipopeptide from high molecular weight contaminants, including pyrogens (e.g., lipopolysaccharide), by subjecting the lipopeptide to conditions under which the lipopeptide is monomeric and then separating the monomeric lipopeptide solution from the high molecular weight contaminants by a size separation technique. In a preferred embodiment, the size separation technique is ultrafiltration, as discussed *supra*. In another preferred embodiment, the lipopeptide is daptomycin or related lipopeptide, such as A54145, the daptomycin-related lipopeptides disclosed *supra*, or an A-21978 antibiotic in which the n-decanoyl fatty acid side chain of daptomycin is replaced by an n-octanoyl,

n-nonanoyl, n-undecanoyl, n-dodecanoyl, n-tridecanoyl or n-tetradecanoyl fatty acid side chain. In an even more preferred embodiment, the lipopeptide is daptomycin.

A preferred embodiment of the process chromatography method using micelles to purify daptomycin is described below:

Streptomyces roseosporus is fermented with a feed of n-decanoic acid as described *supra*. After fermentation, the extracellular solution is clarified as described *supra*.

The clarified preparation is then applied to an anion exchange resin, such as FP-DA 13, as described *supra*. Daptomycin is eluted from the column with one to three column volumes of an elevated salt buffer containing 300 to 500 mM NaCl.

The eluted daptomycin preparation is adjusted to a pH of 2.5 to 5.0 using an acid. In a preferred embodiment, the acid is dilute phosphoric acid. At pH 2.5 to 4.7, 300 to 500 mM NaCl and a temperature of 2-15°C, the daptomycin forms a micelle.

The daptomycin preparation is filtered on a 10,000 to 30,000 NMW ultrafiltration membrane. During ultrafiltration, the daptomycin preparation is washed with a buffer containing 30 mM sodium acetate pH 3.5 and at temperatures of up to 15°C. The initial salt concentration is 300 mM NaCl due to the elution conditions, but the salt concentration decreases as washing continues. Because daptomycin is in micellar form, it is retained on the filter while impurities smaller than the 10,000 to 30,000 (depending upon the filter used), pass through the filter. The daptomycin preparation obtained is approximately 85-90% pure.

As an optional step, the daptomycin preparation may be diluted and its pH raised to 6.5 in order to convert the daptomycin to a monomeric state. The daptomycin preparation is then be passed through a 10,000 NMW ultrafiltration membrane. This optional step decreases pyrogen content significantly.

Methods for Analyzing Daptomycin Purity

Another embodiment of the invention provides analytical methods for measuring the purity of daptomycin.

In the prior art, many of the contaminants that co-purified with daptomycin were unresolved or unidentified because the ability to visualize and measure impurities was limited by the analytical methods and equipment available. See, e.g., United States Patent 4,874,843 and Kirsch et al. The development of more sensitive analytical HPLC systems and techniques permits the resolution of a number of contaminants that exist in daptomycin batches prepared by prior art methods. The higher resolution HPLC methods demonstrate that daptomycin as purified by prior art methods is contaminated with previously identified impurities, such as anhydro-daptomycin and β-isomer, and other, previously unknown contaminants that co-purify with daptomycin (and co-elute under the previously established HPLC detection conditions) during the practice of prior art methods. Identification of these contaminants now permits the development of methods designed to eliminate these contaminants.

As discussed above, anhydro-daptomycin and the β-isomer were previously described as impurities that persistently and consistently occurred during preparation of daptomycin. Using the HPLC analyses described here, an additional approximately twelve impurities produced during the production of daptomycin were distinguished, some of which had previously not been identified. These impurities were not removed after purification by the method disclosed in United States Patent 4,874,843. At least ten of these compounds have been identified (see, e.g., Figs. 2-11). Furthermore, at least six of these compounds are not the direct result of the reaction that produces anhydro-daptomycin and the β-isomer form of daptomycin, but rather are compounds produced by other, unrelated, processes that occur during the fermentation or purification of daptomycin. The method of the instant invention, described below, also significantly reduces the levels of a number of these impurities (see Examples).

Any method known in the art may be used to measure the amount of other compounds in a daptomycin preparation. Methods for identifying daptomycin contaminants include, without limitation, mass spectroscopy, infrared spectroscopy, capillary electrophoresis and nuclear magnetic resonance spectroscopy. A preferred

method for measuring the amount of other compounds in a daptomycin preparation is HPLC.

Two methods were used to measure daptomycin impurities in the instant invention. The first method is a slightly lower resolution method than the second method. In both methods, a Shimadzu or HP HPLC System with PE Nelson's Turbochrom Software Version 4.1 is used. The "first" resolution method is summarized in Table 1 and the "second" resolution method is summarized in Table 2:

TABLE 1

1. Solvent Delivery System:
   - Mode: Isocratic pumping
   - Flow rate: 1.5 mL/min
   - Run time: 30 minutes

2. Solvent A: 34% acetonitrile in 0.5% $NH_4H_2PO_4$ at pH 4.5
   Solvent B: 20% acetonitrile in 0.5% $NH_4H_2PO_4$ at pH 4.5

   The target condition is to retain daptomycin at 15.0 $\pm$ 0.5 minutes. Solvent B may be used together with solvent A to adjust the HPLC mobile phase conditions to achieve the desired retention time.

3. Autosampler cooler: 5 (4 to 6) °C

4. Injection volume: 5 µL to 75 µL (20 µL normal)

5. Column: IB-SIL (Phenomenex), C-8, 5µ, 4.6 mm x 250 mm (or equivalent)

6. Pre-column: IB-SIL (Phenomenex), C-8, 5µ, 4.6 mm x 30 mm (or equivalent)

7. Detection wavelength: 214 nm

8. Column Temperature: ambient

9. Integration: A computer system or integrator capable of measuring peak area.

TABLE 2

1. Solvent Delivery System:
   - Mode: Isocratic pumping
   - Flow rate: 1.5 mL/min
   - Run time: 75 minutes

2. Solvent A: 20% acetonitrile in 0.45% $NH_4H_2PO_4$ at pH 3.25
   Solvent B: 50% acetonitrile in 0.45% $NH_4H_2PO_4$ at pH 3.25

   The target condition is approximately 35% acetonitrile in 0.45% $NH_4H_2PO_4$ at pH 3.25 (50% Solvent B) to retain daptomycin at 36.0 $\pm$ 1.5 minutes; however, the solvent ratio will be used to adjust the HPLC mobile phase composition to achieve the desired retention time.

3. Autosampler cooler: 5 (4 to 6) °C

4. Injection volume: 5 µL to 75 µL (20 µL normal)

5. Column: IB-SIL (Phenomenex), C-8, 5µ, 4.6 mm x 250 mm (or equivalent)

6. Pre-column: IB-SIL (Phenomenex), C-8, 5µ, 4.6 mm x 30 mm (or equivalent)

7. Detection wavelength: 214 nm

8. Column Temperature: 25 (22 to 28) °C

9. Integration: A computer system or integrator capable of measuring peak area.

Purified Lipopeptides, Pharmaceutical Compositions and Methods of Use Thereof

Another object of the instant invention is to provide purified lipopeptides, as well as salts, esters, amides, ethers and protected forms thereof, as well as pharmaceutical formulations comprising purified lipopeptides or its salts. In a preferred embodiment, the lipopeptide is daptomycin or a daptomycin-related lipopeptide, as described *supra*. A further object of the instant invention is to provide pharmaceutical compositions comprising lipopeptide micelles. In a preferred embodiment, the lipopeptide micelles are micelles comprising daptomycin or one or more daptomycin-related lipopeptides. All reference herein to lipopeptide micelles refers not only to all lipopeptide micelles, but specifically contemplates daptomycin, or related lipopeptide, such as A54145, the daptomycin-related lipopeptides disclosed *supra*, or an A-21978 antibiotic in which the n-decanoyl fatty acid side chain of daptomycin is replaced by an n-octanoyl, n-nonanoyl, n-undecanoyl, n-dodecanoyl, n-tridecanoyl or n-tetradecanoyl fatty acid side chain. Further, all references herein to lipopeptide micelles specifically contemplates spherical micelles, mixed micelles and liposomes, as discussed *supra*.

Purified lipopeptides, pharmaceutically acceptable salts thereof, or lipopeptide micelles can be formulated for oral, intravenous, intramuscular, subcutaneous, aerosol, topical or parenteral administration for the therapeutic or prophylactic treatment of diseases, particularly bacterial infections. In a preferred embodiment, the purified lipopeptide is purified daptomycin or a daptomycin-related lipopeptide. Reference herein to "purified daptomycin," "purified daptomycin-related lipopeptide" or "purified lipopeptide" includes pharmaceutically acceptable salts thereof. Daptomycin, daptomycin-related lipopeptide or other lipopeptide micelles can be formulated using any pharmaceutically acceptable carrier or excipient that is compatible with daptomycin or with the lipopeptide of interest. See, e.g., Handbook of Pharmaceutical Additives: An International Guide to More than 6000 Products by Trade Name, Chemical, Function, and Manufacturer, Ashgate Publishing Co., eds., M. Ash and I. Ash, 1996; The Merck Index: An Encyclopedia of Chemicals, Drugs and Biologicals, ed. S. Budavari, annual; Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, PA;

Martindale: The Complete Drug Reference, ed. K. Parfitt, 1999; and Goodman & Gilman's The Pharmaceutical Basis of Therapeutics, Pergamon Press, New York, NY, ed. L. S. Goodman et al.; the contents of which are incorporated herein by reference, for a general description of the methods for administering various antimicrobial agents for human therapy. Purified daptomycin, daptomycin-related lipopeptide or other lipopeptide micelles of this invention can be mixed with conventional pharmaceutical carriers and excipients and used in the form of tablets, capsules, elixirs, suspensions, syrups, wafers, creams and the like. Daptomycin, daptomycin-related lipopeptide or other lipopeptide micelles may be mixed with other therapeutic agents and antibiotics, such as discussed herein. The compositions comprising a compound of this invention will contain from about 0.1 to about 90% by weight of the active compound, and more generally from about 10 to about 30%.

The compositions of the invention can be delivered using controlled (e.g., capsules) or sustained release delivery systems (e.g., bioerodable matrices). Exemplary delayed release delivery systems for drug delivery that are suitable for administration of the compositions of the invention are described in U.S. Patent Nos. 4,452,775 (issued to Kent), 5,239,660 (issued to Leonard), 3,854,480 (issued to Zaffaroni).

The compositions may contain common carriers and excipients, such as corn starch or gelatin, lactose, sucrose, microcrystalline cellulose, kaolin, mannitol, dicalcium phosphate, sodium chloride and alginic acid. The compositions may contain croscarmellose sodium, microcrystalline cellulose, corn starch, sodium starch glycolate and alginic acid.

Tablet binders that can be included are acacia, methylcellulose, sodium carboxymethylcellulose, polyvinylpyrrolidone (Povidone), hydroxypropyl methylcellulose, sucrose, starch and ethylcellulose.

Lubricants that can be used include magnesium stearate or other metallic stearates, stearic acid, silicone fluid, talc, waxes, oils and colloidal silica.

Flavoring agents such as peppermint, oil of wintergreen, cherry flavoring or the like can also be used. It may also be desirable to add a coloring agent to make the dosage form more aesthetic in appearance or to help identify the product.

For oral use, solid formulations such as tablets and capsules are particularly useful. Sustained release or enterically coated preparations may also be devised. For pediatric and geriatric applications, suspensions, syrups and chewable tablets are especially suitable. For oral administration, the pharmaceutical compositions are in the form of, for example, a tablet, capsule, suspension or liquid. The pharmaceutical composition is preferably made in the form of a dosage unit containing a therapeutically-effective amount of the active ingredient. Examples of such dosage units are tablets and capsules. For therapeutic purposes, the tablets and capsules which can contain, in addition to the active ingredient, conventional carriers such as binding agents, for example, acacia gum, gelatin, polyvinylpyrrolidone, sorbitol, or tragacanth; fillers, for example, calcium phosphate, glycine, lactose, maize-starch, sorbitol, or sucrose; lubricants, for example, magnesium stearate, polyethylene glycol, silica, or talc; disintegrants, for example, potato starch, flavoring or coloring agents, or acceptable wetting agents. Oral liquid preparations generally are in the form of aqueous or oily solutions, suspensions, emulsions, syrups or elixirs may contain conventional additives such as suspending agents, emulsifying agents, non-aqueous agents, preservatives, coloring agents and flavoring agents. Oral liquid preparations may comprise lipopeptide micelles or monomeric forms of the lipopeptide. Examples of additives for liquid preparations include acacia, almond oil, ethyl alcohol, fractionated coconut oil, gelatin, glucose syrup, glycerin, hydrogenated edible fats, lecithin, methyl cellulose, methyl or propyl *para*-hydroxybenzoate, propylene glycol, sorbitol, or sorbic acid.

For intravenous (IV) use, a water soluble form of daptomycin, daptomycin-related lipopeptide or other lipopeptide can be dissolved in any of the commonly used intravenous fluids and administered by infusion. For lipopeptide micelles, the lipopeptide is dissolved in an intravenous formulation under conditions in which the lipopeptide is present at a concentration above its cmc. One having ordinary

skill in the art may vary the pH, temperature or salt concentration following the teachings of this invention to obtain an intravenous solution comprising lipopeptide micelles. Further, one may sonicate the lipopeptide solution in order to obtain lipopeptide liposomes. Intravenous formulations may include carriers, excipients or stabilizers including, without limitation, calcium, human serum albumin, citrate, acetate, calcium chloride, carbonate, and other salts. Intravenous fluids include, without limitation, physiological saline or Ringer's solution. Daptomycin or daptomycin-related lipopeptide also may be placed in injectors, cannulae, catheters and lines.

Formulations for parenteral administration can be in the form of aqueous or non-aqueous isotonic sterile injection solutions or suspensions. These solutions or suspensions can be prepared from sterile powders or granules having one or more of the carriers mentioned for use in the formulations for oral administration. Lipopeptide micelles may be particularly desirable for parenteral administration. The compounds can be dissolved in polyethylene glycol, propylene glycol, ethanol, corn oil, benzyl alcohol, sodium chloride, and/or various buffers. For intramuscular preparations, a sterile formulation of a lipopeptide compound or a suitable soluble salt form of the compound, for example the hydrochloride salt, can be dissolved and administered in a pharmaceutical diluent such as Water-for-Injection (WFI), physiological saline or 5% glucose.

Lipopeptide micelles may be particularly desirable for parenteral administration because they are likely to cause no local irritation at the site of injection. Without wishing to be bound by any theory, it is likely that lipopeptide micelles will cause less local irritation than monomeric lipopeptides because the lipid tails, which might cause irritation upon injection, will be sequestered in the interior of the micelle, while the peptide nucleus, which is less likely to cause local irritation than the lipid tail, will be exposed to the tissue. Lipopeptide micelles may be prepared for intramuscular and parenteral preparations by following the teachings of this invention to obtain a preparation comprising lipopeptide micelles. Further, one may sonicate the lipopeptide solution in order to obtain lipopeptide liposomes. A suitable insoluble form of the compound also may be prepared and administered as a suspension in an aqueous base or a

pharmaceutically acceptable oil base, e.g., an ester of a long chain fatty acid such as ethyl oleate.

Injectable depot forms may be made by forming microencapsulated matrices of the compound in biodegradable polymers such as polylactide-polyglycolide. Depending upon the ratio of drug to polymer and the nature of the particular polymer employed, the rate of drug release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the drug in microemulsions that are compatible with body tissues.

For topical use the compounds and micelles of the present invention can also be prepared in suitable forms to be applied to the skin, or mucus membranes of the nose and throat, and can take the form of creams, ointments, liquid sprays or inhalants, lozenges, or throat paints. Such topical formulations further can include chemical compounds such as dimethylsulfoxide (DMSO) to facilitate surface penetration of the active ingredient. For topical preparations, a sterile formulation of daptomycin, daptomycin-related lipopeptide, suitable salt forms thereof, or a lipopeptide micelle may be administered in a cream, ointment, spray or other topical dressing. Topical preparations may also be in the form of bandages that have been impregnated with purified daptomycin, daptomycin-related lipopeptide or a lipopeptide micelle composition.

For application to the eyes or ears, the compounds of the present invention can be presented in liquid or semi-liquid form formulated in hydrophobic or hydrophilic bases as ointments, creams, lotions, paints or powders.

For rectal administration the compounds of the present invention can be administered in the form of suppositories admixed with conventional carriers such as cocoa butter, wax or other glyceride.

For aerosol preparations, a sterile formulation of purified daptomycin or a daptomycin-related lipopeptide or salt form of the compound may be used in inhalers, such as metered dose inhalers, and nebulizers. A sterile formulation of a lipopeptide

micelle may also be used for aerosol preparation. Aerosolized forms may be especially useful for treating respiratory infections, such as pneumonia and sinus-based infections.

Alternatively, the compounds of the present invention can be in powder form for reconstitution in the appropriate pharmaceutically acceptable carrier at the time of delivery. If the powder form is to be reconstituted as lipopeptide micelles, the powder may comprise a buffer and/or salt such that reconstitution with a particular quantity of sterile water or saline will cause the lipopeptide to form micelles. Alternatively, the powder form may contain instructions regarding the quantity and type of pharmaceutically acceptable carrier is to be used to reconstitute the lipopeptide in order to obtain micelles. In another embodiment, the unit dosage form of the compound can be a solution of the compound, a salt thereof, or a lipopeptide micelle in a suitable diluent in sterile, hermetically sealed ampules. The concentration of the compound in the unit dosage may vary, e.g. from about 1 percent to about 50 percent, depending on the compound used and its solubility and the dose desired by the physician. If the compositions contain dosage units, each dosage unit preferably contains from 50-500 mg of the active material. For adult human treatment, the dosage employed preferably ranges from 100 mg to 3 g, per day, depending on the route and frequency of administration.

In a further aspect, this invention provides a method for treating an infection, especially those caused by gram-positive bacteria, in humans and other animals. The term "treating" is used to denote both the prevention of an infection and the control of an established infection after the host animal has become infected. An established infection may be one that is acute or chronic. The method comprises administering to the human or other animal an effective dose of a compound of this invention. An effective dose is generally between about 0.1 and about 25 mg/kg purified daptomycin, daptomycin-related lipopeptide or pharmaceutically acceptable salts thereof. The daptomycin or daptomycin-related lipopeptide may be monomeric or may be part of a lipopeptide micelle. A preferred dose is from about 1 to about 25 mg/kg of purified daptomycin or daptomycin-related lipopeptide or pharmaceutically acceptable salts

thereof. A more preferred dose is from about 1 to 12 mg/kg purified daptomycin or a pharmaceutically acceptable salt thereof.

In one embodiment, the invention provides a method for treating an infection, especially those caused by gram-positive bacteria, in a subject with a therapeutically-effective amount of daptomycin or other antibacterial lipopeptide. The daptomycin or antibacterial lipopeptide may be monomeric or in a lipopeptide micelle. Exemplary procedures for delivering an antibacterial agent are described in U.S. Patent No. 5,041,567, issued to Rogers and in PCT patent application number EP94/02552 (publication no. WO 95/05384), the entire contents of which documents are incorporated in their entirety herein by reference. As used herein the phrase "therapeutically-effective amount" means an amount of daptomycin or antibacterial lipopeptide according to the present invention that prevents the onset, alleviates the symptoms, or stops the progression of a bacterial infection. The term "treating" is defined as administering, to a subject, a therapeutically-effective amount of a compound of the invention, both to prevent the occurrence of an infection and to control or eliminate an infection. The term "subject", as described herein, is defined as a mammal, a plant or a cell culture. In a preferred embodiment, a subject is a human or other animal patient in need of lipopeptide compound treatment.

The lipopeptide antibiotic compound can be administered as a single daily dose or in multiple doses per day. The treatment regime may require administration over extended periods of time, e.g., for several days or for from two to four weeks. The amount per administered dose or the total amount administered will depend on such factors as the nature and severity of the infection, the age and general health of the patient, the tolerance of the patient to the antibiotic and the microorganism or microorganisms involved in the infection. A method of administration is disclosed in United States Serial No. 09/406,568, filed September 24, 1999, herein incorporated by reference, which claims the benefit of U.S. Provisional Application Nos. 60/101,828, filed September 25, 1998, and 60/125,750, filed March 24, 1999.

The methods of the present invention comprise administering purified daptomycin or other lipopeptide antibiotic, or pharmaceutical compositions thereof to a patient in need thereof in an amount that is efficacious in reducing or eliminating the gram-positive bacterial infection. The daptomycin or lipopeptide antibiotic may be either monomeric or may be present in a lipopeptide micelle. The antibiotic may be administered orally, parenterally, by inhalation, topically, rectally, nasally, buccally, vaginally, or by an implanted reservoir, external pump or catheter. The antibiotic may be prepared for opthalmic or aerosolized uses. Purified daptomycin, lipopeptide antibiotic, or pharmaceutical compositions thereof also may be directly injected or administered into an abscess, ventricle or joint. Parenteral administration includes subcutaneous, intravenous, intramuscular, intra-articular, intra-synovial, cisternal, intrathecal, intrahepatic, intralesional and intracranial injection or infusion. In a preferred embodiment, daptomycin or other lipopeptide is administered intravenously, subcutaneously or orally.

The method of the instant invention may be used to treat a patient having a bacterial infection in which the infection is caused or exacerbated by any type of gram-positive bacteria. In a preferred embodiment, purified daptomycin, daptomycin-related lipopeptide, other lipopeptide or pharmaceutical compositions thereof are administered to a patient according to the methods of this invention. In another preferred embodiment, the bacterial infection may be caused or exacerbated by bacteria including, but not limited to, methicillin-susceptible and methicillin-resistant staphylococci (including *Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus haemolyticus, Staphylococcus hominis, Staphylococcus saprophyticus,* and coagulase-negative staphylococci), glycopeptide intermediary- susceptible *Staphylococcus aureus* (GISA), penicillin-susceptible and penicillin-resistant streptococci (including *Streptococcus pneumoniae, Streptococcus pyogenes, Streptococcus agalactiae, Streptococcus avium, Streptococcus bovis, Streptococcus lactis, Streptococcus sangius* and *Streptococci* Group C, *Streptococci* Group G and viridans streptococci), enterococci (including vancomycin-susceptible and vancomycin-resistant strains such as *Enterococcus faecalis* and

Enterococcus faecium), *Clostridium difficile*, *Clostridium clostridiiforme*, *Clostridium innocuum*, *Clostridium perfringens*, *Clostridium ramosum, Haemophilus influenzae, Listeria monocytogenes*, *Corynebacterium jeikeium*, *Bifidobacterium* spp., *Eubacterium aerofaciens, Eubacterium lentum, Lactobacillus acidophilus, Lactobacillus casei, Lactobacilllus plantarum, Lactococcus* spp., *Leuconostoc* spp., *Pediococcus*, *Peptostreptococcus anaerobius*, *Peptostreptococcus asaccarolyticus*, *Peptostreptococcus magnus, Peptostreptococcus micros, Peptostreptococcus prevotii, Peptostreptococcus productus, Propionibacterium acnes,* and *Actinomyces* spp.

The antibacterial activity of daptomycin against classically "resistant" strains is comparable to that against classically "susceptible" strains in *in vitro* experiments. In addition, the minimum inhibitory concentration (MIC) value for daptomycin against susceptible strains is typically 4-fold lower than that of vancomycin. Thus, in a preferred embodiment, purified daptomycin, daptomycin-related lipopeptide antibiotic, or pharmaceutical compositions thereof are administered according to the methods of this invention to a patient who exhibits a bacterial infection that is resistant to other antibiotics, including vancomycin. In addition, unlike glycopeptide antibiotics, daptomycin exhibits rapid, concentration-dependent bactericidal activity against gram-positive organisms. Thus, in a preferred embodiment, purified daptomycin, lipopeptide antibiotic, or pharmaceutical compositions thereof are administered according to the methods of this invention to a patient in need of rapidly acting antibiotic therapy.

The method of the instant invention may be used for a gram-positive bacterial infection of any organ or tissue in the body. These organs or tissue include, without limitation, skeletal muscle, skin, bloodstream, kidneys, heart, lung and bone. The method of the invention may be used to treat, without limitation, skin and soft tissue infections, bacteremia and urinary tract infections. The method of the invention may be used to treat community acquired respiratory infections, including, without limitation, otitis media, sinusitis, chronic bronchitis and pneumonia, including pneumonia caused by drug-resistant *Streptoococcus pneumoniae* or *Haemophilus influenzae*. The method of the invention also may be used to treat mixed infections that comprise different types of

gram-positive bacteria, or which comprise both gram-positive and gram-negative bacteria, including aerobic, caprophilic or anaerobic bacteria. These types of infections include intra-abdominal infections and obstetrical/gynecological infections. The methods of the invention may be used in step-down therapy for hospital infections, including, without limitation, pneumonia, intra-abdominal sepsis, skin and soft tissue infections and bone and joint infections. The method of the invention also may be used to treat an infection including, without limitation, endocarditis, nephritis, septic arthritis and osteomyelitis. In a preferred embodiment, any of the above-described diseases may be treated using purified daptomycin, lipopeptide antibiotic, or pharmaceutical compositions thereof. Further, the diseases may be treated using daptomycin or lipopeptide antibiotic in either a monomeric or micellar form.

Daptomycin, daptomycin-related lipopeptide or other lipopeptide may also be administered in the diet or feed of a patient or animal. If administered as part of a total dietary intake, the amount of daptomycin or other lipopeptide can be less than 1% by weight of the diet and preferably no more than 0.5% by weight. The diet for animals can be normal foodstuffs to which daptomycin or lipopeptide can be added or it can be added to a premix.

The method of the instant invention may also be practiced while concurrently administering one or more antifungal agents and/or one or more antibiotics other than daptomycin or other lipopeptide antibiotic. Co-administration of an antifungal agent and an antibiotic other than daptomycin or another lipopeptide antibiotic may be useful for mixed infections such as those caused by different types of gram-positive bacteria, those caused by both gram-positive and gram-negative bacteria, or those that caused by both bacteria and fungus. Furthermore, daptomycin or other lipopeptide antibiotic may improve the toxicity profile of one or more co-administered antibiotics. It has been shown that administration of daptomycin and an aminoglycoside may ameliorate renal toxicity caused by the aminoglycoside. In a preferred embodiment, an antibiotic and/or antifungal agent may be administered concurrently with purified daptomycin, other

lipopeptide antibiotic, or in pharmaceutical compositions comprising purified daptomycin or another lipopeptide antibiotic.

Co-administration of another therapeutic agent with daptomycin or another lipopeptide antibiotic may be performed using daptomycin or lipopeptide antibiotic in either a monomeric or micellar form. As discussed *supra*, spherical lipopeptide micelles can be used to help solubilize agents that exhibit low aqueous solubility. Further, lipopeptide liposomes can be used to trap agents that are soluble in aqueous media inside the vesicle of the liposomes. By following the teachings of the specification, one having ordinary skill in the art would be able to make lipopeptide micelles comprising therapeutic agents, such as anti-inflammatory agents, anti-fungal agents and other antibiotics.

Antibacterial agents and classes thereof that may be co-administered with daptomycin or other lipopeptide antibiotics include, without limitation, penicillins and related drugs, carbapenems, cephalosporins and related drugs, aminoglycosides, bacitracin, gramicidin, mupirocin, chloramphenicol, thiamphenicol, fusidate sodium, lincomycin, clindamycin, macrolides, novobiocin, polymyxins, rifamycins, spectinomycin, tetracyclines, vancomycin, teicoplanin, streptogramins, anti-folate agents including sulfonamides, trimethoprim and its combinations and pyrimethamine, synthetic antibacterials including nitrofurans, methenamine mandelate and methenamine hippurate, nitroimidazoles, quinolones, fluoroquinolones, isoniazid, ethambutol, pyrazinamide, para-aminosalicylic acid (PAS), cycloserine, capreomycin, ethionamide, prothionamide, thiacetazone, viomycin, eveminomycin, glycopeptide, glycylcylcline, ketolides, oxazolidinone; imipenen, amikacin, netilmicin, fosfomycin, gentamicin, ceftriaxone, Ziracin, LY 333328, CL 331002, HMR 3647, Linezolid, Synercid, Aztreonam, and Metronidazole, Epiroprim, OCA-983, GV-143253, Sanfetrinem sodium, CS-834, Biapenem, A-99058.1, A-165600, A-179796, KA 159, Dynemicin A, DX8739, DU 6681; Cefluprenam, ER 35786, Cefoselis, Sanfetrinem celexetil, HGP-31, Cefpirome, HMR-3647, RU-59863, Mersacidin, KP 736, Rifalazil; Kosan, AM 1732, MEN 10700, Lenapenem, BO 2502A, NE-1530, PR 39, K130, OPC 20000, OPC 2045, Veneprim, PD

138312, PD 140248, CP 111905, Sulopenem, ritipenam acoxyl, RO-65-5788, Cyclothialidine, Sch-40832, SEP-132613, micacocidin A, SB-275833, SR-15402, SUN A0026, TOC 39, carumonam, Cefozopran, Cefetamet pivoxil, and T 3811.

In a preferred embodiment, antibacterial agents that may be co-administered with daptomycin according to this invention include, without limitation, imipenen, amikacin, netilmicin, fosfomycin, gentamicin, ceftriaxone, teicoplanin, Ziracin, LY 333328, CL 331002, HMR 3647, Linezolid, Synercid, Aztreonam, and Metronidazole.

Antifungal agents that may be co-administered with daptomycin or other lipopeptide antibiotic include, without limitation, Caspofungen, Voriconazole, Sertaconazole, IB-367, FK-463, LY-303366, Sch-56592, Sitafloxacin, DB-289 polyenes, such as Amphotericin, Nystatin, Primaricin; azoles, such as Fluconazole, Itraconazole, and Ketoconazole; allylamines, such as Naftifine and Terbinafine; and anti-metabolites such as Flucytosine. Other antifungal agents include without limitation, those disclosed in Fostel et al., Drug Discovery Today 5:25-32 (2000), herein incorporated by reference. Fostel et al. disclose antifungal compounds including Corynecandin, Mer-WF3010, Fusacandins, Artrichitin/LL 15G256γ, Sordarins, Cispentacin, Azoxybacillin, Aureobasidin and Khafrefungin.

Daptomycin or other lipopeptide antibiotic, including daptomycin-related lipopeptides, may be administered according to this method until the bacterial infection is eradicated or reduced. In one embodiment, daptomycin or other lipopeptide is administered for a period of time from 3 days to 6 months. In a preferred embodiment, daptomycin or other lipopeptide is administered for 7 to 56 days. In a more preferred embodiment, daptomycin or other lipopeptide is administered for 7 to 28 days. In an even more preferred embodiment, daptomycin or other lipopeptide is administered for 7 to 14 days. Daptomycin or other lipopeptide may be administered for a longer or shorter time period if it is so desired.

In order that this invention may be more fully understood, the following examples are set forth. These examples are for the purpose of illustration only and are not to be construed as limiting the scope of the invention in any way.

EXAMPLE 1

A fermentation culture of *S. roseosporus* NRRL Strain 15998 is conducted in a controlled decanoic acid feed fermentation at levels that optimize the production of the antibiotic while minimizing the production of contaminants. The residual decanoic acid feed is measured by gas chromatography and the target residual level is 10 ppm decanoic acid from the start of induction (approximately at hour 30) until harvest. Centrifugation of the culture and subsequent analysis of the clarified broth are used to measure the production of daptomycin by HPLC. The harvest titer is typically between 2.1 and 2.6 grams per liter of fermentation broth.

The fermentation is harvested either by microfiltration using a Pall-Sep or by full commercial-scale centrifugation and depth filter. The clarified broth is applied to an anion exchange resin, Mitsubishi FP-DA 13, washed with 30 mM NaCl at pH 6.5 and eluted with 300 mM NaCl at pH 6.0-6.5. Alternatively, the FP-DA 13 column is washed with 60 mM NaCl at pH 6.5 and eluted with 500 mM NaCl at pH 6.0-6.5. The eluate is applied to a HIC resin, HP-20ss, washed with 30% acetonitrile, and eluted with 35% acetonitrile at pH 4.0-5.0. Alternatively, the HIC resin is washed with 45% isopropyl alcohol and eluted with 55-60% isopropyl alcohol. The eluate is applied to FP-DA 13 resin and washed and eluted as before. The final anion exchange step reduces solvent by one third or more. Reverse osmosis diafiltration and concentration at pH 1.5-2.5 is performed using an 0.2 μm filter and the daptomycin preparation is frozen. A final reverse osmosis diafiltration is conducted with Water-For-Injection (WFI) to wash daptomycin and adjust its concentration prior to sterile-filling. Vials or bulk quantities of daptomycin are then lyophilized.

EXAMPLE 2

Daptomycin was produced in a fermentation culture of *S. roseosporus* and partially purified Daptomycin (9.9 Kg) was purified by microfiltration from 5500 liters of fermentation broth by the method described in United States Patent 4,885,243. The partially purified daptomycin was further purified by the method described in US. Pat. No. 4,874,843, and resulted in a bulk daptomycin preparation with a purity of 91%. The daptomycin preparation contained fourteen impurities by HPLC analysis (see Example 10). The daptomycin preparation was applied to a Poros P150 anion exchange resin (PE Biosystems) in Tris buffer pH 7.0 containing 6M urea and allowed to bind to the resin. The resin was washed with three column volumes of buffer prior to initiation of a NaCl gradient in the same buffer. Alternatively, the contaminants can be effectively removed from the column with a fixed salt level of 30 mM NaCl. The elution of purified daptomycin from the resin occurred at approximately 300 mM NaCl during a 0 to 1000 mM NaCl gradient. Daptomycin eluted from the column was greater than 99 % pure as measured by the "first" HPLC method. The purified daptomycin contained only one detectable daptomycin contaminant. Anhydro-daptomycin and ß-isomer were undetectable (less than 0.01% contamination). The level of the unidentified contaminant was greater than 0.1% and less than 0.5%.

EXAMPLE 3

A bulk daptomycin preparation with a purity of 91% was prepared as described in Example 2. The product was applied to a Poros D50 anion exchange resin (PE Biosystems) in an acetate buffer pH 7.0 containing 6M urea. The Poros D50 resin was washed and eluted in the same manner as described in Example 2. Daptomycin eluted from the column was 96.92 % pure as measured by the "second" HPLC method. The product of this invention contained only two of the initial fourteen impurities (less than 0.5% contamination). Anhydro-daptomycin could not be detected in the purified daptomycin preparation (less than 0.01% contamination and with precise quantitation at less than 0.05%).

EXAMPLE 4

A fermentation broth containing daptomycin was produced as described in Example 2. The fermentation broth was clarified by microfiltration. The clarified product was extracted with 20% n-butanol or iso-butanol at pH 4.5 (one part butanol to four parts clarified solution). Re-extraction of the clarified solution was performed to achieve a yield of partially purified daptomycin of greater than 90% of the total daptomycin in the clarified solution. Daptomycin was recovered from the butanol phase by the addition of a pH 6.5 aqueous buffer in a volume that is one-half or more of the volume of butanol to extract daptomycin from the butanol phase into the aqueous phase. The butanol extraction step resulted in a partially purified daptomycin preparation that was purified 5-fold and concentrated 10-fold relative to the clarified solution.

The aqueous daptomycin preparation was then purified by the method disclosed in US. Pat. No. 4,874,843, resulting in daptomycin that was 91% pure. Daptomycin contained fourteen impurities. The product was applied to a Poros D50 resin in a Tris buffer at pH 7.0 containing 6M urea. The resin was washed with three bed volumes of Tris buffer at pH 7.0 containing 6M urea prior to initiation of a NaCl gradient from 0 to 1000 mM in the same buffer. Elution of purified daptomycin from the resin occurred at approximately 300 mM NaCl. Daptomycin was 98% pure as measured by the "second" HPLC method.

EXAMPLE 5

Daptomycin is fermented as described in Example 2. The 5500 liters fermentation broth contains 13 Kg daptomycin. The fermentation broth is directly extracted with 20% n-butanol at pH 4.5, which partitions daptomycin into the butanol. Re-extractions of the fermentation broth with butanol are performed to achieve a yield of greater than 90% of the total daptomycin in the fermentation broth. The butanol phase is extracted with an aqueous acetate buffer at pH 6.5, resulting in daptomycin that is purified 5-fold (35%) and concentrated 10-fold relative to the fermentation broth. The aqueous daptomycin is microfiltered by the method described in United States Patent

4,885,243, then purified by the method of US. Pat. No. 4,874,843. This method results in daptomycin with a purity of approximately 91%. Daptomycin contains 14 impurities by the HPLC method used at the time of the prior art. The product is applied to a Poros D50 resin column in a acetate buffer at pH 7.0 containing 6M urea. Washing and elution of the resin is performed as indicated in Example 2. The product of the chromatographic step is approximately 98% to 99% pure as measured by the second HPLC method.

EXAMPLE 6

Daptomycin was produced in a fermentation culture of *S. roseosporus* except a reduced residual decanoic acid feed was used in order to improve the quality of the fermentation to about 10% purity when clarified by microfiltration or centrifugation. The decanoic acid level was monitored and periodically adjusted to maintain the residual decanoic acid levels at less than 50 ppm and preferably between 1 and 10 ppm during fermentation. The fermentation broth was microfiltered by the method described in United States Patent 4,885,243 to produce 12.1 Kg partially purified daptomycin from 5500 liters of fermentation broth. Clarified fermentation broth was bound to the anion exchanger, FP-DA 13 (Mitsubishi) in acetate buffer at neutral pH, washed in acetate buffer containing 30 mM NaCl, and subsequently eluted with acetate buffer at 300 mM NaCl. This anion exchange step produced daptomycin with a purity of greater than 70%. This partially purified daptomycin was further purified by the method of United States Patent 4,874,843 with the modification that HP-20ss resin was used. Specifically, the partially purified daptomycin was loaded on HP-20ss in acetate buffer containing 10% acetonitrile, washed with acetate buffer containing 30% acetonitrile and eluted with 40% acetonitrile in acetate buffer, resulting in daptomycin with a purity of about 94 to 96% as measured by the "second" HPLC method. The product is subjected to modified buffer enhanced anion exchange chromatography using Poros D50 resin as described in Example 5. Daptomycin is greater than 99 % pure and contains only two of the fourteen impurities produced by methods described in the prior art.

EXAMPLE 7

A daptomycin preparation with a purity of 93% was prepared as described in Example 2. The product was applied to a Poros P150 resin (PE Biosystems) in an acetate buffer pH 6.0 containing 2M urea. The Poros P150 resin was washed with three column volumes of the buffer. Daptomycin was eluted from the resin using a 0 to 400 mM NaCl gradient in the acetate buffer pH 6.0 containing 2M urea. Daptomycin eluted between 150 and 300 mM NaCl. Daptomycin eluted from the column was 99.0 to 99.5 % pure as measured by the "first" HPLC method. Daptomycin contained trace amounts of four impurities that were less than 1% of the total of daptomycin. Anhydro-daptomycin could not be detected in the purified daptomycin preparation (less than 0.02% contamination).

EXAMPLE 8

A daptomycin preparation with a purity of 93% was prepared as described in Example 2. The product was applied to a Poros P150 resin (PE Biosystems) in an acetate buffer pH 6.0 containing 2M urea. The column was washed with six column volumes of 60 mM NaCl in acetate buffer pH 6.0 containing 2M urea (the "wash buffer"). The wash buffer may vary from 50-75 mM NaCl. The wash removes virtually all anhydro-daptomycin. Daptomycin is eluted with sixteen column volumes of 250 mM NaCl in acetate buffer pH 6.0 containing 2M urea. Daptomycin is 98.5 to 99.5% pure as measured by the "first" HPLC method.

EXAMPLE 9

A daptomycin preparation as described in Example 2 was prepared using a method that significantly reduced the concentration of solvent required to perform the HP-20ss chromatography. Unexpectedly, the solvent for elution of daptomycin, 40% acetonitrile or 55-60% isopropyl alcohol, was reduced to 12% and 25%, respectively, when HP-20ss chromatography was conducted at neutral pH rather than acidic pH as described in United States Patent 4,874,843. In a preferred embodiment, pH shifts can be used to recycle the HP-20ss resin without solvent removal.

After elution from a FP-DA13 column at pH 6.5-7.0, daptomycin is loaded on an equilibrated HP-20ss column, such as one that has been equilibrated in 60 mM acetate, pH 6.6. The column is washed with five to eight column bed volumes (CBV) wash buffer. An exemplary wash buffer is 5% isopropyl alcohol/60mM acetate, pH 6.6. Daptomycin is eluted from the column with elution buffer. An exemplary elution buffer is two to three CBV 25% isopropyl alcohol/60 mM acetate pH 6.6. The column is stripped with strip buffer. In one embodiment, the column is stripped with one CBV 40% isopropyl alcohol/60 mM acetate pH 6.6-7.0. The daptomycin solution is adjusted to pH 3.5-4.0 and is reloaded on to the HP-20ss column in order to further enhance purity. In one embodiment, the daptomycin eluted from the HP-20ss column at pH 6.5 is adjusted to pH 3.5 using 0.25M phosphoric acid. The daptomycin solution is reloaded on the previously stripped HP-20ss column that has been equilibrated in 60 mM acetate, pH 3.5.

The column is washed with a pH adjusting buffer such that the pH is 6.5. An exemplary pH adjusting buffer is five to eight CBV 5% isopropyl alcohol/60 mM acetate, pH 6.6. The daptomycin is eluted with elution buffer and may be further purified by anion exchange or other purification methods, if desired. The HP-20ss column is stripped with strip buffer and cleaned prior to reuse. An exemplary cleaning process includes washing with three CBV 0.5M NaOH, washing with one CBV water, and then washing with 0.25M phosphoric acid prior to equilibration. The column may be stored in 0.5M NaOH.

EXAMPLE 10

Bulk daptomycin prepared as described in Example 2 was characterized via semi-preparative HPLC and characterized by liquid chromatography/mass spectroscopy (LC/MS) using both positive and negative ion modes. An impurity profile of the bulk daptomycin prior to chromatography on the Poros P150 anion exchange resin is shown in Table 3 and a chromatogram of the bulk daptomycin preparation is shown in Fig. 12.

Table 3

Impurity ID	Retention Time	Observed MW	Lilly ID	Cubist ID	% of Total Area by HPLC
1	7.96	1638	LY212218	CB-131012	>0.5%, <1.0%
2	9.11	1638		CB-131011	<0.5%, >0.1%
3	11.54	745	LY213928	CB-131008	>0.5%, <1.0%
4	12.28	1624		CB-131006	<0.5%, >0.1%
5	13.10	1618		Unknown-1	<0.5%, >0.1%
6	14.43	587	LY213827	CB-130989	>0.5%, <1.0%
7	14.43	1606		CB-131005	>0.5%, <1.0%
8	15.10	1620	LY213846	CB-131010	>1.0%, <4.0%
Dapto-mycin	16.68	1620	LY146032	CB-109187	>90%
9	17.92	874		Unknown-2	<0.5%, >0.1%
10	19.57	1810		Unknown-3	<0.5%, >0.1%
11	19.57	1635		Unknown-4	<0.5%, >0.1%
12	20.93	859		CB-131009	<0.5%, >0.1%
13	23.11	1602	LY178480	CB-130952	>1.0, < 4.0%
14	24.53	1634	LY109208	CB-131078	<0.1

Impurity 1 (CB-131012), which elutes at approximately 7.96 minutes, (MW: 1638) is proposed to be a lactone hydrolysis product of daptomycin (Fig. 4). The results seem to match LY212218 as previously identified by Lilly as a decyl ring opened derivative of daptomycin.

Impurity 2 (CB-131011), which elutes at approximately 9.11 minutes, (MW: 1638) is also proposed to be a lactone hydrolysis product of the β-isomer (Fig. 5).

Impurity 3 (CB-131008), which elutes at approximately 11.54 minutes, (MW: 745) is proposed to be a linear lipopeptide consisting of a five amino acid chain

containing tryptophan, asparagine, aspartate, threonine and glycine with a decanoic acid chain (Fig. 6). This result seems to match LY213928 as previously identified by Lilly.

Impurity 4 (CB-131006), which elutes at approximately 12.28 minutes, (MW: 1624) is proposed to be an oxidative analog of daptomycin in which the amino acid tryptophan has been oxidized to kynuric acid (Fig. 7).

Impurity 5, which elutes at approximately 13.10 minutes, (MW: 1618) has not yet been assigned a structure.

Impurity 6 (CB-130989) and *Impurity 7* (CB-131005) co-elute at approximately 14.43 minutes. CB-130989 (MW: 587) seems to match LY213827 a linear lipopeptide consisting of a three amino acid chain of tryptophan, asparagine and aspartate with a decanoic acid chain (Fig. 8), as previously identified by Lilly. CB-131005 (MW:1606) corresponds to a daptomycin analog in which the decanoic acid lacks one methyl group (Fig. 9).

Impurity 8 (CB-131010), elutes at approximately 15.10 minutes, (MW: 1620) matches LY213846 (ß-isomer) as previously identified by Lilly (Fig. 2). Levels of ß-isomer are greater than 1%.

Impurity 9, which elutes at approximately 17.92 minutes (MW: 874), has not yet been assigned a structure.

Impurity 10 and 11, which co-elute at approximately 19.57 minutes, have not been assigned a structure.

Impurity 12 (CB-131009), which elutes at 20.93 minutes (MW: 859), is proposed to be a linear lipopeptide consisting of a six amino acid chain of tryptophan, asparagine, aspartate, threonine, glycine and ornithine with a decanoic acid chain (Fig. 10).

Impurity 13 (CB-130952), which elutes at approximately 23.11 minutes (MW: 1602), is proposed to be anhydro-daptomycin (Fig. 3), and appears to be the same as LY178480. Levels of anhydro-daptomycin are greater than 1%.

Impurity 14 (CB-131078), which elutes at approximately 24.53 minutes (MW: 1634), appears to be the same as LY109208, previously identified by Lilly as a

daptomycin analog containing an extra methyl group in the decanoic acid chain (Fig. 11).

The bulk daptomycin may be purified on Poros P150 as described above in Examples 2 or 7-8 or may be purified on Poros D50 as described above in Examples 3-5. After purification on Poros P150 as described in Example 2, a chromatogram (Fig. 13) shows that daptomycin purity is greater than 99.0%, with ß-isomer and anhydro-daptomycin below the level of detection (less than 0.05% of total). There is one unidentified impurity which is present in a quantity of greater than 0.1% but less than 0.5%.

EXAMPLE 11

A fermentation culture of *S. roseosporus* NRRL Strain 15998 is conducted in a controlled decanoic acid feed fermentation at levels that optimize the production of the antibiotic while minimizing the production of contaminants. The residual decanoic acid feed is measured by gas chromatography and the target residual level is 10 ppm decanoic acid from the start of induction (approximately at hour 30) until harvest. Centrifugation of the culture and subsequent analysis of the clarified broth are used to measure the production of daptomycin by HPLC. The harvest titer is typically between 1.0 and 3.0 grams per liter of fermentation broth.

The fermentation is harvested either by microfiltration using a Pall-Sep or by full commercial-scale centrifugation and depth filter. The clarified broth is applied to an anion exchange resin, Mitsubishi FP-DA 13, washed with 30 mM NaCl at pH 6.5 and eluted with 300 mM NaCl at pH 6.0-6.5. Alternatively, the FP-DA 13 column is washed with 60 mM NaCl at pH 6.5 and eluted with 500 mM NaCl at pH 6.0-6.5. The pH is adjusted to 3.0 to 4.8 and the temperature is adjusted to 2-15°C. Under these conditions, daptomycin forms a micelle. The micellar daptomycin solution is purified by washing the micellar preparation while it is retained on a ultrafilter using a 10,000 NMW filter (AG Technology Corp. UF hollow fiber or equivalent) in any configuration. The daptomycin micelles are retained by the filter, but a large number of impurities are eliminated because they pass through the 10,000 NMW filter. Ultrafiltration of

daptomycin micelles increases daptomycin purity from approximately 40% to 80% or greater.

The eluate is applied to a HIC resin, HP-20ss, washed with 30% acetonitrile, and eluted with 35% acetonitrile at pH 4.0-5.0. Alternatively, the HIC resin is washed with 20-30% isopropyl alcohol and eluted with 30-40% isopropyl alcohol at pH 3.5-6.5. Under these conditions of increased solvent and a higher pH of 6.0-7.5, daptomycin reverts to a single, non-micelle state. The eluate is applied to FP-DA 13 resin column and washed and eluted as before. The final anion exchange step reduces solvent by one third or more. Reverse osmosis diafiltration and concentration at pH 1.5-2.5 is performed using an 0.2 μm filter and the daptomycin preparation is frozen. A final reverse osmosis diafiltration is conducted with Water-For-Injection (WFI) to wash daptomycin and adjust its concentration prior to sterile-filling. Vials or bulk quantities of daptomycin are then lyophilized.

EXAMPLE 12

Lyophilized daptomycin purified as described in any of the above-described examples, such as that described in Example 11, is reconstituted in physiologic saline (approximately 140 mM NaCl) at a pH of 4.0-5.0. Under these conditions, daptomycin is present as a micelle, and can be used for injection or intravenous, parenteral, oral or topical administration.

EXAMPLE 13

Daptomycin is produced by fermentation and clarified from the broth by microfiltration as described in Example 11. The clarified broth is applied to an anion exchange resin, Mitsubishi FP-DA 13, washed with 30 mM NaCl at pH 6.5 and eluted with 300 mM NaCl at pH 6.0-6.5 to give a daptomycin preparation that is approximately 40% pure. The eluate is adjusted to pH 3.5 with dilute phosphoric acid such that virtually all of the daptomycin forms micelles. The micelle preparation is loaded on a 10,000 NMW ultrafiltration membrane. The daptomycin preparation is washed with 30 mM

sodium acetate pH 3.5 and at temperatures of up to 15°C. The reduction in volume and washing lowers the contamination level, which results in an 85% pure daptomycin preparation. The daptomycin preparation can be further purified using any of the methods described herein.

EXAMPLE 14

Daptomycin is produced by fermentation, clarified from the broth by microfiltration, and fractionated on the FP-DA 13 resin as described in Example 11. The eluate is adjusted to pH 3.5 with dilute phosphoric acid such that virtually all of the daptomycin forms micelles. The micelle preparation is loaded on a 10,000 NMW ultrafiltration membrane. The daptomycin preparation is washed with 30 mM sodium acetate pH 3.5 and at temperatures of up to 15°C. The reduction in volume and washing lowers the contamination level, which results in an 80-90% pure daptomycin preparation. The daptomycin preparation can be further purified using any of the methods described herein.

EXAMPLE 15

Daptomycin is produced by fermentation and clarified from the broth using microfiltration as described in Example 11. The preparation is purified using hydrophobic interaction chromatography, as described in United States Patent 4,874,843, herein incorporated by reference. In this method, repeated column chromatography on HP-20 and HP-20ss resin is used. Daptomycin purity is 93% with visible impurities on HPLC chromatographs and measurable pyrogen. The product is diluted in water and its pH was adjusted to pH 6.5 with NaOH or the equivalent. The daptomycin preparation is filtered through a 10,000 NMW ultrafiltration membrane. Under these conditions, daptomycin is monomeric and passes through the ultrafiltration membrane. The resulting product remains 93% pure, but several impurities that had been present at 0.1-0.2% are removed by the ultrafiltration membrane. In addition, pyrogen content is reduced to undetectable levels.

EXAMPLE 16

A daptomycin preparation of approximately 93% purity is prepared as described in Example 15. The daptomycin preparation is converted to a micellar state by lowering the pH to 4.7 with HCl or equivalent and chilling the daptomycin preparation to 2-5°C. The product is concentrated from 400 liters to three liters and to a final concentration of approximately 100 mg/ml by filtration on a 10,000 NMW ultrafiltration membrane. Under these conditions, daptomycin is retained by the membrane. This results in a large increase in daptomycin concentration. The purity is approximately 93%.

EXAMPLE 17

A daptomycin preparation is prepared as described in Example 16. Vials are filled with approximately 250 mg daptomycin and lyophilized. The daptomycin is reconstituted in 50 ml of sterile 150 mM saline at a pH of 4.0-5.0 for administration to a human or animal patient. The dose of daptomycin that is administered will depend upon the nature of the infection, the age and weight of the patient, and the species of animal. At a pH of 4.0-5.0 in 150 mM saline, the daptomycin will be present in a micellar state, which is soluble and suitable for intravenous, intramuscular or parenteral injection. The formulation will minimize any local irritation due to the lipopeptide nature of daptomycin.

EXAMPLE 18

Daptomycin micelles were produced using daptomycin at a concentration of 1.0 mg/mL in water at pH 4.0 at 25°C. The size of a daptomycin micelle was measured using a Zetasizer™ (Malvern Instruments, Model 3000 HS). The count rate of 36.3, the cell type was a capillary cell, the detection angle (deg) was 90°, and the wavelength (nm) was 633. Results indicated that the diameter of the micelle was 54 A, which is about twice the diameter of a single monomeric daptomycin molecule. See Fig.

18.

All publications and patent applications cited in this specification are herein incorporated by reference as if each individual publication or patent application were specifically and individually indicated to be incorporated by reference. Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, it will be readily apparent to those of ordinary skill in the art in light of the teachings of this invention that certain changes and modifications may be made thereto without departing from the spirit or scope of the appended claims.

We claim:

1. A composition comprising

(a) essentially pure daptomycin,

(b) daptomycin that is substantially free of anhydro-daptomycin and substantially free of β-isomer of daptomycin,

(c) daptomycin that is essentially free of anhydro-daptomycin and substantially free of β-isomer of daptomycin,

(d) daptomycin that is free of anhydro-daptomycin and substantially free of β-isomer of daptomycin,

(e) daptomycin that is substantially free of each of impurities 1 to 14 defined by peaks 1-14 shown in FIG. 12,

(f) daptomycin that is essentially free of each of impurities 1 to 14 defined by peaks 1-14 shown in FIG. 12, or

(g) substantially pure daptomycin.

2. The composition of claim 1 comprising essentially pure daptomycin.

3. The composition of claim 1 compromising daptomycin that is substantially free of anhydro-daptomycin and substantially free of β-isomer of daptomycin.

4. The composition according to claim 3 that is essentially free of anhydro-daptomycin.

5. The composition according to claim 3 that is free of anhydro-daptomycin.

6. The composition of claim 1 that is substantially free of each of impurities 1 to 14 defined by peaks 1-14 shown in FIG. 12.

7. The composition according to claim 6 that is essentially free of each of impurities 1 to 14 defined by peaks 1-14 shown in FIG. 12.

8. The composition of claim 1, wherein daptomycin purity is measured by HPLC.

9. The composition of claim 1 further comprising a pharmaceutically acceptable carrier or excipient.

10. A pharmaceutical composition according to claim 9, further comprising one or more antibiotics, one or more antifungal agents, or both an antibiotic and an antifungal agent.

11. The composition according to claim 1 wherein the daptomycin is purified by a process comprising the steps of:

a) supplying a fermentation broth;

b) fermenting *Streptomyces roseosporus* with a feed of n-decanoic acid to produce daptomycin in the fermentation broth;

c) clarifying the fermentation broth to obtain a clarified solution;

d) subjecting the clarified solution to anion exchange chromatography to obtain an enriched daptomycin preparation;

e) subjecting the enriched daptomycin preparation to hydrophobic interaction chromatography to obtain a semi-purified daptomycin preparation; and

f) subjecting the semi-purified daptomycin preparation to anion exchange chromatography to obtain the composition of claim 1.

12. The composition according to claim 11, wherein the feed of n-decanoic acid is regulated to achieve a residual concentration of n-decanoic acid of no more than 50 parts per million (ppm) during fermentation.

13. The composition according to claim 11, wherein said clarifying comprises filtration or centrifugation and depth filtration.

14. The composition according to claim 11, wherein the anion exchange chromatography in d) is performed using a resin comprising a copolymer of 2-methacrylic acid and ethyleneglycol dimethacrylate (EDGM).

15. The composition according to claim 11, wherein the hydrophobic interaction chromatography is performed using a resin comprising a co-polymer of cross-linked divinylbenzene/stryene.

16. The composition according to claim 15, wherein the hydrophobic interaction chromatography is performed at neutral pH and a solvent concentration that is reduced compared to the solvent concentration used when performing the hydrophobic interaction chromatography at acidic pH.

17. The composition according to claim 16, wherein the resin is recycled by loading the column at an acidic pH and eluting the column at a neutral pH.

18. The composition according to claim 11, wherein the anion exchange chromatography in f) is performed using a resin comprising a copolymer of 2-methacrylic acid and ethyleneglycol dimethacrylate (EDGM).

19. The composition according to claim 11, wherein the anion exchange chromatography is used to reduce the level of solvent in the clarified solution.

20. The composition according to claim 11, wherein the anion exchange chromatography is performed via continuous flow chromatography.

21. The composition according to claim 11, wherein the process further comprises the step of filtering daptomycin.

22. The composition according to claim 11, wherein the process further comprises the step of depyrogenating daptomycin using ultrafiltration.

23. The composition according to claim 22 wherein said depyrogenating comprises the steps of:

i) providing a daptomycin solution under conditions in which the daptomycin is in a monomeric and nonmicellar state;

ii) filtering the daptomycin solution under conditions in which the daptomycin passes through the filter but pyrogens do not pass through the filter;

iii) subjecting the daptomycin solution to conditions forming a daptomycin aggregate;

iv) filtering the daptomycin aggregate under conditions in which the daptomycin aggregate is retained on the filter; and

v) collecting the daptomycin aggregate.

24. The composition according to claim 22, wherein the process further comprises the step of lyophilizing daptomycin.

25. The composition according to claim 22, wherein the anion exchange chromatography is performed via radial flow chromatography.

26. The composition according claim 11, wherein said clarifying comprises microfiltration or centrifugation.

27. The composition according to claim 11, wherein the process further comprises the steps of filtering and concentrating daptomycin.

28. The composition according to claim 11, wherein the process further comprises the step of separating the enriched daptomycin from low molecular weight material by ultrafiltration.

29. The composition according to claim 28, wherein the process further comprises the step of depyrogenating the daptomycin.

30. The composition of claim 1 comprising substantially pure daptomycin.

31. The pharmaceutical composition of claim 9 comprising essentially pure daptomycin.

32. The pharmaceutical composition of claim 9 comprising daptomycin that is substantially free of anhydro-daptomycin and substantially free of β-isomer of daptomycin.

33. The pharmaceutical composition of claim 9 comprising daptomycin that is essentially free of anhydro-daptomycin and substantially free of β-isomer of daptomycin.

34. The pharmaceutical composition of claim 9 comprising daptomycin that is free of anhydro-daptomycin and substantially free of β-isomer of daptomycin.

35. The pharmaceutical composition of claim 9 comprising daptomycin that is substantially free of each of impurities 1 to 14 defined by peaks 1-14 shown in FIG. 12.

36. The pharmaceutical composition of claim 9 comprising daptomycin that is essentially free of each of impurities 1 to 14 defined by peaks 1-14 shown in FIG.

12.

37. The pharmaceutical composition of claim 9 comprising substantially pure daptomycin.

38. A method for preparing a pharmaceutical composition comprising combining the composition of claim 1 with a pharmaceutically acceptable carrier or excipient.

39. The method of claim 38 wherein the composition is essentially pure daptomycin.

40. The method of claim 38 wherein the composition is daptomycin that is substantially free of anhydro-daptomycin and substantially free of β-isomer of daptomycin.

41. The method of claim 38 wherein the composition is daptomycin that is essentially free of anhydro-daptomycin and substantially free of β-isomer of daptomycin.

42. The method of claim 38 wherein the composition is daptomycin that is free of anhydro-daptomycin and substantially free of β-isomer of daptomycin.

43. The method of claim 38 wherein the composition is daptomycin that is substantially free of each of impurities 1 to 14 defined by peaks 1-14 shown in FIG. 12.

44. The method of claim 38 wherein the composition is daptomycin that is essentially free of each of impurities 1 to 14 defined by peaks 1-14 shown in FIG. 12.

45. The method of claim 38 wherein the composition is substantially pure daptomycin.

46. A pharmaceutical composition prepared by the method of claim 38.

47. The pharmaceutical composition of claim 46 wherein the composition is essentially pure daptomycin.

48. The pharmaceutical composition of claim 46 wherein the composition is daptomycin that is substantially free of anhydro-daptomycin and substantially free of β-isomer of daptomycin.

49. The pharmaceutical composition of claim 46 wherein the composition is daptomycin that is essentially free of anhydro-daptomycin and substantially free of

β-isomer of daptomycin.

50. The pharmaceutical composition of claim 46 wherein the composition is daptomycin that is free of anhydro-daptomycin and substantially free of β-isomer of daptomycin.

51. The pharmaceutical composition of claim 46 wherein the composition is daptomycin that is substantially free of each of impurities 1 to 14 defined by peaks 1-14 shown in FIG. 12.

52. The pharmaceutical composition of claim 46 wherein the composition is daptomycin that is essentially free of each of impurities 1 to 14 defined by peaks 1-14 shown in FIG. 12.

53. The pharmaceutical composition of claim 46 wherein the composition is substantially pure daptomycin.

ABSTRACT

The invention discloses highly purified daptomycin and to pharmaceutical compositions comprising this compound. The invention discloses a method of purifying daptomycin comprising the sequential steps of anion exchange chromatography, hydrophobic interaction chromatography and anion exchange chromatography. The invention also discloses a method of purifying daptomycin by modified buffer enhanced anion exchange chromatography. The invention also discloses an improved method for producing daptomycin by fermentation of *Streptomyces roseosporus*. The invention also discloses high pressure liquid chromatography methods for analysis of daptomycin purity. The invention also discloses lipopeptide micelles and methods of making the micelles. The invention also discloses methods of using lipopeptide micelles for purifying lipopeptide antibiotics, such as daptomycin. The invention also discloses using lipopeptide micelles therapeutically.

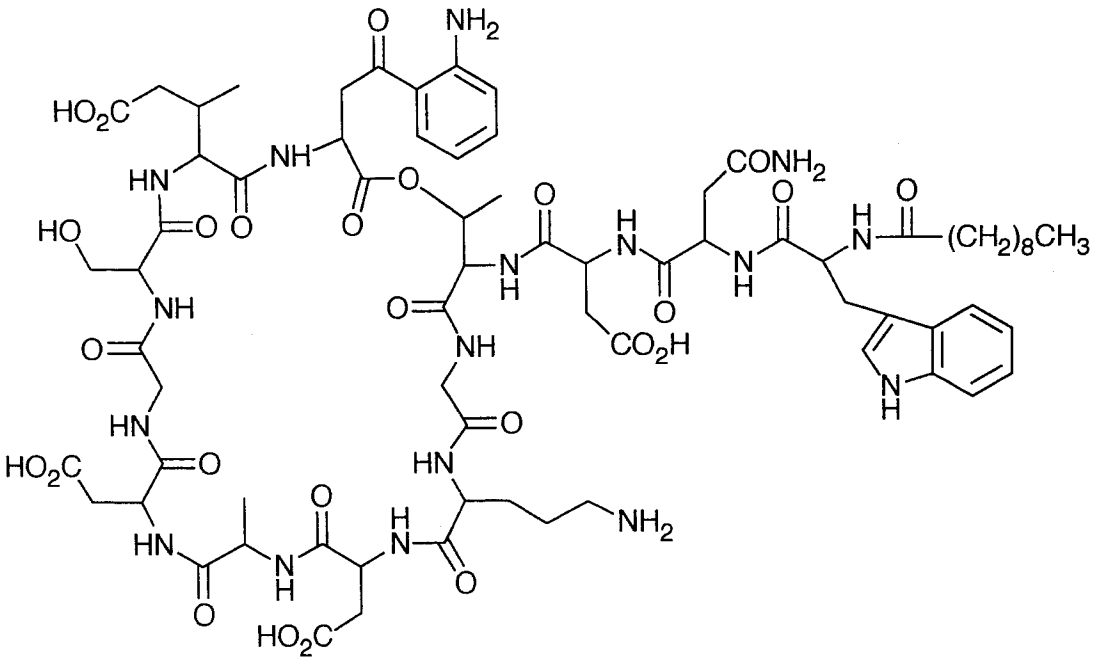


Fig. 1

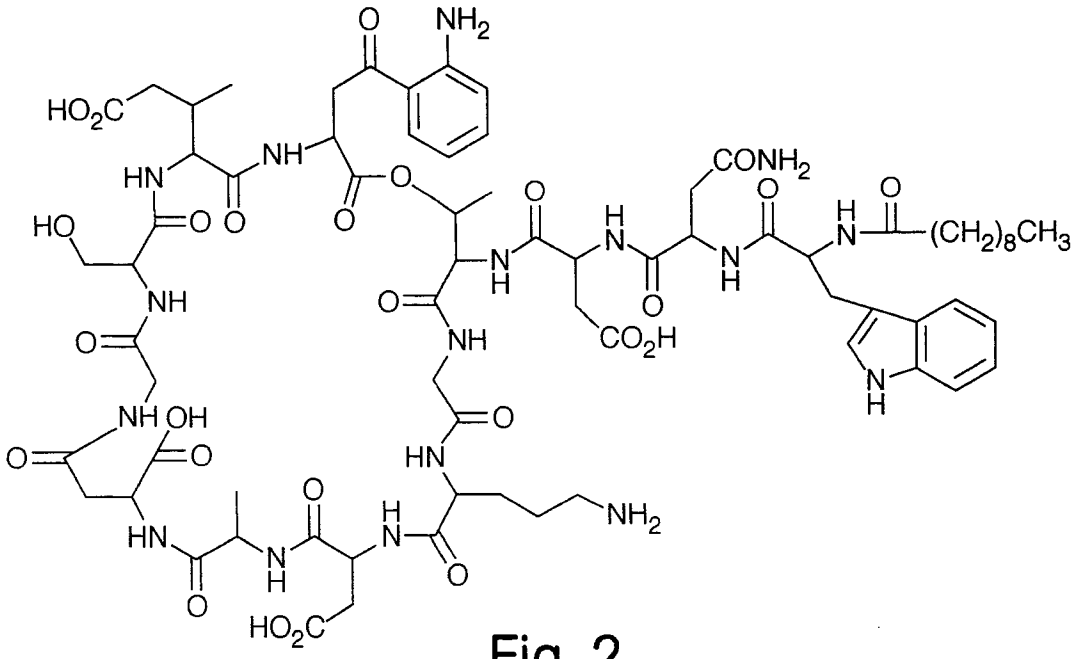


Fig. 2

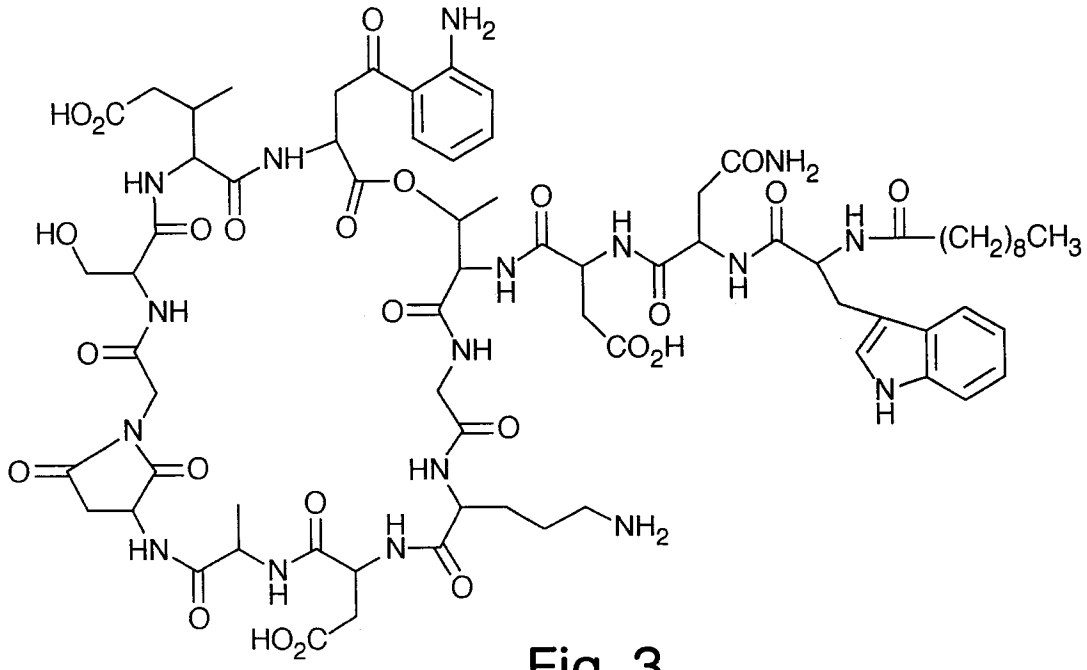


Fig. 3

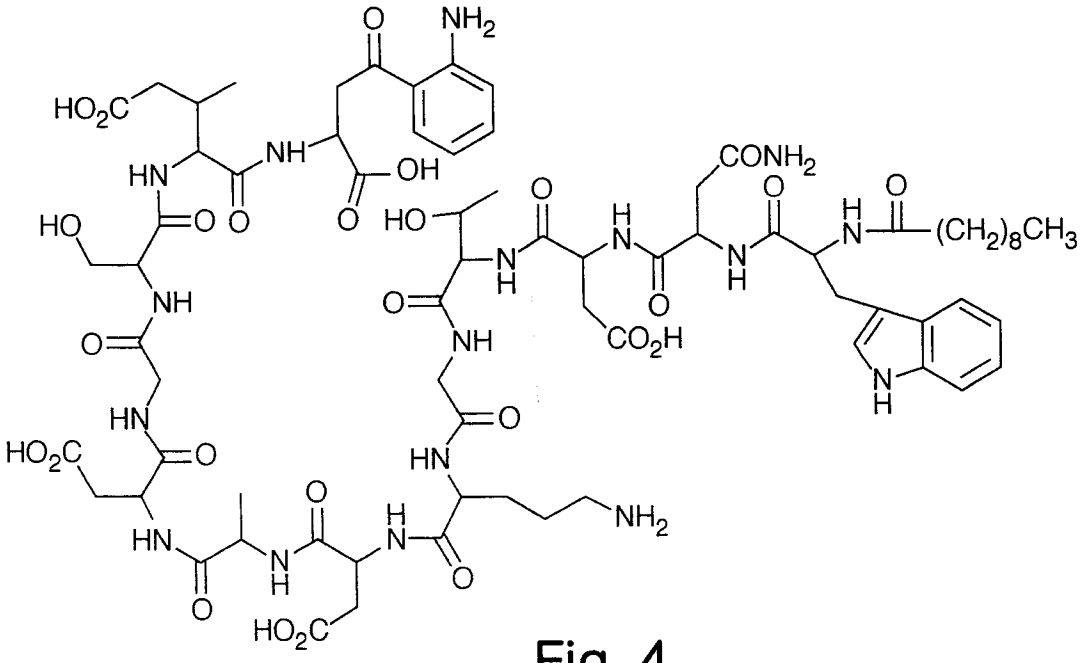


Fig. 4

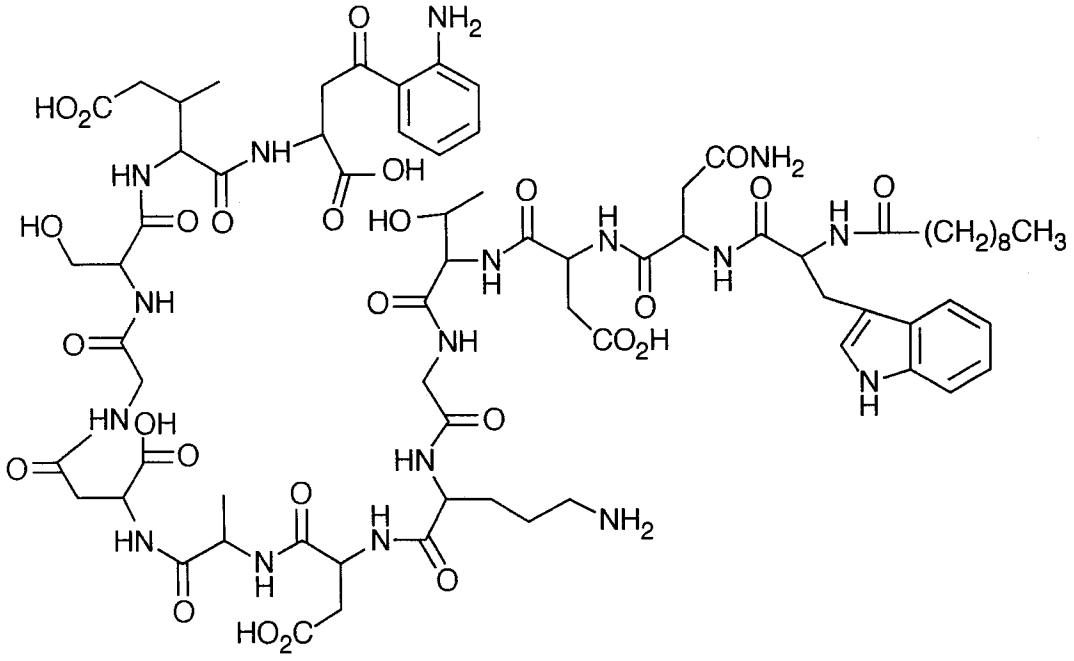


Fig. 5

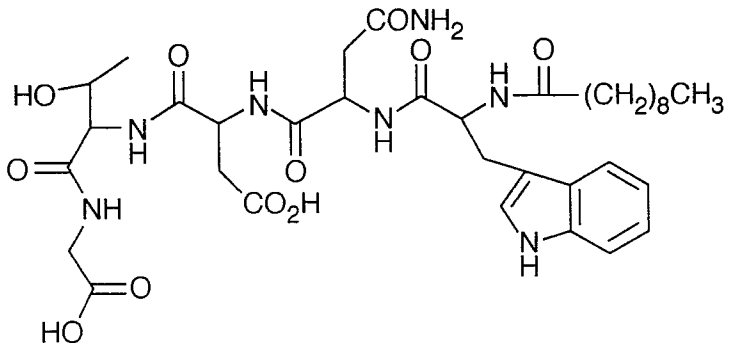


Fig. 6

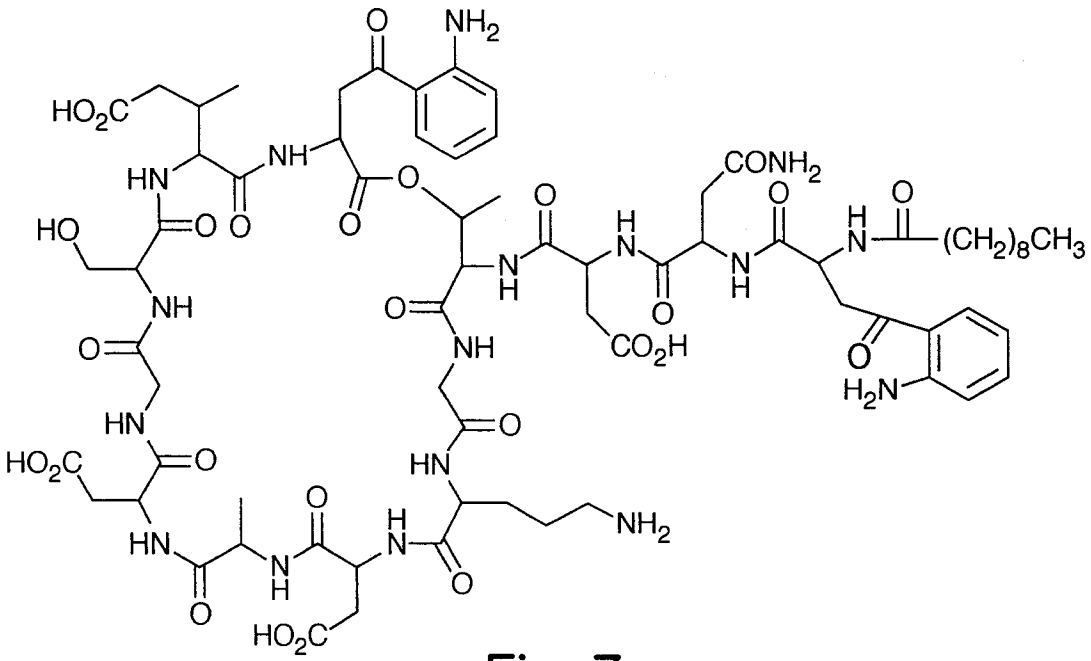


Fig. 7

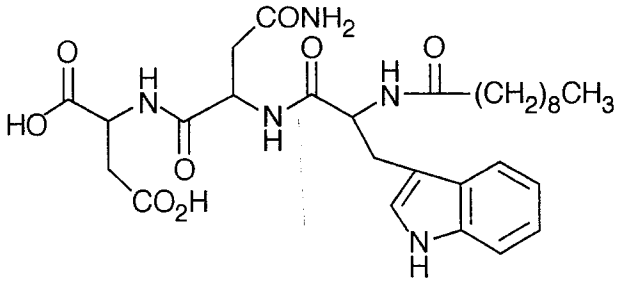


Fig. 8

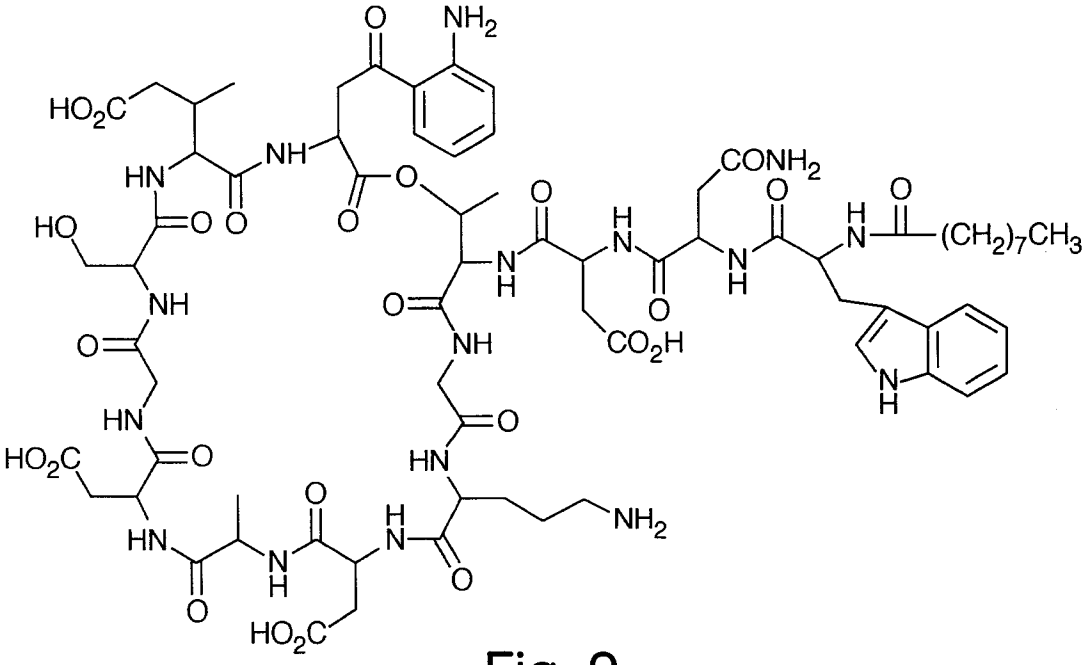


Fig. 9

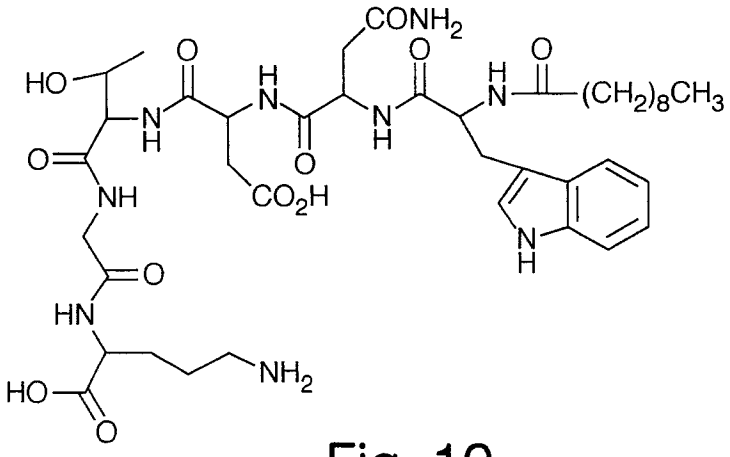


Fig. 10

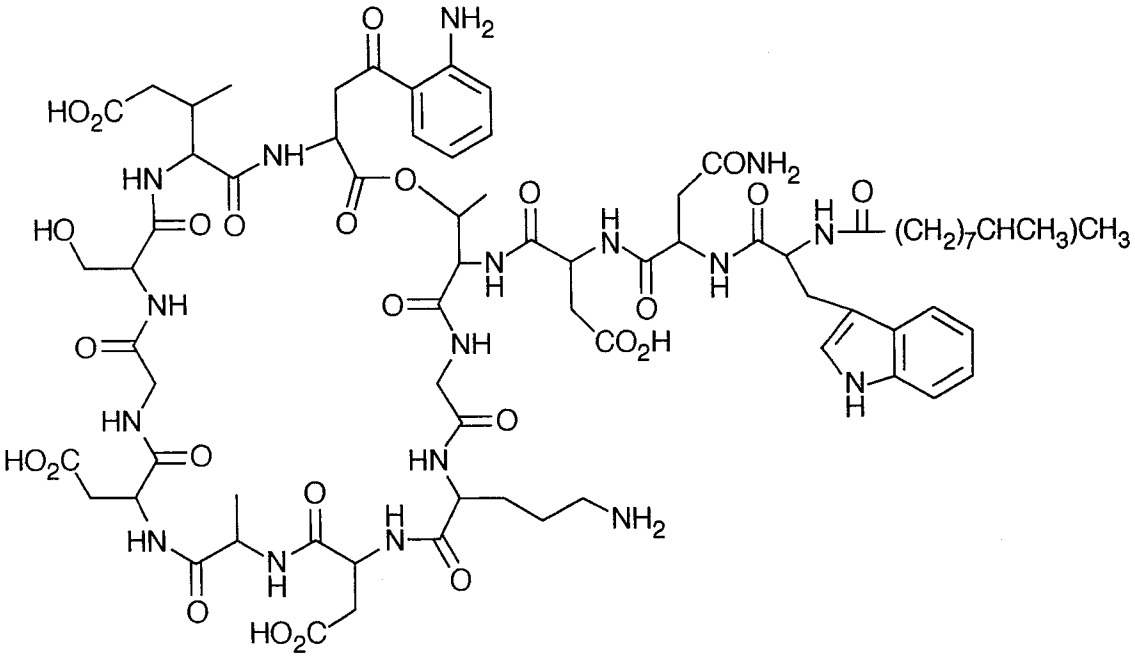
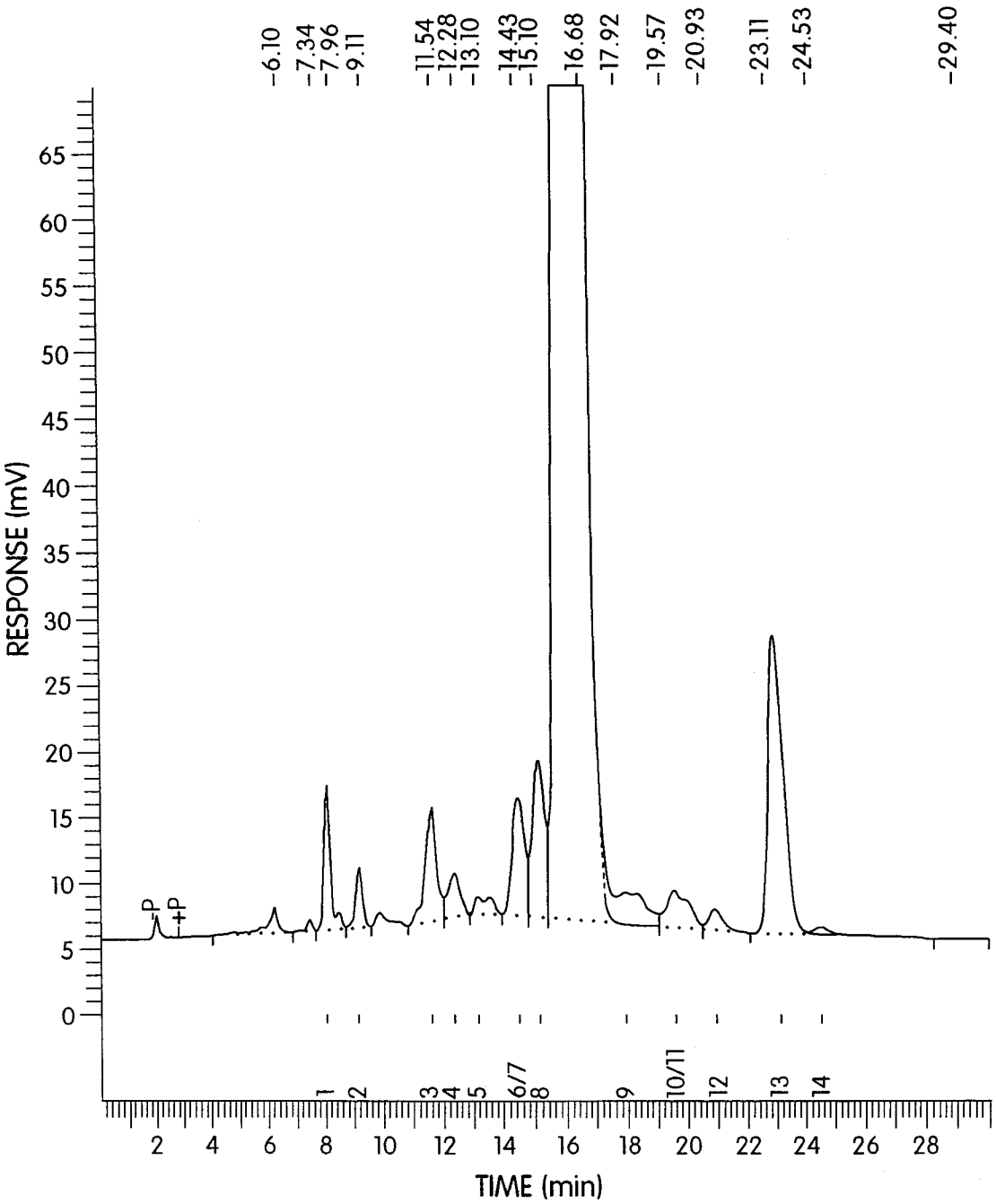


Fig. 11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7.96
9.11
11.54
12.28
13.10
14.43
15.10
16.68
17.92
19.57
20.93
23.11
24.53
29.40
RESPONSE (mV)
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5
10
15
20
25
30
35
40
45
50
55
60
65
P
P
1
2
3
4
5
6/7
8
9
10/11
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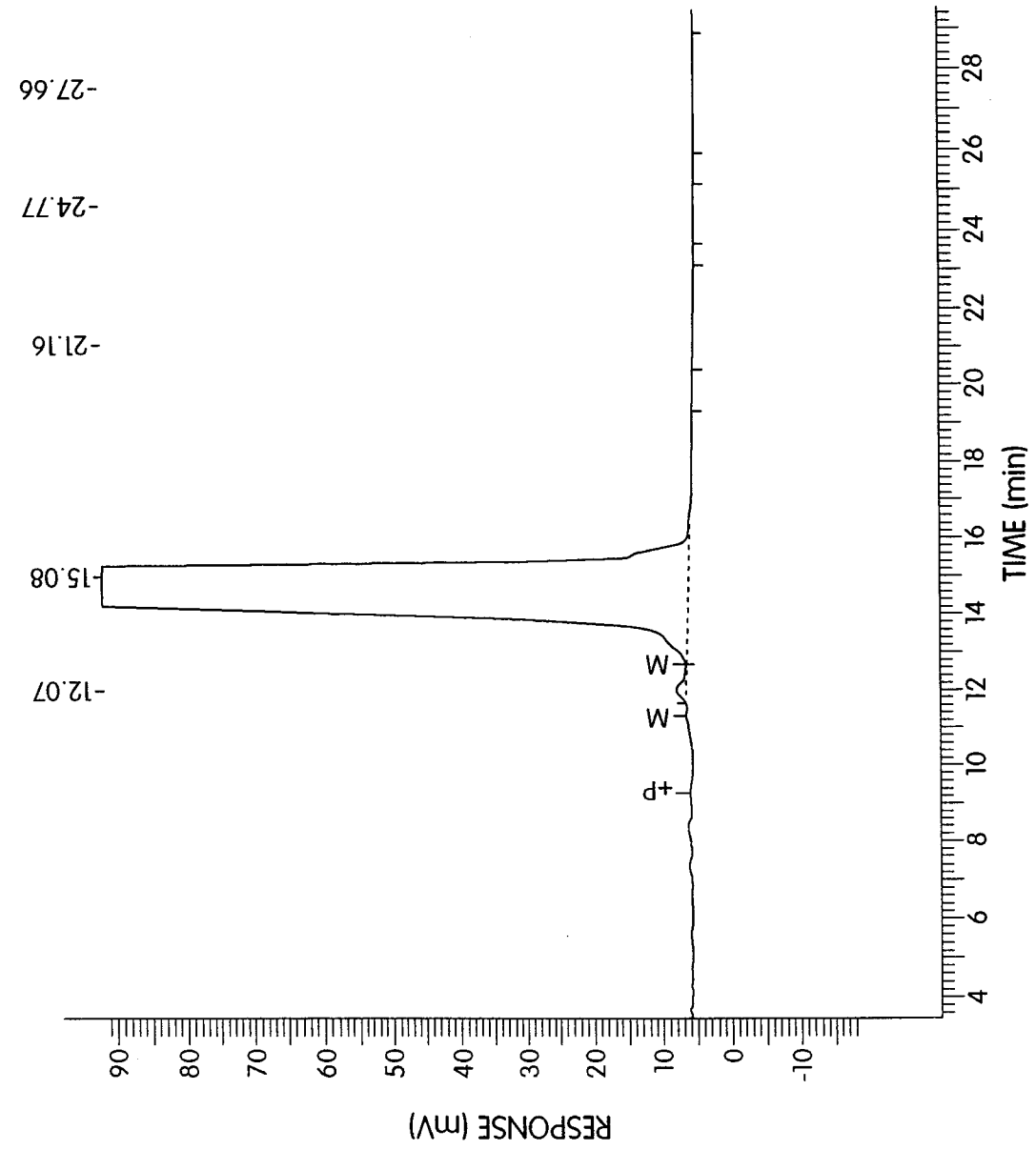
18
20
22
24
26
28
TIME (min)

Fig. 12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60
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30
20
10
0
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TIME (min)
4
6
8
10
12
14
16
18
20
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24
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+P
M
M
12.07
15.08
21.16
24.77
27.66

Fig. 13

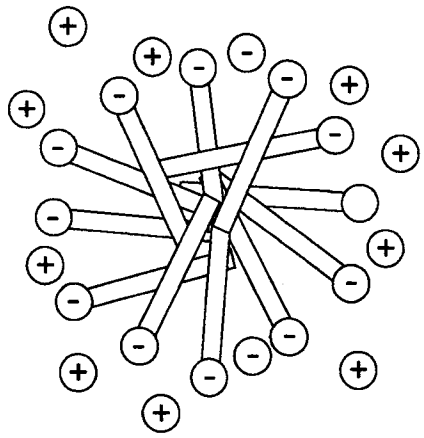


Fig. 14A

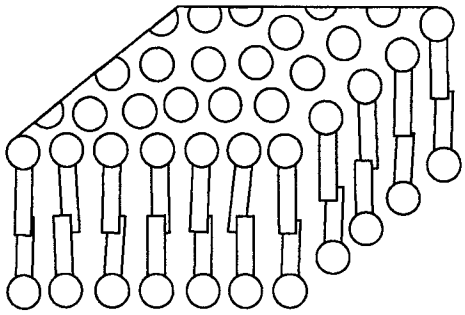


Fig. 14B

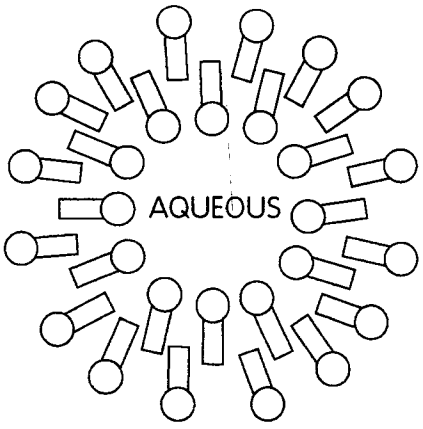
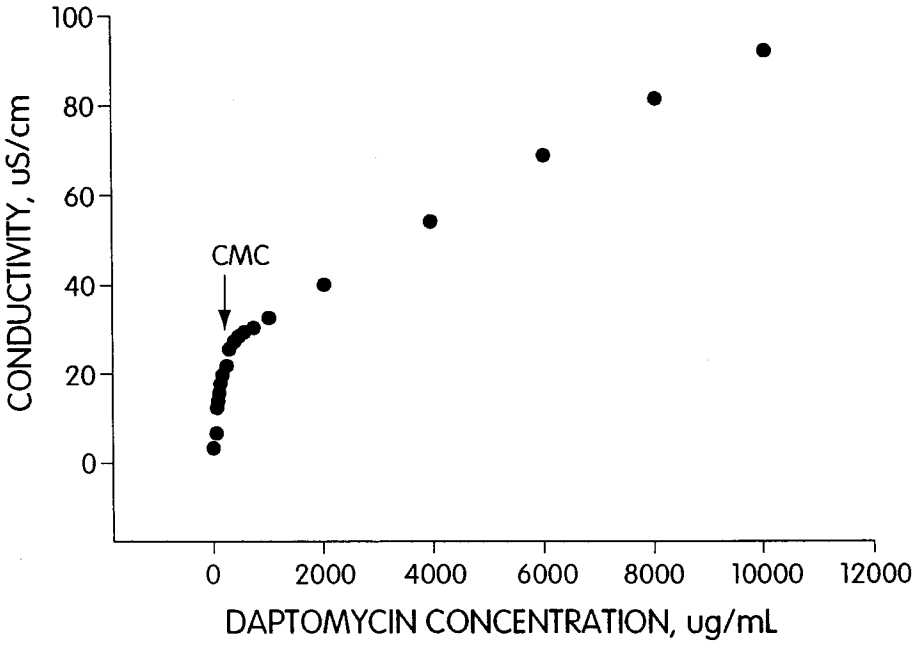


Fig. 14C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60
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CONDUCTIVITY, uS/cm
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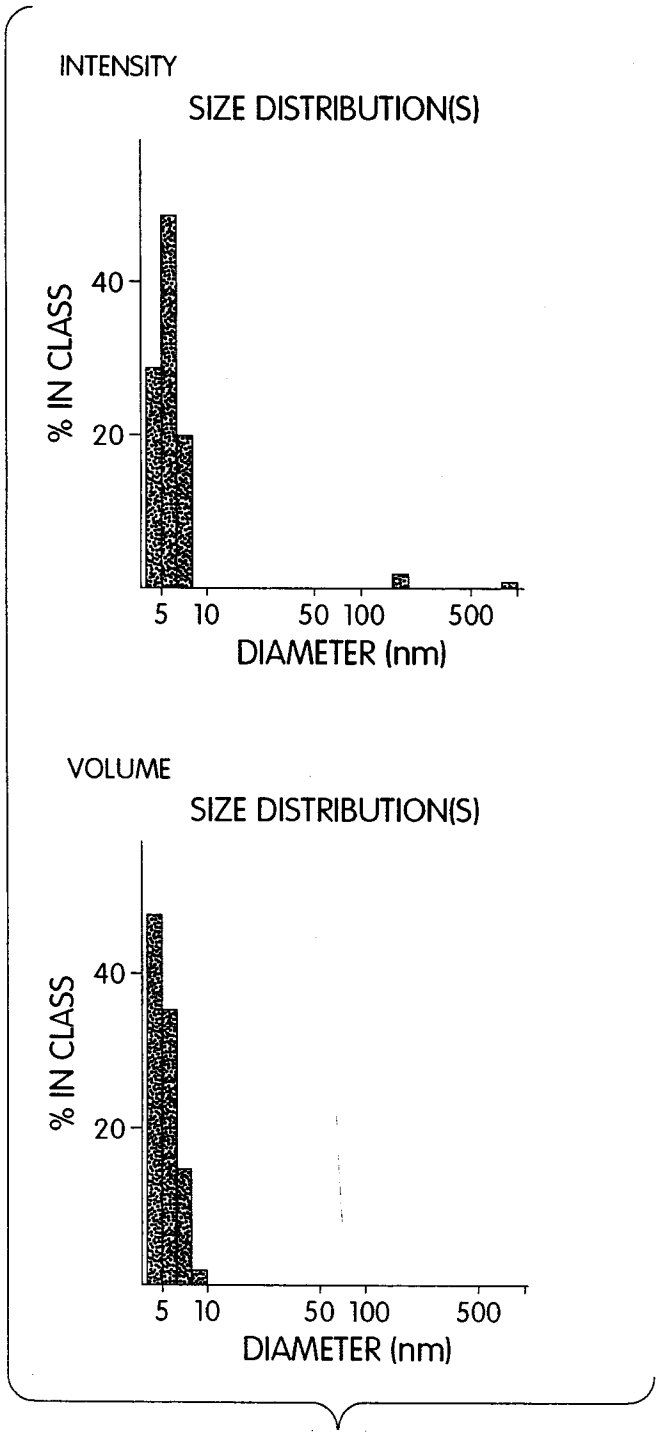
4000
6000
8000
10000
12000
DAPTOMYCIN CONCENTRATION, ug/mL

Fig. 15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20
5
10
50
100
500
DIAMETER (nm)
VOLUME
SIZE DISTRIBUTION(S)
% IN CLASS
40
20
5
10
50
100
500
DIAMETER (nm)

Fig. 16

PTO/SB/01 (08-03)
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DECLARATION FOR UTILITY OR DESIGN PATENT APPLICATION (37 CFR 1.63)

☐ Declaration Submitted With Initial Filing **OR** ☑ Declaration Submitted after Initial Filing (surcharge (37 CFR 1.16 (e)) required)

Attorney Docket Number	C062/D US
First Named Inventor	Kelleher
COMPLETE IF KNOWN	
Application Number	10/747,485
Filing Date	December 29, 2003
Art Unit	1653
Examiner Name	Unknown

I hereby declare that:

Each inventor's residence, mailing address, and citizenship are as stated below next to their name.

I believe the inventor(s) named below to be the original and first inventor(s) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

HIGH PURITY LIPOPEPTIDES

(Title of the Invention)

the specification of which

☐ is attached hereto

OR

☑ was filed on (MM/DD/YYYY) December 29, 2003 as United States Application Number or PCT International Application Number 10/747,485 and was amended on (MM/DD/YYYY) _____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment specifically referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR 1.56, including for continuation-in-part applications, material information which became available between the filing date of the prior application and the national or PCT international filing date of the continuation-in-part application.

I hereby claim foreign priority benefits under 35 U.S.C. 119(a)-(d) or (f), or 365(b) of any foreign application(s) for patent, inventor's or plant breeder's rights certificate(s), or 365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below, by checking the box, any foreign application for patent, inventor's or plant breeder's rights certificate(s), or any PCT international application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application Number(s)	Country	Foreign Filing Date (MM/DD/YYYY)	Priority Not Claimed	Certified Copy Attached? Yes	No
			☐	☐	☐
			☐	☐	☐
			☐	☐	☐
			☐	☐	☐

☐ Additional foreign application numbers are listed on a supplemental priority data sheet PTO/SB/02B attached hereto.

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DECLARATION — Utility or Design Patent Application

Direct all correspondence to: ☑ Customer Number: 34103			*OR* ☐ Correspondence address below
Name			
Address			
City	State	ZIP	
Country	Telephone	Fax	

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

NAME OF SOLE OR FIRST INVENTOR: ☐ A petition has been filed for this unsigned inventor

Given Name (first and middle [if any]) Thomas		Family Name or Surname Kelleher	
Inventor's Signature Thomas J Kelleher			Date 8-21-04
Residence: City Weston	State Massachusetts	Country U.S.A.	Citizenship US
Mailing Address 57 Shell Castle Club, Palmas del Mar			
City Humacao	State Puerto Rico	ZIP 00791	Country U.S.A.

NAME OF SECOND INVENTOR: ☐ A petition has been filed for this unsigned inventor

Given Name (first and middle [if any]) Jan-Ji		Family Name or Surname Lai	
Inventor's Signature			Date
Residence: City Westborough	State Massachusetts	Country U.S.A.	Citizenship US
Mailing Address 5 Roy Street			
City Westborough	State Massachusetts	ZIP 01581	Country U.S.A.

☑ Additional inventors or a legal representative are being named on the 2 supplemental sheet(s) PTO/SB/02A or 02LR attached hereto.

PTO/SB/01 (08-03)
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DECLARATION — Utility or Design Patent Application

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Name

Address

City	State	ZIP

Country	Telephone	Fax

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NAME OF SOLE OR FIRST INVENTOR: ☐ A petition has been filed for this unsigned inventor

Given Name (first and middle [if any])	Family Name or Surname
Thomas	Kelleher

Inventor's Signature | Date

Residence: City	State	Country	Citizenship
Weston	Massachusetts	U.S.A.	US

Mailing Address
57 Shell Castle Club, Palmas del Mar

City	State	ZIP	Country
Humacao	Puerto Rico	00791	U.S.A.

NAME OF SECOND INVENTOR: ☐ A petition has been filed for this unsigned inventor

Given Name (first and middle [if any])	Family Name or Surname
Jan-Ji	Lai

Inventor's Signature Jan-Ji Lai | Date 8/24/04

Residence: City	State	Country	Citizenship
Westborough	Massachusetts	U.S.A.	US

Mailing Address
5 Roy Street

City	State	ZIP	Country
Westborough	Massachusetts	01581	U.S.A.

☑ Additional inventors or a legal representative are being named on the 2 supplemental sheet(s) PTO/SB/02A or 02LR attached hereto.

PTO/SB/02A (08-03)
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DECLARATION

ADDITIONAL INVENTOR(S)
Supplemental Sheet

Name of Additional Joint Inventor, if any:	☐ A petition has been filed for this unsigned inventor		
Given Name (first and middle (if any))	Family Name or Surname		
Joseph P.	DeCourcey		
Inventor's Signature			Date 300804
Charlestown Residence: City	Massachusetts State	U.S.A. Country	US Citizenship
3 Auburn Street Mailing Address			
Mailing Address			
Charlestown City	MA State	02129 Zip	U.S.A. Country

Name of Additional Joint Inventor, if any:	☐ A petition has been filed for this unsigned inventor		
Given Name (first and middle (if any))	Family Name or Surname		
Paul	Lynch		
Inventor's Signature	Date		
Arlington Residence: City	Massachusetts State	U.S.A. Country	US Citizenship
29 Cyprus Road Mailing Address			
Mailing Address			
Arlington City	MA State	02474 Zip	U.S.A. Country

Name of Additional Joint Inventor, if any:	☐ A petition has been filed for this unsigned inventor		
Given Name (first and middle (if any))	Family Name or Surname		
Maurizio	Zenoni		
Inventor's Signature	Date		
Milan Residence: City	State	Italy Country	IT Citizenship
Via Fleming #7 Mailing Address			
Paullo Mailing Address			
Milan City	State	Zip	Italy Country

PTO/SB/02A (08-03)
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DECLARATION

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Supplemental Sheet

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Given Name (first and middle (if any))	Family Name or Surname
Joseph P.	DeCourcey
Inventor's Signature	Date
Charlestown Residence: City	Massachusetts State / U.S.A. Country / US Citizenship
3 Auburn Street Mailing Address	
Mailing Address	
Charlestown City	MA State / 02129 Zip / U.S.A. Country

Name of Additional Joint Inventor, if any:	☐ A petition has been filed for this unsigned inventor
Given Name (first and middle (if any))	Family Name or Surname
Paul	Lynch
Inventor's Signature Paul Lynch	Date 8/24/04
Arlington Residence: City	Massachusetts State / U.S.A. Country / US Citizenship
29 Cyprus Road Mailing Address	
Mailing Address	
Arlington City	MA State / 02474 Zip / U.S.A. Country

Name of Additional Joint Inventor, if any:	☐ A petition has been filed for this unsigned inventor
Given Name (first and middle (if any))	Family Name or Surname
Maurizio	Zenoni
Inventor's Signature	Date
Milan Residence: City	State / Italy Country / IT Citizenship
Via Fleming #7 Mailing Address	
Paullo Mailing Address	
Milan City	State / Zip / Italy Country

This collection of information is required by 35 U.S.C. 115 and 37 CFR 1.63. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 21 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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DECLARATION

ADDITIONAL INVENTOR(S)
Supplemental Sheet

Name of Additional Joint Inventor, if any:	☐ A petition has been filed for this unsigned inventor		
Given Name (first and middle (if any))	Family Name or Surname		
Joseph P.	DeCourcey		
Inventor's Signature			Date
Charlestown Residence: City	Massachusetts State	U.S.A. Country	US Citizenship
3 Auburn Street Mailing Address			
Mailing Address			
Charlestown City	MA State	02129 Zip	U.S.A. Country

Name of Additional Joint Inventor, if any:	☐ A petition has been filed for this unsigned inventor		
Given Name (first and middle (if any))	Family Name or Surname		
Paul	Lynch		
Inventor's Signature	Date		
Arlington Residence: City	Massachusetts State	U.S.A. Country	US Citizenship
29 Cyprus Road Mailing Address			
Mailing Address			
Arlington City	MA State	02474 Zip	U.S.A. Country

Name of Additional Joint Inventor, if any:	☐ A petition has been filed for this unsigned inventor		
Given Name (first and middle (if any))	Family Name or Surname		
Maurizio	Zenoni		
Inventor's Signature Maurizio Zen	Date		
Milan Residence: City	State	Italy Country	IT Citizenship
Via Fleming #7 Mailing Address			
Paullo Mailing Address			
Milan City	State	Zip	Italy Country

PTO/SB/02A (08-03)
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DECLARATION

ADDITIONAL INVENTOR(S)
Supplemental Sheet

Name of Additional Joint Inventor, if any:	☐ A petition has been filed for this unsigned inventor		
Given Name (first and middle (if any))	Family Name or Surname		
Auro	Tagliani		
Inventor's Signature Auro Roberto Tagliani			Date
Pavia Residence: City	State	Italy Country	IT Citizenship
Via Marangoni #1 Mailing Address			
Mailing Address			
Pavia City	State	27100 Zip	Italy Country

Name of Additional Joint Inventor, if any:	☐ A petition has been filed for this unsigned inventor		
Given Name (first and middle (if any))	Family Name or Surname		
Inventor's Signature	Date		
Residence: City	State	Country	Citizenship
Mailing Address			
Mailing Address			
City	State	Zip	Country

Name of Additional Joint Inventor, if any:	☐ A petition has been filed for this unsigned inventor		
Given Name (first and middle (if any))	Family Name or Surname		
Inventor's Signature	Date		
Residence: City	State	Country	Citizenship
Mailing Address			
Mailing Address			
City	State	Zip	Country

Electronic Patent Application Fee Transmittal

Application Number:	
Filing Date:	
Title of Invention:	High Purity Lipopeptides
First Named Inventor/Applicant Name:	Thomas Kelleher
Filer:	Jill Michel-Netka Mandelblatt/Viana Daly
Attorney Docket Number:	

Filed as Small Entity

Utility Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Utility filing Fee (Electronic filing)	4011	1	75	75
Utility Search Fee	2111	1	250	250
Utility Examination Fee	2311	1	100	100
Pages:				
Claims:				
Claims in excess of 20	2202	33	25	825
Miscellaneous-Filing:				
Petition:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
		Total in USD ($)		**1250**

Electronic Acknowledgement Receipt

EFS ID:	1710125
Application Number:	11739180
International Application Number:	
Confirmation Number:	8837
Title of Invention:	High Purity Lipopeptides
First Named Inventor/Applicant Name:	Thomas Kelleher
Customer Number:	34103
Filer:	Jill Michel-Netka Mandelblatt/Viana Daly
Filer Authorized By:	Jill Michel-Netka Mandelblatt
Attorney Docket Number:	
Receipt Date:	24-APR-2007
Filing Date:	
Time Stamp:	12:03:41
Application Type:	Utility

Payment information:

Submitted with Payment	yes
Payment was successfully received in RAM	$1250
RAM confirmation Number	1983
Deposit Account	501986
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows: Charge any Additional Fees required under 37 C.F.R. Section 1.16 and 1.17	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)	Multi Part /.zip	Pages (if appl.)
1		C062-02-03_US_appln_as_filed.pdf	9147860	yes	91

Multipart Description/PDF files in .zip description

Document Description	Start	End
Miscellaneous Incoming Letter	1	1
Fee Worksheet (PTO-06)	2	2
Specification	3	66
Claims	67	72
Abstract	73	73
Drawings	74	84
Oath or Declaration filed	85	91

Warnings:

Information:

2	Fee Worksheet (PTO-06)	fee-info.pdf	8463	no	2

Warnings:

Information:

Total Files Size (in bytes):	9156323

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New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

4/24/07

PTO/SB/06 (12-04)
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PATENT APPLICATION FEE DETERMINATION RECORD	Application or Docket Number 11/739,180

APPLICATION AS FILED – PART I

	(Column 1)	(Column 2)	SMALL ENTITY		OR	OTHER THAN SMALL ENTITY	
FOR	NUMBER FILED	NUMBER EXTRA	RATE ($)	FEE ($)		RATE ($)	FEE ($)
BASIC FEE (37 CFR 1.16(a), (b), or (c))				75			300
SEARCH FEE (37 CFR 1.16(k), (i), or (m))				250			500
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))				100			200
TOTAL CLAIMS (37 CFR 1.16(i))	53 minus 20 =	33	X$ 25	825	OR	X$50	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	1 minus 3 =		X$100			X$200	
APPLICATION SIZE FEE (37 CFR 1.16(s))							
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))			180			360	
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	1250		TOTAL	

APPLICATION AS AMENDED – PART II

		(Column 1)		(Column 2)	(Column 3)	SMALL ENTITY		OR	OTHER THAN SMALL ENTITY	
		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE ($)	ADDI-TIONAL FEE ($)		RATE ($)	ADDI-TIONAL FEE ($)
AMENDMENT A	Total (37 CFR 1.16(i))	*	Minus	**	=	X =		OR	X =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X =		OR	X =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))					180		OR	360	
						TOTAL ADD'T FEE		OR	TOTAL ADD'T FEE	

		(Column 1)		(Column 2)	(Column 3)			OR		
		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE ($)	ADDI-TIONAL FEE ($)		RATE ($)	ADDI-TIONAL FEE ($)
AMENDMENT B	Total (37 CFR 1.16(i))	*	Minus	**	=	X =		OR	X =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X =		OR	X =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))					N/A		OR	N/A	
						TOTAL ADD'T FEE		OR	TOTAL ADD'T FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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