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
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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
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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:	**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	10/10/2013	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
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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
	9/17/2012	for the District of Delaware

PLAINTIFF	DEFENDANT
CUBIST PHARMACEUTICALS, INC.	HOSPIRA, INC.

	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1	6,568,967 B1	10/22/2002	Cubist Pharmaceuticals, Inc.
2	6,852,689 B2	2/8/2005	Cubist Pharmaceuticals, Inc.
3	RE39,071 E	4/18/2006	Cubist Pharmaceuticals, Inc.
4	8,058,238 B2	11/15/2011	Cubist Pharmaceuticals, Inc.
5	8,129,342 B2	3/6/2012	Cubist Pharmaceuticals, Inc.

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
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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

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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 Delaware on the following

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

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
	3/21/2012	for the District of Delaware

PLAINTIFF	DEFENDANT
CUBIST PHARMACEUTICALS, INC.	HOSPIRA, INC.

	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1	8,129,342 B2	3/6/2012	Cubist Pharmaceuticals, Inc.
2			
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4			
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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
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In the above—entitled case, the following decision has been rendered or judgement issued:

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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

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.
12/888,233	03/06/2012	8129342	C062-02/04 US	4046

34103 7590 02/15/2012

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 J. Kelleher, Thousand Oaks, CA;
Jan-Ji Lai, Westborough, MA;
Joseph P. DeCourcey, Boston, MA;
Paul D. Lynch, Arlington, MA;
Maurizio Zenoni, Ferentino Frosinone, ITALY;
Auro R. Tagliani, Pavia, ITALY;

PTO/SB/08a (01-10)
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	12888233
Filing Date	2010-09-22
First Named Inventor	Thomas J. Kelleher
Art Unit	1656
Examiner Name	Chih-Min Kam
Attorney Docket Number	C062-02/04 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./ Change(s) applied to document, /D.A.M./ 1/30/2012	1	6468967		2002-10-22	Oleson Jr., et al. ~~Cubist Pharmaceuticals, Inc.~~	
/CMK./	2	6852689		2005-02-08	Oleson Jr., et al. ~~Cubist Pharmaceuticals, Inc.~~	

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]
/CMK./	1	WO 00/18419	WO		2000-04-06	Cubist Pharmaceuticals, Inc.		☐

If you wish to add additional Foreign Patent Document citation information please click the Add button

NON-PATENT LITERATURE DOCUMENTS

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.
12/888,233	09/22/2010	Thomas J. Kelleher	C062-02/04 US	4046

34103 7590 02/06/2012

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

EXAMINER	
KAM, CHIH MIN	
ART UNIT	**PAPER NUMBER**
1656	

NOTIFICATION DATE	DELIVERY MODE
02/06/2012	ELECTRONIC

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.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patents@cubist.com
jodi.doherty@cubist.com
colleen.lombard@cubist.com

Response to Rule 312 Communication	Application No.	Applicant(s)
	12/888,233	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 –

1. ☒ The amendment filed on *26 January 2012* under 37 CFR 1.312 has been considered, and has been:

a) ☐ entered.

b) ☒ entered as directed to matters of form not affecting the scope of the invention.

c) ☐ disapproved because the amendment was filed after the payment of the issue fee.
Any amendment filed after the date the issue fee is paid must be accompanied by a petition under 37 CFR 1.313(c)(1) and the required fee to withdraw the application from issue.

d) ☐ disapproved. See explanation below.

e) ☐ entered in part. See explanation below.

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

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 01/11/2012

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.
12/888,233	09/22/2010	Thomas J. Kelleher	C062-02/04 US	4046

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	NO	$1740	$300	$0	$2040	04/11/2012

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 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: Cubist Pharmaceuticals, Inc.

(B) RESIDENCE: (CITY and STATE OR COUNTRY): Lexington, Massachusetts 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 50-1986 (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 /Nicholas M. Boivin/ Date January 26, 2012

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:	12888233
Filing Date:	22-Sep-2010
Title of Invention:	HIGH PURITY LIPOPEPTIDES
First Named Inventor/Applicant Name:	Thomas J. Kelleher
Filer:	Nicholas M.C. Boivin/Jodi Doherty
Attorney Docket Number:	C062-02/04 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:	11924066
Application Number:	12888233
International Application Number:	
Confirmation Number:	4046
Title of Invention:	HIGH PURITY LIPOPEPTIDES
First Named Inventor/Applicant Name:	Thomas J. Kelleher
Customer Number:	34103
Filer:	Nicholas M.C. Boivin
Filer Authorized By:	
Attorney Docket Number:	C062-02/04 US
Receipt Date:	26-JAN-2012
Filing Date:	22-SEP-2010
Time Stamp:	10:46:33
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	9183
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		C062_02_04_US_20120126_Amdt_After_Allowance.pdf	54590 481c824840f43de2151763bca6ee4cc65e7673c5	yes	11

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Amendment after Notice of Allowance (Rule 312)	1	1
	Claims	2	10
	Applicant Arguments/Remarks Made in an Amendment	11	11

Warnings:

Information:

2	Issue Fee Payment (PTO-85B)	C062_02_04_US_20120126_Issue_Fee.pdf	192793 baaa2920d51ef106a5a85b9ea83e338a285e70f8	no	1

Warnings:

Information:

3	Fee Worksheet (SB06)	fee-info.pdf	32043 bf48c20933eb8407f3ae1e3a3c59e8b3b8eed3c4	no	2

Warnings:

Information:

Total Files Size (in bytes):	279426

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.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appl. No.	:	12/888,233	Confirmation No.	4046
Applicant	:	Thomas Kelleher		
Filed	:	September 22, 2010		
TC/A.U.	:	1656		
Examiner	:	Chih-Min Kam		
Docket No.	:	C062-02/04 US		
Customer No.	:	34103		

MAIL STOP ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

AMENDMENT AFTER ALLOWANCE PURSUANT TO 37 C.F.R. § 1.312

Please amend the application as indicated on the following pages. This amendment is being filed concurrently with the payment of the issue fee.

AMENDMENTS TO THE CLAIMS

This listing of claims replaces all prior versions and listings of claims in the application:

1. (Currently Amended) A composition obtained by a process comprising the step of forming a daptomycin aggregate, the composition comprising daptomycin of greater than or about 93% purity relative to impurities 1-14 defined by peaks 1-14 shown in FIG. 12 and less than 4% of anhydro-daptomycin and having less than 4% of β-isomer of daptomycin.

2-5. (Canceled)

6. (Original) The composition according to claim 1 that is free of each of impurities 1 to 14 defined by peaks 1-14 shown in FIG. 12.

7. (Previously Presented). The composition according to claim 1 that is essentially free of at least one 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.-22. (Canceled)

23. (Previously Presented) The composition according to claim 1 wherein the process 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. (Previously Presented) The composition according to claim 23, wherein the process further comprises the step of lyophilizing daptomycin.

25.-31. (Canceled).

32. (Previously Presented) The composition of claim 1 comprising daptomycin having less than 1% of β-isomer of daptomycin.

33.-53. (Canceled).

54. (Previously Presented) The composition of claim 1, comprising daptomycin having greater than 93% purity.

55. (Previously Presented) The composition of claim 1, comprising daptomycin having less than 1% of the lactone hydrolysis product of daptomycin.

56. (Currently Amended) The composition of claim 1, comprising daptomycin that is substantially free of ~~beta~~β-isomer of daptomycin.

57. (Previously Presented) The composition of claim 56, comprising daptomycin of greater than 93% purity.

58. (Previously Presented) The composition of claim 1, comprising daptomycin of at least 95% purity.

59. (Previously Presented) The composition of claim 1, comprising daptomycin with a purity of about 94 to 96%.

60. (Previously Presented) The composition of claim 1, comprising daptomycin with a purity of at least 97% purity.

61. (Previously Presented) The composition of claim 1, comprising lyophilized daptomycin having greater than 93% purity relative to impurities 1-14 defined by peaks 1-14 shown in FIG. 12, and having less than 1% of the lactone hydrolysis product of daptomycin.

62. (Currently Amended) The composition of claim 61, wherein the daptomycin is substantially free of ~~beta~~β-isomer of daptomycin.

63. (Previously Presented) A pharmaceutical composition compatible with a pharmaceutically acceptable carrier for the treatment of an infection of the blood, skin or soft tissue, the composition comprising daptomycin obtained by a process comprising the step of forming a daptomycin aggregate, the composition having daptomycin with greater than or about 93% purity relative to impurities 1-14 defined by peaks 1-14 shown in FIG. 12.

64. (Previously Presented) The pharmaceutical composition of claims 63, wherein the daptomycin has greater than 93% purity and less than 4% anhydro daptomycin.

65. (Currently Amended) The pharmaceutical composition of claims 63, wherein the [[the]] pharmaceutically acceptable carrier is selected from the group consisting of physiological saline and Ringer's solution for reconstitution for administration as a single daily dose to the subject.

66. (Previously Presented) The pharmaceutical composition of claims 63, wherein the pharmaceutical composition is compatible with the pharmaceutically acceptable carrier for the treatment of an infection of the blood, skin or soft tissue by administration in a daily dose of 1 to 12 mg/kg of the daptomycin in a reconstituted solution of the composition in the pharmaceutically acceptable carrier.

67. (Currently Amended) The pharmaceutical composition of claim 66, wherein

a) the pharmaceutically acceptable carrier is selected from the group consisting of physiological saline and Ringer's solution for intravenous administration as a single daily dose to the subject;

b) the daptomycin has greater than 93% purity, less than 4% anhydro daptomycin and less than 4% ~~beta~~β-isomer of daptomycin; and

c) the composition comprising daptomycin is obtained by a purification process comprising the steps of forming a daptomycin aggregate and obtaining the daptomycin from the daptomycin aggregate.

68. (Previously Presented) The pharmaceutical composition of claim 67, wherein the process for obtaining the daptomycin includes a purification process comprising the steps of

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

b) forming the daptomycin aggregate comprising a daptomycin micelle in the enriched daptomycin preparation or a composition obtained from the enriched daptomycin preparation; and

c) obtaining daptomycin from the daptomycin aggregate.

69. (Currently Amended) The pharmaceutical composition of claim 68, wherein the daptomycin is obtained from the daptomycin aggregate by a method comprising the steps of

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

b) collecting the daptomycin aggregate.

70. (Previously Presented) The pharmaceutical composition of claim 69, wherein the daptomycin is obtained from the daptomycin aggregate by a method further comprising the steps of

a) subjecting a composition comprising the daptomycin is obtained from the daptomycin aggregate to hydrophobic interaction chromatography to obtain a semi-purified daptomycin preparation; and

b) obtaining the daptomycin from the semi-purified daptomycin preparation.

71. (Previously Presented) A pharmaceutical composition for the treatment of an infection, the composition comprising daptomycin having greater than 93% purity relative to impurities 1-14 defined by peaks 1-14 shown in FIG. 12, the daptomycin purified by a process comprising the formation of micelles comprising daptomycin.

72. (Previously Presented) The pharmaceutical composition of claim 71, wherein the daptomycin is a lyophilized powder comprising daptomycin purified by process comprising the steps of forming a daptomycin micelle and obtaining the daptomycin from the micelles.

73. (Currently Amended) The pharmaceutical composition of claim 71, wherein the daptomycin has less than 4% anhydro daptomycin and less than 4% ~~beta~~β-isomer of daptomycin.

74. (Previously Presented) The pharmaceutical composition of claim 71, wherein the daptomycin has less than 1% of the lactone hydrolysis product of daptomycin.

75. (Currently Amended) The pharmaceutical composition of claim 72, wherein the daptomycin has less than 4% anhydro daptomycin, less than 1% of the lactone hydrolysis product of daptomycin and is essentially free of the ~~beta~~β-isomer of daptomycin.

76. (Previously Presented) A pharmaceutical composition for the treatment of an infection of the blood, skin or soft tissue, the pharmaceutical composition comprising a solution of a pharmaceutically acceptable carrier for intravenous administration and daptomycin, the daptomycin having greater than 93% purity relative to impurities 1-14 defined by peaks 1-14 shown in FIG. 12, and the daptomycin obtained from a purification process comprising the formation of a daptomycin micelle.

77. (Currently Amended) The pharmaceutical composition of claim 76, wherein the daptomycin has less than 4% anhydro daptomycin and less than 4% ~~beta~~β-isomer of daptomycin.

78. (Previously Presented) The pharmaceutical composition of claims 76, wherein the daptomycin has less than 1% of the lactone hydrolysis product of daptomycin.

79. (Currently Amended) The pharmaceutical composition of claim 77, wherein the daptomycin has less than 4% anhydro daptomycin, less than 1% of the lactone hydrolysis project of daptomycin and is essentially free of the ~~beta~~β-isomer of daptomycin.

80. (Previously Presented) The composition of claim 63, wherein the infection of the blood, skin or soft tissue comprises *Staphylococcus aureus*.

81. (Previously Presented) The composition of claim 63, wherein the infection is bacteremia.

82. (Previously Presented) The composition of claim 63, wherein the infection is endocarditis.

83. (Previously Presented) The composition of claim 63, wherein the infection is a skin or soft tissue infection.

84. (Currently Amended) The composition of claim 63, wherein the infection includes bacteria selected from the group consisting *of Staphylococcus aureus*[[.]], *Streptococcus pyogenes*, *Streptococcus agalactiae*, and *Enterococcus faecalis*.

85. (Previously Presented) The composition of claim 71, wherein the infection comprises *Staphylococcus aureus*.

86. (Previously Presented) The composition of claim 71, wherein the infection is bacteremia.

87. (Previously Presented) The composition of claim 71, wherein the infection is endocarditis.

88. (Previously Presented) The composition of claim 71, wherein the infection is a skin or soft tissue infection.

89. (Currently Amended) The composition of claim 71, wherein the infection includes bacteria selected from the group consisting *of Staphylococcus aureus*[[.]], *Streptococcus pyogenes*, *Streptococcus agalactiae*, and *Enterococcus faecalis*.

90. (Previously Presented) The composition of claim 76, wherein the infection comprises *Staphylococcus aureus*.

91. (Previously Presented) The composition of claim 76, wherein the infection is bacteremia.

92. (Previously Presented) The composition of claim 76, wherein the infection is endocarditis.

93. (Previously Presented) The composition of claim 76, wherein the infection is a skin or soft tissue infection.

94. (Currently Amended) The composition of claim 76, wherein the infection includes bacteria selected from the group consisting *of Staphylococcus aureus*[[.]], *Streptococcus pyogenes*, *Streptococcus agalactiae*, and *Enterococcus faecalis*.

95. (Previously Presented) The composition of claim 76, wherein the pharmaceutical composition includes daptomycin in a daily intravenous dose 1 to 12 mg/kg.

96. (Currently Amended) A vial containing a lyophilized powder pharmaceutical composition compatible with a pharmaceutically acceptable carrier for the treatment of an infection by a daily intravenous dose of the lyophilized powder reconstituted in the pharmaceutically acceptable carrier, the composition

a) having daptomycin with greater than or about 93% purity relative to impurities 1-14 defined by peaks 1-14 shown in FIG. 12; and

b) the composition comprising daptomycin purified by a process including the steps of forming a daptomycin aggregate, converting the daptomycin aggregate to monomers and obtaining the daptomycin in the composition from the monomers by a process including one or more steps selected from the group consisting of anion exchange ~~chromatorgraphy~~ chromatography and hydrophobic interaction chromatography.

97. (Currently Amended) A composition obtained by a process comprising the steps of forming a daptomycin aggregate, converting the daptomycin aggregate to monomers and obtaining the daptomycin in the composition from the monomers by a process including one or more steps selected from the group consisting of anion exchange ~~chromatorgraphy~~ chromatography and hydrophobic interaction chromatography, the composition comprising daptomycin of greater than or about 93% purity relative to impurities 1-14 defined by peaks 1-14 shown in FIG. 12.

98. (Previously Presented) The composition of claim 97, comprising daptomycin of greater than 93% purity relative to impurities 1-14 defined by peaks 1-14 shown in FIG. 12.

99. (Previously Presented) The composition of claim 97, wherein the composition is a lyophilized powder compatible with a pharmaceutically acceptable carrier for the treatment of one or more infections selected from the group consisting of infections of the blood, skin and soft tissue, by a daily intravenous dose of 1 to 12 mg/kg of the daptomycin in a reconstituted solution of the lyophilized powder in the pharmaceutically acceptable carrier.

100. (Currently Amended) The composition of claim 98, wherein

a) the composition is a lyophilized powder compatible with a pharmaceutically acceptable carrier for the treatment of an infection by a daily intravenous dose of 1 to 12 mg/kg of the daptomycin in a reconstituted solution of the lyophilized powder in the pharmaceutically acceptable carrier; and

b) the daptomycin has a purity of about 94 to 96% relative to impurities 1-14 defined by peaks 1-14 shown in FIG. 12, the daptomycin having less than 1% of the lactone hydrolysis product of daptomycin, less than 4% anhydro daptomycin and less than 4% of the ~~beta~~β-isomer of daptomycin.

REMARKS

Upon entry of the present amendments, claims 1, 6-8, 23, 24, 32, and 54-100 will remain pending in this application, claims 2-5, 9-22, 25-31, and 33-53 having been previously cancelled without prejudice. Claims 1, 56, 62, 65, 67, 69, 73, 75, 77, 79, 84, 89, 94, 96, 97, and 100 are presently amended.

Applicants request that all claims be allowed in view of the amendments to the claim. In addition, please apply any other necessary charges or credits to Deposit Account No. 50-1986, referencing the above attorney docket number.

Respectfully submitted,

Date: January 26, 2012

/Nicholas M. Boivin/
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Attorney for Applicant

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UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
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NOTICE OF ALLOWANCE AND FEE(S) DUE

34103 7590 01/11/2012

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

EXAMINER
KAM, CHIH MIN

ART UNIT	PAPER NUMBER
1656	

DATE MAILED: 01/11/2012

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/888,233	09/22/2010	Thomas J. Kelleher	C062-02/04 US	4046

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	NO	$1740	$300	$0	$2040	04/11/2012

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 01/11/2012

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.
12/888,233	09/22/2010	Thomas J. Kelleher	C062-02/04 US	4046

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	NO	$1740	$300	$0	$2040	04/11/2012

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.
12/888,233	09/22/2010	Thomas J. Kelleher	C062-02/04 US	4046

34103 7590 01/11/2012

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

EXAMINER	
KAM, CHIH MIN	
ART UNIT	**PAPER NUMBER**
1656	

DATE MAILED: 01/11/2012

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)	
	12/888,233	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 *12/16/2011*.

2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

3. ☒ The allowed claim(s) is/are *1,6-8,23,24,32 and 54-100*.

4. ☐ 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.

5. ☐ 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.

6. ☐ 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).

7. ☐ 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)
2. ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
3. ☐ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date _____
4. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
5. ☐ Notice of Informal Patent Application
6. ☐ Interview Summary (PTO-413), Paper No./Mail Date _____ .
7. ☒ Examiner's Amendment/Comment
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 1, 6-8, 23-24, 32 and 54-100 are pending.

Applicants' amendment filed December 16, 2011 is acknowledged. Applicants' response has been fully considered. Claim 11 has been cancelled. Therefore, claims 1, 6-8, 23-24, 32 and 54-100 are examined.

Withdrawn Claim Rejections - 35 USC § 112

2. The previous rejection of claim 11 under 35 U.S.C.112, second paragraph, is withdrawn in view of applicants' cancellation of the claims and applicants' response at page 10 in the amendment filed December 16, 2011.

Withdrawn Claim Rejections -Obviousness Type Double Patenting

3. The previous rejection of claims 1, 6-8, 11, 23-24, 32 and 54-100 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 2-3, 6, 54, 58, 62, 115, 171, 175, 178 and 179 of co-pending application, 11/739,180 (Now U.S. Patent 8,058,238, claims 1, 3, 8, 10, 21, 49, 50, 176, 180, 183 and 191), is withdrawn in view of applicants' submission of a terminal disclaimer, applicants' cancellation of the claims and applicants' response at page 10 in the amendment filed December 16, 2011.

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 December 29, 2011.

Examiner's Amendment to the Specification:

Please replace the paragraph at page 1, lines 5-11 with the following paragraph:

The present application is a continuation of United States Patent Application No. 11/739,180, filed April 24, 2007, now U.S. Patent 8,058,238, which is a continuation of United States Patent Application No. 10/747,485, filed December 29, 2003, now abandoned, which is a continuation of United States 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.

Examiner's Amendment to the Claims:

Claim 100 has been amended as follows:

100. (Currently Amended) The composition of claim 98, wherein

a) the composition is a lyophilized powder compatible with a pharmaceutically acceptable carrier for the treatment of an infection ~~of the infection~~ by a daily intravenous dose of 1 to 12 mg/kg of the daptomycin in a reconstituted solution of the lyophilized powder in the pharmaceutically acceptable carrier; and

b) the daptomycin has a purity of about 94 to 96% relative to impurities 1-14 defined by peaks 1-14 shown in FIG. 12, the daptomycin having less than 1% of the lactone hydrolysis product of daptomycin, less than 4% anhydro daptomycin and less than 4% of the beta-isomer of 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. Kelleher *et al.* (U.S. Patent 8,058,238) disclose a composition comprising essentially pure daptomycin purified by a process comprising the step of forming a daptomycin aggregate; a composition comprising a daptomycin that is substantially free of each of impurities 1 to 14 defined by peaks 1-14 shown in FIG. 12 and obtained by a process comprising the step of forming a daptomycin aggregate; and a pharmaceutical composition comprising essentially pure daptomycin purified by a process comprising the step of forming a daptomycin aggregate or daptomycin aggregate. An obviousness-type double patenting rejection was made over the patent. Applicants have filed a terminal disclaimer, and the obviousness-type double patenting rejection is withdrawn. 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
December 30, 2011

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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BIB DATA SHEET

CONFIRMATION NO. 4046

SERIAL NUMBER	FILING or 371(c) DATE RULE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
12/888,233	09/22/2010	514	1656	C062-02/04 US

APPLICANTS

Thomas J. Kelleher, Thousand Oaks, CA;
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Maurizio Zenoni, Ferentino Frosinone, ITALY;
Auro R. Tagliani, Pavia, ITALY;

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

This application is a CON of 11/739,180 04/24/2007 ,PAT 8,058,238
which is a CON of 10/747,485 12/29/2003 ABN
which is a CON 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 ****

10/05/2010

Foreign Priority claimed ☐ Yes ☒ No 35 USC 119(a-d) conditions met ☐ Yes ☒ No Verified and Acknowledged /Chih-Min Kam/ Examiner's Signature	☐ Met after Allowance Initials	STATE OR COUNTRY	SHEETS DRAWINGS	TOTAL CLAIMS	INDEPENDENT CLAIMS
		CA	11	53	1

ADDRESS

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

TITLE

High Purity Lipopeptides

FILING FEE RECEIVED		
2936	FEES: Authority has been given in Paper No._____ to charge/credit DEPOSIT ACCOUNT No._____ for following:	☐ All Fees ☐ 1.16 Fees (Filing) ☐ 1.17 Fees (Processing Ext. of time) ☐ 1.18 Fees (Issue) ☐ Other _____ ☐ Credit

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	1274	daptomycin	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2011/12/30 16:24
L2	17	impurities same L1	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2011/12/30 16:24
L3	16	anhydro-daptomycin or beta-daptomycin	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2011/12/30 16:24
L4	22	lactone adj hydrolysis adj product	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2011/12/30 16:24
L5	16	L2 same (L3 or L4)	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2011/12/30 16:24
L6	5	L2 same L4	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2011/12/30 16:24
L7	365259	aggregate	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2011/12/30 16:24
L8	1	L2 same L7	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2011/12/30 16:24
L9	48543	micelles	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2011/12/30 16:25
L10	10	L2 same L9	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2011/12/30 16:25
L11	58462	anion adj exchange	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2011/12/30 16:25
L12	15213	hydrophobic adj interaction adj chromatography	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2011/12/30 16:25
L13	9	L1 same L11 same L12	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2011/12/30 16:25
L14	22	kelleher adj thomas.in.	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2011/12/30 16:25
L15	13	lai adj jan-ji.in.	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2011/12/30 16:25
L16	5	decourcey adj joseph.in.	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2011/12/30 16:25
L17	32	lynch adj paul.in.	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2011/12/30 16:25
L18	83	zenoni adj maurizio.in.	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2011/12/30 16:25
L19	10	tagliani adj auro.in.	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2011/12/30 16:25
L20	138	L14 or L15 or L16 or L17 or L18 or L19	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2011/12/30 16:25
L21	11	L20 and L1	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2011/12/30 16:25

12/30/2011 4:26:26 PM
C:\Users\ckam\Documents\EAST\Workspaces\% daptomycin-1.wsp

=> d his

(FILE 'HOME' ENTERED AT 16:27:27 ON 30 DEC 2011)

FILE 'MEDLINE, CAPLUS, BIOSIS, EMBASE, SCISEARCH, AGRICOLA' ENTERED AT 16:27:52 ON 30 DEC 2011

L1 9085 S DAPTOMYCIN

L2 2 S L1 (P) IMPURITIES

L3 2 DUPLICATE REMOVE L2 (0 DUPLICATES REMOVED)

L4 7 S ANHYDRO-DAPTOMYCIN OR BETA-DAPTOMYCIN

L5 20 S LACTONE HYDROLYSIS PRODUCT

L6 0 S L2 (P) (L4 OR L5)

L7 0 S L2 AND (L4 OR L5)

L8 7 S L1 AND (L4 OR L5)

L9 7 DUPLICATE REMOVE L8 (0 DUPLICATES REMOVED)

L10 7 S L9 NOT L2

L11 472933 S AGGREGATE

L12 152231 S MICELLES

L13 1 S L2 (P) (L11 OR L12)

L14 120967 S ANION EXCHANGE

L15 11680 S HYDROPHOBIC INTERACTION CHROMATOGRAPHY

L16 1 S L2 AND L14 AND L15

L17 58 S KELLEHER THOMAS/AU

L18 31 S LAI JAN-JI/AU

L19 0 S DECOURCEY JOSEPH/AU

L20 24 S LYNCH PAUL/AU

L21 58 S ZENONI MAURIZIO/AU

L22 21 S TAGLIANI AURO/AU

L23 182 S L17 OR L18 OR L19 OR L20 OR L21 OR L22

L24 1 S L23 AND (L2 OR L4)

L25 0 S L24 NOT L2

=> log y

Issue Classification	Application/Control No.	Applicant(s)/Patent under Reexamination	
	12/888,233	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)	/Chih-Min Kam/ 12/30/2011 (Primary Examiner) (Date)	Total Claims Allowed: 54	
(Legal Instruments Examiner) (Date)		O.G. Print Claim(s): 1	O.G. Print Fig.: 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	1		31	15	61	45	91		121		151		181
	2	7	32	16	62	46	92		122		152		182
	3		33	17	63	47	93		123		153		183
	4		34	18	64	48	94		124		154		184
	5		35	19	65	49	95		125		155		185
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3	7		37	21	67	51	97		127		157		187
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	9		39	23	69	54	99		129		159		189
	10		40	24	70	53	100		130		160		190
	11		41	30	71		101		131		161		191
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	18		48	43	78		108		138		168		198
	19		49	42	79		109		139		169		199
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5	23		53	28	83		113		143		173		203
6	24	8	54	29	84		114		144		174		204
	25	9	55	35	85		115		145		175		205
	26	10	56	36	86		116		146		176		206
	27	11	57	37	87		117		147		177		207
	28	12	58	38	88		118		148		178		208
	29	13	59	39	89		119		149		179		209
	30	14	60	44	90		120		150		180		210

Search Notes	Application No.	Applicant(s)	
	12/888,233	KELLEHER ET AL.	
	Examiner	Art Unit	
	CHIH-MIN KAM	1656	

SEARCHED			
Class	Subclass	Date	Examiner
514	9, 11, 2, 14	12/30/2011	CMK
530	317, 322	12/30/2011	CMK
530	344	12/30/2011	CMK
435	886	12/30/2011	CMK

INTERFERENCE SEARCHED			
Class	Subclass	Date	Examiner
514	**9,11,2,14**	**12/30/2011**	**CMK**
530	317;322	12/30/2011	CMK
530	344	12/30/2011	CMK
435/886		12/30/2011	CMK

SEARCH NOTES (INCLUDING SEARCH STRATEGY)		
	DATE	EXMR
EAST Search on USPAT, USPGPUB, DERWENT, EPO, JPO; STN search on MEDLINE, BIOSIS, EMBASE, SCISEARCH, AGRICOLA.	7/25/2011	CMK
Search strategy enclosed, Inventor name search,	7/25/2011	CMK
Parent applications 60/177,170 and 09/735,191, 10/747,48 & 11/739,180 have been reviewed.	7/25/2011	CMK
Update the search	12/7/2011	CMK
Update the search	12/30/2011	CMK

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appl. No.	:	12/888,233	Confirmation No.	4046
Applicant	:	Thomas Kelleher		
Filed	:	September 22, 2010		
TC/A.U.	:	1656		
Examiner	:	Chih-Min Kam		
Docket No.	:	C062-02/04 US		
Customer No.	:	34103		

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

OK to enter
12/31/2011
CMK

RESPONSE AND AMENDMENT

This Amendment is responsive to the Office Action mailed December 15, 2011 (hereafter "the Office Action") in the above-identified application.

Kindly amend the application as follows:

Application Number	Application/Control No.	Applicant(s)/Patent under Reexamination	
	12/888,233	KELLEHER ET AL.	

Document Code - DISQ	Internal Document – DO NOT MAIL

TERMINAL DISCLAIMER	☒ APPROVED	☐ DISAPPROVED
Date Filed : 12-16-2011	This patent is subject to a Terminal Disclaimer	

Approved/Disapproved by:

Dorethea Lawrence

U.S. Patent and Trademark Office

PTO/SB/26 (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
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.

TERMINAL DISCLAIMER TO OBVIATE A DOUBLE PATENTING REJECTION OVER A "PRIOR" PATENT	Docket Number (Optional) C062-02/04 US

In re Application of: Thomas Kelleher

Application No.: 12/888,233

Filed: September 22, 2010

For: High Purity Lipopeptides

The owner*, Cubist Pharmaceuticals, Inc., of 100 percent interest in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application which would extend beyond the expiration date of the full statutory term **prior patent** No. 8,058,236 as the term of said prior patent is defined in 35 U.S.C. 154 and 173, and as the term of said **prior patent** is presently shortened by any terminal disclaimer. The owner hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and the **prior patent** are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

In making the above disclaimer, the owner does not disclaim the terminal part of the term of any patent granted on the instant application that would extend to the expiration date of the full statutory term as defined in 35 U.S.C. 154 and 173 of the **prior patent**, "as the term of said **prior patent** is presently shortened by any terminal disclaimer," in the event that said **prior patent** later:

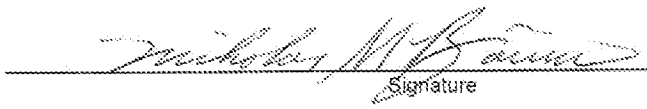
expires for failure to pay a maintenance fee;
is held unenforceable;
is found invalid by a court of competent jurisdiction;
is statutorily disclaimed in whole or terminally disclaimed under 37 CFR 1.321;
has all claims canceled by a reexamination certificate;
is reissued; or
is in any manner terminated prior to the expiration of its full statutory term as presently shortened by any terminal disclaimer.

Check either box 1 or 2 below, if appropriate.

1. ☑ For submissions on behalf of a business/organization (e.g., corporation, partnership, university, government agency, etc.), the undersigned is empowered to act on behalf of the business/organization.

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 Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

2. ☑ The undersigned is an attorney or agent of record. Reg. No. 45,650



Signature — December 16, 2011 (Date)

Nicholas M. Boivin
Typed or printed name

781-860-8660
Telephone Number

☑ Terminal disclaimer fee under 37 CFR 1.20(d) included.

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.

*Statement under 37 CFR 3.73(b) is required if terminal disclaimer is signed by the assignee (owner). Form PTO/SB/96 may be used for making this certification. See MPEP § 324.

Electronic Patent Application Fee Transmittal

Application Number:	12888233
Filing Date:	22-Sep-2010
Title of Invention:	High Purity Lipopeptides
First Named Inventor/Applicant Name:	Thomas J. Kelleher
Filer:	Nicholas M.C. Boivin
Attorney Docket Number:	C062-02/04 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:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
Statutory or terminal disclaimer	1814	1	160	160
		Total in USD ($)		**160**

Electronic Acknowledgement Receipt

EFS ID:	11639221
Application Number:	12888233
International Application Number:	
Confirmation Number:	4046
Title of Invention:	High Purity Lipopeptides
First Named Inventor/Applicant Name:	Thomas J. Kelleher
Customer Number:	34103
Filer:	Nicholas M.C. Boivin
Filer Authorized By:	
Attorney Docket Number:	C062-02/04 US
Receipt Date:	16-DEC-2011
Filing Date:	22-SEP-2010
Time Stamp:	15:26:16
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$160
RAM confirmation Number	2119
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		C062_02_04_US_20111216_Reply.pdf	57492 35272fd8c950b1de8f172989173f6c26115f15af	yes	11

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Amendment After Final	1	1
	Claims	2	9
	Applicant Arguments/Remarks Made in an Amendment	10	11

Warnings:

Information:

2	Terminal Disclaimer Filed	C062_02_04_20111216_Terminal_Disclaimer.pdf	436293 4fda90e027ae9a2ca783e118287e81a76095d709	no	1

Warnings:

Information:

3	Fee Worksheet (SB06)	fee-info.pdf	29731 35108318e9317d9d8ab55f33d156c2e34cb01e20	no	2

Warnings:

Information:

Total Files Size (in bytes):	523516

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.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appl. No.	:	12/888,233	Confirmation No.	4046
Applicant	:	Thomas Kelleher		
Filed	:	September 22, 2010		
TC/A.U.	:	1656		
Examiner	:	Chih-Min Kam		
Docket No.	:	C062-02/04 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 December 15, 2011 (hereafter "the Office Action") in the above-identified application.

Kindly amend the application as follows:

AMENDMENT TO THE CLAIMS

1. (Previously Presented) A composition obtained by a process comprising the step of forming a daptomycin aggregate, the composition comprising daptomycin of greater than or about 93% purity relative to impurities 1-14 defined by peaks 1-14 shown in FIG. 12 and having less than 4% of anhydro-daptomycin and having less than 4% of β isomer of daptomycin.

2-5. (Canceled)

6. (Original) The composition according to claim 1 that is free of each of impurities 1 to 14 defined by peaks 1-14 shown in FIG. 12.

7. (Previously Presented). The composition according to claim 1 that is essentially free of at least one 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. (Canceled).

10. (Canceled).

11. (Canceled).

12.-22. (Canceled)

23. (Previously Presented) The composition according to claim 1 wherein the process 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. (Previously Presented) The composition according to claim 23, wherein the process further comprises the step of lyophilizing daptomycin.

25.-31. (Canceled)

32. (Previously Presented) The composition of claim 1 comprising daptomycin having less than 1% of β-isomer of daptomycin.

33.-53. (Canceled)

54. (Previously Presented) The composition of claim 1, comprising daptomycin having greater than 93% purity.

55. (Previously Presented) The composition of claim 1, comprising daptomycin having less than 1% of the lactone hydrolysis product of daptomycin.

56. (Previously Presented) The composition of claim 1, comprising daptomycin that is substantially free of beta isomer of daptomycin.

57. (Previously Presented) The composition of claim 56, comprising daptomycin of greater than 93% purity.

58. (Previously Presented) The composition of claim 1, comprising daptomycin of at least 95% purity.

59. (Previously Presented) The composition of claim 1, comprising daptomycin with a purity of about 94 to 96%.

60. (Previously Presented) The composition of claim 1, comprising daptomycin of at least 97% purity.

61. (Previously Presented) The composition of claim 1, comprising lyophilized daptomycin having greater than 93% purity relative to impurities 1-14 defined by peaks 1-14 shown in FIG. 12, and having less than 1% of the lactone hydrolysis product of daptomycin.

62. (Previously Presented) The composition of claim 61, wherein the daptomycin is substantially free of beta-isomer of daptomycin.

63. (Previously Presented) A pharmaceutical composition compatible with a pharmaceutically acceptable carrier for the treatment of an infection of the blood, skin or soft tissue, the composition comprising daptomycin obtained by a process comprising the step of forming a daptomycin aggregate, the composition having daptomycin with greater than or about 93% purity relative to impurities 1-14 defined by peaks 1-14 shown in FIG. 12.

64. (Previously Presented) The pharmaceutical composition of claim 63, wherein the daptomycin has greater than 93% purity and less than 4% anhydro daptomycin.

65. (Previously Presented) The pharmaceutical composition of claim 63, wherein the the pharmaceutically acceptable carrier is selected from the group consisting of physiological saline and Ringer's solution for reconstitution for administration as a single daily dose to the subject.

66. (Previously Presented) The pharmaceutical composition of claim 63, wherein the pharmaceutical composition is compatible with the pharmaceutically acceptable carrier for the treatment of an infection of the blood, skin or soft tissue by administration in a daily dose of 1 to 12 mg/kg of the daptomycin in a reconstituted solution of the composition in the pharmaceutically acceptable carrier.

67. (Previously Presented) The pharmaceutical composition of claim 66, wherein

a) the pharmaceutically acceptable carrier is selected from the group consisting of physiological saline and Ringer's solution for intravenous administration as a single daily dose to the subject;

b) the daptomycin has greater than 93% purity, less than 4% anhydro daptomycin and less than 4% beta-isomer of daptomycin; and

c) the composition comprising daptomycin is obtained by a purification process comprising the steps of forming a daptomycin aggregate and obtaining the daptomycin from the daptomycin aggregate.

68. (Previously Presented) The pharmaceutical composition of claim 67, wherein the process for obtaining the daptomycin includes a purification process comprising the steps of

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

b) forming the daptomycin aggregate comprising a daptomycin micelle in the enriched daptomycin preparation or a composition obtained from the enriched daptomycin preparation; and

c) obtaining the daptomycin from the daptomycin aggregate.

69. (Previously Presented) The pharmaceutical composition of claim 68, wherein the daptomycin is obtained from the daptomycin aggregate by a method comprising the steps of

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

b) collecting the daptomycin aggregate.

70. (Previously Presented) The pharmaceutical composition of claim 69, wherein the daptomycin is obtained from the daptomycin aggregate by a method further comprising the steps of

a) subjecting a composition comprising the daptomycin aggregate to hydrophobic interaction chromatography to obtain a semi-purified daptomycin preparation; and

b) obtaining the daptomycin from the semi-purified daptomycin preparation.

71. (Previously Presented) A pharmaceutical composition for the treatment of an infection, the composition comprising daptomycin having greater than

93% purity relative to impurities 1-14 defined by peaks 1-14 shown in FIG. 12, the daptomycin purified by a process comprising the formation of micelles comprising daptomycin.

72. (Previously Presented) The pharmaceutical composition of claim 71, wherein the daptomycin is a lyophilized powder comprising daptomycin purified by process comprising the steps of forming a daptomycin micelle and obtaining the daptomycin from the micelles.

73. (Previously Presented) The pharmaceutical composition of claim 71, wherein the daptomycin has less than 4% anhydro daptomycin and less than 4% beta-isomer of daptomycin.

74. (Previously Presented) The pharmaceutical composition of claim 71, wherein the daptomycin has less than 1% of the lactone hydrolysis product of daptomycin.

75. (Previously Presented) The pharmaceutical composition of claim 72, wherein the daptomycin has less than 4% anhydro daptomycin, less than 1% of the lactone hydrolysis product of daptomycin and is essentially free of the beta-isomer of daptomycin.

76. (Previously Presented) A pharmaceutical composition for the treatment of an infection of the blood, skin or soft tissue, the pharmaceutical composition comprising a solution of a pharmaceutically acceptable carrier for intravenous administration and daptomycin, the daptomycin having greater than 93% purity relative to impurities 1-14 defined by peaks 1-14 shown in FIG. 12, and the daptomycin obtained from a purification process comprising the formation of a daptomycin micelle.

77. (Previously Presented) The pharmaceutical composition of claim 76, wherein the daptomycin has less than 4% anhydro daptomycin and less than 4% beta-isomer of daptomycin.

78. (Previously Presented) The pharmaceutical composition of claim 76, wherein the daptomycin has less than 1% of the lactone hydrolysis product of daptomycin.

79. (Previously Presented) The pharmaceutical composition of claim 77, wherein the daptomycin has less than 4% anhydro daptomycin, less than 1% of the lactone hydrolysis product of daptomycin and is essentially free of the beta-isomer of daptomycin.

80. (Previously Presented) The composition of claim 63, wherein the infection of the blood, skin or soft tissue comprises *Staphylococcus aureus.*

81. (Previously Presented) The composition of claim 63, wherein the infection is bacteremia.

82. (Previously Presented) The composition of claim 63, wherein the infection is endocarditis.

83. (Previously Presented) The composition of claim 63, wherein the infection is a skin or soft tissue infection.

84. (Previously Presented) The composition of claim 63, wherein the infection includes bacteria selected from the group consisting of *Staphylococcus aureus. Streptococcus pyogenes, Streptococcus agalactiae,* and *Enterococcus faecalis.*

85. (Previously Presented) The composition of claim 71, wherein the infection comprises *Staphylococcus aureus.*

86. (Previously Presented) The composition of claim 71, wherein the infection is bacteremia.

87. (Previously Presented) The composition of claim 71, wherein the infection is endocarditis.

88. (Previously Presented) The composition of claim 71, wherein the infection is a skin or soft tissue infection.

89. (Previously Presented) The composition of claim 71, wherein the infection includes bacteria selected from the group consisting of *Staphylococcus aureus. Streptococcus pyogenes, Streptococcus agalactiae,* and *Enterococcus faecalis.*

90. (Previously Presented) The composition of claim 76, wherein the infection comprises *Staphylococcus aureus.*

91. (Previously Presented) The composition of claim 76, wherein the infection is bacteremia.

92. (Previously Presented) The composition of claim 76, wherein the infection is endocarditis.

93. (Previously Presented) The composition of claim 76 wherein the infection is a skin or soft tissue infection.

94. (Previously Presented) The composition of claim 76, wherein the infection includes bacteria selected from the group consisting of *Staphylococcus aureus. Streptococcus pyogenes, Streptococcus agalactiae,* and *Enterococcus faecalis.*

95. (Previously Presented) The composition of claim 76, wherein the pharmaceutical composition includes daptomycin in a daily intravenous dose 1 to 12 mg/kg.

96. (Previously Presented) A vial containing a lyophilized powder pharmaceutical composition compatible with a pharmaceutically acceptable carrier for the treatment of an infection by a daily intravenous dose of the lyophilized powder reconstituted in the pharmaceutically acceptable carrier, the composition

a) having daptomycin with greater than or about 93% purity relative to impurities 1-14 defined by peaks 1-14 shown in FIG. 12; and

b) the composition comprising daptomycin purified by a process including the steps of forming a daptomycin aggregate, converting the daptomycin aggregate to monomers and obtaining the daptomycin in the composition from the monomers by a process including one or more steps selected from the group consisting of anion exchange chromatorgraphy and hydrophobic interaction chromatography.

97. (Previously Presented) A composition obtained by a process comprising the steps of forming a daptomycin aggregate, converting the daptomycin aggregate to monomers and obtaining the daptomycin in the composition from the monomers by a process including one or more steps selected from the group consisting of

anion exchange chromatorgraphy and hydrophobic interaction chromatography, the composition comprising daptomycin of greater than or about 93% purity relative to impurities 1-14 defined by peaks 1-14 shown in FIG. 12.

98. (Previously Presented) The composition of claim 97, comprising daptomycin of greater than 93% purity relative to impurities 1-14 defined by peaks 1-14 shown in FIG. 12.

99. (Previously Presented) The composition of claim 97, wherein the composition is a lyophilized powder compatible with a pharmaceutically acceptable carrier for the treatment of one or more infections selected from the group consisting of infections of the blood, skin and soft tissue, by a daily intravenous dose of 1 to 12 mg/kg of the daptomycin in a reconstituted solution of the lyophilized powder in the pharmaceutically acceptable carrier.

100. (Previously Presented) The composition of claim 98, wherein

a) the composition is a lyophilized powder compatible with a pharmaceutically acceptable carrier for the treatment of an infection of the infection by a daily intravenous dose of 1 to 12 mg/kg of the daptomycin in a reconstituted solution of the lyophilized powder in the pharmaceutically acceptable carrier; and

b) the daptomycin has a purity of about 94 to 96% relative to impurities 1-14 defined by peaks 1-14 shown in FIG. 12, the daptomycin having less than 1% of the lactone hydrolysis product of daptomycin, less than 4% anhydro daptomycin and less than 4% of the beta-isomer of daptomycin.

REMARKS

Applicant requests entry of this Response and Amendment in response to the Final Rejection mailed December 15, 2011. A Response that merely cancels claims, adopts examiner suggestions, and removes issues for appeal is properly entered in response to Final rejection (MPEP 714.13). This Response and Amendment cancels claim 11 and is submitted with a Terminal Disclaimer filed herewith. Accordingly, this Response and Amendment places the instant application in condition for allowance.

Claim Rejections under Obviousness-Type Double Patenting

The Office Action rejects claims 1, 6-8, 11, 23-24, 32 and 54-100 under the judicially-created doctrine of non-statutory obviousness-type double patenting over claims 2-3, 6, 54, 58, 62, 115, 171, 175, 178, and 179 of patent application 11/739,180, now U.S. Patent 8,058,238 (Office Action at pages 4-6). Applicants submit a Terminal Disclaimer of the instant application over patent application 11/739,180, now U.S. Patent 8,058,238, obviating the basis for this rejection. Reconsideration and withdrawal of this rejection is requested.

Claim Rejections under 35 USC 112, 2nd Paragraph

The Office Action rejects claim 11 as being indefinite. Claim 11 is canceled in this Response and Amendment, obviating the basis for this rejection. 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. Please deduct any fee required for entry of this Response and Amendment, and apply any other charges or credits required for entry of this amendment to Deposit Account No. 50-1986, referencing attorney docket number C062-02/04 US. Applicants do not authorize payment of the issue fee at this time with the instructions above.

Respectfully submitted,

Date: December 16, 2011
/Nicholas M. Boivin/
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C062-02-04 US 20111216 response to 20111215 OA.doc

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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 12/888,233	Filing Date 09/22/2010	☐ 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	**330**
☐ 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	**330**

APPLICATION AS AMENDED – PART II

AMENDMENT	12/16/2011	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE ($)	ADDITIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 54	Minus	** 55	= 0	X $ =		OR	X $60=	0
	Independent (37 CFR 1.16(h))	* 6	Minus	***6	= 0	X $ =		OR	X $250=	0
	☐ 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	**0**

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/

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.
12/888,233	09/22/2010	Thomas J. Kelleher	C062-02/04 US	4046

34103 7590 12/15/2011

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

EXAMINER	
KAM, CHIH MIN	

ART UNIT	PAPER NUMBER
1656	

NOTIFICATION DATE	DELIVERY MODE
12/15/2011	ELECTRONIC

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.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patents@cubist.com
jodi.doherty@cubist.com
colleen.lombard@cubist.com

Office Action Summary	Application No.	Applicant(s)	
	12/888,233	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 October 2011*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ 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

5)☒ Claim(s) *1,6-8,11,23,24,32 and 54-100* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1,6-8,11,23,24,32 and 54-100* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☒ The drawing(s) filed on *22 September 2010* 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).

12)☐ 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

13)☐ 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 *10/13/2011;10/24/2011*.
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, 6-8, 11, 23-24, 32 and 54-100 are pending.

Applicants' amendment filed October 13, 2011 is acknowledged. Applicants' response has been fully considered. Claims 1, 11, 23, 24 and 327 have been amended, claims 2-5, 9-10, 12-22, 25-31 and 33-53 have been cancelled, and new claims 54-100 have been added. Therefore, claims 1, 6-8, 11, 23-24, 32 and 54-100 are examined.

Withdrawn Claim Rejections - 35 USC § 102

2. The previous rejection of claims 1, 8-30, 37, 38, 45, 46 and 53 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), is withdrawn in view of applicants' amendment to the claims, applicants' cancellation of the claims, and applicants' response at page 11 in the amendment filed October 13, 2011.

Withdrawn Claim Rejections -Obviousness Type Double Patenting

3. The previous rejection of claims 1, 8-9, 30, 37, 38, 45, 46 and 53 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 pages 11-12 in the amendment filed October 13, 2011.

4. The previous rejection of claims 2-5, 9-10, 12-22, 25-29, 31, 33-36, 38-44 and 46-52 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 2-4, 6, 54, 58, 62 and 115 of co-pending application, 11/739,180 (based on the

amendment dated 5/27/2011), is withdrawn in view of applicants' cancellation of the claims in the amendment filed October 13, 2011.

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. Claim 11 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

6. Claim 11 is indefinite because the claim recites steps of a)-f) to obtain the composition of claim 1, while independent claim 1 recites the composition is obtained by a process comprising the step of forming a daptomycin aggregate, it is not clear how the step of claim 1 is encompassed by the process of claim 11, which merely recites steps of a)-f) for obtaining the composition.

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).

7. Claims 1, 6-8, 11, 23-24, 32 and 54-100 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over at least claims 2-3, 6, 54, 58, 62, 115, 171, 175, 178 and 179 of co-pending application, 11/739,180 (Now U.S. Patent 8,058,238, claims 1, 3, 8, 10, 21, 49, 50, 176, 180, 183 and 191). Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 1, 6-8, 11, 23-24, 32 and 54-100 in the instant application disclose a composition obtained by a process comprising the step of forming a daptomycin aggregate, the composition comprising daptomycin of greater than or about 93% purity relative to impurities 1 to 14 defined by peaks 1-14 shown in FIG. 12, and having less than 4% of anhydro-daptomycin and having less than 4% of β-isomer of daptomycin; a pharmaceutical composition comprising a composition and a pharmaceutically acceptable carrier, wherein the composition comprising daptomycin obtained by a process comprising the step of forming a daptomycin aggregate or a daptomycin micelle, the composition comprising daptomycin of greater than or about 93% purity relative to impurities 1 to 14 defined by peaks 1-14 shown in FIG. 12; and a vial containing the lyopholyzed powder pharmaceutical composition. This is obvious variation in view of at least claims 1, 3, 8, 10, 21, 49, 50, 176, 180, 183 and 191 of the patent which disclose a composition comprising essentially pure daptomycin purified by a process comprising the step of forming a daptomycin aggregate; a composition comprising a daptomycin that is substantially free of each of impurities 1 to 14 defined by peaks 1-14 shown in FIG. 12 and obtained by a process comprising the step of forming a daptomycin aggregate; and a pharmaceutical composition comprising essentially pure daptomycin purified by a process comprising the step of forming a daptomycin aggregate or daptomycin aggregate. Both claims of instant application and the patent are directed to a

composition comprising essentially pure daptomycin purified by a process comprising the step of forming a daptomycin aggregate; ; a composition comprising a daptomycin that is substantially free of each of impurities 1 to 14 defined by peaks 1-14 shown in FIG. 12 and obtained by a process comprising the step of forming a daptomycin aggregate; and a pharmaceutical composition comprising essentially pure daptomycin purified by a process comprising the step of forming a daptomycin aggregate or daptomycin aggregate. Thus, claims 1, 6-8, 11, 23-24, 32 and 54-100 in present application and claims 1, 3, 8, 10, 21, 49, 50, 176, 180, 183 and 191 of the patent are obvious variations of a composition comprising essentially pure daptomycin purified by a process comprising the step of forming a daptomycin aggregate; a composition comprising a daptomycin that is substantially free of each of impurities 1 to 14 defined by peaks 1-14 shown in FIG. 12 and obtained by a process comprising the step of forming a daptomycin aggregate; and a pharmaceutical composition comprising essentially pure daptomycin purified by a process comprising the step of forming a daptomycin aggregate or daptomycin aggregate.

Response to Arguments

Applicants indicate independent claim 1, as amended, and dependent claims therefrom cover a composition obtained by a process comprising the step of forming a daptomycin aggregate, the composition comprising daptomycin of greater than or about 93% purity relative to impurities 1-14 defined by peaks 1-14 shown in FIG. 12 and having less than 4% of anhydro-daptomycin and having less than 4% of β-isomer of daptomycin. Thus, applicants requests reconsideration and withdrawal of this rejection (page 12 of the response).

Applicants' response has been considered, however, the arguments are not found persuasive because the scope of instant claims is overlapped with the scope of the claims of U.S. Patent 8,058,238. For example, claim 8 of the patent recites 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 (i.e., impurity 8 is β-isomer of daptomycin, and impurity 13 is anhydro-daptomycin) and obtained by a process comprising the step of forming a daptomycin aggregate, which has an overlapped scope with instant claim 1. Therefore, the rejection is maintained.

Conclusion

8. No claims are allowed.

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, 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.

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

CMK
December 8, 2011

Notice of References Cited	Application/Control No. 12/888,233	Applicant(s)/Patent Under Reexamination KELLEHER ET AL.	
	Examiner CHIH-MIN KAM	Art Unit 1656	Page 1 of 1

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	B	US-			
	C	US-			
	D	US-			
	E	US-			
	F	US-			
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L1 9013 S DAPTOMYCIN

L2 2 S L1 (P) IMPURITIES

L3 2 DUPLICATE REMOVE L2 (0 DUPLICATES REMOVED)

L4 5 S ANHYDRO-DAPTOMYCIN OR BETA-DAPTOMYCIN

L5 20 S LACTONE HYDROLYSIS PRODUCT

L6 5 S L1 (P) (L4 OR L5)

L7 471237 S AGGREGATE

L8 151646 S MICELLES

L9 5 DUPLICATE REMOVE L6 (0 DUPLICATES REMOVED)

L10 0 S L9 AND (L7 OR L8)

L11 5 S L6 NOT L3

L12 13 S L1 (P) (L7 OR L8)

L13 1 S L2 AND L12

L14 11639 S HYDROPHOBIC INTERACTION CHROMATOGRAPHY

L15 120696 S ANION EXCHANGE

L16 1 S L2 AND L14 AND L15

L17 0 S L9 AND L14 AND L15

L18 226 S KELLEHER T?/AU

L19 13303 S LAI J?/AU

L20 14 S DECOURCEY J?/AU

L21 4074 S LYNCH P?/AU

L22 91 S ZENONI M?/AU

L23 150 S TAGLIANI A?/AU

L24 17840 S L18 OR L19 OR L20 OR L21 OR L22 OR L23

L25 21 S L24 AND L1

L26 0 S L25 AND L4

L27 0 S L25 AND L5

L28 1 S L24 AND L2

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PTO/SB/08a (01-10)
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	12888233
Filing Date	2010-09-22
First Named Inventor	Thomas J. Kelleher
Art Unit	1656
Examiner Name	Chih-Min Kam
Attorney Docket Number	C062-02/04 US

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EXAMINER SIGNATURE

Examiner Signature	/Chih Min Kam/	Date Considered	12/08/2011

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	First Named Inventor	Thomas J. Kelleher
	Art Unit	1656
	Examiner Name	Chih-Min Kam
	Attorney Docket Number	C062-02/04 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).

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☐ 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).

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☒ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

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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	/Nicholas M. Boivin/	Date (YYYY-MM-DD)	2011-10-13
Name/Print	Nicholas M. Boivin	Registration Number	45,650

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L2	1255	daptomycin	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2011/12/07 10:32
L3	17	impurities same L2	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2011/12/07 10:32
L4	16	anhydro-daptomycin or beta-daptomycin	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2011/12/07 10:32
L5	22	lactone adj hydrolysis adj product	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2011/12/07 10:32
L6	16	3 same (4 or 5)	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2011/12/07 10:34
L7	5	3 same 5	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2011/12/07 10:34
L8	362829	aggregate	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2011/12/07 10:36
L9	48234	micelles	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2011/12/07 10:36
L10	1	3 same 8	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2011/12/07 10:36
L11	10	3 same 9	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2011/12/07 10:36
L12	58181	anion adj exchange	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2011/12/07 10:38
L13	15140	hydrophobic adj interaction adj chromatography	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2011/12/07 10:38
L14	9	L2 same L12 same L13	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2011/12/07 10:38
L15	22	kelleher adj thomas.in.	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2011/12/07 10:38
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L18	32	lynch adj paul.in.	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2011/12/07 10:38
L19	83	zenoni adj maurizio.in.	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2011/12/07 10:38
L20	10	tagliani adj auro.in.	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2011/12/07 10:38
L21	138	L15 or L16 or L17 or L18 or L19 or L20	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2011/12/07 10:38
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	12888233
	Filing Date	2010-09-22
	First Named Inventor	Thomas J. Kelleher
	Art Unit	1656
	Examiner Name	Chih-Min Kam
	Attorney Docket Number	C062-02/04 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.	T[5]
/CMK./	1	Cubicin® (daptomycin for injection) Label 1004 - September 2003	☐
/CMK./	2	Cubicin® (daptomycin for injection) Label 1004-1 - Revised August 2004	☐
/CMK./	3	Cubicin® (daptomycin for injection) Label 1004-2 - Revised June 2005	☐
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☒ See attached certification statement.

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Signature	/Nicholas M. Boivin/	Date (YYYY-MM-DD)	2011-10-24
Name/Print	Nicholas M. Boivin	Registration Number	45,650

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Search Notes	Application No.	Applicant(s)	
	12/888,233	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
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Search strategy enclosed, Inventor name search,	7/25/2011	CMK
Parent applications 60/177,170 and 09/735,191, 10/747,48 & 11/739,180have been reviewed.	7/25/2011	CMK
Update the search	12/7/2011	CMK

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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	6468967		2002-10-22	Cubist Pharmaceuticals, Inc.	
	2	6852689		2005-02-08	Cubist Pharmaceuticals, Inc.	

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	1	WO 00/18419	WO		2000-04-06	Cubist Pharmaceuticals, Inc.		☐

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(71) Applicant: CUBIST PHARMACEUTICALS, INC. [US/US]; 24 Emily Street, Cambridge, MA 02139 (US).

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(54) Title: METHODS FOR ADMINISTRATION OF ANTIBIOTICS

(57) Abstract

The invention provides methods for administering a therapeutically effective amount of daptomycin while minimizing skeletal muscle toxicity. The methods provide daptomycin administration at a dosing interval of 24 hours or greater. This long dosing interval minimizes skeletal muscle toxicity and allows for higher peak concentrations of daptomycin, which is related to daptomycin's efficacy. The invention also provides methods of administering lipopeptide antibiotics other than daptomycin while minimizing skeletal muscle toxicity by administering a therapeutically effective amount of the lipopeptide antibiotic at a dosage interval that does not result in muscle toxicity. The invention also provides methods of administering quinupristin/dalfopristin while minimizing skeletal muscle toxicity by administering a therapeutically effective amount of quinupristin/dalfopristin at a dosage interval that does not result in muscle toxicity.

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METHODS FOR ADMINISTRATION OF ANTIBIOTICS

TECHNICAL FIELD OF THE INVENTION

The present invention relates to improved methods of administering lipopeptide antibiotics, such as daptomycin, with potent bactericidal activity against gram-positive bacteria, including antibiotic-resistant strains. The present invention also relates to improved methods of administering quinopristin/dalfopristin, which also has potent bactericidal activity against gram-positive bacteria, including antibiotic-resistant strains.

BACKGROUND OF THE INVENTION

The rapid increase in the incidence of gram-positive infections—including those caused by 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 Tally et al., 1999, Exp. Opin. Invest. Drugs 8:1223-1238, hereafter "Tally"). Daptomycin provides a rapid, concentration-dependent bactericidal effect and a relatively prolonged concentration-dependent post-antibiotic effect *in vivo*.

Daptomycin is described in Baltz in Biotechnology of Antibiotics, 2nd Ed., ed. by W.R. Strohl (New York: Marcel Dekker, Inc.), 1997, pp. 415-435, hereafter "Baltz." Daptomycin is a cyclic lipopeptide antibiotic that can be derived from the fermentation of *Streptomyces roseosporus*. It is comprised of a decanoyl side chain linked to the N-terminal tryptophan of a cyclic 13–amino acid peptide (see Fig. 1a, Baltz et al., *supra*). The compound is currently being developed in both intravenous and oral formulations to treat serious infections caused by bacteria, including, but not limited to, methicillin resistant *Staphylococcus aureus* (MRSA) and vancomycin resistant enterococci (VRE).

Daptomycin's mechanism of action is distinct from that of other classes of antibiotics, which include β-lactams, aminoglycosides, glycopeptides and macrolides. Without wishing to be bound by any theory, daptomycin is believed to kill gram-positive bacteria by disrupting multiple aspects of bacterial plasma membrane function while not penetrating into the cytoplasm. The antibacterial mechanisms of daptomycin may include inhibition of peptidoglycan synthesis, inhibition of lipoteichoic acid synthesis and dissipation of bacterial membrane potential (see, e.g., Baltz, *supra*).

The efficacy and safety of daptomycin has been examined in nonclinical studies and in Phase I and Phase II clinical trials. Daptomycin was well tolerated in human volunteers when given intravenously at 1 or 2 mg/kg every 24 hours. See Baltz, *supra*, and references therein. Furthermore, a single dose of daptomycin was well-tolerated over a dose range of 0.5 to 6 mg/kg. See Baltz, *supra*, and Woodworth et al., 1992, Antimicrob. Agents Chemother. 36:318-25.

However, prolonged treatment with 3 mg/kg daptomycin every 12 hours was shown to cause occasional adverse effects (Baltz, *supra*). Transient muscular weakness and pain were observed in two of five human patients who had been treated with 4 mg/kg daptomycin every 12 hours for 6 to 11 days (Tally, *supra*). In the two subjects who experienced muscular weakness and pain, creatine phosphokinase (CPK) levels had increased one to two days prior to the muscular weakness. Treatment was discontinued three to four days after the initial elevation in CPK was observed. One to two days after discontinuation of daptomycin treatment, CPK levels peaked at levels in excess of 10,000 U/L in one subject and at 20,812 U/L in the second subject (Tally, *supra*). Based upon these studies and the rationale that higher doses of daptomycin were required for efficacy against many types of bacterial infection, clinical studies of daptomycin were discontinued (Baltz, *supra*).

In the above-described clinical trials and in a series of toxicology studies in animals, skeletal muscle was found to be the primary target tissue of daptomycin toxicity. Repeated daily intravenous administration in toxicological studies of high doses of daptomycin in rats and dogs (75 mg/kg/day in rats and 40 mg/kg/day in dogs) caused mild myopathy in the skeletal muscle (Tally, *supra*). It was also found that increases in CPK levels are a sensitive measure of myopathy, and thus can be used to measure daptomycin's effects upon muscle tissue. See Tally et al. *supra*.

Although low doses of daptomycin do not cause muscle toxicity and are effective in treating many gram-positive bacterial infections, certain types of gram-positive bacterial infections, such as deep-seated infections or those caused by certain antibiotic-resistant bacterial strains, may require higher doses of daptomycin for effective treatment. For instance, certain vancomycin-resistant strains of bacteria exhibit a two- to four-fold higher daptomycin minimum inhibitory concentration (MIC) than most vancomycin-susceptible strains. Accordingly, there

is a great need to develop methods for administration of effective amounts of daptomycin that will also minimize adverse skeletal muscle effects.

A non-lipopeptide streptogramin antibiotic combination, quinupristin/dalfopristin, has also shown activity against gram-positive organisms, including antibiotic-resistant bacteria such as methicillin-resistant *Staphylococcus aureus*, glycopeptide intermediary *S. aureus*, and glycopeptide-resistant *Enterococcus faecium* (Rubinstein et al., 1999, J. Antimicrob. Chemother. 44, Topic A, 37-46, hereafter "Rubinstein"). Quinupristin/dalfopristin has been shown to be effective in treatment of nosocomial pneumonia, emergency use studies, complicated skin and skin structure infection and bacteremia (Rubinstein, *supra*). Approximately 13% of the patients treated with 7.5 mg/kg quinupristin/dalfopristin every 8 or 12 hours experienced arthralgia or myalgia, which included muscle pain, and approximately 5% of patients exhibited increased CPK levels (Rubinstein, *supra*). Therefore, it would appear that quinupristin/dalfopristin also causes muscle toxicity.

The aminoglycosides, which make up another class of antibiotics, are also toxic at high doses. They have been administered as a high dose at less frequent intervals rather than at lower doses at more frequent intervals in order to reduce their toxicity (Barclay et al., 1994, Clin. Pharmacokinet. 27:32-48). However, aminoglycosides differ from daptomycin in a number of ways, specifically in the fact that the sites of toxicity are distinct. Aminoglycosides are toxic to the kidney and central nervous system whereas skeletal muscle is the site of toxicity for daptomycin. The mechanisms of toxicity for aminoglycosides and daptomycin are also distinct. In addition, aminoglycosides are structurally dissimilar to daptomycin, act only on gram-negative bacteria, have a different mechanism of antibacterial action from daptomycin and exhibit different mechanisms of resistance. Thus, the possibility that less frequent administration of aminoglycosides results in lower toxicity to the patient does not predict that the same would be true for daptomycin.

SUMMARY OF THE INVENTION

The present invention addresses the problem of skeletal muscle toxicity at high doses of lipopeptide antibiotics such as daptomycin, as well as quinupristin/dalfopristin. The invention provides methods for administering the antibiotic that minimizes skeletal muscle toxicity while simultaneously maintaining a sufficient efficacy level.

The process of the invention is characterized by administering less frequent doses comprising a higher concentration of an antibiotic. This protocol is both safer and more efficacious than administering more frequent doses of the antibiotic at lower concentrations. Thus, in one method of the invention, daptomycin is administered to a patient in need thereof at a dosing interval that minimizes skeletal muscle toxicity. In another method of the invention, a lipopeptide antibiotic other than daptomycin, such as a daptomycin derivative, A54145 or a derivative thereof, is administered to a patient in need thereof at a dosing interval that minimizes skeletal muscle toxicity. In a third method of the invention, quinupristin/dalfopristin is administered to a patient in need thereof at a dosing interval that minimizes skeletal muscle toxicity.

The methods of the invention are characterized by administering a high dose of an antibiotic that causes skeletal muscle toxicity at a dosage interval of 24 hours to once weekly. In one embodiment of the invention, daptomycin is administered at a dose of 3 to 75 mg/kg at a dosage interval of 24 hours to once weekly. In another embodiment of the invention, quinupristin/dalfopristin is administered at a dose of 7.5 to 75 mg/kg at a dosage interval of 24 hours to once weekly.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1. Serum creatine phosphokinase (CPK) levels for Dog Study A (top panel) and Dog Study B (bottom panel). Serum CPK levels were

determined at two hours after daptomycin dosing as an indication of muscle toxicity.

Figure 2. Steady state plasma concentrations of daptomycin on day 18 of dosing as determined by HPLC for Dog Study A (top panel) and Dog Study B (bottom panel).

Figure 3. Relationship between different dosing intervals of daptomycin and its skeletal muscle toxicity (related to CPK levels) and its effectiveness (related to the peak serum concentration, C_{max}, over the minimal inhibitory concentration, MIC, of daptomycin).

DETAILED DESCRIPTION OF THE INVENTION

To investigate the potential effects of dose fractionation on toxicity, two studies were conducted in dogs comparing the effects of repeated intravenous administration once daily (q24h) versus every 8 hours (q8h). These studies were conducted in the dog since this species is most predictive of clinical effects. The objective of the studies was to assess the relationship between pharmacokinetics, including C_{max} and AUC_{24h}, and skeletal muscle toxicity, in order to determine the optimal clinical dosing regimen to minimize potential for skeletal muscle toxicity.

Study A explored whether daptomycin-related skeletal muscle toxicity is related to the peak concentration of daptomycin that occurs in the bloodstream after administration (C_{max}) and not to the total concentration of daptomycin in the bloodstream for 24 hours (AUC_{24h}). In Study A, the daptomycin daily dose was fractionated into multiple administrations per day to reduce C_{max} (see Example 1 and Figure 2, top panel).

Study B examined whether a threshold plasma concentration exists for daptomycin-related skeletal muscle toxicity. Under this hypothesis, administration of the no observed effect dose level at 24 hours (NOELq24h) multiple times per day, such that plasma levels of daptomycin remain below some

undetermined threshold of toxicity, would not be associated with skeletal muscle toxicity (Example 2).

Surprisingly, muscle toxicity was not primarily related to C_{max}. For example, both serum creatine phosphokinase (CPK) levels and the incidence of microscopic myopathy observed at 25 mg/kg administered once every 8 hours (q8h) were greater than those observed at 75 mg/kg administered once every 24 hours (q24h), despite the lower C_{max} for 25 mg/kg q8h (Example 1, Table 2). In contrast, large increases in peak CPK levels were observed when the dose interval was varied from q24h to q8h at a dose of either 5 mg/kg or 25 mg/kg even though C_{max} levels were comparable for each dose at either q24h or q8h (Example 1, Table 2 and Example 2, Table 4). Toxicity also did not appear to be related to AUC_{24h}, since the toxicity observed at 25 mg/kg q8h was greater than at 75 mg/kg q24h at approximately the same AUC.

The results of Studies A and B suggest that the pharmacokinetic parameter defining daptomycin-associated skeletal muscle toxicity in dogs is not related to C_{max}. In addition, toxicity did not appear to be related to AUC or an intrinsically toxic plasma concentration, but appeared to be related to the dosing interval of daptomycin. Without wishing to be bound by any theory, skeletal muscle effects appear to be related to the duration of time at low plasma concentrations of daptomycin available for repair of subclinical damage to the myofibers. Therefore, the data suggest that the dosing interval is the key determinant of muscle toxicity, rather than just the magnitude of the dose itself. Further, since C_{max} and/or AUC were found to be the key pharmacokinetic parameters associated with eradication of infection (J. Leggett et al., Abstract No. 154, page 123, Program and Abstracts of the 27th Interscience Conference on Antimicrobial Agents and Chemotherapy, American Society for Microbiology, Washington, D.C., 1987; A. Louie et al., Abstract No. 1769, N. Safdar et al., Abstract No. 1770, Program and Abstracts of the 39th Interscience Conference on Antimicrobial Agents and Chemotherapy, American Society for Microbiology, San Francisco, CA, September 26-29,1999),

the pharmacological activity of daptomycin is optimized by once-daily dosing. These results suggest that once-daily dosing can minimize daptomycin muscle toxicity, while potentially optimizing its antimicrobial efficacy (Figure 3).

These observations are further supported by the results of a clinical study. The study demonstrated that daptomycin administered at doses of 4 mg/kg q24h, 6 mg/kg q24h or at an initial dose of 6 mg/kg with subsequent doses at 3 mg/kg q12h did not result in an increase in CPK levels related to daptomycin administration and did not result in any muscle weakness or pain in any patient (Example 4). The C_{max} is predicted to be higher (86.8 µg/mL) at a dose regimen of 6 mg/kg q24h than at a dose regimen of 4 mg/kg q12h (69.2 µg/mL). Yet zero of nine patients tested at the dose regimen predicting a higher C_{max} had drug related adverse skeletal muscle effects (Table 5), whereas two of five patients tested at the dose regimen predicting a lower C_{max} had adverse skeletal muscle effects (Tally, *supra*). Thus, the results presented in Example 3 demonstrate that C_{max} is not the cause of skeletal muscle toxicity in humans, further showing that the findings regarding daptomycin dosing in dogs is applicable to humans.

Without wishing to be being bound by any theory, these results may be explained by the hypothesis that skeletal muscle toxicity is related to time between doses for repair of skeletal muscle damage. For instance, Example 1 demonstrates that CPK levels were much higher when dogs were administered 75 mg/kg/day fractionated into three doses per day (25 mg/kg q8h), than when the same dose was administered once per day (75 mg/kg q24h). Once-daily administration may allow greater time between doses (at non-toxic blood levels) for repair of subclinical muscle damage associated with daptomycin. Thus, once-daily dosing results in less toxicity. The new repair hypothesis is consistent with the lack of progression of toxicity after extended durations of dosing. For instance, there is no progression of toxicity for six-month dosing studies compared to one-month dosing studies in rats and dogs. In addition, the new repair hypothesis is consistent with observations that CPK levels decrease despite continued treatment with

daptomycin and the presence of regenerative changes in skeletal muscle (Figure 1). In addition, because C_{max} and/or AUC are the key determinants of efficacy in animal models of infection, the pharmacological activity of daptomycin is optimized by once-daily dosing. Therefore, because safety and efficacy are not dependent upon the same determinant (C_{max}), the safety margin for daptomycin can be increased by altering the dosing regimen.

Based upon these results, the present invention provides methods for administering daptomycin that minimize skeletal muscle toxicity compared to prior methods for administering daptomycin. The methods may be used for human patients in clinical applications and in veterinary applications. The dose and dosage interval for the method is one that is safe and efficacious in clinical or veterinary applications. The method of the invention teaches, in general, that longer dosing intervals can provide for the administration of higher doses of daptomycin.

In one embodiment of the instant invention, the dose is 3 to 75 mg/kg daptomycin. In a preferred embodiment, the dose is 6 to 25 mg/kg. In a more preferred embodiment, the dose for humans patients is 6 to 12 mg/kg. Doses that may be used include 7, 8, 9, 10, 11, 12, 14, 16, 18, 20, 22 or 25 mg/kg. In a preferred embodiment for veterinary applications, the dose is 3 to 25 mg/kg. Other doses higher than, intermediate to or less than these doses may also be used and may be determined by one skilled in the art following the methods of this invention.

In one embodiment of the instant invention, the dosage interval is 24 hours to once weekly. In a preferred embodiment, daptomycin is administered at a dosage interval of once every 24 hours, once every 48 hours, once every 72 hours, once every 96 hours, or once weekly. Administration at less frequent dosage intervals, such as once every 96 hours or once weekly, may be desirable for patients who have impaired renal function or who require hemodialysis. In a more preferred embodiment the dosage interval is 24 to 48 hours. In an even more preferred embodiment, the dosage interval is 24 hours. The preferred dosage interval for veterinary applications may be somewhat shorter or longer than the preferred

dosage intervals for human patients, depending upon whether daptomycin has a shorter or longer half-life, respectively, in a particular animal species than in humans. The present invention also provides a use of daptomycin for the preparation of medicaments for treating a bacterial infection in a patient at the doses and dosage intervals described herein. Other dosage intervals intermediate to or shorter than these dosage intervals for both clinical and veterinary applications may also be used and may be determined by one skilled in the art following the methods of this invention.

In one embodiment of the invention, the method comprises the step of administering a dose of 3 to 75 mg/kg daptomycin once every 24 hours to once weekly. In a preferred embodiment, daptomycin is administered in a dose of 3 to 25 mg/kg once every 24, 48, 72 or 96 hours. In a more preferred embodiment, daptomycin is administered to a human patient in a dose of 3 to 12 mg/kg every 24 to 48 hours. In an even more preferred embodiment, daptomycin is administered in a dose of 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 mg/kg once every 24 hours. In veterinary applications, daptomycin is administered in a dose of 3 to 25 mg/kg every 24 hours.

Daptomycin may be administered according to this method until the bacterial infection is eradicated or reduced. In one embodiment, daptomycin is administered for a period of time from 3 days to 6 months. In a preferred embodiment, daptomycin is administered for 7 to 56 days. In a more preferred embodiment, daptomycin is administered for 7 to 28 days. In an even more preferred embodiment, daptomycin is administered for 7 to 14 days. Daptomycin may be administered for a longer or shorter time period if it is so desired.

Furthermore, although the invention has been exemplified using daptomycin, the results and the method of the instant invention are also applicable to other lipopeptide antibiotics and quinupristin/dalfopristin, or other antibiotics that cause skeletal muscle toxicity. Therefore, the present invention also provides methods for administering other lipopeptide antibiotics that minimize skeletal muscle toxicity while maintaining efficacy. The present invention also provides a

use for lipopeptide antibiotics for the preparation of medicaments for treating a bacterial infection in a patient, wherein the dose is a therapeutically effective amount of the lipopeptide antibiotic at a dosage interval that does not result in muscle toxicity. Lipopeptide antibiotics include, without limitation, daptomycin, daptomycin derivatives, and other antibiotics that comprise a proteinaceous domain and a lipid domain, such as A54145 (Baltz, *supra*), or A54145 derivatives.

The present invention also provides methods for administering quinupristin/dalfopristin that minimize skeletal muscle toxicity while maintaining efficacy. The methods may be used for human patients in clinical applications and in veterinary applications. The dose and dosage interval for the method is one that is safe and efficacious in clinical or veterinary applications. The method of the invention teaches, in general, that a higher dose of quinupristin/dalfopristin can be administered by prolonging the dosing interval. In one embodiment, the dose is 7.5 to 75 mg/kg quinupristin/dalfopristin at a dosage interval of 24 hours to once weekly. In a preferred embodiment, the dose is 7.5 to 30 mg/kg. In a more preferred embodiment, the dose for humans patients is 7.5 to 20 mg/kg. In a more preferred embodiment for veterinary applications, the dose is 7.5 to 50 mg/kg. In a preferred embodiment, the dosage interval is 24, 48, 72 or 96 hours. In a more preferred embodiment the dosage interval is 24 hours. The preferred dosage interval for veterinary applications may be somewhat shorter or longer than the preferred dosage intervals for human patients, depending upon whether quinupristin/dalfopristin has a shorter or longer half-life, respectively, in a particular animal species than in humans. The present invention also provides a use for quinupristin/dalfopristin for the preparation of medicaments for treating a bacterial infection in a patient, wherein the dose is a therapeutically effective amount of quinupristin/dalfopristin at a dosage interval that does not result in muscle toxicity.

The methods of the present invention comprise administering daptomycin, other lipopeptide antibiotics or quinupristin/dalfopristin to a patient in need thereof an amount that is efficacious in reducing or eliminating the gram-

positive bacterial infection and that results in reduced skeletal muscle toxicity compared to other methods of administering daptomycin, other lipopeptide antibiotics or quinupristin/dalfopristin. The antibiotic may be administered orally, parenterally, by inhalation, topically, rectally, nasally, buccally, vaginally, or by an implanted reservoir, external pump or catheter. Daptomycin, other lipopeptide antibiotics or quinupristin/dalfopristin 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, the antibiotic administration is via intravenous, subcutaneous or oral administration.

The methods according to 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, daptomycin, a lipopeptide antibiotic or quinupristin/dalfopristin is 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, daptomycin is 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, daptomycin is administered according to the methods of this invention to a patient in need of rapidly acting antibiotic therapy. Quinupristin/dalfopristin is also useful for treating antibiotic-resistant strains of bacteria, and may be used in emergency use situations.

The methods 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 methods of the invention may be used to treat, without limitation, skin and soft tissue infections, bacteremia and urinary tract infections. The methods 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 methods of the invention 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. 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 methods of the invention also may be used to treat an infection including, without limitation, endocarditis, septic arthritis and osteomyelitis. In a preferred embodiment, any of the above-described diseases may be treated using daptomycin according to the methods of the instant invention. In another preferred embodiment, any of the above-described diseases may be treated using a lipopeptide antibiotic or quinupristin/dalfopristin according to the methods of the instant invention.

The methods of the instant invention may also be practiced while concurrently administering one or more antibiotics other than a lipopeptide antibiotic. Daptomycin exhibits high plasma protein binding and is unable to cross cell membranes. Thus, daptomycin and other lipopeptide antibiotics that exhibit these characteristics are unlikely to cause interactions with other antibiotics. Given this profile, daptomycin would be expected to work synergistically with one or more co-administered antibiotics. Furthermore, daptomycin 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. Quinupristin/dalfopristin may also be administered according to this invention with certain other antibiotics. Quinupristin/dalfopristin inhibits cytochrome P450 3A4-mediated metabolism of certain drugs, such as midazolam, nifedipine, terfenadine and cyclosporin, so these drugs should not be co-adminstered with quinupristin/dalfopristin. In a preferred embodiment, an antibiotic may be administered concurrently while practicing the method of this invention. Antibiotics and classes thereof that may be co-administered with daptomycin or another lipopeptide antibiotic 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 and viomycin. In a preferred embodiment, antibiotics that may be co-administered with daptomycin or other lipopeptide antibiotics according this invention include, without limitation, imipenen, amikacin, netilmicin, fosfomycin, gentamicin, ceftriaxone and teicoplanin.

EXAMPLE 1

STUDY A: EFFECT OF C_{MAX} ON CPK AND SKELETAL MUSCLE TOXICITY

In order to study the effects of C_{max} on skeletal muscle toxicity, dogs (4 male dogs/group) were administered dose regimens of saline q8h, daptomycin 25 mg/kg q24h, daptomycin 75 mg/kg q24h and daptomycin 25 mg/kg q8h intravenously for 20 days. Skeletal muscle toxicity was measured in dogs by increases in CPK levels to above the normal range and by microscopic changes in skeletal tissue.

Steady state plasma concentrations of daptomycin on day 18 of dosing were determined by HPLC. C_{max} levels were approximately the same (1.23-fold higher) at 25 mg/kg q8h compared to 25 mg/kg q24h. C_{max} levels were approximately 2.8-fold higher at 75 mg/kg q24h compared to 25 mg/kg q8h. See Figure 1, top panel (Study A). The AUC was approximately the same (0.37-fold

higher) at 25 mg/kg q8h compared to 75 mg/kg q24h (see Table 2 and Figure 2, top panel).

Throughout the treatment period in Study A, a dose-proportional increase in peak CPK activity was apparent when the dose was increased from 25 to 75 mg/kg at a constant q24h dosing interval. However, an additional 4-fold increase in CPK levels were observed in animals dosed at 25 mg/kg q8h as compared with those dosed at 75 mg/kg q24h, even though the total daily dose for these two regimens was the same. For all dose regimens, CPK peaked after approximately 1 week of treatment, then declined despite continued treatment.

Treated animals were sacrificed at approximately one dosing interval after the last dose and muscle tissue was microscopically examined for indications of myopathy. See Table 1.

TABLE 1

	Dose Regimen			
Site Lesion*	**Saline q8h**	**25 mg/kg q24h**	**75 mg/kg q24h**	**25 mg/kg q8h**
Skeletal muscle				
Myofiber degeneration	0/24	3/24	8/24	14/24
Myofiber regeneration	1/24	2/24	1/24	9/24
Diaphragm				
Myofiber degeneration	0/4	0/4	0/4	1/4
Heart				
Myofiber degeneration	0/4	0/4	0/4	0/4

* The incidence of muscle-related histopathological findings is presented as the number of sites affected divided by the number of sites examined. For skeletal muscle, six sites were examined in each of four dogs for a total of 24 sites.

Skeletal myofiber degeneration increased approximately two-fold at 25 mg/kg q8h compared to 75 mg/kg q75h. In addition, skeletal myofiber degeneration increase five-fold at 25 mg/kg q8h compared to 25 mg/kg q24h. The skeletal myofiber degeneration was of minimal severity, correlating to three- to 25-

fold increases in serum CPK. No microscopic degenerative effect on heart muscle was observed in Study A.

The findings of Study A are summarized in Table 2:

TABLE 2

Dose Regimen	Total Daily Dose (mg/kg)	C_{max} (μg/mL)	AUC_{0-24h} (μg-h/mL)	Peak CPK (U/L)	Incidence of Micro-scopic Myopathy[1]
saline q8h	0	0	0	265	0/28
25 mg/kg q24h	25	190	682	309*	3/28
75 mg/kg q24h	75	540	1840	990	8/28
25 mg/kg q8h	75	238	2526	4000	15/28

* Outlier excluded.

[1] The incidence of microscopic myopathy (last column) shows the number of sites that exhibit minimal degenerative changes divided by the number of sites examined. In this experiment, seven sites were examined in each of four dogs for a total of 28 sites.

In addition, toxicity did not appear to be related to AUC_{0-24h} or a nontoxic plasma concentration threshold. Increases in CPK and incidence of myopathy were greater at 25 mg/kg q8h than at 75 mg/kg q24h despite the lower C_{max}. Further, there was a 5-fold increase in toxicity as measured by the incidence of microscopic myopathy and a greater than 10-fold increase in CPK levels when 25 mg/kg was administered three times a day compared to once daily despite comparable C_{max} levels. Although the AUC was only 0.37-fold higher at a dose regimen of 25 mg/kg q8h as compared to 75 mg/kg q24h, CPK activity and incidence of myopathy increased 2- to 4-fold.

Without wishing to be bound by any theory, skeletal muscle effects appear to be related to the duration of time at low plasma concentrations available for repair of subclinical damage to the myofibers. In comparison to dose fractionation, once-daily dosing resulted in greater time at minimal plasma

concentrations, allowing for more time for repair and, therefore, less toxicity. For example, at a dose regiment of 25 mg/kg q8h, the plasma concentrations never fell below 27 μg/mL, the trough value for this regimen. In contrast, plasma concentrations for the 75 mg/kg q24h regimen were below this level for approximately 12 hours prior to administration of the next dose. This daily period of minimal exposure may explain why the once-daily dosing regimen (75 mg/kg q24h) was associated with less toxicity than fractionated dosing (25 mg/kg q8h).

EXAMPLE 2

STUDY B: EFFECT OF THRESHOLD PLASMA CONCENTRATION ON SKELETAL MUSCLE TOXICITY

In order to study the effects of threshold plasma concentration on skeletal muscle toxicity, dogs (4 male dogs/group) were administered dose regimens of saline q8h, daptomycin 5 mg/kg q24h (approximate NOELq24h) and daptomycin 5 mg/kg q8h intravenously for 20 days.

As in Example 1, steady state plasma concentrations of daptomycin on day 18 of dosing were determined by HPLC. The q8h interval represents 3 half-lives in dogs ($t_{1/2}$ = 2.5 hours) and should have minimal impact on steady state C_{max} as compared to a q24h regimen. The C_{max} for 5 mg/kg q8h and 5 mg/kg q24h was approximately the same for both dose regimens. See Figure 1, bottom panel (Study B). However, the AUC was approximately three-fold higher (2.6-fold higher) at 5 mg/kg q8h compared to 5 mg/kg q24h (see Table 4 and Figure 2, bottom panel).

Serum CPK levels were determined as disclosed in Example 1. There were no changes in CPK levels at 5 mg/kg q24h compared to the saline control. In contrast, CPK levels at 5 mg/kg q8h were elevated compared to 5 mg/kg q24h or saline controls. At 5 mg/kg q8h, CPK levels peaked at levels three- to four-fold higher than baseline after one week of daptomycin treatment, and declined thereafter despite continued treatment, similar to what was seen in Study A. See Figure 1, bottom panel (Study B).

Treated animals were sacrificed at approximately one dosing interval after the last dose and muscle tissue was examined microscopically for indications of myopathy as in Example 1, shown in Table 3.

TABLE 3

	Dose Regimen		
Site Lesion*	**Saline q8h**	**5 mg/kg q24h**	**5 mg/kg q8h**
Skeletal muscle			
Myofiber degeneration	0/24	2/24	11/24
Myofiber regeneration	0/24	3/24	18/24
Diaphragm			
Myofiber degeneration	0/4	1/4	0/4
Heart			
Myofiber degeneration	0/4	0/4	0/4

* The incidence of muscle-related histopathological findings is presented as the number of sites affected divided by the number of sites examined. For skeletal muscle, six sites were examined in each of four dogs for a total of 24 sites.

Skeletal myofiber degeneration increased four-fold at 5 mg/kg q8h compared to 5 mg/kg q24h. Degeneration was of very minimal severity with very few fibers affected, correlating with zero- to four-fold increases in CPK levels. The myofiber degeneration was less severe in Study B than at the higher doses used in Study A. No degenerative effect on heart muscle was observed in Study B.

The findings of Study B are summarized in Table 4:

TABLE 4

Dose Regimen	Total Daily Dose (mg/kg)	C_{max} (μg/mL)	AUC_{0-24h} (μg-h/mL)	Peak CPK (U/L)	Incidence of Microscopic Myopathy[1]
saline q8h	0	0	0	150	0/28
5 mg/kg q24h	5	58	180	150	3/28
5 mg/kg q8h	15	58	412	500	11/28

[1] The incidence of microscopic myopathy (last column) shows the number of sites that exhibit minimal degenerative changes divided by the number of sites examined. In this experiment, seven sites were examined in each of four dogs for a total of 28 sites.

At a q24h dosing interval, the NOEL is approximately 5 mg/kg. This NOELq24h results in no CPK changes and only very minimal histopathological evidence of skeletal muscle toxicity. However, these experiments demonstrate that the NOELq24h does not define a threshold plasma concentration for toxicity because administration every 8 hours (i.e., 5 mg/kg q8h) leads to skeletal muscle toxicity evident by increases in CPK and microscopic myopathy even though the C_{max} was similar to that of the 5 mg/kg q24h regimen. Toxicity may be related to time below a given plasma concentration. For example, time below 10 μg/mL is 6 hours at 5 mg/kg q8h compared to 18 hours at 5 mg/kg q24h. See Figure 1, bottom panel. These results suggest that the peak plasma concentration of daptomycin associated with no observable skeletal muscle toxicity is dependent upon dosing frequency.

EXAMPLE 3

In order to study the effects of C_{max} of quinupristin/dalfopristin on skeletal muscle toxicity, dogs (4 male dogs/group) are administered dose regimens

of saline q8h, quinupristin/dalfopristin 25 mg/kg q24h, quinupristin/dalfopristin 75 mg/kg q24h and quinupristin/dalfopristin 25 mg/kg q8h intravenously for 20 days.

Steady state plasma concentrations of quinupristin/dalfopristin on day 18 of dosing are determined by HPLC. C_{max} levels and AUC are measured as described in Example 1 for 25 mg/kg q8h, 25 mg/kg q24h and 75 mg/kg q24h. Similarly, CPK levels and the incidence of muscle-related histopathological findings are determined as described in Example 1 for 25 mg/kg q8h, 25 mg/kg q24h and 75 mg/kg q24h. For skeletal muscle, six sites are examined in each of four dogs for a total of 24 sites. If no microscopic myopathy or effects on CPK levels are observed at any of the dose regimens, then the doses may be increased. For instance, C_{max} levels and AUC may be measured for 50 mg/kg q8h, 50 mg/kg q24h and 150 mg/kg q24h.

A dosage regimen of 25 mg/kg quinupristin/dalfopristin q8h is expected to result in greater muscle toxicity, as measured by elevated CPK levels and/or a greater incidence of microscopic myopathy, than a dosage regimen of 75 mg/kg quinupristin/dalfopristin q24h. However, C_{max} levels are expected to be higher for 75 mg/kg q24h than C_{max} levels for 25 mg/kg q8h and thus will result in greater efficacy at 75 mg/kg quinupristin/dalfopristin q24h than 25 mg/kg quinupristin/dalfopristin q8h.

EXAMPLE 4

In order to study whether an increased dosing interval would prevent transient skeletal muscle toxicity in patients, daptomycin was administered intravenously to hospitalized adult subjects with serious gram-positive bacteremia or with a variety of infections due to gram-positive bacteria that was resistant to vancomycin or who were otherwise refractory to, or contraindicated for, currently available therapy. The subjects were treated for a period of 7-21 days. Serum CPK levels were determined prior to first antibiotic treatment and every other day for the first seven days of treatment, and daily thereafter.

The results demonstrate that administration of daptomycin to eight patients at a 4 mg/kg dose every 24 hours or to nine patients at a 6 mg/kg dose every 24 hours did not cause an increase in serum CPK levels above the normal range (20-198 U/L) in a majority of patients. See Table 5. Furthermore, even in the few patients who experienced some elevation in CPK levels above normal, the elevation was not considered to be related to daptomycin treatment. None of the patients experienced any muscular pain or weakness and all patients were able to finish the course of daptomycin treatment. Similarly, administration of an initial dose of 6 mg/kg daptomycin followed by 3 mg/kg every 12 hours to three human patients did not cause an increase in CPK levels above normal.

Table 5

Patient	Pre-dose baseline	CPK Range[1] of Observations During Treatment		Total Number of Patients with Presumed Drug-Related Adverse Skeletal Muscle Effects[2]/ Total Evaluated
		Minimum	Maximum	
6MG/KG q 24h				
1	<18	<18	194	0/9
2	129	54	140	
3	NA	<18	56	
4	35	<18	43	
5	<18	<18	<18	
6	44	<18	44	
7	11	6	101	
8	25	8	25	
9	284	171	*1324	
4 MG/KG q 24h				
1	43	33	59	0/8
2	18	18	35	
3	25	19	212	
4	44	<18	48	
5	144	<18	144	
6	23	20	36	
7	37	32	369**	
8	<18	<18	26	
6 MG/KG followed by 3 MG/KG q 12h				
1	78	78	137	0/3
2	29	<18	49	
3	<18	<18	34	

[1] Normal CPK range 20-192; detectable level 18.

[2] CPK > ULN (192 U/L) and with accompanying clinical signs of pain/weakness or CPK > ULN (192 U/L) without accompanying clinical signs of pain/weakness and with no underlying cause for increased CPK levels.

* Increase in CPK began after 1st dose; returned to baseline while continuing daptomycin treatment. Patient also receiving steroid treatment.

** Value occurred after the 13th dose and returned to baseline with continued treatment.

EXAMPLE 5

Different dosage levels at various dosage intervals of daptomycin are administered to human subjects. Daptomycin is administered intravenously to adult subjects with a diagnosis of an infection due to a gram-positive bacteria strain that is resistant to vancomycin or who are otherwise refractory to, or contraindicated for, currently available therapy. The subjects are treated for a period of 7 to 14 days. The treatment may be extended to 28 to 56 days. Different doses of daptomycin are administered at a dosage interval of once every 24 hours, once every 48 hours, once every 72 hours, once every 96 hours, or once weekly. Other dosage intervals intermediate to or shorter than these dosage intervals may also be used. Dosage levels that may be used include 7, 8, 9, 10, 11, 12, 14, 16, 18, 20, 22 or 25 mg/kg. Other dosage levels that are lower than, intermediate to, or higher than these dosage levels also may be used. The efficacy of the treatment is measured by one or more of the following criteria: eradication or reduction of the gram-positive bacteria blood concentrations that are isolated at admission to the study by microbiological measures; the time in days to microbiological resolution or improvement of the bacterial infection; resolution or improvement of clinical signs and symptoms reported at admission; and survival rates at 3 to 4 weeks after the last dose of antibiotic. A dosage level and interval is efficacious when one or more of the above criteria is satisfied. Serum CPK levels were determined prior to first antibiotic treatment and every other day for the first seven days of treatment, and daily thereafter. A dosage level and interval is safe when it does not cause serum CPK levels to rise significantly above normal levels or when the treatment does not cause skeletal muscular pain or weakness.

EXAMPLE 6

The procedures described in Example 5 are followed essentially as described except that quinupristin/dalfopristin is administered to a patient instead of daptomycin, and the dosage levels range from 7.5 to 30 mg/kg q24h. Dosage levels

that may be used include 7.5, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28 or 30 mg/kg. Other dosage levels that are lower than, intermediate to, or higher than these dosage levels also may be used.

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.

CLAIMS

We claim:

1. A method for administering a lipopeptide antibiotic, comprising the step of administering to a patient in need thereof a therapeutically effective amount of the lipopeptide antibiotic at a dosage interval that does not result in muscle toxicity.

2. The method according to claim 1, wherein the lipopeptide antibiotic is administered once every 24 hours to once weekly.

3. The method according to claim 2, wherein the lipopeptide antibiotic is administered once every 24 hours, 48 hours, 72 hours or 96 hours.

4. The method according to claim 1, wherein the lipopeptide antibiotic is selected from the group consisting of daptomycin, a daptomycin derivative, A54145 and a A54145 derivative.

5. The method according to claim 4, wherein the lipopeptide antibiotic is daptomycin.

6. A method for administering daptomycin, comprising the step of administering to a patient in need thereof a therapeutically effective amount of daptomycin in a dose of 3 to 75 mg/kg of daptomycin, wherein the daptomycin is administered once every 24 hours to once weekly.

7. The method according to claim 6, wherein the dose is 3 to 12 mg/kg.

8. The method according to claim 7, wherein the dose is 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 mg/kg.

9. The method according to claim 6, wherein the dose is 10 to 25 mg/kg.

10. The method according to claim 9, wherein the dose is 10, 11, 12, 13, 14, 15, 16, 20 or 25 mg/kg.

11. The method according to either of claim 1 or claim 6, wherein an antibiotic other than a lipopeptide antibiotic is co-administered with the lipopeptide antibiotic.

12. The method according to claim 11 wherein said lipopeptide antibiotic is daptomycin.

13. The method according to claim 11, wherein said antibiotic is selected from the group consisting of 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, sulfonamides, trimethoprim and its combinations, pyrimethamine, synthetic antibacterials, nitrofurans, methenamine mandelate, methenamine hippurate, nitroimidazoles, quinolones, fluoroquinolones, isoniazid, ethambutol, pyrazinamide, para-aminosalicylic acid (PAS), cycloserine, capreomycin, ethionamide, prothionamide, thiacetazone and viomycin.

14. The method according to claim 11, wherein said antibiotic is selected from the group consisting of imipenen, amikacin, netilmicin, fosfomycin, gentamicin and teicoplanin.

15. The method according to claim 11, wherein said administering is via oral, subcutaneous or intravenous administration.

16. A method for administering daptomycin, comprising the step of administering to a patient or animal in need thereof a therapeutically effective amount of daptomycin at a dose of 3 to 75 mg/kg of daptomycin, wherein daptomycin is administered once every 24 hours.

17. The method according to claim 16, wherein the dose is 3 to 12 mg/kg.

18. The method according to claim 17, wherein the dose is 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 mg/kg.

19. The method according to claim 16, wherein the dose is 10 to 25 mg/kg.

20. The method according to claim 19, wherein the dose is 10, 11, 12, 13, 14, 15, 16, 20 or 25 mg/kg.

21. The method according to claim 17, wherein the dose is 25 to 75 mg/kg.

22. The method according to claim 21, wherein the dose is 25, 50 or 75 mg/kg.

23. The method according to claim 16, wherein said method reduces muscle toxicity compared to administration of daptomycin at a more frequent interval than 24 hours.

24. The method according to claim 18, wherein the dose is 4 mg/kg administered once every 24 hours.

25. The method according to claim 18, wherein the dose is 6 mg/kg administered once every 24 hours.

26. The method according to any one of claims 1, 6 or 16, wherein said administering is via oral, subcutaneous or intravenous administration.

27. A method for administering quinupristin/dalfopristin, comprising the step of administering to a patient in need thereof a therapeutically effective amount of quinupristin/dalfopristin at a dosage interval that does not result in muscle toxicity.

28. The method according to claim 27, wherein quinupristin/dalfopristin is administered once every 24 hours to once weekly.

29. The method according to claim 28, wherein quinupristin/dalfopristin is administered once every 24 hours, 48 hours, 72 hours or 96 hours.

30. The method according to claim 27, wherein said quinupristin/dalfopristin is administered at a dose of 7.5 to 30 mg/kg.

31. The method according to claim 27, wherein said quinupristin/dalfopristin is administered at a dose of 7.5, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28 or 30 mg/kg.

32. A pharmaceutical composition comprising a single dose of daptomycin and a pharmaceutically acceptable carrier, wherein said single dose is 7 to 15 mg/kg.

33. A pharmaceutical composition comprising a single dose of quinupristin/dalfopristin and a pharmaceutically acceptable carrier, wherein said single dose is 10 to 30 mg/kg.

34. Use of a lipoprotein antibiotic for the manufacture of a medicament for treating a bacterial infection in a patient in need thereof, wherein a dose for said treating is a therapeutically effective amount of the lipoprotein antibiotic at a dosage interval that does not result in muscle toxicity.

35. The use according to claim 34, wherein the dosage interval is once every 24 hours to once weekly.

36. The use according to claim 35, wherein the dosage interval is once every 24 hours, 48 hours, 72 hours or 96 hours.

37. The use according to claim 34, wherein the lipoprotein antibiotic is selected from the group consisting of daptomycin, a daptomycin derivative, A54145 and a A54145 derivative.

38. The use according to claim 37, wherein the lipoprotein antibiotic is daptomycin.

39. Use of daptomycin for the manufacture of a medicament for treating a bacterial infection in a patient in need thereof, wherein a dose for said use is 3 to 75 mg/kg of daptomycin at a dosage interval of once every 24 hours to once weekly.

40. The use according to claim 39, wherein the dose is 3 to 12 mg/kg.

41. The use according to claim 40, wherein the dose is 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 mg/kg.

42. The use according to claim 39, wherein the dose is 10 to 25 mg/kg.

43. The use according to claim 42, wherein the dose is 10, 11, 12, 13, 14, 15, 16, 20 or 25 mg/kg.

44. The use according to either of claims 34 or 39, further comprising an antibiotic other than a lipoprotein antibiotic for the manufacture of the medicament for treating the bacterial infection in the patient.

45. The use according to claim 44 wherein said lipoprotein antibiotic is daptomycin.

46. The use according to claim 44, wherein said antibiotic is selected from the group consisting of 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 and viomycin.

47. The use according to claim 44, wherein said antibiotic is selected from the group consisting of imipenen, amikacin, netilmicin, fosfomycin, gentamicin and teicoplanin.

48. The use according to claim 44, wherein the dose is an oral, subcutaneous or intravenous dose.

49. Use of daptomycin for the manufacture of a medicament for treating a bacterial infection in a patient in need thereof, wherein a dose for such use is 3 to 75 mg/kg of daptomycin at a dosage interval of once every 24 hours.

50. The use according to claim 49, wherein the dose is 3 to 12 mg/kg.

51. The use according to claim 50, wherein the dose is 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 mg/kg.

52. The use according to claim 49, wherein the dose is 10 to 25 mg/kg.

53. The use according to claim 52, wherein the dose is 10, 11, 12, 13, 14, 15, 16, 20 or 25 mg/kg.

54. The use according to claim 49, wherein the dose is 25 to 75 mg/kg.

55. The use according to claim 54, wherein the dose is 25, 50 or 75 mg/kg.

56. The use according to claim 49, wherein the dosage interval reduces muscle toxicity compared to a dosage interval that is more frequent than 24 hours.

57. The use according to claim 51, wherein the dose is 4 mg/kg and the dosage interval is once every 24 hours.

59. The use according to claim 51, wherein the dose is 6 mg/kg and the dosage interval is once every 24 hours.

60. The use according to any one of claims 34, 39 or 49, wherein the dose is an oral, subcutaneous or intravenous dose.

61. Use of quinupristin/dalfopristin for the manufacture of a medicament for treating a bacterial infection in a patient in need thereof, wherein a dose for such treating is a therapeutically effective amount of quinupristin/dalfopristin at a dosage interval that does not result in muscle toxicity.

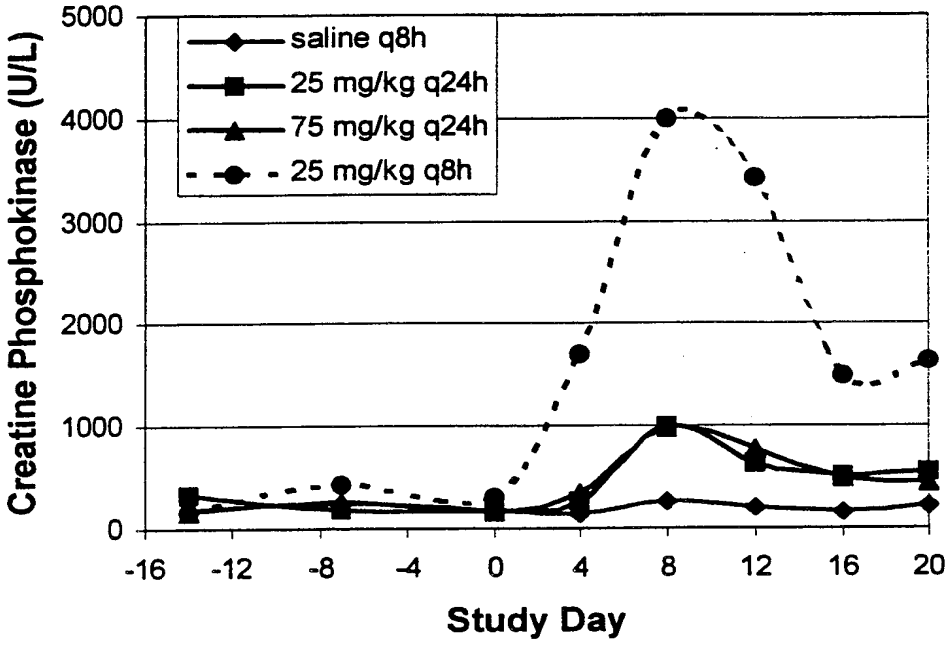
62. The use according to claim 61, wherein the dosage interval is once every 24 hours to once weekly.

63. The use according to claim 62, wherein the dosage interval is once every 24 hours, 48 hours, 72 hours or 96 hours.

64. The use according to claim 61, wherein the dose is 7.5 to 30 mg/kg.

65. The use according to claim 61, wherein the dose is 7.5, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28 or 30 mg/kg.

FIG. 1


Creatine Phosphokinase (U/L)
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4000
3000
2000
1000
0
saline q8h
25 mg/kg q24h
75 mg/kg q24h
25 mg/kg q8h
-16
-12
-8
-4
0
4
8
12
16
20
Study Day

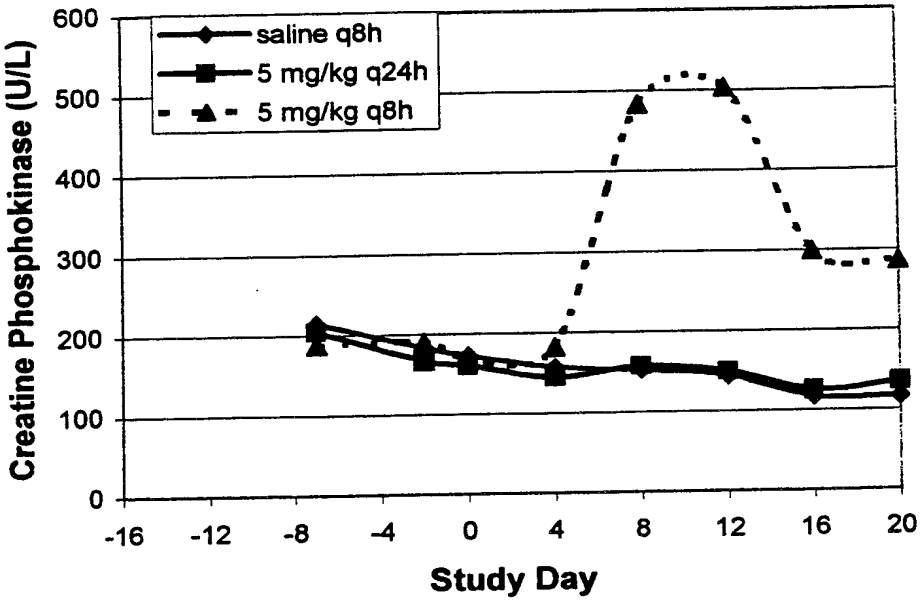
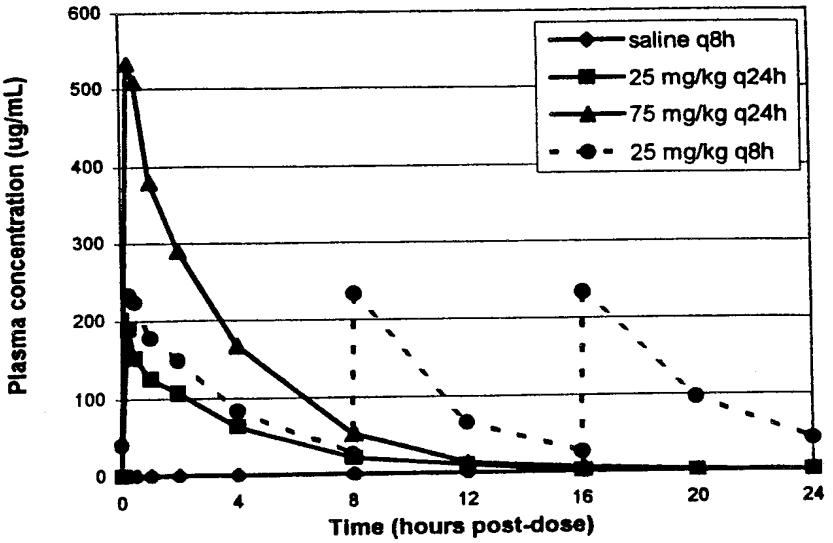
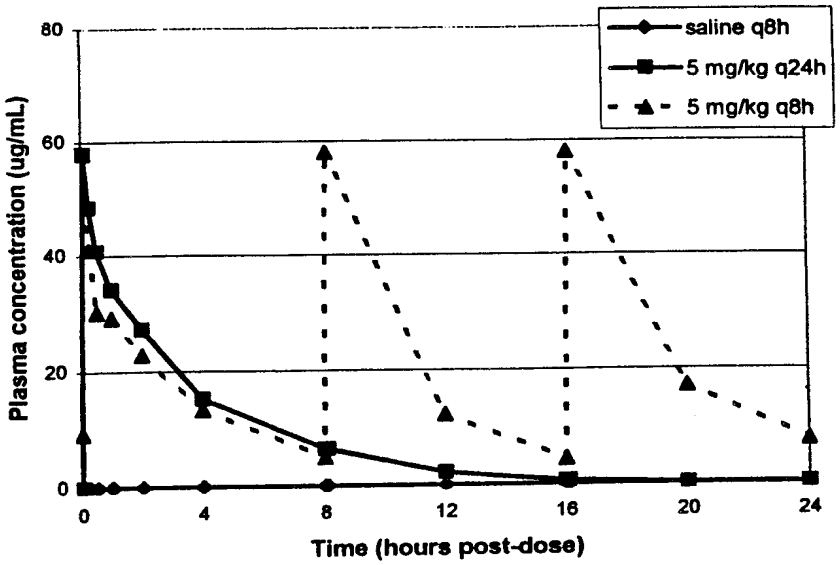

Creatine Phosphokinase (U/L)
600
500
400
300
200
100
0
saline q8h
5 mg/kg q24h
5 mg/kg q8h
-16
-12
-8
-4
0
4
8
12
16
20
Study Day

FIG. 2


saline q8h
25 mg/kg q24h
75 mg/kg q24h
25 mg/kg q8h
Plasma concentration (ug/mL)
600
500
400
300
200
100
0
0
4
8
12
16
20
24
Time (hours post-dose)


saline q8h
5 mg/kg q24h
5 mg/kg q8h
Plasma concentration (ug/mL)
80
60
40
20
0
0
4
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12
16
20
24
Time (hours post-dose)

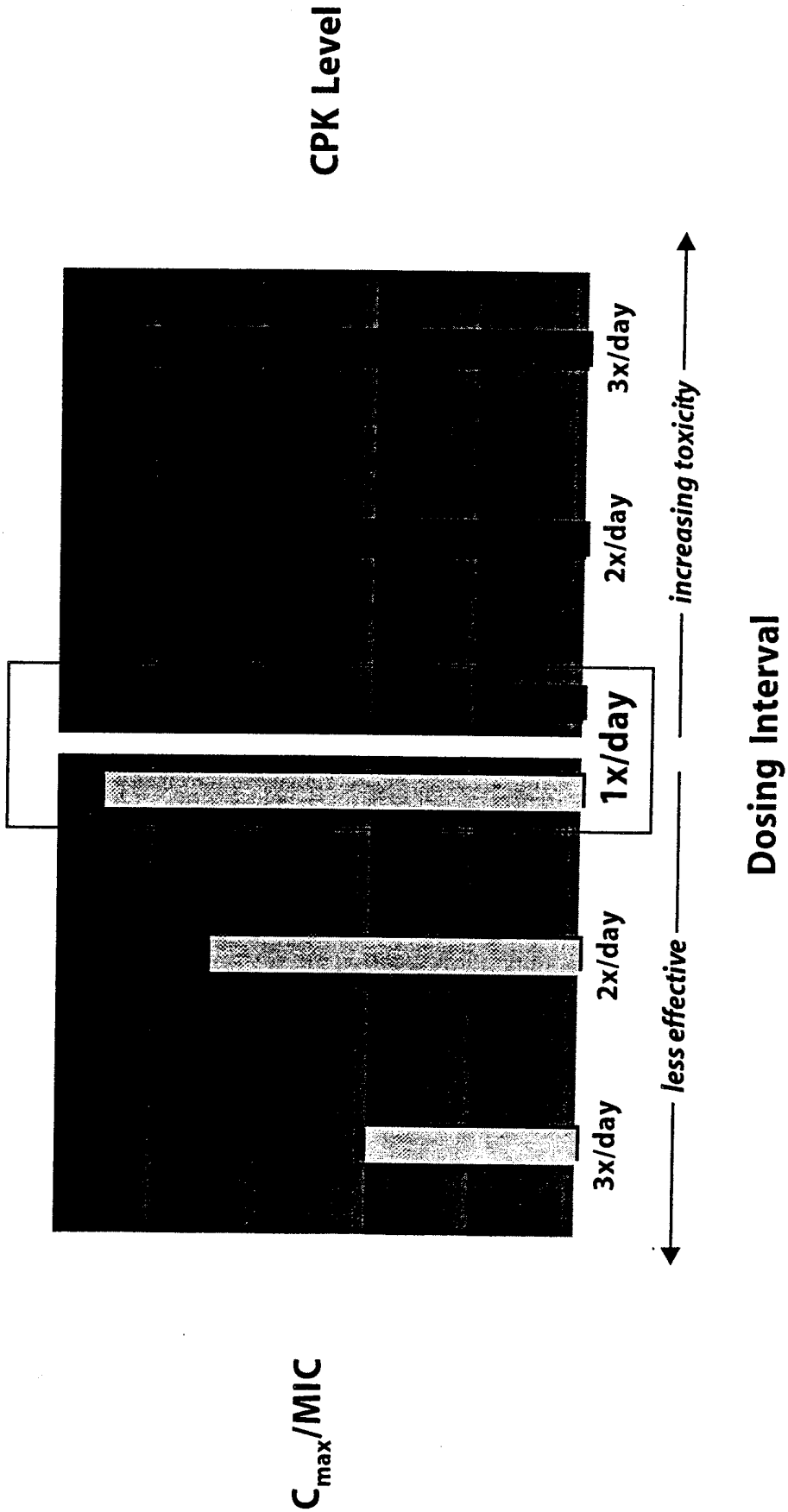
CPK Level
3x/day
2x/day
1x/day
2x/day
3x/day
increasing toxicity
less effective
Dosing Interval
C_{max}/MIC

FIG. 3

Electronic Patent Application Fee Transmittal

Application Number:	12888233
Filing Date:	22-Sep-2010
Title of Invention:	High Purity Lipopeptides
First Named Inventor/Applicant Name:	Thomas J. Kelleher
Filer:	Nicholas M.C. Boivin/Jodi Doherty
Attorney Docket Number:	C062-02/04 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:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
Submission- Information Disclosure Stmt	1806	1	180	180
		Total in USD ($)		**180**

Electronic Acknowledgement Receipt

EFS ID:	11247532
Application Number:	12888233
International Application Number:	
Confirmation Number:	4046
Title of Invention:	High Purity Lipopeptides
First Named Inventor/Applicant Name:	Thomas J. Kelleher
Customer Number:	34103
Filer:	Nicholas M.C. Boivin
Filer Authorized By:	
Attorney Docket Number:	C062-02/04 US
Receipt Date:	24-OCT-2011
Filing Date:	22-SEP-2010
Time Stamp:	13:38:08
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$180
RAM confirmation Number	1
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	Transmittal Letter	C062_02_04_US_20111024_Suppl_IDS_Letter.pdf	16023 adaec8043ae95b84c1d87bc1d48e909c818e003e	no	2
Warnings:					
Information:					
2	Information Disclosure Statement (IDS) Form (SB08)	C062_02_04_US_20111024_Suppl_IDS.pdf	38330 c5e33050989641df39ac33ca0e89e89ffb5b8aad	no	4
Warnings:					
Information:					
This is not an USPTO supplied IDS fillable form					
3	Foreign Reference	WO00018419A2.pdf	899903 3d2268b584d179caec3ff95e767070931a21ca75	no	39
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Information:					
4	Non Patent Literature	Cubicin_1004-1_Revised_Aug_2004.pdf	116647 7190674bef867107775e1bb5e4145ab546663916	no	2
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5	Non Patent Literature	Cubicin_1004-2_Revised_Jun_2005.pdf	111943 7088c5c3faa27d4ba512689d6373cc018ba1258a	no	2
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7	Non Patent Literature	Cubicin_Aug_2010.pdf	286363 2d6d4e659f60ee427e5ee28e32ce9f6b75de5c1a	no	28
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Information:					
8	Fee Worksheet (SB06)	fee-info.pdf	30038 64067fa98dd4f84359279674244aa7675fb7e5f5	no	2
Warnings:					
Information:					

Total Files Size (in bytes):	1616131

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.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appl. No.	:	12/888,233	Confirmation No.	4046
Applicant	:	Thomas J. Kelleher		
Filed	:	September 22, 2010		
TC/A.U.	:	1656		
Examiner	:	Chih Min Kam		
Docket No.	:	C062-02/04 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:

Cubicin® (daptomycin for injection) Label 1004 – September 2003

Cubicin® (daptomycin for injection) Label 1004 -1 – Revised August 2004

Cubicin® (daptomycin for injection) Label 1004 -2 – Revised June 2005

Cubicin® (daptomycin for injection) Label 1004 -10-1 –August 2010

REMARKS

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 C062-02/04 US.

Respectfully submitted,

Dated: October 24, 2011
/Nicholas M. Boivin/
Nicholas M. Boivin, Reg. No. 45,650
Attorney for Applicants

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Cubist Pharmaceuticals, Inc.
65 Hayden Avenue
Lexington, Massachusetts 02421
Tel.: (781) 860-8660
Fax: (781) 860-1407
C062-02-04 US 20111024 Suppl IDS letter.doc

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appl. No.	:	12/888,233	Confirmation No.	4046
Applicant	:	Thomas Kelleher		
Filed	:	September 22, 2010		
TC/A.U.	:	1656		
Examiner	:	Chih-Min Kam		
Docket No.	:	C062-02/04 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 July 29, 2011 (hereafter "the Office Action") in the above-identified application.

Kindly amend the application as follows:

AMENDMENT TO THE CLAIMS

1. (Currently Amended) A composition obtained by a process comprising the step of forming a daptomycin aggregate, the composition comprising daptomycin of greater than or about 93% purity relative to impurities 1-14 defined by peaks 1-14 shown in FIG. 12 and having less than 4%

~~(a) essentially pure daptomycin,~~

~~(b) daptomycin that is substantially free~~ of anhydro-daptomycin and having less than 4% of ~~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~~.

2-5. (Canceled)

6. (Original) The composition according to claim 1 that is free of each of impurities 1 to 14 defined by peaks 1-14 shown in FIG. 12.

7. (Currently Amended). The composition according to claim [[6]]1 that is essentially free of ~~each~~ at least one 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. (Canceled).

10. (Canceled).

11. (Currently Amended) 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.-22. (Canceled)

23. (Currently Amended) The composition according to claim 1[[22]] wherein the process ~~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. (Currently Amended) The composition according to claim 23[[22]], wherein the process further comprises the step of lyophilizing daptomycin.

25.-31. (Canceled)

32. (Currently Amended) The ~~pharmaceutical~~ composition of claim 1[[9]] comprising daptomycin ~~that is substantially free of anhydro-daptomycin and substantially free~~ having less than 1% of β-isomer of daptomycin.

33.-53. (Canceled)

Please enter the following new claims.

54. (New) The composition of claim 1, comprising daptomycin having greater than 93% purity.

55. (New) The composition of claim 1, comprising daptomycin having less than 1% of the lactone hydrolysis product of daptomycin.

56. (New) The composition of claim 1, comprising daptomycin that is substantially free of beta isomer of daptomycin.

57. (New) The composition of claim 56, comprising daptomycin of greater than 93% purity.

58. (New) The composition of claim 1, comprising daptomycin of at least 95% purity.

59. (New) The composition of claim 1, comprising daptomycin with a purity of about 94 to 96%.

60. (New) The composition of claim 1, comprising daptomycin of at least 97% purity.

61. (New) The composition of claim 1, comprising lyophilized daptomycin having greater than 93% purity relative to impurities 1-14 defined by peaks 1-14 shown in FIG. 12, and having less than 1% of the lactone hydrolysis product of daptomycin.

62. (New) The composition of claim 61, wherein the daptomycin is substantially free of beta-isomer of daptomycin.

63. (New) A pharmaceutical composition compatible with a pharmaceutically acceptable carrier for the treatment of an infection of the blood, skin or soft tissue, the composition comprising daptomycin obtained by a process comprising the step of forming a daptomycin aggregate, the composition having daptomycin with greater than or about 93% purity relative to impurities 1-14 defined by peaks 1-14 shown in FIG. 12.

64. (New) The pharmaceutical composition of claim 63, wherein the daptomycin has greater than 93% purity and less than 4% anhydro daptomycin.

65. (New) The pharmaceutical composition of claim 63, wherein the the pharmaceutically acceptable carrier is selected from the group consisting of physiological saline and Ringer's solution for reconstitution for administration as a single daily dose to the subject.

66. (New) The pharmaceutical composition of claim 63, wherein the pharmaceutical composition is compatible with the pharmaceutically acceptable carrier for the treatment of an infection of the blood, skin or soft tissue by administration in a daily dose of 1 to 12 mg/kg of the daptomycin in a reconstituted solution of the composition in the pharmaceutically acceptable carrier.

67. (New) The pharmaceutical composition of claim 66, wherein

a) the pharmaceutically acceptable carrier is selected from the group consisting of physiological saline and Ringer's solution for intravenous administration as a single daily dose to the subject;

b) the daptomycin has greater than 93% purity, less than 4% anhydro daptomycin and less than 4% beta-isomer of daptomycin; and

c) the composition comprising daptomycin is obtained by a purification process comprising the steps of forming a daptomycin aggregate and obtaining the daptomycin from the daptomycin aggregate.

68. (New) The pharmaceutical composition of claim 67, wherein the process for obtaining the daptomycin includes a purification process comprising the steps of

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

b) forming the daptomycin aggregate comprising a daptomycin micelle in the enriched daptomycin preparation or a composition obtained from the enriched daptomycin preparation; and

c) obtaining the daptomycin from the daptomycin aggregate.

69. (New) The pharmaceutical composition of claim 68, wherein the daptomycin is obtained from the daptomycin aggregate by a method comprising the steps of

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

b) collecting the daptomycin aggregate.

70. (New) The pharmaceutical composition of claim 69, wherein the daptomycin is obtained from the daptomycin aggregate by a method further comprising the steps of

a) subjecting a composition comprising the daptomycin aggregate to hydrophobic interaction chromatography to obtain a semi-purified daptomycin preparation; and

b) obtaining the daptomycin from the semi-purified daptomycin preparation.

71. (New) A pharmaceutical composition for the treatment of an infection, the composition comprising daptomycin having greater than 93% purity relative to impurities 1-14 defined by peaks 1-14 shown in FIG. 12, the daptomycin purified by a process comprising the formation of micelles comprising daptomycin.

72. (New) The pharmaceutical composition of claim 71, wherein the daptomycin is a lyophilized powder comprising daptomycin purified by process comprising the steps of forming a daptomycin micelle and obtaining the daptomycin from the micelles.

73. (New) The pharmaceutical composition of claim 71, wherein the daptomycin has less than 4% anhydro daptomycin and less than 4% beta-isomer of daptomycin.

74. (New) The pharmaceutical composition of claim 71, wherein the daptomycin has less than 1% of the lactone hydrolysis product of daptomycin.

75. (New) The pharmaceutical composition of claim 72, wherein the daptomycin has less than 4% anhydro daptomycin, less than 1% of the lactone hydrolysis product of daptomycin and is essentially free of the beta-isomer of daptomycin.

76. (New) A pharmaceutical composition for the treatment of an infection of the blood, skin or soft tissue, the pharmaceutical composition comprising a solution of a pharmaceutically acceptable carrier for intravenous administration and daptomycin, the daptomycin having greater than 93% purity relative to impurities 1-14 defined by peaks 1-14 shown in FIG. 12, and the daptomycin obtained from a purification process comprising the formation of a daptomycin micelle.

77. (New) The pharmaceutical composition of claim 76, wherein the daptomycin has less than 4% anhydro daptomycin and less than 4% beta-isomer of daptomycin.

78. (New) The pharmaceutical composition of claim 76, wherein the daptomycin has less than 1% of the lactone hydrolysis product of daptomycin.

79. (New) The pharmaceutical composition of claim 77, wherein the daptomycin has less than 4% anhydro daptomycin, less than 1% of the lactone hydrolysis product of daptomycin and is essentially free of the beta-isomer of daptomycin.

80. (New) The composition of claim 63, wherein the infection of the blood, skin or soft tissue comprises *Staphylococcus aureus.*

81. (New) The composition of claim 63, wherein the infection is bacteremia.

82. (New) The composition of claim 63, wherein the infection is endocarditis.

83. (New) The composition of claim 63, wherein the infection is a skin or soft tissue infection.

84. (New) The composition of claim 63, wherein the infection includes bacteria selected from the group consisting of *Staphylococcus aureus. Streptococcus pyogenes, Streptococcus agalactiae,* and *Enterococcus faecalis.*

85. (New) The composition of claim 71, wherein the infection comprises *Staphylococcus aureus.*

86. (New) The composition of claim 71, wherein the infection is bacteremia.

87. (New) The composition of claim 71, wherein the infection is endocarditis.

88. (New) The composition of claim 71, wherein the infection is a skin or soft tissue infection.

89. (New) The composition of claim 71, wherein the infection includes bacteria selected from the group consisting of *Staphylococcus aureus. Streptococcus pyogenes, Streptococcus agalactiae,* and *Enterococcus faecalis.*

90. (New) The composition of claim 76, wherein the infection comprises *Staphylococcus aureus.*

91. (New) The composition of claim 76, wherein the infection is bacteremia.

92. (New) The composition of claim 76, wherein the infection is endocarditis.

93. (New) The composition of claim 76 wherein the infection is a skin or soft tissue infection.

94. (New) The composition of claim 76, wherein the infection includes bacteria selected from the group consisting of *Staphylococcus aureus. Streptococcus pyogenes, Streptococcus agalactiae,* and *Enterococcus faecalis.*

95. (New) The composition of claim 76, wherein the pharmaceutical composition includes daptomycin in a daily intravenous dose 1 to 12 mg/kg.

96. (New) A vial containing a lyophilized powder pharmaceutical composition compatible with a pharmaceutically acceptable carrier for the treatment of an infection by a daily intravenous dose of the lyophilized powder reconstituted in the pharmaceutically acceptable carrier, the composition

a) having daptomycin with greater than or about 93% purity relative to impurities 1-14 defined by peaks 1-14 shown in FIG. 12; and

b) the composition comprising daptomycin purified by a process including the steps of forming a daptomycin aggregate, converting the daptomycin aggregate to monomers and obtaining the daptomycin in the composition from the monomers by a process including one or more steps selected from the group consisting of anion exchange chromatorgraphy and hydrophobic interaction chromatography.

97. (New) A composition obtained by a process comprising the steps of forming a daptomycin aggregate, converting the daptomycin aggregate to monomers and obtaining the daptomycin in the composition from the monomers by a process including one or more steps selected from the group consisting of anion exchange chromatorgraphy and hydrophobic interaction chromatography, the composition comprising daptomycin of greater than or about 93% purity relative to impurities 1-14 defined by peaks 1-14 shown in FIG. 12.

98. (New) The composition of claim 97, comprising daptomycin of greater than 93% purity relative to impurities 1-14 defined by peaks 1-14 shown in FIG. 12.

99. (New) The composition of claim 97, wherein the composition is a lyophilized powder compatible with a pharmaceutically acceptable carrier for the treatment of one or more infections selected from the group consisting of infections of the blood, skin and soft tissue, by a daily intravenous dose of 1 to 12 mg/kg of the daptomycin in a reconstituted solution of the lyophilized powder in the pharmaceutically acceptable carrier.

100. (New) The composition of claim 98, wherein

a) the composition is a lyophilized powder compatible with a pharmaceutically acceptable carrier for the treatment of an infection of the infection by a daily intravenous dose of 1 to 12 mg/kg of the daptomycin in a reconstituted solution of the lyophilized powder in the pharmaceutically acceptable carrier; and

b) the daptomycin has a purity of about 94 to 96% relative to impurities 1-14 defined by peaks 1-14 shown in FIG. 12, the daptomycin having less than 1% of the lactone hydrolysis product of daptomycin, less than 4% anhydro daptomycin and less than 4% of the beta-isomer of daptomycin.

REMARKS

Amendments to the Claims

Prior to entry of this Response and Amendment, claims 1-53 were pending in the present application. In this Response and Amendment, Applicant has amended claims 1, 7, 11, 23, 24, 32, and canceled claims 2-5, 9-10, 12-22, 25-31 and 33-53. In addition, Applicant has added new claims 54-100. Support for the claim amendments and new claims can be found throughout the specification as filed. No new matter is added.

Upon entry of the instant claim amendments, claims 1, 6-8, 11, 23, 32, and 54-100 are pending in this application.

Claim Rejections under 35 USC §102

The Office Action rejects claims 1, 8-30, 37, 38, 45, 46 and 53 under 35 USC § 102 as being anticipated by RE39,071 ("Baker") (Office Action at pages 2-3). Applicants respectfully disagree. As amended, independent claim 1 and dependent claims therefrom cover a composition obtained by a process comprising the step of forming a daptomycin aggregate, the composition comprising daptomycin of greater than or about 93% purity relative to impurities 1-14 defined by peaks 1-14 shown in FIG. 12 and having less than 4% of anhydro-daptomycin and having less than 4% of β-isomer of daptomycin. The Office Action does not describe how the cited reference discloses the presently claimed compositions. In rejecting claims for want of novelty or for obviousness, the examiner must cite the particular part relied on and the pertinence of each reference, if not apparent, must be clearly explained and each rejected claim specified. 37 CFR 1.104, MPEP 706. Applicant respectfully requests reconsideration and withdrawal of the rejection under 35 USC §102.

Claim Rejections under Obviousness-Type Double Patenting

The Office Action rejects claims 1, 8-9, 30 37, 38, 45, 46 and 53 over claims 18-20, 26, 28 and 29 of Baker based on the judicially-created doctrine of non-statutory obviousness-type double patenting (Office Action at pages 2-7). The Office Action states

that pending claims 1, 8-9, 30, 37, 38, 45, 46 and 53 "are obvious variations of" issued claims 18-20, 26, 28 and 29 of Baker (Office Action at page 5).

In addition, the Office Action provisionally rejects claims 1-29, 31-36, 38-44 and 46-52 over claims 2-4, 6, 54, 58, 62 and 115 of U.S. Patent Application 11/739,180 (Office Action, pages 5-7).

As amended, independent claim 1 and dependent claims therefrom cover a composition obtained by a process comprising the step of forming a daptomycin aggregate, the composition comprising daptomycin of greater than or about 93% purity relative to impurities 1-14 defined by peaks 1-14 shown in FIG. 12 and having less than 4% of anhydro-daptomycin and having less than 4% of β-isomer of daptomycin.

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. Please deduct any fee required for entry of this Response and Amendment, and apply any other charges or credits required for entry of this amendment to Deposit Account No. 50-1986, referencing attorney docket number C062-02/04 US. Applicants do not authorize payment of the issue fee at this time with the instructions above.

Respectfully submitted,

Date: October 13, 2011

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C062-02-04 US 20111015 response to 20110729 OA (3)

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	12888233
Filing Date	2010-09-22
First Named Inventor	Thomas J. Kelleher
Art Unit	1656
Examiner Name	Chih-Min Kam
Attorney Docket Number	C062-02/04 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
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	20	6696412		2004-02-24	Kelleher	
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	2	EP 178152 A2	EP		1986-04-16	Eli Lilly Co.		☐
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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]
	1	Agreement between Cubist Pharmaceuticals, Inc. and Eli Lilly and Company dated November 7, 1997 (redacted form from SEC Edgar)	☐
	2	Agreement between Cubist Pharmaceuticals, Inc. and Eli Lilly and Company dated October 6, 2000 (redacted form from SEC Edgar)	☐
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	First Named Inventor	Thomas J. Kelleher
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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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	Examiner Name	Chih-Min Kam
	Attorney Docket Number	C062-02/04 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.

☒ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

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	/Nicholas M. Boivin/	Date (YYYY-MM-DD)	2011-10-13
Name/Print	Nicholas M. Boivin	Registration Number	45,650

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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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.

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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.

Electronic Patent Application Fee Transmittal

Application Number:	12888233
Filing Date:	22-Sep-2010
Title of Invention:	High Purity Lipopeptides
First Named Inventor/Applicant Name:	Thomas J. Kelleher
Filer:	Nicholas M.C. Boivin
Attorney Docket Number:	C062-02/04 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	2	60	120
Independent claims in excess of 3	1201	3	250	750
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
Submission- Information Disclosure Stmt	1806	1	180	180
		Total in USD ($)		**1050**

Electronic Acknowledgement Receipt

EFS ID:	11176948
Application Number:	12888233
International Application Number:	
Confirmation Number:	4046
Title of Invention:	High Purity Lipopeptides
First Named Inventor/Applicant Name:	Thomas J. Kelleher
Customer Number:	34103
Filer:	Nicholas M.C. Boivin
Filer Authorized By:	
Attorney Docket Number:	C062-02/04 US
Receipt Date:	13-OCT-2011
Filing Date:	22-SEP-2010
Time Stamp:	11:33:55
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$1050
RAM confirmation Number	8747
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		C062_02_04_US_20111013_Response.pdf	64174 421cc139da10b4639d83c4493106d76a7f4eef14	yes	12
	Multipart Description/PDF files in .zip description				
	Document Description		**Start**	**End**	
	Amendment/Req. Reconsideration-After Non-Final Reject		1	1	
	Claims		2	10	
	Applicant Arguments/Remarks Made in an Amendment		11	12	
Warnings:					
Information:					
2	Information Disclosure Statement (IDS) Form (SB08)	C062_02_04_US_20111013_IDS.pdf	65744 f85c12488d2c1ac1db3bf5447b227323dc311e81	no	9
Warnings:					
Information:					
This is not an USPTO supplied IDS fillable form					
3	Non Patent Literature	Bayer_AAC_32_1988.pdf	1307857 45048646fb3e1e312bd76e4e80197767ad6de334	no	3
Warnings:					
Information:					
4	Non Patent Literature	Eliopoulos_AAC_30_1986.pdf	1869673 c397e9c23b7bc24aab275d6ab4d25a4e6199bbd8	no	4
Warnings:					
Information:					
5	Non Patent Literature	Ramos_AAC_36_1992.pdf	2973641 1b44ac5eb2e6a2550fb06bdb7272f87debc3108c	no	6
Warnings:					
Information:					
6	Fee Worksheet (SB06)	fee-info.pdf	33156 474ddfad7e38cd0ab01acc783d485ea97a54e3dd	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	6314245		

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

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United States Patent and Trademark Office
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www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
12/888,233	09/22/2010	Thomas J. Kelleher	C062-02/04 US

CONFIRMATION NO. 4046

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

PUBLICATION NOTICE

OC00000049502771

Title: High Purity Lipopeptides

Publication No.US-2011-0207658-A1
Publication Date:08/25/2011

NOTICE OF PUBLICATION OF APPLICATION

The above-identified application will be electronically published as a patent application publication pursuant to 37 CFR 1.211, et seq. The patent application publication number and publication date are set forth above.

The publication may be accessed through the USPTO's publically available Searchable Databases via the Internet at www.uspto.gov. The direct link to access the publication is currently http://www.uspto.gov/patft/.

The publication process established by the Office does not provide for mailing a copy of the publication to applicant. A copy of the publication may be obtained from the Office upon payment of the appropriate fee set forth in 37 CFR 1.19(a)(1). Orders for copies of patent application publications are handled by the USPTO's Office of Public Records. The Office of Public Records can be reached by telephone at (703) 308-9726 or (800) 972-6382, by facsimile at (703) 305-8759, by mail addressed to the United States Patent and Trademark Office, Office of Public Records, Alexandria, VA 22313-1450 or via the Internet.

In addition, information on the status of the application, including the mailing date of Office actions and the dates of receipt of correspondence filed in the Office, may also be accessed via the Internet through the Patent Electronic Business Center at www.uspto.gov using the public side of the Patent Application Information and Retrieval (PAIR) system. The direct link to access this status information is currently http://pair.uspto.gov/. Prior to publication, such status information is confidential and may only be obtained by applicant using the private side of PAIR.

Further assistance in electronically accessing the publication, or about PAIR, is available by calling the Patent Electronic Business Center at 1-866-217-9197.

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

UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/888,233	09/22/2010	Thomas J. Kelleher	C062-02/04 US	4046

34103 7590 07/29/2011

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

EXAMINER	
KAM, CHIH MIN	
ART UNIT	**PAPER NUMBER**
1656	

NOTIFICATION DATE	DELIVERY MODE
07/29/2011	ELECTRONIC

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.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patents@cubist.com
jodi.doherty@cubist.com
colleen.lombard@cubist.com

Office Action Summary	Application No.	Applicant(s)
	12/888,233	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) *1-53* 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 *22 September 2010* 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)	4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)	5) ☐ Notice of Informal Patent Application
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.	6) ☐ Other: _____.

Search Notes	Application No.	Applicant(s)	
	12/888,233	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.	7/25/2011	CMK
Search strategy enclosed, Inventor name search,	7/25/2011	CMK
Parent applications 60/177,170 and 09/735,191, 10/747,48 & 11/739,180have been reviewed.	7/25/2011	CMK

DETAILED ACTION

Status of the Claims

1. Claims 1-53 are pending.

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)).

2. Claims 1, 8-30, 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) 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)), 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, 37, 38, 45, 46, 53). 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).

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).

3. Claims 1, 8-9, 30, 37, 38, 45, 46 and 53 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.

This rejection is based on a statement at pages 9-10 of the amendment of the parent application 11/739,180, filed 11/13/2009, which indicates that at the time the claimed invention was made, the subject 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).

Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 1, 8-9, 30, 37, 38, 45, 46 and 53 in the instant application disclose a composition comprising substantially pure daptomycin (i.e., >97% purity daptomycin); a pharmaceutical composition comprising the composition and a pharmaceutically acceptable carrier or excipient; and a method for preparing the pharmaceutical composition. 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, 30, 37, 38, 45, 46 and 53 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.

4. Claims 1-29, 31-36, 38-44 and 46-52 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over at least claims 2-4, 6, 54, 58, 62 and 115 of co-pending application, 11/739,180 (based on the amendment dated 5/27/2011). Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 1-29, 31-36, 38-44 and 46-52 in the instant application disclose 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 (i.e., >97% purity

daptomycin); a pharmaceutical composition comprising the composition and a pharmaceutically acceptable carrier or excipient; and a method for preparing the pharmaceutical composition. This is obvious variation in view of claims 2-4, 6, 54, 58, 62 and 115 of the co-pending application which disclose a composition comprising essentially pure daptomycin, daptomycin that is substantially free of anhydro-daptomycin and substantially free of β-isomer of daptomycin, daptomycin that is essentially free of anhydro-daptomycin and substantially free of β-isomer of daptomycin, daptomycin that is free of anhydro-daptomycin and substantially free of β-isomer of daptomycin, daptomycin that is substantially free of each of impurities 1 to 14 defined by peaks 1-14 shown in FIG. 12, or daptomycin that is essentially free of each of impurities 1 to 14 defined by peaks 1-14 shown in FIG. 12. Both claims of instant application and the patent are directed to a composition comprising essentially pure daptomycin, daptomycin that is substantially free of anhydro-daptomycin and substantially free of β-isomer of daptomycin, daptomycin that is essentially free of anhydro-daptomycin and substantially free of β-isomer of daptomycin, daptomycin that is free of anhydro-daptomycin and substantially free of β-isomer of daptomycin, daptomycin that is substantially free of each of impurities 1 to 14 defined by peaks 1-14 shown in FIG. 12, or daptomycin that is essentially free of each of impurities 1 to 14 defined by peaks 1-14 shown in FIG. 12; or a pharmaceutical composition comprising the composition and a pharmaceutically acceptable carrier or excipient. Thus, claims 1-29, 31-36, 38-44 and 46-52 in present application and claims 2-4, 6, 54, 58, 62 and 115 of the patent are obvious variations of a composition comprising essentially pure daptomycin, daptomycin that is substantially free of anhydro-daptomycin and substantially free of β-isomer of daptomycin, daptomycin that is essentially free of anhydro-daptomycin and substantially free of

β-isomer of daptomycin, daptomycin that is free of anhydro-daptomycin and substantially free of β-isomer of daptomycin, daptomycin that is substantially free of each of impurities 1 to 14 defined by peaks 1-14 shown in FIG. 12, or daptomycin that is essentially free of each of impurities 1 to 14 defined by peaks 1-14 shown in FIG. 12; or a pharmaceutical composition comprising the composition and a pharmaceutically acceptable carrier or excipient.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

5. No claims are allowed.

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

July 26, 2011

Notice of References Cited	Application/Control No. 12/888,233	Applicant(s)/Patent Under Reexamination KELLEHER ET AL.	
	Examiner CHIH-MIN KAM	Art Unit 1656	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
*	A	US-RE39,071 E	04-2006	Baker et al.	514/2.3
	B	US-			
	C	US-			
	D	US-			
	E	US-			
	F	US-			
	G	US-			
	H	US-			
	I	US-			
	J	US-			
	K	US-			
	L	US-			
	M	US-			

FOREIGN PATENT DOCUMENTS

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	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
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*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
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BIB DATA SHEET

CONFIRMATION NO. 4046

SERIAL NUMBER	FILING or 371(c) DATE RULE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
12/888,233	09/22/2010	514	1656	C062-02/04 US

APPLICANTS

Thomas J. Kelleher, Thousand Oaks, CA;
Jan-Ji Lai, Westborough, MA;
Joseph P. DeCourcey, Boston, MA;
Paul D. Lynch, Arlington, MA;
Maurizio Zenoni, Ferentino Frosinone, ITALY;
Auro R. Tagliani, Pavia, ITALY;

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

This application is a CON of 11/739,180 04/24/2007
which is a CON of 10/747,485 12/29/2003 ABN
which is a CON 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 ****

10/05/2010

Foreign Priority claimed ☐ Yes ☒ No 35 USC 119(a-d) conditions met ☐ Yes ☒ No Verified and Acknowledged /Chih-Min Kam/ Examiner's Signature	☐ Met after Allowance Initials	STATE OR COUNTRY	SHEETS DRAWINGS	TOTAL CLAIMS	INDEPENDENT CLAIMS
		CA	11	53	1

ADDRESS

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

TITLE

High Purity Lipopeptides

FILING FEE RECEIVED		
2936	FEES: Authority has been given in Paper No._____ to charge/credit DEPOSIT ACCOUNT No._____ for following:	☐ All Fees ☐ 1.16 Fees (Filing) ☐ 1.17 Fees (Processing Ext. of time) ☐ 1.18 Fees (Issue) ☐ Other _____ ☐ Credit

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	1162	daptomycin	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2011/07/25 18:04
L2	60760	substantially adj pure	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2011/07/25 18:04
L3	15538	essentially adj pure	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2011/07/25 18:04
L4	9	L1 same (L2 or L3)	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2011/07/25 18:04
L5	15	impurities same L1	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2011/07/25 18:07
L6	14	anhydro-daptomycin or beta-daptomycin	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2011/07/25 18:09
L7	56596	anion adj exchange	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2011/07/25 18:10
L8	14634	hydrophobic adj interaction adj chromatography	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2011/07/25 18:10
L9	7	L1 same L7 same L8	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2011/07/25 18:10
L10	108	(Ly adj "146032") or A-21978C or A54145 or A-21978	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2011/07/25 18:12
L11	2	L10 same (L2 or L3)	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2011/07/25 18:12
L12	20	kelleher adj thomas.in.	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2011/07/25 18:14
L13	11	lai adj jan-ji.in.	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2011/07/25 18:14
L14	3	decourcey adj joseph.in.	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2011/07/25 18:14
L15	30	lynch adj paul.in.	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2011/07/25 18:14
L16	78	zenoni adj maurizio.in.	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2011/07/25 18:14
L17	7	tagliani adj auro.in.	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2011/07/25 18:14
L18	132	L12 or L13 or L14 or L15 or L16 or L17	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2011/07/25 18:14
L19	9	L18 and L1	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2011/07/25 18:14

7/ 25/ 2011 6:15:48 PM
C:\ Users\ ckam\ Documents\ EAST\ Workspaces\ % daptomycin-1.wsp

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(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)

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Alexandria, Virginia 22313-1450
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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
12/888,233	09/22/2010		2936	C062-02/04 US	53	1

CONFIRMATION NO. 4046

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

UPDATED FILING RECEIPT

OC000000047659121

Date Mailed: 05/17/2011

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 J. Kelleher, Thousand Oaks, CA;
Jan-Ji Lai, Westborough, MA;
Joseph P. DeCourcey, Boston, MA;
Paul D. Lynch, Arlington, MA;
Maurizio Zenoni, Ferentino Frosinone, ITALY;
Auro R. Tagliani, Pavia, ITALY;

Power of Attorney: The patent practitioners associated with Customer Number 34103

Domestic Priority data as claimed by applicant

This application is a CON of 11/739,180 04/24/2007
which is a CON of 10/747,485 12/29/2003 ABN
which is a CON 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: 10/05/2010

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 12/888,233**

Projected Publication Date: 08/25/2011

Non-Publication Request: No

Early Publication Request: No

Title

High Purity Lipopeptides

Preliminary Class

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

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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.

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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).

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 12/888,233

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	330
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	540
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	220
TOTAL CLAIMS (37 CFR 1.16(i))	53 minus 20 =	* 33			OR	x 52 =	1716
INDEPENDENT CLAIMS (37 CFR 1.16(h))	1 minus 3 =	*				x 220 =	0.00
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, 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).						0.00
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							0.00
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	2806

APPLICATION AS AMENDED - PART II

		(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($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE($)
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))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE($)	ADDITIONAL FEE($)		RATE($)	ADDITIONAL FEE($)
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))							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 found in the appropriate box in column 1.

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
12/888,233	09/22/2010	Thomas J. Kelleher	C062-02/04 US

CONFIRMATION NO. 4046

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

POA ACCEPTANCE LETTER

OC000000047671171

Date Mailed: 05/17/2011

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 05/06/2011.

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.

/ydemisse/

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

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

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

Application Number	12/888,233
Filing Date	September 22, 2010
First Named Inventor	Thomas J. Kelleher
Title	HIGH PURITY LIPOPEPTIDES
Art Unit	
Examiner Name	
Attorney Docket Number	C062-02/04 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	May 6, 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.

This collection of information is required by 37 CFR 1.31, 1.32 and 1.33. 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 3 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.

PTO/SB/01 (04-09)
Approved for use through 09/30/2010. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

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(f)) required)

Attorney Docket Number	C062-02/04 US
First Named Inventor	Thomas J. Kelleher
COMPLETE IF KNOWN	
Application Number	12/888,233
Filing Date	September 22, 2010
Art Unit	
Examiner Name	

I hereby declare that: (1) Each inventor's residence, mailing address, and citizenship are as stated below next to their name; and (2) 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 titled:

HIGH PURITY LIPOPEPTIDES

(Title of the Invention)

the application of which

☐ is attached hereto

OR

☒ was filed on (MM/DD/YYYY) 09/22/2010 as United States Application Number or PCT International Application Number 12/888,233 and was amended on (MM/DD/YYYY) _____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified application, 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.

Authorization To Permit Access To Application by Participating Offices

☐ If checked, the undersigned hereby grants the USPTO authority to provide the European Patent Office (EPO), the Japan Patent Office (JPO), the Korean Intellectual Property Office (KIPO), the World Intellectual Property Office (WIPO), and any other intellectual property offices in which a foreign application claiming priority to the above-identified patent application is filed access to the above-identified patent application. See 37 CFR 1.14(c) and (h). This box should not be checked if the applicant does not wish the EPO, JPO, KIPO, WIPO, or other intellectual property office in which a foreign application claiming priority to the above-identified patent application is filed to have access to the above-identified patent application.

In accordance with 37 CFR 1.14(h)(3), access will be provided to a copy of the above-identified patent application with respect to: 1) the above-identified patent application-as-filed; 2) any foreign application to which the above-identified patent application claims priority under 35 U.S.C. 119(a)-(d) if a copy of the foreign application that satisfies the certified copy requirement of 37 CFR 1.55 has been filed in the above-identified patent application; and 3) any U.S. application-as-filed from which benefit is sought in the above-identified patent application.

In accordance with 37 CFR 1.14(c), access may be provided to information concerning the date of filing the Authorization to Permit Access to Application by Participating Offices.

PTO/SB/01 (04-09)
Approved for use through 09/30/2010. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

DECLARATION — Utility or Design Patent Application

Claim of Foreign Priority Benefits

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 number(s) are listed on a supplemental priority data sheet PTO/SB/02B attached hereto.

PTO/SB/01 (04-09)
Approved for use through 09/30/2010. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

DECLARATION — Utility or Design Patent Application

Direct all correspondence to:	[X] The address associated with Customer Number:	34103	OR	[ ] Correspondence address below

Name		
Address		
City	State	Zip
Country	Telephone	Email

WARNING:

Petitioner/applicant is cautioned to avoid submitting personal information in documents filed in a patent application that may contribute to identity theft. Personal information such as social security numbers, bank account numbers, or credit card numbers (other than a check or credit card authorization form PTO-2038 submitted for payment purposes) is never required by the USPTO to support a petition or an application. If this type of personal information is included in documents submitted to the USPTO, petitioners/applicants should consider redacting such personal information from the documents before submitting them to the USPTO. Petitioner/applicant is advised that the record of a patent application is available to the public after publication of the application (unless a non-publication request in compliance with 37 CFR 1.213(a) is made in the application) or issuance of a patent. Furthermore, the record from an abandoned application may also be available to the public if the application is referenced in a published application or an issued patent (see 37 CFR 1.14). Checks and credit card authorization forms PTO-2038 submitted for payment purposes are not retained in the application file and therefore are not publicly available. Petitioner/applicant is advised that documents which form the record of a patent application (such as the PTO/SB/01) are placed into the Privacy Act system of records DEPARTMENT OF COMMERCE, COMMERCE-PAT-7, System name: *Patent Application Files*. Documents not retained in an application file (such as the PTO-2038) are placed into the Privacy Act system of COMMERCE/PAT-TM-10, System name: *Deposit Accounts and Electronic Funds Transfer Profiles*.

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])	Family Name or Surname
Thomas J.	Kelleher
Inventor's Signature: Thomas J Kelleher	Date: 4-26-11

Residence: City	State	Country	Citizenship
Thousand Oaks	CA	U.S.A.	US
Mailing Address: 1982 Calle Yucca			
City	State	Zip	Country
Thousand Oaks	CA	91360	U.S.A.

[X] 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 (07-07)
Approved for use through 09/30/2010. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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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		
Jan-Ji	Lai		
Inventor's Signature			Date 5/2/2011
Westborough Residence: City	MA State	U.S.A. Country	US Citizenship
5 Roy Street Mailing Address			
Westborough City	MA State	01581 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		
Joseph P.	DeCourcey		
Inventor's Signature			Date
Boston Residence: City	MA State	U.S.A. Country	US Citizenship
175 Blossom Street Unit 1206 Mailing Address			
Boston City	MA State	02114 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 D.	Lynch		
Inventor's Signature			Date
Arlington Residence: City	MA State	U.S.A. Country	US Citizenship
29 Cypress Road Mailing Address			
Arlington City	MA State	02474 Zip	U.S.A. Country

PTO/SB/02A (07-07)
Approved for use through 09/30/2010. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

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		
Jan-Ji	Lai		
Inventor's Signature		Date	
Westborough Residence: City	MA State	U.S.A. Country	US Citizenship
5 Roy Street Mailing Address			
Westborough City	MA State	01581 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		
Joseph P.	DeCourcey		
Inventor's Signature		21-04-11 Date	
Boston Residence: City	MA State	U.S.A. Country	US Citizenship
175 Blossom Street Unit 1206 Mailing Address			
Boston City	MA State	02114 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 D.	Lynch		
Inventor's Signature		Date	
Arlington Residence: City	MA State	U.S.A. Country	US Citizenship
29 Cypress Road Mailing Address			
Arlington City	MA State	02474 Zip	U.S.A. Country

PTO/SB/02A (07-07)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

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		
Jan-Ji	Lai		
Inventor's Signature			Date
Westborough Residence: City	MA State	U.S.A. Country	US Citizenship
5 Roy Street Mailing Address			
Westborough City	MA State	01581 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		
Joseph P.	DeCourcey		
Inventor's Signature			Date
Boston Residence: City	MA State	U.S.A. Country	US Citizenship
175 Blossom Street Unit 1206 Mailing Address			
Boston City	MA State	02114 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 D.	Lynch		
Inventor's Signature			Date 4/27/11
Arlington Residence: City	MA State	U.S.A. Country	US Citizenship
29 Cypress Road Mailing Address			
Arlington City	MA State	02474 Zip	U.S.A. Country

PTO/SB/02A (07-07)
Approved for use through 09/30/2010. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

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		
Maurizio	Zenoni		
Inventor's Signature			Date
Ferentino Frosinone Residence: City	State	Italy Country	IT Citizenship
via Croce Tani Fumone 127/A Mailing Address			
Feretino Frosinone City	State	03010 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		
Auro R.	Tagliani		
Inventor's Signature			Date
Pavia Residence: City	State	Italy Country	IT Citizenship
via Marangoni 1 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			
City	State	Zip	Country

PTO/SB/02A (07-07)
Approved for use through 09/30/2010. OMB 0651-0032
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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		
Maurizio	Zenoni		
Inventor's Signature		Date	
Ferentino Frosinone Residence: City	State	Italy Country	IT Citizenship
via Croce Tani Fumone 127/A Mailing Address			
Feretino Frosinone City	State	03010 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		
Auro R.	Tagliani		
Inventor's Signature Auro Roberto Tagliani		Date	
Pavia Residence: City	State	Italy Country	IT Citizenship
via Marangoni 1 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			
City	State	Zip	Country

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.: 12/888,233 Filed/Issue Date: September 22, 2010

Titled:
High Purity Lipopeptides

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

states that it is:

1. ☐ 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. ☒ A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as follows:

1. From: Inventor(s) Paul D. Lynch To: Perseptive Biosystems, Incorporated

The document was recorded in the United States Patent and Trademark Office at
Reel 012995, Frame 0427, or for which a copy thereof is attached.

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

The document was recorded in the United States Patent and Trademark Office at
Reel 021996, Frame 0376, or for which a copy thereof is attached.

3. From: All remaining Inventor(s) (Kelleher et al.) To: Cubist Pharmaceuticals, Inc.

The document was recorded in the United States Patent and Trademark Office at
Reel 013701, Frame 0774, 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/ May 6, 2011
Signature Date

Nicholas M. Boivin Intellectual Property Counsel
Printed or Typed Name Title

UNITED STATES PATENT AND TRADEMARK OFFICE

AUGUST 19, 2002

PTAS

FISH & NEAVE
JAMES F. HALEY, JR.
1251 AVENUE OF THE AMERICAS
NEW YORK, NY 10020-1104

Under Secretary of Commerce For Intellectual Property and
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Washington, DC 20231
www.uspto.gov

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RECORDATION DATE: 08/15/2002

REEL/FRAME: 012995/0427
NUMBER OF PAGES: 4

BRIEF: ASSIGNMENT OF ASSIGNOR'S INTEREST (SEE DOCUMENT FOR DETAILS).

ASSIGNOR:
LYNCH PAUL D.

DOC DATE: 02/13/2001

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

SERIAL NUMBER: 09735191
PATENT NUMBER:

FILING DATE: 11/28/2000
ISSUE DATE:

LAZENA MARTIN, EXAMINER
ASSIGNMENT DIVISION
OFFICE OF PUBLIC RECORDS

COPY SENT TO CUBIST VIA POUCH MAIL
1/4/03

RECEIVED
SEP 03 2002
FISH & NEAVE - PATENT DEPT.
REFERRED TO
NOTED BY

08-19-2002

8-15-02

Form PTO-1595 (Rev. 03/01) 8-15-02 REC

OMB No. 0651-0027 (exp. 5/31/2002)

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102178759

U.S. DEPARTMENT OF COMMERCE
U.S. Patent and Trademark Office

CUB/009

/ ▼ ▼

To the Honorable Commissioner of Patents and Trademarks: Please record the attached original documents or copy thereof.

1. Name of conveying party(ies):

Paul D. Lynch

Additional name(s) of conveying party(ies) attached? ☐ Yes ☒ No

2. Name and address of receiving party(ies)

Name: Perseptive Biosystems, Incorporated

Internal Address: _____

Street Address: 500 Old Connecticut Path

City: Framingham State: MA Zip: 01701

Additional name(s) & address(es) attached? ☐ Yes ☒ No

3. Nature of conveyance:

☒ Assignment ☐ Merger

☐ Security Agreement ☐ Change of Name

☐ Other _____

Execution Date: 2/13/01

4. Application number(s) or patent number(s):

If this document is being filed together with a new application, the execution date of the application is: _____

A. Patent Application No.(s)
09/735,191

B. Patent No.(s)

Additional numbers attached? ☐ Yes ☒ No

5. Name and address of party to whom correspondence concerning document should be mailed:

Name: James F. Haley, Jr.

Internal Address: Fish & Neave

19/2002 GTON11 00000007 06/1075 09735191

FC:481 40.00 CH
FC:484 120.00 CH

Street Address: 1251 Avenue of the Americas

City: New York State: NY Zip: 10020-1104

6. Total number of applications and patents involved: 1

7. Total fee (37 CFR 3.41).....$ 40.00

☐ Enclosed

☒ Authorized to be charged to deposit account

8. Deposit account number:

06-1075

(Attach duplicate copy of this page if paying by deposit account)

DO NOT USE THIS SPACE

9. Statement and signature.

To the best of my knowledge and belief, the foregoing information is true and correct and any attached copy is a true copy of the original document.

Michele A. Kercher, Reg. No. P51,869	Michele A. Kercher	8/14/02
Name of Person Signing	Signature	Date

Total number of pages including cover sheet, attachments, and documents 4

Mail documents to be recorded with required cover sheet information to:
Commissioner of Patents & Trademarks, Box Assignments
Washington, D.C. 20231

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~~ (i) 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~~ (ii) 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 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 2/13/01(1)
PAUL D. LYNCH

On this 13th day of February, 2001, PAUL D. LYNCH (1) personally appeared before me, a Notary Public in and for Worcester County 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

UNITED STATES PATENT AND TRADEMARK OFFICE

MJ Brown patents
C062-02 01

AUGUST 19, 2002

PTAS

Under Secretary of Commerce For Intellectual Property and
Director of the United States Patent and Trademark Office
Washington, DC 20231
www.uspto.gov

FISH & NEAVE
JAMES F. HALEY, JR.
1251 AVENUE OF THE AMERICAS
NEW YORK, NY 10020-1104

102178758A

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 703-308-9723. PLEASE SEND REQUEST FOR CORRECTION TO: U.S. PATENT AND TRADEMARK OFFICE, ASSIGNMENT DIVISION, BOX ASSIGNMENTS, CG-4, 1213 JEFFERSON DAVIS HWY, SUITE 320, WASHINGTON, D.C. 20231.

RECORDATION DATE: 08/15/2002

REEL/FRAME: 012996/0376
NUMBER OF PAGES: 4

BRIEF: ASSIGNMENT OF ASSIGNOR'S INTEREST (SEE DOCUMENT FOR DETAILS).

ASSIGNOR:
PERSEPTIVE BIOSYSTEMS, INCORPORATED

DOC DATE: 02/13/2001

ASSIGNEE:
CUBIST PHARMACEUTICALS, INCORPORATED
24 EMILY STREET
CAMBRIDGE, MASSACHUSETTS 02139

SERIAL NUMBER: 09735191
PATENT NUMBER:

FILING DATE: 11/28/2000
ISSUE DATE:

SHARON BROOKS, EXAMINER
ASSIGNMENT DIVISION
OFFICE OF PUBLIC RECORDS

RB C062
COPY SENT TO CUBIST VIA POUCH MAIL
M. Weeks 9/4/02

RECEIVED
SEP 0 3 2002
FISH & NEAVE - PATENT DEPT.
REFERRED TO MAK
NOTED BY

8-15-02

08-19-2002

Form PTO-1595 (Rev. 03/01) 8-15-02 RECORD

OMB No. 0651-0027 (exp. 5/31/2002)

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102178758

U.S. DEPARTMENT OF COMMERCE
U.S. Patent and Trademark Office

CUB/009 ▼ ▼

To the Honorable Commissioner of Patents and Trademarks: Please record the attached original documents or copy thereof.

1. Name of conveying party(ies):
Perseptive Biosystems, Incorporated

Additional name(s) of conveying party(ies) attached? ☐ Yes ☒ No

3. Nature of conveyance:
☒ Assignment ☐ Merger
☐ Security Agreement ☐ Change of Name
☐ Other_____

Execution Date: 2/13/01

2. Name and address of receiving party(ies)
Name: Cubist Pharmaceuticals, Incorporated
Internal Address: _____
Street Address: 24 Emily Street
City: Cambridge State: MA Zip: 02139

Additional name(s) & address(es) attached? ☐ Yes ☒ No

4. Application number(s) or patent number(s):
If this document is being filed together with a new application, the execution date of the application is:_____

A. Patent Application No.(s)
09/735,191

B. Patent No.(s)

Additional numbers attached? ☐ Yes ☒ No

5. Name and address of party to whom correspondence concerning document should be mailed:
Name: James F. Haley, Jr.
Internal Address: Fish & Neave

8/19/2002 GTON11 00000069 061075 09735191
1 FC:581 40.00 CH
2 FC:584 20.00 CH

Street Address 1251 Avenue of the Americas

City: New York State: NY Zip: 10020-1104

6. Total number of applications and patents involved: 1

7. Total fee (37 CFR 3.41).....$ 40.00
☐ Enclosed
☒ Authorized to be charged to deposit account

8. Deposit account number:
06-1075

(Attach duplicate copy of this page if paying by deposit account)

DO NOT USE THIS SPACE

9. Statement and signature.
To the best of my knowledge and belief, the foregoing information is true and correct and any attached copy is a true copy of the original document.

Michele A. Kercher, Reg. No. P51,869
Name of Person Signing

Michele A. Kercher
Signature

8/14/02
Date

Total number of pages including cover sheet, attachments, and documents 4

Mail documents to be recorded with required cover sheet information to:
Commissioner of Patents & Trademarks, Box Assignments
Washington, D.C. 20231

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 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

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 [illegible], 2001, Joseph E. Malandrakis personally appeared before me, a Notary Public in and for [illegible], and executed the foregoing Assignment and duly acknowledged to me that such Assignment was executed for the uses and purposes therein expressed.

Notary Public

UNITED STATES PATENT AND TRADEMARK OFFICE

JUNE 04, 2003

PTAS

CUBIST PHARMACEUTICALS, INC.
TIMOTHY J. DOUROS
PATENT GROUP
65 HAYDEN AVENUE
LEXINGTON, MASSACHUSETTS 02421

Under Secretary of Commerce For Intellectual Property and
Director of the United States Patent and Trademark Office
Washington, DC 20231
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RECORDATION DATE: 01/29/2003

REEL/FRAME: 013701/0774
NUMBER OF PAGES: 21

BRIEF: RE-RECORD TO CORRECT THE EXECUTION DATE FOR THE THIRD CONVEYING PARTY, PREVIOUSLY RECORDED ON REEL 012998 FRAME 0851, ASSIGNOR CONFIRMS THE ASSIGNMENT OF THE ENTIRE INTEREST.

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

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

ASSIGNOR:
DECOURCEY, JOSEPH P. DOC DATE: 01/19/2001

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

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

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

SERIAL NUMBER: 09735191
PATENT NUMBER:

FILING DATE: 11/28/2000
ISSUE DATE:

ALLYSON PURNELL, EXAMINER
ASSIGNMENT DIVISION
OFFICE OF PUBLIC RECORDS

UNITED STATES PATENT AND TRADEMARK OFFICE

MS Brown patents
C062-02 US

AUGUST 20, 2002

PTAS

Under Secretary of Commerce For Intellectual Property and
Director of the United States Patent and Trademark Office
Washington, DC 20231
www.uspto.gov

FISH & NEAVE
JAMES F. HALEY, JR.
1251 AVENUE OF THE AMERICAS
NEW YORK, NY 10020-1104

102178757A

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 703-308-9723. PLEASE SEND REQUEST FOR CORRECTION TO: U.S. PATENT AND TRADEMARK OFFICE, ASSIGNMENT DIVISION, BOX ASSIGNMENTS, CG-4, 1213 JEFFERSON DAVIS HWY, SUITE 320, WASHINGTON, D.C. 20231.

RECORDATION DATE: 08/15/2002

REEL/FRAME: 012998/0851
NUMBER OF PAGES: 20

BRIEF: ASSIGNMENT OF ASSIGNOR'S INTEREST (SEE DOCUMENT FOR DETAILS).

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, INCORPORATED
24 EMILY STREET
CAMBRIDGE, MASSACHUSETTS 02139

Cubist Ref C062
COPY SENT TO CUBIST VIA POUCH MAIL
M Mercher 9/4/02

RECEIVED
SEP 0 3 2002
FISH & NEAVE - PATENT DEPT
REFERRED TO MAK
NOTED BY

SERIAL NUMBER: 09735191
PATENT NUMBER:

FILING DATE: 11/28/2000
ISSUE DATE:

JOANN STEWART, EXAMINER
ASSIGNMENT DIVISION
OFFICE OF PUBLIC RECORDS

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

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:

[signature] 1-12-07 (1)
THOMAS J. KELLEHER

On this 12th day of January, 2007, 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.

[signature]
Notary Public

(2)
JAN-JI LAI

On this [illegible] day of [illegible], [illegible], 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: _____

(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: _____

Name: _____

Signature: _____

Name: _____

(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: _____

Signature: _____

Name: _____

(6)
AURO R. TAGLIANI

Witnessed:

Signature: _____

Name: _____

Signature: _____

Name: _____

ACKNOWLEDGEMENT OF ASSIGNEE:

CLBIST PHARMACEUTICALS, INCORPORATED

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

On this 26th day of _____, 1991, Alan D. Watson personally appeared before me, a Notary Public in and for the _____, and duly acknowledged the executed Assignment on behalf of the Assignee.

_____
Notary Public

Electronic Patent Application Fee Transmittal

Application Number:	12888233
Filing Date:	22-Sep-2010
Title of Invention:	High Purity Lipopeptides
First Named Inventor/Applicant Name:	Thomas Kelleher
Filer:	Nicholas M.C. Boivin/Jodi Doherty
Attorney Docket Number:	C062-02/04 US

Filed as Large Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Utility application filing	1011	1	330	330
Utility Search Fee	1111	1	540	540
Utility Examination Fee	1311	1	220	220
Pages:				
Claims:				
Claims in excess of 20	1202	33	52	1716
Miscellaneous-Filing:				
Late filing fee for oath or declaration	1051	1	130	130

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Extension - 5 months with $0 paid	1255	1	2350	2350
Miscellaneous:				
		Total in USD ($)		**5286**

Electronic Acknowledgement Receipt

EFS ID:	10036856
Application Number:	12888233
International Application Number:	
Confirmation Number:	4046
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:	C062-02/04 US
Receipt Date:	06-MAY-2011
Filing Date:	22-SEP-2010
Time Stamp:	14:44:43
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$5286
RAM confirmation Number	1009
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	Miscellaneous Incoming Letter	C062-02-04_US_20110506_Transmittal_Form.pdf	58909 1036293fa59010a68262c5f1fcd16478663041c3	no	1
Warnings:					
Information:					
2	Miscellaneous Incoming Letter	C062-02-04_US_20110506_Fee_Transmittal_Form.pdf	54383 ae76c5aff702da130721fccf8609c836a1eeb9f4	no	1
Warnings:					
Information:					
3	Extension of Time	C062-02-04_US_20110506_Petition_for_Ext.pdf	155988 380c4579eb26cc9d06e5b8712bd6d60327d80a34	no	1
Warnings:					
Information:					
4	Applicant Response to Pre-Exam Formalities Notice	C062-02-04_US_20110506_Resp_to_Miss_Parts.pdf	26022 2d95e682d3c7372a9cf1a4c3d5f0f32b89b5110a	no	2
Warnings:					
Information:					
5	Applicant Response to Pre-Exam Formalities Notice	C062-02-04_US_20110506_Notice_to_File_Missing_Parts_Form.pdf	216797 97822eabe9901374db1dc522101a40257599d6d8	no	2
Warnings:					
Information:					
6	Power of Attorney	C062-02-04_US_20110506_Power_of_Atty.pdf	32140 f5bda79e1f052f83b3637e79b34e0a8e96ca5a14	no	1
Warnings:					
Information:					
7	Oath or Declaration filed	C062-02-04_US_20110506_Declaration.pdf	1115565 62c17a7c02b9f6732762907a1eba261a42736569	no	8
Warnings:					
Information:					
8	Assignee showing of ownership per 37 CFR 3.73(b).	C062-02-04_US_20110506_Statement.pdf	2335318 cc31ee8cdccb1e200d516046d303b136e5078fbf	no	22
Warnings:					
Information:					

9	Fee Worksheet (PTO-875)	fee-info.pdf	39862 223d949a89d3e54049fb53257c96c5ce75d156d2	no	2

Warnings:	
Information:	
Total Files Size (in bytes):	4034984

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.

Doc Code: TRAN.LET

Document Description: Transmittal Letter

PTO/SB/21 (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
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.

TRANSMITTAL FORM

(to be used for all correspondence after initial filing)

Total Number of Pages in This Submission	38

Application Number	12/888,233
Filing Date	September 22, 2010
First Named Inventor	Thomas J. Kelleher
Art Unit	
Examiner Name	
Attorney Docket Number	C062-02/04 US

ENCLOSURES (*Check all that apply*)

- [X] Fee Transmittal Form
  - [X] Fee Attached
- [ ] Amendment/Reply
  - [ ] After Final
  - [ ] Affidavits/declaration(s)
- [X] Extension of Time Request
- [ ] Express Abandonment Request
- [ ] Information Disclosure Statement
- [ ] Certified Copy of Priority Document(s)
- [X] Reply to Missing Parts/ Incomplete Application
  - [X] 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
- [X] 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
- [X] Other Enclosure(s) (please Identify below):

Part 2 of Notice to File Missing Parts of Nonprovisional Application; Declaration signed by the inventors; and Statement under 37 CFR 3.73(b) evidence of title

Remarks

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm Name	Cubist Pharmaceuticals, Inc.		
Signature	/Nicholas M. Boivin/		
Printed name	Nicholas M. Boivin		
Date	May 6, 2011	Reg. No.	45,650

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	

PTO/SB/17 (10-08)
Approved for use through 09/30/2010. OMB 0651-0032
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

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 ($) 2,936.00

Complete if Known	
Application Number	12/888,233
Filing Date	September 22, 2010
First Named Inventor	Thomas J. Kelleher
Examiner Name	
Art Unit	
Attorney Docket No.	C062-02/04 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	330	165	540	270	220	110	1,090.00
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 =	33	x 52.00	=	1,716.00

HP = highest number of total claims paid for, if greater than 20.

Indep. Claims		**Extra Claims**	**Fee ($)**		**Fee Paid ($)**
2	- 3 or HP =	0	x 0	=	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 $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 ($)**		**Fee Paid ($)**
81	- 100 =	-19	/ 50 =	_____ (round **up** to a whole number)	x 270.00	=	0.00

4. OTHER FEE(S)

	Fees Paid ($)
Non-English Specification, $130 fee (no small entity discount)	
Other (e.g., late filing surcharge): _____	130.00

SUBMITTED BY

Signature	/Nicholas M. Boivin/	Registration No. (Attorney/Agent)	45,650	Telephone	781-860-8660
Name (Print/Type)	Nicholas M. Boivin			Date	May 6, 2011

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) C062-02/04 US
Application Number 12/888,233	Filed September 22, 2010
For HIGH PURITY LIPOPEPTIDES	
Art Unit	Examiner

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	$
☐ Four months (37 CFR 1.17(a)(4))	$1730	$865	$
☑ Five months (37 CFR 1.17(a)(5))	$2350	$1175	$ 2,350.00

☐ 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.

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 6, 2011 — Date

Nicholas M. Boivin — 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.

CERTIFICATE OF EFS FILING UNDER 37 CFR §1.8

I hereby certify that this correspondence is being electronically transmitted to the United States Patent and Trademark Office, Commissioner for Patents, via the EFS pursuant to 37 CFR §1.8 on the below date:

Date: May 6, 2011 Name: Jodi Doherty Signature: /Jodi Doherty/

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appl. No.	:	12/888,233	Confirmation No.	4046
Applicant	:	Thomas J. Kelleher et al.		
Filed	:	September 22, 2010		
TC/A.U.	:	Unknown		
Examiner	:	Unknown		
Docket No.	:	C062-02/04 US		
Customer No.	:	34103		

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

RESPONSE TO NOTICE TO FILE MISSING PARTS OF NONPROVISIONAL APPLICATION FILED UNDER 37 CFR 1.53(b) FILING DATE GRANTED

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

Dear Sir:

In accordance with the Notice to File Missing Parts of Nonprovisional Application Filed under 37 CFR 1.53(b) Filing Date Granted mailed October 7, 2010, enclosed herewith for filing are the following documents for the above-referenced patent application:

☒ Fully executed Declarations for Patent Application from inventors (6)

☒ Fully executed Power of Attorney

☐ Fully executed Combined Declaration and Power of Attorney

☒ Petition for 5 Month Extension of Time (37 CFR § 1.136(a)) to File Missing Parts (if by mail, in duplicate)

☒ Other: Statement Under 37 CFR § 3.73(b) with attachments; Correspondence Address Indication Form; Copy of Notice to File Missing Parts

Applicant is: ☐ small entity (per 37 CFR 1.27) ☒ other than small entity

Fees Associated with Payment:

☒ Filing Fee: $330.00

☒ Surcharge: $130.00

☒ Addtl. Claim Fees: $1716.00 for 33 additional claims

☒ Search Fee: $540.00

☒ Examination Fee: $220.00

☐ App. Size Fee: $_____ (for each additional 50 sheets that exceeds 100 sheets, including specification and drawings)

Payment Method:

☐ Payment by credit card in the amount of $_____ to cover the fees listed above. Form PTO-2038 is enclosed for this purpose.

☒ The Commissioner is hereby authorized to charge $2936.00 to cover the fees listed above to Deposit Account No. 50-1986.

☒ The Commissioner is hereby authorized to charge any deficiencies in fees or credit overpayment to Deposit Account No. 50-1986.

Respectfully submitted,

Date: May 6, 2011 /Nicholas M. Boivin/

Nicholas M. Boivin, Reg. No. 45,650
Cubist Pharmaceuticals, Inc.
65 Hayden Avenue
Lexington, Massachusetts 02421
Tel.: (781) 860-8660
Fax: (781) 860-1407

C062-02-04 US 20110506 Resp to Miss Parts.docx

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
12/888,233	09/22/2010	Thomas Kelleher	C062-02/04 US

CONFIRMATION NO. 4046

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

FORMALITIES LETTER

OC000000043852361

Date Mailed: 10/07/2010

NOTICE TO FILE MISSING PARTS OF NONPROVISIONAL APPLICATION

FILED UNDER 37 CFR 1.53(b)

Filing Date Granted

Items Required To Avoid Abandonment:

An application number and filing date have been accorded to this application. The item(s) indicated below, however, are missing. Applicant is given **TWO MONTHS** from the date of this Notice within which to file all required items and pay any fees required below to avoid abandonment. Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a).

- The statutory basic filing fee is missing.
  *Applicant must submit $**330** to complete the basic filing fee for a non-small entity. If appropriate, applicant may make a written assertion of entitlement to small entity status and pay the small entity filing fee (37 CFR 1.27).*
- The oath or declaration is missing.
  A properly signed oath or declaration in compliance with 37 CFR 1.63, identifying the application by the above Application Number and Filing Date, is required.
  Note: If a petition under 37 CFR 1.47 is being filed, an oath or declaration in compliance with 37 CFR 1.63 signed by all available joint inventors, or if no inventor is available by a party with sufficient proprietary interest, is required.

The applicant needs to satisfy supplemental fees problems indicated below.

The required item(s) identified below must be timely submitted to avoid abandonment:

- Additional claim fees of $**1716** as a non-small entity, including any required multiple dependent claim fee, are required. Applicant must submit the additional claim fees or cancel the additional claims for which fees are due.
- To avoid abandonment, a surcharge (for late submission of filing fee, search fee, examination fee or oath or declaration) as set forth in 37 CFR 1.16(f) of $**130** for a non-small entity, must be submitted with the missing items identified in this notice.

SUMMARY OF FEES DUE:

Total additional fee(s) required for this application is $**2936** for a non-small entity
- $**330** Statutory basic filing fee.
- $**130** Surcharge.
- The application search fee has not been paid. Applicant must submit $**540** to complete the search fee.

- The application examination fee has not been paid. Applicant must submit $**220** to complete the examination fee for a non-small entity.
- Total additional claim fee(s) for this application is $**1716**
  - $**1716** for **33** total claims over 20.

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/jmilani/

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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
12/888,233	09/22/2010		0.00	C062-02/04 US	53	1

CONFIRMATION NO. 4046

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

FILING RECEIPT

OC000000043852360

Date Mailed: 10/07/2010

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, Residence Not Provided;

Power of Attorney: None

Domestic Priority data as claimed by applicant

This application is a CON of 11/739,180 04/24/2007
which is a CON of 10/747,485 12/29/2003 ABN
which is a CON 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: 10/05/2010

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 12/888,233**

Projected Publication Date: To Be Determined - pending completion of Missing Parts

Non-Publication Request: No

Early Publication Request: No

Title

High Purity Lipopeptides

Preliminary Class

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

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NOT GRANTED

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
12/888,233	09/22/2010	Thomas Kelleher	C062-02/04 US

CONFIRMATION NO. 4046

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

FORMALITIES LETTER

OC000000043852361

Date Mailed: 10/07/2010

NOTICE TO FILE MISSING PARTS OF NONPROVISIONAL APPLICATION

FILED UNDER 37 CFR 1.53(b)

Filing Date Granted

Items Required To Avoid Abandonment:

An application number and filing date have been accorded to this application. The item(s) indicated below, however, are missing. Applicant is given **TWO MONTHS** from the date of this Notice within which to file all required items and pay any fees required below to avoid abandonment. Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a).

- The statutory basic filing fee is missing.
  *Applicant must submit $**330** to complete the basic filing fee for a non-small entity. If appropriate, applicant may make a written assertion of entitlement to small entity status and pay the small entity filing fee (37 CFR 1.27).*
- The oath or declaration is missing.
  A properly signed oath or declaration in compliance with 37 CFR 1.63, identifying the application by the above Application Number and Filing Date, is required.
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SUMMARY OF FEES DUE:

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PTO/SB/05 (08-08)
Approved for use through 09/30/2010. 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.	C062-02/04 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. ☐ **Fee Transmittal Form** (e.g., PTO/SB/17)
2. ☐ **Applicant claims small entity status.** See 37 CFR 1.27.
3. ☑ **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. ☑ **Drawing(s)** (*35 U.S.C. 113*) [*Total Sheets* 11]
5. **Oath or Declaration** [*Total Sheets* _____]
   a. ☐ Newly executed (original or copy)
   b. ☐ 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**
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Alexandria VA 22313-1450

ACCOMPANYING APPLICATION PARTS

9. ☐ **Assignment Papers** (cover sheet & 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 citations attached
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:*

☑ Continuation ☐ Divisional ☐ Continuation-in-part (CIP) of prior application No.: 11/739,180

Prior application information: *Examiner* Chih-Min Kam *Art Unit:* 1656

19. CORRESPONDENCE ADDRESS

☑ The address associated with Customer Number: 34103 ***OR*** ☐ Correspondence address below

Name					
Address					
City		State		Zip Code	
Country		Telephone		Email	

Signature	/William D. DeVaul/	Date	September 22, 2010
Name (Print/Type)	William D. DeVaul	Registration No. (Attorney/Agent)	42,483

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.
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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 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.

HIGH PURITY LIPOPEPTIDES

CROSS-REFERENCE TO RELATED APPLICATIONS

The present application claims priority to United States Patent Application No. 11/739,180, filed April 24, 2007, which 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 November 28, 2000, now US 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.

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 ± 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.

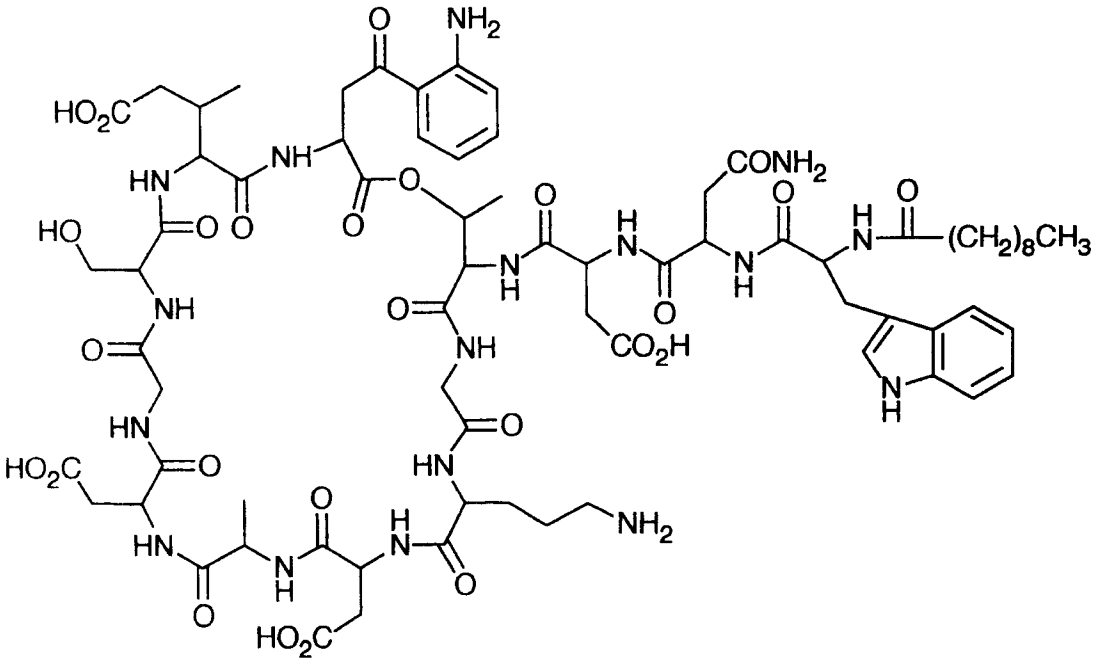

Fig. 1

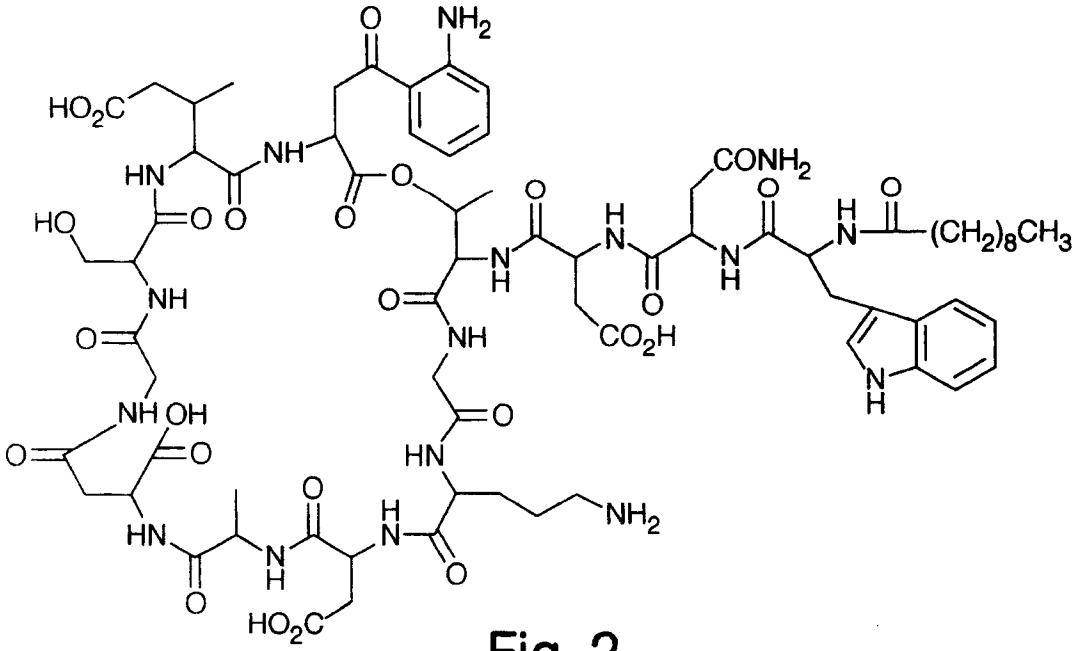

Fig. 2

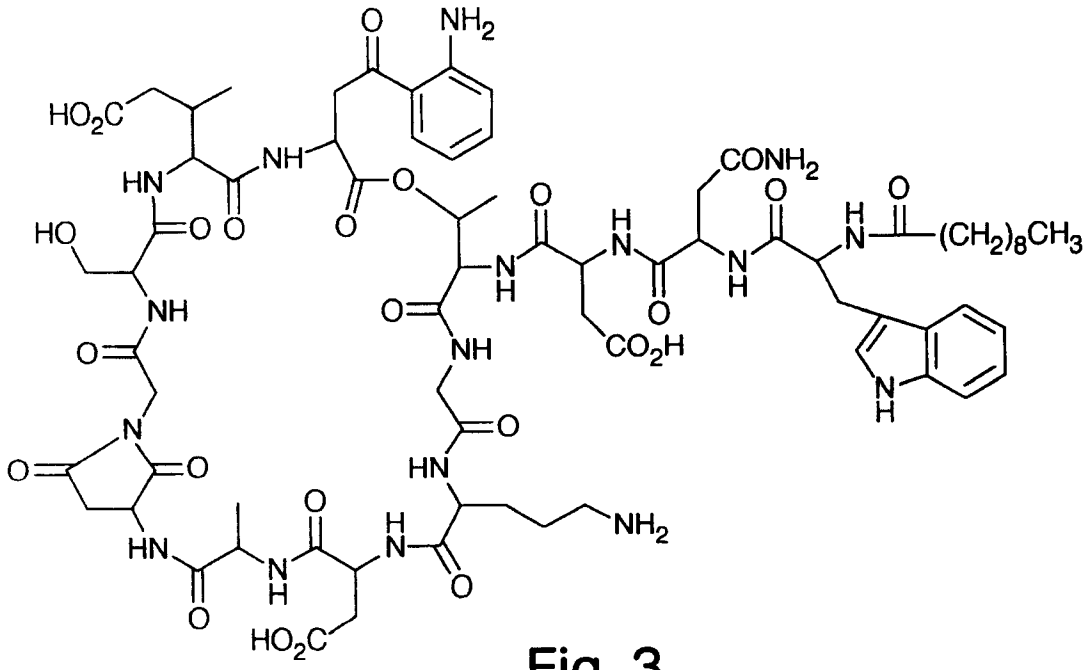

Fig. 3

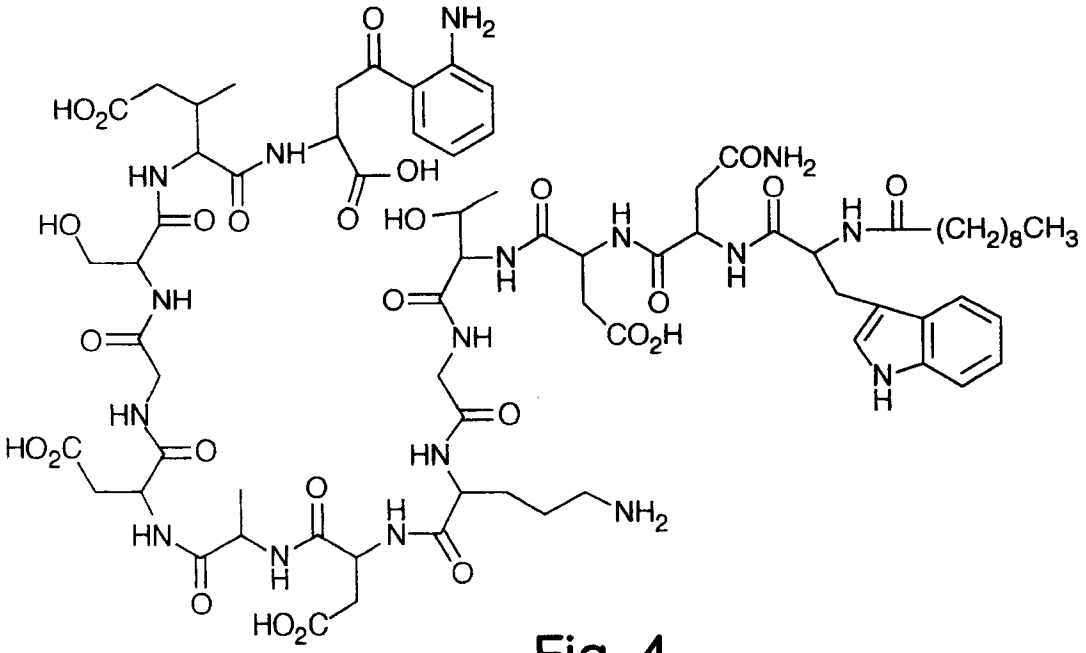

Fig. 4

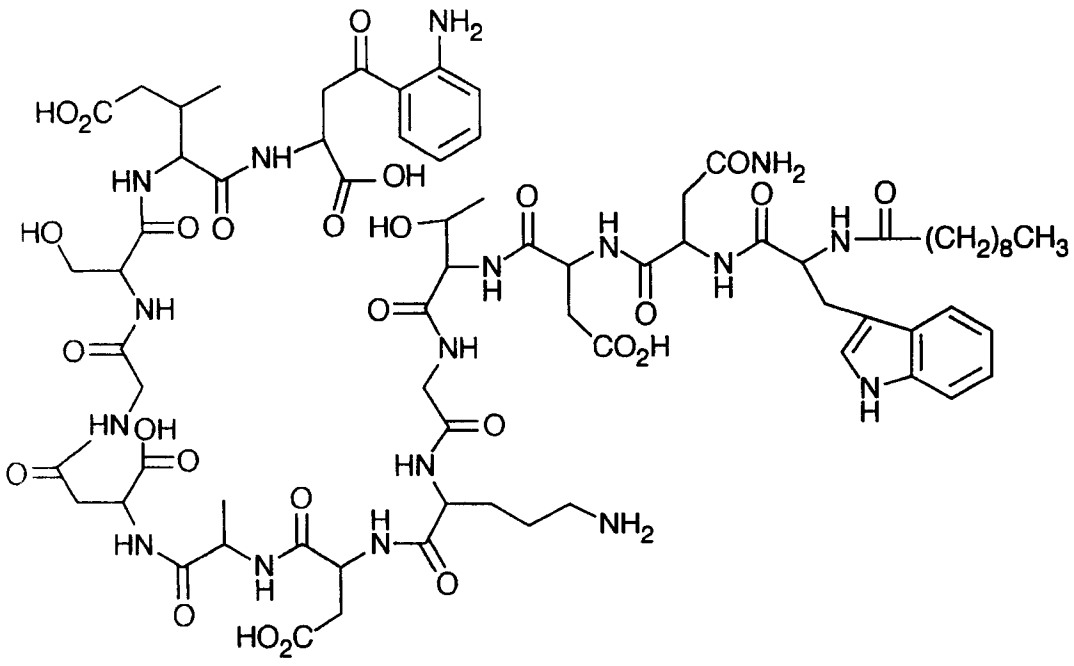

Fig. 5

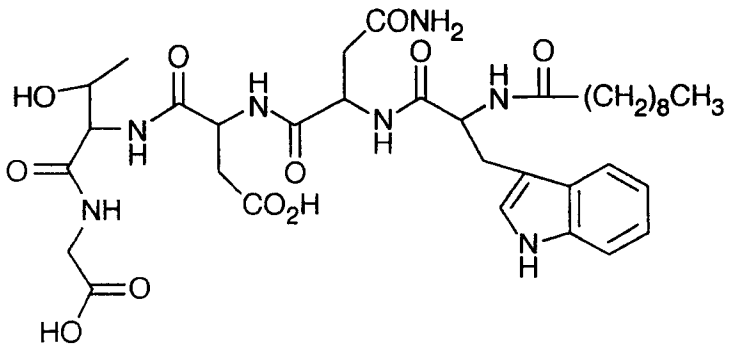

Fig. 6

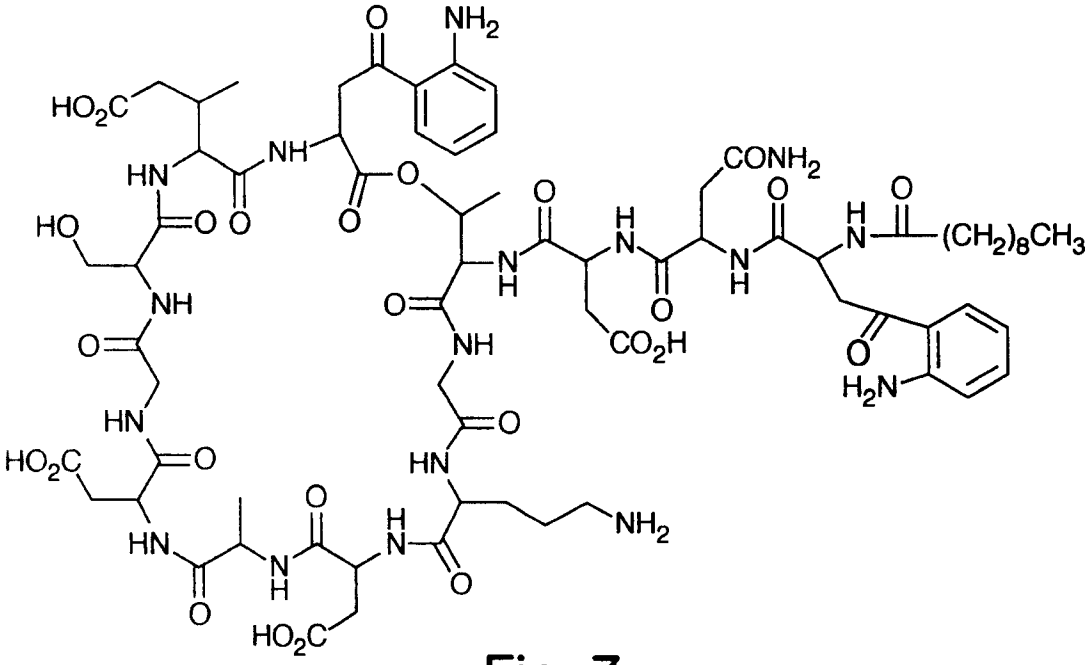

Fig. 7

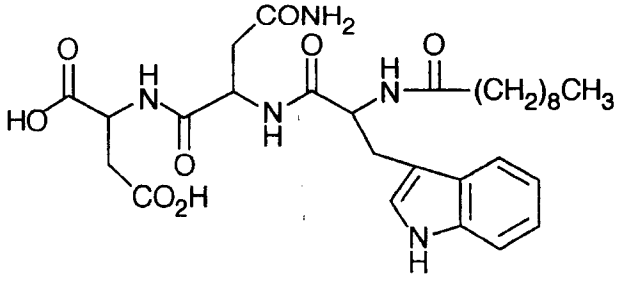

Fig. 8

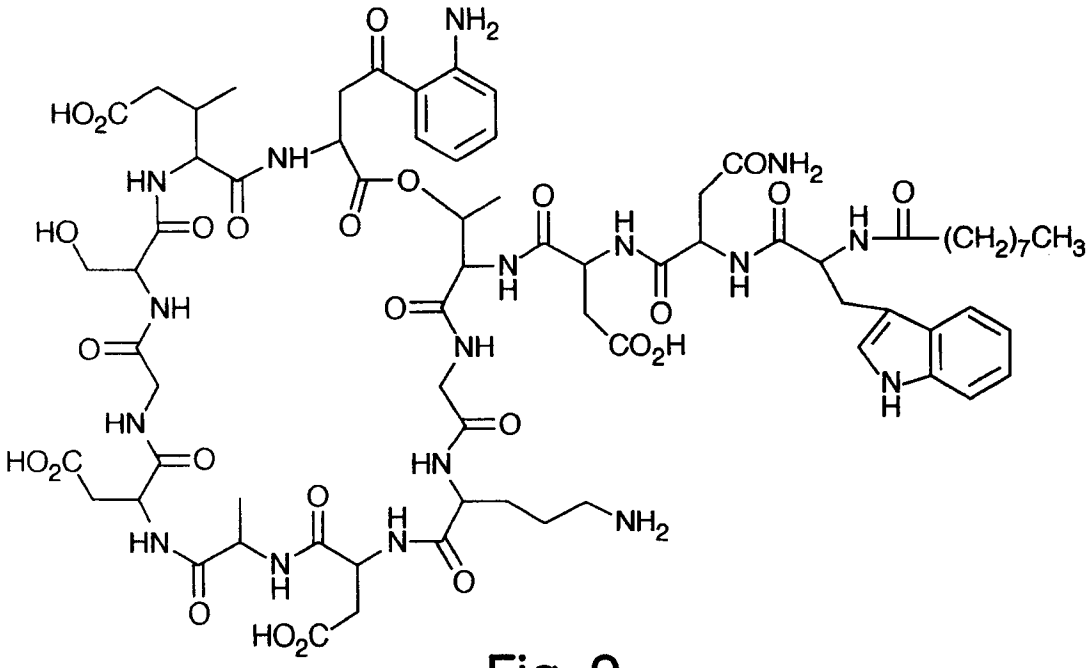

Fig. 9

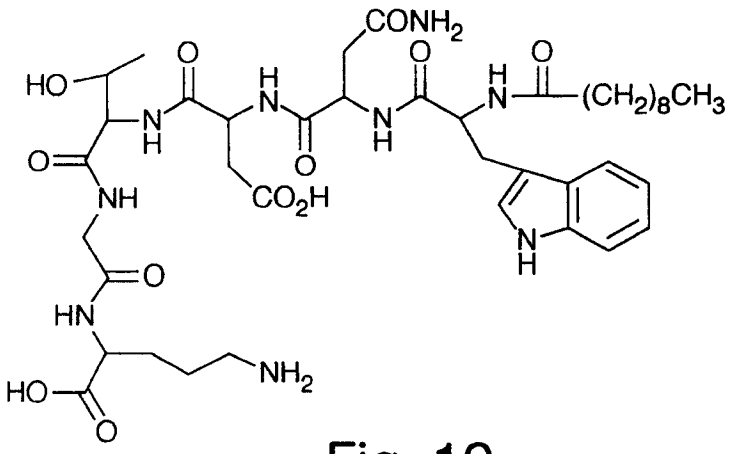

Fig. 10

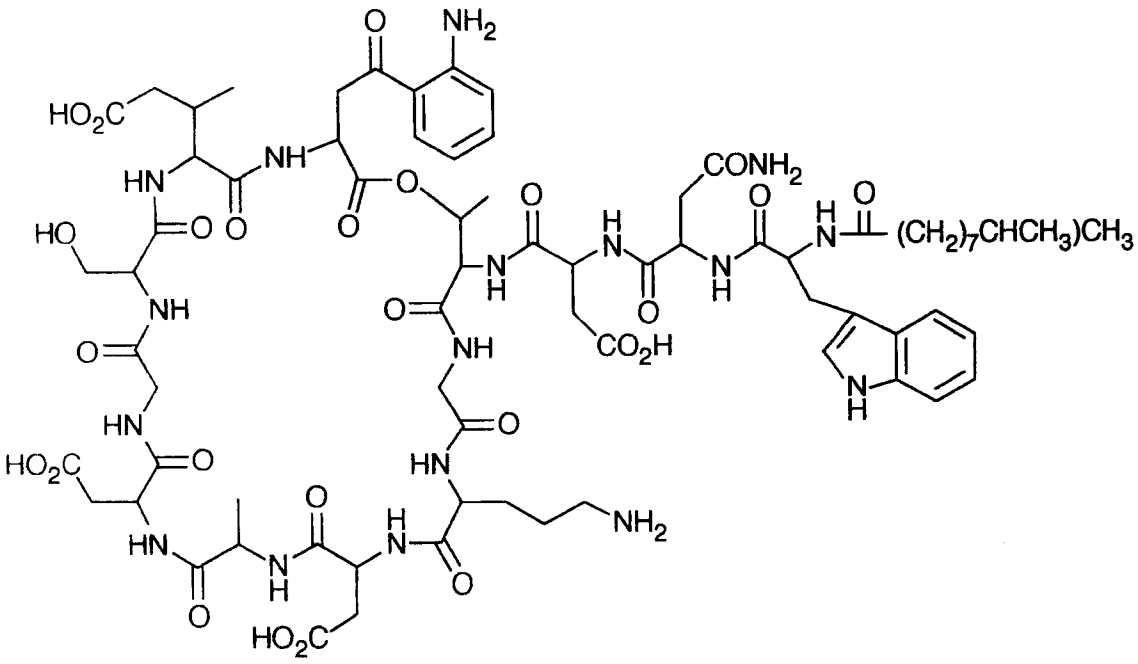

Fig. 11

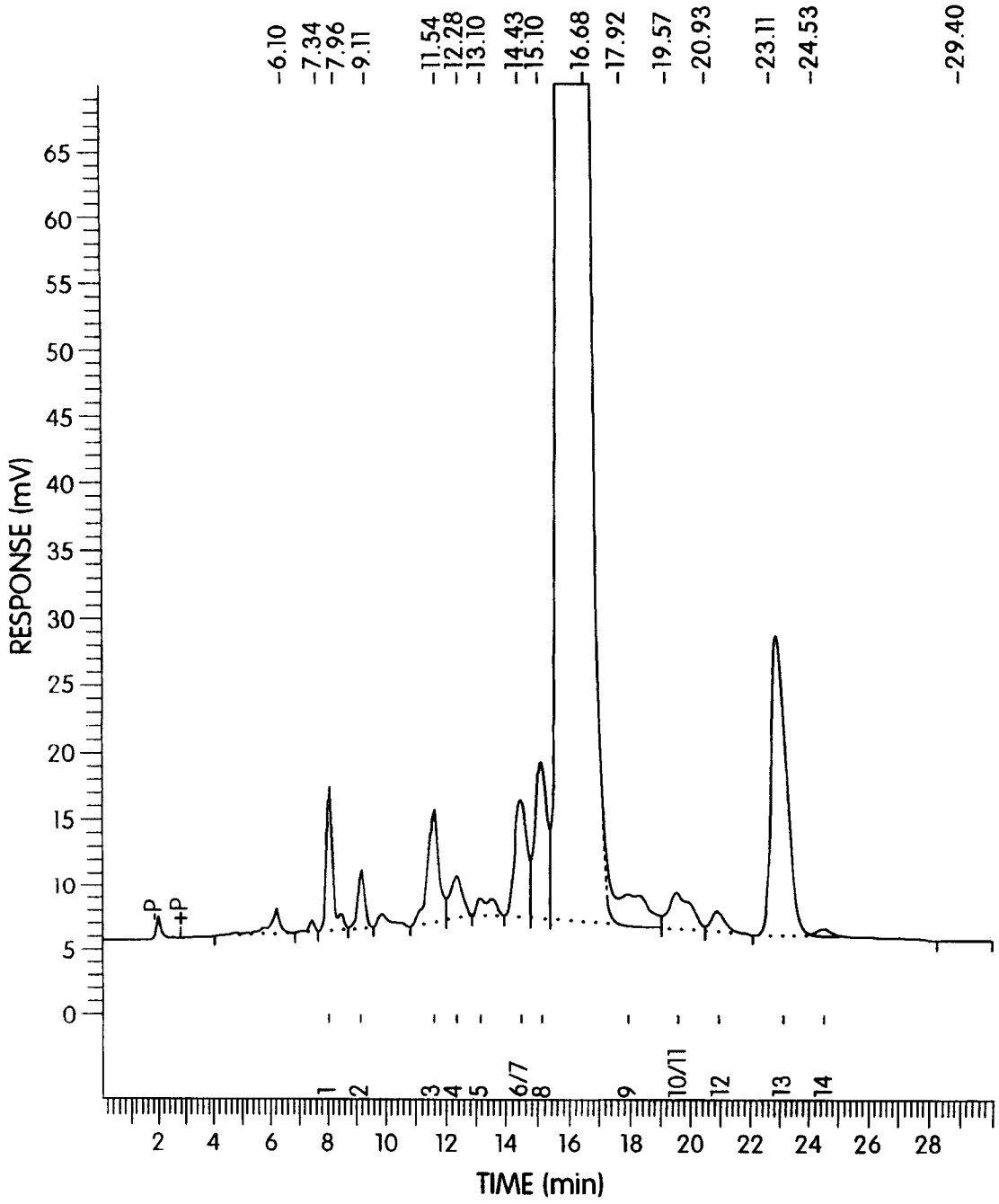
6.10
7.34
7.96
9.11
11.54
12.28
13.10
14.43
15.10
16.68
17.92
19.57
20.93
23.11
24.53
29.40
RESPONSE (mV)
0
5
10
15
20
25
30
35
40
45
50
55
60
65
1
2
3
4
5
6/7
8
9
10/11
12
13
14
2
4
6
8
10
12
14
16
18
20
22
24
26
28
TIME (min)

Fig. 12

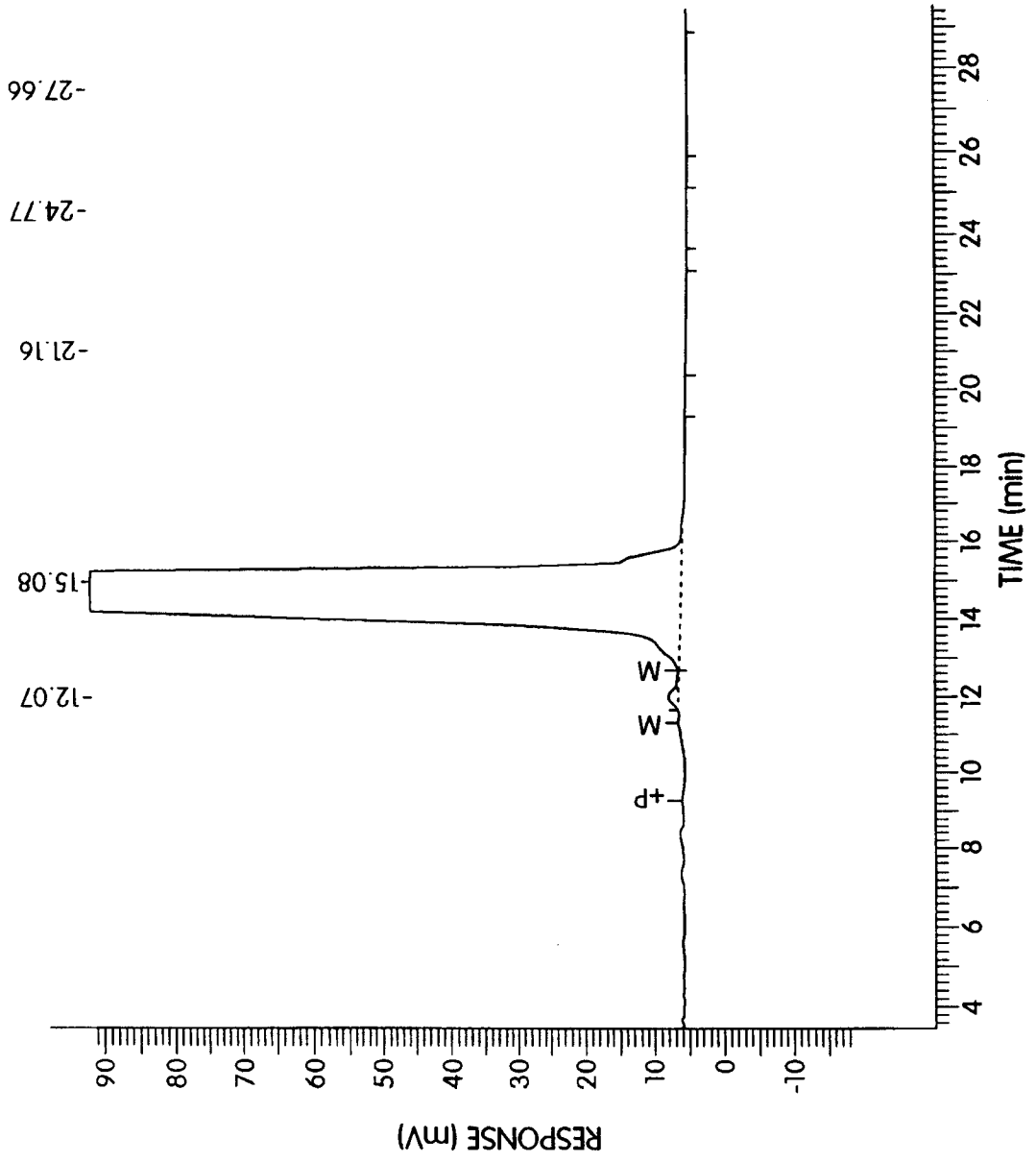
RESPONSE (mV)
90
80
70
60
50
40
30
20
10
0
-10
TIME (min)
4
6
8
10
12
14
16
18
20
22
24
26
28
+P
M
M
12.07
15.08
21.16
24.77
27.66

Fig. 13

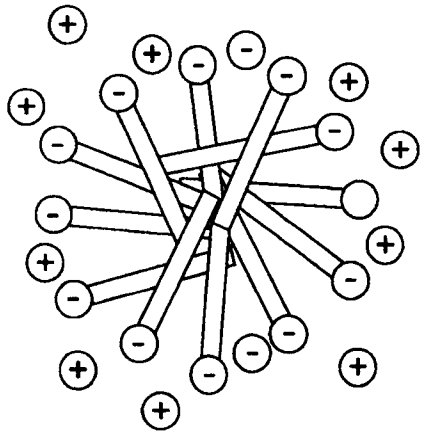

Fig. 14A

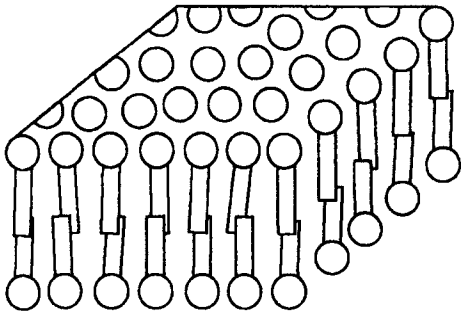

Fig. 14B

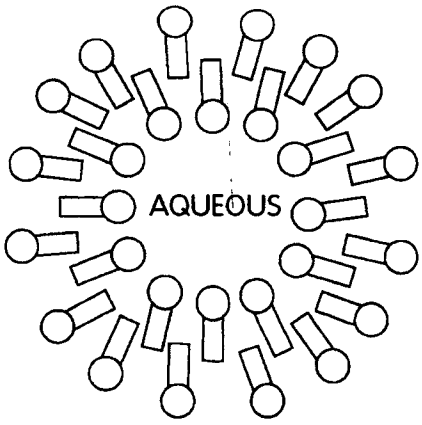

Fig. 14C

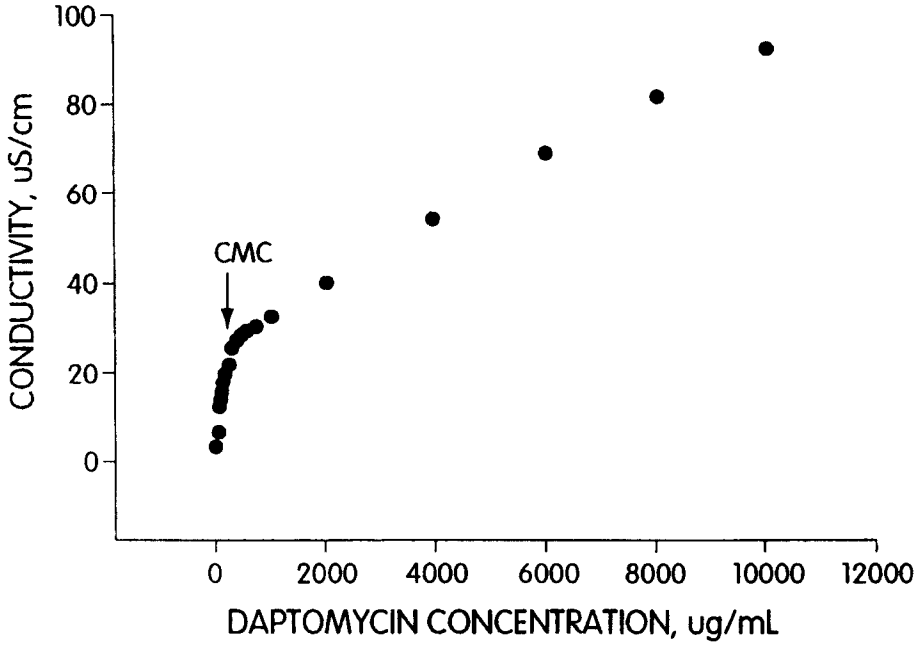
100
80
60
40
20
0
CONDUCTIVITY, uS/cm
CMC
0
2000
4000
6000
8000
10000
12000
DAPTOMYCIN CONCENTRATION, ug/mL

Fig. 15

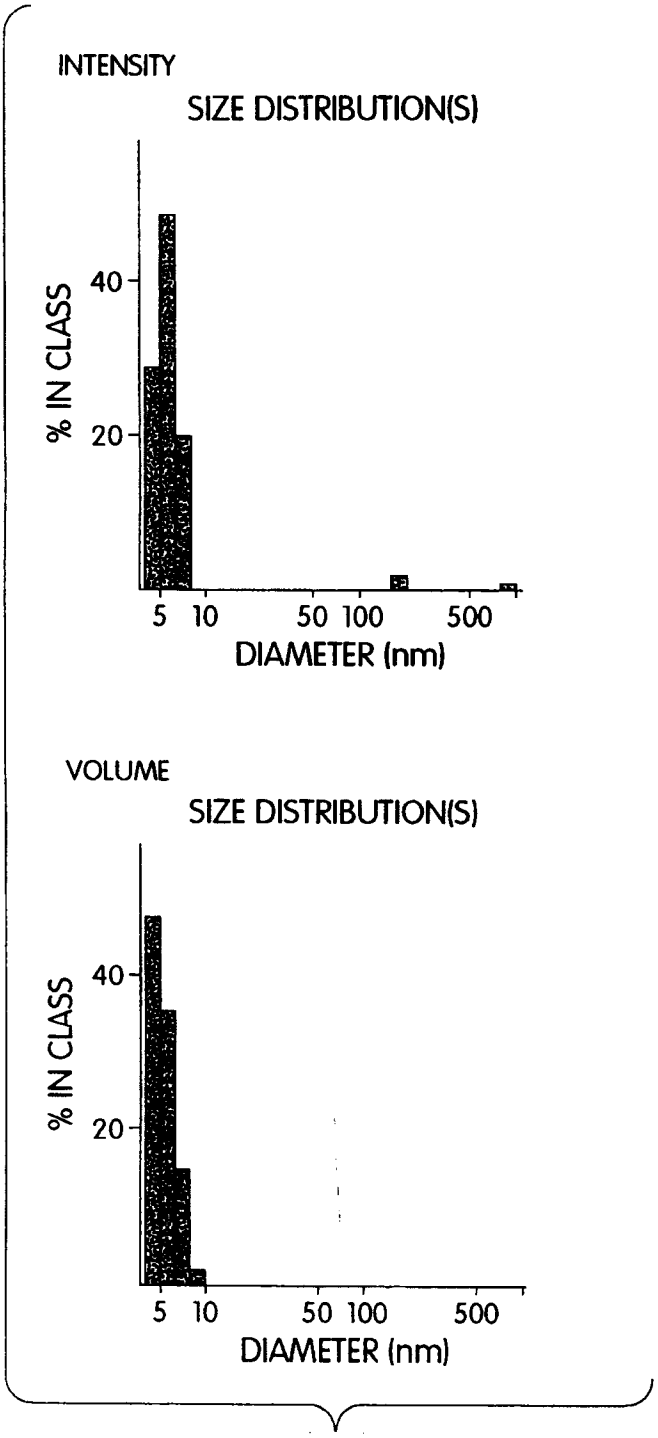
INTENSITY
SIZE DISTRIBUTION(S)
% IN CLASS
40
20
5
10
50
100
500
DIAMETER (nm)
VOLUME
SIZE DISTRIBUTION(S)
% IN CLASS
40
20
5
10
50
100
500
DIAMETER (nm)

Fig. 16

Electronic Acknowledgement Receipt

EFS ID:	8477171
Application Number:	12888233
International Application Number:	
Confirmation Number:	4046
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:	C062-02/04 US
Receipt Date:	22-SEP-2010
Filing Date:	
Time Stamp:	18:13:28
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	Transmittal of New Application	C062-02-04_US_20100922_Transm_Ltr.pdf	302264 996beb1857f9dc97ae4faa4da0dc7c78206dfc59	no	2

Warnings:

Information:

2	Specification	C062-02-04_US_Appln_as_filed.pdf	335388 2a2bc893cb4b32d676864db68c7cf1d874cd2343	no	71
Warnings:					
Information:					
3	Drawings-only black and white line drawings	C062-03-04_US_Figures.pdf	122964 7274ebd1717ae006e41c96859c4cfc7417ae0420	no	11
Warnings:					
Information:					
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PTO/SB/06 (12-04)

Approved for use through 7/31/2006. OMB 0651-0032

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Date: 09/22/10

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 12/888,233

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	330
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	540
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	220
TOTAL CLAIMS (37 CFR 1.16(i))	53 minus 20 =	33	x$26		OR	x$52	1716
INDEPENDENT CLAIMS (37 CFR 1.16(h))	1 minus 3 =	*	x$110			x$220	
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, 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						
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))			195			390	
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	2806

APPLICATION AS AMENDED – PART II

		(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 ($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE ($)
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))					N/A		OR	N/A	
						TOTAL ADD'T FEE		OR	TOTAL ADD'T FEE	

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)	OR	RATE ($)	ADDITIONAL FEE ($)
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.

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