

## Electronic Acknowledgement Receipt

<b>EFS ID:</b>	21540057
<b>Application Number:</b>	13421769
<b>International Application Number:</b>	
<b>Confirmation Number:</b>	3135
<b>Title of Invention:</b>	Formulations of Guanylate Cyclase C Agonists and Methods of Use
<b>First Named Inventor/Applicant Name:</b>	Stephen Comiskey
<b>Customer Number:</b>	58249
<b>Filer:</b>	Anne Elizabeth Fleckenstein
<b>Filer Authorized By:</b>	
<b>Attorney Docket Number:</b>	40737-509001US
<b>Receipt Date:</b>	19-FEB-2015
<b>Filing Date:</b>	15-MAR-2012
<b>Time Stamp:</b>	19:11:03
<b>Application Type:</b>	Utility under 35 USC 111(a)

### Payment information:

Submitted with Payment	no
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### File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Non Patent Literature	Advisory_Committee_Merida.pdf	26183721 <small>1be468f8841752755c75ef8136b2e6f678edc946</small>	no	205

### Warnings:

### Information:

2	Non Patent Literature	Alrefai_et_al_Am_J_Physiol_Gastro_Liver_Physiol_288_G978_2005.pdf	1672523 68769f3687bc63d2de2c671829b625a36187cd26	no	10
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3	Non Patent Literature	Askling_et_al_2001.pdf	9582524 3b9dcb86201ba9f9c1d32cbfa423f02baa57e35b	no	5
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4	Non Patent Literature	Bakre_2000.pdf	16326222 a7f472f3619baaa4f655c5706cc43dd5fd0d789d	no	9
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5	Non Patent Literature	Barbara_2002.pdf	9397719 c394d92a3c073cb59f1c9a45a8c3995df3d2fa4c	no	5
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8	Non Patent Literature	Beltowski_2001.pdf	3876028 a9af723638433fa7362ae25f6551bd7c1d236e58	no	26
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<b>Total Files Size (in bytes):</b>				507719962	

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**New Applications Under 35 U.S.C. 111**

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

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

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

**New International Application Filed with the USPTO as a Receiving Office**

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



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.

<b>PATENT APPLICATION FEE DETERMINATION RECORD</b> Substitute for Form PTO-875	Application or Docket Number <b>13/421,769</b>	Filing Date <b>03/15/2012</b>	<input type="checkbox"/> To be Mailed
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ENTITY:  LARGE  SMALL  MICRO

**APPLICATION AS FILED – PART I**

FOR	NUMBER FILED	NUMBER EXTRA	RATE (\$)	FEE (\$)
<input type="checkbox"/> BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	
<input type="checkbox"/> SEARCH FEE (37 CFR 1.16(k), (l), or (m))	N/A	N/A	N/A	
<input type="checkbox"/> EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X \$ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X \$ =	
<input type="checkbox"/> APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is \$310 (\$155 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).			
<input type="checkbox"/> 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	

**APPLICATION AS AMENDED – PART II**

	(Column 1)	(Column 2)	(Column 3)	PRESENT EXTRA	RATE (\$)	ADDITIONAL FEE (\$)
<b>AMENDMENT</b>	<b>02/19/2015</b>	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR		
	Total (37 CFR 1.16(i))	* 44	Minus	** 42	= 2	X \$40 = 80
	Independent (37 CFR 1.16(h))	* 3	Minus	***3	= 0	X \$210 = 0
	<input type="checkbox"/> Application Size Fee (37 CFR 1.16(s))					
<input type="checkbox"/> FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
					TOTAL ADD'L FEE	<b>80</b>

	(Column 1)	(Column 2)	(Column 3)	PRESENT EXTRA	RATE (\$)	ADDITIONAL FEE (\$)
<b>AMENDMENT</b>		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR		
	Total (37 CFR 1.16(i))	*	Minus	**	=	X \$ =
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X \$ =
	<input type="checkbox"/> Application Size Fee (37 CFR 1.16(s))					
<input type="checkbox"/> FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
					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.

LIE  
/Kelley Dantzer/

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.**

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



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Table with columns: APPLICATION NO., FILING DATE, FIRST NAMED INVENTOR, ATTORNEY DOCKET NO., CONFIRMATION NO., EXAMINER, ART UNIT, PAPER NUMBER, NOTIFICATION DATE, DELIVERY MODE. Includes application details for Stephen Comiskey and examiner LEE, JIA-HAI.

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):

zpatdcdocketing@cooley.com

## Office Action Summary

**Application No.**  
13/421,769

**Applicant(s)**  
COMISKEY ET AL.

**Examiner**  
JIA-HAI LEE

**Art Unit**  
1676

**AIA (First Inventor to File)  
Status**  
No

-- 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 MONTHS 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 02/19/2015.  
 A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on \_\_\_\_\_.
- 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) 1-44 is/are pending in the application.  
     5a) Of the above claim(s) 1,12,13,17-19 and 26-41 is/are withdrawn from consideration.
- 6)  Claim(s) \_\_\_\_\_ is/are allowed.
- 7)  Claim(s) 2-11,14-16,20-25 and 42-44 is/are rejected.
- 8)  Claim(s) \_\_\_\_\_ is/are objected to.
- 9)  Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

\* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see [http://www.uspto.gov/patents/init\\_events/pph/index.jsp](http://www.uspto.gov/patents/init_events/pph/index.jsp) or send an inquiry to [PPHfeedback@uspto.gov](mailto:PPHfeedback@uspto.gov).

### Application Papers

- 10)  The specification is objected to by the Examiner.
- 11)  The drawing(s) filed on \_\_\_\_\_ 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).

### 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).

#### Certified copies:

- 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)).

\*\* 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)  Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b)  
     Paper No(s)/Mail Date 02/19/2015
- 3)  Interview Summary (PTO-413)  
     Paper No(s)/Mail Date. \_\_\_\_\_ .
- 4)  Other: \_\_\_\_\_.

### **DETAILED ACTION**

The present application is being examined under the pre-AIA first to invent provisions.

#### ***Priority***

This application is a CIP of PCT/US2011/051805 filed on 09/15/2011, which claims benefit of 61/383,156 filed on 09/15/2010, claims benefit of 61/387,636 filed on 09/29/2010, and claims benefit of 61/392,186 filed on 10/12/2010.

#### ***Information Disclosure Statement***

The information disclosure statement (IDS) submitted on 02/19/2015 is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement has been considered by the examiner.

#### ***Claim Status***

Claims 1-44 are pending.

Claims 1, 12-13, 17-19, and 26-41 were withdrawn as being directed to a non-elected invention and species, the election having been made on 02/19/2015.

Claims 2-11, 14-16, 20-25, and 42-44 have been examined.

Any objections and/or rejections made in the office action dated 08/19/2014 and not specifically discussed below in its original or modified form here are considered withdrawn.

***Affidavit/ Declaration under 37 CFR 1.132***

The affidavit/declaration under 37 CFR 1.132 filed 07/16/2014 has been fully considered, but it is insufficient to overcome the new ground of rejection. Mihranyan et al. (Int J Pharm. 2004 Jan 28;269(2):433-42.) teach microcrystalline cellulose (MCC) is the most commonly used drug excipients but moisture in microcrystalline cellulose may cause stability problems for moisture sensitive drugs (Abstract; p433, col 1). Mihranyan et al. suggest the use of low moisture grades of commercial MCC product (1.5%, w/w, moisture in Avicel PH 112 and 3%, w/w, moisture in Avicel PH 103, FMC Corp.) for moisture sensitive drugs (p433, col 2). Avicel PH product instruction from FMC (2005) shows the advantages of using Avicel PH products as a drug excipient of inert lower moisture carrier (Table in page 2 and 6) and further suggests the decrease of moisture content can increase stability of moisture-sensitive drugs and flow in making a capsule and tablet at page 12. The stability of peptide drugs was known to be sensitive to temperature, moisture and excipients taught by Lai et al. in the Abstract (J Pharm Sci. 1999 May;88(5):489-500. Review.).

***New grounds of rejections***

***Claim Rejections - 35 USC § 103***

The following is a quotation of pre-AIA 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which

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said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under pre-AIA 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 2-11, 16, 20-21, 23-24, and 42-44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shailubhai et al. (WO 02/078683 A1) in view of Currie et al. (WO 2005/016244) in view of Mhraryan et al. (Int J Pharm. 2004 Jan 28;269(2):433-42.) and in view of Avicel PH product instruction (FMC 2005).

This instant claim 2 is drawn to an oral dosage formulation comprising a guanylate cyclase C agonist peptide of SEQ ID NO: 1 at unit dose 0.01-10 mg with purity greater than 91% and an inert low moisture carrier.

Shailubhai et al. teach a pharmaceutical composition comprising a guanylate cyclase C (GCC) agonist peptide having the sequence of Asn Asp Glu Cys Glu Leu Cys Val Asn Val Ala Cys Thr Gly Cys Leu with 100% homology to SEQ ID NO: 1 of this instant application (p6, line 32) and formulated with pharmaceutically acceptable excipients for oral administration (p17, line 45-49). Shailubhai et al. show the unit dosage of the GCC agonist peptide (p27, claim 22) is between 100 µg - 3 g (p4, line 20-

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24) or 1 µg -10 mg (p7, line 14) and the purity of the GCC agonist peptide is >95% (p21, line 6), reading on claims 1 and 42-43.

With respect to claim 3, Shailubhai et al. show the purity of the GCC agonist peptide is >95% (p21, line 6) in compliance with cGMP level (p21, Table 4).

With respect to claim 4, Shailubhai et al. show the impurity of the GCC agonist peptide is < 5%, calculated as purity between 95%-100% (p21, line 6) in compliance with cGMP level (p21, Table 4).

With respect to claim 6, Shailubhai et al. show the GCC agonist peptide having the sequence of Asn Asp Glu Cys Glu Leu Cys Val Asn Val Ala Cys Thr Gly Cys Leu with 100% homology to SEQ ID NO: 1 of this instant application (p6, line 32).

With respect to claim 7, Shailubhai et al. show the GCC agonist peptide has the dosage of once-a-day unit dose between 10 µg - 2 mg (p20, line 1-8).

With respect to claim 8, Shailubhai et al. show the solid formulation of GCC agonist peptide in a unit dose is powders, tablets, and capsules (p17, line 44-49).

With respect to claims 9, Shailubhai et al. show the pharmaceutically acceptable excipients comprise a pharmaceutical carrier of cellulose (p18, line 11-19).

With respect to claim 21, Shailubhai et al. show the oral dosage formulation of GCC agonist peptide is in the form of a capsule or tablet (p17, line 44-49).

Shailubhai et al. 1) do not specify the cellulose used is an inert carrier of microcrystalline cellulose and 2) do not specify the cellulose used is an inert low moisture carrier.

Currie et al. teach the use of the peptide of SEQ ID NO: 1 consisting of Asn Asp

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Glu Cys Glu Leu Cys Val Asn Val Ala Cys Thr Gly Cys Leu (p27, line 17) for the treatment of gastrointestinal disorders (Abstract). Currie et al. teach the use of pharmaceutically acceptable inert carriers such as microcrystalline cellulose purchased from FMC corporation (p48, line 22-23) and lubricants to insure the stability of the peptide formulation (p48, line 1-5; 12-15). Currie et al. teach the oral peptide formulation is administered in a liposomal formulation or a capsule comprising a suspension in an aqueous liquid (p46, line 12-17), reading on claims 2, 16, and 23-24.

Mihrianyan et al. (Int J Pharm. 2004 Jan 28;269(2):433-42.) teach microcrystalline cellulose (MCC) is the most commonly used drug excipients as taught by Currie et al. (p48, line 22), but moisture in microcrystalline cellulose may cause stability problems for moisture sensitive drugs (Abstract; p433, col 1), reading on peptide drugs. Mihrianyan et al. suggest the use of low moisture grades of commercial MCC (1.5%, w/w, moisture in Avicel PH 112 and 3%, w/w, moisture in Avicel PH 103, FMC Corp.) for moisture sensitive drugs (Abstract, p433, col 2), reading on claims 2, 9-10, and 16. With respect to claims 20 and 44, it is noted the same peptide composition having the same components must have the same properties. These properties are presumed to be present in any composition that meets the structural requirements of the claim, absent evidence to the contrary. If this is not the case, then applicant is either missing essential subject matter from the claims, not enabled for the full scope of the claims, or both. Mihrianyan et al. suggest inorganic acid (HCL) hydrolyzes cellulose materials; thus, one of ordinary skill in the art would make drug cellulose composition free of inorganic acid (p434, 2.13), reading on claim 5. The inherent property of particle size is



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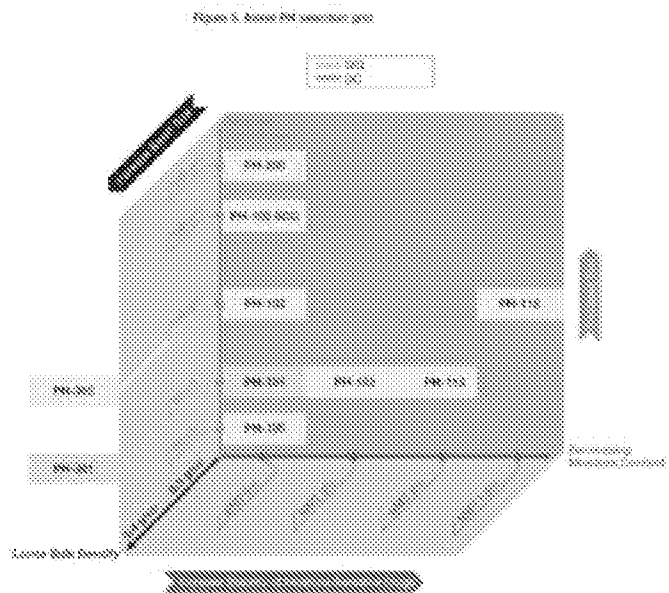
50 µM for Avicel PH 103 and 100 µM for Avicel PH 112, reading on claim 11 evidenced in Avicel PH product instruction (Table in page 6).

Avicel PH product instruction shows the advantages and inherent properties of particle size in using Avicel PH products as a drug excipient (Table in page 2 and 6) including the decrease of moisture content can increase stability of moisture-sensitive drugs (e.g., GCC agonist peptide ) as well as increase flow in making a capsule and tablet (page 12). Thus, one of ordinary would use a commercial product of an inert low moisture microcrystalline cellulose (e.g., PH 112) according to the FMC's manufacturer recommendation.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine

Shailubhai's a guanylate cyclase C agonist peptide SEQ ID NO: 1 with Currie's teaching of pharmaceutically acceptable inert carriers because Shailubhai's peptide of SEQ ID NO: 1 is identical to Currie's peptide (p27, line 17) and Currie et al. teach the use of a commercial pharmaceutically acceptable

inert carrier of microcrystalline cellulose (e.g., PH 103) purchased from FMC corporation (p48, line 22-23) to insure the stability of the peptide formulation (p48, line 1-5; 12-15; line 22). It would be further obvious to combine the teachings (Shailubhai in view of



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Currie) with Mihranyan's low moisture grades of microcrystalline cellulose (1.5%, w/w, moisture in Avicel PH 112 and 3%, w/w, moisture in Avicel PH 103) sold by FMC Corp (p433, col 2). because Shailubhai in view of Currie teach a guanylate cyclase C agonist peptide (SEQ ID NO: 1) formulated with an inert carrier of microcrystalline cellulose from in an oral dosage composition and Mihranyan et al. teach moisture in microcrystalline cellulose may cause stability problems for moisture sensitive drugs (e.g., peptide drug) and suggest the use low moisture grades of microcrystalline cellulose (1.5%, w/w, moisture in Avicel PH 112 and 3%, w/w, moisture in Avicel PH 103) sold by FMC Corp consistent with Currie's teaching (p48, line 22-23). Avicel PH product instruction from FMC would demonstrate the common knowledge of an inert low moisture grades of microcrystalline cellulose excipient and inherent properties of Avicel PH products used in drug manufacturing. The teaching/suggestion/motivation to combine the references is described above to establish a prima facie case of obviousness met the requirement described in MPEP 2143 and the combination would have yielded nothing more than predictable success to one of ordinary skill in the art at the time of the invention.

Claims 2, 14-16, 20-22, 25, and 44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shailubhai et al. (WO 02/078683 A1) in view of Currie et al. (WO 2005/016244) in view of Mihranyan et al. (Int J Pharm. 2004 Jan 28;269(2):433-42.) and in view of Avicel PH product instruction (FMC 2005) as applied to claims 2-11, 16, 21, 23-24, and 42-43 and further in view of Fretzen et al. (WO 2010/027404 A2).

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This instant claim 2 is drawn to an oral dosage formulation comprising a guanylate cyclase C agonist peptide of SEQ ID NO: 1 at unit dose 0.01-10 mg with purity greater than 91% and an inert low moisture carrier.

Shailubhai in view of Currie in view of Mihranyan and in view of Avicel PH product instruction teach an oral dosage formulation comprising a guanylate cyclase C agonist peptide of SEQ ID NO: 1 at unit dose 0.01-10 mg with purity greater than 91% and an inert low moisture carrier (e.g., Avicel PH 112) described above.

Shailubhai in view of Currie in view of Mihranyan and in view of Avicel PH product instruction do not specify the ratio for an excipient of an amino acid to a therapeutic peptide in the therapeutic composition.

Fretzen et al. teach a peptide formulation for oral administration comprises (a) an aqueous coating solution, a therapeutic peptide, a sterically hindered primary amine (e.g., amino acid of leucine) and (b) a pharmaceutically acceptable/SATYANARAYANA R GUDIBANDE/

Primary Examiner, Art Unit 1676 carrier of filler (p6, line 10-18) to form the tablets or to be placed into capsules (p6, line 24-25). Fretzen et al. suggest the lubricant of the peptide composition can be the amino acid leucine (p9, line 8).

With respect to claims 14-15, Fretzen et al. suggest the molar ratio of an amino acid of leucine (comprising a primary amine) to the therapeutic peptide is ranged from 5:1 to 50:1 (p7, line 32-34 bridging to p8, line 1-5).

With respect to claim 16, Fretzen et al. suggest a formulation consists of a therapeutic peptide, an inert carrier of a microcrystalline cellulose (p9, line 1-6) and a

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lubricant of an amino acid leucine (p9, line 8).

With respect to claims 20 and 44, Fretzen et al. further suggest the formulated peptide is stabilized against degradation, less than 2% degradation, after 18-24 months of storage at 25°C and 60% relative humidity (p2, line 15-21).

With respect to claim 21, Fretzen et al. suggest final pharmaceutical composition is in the form of tablets or to be placed into capsules (p6, line 24-25).

With respect to claim 22, Fretzen et al. suggest the use of a blister pack with individual doses of a tablet for pressing out of the pack according to a therapeutic schedule (p16, line 2-3).

With respect to claim 25, Fretzen et al. suggest the use of special oil, e.g., mineral oil or vegetable oil, as a lubricant and/or glidant in the oral dosage composition (p9, line 9).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings (Shailubhai et al. in view of Currie et al. in view of Mihranyan et al. and in view of Avicel PH product instruction) with Fretzen teaching of leucine in a peptide formulation because Shailubhai et al. in view of Currie et al. in view of Mihranyan et al. and in view of Avicel PH product instruction teach an oral dosage formulation comprising the peptide of SEQ ID NO: 1 and an inert low moisture carrier of microcrystalline cellulose excipient and Fretzen et al. teach microcrystalline cellulose can be used as a filler together with a glidant/lubricant of leucine and the ratio of leucine to a therapeutic peptide in a composition (p9, line 19-21). The teaching/suggestion/motivation to combine the references is described above

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to establish a prima facie case of obviousness met the requirement described in MPEP 2143 and the combination would have yielded nothing more than predictable success to one of ordinary skill in the art at the time of the invention.

DP

### ***Conclusion***

No claim is 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 JIA-HAI LEE whose telephone number is (571)270-1691. The examiner can normally be reached on Mon-Fri.

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Karlheinz R. Skowronek can be reached on 571-272-9047. 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). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/J. L./  
Examiner, Art Unit 1676

28-April-2015

/SATYANARAYANA R GUDIBANDE/  
Primary Examiner, Art Unit 1676

<b>Notice of References Cited</b>	Application/Control No. 13/421,769	Applicant(s)/Patent Under Reexamination COMISKEY ET AL.	
	Examiner JIA-HAI LEE	Art Unit 1676	Page 1 of 1

**U.S. PATENT DOCUMENTS**

*	Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
	A US-			
	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**

*	Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	Classification
	N WO 2005/016244 A2	02-2005	US	Currie	A61K
	O				
	P				
	Q				
	R				
	S				
	T				

**NON-PATENT DOCUMENTS**

*	Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U Mhraryan et al. Moisture sorption by cellulose powders of varying crystallinity. Int J Pharm. 2004 Jan 28;269(2):433-42.
	V Lai et al. Solid-State Chemical Stability of Proteins and Peptides. J Pharm Sci. 1999 May;88(5):489-500. Review.
	W FMC biopolymer of Avice PH production instruction (2005).
	X

\*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.







ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

**Declarations under Rule 4.17:**

- *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)*
- *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)*

- *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)*
- *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)*

**Published:**

- *without international search report and to be republished upon receipt of that report*

*For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

## METHODS AND COMPOSITIONS FOR THE TREATMENT OF GASTROINTESTINAL DISORDERS

### TECHNICAL FIELD

This invention relates to methods and compositions for treating gastrointestinal disorders,  
5 obesity, congestive heart failure, benign prostatic hyperplasia and other disorders.

### BACKGROUND

Irritable bowel syndrome (IBS) is a common chronic disorder of the intestine that affects 20 to  
60 million individuals in the US alone (Lehman Brothers, Global Healthcare-Irritable Bowel  
10 Syndrome Industry Update, September 1999). IBS is the most common disorder diagnosed by  
gastroenterologists (28% of patients examined) and accounts for 12% of visits to primary care  
physicians (Camilleri 2001 *Gastroenterology* 120:652-668). In the US, the economic impact of  
IBS is estimated at \$25 billion annually, through direct costs of health care use and indirect costs  
of absenteeism from work (Talley 1995 *Gastroenterology* 109:1736-1741). Patients with IBS  
15 have three times more absenteeism from work and report a reduced quality of life. Sufferers may  
be unable or unwilling to attend social events, maintain employment, or travel even short  
distances (Drossman 1993 *Dig Dis Sci* 38:1569-1580). There is a tremendous unmet medical  
need in this population since few prescription options exist to treat IBS.

Patients with IBS suffer from abdominal pain and a disturbed bowel pattern. Three subgroups of  
20 IBS patients have been defined based on the predominant bowel habit: constipation-predominant  
(c-IBS), diarrhea-predominant (d-IBS) or alternating between the two (a-IBS). Estimates of  
individuals who suffer from c-IBS range from 20-50% of the IBS patients with 30% frequently  
cited. In contrast to the other two subgroups that have a similar gender ratio, c-IBS is more  
common in women (ratio of 3:1) (Talley et al. 1995 *Am J Epidemiol* 142:76-83).

25 The definition and diagnostic criteria for IBS have been formalized in the "Rome Criteria"  
(Drossman et al. 1999 *Gut* 45:Suppl II:1-81), which are well accepted in clinical practice.  
However, the complexity of symptoms has not been explained by anatomical abnormalities or

metabolic changes. This has led to the classification of IBS as a functional GI disorder, which is diagnosed on the basis of the Rome criteria and limited evaluation to exclude organic disease(Ringel et al. 2001 *Annu Rev Med* 52: 319-338). IBS is considered to be a “biopsychosocial” disorder resulting from a combination of three interacting mechanisms:

5 altered bowel motility, an increased sensitivity of the intestine or colon to pain stimuli (visceral sensitivity) and psychosocial factors (Camilleri 2001 *Gastroenterology* 120:652-668). Recently, there has been increasing evidence for a role of inflammation in the etiology of IBS. Reports indicate that subsets of IBS patients have small but significant increases in colonic inflammatory and mast cells, increased inducible nitric oxide (NO) and synthase (iNOS) and altered expression

10 of inflammatory cytokines (reviewed by Talley 2000, Medscape Coverage of DDW Week).

#### SUMMARY OF THE INVENTION

The present invention features compositions and related methods for treating IBS and other gastrointestinal disorders and conditions (e.g., gastrointestinal motility disorders, functional gastrointestinal disorders, gastroesophageal reflux disease (GERD), duodenogastric reflux,

15 Crohn’s disease, ulcerative colitis, inflammatory bowel disease, functional heartburn, dyspepsia (including functional dyspepsia or nonulcer dyspepsia), gastroparesis, chronic intestinal pseudo-obstruction (or colonic pseudoobstruction), and disorders and conditions associated with constipation, e.g., constipation associated with use of opiate pain killers, post-surgical constipation, and constipation associated with neuropathic disorders as well as other conditions

20 and disorders. The compositions feature peptides that activate the guanylate cyclase C (GC-C) receptor.

The present invention also features compositions and related methods for treating obesity, congestive heart failure and benign prostatic hyperplasia (BPH).

Without being bound by any particular theory, in the case of IBS and other gastrointestinal

25 disorders the peptides are useful because they can increase gastrointestinal motility.

Without being bound by any particular theory, in the case of IBS and other gastrointestinal disorders the peptides are useful, in part, because they can decrease inflammation.

Without being bound by any particular theory, in the case of IBS and other gastrointestinal disorders the peptides are also useful because they can decrease gastrointestinal pain or visceral pain.

The invention features pharmaceutical compositions comprising certain peptides that are capable of activating the guanylate-cyclase C (GC-C) receptor. Also within the invention are pharmaceutical compositions comprising a peptide of the invention as well as combination compositions comprising a peptide of the invention and one or more additional therapeutic agents, e.g., an agent for treating constipation (e.g., a chloride channel activator such as SPI-0211; Sucampo Pharmaceuticals, Inc.; Bethesda, MD, a laxative such as MiraLax; Braintree Laboratories, Braintree MA) or some other gastrointestinal disorder. Examples of additional therapeutic agents include: acid reducing agents such as proton pump inhibitors (e.g. omeprazole, esomeprazole, lansoprazole, pantorazole and rabeprazole), H2 receptor blockers (e.g., cimetidine, ranitidine, famotidine and nizatidine), pro-motility agents such as motilin agonists (e.g., GM-611 or mitemincinal fumarate), 5HT receptor agonists (e.g. 5HT4 receptor agonists such as Zelnorm<sup>®</sup>; 5HT3 receptor agonists such as MKC-733), 5HT receptor antagonists (e.g., 5HT1, 5HT2, 5HT3 (e.g., alosetron), 5HT4 receptor antagonists, muscarinic receptor agonists, anti-inflammatory agents, antispasmodics, antidepressants, centrally-acting analgesic agents such as opioid receptor agonists, opioid receptor antagonists (e.g., naltrexone), agents for the treatment of Inflammatory bowel disease, Crohn's disease and ulcerative colitis (e.g., Traficet-EN<sup>TM</sup> (ChemoCentryx, Inc.; San Carlos, CA)), agents that treat gastrointestinal or visceral pain, and cGMP phosphodiesterase inhibitors (e.g., motapizone, zaprinast, and suldinac sulfone). The peptides of the invention can also be used in combination with agents such as tianeptine (Stablon<sup>®</sup>) and other agents described in U.S. 6,683,072, (E)-4 (1,3bis(cyclohexylmethyl)-1,2,3,4,-tetrahydro-2,6-diono-9H-purin-8-yl)cinnamic acid nonaethylene glycol methyl ether ester and related compounds described in WO 02/067942. The peptides can also be used in combination with treatments entailing the administration of microorganisms useful in the treatment of gastrointestinal disorders such as IBS. Probactrix<sup>®</sup>

(The BioBalance Corporation; New York, NY) is one example of a formulation that contains microorganisms useful in the treatment of gastrointestinal disorders. The peptides can also be used in combination with purgatives that draw fluids to the intestine (e.g., Visicol<sup>®</sup>, a combination of sodium phosphate monobasic monohydrate and sodium phosphate dibasic anhydrate).

In addition, the pharmaceutical compositions can include one or more agents selected from the group consisting of: Ca channel blockers (e.g., ziconotide), complete or partial 5HT receptor antagonists (for example 5HT3 (e.g., alosetron, ATI-7000; Aryx Therapeutics, Santa Clara CA), 5HT4, 5HT2, and 5HT1 receptor antagonists), complete or partial 5HT receptor agonists including 5HT3, 5HT2, 5HT4 (e.g., tegaserod, mosapride and renzapride), 5HT1 receptor agonists, CRF receptor agonists (NBI-34041),  $\beta$ -3 adrenoreceptor agonists, opioid receptor agonists (e.g., loperamide, fedotozine, and fentanyl, naloxone, naltrexone, methyl naloxone, nalmeferne, cypridime, beta funaltrexamine, naloxonazine, naltrindole, and nor-binaltorphimine, morphine, diphenyloxylate, enkephalin pentapeptide, asimadoline, and trimebutine), NK1 receptor antagonists (e.g., ezlopitant and SR-14033), CCK receptor agonists (e.g., loxiglumide), NK1 receptor antagonists, NK3 receptor antagonists (e.g., talnetant, osanetant (SR-142801), SSR-241586), norepinephrine-serotonin reuptake inhibitors (NSRI; e.g., milnacipran), vanilloid and cannabinoid receptor agonists (e.g., arvanil), sialorphan, sialorphan-related peptides comprising the amino acid sequence QHNPR (SEQ ID NO: ) for example, VQHNPR (SEQ ID NO: ); VRQHNPR (SEQ ID NO: ); VRGQHNPR (SEQ ID NO: ); VRGPQHNPR (SEQ ID NO: ); VRGPRQHNPR (SEQ ID NO: ); VRGPRRQHNPR (SEQ ID NO: ); and RQHNPR (SEQ ID NO: ), compounds or peptides that are inhibitors of neprilysin, frakefamide (H-Tyr-D-Ala-Phe(F)-Phe-NH<sub>2</sub>; WO 01/019849 A1), loperamide, Tyr-Arg (kyotorphin), CCK receptor agonists (caerulein), conotoxin peptides, peptide analogs of thymulin, loxiglumide, dexloxiglumide (the R-isomer of loxiglumide) (WO 88/05774). These peptides and compounds can be administered with the peptides of the invention (simultaneously or sequentially). They can also be covalently linked to a peptide of the invention to create therapeutic conjugates.

The invention includes methods for treating various gastrointestinal disorders by administering a peptide that acts as a partial or complete agonist of the GC-C receptor. The peptide contains up to four cysteines that form one or two disulfide bonds. In certain embodiments the disulfide bonds are replaced by other covalent cross-links and in some cases the cysteines are substituted  
5 by other residues to provide for alternative covalent cross-links. The peptides may also include at least one trypsin or chymotrypsin cleavage site and/or a carboxy-terminal analgesic peptide or small molecule, e.g., AspPhe or some other analgesic peptide. When present within the peptide, the analgesic peptide or small molecule may be preceded by a chymotrypsin or trypsin cleavage site that allows release of the analgesic peptide or small molecule. The peptides and methods of  
10 the invention are also useful for treating pain and inflammation associated with various disorders, including gastrointestinal disorders. Certain peptides include a functional chymotrypsin or trypsin cleavage site located so as to allow inactivation of the peptide upon cleavage. Certain peptides having a functional cleavage site undergo cleavage and gradual inactivation in the digestive tract, and this is desirable in some circumstances. In certain  
15 peptides, a functional chymotrypsin site is altered, increasing the stability of the peptide *in vivo* (e.g., guanylin).

The invention includes methods for treating other disorders such as congestive heart failure and benign prostatic hyperplasia by administering a peptide or small molecule (parenterally or orally)  
20 that acts as an agonist of the GC-C receptor. Such agents can be used in combination with natriuretic peptides (e.g., atrial natriuretic peptide, brain natriuretic peptide or C-type natriuretic peptide), a diuretic, or an inhibitor of angiotensin converting enzyme.

The invention features methods and compositions for increasing intestinal motility. Intestinal motility involves spontaneous coordinated distentions and contractions of the stomach,  
25 intestines, colon and rectum to move food through the gastrointestinal tract during the digestive process.

The peptide can contain additional carboxy terminal or amino terminal amino acids or both. For example, the peptide can include an amino terminal sequence that facilitates recombinant production of the peptide and is cleaved prior to administration of the peptide to a patient. The

peptide can also include other amino terminal or carboxy terminal amino acids. In some cases the additional amino acids protect the peptide, stabilize the peptide or alter the activity of the peptide. In some cases some or all of these additional amino acids are removed prior to administration of the peptide to a patient. The peptide can include 1, 2, 3, 4, 5, 10, 15, 20, 25,  
 5 30, 40, 50, 60, 70 80, 90, 100 or more amino acids at its amino terminus or carboxy terminus or both. The number of flanking amino acids need not be the same. For example, there can be 10 additional amino acids at the amino terminus of the peptide and none at the carboxy terminus.

In certain embodiments the peptides include either one or two or more contiguous negatively charged amino acids (e.g., Asp or Glu) or one or two or more contiguous positively charged residues (e.g., Lys or Arg) or one or two or more contiguous positively or negatively charged amino acids at the carboxy terminus. In these embodiments all of the flanking amino acids at the carboxy terminus are either positively or negatively charged. In other embodiments the carboxy terminal charged amino acids are preceded by a Leu. For example, the following amino acid sequences can be added to the carboxy terminus of the peptide: Asp; Asp Lys; Lys Lys Lys Lys  
 10 Lys Lys; Asp Lys Lys Lys Lys Lys Lys; Leu Lys Lys; and Leu Asp. It is also possible to simply add Leu at the carboxy terminus.

In a first aspect, the invention features a polypeptide comprising, consisting of, or consisting essentially of the amino acid sequence: Xaa<sub>1</sub> Xaa<sub>2</sub> Xaa<sub>3</sub> Cys<sub>4</sub> Xaa<sub>5</sub> Xaa<sub>6</sub> Xaa<sub>7</sub> Xaa<sub>8</sub> Xaa<sub>9</sub> Xaa<sub>10</sub>  
 Xaa<sub>11</sub> Cys<sub>12</sub> Xaa<sub>13</sub> Xaa<sub>14</sub> Xaa<sub>15</sub> Xaa<sub>16</sub> (SEQ ID NO:1) wherein:

20 Xaa<sub>1</sub> is Ser, Asn, Tyr, Ala, Gln, Pro, Lys, Gly, or Thr, or is missing;

Xaa<sub>2</sub> is His, Asp, Glu, Ala, Ser, Asn, Gly, or is missing;

Xaa<sub>3</sub> is Thr, Asp, Ser, Glu, Pro, Val or Leu;

Xaa<sub>5</sub> is Asp, Ile or Glu;

Xaa<sub>6</sub> is Ile, Trp or Leu;

25 Xaa<sub>7</sub> is Cys, Ser, or Tyr;

Xaa<sub>8</sub> is Ala, Val, Thr, Ile, Met or is missing;

Xaa<sub>9</sub> is a) any amino acid, b) Phe, Tyr, Asn, Trp, c) an amino acid other than Phe, Trp, or Tyr, d) non-aromatic amino acid or e) is missing;

Xaa<sub>10</sub> is Ala, Val, Met, Thr or Ile;

Xaa<sub>11</sub> is Ala or Val;

Xaa<sub>13</sub> is Ala or Thr;

Xaa<sub>14</sub> is Gly, Ala or Ser;

Xaa<sub>15</sub> is Cys, Tyr or is missing; and

5 Xaa<sub>16</sub> is: a) Trp, Tyr or Phe to create a chymotrypsin cleavage site; b) Lys or Arg to create a trypsin cleavage site; c) is missing or d) His or Leu or Ser.

In some embodiments, Xaa<sub>1</sub> is preceded by Lys or Tyr.

In certain embodiments, a Cys is replaced by any amino acid other than Cys. Certain such polypeptides will have fewer disulfide bonds.

10 In a related aspect the invention features a composition comprising a polypeptide comprising, consisting of, or consisting essentially of the amino acid sequence: Xaa<sub>1</sub> Xaa<sub>2</sub> Xaa<sub>3</sub> Cys<sub>4</sub> Xaa<sub>5</sub> Xaa<sub>6</sub> Xaa<sub>7</sub> Xaa<sub>8</sub> Xaa<sub>9</sub> Xaa<sub>10</sub> Xaa<sub>11</sub> Cys<sub>12</sub> Xaa<sub>13</sub> Xaa<sub>14</sub> Xaa<sub>15</sub> Xaa<sub>16</sub> (SEQ ID NO:1) wherein: Xaa<sub>1</sub> is Ser, Asn, Tyr, Ala, Gln, Pro, Lys, Gly, or Thr, or is missing; Xaa<sub>2</sub> is His, Asp, Glu, Ala, Ser, Asn, Gly, Pro or is missing; Xaa<sub>3</sub> is Thr, Asp, Ser, Glu, Pro, Val or Leu; Xaa<sub>5</sub> is Asp, Ile or Glu;

15 Xaa<sub>6</sub> is Ile, Trp or Leu; Xaa<sub>7</sub> is Cys, Ser, or Tyr; Xaa<sub>8</sub> is Ala, Val, Thr, Ile, Met or is missing; Xaa<sub>9</sub> is Phe, Tyr, Asn, Trp, an amino acid other than Phe, Trp, or Tyr, is a non-aromatic amino acid or is missing; Xaa<sub>10</sub> is Ala, Val, Met, Thr or Ile; Xaa<sub>11</sub> is Ala or Val; Xaa<sub>13</sub> is Ala or Thr; Xaa<sub>14</sub> is Gly, Ala or Ser; Xaa<sub>15</sub> is Cys, Tyr or is missing; and Xaa<sub>16</sub> is: a) Trp, Tyr or Phe to create a chymotrypsin cleavage site; b) Lys or Arg to create a trypsin cleavage site; c) is missing or d) His

20 or Leu or Ser and a pharmaceutically acceptable carrier. In related aspects, the invention features a pharmaceutically acceptable tablet, pill, capsule comprising the peptide.

In a related aspect, the invention features a polypeptide comprising, consisting of, or consisting essentially of the amino acid sequence: Xaa<sub>1</sub> Xaa<sub>2</sub> Xaa<sub>3</sub> Cys<sub>4</sub> Xaa<sub>5</sub> Xaa<sub>6</sub> Xaa<sub>7</sub> Xaa<sub>8</sub> Xaa<sub>9</sub> Xaa<sub>10</sub>

25 Xaa<sub>11</sub> Cys<sub>12</sub> Xaa<sub>13</sub> Xaa<sub>14</sub> Xaa<sub>15</sub> Xaa<sub>16</sub> (SEQ ID NO:1) wherein:

Xaa<sub>1</sub> is Asn, any amino acid or is missing;

Xaa<sub>2</sub> is Asp, Glu, any amino acid or is missing;

Xaa<sub>3</sub> is Asp or Glu;



Xaa<sub>5</sub> is any amino acid or Glu;

Xaa<sub>6</sub> is any amino acid or Leu;

Xaa<sub>7</sub> is Cys;

Xaa<sub>8</sub> is any amino acid or Val;

5 Xaa<sub>9</sub> is Asn, Gln, Tyr;

Xaa<sub>10</sub> is any amino acid or Val;

Xaa<sub>11</sub> is any amino acid or Ala;

Xaa<sub>13</sub> is any amino acid or Thr;

Xaa<sub>14</sub> is any amino acid or Gly;

10 Xaa<sub>15</sub> is Cys;

Xaa<sub>16</sub> is any amino acid, Leu or missing

In a related aspect, the invention features a polypeptide comprising, consisting of, or consisting essentially of the amino acid sequence: Asn<sub>1</sub> Xaa<sub>2</sub> Xaa<sub>3</sub> Xaa<sub>4</sub> Glu<sub>5</sub> Leu<sub>6</sub> Xaa<sub>7</sub> Val<sub>8</sub> Asn<sub>9</sub> Xaa<sub>10</sub> Xaa<sub>11</sub> Xaa<sub>12</sub> Thr<sub>13</sub> Xaa<sub>14</sub> Xaa<sub>15</sub> Leu<sub>16</sub> (SEQ ID NO: \_\_)

15 Xaa<sub>2</sub> is Asp or Glu;

Xaa<sub>3</sub> is Asp or Glu;

Xaa<sub>4</sub> is Cys or Mpt (mercaptoproline) or Pen (penicillamine) or Dpr (diaminopropionic acid) or Asp or Glu;

20 Xaa<sub>7</sub> is Cys or Mpt (mercaptoproline) or Pen (penicillamine) or Dpr (diaminopropionic acid) or Asp or Glu;

Xaa<sub>10</sub> is Val or Pro;

Xaa<sub>11</sub> is Ala or Aib (alpha-aminoisobutyric acid);

Xaa<sub>12</sub> is Cys or Mpt (mercaptoproline) or Pen (penicillamine) or Dpr (diaminopropionic acid) or Asp or Glu;

25 Xaa<sub>14</sub> is Gly or Ala;

Xaa<sub>15</sub> is Cys or Mpt (mercaptoproline) or Pen (penicillamine) or Dpr (diaminopropionic acid) or Asp or Glu; and

30 In certain embodiments, where Xaa<sub>15</sub> is other than Cys or is missing, Xaa<sub>7</sub> is Ser or an amino acid other than Cys.

In certain embodiments 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 of Xaa<sub>1</sub>, Xaa<sub>2</sub>, Xaa<sub>3</sub>, Xaa<sub>5</sub>, Xaa<sub>6</sub>, Xaa<sub>7</sub>, Xaa<sub>8</sub>, Xaa<sub>9</sub>, Xaa<sub>10</sub>, Xaa<sub>11</sub>, Xaa<sub>13</sub>, Xaa<sub>14</sub>, and Xaa<sub>16</sub> are any amino acid other than Cys.

In certain embodiments, Xaa<sub>9</sub> is any amino acid other than Gln. In other embodiments where Xaa<sub>2</sub> and Xaa<sub>3</sub> are Glu, Xaa<sub>9</sub> is any amino acid other than Gln.

- 5 In certain embodiments Xaa<sub>1</sub> and Xaa<sub>2</sub> are missing; Xaa<sub>3</sub> is Thr; Xaa<sub>5</sub> is Glu; Xaa<sub>6</sub> is Ile or Leu; Xaa<sub>8</sub> is Ala, Val, or Ile; Xaa<sub>9</sub> is Phe or Tyr; Xaa<sub>10</sub> is Ala or Val; Xaa<sub>11</sub> is Ala; Xaa<sub>13</sub> is Ala or Thr; Xaa<sub>14</sub> is Gly; and Xaa<sub>16</sub> is Trp, Tyr, Phe, Lys, Arg or is missing.

In certain embodiments the polypeptide comprising, consisting of, or consisting essentially of the amino acid sequence: Xaa<sub>1</sub> Xaa<sub>2</sub> Xaa<sub>3</sub> Cys<sub>4</sub> Xaa<sub>5</sub> Xaa<sub>6</sub> Xaa<sub>7</sub> Xaa<sub>8</sub> Xaa<sub>9</sub> Xaa<sub>10</sub> Xaa<sub>11</sub> Cys<sub>12</sub> Xaa<sub>13</sub>  
 10 Xaa<sub>14</sub> Xaa<sub>15</sub> Xaa<sub>16</sub> (SEQ ID NO:1) is not cleaved after Xaa<sub>9</sub> by chymotrypsin. In these embodiments wherein:

Xaa<sub>1</sub> is Ser, Asn, Tyr, Ala, Gln, Pro, Lys, Gly, or Thr, or is missing;

Xaa<sub>2</sub> is His, Asp, Glu, Ala, Ser, Asn, or Gly, or is missing;

Xaa<sub>3</sub> is Thr, Asp, Ser, Glu, Pro, Val or Leu or is missing;

15 Xaa<sub>5</sub> is Asp, Ile or Glu;

Xaa<sub>6</sub> is Ile, Trp or Leu;

Xaa<sub>7</sub> is Cys, Ser, or Tyr;

Xaa<sub>8</sub> is Ala, Val, Thr, Ile, Met or is missing;

Xaa<sub>9</sub> is either: a) any amino acid other than Phe and Tyr, b) any amino acid other than  
 20 Phe, Tyr, and Trp, c) any amino acid other than Phe, Tyr, Trp, Ile, Leu and Val; d) any amino acid other than Phe, Tyr, Trp, Ile, Leu, Val, and His; d) any non-aromatic amino acid or e) is missing;

Xaa<sub>10</sub> is Ala, Val, Met, Thr or Ile;

Xaa<sub>11</sub> is Ala or Val;

Xaa<sub>13</sub> is Ala or Thr;

25 Xaa<sub>14</sub> is Gly, Ala or Ser;

Xaa<sub>15</sub> is Cys, Tyr or is missing; and

Xaa<sub>16</sub> is: a) Trp, Tyr or Phe to create a chymotrypsin cleavage site; b) Lys or Arg to create a trypsin cleavage site; c) is missing or d) His or Leu or Ser.

In addition, the invention features variants of Xaa<sub>1</sub> Xaa<sub>2</sub> Xaa<sub>3</sub> Cys<sub>4</sub> Xaa<sub>5</sub> Xaa<sub>6</sub> Xaa<sub>7</sub> Xaa<sub>8</sub> Xaa<sub>9</sub> Xaa<sub>10</sub> Xaa<sub>11</sub> Cys<sub>12</sub> Xaa<sub>13</sub> Xaa<sub>14</sub> Xaa<sub>15</sub> Xaa<sub>16</sub> (SEQ ID NO:1) that is not cleaved after Xaa<sub>9</sub> by chymotrypsin due to the addition of an amino terminal lysine. An example of such a molecule is a human guanylin variant having an amino terminal lysine: KPGTCEICAYAACTGC (SEQ ID  
 5 NO: ).

In certain embodiments of the peptide comprising, consisting of, or consisting essentially of the amino acid sequence: Xaa<sub>1</sub> Xaa<sub>2</sub> Xaa<sub>3</sub> Cys<sub>4</sub> Xaa<sub>5</sub> Xaa<sub>6</sub> Xaa<sub>7</sub> Xaa<sub>8</sub> Xaa<sub>9</sub> Xaa<sub>10</sub> Xaa<sub>11</sub> Cys<sub>12</sub> Xaa<sub>13</sub> Xaa<sub>14</sub> Xaa<sub>15</sub> Xaa<sub>16</sub> (SEQ ID NO:1) that is not cleaved after Xaa<sub>9</sub> by chymotrypsin, Xaa<sub>7</sub> and Xaa<sub>15</sub> are both Cys.

10 Also within the invention are variants of PGTCEICAYAACTGC (human guanylin) (SEQ ID NO: ) wherein Y is substituted by any amino acid other than a) Phe; b) any amino acid other than Phe and Trp; c) any amino acid other than Phe, Trp, Ile, Leu and Val; d) any amino acid other than Phe, Trp, Ile, Leu, Val and His; e) any non-aromatic amino acid or f) is missing.

15 In certain embodiments the polypeptide comprising, consisting of, or consisting essentially of the amino acid sequence: Xaa<sub>1</sub> Xaa<sub>2</sub> Xaa<sub>3</sub> Cys<sub>4</sub> Xaa<sub>5</sub> Xaa<sub>6</sub> Xaa<sub>7</sub> Xaa<sub>8</sub> Xaa<sub>9</sub> Xaa<sub>10</sub> Xaa<sub>11</sub> Cys<sub>12</sub> Xaa<sub>13</sub> Xaa<sub>14</sub> Xaa<sub>15</sub> Xaa<sub>16</sub> (SEQ ID NO:1) is not cleaved after Xaa<sub>9</sub> by either chymotrypsin or trypsin.

In these embodiments wherein:

Xaa<sub>1</sub> is Ser, Asn, Tyr, Ala, Gln, Pro, Lys, Gly, or Thr, or is missing;

20 Xaa<sub>2</sub> is His, Asp, Glu, Ala, Ser, Asn, or Gly, or is missing;

Xaa<sub>3</sub> is Thr, Asp, Ser, Glu, Pro, Val or Leu or is missing;

Xaa<sub>5</sub> is Asp, Ile or Glu;

Xaa<sub>6</sub> is Ile, Trp or Leu;

Xaa<sub>7</sub> is Cys, Ser, or Tyr;

25 Xaa<sub>8</sub> is Ala, Val, Thr, Ile, Met or is missing;

Xaa<sub>9</sub> is either: a) any amino acid other than Lys, Arg, Phe and Tyr, b) any amino acid other than Lys, Arg, Phe, Tyr, and Trp, c) any amino acid other than Lys, Arg, Phe, Tyr, Trp, Ile, Leu and Val; d) any amino acid other than Lys, Arg, Phe, Tyr, Trp, Ile, Leu, Val, and His; or e) is missing;

Xaa<sub>10</sub> is Ala, Val, Met, Thr or Ile;

Xaa<sub>11</sub> is Ala or Val;

Xaa<sub>13</sub> is Ala or Thr;

Xaa<sub>14</sub> is Gly, Ala or Ser;

5 Xaa<sub>15</sub> is Cys, Tyr or is missing; and

Xaa<sub>16</sub> is: a) Trp, Tyr or Phe to create a chymotrypsin cleavage site; b) Lys or Arg to create a trypsin cleavage site; c) is missing or d) His or Leu or Ser.

In certain embodiments of the peptide comprising, consisting of, or consisting essentially of the amino acid sequence: Xaa<sub>1</sub> Xaa<sub>2</sub> Xaa<sub>3</sub> Cys<sub>4</sub> Xaa<sub>5</sub> Xaa<sub>6</sub> Xaa<sub>7</sub> Xaa<sub>8</sub> Xaa<sub>9</sub> Xaa<sub>10</sub> Xaa<sub>11</sub> Cys<sub>12</sub> Xaa<sub>13</sub>  
 10 Xaa<sub>14</sub> Xaa<sub>15</sub> Xaa<sub>16</sub> (SEQ ID NO:1) that is not cleaved after Xaa<sub>9</sub> by chymotrypsin or trypsin, Xaa<sub>7</sub> and Xaa<sub>15</sub> are both Cys.

Useful variants of PGTCEICAYAACTGC (human guanylin) (SEQ ID NO: ) that should not be cleaved by chymotrypsin include:

PGTCEICASAACTGC (SEQ ID NO: )

15 PGTCEICATAACTGC (SEQ ID NO: )

PGTCEICANAACTGC (SEQ ID NO: )

PGTCEICAQAACTGC (SEQ ID NO: )

PGTCEICARAACTGC (SEQ ID NO: )

PGTCEICAEAACTGC (SEQ ID NO: )

20 PGTCEICADAACTGC (SEQ ID NO: )

PGTCEICAGAACTGC (SEQ ID NO: )

PGTCEICAAAACTGC (SEQ ID NO: )

PGTCEICAMAACTGC (SEQ ID NO: ).

25 Additional variants which are not likely to be cleaved by chymotrypsin under certain conditions include:

PGTCEICAIAACTGC (SEQ ID NO: )

PGTCEICALAACTGC (SEQ ID NO: )

PGTCEICAVAACTGC (SEQ ID NO: )

PGTCEICAHAACTGC (SEQ ID NO: )

The invention also features deletion variants of any of the peptides described herein in which one, two, three or four amino acids, other than a Cys, are deleted. Where two (or more) amino acids are deleted and the peptide comprises the sequence: Cys<sub>a</sub> Xaa Xaa Cys<sub>b</sub> Xaa Xaa Xaa Xaa Cys<sub>c</sub> Xaa Xaa Cys<sub>d</sub>, in some embodiments two or more deletions can be located between Cys<sub>a</sub> and Cys<sub>b</sub> or between Cys<sub>b</sub> and Cys<sub>c</sub> or between Cys<sub>c</sub> and Cys<sub>d</sub>. Thus, there can be two or more deletions between two Cys. However, in other embodiments there is at most one deletion between each Cys, i.e., there is no more than one deletion between each of Cys<sub>a</sub> and Cys<sub>b</sub>, Cys<sub>b</sub> and Cys<sub>c</sub>, and Cys<sub>c</sub> and Cys<sub>d</sub>. Thus, the invention includes any of the peptides described herein comprising the sequence Cys<sub>a</sub> Xaa Xaa Cys<sub>b</sub> Xaa Xaa Xaa Xaa Cys<sub>c</sub> Xaa Xaa Cys<sub>d</sub> wherein: a) one amino acid between Cys<sub>a</sub> and Cys<sub>b</sub> is deleted; b) one amino acid between Cys<sub>b</sub> and Cys<sub>c</sub> is deleted; c) one amino acid between Cys<sub>c</sub> and Cys<sub>d</sub> is deleted; d) one amino acid between Cys<sub>a</sub> and Cys<sub>b</sub> is deleted and one amino acid between Cys<sub>b</sub> and Cys<sub>c</sub> is deleted; e) one amino acid between Cys<sub>a</sub> and Cys<sub>b</sub> is deleted and one amino acid between Cys<sub>c</sub> and Cys<sub>d</sub> is deleted; f) one amino acid between Cys<sub>b</sub> and Cys<sub>c</sub> is deleted and one amino acid between Cys<sub>c</sub> and Cys<sub>d</sub> is deleted; or g) one amino acid between Cys<sub>a</sub> and Cys<sub>b</sub> is deleted, one amino acid between Cys<sub>b</sub> and Cys<sub>c</sub> is deleted, and one amino acid between Cys<sub>c</sub> and Cys<sub>d</sub> is deleted. In addition, one or more amino acids preceding Cys<sub>a</sub> and/or one or more amino acids following Cys<sub>d</sub> can be deleted. The various deletion variants are peptides that bind to and/or activate the GC-C receptor.

The invention also features deletion variants of any of the peptides described herein in which one, two, three or four amino acids (or non-natural amino acids or natural or non-natural amino acid analogs), other than a Cys (or an amino acid substituted for Cys, e.g., an amino acid capable of forming a covalent bond to another amino acid) is deleted. Thus, additional variants include those in which a Cys is substituted by an amino acid capable of forming a covalent linkage with another amino acid (e.g., a Cys or a substitute therefore). Such amino acids include: Mpt (mercaptoproline) or Pen (penicillamine) or Dpr (diaminopropionic acid).

FIG. 1 includes deletion variants of human guanylin in which one, two, three or four amino acids are deleted. The deleted amino acids are between Cys<sub>a</sub> and Cys<sub>d</sub> as well as amino terminal to Cys<sub>a</sub>.

The invention also features insertion variants of any of the peptides described herein in which  
5 one, two, three or four amino acids are inserted.

Where two (or more) amino acids are inserted and the peptide comprises the sequence: Cys<sub>a</sub> Xaa Xaa Cys<sub>b</sub> Xaa Xaa Xaa Xaa Cys<sub>c</sub> Xaa Xaa Cys<sub>d</sub>, in some embodiments two or more insertions can be located between Cys<sub>a</sub> and Cys<sub>b</sub> or between Cys<sub>b</sub> and Cys<sub>c</sub> or between Cys<sub>c</sub> and Cys<sub>d</sub>.

10 However, in other embodiments there is at most one insertion between each of Cys<sub>a</sub> and Cys<sub>b</sub> or between Cys<sub>b</sub> and Cys<sub>c</sub> or between Cys<sub>c</sub> and Cys<sub>d</sub>. Thus, the invention includes any of the peptides described herein comprising the sequence Cys<sub>a</sub> Xaa Xaa Cys<sub>b</sub> Xaa Xaa Xaa Xaa Cys<sub>c</sub> Xaa Xaa Cys<sub>d</sub> wherein: a) one amino acid is inserted between Cys<sub>a</sub> and Cys<sub>b</sub>; b) one amino acid is inserted between Cys<sub>b</sub> and Cys<sub>c</sub>; c) one amino acid is inserted between Cys<sub>c</sub> and Cys<sub>d</sub>; d) one  
15 amino acid is inserted between Cys<sub>a</sub> and Cys<sub>b</sub> and one amino acid is inserted between Cys<sub>b</sub> and Cys<sub>c</sub>; e) one amino acid is inserted between Cys<sub>a</sub> and Cys<sub>b</sub> and one amino acid is inserted between Cys<sub>c</sub> and Cys<sub>d</sub>; f) one amino acid is inserted between Cys<sub>b</sub> and Cys<sub>c</sub> and one amino acid is inserted between Cys<sub>c</sub> and Cys<sub>d</sub> or g) one amino acid is inserted between Cys<sub>a</sub> and Cys<sub>b</sub>, one amino acid is inserted between Cys<sub>b</sub> and Cys<sub>c</sub>, and one amino acid is inserted between Cys<sub>c</sub> and  
20 Cys<sub>d</sub>. In addition, one or more amino acids can be inserted preceding Cys<sub>a</sub> and/or one or more amino acids can be inserted following Cys<sub>d</sub>. The insertions can be any natural or non-natural occurring amino acid (e.g., Gly or Ala) or amino acid analog and where there are more than one insertions present, they can be the same or different. The various deletion variants are peptides that bind to and/or activate the GC-C receptor.

25

For example, the invention includes the following insertion variants of PGTCGEICAYAACTGC (human guanylin) (SEQ ID NO: ) include:

PGTCEGICAYAACTGC (SEQ ID NO: )

30 PGTCEIGCAYAACTGC (SEQ ID NO: )

PGTCEICGAYAACTGC (SEQ ID NO: )  
 PGTCEICAGYAACTGC (SEQ ID NO: )  
 PGTCEICAYGAACTGC (SEQ ID NO: )  
 PGTCEICAYAGACTGC (SEQ ID NO: )  
 5 PGTCEICAYAAGCTGC (SEQ ID NO: )  
 PGTCEICAYAACGTGC (SEQ ID NO: )  
 PGTCEICAYAAGTGC (SEQ ID NO: )  
 PGTCAEICAYAACTGC (SEQ ID NO: )  
 PGTCEAICAYAACTGC (SEQ ID NO: )  
 10 PGTCEIACAYAACTGC (SEQ ID NO: )  
 PGTCEICAAYAAGTGC (SEQ ID NO: )  
 PGTCEICAYAACTGC (SEQ ID NO: )  
 PGTCEICAYAACTGC (SEQ ID NO: )  
 PGTCEICAYAACTGC (SEQ ID NO: )  
 15 PGTCEICAYAACTGAC (SEQ ID NO: )  
 PGTCAEICAAYAAGTGC (SEQ ID NO: )  
 PGTCEAICAAYAAGTGC (SEQ ID NO: )  
 PGTCEIACAAYAAGTGC (SEQ ID NO: )

20 Other insertion variants of human guanylin can have up to four amino acids (i.e., 0, 1, 2, 3 or 4 natural or non-natural amino acids) inserted after each of the 15 amino acids in human guanylin. Thus, the invention includes peptides having the sequence: Pro Xaa<sub>(0-4)</sub> Gly Xaa<sub>(0-4)</sub> Thr Xaa<sub>(0-4)</sub> Cys Xaa<sub>(0-4)</sub> Glu Xaa<sub>(0-4)</sub> Ile Xaa<sub>(0-4)</sub> Cys Xaa<sub>(0-4)</sub> Ala Xaa<sub>(0-4)</sub> Tyr Xaa<sub>(0-4)</sub> Ala Xaa<sub>(0-4)</sub> Ala Xaa<sub>(0-4)</sub> Cys Xaa<sub>(0-4)</sub> Thr Xaa<sub>(0-4)</sub> Gly Xaa<sub>(0-4)</sub> Cys Xaa<sub>(0-4)</sub> (SEQ ID NO: ). The inserted amino acids can  
 25 be any amino acid and can be the same or different. In certain embodiments the inserted amino acids are all Gly or all Ala or a combination of Gly and Ala.

FIG. 2 depicts insertion variants of human guanylin in which one, two, three or four amino acids are inserted. The inserted amino acids are between Cys<sub>a</sub> and Cys<sub>d</sub> as well as amino terminal to  
 30 Cys<sub>a</sub> and carboxy terminal to Cys<sub>d</sub>.

The invention also features variants of peptides having the sequence Xaa<sub>1</sub> Xaa<sub>2</sub> Xaa<sub>3</sub> Cys<sub>4</sub> Xaa<sub>5</sub> Xaa<sub>6</sub> Xaa<sub>7</sub> Xaa<sub>8</sub> Xaa<sub>9</sub> Xaa<sub>10</sub> Xaa<sub>11</sub> Cys<sub>12</sub> Xaa<sub>13</sub> Xaa<sub>14</sub> Xaa<sub>15</sub> Xaa<sub>16</sub> (SEQ ID NO:1), e.g., variants of PGTCEICAYAACTGC human guanylin (SEQ ID NO: ) in which up to four amino acids are  
5 deleted and/or up to four amino acids are inserted. The insertions and deletions can be between Cys<sub>4</sub> and Cys<sub>12</sub> in SEQ ID NO:1 or they can be amino terminal to Cys<sub>4</sub> and/or carboxy terminal to Cys<sub>12</sub> in SEQ ID NO:1

When Xaa<sub>16</sub> is Trp, Tyr or Phe, the peptide has a chymotrypsin cleavage site that is located at a position where cleavage will liberate the portion of the peptide carboxy-terminal to Xaa<sub>16</sub>. When  
10 Xaa<sub>16</sub> is Lys or Arg, the peptide has a trypsin cleavage site that is located at a position where cleavage will liberate portion of the peptide carboxy-terminal to Xaa<sub>16</sub>. Thus, if the peptide includes an analgesic peptide carboxy-terminal to Xaa<sub>16</sub>, the peptide will be liberated in the digestive tract upon exposure to the appropriate protease. Among the analgesic peptides which can be included in the peptide are: AspPhe, endomorphin-1, endomorphin-2, nocistatin, dalargin,  
15 lupron, and substance P and other analgesic peptides described herein.

When Xaa<sub>1</sub> or the amino-terminal amino acid of the peptide of the invention (e.g., Xaa<sub>2</sub> or Xaa<sub>3</sub>) is Trp, Tyr or Phe, the peptide has a chymotrypsin cleavage site that is located at a position where cleavage will liberate the portion of the peptide amino-terminal to Xaa<sub>1</sub> (or Xaa<sub>2</sub> or Xaa<sub>3</sub>) along  
20 with Xaa<sub>1</sub>, Xaa<sub>2</sub> or Xaa<sub>3</sub>. When Xaa<sub>1</sub> or the amino-terminal amino acid of the peptide of the invention (e.g., Xaa<sub>2</sub> or Xaa<sub>3</sub>) is Lys or Arg, the peptide has a trypsin cleavage site that is located at a position where cleavage will liberate portion of the peptide amino-terminal to Xaa<sub>1</sub> along with Xaa<sub>1</sub>, Xaa<sub>2</sub> or Xaa<sub>3</sub>). Thus, for example, if the peptide includes an analgesic peptide amino-terminal to Xaa<sub>1</sub>, the peptide will be liberated in the digestive tract upon exposure to the appropriate protease. Among the analgesic peptides which can be included in the peptide are:  
25 AspPhe, endomorphin-1, endomorphin-2, nocistatin, dalargin, lupron, and substance p and other analgesic peptides described herein.

The peptides can linked, e.g., covalently linked to any of a variety of other analgesic peptides or analgesic compounds. Thus, a peptide described herein can be linked to a second therapeutic



agent, e.g., an agent for treating constipation (e.g., a chloride channel activator such as SPI-0211; Sucampo Pharmaceuticals, Inc.; Bethesda, MD, a laxative such as MiraLax; Braintree Laboratories, Braintree MA) or some other gastrointestinal disorder. Examples of a second therapeutic agent include: acid reducing agents such as proton pump inhibitors (e.g., omeprazole, esomeprazole, lansoprazole, pantoprazole and rabeprazole), H<sub>2</sub> receptor blockers (e.g., cimetidine, ranitidine, famotidine and nizatidine), pro-motility agents such as motilin agonists (e.g., GM-611 or mitemincinal fumarate), 5HT receptor agonists (e.g., 5HT<sub>4</sub> receptor agonists such as Zelnorm<sup>®</sup>; 5HT<sub>3</sub> receptor agonists such as MKC-733), 5HT receptor antagonists (e.g., 5HT<sub>1</sub>, 5HT<sub>2</sub>, 5HT<sub>3</sub> (e.g., alosetron), 5HT<sub>4</sub> receptor antagonists, muscarinic receptor agonists, anti-inflammatory agents, antispasmodics, antidepressants, centrally-acting analgesic agents such as opioid receptor agonists, opioid receptor antagonists (e.g., naltrexone), agents for the treatment of Inflammatory bowel disease, Crohn's disease and ulcerative colitis (e.g., Traficet-EN<sup>™</sup> (ChemoCentryx, Inc.; San Carlos, CA), agents that treat gastrointestinal or visceral pain, and cGMP phosphodiesterase inhibitors (motapizone, zaprinast, and suldinac sulfone). The peptides of the invention can also be linked to agents such a tianeptine (Stablon<sup>®</sup>) and other agents described in U.S. 6,683,072; (E)-4 (1,3bis(cyclohexylmethyl)-1,2,3,4,-tetrahydro-2,6-diono-9H-purin-8-yl)cinnamic acid nonaethylene glycol methyl ether ester and related compounds described in WO 02/067942. The peptides can be linked to an agent selected from the group consisting of: Ca channel blockers (e.g., ziconotide), complete or partial 5HT receptor antagonists (for example 5HT<sub>3</sub> (e.g., alosetron, ATI-7000; Aryx Therapeutics, Santa Clara CA), 5HT<sub>4</sub>, 5HT<sub>2</sub>, and 5HT<sub>1</sub> receptor antagonists), complete or partial 5HT receptor agonists including 5HT<sub>3</sub>, 5HT<sub>2</sub>, 5HT<sub>4</sub> (e.g., tegaserod, mosapride and renzapride) and 5HT<sub>1</sub> receptor agonists, CRF receptor agonists (NBI-34041),  $\beta$ -3 adrenoreceptor agonists, opioid receptor agonists (e.g., loperamide, fedotozine, and fentanyl, naloxone, naltrexone, methyl naloxone, nalmefene, cypridime, beta funaltrexamine, naloxonazine, naltrindole, and nor-binaltorphimine, morphine, diphenyloxylate, enkephalin pentapeptide, asimadoline, and trimebutine), NK1 receptor antagonists (e.g., ezlopitant and SR-14033), CCK receptor agonists (e.g., loxiglumide), NK1 receptor antagonists, NK3 receptor antagonists (e.g., talnetant, osanetant (SR-142801), SSR-241586), norepinephrine-serotonin reuptake inhibitors (NSRI; e.g., milnacipran), vanilloid and cannabinoid receptor agonists (e.g., arvanil), sialorphin, sialorphin-related peptides

comprising the amino acid sequence QHNPR (SEQ ID NO: ) for example, VQHNPR (SEQ ID NO: ); VRQHNPR (SEQ ID NO: ); VRGQHNPR (SEQ ID NO: ); VRGPQHNPR (SEQ ID NO: ); VRGPRQHNPR (SEQ ID NO: ); VRGPRRQHNPR (SEQ ID NO: ); and RQHNPR (SEQ ID NO: ), compounds or peptides that are inhibitors of neprilysin, frakefamide (H-Tyr-D-Ala-Phe(F)-Phe-NH<sub>2</sub>; WO 01/019849 A1), loperamide, Tyr-Arg (kyotorphin), CCK receptor agonists (caerulein), conotoxin peptides, peptide analogs of thymulin, loxiglumide, dexloxiglumide (the R-isomer of loxiglumide) (WO 88/05774) and other analgesic peptides or compounds.

10 Amino acid, non-amino acid, peptide and non-peptide spacers can be interposed between a peptides of the invention and a peptide that has some other biological function, e.g., an analgesic peptide or a peptide used to treat obesity. The linker can be one that is cleaved from the flanking peptides *in vivo* or one that remains linked to the flanking peptides *in vivo*. For example, glycine, beta-alanine, glycyl-glycine, glycyl-beta-alanine, gamma-aminobutyric acid, 6-aminocaproic acid, L-phenylalanine, L-tryptophan and glycyl-L-valil-L-phenylalanine can be used as a spacer (Chaltin et al. 2003 Helvetica Chimica Acta 86:533-547; Caliceti et al. 1993 FARMCO 48:919-32) as can polyethylene glycols (Butterworth et al. 1987 J. Med. Chem 30:1295-302) and maleimide derivatives (King et al. 2002 Tetrahedron Lett. 43:1987-1990). Various other linkers are described in the literature (Nestler 1996 Molecular Diversity 2:35-42; 15 Finn et al. 1984 Biochemistry 23:2554-8; Cook et al. 1994 Tetrahedron Lett. 35:6777-80; Brokx et al. 2002 Journal of Controlled Release 78:115-123; Griffin et al. 2003 J. Am. Chem. Soc. 125:6517-6531; Robinson et al. 1998 Proc. Natl. Acad. Sci. USA 95:5929-5934.

The peptides can include the amino acid sequence of a peptide that occurs naturally in a vertebrate (e.g., mammalian) species or in a bacterial species. In addition, the peptides can be partially or completely non-naturally occurring peptides. Also within the invention are peptidomimetics corresponding to the peptides of the invention.

When fully folded, disulfide bonds are present between the first and third cysteines and between 30 the second and fourth cysteines, e.g., there is a disulfide bond between Cys<sub>4</sub> and Cys<sub>12</sub> and a

disulfide bond between Xaa<sub>7</sub> and Xaa<sub>15</sub> (when Xaa<sub>7</sub> is a Cys and Xaa<sub>15</sub> is a Cys). In some embodiments, the peptide has only one disulfide bond, e.g., between the first and third cysteines (i.e., Cys<sub>4</sub> and Cys<sub>12</sub>; corresponds to the first and second cysteines when Xaa<sub>7</sub> is other than Cys). In certain embodiments one or more Cys can be replaced by Mpt (mercaptoproline) or Pen  
5 (penicillamine) or Dpr (diaminopropionic acid) or some other amino acid that can covalently link to another amino acid (e.g., Cys, Mpt, Pen or Dpr). In some embodiments, one or both members of a pair of Cys residues which normally form a disulfide bond can be replaced by homocysteine, 3-mercaptoproline (Kolodziej et al. 1996 *Int J Pept Protein Res* 48:274); β, β dimethylcysteine (Hunt et al. 1993 *Int J Pept Protein Res* 42:249) or diaminopropionic acid (Smith et al. 1978 *J  
10 Med Chem* 21:117) to form alternative internal cross-links at the positions of the normal disulfide bonds.

In addition, one or more disulfide bonds can be replaced by alternative covalent cross-links, e.g., an amide bond, an ester linkage, an alkyl linkage, a thio ester linkage, a lactam bridge, a carbamoyl linkage, a urea linkage, a thiourea linkage, a phosphonate ester linkage, an alkyl  
15 linkage, and alkenyl linkage, an ether, a thioether linkage, or an amino linkage. For example, Ledu et al. (Proceedings Nat'l Acad. Sci. 100:11263-78, 2003) described methods for preparing lactam and amide cross-links. Schafmeister et al. (J. Am. Chem. Soc. 122:5891, 2000) describes stable, all carbon cross-links. In some cases, the generation of such alternative cross-links requires replacing the Cys residues with other residues such as Lys or Glu or non-naturally  
20 occurring amino acids.

In certain embodiments one or more amino acids can be replaced by a non-naturally occurring amino acid or a naturally or non-naturally occurring amino acid analog. For example, an aromatic amino acid can be replaced by 3,4-dihydroxy-L-phenylalanine, 3-iodo-L-tyrosine, triiodothyronine, L-thyroxine, phenylglycine (Phg) or nor-tyrosine (norTyr). Phg and norTyr and  
25 other amino acids including Phe and Tyr can be substituted by, e.g., a halogen, -CH<sub>3</sub>, -OH, -CH<sub>2</sub>NH<sub>3</sub>, -C(O)H, -CH<sub>2</sub>CH<sub>3</sub>, -CN, -CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>, -SH, or another group.

Further examples of unnatural amino acids include: an unnatural analogue of tyrosine; an unnatural analogue of glutamine; an unnatural analogue of phenylalanine; an unnatural analogue

of serine; an unnatural analogue of threonine; an alkyl, aryl, acyl, azido, cyano, halo, hydrazine, hydrazide, hydroxyl, alkenyl, alkynyl, ether, thiol, sulfonyl, seleno, ester, thioacid, borate, boronate, phospho, phosphono, phosphine, heterocyclic, enone, imine, aldehyde, hydroxylamine, keto, or amino substituted amino acid, or any combination thereof; an amino acid with a  
5 photoactivatable cross-linker; a spin-labeled amino acid; a fluorescent amino acid; an amino acid with a novel functional group; an amino acid that covalently or noncovalently interacts with another molecule; a metal binding amino acid; a metal-containing amino acid; a radioactive amino acid; a photocaged and/or photoisomerizable amino acid; a biotin or biotin-analogue containing amino acid; a glycosylated or carbohydrate modified amino acid; a keto containing  
10 amino acid; amino acids comprising polyethylene glycol or polyether; a heavy atom substituted amino acid (e.g., an amino acid containing deuterium, tritium,  $^{13}\text{C}$ ,  $^{15}\text{N}$ , or  $^{18}\text{O}$ ); a chemically cleavable or photocleavable amino acid; an amino acid with an elongated side chain; an amino acid containing a toxic group; a sugar substituted amino acid, e.g., a sugar substituted serine or the like; a carbon-linked sugar-containing amino acid; a redox-active amino acid; an  $\alpha$ -hydroxy  
15 containing acid; an amino thio acid containing amino acid; an  $\alpha$ ,  $\alpha$  disubstituted amino acid; a  $\beta$ -amino acid; a cyclic amino acid other than proline; an O-methyl-L-tyrosine; an L-3-(2-naphthyl)alanine; a 3-methyl-phenylalanine; a *p*-acetyl-L-phenylalanine; an O-4-allyl-L-tyrosine; a 4-propyl-L-tyrosine; a tri-O-acetyl-GlcNAc $\beta$ -serine; an L-Dopa; a fluorinated phenylalanine; an isopropyl-L-phenylalanine; a *p*-azido-L-phenylalanine; a *p*-acyl-L-phenylalanine; a *p*-  
20 benzoyl-L-phenylalanine; an L-phosphoserine; a phosphoserine; a phosphotyrosine; a *p*-iodo-phenylalanine; a 4-fluorophenylglycine; a *p*-bromophenylalanine; a *p*-amino-L-phenylalanine; an isopropyl-L-phenylalanine; L-3-(2-naphthyl)alanine; an amino-, isopropyl-, or O-allyl-containing phenylalanine analogue; a dopa, O-methyl-L-tyrosine; a glycosylated amino acid; a *p*-(propargyloxy)phenylalanine, dimethyl-Lysine, hydroxy-proline, mercaptopropionic  
25 acid, methyl-lysine, 3-nitro-tyrosine, norleucine, pyro-glutamic acid, Z (Carbobenzoxyl),  $\epsilon$ -Acetyl-Lysine,  $\beta$ -alanine, aminobenzoyl derivative, aminobutyric acid (Abu), citrulline, aminohexanoic acid, aminoisobutyric acid, cyclohexylalanine, d-cyclohexylalanine, hydroxyproline, nitro-arginine, nitro-phenylalanine, nitro-tyrosine, norvaline, octahydroindole carboxylate, ornithine, penicillamine, tetrahydroisoquinoline, acetamidomethyl protected amino

acids and a pegylated amino acid. Further examples of unnatural amino acids can be found in U.S. 20030108885, U.S. 20030082575, and the references cited therein.

5 In some embodiments, an amino acid can be replaced by a naturally-occurring, non-essential amino acid, e.g., taurine.

Methods to manufacture peptides containing unnatural amino acids can be found in, for example, U.S. 20030108885, U.S. 20030082575, Deiters et al., J Am Chem Soc. (2003) 125:11782-3, Chin et al., Science (2003) 301:964-7, and the references cited therein.

10

Peptides that include non-natural amino acids can also be prepared using the methods described in WO02086075.

The peptides of the invention can be modified using standard modifications. Modifications may occur at the amino (N-), carboxy (C-) terminus, internally or a combination of any of the preceding. In one aspect of the invention, there may be more than one type of modification on the peptide. Modifications include but are not limited to: acetylation, amidation, biotinylation, cinnamoylation, farnesylation, formylation, myristoylation, palmitoylation, phosphorylation (Ser, Tyr or Thr), stearoylation, succinylation, sulfurylation and cyclisation (via disulfide bridges or amide cyclisation), and modification by Cy3 or Cy5. The peptides of the invention may also be modified by 2, 4-dinitrophenyl (DNP), DNP-lysine, modification by 7-Amino-4-methyl-coumarin (AMC), fluorescein, NBD (7-Nitrobenz-2-Oxa-1,3-Diazole), p-nitro-anilide, rhodamine B, EDANS (5-((2-aminoethyl)amino)naphthalene-1-sulfonic acid), dabcy1, dabsyl, dansyl, texas red, Fmoc, and Tamra (Tetramethylrhodamine). The peptides of the invention may also be conjugated to, for example, BSA or KLH (Keyhole Limpet Hemocyanin).

The invention also features a purified polypeptide comprising, consisting of or consisting essentially of the amino acid sequence: Xaa<sub>1</sub> Xaa<sub>2</sub> Xaa<sub>3</sub> Cys<sub>4</sub> Xaa<sub>5</sub> Xaa<sub>6</sub> Xaa<sub>7</sub> Xaa<sub>8</sub> Xaa<sub>9</sub> Xaa<sub>10</sub> Xaa<sub>11</sub> Cys<sub>12</sub> Xaa<sub>13</sub> Xaa<sub>14</sub> Xaa<sub>15</sub> Xaa<sub>16</sub> (SEQ ID NO:1) wherein:

30 Xaa<sub>1</sub> is any amino acid or is missing;

Xaa<sub>2</sub> is any amino acid or is missing;

Xaa<sub>3</sub> is any amino acid or is missing;

Xaa<sub>5</sub> is Glu;

Xaa<sub>6</sub> is Tyr, Trp, Phe or Leu;

5 Xaa<sub>7</sub> is Cys;

Xaa<sub>8</sub> is any of the 20 naturally-occurring amino acids other than Cys or is missing;

Xaa<sub>9</sub> is any of the 20 naturally-occurring amino acids;

Xaa<sub>10</sub> is Pro or Gly;

Xaa<sub>11</sub> is any of the 20 naturally-occurring amino acids;

10 Xaa<sub>13</sub> is Thr, Val or Gly;

Xaa<sub>14</sub> is Gly or Ala;

Xaa<sub>15</sub> is Cys; and

Xaa<sub>16</sub> is any of the 20 naturally-occurring amino acids or is missing.

In various embodiments: Xaa<sub>9</sub> is Asn; Xaa<sub>11</sub> is Ala or Thr; Xaa<sub>8</sub> is missing; and Xaa<sub>16</sub> is Tyr.

15 In other embodiments Xaa<sub>4</sub> is immediately preceded by an amino acid sequence selected from:  
 Ser His Thr; Pro Ser Thr; Thr; Pro Asp Pro; Ile Ala Glu Asp Ser His Thr; Ile Ala Gln Asp Pro Ser  
 Thr; Ala Asn Thr; Asn Thr; Asp Pro Asn Thr; Lys Asn Thr; Pro Asn Thr; Ile Ala Gln Asp Pro Asn  
 Thr; Lys Pro Asn Thr; Asp Pro Gly Thr; Glu Asp Pro Gly Thr; Pro Gly Thr; Pro Ala Thr; Val Ala  
 Ala Arg Ala Asp Leu; Gly Asp Asp; Asn Asp Glu; Gln Glu Asp; Asn Asp Asp; Arg Thr Ile Ala  
 20 Asn Asp Asp; Thr Ile Ala Asn Asp Asp; Asp Asp; Arg Thr Met Asp Asn Asp Glu; Arg Thr Ile Ala  
 Gly Asp Asp; Arg Thr Ile Ala Asn Asp; Asp; Glu Asp; Arg Ser Ile Ser Gln Glu Asp; Thr Asp Glu;  
 Arg Thr Ile Ala Thr Asp Glu; Glu; Ile Ile Thr Pro Pro Asp Pro; Gln Glu Leu; Lys Asp Asp; Gln  
 Glu Glu; Arg Tyr Ile Asn Gln Glu Glu; Ala Ser Ser Tyr Ala Ser; and Thr Ser Ser Tyr Ala Ser.

The invention further features a purified polypeptide comprising, consisting of or consisting  
 25 essentially the amino acid sequence: Xaa<sub>1</sub> Xaa<sub>2</sub> Xaa<sub>3</sub> Cys<sub>4</sub> Xaa<sub>5</sub> Xaa<sub>6</sub> Xaa<sub>7</sub> Xaa<sub>8</sub> Xaa<sub>9</sub> Xaa<sub>10</sub>  
 Xaa<sub>11</sub> Cys<sub>12</sub> Xaa<sub>13</sub> Xaa<sub>14</sub> Xaa<sub>15</sub> Xaa<sub>16</sub> (SEQ ID NO:1) wherein:

Xaa<sub>1</sub> is: a) Ser, Asn, Tyr, Ala, Gln, Pro, Lys, Gly, or Thr, or is missing; b)

preceded by Lys or Tyr; c) any amino acid; d) missing; e) any amino acid other than Cys; or f) Lys or Arg;

Xaa<sub>2</sub> is: a) His, Asp, Glu, Ala, Ser, Asn, Gly, or is missing; b) His, Asp, Glu, Ala, Ser, Asn, Gly, Pro or is missing; c) Asp, Glu, any amino acid or is missing; d) Asp or Glu; e) any amino acid other than Cys; e) Glu; f) missing; g) Trp, Tyr or Phe; or h) Lys or Arg;

Xaa<sub>3</sub> is: a) Thr, Asp, Ser, Glu, Pro, Val or Leu; Asp or Glu; b) any amino acid other than Cys; c) Glu; d) Thr; e) Thr, Asp, Ser, Glu, Pro, Val or Leu or is missing; f) Trp, Tyr or Phe; or g) Lys or Arg;

Xaa<sub>4</sub> is: a) Cys, Mpt (mercaptoproline), Pen (penicillamine), Dpr (diaminopropionic acid), Asp, or Glu;

Xaa<sub>5</sub> is: a) any amino acid; b) Glu, Asp, Gln, Gly or Pro; c) Glu; d) Glu or Asp; e) Asp, Ile or Glu; f) any amino acid; or g) any amino acid other than Cys;

Xaa<sub>6</sub> is: a) Leu, Ile, Val, Ala, Lys, Arg, Trp, Tyr or Phe; b) Leu, Ile, Val, Lys, Arg, Trp, Tyr or Phe; Leu, Ile, Lys, Arg, Trp, Tyr or Phe; c) Leu, Ile, Val, Trp, Tyr or Phe; d) Trp, Tyr, Phe or Leu; e) Leu, Ile or Val; f) Ile, Trp or Leu; g) Trp, Tyr or Phe; h) Ile or Leu; i) Tyr; j) any amino acid; k) any amino acid except Leu; l) any natural or non-natural aromatic amino acid; or m) any amino acid other than Cys;

Xaa<sub>7</sub> is: a) Cys, Ser, or Tyr; Cys; b) Cys, Mpt (mercaptoproline), Pen (penicillamine), Dpr (diaminopropionic acid), Asp or Glu; c) Ser; or d) an amino acid other than Cys;

Xaa<sub>8</sub> is: a) Ala, Val, or Ile; b) Ala, Val, Thr, Ile, Met or is missing; c) any amino acid; d) Val; e) any amino acid other than Cys; or f) missing;

Xaa<sub>9</sub> is: a) any amino acid; b) any amino acid other than Phe and Tyr; c) any amino acid other than Phe, Tyr, and Trp; d) any amino acid other than Phe, Tyr, Trp, Ile, Leu and Val; e) any amino acid other than Phe, Tyr, Trp, Ile, Leu, Val, and His; f) any amino acid other than Gln; g) any amino acid other than Lys, Arg, Phe, Tyr, and Trp; h) any amino acid other than Lys, Arg, Phe, Tyr, Trp, Ile, Leu and Val; i) any amino acid other than Lys, Arg, Phe, Tyr, Trp, Ile, Leu, Val, and His; j) any non-aromatic amino acid; k) missing; l) Phe, Tyr, Asn, or Trp; m) Asn, Tyr, Asp or Ala; n) Asn, Gln, or Tyr; o) Phe or Tyr; p) Asn; or q) any amino acid other than Cys;

Xaa<sub>10</sub> is: a) Ala, Pro or Gly; b) Pro or Gly; c) Pro; d) Ala, Val, Met, Thr or Ile; e) any amino acid; f) Val; g) Val or Pro; h) Ala or Val; i) any amino acid other than Cys; j) Pro; or k) Gly;

Xaa<sub>11</sub> is: a) any amino acid; b) Ala, Leu, Ser, Gly, Val, Glu, Gln, Ile, Leu, Lys, Arg, or Asp; c) Ala or Gly; d) Ala; e) Ala or Val; f) any amino acid; g) Ala or Aib (alpha-aminoisobutyric acid); h) any amino acid other than Cys; i) Ala or Thr; or j) Thr.

Xaa<sub>12</sub> is: a) Cys, Mpt (mercaptoproline), Pen (penicillamine), Dpr (diaminopropionic acid), Asp, or Glu; or b) any amino acid other than Cys;

Xaa<sub>13</sub> is: a) Thr, Ala, Asn, Lys, Arg, or Trp; b) Thr, Ala, Lys, Arg, or Trp; c) any amino acid; d) any non-aromatic amino acid; e) Thr, Ala, or Trp; f) Trp, Tyr or Phe; g) Thr or Ala; h) any amino acid; i) Thr; j) any amino acid other than Cys; k) Thr, Val, or Gly; l) Thr or Val, m) Thr or Gly, n) Val or Thr; o) Val; p) Thr; or q) Gly;

Xaa<sub>14</sub> is: a) Gly, Pro or Ala; b) Gly; c) any amino acid; d) Gly, Ala or Ser; e) Gly or Ala; f) any amino acid other than Cys; or g) Ala;

Xaa<sub>15</sub> is: a) Cys, Tyr or is missing; b) Cys; c) Cys, Mpt (mercaptoproline), Pen (penicillamine), Dpr (diaminopropionic acid), Asp, Glu; or d) any amino acid other than Cys or is missing; and

Xaa<sub>16</sub> is: a) Trp, Tyr, Phe, Asn, Ile, Val, His or Leu; b) Trp, Tyr, Phe, Asn or Leu; c) Trp, Tyr, Phe or Leu; d) Trp, Tyr, or Phe; e) Leu, Ile or Val; f) His, Leu or Ser; g) Tyr or Leu; Lys or Arg; h) His; i) any amino acid, j) Leu, or missing; k) Trp, Tyr, Phe, Lys, Arg or is missing; l) missing; m) any amino acid other than Cys; or n) Tyr.

Also featured is purified polypeptide comprising, consisting of or consisting essentially of the amino acid sequence: Xaa<sub>1</sub> Xaa<sub>2</sub> Xaa<sub>3</sub> Xaa<sub>4</sub> Xaa<sub>5</sub> Xaa<sub>6</sub> Xaa<sub>7</sub> Xaa<sub>8</sub> Xaa<sub>9</sub> Xaa<sub>10</sub> Xaa<sub>11</sub> Xaa<sub>12</sub> Xaa<sub>13</sub> Xaa<sub>14</sub> Xaa<sub>15</sub> Xaa<sub>16</sub> (SEQ ID NO:1) wherein:

Xaa<sub>1</sub> is any amino acid or is missing;

Xaa<sub>2</sub> is any amino acid or is missing;

Xaa<sub>3</sub> is any amino acid or is missing;

Xaa<sub>4</sub> is Cys, Mpt (mercaptoproline), Pen (penicillamine), Dpr (diaminopropionic acid), Asp or Glu;



Xaa<sub>5</sub> is Glu;

Xaa<sub>6</sub> is Tyr, Trp, Phe or Leu;

Xaa<sub>7</sub> is Cys, Mpt (mercaptoproline), Pen (penicillamine), Dpr (diaminopropionic acid),  
Asp or Glu;

5 Xaa<sub>8</sub> is any amino acid other than Cys or is missing;

Xaa<sub>9</sub> is any amino acid;

Xaa<sub>10</sub> is Pro or Gly;

Xaa<sub>11</sub> is any amino acid;

Xaa<sub>12</sub> is Cys, Mpt (mercaptoproline), Pen (penicillamine), Dpr (diaminopropionic acid),

10 Asp or Glu;

Xaa<sub>13</sub> is Thr, Val or Gly;

Xaa<sub>14</sub> is Gly or Ala;

Xaa<sub>15</sub> is Cys, Mpt (mercaptoproline), Pen (penicillamine), Dpr (diaminopropionic acid),

Asp or Glu; and

15 Xaa<sub>16</sub> is any amino acid or is missing.

The various peptides can be present with a counterion. Useful counterions include salts of:  
acetate, benzenesulfonate, benzoate, calcium edetate, camsylate, carbonate, citrate, edetate  
(EDTA), edisylate, embonate, esylate, fumarate, gluceptate, gluconate, glutamate,

20 glycollylarsanilate, hexylresorcinate, iodide, bromide, chloride, hydroxynaphthoate, isethionate,  
lactate, lactobionate, estolate, maleate, malate, mandelate, mesylate, mucate, napsylate, nitrate,  
pantothenate, phosphate, salicylate, stearate, succinate, sulfate, tartarate, theoclate,  
acetamidobenzoate, adipate, alginate, aminosaliclate, anhydromethylenecitrate, ascorbate,  
aspartate, camphorate, caprate, caproate, caprylate, cinnamate, cyclamate, dichloroacetate,  
25 formate, gentisate, glucuronate, glycerophosphate, glycolate, hippurate, fluoride, malonate,  
napadisylate, nicotinate, oleate, orotate, oxalate, oxoglutarate, palmitate, pectinate, pectinate  
polymer, phenylethylbarbiturate, picrate, propionate, pidolate, sebacate, rhodanide, tosylate,  
tannate

30

In a second aspect, the invention also features a therapeutic or prophylactic method comprising administering a composition comprising a purified peptide comprising, consisting essentially or consisting of the amino acid sequence of SEQ ID NO:1. For the treatment of gastrointestinal disorders, the peptide can be administered orally, by rectal suppository or parenterally.

- 5 In various embodiments, the patient is suffering from a gastrointestinal disorder; the patient is suffering from a disorder selected from the group consisting of: a gastrointestinal motility disorder, irritable bowel syndrome, a functional gastrointestinal disorder, gastroesophageal reflux disease, duodenogastric reflux, functional heartburn, dyspepsia, functional dyspepsia, nonulcer dyspepsia, gastroparesis, chronic intestinal pseudo-obstruction, colonic pseudo-obstruction,
- 10 obesity, congestive heart failure, or benign prostatic hyperplasia; the composition is administered orally; the peptide comprises 150, 140, 130, 120, 110, 100, 90, 80, 70, 60, 50, 40, or 30 or fewer amino acids. In other embodiments, the peptide comprises 20 or fewer amino acids, and the peptide comprises no more than 5 amino acids prior to Cys<sub>4</sub>. In other embodiments the peptide comprises no more than 20, 15, 10, or 5 peptides subsequent to Cys<sub>15</sub>. In certain embodiments
- 15 Xaa<sub>16</sub> is a chymotrypsin or trypsin cleavage site and an analgesic peptide is present immediately following Xaa<sub>16</sub>.

Among the useful peptides are those comprising, consisting of or consisting essentially of any of the following amino acid sequences:

SHTCEICAF AACAGC (opossum guanylin) (SEQ ID NO: );

20 PGTCEICAYAACTGC (human guanylin) (SEQ ID NO: );

PSTCEICAYAAACAGC (pig guanylin) (SEQ ID NO: );

PNTCEICAYAACTGC (rat guanylin) (SEQ ID NO: );

PDPCEICANA ACTGCL (European eel guanylin, inferred) (SEQ ID NO: );

NDDCELCVNVACTGCL (human uroguanylin) (SEQ ID NO: );

- QEECELCINMACTGY (opossum lymphoguanylin) (SEQ ID NO: );
- GDDCELCVNVACTGCS (pig uroguanylin) (SEQ ID NO: );
- NDECELCVNIACTGC (guinea pig uroguanylin) (SEQ ID NO: );
- TDECELCINVACTGC (rat uroguanylin) (SEQ ID NO: );
- 5 QEDCELCINVACTGC (opossum uroguanylin) (SEQ ID NO: );
- MPSTQYIRRPASSYASCIWCTTACASCHGRTTKPSLAT (EAST 1) (SEQ ID NO: );
- MPSTQYIRRPASSYASCIWCATACASCHGRTTKPSLAT (SEQ ID NO: );
- MPSTQYIRRPASSYASCIWCATACASCHGRTTKPSLAT (SEQ ID NO: );
- MPSTQYIRRPASSYASCIWCATVCASCHGRTTKPSLAT (SEQ ID NO: );
- 10 MPSTQYIRRPASSYASCIWYATACASCHGRTTEPSLAT (SEQ ID NO: );
- QEECELSINMACTGY (opossum lymphoguanylin analog) (SEQ ID NO: );
- YDECEICMFAACTGC (Japanese eel guanylin) (SEQ ID NO: );
- VCEICAFAACTGC (Zebrafish guanylin, inferred) (SEQ ID NO: );
- ADLCEICAFAACTGCL (Japanese eel renoguanylin, inferred) (SEQ ID NO: );
- 15 PGTCEICAYAACTGCL (SEQ ID NO: );
- PGTCEICAYAACTGCLKK (SEQ ID NO: );
- PNTCEICAYAACTGCKKKKKKK (SEQ ID NO: );
- PNTCEICAYAACTGCD (SEQ ID NO: );
- PNTCEICAYAACTGCDK (SEQ ID NO: );

YPNTCEICAYAACTGC (SEQ ID NO: );

KNTCEICAYAACTGC (SEQ ID NO: );

KPNTCEICAYAACTGC (SEQ ID NO: );

EDPGTCEICAYAACTGC (SEQ ID NO: );

5 VTVQDG NFSFSLESVK KLKDLQEPQE PRVGKLRNFA PIPGEPVVPI LCSNPNFPPEE  
LKPLCKEPNA QEILQRLEEIAEDPGTCEICAYAACTGC (SEQ ID NO: );

DPGTCEICAYAACTGC (SEQ ID NO: );

MNAFLLSALC LLGAWAALAG GVTVQDGNFS FSLESVKKLK DLQEPQEPRV  
GKLRNFAPIP GEPVVPILCS NPNFPPEELKP LCKEPNAQEI LQRLEEIAED

10 PGTCEICAYAACTGC (SEQ ID NO: );

MNAFLLFALC LLGAWAALAG GVTVQDGNFS FSLEPRVGKL RNFAPIPGEP  
VVPILCSNPN FPEELKPLCK EPNAQEILQR LEEIAEDPGTCEICAYAACTGC (SEQ ID  
NO: );

15 TGSMNAFLLF ALCLLGAWAA LAGGVTVQDG NFSFSLEPRV GKLRNFAPIP  
GEPVVPILCS NPNFPPEELKP LCKEPNAQEI LQRLEEIAEDPGTCEICAYAACTGCLEG  
(SEQ ID NO: );

NDECELCVNVACTGCL (SEQ ID NO: ); line 17

ECELCVNVACTGCL (SEQ ID NO: );

EDCELCINVACTGC (SEQ ID NO: );

20 NDDCELCVACTGCL (SEQ ID NO: );

FKTLRTIANDDCELCVNVACTGCL (SEQ ID NO: );

FKTLRTIANDDCLCVNVACTGCL (SEQ ID NO: );

DDCELCVNVACTGCL (SEQ ID NO: );

DCELCVNVACTGCL (SEQ ID NO: );

CELCVNVACTGCL (SEQ ID NO: );

KDDCELCVNVACTGCL (SEQ ID NO: );

5 PNTCEICANPACTGC (SEQ ID NO: ).

The peptides can include the amino acid sequence of a peptide that occurs naturally in a vertebrate (e.g., mammalian) species or in a bacterial species. In addition, the peptides can be partially or completely non-naturally occurring peptides.

10 In a third aspect, the invention features a method for treating a patient suffering from constipation, the method comprising administering a composition comprising a peptide comprising, consisting essentially or consisting of the amino acid sequence of SEQ ID NO:1. Clinically accepted criteria that define constipation range from the frequency of bowel movements, the consistency of feces and the ease of bowel movement. One common definition  
15 of constipation is less than three bowel movements per week. Other definitions include abnormally hard stools or defecation that requires excessive straining (Schiller 2001 *Aliment Pharmacol Ther* 15:749-763). Constipation may be idiopathic (functional constipation or slow transit constipation) or secondary to other causes including neurologic, metabolic or endocrine disorders. These disorders include diabetes mellitus, hypothyroidism, hyperthyroidism,  
20 hypocalcaemia, Multiple sclerosis, Parkinson's disease, spinal cord lesions, Neurofibromatosis, autonomic neuropathy, Chagas disease, Hirschsprung disease and cystic fibrosis. Constipation may also be the result of surgery or due to the use of drugs such as analgesics (like opioids), antihypertensives, anticonvulsants, antidepressants, antispasmodics and antipsychotics.

In various embodiments, the constipation is associated with use of a therapeutic agent; the  
25 constipation is associated with a neuropathic disorder; the constipation is post-surgical constipation; the constipation is associated with a gastrointestinal disorder; the constipation is idiopathic (functional constipation or slow transit constipation); the constipation is associated

with neuropathic, metabolic or endocrine disorder (e.g., diabetes mellitus, hypothyroidism, hyperthyroidism, hypocalcaemia, Multiple Sclerosis, Parkinson's disease, spinal cord lesions, neurofibromatosis, autonomic neuropathy, Chagas disease, Hirschsprung disease or cystic fibrosis). Constipation may also be the result of surgery or due to the use of drugs such as  
5 analgesics (e.g., opioids), antihypertensives, anticonvulsants, antidepressants, antispasmodics and antipsychotics.

In a fourth aspect, the invention features a method for treating a patient suffering a gastrointestinal disorder, the method comprising administering to the patient a composition comprising a purified peptide comprising, consisting essentially of or consisting of the amino  
10 acid sequence of SEQ ID NO:1.

In various embodiments, the patient is suffering from a gastrointestinal disorder; the patient is suffering from a disorder selected from the group consisting of: a gastrointestinal motility disorder, irritable bowel syndrome, a functional gastrointestinal disorder, gastroesophageal reflux disease, functional heartburn, dyspepsia, functional dyspepsia, nonulcer dyspepsia, gastroparesis,  
15 chronic intestinal pseudo-obstruction, colonic pseudo-obstruction; Crohn's disease, ulcerative colitis, Inflammatory bowel disease, colonic pseudo-obstruction, obesity, congestive heart failure, and benign prostatic hyperplasia.

In a fifth aspect, the invention features a method for increasing gastrointestinal motility in a  
20 patient, the method comprising administering to the patient a composition comprising a purified peptide comprising, consisting essentially of or consisting of the amino acid sequence of SEQ ID NO:1.

In a sixth aspect, the invention features a method for decreasing gastrointestinal pain or visceral pain in a patient, the method comprising administering to the patient a composition comprising a  
25 purified peptide comprising, consisting essentially of or consisting of the amino acid sequence of SEQ ID NO:1.

In a seventh aspect, the invention features a method for increasing the activity of an intestinal guanylate cyclase (GC-C) receptor in a patient, the method comprising administering to the patient a composition comprising a purified peptide comprising, consisting essentially of or consisting of the amino acid sequence of SEQ ID NO:1.

- 5 In an eighth aspect, the invention features an isolated nucleic acid molecule comprising a nucleotide sequence encoding a peptide comprising, consisting essentially of or consisting of the amino acid sequence of SEQ ID NO:1.

In a ninth aspect, the invention features a composition comprising a purified polypeptide comprising, consisting essentially of or consisting of the amino acid sequence of SEQ ID NO:1.

- 10 In an embodiment, the composition is a pharmaceutical composition.

In a tenth aspect, the invention features a method for treating obesity, the method comprising administering a composition comprising a purified peptide comprising, consisting essentially of or consisting of the amino acid sequence of SEQ ID NO:1. The peptide can be administered in combination with one or more agents for treatment of obesity, for example, gut hormone fragment peptide YY<sub>3-36</sub> (PYY<sub>3-36</sub>) (*N. Engl. J. Med.* 349:941, 2003; ikpeapge daspeelnry yaslryhlnl vtrqry) or a variant thereof, glp-1 (glucagon-like peptide-1), exendin-4 (an inhibitor of glp-1), sibutramine, phentermine, phendimetrazine, benzphetamine hydrochloride (Didrex), orlistat (Xenical), diethylpropion hydrochloride (Tenuate), fluoxetine (Prozac), bupropion, ephedra, chromium, garcinia cambogia, benzocaine, bladderwrack (*focus vesiculosus*), chitosan, nomame herba, galega (Goat's Rue, French Lilac), conjugated linoleic acid, L-carnitine, fiber (psyllium, plantago, guar fiber), caffeine, dehydroepiandrosterone, germander (*teucrium chamaedrys*), B-hydroxy- $\beta$ -methylbutyrate, ATL-962 (Alizyme PLC), and pyruvate. A peptide useful for treating obesity can be administered as a co-therapy with a peptide of the invention either as a distinct molecule or as part of a fusion protein with a peptide of the invention. Thus, 25 for example, PYY<sub>3-36</sub> can be fused to the carboxy or amino terminus of a peptide of the invention. Such a fusion protein can include a chymotrypsin or trypsin cleavage site that can permit cleavage to separate the two peptides. A peptide useful for treating obesity can be administered as a co-therapy with electrostimulation (U.S. 20040015201).

In an eleventh aspect, the invention features a method for treating congestive heart failure, the method comprising: administering to the patient a composition comprising a purified peptide comprising, consisting essentially of or consisting of the amino acid sequence of SEQ ID NO:1. The peptide can be administered in combination with one or more agents for treatment of  
5 congestive heart failure, for example, a natriuretic peptide such as atrial natriuretic peptide, brain natriuretic peptide or C-type natriuretic peptide), a diuretic, or an inhibitor of angiotensin converting enzyme.

In a twelfth aspect, the invention features a method for treating benign prostatic hyperplasia, the method comprising: administering to the patient a composition comprising a purified peptide  
10 comprising, consisting essentially of or consisting of the amino acid sequence of SEQ ID NO:1. The peptide can be administered in combination with one or more agents for treatment of BPH, for example, a 5-alpha reductase inhibitor (e.g., finasteride) or an alpha adrenergic inhibitor (e.g., doxazosine).

In a thirteenth aspect, the invention features a method for treating a patient suffering a  
15 gastrointestinal disorder, the method comprising administering to the patient a composition comprising a complete or partial agonist of the GC-C receptor. In various embodiments, the patient is suffering from a gastrointestinal disorder; the patient is suffering from a disorder selected from the group consisting of: a gastrointestinal motility disorder, irritable bowel syndrome, a functional gastrointestinal disorder, gastroesophageal reflux disease, functional  
20 heartburn, dyspepsia, functional dyspepsia, nonulcer dyspepsia, gastroparesis, chronic intestinal pseudo-obstruction, and colonic pseudo-obstruction.

In a fourteenth aspect, the invention features a method for treating a patient suffering from constipation, the method comprising administering a composition comprising a complete or partial agonist of the GC-C receptor.

25 In a fifteenth aspect, the invention features a method for increasing gastrointestinal motility in a patient, the method comprising administering to the patient a composition comprising a complete or partial agonist of the GC-C receptor.



In a sixteenth aspect, the invention features a method for decreasing gastrointestinal pain or visceral pain in a patient, the method comprising administering to the patient a composition comprising a complete or partial agonist of the GC-C receptor.

In a seventeenth aspect, the invention features a method for treating congestive heart failure, the method comprising administering a complete or partial agonist of the GC-C receptor. GC-C agonists can act in the kidney and adrenal gland to control natriuresis, kaliuresis, and diuresis thereby reducing the build-up of fluid associated with congestive heart failure (Lorenz et al. *J Clin Invest* 112:1138, 2003; Carrithers et al. *Kidney Int* 65:40, 2004). The agonist can be administered in combination with one or more agents for treatment of congestive heart failure, for example, a natriuretic peptide such as atrial natriuretic peptide, brain natriuretic peptide or C-type natriuretic peptide), a diuretic, or an inhibitor of angiotensin converting enzyme.

In an eighteenth aspect, the invention features a method for treating BPH, the method comprising administering a complete or partial agonist of the GC-C receptor. GC-C agonists acting in the prostate can reduce cellular hypertrophy and complications associated with cellular hypertrophy. The agonist can be administered in combination with one or more agents for treatment of BPH, for example, a 5-alpha reductase inhibitor (e.g., finasteride) or an alpha adrenergic inhibitor (e.g., doxazosine).

In a nineteenth aspect, the invention features a method for treating obesity, the method comprising administering a complete or partial agonist of the GC-C receptor. The agonist can be administered in combination with one or more agents for treatment of obesity, for example, sibutramine.

The peptides and agonists of the GC-C receptor can be used to treat constipation or decreased intestinal motility, slow digestion or slow stomach emptying. The peptides can be used to relieve one or more symptoms of IBS (bloating, pain, constipation), GERD (acid reflux into the esophagus), duodenogastric reflux, functional dyspepsia, or gastroparesis (nausea, vomiting, bloating, delayed gastric emptying) and other disorders described herein.

Clinically accepted criteria that define constipation range from the frequency of bowel movements, the consistency of feces and the ease of bowel movement. One common definition of constipation is less than three bowel movements per week. Other definitions include abnormally hard stools or defecation that requires excessive straining (Schiller 2001, *Aliment Pharmacol Ther* 15:749-763). Constipation may be idiopathic (functional constipation or slow transit constipation) or secondary to other causes including neurologic, metabolic or endocrine disorders. These disorders include diabetes mellitus, hypothyroidism, hyperthyroidism, hypocalcaemia, Multiple Sclerosis, Parkinson's disease, spinal cord lesions, Neurofibromatosis, autonomic neuropathy, Chagas disease, Hirschsprung's disease and cystic fibrosis. Constipation may also be the result of surgery or due to the use of drugs such as analgesics (like opioids), antihypertensives, anticonvulsants, antidepressants, antispasmodics and antipsychotics.

In a twentieth aspect, the invention features isolated nucleic acid molecules comprising or consisting of a sequence encoding a peptide of the invention. The invention also features vectors, e.g., expression vectors that include such nucleic acid molecules and can be used to express a peptide of the invention in a cultured cell (e.g., a eukaryotic cell or a prokaryotic cell). The vector can further include one or more regulatory elements, e.g., a heterologous promoter or elements required for translation operably linked to the sequence encoding the peptide. In some cases the nucleic acid molecule will encode an amino acid sequence that includes the amino acid sequence of a peptide of the invention. For example, the nucleic acid molecule can encode a preprotein or a preproprotein that can be processed to produce a peptide of the invention.

A vector that includes a nucleotide sequence encoding a peptide of the invention or a peptide or polypeptide comprising a peptide of the invention may be either RNA or DNA, single- or double-stranded, prokaryotic, eukaryotic, or viral. Vectors can include transposons, viral vectors, episomes, (e.g., plasmids), chromosomes inserts, and artificial chromosomes (e.g. BACs or YACs). Suitable bacterial hosts for expression of the encode peptide or polypeptide include, but are not limited to, *E. coli*. Suitable eukaryotic hosts include yeast such as *S. cerevisiae*, other fungi, vertebrate cells, invertebrate cells (e.g., insect cells), plant cells, human cells, human tissue cells, and whole eukaryotic organisms. (e.g., a transgenic plant or a transgenic animal). Further, the vector nucleic acid can be used to generate a virus such as vaccinia or baculovirus.

As noted above the invention includes vectors and genetic constructs suitable for production of a peptide of the invention or a peptide or polypeptide comprising such a peptide. Generally, the genetic construct also includes, in addition to the encoding nucleic acid molecule, elements that allow expression, such as a promoter and regulatory sequences. The expression vectors may contain transcriptional control sequences that control transcriptional initiation, such as promoter, enhancer, operator, and repressor sequences. A variety of transcriptional control sequences are well known to those in the art and may be functional in, but are not limited to, a bacterium, yeast, plant, or animal cell. The expression vector can also include a translation regulatory sequence (e.g., an untranslated 5' sequence, an untranslated 3' sequence, a poly A addition site, or an internal ribosome entry site), a splicing sequence or splicing regulatory sequence, and a transcription termination sequence. The vector can be capable of autonomous replication or it can integrate into host DNA.

The invention also includes isolated host cells harboring one of the forgoing nucleic acid molecules and methods for producing a peptide by culturing such a cell and recovering the peptide or a precursor of the peptide. Recovery of the peptide or precursor may refer to collecting the growth solution and need not involve additional steps of purification. Proteins of the present invention, however, can be purified using standard purification techniques, such as, but not limited to, affinity chromatography, thermoprecipitation, immunoaffinity chromatography, ammonium sulfate precipitation, ion exchange chromatography, filtration, electrophoresis and hydrophobic interaction chromatography.

In a twenty first aspect, the invention features a method of increasing the level of cyclic guanosine 3'-monophosphate (cGMP) in an organ, tissue (e.g, the intestinal mucosa), or cell (e.g., a cell bearing GC-A receptor) by administering a composition that includes a peptide of the invention.

The details of one or more embodiments of the invention are set forth in the accompanying description and claims. The publications and patents referenced herein are incorporated by reference.

## DRAWINGS

5 FIG.1 depicts deletion variants of human guanylin in which one, two, three or four amino acids are deleted. The deleted amino acids are between Cys<sub>a</sub> and Cys<sub>d</sub> as well as amino terminal to Cys<sub>a</sub>.

FIG. 2 depicts insertion variants of human guanylin in which one, two, three or four amino acids are inserted. The inserted amino acids are between Cys<sub>a</sub> and Cys<sub>d</sub> as well as amino terminal to  
10 Cys<sub>a</sub> and carboxy terminal to Cys<sub>d</sub>.

FIG. 3 depicts various polypeptides which include the amino acid sequence: Xaa<sub>1</sub> Xaa<sub>2</sub> Xaa<sub>3</sub> Cys<sub>4</sub> Xaa<sub>5</sub> Xaa<sub>6</sub> Xaa<sub>7</sub> Xaa<sub>8</sub> Xaa<sub>9</sub> Xaa<sub>10</sub> Xaa<sub>11</sub> Cys<sub>12</sub> Xaa<sub>13</sub> Xaa<sub>14</sub> Xaa<sub>15</sub> Xaa<sub>16</sub> (SEQ ID NO:1) wherein:  
Xaa<sub>1</sub> is any amino acid or is missing; Xaa<sub>2</sub> is any amino acid or is missing; Xaa<sub>3</sub> is any amino acid or is missing; Xaa<sub>5</sub> is Glu; Xaa<sub>6</sub> is Tyr, Trp, Phe or Leu; Xaa<sub>7</sub> is Cys;  
15 Xaa<sub>8</sub> is any of the 20 naturally-occurring amino acids other than Cys or is missing; Xaa<sub>9</sub> is any of the 20 naturally-occurring amino acids; Xaa<sub>10</sub> is Pro or Gly; Xaa<sub>11</sub> is any of the 20 naturally-occurring amino acids; Xaa<sub>13</sub> is Thr, Val or Gly; Xaa<sub>14</sub> is Gly or Ala; Xaa<sub>15</sub> is Cys; and Xaa<sub>16</sub> is any of the 20 naturally-occurring amino acids or is missing.

20

## DETAILED DESCRIPTION

The peptides of the invention bind to the guanylate cyclase (GC-C) receptor, a key regulator of fluid and electrolyte balance in the intestine and kidney. When stimulated, this receptor, which is located on the apical membrane of the intestinal epithelial surface, causes an increase in intestinal epithelial cyclic GMP (cGMP). This increase in cGMP is believed to cause a decrease  
25 in water and sodium absorption and an increase in chloride and potassium ion secretion, leading to changes in intestinal fluid and electrolyte transport and increased intestinal motility. The

intestinal GC-C receptor possesses an extracellular ligand binding region, a transmembrane region, an intracellular protein kinase-like region and a cyclase catalytic domain. Proposed functions for the GC-C receptor are the fluid and electrolyte homeostasis, the regulation of epithelial cell proliferation and the induction of apoptosis (Shaibhubhai 2002 *Curr Opin Drug*  
5 *Dis Devel* 5:261-268).

In addition to being expressed in gastrointestinal epithelial cells, GC-C is expressed in extra-intestinal tissues including kidney, lung, pancreas, pituitary, adrenal, developing liver, heart and male and female reproductive tissues (reviewed in Vaandrager 2002 *Mol Cell Biochem* 230:73-  
10 83). This suggests that the GC-C receptor agonists can be used in the treatment of disorders outside the GI tract, for example, congestive heart failure and benign prostatic hyperplasia.

Ghrelin, a peptide hormone secreted by the stomach, is a key regulator of appetite in humans. Ghrelin expression levels are regulated by fasting and by gastric emptying. (Kim et al., 2003, *Neurorept* 14:1317-20; Gualillo et al., 2003, *FEBS Letts* 552: 105-9). Thus, by increasing gastrointestinal motility, GC-C receptor agonists may also be used to regulate obesity.

15 In humans, the GC-C receptor is activated by guanylin (Gn) (U.S. Patent 5,96,097), uroguanylin (Ugn) (U.S. Patent 5,140,102) and lymphoguanylin (Forte et al. 1999 *Endocrinology* 140:1800-1806).

Many gastrointestinal disorders, including IBS, are associated with abdominal or visceral pain. Certain of the peptides of the invention include the analgesic or anti-nociceptive tags such as the  
20 carboxy-terminal sequence AspPhe immediately following a Trp, Tyr or Phe (i.e., a chymotrypsin cleavage site) or following Lys or Arg (a trypsin cleavage site). Chymotrypsin in the intestinal tract will cleave such peptides immediately carboxy terminal to the Trp, Phe or Tyr residue, releasing the dipeptide, AspPhe. This dipeptide has been shown to have analgesic  
25 activity in animal models (Abdikkahi et al. 2001 *Fundam Clin Pharmacol* 15:117-23; Nikfar et al 1997, 29:583-6; Edmundson et al 1998 *Clin Pharmacol Ther* 63:580-93). In this manner such peptides can treat both pain and inflammation. Other analgesic peptides can be present at the carboxy terminus of the peptide (following a cleavage site) including: endomorphin-1,

endomorphin-2, nocistatin, dalargin, lupron, and substance P. As described in greater detail below, various analgesic peptides and compounds can be covalently linked to or used in combination therapy with the therapeutic peptides described herein.

5 In the human body an inactive form of chymotrypsin, chymotrypsinogen is produced in the pancreas. When this inactive enzyme reaches the small intestine it is converted to active chymotrypsin by the excision of two di-peptides. Active chymotrypsin will cleave peptides at the peptide bond on the carboxy-terminal side of Trp, Tyr or Phe. The presence of active chymotrypsin in the intestinal tract will lead to cleavage of certain of the peptides of the invention having an appropriately positioned chymotrypsin cleavage site. Certain of the peptides  
10 of the invention include a Trp, Tyr or Phe immediately followed by a carboxy-terminal analgesic peptide. It is expected that chymotrypsin cleavage will release the analgesic peptide from peptide of the invention having an appropriately positioned chymotrypsin cleavage site as the peptide passes through the intestinal tract.

Trypsinogen, like chymotrypsin, is a serine protease that is produced in the pancreas and is  
15 present in the digestive tract. The active form, trypsin, will cleave peptides having a Lys or Arg. The presence of active trypsin in the intestinal tract will lead to cleavage of certain of the peptides of the invention having an appropriately positioned trypsin cleavage site. It is expected that chymotrypsin cleavage will release the analgesic peptide from peptide of the invention having an appropriately positioned trypsin cleavage site as the peptide passes through the  
20 intestinal tract.

In some cases, the peptides of the invention are produced as a prepro protein. The prepro protein can include any suitable prepro sequence, including, for example, mnaflsalc llgawaalag gvtvqdg nfs fslesvkkklk dlqepqprv gklrmfapip gepvvpilcs npnfpeelkp lckepnaqei lqrleeiaed (SEQ ID NO: ) and mgcraasgll pgvavvllll lqstqsvyiq yqgfrvqlcs mkklsdlea q wapsprlqaq sllpavchhp  
25 alp qdlqpvc asqeassifk tlrta (SEQ ID NO: ) or a bacterial leader sequence such as: mkksilfiflsvlsfspa qdakpvesskekitleskkcniakksnks gpesmn. Where the peptide is produced by a bacterial cell, e.g., *E. coli*, the forgoing leader sequence will be cleaved and the mature peptide will be efficiently secreted from the bacterial cell. U.S. Patent No. 5,395,490 describes vectors,

expression systems and methods for the efficient production of certain mature peptides having disulfide bonds in bacterial cells and methods for achieving efficient secretion of such mature peptides. The vectors, expression systems and methods described in U.S. Patent No. 5,395,490 can be used to produce the polypeptides of the present invention.

5 Variant Peptides

The invention includes variant peptides that can include one, two, three, four, or five or more (e.g., 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15) amino acid substitutions compared to any of the peptides described above. The substitution(s) can be conservative or non-conservative. The naturally-occurring amino acids can be substituted by D-isomers of any amino acid, non-natural  
10 amino acids, natural and non-natural amino acid analogs, and other groups. A conservative amino acid substitution results in the alteration of an amino acid for a similar acting amino acid, or amino acid of like charge, polarity, or hydrophobicity. At some positions, even conservative amino acid substitutions can reduce the activity of the peptide. A conservative substitution can substitute a naturally-occurring amino acid for a non-naturally-occurring amino acid. Among the  
15 naturally occurring amino acid substitutions generally considered conservative are:

For Amino Acid	Code	Replace with any of
Alanine	Ala	Gly, Cys, Ser
Arginine	Arg	Lys, His
Asparagine	Asn	Asp, Glu, Gln,
Aspartic Acid	Asp	Asn, Glu, Gln
Cysteine	Cys	Met, Thr, Ser
Glutamine	Gln	Asn, Glu, Asp
Glutamic Acid	Glu	Asp, Asn, Gln
Glycine	Gly	Ala
Histidine	His	Lys, Arg
Isoleucine	Ile	Val, Leu, Met
Leucine	Leu	Val, Ile, Met
Lysine	Lys	Arg, His
Methionine	Met	Ile, Leu, Val
Phenylalanine	Phe	Tyr, His, Trp
Proline	Pro	
Serine	Ser	Thr, Cys, Ala
Threonine	Thr	Ser, Met, Val
Tryptophan	Trp	Phe, Tyr
Tyrosine	Tyr	Phe, His
Valine	Val	Leu, Ile, Met

In some circumstances it can be desirable to treat patients with a variant peptide that binds to and activates intestinal GC-C receptor, but is less active or more active than the non-variant form of the peptide. Reduced activity can arise from reduced affinity for the receptor or a reduced ability to activate the receptor once bound or reduced stability of the peptide. Increased activity can arise from increased affinity for the receptor or an increased ability to activate the receptor once bound or increased stability of the peptide.

In some peptides one or both members of one or both pairs of Cys residues which normally form a disulfide bond can be replaced by homocysteine, 3-mercaptoproline (Kolodziej et al. 1996 *Int J Pept Protein Res* 48:274);  $\beta$ ,  $\beta$  dimethylcysteine (Hunt et al. 1993 *Int J Pept Protein Res* 42:249) or diaminopropionic acid (Smith et al. 1978 *J Med Chem* 21:117) to form alternative internal cross-links at the positions of the normal disulfide bonds.



### Production of peptides

Useful peptides can be produced either in bacteria including, without limitation, *E. coli*, or in other existing systems for peptide or protein production (e.g., *Bacillus subtilis*, baculovirus expression systems using *Drosophila* Sf9 cells, yeast or filamentous fungal expression systems, mammalian cell expression systems), or they can be chemically synthesized.

If the peptide or variant peptide is to be produced in bacteria, e.g., *E. coli*, the nucleic acid molecule encoding the peptide may also encode a leader sequence that permits the secretion of the mature peptide from the cell. Thus, the sequence encoding the peptide can include the pre sequence and the pro sequence of, for example, a naturally-occurring bacterial ST peptide. The secreted, mature peptide can be purified from the culture medium.

The sequence encoding a peptide of the invention is can be inserted into a vector capable of delivering and maintaining the nucleic acid molecule in a bacterial cell. The DNA molecule may be inserted into an autonomously replicating vector (suitable vectors include, for example, pGEM3Z and pcDNA3, and derivatives thereof). The vector nucleic acid may be a bacterial or bacteriophage DNA such as bacteriophage lambda or M13 and derivatives thereof. Construction of a vector containing a nucleic acid described herein can be followed by transformation of a host cell such as a bacterium. Suitable bacterial hosts include but are not limited to, *E. coli*, *B subtilis*, *Pseudomonas*, *Salmonella*. The genetic construct also includes, in addition to the encoding nucleic acid molecule, elements that allow expression, such as a promoter and regulatory sequences. The expression vectors may contain transcriptional control sequences that control transcriptional initiation, such as promoter, enhancer, operator, and repressor sequences. A variety of transcriptional control sequences are well known to those in the art. The expression vector can also include a translation regulatory sequence (e.g., an untranslated 5' sequence, an untranslated 3' sequence, or an internal ribosome entry site). The vector can be capable of autonomous replication or it can integrate into host DNA to ensure stability during peptide production.

The protein coding sequence that includes a peptide of the invention can also be fused to a nucleic acid encoding a polypeptide affinity tag, e.g., glutathione S-transferase (GST), maltose E binding protein, protein A, FLAG tag, hexa-histidine, myc tag or the influenza HA tag, in order to facilitate purification. The affinity tag or reporter fusion joins the reading frame of the peptide  
5 of interest to the reading frame of the gene encoding the affinity tag such that a translational fusion is generated. Expression of the fusion gene results in translation of a single polypeptide that includes both the peptide of interest and the affinity tag. In some instances where affinity tags are utilized, DNA sequence encoding a protease recognition site will be fused between the reading frames for the affinity tag and the peptide of interest.

10 Genetic constructs and methods suitable for production of immature and mature forms of the peptides and variants of the invention in protein expression systems other than bacteria, and well known to those skilled in the art, can also be used to produce peptides in a biological system.

Mature peptides and variants thereof can be synthesized by the solid-phase method using an automated peptide synthesizer. For example, the peptide can be synthesized on Cyc(4-CH<sub>2</sub> BxI)-  
15 OCH<sub>2</sub>-4-(oxymethyl)-phenylacetamidomethyl resin using a double coupling program.

Protecting groups must be used appropriately to create the correct disulfide bond pattern. For example, the following protecting groups can be used: t-butyloxycarbonyl (alpha-amino groups); acetamidomethyl (thiol groups of Cys residues B and E); 4-methylbenzyl (thiol groups of Cys residues C and F); benzyl (gamma-carboxyl of glutamic acid and the hydroxyl group of threonine, if  
20 present); and bromobenzyl (phenolic group of tyrosine, if present). Coupling is effected with symmetrical anhydride of t-butoxycarbonylamino acids or hydroxybenzotriazole ester (for asparagine or glutamine residues), and the peptide is deprotected and cleaved from the solid support in hydrogen fluoride, dimethyl sulfide, anisole, and p-thiocresol using 8/1/1/0.5 ratio (v/v/v/w) at 0°C for 60 min. After removal of hydrogen fluoride and dimethyl sulfide by  
25 reduced pressure and anisole and p-thiocresol by extraction with ethyl ether and ethyl acetate sequentially, crude peptides are extracted with a mixture of 0.5M sodium phosphate buffer, pH 8.0 and N,N-dimethylformamide using 1/1 ratio, v/v. The disulfide bond for Cys residues B and E is the formed using dimethyl sulfoxide (Tam et al. (1991) *J. Am. Chem. Soc.* 113:6657-62). The resulting peptide is the purified by reverse-phase chromatography. The disulfide bond

between Cys residues C and F is formed by first dissolving the peptide in 50% acetic acid in water. Saturated iodine solution in glacial acetic acid is added (1 ml iodine solution per 100 ml solution). After incubation at room temperature for 2 days in an enclosed glass container, the solution is diluted five-fold with deionized water and extracted with ethyl ether four times for  
5 removal of unreacted iodine. After removal of the residual amount of ethyl ether by rotary evaporation the solution of crude product is lyophilized and purified by successive reverse-phase chromatography.

#### Intestinal GC-C Receptor Binding and Activity Assays

The ability of peptides, variant peptides and other compounds to bind to and activate the  
10 intestinal GC-C receptor can be tested using the T84 human colon carcinoma cell line (American Type Culture Collection (Bethesda, Md.).

Briefly, cells are grown to confluency in 24-well culture plates with a 1:1 mixture of Ham's F12 medium and Dulbecco's modified Eagle's medium (DMEM), supplemented with 5% fetal calf  
15 serum and are used at between passages 54 and 60.

Monolayers of T84 cells in 24-well plates are washed twice with 1 ml/well DMEM, then incubated at 37°C for 10 min with 0.45 ml DMEM containing 1 mM isobutylmethylxanthine (IBMX), a cyclic nucleotide phosphodiesterase inhibitor. Test peptides (50µl) are then added  
20 and incubated for 30 minutes at 37°C. The media is aspirated and the reaction is terminated by the addition of ice cold 0.5 ml of 0.1N HCl. The samples are held on ice for 20 minutes and then evaporated to dryness using a heat gun or vacuum centrifugation. The dried samples are resuspended in 0.5ml of phosphate buffer provided in the Cayman Chemical Cyclic GMP EIA kit (Cayman Chemical, Ann Arbor, MI). Cyclic GMP is measured by EIA according to  
25 procedures outlined in the Cayman Chemical Cyclic GMP EIA kit.

For the binding assay, T84 cell monolayers in 24-well plates are washed twice with 1 ml of binding buffer (DMEM containing 0.05% bovine serum albumin and 25 mM HEPES, pH 7.2), then incubated for 30 min at 37°C in the presence of mature radioactively labeled *E. coli* ST

peptide and the test material at various concentrations. The cells are then washed 4 times with 1 ml of DMEM and solubilized with 0.5 ml/well 1N NaOH. The level of radioactivity in the solubilized material is then determined using standard methods.

#### Murine gastrointestinal transit (GIT) assay

5 In order to determine whether a test compound or a peptide, increases the rate of gastrointestinal transit, the test compound can be tested in the murine gastrointestinal transit (GIT) assay (Moon et al. *Infection and Immunity* 25:127, 1979). In this assay, charcoal, which can be readily visualized in the gastrointestinal tract is administered to mice after the administration of a test compound. The distance traveled by the charcoal is measured and expressed as a percentage of  
10 the total length of the colon.

Mice are fasted with free access to water for 12 to 16 hours before the treatment with peptide or control buffer. The peptides are orally administered at 1 µg/kg – 1mg/kg of peptide in buffer (20mM Tris pH 7.5) seven minutes before being given an oral dose of 5% Activated Carbon  
15 (Aldrich 242276-250G). Control mice are administered buffer only before being given a dose of Activated Carbon. After 15 minutes, the mice are sacrificed and their intestines from the stomach to the cecum are dissected. The total length of the intestine as well as the distance traveled from the stomach to the charcoal front is measured for each animal and the results are expressed as the percent of the total length of the intestine traveled by the charcoal front. Results  
20 are reported as the average of 10 mice ± standard deviation. A comparison of the distance traveled by the charcoal between the mice treated with peptide versus the mice treated with vehicle alone is performed using a Student's t test and a statistically significant difference is considered for P<0.05. Positive controls for this assay may include commercially available wild-type ST peptide (Sigma-Aldrich, St Louis, MO) and Zelnorm®, a drug approved for IBS that is  
25 an agonist for the serotonin receptor 5HT4.

#### Suckling mouse model of intestinal secretion (SuMi assay)

The peptides of the invention can be tested for their ability to increase intestinal secretion using a suckling mouse model of intestinal secretion. In this model a test compound is administered to

suckling mice that are between seven and nine days old. After the mice are sacrificed, the gastrointestinal tract from the stomach to the cecum is dissected (“guts”). The remains (“carcass”) as well as the guts are weighed and the ratio of guts to carcass weight is calculated. If the ratio is above 0.09, one can conclude that the test compound increases intestinal secretion.

5 Controls for this assay may include wild-type ST peptide and Zelnorm®

#### Phenylbenzoquinone-induced writhing model

The PBQ-induced writhing model can be used to assess pain control activity of the peptides and GC-C receptor agonists of the invention. This model is described by Siegmund et al. (1957 Proc. Soc. Exp. Bio. Med. 95:729-731). Briefly, one hour after oral dosing with a test compound, e.g.,  
10 a peptide, morphine or vehicle, 0.02% phenylbenzoquinone (PBQ) solution (12.5 mL/kg) is injected by intraperitoneal route into the mouse. The number of stretches and writhings are recorded from the 5<sup>th</sup> to the 10<sup>th</sup> minute after PBQ injection, and can also be counted between the 35<sup>th</sup> and 40<sup>th</sup> minute and between the 60<sup>th</sup> and 65<sup>th</sup> minute to provide a kinetic assessment. The results are expressed as the number of stretches and writhings (mean ± SEM) and the percentage  
15 of variation of the nociceptive threshold calculated from the mean value of the vehicle-treated group. The statistical significance of any differences between the treated groups and the control group is determined by a Dunnett’s test using the residual variance after a one-way analysis of variance (P < 0.05) using SigmaStat Software.

#### 20 Colonic hyperalgesia animal models

Hypersensitivity to colorectal distension is a common feature in patients with IBS and may be responsible for the major symptom of pain. Both inflammatory and non-inflammatory animal models of visceral hyperalgesia to distension have been developed to investigate the effect of compounds on visceral pain in IBS.

25

##### I. Trinitrobenzenesulphonic acid (TNBS)-induced rectal allodynia model

Male Wistar rats (220-250 g) are premedicated with 0.5 mg/kg of acepromazine injected intraperitoneally (IP) and anesthetized by intramuscular administration of 100 mg/kg of

ketamine. Pairs of nichrome wire electrodes (60 cm in length and 80  $\mu\text{m}$  in diameter) are implanted in the striated muscle of the abdomen, 2 cm laterally from the white line. The free ends of electrodes are exteriorized on the back of the neck and protected by a plastic tube attached to the skin. Electromyographic (EMG) recordings are started 5 days after surgery.

5 Electrical activity of abdominal striated muscle is recorded with an electroencephalograph machine (Mini VIII, Alvar, Paris, France) using a short time constant (0.03 sec.) to remove low-frequency signals (<3 Hz).

Ten days post surgical implantation, trinitrobenzenesulphonic acid (TNBS) is administered to induce rectal inflammation. TNBS (80 mg  $\text{kg}^{-1}$  in 0.3 ml 50 % ethanol) is administered intrarectally through a silicone rubber catheter introduced at 3 cm from the anus under light diethyl-ether anesthesia, as described (Morteau et al. 1994 Dig Dis Sci 39:1239). Following TNBS administration, rats are placed in plastic tunnels where they are severely limited in mobility for several days before colorectal distension (CRD). Experimental compound is administered one hour before CRD which is performed by insertion into the rectum, at 1 cm of the anus, a 4 cm long balloon made from a latex condom (Gue et al, 1997 *Neurogastroenterol. Motil.* 9:271). The balloon is fixed on a rigid catheter taken from an embolectomy probe (Fogarty). The catheter attached balloon is fixed at the base of the tail. The balloon, connected to a barostat is inflated progressively by step of 15 mmHg, from 0 to 60 mmHg, each step of inflation lasting 5 min. Evaluation of rectal sensitivity, as measured by EMG, is performed before (1-2 days) and 3 days following rectal instillation of TNBS.

The number of spike bursts that corresponds to abdominal contractions is determined per 5 min periods. Statistical analysis of the number of abdominal contractions and evaluation of the dose-effects relationships is performed by a one way analysis of variance (ANOVA) followed by a post-hoc (Student or Dunnett tests) and regression analysis for ED50 if appropriate.

## II. Stress-induced hyperalgesia model

Male Wistar Rats (200-250 g) are surgically implanted with nichrome wire electrodes as in the TNBS model. Ten days post surgical implantation, partial restraint stress (PRS), is performed as

described by Williams et al. for two hours (Williams et al. 1988 Gastroenterology 64:611). Briefly, under light anaesthesia with ethyl-ether, the foreshoulders, upper forelimbs and thoracic trunk are wrapped in a confining harness of paper tape to restrict, but not prevent body movements. Control sham-stress animals are anaesthetized but not wrapped. Thirty minutes  
5 before the end of the PRS session, the animals are administered test-compound or vehicle. Thirty minutes to one hour after PRS completion, the CRD distension procedure is performed as described above for the TNBS model with barostat at pressures of 15, 30, 45 and 60mm Hg. Statistical analysis on the number of bursts is determined and analyzed as in the TNBS model above.

10

#### Administration of peptides and GC-C receptor agonists

For treatment of gastrointestinal disorders, the peptides and agonists of the invention are can be administered orally, e.g., as a tablet or cachet containing a predetermined amount of the active ingredient, pellet, gel, paste, syrup, bolus, electuary, slurry, capsule; powder; granules; as  
15 a solution or a suspension in an aqueous liquid or a non-aqueous liquid; as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion, via a liposomal formulation (see, e.g., EP 736299) or in some other form. Orally administered compositions can include binders, lubricants, inert diluents, lubricating, surface active or dispersing agents, flavoring agents, and humectants. Orally administered formulations such as tablets may optionally be coated or scored and may be  
20 formulated so as to provide sustained, delayed or controlled release of the active ingredient therein. The peptides and agonists can be co-administered with other agents used to treat gastrointestinal disorders including but not limited to acid suppressing agents such as Histamine-2 receptor agonists (H2As) and proton pump inhibitors (PPIs). The peptides and agonists can also be administered by rectal suppository. For the treatment of disorders outside the  
25 gastrointestinal tract such as congestive heart failure and benign prostatic hypertrophy, peptides and agonists can be administered parenterally or orally.

The peptides described herein can be used alone or in combination with other agents. For example, the peptides can be administered together with one or more analgesic peptides or  
30 compounds. The analgesic peptide and/or compound can be covalently attached to a peptide

described herein or it can be a separate agent that is administered together with or sequentially with a peptide described herein in a combination therapy.

Combination therapy can be achieved by administering two or more agents, e.g., a peptide described herein and an analgesic peptide or compound, each of which is formulated and administered separately, or by administering two or more agents in a single formulation. Other combinations are also encompassed by combination therapy. For example, two agents can be formulated together and administered in conjunction with a separate formulation containing a third agent. While the two or more agents in the combination therapy can be administered simultaneously, they need not be. For example, administration of a first agent (or combination of agents) can precede administration of a second agent (or combination of agents) by minutes, hours, days, or weeks. Thus, the two or more agents can be administered within minutes of each other or within 1, 2, 3, 6, 9, 12, 15, 18, or 24 hours of each other or within 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 14 days of each other or within 2, 3, 4, 5, 6, 7, 8, 9, or 10 weeks of each other. In some cases even longer intervals are possible. While in many cases it is desirable that the two or more agents used in a combination therapy be present in within the patient's body at the same time, this need not be so.

Combination therapy can also include two or more administrations of one or more of the agents used in the combination. For example, if agent X and agent Y are used in a combination, one could administer them sequentially in any combination one or more times, e.g., in the order X-Y-X, X-X-Y, Y-X-Y, Y-Y-X, X-X-Y-Y, etc.

The agents, alone or in combination, can be combined with any pharmaceutically acceptable carrier or medium. Thus, they can be combined with materials that do not produce an adverse, allergic or otherwise unwanted reaction when administered to a patient. The carriers or mediums used can include solvents, dispersants, coatings, absorption promoting agents, controlled release agents, and one or more inert excipients (which include starches, polyols, granulating agents, microcrystalline cellulose, diluents, lubricants, binders, disintegrating agents, and the like), etc. If desired, tablet dosages of the disclosed compositions may be coated by standard aqueous or nonaqueous techniques.



Compositions of the present invention may also optionally include other therapeutic ingredients, anti-caking agents, preservatives, sweetening agents, colorants, flavors, desiccants, plasticizers, dyes, and the like. Any such optional ingredient must be compatible with the compound of the invention to insure the stability of the formulation.

The composition may contain other additives as needed, including for example lactose, glucose, fructose, galactose, trehalose, sucrose, maltose, raffinose, maltitol, melezitose, stachyose, lactitol, palatinite, starch, xylitol, mannitol, myoinositol, and the like, and hydrates thereof, and amino acids, for example alanine, glycine and betaine, and peptides and proteins, for example albumen.

Examples of excipients for use as the pharmaceutically acceptable carriers and the pharmaceutically acceptable inert carriers and the aforementioned additional ingredients include, but are not limited to binders, fillers, disintegrants, lubricants, anti-microbial agents, and coating agents such as:

BINDERS: corn starch, potato starch, other starches, gelatin, natural and synthetic gums such as acacia, sodium alginate, alginic acid, other alginates, powdered tragacanth, guar gum, cellulose and its derivatives (*e.g.*, ethyl cellulose, cellulose acetate, carboxymethyl cellulose calcium, sodium carboxymethyl cellulose), polyvinyl pyrrolidone, methyl cellulose, pre-gelatinized starch (*e.g.*, STARCH 1500® and STARCH 1500 LM®, sold by Colorcon, Ltd.), hydroxypropyl methyl cellulose, microcrystalline cellulose (*e.g.* AVICEL™, such as, AVICEL-PH-101™, -103™ and -105™, sold by FMC Corporation, Marcus Hook, PA, USA), or mixtures thereof,

FILLERS: talc, calcium carbonate (*e.g.*, granules or powder), dibasic calcium phosphate, tribasic calcium phosphate, calcium sulfate (*e.g.*, granules or powder), microcrystalline cellulose, powdered cellulose, dextrans, kaolin, mannitol, silicic acid, sorbitol, starch, pre-gelatinized starch, or mixtures thereof,

DISINTEGRANTS: agar-agar, alginic acid, calcium carbonate, microcrystalline cellulose,

croscarmellose sodium, crospovidone, polacrillin potassium, sodium starch glycolate, potato or tapioca starch, other starches, pre-gelatinized starch, clays, other algins, other celluloses, gums, or mixtures thereof,

5 LUBRICANTS: calcium stearate, magnesium stearate, mineral oil, light mineral oil, glycerin, sorbitol, mannitol, polyethylene glycol, other glycols, stearic acid, sodium lauryl sulfate, talc, hydrogenated vegetable oil (*e.g.*, peanut oil, cottonseed oil, sunflower oil, sesame oil, olive oil, corn oil and soybean oil), zinc stearate, ethyl oleate, ethyl laurate, agar, syloid silica gel (AEROSIL 200, W.R. Grace Co., Baltimore, MD USA), a coagulated aerosol of synthetic silica  
10 (Deaussa Co., Plano, TX USA), a pyrogenic silicon dioxide (CAB-O-SIL, Cabot Co., Boston, MA USA), or mixtures thereof,

ANTI-CAKING AGENTS: calcium silicate, magnesium silicate, silicon dioxide, colloidal silicon dioxide, talc, or mixtures thereof,

15

ANTIMICROBIAL AGENTS: benzalkonium chloride, benzethonium chloride, benzoic acid, benzyl alcohol, butyl paraben, cetylpyridinium chloride, cresol, chlorobutanol, dehydroacetic acid, ethylparaben, methylparaben, phenol, phenylethyl alcohol, phenoxyethanol, phenylmercuric acetate, phenylmercuric nitrate, potassium sorbate, propylparaben, sodium  
20 benzoate, sodium dehydroacetate, sodium propionate, sorbic acid, thimersol, thymo, or mixtures thereof, and

COATING AGENTS: sodium carboxymethyl cellulose, cellulose acetate phthalate, ethylcellulose, gelatin, pharmaceutical glaze, hydroxypropyl cellulose, hydroxypropyl  
25 methylcellulose, hydroxypropyl methyl cellulose phthalate, methylcellulose, polyethylene glycol, polyvinyl acetate phthalate, shellac, sucrose, titanium dioxide, carnauba wax, microcrystalline wax, or mixtures thereof.

The agents either in their free form or as a salt can be combined with a polymer such as  
30 polylactic-glycolic acid (PLGA), poly-(I)-lactic-glycolic-tartaric acid (P(I)LGT) (WO

01/12233), polyglycolic acid (U.S. 3,773,919), polylactic acid (U.S. 4,767,628), poly( $\epsilon$ -caprolactone) and poly(alkylene oxide) (U.S. 20030068384) to create a sustained release formulation. Such formulations can be used to implants that release a peptide or another agent over a period of a few days, a few weeks or several months depending on the polymer, the particle size of the polymer, and the size of the implant (see, e.g., U.S. 6,620,422). Other sustained release formulations and polymers for use in such formulations are described in EP 0 467 389 A2, WO 93/24150, U.S. 5,612,052, WO 97/40085, WO 03/075887, WO 01/01964A2, U.S. 5,922,356, WO 94/155587, WO 02/074247A2, WO 98/25642, U.S. 5,968,895, U.S. 6,180,608, U.S. 20030171296, U.S. 20020176841, U.S. 5,672,659, U.S. 5,893,985, U.S. 5,134,122, U.S. 5,192,741, U.S. 5,192,741, U.S. 4,668,506, U.S. 4,713,244, U.S. 5,445,832 U.S. 4,931,279, U.S. 5,980,945, WO 02/058672, WO 9726015, WO 97/04744, and US20020019446. In such sustained release formulations microparticles of peptide are combined with microparticles of polymer. One or more sustained release implants can be placed in the large intestine, the small intestine or both. U.S. 6,011,011 and WO 94/06452 describe a sustained release formulation providing either polyethylene glycols (i.e. PEG 300 and PEG 400) or triacetin. WO 03/053401 describes a formulation which may both enhance bioavailability and provide controlled release of the agent within the GI tract. Additional controlled release formulations are described in WO 02/38129, EP 326 151, U.S. 5,236,704, WO 02/30398, WO 98/13029; U.S. 20030064105, U.S. 20030138488A1, U.S. 20030216307A1, U.S. 6,667,060, WO 01/49249, WO 01/49311, WO 01/49249, WO 01/49311, and U.S. 5,877,224.

The agents can be administered, e.g., by intravenous injection, intramuscular injection, subcutaneous injection, intraperitoneal injection, topical, sublingual, intraarticular (in the joints), intradermal, buccal, ophthalmic (including intraocular), intranasally (including using a cannula), or by other routes. The agents can be administered orally, e.g., as a tablet or cachet containing a predetermined amount of the active ingredient, gel, pellet, paste, syrup, bolus, electuary, slurry, capsule, powder, granules, as a solution or a suspension in an aqueous liquid or a non-aqueous liquid, as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion, via a micellar formulation (see, e.g. WO 97/11682) via a liposomal formulation (see, e.g., EP 736299, WO 99/59550 and WO 97/13500), via formulations described in WO 03/094886 or in some other

form. Orally administered compositions can include binders, lubricants, inert diluents, lubricating, surface active or dispersing agents, flavoring agents, and humectants. Orally administered formulations such as tablets may optionally be coated or scored and may be formulated so as to provide sustained, delayed or controlled release of the active ingredient  
5 therein. The agents can also be administered transdermally (i.e. via reservoir-type or matrix-type patches, microneedles, thermal poration, hypodermic needles, iontophoresis, electroporation, ultrasound or other forms of sonophoresis, jet injection, or a combination of any of the preceding methods (Prausnitz et al. 2004, Nature Reviews Drug Discovery 3:115-124)). The agents can be administered using high-velocity transdermal particle injection techniques using the hydrogel  
10 particle formulation described in U.S. 20020061336. Additional particle formulations are described in WO 00/45792, WO 00/53160, and WO 02/19989. An example of a transdermal formulation containing plaster and the absorption promoter dimethylisosorbide can be found in WO 89/04179. WO 96/11705 provides formulations suitable for transdermal administration. The agents can be administered in the form a suppository or by other vaginal or rectal means.  
15 The agents can be administered in a transmembrane formulation as described in WO 90/07923. The agents can be administered non-invasively via the dehydrated particles described in U.S. 6,485,706. The agent can be administered in an enteric-coated drug formulation as described in WO 02/49621. The agents can be administered intranasally using the formulation described in U.S. 5,179,079. Formulations suitable for parenteral injection are described in WO 00/62759.  
20 The agents can be administered using the casein formulation described in U. S. 20030206939 and WO 00/06108. The agents can be administered using the particulate formulations described in U.S. 20020034536.

The agents, alone or in combination with other suitable components, can be administered by  
25 pulmonary route utilizing several techniques including but not limited to intratracheal instillation (delivery of solution into the lungs by syringe), intratracheal delivery of liposomes, insufflation (administration of powder formulation by syringe or any other similar device into the lungs) and aerosol inhalation. Aerosols (e.g., jet or ultrasonic nebulizers, metered-dose inhalers (MDIs), and dry-powder inhalers (DPIs)) can also be used in intranasal applications. Aerosol  
30 formulations are stable dispersions or suspensions of solid material and liquid droplets in a

gaseous medium and can be placed into pressurized acceptable propellants, such as hydrofluoroalkanes (HFAs, i.e. HFA-134a and HFA-227, or a mixture thereof), dichlorodifluoromethane (or other chlorofluocarbon propellants such as a mixture of Propellants 11, 12, and/or 114), propane, nitrogen, and the like. Pulmonary formulations may include permeation enhancers such as fatty acids, and saccharides, chelating agents, enzyme inhibitors (e.g., protease inhibitors), adjuvants (e.g., glycocholate, surfactin, span 85, and nafamostat), preservatives (e.g., benzalkonium chloride or chlorobutanol), and ethanol (normally up to 5% but possibly up to 20%, by weight). Ethanol is commonly included in aerosol compositions as it can improve the function of the metering valve and in some cases also improve the stability of the dispersion. Pulmonary formulations may also include surfactants which include but are not limited to bile salts and those described in U.S. 6,524,557 and references therein. The surfactants described in U.S. 6,524,557, e.g., a C8-C16 fatty acid salt, a bile salt, a phospholipid, or alkyl saccharide are advantageous in that some of them also reportedly enhance absorption of the peptide in the formulation. Also suitable in the invention are dry powder formulations comprising a therapeutically effective amount of active compound blended with an appropriate carrier and adapted for use in connection with a dry-powder inhaler. Absorption enhancers which can be added to dry powder formulations of the present invention include those described in U.S. 6,632,456. WO 02/080884 describes new methods for the surface modification of powders. Aerosol formulations may include U.S. 5,230,884, U.S. 5,292,499, WO 01/78694, WO 01/78696, U.S. 2003019437, U. S. 20030165436, and WO 96/40089 (which includes vegetable oil). Sustained release formulations suitable for inhalation are described in U.S. 20010036481A1, 20030232019A1, and U.S. 20040018243A1 as well as in WO 01/13891, WO 02/067902, WO 03/072080, and WO 03/079885. Pulmonary formulations containing microparticles are described in WO 03/015750, U.S. 20030008013, and WO 00/00176. Pulmonary formulations containing stable glassy state powder are described in U.S. 20020141945 and U.S. 6,309,671. Other aerosol formulations are described in EP 1338272A1 WO 90/09781, U. S. 5,348,730, U.S. 6,436,367, WO 91/04011, and U.S. 6,294,153 and U.S. 6,290,987 describes a liposomal based formulation that can be administered via aerosol or other means. Powder formulations for inhalation are described in U.S. 20030053960 and WO 01/60341. The agents can be administered intranasally as described in U.S. 20010038824.

Solutions of medicament in buffered saline and similar vehicles are commonly employed to generate an aerosol in a nebulizer. Simple nebulizers operate on Bernoulli's principle and employ a stream of air or oxygen to generate the spray particles. More complex nebulizers employ ultrasound to create the spray particles. Both types are well known in the art and are described in standard textbooks of pharmacy such as Sprowls' American Pharmacy and Remington's The Science and Practice of Pharmacy. Other devices for generating aerosols employ compressed gases, usually hydrofluorocarbons and chlorofluorocarbons, which are mixed with the medicament and any necessary excipients in a pressurized container, these devices are likewise described in standard textbooks such as Sprowls and Remington.

The agents can be a free acid or base, or a pharmacologically acceptable salt thereof. Solids can be dissolved or dispersed immediately prior to administration or earlier. In some circumstances the preparations include a preservative to prevent the growth of microorganisms. The pharmaceutical forms suitable for injection can include sterile aqueous or organic solutions or dispersions which include, e.g., water, an alcohol, an organic solvent, an oil or other solvent or dispersant (e.g., glycerol, propylene glycol, polyethylene glycol, and vegetable oils). The formulations may contain antioxidants, buffers, bacteriostats, and solutes that render the formulation isotonic with the blood of the intended recipient, and aqueous and non-aqueous sterile suspensions that can include suspending agents, solubilizers, thickening agents, stabilizers, and preservatives. Pharmaceutical agents can be sterilized by filter sterilization or by other suitable means.

The agent can be fused to immunoglobulins or albumin, or incorporated into a liposome to improve half-life. The agent can also be conjugated to polyethylene glycol (PEG) chains. Methods for pegylation and additional formulations containing PEG-conjugates (i.e. PEG-based hydrogels, PEG modified liposomes) can be found in Harris and Chess, Nature Reviews Drug Discovery 2: 214-221 and the references therein. The peptides of the invention may also be conjugated to, for example, alkyl groups (e.g., C1-C20 straight or branched alkyl groups); fatty acid radicals; and combinations of PEG, alkyl groups and fatty acid radicals (see U.S. Patent 6,309,633; Soltero et al., 2001 Innovations in Pharmaceutical Technology 106-110). The agent

can be administered via a nanocochleate or cochleate delivery vehicle (BioDelivery Sciences International). The agents can be delivered transmucosally (i.e. across a mucosal surface such as the vagina, eye or nose) using formulations such as that described in U.S. 5,204,108. The agents can be formulated in microcapsules as described in WO 88/01165. The agent can be  
5 administered intra-orally using the formulations described in U.S. 20020055496, WO 00/47203, and U.S. 6,495,120. The agent can be delivered using nanoemulsion formulations described in WO 01/91728A2.

Suitable pharmaceutical compositions in accordance with the invention will generally include an  
10 amount of the active compound(s) with an acceptable pharmaceutical diluent or excipient, such as a sterile aqueous solution, to give a range of final concentrations, depending on the intended use. The techniques of preparation are generally well known in the art, as exemplified by Remington's Pharmaceutical Sciences (18th Edition, Mack Publishing Company, 1995).

15 The agents described herein and combination therapy agents can be packaged as a kit that includes single or multiple doses of two or more agents, each packaged or formulated individually, or single or multiple doses of two or more agents packaged or formulated in combination. Thus, one or more agents can be present in first container, and the kit can optionally include one or more agents in a second container. The container or containers are  
20 placed within a package, and the package can optionally include administration or dosage instructions. A kit can include additional components such as syringes or other means for administering the agents as well as diluents or other means for formulation.

Methods to increase chemical and/or physical stability of the agents the described herein are  
25 found in U.S. 6,541,606, U.S. 6,068,850, U.S. 6,124,261, U.S. 5,904,935, and WO 00/15224, U.S. 20030069182 (via the additon of nicotinamide), U.S. 20030175230A1, U.S. 20030175230A1, U.S. 20030175239A1, U.S. 20020045582, U.S. 20010031726, WO 02/26248, WO 03/014304, WO 98/00152A1, WO 98/00157A1, WO 90/12029, WO 00/04880, and WO 91/04743, WO 97/04796 and the references cited therein.

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Methods to increase bioavailability of the agents described herein are found in U.S. 6,008,187, U.S. 5,424,289, U.S. 20030198619, WO 90/01329, WO 01/49268, WO 00/32172, and WO 02/064166. Glycyrrhizinate can also be used as an absorption enhancer (see, e.g., EP397447). WO 03/004062 discusses Ulex europaeus I (UEAI) and UEAI mimetics which may be used to  
5 target the agents of the invention to the GI tract.

### Analgesic Agents

The peptides described herein can be used in combination therapy with an analgesic agent, e.g.,  
10 an analgesic compound or an analgesic peptide. The analgesic agent can optionally be covalently attached to a peptide described herein. Among the useful analgesic agents are: Ca channel blockers, 5HT receptor antagonists (for example 5HT3, 5HT4 and 5HT1 receptor antagonists), opioid receptor agonists (loperamide, fedotozine, and fentanyl), NK1 receptor antagonists, CCK receptor agonists (e.g., loxiglumide), NK1 receptor antagonists, NK3 receptor  
15 antagonists, norepinephrine-serotonin reuptake inhibitors (NSRI), vanilloid and cannabanoid receptor agonists, and sialorphin. Analgesics agents in the various classes are described in the literature.

Among the useful analgesic peptides are sialorphin-related peptides, including those comprising  
20 the amino acid sequence QHNPR (SEQ ID NO: ), including: VQHNPR (SEQ ID NO: ); VRQHNPR (SEQ ID NO: ); VRGQHNPR (SEQ ID NO: ); VRGPQHNPR (SEQ ID NO: ); VRGPRQHNPR (SEQ ID NO: ); VRGPRRQHNPR (SEQ ID NO: ); and RQHNPR (SEQ ID NO: ). Sialorphin-related peptides bind to neprilysin and inhibit neprilysin-mediated  
25 breakdown of substance P and Met-enkephalin. Thus, compounds or peptides that are inhibitors of neprilysin are useful analgesic agents which can be administered with the peptides of the invention in a co-therapy or linked to the peptides of the invention, e.g., by a covalent bond. Sialorphin and related peptides are described in U.S. Patent 6,589,750; U.S. 20030078200 A1; and WO 02/051435 A2.



Opioid receptor antagonists and agonists can be administered with the peptides of the invention in co-therapy or linked to the peptide of the invention, e.g., by a covalent bond. For example, opioid receptor antagonists such as naloxone, naltrexone, methyl naloxone, nalmefene, cypridime, beta funaltrexamine, naloxonazine, naltrindole, and nor-binaltorphimine are thought to be useful in the treatment of IBS. It can be useful to formulate opioid antagonists of this type is a delayed and sustained release formulation such that initial release of the antagonist is in the mid to distal small intestine and/or ascending colon. Such antagonists are described in WO 01/32180 A2. Enkephalin pentapeptide (HOE825; Tyr-D-Lys-Gly-Phe-L-homoserine) is an agonist of the mu and delta opioid receptors and is thought to be useful for increasing intestinal motility (Eur. J. Pharm. 219:445, 1992), and this peptide can be used in conjunction with the peptides of the invention. Also useful is trimebutine which is thought to bind to mu/delta/kappa opioid receptors and activate release of motilin and modulate the release of gastrin, vasoactive intestinal peptide, gastrin and glucagons. Kappa opioid receptor agonists such as fedotozine, ketocyclazocine, and compounds described in WO 03/097051 A2 can be used with or linked to the peptides of the invention. In addition, mu opioid receptor agonists such as morphine, diphenyloxylyate, frakefamide (H-Tyr-D-Ala-Phe(F)-Phe-NH<sub>2</sub>; WO 01/019849 A1) and loperamide can be used.

Tyr-Arg (kyotorphin) is a dipeptide that acts by stimulating the release of met-enkephalins to elicit an analgesic effect (J. Biol. Chem. 262:8165, 1987). Kyotorphin can be used with or linked to the peptides of the invention.

CCK receptor agonists such as caerulein from amphibians and other species are useful analgesic agents that can be used with or linked to the peptides of the invention.

Conotoxin peptides represent a large class of analgesic peptides that act at voltage gated Ca channels, NMDA receptors or nicotinic receptors. These peptides can be used with or linked to the peptides of the invention.

Peptide analogs of thymulin (FR 2830451) can have analgesic activity and can be used with or linked to the peptides of the invention.

5 CCK (CCKa or CCKb) receptor antagonists, including loxiglumide and dexloxiglumide (the R-isomer of loxiglumide) (WO 88/05774) can have analgesic activity and can be used with or linked to the peptides of the invention.

Other useful analgesic agents include 5-HT<sub>4</sub> agonists such as tegaserod/zelnorm and lirexapride. Such agonists are described in: EP1321142 A1, WO 03/053432A1, EP 505322 A1, EP 505322  
10 B1, U.S. 5,510,353, EP 507672 A1, EP 507672 B1, and U.S. 5,273,983.

Calcium channel blockers such as ziconotide and related compounds described in, for example, EP 625162B1, U.S. 5,364,842, U.S. 5,587,454, U.S. 5,824,645, U.S. 5,859,186, U.S. 5,994,305, U.S. 6,087,091, U.S. 6,136,786, WO 93/13128 A1, EP 1336409 A1, EP 835126 A1, EP 835126  
15 B1, U.S. 5,795,864, U.S. 5,891,849, U.S. 6,054,429, WO 97/01351 A1, can be used with or linked to the peptides of the invention.

Various antagonists of the NK-1, NK-2, and NK-3 receptors (for a review see Giardina et al. 2003 *Drugs* 6:758) can be used with or linked to the peptides of the invention.

20 NK1 receptor antagonists such as: aprepitant (Merck & Co Inc), vofopitant, ezlopitant (Pfizer, Inc.), R-673 (Hoffmann-La Roche Ltd), SR-14033 and related compounds described in, for example, EP 873753 A1, U.S. 20010006972 A1, U.S. 20030109417 A1, WO 01/52844 A1, can be used with or linked to the peptides of the invention.

25 NK-2 receptor antagonists such as nepadutant (Menarini Ricerche SpA), saredutant (Sanofi-Synthelabo), SR-144190 (Sanofi-Synthelabo) and UK-290795 (Pfizer Inc) can be used with or linked to the peptides of the invention.

NK3 receptor antagonists such as osanetant (Sanofi-Synthelabo), talnetant and related compounds described in, for example, WO 02/094187 A2, EP 876347 A1, WO 97/21680 A1, U.S. 6,277,862, WO 98/11090, WO 95/28418, WO 97/19927, and Boden et al. (*J Med Chem.* 39:1664-75, 1996) can be used with or linked to the peptides of the invention.

5

Norepinephrine-serotonin reuptake inhibitors such as milnacipran and related compounds described in WO 03/077897 A1 can be used with or linked to the peptides of the invention.

Vanilloid receptor antagonists such as arvanil and related compounds described in WO 01/64212  
10 A1 can be used with or linked to the peptides of the invention.

Where the analgesic is a peptide and is covalently linked to a peptide described herein the resulting peptide may also include at least one trypsin or chymotrypsin cleavage site. When present within the peptide, the analgesic peptide may be preceded by (if it is at the carboxy  
15 terminus) or followed by (if it is at the amino terminus) a chymotrypsin or trypsin cleavage site that allows release of the analgesic peptide.

In addition to sialorphin-related peptides, analgesic peptides include: AspPhe, endomorphin-1, endomorphin-2, nocistatin, dalargin, lupron, zicnotide, and substance P.

20

### Methods of Treatment

The peptides of the invention can be used alone or in combination therapy for the treatment or prevention of cancer, pre-cancerous growths, or metastatic growths. For example, they can be  
25 used for the prevention or treatment of: colorectal/local metastasized colorectal cancer, gastrointestinal tract cancer, lung cancer, cancer or pre-cancerous growths or metastatic growths of epithelial cells, polyps, breast, colorectal, lung, ovarian, pancreatic, prostatic, renal, stomach, bladder, liver, esophageal and testicular carcinoma, carcinoma (e.g., basal cell, basosquamous, Brown-Pearce, ductal carcinoma, Ehrlich tumor, Krebs, Merkel cell, small or non-small cell  
30 lung, oat cell, papillary, bronchiolar, squamous cell, transitional cell, Walker), leukemia (e.g., B-

cell, T-cell, HTLV, acute or chronic lymphocytic, mast cell, myeloid), histiocytoma, histiocytosis, Hodgkin's disease, non-Hodgkin's lymphoma, plasmacytoma, reticuloendotheliosis, adenoma, adeno-carcinoma, adenofibroma, adenolymphoma, ameloblastoma, angiokeratoma, angiolymphoid hyperplasia with eosinophilia, sclerosing angioma, angiomatosis, apudoma, 5 branchionia, malignant carcinoid syndrome, carcinoid heart disease, carcinosarcoma, cementoma, cholangioma, cholesteatoma, chondrosarcoma, chondroblastoma, chondrosarcoma, chordoma, choristoma, craniopharyngioma, chondroma, cylindroma, cystadenocarcinoma, cystadenoma, cystosarcoma phyllodes, dysgenninoma, ependymoma, Ewing sarcoma, fibroma, fibrosarcoma, giant cell tumor, ganglioneuroma, glioblastoma, glomangioma, granulosa cell 10 tumor, gynandroblastoma, hamartoma, hemangioendothelioma, hemangioma, hemangiopericytoma, hemangiosarcoma, hepatoma, islet cell tumor, Kaposi sarcoma, leiomyoma, leiomyosarcoma, leukosarcoma, Leydig cell tumor, lipoma, liposarcoma, lymphangioma, lymphangiomyoma, lymphangiosarcoma, medulloblastoma, meningioma, mesenchymoma, mesonephroma, mesothelioma, myoblastoma, myoma, myosarcoma, myxoma, myxosarcoma, 15 neurilemmoma, neuroma, neuroblastoma, neuroepithelioma, neurofibroma, neurofibromatosis, odontoma, osteoma, osteosarcoma, papilloma, paraganglioma, paraganglionia. nonchromaffin, pinealoma, rhabdomyoma, rhabdomyosarcoma, Sertoli cell tumor, teratoma, theca cell tumor, and other diseases in which cells have become dysplastic, immortalized, or transformed.

20 The peptides of the invention can be used alone or in combination therapy for the treatment or prevention of: Familial Adenomatous Polyposis (FAP) (autosomal dominant syndrome) that precedes colon cancer, hereditary nonpolyposis colorectal cancer (HNPCC), and inherited autosomal dominant syndrome.

25 For treatment or prevention of cancer, pre-cancerous growths and metastatic growths, the peptides can be used alone or in combination therapy with radiation or chemotherapeutic agents, an inhibitor of a cGMP-dependent phosphodiesterase or a selective cyclooxygenase-2 inhibitor (a number of selective cyclooxygenase-2 inhibitors are described in WO02062369, hereby incorporated by reference).

30

The peptides can be for treatment or prevention of inflammation. Thus, they can be used alone or in combination with inhibitors of cGMP-dependent phosphodiesterase or a selective cyclooxygenase-2 inhibitor for treatment of: organ inflammation, IBD (e.g, Crohn's disease, ulcerative colitis), asthma, nephritis, hepatitis, pancreatitis, bronchitis, cystic fibrosis, ischemic  
5 bowel diseases, intestinal inflammations/allergies, coeliac disease, proctitis, eosinophilic gastroenteritis, mastocytosis, and other inflammatory disorders.

The peptides can also be used alone or in combination therapy to treat or prevent insulin-related disorders, for example: II diabetes mellitus, hyperglycemia, obesity, disorders associated with  
10 disturbances in glucose or electrolyte transport and insulin secretion in cells, or endocrine disorders. They can be also used in insulin resistance treatment and post-surgical and non-post surgery decrease in insulin responsiveness.

The peptides can be used alone or in combination therapy to prevent or treat respiratory  
15 disorders, including, inhalation, ventilation and mucus secretion disorders, pulmonary hypertension, chronic obstruction of vessels and airways, and irreversible obstructions of vessels and bronchi.

The peptides can be used in combination therapy with a phosphodiesterase inhibitor (examples  
20 of such inhibitors can be found in U.S. 6,333,354, hereby incorporated by reference).

The peptides can also be used alone or in combination therapy to prevent or treat: retinopathy, nephropathy, diabetic angiopathy, and edema formation

25 The peptides can also be used alone or in combination therapy to prevent or treat neurological disorders, for example, headache, anxiety, movement disorders, aggression, psychosis, seizures, panic attacks, hysteria, sleep disorders, depression, schizoaffective disorders, sleep apnea, attention deficit syndromes, memory loss, and narcolepsy. They may also be used as a sedative.

The peptides and detectably labeled peptides can be used as markers to identify, detect, stage, or diagnosis diseases and conditions of the small intestine, including:

5 Crohn's disease, colitis, inflammatory bowel disease, tumors, benign tumors, such as benign stromal tumors, adenoma, angioma, adenomatous (pedunculated and sessile) polyps, malignant, carcinoid tumors, endocrine cell tumors, lymphoma, adenocarcinoma, foregut, midgut, and hindgut carcinoma, gastrointestinal stromal tumor (GIST), such as leiomyoma, cellular leiomyoma, leiomyoblastoma, and leiomyosarcoma, gastrointestinal autonomic nerve tumor, malabsorption syndromes, celiac diseases, diverticulosis, Meckel's diverticulum, colonic diverticula, megacolon, Hirschsprung's disease, irritable bowel syndrome, mesenteric ischemia, ischemic colitis, colorectal cancer, colonic polyposis, polyp syndrome, intestinal adenocarcinoma, Liddle syndrome, Brody myopathy, infantile convulsions, and choreoathetosis

15 The peptides can be conjugated to another molecule (e.g, a diagnostic or therapeutic molecule) to target cells bearing the GCC receptor, e.g., cystic fibrosis lesions and specific cells lining the intestinal tract. Thus, they can be used to target radioactive moieties or therapeutic moieties to the intestine to aid in imaging and diagnosing or treating colorectal/metastasized or local colorectal cancer and to deliver normal copies of the p53 tumor suppressor gene to the intestinal tract.

20 The peptides can be used alone or in combination therapy to treat erectile dysfunction.

The peptides can be used alone or in combination therapy to treat inner ear disorders, e.g., to treat Meniere's disease, including symptoms of the disease such as vertigo, hearing loss, tinnitus, sensation of fullness in the ear, and to maintain fluid homeostasis in the inner ear.

25 The peptides can be used alone or in combination therapy to treat disorders associated with fluid and sodium retention, e.g., diseases of the electrolyte-water/electrolyte transport system within the kidney, gut and urogenital system, congestive heart failure, hypertension, hypotension, liver cirrhosis, and nephrotic syndrome. In addition they can be used to facilitate diuresis or control intestinal fluid.

30

The peptides can be used alone or in combination therapy to treat disorders associated with chloride or bicarbonate secretion, e.g., Cystic Fibrosis.

- 5 The peptides can be used alone or in combination therapy to treat disorders associated with bile secretion. In addition, they can be used to facilitate or control chloride and bile fluid secretion in the gall bladder.

- 10 The peptides can be used alone or in combination therapy to treat disorders associated with liver cell regeneration.

What is claimed is:

1. A purified polypeptide comprising the amino acid sequence: Xaa<sub>1</sub> Xaa<sub>2</sub> Xaa<sub>3</sub> Cys<sub>4</sub> Xaa<sub>5</sub> Xaa<sub>6</sub> Xaa<sub>7</sub> Xaa<sub>8</sub> Xaa<sub>9</sub> Xaa<sub>10</sub> Xaa<sub>11</sub> Cys<sub>12</sub> Xaa<sub>13</sub> Xaa<sub>14</sub> Xaa<sub>15</sub> Xaa<sub>16</sub> (SEQ ID NO:1) wherein:
  - Xaa<sub>1</sub> is Ser, Asn, Tyr, Ala, Gln, Pro, Lys, Gly, or Thr, or is missing;
  - 5 Xaa<sub>2</sub> is His, Asp, Glu, Ala, Ser, Asn, Gly, or is missing;
  - Xaa<sub>3</sub> is Thr, Asp, Ser, Glu, Pro, Val or Leu;
  - Xaa<sub>5</sub> is Asp, Ile or Glu;
  - Xaa<sub>6</sub> is Ile, Trp or Leu;
  - Xaa<sub>7</sub> is Cys, Ser, or Tyr;
  - 10 Xaa<sub>8</sub> is Ala, Val, Thr, Ile, Met or is missing;
  - Xaa<sub>9</sub> is a) any amino acid, b) Phe, Tyr, Asn, Trp, c) an amino acid other than Phe, Trp, or Tyr, d) non-aromatic amino acid or e) is missing;
  - Xaa<sub>10</sub> is Ala, Val, Met, Thr or Ile;
  - Xaa<sub>11</sub> is Ala or Val;
  - 15 Xaa<sub>13</sub> is Ala or Thr;
  - Xaa<sub>14</sub> is Gly, Ala or Ser;
  - Xaa<sub>15</sub> is Cys, Tyr or is missing; and
  - Xaa<sub>16</sub> is: a) Trp, Tyr or Phe to create a chymotrypsin cleavage site; b) Lys or Arg to create a trypsin cleavage site; c) is missing or d) His or Leu or Ser.
- 20 2. The purified polypeptide of claim 1 wherein Xaa<sub>1</sub> is preceded by Lys or Tyr.
3. A composition comprising the polypeptide of claim 1 and a pharmaceutically acceptable carrier.
4. A composition comprising a polypeptide comprising the amino acid sequence: Xaa<sub>1</sub> Xaa<sub>2</sub> Xaa<sub>3</sub> Cys<sub>4</sub> Xaa<sub>5</sub> Xaa<sub>6</sub> Xaa<sub>7</sub> Xaa<sub>8</sub> Xaa<sub>9</sub> Xaa<sub>10</sub> Xaa<sub>11</sub> Cys<sub>12</sub> Xaa<sub>13</sub> Xaa<sub>14</sub> Xaa<sub>15</sub> Xaa<sub>16</sub> (SEQ ID  
25 NO:1) wherein:
  - Xaa<sub>1</sub> is Ser, Asn, Tyr, Ala, Gln, Pro, Lys, Gly, or Thr, or is missing;
  - Xaa<sub>2</sub> is His, Asp, Glu, Ala, Ser, Asn, Gly, Pro or is missing;
  - Xaa<sub>3</sub> is Thr, Asp, Ser, Glu, Pro, Val or Leu;



Xaa<sub>5</sub> is Asp, Ile or Glu;

Xaa<sub>6</sub> is Ile, Trp or Leu;

Xaa<sub>7</sub> is Cys, Ser, or Tyr;

Xaa<sub>8</sub> is Ala, Val, Thr, Ile, Met or is missing;

5 Xaa<sub>9</sub> is Phe, Tyr, Asn, Trp, an amino acid other than Phe, Trp, or Tyr, is a non-aromatic amino acid or is missing;

Xaa<sub>10</sub> is Ala, Val, Met, Thr or Ile;

Xaa<sub>11</sub> is Ala or Val;

Xaa<sub>13</sub> is Ala or Thr; Xaa<sub>14</sub> is Gly, Ala or Ser;

10 Xaa<sub>15</sub> is Cys, Tyr or is missing;

Xaa<sub>16</sub> is: a) Trp, Tyr or Phe to create a chymotrypsin cleavage site; b) Lys or Arg to create a trypsin cleavage site; c) is missing or d) His or Leu or Ser and a pharmaceutically acceptable carrier.

15 5. A purified polypeptide comprising the amino acid sequence: Xaa<sub>1</sub> Xaa<sub>2</sub> Xaa<sub>3</sub> Cys<sub>4</sub> Xaa<sub>5</sub> Xaa<sub>6</sub> Xaa<sub>7</sub> Xaa<sub>8</sub> Xaa<sub>9</sub> Xaa<sub>10</sub> Xaa<sub>11</sub> Cys<sub>12</sub> Xaa<sub>13</sub> Xaa<sub>14</sub> Xaa<sub>15</sub> Xaa<sub>16</sub> (SEQ ID NO:1) wherein:

Xaa<sub>1</sub> is Asn, any amino acid or is missing;

Xaa<sub>2</sub> is Asp, Glu, any amino acid or is missing;

Xaa<sub>3</sub> is Asp or Glu;

20 Xaa<sub>5</sub> is any amino acid or Glu;

Xaa<sub>6</sub> is any amino acid or Leu;

Xaa<sub>7</sub> is Cys;

Xaa<sub>8</sub> is any amino acid or Val;

Xaa<sub>9</sub> is Asn, Gln, Tyr;

25 Xaa<sub>10</sub> is any amino acid or Val;

Xaa<sub>11</sub> is any amino acid or Ala;

Xaa<sub>13</sub> is any amino acid or Thr;

Xaa<sub>14</sub> is any amino acid or Gly;

Xaa<sub>15</sub> is Cys;

30 Xaa<sub>16</sub> is any amino acid, Leu or missing

6. A purified polypeptide comprising the amino acid sequence: Asn<sub>1</sub> Xaa<sub>2</sub> Xaa<sub>3</sub> Xaa<sub>4</sub> Glu<sub>5</sub> Leu<sub>6</sub> Xaa<sub>7</sub> Val<sub>8</sub> Asn<sub>9</sub> Xaa<sub>10</sub> Xaa<sub>11</sub> Xaa<sub>12</sub> Thr<sub>13</sub> Xaa<sub>14</sub> Xaa<sub>15</sub> Leu<sub>16</sub> (SEQ ID NO: \_\_)
- Xaa<sub>2</sub> is Asp or Glu;
- Xaa<sub>3</sub> is Asp or Glu;
- 5 Xaa<sub>4</sub> is Cys or Mpt (mercaptoproline) or Pen (penicillamine) or Dpr (diaminopropionic acid) or Asp or Glu;
- Xaa<sub>7</sub> is Cys or Mpt (mercaptoproline) or Pen (penicillamine) or Dpr (diaminopropionic acid) or Asp or Glu;
- Xaa<sub>10</sub> is Val or Pro;
- 10 Xaa<sub>11</sub> is Ala or Aib (alpha-aminoisobutyric acid);
- Xaa<sub>12</sub> is Cys or Mpt (mercaptoproline) or Pen (penicillamine) or Dpr (diaminopropionic acid) or Asp or Glu;
- Xaa<sub>14</sub> is Gly or Ala;
- Xaa<sub>15</sub> is Cys or Mpt (mercaptoproline) or Pen (penicillamine) or Dpr (diaminopropionic acid) or Asp or Glu; and
- 15
7. The polypeptide of claim 1 wherein Xaa<sub>15</sub> is other than Cys or is missing and Xaa<sub>7</sub> is Ser or an amino acid other than Cys.
8. The polypeptide of claim 1 wherein at least 5 of Xaa<sub>1</sub>, Xaa<sub>2</sub>, Xaa<sub>3</sub>, Xaa<sub>5</sub>, Xaa<sub>6</sub>, Xaa<sub>7</sub>, Xaa<sub>8</sub>,  
20 Xaa<sub>9</sub>, Xaa<sub>10</sub>, Xaa<sub>11</sub>, Xaa<sub>13</sub>, Xaa<sub>14</sub>, and Xaa<sub>16</sub> are any amino acid other than Cys.
9. The polypeptide of claim 1 wherein: Xaa<sub>9</sub> is any amino acid other than Gln.
10. The polypeptide of claim 1 wherein Xaa<sub>2</sub> and Xaa<sub>3</sub> are Glu.
11. A polypeptide comprising the amino acid sequence of claim 1 wherein the polypeptide is not cleaved after Xaa<sub>9</sub> by chymotrypsin.
- 25 12. The polypeptide of claim 1 wherein the polypeptide does not comprise the amino acid sequence PGTCEICAYAACTGC.

13. A purified polypeptide comprising the amino acid sequence KPGTCEICAYAACTGC.
14. A purified polypeptide selected from the group consisting of:
- a) a polypeptide comprising the amino acid sequence PGTCEICAXAACTGC wherein X is any amino acid other than Phe;
- 5 b) a polypeptide comprising the amino acid sequence PGTCEICAXAACTGC wherein X is any amino acid other than Phe and Trp;
- c) a polypeptide comprising the amino acid sequence PGTCEICAXAACTGC wherein X is any amino acid other than Phe, Trp, Ile, Leu and Val;
- d) a polypeptide comprising the amino acid sequence PGTCEICAXAACTGC wherein X is any amino acid other than Phe, Trp, Ile, Leu, Val and His;
- 10 e) a polypeptide comprising the amino acid sequence PGTCEICAXAACTGC wherein X is any non-aromatic amino acid or
- f) a polypeptide comprising the amino acid sequence PGTCEICAXAACTGC wherein X is missing.
- 15
15. A purified polypeptide comprising an amino acid sequence selected from the group consisting of:
- PGTCEICASAACTGC (SEQ ID NO: )
- PGTCEICATAACTGC (SEQ ID NO: )
- 20 PGTCEICANAACTGC (SEQ ID NO: )
- PGTCEICAQAACTGC (SEQ ID NO: )
- PGTCEICARAACTGC (SEQ ID NO: )
- PGTCEICAEAACTGC (SEQ ID NO: )
- PGTCEICADAACTGC (SEQ ID NO: )
- 25 PGTCEICAGAACTGC (SEQ ID NO: )
- PGTCEICAAAACTGC (SEQ ID NO: )
- PGTCEICAMAACTGC (SEQ ID NO: )
- PGTCEICAIAACTGC (SEQ ID NO: )
- PGTCEICALAACTGC (SEQ ID NO: )
- 30 PGTCEICAVAACTGC (SEQ ID NO: ) and

PGTCEICAHAACTGC (SEQ ID NO: )

16. A purified polypeptide comprising an amino acid sequence shown in Figure 1.
- 5 17. A purified polypeptide comprising an amino acid sequence shown in Figure 2 wherein Xaa is any amino acid.
18. The purified polypeptide of claim 17 wherein Xaa is any amino acid other than Cys.
- 10 19. A purified polypeptide comprising an amino acid sequence selected from the group consisting of:
- PGTCEGICAYAACTGC (SEQ ID NO: )
- PGTCEIGCAYAACTGC (SEQ ID NO: )
- PGTCEICGAYAACTGC (SEQ ID NO: )
- 15 PGTCEICAGYAACTGC (SEQ ID NO: )
- PGTCEICAYGAACTGC (SEQ ID NO: )
- PGTCEICAYAGACTGC (SEQ ID NO: )
- PGTCEICAYAAGCTGC (SEQ ID NO: )
- PGTCEICAYAACGTGC (SEQ ID NO: )
- 20 PGTCEICAYAACTGGC (SEQ ID NO: )
- PGTCAEICAYAACTGC (SEQ ID NO: )
- PGTCEAICAYAACTGC (SEQ ID NO: )
- PGTCEIACAYAACTGC (SEQ ID NO: )
- PGTCEICAAYAACTGC (SEQ ID NO: )
- 25 PGTCEICAYAAACTGC (SEQ ID NO: )
- PGTCEICAYAACATGC (SEQ ID NO: )
- PGTCEICAYAACTAGC (SEQ ID NO: )
- PGTCEICAYAACTGAC (SEQ ID NO: )
- PGTCAEICAAYAACTGC (SEQ ID NO: )
- 30 PGTCEAICAAYAACTGC (SEQ ID NO: ) and

PGTCEIACAAYA ACTGC (SEQ ID NO: ).

20. The polypeptide of claim 1 further comprising an amino acid sequence selected from:  
Asp Phe, the amino acid sequence of endomorphin-1, the amino acid sequence of endomorphin-  
5 2, the amino acid sequence of nocistatin, the amino acid sequence of dalargin, the amino acid  
sequence of lupron, and the amino acid sequence of substance P.

21. A method for treating a gastrointestinal disorder comprising administering a composition  
comprising the purified polypeptide of claim 1.

22. The method of claim 21 wherein the gastrointestinal disorder is: a gastrointestinal  
10 motility disorder, irritable bowel syndrome, a functional gastrointestinal disorder,  
gastroesophageal reflux disease, duodenogastric reflux, functional heartburn, dyspepsia,  
functional dyspepsia, nonulcer dyspepsia, gastroparesis, chronic intestinal pseudo-obstruction, or  
colonic pseudo-obstruction.

23. A method for treating obesity comprising administering a composition comprising the  
15 purified polypeptide of claim 1.

24. A method for treating congestive heart failure comprising administering a composition  
comprising the purified polypeptide of claim 1.

25. A method for treating benign prostatic hyperplasia comprising administering a  
composition comprising the purified polypeptide of claim 1.

20 26. A method for treating constipation comprising administering a composition comprising  
the purified polypeptide of claim 1

27. The method of claim 21 wherein the polypeptide does not comprise the amino acid  
sequence PGTCEICAYA ACTGC or the amino acid sequence

NDDCELCVNVACTGCL.

28. A method for increasing gastrointestinal motility in a patient, the method comprising administering to the patient the polypeptide of claim 1.
29. A method for decreasing gastrointestinal pain or visceral pain in a patient, the method  
5 comprising administering to the patient the polypeptide of claim 1.
30. A method for increasing the activity of an intestinal guanylate cyclase (GC-C) receptor in a patient, the method comprising administering to the patient the polypeptide of claim 1.
31. A method for treating a patient suffering a gastrointestinal disorder, the method  
10 comprising administering to the patient a composition comprising a complete or partial agonist of the GC-C receptor.
32. A method for treating a patient suffering from constipation, the method comprising administering a composition comprising a complete or partial agonist of the GC-C receptor.
33. A method for increasing gastrointestinal motility in a patient, the method comprising  
15 administering to the patient a composition comprising a complete or partial agonist of the GC-C receptor.
34. A method for decreasing gastrointestinal pain or visceral pain in a patient, the method comprising administering to the patient a composition comprising a complete or partial agonist of the GC-C receptor.
35. A method for treating congestive heart failure, the method comprising administering a  
20 complete or partial agonist of the GC-C receptor.
36. A method for treating benign prostatic hyperplasia, the method comprising administering a complete or partial agonist of the GC-C receptor.

37. A method for treating obesity, the method comprising administering a complete or partial agonist of the GC-C receptor.
38. A purified polypeptide comprising the amino acid sequence: Xaa<sub>1</sub> Xaa<sub>2</sub> Xaa<sub>3</sub> Cys<sub>4</sub> Xaa<sub>5</sub> Xaa<sub>6</sub> Xaa<sub>7</sub> Xaa<sub>8</sub> Xaa<sub>9</sub> Xaa<sub>10</sub> Xaa<sub>11</sub> Cys<sub>12</sub> Xaa<sub>13</sub> Xaa<sub>14</sub> Xaa<sub>15</sub> Xaa<sub>16</sub> (SEQ ID NO:1) wherein:
- 5 Xaa<sub>1</sub> is any amino acid or is missing;  
Xaa<sub>2</sub> is any amino acid or is missing;  
Xaa<sub>3</sub> is any amino acid or is missing;  
Xaa<sub>5</sub> is Glu;  
Xaa<sub>6</sub> is Tyr, Trp, Phe or Leu;
- 10 Xaa<sub>7</sub> is Cys;  
Xaa<sub>8</sub> is any of the 20 naturally-occurring amino acids other than Cys or is missing;  
Xaa<sub>9</sub> is any of the 20 naturally-occurring amino acids;  
Xaa<sub>10</sub> is Pro or Gly;  
Xaa<sub>11</sub> is any of the 20 naturally-occurring amino acids;
- 15 Xaa<sub>13</sub> is Thr, Val or Gly;  
Xaa<sub>14</sub> is Gly or Ala;  
Xaa<sub>15</sub> is Cys; and  
Xaa<sub>16</sub> is any of the 20 naturally-occurring amino acids or is missing.
39. The purified polypeptide of claim 38 wherein Xaa<sub>9</sub> is Asn.
- 20 40. The purified polypeptide of claim 38 wherein Xaa<sub>11</sub> is Ala or Thr.
41. The purified polypeptide of claim 38 wherein Xaa<sub>8</sub> is missing.
42. The purified polypeptide of claim 38 wherein Xaa<sub>16</sub> is Tyr.
- 25 43. The purified polypeptide of claim 38 wherein Xaa<sub>4</sub> is immediately preceded by an amino acid sequence selected from: Ser His Thr; Pro Ser Thr; Thr; Pro Asp Pro; Ile Ala Glu Asp Ser His

Thr; Ile Ala Gln Asp Pro Ser Thr; Ala Asn Thr; Asn Thr; Asp Pro Asn Thr; Lys Asn Thr; Pro Asn Thr; Ile Ala Gln Asp Pro Asn Thr; Lys Pro Asn Thr; Asp Pro Gly Thr; Glu Asp Pro Gly Thr; Pro Gly Thr; Pro Ala Thr; Val Ala Ala Arg Ala Asp Leu; Gly Asp Asp; Asn Asp Glu; Gln Glu Asp; Asn Asp Asp; Arg Thr Ile Ala Asn Asp Asp; Thr Ile Ala Asn Asp Asp; Asp Asp; Arg Thr Met Asp  
 5 Asn Asp Glu; Arg Thr Ile Ala Gly Asp Asp; Arg Thr Ile Ala Asn Asp; Asp; Glu Asp; Arg Ser Ile Ser Gln Glu Asp; Thr Asp Glu; Arg Thr Ile Ala Thr Asp Glu; Glu; Ile Ile Thr Pro Pro Asp Pro; Gln Glu Leu; Lys Asp Asp; Gln Glu Glu; Arg Tyr Ile Asn Gln Glu Glu; Ala Ser Ser Tyr Ala Ser; and Thr Ser Ser Tyr Ala Ser.

10 44. A pharmaceutical composition comprising the polypeptide of claim 38 and a pharmaceutically acceptable carrier.

45. A purified polypeptide comprising the amino acid sequence: Xaa<sub>1</sub> Xaa<sub>2</sub> Xaa<sub>3</sub> Cys<sub>4</sub> Xaa<sub>5</sub> Xaa<sub>6</sub> Xaa<sub>7</sub> Xaa<sub>8</sub> Xaa<sub>9</sub> Xaa<sub>10</sub> Xaa<sub>11</sub> Cys<sub>12</sub> Xaa<sub>13</sub> Xaa<sub>14</sub> Xaa<sub>15</sub> Xaa<sub>16</sub> (SEQ ID NO:1) wherein:

Xaa<sub>1</sub> is: a) Ser, Asn, Tyr, Ala, Gln, Pro, Lys, Gly, or Thr, or is missing; b) preceded by Lys or Tyr; c) any amino acid; d) missing; e) any amino acid other than Cys; or f) Lys or Arg;

Xaa<sub>2</sub> is: a) His, Asp, Glu, Ala, Ser, Asn, Gly, or is missing; b) His, Asp, Glu, Ala, Ser, Asn, Gly, Pro or is missing; c) Asp, Glu, any amino acid or is missing; d) Asp or Glu; e) any amino acid other than Cys; e) Glu; f) missing; g) Trp, Tyr or Phe; or h) Lys or Arg;

20 Xaa<sub>3</sub> is: a) Thr, Asp, Ser, Glu, Pro, Val or Leu; Asp or Glu; b) any amino acid other than Cys; c) Glu; d) Thr; e) Thr, Asp, Ser, Glu, Pro, Val or Leu or is missing; f) Trp, Tyr or Phe; or g) Lys or Arg;

Xaa<sub>4</sub> is: a) Cys, Mpt (mercaptoproline), Pen (penicillamine), Dpr (diaminopropionic acid), Asp, or Glu;

25 Xaa<sub>5</sub> is: a) any amino acid; b) Glu, Asp, Gln, Gly or Pro; c) Glu; d) Glu or Asp; e) Asp, Ile or Glu; f) any amino acid; or g) any amino acid other than Cys;

Xaa<sub>6</sub> is: a) Leu, Ile, Val, Ala, Lys, Arg, Trp, Tyr or Phe; b) Leu, Ile, Val, Lys, Arg, Trp, Tyr or Phe; Leu, Ile, Lys, Arg, Trp, Tyr or Phe; c) Leu, Ile, Val, Trp, Tyr or Phe; d) Trp, Tyr, Phe or Leu; e) Leu, Ile or Val; f) Ile, Trp or Leu; g) Trp, Tyr or Phe; h) Ile or Leu; i) Tyr; j) any



amino acid; k) any amino acid except Leu; l) any natural or non-natural aromatic amino acid; or m) any amino acid other than Cys;

Xaa<sub>7</sub> is: a) Cys, Ser, or Tyr; Cys; b) Cys, Mpt (mercaptoproline), Pen (penicillamine), Dpr (diaminopropionic acid), Asp or Glu; c) Ser; or d) an amino acid other than Cys;

5 Xaa<sub>8</sub> is: a) Ala, Val, or Ile; b) Ala, Val, Thr, Ile, Met or is missing; c) any amino acid; d) Val; e) any amino acid other than Cys; or f) missing;

Xaa<sub>9</sub> is: a) any amino acid; b) any amino acid other than Phe and Tyr; c) any amino acid other than Phe, Tyr, and Trp; d) any amino acid other than Phe, Tyr, Trp, Ile, Leu and Val; e) any amino acid other than Phe, Tyr, Trp, Ile, Leu, Val, and His; f) any amino acid other than Gln; g) 10 any amino acid other than Lys, Arg, Phe, Tyr, and Trp; h) any amino acid other than Lys, Arg, Phe, Tyr, Trp, Ile, Leu and Val; i) any amino acid other than Lys, Arg, Phe, Tyr, Trp, Ile, Leu, Val, and His; j) any non-aromatic amino acid; k) missing; l) Phe, Tyr, Asn, or Trp; m) Asn, Tyr, Asp or Ala; n) Asn, Gln, or Tyr; o) Phe or Tyr; p) Asn; or q) any amino acid other than Cys;

Xaa<sub>10</sub> is: a) Ala, Pro or Gly; b) Pro or Gly; c) Pro; d) Ala, Val, Met, Thr or Ile; e) any 15 amino acid; f) Val; g) Val or Pro; h) Ala or Val; i) any amino acid other than Cys; j) Pro; or k) Gly;

Xaa<sub>11</sub> is: a) any amino acid; b) Ala, Leu, Ser, Gly, Val, Glu, Gln, Ile, Leu, Lys, Arg, or Asp; c) Ala or Gly; d) Ala; e) Ala or Val; f) any amino acid; g) Ala or Aib (alpha-aminoisobutyric acid); h) any amino acid other than Cys; i) Ala or Thr; or j) Thr.

20 Xaa<sub>12</sub> is: a) Cys, Mpt (mercaptoproline), Pen (penicillamine), Dpr (diaminopropionic acid), Asp, or Glu; or b) any amino acid other than Cys;

Xaa<sub>13</sub> is: a) Thr, Ala, Asn, Lys, Arg, or Trp; b) Thr, Ala, Lys, Arg, or Trp; c) any amino acid; d) any non-aromatic amino acid; e) Thr, Ala, or Trp; f) Trp, Tyr or Phe; g) Thr or Ala; h) any amino acid; i) Thr; j) any amino acid other than Cys; k) Thr, Val, or Gly; l) Thr or Val, m) 25 Thr or Gly, n) Val or Thr; o) Val; p) Thr; or q) Gly;

Xaa<sub>14</sub> is: a) Gly, Pro or Ala; b) Gly; c) any amino acid; d) Gly, Ala or Ser; e) Gly or Ala; f) any amino acid other than Cys; or g) Ala;

Xaa<sub>15</sub> is: a) Cys, Tyr or is missing; b) Cys; c) Cys, Mpt (mercaptoproline), Pen (penicillamine), Dpr (diaminopropionic acid), Asp, Glu; or d) any amino acid other than Cys or 30 is missing; and

Xaa<sub>16</sub> is: a) Trp, Tyr, Phe, Asn, Ile, Val, His or Leu; b) Trp, Tyr, Phe, Asn or Leu; c) Trp, Tyr, Phe or Leu; d) Trp, Tyr, or Phe; e) Leu, Ile or Val; f) His, Leu or Ser; g) Tyr or Leu; Lys or Arg; h) His; i) any amino acid, j) Leu, or missing; k) Trp, Tyr, Phe, Lys, Arg or is missing; l) missing; m) any amino acid other than Cys; or n) Tyr.

5

46. A composition comprising the polypeptide of claim 45 and a pharmaceutically acceptable carrier.

47. A purified polypeptide comprising the amino acid sequence: Xaa<sub>1</sub> Xaa<sub>2</sub> Xaa<sub>3</sub> Xaa<sub>4</sub> Xaa<sub>5</sub>  
10 Xaa<sub>6</sub> Xaa<sub>7</sub> Xaa<sub>8</sub> Xaa<sub>9</sub> Xaa<sub>10</sub> Xaa<sub>11</sub> Xaa<sub>12</sub> Xaa<sub>13</sub> Xaa<sub>14</sub> Xaa<sub>15</sub> Xaa<sub>16</sub> (SEQ ID NO:1) wherein:

Xaa<sub>1</sub> is any amino acid or is missing;

Xaa<sub>2</sub> is any amino acid or is missing;

Xaa<sub>3</sub> is any amino acid or is missing;

Xaa<sub>4</sub> is Cys, Mpt (mercaptoproline), Pen (penicillamine), Dpr (diaminopropionic acid),

15 Asp or Glu;

Xaa<sub>5</sub> is Glu;

Xaa<sub>6</sub> is Tyr, Trp, Phe or Leu;

Xaa<sub>7</sub> is Cys, Mpt (mercaptoproline), Pen (penicillamine), Dpr (diaminopropionic acid),

Asp or Glu;

20 Xaa<sub>8</sub> is any amino acid other than Cys or is missing;

Xaa<sub>9</sub> is any amino acid;

Xaa<sub>10</sub> is Pro or Gly;

Xaa<sub>11</sub> is any amino acid;

Xaa<sub>12</sub> is Cys, Mpt (mercaptoproline), Pen (penicillamine), Dpr (diaminopropionic acid),

25 Asp or Glu;

Xaa<sub>13</sub> is Thr, Val or Gly;

Xaa<sub>14</sub> is Gly or Ala;

Xaa<sub>15</sub> is Cys, Mpt (mercaptoproline), Pen (penicillamine), Dpr (diaminopropionic acid),

Asp or Glu; and

30 Xaa<sub>16</sub> is any amino acid or is missing.



























FIG. 1 (sheet 13 of 13)

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Pro Gly Thr Cys Gly Glu Ile Cys --- Tyr --- --- Cys Thr --- Cys (SEQ ID NO: )
Pro Gly Thr Cys Gly Glu Ile Cys --- Tyr --- Ala Cys --- Gly Cys (SEQ ID NO: )
Pro Gly Thr Cys Gly Glu Ile Cys --- Tyr --- Ala Cys --- --- Cys (SEQ ID NO: )
Pro Gly Thr Cys Gly Glu Ile Cys --- Tyr --- Ala Cys Thr --- Cys (SEQ ID NO: )
Pro Gly Thr Cys Gly Glu Ile Cys --- Tyr Ala --- Cys --- Gly Cys (SEQ ID NO: )
Pro Gly Thr Cys Gly Glu Ile Cys --- Tyr Ala --- Cys --- --- Cys (SEQ ID NO: )
Pro Gly Thr Cys Gly Glu Ile Cys --- Tyr Ala --- Cys Thr --- Cys (SEQ ID NO: )
Pro Gly Thr Cys Gly Glu Ile Cys --- Tyr Ala Ala --- Gly Cys (SEQ ID NO: )
Pro Gly Thr Cys Gly Glu Ile Cys --- Tyr Ala Ala Cys --- --- Cys (SEQ ID NO: )
Pro Gly Thr Cys Gly Glu Ile Cys --- Tyr Ala Ala Cys Thr --- Cys (SEQ ID NO: )
Pro Gly Thr Cys Gly Glu Ile Cys Ala --- Ala Ala Cys Thr Gly Cys (SEQ ID NO: )
Pro Gly Thr Cys Gly Glu Ile Cys Ala --- --- Ala Cys Thr Gly Cys (SEQ ID NO: )
Pro Gly Thr Cys Gly Glu Ile Cys Ala --- --- --- Cys Thr Gly Cys (SEQ ID NO: )
Pro Gly Thr Cys Gly Glu Ile Cys Ala --- --- --- Cys --- Gly Cys (SEQ ID NO: )
Pro Gly Thr Cys Gly Glu Ile Cys Ala --- --- --- Cys Thr --- Cys (SEQ ID NO: )
Pro Gly Thr Cys Gly Glu Ile Cys Ala --- --- Ala Cys --- Gly Cys (SEQ ID NO: )
Pro Gly Thr Cys Gly Glu Ile Cys Ala --- --- Ala Cys --- --- Cys (SEQ ID NO: )
Pro Gly Thr Cys Gly Glu Ile Cys Ala --- --- Ala Cys Thr --- Cys (SEQ ID NO: )
Pro Gly Thr Cys Gly Glu Ile Cys Ala --- Ala --- Cys --- Gly Cys (SEQ ID NO: )
Pro Gly Thr Cys Gly Glu Ile Cys Ala --- Ala --- Cys --- --- Cys (SEQ ID NO: )
Pro Gly Thr Cys Gly Glu Ile Cys Ala --- Ala Ala Cys Thr --- Cys (SEQ ID NO: )
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr --- Ala Cys Thr Gly Cys (SEQ ID NO: )
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr --- --- Cys Thr Gly Cys (SEQ ID NO: )
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr --- --- Cys --- Gly Cys (SEQ ID NO: )
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr --- --- Cys --- --- Cys (SEQ ID NO: )
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr --- --- Cys Thr --- Cys (SEQ ID NO: )
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr --- Ala Cys --- Gly Cys (SEQ ID NO: )
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr --- Ala Cys --- --- Cys (SEQ ID NO: )
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr --- Ala Cys Thr --- Cys (SEQ ID NO: )
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala --- Cys Thr Gly Cys (SEQ ID NO: )
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala --- Cys --- Gly Cys (SEQ ID NO: )
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala --- Cys --- --- Cys (SEQ ID NO: )
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala --- Cys Thr --- Cys (SEQ ID NO: )
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys --- Gly Cys (SEQ ID NO: )
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys --- --- Cys (SEQ ID NO: )
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr --- Cys (SEQ ID NO: )

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FIG. 2 (sheet 91 of 91)

Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Xaa' Cys Xaa' (SEQ ID NO: )  
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Xaa' Cys Xaa' Xaa' (SEQ ID NO: )  
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Xaa' Cys Xaa' Xaa' Xaa' (SEQ ID NO: )  
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys Xaa' (SEQ ID NO: )  
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys Xaa' Xaa' (SEQ ID NO: )  
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys Xaa' Xaa' Xaa' (SEQ ID NO: )  
Pro Gly Thr Cys Gly Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys Xaa' Xaa' Xaa' Xaa' (SEQ ID NO: )

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FIGURE 3 (sheet 3 of 68)

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Cys Glu Tyr Cys Gln Asn Gly Thr Cys Thr Gly Cys Tyr  
 Cys Glu Tyr Cys Gln Asn Gly Thr Cys Thr Ala Cys Tyr  
 Cys Glu Tyr Cys Gln Asn Gly Thr Cys Val Gly Cys Tyr  
 Cys Glu Tyr Cys Gln Asn Gly Thr Cys Val Ala Cys Tyr  
 Cys Glu Tyr Cys Gln Asn Gly Thr Cys Gly Gly Cys Tyr  
 Cys Glu Tyr Cys Gln Asn Gly Thr Cys Gly Ala Cys Tyr  
 Cys Glu Tyr Cys Glu Asn Pro Ala Cys Thr Gly Cys Tyr  
 Cys Glu Tyr Cys Glu Asn Pro Ala Cys Thr Ala Cys Tyr  
 Cys Glu Tyr Cys Glu Asn Pro Ala Cys Val Gly Cys Tyr  
 Cys Glu Tyr Cys Glu Asn Pro Ala Cys Val Ala Cys Tyr  
 Cys Glu Tyr Cys Glu Asn Pro Ala Cys Gly Gly Cys Tyr  
 Cys Glu Tyr Cys Glu Asn Pro Ala Cys Gly Ala Cys Tyr  
 Cys Glu Tyr Cys Glu Asn Pro Thr Cys Thr Gly Cys Tyr  
 Cys Glu Tyr Cys Glu Asn Pro Thr Cys Thr Ala Cys Tyr  
 Cys Glu Tyr Cys Glu Asn Pro Thr Cys Val Gly Cys Tyr  
 Cys Glu Tyr Cys Glu Asn Pro Thr Cys Val Ala Cys Tyr  
 Cys Glu Tyr Cys Glu Asn Pro Thr Cys Gly Gly Cys Tyr  
 Cys Glu Tyr Cys Glu Asn Pro Thr Cys Gly Ala Cys Tyr  
 Cys Glu Tyr Cys Glu Asn Gly Ala Cys Thr Gly Cys Tyr  
 Cys Glu Tyr Cys Glu Asn Gly Ala Cys Val Gly Cys Tyr  
 Cys Glu Tyr Cys Glu Asn Gly Ala Cys Val Ala Cys Tyr  
 Cys Glu Tyr Cys Glu Asn Gly Ala Cys Gly Gly Cys Tyr  
 Cys Glu Tyr Cys Glu Asn Gly Ala Cys Gly Ala Cys Tyr  
 Cys Glu Tyr Cys Glu Asn Gly Ala Cys Thr Gly Cys Tyr  
 Cys Glu Tyr Cys Glu Asn Gly Thr Cys Thr Ala Cys Tyr  
 Cys Glu Tyr Cys Glu Asn Gly Thr Cys Val Gly Cys Tyr  
 Cys Glu Tyr Cys Gly Asn Pro Thr Cys Val Ala Cys Tyr  
 Cys Glu Tyr Cys Gly Asn Pro Thr Cys Val Ala Cys Tyr  
 Cys Glu Tyr Cys Gly Asn Pro Thr Cys Val Ala Cys Tyr  
 Cys Glu Tyr Cys Gly Asn Pro Thr Cys Val Ala Cys Tyr  
 Cys Glu Tyr Cys Gly Asn Pro Thr Cys Val Ala Cys Tyr  
 Cys Glu Tyr Cys Gly Asn Pro Thr Cys Val Ala Cys Tyr  
 Cys Glu Tyr Cys Gly Asn Pro Thr Cys Val Ala Cys Tyr  
 Cys Glu Tyr Cys Gly Asn Pro Thr Cys Val Ala Cys Tyr  
 Cys Glu Tyr Cys Gly Asn Gly Ala Cys Thr Gly Cys Tyr  
 Cys Glu Tyr Cys Gly Asn Gly Ala Cys Thr Ala Cys Tyr  
 Cys Glu Tyr Cys Gly Asn Gly Ala Cys Val Gly Cys Tyr  
 Cys Glu Tyr Cys Gly Asn Gly Ala Cys Val Ala Cys Tyr  
 Cys Glu Tyr Cys Gly Asn Gly Ala Cys Gly Gly Cys Tyr  
 Cys Glu Tyr Cys Gly Asn Gly Ala Cys Gly Ala Cys Tyr  
 Cys Glu Tyr Cys Gly Asn Gly Thr Cys Thr Gly Cys Tyr  
 Cys Glu Tyr Cys Gly Asn Gly Thr Cys Thr Ala Cys Tyr  
 Cys Glu Tyr Cys Gly Asn Gly Thr Cys Val Gly Cys Tyr  
 Cys Glu Tyr Cys Gly Asn Gly Thr Cys Val Ala Cys Tyr  
 Cys Glu Tyr Cys Gly Asn Gly Thr Cys Gly Gly Cys Tyr  
 Cys Glu Tyr Cys Gly Asn Gly Thr Cys Gly Ala Cys Tyr  
 Cys Glu Tyr Cys His Asn Pro Ala Cys Thr Gly Cys Tyr  
 Cys Glu Tyr Cys His Asn Pro Ala Cys Thr Ala Cys Tyr  
 Cys Glu Tyr Cys His Asn Pro Ala Cys Val Gly Cys Tyr

Cys Glu Tyr Cys His Asn Pro Ala Cys Val Ala Cys Tyr  
Cys Glu Tyr Cys His Asn Pro Ala Cys Gly Gly Cys Tyr  
Cys Glu Tyr Cys His Asn Pro Ala Cys Gly Ala Cys Tyr  
Cys Glu Tyr Cys His Asn Pro Thr Cys Thr Gly Cys Tyr  
Cys Glu Tyr Cys His Asn Pro Thr Cys Thr Ala Cys Tyr  
Cys Glu Tyr Cys His Asn Pro Thr Cys Val Gly Cys Tyr  
Cys Glu Tyr Cys His Asn Pro Thr Cys Val Ala Cys Tyr  
Cys Glu Tyr Cys His Asn Pro Thr Cys Gly Gly Cys Tyr  
Cys Glu Tyr Cys His Asn Pro Thr Cys Gly Ala Cys Tyr  
Cys Glu Tyr Cys His Asn Gly Ala Cys Thr Gly Cys Tyr  
Cys Glu Tyr Cys His Asn Gly Ala Cys Thr Ala Cys Tyr  
Cys Glu Tyr Cys His Asn Gly Ala Cys Val Gly Cys Tyr  
Cys Glu Tyr Cys His Asn Gly Ala Cys Val Ala Cys Tyr  
Cys Glu Tyr Cys His Asn Gly Ala Cys Val Ala Cys Tyr  
Cys Glu Tyr Cys His Asn Gly Ala Cys Gly Gly Cys Tyr  
Cys Glu Tyr Cys His Asn Gly Thr Cys Thr Gly Cys Tyr  
Cys Glu Tyr Cys His Asn Gly Thr Cys Thr Ala Cys Tyr  
Cys Glu Tyr Cys His Asn Gly Thr Cys Val Gly Cys Tyr  
Cys Glu Tyr Cys His Asn Gly Thr Cys Val Ala Cys Tyr  
Cys Glu Tyr Cys His Asn Gly Thr Cys Gly Gly Cys Tyr  
Cys Glu Tyr Cys His Asn Gly Thr Cys Gly Ala Cys Tyr  
Cys Glu Tyr Cys His Asn Gly Thr Cys Thr Gly Cys Tyr  
Cys Glu Tyr Cys Ile Asn Pro Ala Cys Thr Gly Cys Tyr  
Cys Glu Tyr Cys Ile Asn Pro Ala Cys Thr Ala Cys Tyr  
Cys Glu Tyr Cys Ile Asn Pro Ala Cys Val Gly Cys Tyr  
Cys Glu Tyr Cys Ile Asn Pro Ala Cys Val Ala Cys Tyr  
Cys Glu Tyr Cys Ile Asn Pro Ala Cys Gly Gly Cys Tyr  
Cys Glu Tyr Cys Ile Asn Pro Thr Cys Gly Ala Cys Tyr  
Cys Glu Tyr Cys Ile Asn Gly Ala Cys Thr Gly Cys Tyr  
Cys Glu Tyr Cys Ile Asn Gly Ala Cys Thr Ala Cys Tyr  
Cys Glu Tyr Cys Ile Asn Gly Ala Cys Val Gly Cys Tyr  
Cys Glu Tyr Cys Ile Asn Gly Ala Cys Val Ala Cys Tyr  
Cys Glu Tyr Cys Ile Asn Gly Ala Cys Gly Gly Cys Tyr  
Cys Glu Tyr Cys Ile Asn Gly Ala Cys Gly Ala Cys Tyr  
Cys Glu Tyr Cys Ile Asn Gly Thr Cys Thr Gly Cys Tyr  
Cys Glu Tyr Cys Ile Asn Gly Thr Cys Thr Ala Cys Tyr  
Cys Glu Tyr Cys Ile Asn Gly Thr Cys Val Gly Cys Tyr  
Cys Glu Tyr Cys Ile Asn Gly Thr Cys Val Ala Cys Tyr  
Cys Glu Tyr Cys Ile Asn Gly Thr Cys Gly Gly Cys Tyr  
Cys Glu Tyr Cys Ile Asn Gly Thr Cys Gly Ala Cys Tyr  
Cys Glu Tyr Cys Leu Asn Pro Ala Cys Thr Gly Cys Tyr  
Cys Glu Tyr Cys Leu Asn Pro Ala Cys Thr Ala Cys Tyr  
Cys Glu Tyr Cys Leu Asn Pro Ala Cys Val Gly Cys Tyr  
Cys Glu Tyr Cys Leu Asn Pro Ala Cys Val Ala Cys Tyr  
Cys Glu Tyr Cys Leu Asn Pro Ala Cys Gly Gly Cys Tyr  
Cys Glu Tyr Cys Leu Asn Pro Ala Cys Gly Ala Cys Tyr  
Cys Glu Tyr Cys Leu Asn Pro Thr Cys Thr Gly Cys Tyr  
Cys Glu Tyr Cys Leu Asn Pro Thr Cys Thr Ala Cys Tyr  
Cys Glu Tyr Cys Leu Asn Pro Thr Cys Val Gly Cys Tyr  
Cys Glu Tyr Cys Leu Asn Pro Thr Cys Val Ala Cys Tyr  
Cys Glu Tyr Cys Leu Asn Pro Thr Cys Gly Gly Cys Tyr  
Cys Glu Tyr Cys Leu Asn Pro Thr Cys Gly Ala Cys Tyr

Cys Glu Tyr Cys Leu Asn Gly Ala Cys Thr Gly Cys Tyr  
 Cys Glu Tyr Cys Leu Asn Gly Ala Cys Thr Ala Cys Tyr  
 Cys Glu Tyr Cys Leu Asn Gly Ala Cys Val Gly Cys Tyr  
 Cys Glu Tyr Cys Leu Asn Gly Ala Cys Val Ala Cys Tyr  
 Cys Glu Tyr Cys Leu Asn Gly Ala Cys Gly Gly Cys Tyr  
 Cys Glu Tyr Cys Leu Asn Gly Ala Cys Gly Ala Cys Tyr  
 Cys Glu Tyr Cys Leu Asn Gly Thr Cys Thr Gly Cys Tyr  
 Cys Glu Tyr Cys Leu Asn Gly Thr Cys Thr Ala Cys Tyr  
 Cys Glu Tyr Cys Leu Asn Gly Thr Cys Val Gly Cys Tyr  
 Cys Glu Tyr Cys Leu Asn Gly Thr Cys Val Ala Cys Tyr  
 Cys Glu Tyr Cys Leu Asn Gly Thr Cys Gly Gly Cys Tyr  
 Cys Glu Tyr Cys Leu Asn Gly Thr Cys Gly Ala Cys Tyr  
 Cys Glu Tyr Cys Lys Asn Pro Ala Cys Thr Gly Cys Tyr  
 Cys Glu Tyr Cys Lys Asn Pro Ala Cys Thr Ala Cys Tyr  
 Cys Glu Tyr Cys Lys Asn Pro Ala Cys Val Gly Cys Tyr  
 Cys Glu Tyr Cys Lys Asn Pro Ala Cys Val Ala Cys Tyr  
 Cys Glu Tyr Cys Lys Asn Pro Ala Cys Gly Gly Cys Tyr  
 Cys Glu Tyr Cys Lys Asn Pro Ala Cys Gly Ala Cys Tyr  
 Cys Glu Tyr Cys Lys Asn Pro Thr Cys Thr Gly Cys Tyr  
 Cys Glu Tyr Cys Lys Asn Pro Thr Cys Thr Ala Cys Tyr  
 Cys Glu Tyr Cys Lys Asn Pro Thr Cys Val Gly Cys Tyr  
 Cys Glu Tyr Cys Lys Asn Pro Thr Cys Val Ala Cys Tyr  
 Cys Glu Tyr Cys Lys Asn Pro Thr Cys Gly Gly Cys Tyr  
 Cys Glu Tyr Cys Lys Asn Pro Thr Cys Gly Ala Cys Tyr  
 Cys Glu Tyr Cys Lys Asn Gly Ala Cys Thr Gly Cys Tyr  
 Cys Glu Tyr Cys Lys Asn Gly Ala Cys Thr Ala Cys Tyr  
 Cys Glu Tyr Cys Lys Asn Gly Ala Cys Val Gly Cys Tyr  
 Cys Glu Tyr Cys Lys Asn Gly Ala Cys Val Ala Cys Tyr  
 Cys Glu Tyr Cys Lys Asn Gly Ala Cys Gly Gly Cys Tyr  
 Cys Glu Tyr Cys Lys Asn Gly Ala Cys Gly Ala Cys Tyr  
 Cys Glu Tyr Cys Lys Asn Gly Thr Cys Thr Gly Cys Tyr  
 Cys Glu Tyr Cys Lys Asn Gly Thr Cys Thr Ala Cys Tyr  
 Cys Glu Tyr Cys Met Asn Pro Ala Cys Thr Gly Cys Tyr  
 Cys Glu Tyr Cys Met Asn Pro Ala Cys Thr Ala Cys Tyr  
 Cys Glu Tyr Cys Met Asn Pro Ala Cys Val Gly Cys Tyr  
 Cys Glu Tyr Cys Met Asn Pro Ala Cys Val Ala Cys Tyr  
 Cys Glu Tyr Cys Met Asn Pro Ala Cys Gly Gly Cys Tyr  
 Cys Glu Tyr Cys Met Asn Pro Ala Cys Gly Ala Cys Tyr  
 Cys Glu Tyr Cys Met Asn Pro Thr Cys Thr Gly Cys Tyr  
 Cys Glu Tyr Cys Met Asn Pro Thr Cys Thr Ala Cys Tyr  
 Cys Glu Tyr Cys Met Asn Pro Thr Cys Val Gly Cys Tyr  
 Cys Glu Tyr Cys Met Asn Pro Thr Cys Val Ala Cys Tyr  
 Cys Glu Tyr Cys Met Asn Pro Thr Cys Gly Gly Cys Tyr  
 Cys Glu Tyr Cys Met Asn Pro Thr Cys Gly Ala Cys Tyr  
 Cys Glu Tyr Cys Met Asn Gly Ala Cys Thr Gly Cys Tyr  
 Cys Glu Tyr Cys Met Asn Gly Ala Cys Thr Ala Cys Tyr  
 Cys Glu Tyr Cys Met Asn Gly Ala Cys Val Gly Cys Tyr  
 Cys Glu Tyr Cys Met Asn Gly Ala Cys Val Ala Cys Tyr  
 Cys Glu Tyr Cys Met Asn Gly Ala Cys Gly Gly Cys Tyr  
 Cys Glu Tyr Cys Met Asn Gly Ala Cys Gly Ala Cys Tyr  
 Cys Glu Tyr Cys Met Asn Gly Thr Cys Thr Gly Cys Tyr  
 Cys Glu Tyr Cys Met Asn Gly Thr Cys Thr Ala Cys Tyr  
 Cys Glu Tyr Cys Met Asn Gly Thr Cys Val Gly Cys Tyr

FIGURE 3 (sheet 6 of 68)

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Cys Glu Tyr Cys Met Asn Gly Thr Cys Val Ala Cys Tyr  
 Cys Glu Tyr Cys Met Asn Gly Thr Cys Gly Gly Cys Tyr  
 Cys Glu Tyr Cys Met Asn Gly Thr Cys Gly Ala Cys Tyr  
 Cys Glu Tyr Cys Phe Asn Pro Ala Cys Thr Gly Cys Tyr  
 Cys Glu Tyr Cys Phe Asn Pro Ala Cys Thr Ala Cys Tyr  
 Cys Glu Tyr Cys Phe Asn Pro Ala Cys Val Gly Cys Tyr  
 Cys Glu Tyr Cys Phe Asn Pro Ala Cys Val Ala Cys Tyr  
 Cys Glu Tyr Cys Phe Asn Pro Ala Cys Gly Gly Cys Tyr  
 Cys Glu Tyr Cys Phe Asn Pro Ala Cys Gly Ala Cys Tyr  
 Cys Glu Tyr Cys Phe Asn Pro Thr Cys Thr Gly Cys Tyr  
 Cys Glu Tyr Cys Phe Asn Pro Thr Cys Thr Ala Cys Tyr  
 Cys Glu Tyr Cys Phe Asn Pro Thr Cys Val Gly Cys Tyr  
 Cys Glu Tyr Cys Phe Asn Pro Thr Cys Val Ala Cys Tyr  
 Cys Glu Tyr Cys Phe Asn Pro Thr Cys Gly Gly Cys Tyr  
 Cys Glu Tyr Cys Phe Asn Pro Thr Cys Gly Ala Cys Tyr  
 Cys Glu Tyr Cys Phe Asn Gly Ala Cys Thr Gly Cys Tyr  
 Cys Glu Tyr Cys Phe Asn Gly Ala Cys Thr Ala Cys Tyr  
 Cys Glu Tyr Cys Phe Asn Gly Ala Cys Val Gly Cys Tyr  
 Cys Glu Tyr Cys Phe Asn Gly Ala Cys Val Ala Cys Tyr  
 Cys Glu Tyr Cys Phe Asn Gly Ala Cys Gly Gly Cys Tyr  
 Cys Glu Tyr Cys Phe Asn Gly Ala Cys Gly Ala Cys Tyr  
 Cys Glu Tyr Cys Phe Asn Gly Thr Cys Thr Gly Cys Tyr  
 Cys Glu Tyr Cys Phe Asn Gly Thr Cys Thr Ala Cys Tyr  
 Cys Glu Tyr Cys Phe Asn Gly Thr Cys Val Gly Cys Tyr  
 Cys Glu Tyr Cys Phe Asn Gly Thr Cys Val Ala Cys Tyr  
 Cys Glu Tyr Cys Phe Asn Gly Thr Cys Gly Gly Cys Tyr  
 Cys Glu Tyr Cys Pro Asn Pro Ala Cys Thr Gly Cys Tyr  
 Cys Glu Tyr Cys Pro Asn Pro Ala Cys Thr Ala Cys Tyr  
 Cys Glu Tyr Cys Pro Asn Pro Ala Cys Val Ala Cys Tyr  
 Cys Glu Tyr Cys Pro Asn Pro Ala Cys Gly Gly Cys Tyr  
 Cys Glu Tyr Cys Pro Asn Pro Thr Cys Thr Gly Cys Tyr  
 Cys Glu Tyr Cys Pro Asn Pro Thr Cys Thr Ala Cys Tyr  
 Cys Glu Tyr Cys Pro Asn Pro Thr Cys Val Gly Cys Tyr  
 Cys Glu Tyr Cys Pro Asn Pro Thr Cys Val Ala Cys Tyr  
 Cys Glu Tyr Cys Pro Asn Pro Thr Cys Gly Gly Cys Tyr  
 Cys Glu Tyr Cys Pro Asn Gly Ala Cys Thr Gly Cys Tyr  
 Cys Glu Tyr Cys Pro Asn Gly Ala Cys Thr Ala Cys Tyr  
 Cys Glu Tyr Cys Pro Asn Gly Ala Cys Val Gly Cys Tyr  
 Cys Glu Tyr Cys Pro Asn Gly Ala Cys Val Ala Cys Tyr  
 Cys Glu Tyr Cys Pro Asn Gly Ala Cys Gly Gly Cys Tyr  
 Cys Glu Tyr Cys Pro Asn Gly Ala Cys Gly Ala Cys Tyr  
 Cys Glu Tyr Cys Pro Asn Gly Thr Cys Thr Gly Cys Tyr  
 Cys Glu Tyr Cys Pro Asn Gly Thr Cys Thr Ala Cys Tyr  
 Cys Glu Tyr Cys Pro Asn Gly Thr Cys Val Gly Cys Tyr  
 Cys Glu Tyr Cys Pro Asn Gly Thr Cys Val Ala Cys Tyr  
 Cys Glu Tyr Cys Pro Asn Gly Thr Cys Gly Gly Cys Tyr  
 Cys Glu Tyr Cys Pro Asn Gly Thr Cys Gly Ala Cys Tyr  
 Cys Glu Tyr Cys Ser Asn Pro Ala Cys Thr Gly Cys Tyr  
 Cys Glu Tyr Cys Ser Asn Pro Ala Cys Thr Ala Cys Tyr  
 Cys Glu Tyr Cys Ser Asn Pro Ala Cys Val Gly Cys Tyr  
 Cys Glu Tyr Cys Ser Asn Pro Ala Cys Val Ala Cys Tyr  
 Cys Glu Tyr Cys Ser Asn Pro Ala Cys Gly Gly Cys Tyr  
 Cys Glu Tyr Cys Ser Asn Pro Ala Cys Gly Ala Cys Tyr



FIGURE 3 (sheet 7 of 68)

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Cys Glu Tyr Cys Ser Asn Pro Thr Cys Thr Gly Cys Tyr  
 Cys Glu Tyr Cys Ser Asn Pro Thr Cys Thr Ala Cys Tyr  
 Cys Glu Tyr Cys Ser Asn Pro Thr Cys Val Gly Cys Tyr  
 Cys Glu Tyr Cys Ser Asn Pro Thr Cys Val Ala Cys Tyr  
 Cys Glu Tyr Cys Ser Asn Pro Thr Cys Gly Gly Cys Tyr  
 Cys Glu Tyr Cys Ser Asn Pro Thr Cys Gly Ala Cys Tyr  
 Cys Glu Tyr Cys Ser Asn Gly Ala Cys Thr Gly Cys Tyr  
 Cys Glu Tyr Cys Ser Asn Gly Ala Cys Thr Ala Cys Tyr  
 Cys Glu Tyr Cys Ser Asn Gly Ala Cys Val Gly Cys Tyr  
 Cys Glu Tyr Cys Ser Asn Gly Ala Cys Val Ala Cys Tyr  
 Cys Glu Tyr Cys Ser Asn Gly Ala Cys Gly Gly Cys Tyr  
 Cys Glu Tyr Cys Ser Asn Gly Ala Cys Gly Ala Cys Tyr  
 Cys Glu Tyr Cys Ser Asn Gly Thr Cys Thr Gly Cys Tyr  
 Cys Glu Tyr Cys Ser Asn Gly Thr Cys Thr Ala Cys Tyr  
 Cys Glu Tyr Cys Ser Asn Gly Thr Cys Val Gly Cys Tyr  
 Cys Glu Tyr Cys Ser Asn Gly Thr Cys Val Ala Cys Tyr  
 Cys Glu Tyr Cys Ser Asn Gly Thr Cys Gly Gly Cys Tyr  
 Cys Glu Tyr Cys Ser Asn Gly Thr Cys Gly Ala Cys Tyr  
 Cys Glu Tyr Cys Thr Asn Pro Ala Cys Thr Gly Cys Tyr  
 Cys Glu Tyr Cys Thr Asn Pro Ala Cys Thr Ala Cys Tyr  
 Cys Glu Tyr Cys Thr Asn Pro Ala Cys Val Gly Cys Tyr  
 Cys Glu Tyr Cys Thr Asn Pro Ala Cys Val Ala Cys Tyr  
 Cys Glu Tyr Cys Thr Asn Pro Ala Cys Gly Gly Cys Tyr  
 Cys Glu Tyr Cys Thr Asn Pro Ala Cys Gly Ala Cys Tyr  
 Cys Glu Tyr Cys Thr Asn Pro Thr Cys Thr Gly Cys Tyr  
 Cys Glu Tyr Cys Thr Asn Pro Thr Cys Thr Ala Cys Tyr  
 Cys Glu Tyr Cys Thr Asn Pro Thr Cys Val Gly Cys Tyr  
 Cys Glu Tyr Cys Thr Asn Gly Thr Cys Val Ala Cys Tyr  
 Cys Glu Tyr Cys Thr Asn Gly Thr Cys Gly Gly Cys Tyr  
 Cys Glu Tyr Cys Thr Asn Gly Thr Cys Gly Ala Cys Tyr  
 Cys Glu Tyr Cys Thr Asn Gly Thr Cys Thr Gly Cys Tyr  
 Cys Glu Tyr Cys Thr Asn Gly Thr Cys Thr Ala Cys Tyr  
 Cys Glu Tyr Cys Thr Asn Gly Thr Cys Val Gly Cys Tyr  
 Cys Glu Tyr Cys Thr Asn Gly Thr Cys Val Ala Cys Tyr  
 Cys Glu Tyr Cys Thr Asn Gly Thr Cys Gly Gly Cys Tyr  
 Cys Glu Tyr Cys Trp Asn Pro Ala Cys Thr Gly Cys Tyr  
 Cys Glu Tyr Cys Trp Asn Pro Ala Cys Thr Ala Cys Tyr  
 Cys Glu Tyr Cys Trp Asn Pro Ala Cys Val Gly Cys Tyr  
 Cys Glu Tyr Cys Trp Asn Pro Ala Cys Val Ala Cys Tyr  
 Cys Glu Tyr Cys Trp Asn Pro Ala Cys Gly Gly Cys Tyr  
 Cys Glu Tyr Cys Trp Asn Pro Ala Cys Gly Ala Cys Tyr  
 Cys Glu Tyr Cys Trp Asn Pro Thr Cys Thr Gly Cys Tyr  
 Cys Glu Tyr Cys Trp Asn Pro Thr Cys Thr Ala Cys Tyr  
 Cys Glu Tyr Cys Trp Asn Pro Thr Cys Val Gly Cys Tyr  
 Cys Glu Tyr Cys Trp Asn Pro Thr Cys Val Ala Cys Tyr  
 Cys Glu Tyr Cys Trp Asn Pro Thr Cys Gly Gly Cys Tyr  
 Cys Glu Tyr Cys Trp Asn Pro Thr Cys Gly Ala Cys Tyr  
 Cys Glu Tyr Cys Trp Asn Gly Ala Cys Thr Gly Cys Tyr  
 Cys Glu Tyr Cys Trp Asn Gly Ala Cys Thr Ala Cys Tyr  
 Cys Glu Tyr Cys Trp Asn Gly Ala Cys Val Gly Cys Tyr

Cys Glu Tyr Cys Trp Asn Gly Ala Cys Val Ala Cys Tyr  
 Cys Glu Tyr Cys Trp Asn Gly Ala Cys Gly Gly Cys Tyr  
 Cys Glu Tyr Cys Trp Asn Gly Ala Cys Gly Ala Cys Tyr  
 Cys Glu Tyr Cys Trp Asn Gly Thr Cys Thr Gly Cys Tyr  
 Cys Glu Tyr Cys Trp Asn Gly Thr Cys Thr Ala Cys Tyr  
 Cys Glu Tyr Cys Trp Asn Gly Thr Cys Val Gly Cys Tyr  
 Cys Glu Tyr Cys Trp Asn Gly Thr Cys Val Ala Cys Tyr  
 Cys Glu Tyr Cys Trp Asn Gly Thr Cys Gly Gly Cys Tyr  
 Cys Glu Tyr Cys Trp Asn Gly Thr Cys Gly Ala Cys Tyr  
 Cys Glu Tyr Cys Tyr Asn Pro Ala Cys Thr Gly Cys Tyr  
 Cys Glu Tyr Cys Tyr Asn Pro Ala Cys Thr Ala Cys Tyr  
 Cys Glu Tyr Cys Tyr Asn Pro Ala Cys Val Gly Cys Tyr  
 Cys Glu Tyr Cys Tyr Asn Pro Ala Cys Val Ala Cys Tyr  
 Cys Glu Tyr Cys Tyr Asn Pro Ala Cys Gly Gly Cys Tyr  
 Cys Glu Tyr Cys Tyr Asn Pro Ala Cys Gly Ala Cys Tyr  
 Cys Glu Tyr Cys Tyr Asn Pro Thr Cys Thr Gly Cys Tyr  
 Cys Glu Tyr Cys Tyr Asn Pro Thr Cys Thr Ala Cys Tyr  
 Cys Glu Tyr Cys Tyr Asn Pro Thr Cys Val Gly Cys Tyr  
 Cys Glu Tyr Cys Tyr Asn Pro Thr Cys Val Ala Cys Tyr  
 Cys Glu Tyr Cys Tyr Asn Pro Thr Cys Gly Gly Cys Tyr  
 Cys Glu Tyr Cys Tyr Asn Gly Ala Cys Thr Ala Cys Tyr  
 Cys Glu Tyr Cys Tyr Asn Gly Ala Cys Gly Ala Cys Tyr  
 Cys Glu Tyr Cys Tyr Asn Gly Thr Cys Thr Gly Cys Tyr  
 Cys Glu Tyr Cys Tyr Asn Gly Thr Cys Thr Ala Cys Tyr  
 Cys Glu Tyr Cys Tyr Asn Gly Thr Cys Val Ala Cys Tyr  
 Cys Glu Tyr Cys Tyr Asn Gly Thr Cys Val Gly Cys Tyr  
 Cys Glu Tyr Cys Tyr Asn Gly Thr Cys Val Ala Cys Tyr  
 Cys Glu Tyr Cys Tyr Asn Gly Thr Cys Gly Gly Cys Tyr  
 Cys Glu Tyr Cys Tyr Asn Gly Thr Cys Val Ala Cys Tyr  
 Cys Glu Tyr Cys Tyr Asn Gly Thr Cys Thr Ala Cys Tyr  
 Cys Glu Tyr Cys Tyr Asn Gly Thr Cys Val Gly Cys Tyr  
 Cys Glu Tyr Cys Tyr Asn Gly Thr Cys Val Ala Cys Tyr  
 Cys Glu Tyr Cys Tyr Asn Gly Thr Cys Gly Gly Cys Tyr  
 Cys Glu Tyr Cys Tyr Asn Gly Thr Cys Gly Ala Cys Tyr



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Cys Glu Trp Cys Arg Asn Pro Thr Cys Val Ala Cys Tyr  
 Cys Glu Trp Cys Arg Asn Pro Thr Cys Gly Gly Cys Tyr  
 Cys Glu Trp Cys Arg Asn Pro Thr Cys Gly Ala Cys Tyr  
 Cys Glu Trp Cys Arg Asn Gly Ala Cys Thr Gly Cys Tyr  
 Cys Glu Trp Cys Arg Asn Gly Ala Cys Thr Ala Cys Tyr  
 Cys Glu Trp Cys Arg Asn Gly Ala Cys Val Gly Cys Tyr  
 Cys Glu Trp Cys Arg Asn Gly Ala Cys Val Ala Cys Tyr  
 Cys Glu Trp Cys Arg Asn Gly Ala Cys Gly Gly Cys Tyr  
 Cys Glu Trp Cys Arg Asn Gly Ala Cys Gly Ala Cys Tyr  
 Cys Glu Trp Cys Arg Asn Gly Thr Cys Thr Gly Cys Tyr  
 Cys Glu Trp Cys Arg Asn Gly Thr Cys Thr Ala Cys Tyr  
 Cys Glu Trp Cys Arg Asn Gly Thr Cys Val Gly Cys Tyr  
 Cys Glu Trp Cys Arg Asn Gly Thr Cys Val Ala Cys Tyr  
 Cys Glu Trp Cys Arg Asn Gly Thr Cys Gly Gly Cys Tyr  
 Cys Glu Trp Cys Arg Asn Gly Thr Cys Gly Ala Cys Tyr  
 Cys Glu Trp Cys Arg Asn Gly Thr Cys Gly Ala Cys Tyr  
 Cys Glu Trp Cys Asn Asn Pro Ala Cys Thr Gly Cys Tyr  
 Cys Glu Trp Cys Asn Asn Pro Ala Cys Thr Ala Cys Tyr  
 Cys Glu Trp Cys Asn Asn Pro Ala Cys Val Gly Cys Tyr  
 Cys Glu Trp Cys Asn Asn Pro Ala Cys Val Ala Cys Tyr  
 Cys Glu Trp Cys Asn Asn Pro Ala Cys Gly Gly Cys Tyr  
 Cys Glu Trp Cys Asn Asn Pro Ala Cys Gly Ala Cys Tyr  
 Cys Glu Trp Cys Asn Asn Pro Thr Cys Thr Gly Cys Tyr  
 Cys Glu Trp Cys Asn Asn Pro Thr Cys Thr Ala Cys Tyr  
 Cys Glu Trp Cys Asn Asn Pro Thr Cys Val Gly Cys Tyr  
 Cys Glu Trp Cys Asn Asn Pro Thr Cys Val Ala Cys Tyr  
 Cys Glu Trp Cys Asn Asn Pro Thr Cys Gly Gly Cys Tyr  
 Cys Glu Trp Cys Asn Asn Gly Thr Cys Thr Gly Cys Tyr  
 Cys Glu Trp Cys Asn Asn Gly Thr Cys Thr Ala Cys Tyr  
 Cys Glu Trp Cys Asn Asn Gly Thr Cys Val Gly Cys Tyr  
 Cys Glu Trp Cys Asn Asn Gly Thr Cys Val Ala Cys Tyr  
 Cys Glu Trp Cys Asn Asn Gly Thr Cys Gly Gly Cys Tyr  
 Cys Glu Trp Cys Asn Asn Gly Thr Cys Gly Ala Cys Tyr  
 Cys Glu Trp Cys Asp Asn Pro Ala Cys Thr Gly Cys Tyr  
 Cys Glu Trp Cys Asp Asn Pro Ala Cys Thr Ala Cys Tyr  
 Cys Glu Trp Cys Asp Asn Pro Ala Cys Val Gly Cys Tyr  
 Cys Glu Trp Cys Asp Asn Pro Ala Cys Val Ala Cys Tyr  
 Cys Glu Trp Cys Asp Asn Pro Ala Cys Gly Gly Cys Tyr  
 Cys Glu Trp Cys Asp Asn Pro Ala Cys Gly Ala Cys Tyr  
 Cys Glu Trp Cys Asp Asn Pro Thr Cys Thr Gly Cys Tyr  
 Cys Glu Trp Cys Asp Asn Pro Thr Cys Thr Ala Cys Tyr  
 Cys Glu Trp Cys Asp Asn Pro Thr Cys Val Gly Cys Tyr  
 Cys Glu Trp Cys Asp Asn Pro Thr Cys Val Ala Cys Tyr  
 Cys Glu Trp Cys Asp Asn Pro Thr Cys Gly Gly Cys Tyr  
 Cys Glu Trp Cys Asp Asn Gly Ala Cys Thr Gly Cys Tyr  
 Cys Glu Trp Cys Asp Asn Gly Ala Cys Thr Ala Cys Tyr  
 Cys Glu Trp Cys Asp Asn Gly Ala Cys Val Gly Cys Tyr  
 Cys Glu Trp Cys Asp Asn Gly Ala Cys Val Ala Cys Tyr  
 Cys Glu Trp Cys Asp Asn Gly Ala Cys Gly Gly Cys Tyr  
 Cys Glu Trp Cys Asp Asn Gly Ala Cys Gly Ala Cys Tyr



FIGURE 3 (sheet 12 of 68)

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Cys Glu Trp Cys Gly Asn Pro Ala Cys Val Ala Cys Tyr  
 Cys Glu Trp Cys Gly Asn Pro Ala Cys Gly Gly Cys Tyr  
 Cys Glu Trp Cys Gly Asn Pro Ala Cys Gly Ala Cys Tyr  
 Cys Glu Trp Cys Gly Asn Pro Thr Cys Thr Gly Cys Tyr  
 Cys Glu Trp Cys Gly Asn Pro Thr Cys Thr Ala Cys Tyr  
 Cys Glu Trp Cys Gly Asn Pro Thr Cys Val Gly Cys Tyr  
 Cys Glu Trp Cys Gly Asn Pro Thr Cys Val Ala Cys Tyr  
 Cys Glu Trp Cys Gly Asn Pro Thr Cys Gly Gly Cys Tyr  
 Cys Glu Trp Cys Gly Asn Pro Thr Cys Gly Ala Cys Tyr  
 Cys Glu Trp Cys Gly Asn Gly Ala Cys Thr Gly Cys Tyr  
 Cys Glu Trp Cys Gly Asn Gly Ala Cys Thr Ala Cys Tyr  
 Cys Glu Trp Cys Gly Asn Gly Ala Cys Val Gly Cys Tyr  
 Cys Glu Trp Cys Gly Asn Gly Thr Cys Val Gly Cys Tyr  
 Cys Glu Trp Cys Gly Asn Gly Thr Cys Val Ala Cys Tyr  
 Cys Glu Trp Cys Gly Asn Gly Thr Cys Gly Gly Cys Tyr  
 Cys Glu Trp Cys Gly Asn Gly Thr Cys Gly Ala Cys Tyr  
 Cys Glu Trp Cys His Asn Pro Ala Cys Thr Gly Cys Tyr  
 Cys Glu Trp Cys His Asn Pro Ala Cys Thr Ala Cys Tyr  
 Cys Glu Trp Cys His Asn Pro Ala Cys Val Gly Cys Tyr  
 Cys Glu Trp Cys His Asn Pro Ala Cys Val Ala Cys Tyr  
 Cys Glu Trp Cys His Asn Pro Ala Cys Gly Gly Cys Tyr  
 Cys Glu Trp Cys His Asn Pro Ala Cys Gly Ala Cys Tyr  
 Cys Glu Trp Cys His Asn Pro Thr Cys Thr Gly Cys Tyr  
 Cys Glu Trp Cys His Asn Pro Thr Cys Thr Ala Cys Tyr  
 Cys Glu Trp Cys His Asn Pro Thr Cys Val Gly Cys Tyr  
 Cys Glu Trp Cys His Asn Pro Thr Cys Val Ala Cys Tyr  
 Cys Glu Trp Cys His Asn Pro Thr Cys Gly Gly Cys Tyr  
 Cys Glu Trp Cys His Asn Gly Ala Cys Gly Ala Cys Tyr  
 Cys Glu Trp Cys His Asn Gly Thr Cys Thr Gly Cys Tyr  
 Cys Glu Trp Cys His Asn Gly Thr Cys Thr Ala Cys Tyr  
 Cys Glu Trp Cys His Asn Gly Thr Cys Val Gly Cys Tyr  
 Cys Glu Trp Cys His Asn Gly Thr Cys Val Ala Cys Tyr  
 Cys Glu Trp Cys His Asn Gly Thr Cys Gly Gly Cys Tyr  
 Cys Glu Trp Cys His Asn Gly Thr Cys Gly Ala Cys Tyr  
 Cys Glu Trp Cys Ile Asn Pro Ala Cys Thr Gly Cys Tyr  
 Cys Glu Trp Cys Ile Asn Pro Ala Cys Thr Ala Cys Tyr  
 Cys Glu Trp Cys Ile Asn Pro Ala Cys Val Gly Cys Tyr  
 Cys Glu Trp Cys Ile Asn Pro Ala Cys Val Ala Cys Tyr  
 Cys Glu Trp Cys Ile Asn Pro Ala Cys Gly Gly Cys Tyr  
 Cys Glu Trp Cys Ile Asn Pro Ala Cys Gly Ala Cys Tyr  
 Cys Glu Trp Cys Ile Asn Pro Thr Cys Thr Gly Cys Tyr  
 Cys Glu Trp Cys Ile Asn Pro Thr Cys Thr Ala Cys Tyr  
 Cys Glu Trp Cys Ile Asn Pro Thr Cys Val Gly Cys Tyr  
 Cys Glu Trp Cys Ile Asn Pro Thr Cys Val Ala Cys Tyr  
 Cys Glu Trp Cys Ile Asn Pro Thr Cys Gly Gly Cys Tyr  
 Cys Glu Trp Cys Ile Asn Pro Thr Cys Gly Ala Cys Tyr

FIGURE 3 (sheet 15 of 68)

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Cys Glu Trp Cys Ile Asn Gly Ala Cys Thr Gly Cys Tyr  
 Cys Glu Trp Cys Ile Asn Gly Ala Cys Thr Ala Cys Tyr  
 Cys Glu Trp Cys Ile Asn Gly Ala Cys Val Gly Cys Tyr  
 Cys Glu Trp Cys Ile Asn Gly Ala Cys Val Ala Cys Tyr  
 Cys Glu Trp Cys Ile Asn Gly Ala Cys Gly Gly Cys Tyr  
 Cys Glu Trp Cys Ile Asn Gly Ala Cys Gly Ala Cys Tyr  
 Cys Glu Trp Cys Ile Asn Gly Thr Cys Thr Gly Cys Tyr  
 Cys Glu Trp Cys Ile Asn Gly Thr Cys Thr Ala Cys Tyr  
 Cys Glu Trp Cys Ile Asn Gly Thr Cys Val Gly Cys Tyr  
 Cys Glu Trp Cys Ile Asn Gly Thr Cys Val Ala Cys Tyr  
 Cys Glu Trp Cys Ile Asn Gly Thr Cys Gly Gly Cys Tyr  
 Cys Glu Trp Cys Ile Asn Gly Thr Cys Gly Ala Cys Tyr  
 Cys Glu Trp Cys Leu Asn Pro Ala Cys Thr Gly Cys Tyr  
 Cys Glu Trp Cys Leu Asn Pro Ala Cys Thr Ala Cys Tyr  
 Cys Glu Trp Cys Leu Asn Pro Ala Cys Val Gly Cys Tyr  
 Cys Glu Trp Cys Leu Asn Pro Ala Cys Val Ala Cys Tyr  
 Cys Glu Trp Cys Leu Asn Pro Ala Cys Gly Gly Cys Tyr  
 Cys Glu Trp Cys Leu Asn Pro Ala Cys Gly Ala Cys Tyr  
 Cys Glu Trp Cys Leu Asn Pro Thr Cys Thr Gly Cys Tyr  
 Cys Glu Trp Cys Leu Asn Pro Thr Cys Thr Ala Cys Tyr  
 Cys Glu Trp Cys Leu Asn Pro Thr Cys Val Gly Cys Tyr  
 Cys Glu Trp Cys Leu Asn Pro Thr Cys Val Ala Cys Tyr  
 Cys Glu Trp Cys Leu Asn Pro Thr Cys Gly Gly Cys Tyr  
 Cys Glu Trp Cys Leu Asn Pro Thr Cys Gly Ala Cys Tyr  
 Cys Glu Trp Cys Leu Asn Gly Ala Cys Thr Gly Cys Tyr  
 Cys Glu Trp Cys Leu Asn Gly Ala Cys Thr Ala Cys Tyr  
 Cys Glu Trp Cys Leu Asn Gly Ala Cys Val Gly Cys Tyr  
 Cys Glu Trp Cys Leu Asn Gly Ala Cys Val Ala Cys Tyr  
 Cys Glu Trp Cys Leu Asn Gly Thr Cys Thr Gly Cys Tyr  
 Cys Glu Trp Cys Leu Asn Gly Thr Cys Thr Ala Cys Tyr  
 Cys Glu Trp Cys Leu Asn Gly Thr Cys Val Gly Cys Tyr  
 Cys Glu Trp Cys Leu Asn Gly Thr Cys Thr Ala Cys Tyr  
 Cys Glu Trp Cys Leu Asn Gly Thr Cys Thr Ala Cys Tyr  
 Cys Glu Trp Cys Lys Asn Pro Ala Cys Thr Gly Cys Tyr  
 Cys Glu Trp Cys Lys Asn Pro Ala Cys Thr Ala Cys Tyr  
 Cys Glu Trp Cys Lys Asn Pro Ala Cys Val Gly Cys Tyr  
 Cys Glu Trp Cys Lys Asn Pro Ala Cys Val Ala Cys Tyr  
 Cys Glu Trp Cys Lys Asn Pro Ala Cys Gly Gly Cys Tyr  
 Cys Glu Trp Cys Lys Asn Pro Ala Cys Gly Ala Cys Tyr  
 Cys Glu Trp Cys Lys Asn Pro Thr Cys Thr Gly Cys Tyr  
 Cys Glu Trp Cys Lys Asn Pro Thr Cys Thr Ala Cys Tyr  
 Cys Glu Trp Cys Lys Asn Pro Thr Cys Val Gly Cys Tyr  
 Cys Glu Trp Cys Lys Asn Pro Thr Cys Val Ala Cys Tyr  
 Cys Glu Trp Cys Lys Asn Pro Thr Cys Gly Gly Cys Tyr  
 Cys Glu Trp Cys Lys Asn Pro Thr Cys Gly Ala Cys Tyr  
 Cys Glu Trp Cys Lys Asn Gly Ala Cys Thr Gly Cys Tyr  
 Cys Glu Trp Cys Lys Asn Gly Ala Cys Thr Ala Cys Tyr  
 Cys Glu Trp Cys Lys Asn Gly Ala Cys Val Gly Cys Tyr  
 Cys Glu Trp Cys Lys Asn Gly Ala Cys Val Ala Cys Tyr  
 Cys Glu Trp Cys Lys Asn Gly Ala Cys Gly Gly Cys Tyr  
 Cys Glu Trp Cys Lys Asn Gly Ala Cys Gly Ala Cys Tyr  
 Cys Glu Trp Cys Lys Asn Gly Thr Cys Thr Gly Cys Tyr  
 Cys Glu Trp Cys Lys Asn Gly Thr Cys Thr Ala Cys Tyr  
 Cys Glu Trp Cys Lys Asn Gly Thr Cys Val Gly Cys Tyr

FIGURE 3 (sheet 14 of 68)

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Cys Glu Trp Cys Lys Asn Gly Thr Cys Val Ala Cys Tyr  
 Cys Glu Trp Cys Lys Asn Gly Thr Cys Gly Gly Cys Tyr  
 Cys Glu Trp Cys Lys Asn Gly Thr Cys Gly Ala Cys Tyr  
 Cys Glu Trp Cys Met Asn Pro Ala Cys Thr Gly Cys Tyr  
 Cys Glu Trp Cys Met Asn Pro Ala Cys Thr Ala Cys Tyr  
 Cys Glu Trp Cys Met Asn Pro Ala Cys Val Gly Cys Tyr  
 Cys Glu Trp Cys Met Asn Pro Ala Cys Val Ala Cys Tyr  
 Cys Glu Trp Cys Met Asn Pro Ala Cys Gly Gly Cys Tyr  
 Cys Glu Trp Cys Met Asn Pro Ala Cys Gly Ala Cys Tyr  
 Cys Glu Trp Cys Met Asn Pro Thr Cys Thr Gly Cys Tyr  
 Cys Glu Trp Cys Met Asn Pro Thr Cys Thr Ala Cys Tyr  
 Cys Glu Trp Cys Met Asn Pro Thr Cys Val Gly Cys Tyr  
 Cys Glu Trp Cys Met Asn Pro Thr Cys Val Ala Cys Tyr  
 Cys Glu Trp Cys Met Asn Pro Thr Cys Gly Gly Cys Tyr  
 Cys Glu Trp Cys Met Asn Pro Thr Cys Gly Ala Cys Tyr  
 Cys Glu Trp Cys Met Asn Gly Ala Cys Thr Gly Cys Tyr  
 Cys Glu Trp Cys Met Asn Gly Ala Cys Thr Ala Cys Tyr  
 Cys Glu Trp Cys Met Asn Gly Ala Cys Val Gly Cys Tyr  
 Cys Glu Trp Cys Met Asn Gly Ala Cys Val Ala Cys Tyr  
 Cys Glu Trp Cys Met Asn Gly Ala Cys Gly Gly Cys Tyr  
 Cys Glu Trp Cys Met Asn Gly Thr Cys Thr Gly Cys Tyr  
 Cys Glu Trp Cys Met Asn Gly Thr Cys Thr Ala Cys Tyr  
 Cys Glu Trp Cys Met Asn Gly Thr Cys Val Gly Cys Tyr  
 Cys Glu Trp Cys Met Asn Gly Thr Cys Val Ala Cys Tyr  
 Cys Glu Trp Cys Met Asn Gly Thr Cys Gly Gly Cys Tyr  
 Cys Glu Trp Cys Met Asn Gly Thr Cys Gly Ala Cys Tyr  
 Cys Glu Trp Cys Phe Asn Pro Ala Cys Thr Gly Cys Tyr  
 Cys Glu Trp Cys Phe Asn Pro Ala Cys Thr Ala Cys Tyr  
 Cys Glu Trp Cys Phe Asn Pro Ala Cys Val Gly Cys Tyr  
 Cys Glu Trp Cys Phe Asn Pro Ala Cys Val Ala Cys Tyr  
 Cys Glu Trp Cys Phe Asn Pro Ala Cys Gly Gly Cys Tyr  
 Cys Glu Trp Cys Phe Asn Pro Ala Cys Gly Ala Cys Tyr  
 Cys Glu Trp Cys Phe Asn Pro Thr Cys Thr Gly Cys Tyr  
 Cys Glu Trp Cys Phe Asn Pro Thr Cys Thr Ala Cys Tyr  
 Cys Glu Trp Cys Phe Asn Pro Thr Cys Val Gly Cys Tyr  
 Cys Glu Trp Cys Phe Asn Pro Thr Cys Val Ala Cys Tyr  
 Cys Glu Trp Cys Phe Asn Pro Thr Cys Gly Gly Cys Tyr  
 Cys Glu Trp Cys Phe Asn Pro Thr Cys Gly Ala Cys Tyr  
 Cys Glu Trp Cys Phe Asn Gly Ala Cys Thr Gly Cys Tyr  
 Cys Glu Trp Cys Phe Asn Gly Ala Cys Thr Ala Cys Tyr  
 Cys Glu Trp Cys Phe Asn Gly Ala Cys Val Gly Cys Tyr  
 Cys Glu Trp Cys Phe Asn Gly Ala Cys Val Ala Cys Tyr  
 Cys Glu Trp Cys Phe Asn Gly Ala Cys Gly Gly Cys Tyr  
 Cys Glu Trp Cys Phe Asn Gly Ala Cys Gly Ala Cys Tyr  
 Cys Glu Trp Cys Phe Asn Gly Thr Cys Thr Gly Cys Tyr  
 Cys Glu Trp Cys Phe Asn Gly Thr Cys Thr Ala Cys Tyr  
 Cys Glu Trp Cys Phe Asn Gly Thr Cys Val Gly Cys Tyr  
 Cys Glu Trp Cys Phe Asn Gly Thr Cys Val Ala Cys Tyr  
 Cys Glu Trp Cys Phe Asn Gly Thr Cys Gly Gly Cys Tyr  
 Cys Glu Trp Cys Phe Asn Gly Thr Cys Gly Ala Cys Tyr  
 Cys Glu Trp Cys Pro Asn Pro Ala Cys Thr Gly Cys Tyr  
 Cys Glu Trp Cys Pro Asn Pro Ala Cys Thr Ala Cys Tyr  
 Cys Glu Trp Cys Pro Asn Pro Ala Cys Val Gly Cys Tyr  
 Cys Glu Trp Cys Pro Asn Pro Ala Cys Val Ala Cys Tyr  
 Cys Glu Trp Cys Pro Asn Pro Ala Cys Gly Gly Cys Tyr  
 Cys Glu Trp Cys Pro Asn Pro Ala Cys Gly Ala Cys Tyr



FIGURE 3 (sheet 15 of 68)

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Cys Glu Trp Cys Pro Asn Pro Thr Cys Thr Gly Cys Tyr  
Cys Glu Trp Cys Pro Asn Pro Thr Cys Thr Ala Cys Tyr  
Cys Glu Trp Cys Pro Asn Pro Thr Cys Val Gly Cys Tyr  
Cys Glu Trp Cys Pro Asn Pro Thr Cys Val Ala Cys Tyr  
Cys Glu Trp Cys Pro Asn Pro Thr Cys Gly Gly Cys Tyr  
Cys Glu Trp Cys Pro Asn Pro Thr Cys Gly Ala Cys Tyr  
Cys Glu Trp Cys Pro Asn Gly Ala Cys Thr Gly Cys Tyr  
Cys Glu Trp Cys Pro Asn Gly Ala Cys Thr Ala Cys Tyr  
Cys Glu Trp Cys Pro Asn Gly Ala Cys Val Gly Cys Tyr  
Cys Glu Trp Cys Pro Asn Gly Ala Cys Val Ala Cys Tyr  
Cys Glu Trp Cys Pro Asn Gly Ala Cys Gly Gly Cys Tyr  
Cys Glu Trp Cys Pro Asn Gly Ala Cys Gly Ala Cys Tyr  
Cys Glu Trp Cys Pro Asn Gly Thr Cys Thr Gly Cys Tyr  
Cys Glu Trp Cys Pro Asn Gly Thr Cys Thr Ala Cys Tyr  
Cys Glu Trp Cys Pro Asn Gly Thr Cys Val Gly Cys Tyr  
Cys Glu Trp Cys Pro Asn Gly Thr Cys Val Ala Cys Tyr  
Cys Glu Trp Cys Pro Asn Gly Thr Cys Gly Gly Cys Tyr  
Cys Glu Trp Cys Pro Asn Pro Thr Cys Gly Ala Cys Tyr  
Cys Glu Trp Cys Ser Asn Pro Ala Cys Thr Gly Cys Tyr  
Cys Glu Trp Cys Ser Asn Pro Ala Cys Thr Ala Cys Tyr  
Cys Glu Trp Cys Ser Asn Pro Ala Cys Val Gly Cys Tyr  
Cys Glu Trp Cys Ser Asn Pro Ala Cys Val Ala Cys Tyr  
Cys Glu Trp Cys Ser Asn Pro Ala Cys Gly Gly Cys Tyr  
Cys Glu Trp Cys Ser Asn Pro Ala Cys Gly Ala Cys Tyr  
Cys Glu Trp Cys Ser Asn Pro Ala Cys Gly Ala Cys Tyr  
Cys Glu Trp Cys Ser Asn Pro Thr Cys Thr Gly Cys Tyr  
Cys Glu Trp Cys Ser Asn Pro Thr Cys Thr Ala Cys Tyr  
Cys Glu Trp Cys Ser Asn Pro Thr Cys Val Gly Cys Tyr  
Cys Glu Trp Cys Ser Asn Pro Thr Cys Val Ala Cys Tyr  
Cys Glu Trp Cys Ser Asn Pro Thr Cys Gly Gly Cys Tyr  
Cys Glu Trp Cys Ser Asn Gly Thr Cys Gly Ala Cys Tyr  
Cys Glu Trp Cys Ser Asn Gly Thr Cys Gly Ala Cys Tyr  
Cys Glu Trp Cys Ser Asn Gly Thr Cys Thr Gly Cys Tyr  
Cys Glu Trp Cys Ser Asn Gly Thr Cys Thr Ala Cys Tyr  
Cys Glu Trp Cys Ser Asn Gly Thr Cys Val Gly Cys Tyr  
Cys Glu Trp Cys Ser Asn Gly Thr Cys Val Ala Cys Tyr  
Cys Glu Trp Cys Ser Asn Gly Thr Cys Gly Ala Cys Tyr  
Cys Glu Trp Cys Thr Asn Pro Ala Cys Thr Gly Cys Tyr  
Cys Glu Trp Cys Thr Asn Pro Ala Cys Thr Ala Cys Tyr  
Cys Glu Trp Cys Thr Asn Pro Ala Cys Val Gly Cys Tyr  
Cys Glu Trp Cys Thr Asn Pro Ala Cys Val Ala Cys Tyr  
Cys Glu Trp Cys Thr Asn Pro Ala Cys Gly Gly Cys Tyr  
Cys Glu Trp Cys Thr Asn Pro Thr Cys Val Gly Cys Tyr  
Cys Glu Trp Cys Thr Asn Pro Thr Cys Thr Ala Cys Tyr  
Cys Glu Trp Cys Thr Asn Pro Thr Cys Thr Ala Cys Tyr  
Cys Glu Trp Cys Thr Asn Pro Thr Cys Val Gly Cys Tyr  
Cys Glu Trp Cys Thr Asn Pro Thr Cys Gly Gly Cys Tyr  
Cys Glu Trp Cys Thr Asn Pro Thr Cys Gly Ala Cys Tyr  
Cys Glu Trp Cys Thr Asn Gly Ala Cys Thr Gly Cys Tyr  
Cys Glu Trp Cys Thr Asn Gly Ala Cys Thr Ala Cys Tyr  
Cys Glu Trp Cys Thr Asn Gly Ala Cys Val Gly Cys Tyr

FIGURE 3 (sheet 16 of 68)

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Cys Glu Trp Cys Thr Asn Gly Ala Cys Val Ala Cys Tyr  
Cys Glu Trp Cys Thr Asn Gly Ala Cys Gly Gly Cys Tyr  
Cys Glu Trp Cys Thr Asn Gly Ala Cys Gly Ala Cys Tyr  
Cys Glu Trp Cys Thr Asn Gly Thr Cys Thr Gly Cys Tyr  
Cys Glu Trp Cys Thr Asn Gly Thr Cys Thr Ala Cys Tyr  
Cys Glu Trp Cys Thr Asn Gly Thr Cys Val Gly Cys Tyr  
Cys Glu Trp Cys Thr Asn Gly Thr Cys Val Ala Cys Tyr  
Cys Glu Trp Cys Thr Asn Gly Thr Cys Gly Gly Cys Tyr  
Cys Glu Trp Cys Thr Asn Gly Thr Cys Gly Ala Cys Tyr  
Cys Glu Trp Cys Trp Asn Pro Ala Cys Thr Gly Cys Tyr  
Cys Glu Trp Cys Trp Asn Pro Ala Cys Thr Ala Cys Tyr  
Cys Glu Trp Cys Trp Asn Pro Ala Cys Val Gly Cys Tyr  
Cys Glu Trp Cys Trp Asn Pro Ala Cys Val Ala Cys Tyr  
Cys Glu Trp Cys Trp Asn Pro Ala Cys Gly Gly Cys Tyr  
Cys Glu Trp Cys Trp Asn Pro Ala Cys Gly Ala Cys Tyr  
Cys Glu Trp Cys Trp Asn Pro Thr Cys Thr Gly Cys Tyr  
Cys Glu Trp Cys Trp Asn Pro Thr Cys Thr Ala Cys Tyr  
Cys Glu Trp Cys Trp Asn Pro Thr Cys Val Gly Cys Tyr  
Cys Glu Trp Cys Trp Asn Pro Thr Cys Val Ala Cys Tyr  
Cys Glu Trp Cys Trp Asn Pro Thr Cys Gly Gly Cys Tyr  
Cys Glu Trp Cys Trp Asn Gly Ala Cys Gly Ala Cys Tyr  
Cys Glu Trp Cys Trp Asn Gly Thr Cys Thr Gly Cys Tyr  
Cys Glu Trp Cys Trp Asn Gly Thr Cys Thr Ala Cys Tyr  
Cys Glu Trp Cys Trp Asn Gly Thr Cys Val Gly Cys Tyr  
Cys Glu Trp Cys Trp Asn Gly Thr Cys Val Ala Cys Tyr  
Cys Glu Trp Cys Trp Asn Gly Thr Cys Gly Gly Cys Tyr  
Cys Glu Trp Cys Trp Asn Gly Thr Cys Gly Ala Cys Tyr  
Cys Glu Trp Cys Tyr Asn Pro Ala Cys Thr Gly Cys Tyr  
Cys Glu Trp Cys Tyr Asn Pro Ala Cys Thr Ala Cys Tyr  
Cys Glu Trp Cys Tyr Asn Pro Ala Cys Val Gly Cys Tyr  
Cys Glu Trp Cys Tyr Asn Pro Ala Cys Val Ala Cys Tyr  
Cys Glu Trp Cys Tyr Asn Pro Ala Cys Gly Gly Cys Tyr  
Cys Glu Trp Cys Tyr Asn Pro Ala Cys Gly Ala Cys Tyr  
Cys Glu Trp Cys Tyr Asn Pro Thr Cys Thr Gly Cys Tyr  
Cys Glu Trp Cys Tyr Asn Pro Thr Cys Thr Ala Cys Tyr  
Cys Glu Trp Cys Tyr Asn Pro Thr Cys Val Gly Cys Tyr  
Cys Glu Trp Cys Tyr Asn Pro Thr Cys Val Ala Cys Tyr  
Cys Glu Trp Cys Tyr Asn Pro Thr Cys Gly Gly Cys Tyr  
Cys Glu Trp Cys Tyr Asn Pro Thr Cys Gly Ala Cys Tyr  
Cys Glu Trp Cys Tyr Asn Gly Thr Cys Thr Gly Cys Tyr  
Cys Glu Trp Cys Tyr Asn Gly Thr Cys Thr Ala Cys Tyr  
Cys Glu Trp Cys Tyr Asn Gly Thr Cys Val Gly Cys Tyr  
Cys Glu Trp Cys Tyr Asn Gly Thr Cys Val Ala Cys Tyr  
Cys Glu Trp Cys Tyr Asn Gly Thr Cys Gly Gly Cys Tyr  
Cys Glu Trp Cys Tyr Asn Gly Thr Cys Gly Ala Cys Tyr

Cys Glu Trp Cys Val Asn Pro Ala Cys Thr Gly Cys Tyr  
 Cys Glu Trp Cys Val Asn Pro Ala Cys Thr Ala Cys Tyr  
 Cys Glu Trp Cys Val Asn Pro Ala Cys Val Gly Cys Tyr  
 Cys Glu Trp Cys Val Asn Pro Ala Cys Val Ala Cys Tyr  
 Cys Glu Trp Cys Val Asn Pro Ala Cys Gly Gly Cys Tyr  
 Cys Glu Trp Cys Val Asn Pro Ala Cys Gly Ala Cys Tyr  
 Cys Glu Trp Cys Val Asn Pro Thr Cys Thr Gly Cys Tyr  
 Cys Glu Trp Cys Val Asn Pro Thr Cys Thr Ala Cys Tyr  
 Cys Glu Trp Cys Val Asn Pro Thr Cys Val Gly Cys Tyr  
 Cys Glu Trp Cys Val Asn Pro Thr Cys Val Ala Cys Tyr  
 Cys Glu Trp Cys Val Asn Pro Thr Cys Gly Gly Cys Tyr  
 Cys Glu Trp Cys Val Asn Pro Thr Cys Gly Ala Cys Tyr  
 Cys Glu Trp Cys Val Asn Gly Ala Cys Thr Gly Cys Tyr  
 Cys Glu Trp Cys Val Asn Gly Ala Cys Thr Ala Cys Tyr  
 Cys Glu Trp Cys Val Asn Gly Ala Cys Val Gly Cys Tyr  
 Cys Glu Trp Cys Val Asn Gly Ala Cys Val Ala Cys Tyr  
 Cys Glu Trp Cys Val Asn Gly Ala Cys Gly Gly Cys Tyr  
 Cys Glu Trp Cys Val Asn Gly Thr Cys Thr Gly Cys Tyr  
 Cys Glu Trp Cys Val Asn Gly Thr Cys Thr Ala Cys Tyr  
 Cys Glu Trp Cys Val Asn Gly Thr Cys Val Gly Cys Tyr  
 Cys Glu Trp Cys Val Asn Gly Thr Cys Val Ala Cys Tyr  
 Cys Glu Trp Cys Val Asn Gly Thr Cys Gly Gly Cys Tyr  
 Cys Glu Trp Cys Val Asn Gly Thr Cys Gly Ala Cys Tyr  
 Cys Glu Trp Cys Val Asn Gly Thr Cys Thr Gly Cys Tyr  
 Cys Glu Trp Cys Val Asn Gly Thr Cys Thr Ala Cys Tyr  
 Cys Glu Trp Cys Val Asn Gly Thr Cys Val Gly Cys Tyr  
 Cys Glu Trp Cys Val Asn Gly Thr Cys Val Ala Cys Tyr  
 Cys Glu Trp Cys Val Asn Gly Thr Cys Gly Gly Cys Tyr  
 Cys Glu Trp Cys Val Asn Gly Thr Cys Gly Ala Cys Tyr  
 Cys Glu Trp Cys Val Asn Gly Thr Cys Gly Ala Cys Tyr  
 Cys Glu Trp Cys Val Asn Gly Thr Cys Thr Gly Cys Tyr  
 Cys Glu Trp Cys Val Asn Gly Thr Cys Thr Ala Cys Tyr  
 Cys Glu Trp Cys Val Asn Gly Thr Cys Val Gly Cys Tyr  
 Cys Glu Trp Cys Val Asn Gly Thr Cys Val Ala Cys Tyr  
 Cys Glu Trp Cys Val Asn Gly Thr Cys Gly Gly Cys Tyr  
 Cys Glu Trp Cys Val Asn Gly Thr Cys Gly Ala Cys Tyr  
 Cys Glu Phe Cys Ala Asn Pro Ala Cys Thr Gly Cys Tyr  
 Cys Glu Phe Cys Ala Asn Pro Ala Cys Thr Ala Cys Tyr  
 Cys Glu Phe Cys Ala Asn Pro Ala Cys Val Gly Cys Tyr  
 Cys Glu Phe Cys Ala Asn Pro Ala Cys Val Ala Cys Tyr  
 Cys Glu Phe Cys Ala Asn Pro Ala Cys Gly Gly Cys Tyr  
 Cys Glu Phe Cys Ala Asn Pro Ala Cys Gly Ala Cys Tyr  
 Cys Glu Phe Cys Ala Asn Pro Thr Cys Thr Gly Cys Tyr  
 Cys Glu Phe Cys Ala Asn Pro Thr Cys Thr Ala Cys Tyr  
 Cys Glu Phe Cys Ala Asn Pro Thr Cys Val Gly Cys Tyr  
 Cys Glu Phe Cys Ala Asn Pro Thr Cys Gly Gly Cys Tyr  
 Cys Glu Phe Cys Ala Asn Pro Thr Cys Gly Ala Cys Tyr

FIGURE 3 (sheet 18 of 68)

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Cys Glu Phe Cys Ala Asn Pro Thr Cys Val Ala Cys Tyr  
 Cys Glu Phe Cys Ala Asn Pro Thr Cys Gly Gly Cys Tyr  
 Cys Glu Phe Cys Ala Asn Pro Thr Cys Gly Ala Cys Tyr  
 Cys Glu Phe Cys Ala Asn Gly Ala Cys Thr Gly Cys Tyr  
 Cys Glu Phe Cys Ala Asn Gly Ala Cys Thr Ala Cys Tyr  
 Cys Glu Phe Cys Ala Asn Gly Ala Cys Val Gly Cys Tyr  
 Cys Glu Phe Cys Ala Asn Gly Ala Cys Val Ala Cys Tyr  
 Cys Glu Phe Cys Ala Asn Gly Ala Cys Gly Gly Cys Tyr  
 Cys Glu Phe Cys Ala Asn Gly Ala Cys Gly Ala Cys Tyr  
 Cys Glu Phe Cys Ala Asn Gly Thr Cys Thr Gly Cys Tyr  
 Cys Glu Phe Cys Ala Asn Gly Thr Cys Thr Ala Cys Tyr  
 Cys Glu Phe Cys Ala Asn Gly Thr Cys Val Gly Cys Tyr  
 Cys Glu Phe Cys Ala Asn Gly Thr Cys Val Ala Cys Tyr  
 Cys Glu Phe Cys Ala Asn Gly Thr Cys Gly Gly Cys Tyr  
 Cys Glu Phe Cys Ala Asn Gly Thr Cys Gly Ala Cys Tyr  
 Cys Glu Phe Cys Arg Asn Pro Ala Cys Thr Gly Cys Tyr  
 Cys Glu Phe Cys Arg Asn Pro Ala Cys Thr Ala Cys Tyr  
 Cys Glu Phe Cys Arg Asn Pro Ala Cys Val Gly Cys Tyr  
 Cys Glu Phe Cys Arg Asn Pro Ala Cys Val Ala Cys Tyr  
 Cys Glu Phe Cys Arg Asn Pro Ala Cys Gly Gly Cys Tyr  
 Cys Glu Phe Cys Arg Asn Pro Ala Cys Gly Ala Cys Tyr  
 Cys Glu Phe Cys Arg Asn Pro Thr Cys Thr Gly Cys Tyr  
 Cys Glu Phe Cys Arg Asn Pro Thr Cys Thr Ala Cys Tyr  
 Cys Glu Phe Cys Arg Asn Pro Thr Cys Val Gly Cys Tyr  
 Cys Glu Phe Cys Arg Asn Pro Thr Cys Val Ala Cys Tyr  
 Cys Glu Phe Cys Arg Asn Pro Thr Cys Gly Gly Cys Tyr  
 Cys Glu Phe Cys Arg Asn Pro Thr Cys Gly Ala Cys Tyr  
 Cys Glu Phe Cys Arg Asn Gly Thr Cys Thr Gly Cys Tyr  
 Cys Glu Phe Cys Arg Asn Gly Thr Cys Thr Ala Cys Tyr  
 Cys Glu Phe Cys Arg Asn Gly Thr Cys Val Gly Cys Tyr  
 Cys Glu Phe Cys Arg Asn Gly Thr Cys Val Ala Cys Tyr  
 Cys Glu Phe Cys Arg Asn Gly Thr Cys Gly Gly Cys Tyr  
 Cys Glu Phe Cys Arg Asn Gly Thr Cys Gly Ala Cys Tyr  
 Cys Glu Phe Cys Asn Asn Pro Ala Cys Thr Gly Cys Tyr  
 Cys Glu Phe Cys Asn Asn Pro Ala Cys Val Gly Cys Tyr  
 Cys Glu Phe Cys Asn Asn Pro Ala Cys Val Ala Cys Tyr  
 Cys Glu Phe Cys Asn Asn Pro Ala Cys Gly Gly Cys Tyr  
 Cys Glu Phe Cys Asn Asn Pro Ala Cys Gly Ala Cys Tyr  
 Cys Glu Phe Cys Asn Asn Pro Thr Cys Thr Gly Cys Tyr  
 Cys Glu Phe Cys Asn Asn Pro Thr Cys Thr Ala Cys Tyr  
 Cys Glu Phe Cys Asn Asn Pro Thr Cys Val Gly Cys Tyr  
 Cys Glu Phe Cys Asn Asn Pro Thr Cys Val Ala Cys Tyr  
 Cys Glu Phe Cys Asn Asn Pro Thr Cys Gly Gly Cys Tyr  
 Cys Glu Phe Cys Asn Asn Gly Ala Cys Thr Gly Cys Tyr  
 Cys Glu Phe Cys Asn Asn Gly Ala Cys Thr Ala Cys Tyr  
 Cys Glu Phe Cys Asn Asn Gly Ala Cys Val Gly Cys Tyr  
 Cys Glu Phe Cys Asn Asn Gly Ala Cys Val Ala Cys Tyr  
 Cys Glu Phe Cys Asn Asn Gly Ala Cys Gly Gly Cys Tyr  
 Cys Glu Phe Cys Asn Asn Gly Ala Cys Gly Ala Cys Tyr



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Cys Glu Phe Cys Glu Asn Pro Ala Cys Val Ala Cys Tyr  
Cys Glu Phe Cys Glu Asn Pro Ala Cys Gly Gly Cys Tyr  
Cys Glu Phe Cys Glu Asn Pro Ala Cys Gly Ala Cys Tyr  
Cys Glu Phe Cys Glu Asn Pro Thr Cys Thr Gly Cys Tyr  
Cys Glu Phe Cys Glu Asn Pro Thr Cys Thr Ala Cys Tyr  
Cys Glu Phe Cys Glu Asn Pro Thr Cys Val Gly Cys Tyr  
Cys Glu Phe Cys Glu Asn Pro Thr Cys Val Ala Cys Tyr  
Cys Glu Phe Cys Glu Asn Pro Thr Cys Gly Gly Cys Tyr  
Cys Glu Phe Cys Glu Asn Pro Thr Cys Gly Ala Cys Tyr  
Cys Glu Phe Cys Glu Asn Gly Ala Cys Thr Gly Cys Tyr  
Cys Glu Phe Cys Glu Asn Gly Ala Cys Thr Ala Cys Tyr  
Cys Glu Phe Cys Glu Asn Gly Ala Cys Val Gly Cys Tyr  
Cys Glu Phe Cys Glu Asn Gly Ala Cys Val Ala Cys Tyr  
Cys Glu Phe Cys Glu Asn Gly Ala Cys Gly Gly Cys Tyr  
Cys Glu Phe Cys Glu Asn Gly Thr Cys Thr Gly Cys Tyr  
Cys Glu Phe Cys Glu Asn Gly Thr Cys Thr Ala Cys Tyr  
Cys Glu Phe Cys Glu Asn Gly Thr Cys Val Gly Cys Tyr  
Cys Glu Phe Cys Glu Asn Gly Thr Cys Val Ala Cys Tyr  
Cys Glu Phe Cys Gly Asn Pro Ala Cys Thr Gly Cys Tyr  
Cys Glu Phe Cys Gly Asn Pro Ala Cys Val Ala Cys Tyr  
Cys Glu Phe Cys Gly Asn Pro Thr Cys Gly Gly Cys Tyr  
Cys Glu Phe Cys Gly Asn Pro Thr Cys Thr Gly Cys Tyr  
Cys Glu Phe Cys Gly Asn Pro Thr Cys Thr Ala Cys Tyr  
Cys Glu Phe Cys Gly Asn Pro Thr Cys Val Gly Cys Tyr  
Cys Glu Phe Cys Gly Asn Gly Thr Cys Val Ala Cys Tyr  
Cys Glu Phe Cys Gly Asn Gly Thr Cys Gly Gly Cys Tyr  
Cys Glu Phe Cys Gly Asn Gly Thr Cys Gly Ala Cys Tyr  
Cys Glu Phe Cys Gly Asn Gly Thr Cys Thr Gly Cys Tyr  
Cys Glu Phe Cys Gly Asn Gly Thr Cys Thr Ala Cys Tyr  
Cys Glu Phe Cys Gly Asn Gly Thr Cys Val Gly Cys Tyr  
Cys Glu Phe Cys Gly Asn Gly Thr Cys Val Ala Cys Tyr  
Cys Glu Phe Cys Gly Asn Gly Thr Cys Gly Gly Cys Tyr  
Cys Glu Phe Cys Gly Asn Gly Thr Cys Gly Ala Cys Tyr  
Cys Glu Phe Cys His Asn Pro Ala Cys Thr Gly Cys Tyr  
Cys Glu Phe Cys His Asn Pro Ala Cys Thr Ala Cys Tyr  
Cys Glu Phe Cys His Asn Pro Ala Cys Val Gly Cys Tyr  
Cys Glu Phe Cys His Asn Pro Ala Cys Val Ala Cys Tyr  
Cys Glu Phe Cys His Asn Pro Ala Cys Gly Gly Cys Tyr  
Cys Glu Phe Cys His Asn Pro Ala Cys Gly Ala Cys Tyr  
Cys Glu Phe Cys His Asn Pro Thr Cys Thr Gly Cys Tyr  
Cys Glu Phe Cys His Asn Pro Thr Cys Thr Ala Cys Tyr  
Cys Glu Phe Cys His Asn Pro Thr Cys Val Gly Cys Tyr  
Cys Glu Phe Cys His Asn Pro Thr Cys Val Ala Cys Tyr  
Cys Glu Phe Cys His Asn Pro Thr Cys Gly Gly Cys Tyr  
Cys Glu Phe Cys His Asn Pro Thr Cys Gly Ala Cys Tyr

Cys Glu Phe Cys His Asn Gly Ala Cys Thr Gly Cys Tyr  
 Cys Glu Phe Cys His Asn Gly Ala Cys Thr Ala Cys Tyr  
 Cys Glu Phe Cys His Asn Gly Ala Cys Val Gly Cys Tyr  
 Cys Glu Phe Cys His Asn Gly Ala Cys Val Ala Cys Tyr  
 Cys Glu Phe Cys His Asn Gly Ala Cys Gly Gly Cys Tyr  
 Cys Glu Phe Cys His Asn Gly Ala Cys Gly Ala Cys Tyr  
 Cys Glu Phe Cys His Asn Gly Thr Cys Thr Gly Cys Tyr  
 Cys Glu Phe Cys His Asn Gly Thr Cys Thr Ala Cys Tyr  
 Cys Glu Phe Cys His Asn Gly Thr Cys Val Gly Cys Tyr  
 Cys Glu Phe Cys His Asn Gly Thr Cys Val Ala Cys Tyr  
 Cys Glu Phe Cys His Asn Gly Thr Cys Gly Gly Cys Tyr  
 Cys Glu Phe Cys His Asn Gly Thr Cys Gly Ala Cys Tyr  
 Cys Glu Phe Cys Ile Asn Pro Ala Cys Thr Gly Cys Tyr  
 Cys Glu Phe Cys Ile Asn Pro Ala Cys Thr Ala Cys Tyr  
 Cys Glu Phe Cys Ile Asn Pro Ala Cys Val Gly Cys Tyr  
 Cys Glu Phe Cys Ile Asn Pro Ala Cys Val Ala Cys Tyr  
 Cys Glu Phe Cys Ile Asn Pro Ala Cys Gly Gly Cys Tyr  
 Cys Glu Phe Cys Ile Asn Pro Ala Cys Gly Ala Cys Tyr  
 Cys Glu Phe Cys Ile Asn Pro Thr Cys Thr Gly Cys Tyr  
 Cys Glu Phe Cys Ile Asn Pro Thr Cys Thr Ala Cys Tyr  
 Cys Glu Phe Cys Ile Asn Pro Thr Cys Val Gly Cys Tyr  
 Cys Glu Phe Cys Ile Asn Pro Thr Cys Val Ala Cys Tyr  
 Cys Glu Phe Cys Ile Asn Pro Thr Cys Gly Gly Cys Tyr  
 Cys Glu Phe Cys Ile Asn Pro Thr Cys Gly Ala Cys Tyr  
 Cys Glu Phe Cys Ile Asn Gly Ala Cys Thr Ala Cys Tyr  
 Cys Glu Phe Cys Ile Asn Gly Ala Cys Val Gly Cys Tyr  
 Cys Glu Phe Cys Ile Asn Gly Ala Cys Gly Gly Cys Tyr  
 Cys Glu Phe Cys Ile Asn Gly Ala Cys Gly Ala Cys Tyr  
 Cys Glu Phe Cys Ile Asn Gly Thr Cys Thr Gly Cys Tyr  
 Cys Glu Phe Cys Ile Asn Gly Thr Cys Thr Ala Cys Tyr  
 Cys Glu Phe Cys Ile Asn Gly Thr Cys Val Gly Cys Tyr  
 Cys Glu Phe Cys Ile Asn Gly Thr Cys Val Ala Cys Tyr  
 Cys Glu Phe Cys Ile Asn Gly Thr Cys Gly Gly Cys Tyr  
 Cys Glu Phe Cys Ile Asn Gly Thr Cys Gly Ala Cys Tyr  
 Cys Glu Phe Cys Leu Asn Pro Ala Cys Thr Gly Cys Tyr  
 Cys Glu Phe Cys Leu Asn Pro Ala Cys Thr Ala Cys Tyr  
 Cys Glu Phe Cys Leu Asn Pro Ala Cys Val Gly Cys Tyr  
 Cys Glu Phe Cys Leu Asn Pro Ala Cys Val Ala Cys Tyr  
 Cys Glu Phe Cys Leu Asn Pro Ala Cys Gly Gly Cys Tyr  
 Cys Glu Phe Cys Leu Asn Pro Ala Cys Gly Ala Cys Tyr  
 Cys Glu Phe Cys Leu Asn Pro Thr Cys Thr Gly Cys Tyr  
 Cys Glu Phe Cys Leu Asn Pro Thr Cys Thr Ala Cys Tyr  
 Cys Glu Phe Cys Leu Asn Pro Thr Cys Val Gly Cys Tyr  
 Cys Glu Phe Cys Leu Asn Pro Thr Cys Val Ala Cys Tyr  
 Cys Glu Phe Cys Leu Asn Pro Thr Cys Gly Gly Cys Tyr  
 Cys Glu Phe Cys Leu Asn Pro Thr Cys Gly Ala Cys Tyr  
 Cys Glu Phe Cys Leu Asn Gly Ala Cys Thr Gly Cys Tyr  
 Cys Glu Phe Cys Leu Asn Gly Ala Cys Thr Ala Cys Tyr  
 Cys Glu Phe Cys Leu Asn Gly Ala Cys Val Gly Cys Tyr  
 Cys Glu Phe Cys Leu Asn Gly Ala Cys Val Ala Cys Tyr  
 Cys Glu Phe Cys Leu Asn Gly Ala Cys Gly Gly Cys Tyr  
 Cys Glu Phe Cys Leu Asn Gly Ala Cys Gly Ala Cys Tyr  
 Cys Glu Phe Cys Leu Asn Gly Thr Cys Thr Gly Cys Tyr  
 Cys Glu Phe Cys Leu Asn Gly Thr Cys Thr Ala Cys Tyr  
 Cys Glu Phe Cys Leu Asn Gly Thr Cys Val Gly Cys Tyr

FIGURE 3 (sheet 22 of 68)

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Cys Glu Phe Cys Leu Asn Gly Thr Cys Val Ala Cys Tyr  
 Cys Glu Phe Cys Leu Asn Gly Thr Cys Gly Gly Cys Tyr  
 Cys Glu Phe Cys Leu Asn Gly Thr Cys Gly Ala Cys Tyr  
 Cys Glu Phe Cys Lys Asn Pro Ala Cys Thr Gly Cys Tyr  
 Cys Glu Phe Cys Lys Asn Pro Ala Cys Thr Ala Cys Tyr  
 Cys Glu Phe Cys Lys Asn Pro Ala Cys Val Gly Cys Tyr  
 Cys Glu Phe Cys Lys Asn Pro Ala Cys Val Ala Cys Tyr  
 Cys Glu Phe Cys Lys Asn Pro Ala Cys Gly Gly Cys Tyr  
 Cys Glu Phe Cys Lys Asn Pro Ala Cys Gly Ala Cys Tyr  
 Cys Glu Phe Cys Lys Asn Pro Thr Cys Thr Gly Cys Tyr  
 Cys Glu Phe Cys Lys Asn Pro Thr Cys Thr Ala Cys Tyr  
 Cys Glu Phe Cys Lys Asn Pro Thr Cys Val Gly Cys Tyr  
 Cys Glu Phe Cys Lys Asn Pro Thr Cys Val Ala Cys Tyr  
 Cys Glu Phe Cys Lys Asn Pro Thr Cys Gly Gly Cys Tyr  
 Cys Glu Phe Cys Lys Asn Pro Thr Cys Gly Ala Cys Tyr  
 Cys Glu Phe Cys Lys Asn Gly Ala Cys Thr Gly Cys Tyr  
 Cys Glu Phe Cys Lys Asn Gly Ala Cys Thr Ala Cys Tyr  
 Cys Glu Phe Cys Lys Asn Gly Ala Cys Val Gly Cys Tyr  
 Cys Glu Phe Cys Lys Asn Gly Ala Cys Val Ala Cys Tyr  
 Cys Glu Phe Cys Lys Asn Gly Ala Cys Gly Gly Cys Tyr  
 Cys Glu Phe Cys Lys Asn Gly Ala Cys Gly Ala Cys Tyr  
 Cys Glu Phe Cys Lys Asn Gly Thr Cys Thr Gly Cys Tyr  
 Cys Glu Phe Cys Lys Asn Gly Thr Cys Thr Ala Cys Tyr  
 Cys Glu Phe Cys Lys Asn Gly Thr Cys Val Gly Cys Tyr  
 Cys Glu Phe Cys Lys Asn Gly Thr Cys Val Ala Cys Tyr  
 Cys Glu Phe Cys Lys Asn Gly Thr Cys Gly Gly Cys Tyr  
 Cys Glu Phe Cys Lys Asn Gly Thr Cys Gly Ala Cys Tyr  
 Cys Glu Phe Cys Met Asn Pro Ala Cys Thr Gly Cys Tyr  
 Cys Glu Phe Cys Met Asn Pro Ala Cys Thr Ala Cys Tyr  
 Cys Glu Phe Cys Met Asn Pro Ala Cys Gly Gly Cys Tyr  
 Cys Glu Phe Cys Met Asn Pro Ala Cys Gly Ala Cys Tyr  
 Cys Glu Phe Cys Met Asn Pro Thr Cys Thr Gly Cys Tyr  
 Cys Glu Phe Cys Met Asn Pro Thr Cys Thr Ala Cys Tyr  
 Cys Glu Phe Cys Met Asn Pro Thr Cys Val Gly Cys Tyr  
 Cys Glu Phe Cys Met Asn Pro Thr Cys Val Ala Cys Tyr  
 Cys Glu Phe Cys Met Asn Pro Thr Cys Gly Gly Cys Tyr  
 Cys Glu Phe Cys Met Asn Gly Ala Cys Gly Ala Cys Tyr  
 Cys Glu Phe Cys Met Asn Gly Ala Cys Thr Gly Cys Tyr  
 Cys Glu Phe Cys Met Asn Gly Ala Cys Thr Ala Cys Tyr  
 Cys Glu Phe Cys Met Asn Gly Ala Cys Val Gly Cys Tyr  
 Cys Glu Phe Cys Met Asn Gly Ala Cys Val Ala Cys Tyr  
 Cys Glu Phe Cys Met Asn Gly Ala Cys Gly Gly Cys Tyr  
 Cys Glu Phe Cys Met Asn Gly Ala Cys Gly Ala Cys Tyr  
 Cys Glu Phe Cys Met Asn Gly Thr Cys Thr Gly Cys Tyr  
 Cys Glu Phe Cys Met Asn Gly Thr Cys Thr Ala Cys Tyr  
 Cys Glu Phe Cys Met Asn Gly Thr Cys Val Gly Cys Tyr  
 Cys Glu Phe Cys Met Asn Gly Thr Cys Val Ala Cys Tyr  
 Cys Glu Phe Cys Met Asn Gly Thr Cys Gly Gly Cys Tyr  
 Cys Glu Phe Cys Met Asn Gly Thr Cys Gly Ala Cys Tyr  
 Cys Glu Phe Cys Phe Asn Pro Ala Cys Thr Gly Cys Tyr  
 Cys Glu Phe Cys Phe Asn Pro Ala Cys Thr Ala Cys Tyr  
 Cys Glu Phe Cys Phe Asn Pro Ala Cys Val Gly Cys Tyr  
 Cys Glu Phe Cys Phe Asn Pro Ala Cys Val Ala Cys Tyr  
 Cys Glu Phe Cys Phe Asn Pro Ala Cys Gly Gly Cys Tyr  
 Cys Glu Phe Cys Phe Asn Pro Ala Cys Gly Ala Cys Tyr



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Cys Glu Phe Cys Phe Asn Pro Thr Cys Thr Gly Cys Tyr  
 Cys Glu Phe Cys Phe Asn Pro Thr Cys Thr Ala Cys Tyr  
 Cys Glu Phe Cys Phe Asn Pro Thr Cys Val Gly Cys Tyr  
 Cys Glu Phe Cys Phe Asn Pro Thr Cys Val Ala Cys Tyr  
 Cys Glu Phe Cys Phe Asn Pro Thr Cys Gly Gly Cys Tyr  
 Cys Glu Phe Cys Phe Asn Pro Thr Cys Gly Ala Cys Tyr  
 Cys Glu Phe Cys Phe Asn Gly Ala Cys Thr Gly Cys Tyr  
 Cys Glu Phe Cys Phe Asn Gly Ala Cys Thr Ala Cys Tyr  
 Cys Glu Phe Cys Phe Asn Gly Ala Cys Val Gly Cys Tyr  
 Cys Glu Phe Cys Phe Asn Gly Ala Cys Val Ala Cys Tyr  
 Cys Glu Phe Cys Phe Asn Gly Ala Cys Gly Gly Cys Tyr  
 Cys Glu Phe Cys Phe Asn Gly Ala Cys Gly Ala Cys Tyr  
 Cys Glu Phe Cys Phe Asn Gly Thr Cys Thr Gly Cys Tyr  
 Cys Glu Phe Cys Phe Asn Gly Thr Cys Thr Ala Cys Tyr  
 Cys Glu Phe Cys Phe Asn Gly Thr Cys Val Gly Cys Tyr  
 Cys Glu Phe Cys Phe Asn Gly Thr Cys Val Ala Cys Tyr  
 Cys Glu Phe Cys Phe Asn Gly Thr Cys Gly Gly Cys Tyr  
 Cys Glu Phe Cys Phe Asn Gly Thr Cys Gly Ala Cys Tyr  
 Cys Glu Phe Cys Phe Asn Gly Thr Cys Gly Ala Cys Tyr  
 Cys Glu Phe Cys Phe Asn Gly Thr Cys Thr Gly Cys Tyr  
 Cys Glu Phe Cys Pro Asn Pro Ala Cys Thr Gly Cys Tyr  
 Cys Glu Phe Cys Pro Asn Pro Ala Cys Thr Ala Cys Tyr  
 Cys Glu Phe Cys Pro Asn Pro Ala Cys Val Gly Cys Tyr  
 Cys Glu Phe Cys Pro Asn Pro Ala Cys Val Ala Cys Tyr  
 Cys Glu Phe Cys Pro Asn Pro Ala Cys Gly Gly Cys Tyr  
 Cys Glu Phe Cys Pro Asn Pro Ala Cys Gly Ala Cys Tyr  
 Cys Glu Phe Cys Pro Asn Pro Thr Cys Thr Gly Cys Tyr  
 Cys Glu Phe Cys Pro Asn Pro Thr Cys Thr Ala Cys Tyr  
 Cys Glu Phe Cys Pro Asn Pro Thr Cys Val Gly Cys Tyr  
 Cys Glu Phe Cys Pro Asn Pro Thr Cys Val Ala Cys Tyr  
 Cys Glu Phe Cys Pro Asn Gly Thr Cys Gly Gly Cys Tyr  
 Cys Glu Phe Cys Pro Asn Gly Thr Cys Gly Ala Cys Tyr  
 Cys Glu Phe Cys Pro Asn Gly Thr Cys Gly Ala Cys Tyr  
 Cys Glu Phe Cys Pro Asn Gly Thr Cys Thr Gly Cys Tyr  
 Cys Glu Phe Cys Pro Asn Gly Thr Cys Thr Ala Cys Tyr  
 Cys Glu Phe Cys Pro Asn Gly Thr Cys Val Gly Cys Tyr  
 Cys Glu Phe Cys Pro Asn Gly Thr Cys Val Ala Cys Tyr  
 Cys Glu Phe Cys Pro Asn Gly Thr Cys Gly Gly Cys Tyr  
 Cys Glu Phe Cys Pro Asn Gly Thr Cys Gly Ala Cys Tyr  
 Cys Glu Phe Cys Ser Asn Pro Ala Cys Thr Gly Cys Tyr  
 Cys Glu Phe Cys Ser Asn Pro Ala Cys Thr Ala Cys Tyr  
 Cys Glu Phe Cys Ser Asn Pro Ala Cys Val Gly Cys Tyr  
 Cys Glu Phe Cys Ser Asn Pro Ala Cys Val Ala Cys Tyr  
 Cys Glu Phe Cys Ser Asn Pro Ala Cys Gly Gly Cys Tyr  
 Cys Glu Phe Cys Ser Asn Pro Ala Cys Gly Ala Cys Tyr  
 Cys Glu Phe Cys Ser Asn Pro Thr Cys Thr Gly Cys Tyr  
 Cys Glu Phe Cys Ser Asn Pro Thr Cys Thr Ala Cys Tyr  
 Cys Glu Phe Cys Ser Asn Pro Thr Cys Val Gly Cys Tyr  
 Cys Glu Phe Cys Ser Asn Pro Thr Cys Val Ala Cys Tyr  
 Cys Glu Phe Cys Ser Asn Pro Thr Cys Gly Gly Cys Tyr  
 Cys Glu Phe Cys Ser Asn Pro Thr Cys Gly Ala Cys Tyr  
 Cys Glu Phe Cys Ser Asn Gly Ala Cys Thr Gly Cys Tyr  
 Cys Glu Phe Cys Ser Asn Gly Ala Cys Thr Ala Cys Tyr  
 Cys Glu Phe Cys Ser Asn Gly Ala Cys Val Gly Cys Tyr

FIGURE 5 (sheet 24 of 68)

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Cys Glu Phe Cys Ser Asn Gly Ala Cys Val Ala Cys Tyr  
 Cys Glu Phe Cys Ser Asn Gly Ala Cys Gly Gly Cys Tyr  
 Cys Glu Phe Cys Ser Asn Gly Ala Cys Gly Ala Cys Tyr  
 Cys Glu Phe Cys Ser Asn Gly Thr Cys Thr Gly Cys Tyr  
 Cys Glu Phe Cys Ser Asn Gly Thr Cys Thr Ala Cys Tyr  
 Cys Glu Phe Cys Ser Asn Gly Thr Cys Val Gly Cys Tyr  
 Cys Glu Phe Cys Ser Asn Gly Thr Cys Val Ala Cys Tyr  
 Cys Glu Phe Cys Ser Asn Gly Thr Cys Gly Gly Cys Tyr  
 Cys Glu Phe Cys Ser Asn Gly Thr Cys Gly Ala Cys Tyr  
 Cys Glu Phe Cys Thr Asn Pro Ala Cys Thr Gly Cys Tyr  
 Cys Glu Phe Cys Thr Asn Pro Ala Cys Thr Ala Cys Tyr  
 Cys Glu Phe Cys Thr Asn Pro Ala Cys Val Gly Cys Tyr  
 Cys Glu Phe Cys Thr Asn Pro Ala Cys Val Ala Cys Tyr  
 Cys Glu Phe Cys Thr Asn Pro Ala Cys Gly Gly Cys Tyr  
 Cys Glu Phe Cys Thr Asn Pro Ala Cys Gly Ala Cys Tyr  
 Cys Glu Phe Cys Thr Asn Pro Thr Cys Thr Gly Cys Tyr  
 Cys Glu Phe Cys Thr Asn Pro Thr Cys Thr Ala Cys Tyr  
 Cys Glu Phe Cys Thr Asn Pro Thr Cys Val Gly Cys Tyr  
 Cys Glu Phe Cys Thr Asn Pro Thr Cys Val Ala Cys Tyr  
 Cys Glu Phe Cys Thr Asn Gly Thr Cys Gly Gly Cys Tyr  
 Cys Glu Phe Cys Thr Asn Gly Ala Cys Gly Ala Cys Tyr  
 Cys Glu Phe Cys Thr Asn Gly Thr Cys Thr Gly Cys Tyr  
 Cys Glu Phe Cys Thr Asn Gly Thr Cys Thr Ala Cys Tyr  
 Cys Glu Phe Cys Thr Asn Gly Thr Cys Val Gly Cys Tyr  
 Cys Glu Phe Cys Thr Asn Gly Thr Cys Val Ala Cys Tyr  
 Cys Glu Phe Cys Thr Asn Gly Thr Cys Gly Gly Cys Tyr  
 Cys Glu Phe Cys Trp Asn Pro Ala Cys Thr Gly Cys Tyr  
 Cys Glu Phe Cys Trp Asn Pro Ala Cys Thr Ala Cys Tyr  
 Cys Glu Phe Cys Trp Asn Pro Ala Cys Val Gly Cys Tyr  
 Cys Glu Phe Cys Trp Asn Pro Ala Cys Val Ala Cys Tyr  
 Cys Glu Phe Cys Trp Asn Pro Ala Cys Gly Gly Cys Tyr  
 Cys Glu Phe Cys Trp Asn Pro Ala Cys Gly Ala Cys Tyr  
 Cys Glu Phe Cys Trp Asn Pro Thr Cys Thr Gly Cys Tyr  
 Cys Glu Phe Cys Trp Asn Pro Thr Cys Thr Ala Cys Tyr  
 Cys Glu Phe Cys Trp Asn Pro Thr Cys Val Gly Cys Tyr  
 Cys Glu Phe Cys Trp Asn Pro Thr Cys Val Ala Cys Tyr  
 Cys Glu Phe Cys Trp Asn Gly Ala Cys Gly Gly Cys Tyr  
 Cys Glu Phe Cys Trp Asn Gly Ala Cys Gly Ala Cys Tyr  
 Cys Glu Phe Cys Trp Asn Gly Thr Cys Thr Gly Cys Tyr  
 Cys Glu Phe Cys Trp Asn Gly Thr Cys Thr Ala Cys Tyr  
 Cys Glu Phe Cys Trp Asn Gly Thr Cys Val Gly Cys Tyr  
 Cys Glu Phe Cys Trp Asn Gly Thr Cys Val Ala Cys Tyr  
 Cys Glu Phe Cys Trp Asn Gly Thr Cys Gly Gly Cys Tyr  
 Cys Glu Phe Cys Trp Asn Gly Thr Cys Gly Ala Cys Tyr

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FIGURE 3 (sheet 25 of 68)

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Cys Glu Phe Cys Tyr Asn Pro Ala Cys Thr Gly Cys Tyr  
Cys Glu Phe Cys Tyr Asn Pro Ala Cys Thr Ala Cys Tyr  
Cys Glu Phe Cys Tyr Asn Pro Ala Cys Val Gly Cys Tyr  
Cys Glu Phe Cys Tyr Asn Pro Ala Cys Val Ala Cys Tyr  
Cys Glu Phe Cys Tyr Asn Pro Ala Cys Gly Gly Cys Tyr  
Cys Glu Phe Cys Tyr Asn Pro Ala Cys Gly Ala Cys Tyr  
Cys Glu Phe Cys Tyr Asn Pro Thr Cys Thr Gly Cys Tyr  
Cys Glu Phe Cys Tyr Asn Pro Thr Cys Thr Ala Cys Tyr  
Cys Glu Phe Cys Tyr Asn Pro Thr Cys Val Gly Cys Tyr  
Cys Glu Phe Cys Tyr Asn Pro Thr Cys Val Ala Cys Tyr  
Cys Glu Phe Cys Tyr Asn Pro Thr Cys Gly Gly Cys Tyr  
Cys Glu Phe Cys Tyr Asn Pro Thr Cys Gly Ala Cys Tyr  
Cys Glu Phe Cys Tyr Asn Gly Ala Cys Thr Ala Cys Tyr  
Cys Glu Phe Cys Tyr Asn Gly Ala Cys Val Gly Cys Tyr  
Cys Glu Phe Cys Tyr Asn Gly Ala Cys Val Ala Cys Tyr  
Cys Glu Phe Cys Tyr Asn Gly Thr Cys Thr Gly Cys Tyr  
Cys Glu Phe Cys Tyr Asn Gly Thr Cys Thr Ala Cys Tyr  
Cys Glu Phe Cys Tyr Asn Gly Thr Cys Val Ala Cys Tyr  
Cys Glu Phe Cys Tyr Asn Gly Thr Cys Val Ala Cys Tyr  
Cys Glu Phe Cys Tyr Asn Gly Thr Cys Gly Gly Cys Tyr  
Cys Glu Phe Cys Tyr Asn Gly Thr Cys Gly Ala Cys Tyr  
Cys Glu Phe Cys Tyr Asn Gly Thr Cys Thr Gly Cys Tyr  
Cys Glu Phe Cys Tyr Asn Gly Thr Cys Thr Ala Cys Tyr  
Cys Glu Phe Cys Tyr Asn Gly Thr Cys Val Gly Cys Tyr  
Cys Glu Phe Cys Tyr Asn Gly Thr Cys Gly Gly Cys Tyr  
Cys Glu Phe Cys Tyr Asn Gly Thr Cys Gly Ala Cys Tyr  
Cys Glu Phe Cys --- Asn Pro Ala Cys Thr Gly Cys Tyr  
Cys Glu Phe Cys --- Asn Pro Ala Cys Thr Ala Cys Tyr  
Cys Glu Phe Cys --- Asn Pro Ala Cys Val Gly Cys Tyr  
Cys Glu Phe Cys --- Asn Pro Ala Cys Val Ala Cys Tyr  
Cys Glu Phe Cys --- Asn Pro Ala Cys Gly Gly Cys Tyr  
Cys Glu Phe Cys --- Asn Pro Ala Cys Gly Ala Cys Tyr  
Cys Glu Phe Cys --- Asn Pro Thr Cys Thr Gly Cys Tyr  
Cys Glu Phe Cys --- Asn Pro Thr Cys Thr Ala Cys Tyr  
Cys Glu Phe Cys --- Asn Pro Thr Cys Val Gly Cys Tyr



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Cys Glu Leu Cys Arg Asn Gly Thr Cys Thr Gly Cys Tyr  
 Cys Glu Leu Cys Arg Asn Gly Thr Cys Thr Ala Cys Tyr  
 Cys Glu Leu Cys Arg Asn Gly Thr Cys Val Gly Cys Tyr  
 Cys Glu Leu Cys Arg Asn Gly Thr Cys Val Ala Cys Tyr  
 Cys Glu Leu Cys Arg Asn Gly Thr Cys Gly Gly Cys Tyr  
 Cys Glu Leu Cys Arg Asn Gly Thr Cys Gly Ala Cys Tyr  
 Cys Glu Leu Cys Asn Asn Pro Ala Cys Thr Gly Cys Tyr  
 Cys Glu Leu Cys Asn Asn Pro Ala Cys Thr Ala Cys Tyr  
 Cys Glu Leu Cys Asn Asn Pro Ala Cys Val Gly Cys Tyr  
 Cys Glu Leu Cys Asn Asn Pro Ala Cys Val Ala Cys Tyr  
 Cys Glu Leu Cys Asn Asn Pro Ala Cys Gly Gly Cys Tyr  
 Cys Glu Leu Cys Asn Asn Pro Ala Cys Gly Ala Cys Tyr  
 Cys Glu Leu Cys Asn Asn Pro Thr Cys Thr Gly Cys Tyr  
 Cys Glu Leu Cys Asn Asn Pro Thr Cys Thr Ala Cys Tyr  
 Cys Glu Leu Cys Asn Asn Pro Thr Cys Val Gly Cys Tyr  
 Cys Glu Leu Cys Asn Asn Pro Thr Cys Val Ala Cys Tyr  
 Cys Glu Leu Cys Asn Asn Pro Thr Cys Gly Gly Cys Tyr  
 Cys Glu Leu Cys Asn Asn Gly Ala Cys Thr Gly Cys Tyr  
 Cys Glu Leu Cys Asn Asn Gly Ala Cys Thr Ala Cys Tyr  
 Cys Glu Leu Cys Asn Asn Gly Ala Cys Val Gly Cys Tyr  
 Cys Glu Leu Cys Asn Asn Gly Ala Cys Val Ala Cys Tyr  
 Cys Glu Leu Cys Asn Asn Gly Ala Cys Gly Gly Cys Tyr  
 Cys Glu Leu Cys Asn Asn Gly Ala Cys Gly Ala Cys Tyr  
 Cys Glu Leu Cys Asn Asn Gly Thr Cys Thr Gly Cys Tyr  
 Cys Glu Leu Cys Asn Asn Gly Thr Cys Thr Ala Cys Tyr  
 Cys Glu Leu Cys Asn Asn Gly Thr Cys Val Gly Cys Tyr  
 Cys Glu Leu Cys Asn Asn Gly Thr Cys Val Ala Cys Tyr  
 Cys Glu Leu Cys Asp Asn Pro Ala Cys Thr Gly Cys Tyr  
 Cys Glu Leu Cys Asp Asn Pro Ala Cys Thr Ala Cys Tyr  
 Cys Glu Leu Cys Asp Asn Pro Ala Cys Val Gly Cys Tyr  
 Cys Glu Leu Cys Asp Asn Pro Ala Cys Val Ala Cys Tyr  
 Cys Glu Leu Cys Asp Asn Pro Ala Cys Gly Gly Cys Tyr  
 Cys Glu Leu Cys Asp Asn Pro Ala Cys Gly Ala Cys Tyr  
 Cys Glu Leu Cys Asp Asn Pro Thr Cys Thr Gly Cys Tyr  
 Cys Glu Leu Cys Asp Asn Pro Thr Cys Thr Ala Cys Tyr  
 Cys Glu Leu Cys Asp Asn Pro Thr Cys Val Gly Cys Tyr  
 Cys Glu Leu Cys Asp Asn Pro Thr Cys Val Ala Cys Tyr  
 Cys Glu Leu Cys Asp Asn Gly Ala Cys Thr Gly Cys Tyr  
 Cys Glu Leu Cys Asp Asn Gly Ala Cys Thr Ala Cys Tyr  
 Cys Glu Leu Cys Asp Asn Gly Ala Cys Gly Gly Cys Tyr  
 Cys Glu Leu Cys Asp Asn Gly Ala Cys Gly Ala Cys Tyr  
 Cys Glu Leu Cys Asp Asn Gly Thr Cys Thr Gly Cys Tyr  
 Cys Glu Leu Cys Asp Asn Gly Thr Cys Thr Ala Cys Tyr  
 Cys Glu Leu Cys Asp Asn Gly Thr Cys Val Gly Cys Tyr  
 Cys Glu Leu Cys Asp Asn Gly Thr Cys Val Ala Cys Tyr  
 Cys Glu Leu Cys Asp Asn Gly Thr Cys Gly Gly Cys Tyr  
 Cys Glu Leu Cys Asp Asn Gly Thr Cys Gly Ala Cys Tyr  
 Cys Glu Leu Cys Gln Asn Pro Ala Cys Thr Gly Cys Tyr  
 Cys Glu Leu Cys Gln Asn Pro Ala Cys Thr Ala Cys Tyr  
 Cys Glu Leu Cys Gln Asn Pro Ala Cys Val Gly Cys Tyr

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Cys Glu Leu Cys Gln Asn Pro Ala Cys Val Ala Cys Tyr  
 Cys Glu Leu Cys Gln Asn Pro Ala Cys Gly Gly Cys Tyr  
 Cys Glu Leu Cys Gln Asn Pro Ala Cys Gly Ala Cys Tyr  
 Cys Glu Leu Cys Gln Asn Pro Thr Cys Thr Gly Cys Tyr  
 Cys Glu Leu Cys Gln Asn Pro Thr Cys Thr Ala Cys Tyr  
 Cys Glu Leu Cys Gln Asn Pro Thr Cys Val Gly Cys Tyr  
 Cys Glu Leu Cys Gln Asn Pro Thr Cys Val Ala Cys Tyr  
 Cys Glu Leu Cys Gln Asn Pro Thr Cys Gly Gly Cys Tyr  
 Cys Glu Leu Cys Gln Asn Pro Thr Cys Gly Ala Cys Tyr  
 Cys Glu Leu Cys Gln Asn Gly Ala Cys Thr Gly Cys Tyr  
 Cys Glu Leu Cys Gln Asn Gly Ala Cys Thr Ala Cys Tyr  
 Cys Glu Leu Cys Gln Asn Gly Ala Cys Val Gly Cys Tyr  
 Cys Glu Leu Cys Gln Asn Gly Ala Cys Val Ala Cys Tyr  
 Cys Glu Leu Cys Gln Asn Gly Ala Cys Gly Gly Cys Tyr  
 Cys Glu Leu Cys Gln Asn Gly Ala Cys Gly Ala Cys Tyr  
 Cys Glu Leu Cys Gln Asn Gly Thr Cys Thr Gly Cys Tyr  
 Cys Glu Leu Cys Gln Asn Gly Thr Cys Thr Ala Cys Tyr  
 Cys Glu Leu Cys Gln Asn Gly Thr Cys Val Gly Cys Tyr  
 Cys Glu Leu Cys Gln Asn Gly Thr Cys Val Ala Cys Tyr  
 Cys Glu Leu Cys Gln Asn Gly Thr Cys Gly Gly Cys Tyr  
 Cys Glu Leu Cys Gln Asn Gly Thr Cys Gly Ala Cys Tyr  
 Cys Glu Leu Cys Gln Asn Gly Thr Cys Thr Gly Cys Tyr  
 Cys Glu Leu Cys Gln Asn Gly Thr Cys Thr Ala Cys Tyr  
 Cys Glu Leu Cys Gln Asn Gly Thr Cys Val Gly Cys Tyr  
 Cys Glu Leu Cys Gln Asn Gly Thr Cys Val Ala Cys Tyr  
 Cys Glu Leu Cys Gln Asn Gly Ala Cys Gly Gly Cys Tyr  
 Cys Glu Leu Cys Gln Asn Gly Ala Cys Gly Ala Cys Tyr  
 Cys Glu Leu Cys Gln Asn Gly Thr Cys Thr Gly Cys Tyr  
 Cys Glu Leu Cys Gln Asn Gly Thr Cys Thr Ala Cys Tyr  
 Cys Glu Leu Cys Gln Asn Gly Thr Cys Val Gly Cys Tyr  
 Cys Glu Leu Cys Gln Asn Gly Thr Cys Val Ala Cys Tyr  
 Cys Glu Leu Cys Gln Asn Gly Thr Cys Gly Gly Cys Tyr  
 Cys Glu Leu Cys Gly Asn Pro Ala Cys Thr Gly Cys Tyr  
 Cys Glu Leu Cys Gly Asn Pro Ala Cys Thr Ala Cys Tyr  
 Cys Glu Leu Cys Gly Asn Pro Ala Cys Val Gly Cys Tyr  
 Cys Glu Leu Cys Gly Asn Pro Ala Cys Val Ala Cys Tyr  
 Cys Glu Leu Cys Gly Asn Pro Ala Cys Gly Gly Cys Tyr  
 Cys Glu Leu Cys Gly Asn Pro Ala Cys Gly Ala Cys Tyr  
 Cys Glu Leu Cys Gly Asn Pro Thr Cys Thr Gly Cys Tyr  
 Cys Glu Leu Cys Gly Asn Pro Thr Cys Thr Ala Cys Tyr  
 Cys Glu Leu Cys Gly Asn Pro Thr Cys Val Gly Cys Tyr  
 Cys Glu Leu Cys Gly Asn Pro Thr Cys Val Ala Cys Tyr  
 Cys Glu Leu Cys Gly Asn Pro Thr Cys Gly Gly Cys Tyr  
 Cys Glu Leu Cys Gly Asn Pro Thr Cys Gly Ala Cys Tyr

Cys Glu Leu Cys Gly Asn Gly Ala Cys Thr Gly Cys Tyr  
Cys Glu Leu Cys Gly Asn Gly Ala Cys Thr Ala Cys Tyr  
Cys Glu Leu Cys Gly Asn Gly Ala Cys Val Gly Cys Tyr  
Cys Glu Leu Cys Gly Asn Gly Ala Cys Val Ala Cys Tyr  
Cys Glu Leu Cys Gly Asn Gly Ala Cys Gly Gly Cys Tyr  
Cys Glu Leu Cys Gly Asn Gly Ala Cys Gly Ala Cys Tyr  
Cys Glu Leu Cys Gly Asn Gly Thr Cys Thr Gly Cys Tyr  
Cys Glu Leu Cys Gly Asn Gly Thr Cys Thr Ala Cys Tyr  
Cys Glu Leu Cys Gly Asn Gly Thr Cys Val Gly Cys Tyr  
Cys Glu Leu Cys Gly Asn Gly Thr Cys Val Ala Cys Tyr  
Cys Glu Leu Cys Gly Asn Gly Thr Cys Gly Gly Cys Tyr  
Cys Glu Leu Cys Gly Asn Gly Thr Cys Gly Ala Cys Tyr  
Cys Glu Leu Cys His Asn Pro Ala Cys Thr Gly Cys Tyr  
Cys Glu Leu Cys His Asn Pro Ala Cys Thr Ala Cys Tyr  
Cys Glu Leu Cys His Asn Pro Ala Cys Val Gly Cys Tyr  
Cys Glu Leu Cys His Asn Pro Ala Cys Val Ala Cys Tyr  
Cys Glu Leu Cys His Asn Pro Ala Cys Gly Gly Cys Tyr  
Cys Glu Leu Cys His Asn Pro Ala Cys Gly Ala Cys Tyr  
Cys Glu Leu Cys His Asn Pro Thr Cys Thr Gly Cys Tyr  
Cys Glu Leu Cys His Asn Pro Thr Cys Thr Ala Cys Tyr  
Cys Glu Leu Cys His Asn Pro Thr Cys Thr Ala Cys Tyr  
Cys Glu Leu Cys His Asn Pro Thr Cys Val Gly Cys Tyr  
Cys Glu Leu Cys His Asn Pro Thr Cys Val Ala Cys Tyr  
Cys Glu Leu Cys His Asn Pro Thr Cys Gly Gly Cys Tyr  
Cys Glu Leu Cys His Asn Pro Thr Cys Gly Ala Cys Tyr  
Cys Glu Leu Cys His Asn Gly Ala Cys Thr Ala Cys Tyr  
Cys Glu Leu Cys His Asn Gly Ala Cys Val Gly Cys Tyr  
Cys Glu Leu Cys His Asn Gly Ala Cys Gly Gly Cys Tyr  
Cys Glu Leu Cys His Asn Gly Thr Cys Thr Gly Cys Tyr  
Cys Glu Leu Cys His Asn Gly Thr Cys Thr Ala Cys Tyr  
Cys Glu Leu Cys His Asn Gly Thr Cys Val Gly Cys Tyr  
Cys Glu Leu Cys His Asn Gly Thr Cys Val Ala Cys Tyr  
Cys Glu Leu Cys Ile Asn Pro Ala Cys Thr Gly Cys Tyr  
Cys Glu Leu Cys Ile Asn Pro Ala Cys Thr Ala Cys Tyr  
Cys Glu Leu Cys Ile Asn Pro Ala Cys Val Gly Cys Tyr  
Cys Glu Leu Cys Ile Asn Pro Ala Cys Gly Gly Cys Tyr  
Cys Glu Leu Cys Ile Asn Pro Ala Cys Gly Ala Cys Tyr  
Cys Glu Leu Cys Ile Asn Pro Thr Cys Thr Gly Cys Tyr  
Cys Glu Leu Cys Ile Asn Pro Thr Cys Thr Ala Cys Tyr  
Cys Glu Leu Cys Ile Asn Pro Thr Cys Val Gly Cys Tyr  
Cys Glu Leu Cys Ile Asn Pro Thr Cys Val Ala Cys Tyr  
Cys Glu Leu Cys Ile Asn Pro Thr Cys Gly Gly Cys Tyr  
Cys Glu Leu Cys Ile Asn Gly Ala Cys Thr Gly Cys Tyr  
Cys Glu Leu Cys Ile Asn Gly Ala Cys Thr Ala Cys Tyr  
Cys Glu Leu Cys Ile Asn Gly Ala Cys Val Gly Cys Tyr  
Cys Glu Leu Cys Ile Asn Gly Ala Cys Val Ala Cys Tyr  
Cys Glu Leu Cys Ile Asn Gly Ala Cys Gly Gly Cys Tyr  
Cys Glu Leu Cys Ile Asn Gly Ala Cys Gly Ala Cys Tyr  
Cys Glu Leu Cys Ile Asn Gly Thr Cys Thr Gly Cys Tyr  
Cys Glu Leu Cys Ile Asn Gly Thr Cys Thr Ala Cys Tyr  
Cys Glu Leu Cys Ile Asn Gly Thr Cys Val Gly Cys Tyr

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Cys Glu Leu Cys Ile Asn Gly Thr Cys Val Ala Cys Tyr  
 Cys Glu Leu Cys Ile Asn Gly Thr Cys Gly Gly Cys Tyr  
 Cys Glu Leu Cys Ile Asn Gly Thr Cys Gly Ala Cys Tyr  
 Cys Glu Leu Cys Leu Asn Pro Ala Cys Thr Gly Cys Tyr  
 Cys Glu Leu Cys Leu Asn Pro Ala Cys Thr Ala Cys Tyr  
 Cys Glu Leu Cys Leu Asn Pro Ala Cys Val Gly Cys Tyr  
 Cys Glu Leu Cys Leu Asn Pro Ala Cys Val Ala Cys Tyr  
 Cys Glu Leu Cys Leu Asn Pro Ala Cys Gly Gly Cys Tyr  
 Cys Glu Leu Cys Leu Asn Pro Ala Cys Gly Ala Cys Tyr  
 Cys Glu Leu Cys Leu Asn Pro Thr Cys Thr Gly Cys Tyr  
 Cys Glu Leu Cys Leu Asn Pro Thr Cys Thr Ala Cys Tyr  
 Cys Glu Leu Cys Leu Asn Pro Thr Cys Val Gly Cys Tyr  
 Cys Glu Leu Cys Leu Asn Pro Thr Cys Val Ala Cys Tyr  
 Cys Glu Leu Cys Leu Asn Pro Thr Cys Gly Gly Cys Tyr  
 Cys Glu Leu Cys Leu Asn Pro Thr Cys Gly Ala Cys Tyr  
 Cys Glu Leu Cys Leu Asn Gly Ala Cys Thr Gly Cys Tyr  
 Cys Glu Leu Cys Leu Asn Gly Ala Cys Thr Ala Cys Tyr  
 Cys Glu Leu Cys Leu Asn Gly Ala Cys Val Gly Cys Tyr  
 Cys Glu Leu Cys Leu Asn Gly Ala Cys Val Ala Cys Tyr  
 Cys Glu Leu Cys Leu Asn Gly Ala Cys Gly Gly Cys Tyr  
 Cys Glu Leu Cys Leu Asn Gly Ala Cys Gly Ala Cys Tyr  
 Cys Glu Leu Cys Leu Asn Gly Thr Cys Thr Gly Cys Tyr  
 Cys Glu Leu Cys Leu Asn Gly Thr Cys Thr Ala Cys Tyr  
 Cys Glu Leu Cys Leu Asn Gly Thr Cys Val Gly Cys Tyr  
 Cys Glu Leu Cys Leu Asn Gly Thr Cys Val Ala Cys Tyr  
 Cys Glu Leu Cys Leu Asn Gly Thr Cys Gly Gly Cys Tyr  
 Cys Glu Leu Cys Lys Asn Pro Ala Cys Thr Gly Cys Tyr  
 Cys Glu Leu Cys Lys Asn Pro Ala Cys Thr Ala Cys Tyr  
 Cys Glu Leu Cys Lys Asn Pro Ala Cys Val Gly Cys Tyr  
 Cys Glu Leu Cys Lys Asn Pro Ala Cys Val Ala Cys Tyr  
 Cys Glu Leu Cys Lys Asn Pro Ala Cys Gly Gly Cys Tyr  
 Cys Glu Leu Cys Lys Asn Pro Ala Cys Gly Ala Cys Tyr  
 Cys Glu Leu Cys Lys Asn Pro Thr Cys Thr Gly Cys Tyr  
 Cys Glu Leu Cys Lys Asn Pro Thr Cys Thr Ala Cys Tyr  
 Cys Glu Leu Cys Lys Asn Pro Thr Cys Val Gly Cys Tyr  
 Cys Glu Leu Cys Lys Asn Pro Thr Cys Val Ala Cys Tyr  
 Cys Glu Leu Cys Lys Asn Pro Thr Cys Gly Gly Cys Tyr  
 Cys Glu Leu Cys Lys Asn Gly Ala Cys Thr Gly Cys Tyr  
 Cys Glu Leu Cys Lys Asn Gly Ala Cys Thr Ala Cys Tyr  
 Cys Glu Leu Cys Lys Asn Gly Ala Cys Val Gly Cys Tyr  
 Cys Glu Leu Cys Lys Asn Gly Ala Cys Val Ala Cys Tyr  
 Cys Glu Leu Cys Lys Asn Gly Ala Cys Gly Gly Cys Tyr  
 Cys Glu Leu Cys Lys Asn Gly Ala Cys Gly Ala Cys Tyr  
 Cys Glu Leu Cys Lys Asn Gly Thr Cys Thr Gly Cys Tyr  
 Cys Glu Leu Cys Lys Asn Gly Thr Cys Thr Ala Cys Tyr  
 Cys Glu Leu Cys Lys Asn Gly Thr Cys Val Gly Cys Tyr  
 Cys Glu Leu Cys Lys Asn Gly Thr Cys Val Ala Cys Tyr  
 Cys Glu Leu Cys Lys Asn Gly Thr Cys Gly Gly Cys Tyr  
 Cys Glu Leu Cys Lys Asn Gly Thr Cys Gly Ala Cys Tyr  
 Cys Glu Leu Cys Met Asn Pro Ala Cys Thr Gly Cys Tyr  
 Cys Glu Leu Cys Met Asn Pro Ala Cys Thr Ala Cys Tyr  
 Cys Glu Leu Cys Met Asn Pro Ala Cys Val Gly Cys Tyr  
 Cys Glu Leu Cys Met Asn Pro Ala Cys Val Ala Cys Tyr  
 Cys Glu Leu Cys Met Asn Pro Ala Cys Gly Gly Cys Tyr  
 Cys Glu Leu Cys Met Asn Pro Ala Cys Gly Ala Cys Tyr



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Cys Glu Leu Cys Met Asn Pro Thr Cys Thr Gly Cys Tyr  
 Cys Glu Leu Cys Met Asn Pro Thr Cys Thr Ala Cys Tyr  
 Cys Glu Leu Cys Met Asn Pro Thr Cys Val Gly Cys Tyr  
 Cys Glu Leu Cys Met Asn Pro Thr Cys Val Ala Cys Tyr  
 Cys Glu Leu Cys Met Asn Pro Thr Cys Gly Gly Cys Tyr  
 Cys Glu Leu Cys Met Asn Pro Thr Cys Gly Ala Cys Tyr  
 Cys Glu Leu Cys Met Asn Gly Ala Cys Thr Gly Cys Tyr  
 Cys Glu Leu Cys Met Asn Gly Ala Cys Thr Ala Cys Tyr  
 Cys Glu Leu Cys Met Asn Gly Ala Cys Val Gly Cys Tyr  
 Cys Glu Leu Cys Met Asn Gly Ala Cys Val Ala Cys Tyr  
 Cys Glu Leu Cys Met Asn Gly Ala Cys Gly Gly Cys Tyr  
 Cys Glu Leu Cys Met Asn Gly Ala Cys Gly Ala Cys Tyr  
 Cys Glu Leu Cys Met Asn Gly Thr Cys Thr Gly Cys Tyr  
 Cys Glu Leu Cys Met Asn Gly Thr Cys Thr Ala Cys Tyr  
 Cys Glu Leu Cys Met Asn Gly Thr Cys Val Gly Cys Tyr  
 Cys Glu Leu Cys Met Asn Gly Thr Cys Val Ala Cys Tyr  
 Cys Glu Leu Cys Met Asn Gly Thr Cys Gly Gly Cys Tyr  
 Cys Glu Leu Cys Met Asn Gly Thr Cys Gly Ala Cys Tyr  
 Cys Glu Leu Cys Phe Asn Pro Ala Cys Thr Gly Cys Tyr  
 Cys Glu Leu Cys Phe Asn Pro Ala Cys Thr Ala Cys Tyr  
 Cys Glu Leu Cys Phe Asn Pro Ala Cys Val Gly Cys Tyr  
 Cys Glu Leu Cys Phe Asn Pro Ala Cys Val Ala Cys Tyr  
 Cys Glu Leu Cys Phe Asn Pro Ala Cys Gly Gly Cys Tyr  
 Cys Glu Leu Cys Phe Asn Pro Ala Cys Gly Ala Cys Tyr  
 Cys Glu Leu Cys Phe Asn Pro Thr Cys Thr Gly Cys Tyr  
 Cys Glu Leu Cys Phe Asn Pro Thr Cys Thr Ala Cys Tyr  
 Cys Glu Leu Cys Phe Asn Pro Thr Cys Val Gly Cys Tyr  
 Cys Glu Leu Cys Phe Asn Pro Thr Cys Val Ala Cys Tyr  
 Cys Glu Leu Cys Phe Asn Pro Thr Cys Gly Gly Cys Tyr  
 Cys Glu Leu Cys Phe Asn Pro Thr Cys Gly Ala Cys Tyr  
 Cys Glu Leu Cys Phe Asn Gly Ala Cys Thr Gly Cys Tyr  
 Cys Glu Leu Cys Phe Asn Gly Ala Cys Val Gly Cys Tyr  
 Cys Glu Leu Cys Phe Asn Gly Ala Cys Val Ala Cys Tyr  
 Cys Glu Leu Cys Phe Asn Gly Ala Cys Gly Gly Cys Tyr  
 Cys Glu Leu Cys Phe Asn Gly Ala Cys Gly Ala Cys Tyr  
 Cys Glu Leu Cys Phe Asn Gly Thr Cys Thr Gly Cys Tyr  
 Cys Glu Leu Cys Phe Asn Gly Thr Cys Thr Ala Cys Tyr  
 Cys Glu Leu Cys Phe Asn Gly Thr Cys Val Gly Cys Tyr  
 Cys Glu Leu Cys Phe Asn Gly Thr Cys Val Ala Cys Tyr  
 Cys Glu Leu Cys Phe Asn Gly Thr Cys Gly Gly Cys Tyr  
 Cys Glu Leu Cys Phe Asn Gly Thr Cys Gly Ala Cys Tyr  
 Cys Glu Leu Cys Pro Asn Pro Ala Cys Thr Gly Cys Tyr  
 Cys Glu Leu Cys Pro Asn Pro Ala Cys Thr Ala Cys Tyr  
 Cys Glu Leu Cys Pro Asn Pro Ala Cys Val Gly Cys Tyr  
 Cys Glu Leu Cys Pro Asn Pro Ala Cys Val Ala Cys Tyr  
 Cys Glu Leu Cys Pro Asn Pro Ala Cys Gly Gly Cys Tyr  
 Cys Glu Leu Cys Pro Asn Pro Ala Cys Gly Ala Cys Tyr  
 Cys Glu Leu Cys Pro Asn Pro Thr Cys Thr Gly Cys Tyr  
 Cys Glu Leu Cys Pro Asn Pro Thr Cys Thr Ala Cys Tyr  
 Cys Glu Leu Cys Pro Asn Pro Thr Cys Val Gly Cys Tyr  
 Cys Glu Leu Cys Pro Asn Pro Thr Cys Val Ala Cys Tyr  
 Cys Glu Leu Cys Pro Asn Pro Thr Cys Gly Gly Cys Tyr  
 Cys Glu Leu Cys Pro Asn Pro Thr Cys Gly Ala Cys Tyr  
 Cys Glu Leu Cys Pro Asn Gly Ala Cys Thr Gly Cys Tyr  
 Cys Glu Leu Cys Pro Asn Gly Ala Cys Thr Ala Cys Tyr  
 Cys Glu Leu Cys Pro Asn Gly Ala Cys Val Gly Cys Tyr

Cys Glu Leu Cys Pro Asn Gly Ala Cys Val Ala Cys Tyr  
 Cys Glu Leu Cys Pro Asn Gly Ala Cys Gly Gly Cys Tyr  
 Cys Glu Leu Cys Pro Asn Gly Ala Cys Gly Ala Cys Tyr  
 Cys Glu Leu Cys Pro Asn Gly Thr Cys Thr Gly Cys Tyr  
 Cys Glu Leu Cys Pro Asn Gly Thr Cys Thr Ala Cys Tyr  
 Cys Glu Leu Cys Pro Asn Gly Thr Cys Val Gly Cys Tyr  
 Cys Glu Leu Cys Pro Asn Gly Thr Cys Val Ala Cys Tyr  
 Cys Glu Leu Cys Pro Asn Gly Thr Cys Gly Gly Cys Tyr  
 Cys Glu Leu Cys Pro Asn Gly Thr Cys Gly Ala Cys Tyr  
 Cys Glu Leu Cys Ser Asn Pro Ala Cys Thr Gly Cys Tyr  
 Cys Glu Leu Cys Ser Asn Pro Ala Cys Thr Ala Cys Tyr  
 Cys Glu Leu Cys Ser Asn Pro Ala Cys Val Gly Cys Tyr  
 Cys Glu Leu Cys Ser Asn Pro Ala Cys Val Ala Cys Tyr  
 Cys Glu Leu Cys Ser Asn Pro Ala Cys Gly Gly Cys Tyr  
 Cys Glu Leu Cys Ser Asn Pro Ala Cys Gly Gly Cys Tyr  
 Cys Glu Leu Cys Ser Asn Pro Ala Cys Gly Ala Cys Tyr  
 Cys Glu Leu Cys Ser Asn Pro Thr Cys Thr Gly Cys Tyr  
 Cys Glu Leu Cys Ser Asn Pro Thr Cys Thr Ala Cys Tyr  
 Cys Glu Leu Cys Ser Asn Pro Thr Cys Val Gly Cys Tyr  
 Cys Glu Leu Cys Ser Asn Pro Thr Cys Val Ala Cys Tyr  
 Cys Glu Leu Cys Ser Asn Pro Thr Cys Gly Gly Cys Tyr  
 Cys Glu Leu Cys Ser Asn Pro Thr Cys Gly Ala Cys Tyr  
 Cys Glu Leu Cys Ser Asn Gly Ala Cys Thr Gly Cys Tyr  
 Cys Glu Leu Cys Ser Asn Gly Ala Cys Thr Ala Cys Tyr  
 Cys Glu Leu Cys Ser Asn Gly Ala Cys Val Gly Cys Tyr  
 Cys Glu Leu Cys Ser Asn Gly Ala Cys Val Ala Cys Tyr  
 Cys Glu Leu Cys Ser Asn Gly Ala Cys Gly Gly Cys Tyr  
 Cys Glu Leu Cys Ser Asn Gly Thr Cys Thr Gly Cys Tyr  
 Cys Glu Leu Cys Thr Asn Pro Ala Cys Thr Gly Cys Tyr  
 Cys Glu Leu Cys Thr Asn Pro Ala Cys Thr Ala Cys Tyr  
 Cys Glu Leu Cys Thr Asn Pro Ala Cys Val Gly Cys Tyr  
 Cys Glu Leu Cys Thr Asn Pro Ala Cys Val Ala Cys Tyr  
 Cys Glu Leu Cys Thr Asn Pro Ala Cys Gly Gly Cys Tyr  
 Cys Glu Leu Cys Thr Asn Pro Ala Cys Gly Ala Cys Tyr  
 Cys Glu Leu Cys Thr Asn Pro Thr Cys Thr Gly Cys Tyr  
 Cys Glu Leu Cys Thr Asn Pro Thr Cys Thr Ala Cys Tyr  
 Cys Glu Leu Cys Thr Asn Pro Thr Cys Val Gly Cys Tyr  
 Cys Glu Leu Cys Thr Asn Pro Thr Cys Val Ala Cys Tyr  
 Cys Glu Leu Cys Thr Asn Pro Thr Cys Gly Gly Cys Tyr  
 Cys Glu Leu Cys Thr Asn Pro Thr Cys Gly Ala Cys Tyr  
 Cys Glu Leu Cys Thr Asn Gly Ala Cys Thr Ala Cys Tyr  
 Cys Glu Leu Cys Thr Asn Gly Ala Cys Val Gly Cys Tyr  
 Cys Glu Leu Cys Thr Asn Gly Ala Cys Val Ala Cys Tyr  
 Cys Glu Leu Cys Thr Asn Gly Ala Cys Gly Gly Cys Tyr  
 Cys Glu Leu Cys Thr Asn Gly Ala Cys Gly Ala Cys Tyr  
 Cys Glu Leu Cys Thr Asn Gly Thr Cys Thr Gly Cys Tyr  
 Cys Glu Leu Cys Thr Asn Gly Thr Cys Thr Ala Cys Tyr  
 Cys Glu Leu Cys Thr Asn Gly Thr Cys Val Gly Cys Tyr  
 Cys Glu Leu Cys Thr Asn Gly Thr Cys Val Ala Cys Tyr  
 Cys Glu Leu Cys Thr Asn Gly Thr Cys Gly Gly Cys Tyr  
 Cys Glu Leu Cys Thr Asn Gly Thr Cys Gly Ala Cys Tyr

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Cys Glu Leu Cys Trp Asn Pro Ala Cys Thr Gly Cys Tyr  
 Cys Glu Leu Cys Trp Asn Pro Ala Cys Thr Ala Cys Tyr  
 Cys Glu Leu Cys Trp Asn Pro Ala Cys Val Gly Cys Tyr  
 Cys Glu Leu Cys Trp Asn Pro Ala Cys Val Ala Cys Tyr  
 Cys Glu Leu Cys Trp Asn Pro Ala Cys Gly Gly Cys Tyr  
 Cys Glu Leu Cys Trp Asn Pro Ala Cys Gly Ala Cys Tyr  
 Cys Glu Leu Cys Trp Asn Pro Thr Cys Thr Gly Cys Tyr  
 Cys Glu Leu Cys Trp Asn Pro Thr Cys Thr Ala Cys Tyr  
 Cys Glu Leu Cys Trp Asn Pro Thr Cys Val Gly Cys Tyr  
 Cys Glu Leu Cys Trp Asn Pro Thr Cys Val Ala Cys Tyr  
 Cys Glu Leu Cys Trp Asn Pro Thr Cys Gly Gly Cys Tyr  
 Cys Glu Leu Cys Trp Asn Pro Thr Cys Gly Ala Cys Tyr  
 Cys Glu Leu Cys Trp Asn Gly Ala Cys Thr Ala Cys Tyr  
 Cys Glu Leu Cys Trp Asn Gly Ala Cys Val Gly Cys Tyr  
 Cys Glu Leu Cys Trp Asn Gly Ala Cys Val Ala Cys Tyr  
 Cys Glu Leu Cys Trp Asn Gly Ala Cys Gly Gly Cys Tyr  
 Cys Glu Leu Cys Trp Asn Gly Ala Cys Gly Ala Cys Tyr  
 Cys Glu Leu Cys Trp Asn Gly Thr Cys Thr Gly Cys Tyr  
 Cys Glu Leu Cys Tyr Asn Pro Ala Cys Thr Gly Cys Tyr  
 Cys Glu Leu Cys Tyr Asn Pro Ala Cys Thr Ala Cys Tyr  
 Cys Glu Leu Cys Tyr Asn Pro Ala Cys Val Gly Cys Tyr  
 Cys Glu Leu Cys Tyr Asn Pro Thr Cys Val Ala Cys Tyr  
 Cys Glu Leu Cys Tyr Asn Pro Thr Cys Gly Gly Cys Tyr  
 Cys Glu Leu Cys Tyr Asn Pro Thr Cys Gly Ala Cys Tyr  
 Cys Glu Leu Cys Tyr Asn Gly Ala Cys Thr Gly Cys Tyr  
 Cys Glu Leu Cys Tyr Asn Gly Ala Cys Val Gly Cys Tyr  
 Cys Glu Leu Cys Tyr Asn Gly Ala Cys Gly Gly Cys Tyr  
 Cys Glu Leu Cys Tyr Asn Gly Ala Cys Gly Ala Cys Tyr  
 Cys Glu Leu Cys Tyr Asn Gly Thr Cys Thr Gly Cys Tyr  
 Cys Glu Leu Cys Tyr Asn Gly Thr Cys Thr Ala Cys Tyr  
 Cys Glu Leu Cys Tyr Asn Gly Thr Cys Val Gly Cys Tyr  
 Cys Glu Leu Cys Tyr Asn Gly Thr Cys Val Ala Cys Tyr  
 Cys Glu Leu Cys Tyr Asn Gly Thr Cys Gly Gly Cys Tyr  
 Cys Glu Leu Cys Tyr Asn Gly Thr Cys Gly Ala Cys Tyr  
 Cys Glu Leu Cys Val Asn Pro Ala Cys Thr Gly Cys Tyr  
 Cys Glu Leu Cys Val Asn Pro Ala Cys Thr Ala Cys Tyr  
 Cys Glu Leu Cys Val Asn Pro Ala Cys Val Gly Cys Tyr  
 Cys Glu Leu Cys Val Asn Pro Ala Cys Val Ala Cys Tyr  
 Cys Glu Leu Cys Val Asn Pro Ala Cys Gly Gly Cys Tyr  
 Cys Glu Leu Cys Val Asn Pro Ala Cys Gly Ala Cys Tyr  
 Cys Glu Leu Cys Val Asn Pro Thr Cys Thr Gly Cys Tyr  
 Cys Glu Leu Cys Val Asn Pro Thr Cys Thr Ala Cys Tyr  
 Cys Glu Leu Cys Val Asn Pro Thr Cys Val Gly Cys Tyr

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Cys Glu Leu Cys Val Asn Pro Thr Cys Val Ala Cys Tyr  
 Cys Glu Leu Cys Val Asn Pro Thr Cys Gly Gly Cys Tyr  
 Cys Glu Leu Cys Val Asn Pro Thr Cys Gly Ala Cys Tyr  
 Cys Glu Leu Cys Val Asn Gly Ala Cys Thr Gly Cys Tyr  
 Cys Glu Leu Cys Val Asn Gly Ala Cys Thr Ala Cys Tyr  
 Cys Glu Leu Cys Val Asn Gly Ala Cys Val Gly Cys Tyr  
 Cys Glu Leu Cys Val Asn Gly Ala Cys Val Ala Cys Tyr  
 Cys Glu Leu Cys Val Asn Gly Ala Cys Gly Gly Cys Tyr  
 Cys Glu Leu Cys Val Asn Gly Ala Cys Gly Ala Cys Tyr  
 Cys Glu Leu Cys Val Asn Gly Thr Cys Thr Gly Cys Tyr  
 Cys Glu Leu Cys Val Asn Gly Thr Cys Thr Ala Cys Tyr  
 Cys Glu Leu Cys Val Asn Gly Thr Cys Val Gly Cys Tyr  
 Cys Glu Leu Cys Val Asn Gly Thr Cys Val Ala Cys Tyr  
 Cys Glu Leu Cys Val Asn Gly Thr Cys Gly Gly Cys Tyr  
 Cys Glu Leu Cys Val Asn Gly Thr Cys Gly Ala Cys Tyr  
 Cys Glu Leu Cys Val Asn Gly Thr Cys Thr Gly Cys Tyr  
 Cys Glu Leu Cys Val Asn Gly Thr Cys Thr Ala Cys Tyr  
 Cys Glu Leu Cys Val Asn Gly Thr Cys Val Gly Cys Tyr  
 Cys Glu Leu Cys Val Asn Gly Thr Cys Val Ala Cys Tyr  
 Cys Glu Leu Cys Val Asn Gly Thr Cys Gly Gly Cys Tyr  
 Cys Glu Leu Cys Val Asn Gly Thr Cys Gly Ala Cys Tyr  
 Cys Glu Leu Cys Val Asn Gly Thr Cys Thr Gly Cys Tyr  
 Cys Glu Leu Cys Val Asn Gly Thr Cys Thr Ala Cys Tyr  
 Cys Glu Leu Cys Val Asn Gly Thr Cys Val Gly Cys Tyr  
 Cys Glu Leu Cys Val Asn Gly Thr Cys Val Ala Cys Tyr  
 Cys Glu Leu Cys Val Asn Gly Thr Cys Gly Gly Cys Tyr  
 Cys Glu Leu Cys Val Asn Gly Thr Cys Gly Ala Cys Tyr  
 Cys Glu Tyr Cys Ala Asn Pro Ala Cys Thr Gly Cys  
 Cys Glu Tyr Cys Ala Asn Pro Ala Cys Thr Ala Cys  
 Cys Glu Tyr Cys Ala Asn Pro Ala Cys Val Gly Cys  
 Cys Glu Tyr Cys Ala Asn Pro Ala Cys Val Ala Cys  
 Cys Glu Tyr Cys Ala Asn Pro Ala Cys Gly Gly Cys  
 Cys Glu Tyr Cys Ala Asn Pro Ala Cys Gly Ala Cys  
 Cys Glu Tyr Cys Ala Asn Pro Thr Cys Thr Gly Cys  
 Cys Glu Tyr Cys Ala Asn Pro Thr Cys Thr Ala Cys  
 Cys Glu Tyr Cys Ala Asn Pro Thr Cys Val Gly Cys  
 Cys Glu Tyr Cys Ala Asn Pro Thr Cys Val Ala Cys  
 Cys Glu Tyr Cys Ala Asn Pro Thr Cys Gly Gly Cys  
 Cys Glu Tyr Cys Ala Asn Pro Thr Cys Gly Ala Cys  
 Cys Glu Tyr Cys Ala Asn Gly Ala Cys Thr Gly Cys  
 Cys Glu Tyr Cys Ala Asn Gly Ala Cys Thr Ala Cys  
 Cys Glu Tyr Cys Ala Asn Gly Ala Cys Val Gly Cys  
 Cys Glu Tyr Cys Ala Asn Gly Ala Cys Val Ala Cys  
 Cys Glu Tyr Cys Ala Asn Gly Ala Cys Gly Gly Cys  
 Cys Glu Tyr Cys Ala Asn Gly Ala Cys Gly Ala Cys

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Cys Glu Tyr Cys Ala Asn Gly Thr Cys Thr Gly Cys  
 Cys Glu Tyr Cys Ala Asn Gly Thr Cys Thr Ala Cys  
 Cys Glu Tyr Cys Ala Asn Gly Thr Cys Val Gly Cys  
 Cys Glu Tyr Cys Ala Asn Gly Thr Cys Val Ala Cys  
 Cys Glu Tyr Cys Ala Asn Gly Thr Cys Gly Gly Cys  
 Cys Glu Tyr Cys Ala Asn Gly Thr Cys Gly Ala Cys  
 Cys Glu Tyr Cys Arg Asn Pro Ala Cys Thr Gly Cys  
 Cys Glu Tyr Cys Arg Asn Pro Ala Cys Thr Ala Cys  
 Cys Glu Tyr Cys Arg Asn Pro Ala Cys Val Gly Cys  
 Cys Glu Tyr Cys Arg Asn Pro Ala Cys Val Ala Cys  
 Cys Glu Tyr Cys Arg Asn Pro Ala Cys Gly Gly Cys  
 Cys Glu Tyr Cys Arg Asn Pro Ala Cys Gly Ala Cys  
 Cys Glu Tyr Cys Arg Asn Pro Thr Cys Thr Gly Cys  
 Cys Glu Tyr Cys Arg Asn Pro Thr Cys Thr Ala Cys  
 Cys Glu Tyr Cys Arg Asn Pro Thr Cys Val Gly Cys  
 Cys Glu Tyr Cys Arg Asn Pro Thr Cys Val Ala Cys  
 Cys Glu Tyr Cys Arg Asn Pro Thr Cys Gly Gly Cys  
 Cys Glu Tyr Cys Arg Asn Pro Thr Cys Gly Ala Cys  
 Cys Glu Tyr Cys Arg Asn Gly Ala Cys Thr Gly Cys  
 Cys Glu Tyr Cys Arg Asn Gly Ala Cys Val Gly Cys  
 Cys Glu Tyr Cys Arg Asn Gly Ala Cys Val Ala Cys  
 Cys Glu Tyr Cys Arg Asn Gly Ala Cys Gly Gly Cys  
 Cys Glu Tyr Cys Arg Asn Gly Ala Cys Gly Ala Cys  
 Cys Glu Tyr Cys Arg Asn Gly Ala Cys Gly Ala Cys  
 Cys Glu Tyr Cys Arg Asn Gly Thr Cys Thr Gly Cys  
 Cys Glu Tyr Cys Arg Asn Gly Thr Cys Thr Ala Cys  
 Cys Glu Tyr Cys Arg Asn Gly Thr Cys Val Gly Cys  
 Cys Glu Tyr Cys Arg Asn Gly Thr Cys Val Ala Cys  
 Cys Glu Tyr Cys Arg Asn Gly Thr Cys Gly Gly Cys  
 Cys Glu Tyr Cys Arg Asn Gly Ala Cys Gly Ala Cys  
 Cys Glu Tyr Cys Arg Asn Gly Thr Cys Thr Gly Cys  
 Cys Glu Tyr Cys Arg Asn Gly Thr Cys Thr Ala Cys  
 Cys Glu Tyr Cys Arg Asn Gly Thr Cys Val Gly Cys  
 Cys Glu Tyr Cys Arg Asn Gly Thr Cys Val Ala Cys  
 Cys Glu Tyr Cys Arg Asn Gly Thr Cys Gly Gly Cys  
 Cys Glu Tyr Cys Arg Asn Gly Thr Cys Gly Ala Cys  
 Cys Glu Tyr Cys Asp Asn Pro Ala Cys Thr Gly Cys  
 Cys Glu Tyr Cys Asp Asn Pro Ala Cys Thr Ala Cys  
 Cys Glu Tyr Cys Asp Asn Pro Ala Cys Val Gly Cys

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Cys Glu Tyr Cys Asp Asn Pro Ala Cys Val Ala Cys  
 Cys Glu Tyr Cys Asp Asn Pro Ala Cys Gly Gly Cys  
 Cys Glu Tyr Cys Asp Asn Pro Ala Cys Gly Ala Cys  
 Cys Glu Tyr Cys Asp Asn Pro Thr Cys Thr Gly Cys  
 Cys Glu Tyr Cys Asp Asn Pro Thr Cys Thr Ala Cys  
 Cys Glu Tyr Cys Asp Asn Pro Thr Cys Val Gly Cys  
 Cys Glu Tyr Cys Asp Asn Pro Thr Cys Val Ala Cys  
 Cys Glu Tyr Cys Asp Asn Pro Thr Cys Gly Gly Cys  
 Cys Glu Tyr Cys Asp Asn Pro Thr Cys Gly Ala Cys  
 Cys Glu Tyr Cys Asp Asn Gly Ala Cys Thr Gly Cys  
 Cys Glu Tyr Cys Asp Asn Gly Ala Cys Thr Ala Cys  
 Cys Glu Tyr Cys Asp Asn Gly Ala Cys Val Gly Cys  
 Cys Glu Tyr Cys Asp Asn Gly Ala Cys Val Ala Cys  
 Cys Glu Tyr Cys Asp Asn Gly Ala Cys Gly Gly Cys  
 Cys Glu Tyr Cys Asp Asn Gly Ala Cys Gly Ala Cys  
 Cys Glu Tyr Cys Asp Asn Gly Thr Cys Thr Gly Cys  
 Cys Glu Tyr Cys Asp Asn Gly Thr Cys Thr Ala Cys  
 Cys Glu Tyr Cys Asp Asn Gly Thr Cys Val Gly Cys  
 Cys Glu Tyr Cys Asp Asn Gly Thr Cys Val Ala Cys  
 Cys Glu Tyr Cys Asp Asn Gly Thr Cys Val Ala Cys  
 Cys Glu Tyr Cys Asp Asn Gly Thr Cys Gly Gly Cys  
 Cys Glu Tyr Cys Asp Asn Gly Thr Cys Gly Ala Cys  
 Cys Glu Tyr Cys Asp Asn Gly Thr Cys Thr Gly Cys  
 Cys Glu Tyr Cys Asp Asn Gly Thr Cys Thr Ala Cys  
 Cys Glu Tyr Cys Asp Asn Gly Thr Cys Val Gly Cys  
 Cys Glu Tyr Cys Asp Asn Gly Thr Cys Val Ala Cys  
 Cys Glu Tyr Cys Asp Asn Gly Thr Cys Gly Gly Cys  
 Cys Glu Tyr Cys Asp Asn Gly Thr Cys Gly Ala Cys  
 Cys Glu Tyr Cys Glu Asn Pro Ala Cys Thr Gly Cys  
 Cys Glu Tyr Cys Glu Asn Pro Ala Cys Thr Ala Cys  
 Cys Glu Tyr Cys Glu Asn Pro Ala Cys Val Gly Cys  
 Cys Glu Tyr Cys Glu Asn Pro Ala Cys Val Ala Cys  
 Cys Glu Tyr Cys Glu Asn Pro Ala Cys Gly Gly Cys  
 Cys Glu Tyr Cys Glu Asn Pro Ala Cys Gly Ala Cys  
 Cys Glu Tyr Cys Glu Asn Pro Thr Cys Thr Gly Cys  
 Cys Glu Tyr Cys Glu Asn Pro Thr Cys Thr Ala Cys  
 Cys Glu Tyr Cys Glu Asn Pro Thr Cys Val Gly Cys  
 Cys Glu Tyr Cys Glu Asn Pro Thr Cys Val Ala Cys  
 Cys Glu Tyr Cys Glu Asn Pro Thr Cys Gly Gly Cys  
 Cys Glu Tyr Cys Glu Asn Pro Thr Cys Gly Ala Cys

FIGURE 3 (sheet 37 of 68)

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Cys Glu Tyr Cys Glu Asn Gly Ala Cys Thr Gly Cys  
 Cys Glu Tyr Cys Glu Asn Gly Ala Cys Thr Ala Cys  
 Cys Glu Tyr Cys Glu Asn Gly Ala Cys Val Gly Cys  
 Cys Glu Tyr Cys Glu Asn Gly Ala Cys Val Ala Cys  
 Cys Glu Tyr Cys Glu Asn Gly Ala Cys Gly Gly Cys  
 Cys Glu Tyr Cys Glu Asn Gly Ala Cys Gly Ala Cys  
 Cys Glu Tyr Cys Glu Asn Gly Thr Cys Thr Gly Cys  
 Cys Glu Tyr Cys Glu Asn Gly Thr Cys Thr Ala Cys  
 Cys Glu Tyr Cys Glu Asn Gly Thr Cys Val Gly Cys  
 Cys Glu Tyr Cys Glu Asn Gly Thr Cys Val Ala Cys  
 Cys Glu Tyr Cys Glu Asn Gly Thr Cys Gly Gly Cys  
 Cys Glu Tyr Cys Glu Asn Gly Thr Cys Gly Ala Cys  
 Cys Glu Tyr Cys Glu Asn Gly Thr Cys Gly Ala Cys  
 Cys Glu Tyr Cys Gly Asn Pro Ala Cys Thr Gly Cys  
 Cys Glu Tyr Cys Gly Asn Pro Ala Cys Thr Ala Cys  
 Cys Glu Tyr Cys Gly Asn Pro Ala Cys Val Gly Cys  
 Cys Glu Tyr Cys Gly Asn Pro Ala Cys Val Ala Cys  
 Cys Glu Tyr Cys Gly Asn Pro Ala Cys Gly Gly Cys  
 Cys Glu Tyr Cys Gly Asn Pro Ala Cys Gly Ala Cys  
 Cys Glu Tyr Cys Gly Asn Pro Thr Cys Thr Gly Cys  
 Cys Glu Tyr Cys Gly Asn Pro Thr Cys Thr Ala Cys  
 Cys Glu Tyr Cys Gly Asn Pro Thr Cys Val Gly Cys  
 Cys Glu Tyr Cys Gly Asn Pro Thr Cys Val Ala Cys  
 Cys Glu Tyr Cys Gly Asn Pro Thr Cys Gly Gly Cys  
 Cys Glu Tyr Cys Gly Asn Pro Thr Cys Gly Ala Cys  
 Cys Glu Tyr Cys His Asn Pro Ala Cys Thr Gly Cys  
 Cys Glu Tyr Cys His Asn Pro Ala Cys Thr Ala Cys  
 Cys Glu Tyr Cys His Asn Pro Ala Cys Val Gly Cys  
 Cys Glu Tyr Cys His Asn Pro Ala Cys Val Ala Cys  
 Cys Glu Tyr Cys His Asn Pro Ala Cys Gly Gly Cys  
 Cys Glu Tyr Cys His Asn Pro Ala Cys Gly Ala Cys  
 Cys Glu Tyr Cys His Asn Pro Thr Cys Thr Gly Cys  
 Cys Glu Tyr Cys His Asn Pro Thr Cys Thr Ala Cys  
 Cys Glu Tyr Cys His Asn Pro Thr Cys Val Gly Cys  
 Cys Glu Tyr Cys His Asn Pro Thr Cys Val Ala Cys  
 Cys Glu Tyr Cys His Asn Pro Thr Cys Gly Gly Cys  
 Cys Glu Tyr Cys His Asn Gly Ala Cys Thr Gly Cys  
 Cys Glu Tyr Cys His Asn Gly Ala Cys Thr Ala Cys  
 Cys Glu Tyr Cys His Asn Gly Ala Cys Val Gly Cys  
 Cys Glu Tyr Cys His Asn Gly Ala Cys Val Ala Cys  
 Cys Glu Tyr Cys His Asn Gly Ala Cys Gly Gly Cys  
 Cys Glu Tyr Cys His Asn Gly Ala Cys Gly Ala Cys  
 Cys Glu Tyr Cys His Asn Gly Thr Cys Thr Gly Cys  
 Cys Glu Tyr Cys His Asn Gly Thr Cys Thr Ala Cys  
 Cys Glu Tyr Cys His Asn Gly Thr Cys Val Gly Cys





Cys Glu Tyr Cys Lys Asn Pro Thr Cys Thr Gly Cys  
Cys Glu Tyr Cys Lys Asn Pro Thr Cys Thr Ala Cys  
Cys Glu Tyr Cys Lys Asn Pro Thr Cys Val Gly Cys  
Cys Glu Tyr Cys Lys Asn Pro Thr Cys Val Ala Cys  
Cys Glu Tyr Cys Lys Asn Pro Thr Cys Gly Gly Cys  
Cys Glu Tyr Cys Lys Asn Pro Thr Cys Gly Ala Cys  
Cys Glu Tyr Cys Lys Asn Gly Ala Cys Thr Gly Cys  
Cys Glu Tyr Cys Lys Asn Gly Ala Cys Thr Ala Cys  
Cys Glu Tyr Cys Lys Asn Gly Ala Cys Val Gly Cys  
Cys Glu Tyr Cys Lys Asn Gly Ala Cys Val Ala Cys  
Cys Glu Tyr Cys Lys Asn Gly Ala Cys Gly Gly Cys  
Cys Glu Tyr Cys Lys Asn Gly Ala Cys Gly Ala Cys  
Cys Glu Tyr Cys Lys Asn Gly Ala Cys Gly Ala Cys  
Cys Glu Tyr Cys Lys Asn Gly Thr Cys Thr Gly Cys  
Cys Glu Tyr Cys Lys Asn Gly Thr Cys Thr Ala Cys  
Cys Glu Tyr Cys Lys Asn Gly Thr Cys Val Gly Cys  
Cys Glu Tyr Cys Lys Asn Gly Thr Cys Val Ala Cys  
Cys Glu Tyr Cys Met Asn Pro Ala Cys Thr Gly Cys  
Cys Glu Tyr Cys Met Asn Pro Ala Cys Thr Ala Cys  
Cys Glu Tyr Cys Met Asn Pro Ala Cys Val Gly Cys  
Cys Glu Tyr Cys Met Asn Pro Ala Cys Val Ala Cys  
Cys Glu Tyr Cys Met Asn Pro Ala Cys Gly Gly Cys  
Cys Glu Tyr Cys Met Asn Pro Ala Cys Gly Ala Cys  
Cys Glu Tyr Cys Met Asn Pro Thr Cys Thr Gly Cys  
Cys Glu Tyr Cys Met Asn Pro Thr Cys Thr Ala Cys  
Cys Glu Tyr Cys Met Asn Pro Thr Cys Val Gly Cys  
Cys Glu Tyr Cys Met Asn Gly Thr Cys Val Ala Cys  
Cys Glu Tyr Cys Met Asn Gly Thr Cys Gly Gly Cys  
Cys Glu Tyr Cys Met Asn Gly Thr Cys Gly Ala Cys  
Cys Glu Tyr Cys Met Asn Gly Thr Cys Thr Gly Cys  
Cys Glu Tyr Cys Met Asn Gly Thr Cys Thr Ala Cys  
Cys Glu Tyr Cys Met Asn Gly Thr Cys Val Gly Cys  
Cys Glu Tyr Cys Met Asn Gly Thr Cys Val Ala Cys  
Cys Glu Tyr Cys Phe Asn Pro Ala Cys Thr Gly Cys  
Cys Glu Tyr Cys Phe Asn Pro Ala Cys Thr Ala Cys  
Cys Glu Tyr Cys Phe Asn Pro Ala Cys Val Gly Cys  
Cys Glu Tyr Cys Phe Asn Pro Ala Cys Val Ala Cys  
Cys Glu Tyr Cys Phe Asn Pro Ala Cys Gly Gly Cys  
Cys Glu Tyr Cys Phe Asn Pro Ala Cys Gly Ala Cys  
Cys Glu Tyr Cys Phe Asn Pro Thr Cys Thr Gly Cys  
Cys Glu Tyr Cys Phe Asn Pro Thr Cys Thr Ala Cys  
Cys Glu Tyr Cys Phe Asn Pro Thr Cys Val Gly Cys  
Cys Glu Tyr Cys Phe Asn Pro Thr Cys Val Ala Cys  
Cys Glu Tyr Cys Phe Asn Pro Thr Cys Gly Gly Cys  
Cys Glu Tyr Cys Phe Asn Pro Thr Cys Gly Ala Cys  
Cys Glu Tyr Cys Phe Asn Gly Ala Cys Thr Gly Cys  
Cys Glu Tyr Cys Phe Asn Gly Ala Cys Thr Ala Cys  
Cys Glu Tyr Cys Phe Asn Gly Ala Cys Val Gly Cys

FIGURE 3 (sheet 40 of 68)

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Cys Glu Tyr Cys Phe Asn Gly Ala Cys Val Ala Cys  
 Cys Glu Tyr Cys Phe Asn Gly Ala Cys Gly Gly Cys  
 Cys Glu Tyr Cys Phe Asn Gly Ala Cys Gly Ala Cys  
 Cys Glu Tyr Cys Phe Asn Gly Thr Cys Thr Gly Cys  
 Cys Glu Tyr Cys Phe Asn Gly Thr Cys Thr Ala Cys  
 Cys Glu Tyr Cys Phe Asn Gly Thr Cys Val Gly Cys  
 Cys Glu Tyr Cys Phe Asn Gly Thr Cys Val Ala Cys  
 Cys Glu Tyr Cys Phe Asn Gly Thr Cys Gly Gly Cys  
 Cys Glu Tyr Cys Phe Asn Gly Thr Cys Gly Ala Cys  
 Cys Glu Tyr Cys Pro Asn Pro Ala Cys Thr Gly Cys  
 Cys Glu Tyr Cys Pro Asn Pro Ala Cys Thr Ala Cys  
 Cys Glu Tyr Cys Pro Asn Pro Ala Cys Val Gly Cys  
 Cys Glu Tyr Cys Pro Asn Pro Ala Cys Val Ala Cys  
 Cys Glu Tyr Cys Pro Asn Pro Ala Cys Gly Gly Cys  
 Cys Glu Tyr Cys Pro Asn Pro Ala Cys Gly Ala Cys  
 Cys Glu Tyr Cys Pro Asn Pro Thr Cys Thr Gly Cys  
 Cys Glu Tyr Cys Pro Asn Pro Thr Cys Thr Ala Cys  
 Cys Glu Tyr Cys Pro Asn Pro Thr Cys Val Gly Cys  
 Cys Glu Tyr Cys Pro Asn Pro Thr Cys Val Ala Cys  
 Cys Glu Tyr Cys Pro Asn Pro Thr Cys Gly Gly Cys  
 Cys Glu Tyr Cys Pro Asn Gly Ala Cys Thr Gly Cys  
 Cys Glu Tyr Cys Pro Asn Gly Ala Cys Thr Ala Cys  
 Cys Glu Tyr Cys Pro Asn Gly Ala Cys Val Gly Cys  
 Cys Glu Tyr Cys Pro Asn Gly Ala Cys Val Ala Cys  
 Cys Glu Tyr Cys Pro Asn Gly Ala Cys Gly Gly Cys  
 Cys Glu Tyr Cys Pro Asn Gly Ala Cys Gly Ala Cys  
 Cys Glu Tyr Cys Pro Asn Gly Thr Cys Thr Gly Cys  
 Cys Glu Tyr Cys Pro Asn Gly Thr Cys Thr Ala Cys  
 Cys Glu Tyr Cys Pro Asn Gly Thr Cys Val Gly Cys  
 Cys Glu Tyr Cys Pro Asn Gly Thr Cys Val Ala Cys  
 Cys Glu Tyr Cys Pro Asn Gly Thr Cys Gly Gly Cys  
 Cys Glu Tyr Cys Ser Asn Pro Ala Cys Thr Gly Cys  
 Cys Glu Tyr Cys Ser Asn Pro Ala Cys Thr Ala Cys  
 Cys Glu Tyr Cys Ser Asn Pro Ala Cys Val Gly Cys  
 Cys Glu Tyr Cys Ser Asn Pro Ala Cys Val Ala Cys  
 Cys Glu Tyr Cys Ser Asn Pro Ala Cys Gly Gly Cys  
 Cys Glu Tyr Cys Ser Asn Pro Ala Cys Gly Ala Cys  
 Cys Glu Tyr Cys Ser Asn Pro Thr Cys Thr Gly Cys  
 Cys Glu Tyr Cys Ser Asn Pro Thr Cys Thr Ala Cys  
 Cys Glu Tyr Cys Ser Asn Pro Thr Cys Val Gly Cys  
 Cys Glu Tyr Cys Ser Asn Pro Thr Cys Val Ala Cys  
 Cys Glu Tyr Cys Ser Asn Gly Ala Cys Gly Gly Cys  
 Cys Glu Tyr Cys Ser Asn Gly Ala Cys Gly Ala Cys  
 Cys Glu Tyr Cys Ser Asn Gly Thr Cys Thr Gly Cys  
 Cys Glu Tyr Cys Ser Asn Gly Thr Cys Thr Ala Cys  
 Cys Glu Tyr Cys Ser Asn Gly Thr Cys Val Gly Cys  
 Cys Glu Tyr Cys Ser Asn Gly Thr Cys Val Ala Cys  
 Cys Glu Tyr Cys Ser Asn Gly Thr Cys Gly Gly Cys  
 Cys Glu Tyr Cys Ser Asn Gly Thr Cys Gly Ala Cys

FIGURE 3 (sheet 41 of 68)

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Cys Glu Tyr Cys Thr Asn Pro Ala Cys Thr Gly Cys  
Cys Glu Tyr Cys Thr Asn Pro Ala Cys Thr Ala Cys  
Cys Glu Tyr Cys Thr Asn Pro Ala Cys Val Gly Cys  
Cys Glu Tyr Cys Thr Asn Pro Ala Cys Val Ala Cys  
Cys Glu Tyr Cys Thr Asn Pro Ala Cys Gly Gly Cys  
Cys Glu Tyr Cys Thr Asn Pro Ala Cys Gly Ala Cys  
Cys Glu Tyr Cys Thr Asn Pro Thr Cys Thr Gly Cys  
Cys Glu Tyr Cys Thr Asn Pro Thr Cys Thr Ala Cys  
Cys Glu Tyr Cys Thr Asn Pro Thr Cys Val Gly Cys  
Cys Glu Tyr Cys Thr Asn Pro Thr Cys Val Ala Cys  
Cys Glu Tyr Cys Thr Asn Pro Thr Cys Gly Gly Cys  
Cys Glu Tyr Cys Thr Asn Pro Thr Cys Gly Ala Cys  
Cys Glu Tyr Cys Thr Asn Gly Ala Cys Val Gly Cys  
Cys Glu Tyr Cys Thr Asn Gly Ala Cys Gly Gly Cys  
Cys Glu Tyr Cys Thr Asn Gly Thr Cys Thr Gly Cys  
Cys Glu Tyr Cys Thr Asn Gly Thr Cys Thr Ala Cys  
Cys Glu Tyr Cys Thr Asn Gly Thr Cys Val Gly Cys  
Cys Glu Tyr Cys Thr Asn Gly Thr Cys Val Ala Cys  
Cys Glu Tyr Cys Thr Asn Gly Thr Cys Gly Gly Cys  
Cys Glu Tyr Cys Thr Asn Gly Thr Cys Gly Ala Cys  
Cys Glu Tyr Cys Trp Asn Pro Ala Cys Thr Gly Cys  
Cys Glu Tyr Cys Trp Asn Pro Ala Cys Thr Ala Cys  
Cys Glu Tyr Cys Trp Asn Pro Ala Cys Val Gly Cys  
Cys Glu Tyr Cys Trp Asn Pro Ala Cys Val Ala Cys  
Cys Glu Tyr Cys Trp Asn Pro Ala Cys Gly Gly Cys  
Cys Glu Tyr Cys Trp Asn Pro Ala Cys Gly Ala Cys  
Cys Glu Tyr Cys Trp Asn Pro Thr Cys Thr Gly Cys  
Cys Glu Tyr Cys Trp Asn Pro Thr Cys Thr Ala Cys  
Cys Glu Tyr Cys Trp Asn Pro Thr Cys Val Gly Cys  
Cys Glu Tyr Cys Trp Asn Pro Thr Cys Val Ala Cys  
Cys Glu Tyr Cys Trp Asn Pro Thr Cys Gly Gly Cys  
Cys Glu Tyr Cys Trp Asn Gly Ala Cys Thr Ala Cys  
Cys Glu Tyr Cys Trp Asn Gly Ala Cys Val Gly Cys  
Cys Glu Tyr Cys Trp Asn Gly Ala Cys Val Ala Cys  
Cys Glu Tyr Cys Trp Asn Gly Ala Cys Gly Gly Cys  
Cys Glu Tyr Cys Trp Asn Gly Ala Cys Gly Ala Cys  
Cys Glu Tyr Cys Trp Asn Gly Thr Cys Thr Gly Cys  
Cys Glu Tyr Cys Trp Asn Gly Thr Cys Thr Ala Cys  
Cys Glu Tyr Cys Trp Asn Gly Thr Cys Val Gly Cys  
Cys Glu Tyr Cys Trp Asn Gly Thr Cys Val Ala Cys  
Cys Glu Tyr Cys Trp Asn Gly Thr Cys Gly Gly Cys  
Cys Glu Tyr Cys Tyr Asn Pro Ala Cys Thr Gly Cys  
Cys Glu Tyr Cys Tyr Asn Pro Ala Cys Thr Ala Cys  
Cys Glu Tyr Cys Tyr Asn Pro Ala Cys Val Gly Cys  
Cys Glu Tyr Cys Tyr Asn Pro Ala Cys Val Ala Cys  
Cys Glu Tyr Cys Tyr Asn Pro Ala Cys Gly Gly Cys  
Cys Glu Tyr Cys Tyr Asn Pro Ala Cys Gly Ala Cys  
Cys Glu Tyr Cys Tyr Asn Pro Thr Cys Thr Gly Cys  
Cys Glu Tyr Cys Tyr Asn Pro Thr Cys Thr Ala Cys  
Cys Glu Tyr Cys Tyr Asn Pro Thr Cys Val Gly Cys

FIGURE 3 (sheet 42 of 68)

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Cys Glu Tyr Cys Tyr Asn Pro Thr Cys Val Ala Cys  
 Cys Glu Tyr Cys Tyr Asn Pro Thr Cys Gly Gly Cys  
 Cys Glu Tyr Cys Tyr Asn Pro Thr Cys Gly Ala Cys  
 Cys Glu Tyr Cys Tyr Asn Gly Ala Cys Thr Gly Cys  
 Cys Glu Tyr Cys Tyr Asn Gly Ala Cys Thr Ala Cys  
 Cys Glu Tyr Cys Tyr Asn Gly Ala Cys Val Gly Cys  
 Cys Glu Tyr Cys Tyr Asn Gly Ala Cys Val Ala Cys  
 Cys Glu Tyr Cys Tyr Asn Gly Ala Cys Gly Gly Cys  
 Cys Glu Tyr Cys Tyr Asn Gly Ala Cys Gly Ala Cys  
 Cys Glu Tyr Cys Tyr Asn Gly Thr Cys Thr Gly Cys  
 Cys Glu Tyr Cys Tyr Asn Gly Thr Cys Thr Ala Cys  
 Cys Glu Tyr Cys Tyr Asn Gly Thr Cys Val Gly Cys  
 Cys Glu Tyr Cys Tyr Asn Gly Thr Cys Val Ala Cys  
 Cys Glu Tyr Cys Tyr Asn Gly Thr Cys Val Ala Cys  
 Cys Glu Tyr Cys Tyr Asn Gly Thr Cys Gly Gly Cys  
 Cys Glu Tyr Cys Tyr Asn Gly Thr Cys Gly Ala Cys  
 Cys Glu Tyr Cys Tyr Asn Gly Thr Cys Thr Gly Cys  
 Cys Glu Tyr Cys Val Asn Pro Ala Cys Thr Gly Cys  
 Cys Glu Tyr Cys Val Asn Pro Ala Cys Thr Ala Cys  
 Cys Glu Tyr Cys Val Asn Pro Ala Cys Val Gly Cys  
 Cys Glu Tyr Cys Val Asn Pro Ala Cys Val Ala Cys  
 Cys Glu Tyr Cys Val Asn Pro Ala Cys Gly Gly Cys  
 Cys Glu Tyr Cys Val Asn Pro Ala Cys Gly Ala Cys  
 Cys Glu Tyr Cys Val Asn Pro Thr Cys Thr Gly Cys  
 Cys Glu Tyr Cys Val Asn Gly Thr Cys Thr Ala Cys  
 Cys Glu Tyr Cys Val Asn Gly Thr Cys Thr Ala Cys  
 Cys Glu Tyr Cys Val Asn Gly Thr Cys Val Gly Cys  
 Cys Glu Tyr Cys Val Asn Gly Thr Cys Val Ala Cys  
 Cys Glu Tyr Cys Val Asn Gly Thr Cys Gly Gly Cys  
 Cys Glu Tyr Cys Val Asn Gly Thr Cys Gly Ala Cys  
 Cys Glu Tyr Cys --- Asn Pro Ala Cys Thr Gly Cys  
 Cys Glu Tyr Cys --- Asn Pro Ala Cys Thr Ala Cys  
 Cys Glu Tyr Cys --- Asn Pro Ala Cys Val Gly Cys  
 Cys Glu Tyr Cys --- Asn Pro Ala Cys Val Ala Cys  
 Cys Glu Tyr Cys --- Asn Pro Ala Cys Gly Gly Cys  
 Cys Glu Tyr Cys --- Asn Pro Ala Cys Gly Ala Cys  
 Cys Glu Tyr Cys --- Asn Pro Thr Cys Thr Gly Cys  
 Cys Glu Tyr Cys --- Asn Pro Thr Cys Thr Ala Cys  
 Cys Glu Tyr Cys --- Asn Pro Thr Cys Val Gly Cys  
 Cys Glu Tyr Cys --- Asn Pro Thr Cys Val Ala Cys  
 Cys Glu Tyr Cys --- Asn Pro Thr Cys Gly Gly Cys  
 Cys Glu Tyr Cys --- Asn Pro Thr Cys Gly Ala Cys  
 Cys Glu Tyr Cys --- Asn Gly Ala Cys Thr Gly Cys  
 Cys Glu Tyr Cys --- Asn Gly Ala Cys Thr Ala Cys  
 Cys Glu Tyr Cys --- Asn Gly Ala Cys Val Gly Cys  
 Cys Glu Tyr Cys --- Asn Gly Ala Cys Val Ala Cys  
 Cys Glu Tyr Cys --- Asn Gly Ala Cys Gly Gly Cys  
 Cys Glu Tyr Cys --- Asn Gly Ala Cys Gly Ala Cys

FIGURE 3 (sheet 43 of 68)

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Cys Glu Tyr Cys --- Asn Gly Thr Cys Thr Gly Cys  
 Cys Glu Tyr Cys --- Asn Gly Thr Cys Thr Ala Cys  
 Cys Glu Tyr Cys --- Asn Gly Thr Cys Val Gly Cys  
 Cys Glu Tyr Cys --- Asn Gly Thr Cys Val Ala Cys  
 Cys Glu Tyr Cys --- Asn Gly Thr Cys Gly Gly Cys  
 Cys Glu Tyr Cys --- Asn Gly Thr Cys Gly Ala Cys  
 Cys Glu Trp Cys Ala Asn Pro Ala Cys Thr Gly Cys  
 Cys Glu Trp Cys Ala Asn Pro Ala Cys Thr Ala Cys  
 Cys Glu Trp Cys Ala Asn Pro Ala Cys Val Gly Cys  
 Cys Glu Trp Cys Ala Asn Pro Ala Cys Val Ala Cys  
 Cys Glu Trp Cys Ala Asn Pro Ala Cys Gly Gly Cys  
 Cys Glu Trp Cys Ala Asn Pro Ala Cys Gly Ala Cys  
 Cys Glu Trp Cys Ala Asn Pro Thr Cys Thr Gly Cys  
 Cys Glu Trp Cys Ala Asn Pro Thr Cys Thr Ala Cys  
 Cys Glu Trp Cys Ala Asn Pro Thr Cys Val Gly Cys  
 Cys Glu Trp Cys Ala Asn Pro Thr Cys Val Ala Cys  
 Cys Glu Trp Cys Ala Asn Pro Thr Cys Gly Gly Cys  
 Cys Glu Trp Cys Ala Asn Pro Thr Cys Gly Ala Cys  
 Cys Glu Trp Cys Ala Asn Gly Ala Cys Thr Gly Cys  
 Cys Glu Trp Cys Ala Asn Gly Ala Cys Val Gly Cys  
 Cys Glu Trp Cys Ala Asn Gly Ala Cys Val Ala Cys  
 Cys Glu Trp Cys Ala Asn Gly Ala Cys Gly Gly Cys  
 Cys Glu Trp Cys Ala Asn Gly Ala Cys Gly Ala Cys  
 Cys Glu Trp Cys Ala Asn Gly Thr Cys Thr Gly Cys  
 Cys Glu Trp Cys Ala Asn Gly Thr Cys Thr Ala Cys  
 Cys Glu Trp Cys Ala Asn Gly Thr Cys Val Gly Cys  
 Cys Glu Trp Cys Ala Asn Gly Thr Cys Val Ala Cys  
 Cys Glu Trp Cys Arg Asn Pro Ala Cys Thr Gly Cys  
 Cys Glu Trp Cys Arg Asn Pro Ala Cys Thr Ala Cys  
 Cys Glu Trp Cys Arg Asn Pro Ala Cys Val Gly Cys  
 Cys Glu Trp Cys Arg Asn Pro Ala Cys Val Ala Cys  
 Cys Glu Trp Cys Arg Asn Pro Ala Cys Gly Gly Cys  
 Cys Glu Trp Cys Arg Asn Pro Ala Cys Gly Ala Cys  
 Cys Glu Trp Cys Arg Asn Pro Thr Cys Thr Gly Cys  
 Cys Glu Trp Cys Arg Asn Pro Thr Cys Thr Ala Cys  
 Cys Glu Trp Cys Arg Asn Pro Thr Cys Val Gly Cys  
 Cys Glu Trp Cys Arg Asn Pro Thr Cys Val Ala Cys  
 Cys Glu Trp Cys Arg Asn Pro Thr Cys Gly Gly Cys  
 Cys Glu Trp Cys Arg Asn Pro Thr Cys Gly Ala Cys  
 Cys Glu Trp Cys Arg Asn Gly Ala Cys Thr Gly Cys  
 Cys Glu Trp Cys Arg Asn Gly Ala Cys Thr Ala Cys  
 Cys Glu Trp Cys Arg Asn Gly Ala Cys Val Gly Cys  
 Cys Glu Trp Cys Arg Asn Gly Ala Cys Val Ala Cys  
 Cys Glu Trp Cys Arg Asn Gly Ala Cys Gly Gly Cys  
 Cys Glu Trp Cys Arg Asn Gly Thr Cys Thr Gly Cys  
 Cys Glu Trp Cys Arg Asn Gly Thr Cys Thr Ala Cys  
 Cys Glu Trp Cys Arg Asn Gly Thr Cys Val Gly Cys  
 Cys Glu Trp Cys Arg Asn Gly Thr Cys Val Ala Cys  
 Cys Glu Trp Cys Arg Asn Gly Thr Cys Gly Gly Cys  
 Cys Glu Trp Cys Arg Asn Gly Thr Cys Gly Ala Cys  
 Cys Glu Trp Cys Asn Asn Pro Ala Cys Thr Gly Cys  
 Cys Glu Trp Cys Asn Asn Pro Ala Cys Thr Ala Cys  
 Cys Glu Trp Cys Asn Asn Pro Ala Cys Val Gly Cys

FIGURE 3 (sheet 44 of 68)

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Cys Glu Trp Cys Asn Asn Pro Ala Cys Val Ala Cys  
 Cys Glu Trp Cys Asn Asn Pro Ala Cys Gly Gly Cys  
 Cys Glu Trp Cys Asn Asn Pro Ala Cys Gly Ala Cys  
 Cys Glu Trp Cys Asn Asn Pro Thr Cys Thr Gly Cys  
 Cys Glu Trp Cys Asn Asn Pro Thr Cys Thr Ala Cys  
 Cys Glu Trp Cys Asn Asn Pro Thr Cys Val Gly Cys  
 Cys Glu Trp Cys Asn Asn Pro Thr Cys Val Ala Cys  
 Cys Glu Trp Cys Asn Asn Pro Thr Cys Gly Gly Cys  
 Cys Glu Trp Cys Asn Asn Pro Thr Cys Gly Ala Cys  
 Cys Glu Trp Cys Asn Asn Pro Thr Cys Gly Ala Cys  
 Cys Glu Trp Cys Asn Asn Gly Ala Cys Thr Gly Cys  
 Cys Glu Trp Cys Asn Asn Gly Ala Cys Thr Ala Cys  
 Cys Glu Trp Cys Asn Asn Gly Ala Cys Val Gly Cys  
 Cys Glu Trp Cys Asn Asn Gly Ala Cys Val Ala Cys  
 Cys Glu Trp Cys Asn Asn Gly Ala Cys Gly Gly Cys  
 Cys Glu Trp Cys Asn Asn Gly Ala Cys Gly Ala Cys  
 Cys Glu Trp Cys Asn Asn Gly Thr Cys Thr Gly Cys  
 Cys Glu Trp Cys Asn Asn Gly Thr Cys Thr Ala Cys  
 Cys Glu Trp Cys Asn Asn Gly Thr Cys Val Gly Cys  
 Cys Glu Trp Cys Asn Asn Gly Thr Cys Val Ala Cys  
 Cys Glu Trp Cys Asp Asn Pro Ala Cys Thr Gly Cys  
 Cys Glu Trp Cys Asp Asn Pro Ala Cys Thr Ala Cys  
 Cys Glu Trp Cys Asp Asn Pro Ala Cys Val Gly Cys  
 Cys Glu Trp Cys Asp Asn Pro Ala Cys Val Ala Cys  
 Cys Glu Trp Cys Asp Asn Pro Ala Cys Gly Gly Cys  
 Cys Glu Trp Cys Asp Asn Pro Ala Cys Gly Ala Cys  
 Cys Glu Trp Cys Asp Asn Pro Thr Cys Thr Gly Cys  
 Cys Glu Trp Cys Asp Asn Pro Thr Cys Thr Ala Cys  
 Cys Glu Trp Cys Asp Asn Pro Thr Cys Thr Ala Cys  
 Cys Glu Trp Cys Asp Asn Pro Thr Cys Val Gly Cys  
 Cys Glu Trp Cys Asp Asn Pro Thr Cys Val Ala Cys  
 Cys Glu Trp Cys Asp Asn Gly Ala Cys Val Ala Cys  
 Cys Glu Trp Cys Asp Asn Gly Ala Cys Gly Gly Cys  
 Cys Glu Trp Cys Asp Asn Gly Ala Cys Gly Ala Cys  
 Cys Glu Trp Cys Asp Asn Gly Thr Cys Thr Gly Cys  
 Cys Glu Trp Cys Asp Asn Gly Thr Cys Thr Ala Cys  
 Cys Glu Trp Cys Asp Asn Gly Thr Cys Val Gly Cys  
 Cys Glu Trp Cys Asp Asn Gly Thr Cys Val Ala Cys  
 Cys Glu Trp Cys Asp Asn Gly Thr Cys Gly Gly Cys  
 Cys Glu Trp Cys Asp Asn Gly Thr Cys Gly Ala Cys  
 Cys Glu Trp Cys Gln Asn Pro Ala Cys Thr Gly Cys  
 Cys Glu Trp Cys Gln Asn Pro Ala Cys Thr Ala Cys  
 Cys Glu Trp Cys Gln Asn Pro Ala Cys Val Gly Cys  
 Cys Glu Trp Cys Gln Asn Pro Ala Cys Val Ala Cys  
 Cys Glu Trp Cys Gln Asn Pro Ala Cys Gly Gly Cys  
 Cys Glu Trp Cys Gln Asn Pro Ala Cys Gly Ala Cys  
 Cys Glu Trp Cys Gln Asn Pro Thr Cys Thr Gly Cys  
 Cys Glu Trp Cys Gln Asn Pro Thr Cys Thr Ala Cys  
 Cys Glu Trp Cys Gln Asn Pro Thr Cys Val Gly Cys  
 Cys Glu Trp Cys Gln Asn Pro Thr Cys Val Ala Cys  
 Cys Glu Trp Cys Gln Asn Pro Thr Cys Gly Gly Cys  
 Cys Glu Trp Cys Gln Asn Pro Thr Cys Gly Ala Cys

FIGURE 3 (sheet 45 of 68)

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Cys Glu Trp Cys Gln Asn Gly Ala Cys Thr Gly Cys  
Cys Glu Trp Cys Gln Asn Gly Ala Cys Thr Ala Cys  
Cys Glu Trp Cys Gln Asn Gly Ala Cys Val Gly Cys  
Cys Glu Trp Cys Gln Asn Gly Ala Cys Val Ala Cys  
Cys Glu Trp Cys Gln Asn Gly Ala Cys Gly Gly Cys  
Cys Glu Trp Cys Gln Asn Gly Ala Cys Gly Ala Cys  
Cys Glu Trp Cys Gln Asn Gly Thr Cys Thr Gly Cys  
Cys Glu Trp Cys Gln Asn Gly Thr Cys Thr Ala Cys  
Cys Glu Trp Cys Gln Asn Gly Thr Cys Val Gly Cys  
Cys Glu Trp Cys Gln Asn Gly Thr Cys Val Ala Cys  
Cys Glu Trp Cys Gln Asn Gly Thr Cys Val Ala Cys  
Cys Glu Trp Cys Gln Asn Gly Thr Cys Gly Gly Cys  
Cys Glu Trp Cys Gln Asn Gly Thr Cys Gly Ala Cys  
Cys Glu Trp Cys Gln Asn Gly Thr Cys Gly Ala Cys  
Cys Glu Trp Cys Gln Asn Gly Thr Cys Thr Gly Cys  
Cys Glu Trp Cys Gln Asn Gly Thr Cys Thr Ala Cys  
Cys Glu Trp Cys Gln Asn Gly Thr Cys Val Gly Cys  
Cys Glu Trp Cys Gln Asn Gly Thr Cys Val Ala Cys  
Cys Glu Trp Cys Gln Asn Gly Thr Cys Gly Gly Cys  
Cys Glu Trp Cys Gln Asn Gly Thr Cys Gly Ala Cys  
Cys Glu Trp Cys Gln Asn Gly Thr Cys Gly Ala Cys  
Cys Glu Trp Cys Gln Asn Gly Thr Cys Thr Gly Cys  
Cys Glu Trp Cys Gln Asn Gly Thr Cys Thr Ala Cys  
Cys Glu Trp Cys Gln Asn Gly Thr Cys Thr Ala Cys  
Cys Glu Trp Cys Gln Asn Gly Ala Cys Thr Ala Cys  
Cys Glu Trp Cys Gly Asn Pro Ala Cys Thr Gly Cys  
Cys Glu Trp Cys Gly Asn Pro Ala Cys Val Gly Cys  
Cys Glu Trp Cys Gly Asn Pro Ala Cys Val Ala Cys  
Cys Glu Trp Cys Gly Asn Pro Ala Cys Gly Gly Cys  
Cys Glu Trp Cys Gly Asn Pro Ala Cys Gly Ala Cys  
Cys Glu Trp Cys Gly Asn Pro Thr Cys Thr Gly Cys  
Cys Glu Trp Cys Gly Asn Pro Thr Cys Thr Ala Cys  
Cys Glu Trp Cys Gly Asn Pro Thr Cys Val Gly Cys  
Cys Glu Trp Cys Gly Asn Pro Thr Cys Val Ala Cys  
Cys Glu Trp Cys Gly Asn Pro Thr Cys Gly Gly Cys  
Cys Glu Trp Cys Gly Asn Gly Ala Cys Thr Ala Cys  
Cys Glu Trp Cys Gly Asn Gly Ala Cys Thr Ala Cys  
Cys Glu Trp Cys Gly Asn Gly Ala Cys Val Gly Cys  
Cys Glu Trp Cys Gly Asn Gly Ala Cys Val Ala Cys  
Cys Glu Trp Cys Gly Asn Gly Ala Cys Gly Gly Cys  
Cys Glu Trp Cys Gly Asn Gly Ala Cys Gly Ala Cys  
Cys Glu Trp Cys Gly Asn Gly Thr Cys Thr Gly Cys  
Cys Glu Trp Cys Gly Asn Gly Thr Cys Thr Ala Cys  
Cys Glu Trp Cys Gly Asn Gly Thr Cys Val Gly Cys

FIGURE 3 (sheet 46 of 68)

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Cys Glu Trp Cys Gly Asn Gly Thr Cys Val Ala Cys  
 Cys Glu Trp Cys Gly Asn Gly Thr Cys Gly Gly Cys  
 Cys Glu Trp Cys Gly Asn Gly Thr Cys Gly Ala Cys  
 Cys Glu Trp Cys His Asn Pro Ala Cys Thr Gly Cys  
 Cys Glu Trp Cys His Asn Pro Ala Cys Thr Ala Cys  
 Cys Glu Trp Cys His Asn Pro Ala Cys Val Gly Cys  
 Cys Glu Trp Cys His Asn Pro Ala Cys Val Ala Cys  
 Cys Glu Trp Cys His Asn Pro Ala Cys Gly Gly Cys  
 Cys Glu Trp Cys His Asn Pro Ala Cys Gly Ala Cys  
 Cys Glu Trp Cys His Asn Pro Thr Cys Thr Gly Cys  
 Cys Glu Trp Cys His Asn Pro Thr Cys Thr Ala Cys  
 Cys Glu Trp Cys His Asn Pro Thr Cys Val Gly Cys  
 Cys Glu Trp Cys His Asn Pro Thr Cys Val Ala Cys  
 Cys Glu Trp Cys His Asn Pro Thr Cys Gly Gly Cys  
 Cys Glu Trp Cys His Asn Pro Thr Cys Gly Ala Cys  
 Cys Glu Trp Cys His Asn Gly Ala Cys Thr Gly Cys  
 Cys Glu Trp Cys His Asn Gly Ala Cys Thr Ala Cys  
 Cys Glu Trp Cys His Asn Gly Ala Cys Val Gly Cys  
 Cys Glu Trp Cys His Asn Gly Ala Cys Val Ala Cys  
 Cys Glu Trp Cys His Asn Gly Ala Cys Gly Gly Cys  
 Cys Glu Trp Cys His Asn Gly Thr Cys Thr Gly Cys  
 Cys Glu Trp Cys His Asn Gly Thr Cys Thr Ala Cys  
 Cys Glu Trp Cys His Asn Gly Thr Cys Val Gly Cys  
 Cys Glu Trp Cys His Asn Gly Thr Cys Val Ala Cys  
 Cys Glu Trp Cys His Asn Gly Thr Cys Gly Gly Cys  
 Cys Glu Trp Cys His Asn Gly Thr Cys Gly Ala Cys  
 Cys Glu Trp Cys His Asn Gly Thr Cys Thr Gly Cys  
 Cys Glu Trp Cys His Asn Gly Thr Cys Thr Ala Cys  
 Cys Glu Trp Cys Ile Asn Pro Ala Cys Thr Ala Cys  
 Cys Glu Trp Cys Ile Asn Pro Ala Cys Val Gly Cys  
 Cys Glu Trp Cys Ile Asn Pro Ala Cys Val Ala Cys  
 Cys Glu Trp Cys Ile Asn Pro Ala Cys Gly Gly Cys  
 Cys Glu Trp Cys Ile Asn Pro Ala Cys Gly Ala Cys  
 Cys Glu Trp Cys Ile Asn Pro Thr Cys Thr Gly Cys  
 Cys Glu Trp Cys Ile Asn Pro Thr Cys Thr Ala Cys  
 Cys Glu Trp Cys Ile Asn Pro Thr Cys Val Gly Cys  
 Cys Glu Trp Cys Ile Asn Pro Thr Cys Val Ala Cys  
 Cys Glu Trp Cys Ile Asn Pro Thr Cys Gly Gly Cys  
 Cys Glu Trp Cys Ile Asn Pro Thr Cys Gly Ala Cys  
 Cys Glu Trp Cys Ile Asn Gly Ala Cys Thr Gly Cys  
 Cys Glu Trp Cys Ile Asn Gly Ala Cys Thr Ala Cys  
 Cys Glu Trp Cys Ile Asn Gly Ala Cys Val Gly Cys  
 Cys Glu Trp Cys Ile Asn Gly Ala Cys Val Ala Cys  
 Cys Glu Trp Cys Ile Asn Gly Ala Cys Gly Gly Cys  
 Cys Glu Trp Cys Ile Asn Gly Ala Cys Gly Ala Cys  
 Cys Glu Trp Cys Ile Asn Gly Thr Cys Thr Gly Cys  
 Cys Glu Trp Cys Ile Asn Gly Thr Cys Thr Ala Cys  
 Cys Glu Trp Cys Ile Asn Gly Thr Cys Val Gly Cys  
 Cys Glu Trp Cys Ile Asn Gly Thr Cys Val Ala Cys  
 Cys Glu Trp Cys Ile Asn Gly Thr Cys Gly Gly Cys  
 Cys Glu Trp Cys Ile Asn Gly Thr Cys Gly Ala Cys  
 Cys Glu Trp Cys Leu Asn Pro Ala Cys Thr Gly Cys  
 Cys Glu Trp Cys Leu Asn Pro Ala Cys Thr Ala Cys  
 Cys Glu Trp Cys Leu Asn Pro Ala Cys Val Gly Cys  
 Cys Glu Trp Cys Leu Asn Pro Ala Cys Val Ala Cys  
 Cys Glu Trp Cys Leu Asn Pro Ala Cys Gly Gly Cys  
 Cys Glu Trp Cys Leu Asn Pro Ala Cys Gly Ala Cys



Cys Glu Trp Cys Leu Asn Pro Thr Cys Thr Gly Cys  
Cys Glu Trp Cys Leu Asn Pro Thr Cys Thr Ala Cys  
Cys Glu Trp Cys Leu Asn Pro Thr Cys Val Gly Cys  
Cys Glu Trp Cys Leu Asn Pro Thr Cys Val Ala Cys  
Cys Glu Trp Cys Leu Asn Pro Thr Cys Gly Gly Cys  
Cys Glu Trp Cys Leu Asn Gly Ala Cys Thr Gly Cys  
Cys Glu Trp Cys Leu Asn Gly Ala Cys Thr Ala Cys  
Cys Glu Trp Cys Leu Asn Gly Ala Cys Val Gly Cys  
Cys Glu Trp Cys Leu Asn Gly Ala Cys Val Ala Cys  
Cys Glu Trp Cys Leu Asn Gly Ala Cys Gly Gly Cys  
Cys Glu Trp Cys Leu Asn Gly Ala Cys Gly Ala Cys  
Cys Glu Trp Cys Leu Asn Gly Thr Cys Thr Gly Cys  
Cys Glu Trp Cys Leu Asn Gly Thr Cys Thr Ala Cys  
Cys Glu Trp Cys Leu Asn Gly Thr Cys Val Gly Cys  
Cys Glu Trp Cys Leu Asn Gly Thr Cys Val Ala Cys  
Cys Glu Trp Cys Leu Asn Gly Thr Cys Gly Gly Cys  
Cys Glu Trp Cys Lys Asn Pro Ala Cys Thr Gly Cys  
Cys Glu Trp Cys Lys Asn Pro Ala Cys Thr Ala Cys  
Cys Glu Trp Cys Lys Asn Pro Ala Cys Val Gly Cys  
Cys Glu Trp Cys Lys Asn Pro Ala Cys Val Ala Cys  
Cys Glu Trp Cys Lys Asn Pro Ala Cys Gly Gly Cys  
Cys Glu Trp Cys Lys Asn Pro Ala Cys Gly Ala Cys  
Cys Glu Trp Cys Lys Asn Pro Thr Cys Thr Gly Cys  
Cys Glu Trp Cys Lys Asn Pro Thr Cys Thr Ala Cys  
Cys Glu Trp Cys Lys Asn Pro Thr Cys Val Gly Cys  
Cys Glu Trp Cys Lys Asn Gly Thr Cys Val Ala Cys  
Cys Glu Trp Cys Lys Asn Gly Thr Cys Gly Gly Cys  
Cys Glu Trp Cys Lys Asn Gly Thr Cys Gly Ala Cys  
Cys Glu Trp Cys Met Asn Pro Ala Cys Thr Gly Cys  
Cys Glu Trp Cys Met Asn Pro Ala Cys Thr Ala Cys  
Cys Glu Trp Cys Met Asn Pro Ala Cys Val Gly Cys  
Cys Glu Trp Cys Met Asn Pro Ala Cys Val Ala Cys  
Cys Glu Trp Cys Met Asn Pro Ala Cys Gly Gly Cys  
Cys Glu Trp Cys Met Asn Pro Ala Cys Gly Ala Cys  
Cys Glu Trp Cys Met Asn Pro Thr Cys Thr Gly Cys  
Cys Glu Trp Cys Met Asn Pro Thr Cys Thr Ala Cys  
Cys Glu Trp Cys Met Asn Pro Thr Cys Val Gly Cys  
Cys Glu Trp Cys Met Asn Pro Thr Cys Val Ala Cys  
Cys Glu Trp Cys Met Asn Pro Thr Cys Gly Gly Cys  
Cys Glu Trp Cys Met Asn Pro Thr Cys Gly Ala Cys  
Cys Glu Trp Cys Met Asn Gly Ala Cys Thr Gly Cys  
Cys Glu Trp Cys Met Asn Gly Ala Cys Thr Ala Cys  
Cys Glu Trp Cys Met Asn Gly Ala Cys Val Gly Cys

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Cys Glu Trp Cys Met Asn Gly Ala Cys Val Ala Cys  
 Cys Glu Trp Cys Met Asn Gly Ala Cys Gly Gly Cys  
 Cys Glu Trp Cys Met Asn Gly Ala Cys Gly Ala Cys  
 Cys Glu Trp Cys Met Asn Gly Thr Cys Thr Gly Cys  
 Cys Glu Trp Cys Met Asn Gly Thr Cys Thr Ala Cys  
 Cys Glu Trp Cys Met Asn Gly Thr Cys Val Gly Cys  
 Cys Glu Trp Cys Met Asn Gly Thr Cys Val Ala Cys  
 Cys Glu Trp Cys Met Asn Gly Thr Cys Gly Gly Cys  
 Cys Glu Trp Cys Met Asn Gly Thr Cys Gly Ala Cys  
 Cys Glu Trp Cys Phe Asn Pro Ala Cys Thr Gly Cys  
 Cys Glu Trp Cys Phe Asn Pro Ala Cys Thr Ala Cys  
 Cys Glu Trp Cys Phe Asn Pro Ala Cys Val Gly Cys  
 Cys Glu Trp Cys Phe Asn Pro Ala Cys Val Ala Cys  
 Cys Glu Trp Cys Phe Asn Pro Ala Cys Gly Gly Cys  
 Cys Glu Trp Cys Phe Asn Pro Ala Cys Gly Ala Cys  
 Cys Glu Trp Cys Phe Asn Pro Thr Cys Thr Gly Cys  
 Cys Glu Trp Cys Phe Asn Pro Thr Cys Thr Ala Cys  
 Cys Glu Trp Cys Phe Asn Pro Thr Cys Val Gly Cys  
 Cys Glu Trp Cys Phe Asn Pro Thr Cys Val Ala Cys  
 Cys Glu Trp Cys Phe Asn Pro Thr Cys Gly Gly Cys  
 Cys Glu Trp Cys Phe Asn Pro Thr Cys Gly Ala Cys  
 Cys Glu Trp Cys Phe Asn Gly Ala Cys Thr Gly Cys  
 Cys Glu Trp Cys Phe Asn Gly Ala Cys Thr Ala Cys  
 Cys Glu Trp Cys Phe Asn Gly Ala Cys Val Gly Cys  
 Cys Glu Trp Cys Phe Asn Gly Ala Cys Gly Gly Cys  
 Cys Glu Trp Cys Phe Asn Gly Ala Cys Gly Ala Cys  
 Cys Glu Trp Cys Phe Asn Gly Thr Cys Thr Gly Cys  
 Cys Glu Trp Cys Pro Asn Pro Ala Cys Thr Gly Cys  
 Cys Glu Trp Cys Pro Asn Pro Ala Cys Thr Ala Cys  
 Cys Glu Trp Cys Pro Asn Pro Ala Cys Val Gly Cys  
 Cys Glu Trp Cys Pro Asn Pro Ala Cys Val Ala Cys  
 Cys Glu Trp Cys Pro Asn Pro Ala Cys Gly Gly Cys  
 Cys Glu Trp Cys Pro Asn Pro Ala Cys Gly Ala Cys  
 Cys Glu Trp Cys Pro Asn Pro Thr Cys Thr Gly Cys  
 Cys Glu Trp Cys Pro Asn Pro Thr Cys Thr Ala Cys  
 Cys Glu Trp Cys Pro Asn Pro Thr Cys Val Gly Cys  
 Cys Glu Trp Cys Pro Asn Pro Thr Cys Val Ala Cys  
 Cys Glu Trp Cys Pro Asn Pro Thr Cys Gly Gly Cys  
 Cys Glu Trp Cys Pro Asn Pro Thr Cys Gly Ala Cys  
 Cys Glu Trp Cys Pro Asn Gly Ala Cys Thr Gly Cys  
 Cys Glu Trp Cys Pro Asn Gly Ala Cys Thr Ala Cys  
 Cys Glu Trp Cys Pro Asn Gly Ala Cys Val Gly Cys  
 Cys Glu Trp Cys Pro Asn Gly Ala Cys Val Ala Cys  
 Cys Glu Trp Cys Pro Asn Gly Ala Cys Gly Gly Cys  
 Cys Glu Trp Cys Pro Asn Gly Ala Cys Gly Ala Cys  
 Cys Glu Trp Cys Pro Asn Gly Thr Cys Thr Gly Cys  
 Cys Glu Trp Cys Pro Asn Gly Thr Cys Thr Ala Cys  
 Cys Glu Trp Cys Pro Asn Gly Thr Cys Val Gly Cys  
 Cys Glu Trp Cys Pro Asn Gly Thr Cys Val Ala Cys  
 Cys Glu Trp Cys Pro Asn Gly Thr Cys Gly Gly Cys  
 Cys Glu Trp Cys Pro Asn Gly Thr Cys Gly Ala Cys

FIGURE 3 (sheet 49 of 68)

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Cys Glu Trp Cys Ser Asn Pro Ala Cys Thr Gly Cys  
Cys Glu Trp Cys Ser Asn Pro Ala Cys Thr Ala Cys  
Cys Glu Trp Cys Ser Asn Pro Ala Cys Val Gly Cys  
Cys Glu Trp Cys Ser Asn Pro Ala Cys Val Ala Cys  
Cys Glu Trp Cys Ser Asn Pro Ala Cys Gly Gly Cys  
Cys Glu Trp Cys Ser Asn Pro Ala Cys Gly Ala Cys  
Cys Glu Trp Cys Ser Asn Pro Thr Cys Thr Gly Cys  
Cys Glu Trp Cys Ser Asn Pro Thr Cys Thr Ala Cys  
Cys Glu Trp Cys Ser Asn Pro Thr Cys Val Gly Cys  
Cys Glu Trp Cys Ser Asn Pro Thr Cys Val Ala Cys  
Cys Glu Trp Cys Ser Asn Pro Thr Cys Gly Gly Cys  
Cys Glu Trp Cys Ser Asn Pro Thr Cys Gly Ala Cys  
Cys Glu Trp Cys Ser Asn Gly Ala Cys Thr Gly Cys  
Cys Glu Trp Cys Ser Asn Gly Ala Cys Thr Ala Cys  
Cys Glu Trp Cys Ser Asn Gly Ala Cys Val Gly Cys  
Cys Glu Trp Cys Ser Asn Gly Ala Cys Val Ala Cys  
Cys Glu Trp Cys Ser Asn Gly Ala Cys Gly Gly Cys  
Cys Glu Trp Cys Ser Asn Gly Thr Cys Thr Gly Cys  
Cys Glu Trp Cys Ser Asn Gly Thr Cys Thr Ala Cys  
Cys Glu Trp Cys Ser Asn Gly Thr Cys Val Gly Cys  
Cys Glu Trp Cys Ser Asn Gly Thr Cys Val Ala Cys  
Cys Glu Trp Cys Ser Asn Gly Thr Cys Gly Gly Cys  
Cys Glu Trp Cys Ser Asn Gly Thr Cys Gly Ala Cys  
Cys Glu Trp Cys Thr Asn Pro Ala Cys Thr Gly Cys  
Cys Glu Trp Cys Thr Asn Pro Ala Cys Thr Ala Cys  
Cys Glu Trp Cys Thr Asn Pro Ala Cys Val Gly Cys  
Cys Glu Trp Cys Thr Asn Pro Ala Cys Val Ala Cys  
Cys Glu Trp Cys Thr Asn Pro Thr Cys Val Ala Cys  
Cys Glu Trp Cys Thr Asn Pro Thr Cys Gly Gly Cys  
Cys Glu Trp Cys Thr Asn Pro Thr Cys Gly Ala Cys  
Cys Glu Trp Cys Thr Asn Gly Ala Cys Thr Gly Cys  
Cys Glu Trp Cys Thr Asn Gly Ala Cys Val Gly Cys  
Cys Glu Trp Cys Thr Asn Gly Ala Cys Val Ala Cys  
Cys Glu Trp Cys Thr Asn Gly Ala Cys Gly Gly Cys  
Cys Glu Trp Cys Thr Asn Gly Ala Cys Gly Ala Cys  
Cys Glu Trp Cys Thr Asn Gly Thr Cys Thr Gly Cys  
Cys Glu Trp Cys Thr Asn Gly Thr Cys Thr Ala Cys  
Cys Glu Trp Cys Thr Asn Gly Thr Cys Val Gly Cys  
Cys Glu Trp Cys Thr Asn Gly Thr Cys Val Ala Cys  
Cys Glu Trp Cys Thr Asn Gly Thr Cys Gly Gly Cys  
Cys Glu Trp Cys Thr Asn Gly Thr Cys Gly Ala Cys  
Cys Glu Trp Cys Trp Asn Pro Ala Cys Thr Gly Cys  
Cys Glu Trp Cys Trp Asn Pro Ala Cys Thr Ala Cys  
Cys Glu Trp Cys Trp Asn Pro Ala Cys Val Gly Cys  
Cys Glu Trp Cys Trp Asn Pro Ala Cys Val Ala Cys  
Cys Glu Trp Cys Trp Asn Pro Ala Cys Gly Gly Cys  
Cys Glu Trp Cys Trp Asn Pro Ala Cys Gly Ala Cys  
Cys Glu Trp Cys Trp Asn Pro Thr Cys Thr Gly Cys  
Cys Glu Trp Cys Trp Asn Pro Thr Cys Thr Ala Cys  
Cys Glu Trp Cys Trp Asn Pro Thr Cys Val Gly Cys

FIGURE 3 (sheet 50 of 68)

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Cys Glu Trp Cys Trp Asn Pro Thr Cys Val Ala Cys  
Cys Glu Trp Cys Trp Asn Pro Thr Cys Gly Gly Cys  
Cys Glu Trp Cys Trp Asn Pro Thr Cys Gly Ala Cys  
Cys Glu Trp Cys Trp Asn Gly Ala Cys Thr Gly Cys  
Cys Glu Trp Cys Trp Asn Gly Ala Cys Thr Ala Cys  
Cys Glu Trp Cys Trp Asn Gly Ala Cys Val Gly Cys  
Cys Glu Trp Cys Trp Asn Gly Ala Cys Val Ala Cys  
Cys Glu Trp Cys Trp Asn Gly Ala Cys Gly Gly Cys  
Cys Glu Trp Cys Trp Asn Gly Ala Cys Gly Gly Cys  
Cys Glu Trp Cys Trp Asn Gly Thr Cys Thr Gly Cys  
Cys Glu Trp Cys Trp Asn Gly Thr Cys Thr Ala Cys  
Cys Glu Trp Cys Trp Asn Gly Thr Cys Val Gly Cys  
Cys Glu Trp Cys Tyr Asn Pro Ala Cys Thr Gly Cys  
Cys Glu Trp Cys Tyr Asn Pro Ala Cys Thr Ala Cys  
Cys Glu Trp Cys Tyr Asn Pro Ala Cys Val Gly Cys  
Cys Glu Trp Cys Tyr Asn Pro Ala Cys Val Ala Cys  
Cys Glu Trp Cys Tyr Asn Pro Ala Cys Gly Gly Cys  
Cys Glu Trp Cys Tyr Asn Pro Ala Cys Gly Ala Cys  
Cys Glu Trp Cys Tyr Asn Pro Thr Cys Thr Gly Cys  
Cys Glu Trp Cys Tyr Asn Pro Thr Cys Thr Ala Cys  
Cys Glu Trp Cys Tyr Asn Pro Thr Cys Val Gly Cys  
Cys Glu Trp Cys Tyr Asn Pro Thr Cys Gly Gly Cys  
Cys Glu Trp Cys Tyr Asn Gly Ala Cys Thr Gly Cys  
Cys Glu Trp Cys Tyr Asn Gly Ala Cys Thr Ala Cys  
Cys Glu Trp Cys Tyr Asn Gly Thr Cys Thr Ala Cys  
Cys Glu Trp Cys Tyr Asn Gly Thr Cys Val Gly Cys  
Cys Glu Trp Cys Tyr Asn Gly Thr Cys Val Ala Cys  
Cys Glu Trp Cys Tyr Asn Gly Thr Cys Gly Gly Cys  
Cys Glu Trp Cys Tyr Asn Gly Thr Cys Gly Ala Cys  
Cys Glu Trp Cys Val Asn Pro Ala Cys Thr Gly Cys  
Cys Glu Trp Cys Val Asn Pro Ala Cys Thr Ala Cys  
Cys Glu Trp Cys Val Asn Pro Ala Cys Val Gly Cys  
Cys Glu Trp Cys Val Asn Pro Ala Cys Val Ala Cys  
Cys Glu Trp Cys Val Asn Pro Ala Cys Gly Gly Cys  
Cys Glu Trp Cys Val Asn Pro Ala Cys Gly Ala Cys  
Cys Glu Trp Cys Val Asn Pro Thr Cys Thr Gly Cys  
Cys Glu Trp Cys Val Asn Pro Thr Cys Thr Ala Cys  
Cys Glu Trp Cys Val Asn Pro Thr Cys Val Gly Cys  
Cys Glu Trp Cys Val Asn Pro Thr Cys Val Ala Cys  
Cys Glu Trp Cys Val Asn Pro Thr Cys Gly Gly Cys  
Cys Glu Trp Cys Val Asn Pro Thr Cys Gly Ala Cys  
Cys Glu Trp Cys Val Asn Gly Ala Cys Thr Gly Cys  
Cys Glu Trp Cys Val Asn Gly Ala Cys Thr Ala Cys  
Cys Glu Trp Cys Val Asn Gly Ala Cys Val Gly Cys  
Cys Glu Trp Cys Val Asn Gly Ala Cys Val Ala Cys  
Cys Glu Trp Cys Val Asn Gly Ala Cys Gly Gly Cys  
Cys Glu Trp Cys Val Asn Gly Ala Cys Gly Ala Cys

FIGURE 3 (sheet 51 of 68)

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Cys Glu Trp Cys Val Asn Gly Thr Cys Thr Gly Cys  
 Cys Glu Trp Cys Val Asn Gly Thr Cys Thr Ala Cys  
 Cys Glu Trp Cys Val Asn Gly Thr Cys Val Gly Cys  
 Cys Glu Trp Cys Val Asn Gly Thr Cys Val Ala Cys  
 Cys Glu Trp Cys Val Asn Gly Thr Cys Gly Gly Cys  
 Cys Glu Trp Cys Val Asn Gly Thr Cys Gly Ala Cys  
 Cys Glu Trp Cys --- Asn Pro Ala Cys Thr Gly Cys  
 Cys Glu Trp Cys --- Asn Pro Ala Cys Thr Ala Cys  
 Cys Glu Trp Cys --- Asn Pro Ala Cys Val Gly Cys  
 Cys Glu Trp Cys --- Asn Pro Ala Cys Val Ala Cys  
 Cys Glu Trp Cys --- Asn Pro Ala Cys Gly Gly Cys  
 Cys Glu Trp Cys --- Asn Pro Ala Cys Gly Ala Cys  
 Cys Glu Trp Cys --- Asn Pro Thr Cys Thr Gly Cys  
 Cys Glu Trp Cys --- Asn Pro Thr Cys Thr Ala Cys  
 Cys Glu Trp Cys --- Asn Pro Thr Cys Val Gly Cys  
 Cys Glu Trp Cys --- Asn Pro Thr Cys Val Ala Cys  
 Cys Glu Trp Cys --- Asn Pro Thr Cys Gly Gly Cys  
 Cys Glu Trp Cys --- Asn Pro Thr Cys Gly Ala Cys  
 Cys Glu Trp Cys --- Asn Gly Ala Cys Thr Gly Cys  
 Cys Glu Trp Cys --- Asn Gly Ala Cys Thr Ala Cys  
 Cys Glu Trp Cys --- Asn Gly Ala Cys Val Gly Cys  
 Cys Glu Trp Cys --- Asn Gly Ala Cys Val Ala Cys  
 Cys Glu Trp Cys --- Asn Gly Ala Cys Gly Gly Cys  
 Cys Glu Trp Cys --- Asn Gly Ala Cys Gly Ala Cys  
 Cys Glu Trp Cys --- Asn Gly Thr Cys Thr Gly Cys  
 Cys Glu Trp Cys --- Asn Gly Thr Cys Thr Ala Cys  
 Cys Glu Trp Cys --- Asn Gly Thr Cys Val Gly Cys  
 Cys Glu Trp Cys --- Asn Gly Thr Cys Val Ala Cys  
 Cys Glu Trp Cys --- Asn Gly Thr Cys Gly Gly Cys  
 Cys Glu Trp Cys --- Asn Gly Thr Cys Gly Ala Cys  
 Cys Glu Phe Cys Ala Asn Pro Ala Cys Thr Gly Cys  
 Cys Glu Phe Cys Ala Asn Pro Ala Cys Thr Ala Cys  
 Cys Glu Phe Cys Ala Asn Pro Ala Cys Val Gly Cys  
 Cys Glu Phe Cys Ala Asn Pro Ala Cys Val Ala Cys  
 Cys Glu Phe Cys Ala Asn Pro Ala Cys Gly Gly Cys  
 Cys Glu Phe Cys Ala Asn Pro Ala Cys Gly Ala Cys  
 Cys Glu Phe Cys Ala Asn Pro Thr Cys Thr Gly Cys  
 Cys Glu Phe Cys Ala Asn Pro Thr Cys Thr Ala Cys  
 Cys Glu Phe Cys Ala Asn Pro Thr Cys Val Gly Cys  
 Cys Glu Phe Cys Ala Asn Pro Thr Cys Val Ala Cys  
 Cys Glu Phe Cys Ala Asn Pro Thr Cys Gly Gly Cys  
 Cys Glu Phe Cys Ala Asn Pro Thr Cys Gly Ala Cys  
 Cys Glu Phe Cys Ala Asn Gly Ala Cys Thr Gly Cys  
 Cys Glu Phe Cys Ala Asn Gly Ala Cys Thr Ala Cys  
 Cys Glu Phe Cys Ala Asn Gly Ala Cys Val Gly Cys  
 Cys Glu Phe Cys Ala Asn Gly Ala Cys Val Ala Cys  
 Cys Glu Phe Cys Ala Asn Gly Ala Cys Gly Gly Cys  
 Cys Glu Phe Cys Ala Asn Gly Ala Cys Gly Ala Cys  
 Cys Glu Phe Cys Ala Asn Gly Thr Cys Thr Gly Cys  
 Cys Glu Phe Cys Ala Asn Gly Thr Cys Thr Ala Cys  
 Cys Glu Phe Cys Ala Asn Gly Thr Cys Val Gly Cys  
 Cys Glu Phe Cys Ala Asn Gly Thr Cys Val Ala Cys  
 Cys Glu Phe Cys Ala Asn Gly Thr Cys Gly Gly Cys  
 Cys Glu Phe Cys Ala Asn Gly Thr Cys Gly Ala Cys  
 Cys Glu Phe Cys Arg Asn Pro Ala Cys Thr Gly Cys  
 Cys Glu Phe Cys Arg Asn Pro Ala Cys Thr Ala Cys  
 Cys Glu Phe Cys Arg Asn Pro Ala Cys Val Gly Cys

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Cys Glu Phe Cys Arg Asn Pro Ala Cys Val Ala Cys  
 Cys Glu Phe Cys Arg Asn Pro Ala Cys Gly Gly Cys  
 Cys Glu Phe Cys Arg Asn Pro Ala Cys Gly Ala Cys  
 Cys Glu Phe Cys Arg Asn Pro Thr Cys Thr Gly Cys  
 Cys Glu Phe Cys Arg Asn Pro Thr Cys Thr Ala Cys  
 Cys Glu Phe Cys Arg Asn Pro Thr Cys Val Gly Cys  
 Cys Glu Phe Cys Arg Asn Pro Thr Cys Val Ala Cys  
 Cys Glu Phe Cys Arg Asn Pro Thr Cys Gly Gly Cys  
 Cys Glu Phe Cys Arg Asn Pro Thr Cys Gly Ala Cys  
 Cys Glu Phe Cys Arg Asn Gly Ala Cys Thr Gly Cys  
 Cys Glu Phe Cys Arg Asn Gly Ala Cys Thr Ala Cys  
 Cys Glu Phe Cys Arg Asn Gly Ala Cys Val Gly Cys  
 Cys Glu Phe Cys Arg Asn Gly Ala Cys Val Ala Cys  
 Cys Glu Phe Cys Arg Asn Gly Ala Cys Gly Gly Cys  
 Cys Glu Phe Cys Arg Asn Gly Ala Cys Gly Ala Cys  
 Cys Glu Phe Cys Arg Asn Gly Thr Cys Thr Gly Cys  
 Cys Glu Phe Cys Arg Asn Gly Thr Cys Thr Ala Cys  
 Cys Glu Phe Cys Arg Asn Gly Thr Cys Val Gly Cys  
 Cys Glu Phe Cys Arg Asn Gly Thr Cys Val Ala Cys  
 Cys Glu Phe Cys Arg Asn Gly Thr Cys Gly Gly Cys  
 Cys Glu Phe Cys Arg Asn Gly Thr Cys Gly Ala Cys  
 Cys Glu Phe Cys Arg Asn Gly Thr Cys Thr Gly Cys  
 Cys Glu Phe Cys Asn Asn Pro Ala Cys Thr Gly Cys  
 Cys Glu Phe Cys Asn Asn Pro Ala Cys Val Gly Cys  
 Cys Glu Phe Cys Asn Asn Pro Ala Cys Val Ala Cys  
 Cys Glu Phe Cys Asn Asn Pro Ala Cys Gly Gly Cys  
 Cys Glu Phe Cys Asn Asn Pro Ala Cys Gly Ala Cys  
 Cys Glu Phe Cys Asn Asn Pro Thr Cys Thr Gly Cys  
 Cys Glu Phe Cys Asn Asn Pro Thr Cys Thr Ala Cys  
 Cys Glu Phe Cys Asn Asn Pro Thr Cys Val Gly Cys  
 Cys Glu Phe Cys Asn Asn Pro Thr Cys Val Ala Cys  
 Cys Glu Phe Cys Asn Asn Gly Ala Cys Gly Gly Cys  
 Cys Glu Phe Cys Asn Asn Gly Ala Cys Val Ala Cys  
 Cys Glu Phe Cys Asn Asn Gly Ala Cys Gly Gly Cys  
 Cys Glu Phe Cys Asn Asn Gly Ala Cys Val Ala Cys  
 Cys Glu Phe Cys Asn Asn Gly Ala Cys Gly Gly Cys  
 Cys Glu Phe Cys Asn Asn Gly Ala Cys Val Ala Cys  
 Cys Glu Phe Cys Asp Asn Pro Ala Cys Thr Gly Cys  
 Cys Glu Phe Cys Asp Asn Pro Ala Cys Thr Ala Cys  
 Cys Glu Phe Cys Asp Asn Pro Ala Cys Val Gly Cys  
 Cys Glu Phe Cys Asp Asn Pro Ala Cys Val Ala Cys  
 Cys Glu Phe Cys Asp Asn Pro Ala Cys Gly Gly Cys  
 Cys Glu Phe Cys Asp Asn Pro Ala Cys Gly Ala Cys  
 Cys Glu Phe Cys Asp Asn Pro Thr Cys Thr Gly Cys  
 Cys Glu Phe Cys Asp Asn Pro Thr Cys Thr Ala Cys  
 Cys Glu Phe Cys Asp Asn Pro Thr Cys Val Gly Cys  
 Cys Glu Phe Cys Asp Asn Pro Thr Cys Val Ala Cys  
 Cys Glu Phe Cys Asp Asn Pro Thr Cys Gly Gly Cys  
 Cys Glu Phe Cys Asp Asn Pro Thr Cys Gly Ala Cys

FIGURE 3 (sheet 53 of 68)

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Cys Glu Phe Cys Asp Asn Gly Ala Cys Thr Gly Cys  
 Cys Glu Phe Cys Asp Asn Gly Ala Cys Thr Ala Cys  
 Cys Glu Phe Cys Asp Asn Gly Ala Cys Val Gly Cys  
 Cys Glu Phe Cys Asp Asn Gly Ala Cys Val Ala Cys  
 Cys Glu Phe Cys Asp Asn Gly Ala Cys Gly Gly Cys  
 Cys Glu Phe Cys Asp Asn Gly Ala Cys Gly Ala Cys  
 Cys Glu Phe Cys Asp Asn Gly Thr Cys Thr Gly Cys  
 Cys Glu Phe Cys Asp Asn Gly Thr Cys Thr Ala Cys  
 Cys Glu Phe Cys Asp Asn Gly Thr Cys Val Gly Cys  
 Cys Glu Phe Cys Asp Asn Gly Thr Cys Val Ala Cys  
 Cys Glu Phe Cys Asp Asn Gly Thr Cys Gly Gly Cys  
 Cys Glu Phe Cys Asp Asn Gly Thr Cys Gly Ala Cys  
 Cys Glu Phe Cys Gln Asn Pro Ala Cys Thr Gly Cys  
 Cys Glu Phe Cys Gln Asn Pro Ala Cys Thr Ala Cys  
 Cys Glu Phe Cys Gln Asn Pro Ala Cys Val Gly Cys  
 Cys Glu Phe Cys Gln Asn Pro Ala Cys Val Ala Cys  
 Cys Glu Phe Cys Gln Asn Pro Ala Cys Gly Gly Cys  
 Cys Glu Phe Cys Gln Asn Pro Ala Cys Gly Ala Cys  
 Cys Glu Phe Cys Gln Asn Pro Thr Cys Thr Gly Cys  
 Cys Glu Phe Cys Gln Asn Pro Thr Cys Thr Ala Cys  
 Cys Glu Phe Cys Gln Asn Pro Thr Cys Val Gly Cys  
 Cys Glu Phe Cys Gln Asn Pro Thr Cys Val Ala Cys  
 Cys Glu Phe Cys Gln Asn Pro Thr Cys Gly Gly Cys  
 Cys Glu Phe Cys Gln Asn Pro Thr Cys Gly Ala Cys  
 Cys Glu Phe Cys Gln Asn Gly Ala Cys Thr Gly Cys  
 Cys Glu Phe Cys Gln Asn Gly Ala Cys Thr Ala Cys  
 Cys Glu Phe Cys Gln Asn Gly Ala Cys Val Gly Cys  
 Cys Glu Phe Cys Gln Asn Gly Ala Cys Val Ala Cys  
 Cys Glu Phe Cys Gln Asn Gly Ala Cys Gly Gly Cys  
 Cys Glu Phe Cys Gln Asn Gly Ala Cys Gly Ala Cys  
 Cys Glu Phe Cys Gln Asn Gly Thr Cys Thr Gly Cys  
 Cys Glu Phe Cys Gln Asn Gly Thr Cys Thr Ala Cys  
 Cys Glu Phe Cys Gln Asn Gly Thr Cys Thr Ala Cys  
 Cys Glu Phe Cys Gln Asn Gly Thr Cys Val Gly Cys

FIGURE 3 (sheet 54 of 68)

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Cys Glu Phe Cys Glu Asn Gly Thr Cys Val Ala Cys  
 Cys Glu Phe Cys Glu Asn Gly Thr Cys Gly Gly Cys  
 Cys Glu Phe Cys Glu Asn Gly Thr Cys Gly Ala Cys  
 Cys Glu Phe Cys Gly Asn Pro Ala Cys Thr Gly Cys  
 Cys Glu Phe Cys Gly Asn Pro Ala Cys Thr Ala Cys  
 Cys Glu Phe Cys Gly Asn Pro Ala Cys Val Gly Cys  
 Cys Glu Phe Cys Gly Asn Pro Ala Cys Val Ala Cys  
 Cys Glu Phe Cys Gly Asn Pro Ala Cys Gly Gly Cys  
 Cys Glu Phe Cys Gly Asn Pro Ala Cys Gly Ala Cys  
 Cys Glu Phe Cys Gly Asn Pro Thr Cys Thr Gly Cys  
 Cys Glu Phe Cys Gly Asn Pro Thr Cys Thr Ala Cys  
 Cys Glu Phe Cys Gly Asn Pro Thr Cys Val Gly Cys  
 Cys Glu Phe Cys Gly Asn Pro Thr Cys Val Ala Cys  
 Cys Glu Phe Cys Gly Asn Pro Thr Cys Gly Gly Cys  
 Cys Glu Phe Cys Gly Asn Pro Thr Cys Gly Ala Cys  
 Cys Glu Phe Cys Gly Asn Gly Ala Cys Thr Gly Cys  
 Cys Glu Phe Cys Gly Asn Gly Ala Cys Thr Ala Cys  
 Cys Glu Phe Cys Gly Asn Gly Thr Cys Val Gly Cys  
 Cys Glu Phe Cys Gly Asn Gly Thr Cys Val Ala Cys  
 Cys Glu Phe Cys Gly Asn Gly Thr Cys Gly Gly Cys  
 Cys Glu Phe Cys Gly Asn Gly Thr Cys Gly Ala Cys  
 Cys Glu Phe Cys His Asn Pro Ala Cys Thr Gly Cys  
 Cys Glu Phe Cys His Asn Pro Ala Cys Thr Ala Cys  
 Cys Glu Phe Cys His Asn Pro Ala Cys Val Gly Cys  
 Cys Glu Phe Cys His Asn Pro Ala Cys Val Ala Cys  
 Cys Glu Phe Cys His Asn Pro Ala Cys Gly Gly Cys  
 Cys Glu Phe Cys His Asn Pro Ala Cys Gly Ala Cys  
 Cys Glu Phe Cys His Asn Pro Thr Cys Thr Gly Cys  
 Cys Glu Phe Cys His Asn Pro Thr Cys Thr Ala Cys  
 Cys Glu Phe Cys His Asn Pro Thr Cys Val Gly Cys  
 Cys Glu Phe Cys His Asn Pro Thr Cys Val Ala Cys  
 Cys Glu Phe Cys His Asn Pro Thr Cys Gly Gly Cys  
 Cys Glu Phe Cys His Asn Pro Thr Cys Gly Ala Cys  
 Cys Glu Phe Cys His Asn Gly Ala Cys Thr Gly Cys  
 Cys Glu Phe Cys His Asn Gly Ala Cys Thr Ala Cys  
 Cys Glu Phe Cys His Asn Gly Ala Cys Val Gly Cys  
 Cys Glu Phe Cys His Asn Gly Ala Cys Val Ala Cys  
 Cys Glu Phe Cys His Asn Gly Ala Cys Gly Gly Cys  
 Cys Glu Phe Cys His Asn Gly Thr Cys Thr Gly Cys  
 Cys Glu Phe Cys His Asn Gly Thr Cys Thr Ala Cys  
 Cys Glu Phe Cys His Asn Gly Thr Cys Val Gly Cys  
 Cys Glu Phe Cys His Asn Gly Thr Cys Val Ala Cys  
 Cys Glu Phe Cys His Asn Gly Thr Cys Gly Gly Cys  
 Cys Glu Phe Cys His Asn Gly Thr Cys Gly Ala Cys  
 Cys Glu Phe Cys Ile Asn Pro Ala Cys Thr Gly Cys  
 Cys Glu Phe Cys Ile Asn Pro Ala Cys Thr Ala Cys  
 Cys Glu Phe Cys Ile Asn Pro Ala Cys Val Gly Cys  
 Cys Glu Phe Cys Ile Asn Pro Ala Cys Val Ala Cys  
 Cys Glu Phe Cys Ile Asn Pro Ala Cys Gly Gly Cys  
 Cys Glu Phe Cys Ile Asn Pro Ala Cys Gly Ala Cys



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Cys Glu Phe Cys Ile Asn Pro Thr Cys Thr Gly Cys  
Cys Glu Phe Cys Ile Asn Pro Thr Cys Thr Ala Cys  
Cys Glu Phe Cys Ile Asn Pro Thr Cys Val Gly Cys  
Cys Glu Phe Cys Ile Asn Pro Thr Cys Val Ala Cys  
Cys Glu Phe Cys Ile Asn Pro Thr Cys Gly Gly Cys  
Cys Glu Phe Cys Ile Asn Pro Thr Cys Gly Ala Cys  
Cys Glu Phe Cys Ile Asn Gly Ala Cys Thr Gly Cys  
Cys Glu Phe Cys Ile Asn Gly Ala Cys Thr Ala Cys  
Cys Glu Phe Cys Ile Asn Gly Ala Cys Val Gly Cys  
Cys Glu Phe Cys Ile Asn Gly Ala Cys Val Ala Cys  
Cys Glu Phe Cys Ile Asn Gly Ala Cys Gly Gly Cys  
Cys Glu Phe Cys Ile Asn Gly Ala Cys Gly Ala Cys  
Cys Glu Phe Cys Ile Asn Gly Thr Cys Thr Gly Cys  
Cys Glu Phe Cys Ile Asn Gly Thr Cys Thr Ala Cys  
Cys Glu Phe Cys Ile Asn Gly Thr Cys Val Gly Cys  
Cys Glu Phe Cys Ile Asn Gly Thr Cys Val Ala Cys  
Cys Glu Phe Cys Ile Asn Gly Thr Cys Gly Gly Cys  
Cys Glu Phe Cys Ile Asn Gly Thr Cys Gly Ala Cys  
Cys Glu Phe Cys Leu Asn Pro Ala Cys Thr Gly Cys  
Cys Glu Phe Cys Leu Asn Pro Ala Cys Thr Ala Cys  
Cys Glu Phe Cys Leu Asn Pro Ala Cys Val Gly Cys  
Cys Glu Phe Cys Leu Asn Pro Ala Cys Val Ala Cys  
Cys Glu Phe Cys Leu Asn Pro Ala Cys Gly Gly Cys  
Cys Glu Phe Cys Leu Asn Pro Ala Cys Gly Ala Cys  
Cys Glu Phe Cys Leu Asn Pro Ala Cys Gly Ala Cys  
Cys Glu Phe Cys Leu Asn Pro Thr Cys Thr Gly Cys  
Cys Glu Phe Cys Leu Asn Pro Thr Cys Thr Ala Cys  
Cys Glu Phe Cys Leu Asn Pro Thr Cys Thr Ala Cys  
Cys Glu Phe Cys Leu Asn Pro Thr Cys Val Gly Cys  
Cys Glu Phe Cys Leu Asn Gly Thr Cys Val Ala Cys  
Cys Glu Phe Cys Leu Asn Gly Thr Cys Gly Gly Cys  
Cys Glu Phe Cys Leu Asn Gly Thr Cys Gly Ala Cys  
Cys Glu Phe Cys Lys Asn Pro Ala Cys Thr Gly Cys  
Cys Glu Phe Cys Lys Asn Pro Ala Cys Thr Ala Cys  
Cys Glu Phe Cys Lys Asn Pro Ala Cys Val Gly Cys  
Cys Glu Phe Cys Lys Asn Pro Ala Cys Val Ala Cys  
Cys Glu Phe Cys Lys Asn Pro Ala Cys Gly Gly Cys  
Cys Glu Phe Cys Lys Asn Pro Ala Cys Gly Ala Cys  
Cys Glu Phe Cys Lys Asn Pro Thr Cys Thr Gly Cys  
Cys Glu Phe Cys Lys Asn Pro Thr Cys Thr Ala Cys  
Cys Glu Phe Cys Lys Asn Pro Thr Cys Val Gly Cys  
Cys Glu Phe Cys Lys Asn Pro Thr Cys Val Ala Cys  
Cys Glu Phe Cys Lys Asn Pro Thr Cys Gly Gly Cys  
Cys Glu Phe Cys Lys Asn Pro Thr Cys Gly Ala Cys  
Cys Glu Phe Cys Lys Asn Gly Ala Cys Thr Gly Cys  
Cys Glu Phe Cys Lys Asn Gly Ala Cys Thr Ala Cys  
Cys Glu Phe Cys Lys Asn Gly Ala Cys Val Gly Cys

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Cys Glu Phe Cys Lys Asn Gly Ala Cys Val Ala Cys  
 Cys Glu Phe Cys Lys Asn Gly Ala Cys Gly Gly Cys  
 Cys Glu Phe Cys Lys Asn Gly Ala Cys Gly Ala Cys  
 Cys Glu Phe Cys Lys Asn Gly Thr Cys Thr Gly Cys  
 Cys Glu Phe Cys Lys Asn Gly Thr Cys Thr Ala Cys  
 Cys Glu Phe Cys Lys Asn Gly Thr Cys Val Gly Cys  
 Cys Glu Phe Cys Lys Asn Gly Thr Cys Val Ala Cys  
 Cys Glu Phe Cys Lys Asn Gly Thr Cys Gly Gly Cys  
 Cys Glu Phe Cys Lys Asn Gly Thr Cys Gly Ala Cys  
 Cys Glu Phe Cys Met Asn Pro Ala Cys Thr Gly Cys  
 Cys Glu Phe Cys Met Asn Pro Ala Cys Thr Ala Cys  
 Cys Glu Phe Cys Met Asn Pro Ala Cys Val Gly Cys  
 Cys Glu Phe Cys Met Asn Pro Ala Cys Val Ala Cys  
 Cys Glu Phe Cys Met Asn Pro Ala Cys Gly Gly Cys  
 Cys Glu Phe Cys Met Asn Pro Ala Cys Gly Gly Cys  
 Cys Glu Phe Cys Met Asn Pro Ala Cys Gly Ala Cys  
 Cys Glu Phe Cys Met Asn Pro Thr Cys Thr Gly Cys  
 Cys Glu Phe Cys Met Asn Pro Thr Cys Thr Ala Cys  
 Cys Glu Phe Cys Met Asn Pro Thr Cys Val Gly Cys  
 Cys Glu Phe Cys Met Asn Pro Thr Cys Val Ala Cys  
 Cys Glu Phe Cys Met Asn Gly Thr Cys Gly Gly Cys  
 Cys Glu Phe Cys Met Asn Gly Thr Cys Gly Ala Cys  
 Cys Glu Phe Cys Met Asn Gly Thr Cys Thr Gly Cys  
 Cys Glu Phe Cys Met Asn Gly Thr Cys Thr Ala Cys  
 Cys Glu Phe Cys Met Asn Gly Thr Cys Val Gly Cys  
 Cys Glu Phe Cys Met Asn Gly Thr Cys Val Ala Cys  
 Cys Glu Phe Cys Met Asn Gly Thr Cys Gly Gly Cys  
 Cys Glu Phe Cys Met Asn Gly Thr Cys Gly Ala Cys  
 Cys Glu Phe Cys Phe Asn Pro Ala Cys Thr Gly Cys  
 Cys Glu Phe Cys Phe Asn Pro Ala Cys Thr Ala Cys  
 Cys Glu Phe Cys Phe Asn Pro Ala Cys Val Gly Cys  
 Cys Glu Phe Cys Phe Asn Pro Ala Cys Val Ala Cys  
 Cys Glu Phe Cys Phe Asn Pro Ala Cys Gly Gly Cys  
 Cys Glu Phe Cys Phe Asn Pro Ala Cys Gly Ala Cys  
 Cys Glu Phe Cys Phe Asn Pro Thr Cys Thr Gly Cys  
 Cys Glu Phe Cys Phe Asn Pro Thr Cys Thr Ala Cys  
 Cys Glu Phe Cys Phe Asn Pro Thr Cys Val Gly Cys  
 Cys Glu Phe Cys Phe Asn Pro Thr Cys Val Ala Cys  
 Cys Glu Phe Cys Phe Asn Pro Thr Cys Gly Gly Cys  
 Cys Glu Phe Cys Phe Asn Pro Thr Cys Gly Ala Cys  
 Cys Glu Phe Cys Phe Asn Gly Ala Cys Thr Gly Cys  
 Cys Glu Phe Cys Phe Asn Gly Ala Cys Thr Ala Cys  
 Cys Glu Phe Cys Phe Asn Gly Ala Cys Val Gly Cys  
 Cys Glu Phe Cys Phe Asn Gly Ala Cys Val Ala Cys  
 Cys Glu Phe Cys Phe Asn Gly Ala Cys Gly Gly Cys  
 Cys Glu Phe Cys Phe Asn Gly Ala Cys Gly Ala Cys  
 Cys Glu Phe Cys Phe Asn Gly Thr Cys Thr Gly Cys  
 Cys Glu Phe Cys Phe Asn Gly Thr Cys Thr Ala Cys  
 Cys Glu Phe Cys Phe Asn Gly Thr Cys Val Gly Cys  
 Cys Glu Phe Cys Phe Asn Gly Thr Cys Val Ala Cys  
 Cys Glu Phe Cys Phe Asn Gly Thr Cys Gly Gly Cys  
 Cys Glu Phe Cys Phe Asn Gly Thr Cys Gly Ala Cys

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Cys Glu Phe Cys Pro Asn Pro Ala Cys Thr Gly Cys  
 Cys Glu Phe Cys Pro Asn Pro Ala Cys Thr Ala Cys  
 Cys Glu Phe Cys Pro Asn Pro Ala Cys Val Gly Cys  
 Cys Glu Phe Cys Pro Asn Pro Ala Cys Val Ala Cys  
 Cys Glu Phe Cys Pro Asn Pro Ala Cys Gly Gly Cys  
 Cys Glu Phe Cys Pro Asn Pro Ala Cys Gly Ala Cys  
 Cys Glu Phe Cys Pro Asn Pro Thr Cys Thr Gly Cys  
 Cys Glu Phe Cys Pro Asn Pro Thr Cys Thr Ala Cys  
 Cys Glu Phe Cys Pro Asn Pro Thr Cys Val Gly Cys  
 Cys Glu Phe Cys Pro Asn Pro Thr Cys Val Ala Cys  
 Cys Glu Phe Cys Pro Asn Pro Thr Cys Gly Gly Cys  
 Cys Glu Phe Cys Pro Asn Pro Thr Cys Gly Ala Cys  
 Cys Glu Phe Cys Pro Asn Gly Ala Cys Thr Ala Cys  
 Cys Glu Phe Cys Pro Asn Gly Ala Cys Val Gly Cys  
 Cys Glu Phe Cys Pro Asn Gly Ala Cys Val Ala Cys  
 Cys Glu Phe Cys Pro Asn Gly Ala Cys Gly Gly Cys  
 Cys Glu Phe Cys Pro Asn Gly Ala Cys Gly Ala Cys  
 Cys Glu Phe Cys Pro Asn Gly Thr Cys Thr Gly Cys  
 Cys Glu Phe Cys Pro Asn Gly Thr Cys Thr Ala Cys  
 Cys Glu Phe Cys Pro Asn Gly Thr Cys Val Gly Cys  
 Cys Glu Phe Cys Pro Asn Gly Thr Cys Val Ala Cys  
 Cys Glu Phe Cys Pro Asn Gly Thr Cys Val Ala Cys  
 Cys Glu Phe Cys Pro Asn Gly Thr Cys Gly Gly Cys  
 Cys Glu Phe Cys Pro Asn Gly Thr Cys Gly Ala Cys  
 Cys Glu Phe Cys Pro Asn Gly Thr Cys Gly Ala Cys  
 Cys Glu Phe Cys Pro Asn Gly Thr Cys Thr Gly Cys  
 Cys Glu Phe Cys Pro Asn Gly Thr Cys Thr Ala Cys  
 Cys Glu Phe Cys Pro Asn Gly Thr Cys Val Gly Cys  
 Cys Glu Phe Cys Pro Asn Gly Thr Cys Val Ala Cys  
 Cys Glu Phe Cys Pro Asn Gly Thr Cys Gly Gly Cys  
 Cys Glu Phe Cys Pro Asn Gly Thr Cys Gly Ala Cys  
 Cys Glu Phe Cys Pro Asn Gly Thr Cys Gly Ala Cys  
 Cys Glu Phe Cys Pro Asn Gly Thr Cys Thr Gly Cys  
 Cys Glu Phe Cys Pro Asn Gly Thr Cys Thr Ala Cys  
 Cys Glu Phe Cys Pro Asn Gly Thr Cys Val Gly Cys  
 Cys Glu Phe Cys Thr Asn Pro Ala Cys Thr Gly Cys  
 Cys Glu Phe Cys Thr Asn Pro Ala Cys Thr Ala Cys  
 Cys Glu Phe Cys Thr Asn Pro Ala Cys Val Gly Cys  
 Cys Glu Phe Cys Thr Asn Pro Ala Cys Val Ala Cys  
 Cys Glu Phe Cys Thr Asn Pro Ala Cys Gly Gly Cys  
 Cys Glu Phe Cys Thr Asn Pro Ala Cys Gly Ala Cys  
 Cys Glu Phe Cys Thr Asn Pro Thr Cys Thr Gly Cys  
 Cys Glu Phe Cys Thr Asn Pro Thr Cys Thr Ala Cys  
 Cys Glu Phe Cys Thr Asn Pro Thr Cys Val Gly Cys

FIGURE 3 (sheet 58 of 68)

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Cys Glu Phe Cys Thr Asn Pro Thr Cys Val Ala Cys  
Cys Glu Phe Cys Thr Asn Pro Thr Cys Gly Gly Cys  
Cys Glu Phe Cys Thr Asn Pro Thr Cys Gly Ala Cys  
Cys Glu Phe Cys Thr Asn Gly Ala Cys Thr Gly Cys  
Cys Glu Phe Cys Thr Asn Gly Ala Cys Thr Ala Cys  
Cys Glu Phe Cys Thr Asn Gly Ala Cys Val Gly Cys  
Cys Glu Phe Cys Thr Asn Gly Ala Cys Val Ala Cys  
Cys Glu Phe Cys Thr Asn Gly Ala Cys Gly Gly Cys  
Cys Glu Phe Cys Thr Asn Gly Ala Cys Gly Ala Cys  
Cys Glu Phe Cys Thr Asn Gly Thr Cys Thr Gly Cys  
Cys Glu Phe Cys Thr Asn Gly Thr Cys Thr Ala Cys  
Cys Glu Phe Cys Thr Asn Gly Thr Cys Val Gly Cys  
Cys Glu Phe Cys Thr Asn Gly Thr Cys Val Ala Cys  
Cys Glu Phe Cys Thr Asn Gly Thr Cys Gly Gly Cys  
Cys Glu Phe Cys Thr Asn Gly Thr Cys Gly Ala Cys  
Cys Glu Phe Cys Trp Asn Pro Ala Cys Thr Gly Cys  
Cys Glu Phe Cys Trp Asn Pro Ala Cys Thr Ala Cys  
Cys Glu Phe Cys Trp Asn Pro Ala Cys Val Gly Cys  
Cys Glu Phe Cys Trp Asn Pro Ala Cys Val Ala Cys  
Cys Glu Phe Cys Trp Asn Pro Ala Cys Gly Gly Cys  
Cys Glu Phe Cys Trp Asn Pro Ala Cys Gly Ala Cys  
Cys Glu Phe Cys Trp Asn Pro Thr Cys Thr Gly Cys  
Cys Glu Phe Cys Trp Asn Gly Thr Cys Thr Ala Cys  
Cys Glu Phe Cys Trp Asn Gly Thr Cys Val Gly Cys  
Cys Glu Phe Cys Trp Asn Gly Thr Cys Val Ala Cys  
Cys Glu Phe Cys Trp Asn Gly Thr Cys Gly Gly Cys  
Cys Glu Phe Cys Trp Asn Gly Thr Cys Gly Ala Cys  
Cys Glu Phe Cys Tyr Asn Pro Ala Cys Thr Gly Cys  
Cys Glu Phe Cys Tyr Asn Pro Ala Cys Thr Ala Cys  
Cys Glu Phe Cys Tyr Asn Pro Ala Cys Val Gly Cys  
Cys Glu Phe Cys Tyr Asn Pro Ala Cys Val Ala Cys  
Cys Glu Phe Cys Tyr Asn Pro Ala Cys Gly Gly Cys  
Cys Glu Phe Cys Tyr Asn Pro Ala Cys Gly Ala Cys  
Cys Glu Phe Cys Tyr Asn Pro Thr Cys Thr Gly Cys  
Cys Glu Phe Cys Tyr Asn Pro Thr Cys Thr Ala Cys  
Cys Glu Phe Cys Tyr Asn Pro Thr Cys Val Gly Cys  
Cys Glu Phe Cys Tyr Asn Pro Thr Cys Val Ala Cys  
Cys Glu Phe Cys Tyr Asn Pro Thr Cys Gly Gly Cys  
Cys Glu Phe Cys Tyr Asn Pro Thr Cys Gly Ala Cys  
Cys Glu Phe Cys Tyr Asn Gly Ala Cys Thr Ala Cys  
Cys Glu Phe Cys Tyr Asn Gly Ala Cys Val Gly Cys  
Cys Glu Phe Cys Tyr Asn Gly Ala Cys Val Ala Cys  
Cys Glu Phe Cys Tyr Asn Gly Ala Cys Gly Gly Cys  
Cys Glu Phe Cys Tyr Asn Gly Ala Cys Gly Ala Cys

FIGURE 3 (sheet 59 of 68)

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Cys Glu Phe Cys Tyr Asn Gly Thr Cys Thr Gly Cys  
 Cys Glu Phe Cys Tyr Asn Gly Thr Cys Thr Ala Cys  
 Cys Glu Phe Cys Tyr Asn Gly Thr Cys Val Gly Cys  
 Cys Glu Phe Cys Tyr Asn Gly Thr Cys Val Ala Cys  
 Cys Glu Phe Cys Tyr Asn Gly Thr Cys Gly Gly Cys  
 Cys Glu Phe Cys Tyr Asn Gly Thr Cys Gly Ala Cys  
 Cys Glu Phe Cys Val Asn Pro Ala Cys Thr Gly Cys  
 Cys Glu Phe Cys Val Asn Pro Ala Cys Thr Ala Cys  
 Cys Glu Phe Cys Val Asn Pro Ala Cys Val Gly Cys  
 Cys Glu Phe Cys Val Asn Pro Ala Cys Val Ala Cys  
 Cys Glu Phe Cys Val Asn Pro Ala Cys Gly Gly Cys  
 Cys Glu Phe Cys Val Asn Pro Ala Cys Gly Ala Cys  
 Cys Glu Phe Cys Val Asn Pro Thr Cys Thr Gly Cys  
 Cys Glu Phe Cys Val Asn Pro Thr Cys Thr Ala Cys  
 Cys Glu Phe Cys Val Asn Pro Thr Cys Val Gly Cys  
 Cys Glu Phe Cys Val Asn Pro Thr Cys Val Ala Cys  
 Cys Glu Phe Cys Val Asn Pro Thr Cys Gly Gly Cys  
 Cys Glu Phe Cys Val Asn Pro Thr Cys Gly Ala Cys  
 Cys Glu Phe Cys Val Asn Gly Ala Cys Thr Gly Cys  
 Cys Glu Phe Cys Val Asn Gly Ala Cys Thr Ala Cys  
 Cys Glu Phe Cys Val Asn Gly Ala Cys Val Gly Cys  
 Cys Glu Phe Cys Val Asn Gly Ala Cys Val Ala Cys  
 Cys Glu Phe Cys Val Asn Gly Ala Cys Gly Gly Cys  
 Cys Glu Phe Cys Val Asn Gly Ala Cys Gly Ala Cys  
 Cys Glu Phe Cys Val Asn Gly Thr Cys Thr Gly Cys  
 Cys Glu Phe Cys Val Asn Gly Thr Cys Thr Ala Cys  
 Cys Glu Phe Cys Val Asn Gly Thr Cys Val Gly Cys  
 Cys Glu Phe Cys Val Asn Gly Thr Cys Val Ala Cys  
 Cys Glu Phe Cys Val Asn Gly Thr Cys Gly Gly Cys  
 Cys Glu Phe Cys Val Asn Gly Thr Cys Gly Ala Cys  
 Cys Glu Phe Cys Val Asn Gly Thr Cys Gly Ala Cys  
 Cys Glu Phe Cys Val Asn Gly Thr Cys Thr Gly Cys  
 Cys Glu Phe Cys Val Asn Gly Thr Cys Thr Ala Cys  
 Cys Glu Phe Cys Val Asn Gly Thr Cys Val Gly Cys  
 Cys Glu Phe Cys Val Asn Gly Thr Cys Val Ala Cys  
 Cys Glu Phe Cys Val Asn Gly Ala Cys Gly Gly Cys  
 Cys Glu Phe Cys Val Asn Gly Ala Cys Gly Ala Cys  
 Cys Glu Phe Cys Val Asn Gly Thr Cys Thr Gly Cys  
 Cys Glu Phe Cys Val Asn Gly Thr Cys Thr Ala Cys  
 Cys Glu Phe Cys Val Asn Gly Thr Cys Val Ala Cys  
 Cys Glu Phe Cys Val Asn Gly Thr Cys Gly Gly Cys  
 Cys Glu Phe Cys Val Asn Gly Thr Cys Gly Ala Cys  
 Cys Glu Leu Cys Ala Asn Pro Ala Cys Thr Gly Cys  
 Cys Glu Leu Cys Ala Asn Pro Ala Cys Thr Ala Cys  
 Cys Glu Leu Cys Ala Asn Pro Ala Cys Val Gly Cys

FIGURE 3 (sheet 60 of 68)

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Cys Glu Leu Cys Ala Asn Pro Ala Cys Val Ala Cys  
 Cys Glu Leu Cys Ala Asn Pro Ala Cys Gly Gly Cys  
 Cys Glu Leu Cys Ala Asn Pro Ala Cys Gly Ala Cys  
 Cys Glu Leu Cys Ala Asn Pro Thr Cys Thr Gly Cys  
 Cys Glu Leu Cys Ala Asn Pro Thr Cys Thr Ala Cys  
 Cys Glu Leu Cys Ala Asn Pro Thr Cys Val Gly Cys  
 Cys Glu Leu Cys Ala Asn Pro Thr Cys Gly Gly Cys  
 Cys Glu Leu Cys Ala Asn Pro Thr Cys Gly Ala Cys  
 Cys Glu Leu Cys Ala Asn Gly Ala Cys Thr Gly Cys  
 Cys Glu Leu Cys Ala Asn Gly Ala Cys Thr Ala Cys  
 Cys Glu Leu Cys Ala Asn Gly Ala Cys Val Gly Cys  
 Cys Glu Leu Cys Ala Asn Gly Ala Cys Val Ala Cys  
 Cys Glu Leu Cys Ala Asn Gly Ala Cys Gly Gly Cys  
 Cys Glu Leu Cys Ala Asn Gly Ala Cys Gly Ala Cys  
 Cys Glu Leu Cys Ala Asn Gly Thr Cys Thr Gly Cys  
 Cys Glu Leu Cys Ala Asn Gly Thr Cys Thr Ala Cys  
 Cys Glu Leu Cys Ala Asn Gly Thr Cys Val Gly Cys  
 Cys Glu Leu Cys Ala Asn Gly Thr Cys Val Ala Cys  
 Cys Glu Leu Cys Ala Asn Gly Thr Cys Gly Gly Cys  
 Cys Glu Leu Cys Ala Asn Gly Thr Cys Gly Ala Cys  
 Cys Glu Leu Cys Arg Asn Pro Ala Cys Thr Gly Cys  
 Cys Glu Leu Cys Arg Asn Pro Ala Cys Thr Ala Cys  
 Cys Glu Leu Cys Arg Asn Pro Ala Cys Val Gly Cys  
 Cys Glu Leu Cys Arg Asn Pro Ala Cys Val Ala Cys  
 Cys Glu Leu Cys Arg Asn Pro Ala Cys Gly Gly Cys  
 Cys Glu Leu Cys Arg Asn Pro Ala Cys Gly Ala Cys  
 Cys Glu Leu Cys Arg Asn Pro Thr Cys Thr Gly Cys  
 Cys Glu Leu Cys Arg Asn Pro Thr Cys Thr Ala Cys  
 Cys Glu Leu Cys Arg Asn Pro Thr Cys Val Gly Cys  
 Cys Glu Leu Cys Arg Asn Pro Thr Cys Val Ala Cys  
 Cys Glu Leu Cys Arg Asn Gly Ala Cys Val Ala Cys  
 Cys Glu Leu Cys Arg Asn Gly Ala Cys Gly Gly Cys  
 Cys Glu Leu Cys Arg Asn Gly Ala Cys Gly Ala Cys  
 Cys Glu Leu Cys Arg Asn Gly Thr Cys Thr Gly Cys  
 Cys Glu Leu Cys Arg Asn Gly Thr Cys Thr Ala Cys  
 Cys Glu Leu Cys Arg Asn Gly Thr Cys Val Gly Cys  
 Cys Glu Leu Cys Arg Asn Gly Thr Cys Val Ala Cys  
 Cys Glu Leu Cys Arg Asn Gly Thr Cys Gly Gly Cys  
 Cys Glu Leu Cys Arg Asn Gly Thr Cys Gly Ala Cys  
 Cys Glu Leu Cys Asn Asn Pro Ala Cys Thr Gly Cys  
 Cys Glu Leu Cys Asn Asn Pro Ala Cys Thr Ala Cys  
 Cys Glu Leu Cys Asn Asn Pro Ala Cys Val Gly Cys  
 Cys Glu Leu Cys Asn Asn Pro Ala Cys Val Ala Cys  
 Cys Glu Leu Cys Asn Asn Pro Ala Cys Gly Gly Cys  
 Cys Glu Leu Cys Asn Asn Pro Ala Cys Gly Ala Cys  
 Cys Glu Leu Cys Asn Asn Pro Thr Cys Thr Gly Cys  
 Cys Glu Leu Cys Asn Asn Pro Thr Cys Thr Ala Cys  
 Cys Glu Leu Cys Asn Asn Pro Thr Cys Val Gly Cys  
 Cys Glu Leu Cys Asn Asn Pro Thr Cys Val Ala Cys  
 Cys Glu Leu Cys Asn Asn Pro Thr Cys Gly Gly Cys  
 Cys Glu Leu Cys Asn Asn Pro Thr Cys Gly Ala Cys

FIGURE 3 (Sheet 61 of 68)

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Cys Glu Leu Cys Asn Asn Gly Ala Cys Thr Gly Cys  
 Cys Glu Leu Cys Asn Asn Gly Ala Cys Thr Ala Cys  
 Cys Glu Leu Cys Asn Asn Gly Ala Cys Val Gly Cys  
 Cys Glu Leu Cys Asn Asn Gly Ala Cys Val Ala Cys  
 Cys Glu Leu Cys Asn Asn Gly Ala Cys Gly Gly Cys  
 Cys Glu Leu Cys Asn Asn Gly Thr Cys Thr Gly Cys  
 Cys Glu Leu Cys Asn Asn Gly Thr Cys Thr Ala Cys  
 Cys Glu Leu Cys Asn Asn Gly Thr Cys Val Gly Cys  
 Cys Glu Leu Cys Asn Asn Gly Thr Cys Val Ala Cys  
 Cys Glu Leu Cys Asn Asn Gly Thr Cys Gly Gly Cys  
 Cys Glu Leu Cys Asn Asn Gly Thr Cys Gly Ala Cys  
 Cys Glu Leu Cys Asp Asn Pro Ala Cys Thr Gly Cys  
 Cys Glu Leu Cys Asp Asn Pro Ala Cys Thr Ala Cys  
 Cys Glu Leu Cys Asp Asn Pro Ala Cys Val Gly Cys  
 Cys Glu Leu Cys Asp Asn Pro Ala Cys Val Ala Cys  
 Cys Glu Leu Cys Asp Asn Pro Ala Cys Gly Gly Cys  
 Cys Glu Leu Cys Asp Asn Pro Ala Cys Gly Gly Cys  
 Cys Glu Leu Cys Asp Asn Pro Thr Cys Thr Gly Cys  
 Cys Glu Leu Cys Asp Asn Pro Thr Cys Thr Ala Cys  
 Cys Glu Leu Cys Asp Asn Pro Thr Cys Val Gly Cys  
 Cys Glu Leu Cys Asp Asn Pro Thr Cys Val Ala Cys  
 Cys Glu Leu Cys Asp Asn Pro Thr Cys Gly Gly Cys  
 Cys Glu Leu Cys Asp Asn Pro Thr Cys Gly Ala Cys  
 Cys Glu Leu Cys Asp Asn Gly Ala Cys Thr Gly Cys  
 Cys Glu Leu Cys Asp Asn Gly Ala Cys Val Gly Cys  
 Cys Glu Leu Cys Asp Asn Gly Ala Cys Val Ala Cys  
 Cys Glu Leu Cys Asp Asn Gly Ala Cys Gly Gly Cys  
 Cys Glu Leu Cys Asp Asn Gly Ala Cys Gly Ala Cys  
 Cys Glu Leu Cys Asp Asn Gly Thr Cys Thr Gly Cys  
 Cys Glu Leu Cys Asp Asn Gly Thr Cys Thr Ala Cys  
 Cys Glu Leu Cys Asp Asn Gly Thr Cys Val Gly Cys  
 Cys Glu Leu Cys Asp Asn Gly Thr Cys Val Gly Cys  
 Cys Glu Leu Cys Asp Asn Gly Thr Cys Thr Gly Cys  
 Cys Glu Leu Cys Asp Asn Gly Thr Cys Thr Ala Cys  
 Cys Glu Leu Cys Asp Asn Gly Thr Cys Val Gly Cys

FIGURE 3 (sheet 62 of 68)

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Cys Glu Leu Cys Gln Asn Gly Thr Cys Val Ala Cys  
 Cys Glu Leu Cys Gln Asn Gly Thr Cys Gly Gly Cys  
 Cys Glu Leu Cys Gln Asn Gly Thr Cys Gly Ala Cys  
 Cys Glu Leu Cys Glu Asn Pro Ala Cys Thr Gly Cys  
 Cys Glu Leu Cys Glu Asn Pro Ala Cys Thr Ala Cys  
 Cys Glu Leu Cys Glu Asn Pro Ala Cys Val Gly Cys  
 Cys Glu Leu Cys Glu Asn Pro Ala Cys Val Ala Cys  
 Cys Glu Leu Cys Glu Asn Pro Ala Cys Gly Gly Cys  
 Cys Glu Leu Cys Glu Asn Pro Ala Cys Gly Ala Cys  
 Cys Glu Leu Cys Glu Asn Pro Thr Cys Thr Gly Cys  
 Cys Glu Leu Cys Glu Asn Pro Thr Cys Thr Ala Cys  
 Cys Glu Leu Cys Glu Asn Pro Thr Cys Val Gly Cys  
 Cys Glu Leu Cys Glu Asn Pro Thr Cys Val Ala Cys  
 Cys Glu Leu Cys Glu Asn Pro Thr Cys Gly Gly Cys  
 Cys Glu Leu Cys Glu Asn Pro Thr Cys Gly Ala Cys  
 Cys Glu Leu Cys Glu Asn Gly Ala Cys Thr Gly Cys  
 Cys Glu Leu Cys Glu Asn Gly Ala Cys Thr Ala Cys  
 Cys Glu Leu Cys Glu Asn Gly Ala Cys Val Gly Cys  
 Cys Glu Leu Cys Glu Asn Gly Ala Cys Val Ala Cys  
 Cys Glu Leu Cys Glu Asn Gly Ala Cys Gly Gly Cys  
 Cys Glu Leu Cys Gly Asn Pro Ala Cys Thr Gly Cys  
 Cys Glu Leu Cys Gly Asn Pro Ala Cys Thr Ala Cys  
 Cys Glu Leu Cys Gly Asn Pro Ala Cys Val Gly Cys  
 Cys Glu Leu Cys Gly Asn Pro Thr Cys Thr Gly Cys  
 Cys Glu Leu Cys Gly Asn Pro Thr Cys Thr Ala Cys  
 Cys Glu Leu Cys Gly Asn Pro Thr Cys Val Gly Cys  
 Cys Glu Leu Cys Gly Asn Pro Thr Cys Val Ala Cys  
 Cys Glu Leu Cys Gly Asn Pro Thr Cys Gly Gly Cys  
 Cys Glu Leu Cys Gly Asn Pro Thr Cys Gly Ala Cys  
 Cys Glu Leu Cys Gly Asn Gly Ala Cys Thr Gly Cys  
 Cys Glu Leu Cys Gly Asn Gly Ala Cys Thr Ala Cys  
 Cys Glu Leu Cys Gly Asn Gly Ala Cys Val Gly Cys  
 Cys Glu Leu Cys Gly Asn Gly Ala Cys Val Ala Cys  
 Cys Glu Leu Cys Gly Asn Gly Ala Cys Gly Gly Cys  
 Cys Glu Leu Cys Gly Asn Gly Ala Cys Gly Ala Cys  
 Cys Glu Leu Cys Gly Asn Gly Thr Cys Thr Gly Cys  
 Cys Glu Leu Cys Gly Asn Gly Thr Cys Thr Ala Cys  
 Cys Glu Leu Cys Gly Asn Gly Thr Cys Val Gly Cys  
 Cys Glu Leu Cys Gly Asn Gly Thr Cys Val Ala Cys  
 Cys Glu Leu Cys Gly Asn Gly Thr Cys Gly Gly Cys  
 Cys Glu Leu Cys Gly Asn Gly Thr Cys Gly Ala Cys  
 Cys Glu Leu Cys His Asn Pro Ala Cys Thr Gly Cys  
 Cys Glu Leu Cys His Asn Pro Ala Cys Thr Ala Cys  
 Cys Glu Leu Cys His Asn Pro Ala Cys Val Gly Cys  
 Cys Glu Leu Cys His Asn Pro Ala Cys Val Ala Cys  
 Cys Glu Leu Cys His Asn Pro Ala Cys Gly Gly Cys  
 Cys Glu Leu Cys His Asn Pro Ala Cys Gly Ala Cys



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Cys Glu Leu Cys His Asn Pro Thr Cys Thr Gly Cys  
 Cys Glu Leu Cys His Asn Pro Thr Cys Thr Ala Cys  
 Cys Glu Leu Cys His Asn Pro Thr Cys Val Gly Cys  
 Cys Glu Leu Cys His Asn Pro Thr Cys Val Ala Cys  
 Cys Glu Leu Cys His Asn Pro Thr Cys Gly Gly Cys  
 Cys Glu Leu Cys His Asn Pro Thr Cys Gly Ala Cys  
 Cys Glu Leu Cys His Asn Gly Ala Cys Thr Gly Cys  
 Cys Glu Leu Cys His Asn Gly Ala Cys Thr Ala Cys  
 Cys Glu Leu Cys His Asn Gly Ala Cys Val Gly Cys  
 Cys Glu Leu Cys His Asn Gly Ala Cys Val Ala Cys  
 Cys Glu Leu Cys His Asn Gly Ala Cys Gly Gly Cys  
 Cys Glu Leu Cys His Asn Gly Ala Cys Gly Ala Cys  
 Cys Glu Leu Cys His Asn Gly Thr Cys Thr Gly Cys  
 Cys Glu Leu Cys His Asn Gly Thr Cys Thr Ala Cys  
 Cys Glu Leu Cys His Asn Gly Thr Cys Val Gly Cys  
 Cys Glu Leu Cys His Asn Gly Thr Cys Val Ala Cys  
 Cys Glu Leu Cys His Asn Gly Thr Cys Gly Gly Cys  
 Cys Glu Leu Cys His Asn Gly Thr Cys Gly Ala Cys  
 Cys Glu Leu Cys His Asn Gly Thr Cys Thr Gly Cys  
 Cys Glu Leu Cys His Asn Gly Thr Cys Thr Ala Cys  
 Cys Glu Leu Cys His Asn Gly Thr Cys Val Gly Cys  
 Cys Glu Leu Cys His Asn Gly Thr Cys Val Ala Cys  
 Cys Glu Leu Cys His Asn Gly Thr Cys Gly Gly Cys  
 Cys Glu Leu Cys His Asn Gly Ala Cys Gly Ala Cys  
 Cys Glu Leu Cys His Asn Gly Thr Cys Thr Gly Cys  
 Cys Glu Leu Cys His Asn Gly Thr Cys Thr Ala Cys  
 Cys Glu Leu Cys His Asn Gly Thr Cys Val Gly Cys  
 Cys Glu Leu Cys His Asn Gly Thr Cys Val Ala Cys  
 Cys Glu Leu Cys His Asn Gly Thr Cys Gly Gly Cys  
 Cys Glu Leu Cys His Asn Gly Thr Cys Gly Ala Cys  
 Cys Glu Leu Cys His Asn Gly Thr Cys Thr Gly Cys  
 Cys Glu Leu Cys His Asn Gly Thr Cys Thr Ala Cys  
 Cys Glu Leu Cys His Asn Gly Ala Cys Thr Gly Cys  
 Cys Glu Leu Cys His Asn Gly Ala Cys Thr Ala Cys  
 Cys Glu Leu Cys His Asn Gly Ala Cys Val Gly Cys  
 Cys Glu Leu Cys His Asn Pro Ala Cys Val Ala Cys  
 Cys Glu Leu Cys His Asn Pro Ala Cys Gly Gly Cys  
 Cys Glu Leu Cys His Asn Pro Ala Cys Gly Ala Cys  
 Cys Glu Leu Cys His Asn Pro Thr Cys Thr Gly Cys  
 Cys Glu Leu Cys His Asn Pro Thr Cys Thr Ala Cys  
 Cys Glu Leu Cys His Asn Pro Thr Cys Val Gly Cys  
 Cys Glu Leu Cys His Asn Pro Thr Cys Val Ala Cys  
 Cys Glu Leu Cys His Asn Pro Thr Cys Gly Gly Cys  
 Cys Glu Leu Cys His Asn Pro Thr Cys Gly Ala Cys  
 Cys Glu Leu Cys His Asn Gly Ala Cys Thr Gly Cys  
 Cys Glu Leu Cys His Asn Gly Ala Cys Thr Ala Cys  
 Cys Glu Leu Cys His Asn Gly Ala Cys Val Gly Cys



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Cys Glu Leu Cys Phe Asn Pro Ala Cys Thr Gly Cys  
 Cys Glu Leu Cys Phe Asn Pro Ala Cys Thr Ala Cys  
 Cys Glu Leu Cys Phe Asn Pro Ala Cys Val Gly Cys  
 Cys Glu Leu Cys Phe Asn Pro Ala Cys Val Ala Cys  
 Cys Glu Leu Cys Phe Asn Pro Ala Cys Gly Gly Cys  
 Cys Glu Leu Cys Phe Asn Pro Ala Cys Gly Ala Cys  
 Cys Glu Leu Cys Phe Asn Pro Thr Cys Thr Gly Cys  
 Cys Glu Leu Cys Phe Asn Pro Thr Cys Thr Ala Cys  
 Cys Glu Leu Cys Phe Asn Pro Thr Cys Val Gly Cys  
 Cys Glu Leu Cys Phe Asn Pro Thr Cys Val Ala Cys  
 Cys Glu Leu Cys Phe Asn Pro Thr Cys Gly Gly Cys  
 Cys Glu Leu Cys Phe Asn Pro Thr Cys Gly Ala Cys  
 Cys Glu Leu Cys Phe Asn Gly Ala Cys Thr Gly Cys  
 Cys Glu Leu Cys Phe Asn Gly Ala Cys Thr Ala Cys  
 Cys Glu Leu Cys Phe Asn Gly Ala Cys Val Gly Cys  
 Cys Glu Leu Cys Phe Asn Gly Ala Cys Val Ala Cys  
 Cys Glu Leu Cys Phe Asn Gly Ala Cys Gly Gly Cys  
 Cys Glu Leu Cys Phe Asn Gly Ala Cys Gly Ala Cys  
 Cys Glu Leu Cys Phe Asn Gly Thr Cys Thr Gly Cys  
 Cys Glu Leu Cys Phe Asn Gly Thr Cys Thr Ala Cys  
 Cys Glu Leu Cys Phe Asn Gly Thr Cys Val Gly Cys  
 Cys Glu Leu Cys Phe Asn Gly Thr Cys Val Ala Cys  
 Cys Glu Leu Cys Phe Asn Gly Thr Cys Gly Gly Cys  
 Cys Glu Leu Cys Phe Asn Gly Thr Cys Gly Ala Cys  
 Cys Glu Leu Cys Pro Asn Pro Ala Cys Thr Gly Cys  
 Cys Glu Leu Cys Pro Asn Pro Ala Cys Thr Ala Cys  
 Cys Glu Leu Cys Pro Asn Pro Ala Cys Val Gly Cys  
 Cys Glu Leu Cys Pro Asn Pro Ala Cys Val Ala Cys  
 Cys Glu Leu Cys Pro Asn Pro Ala Cys Gly Gly Cys  
 Cys Glu Leu Cys Pro Asn Pro Ala Cys Gly Ala Cys  
 Cys Glu Leu Cys Pro Asn Pro Thr Cys Thr Gly Cys  
 Cys Glu Leu Cys Pro Asn Pro Thr Cys Thr Ala Cys  
 Cys Glu Leu Cys Pro Asn Pro Thr Cys Val Gly Cys  
 Cys Glu Leu Cys Pro Asn Pro Thr Cys Val Ala Cys  
 Cys Glu Leu Cys Pro Asn Gly Ala Cys Gly Gly Cys  
 Cys Glu Leu Cys Pro Asn Gly Ala Cys Gly Ala Cys  
 Cys Glu Leu Cys Pro Asn Gly Thr Cys Thr Gly Cys  
 Cys Glu Leu Cys Pro Asn Gly Thr Cys Thr Ala Cys  
 Cys Glu Leu Cys Pro Asn Gly Thr Cys Val Gly Cys  
 Cys Glu Leu Cys Pro Asn Gly Thr Cys Val Ala Cys  
 Cys Glu Leu Cys Pro Asn Gly Thr Cys Gly Gly Cys  
 Cys Glu Leu Cys Pro Asn Gly Thr Cys Gly Ala Cys  
 Cys Glu Leu Cys Ser Asn Pro Ala Cys Thr Gly Cys  
 Cys Glu Leu Cys Ser Asn Pro Ala Cys Thr Ala Cys  
 Cys Glu Leu Cys Ser Asn Pro Ala Cys Val Gly Cys  
 Cys Glu Leu Cys Ser Asn Pro Ala Cys Val Ala Cys  
 Cys Glu Leu Cys Ser Asn Pro Ala Cys Gly Gly Cys  
 Cys Glu Leu Cys Ser Asn Pro Ala Cys Gly Ala Cys  
 Cys Glu Leu Cys Ser Asn Pro Thr Cys Thr Gly Cys  
 Cys Glu Leu Cys Ser Asn Pro Thr Cys Thr Ala Cys  
 Cys Glu Leu Cys Ser Asn Pro Thr Cys Val Gly Cys

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Cys Glu Leu Cys Ser Asn Pro Thr Cys Val Ala Cys  
 Cys Glu Leu Cys Ser Asn Pro Thr Cys Gly Gly Cys  
 Cys Glu Leu Cys Ser Asn Pro Thr Cys Gly Ala Cys  
 Cys Glu Leu Cys Ser Asn Gly Ala Cys Thr Gly Cys  
 Cys Glu Leu Cys Ser Asn Gly Ala Cys Thr Ala Cys  
 Cys Glu Leu Cys Ser Asn Gly Ala Cys Val Gly Cys  
 Cys Glu Leu Cys Ser Asn Gly Ala Cys Val Ala Cys  
 Cys Glu Leu Cys Ser Asn Gly Ala Cys Gly Gly Cys  
 Cys Glu Leu Cys Ser Asn Gly Ala Cys Gly Ala Cys  
 Cys Glu Leu Cys Ser Asn Gly Thr Cys Thr Gly Cys  
 Cys Glu Leu Cys Ser Asn Gly Thr Cys Thr Ala Cys  
 Cys Glu Leu Cys Ser Asn Gly Thr Cys Val Gly Cys  
 Cys Glu Leu Cys Ser Asn Gly Thr Cys Val Ala Cys  
 Cys Glu Leu Cys Ser Asn Gly Thr Cys Gly Gly Cys  
 Cys Glu Leu Cys Ser Asn Gly Thr Cys Gly Ala Cys  
 Cys Glu Leu Cys Thr Asn Pro Ala Cys Thr Gly Cys  
 Cys Glu Leu Cys Thr Asn Pro Ala Cys Thr Ala Cys  
 Cys Glu Leu Cys Thr Asn Pro Ala Cys Val Gly Cys  
 Cys Glu Leu Cys Thr Asn Pro Ala Cys Val Ala Cys  
 Cys Glu Leu Cys Thr Asn Pro Ala Cys Gly Gly Cys  
 Cys Glu Leu Cys Thr Asn Pro Ala Cys Gly Ala Cys  
 Cys Glu Leu Cys Thr Asn Pro Thr Cys Thr Gly Cys  
 Cys Glu Leu Cys Thr Asn Pro Thr Cys Thr Ala Cys  
 Cys Glu Leu Cys Thr Asn Pro Thr Cys Val Gly Cys  
 Cys Glu Leu Cys Thr Asn Pro Thr Cys Val Ala Cys  
 Cys Glu Leu Cys Thr Asn Pro Thr Cys Gly Gly Cys  
 Cys Glu Leu Cys Thr Asn Gly Thr Cys Gly Ala Cys  
 Cys Glu Leu Cys Trp Asn Pro Ala Cys Thr Gly Cys  
 Cys Glu Leu Cys Trp Asn Pro Ala Cys Thr Ala Cys  
 Cys Glu Leu Cys Trp Asn Pro Ala Cys Val Gly Cys  
 Cys Glu Leu Cys Trp Asn Pro Ala Cys Val Ala Cys  
 Cys Glu Leu Cys Trp Asn Pro Ala Cys Gly Gly Cys  
 Cys Glu Leu Cys Trp Asn Pro Ala Cys Gly Ala Cys  
 Cys Glu Leu Cys Trp Asn Pro Thr Cys Thr Gly Cys  
 Cys Glu Leu Cys Trp Asn Pro Thr Cys Thr Ala Cys  
 Cys Glu Leu Cys Trp Asn Pro Thr Cys Val Gly Cys  
 Cys Glu Leu Cys Trp Asn Pro Thr Cys Val Ala Cys  
 Cys Glu Leu Cys Trp Asn Pro Thr Cys Gly Gly Cys  
 Cys Glu Leu Cys Trp Asn Gly Ala Cys Thr Gly Cys  
 Cys Glu Leu Cys Trp Asn Gly Ala Cys Thr Ala Cys  
 Cys Glu Leu Cys Trp Asn Gly Ala Cys Val Gly Cys  
 Cys Glu Leu Cys Trp Asn Gly Ala Cys Val Ala Cys  
 Cys Glu Leu Cys Trp Asn Gly Ala Cys Gly Gly Cys  
 Cys Glu Leu Cys Trp Asn Gly Ala Cys Gly Ala Cys

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Cys Glu Leu Cys Trp Asn Gly Thr Cys Thr Gly Cys  
Cys Glu Leu Cys Trp Asn Gly Thr Cys Thr Ala Cys  
Cys Glu Leu Cys Trp Asn Gly Thr Cys Val Gly Cys  
Cys Glu Leu Cys Trp Asn Gly Thr Cys Val Ala Cys  
Cys Glu Leu Cys Trp Asn Gly Thr Cys Gly Gly Cys  
Cys Glu Leu Cys Trp Asn Gly Thr Cys Gly Ala Cys  
Cys Glu Leu Cys Tyr Asn Pro Ala Cys Thr Gly Cys  
Cys Glu Leu Cys Tyr Asn Pro Ala Cys Thr Ala Cys  
Cys Glu Leu Cys Tyr Asn Pro Ala Cys Val Gly Cys  
Cys Glu Leu Cys Tyr Asn Pro Ala Cys Val Ala Cys  
Cys Glu Leu Cys Tyr Asn Pro Ala Cys Gly Gly Cys  
Cys Glu Leu Cys Tyr Asn Pro Ala Cys Gly Ala Cys  
Cys Glu Leu Cys Tyr Asn Pro Thr Cys Thr Gly Cys  
Cys Glu Leu Cys Tyr Asn Pro Thr Cys Thr Ala Cys  
Cys Glu Leu Cys Tyr Asn Pro Thr Cys Val Gly Cys  
Cys Glu Leu Cys Tyr Asn Pro Thr Cys Val Ala Cys  
Cys Glu Leu Cys Tyr Asn Pro Thr Cys Gly Gly Cys  
Cys Glu Leu Cys Tyr Asn Gly Thr Cys Gly Ala Cys  
Cys Glu Leu Cys Tyr Asn Gly Thr Cys Gly Ala Cys  
Cys Glu Leu Cys Tyr Asn Gly Thr Cys Val Gly Cys  
Cys Glu Leu Cys Tyr Asn Gly Thr Cys Val Ala Cys  
Cys Glu Leu Cys Tyr Asn Gly Thr Cys Gly Gly Cys  
Cys Glu Leu Cys Tyr Asn Gly Thr Cys Gly Ala Cys  
Cys Glu Leu Cys Tyr Asn Gly Thr Cys Thr Gly Cys  
Cys Glu Leu Cys Tyr Asn Gly Thr Cys Thr Ala Cys  
Cys Glu Leu Cys Tyr Asn Gly Thr Cys Val Gly Cys  
Cys Glu Leu Cys Tyr Asn Gly Thr Cys Val Ala Cys  
Cys Glu Leu Cys Tyr Asn Gly Thr Cys Gly Gly Cys  
Cys Glu Leu Cys Tyr Asn Gly Thr Cys Gly Ala Cys  
Cys Glu Leu Cys Tyr Asn Gly Thr Cys Thr Gly Cys  
Cys Glu Leu Cys Tyr Asn Gly Thr Cys Thr Ala Cys  
Cys Glu Leu Cys Tyr Asn Gly Thr Cys Val Gly Cys  
Cys Glu Leu Cys Tyr Asn Gly Thr Cys Val Ala Cys  
Cys Glu Leu Cys Tyr Asn Gly Thr Cys Gly Gly Cys  
Cys Glu Leu Cys Tyr Asn Gly Thr Cys Gly Ala Cys  
Cys Glu Leu Cys --- Asn Pro Ala Cys Thr Gly Cys  
Cys Glu Leu Cys --- Asn Pro Ala Cys Thr Ala Cys  
Cys Glu Leu Cys --- Asn Pro Ala Cys Val Gly Cys

FIGURE 3 (sheet 68 of 68)

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Cys Glu Leu Cys --- Asn Pro Ala Cys Val Ala Cys  
 Cys Glu Leu Cys --- Asn Pro Ala Cys Gly Gly Cys  
 Cys Glu Leu Cys --- Asn Pro Ala Cys Gly Ala Cys  
 Cys Glu Leu Cys --- Asn Pro Thr Cys Thr Gly Cys  
 Cys Glu Leu Cys --- Asn Pro Thr Cys Thr Ala Cys  
 Cys Glu Leu Cys --- Asn Pro Thr Cys Val Gly Cys  
 Cys Glu Leu Cys --- Asn Pro Thr Cys Val Ala Cys  
 Cys Glu Leu Cys --- Asn Pro Thr Cys Gly Gly Cys  
 Cys Glu Leu Cys --- Asn Pro Thr Cys Gly Ala Cys  
 Cys Glu Leu Cys --- Asn Gly Ala Cys Thr Gly Cys  
 Cys Glu Leu Cys --- Asn Gly Ala Cys Thr Ala Cys  
 Cys Glu Leu Cys --- Asn Gly Ala Cys Val Gly Cys  
 Cys Glu Leu Cys --- Asn Gly Ala Cys Val Ala Cys  
 Cys Glu Leu Cys --- Asn Gly Ala Cys Gly Gly Cys  
 Cys Glu Leu Cys --- Asn Gly Ala Cys Gly Ala Cys  
 Cys Glu Leu Cys --- Asn Gly Thr Cys Thr Gly Cys  
 Cys Glu Leu Cys --- Asn Gly Thr Cys Thr Ala Cys  
 Cys Glu Leu Cys --- Asn Gly Thr Cys Val Gly Cys  
 Cys Glu Leu Cys --- Asn Gly Thr Cys Val Ala Cys  
 Cys Glu Leu Cys --- Asn Gly Thr Cys Gly Gly Cys  
 Cys Glu Leu Cys --- Asn Gly Thr Cys Gly Ala Cys

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**SHEET 1 OF 19**

<b>INFORMATION DISCLOSURE                  STATEMENT LIST</b> (Use as many sheets as necessary)	Complete if Known	
	Application Number	13/421,769
	Filing Date	March 15, 2012
	First Named Inventor	Stephen Comiskey
	Art Unit	1676
	Examiner Name	Jia-Hai Lee
	Attorney Docket Number	SYPA-009/X001US 321994-2142

**U.S. PATENT DOCUMENTS**

Examiner Initials*	Cite No. <sup>1</sup>	Document Number Number-Kind Code <sup>2</sup> (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	1.	2002/0128176 A1	09-12-2002	Forssmann et al.	
	<del>2.</del>	<del>2002/0078683</del>	<del>06-27-2002</del>	<del>Katayama et al.</del>	
	3.	2002/0133168	09-19-2002	Smeldley et al.	
	4.	2002/0143015	10-03-2002	Fryburg et al.	
	5.	2003/0073628	04-17-2003	Shailubhai et al.	
	6.	2004/0015140 A1	01-22-2004	Shields	
	7.	2005/0016244	01-27-2005	Hergemoller	
	8.	2005/0032684 A1	02-10-2005	Cetin et al.	
	9.	2005/0107734	05-19-2005	Coroneo	
	10.	2005/0266047	12-01-2005	Tu et al	
	11.	005/0267297	12-01-2005	Berlin	
	12.	2006/0086653	04-27-2006	St. Germain	
	13.	2006/0094658	05-04-2006	Currie	
	14.	2007/0101158	05-03-2007	Elliott	
	15.	2008/0137318	06-12-2008	Rangaraj et al.	
	16.	2008/0151257	06-26-2008	Yasuda et al.	
	17.	2009/0048175 A1	02-19-2009	Shailubhai et al.	
	18.	2009/0192083 A1	07-30-2009	Currie	
	19.	2009/0253634 A1	10-08-2009	Currie et al.	
	20.	2010/0069306 A1	03-18-2010	Shailubhai et al.	

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	21.	2010/0093635 A1	04-15-2010	Shailubhai	
	22.	2010/0120694 A1	05-13-2010	Shailubhai et al.	
	23.	2010/0152118 A1	06-17-2010	Shailubhai	
	24.	2010/0221329 A1	09-02-2010	Shailubhai et al.	
	25.	2012/0196797 A1	08-02-2012	Currie et al.	
	26.	2012/0237593 A1	09-20-2012	Comiskey et al.	
	27.	2012/0289460 A1	11-15-2012	Shailubhai	
	28.	2013/0274204 A1	10-17-2013	Shailubhai et al.	
	29.	2014/0024605 A1	01-23-2014	Shailubhai et al.	
	30.	2014/0121169 A1	05-01-2014	Shailubhai et al.	
	31.	2014/0135274 A1	05-15-2014	Shailubhai	
	32.	2014/0287002 A1	09-25-2014	Shailubhai	
	33.	2014/0329738 A1	11-06-2014	Shailubhai et al.	
	34.	5,106,834	04-21-1992	Bovy et al.	
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	36.	5,489,670	02-06-1994	Currie et al.	
	37.	5,518,888	05-21-1996	Waldman et al.	
	38.	5,578,709	11-26-1996	Woiszwillio et al.	
	39.	5,601,990	02-11-1997	Waldman et al.	
	40.	5,731,159	03-24-1998	Waldman et al.	

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	First Named Inventor	Stephen Comiskey
	Art Unit	1676
	Examiner Name	Jia-Hai Lee
	Attorney Docket Number	SYPA-009/X001US 321994-2142

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	41.	5,721,238	02-24-1998	Heiker et al.	
	42.	5,879,656	03-9-1999	Waldman et al.	
	43.	5,928,873	07-29-1999	Waldman et al.	
	44.	5,969,097	10-19-1999	Wiegand et al.	
	45.	6,060,037	05-09-2000	Waldman et al.	
	46.	6,235,782 B2	05-22-2001	Pamukcu et al.	
	47.	7,041,786 B2	05-09-2006	Shailubhai et al.	
	48.	7,375,083 B2	05-20-2008	Mickle et al.	
	49.	7,494,979 B2	02-24-2009	Currie et al.	
	50.	7,799,897 B2	09-21-2010	Jacob et al.	
	51.	7,879,802 B2	02-01-2011	Shailubhai et al.	
	52.	8,034,782 B2	10-11-2011	Shailubhai	
	53.	8,114,831 B2	02-14-2012	Shailubhai et al.	
	54.	8,207,295 B2	06-26-2012	Shailubhai et al.	
	55.	8,357,775 B2	01-22-2013	Shailubhai et al.	
	56.	8,367,800 B2	02-05-2013	Shailubhai	
	57.	8,497,348 B2	07-30-2013	Shailubhai et al.	
	58.	8,637,451 B2	01-28-2014	Shailubhai et al.	
	59.	8,716,224 B2	05-06-2014	Shailubhai et al.	

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	Application Number	13/421,769
	Filing Date	March 15, 2012
	First Named Inventor	Stephen Comiskey
	Art Unit	1676
	Examiner Name	Jia-Hai Lee
	Attorney Docket Number	SYPA-009/X001US 321994-2142

FOREIGN PATENT DOCUMENTS						
Examiner Initials*	Cite No. <sup>1</sup>	Foreign Patent Document Country Code <sup>3</sup> -Number <sup>4</sup> -Kind Code <sup>5</sup> (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T <sup>6</sup>
	60.	DE 19744027	04-08-1999	Hoechst Marion Rouseel Deutschland GmbH		
	61.	WO 88/05306	07-28-1988	The General Hospital Corporation		
	62.	WO 93/12068 A1	06-24-1993	Brigham and Women's Hospital		
	63.	WP 1999/026567 A1	06-03-1999	Optonol Ltd		
	64.	WO 01/25266 A1	04-12-2001	Pharmacia Corporation		
	65.	WO 02/062369 A2	08-15-2002	Pharmacia Corporation		
	66.	WO 2002/078683 A1	10-10-2002	Synergy Pharmaceuticals, Inc.		
	67.	WO 2002/098912 A3	12-12-2002	Cetin		
	68.	WO 2004/069165	08-19-2004	Microbia Inc. et al.		
	69.	WO 2005/016244 A2	02-24-2005	Microbia, Inc. et al.		
	70.	WO 2005/087797	09-22-2005	Microbia, Inc. et al.		
	71.	WO 2006/086653 A2	08-17-2006	Microbia, Inc. et al.		
	72.	WO 2007/101158 A2	09-07-2007	Microbia, Inc. et al.		
	73.	WO 2007/022531	02-22-2007	Microbia, Inc. et al.		
	74.	WO 2008/106429	09-04-2008	Microbia, Inc. et al.		
	75.	WO 2008/137318 A1	11-13-2008	Ironwood Pharmaceuticals, Inc. et al.		

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	Filing Date	March 15, 2012
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	Art Unit	1676
	Examiner Name	Jia-Hai Lee
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	76.	WO 2008/151257 A2	12-11-2008	Synergy Pharmaceuticals Inc. et al.		
	77.	WO 2009/149278 A1	12-10-2009	Synergy Pharmaceuticals Inc. et al.		
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	79.	WO 2010/009319 A2	01-21-2010	Synergy Pharmaceuticals Inc. et al.		
	80.	WO 2010/027404 A2	03-11-2010	Ironwood Pharmaceuticals Inc. et al.		
	81.	WO 2010/065751 A2	06-10-2010	Synergy Pharmaceuticals Inc. et al.		
	82.	WO 2011/020054 A1	02-17-2011	Ironwood Pharmaceuticals Inc. et al.		
	83.	WO 2012/037380 A2	03-22-2012	Synergy Pharmaceuticals Inc. et al.		

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	84.	Advisory Committee Briefing document for Merida [sibutramine hydrochloride monohydrate], Abbott, August 13, 2010 (205 pages)	

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	85.	Alrefai et al., "Cholesterol modulates human intestinal sodium-dependent bile acid transporter," Am. J. Physiol. Gastrointest. Liver Physiol. 288:G978-G985 (2005)	
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	87.	Bakre et al. "Expression and regulation of the cGMP-binding, cGMP-specific phosphodiesterase (PDE5) in human colonic epithelial cells: role in the induction of cellular refractoriness to the heat-stable enterotoxin peptide" J. Cell Biol. 77:159-167 (2000)	
	88.	Barbara et al. " A role for inflammation in irritable bowel syndrome": Gut, 51(Suppl. 1): 141-144 (2002)	
	89.	Basoglu et al. In: "Proceedings of the Second FEPS Congress, June 29-July 4, 1999, Prague, Czech Republic, If2.cuni.cz/physiolres/feeps/basoglu.htm. (3 pages)	
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	97.	Camilleri et al. "Management of the irritable bowel syndrome" Gastroenterol. 120:652-668 (2001)	

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**SHEET 7 OF 19**

<b>INFORMATION DISCLOSURE                  STATEMENT LIST</b> (Use as many sheets as necessary)	Complete if Known	
	Application Number	13/421,769
	Filing Date	March 15, 2012
	First Named Inventor	Stephen Comiskey
	Art Unit	1676
	Examiner Name	Jia-Hai Lee
	Attorney Docket Number	SYPA-009/X001US 321994-2142

**NON PATENT LITERATURE DOCUMENTS**

Examiner's Initials	Cite No. <sup>1</sup>	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T <sup>6</sup>
	98.	Carrithers et al., "Guanylyl cyclase C is a selective marker for metastatic colorectal tumors in human extraintestinal tissues" Proc. Natl. Acad. Sci. USA 93:14827-14832. (1996)	
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	First Named Inventor	Stephen Comiskey
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	Examiner Name	Jia-Hai Lee
	Attorney Docket Number	SYPA-009/X001US 321994-2142

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	120	European Patent 1,379,224:: Summons to attend oral hearing dated June 6, 2011 (23 pages)	
	121	European Patent 1,379,224: Response to Communication from Opposition division dated October 8, 2010 (44 pages)	
	122	European Patent 1,379,224: Written submission dated October 7, 2011 in response to the June 24, 2011 preliminary opinion of the Opposition Division (7 pages)	

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	123	European Patent 1,379,224: Written submission dated October 14, 2011 by Ironwood (27 pages)	
	124	European Patent 1,379,224: Written submission dated October 14, 2011 (7 pages)	
	125	European Patent 1,379,224: Written submission dated October 25, 2011(5 pages)	
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	138	Genbank 1UYBA- Chain A, Solution Structure B – Form uroguanylin. March 15, 2010. 2 pages	
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	149	Gulcan et al. "The predictive value of CRP levels on future severe renal disease in overweight and obese subjects without diabetes mellitus and hypertension. Am. J. Med. Sci 334:444-451 (2007).	
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	162	http:www.nlm.nih.gov/medlineplus/obesity.html: 1999-2011; last visited 09/25/2012 (6 pages)	
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<b>INFORMATION DISCLOSURE                  STATEMENT LIST</b> (Use as many sheets as necessary)	Complete if Known	
	Application Number	13/421,769
	Filing Date	March 15, 2012
	First Named Inventor	Stephen Comiskey
	Art Unit	1676
	Examiner Name	Jia-Hai Lee
	Attorney Docket Number	SYPA-009/X001US 321994-2142

**NON PATENT LITERATURE DOCUMENTS**

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	174	Kelland "Of mice and men": values and liabilities of the athymic nude mouse model in anticancer drug development" Eur. J. Cancer 40(6):827-836 (2004).	
	175	Kita et al. :Characterization of human uroguanylin; A member of the guanylin peptide family" Am. J. Physiol. 266:F342-8 (1994)	
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	Filing Date	March 15, 2012
	First Named Inventor	Stephen Comiskey
	Art Unit	1676
	Examiner Name	Jia-Hai Lee
	Attorney Docket Number	SYPA-009/X001US 321994-2142

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	Filing Date	March 15, 2012
	First Named Inventor	Stephen Comiskey
	Art Unit	1676
	Examiner Name	Jia-Hai Lee
	Attorney Docket Number	SYPA-009/X001US 321994-2142

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	198	Ohbayashi et al., "Effects of uroguanylin and guanylin against antigen-induced bronchoconstriction and airway microvascular leakage in sensitized guinea-pigs" Life Sci., 62(20):1883-1844 (1998)	
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	Filing Date	March 15, 2012
	First Named Inventor	Stephen Comiskey
	Art Unit	1676
	Examiner Name	Jia-Hai Lee
	Attorney Docket Number	SYPA-009/X001US 321994-2142

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	211	Schulz et al., "Guanylyl Cyclase Is a Heat-Stable Enterotoxin Receptor," Cell 63:941-948 (1990)	
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	240	Weber et al. "Activation of NF-κB in airway epithelial cells is dependent on CFTR trafficking and Cl channel function" Am. J. Physiol. Lung Cell Mol. Biol. 281(1):L71-78 (2001).	
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	244	Wong et al. "Histogenesis of human colorectal adenomas and hyperplastic polyps: the role of cell proliferation and crypt fission" Gut 50:212-217 (2002)	
	245	Written Opinion of the International Searching Authority, PCT Appl. No. PCT/US2011/051805, 5 pages (June 21, 2012)	

<b>Examiner Signature:</b>	<b>Date Considered</b>
EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.	

<sup>1</sup>EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. <sup>2</sup> Applicant's unique citation designation number (optional). <sup>3</sup> See Kinds Codes of USPTO Patent Documents at [www.uspto.gov](http://www.uspto.gov) or MPEP 901.04. <sup>4</sup> Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). <sup>5</sup> For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. <sup>6</sup> Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. <sup>7</sup> Applicant is to place a check mark here if English language Translation is attached.

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 2 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, 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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**SHEET 19 OF 19**

<b>INFORMATION DISCLOSURE                  STATEMENT LIST</b> (Use as many sheets as necessary)	Complete if Known	
	Application Number	13/421,769
	Filing Date	March 15, 2012
	First Named Inventor	Stephen Comiskey
	Art Unit	1676
	Examiner Name	Jia-Hai Lee
	Attorney Docket Number	SYPA-009/X001US 321994-2142


NON PATENT LITERATURE DOCUMENTS			
Examiner's Initials	Cite No. <sup>1</sup>	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T <sup>6</sup>
	246	Written Opinion of the International Searching Authority, PCT Appl. No. PCT/US2013/030551, 6 pages (June 18, 2013)	
	247	Wu et al. "Atrial natriuretic peptide induces apoptosis in neonatal rat cardia myocytes" J. Biol. Chem. 272(23):14860-14866 (1997)	
	248	Zhang et al. "Gene expression profiles in normal and cancer cells" Science 276:1268-1272 (1997)	
	249	Zimmerman et al. "Influence of local interactions on protein structure. I. Conformational energy studies of N-acetyl-N-methylamides of pro-X and X-pro dipeptides" Biopolymers, 16:811-843 (1977)	

<b>Examiner Signature:</b>	/Jia-hai Lee/	<b>Date Considered</b>	04/27/2015
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\*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. <sup>1</sup> Applicant's unique citation designation number (optional). <sup>2</sup> See Kinds Codes of USPTO Patent Documents at [www.uspto.gov](http://www.uspto.gov) or MPEP 901.04. <sup>3</sup> Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). <sup>4</sup> For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. <sup>5</sup> Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. <sup>6</sup> Applicant is to place a check mark here if English language Translation is attached.

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 2 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, 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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<b>Search Notes</b>  	<b>Application/Control No.</b>  13421769	<b>Applicant(s)/Patent Under Reexamination</b>  COMISKEY ET AL.
	<b>Examiner</b>  JIA-HAI LEE	<b>Art Unit</b>  1676

CPC- SEARCHED		
Symbol	Date	Examiner
(A61K2300/00 OR A61K38/10 OR A61K31/215 OR A61K8/731 OR C07D213/81 OR C07D213/56).CPC.	4/28/2015	JL

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner

US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES		
Search Notes	Date	Examiner
EAST, Database: USPATFUL, USPGPUB, EPO, JPO, DERWENT, Search history enclosed	4/28/2015	JL
STN, Databases: Biosis, Embase, Medline, Caplus, Search history enclosed	4/28/2015	JL
PALM Inventor Search	4/28/2015	JL
STIC search, results available on SCORE	05/29/2014	JL

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner

/J.L./ Examiner.Art Unit 1676	
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## EAST Search History

## EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	42331	(guanylate near cyclase near C) or GOC	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/04/28 20:14
L3	270	L1 with agonist	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/04/28 20:15
L4	72	L3 and @py<"2011"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/04/28 20:15
L5	30	GOC agonist peptide	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/04/28 20:15
L6	30	GOC agonist peptide	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/04/28 20:15
L7	11	L6 and tablet and process	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/04/28 20:15
L8	665	(blister pack) with liquid	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/04/28 20:15
L9	101	L8 with capsule	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/04/28 20:15
L10	0	L9 same peptide	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/04/28 20:15
L11	50	L9 and peptide	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/04/28 20:15

L12	48	L11 and oral	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/04/28 20:15
L13	2	L12 and cyclase	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/04/28 20:15
L14	17	(oral dosage) same (inorganic acid) same (carboxylic acid)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/04/28 20:15
L15	21070	excipient same (leucine or histidine or arginine or amine)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/04/28 20:15
L16	13721	L15 and oral	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/04/28 20:15
L17	1976	L15 same oral	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/04/28 20:15
L18	843	L17 and peptide	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/04/28 20:15
L19	550	L18 and lubricant	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/04/28 20:15
L20	544	L19 and pharmaceutical	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/04/28 20:15
L21	339	L20 and blister	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/04/28 20:15
L22	339	L21 and capsule	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/04/28 20:15
L23	138	L22 and @py< "2010"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/04/28 20:15

L24	134	L23 and liquid	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/04/28 20:15
L25	102	(Stephen near3 Comiskey).in.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/04/28 20:15
L26	2	L25 and (Oral dosage)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/04/28 20:15
L27	208	(Rong near3 Feng).in.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/04/28 20:15
L28	6	L27 and (oral)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/04/28 20:15
L29	124	(John near3 Foss).in.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/04/28 20:15
L30	2	L29 and oral	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/04/28 20:15
L31	157	(Kunwar near3 Shailubhai).in.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/04/28 20:15
L32	50	L31 and oral	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/04/28 20:15
L33	35	L32 and arginine	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/04/28 20:15
L34	1	peptide same (liquid formulation) same (blister pack)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/04/28 20:15
L35	104	(liquid formulation) same (blister pack)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/04/28 20:15

L36	79	L35 and peptide	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/04/28 20:15
L37	34	L36 and @py<"2010"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/04/28 20:15
L38	7432	guanylate cyclase	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/04/28 20:15
L39	1	L35 and L38	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/04/28 20:15
L40	220	L38 and (liquid formulation)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/04/28 20:15
L41	63	L40 and blister	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/04/28 20:15
L42	28	L41 and @py<"2010"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/04/28 20:15
L43	43	L40 AND ( (A61K2300/00 OR A61K38/10 OR A61K31/215 OR A61K8/731 OR C07D213/81 OR C07D213/56).CPC. )	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/04/28 20:15
L44	15	(low near moisture near carrier)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/04/28 20:15
L45	41	(synergy near2 pharmaceuticals).asn.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/04/28 20:18
L47	32	L45 and L1	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/04/28 20:19

4/ 28/ 2015 8:22:07 PM

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(FILE 'HOME' ENTERED AT 21:36:08 ON 28 APR 2015)

FILE 'REGISTRY' ENTERED AT 21:36:27 ON 28 APR 2015

L1 77 SEA SPE=ON ABB=ON PLU=ON NDECELVCNVACTGCL/SQSP AND SQL=16  
L2 0 SEA SPE=ON ABB=ON PLU=ON GUANYLATE CYCLASE C AGONIST

FILE 'CAPLUS, EMBASE, BIOSIS, MEDLINE' ENTERED AT 21:37:40 ON 28 APR 2015

L3 57 SEA SPE=ON ABB=ON PLU=ON L1  
L4 41880 SEA SPE=ON ABB=ON PLU=ON GUANYLATE CYCLASE  
L5 0 SEA SPE=ON ABB=ON PLU=ON LOW MOISTURE CARRIER  
L6 0 SEA SPE=ON ABB=ON PLU=ON (LOW MOISTURE CARRIER)  
L7 25625 SEA SPE=ON ABB=ON PLU=ON MICROCRYSTALLINE CELLULOSE  
L8 84264 SEA SPE=ON ABB=ON PLU=ON EXCIPIENT  
L9 3088 SEA SPE=ON ABB=ON PLU=ON L7 (L) L8  
L10 0 SEA SPE=ON ABB=ON PLU=ON L3 AND L9  
L11 0 SEA SPE=ON ABB=ON PLU=ON L3 AND L7  
L12 34 SEA SPE=ON ABB=ON PLU=ON L3 AND L4  
E COMISKEY STEP?/AU  
L13 39 SEA SPE=ON ABB=ON PLU=ON ("COMISKEY STEPHEN"/AU OR "COMISKEY  
STEPHEN DR"/AU OR "COMISKEY STEPHEN J"/AU OR "COMISKEY  
STEPHEN JOHN"/AU OR "COMISKEY STEPHEN W"/AU)  
E FENG RON?/AU  
L14 95 SEA SPE=ON ABB=ON PLU=ON "FENG RONG"/AU  
E FOSS JON?/AU  
E FOSS JOH?/AU  
L15 109 SEA SPE=ON ABB=ON PLU=ON ("FOSS JOHN"/AU OR "FOSS JOHN  
A"/AU OR "FOSS JOHN DR"/AU OR "FOSS JOHN E"/AU OR "FOSS JOHN  
F"/AU OR "FOSS JOHN G"/AU OR "FOSS JOHN W"/AU)  
E SHAILUBHAI KUNW?/AU  
L16 112 SEA SPE=ON ABB=ON PLU=ON ("SHAILUBHAI KUNW?"/AU OR "SHAILUBH  
AI KUNWAR"/AU OR "SHAILUBHAI KUNWAR DR"/AU)  
L17 281 SEA SPE=ON ABB=ON PLU=ON L13 OR L14 OR L15 OR L16  
L18 219 DUP REM L17 (62 DUPLICATES REMOVED)  
L\*\*\* DEL 158 S L13 OR L14 OR L15 OR L16  
L\*\*\* DEL 35 S L13 OR L14 OR L15 OR L16  
L\*\*\* DEL 79 S L13 OR L14 OR L15 OR L16  
L\*\*\* DEL 79 S L13 OR L14 OR L15 OR L16  
L19 56 SEA SPE=ON ABB=ON PLU=ON L18 AND L4  
L20 1 SEA SPE=ON ABB=ON PLU=ON L19 AND L9  
L21 9 SEA SPE=ON ABB=ON PLU=ON L12 AND L8  
L22 0 SEA SPE=ON ABB=ON PLU=ON L20 AND L21  
L23 10 SEA SPE=ON ABB=ON PLU=ON L20 OR L21  
D L23 1-10 IBIB ABS

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## Request for Continued Examination (RCE) Transmittal

Address to:  
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Alexandria, VA 22313-1450

Application Number	13/421,769
Filing Date	March 15, 2012
First Named Inventor	Stephen COMISKEY
Art Unit	1676
Examiner Name	LEE, Jia-Hai
Attorney Docket Number	SYPA-009/X01US 321994-2142

### This is a Request for Continued Examination (RCE) under 37 CFR 1.114 of the above-identified application.

Request for Continued Examination (RCE) practice under 37 CFR 1.114 does not apply to any utility or plant application filed prior to June 8, 1995, to any international application that does not comply with the requirements of 35 U.S.C. 371, or to any design application. See Instruction Sheet for RCEs (not to be submitted to the USPTO on page 2.)

1. **Submission required under 37 CFR 1.114** Note: If the RCE is proper, any previously filed unentered amendments and amendments enclosed with the RCE will be entered in the order in which they were filed unless applicant instructs otherwise. If applicant does not wish to have any previously filed unentered amendment(s) entered, applicant must request non-entry of such amendment(s).
- a.  Previously submitted. If a final Office action is outstanding, any amendments filed after the final Office action may be considered as a submission even if this box is not checked.
- i.  Consider the arguments in the Appeal Brief or Reply Brief previously filed on \_\_\_\_\_
- ii.  Other \_\_\_\_\_
- b.  Enclosed
- i.  Amendment/Reply
- ii.  Affidavit(s)/ Declaration(s)
- iii.  Information Disclosure Statement (IDS)
- iv.  Other \_\_\_\_\_
2. **Miscellaneous**
- Suspension of action on the above-identified application is requested under 37 CFR 1.103(c) for a
- a.  period of \_\_\_\_\_ months. (Period of suspension shall not exceed 3 months; Fee under 37 CFR 1.17(i) required)
- b.  Other \_\_\_\_\_
3. **Fees** The RCE fee under 37 CFR 1.17(e) is required by 37 CFR 1.114 when the RCE is filed.
- The Director is hereby authorized to charge the following fees, any underpayment of fees, or credit any overpayments, to
- a.  Deposit Account No. 50-1283.
- i.  RCE fee required under 37 CFR 1.17(e)
- ii.  Extension of time fee (37 CFR 1.136 and 1.17)
- iii.  Other \_\_\_\_\_
- b.  Check in the amount of \$ \_\_\_\_\_ enclosed
- c.  Payment by credit card (Form PTO-2038 enclosed)

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

#### SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT REQUIRED

Signature	/Anne E. Fleckenstein/	Date	November 20, 2015
Name (Print/Type)	Anne E. Fleckenstein	Registration No.	62,951

#### CERTIFICATE OF MAILING OR TRANSMISSION

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Mail Stop RCE, Commissioner for Patents, P. O. Box 1450, Alexandria, VA 22313-1450 or facsimile transmitted to the U.S. Patent and Trademark Office on the date shown below.

Signature		Date	
Name (Print/Type)		Date	

This collection of information is required by 37 CFR 1.114. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Mail Stop RCE, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

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## Instruction Sheet for RCEs

(not to be submitted to the USPTO)

### NOTES:

An RCE is not a new application, and filing an RCE will not result in an application being accorded a new filing date.

#### **Filing Qualifications:**

The application must be a utility or plant application filed on or after June 8, 1995. The application cannot be a provisional application, a utility or plant application filed before June 8, 1995, an international application that does not comply with the requirements of 35 U.S.C. 371, a design application, or a patent under reexamination. See 37 CFR 1.114(e). An international application does not comply with the requirements of 35 U.S.C. 371 until the requirements under 35 U.S.C. 371(c), including the requirement for the inventor's oath or declaration under 35 U.S.C. 371(c)(4), have been complied with.

#### **Filing Requirements:**

***Prosecution in the application must be closed.*** Prosecution is closed if the application is under appeal, or the last Office action is a final action, a notice of allowance, or an action that otherwise closes prosecution in the application (e.g., an Office action under *Ex parte Quayle* ). See 37 CFR 1.114(b).

***A submission and a fee are required at the time the RCE is filed.*** If reply to an Office action under 35 U.S.C. 132 is outstanding (e.g., the application is under final rejection), the submission must meet the reply requirements of 37 CFR 1.111. If there is no outstanding Office action, the submission can be an information disclosure statement, an amendment, new arguments, or new evidence. See 37 CFR 1.114(c). The submission may be a previously filed amendment ( e.g., an amendment after final rejection).

### WARNINGS:

#### **Request for Suspension of Action:**

All RCE filing requirements must be met before suspension of action is granted. A request for a suspension of action under 37 C FR 1.103(c) does not satisfy the submission requirement and does not permit the filing of the required submission to be suspended.

#### **Improper RCE will NOT toll Any Time Period:**

***Before Appeal*** - If the RCE is improper (e.g., prosecution in the application is not closed or the submission or fee has not been filed) and the application is not under appeal, the time period set forth in the last Office action will continue to run and the application will be abandoned after the statutory time period has expired if a reply to the Office action is not timely filed. No additional time will be given to correct the improper RCE.

***Under Appeal*** - If the RCE is improper (e.g., the submission or the fee has not been filed) and the application is under appeal, the improper RCE is effective to withdraw the appeal. Withdrawal of the appeal results in the allowance or abandonment of the application depending on the status of the claims. If there are no allowed claims, the application is abandoned. If there is at least one allowed claim, the application will be passed to issue on the allowed claim(s). See MPEP 1215.01.

**See MPEP 706.07(h) for further information on the RCE practice.**

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In Re Application of: Stephen Comiskey *et al* Confirmation No.: 3135

Application No.: 13/421,769 Group Art Unit: 1676

Filed: March 15, 2012 Examiner: LEE, Jia-Hai

FOR: **FORMULATIONS OF GUANYLATE CYCLASE C AGONISTS AND METHODS OF USE**

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**EFS**

**Mail Stop Amendment**

Commissioner for Patents

P.O. Box 1450

Alexandria, VA 22313-1450

**RESPONSE TO FINAL OFFICE ACTION AND REQUEST FOR CONTINUED  
EXAMINATION**

In response to the Final Office Action mailed May 20, 2015 please enter the following amendments and remarks. A request for a three-month extension of time is submitted concurrently herewith, making this response timely filed by November 20, 2015.

**Amendments to the Claims** begin on page 2.

**Remarks** begin on page 7.

**Amendments to the Claims:**

*This listing of claims will replace all prior listings in the application. Please amend the claims as follows.*

1. (Withdrawn –Previously Presented) An oral dosage formulation comprising at least one Guanylate Cyclase C (GCC) agonist peptide and one or more pharmaceutically acceptable excipients, wherein the amount of GCC agonist peptide per unit dose is from 0.01 mg to 10 mg, and the GCC agonist peptide is selected from the group consisting of SEQ ID NOs: 9 and 8.
2. (Currently Amended) An oral dosage formulation comprising at least one Guanylate Cyclase C (GCC) agonist peptide and one or more pharmaceutically acceptable excipients, wherein the amount of GCC agonist peptide per unit dose is from 0.01 mg to 10 mg, the GCC agonist peptide is selected from the group consisting of SEQ ID NOs: 1-54 and 56-249, the GCC agonist peptide has a chromatographic purity of no less than 91% after storage for at least three months, and the formulation comprises an inert low moisture carrier.
3. (Previously Presented) The oral dosage formulation of claim 2, wherein the GCC agonist peptide has a chromatographic purity of no less than 92% to 95%.
4. (Previously Presented) The oral dosage formulation of claim 2, wherein the GCC agonist peptide has a total impurity content of no greater than 9%.
5. (Original) The oral dosage formulation of claim 2, wherein the formulation is substantially free of inorganic acids and carboxylic acids.
6. (Original) The oral dosage formulation of claim 2, wherein the GCC agonist peptide is selected from the group consisting of SEQ ID NOs: 1, 8, 9, or 56.
7. (Previously Presented) The oral dosage formulation of claim 2, wherein the amount of GCC agonist peptide per unit dose is selected from the group consisting of 0.1 mg, 0.3 mg, 1.0 mg, 3.0 mg, 6.0 mg, 9.0 mg or 9.5 mg.

8. (Original) The oral dosage formulation of claim 2, wherein the formulation is a solid formulation and the unit dose is a powder, granule, sachet, troche, tablet, or capsule.
9. (Original) The oral dosage formulation of claim 2, wherein the one or more pharmaceutically acceptable excipients comprise an inert carrier.
10. (Previously Presented) The oral dosage formulation of claim 9, wherein the inert carrier is a microcrystalline cellulose.
11. (Original) The oral dosage formulation of claim 10, wherein the inert carrier has a particle size of from 50 to 900 microns.
12. (Withdrawn) The oral dosage formulation of claim 2, wherein the one or more pharmaceutically acceptable excipients comprise a divalent cation salt.
13. (Withdrawn) The oral dosage formulation of claim 12, wherein the salt is calcium chloride or calcium ascorbate.
14. (Original) The oral dosage formulation of claim 2, wherein the one or more pharmaceutically acceptable excipients comprise an amino acid or amine, and the molar ratio between the amino acid and GCC agonist peptide is 2:1 to 30:1.
15. (Original) The oral dosage formulation of claim 14, wherein the amino acid is leucine, histidine, or arginine.
16. (Previously Presented) The oral dosage formulation of claim 2, wherein the formulation consists of the GCC agonist peptide, the inert low moisture carrier, and a lubricant.
17. (Withdrawn) The oral dosage formulation of claim 2, wherein the formulation consists of the GCC agonist peptide, an inert carrier, a divalent cation salt, an amino acid, a coating agent and optionally a lubricant.
18. (Withdrawn) The oral dosage of formulation of claim 17, wherein the inert carrier is microcrystalline cellulose and the lubricant is magnesium stearate.
19. (Withdrawn) The oral dosage of formulation of claim 18, wherein the divalent cation salt is calcium chloride or calcium ascorbate, the amino acid is leucine, histidine, or arginine, and the coating agent is hypromellose.

20. (Original) The oral dosage formulation of claim 2, wherein the GCC agonist peptide is stabilized against degradation for a period of at least 18 months at 30 °C and 65% relative humidity, or at least 18 months at 25 °C and 60% relative humidity, or at least 18 months at 2-8 °C.
21. (Original) The oral dosage formulation of claim 2, wherein the formulation is in the form of a capsule or tablet.
22. (Original) The oral dosage formulation of claim 21, wherein the capsule or tablet is in a blister pack or strip.
23. (Original) The oral dosage formulation of claim 22, wherein the GCC agonist peptide is in solution or suspension in a lipophilic liquid.
24. (Original) The oral dosage formulation of claim 23, wherein the unit dosage form is a liquid-filled capsule.
25. (Previously Presented) The oral dosage formulation of claim 23, wherein the liquid is a refined specialty oil or a medium chain triglyceride or related ester.
26. (Withdrawn) A process for making an oral dosage formulation comprising at least one GCC agonist peptide, the method comprising:
  - a) providing an aqueous solution comprising: a GCC agonist peptide selected from the group consisting of SEQ ID NOs: 1-54 and 56-249, and one or more pharmaceutically acceptable excipients, wherein the concentration of the GCC agonist peptide ranges from 10 to 60 mg/mL; and
  - b) applying the aqueous solution to a pharmaceutically acceptable carrier to generate a GCC agonist peptide-coated carrier.
27. (Withdrawn) The process of claim 26, wherein the one or more pharmaceutically acceptable excipients comprise a divalent cation salt wherein the divalent cation is selected from  $\text{Ca}^{2+}$ ,  $\text{Mg}^{2+}$ ,  $\text{Zn}^{2+}$ , and  $\text{Mn}^{2+}$

28. (Withdrawn) The process of claim 26, wherein the one or more pharmaceutically acceptable excipients comprise an amino acid selected from leucine, histidine, and arginine.
29. (Withdrawn) The process of claim 26, wherein the one or more pharmaceutically acceptable excipients comprise a coating agent.
30. (Withdrawn) The process of claim 29, wherein the coating agent is hypromellose.
31. (Withdrawn) The process of claim 26, wherein the aqueous solution has a pH greater than 4 or 5.
32. (Withdrawn) The process of claim 26, wherein the GCC agonist peptide is selected from the group consisting of SEQ ID NOs: 1, 8, 9, and 56.
33. (Withdrawn) The process of claim 26, wherein the aqueous solution is substantially free of inorganic acids and carboxylic acids.
34. (Withdrawn) The process of claim 26, further comprising drying the GCC agonist peptide-coated carrier.
35. (Withdrawn) An oral dosage formulation made by the process of claim 26, wherein the GCC agonist peptide is stabilized against degradation for a period of at least 18 months at 30 °C and 65% relative humidity, or at least 18 months at 25 °C and 60% relative humidity, or at least 18 months at 2-8 °C.
36. (Withdrawn) A method for treating or preventing a disease or disorder in a subject in need thereof, comprising administering to the subject an oral dosage formulation of claim 2.
37. (Withdrawn) The method of claim 36, wherein the disease or disorder is a gastrointestinal disease or disorder selected from the group consisting of irritable bowel syndrome, chronic idiopathic constipation, non-ulcer dyspepsia, chronic intestinal pseudo-obstruction, functional dyspepsia, colonic pseudo-obstruction, duodenogastric reflux, gastro esophageal reflux disease, constipation, gastroparesis, heartburn, gastric cancer, and *H. pylori* infection.

38. (Withdrawn) The method of claim 36, wherein the GCC agonist peptide is selected from the group consisting of SEQ ID NOs: 1, 8, 9, or 56.
39. (Withdrawn) The method of claim 36, further comprising administering to the subject an effective amount of an inhibitor of a cGMP-specific phosphodiesterase.
40. (Withdrawn) The method of claim 36, further comprising administering to the subject an effective amount of at least one laxative.
41. (Withdrawn) The method of claim 36, further comprising administering to the subject an effective amount of at least one anti-inflammatory agent.
42. (Withdrawn) A pharmaceutical composition comprising the oral dosage formulation of claim 2.
43. (Previously Presented) The oral dosage formulation of claim 2, wherein the GCC agonist peptide is SEQ ID NO: 1 and the per unit dose is 3.0 mg or 6.0 mg.
44. (Previously Presented) The oral dosage formulation of claim 43, wherein the GCC agonist peptide is stabilized against degradation for a period of at least 18 months at 30 °C and 65% relative humidity, or at least 18 months at 25 °C and 60% relative humidity, or at least 18 months at 2-8 °C.

## **REMARKS**

### ***Status of the Claims***

Claims 1-44 are pending. Claim 2 is amended herein to recite the GCC agonist peptide has a chromatographic purity of no less than 91% after storage for at least three months. Support for this amendment can be found throughout the specification as filed, and specifically for example, at paragraph [040]. No new matter is added.

### ***Rejection of claims 2-11, 16, 20-21, 23-24 and 42-44 under 35 U.S.C. § 103***

The Examiner rejected claims 2-11, 16, 20-21, 23-24 and 42-44 under 35 U.S.C. § 103(a) as allegedly being obvious over Shailubhai *et al.* (WO 2002/078683) in view of Currie *et al.* (WO 2005/016244) in view of Mihranyan *et al.* (Int. J. Pharm. 2004. Jan 28; 269(2): 433-42) and in view of Avicel PH product instruction (FMC 2005). Office Action at page 4. Specifically, the Examiner argues Shailubhai teaches a pharmaceutical composition comprising a GCC agonist peptide with 100% sequence homology to SEQ ID NO: 1, the unit dosage of the GCC agonist peptide is between 100µg to 3g, and the purity of the GCC agonist peptide is greater than 95%. *Id.* at pages 4-5. The Examiner further states that Currie teaches the use of a peptide of SEQ ID NO: 1 for the treatment of gastrointestinal disorders and the use of pharmaceutically acceptable inert carriers such as microcrystalline cellulose. *Id.* at pages 5-6. The Examiner stated Mihranyan teaches microcrystalline cellulose (MCC) is the most commonly used drug excipients as taught by Currie *et al.*, and suggest the use of low moisture grades of commercial MCC for moisture sensitive drugs. *Id.* at page 6. Finally, the Examiner argues the Avicel PH product instruction teaches decreasing the moisture content can increase stability of moisture-sensitive drugs. *Id.* at page 7. The Examiner argues it would have been obvious to the skilled artisan to combine Shailubhai's guanylate cyclase C agonist peptide SEQ ID NO: 1 with Currie's teaching of pharmaceutically acceptable inert carriers, and to use a low moisture MCC to insure the stability of peptide formulation. *Id.*

The Examiner also rejected claims 2, 14-16, 20-22, 25, and 44 under 35 U.S.C. § 103(a) as allegedly being obvious over Shailubhai *et al.* (WO 02/078683) in view of Currie *et al.* (WO



2005/016244) in view of Mihranyan *et al.* and in view of Avicel PH product instruction as applied to claims 2-11, 16, 21, 23-24, and 42-43 and further in view of Fretzen *et al.* (WO 2010/027404). *Id.* at page 8. The Examiner contends Fretzen teaches a peptide formulation for oral administration comprising an aqueous coating solution, a therapeutic peptide, a sterically hindered primary amine and a pharmaceutically acceptable carrier or filler to form tablets or to be placed in capsules. *Id.* at page 9. The Examiner argues it would have been obvious to one of ordinary skill in the art to combine the teachings of Shailubhai, Currie, Mihranyan, and the Avicel PH product instruction with Fretzen to arrive at the claimed invention. *Id.* at page 10.

Applicants respectfully disagree. The present claims recite the GCC agonist peptide has a chromatographic purity of no less than 91% after storage for at least three months. This element is neither taught nor suggested in the cited art. The Examiner has failed to make a *prima facie* case of obviousness. A *prima facie* case of “obviousness requires a suggestion of all limitations in a claim.” *CFMT, Inc. v. Yieldup Intern. Corp.*, 349 F.3d 1333, 1342 (Fed. Cir. 2003) (citing *In re Royka*, 490 F.2d 981, 985 (CCPA 1974)). Shailubhai does not teach or suggest a formulation where the GCC agonist peptide has a chromatographic purity of no less than 91% after storage for at least three months. Nothing in Shailubhai teaches or suggests a formulation with such characteristics.

Nor do Currie, Mihranyan, the Avicel PH product instruction, or Fretzen cure the deficiencies of Shailubhai. None of the cited art teaches or suggests a formulation where the GCC agonist peptide has a chromatographic purity of no less than 91% after storage for at least three months. The cited art therefore does not provide a suggestion of all elements of claim 2. Nor do they provide any reason to arrive at the subject matter of claim 2. The Examiner has therefore not made a *prima facie* case of obviousness with respect to claim 2. Claims 2-11, 14-16, 20-25 and 42-44 depend from claim 2 and are therefore not obvious for the same reasons.

Further, Mihranyan teaches away from using low moisture grades of MCC (e.g. Avicel PH 112 and Avicel PH 103). The Examiner cites Mihranyan as suggesting the use of low moisture grades of commercial MCC. Office Action at page 6. However, Mihranyan notes that these low moisture grades of MCC appear hygroscopic. *See* page 433, second column, first paragraph. The skilled artisan looking for low moisture carriers to use in a formulation with a

moisture-sensitive compound would not have been motivated to select a carrier which has been demonstrated itself to attract water, especially for use in formulations that are stored for at least 3 months. Nor does the other cited art cure this deficiency. Indeed, the Avicel PH product instruction only provides data for moisture content of formulations comprising low-moisture grades of Avicel PH for up to 24 hours. *See* Figure 3 on page 10, and the Figure on page 16. There is no data disclosing moisture contents after longer periods of storage.

There is no objective reason provided by the teachings of Shailubhai and Currie in view of Mihranyan, the Avicel PH product instruction, and Fretzen that would lead the skilled artisan to combine these references, nor is there any evidence that the resultant combination of these references would lead the skilled artisan to arrive at the claimed invention with predictable results. These references, when considered in their entirety, fail to provide the skilled artisan with a reasonable expectation that an oral dosage formulation of the specifically recited Guanylate Cyclase C (GCC) agonist peptide and an inert low moisture carrier, as recited in claim 2, would have increased stability compared to any other inert carrier. This is especially true given the teaching of the instant specification and the surprising results detailed in the Comiskey Declaration submitted in this application February 19, 2015. As discussed in the Comiskey Declaration, the improved stability of the GCC agonist formulation comprising a low-moisture inert carrier shows superior results compared with formulations taught in the art and are more stable than expected compared to formulations comprising a regular-grade carrier. (Comiskey Decl. at ¶5) As described in the Comiskey Decl., formulations with a low moisture carrier decreased the amount of impurities dramatically, and more than had been expected. (Comiskey Decl. at ¶ 6 and 7). These data demonstrate that the claimed formulation provides an unexpectedly superior result relative to the formulations taught in the cited prior art.

In view of the foregoing, Applicants therefore respectfully request that the rejection be withdrawn.

**CONCLUSION**

In view of the foregoing, Applicant respectfully submits that no further impediments exist to the allowance of this application. However, the Examiner is requested to call the undersigned if any questions or comments arise.

The Director is hereby authorized to charge any appropriate fees, including those under 37 C.F.R. §§1.16, 1.17, and 1.21, that may be required by this paper, and to credit any overpayment, to Deposit Account No. 50-1283.

Dated: November 20, 2015

Respectfully submitted,

**COOLEY LLP**

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## Electronic Patent Application Fee Transmittal

<b>Application Number:</b>	13421769			
<b>Filing Date:</b>	15-Mar-2012			
<b>Title of Invention:</b>	Formulations of Guanylate Cyclase C Agonists and Methods of Use			
<b>First Named Inventor/Applicant Name:</b>	Stephen Comiskey			
<b>Filer:</b>	Anne Elizabeth Fleckenstein			
<b>Attorney Docket Number:</b>	SYPA-009X01US 321994-2142			
Filed as Small Entity				
<b>Filing Fees for Utility under 35 USC 111(a)</b>				
<b>Description</b>	<b>Fee Code</b>	<b>Quantity</b>	<b>Amount</b>	<b>Sub-Total in USD(\$)</b>
<b>Basic Filing:</b>				
<b>Pages:</b>				
<b>Claims:</b>				
<b>Miscellaneous-Filing:</b>				
<b>Petition:</b>				
<b>Patent-Appeals-and-Interference:</b>				
<b>Post-Allowance-and-Post-Issuance:</b>				
<b>Extension-of-Time:</b>				

Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Extension - 3 months with \$0 paid	2253	1	700	700
<b>Miscellaneous:</b>				
Request for Continued Examination	2801	1	600	600
<b>Total in USD (\$)</b>				<b>1300</b>

## Electronic Acknowledgement Receipt

<b>EFS ID:</b>	24142480
<b>Application Number:</b>	13421769
<b>International Application Number:</b>	
<b>Confirmation Number:</b>	3135
<b>Title of Invention:</b>	Formulations of Guanylate Cyclase C Agonists and Methods of Use
<b>First Named Inventor/Applicant Name:</b>	Stephen Comiskey
<b>Customer Number:</b>	58249
<b>Filer:</b>	Anne Elizabeth Fleckenstein
<b>Filer Authorized By:</b>	
<b>Attorney Docket Number:</b>	SYPA-009X01US 321994-2142
<b>Receipt Date:</b>	20-NOV-2015
<b>Filing Date:</b>	15-MAR-2012
<b>Time Stamp:</b>	15:58:27
<b>Application Type:</b>	Utility under 35 USC 111(a)

### Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	\$1300
RAM confirmation Number	2754
Deposit Account	501283
Authorized User	COOLEY LLP

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 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	Request for Continued Examination (RCE)	SYPA_009_X01US_RCE.pdf	156464 db3ecde9443972223df3c78c78859a4085d726a4	no	2

**Warnings:**

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**Information:**

2	Amendment Submitted/Entered with Filing of CPA/RCE	SYPA_009_X01US_Response.pdf	156649 699bee9dab3b8db245170c923cbb43c97507602f	no	10
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**Warnings:**

**Information:**

3	Fee Worksheet (SB06)	fee-info.pdf	32335 775ed4803e503b841597afcd623d5b7eaa31d051	no	2
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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**

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**New International Application Filed with the USPTO as a Receiving Office**

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

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<b>PATENT APPLICATION FEE DETERMINATION RECORD</b> Substitute for Form PTO-875	Application or Docket Number <b>13/421,769</b>	Filing Date <b>03/15/2012</b>	<input type="checkbox"/> To be Mailed
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ENTITY:  LARGE  SMALL  MICRO

**APPLICATION AS FILED – PART I**

FOR	NUMBER FILED	NUMBER EXTRA	RATE (\$)	FEE (\$)
<input type="checkbox"/> BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	
<input type="checkbox"/> SEARCH FEE (37 CFR 1.16(k), (l), or (m))	N/A	N/A	N/A	
<input type="checkbox"/> EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X \$ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X \$ =	
<input type="checkbox"/> APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is \$310 (\$155 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).			
<input type="checkbox"/> 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	

**APPLICATION AS AMENDED – PART II**

	(Column 1)	(Column 2)	(Column 3)	PRESENT EXTRA	RATE (\$)	ADDITIONAL FEE (\$)
<b>AMENDMENT</b>	<b>11/20/2015</b>	CLAIMS REMAINING AFTER AMENDMENT	HIGHEST NUMBER PREVIOUSLY PAID FOR			
	Total (37 CFR 1.16(i))	* 44	Minus	** 44	= 0	X \$40 = 0
	Independent (37 CFR 1.16(h))	* 3	Minus	***3	= 0	X \$210 = 0
	<input type="checkbox"/> Application Size Fee (37 CFR 1.16(s))					
<input type="checkbox"/> FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
					TOTAL ADD'L FEE	<b>0</b>

	(Column 1)	(Column 2)	(Column 3)	PRESENT EXTRA	RATE (\$)	ADDITIONAL FEE (\$)
<b>AMENDMENT</b>		CLAIMS REMAINING AFTER AMENDMENT	HIGHEST NUMBER PREVIOUSLY PAID FOR			
	Total (37 CFR 1.16(i))	*	Minus	**	=	X \$ =
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X \$ =
	<input type="checkbox"/> Application Size Fee (37 CFR 1.16(s))					
<input type="checkbox"/> FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
					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.

LIE  
 /MARSHA RICHARDS/

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**SHEET 1 OF 1**

<b>INFORMATION DISCLOSURE STATEMENT LIST</b> (Use as many sheets as necessary)	Complete if Known	
	Application Number	13/421,769
	Filing Date	March 15, 2012
	First Named Inventor	Stephen Comiskey
	Art Unit	1676
	Examiner Name	Jia-Hai Lee
	Attorney Docket Number	SYPA-009/X001US 321994-2142

**U.S. PATENT DOCUMENTS**

Examiner Initials*	Cite No. <sup>1</sup>	Document Number Number-Kind Code <sup>2</sup> (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	1.	2015/0366935 A1	12-24-2015	Comiskey et al.	

<b>Examiner Signature:</b>		<b>Date Considered</b>	
EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.			

\*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. <sup>1</sup> Applicant's unique citation designation number (optional). <sup>2</sup> See Kinds Codes of USPTO Patent Documents at [www.uspto.gov](http://www.uspto.gov) or MPEP 901.04. <sup>3</sup> Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). <sup>4</sup> For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. <sup>5</sup> Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. <sup>6</sup> Applicant is to place a check mark here if English language Translation is attached.

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 2 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, 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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<b>EFS ID:</b>	24496419
<b>Application Number:</b>	13421769
<b>International Application Number:</b>	
<b>Confirmation Number:</b>	3135
<b>Title of Invention:</b>	Formulations of Guanylate Cyclase C Agonists and Methods of Use
<b>First Named Inventor/Applicant Name:</b>	Stephen Comiskey
<b>Customer Number:</b>	58249
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<b>Filer Authorized By:</b>	Anne Elizabeth Fleckenstein
<b>Attorney Docket Number:</b>	SYPA-009X01US 321994-2142
<b>Receipt Date:</b>	30-DEC-2015
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<b>Time Stamp:</b>	19:48:25
<b>Application Type:</b>	Utility under 35 USC 111(a)

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### File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Transmittal Letter	009_X01US_IDS.pdf	78971 <small>ec322655009e90c1959a6e855a439670bba8cb09</small>	no	2

### Warnings:

### Information:

2	Information Disclosure Statement (IDS) Form (SB08)	009_X01US_SB08.pdf	161690	no	1
			52ef83cf86ba3ef4d1db94a119e1e6bb1aa1982a		

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**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.**

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**New International Application Filed with the USPTO as a Receiving Office**

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**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In Re Application of: COMISKEY, Stephen, Confirmation No.: 3135  
et al.

Application No.: 13/421,769 Group Art Unit: 1676

Filed: March 15, 2012 Examiner: Jia-Hai LEE

FOR: **FORMULATIONS OF GUANYLATE CYCLASE C AGONISTS AND METHODS OF USE**

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**VIA EFS**

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

**INFORMATION DISCLOSURE STATEMENT UNDER 37 C.F.R. §1.97(b)**

In accordance with the duty of disclosure set forth in 37 C.F.R. §1.56, Applicant(s) hereby submits the following information in conformance with 37 C.F.R. §§1.97 and 1.98.

- Pursuant to 37 C.F.R. §1.98, a copy of each non-US patent document cited in the attached Form PTO/SB/08 is enclosed.
- No copies of the publications listed on the attached Form PTO/SB/08 are being provided pursuant to 37 C.F.R. §1.98(d) because the publications were previously cited by or submitted to the Office in prior Application Serial No. \_\_\_\_\_ to which the above-identified application claims priority under 35 U.S.C. §120.
- No copies of any U.S. patents or U.S. patent application publications listed on the attached Form PTO/SB/08 are being provided pursuant to 37 C.F.R. §1.98.
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