(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
7 April 2011 (07.04.2011)

PCT

(10) International Publication Number
WO 2011/039634 A2

(51) International Patent Classification:
C12N 9/00 (2006.01)

(21) International Application Number:
PCT/IB2010/002589

(22) International Filing Date:
29 September 2010 (29.09.2010)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/246,847 29 September 2009 (29.09.2009) US

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR), OAPI (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 (Rule 48.2(g))*

WO 2011/039634 A2

(54) **Title**: HYDROLYSIS OF MANNOSE-1-PHOSPHO-6-MANNOSE LINKAGE TO PHOSPHO-6-MANNOSE

(57) **Abstract**: Described herein are methods and genetically engineered cells useful for uncapping a mannose-6-phosphate residue on an oligosaccharide.

HYDROLYSIS OF MANNOSE-1-PHOSPHO-6-MANNOSE LINKAGE TO PHOSPHO-6-MANNOSE

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims priority to U.S. Application Serial No. 61/246,847, filed on September 29, 2009. The disclosure of the prior application is incorporated by reference in its entirety.

TECHNICAL FIELD

The invention relates to methods of hydrolyzing mannose-1-phospho-6-mannose linkages on glycoproteins, and more particularly, to using a mannosidase to hydrolyze mannose-1-phospho-6-mannose linkages to uncap the phospho-6-mannose residues on the glycoprotein.

BACKGROUND

High performance expression systems are required to produce most biopharmaceuticals (e.g., recombinant proteins) currently under development. The biological activity of many of these biopharmaceuticals is dependent on their post-translational modification (e.g., phosphorylation or glycosylation). A yeast-based expression system combines the ease of genetic manipulation and fermentation of a microbial organism with the capability to secrete and to modify proteins. However, recombinant glycoproteins produced in yeast cells exhibit mainly heterogeneous high-mannose and hyper-mannose glycan structures, which can be detrimental to protein function, downstream processing, and subsequent therapeutic use, particularly where glycosylation plays a biologically significant role.

U.S. Application Serial No. 12/062,469 is incorporated by reference in its entirety.

SUMMARY

The present invention is based, at least in part, on the discovery of a mannosidase that is capable of hydrolyzing mannose-1-phospho-6-mannose linkages on glycoproteins. As such, the mannosidase can be used to obtain glycoproteins containing uncapped

terminal mannose-6-phosphate residues. *In vitro* and *in vivo* methods of obtaining such glycoproteins are described herein. Genetically engineered cells can be used in the methods to produce target molecules having uncapped terminal mannose-6-phosphate residues.

In one aspect, this document features a method for uncapping a mannose-6-phosphate residue on an oligosaccharide. The method includes providing the oligosaccharide having a mannose-1-phospho-6-mannose linkage; and contacting the oligosaccharide with a mannosidase capable of hydrolyzing the mannose-1-phospho-6-mannose linkage to phospho-6-mannose. The contacting step can be performed using a purified mannosidase, a recombinant mannosidase, a cell lysate containing the recombinant mannosidase, or a fungal cell containing the recombinant mannosidase. The mannosidase can include a targeting sequence. The oligosaccharide can be attached to a protein (e.g., a human protein expressed in a fungal organism).

In another aspect, this document features a method of producing a target protein having terminal phospho-6-mannose residues. The method includes providing a fungal cell genetically engineered to include a nucleic acid encoding a mannosidase, the mannosidase capable of hydrolyzing a mannose-1-phospho-6-mannose linkage to phospho-6-mannose; and introducing into the cell a nucleic acid encoding a target protein, wherein the cell produces the target protein comprising the terminal phospho-6-mannose residues.

This document also features a method of producing a target protein having terminal phospho-6-mannose residues in a fungal organism. The method includes providing a fungal cell genetically engineered to include a nucleic acid encoding a mannosidase capable of hydrolyzing a mannose-1-phospho-6-mannose linkage to phospho-6-mannose, wherein the fungal cell further includes a nucleic acid encoding a target protein; and isolating the target protein having the terminal phospho-6-mannose residues. The fungal cell further can include a nucleic acid encoding a polypeptide capable of promoting mannosyl phosphorylation and/or can be genetically engineered to be deficient in OCH1 activity.

This document also features an isolated fungal cell genetically engineered to produce glycoproteins comprising terminal phospho-6-mannose residues. The fungal cell

includes a nucleic acid encoding a mannosidase, wherein expression of the mannosidase in the fungal cell produces glycoproteins comprising the terminal phospho-6-mannose residues. The fungal cell further can include a nucleic acid encoding a target glycoprotein protein.

In another aspect, this document features a substantially pure culture of *Yarrowia lipolytica*, *Pichia pastoris*, *Hansenula polymorpha*, *Arxula adeninivorans*, *Pichia methanolica*, *Oogataea minuta*, or *Aspergillus niger* cells, a substantial number of which are genetically engineered to produce glycoproteins comprising a terminal phospho-6-mannose residue, the cells comprising a nucleic acid encoding a mannosidase capable of hydrolyzing a mannose-1-phospho-6-mannose linkage to phospho-6-mannose.

In any of the embodiments described herein, the fungal organism can be *Yarrowia lipolytica* or *Arxula adeninivorans*. The fungal organism can be a methylotrophic yeast such as *Pichia pastoris*, *Pichia methanolica*, *Oogataea minuta*, or *Hansenula polymorpha*. The fungal organism can be a filamentous fungus (e.g., a filamentous fungus selected from the group consisting of *Aspergillus caesiellus, Aspergillus candidus, Aspergillus carneus, Aspergillus clavatus, Aspergillus deflectus, Aspergillus flavus, Aspergillus fumigatus, Aspergillus glaucus, Aspergillus nidulans, Aspergillus niger, Aspergillus ochraceus, Aspergillus oryzae, Aspergillus parasiticus, Aspergillus penicilloides, Aspergillus restrictus, Aspergillus sojae, Aspergillus sydowi, Aspergillus tamari, Aspergillus terreus, Aspergillus ustus,* and *Aspergillus versicolor*).

In any of embodiments described herein, the protein can be a pathogen protein, a lysosomal protein, a growth factor, a cytokine, a chemokine, an antibody or antigen-binding fragment thereof, or a fusion protein. The lysosomal protein can be a lysosomal enzyme (e.g., a lysosomal enzyme associated with a lysosomal storage disorder (LSD) such as acid alpha glucosidase or alpha galactosidase). The LSD can be Fabry's disease, mucopolysaccharidosis I, Farber disease, Gaucher disease, GM1-gangliosidosis, Tay-Sachs disease, Sandhoff disease, GM2 activator disease, Krabbe disease, metachromatic leukodystrophy, Niemann-Pick disease, Scheie disease, Hunter disease, Sanfilippo disease, Morquio disease, Maroteaux-Lamy disease, hyaluronidase deficiency, aspartylglucosaminuria, fucosidosis, mannosidosis, Schindler disease, sialidosis type 1, Pompe disease, Pycnodysostosis, ceroid lipofuscinosis, cholesterol ester storage disease,

Wolman disease, Multiple sulfatase deficiency, galactosialidosis, mucolipidosis, cystinosis, sialic acid storage disorder, chylomicron retention disease with Marinesco-Sjögren syndrome, Hermansky-Pudlak syndrome, Chediak-Higashi syndrome, Danon disease, or Geleophysic dysplasia. For example, the LSD can be Pompe disease or Fabry's disease.

In any of the embodiments described herein, for the mannosidase, the three dimensional protein coordinates of the atoms in the amino acid side chains located in the minimal catalytic center fall within 1.5 Å deviation of the coordinates of the equivalent atoms in FIG. 33.

In any of the embodiments described herein, the mannosidase can include an amino acid sequence having at least 90% identity(e.g., at least 95% or 98% identity) to the amino acid sequence set forth in residues 1 to 774 of SEQ ID NO:50 or to the amino acid sequence set forth in SEQ ID NO:50.

In any of the embodiments described herein, the mannosidase can include an amino acid sequence having (i) a GVGXXGXGG motif, where X is Gly, Ala, Ser, Thr, or Cys; (ii) a VRXE motif, where X is any amino acid other than Pro; (iii) an X_1YQGX_2 motif, where X_1 is Leu, Ile, Val, Ala, Phe, Tyr or Met, and X_2 is Thr, Ser, or Asn; or (iv) a GDXGN motif, where X can be any amino acid other than Pro.

In any of the embodiments described herein, the mannosidase can be a *C. cellulans*, *Streptomyces coelicolor*, or *Streptomyces lividans* mannosidase.

In any of the embodiments described herein, the fungal cell further can include a nucleic acid encoding a polypeptide capable of promoting mannosyl phosphorylation (e.g., a MNN4 polypeptide such as *Yarrowia lipolytica*, *S. cerevisiae*, *Ogataea minuta*, *Pichia pastoris*, or *C. albicans* polypeptide) and/or can be genetically engineered to be deficient in OCH1 activity. For example, the polypeptide capable of promoting mannosyl phosphorylation can be a *P. pastoris* PNO1 polypeptide.

In any of the embodiments described herein, the mannosidase can include a secretion signal and/or a targeting signal to target the mannosidase to an intracellular compartment. The target protein and the mannosidase can be co-secreted.

This document also features an isolated glycoprotein that includes terminal phospho-6-mannose residues, wherein the protein is produced by the methods described herein.

In yet another aspect, this document features a composition that includes a glycoprotein, wherein at least 47% of the N-glycans on the glycoprotein have terminal phospho-6-mannose residues. For example, at least 50%, 75%, 80%, 85%, or 90% of the N-glycans on the glycoprotein can have terminal phospho-6-mannose residues.

This document also features an isolated nucleic acid that includes a nucleotide sequence set forth in SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, or SEQ ID NO:14, or a nucleotide sequence that is at least 90% identical to SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, or SEQ ID NO:20. This document also features a vector that includes a promoter operably linked to such a nucleic acid, wherein the nucleic acid encodes a mannosidase. The nucleic acid further can include a secretion signal or targeting sequence to target the mannosidase to an intracellular compartment.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, the exemplary methods and materials are described below. All publications, patent applications, patents, Genbank® Accession Nos, and other references mentioned herein are incorporated by reference in their entirety. In case of conflict, the present application, including definitions, will control. The materials, methods, and examples are illustrative only and not intended to be limiting.

Other features and advantages of the invention will be apparent from the following detailed description, and from the claims.

Brief Description of the Drawings7

FIG. 1 is a schematic of the pYLTmAX and pYLTmAXMnn4 constructs.

FIG. 2 is a series of electroferograms depicting sugar analysis of MTLY60Δoch1(1 wild type copy of Mnn4), MTLY60Δoch1+Hp4dMnn4 (1WT +1 extra

copy of Mnn4) and MTLY60Δoch1+Hp4dMnn4+TEFMnn4. P represents the monophosphorylated peak, PP represents the diphosphorylated peak, and Man8 represents the $Man_8GlcNAc_2$ peak.

FIG. 3 is a schematic of mammalian and yeast glycan phosphorylation pathways. The mammalian glycan phosphorylation pathway involves addition of a phospho-GlcNAc catalyzed by GlcNAc-phosphotransferase to $Man_8GlcNAc_2$ glycans followed by decapping of the GlcNAc to expose the phosphate by an uncovering enzyme. In contrast, yeast glycan phosphorylation involves addition of a phospho-mannose to $Man_8GlcNAc_2$ glycans, but no endogenous enzyme is present to uncap the mannose to expose the phosphate.

FIG. 4 is a series of electroferograms depicting N-glycans derived from strain MTLY60Δoch1+Hp4dMnn4+TEFMnn4 treated for different time frames (7 hrs, 8 hrs, or overnight (ON)) with supernatants from *C. cellulans* medium.

FIG. 5 is a series of electroferograms depicting N-glycans derived from an MNN4 overexpressing strain treated with *C. cellulans* supernatant (SN) with and without phosphatase (CIP) incubation.

FIG. 6 is a graph of the absorbance units (mAU) of elution fractions at the indicated MW. Each elution fraction contained ~500 µl.

FIG. 7 is a representation of a SDS-polyacrylamide gel after electrophoresis of elution fractions from silica-based gel filtration (250 µl of each fraction was DOC/TCA precipitated). The boxed bands were cut out for peptide mass fingerprinting and de novo sequencing using tandem mass spectrometry (MS/MS).

FIG. 8A is the nucleotide sequence (SEQ ID NO:6) encoding CcMan1 (i.e., mannosidase candidate 1 from *C. Cellulans*) (on contig 1003), which was identified in the MS/MS de novo sequencing. FIG. 8B is the amino acid sequence (SEQ ID NO:7) of CcMan 1, including the signal sequence (in bold). The predicted molecular weight of the CcMan 1 polypeptide without the signal sequence is 92.6 kDa.

FIG. 9A is the nucleotide sequence (SEQ ID NO:8) encoding CcMan2 (on contig 774) and FIG. 9B is the amino acid sequence of CcMan2 (SEQ ID NO:9) with signal sequence (in bold). The predicted molecular weight of the CcMan2 polypeptide without the signal sequence is 121.6 kDa.

FIG. 10A is the nucleotide sequence (SEQ ID NO:10) encoding CcMan3 (on contig 774) and FIG. 10 B is the amino acid sequence of CcMan3 (SEQ ID NO:11) with signal sequence (in bold). The predicted molecular weight of the CcMan3 polypeptide without the signal sequence is 116 kDa.

FIG. 11A is the nucleotide sequence (SEQ ID NO:12) encoding CcMan4 (on contig 1237) and FIG. 11B is the amino acid sequence of CcMan4 (SEQ ID NO:13) with signal sequence (in bold). The predicted molecular weight of the CcMan4 polypeptide without the signal sequence is 184 kDa.

FIG. 12A is the nucleotide sequence (SEQ ID NO:14) encoding CcMan5 (on contig 896). FIG. 12B is the amino acid sequence of CcMan5 with signal sequence (in bold) (SEQ ID NO:15) and FIG. 12C is the amino acid sequence of CcMan5 without signal sequence (SEQ ID NO:50). The predicted molecular weight of the CcMan5 polypeptide without the signal sequence is 173 kDa.

FIG. 13 contains examples of expression plasmids for the expression of CcMan1-5 in the periplasm of *E. coli* (pET25-Man), as secreted proteins in *Yarrowia lipolytica* (pYLPSecCcMan1-5), as proteins targeted to the secretory pathway of *Yarrowia lipolytica*, tagged to the N-terminus (pYLPNtCcMan1-5) or tagged to the C-terminus (pYLPCtCcMan1-5).

FIG. 14 is the nucleotide sequence of CcMan1 that has been codon optimized for expression in *E. coli* (SEQ ID NO:16).

FIG. 15 is the nucleotide sequence of CcMan2 that has been codon optimized for expression *E. coli* (SEQ ID NO:17).

FIG. 16 is the nucleotide sequence of CcMan3 that has been codon optimized for expression in *E. coli* (SEQ ID NO:18).

FIG. 17 is the nucleotide sequence of CcMan4 that has been codon optimized for expression in *E. coli* (SEQ ID NO:19).

FIG. 18 is the nucleotide sequence of CcMan5 that has been codon optimized for expression in *E. coli* (SEQ ID NO:20).

FIG. 19 is a schematic of the pLSAH36 and pLSH36 vectors and the cloning strategy for introducing the *C. cellulans* genes into the vectors.

FIG. 20 is a series of electroferograms depicting analysis of the periplasmic fraction of CcMan4 and CcMan5 expressing *E. coli* cells. Analysis was performed using DNA sequencer-assisted, fluorophore-assisted carbohydrate electrophoresis (DSA-FACE). The first and second panels represent the dextran ladder and the sugars from RNaseB, respectively. The third panel is the untreated Mnn4 sugars with "P" corresponding to the mono mannophosphorylated $Man_8GlcNAc_2$ peak, "PP" corresponding to the double mannophosphorylated $Man_8GlcNAc_2$ peak, and "Man8" corresponding to the $Man_8GlcNAc_2$ peak. Panels 4 to 9 are the results obtained with Mnn4 glycans incubated with the indicated periplasm, with or without a subsequent calf intestinal phosphatase (CIP) digest.

FIG. 21 is a schematic alignment of CcMan4 (1759 AA) and CcMan5 (1650 AA) with Bt3990 (744 AA) and Bt2199 (739 AA) mannosidases described in Zhu *et al.*, *Nat. Chem. Biol.*, 6(2):125-32. Epub 2009 Dec 27 (2010).

FIG. 22 is a series of electroferograms depicting the analysis of the CcMan4 and CcMan5 enzymes obtained from expressing *E. coli* cells. Analysis was performed using DSA-FACE using MNN4 overexpressing strain derived glycans (referred to as MNN4 glycans or MNN4 sugars) as a substrate. The first panel represents the dextran ladder and the second panel represents the untreated Mnn4 sugars. In the third through sixth panels, the sugars were incubated with the CcMan4domain periplasmic fraction not induced, induced overnight at 18°C with IPTG, the CcMan5domain periplasmic fraction not induced, and induced overnight at 18°C with IPTG, respectively. The last panel represents the sugars from RNaseB.

FIG. 23 is a ribbon representation of $CcMan5_{1-774}$. $CcMan5_{1-744}$ consists of a N-terminal β-sandwich domain (residues 8-271; light gray), an α-helical linker (residues 272-290; black) and a (αα)6 barrel domain (residues 291-771; dark gray). The catalytic Ca2+ is shown as a sphere.

FIG. 24 is a ribbon representation of the $CcMan5_{1-774}$ protein backbone with side chains lining the substrate binding site shown in stick representation. Carbon, oxygen and nitrogen atoms are colored light gray, gray, and dark gray, respectively The Ca^{2+} ion and waters W1, W2, W3 and W4 in the catalytic center are shown as spheres.

FIG. 25 is a ribbon representation of the $CcMan5_{1-774}$ protein backbone with side chains lining the substrate binding site and the modeled position of mannose-1-phospho-6-mannose (labeled Man-P-Man) shown in stick representation. Carbon, oxygen and nitrogen atoms are coloured light gray, gray, and dark gray, respectively. The Ca2+ ion and water molecules W1, W2, W3 and W4 in the catalytic center are shown as spheres (for comparison, the positions of W2 and W3 which will be displaced by the substrate O2 and O3 hydroxyl groups are still shown). Yellow, red and black dashed lines indicate coordination bonds with Ca2+, H-bonds with the proposed nucleophilic water (W4) and H-binds with the -1 site mannose and phosphate, respectively. The -1 site mannose is modeled in its ground state chair conformation. During catalysis, its O2 hydroxyl will occupy a position nearer that seen for W2, in the equatorial coordination plane of Ca2+ ion, thereby leading to a distortion to a half-chair conformation in the mannose -1 ring and facilitating in line attack of the nucleophilic water (W4) on the C1 carbon (arrow).

FIG. 26A is the *Y. lipolytica* codon optimized nucleotide sequence encoding α-GalactosidaseA with lip2 pre sequence in bold and the Myc His tag underlined (SEQ ID NO:22). FIG. 26B is the amino acid sequence of α-GalactosidaseA with lip2 pre sequence in bold and the Myc His tag underlined (SEQ ID NO:23).

FIG. 27A is the codon optimized nucleotide sequence of human alpha glucosidase (GAA) with lip2 pre sequence in bold (SEQ ID NO:24). FIG. 27B is the amino acid sequence of human GAA with lip2 pre sequence in bold (SEQ ID NO:25), where the * represents the stop codon.

FIG. 28 is a schematic of a *Y. lipolytica* expression vector used for cloning of huGAA.

FIG. 29 is a series of electroferograms depicting analysis of treatment of huGAA with CcMan5 derived from the periplasmic fraction of *E. coli* cells. Analysis was performed using DSA-FACE.

FIG. 30 is a depiction of the minimal catalytic center of CcMan5. The numbering of equivalent residues in SEQ ID NO:50 is given in parenthesis. 1: Q (Q536); 2: N/D-E/Q (N588-Q589); 3: D/E (D355); 4: R (R405); 5: D/E-X-D/E (D660-X-D662); 6: G-G (G71-G72); and 7: T/S/G (T626).

FIG. 31 is an alignment of the amino acid sequence of CcMan5 (SEQ ID NO:50, the amino acid sequence set forth in SEQ ID NO:15 without the signal peptide) and 10 of its homologs using MUSCLE (MUltiple Sequence Comparison by Log-Expectation). NP_630514 *Streptomyces*, SEQ ID NO:26; ZP_02866543 *Clostridium*, SEQ ID NO:27; NP_812442 *Bacteroides*, SEQ ID NO:28; YP_003584502 *Zunongwangia*, SEQ ID NO:29; YP_003120664 *Chitinophaga* , SEQ ID NO:30; AAK22560 *Caulobacter*, SEQ ID NO:31; ACL94075 *Caulobacter* , SEQ ID NO:32; ACT03290 *Paenibacillus*, SEQ ID NO:33; ACU59240 *Chitinophaga*, SEQ ID NO:34; ACU05553 *Pedobacter*, SEQ ID NO:35.

FIG. 32 is an alignment of the amino acid sequence of CcMan5 (SEQ ID NO:50) and 19 of its homologs using MUSCLE. *Streptomyces* NP_630514, SEQ ID NO:26; *Streptomyces* ZP_02866543, SEQ ID NO:36, ZP_06527366 *Streptomyces*, SEQ ID NO:37; YP_003013376 Paenibacillus, SEQ ID NO:38; NP_812442 *Bacteroides*, SEQ ID NO:28; ZP_04848482 Bacteroides, SEQ ID NO:39; ZP_03677957 *Bacteroides*, SEQ ID NO:40; YP_003584502 *Zunongwangia*, SEQ ID NO:29; ZP_01061975 *Leeuwenhoekiella*, SEQ ID NO:41; ZP_07083984 *Sphingobacterium*, SEQ ID NO:42; YP_003120664 *Chitinophaga* , SEQ ID NO:30; ZP_01885202 *Pedobacter*, SEQ ID NO:43; ZP_02866543 *Clostridium*, SEQ ID NO:27; XP_367221 *Magnaporthe*, SEQ ID NO:44; ZP_07042437 *Bacteroides*, SEQ ID NO:45; ZP_05759807 *Bacteroides*, SEQ ID NO:46; ZP_05287524 *Bacteroides*, SEQ ID NO:47; ZP_06076108 *Bacteroides*, SEQ ID NO:48; YP_001302992 *Parabacteroides*, SEQ ID NO:49.

FIG. 33 contains the structural coordinates of the residues surrounding the active site of $CcMan5_{1-774}$.

FIG. 34 contains the protein C alpha atoms and the catalytic Ca2+ atoms of the two $CcMan5_{1-774}$ molecules in the asymmetric unit in PDB entry 2xsg and describes the overall fold of the protein.

DETAILED DESCRIPTION

In general, this document provides methods and materials for hydrolyzing mannose-1-phospho-6-mannose linkages on glycoproteins to produce target molecules (e.g., target proteins) having uncapped phospho-6-mannose (M6P) residues. The

methods and materials described herein are particularly useful for producing agents for treating patients with lysosomal storage disorders (LSDs), a diverse group of hereditary metabolic disorders characterized by the accumulation of storage products in the lysosomes due to impaired activity of catabolic enzymes involved in their degradation. The build-up of storage products leads to cell dysfunction and progressive clinical manifestations. Deficiencies in catabolic enzymes can be corrected by enzyme replacement therapy (ERT), provided that the administered enzyme can be targeted to the lysosomes of the diseased cells. Lysosomal enzymes typically are glycoproteins that are synthesized in the endoplasmic reticulum (ER), transported via the secretory pathway to the Golgi, and then recruited to the lysosomes. One way in which lysosomal enzymes are delivered to the lysosome is via a cation-dependent (CD) mannose 6-phosphate receptor (MPR). M6P terminal glycans are recognized in the trans-Golgi network (TGN) by two MPRs that mediate the sorting of lysosomal enzymes from the secretory pathway and deliver the enzyme to the lysosome. Using the methods and materials described herein, a microbial based production process can be used to obtain therapeutic proteins with uncapped M6P glycans, which can be delivered to lysosomes by exploiting the same M6P dependent pathway. Thus, the methods and materials described herein are useful for preparing glycoproteins for the treatment of metabolic disorders such as LSDs.

Mannosidases

This document provides isolated nucleic acids encoding mannosidase polypeptides capable of hydrolyzing terminal mannose-1-phospho-6-mannose linkages on oligosaccharides, as well as isolated mannosidases capable of hydrolyzing terminal mannose-1-phospho-6-mannose linkages on oligosaccharides. The terms "nucleic acid" and "polynucleotide" are used interchangeably herein, and refer to both RNA and DNA, including cDNA, genomic DNA, synthetic DNA, and DNA (or RNA) containing nucleic acid analogs. Polynucleotides can have any three-dimensional structure. A nucleic acid can be double-stranded or single-stranded (i.e., a sense strand or an antisense strand). Non-limiting examples of polynucleotides include genes, gene fragments, exons, introns, messenger RNA (mRNA), transfer RNA, ribosomal RNA, siRNA, micro-RNA, ribozymes, cDNA, recombinant polynucleotides, branched polynucleotides, plasmids,

vectors, isolated DNA of any sequence, isolated RNA of any sequence, nucleic acid probes, and primers, as well as nucleic acid analogs.

"Polypeptide" and "protein" are used interchangeably herein and mean any peptide-linked chain of amino acids, regardless of length or post-translational modification. Typically, a polypeptide described herein (e.g., a mannosidase or a target protein having uncapped M6P residues) is isolated when it constitutes at least 60%, by weight, of the total protein in a preparation, e.g., 60% of the total protein in a sample. In some embodiments, a polypeptide described herein consists of at least 75%, at least 90%, or at least 99%, by weight, of the total protein in a preparation.

An "isolated nucleic acid" refers to a nucleic acid that is separated from other nucleic acid molecules that are present in a naturally-occurring genome, including nucleic acids that normally flank one or both sides of the nucleic acid in a naturally-occurring genome (e.g., a yeast genome). The term "isolated" as used herein with respect to nucleic acids also includes any non-naturally-occurring nucleic acid sequence, since such non-naturally-occurring sequences are not found in nature and do not have immediately contiguous sequences in a naturally-occurring genome.

An isolated nucleic acid can be, for example, a DNA molecule, provided one of the nucleic acid sequences normally found immediately flanking that DNA molecule in a naturally-occurring genome is removed or absent. Thus, an isolated nucleic acid includes, without limitation, a DNA molecule that exists as a separate molecule (e.g., a chemically synthesized nucleic acid, or a cDNA or genomic DNA fragment produced by PCR or restriction endonuclease treatment) independent of other sequences as well as DNA that is incorporated into a vector, an autonomously replicating plasmid, a virus (e.g., any paramyxovirus, retrovirus, lentivirus, adenovirus, or herpes virus), or into the genomic DNA of a prokaryote or eukaryote. In addition, an isolated nucleic acid can include an engineered nucleic acid such as a DNA molecule that is part of a hybrid or fusion nucleic acid. A nucleic acid existing among hundreds to millions of other nucleic acids within, for example, cDNA libraries or genomic libraries, or gel slices containing a genomic DNA restriction digest, is not considered an isolated nucleic acid.

The term "exogenous" as used herein with reference to nucleic acid and a particular host cell refers to any nucleic acid that does not occur in (and cannot be

obtained from) that particular cell as found in nature. Thus, a non-naturally-occurring nucleic acid is considered to be exogenous to a host cell once introduced into the host cell. It is important to note that non-naturally-occurring nucleic acids can contain nucleic acid subsequences or fragments of nucleic acid sequences that are found in nature provided that the nucleic acid as a whole does not exist in nature. For example, a nucleic acid molecule containing a genomic DNA sequence within an expression vector is non-naturally-occurring nucleic acid, and thus is exogenous to a host cell once introduced into the host cell, since that nucleic acid molecule as a whole (genomic DNA plus vector DNA) does not exist in nature. Thus, any vector, autonomously replicating plasmid, or virus (e.g., retrovirus, adenovirus, or herpes virus) that as a whole does not exist in nature is considered to be non-naturally-occurring nucleic acid. It follows that genomic DNA fragments produced by PCR or restriction endonuclease treatment as well as cDNAs are considered to be non-naturally-occurring nucleic acid since they exist as separate molecules not found in nature. It also follows that any nucleic acid containing a promoter sequence and polypeptide-encoding sequence (e.g., cDNA or genomic DNA) in an arrangement not found in nature is non-naturally-occurring nucleic acid. A nucleic acid that is naturally-occurring can be exogenous to a particular cell. For example, an entire chromosome isolated from a cell of yeast x is an exogenous nucleic acid with respect to a cell of yeast y once that chromosome is introduced into a cell of yeast.

A nucleic acid encoding a mannosidase can have at least 70% sequence identity (e.g., at least 80%, 85%, 90%, 95%, 97%, 98%, 99%, or 100% sequence identity) to a nucleotide sequence set forth in SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, or SEQ ID NO:14. In some embodiments, nucleic acids described herein can encode mannosidase polypeptides that have at least 70% (e.g., at least 75, 80, 85, 90, 95, 99, or 100 percent) identity to an amino acid sequence set forth in SEQ ID NOs: 7, 9, 11, 13, 15, 50. For example, a nucleic acid can encode a mannosidase having at least 90% (e.g., at least 95 or 98%) identity to the amino acid sequence set forth in SEQ ID NO:15 or SEQ ID NO:50, or a portion thereof. For example, a nucleic acid can encode a mannosidase having at least 90% identity to amino acid residues 1 to 774 of SEQ ID NO:50. The percent identity between a particular amino acid sequence and the amino acid sequence set forth in SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13,

SEQ ID NO:15, or SEQ ID NO:50 is determined as follows. First, the amino acid sequences are aligned using the BLAST 2 Sequences (Bl2seq) program from the stand-alone version of BLASTZ containing BLASTP version 2.0.14. This stand-alone version of BLASTZ can be obtained from Fish & Richardson's web site (e.g., www.fr.com/blast/) or the U.S. government's National Center for Biotechnology Information web site (www.ncbi.nlm.nih.gov). Instructions explaining how to use the Bl2seq program can be found in the readme file accompanying BLASTZ. Bl2seq performs a comparison between two amino acid sequences using the BLASTP algorithm. To compare two amino acid sequences, the options of Bl2seq are set as follows: -i is set to a file containing the first amino acid sequence to be compared (e.g., C:\seq1.txt); -j is set to a file containing the second amino acid sequence to be compared (e.g., C:\seq2.txt); -p is set to blastp; -o is set to any desired file name (e.g., C:\output.txt); and all other options are left at their default setting. For example, the following command can be used to generate an output file containing a comparison between two amino acid sequences: C:\Bl2seq –i c:\seq1.txt –j c:\seq2.txt –p blastp –o c:\output.txt. If the two compared sequences share homology, then the designated output file will present those regions of homology as aligned sequences. If the two compared sequences do not share homology, then the designated output file will not present aligned sequences. Similar procedures can be following for nucleic acid sequences except that blastn is used.

Once aligned, the number of matches is determined by counting the number of positions where an identical amino acid residue is presented in both sequences. The percent identity is determined by dividing the number of matches by the length of the full-length mannosidase polypeptide amino acid sequence followed by multiplying the resulting value by 100. For example, an amino acid sequence that has 700 matches when aligned with the sequence set forth in SEQ ID NO:7 is 77.8 percent identical to the sequence set forth in SEQ ID NO:7 (i.e., 700÷900*100 = 77.8).

It is noted that the percent identity value is rounded to the nearest tenth. For example, 78.11, 78.12, 78.13, and 78.14 is rounded down to 78.1, while 78.15, 78.16, 78.17, 78.18, and 78.19 is rounded up to 78.2. It also is noted that the length value will always be an integer.

It will be appreciated that a number of nucleic acids can encode a polypeptide

having a particular amino acid sequence. The degeneracy of the genetic code is well known to the art; i.e., for many amino acids, there is more than one nucleotide triplet that serves as the codon for the amino acid. For example, codons in the coding sequence for a given mannosidase polypeptide can be modified such that optimal expression in a particular species (e.g., bacteria or fungus) is obtained, using appropriate codon bias tables for that species. For example, the nucleic acids set forth in SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, or SEQ ID NO:14 can be codon optimized for *E. coli* expression as set forth in FIGs. 14-18 (see SEQ ID NOs:16-20).

Hybridization also can be used to assess homology between two nucleic acid sequences. A nucleic acid sequence described herein, or a fragment or variant thereof, can be used as a hybridization probe according to standard hybridization techniques. The hybridization of a probe of interest (e.g., a probe containing a portion of a CcMan5 nucleotide sequence) to DNA or RNA from a test source is an indication of the presence of DNA or RNA (e.g., a CcMan5 nucleotide sequence) corresponding to the probe in the test source. Hybridization conditions are known to those skilled in the art and can be found in Current Protocols in Molecular Biology, John Wiley & Sons, N.Y., 6.3.1-6.3.6, 1991. Moderate hybridization conditions are defined as equivalent to hybridization in 2X sodium chloride/sodium citrate (SSC) at 30°C, followed by a wash in 1 X SSC, 0.1% SDS at 50°C. Highly stringent conditions are defined as equivalent to hybridization in 6X sodium chloride/sodium citrate (SSC) at 45°C, followed by a wash in 0.2 X SSC, 0.1% SDS at 65°C.

Mannosidase polypeptides capable of hydrolyzing terminal mannose-1-phospho-6-mannose linkages on oligosaccharides also can be identified based on the three dimensional structure described herein for a portion of a mannosidase from *C. cellulans* (residues 1 to 774 of SEQ ID NO:50, also referred to as $CcMan5_{1-774}$). The three dimensional structure can be determined by, for example, X-ray diffraction of a crystal of $CcMan5_{1-774}$. Structural coordinates of $CcMan5_{1-774}$ (e.g., the coordinates of $CcMan5_{1-774}$ deposited with the Protein Data Bank (world wide web at PDB.org under PDB ID No. 2xs), the coordinates set forth in FIG. 33 for the catalytic center of CcMan5, or the coordinates set forth in FIG. 34 for the protein C alpha atoms and the catalytic Ca2+ atoms of the two $CcMan5_{1-774}$ molecules in the asymmetric unit in PDB entry 2xsg) are

useful for a number of applications, including, but not limited to, the characterization of a three dimensional structure of a mannosidase capable of hydrolyzing terminal mannose-1-phospho-6-mannose linkages on oligosaccharides, as well as the visualization, identification and characterization of regions of the mannosidase that are involved in acceptance of mannose-6-phosphate-alpha,1-mannose (hereafter referred to as Man-P-Man) as a substrate, and conferring its ability to hydrolyse Man-P-Man to produce a terminal phospho-6-mannose. "Structural coordinates" are the Cartesian coordinates corresponding to an atom's spatial relationship to other atoms in a molecule or molecular complex. Structural coordinates can be obtained using x-ray crystallography techniques or NMR techniques, or can be derived using molecular replacement analysis or homology modeling. Various software programs allow for the graphical representation of a set of structural coordinates to obtain a three dimensional representation of a molecule or molecular complex. The structural coordinates of the structures described herein can be modified from the original set provided in FIG. 33 or FIG. 34 by mathematical manipulation, such as by inversion or integer additions or subtractions. As such, it is recognized that the structural coordinates of the present invention are relative, and are in no way specifically limited by the actual x, y, z coordinates of FIG. 33 or FIG. 34.

As set forth in Example 8, the structure of $CcMan5_{1-774}$ consists of two domains, an N-terminal β-sandwich domain (residues 8 to 271 of SEQ ID NO:50) and a C-terminal (αα)6 barrel domain (residues 291 to 771 of SEQ ID NO:50), connected via an α-helical linker (residues 272 to 290 of SEQ ID NO:50). The interface between both domains gives shape to a shallow cavity that harbors a conserved catalytic Ca^{2+} ion and gives shape to the -1 substrate binding site (nomenclature as described by Davies *et al.*, *Biochem. J.* 321:557-9 (1997)) and the catalytic center. Residues 22, 25, 71, 72, 195, 196, 354, 405, 535, 536, 588, 589, 626, 658, 660, and 662 of SEQ ID NO: 50 form the substrate binding site.

The three dimensional structure of $CcMan5_{1-774}$ can be characterized in part, or all, using the structural coordinates of PDB ID No. 2xs, or an extract of which that is presented in FIG. 33, comprising the residues surrounding the active site of $CcMan5_{1-774}$, or an extract of which that is presented in FIG. 34, comprising the protein C alpha atoms and the catalytic Ca2+ atoms of the two $CcMan5_{1-774}$ molecules in the asymmetric unit in

PDB entry 2xsg, and describing the overall fold of the protein. For example, the three-dimensional structure of $CcMan5_{1-774}$ can be characterized by the structural coordinates of amino acid residues 7 to 771 according to PDB ID No. 2xs, ± a root mean square deviation from the conserved backbone atoms of said amino acids of not more than 2Å. In some embodiments, the three dimensional structure of $CcMan5_{1-774}$ comprises the complete structural coordinates of the amino acids according to PDB ID No. 2xs, ± a root mean square deviation from the conserved backbone atoms of said amino acids of not more than 2Å (e.g., not more than 1.5 Å, 1.0Å or 0.5Å). As used herein, "root mean square deviation" is the square root of the arithmetic mean of the squares of the deviations from the mean, and is a way of expressing deviation or variation from the structural coordinates described herein. The present disclosure includes all embodiments comprising conservative substitutions of the noted amino acid residues resulting in same structural coordinates within the stated root mean square deviation.

The structural coordinates provided herein can be used to characterize a three dimensional structure of a mannosidase polypeptide. From such a structure, substrate binding sites, for example, can be computationally visualized, identified and characterized based on the surface structure of the molecule, surface charge, steric arrangement, the presence of reactive amino acids, regions of hydrophobicity or hydrophilicity, etc.

In order to use the structural coordinates generated for a structure described herein as set forth in FIGs. 33, FIG. 34, or PDB ID No. 2xs, the relevant coordinates can be displayed as, or converted to, a three dimensional shape or graphical representation. Software programs are commercially available that are capable of generating three dimensional graphical representations of molecules or portions thereof from a set of structural coordinates. Examples of commercially available software programs include, without limitation, the following: GRID (Oxford University, Oxford, UK) ; MCSS (Molecular Simulations, San Diego, CA); AUTODOCK (Scripps Research Institute, La Jolla, CA); DOCK (University of California, San Francisco, CA); Flo99 (Thistlesoft, Morris Township, NJ); Ludi (Molecular Simulations, San Diego, CA); QUANTA (Molecular Simulations, San Diego, CA); Insight (Molecular Simulations, San Diego,

CA); SYBYL (TRIPOS, Inc., St. Louis. MO); and LEAPFROG (TRIPOS, Inc., St. Louis, MO).

The structural coordinates described herein can be used with standard homology modeling techniques in order to determine the unknown three-dimensional structure of a molecule or molecular complex. Homology modeling involves constructing a model of an unknown structure using structural coordinates of one or more related protein molecules, molecular complexes or parts thereof. Homology modeling can be conducted by fitting common or homologous portions of the protein whose three dimensional structure is to be solved to the three dimensional structure of homologous structural elements in the known molecule, specifically using the relevant (i.e., homologous) structural coordinates provided by FIGs. 33 and 34 herein. Homology may be determined using amino acid sequence identity, homologous secondary structure elements, and/or homologous tertiary folds. Homology modeling can include rebuilding part or all of a three dimensional structure with replacement of amino acids (or other components) by those of the related structure to be solved. Accordingly, a three dimensional structure for the unknown molecule may be generated using the three dimensional structure of $CcMan5_{1-774}$ described herein, and refined using a number of techniques well known in the art.

Based on the three dimensional structure described herein, substitutions can be made in some of the atoms or side groups of $CcMan5_{1-774}$ or other mannosidases in order to improve or modify its selectivity. For example, CcMan5 contains a non-acidic residue at positions 536 and 588, which may allow the mannosidase to tolerate the phosphate linkage to the anomeric oxygen in Man-P-Man substrates. As such, corresponding residues in other mannosidases can be changed to non-acidic residues to increase the ability of the mannosidase to accept Man-P-Man substrates.

Other mannosidase polypeptide candidates suitable for use herein can be identified by analysis of nucleotide and polypeptide sequence alignments. For example, performing a query on a database of nucleotide or polypeptide sequences can identify homologs and/or orthologs of mannosidase polypeptides. Sequence analysis can involve BLAST, Reciprocal BLAST, or PSI-BLAST analysis of nonredundant databases using known mannosidase amino acid sequences. Those polypeptides in the database that have

greater than 40% sequence identity can be identified as candidates for further evaluation for suitability as a mannosidase polypeptide. Amino acid sequence similarity allows for conservative amino acid substitutions, such as substitution of one hydrophobic residue for another or substitution of one polar residue for another. If desired, manual inspection of such candidates can be carried out in order to narrow the number of candidates to be further evaluated. Manual inspection can be performed by selecting those candidates that appear to have domains suspected of being present in mannosidases capable of hydrolyzing terminal mannose-1-phospho-6-mannose linkages, e.g., one or more (e.g., 1, 2, 3, 4 or more) conserved domains or functional regions (e.g., substrate binding cavity). Such domains can include a glycine-rich motif GVGXXGXGG, where X is Gly, Ser, Thr, Val, Ala, Cys or Gln (or other amino acid with a small side chain). This motif is found at residues 69-77 of SEQ ID NO:50. This region makes a loop that provides essential hydrogen bonds to the -1 mannose and phosphate-binding subsite in the active site of the enzyme.

Another example of a conserved motif includes a VRXE motif, where Arg (R) makes a hydrogen bond to the -1 ring and possibly the +1 ring, Glu (E) is in a salt bridge to this R residue, probably shaping this motif; and X is Trp or any of the 20 amino acids except Pro. This motif is found at residues 404-407 of SEQ ID NO:50.

A suitable motif also can be an X_1YQGX_2 motif, where X_1 can be Leu, Ile, Val Ala, Phe, Tyr or Met, and X_2 can be Thr, Ser or Asn. This motif is found at residues 534-538 of SEQ ID NO:50. The Gln (Q) in this motif is important as an E is present in mannosidases that do not have the ability to hydrolyze terminal mannose-1-phospho-6-mannose linkages on oligosaccharides. The Tyr (Y) in this motif also is thought to be important for the +1 site formation.

In addition, a region defined by residues 22, 25, 71, 72, 195, 196, 354, 405, 535, 536, 588, 589, 626, 658, 660, and 662 of SEQ ID NO:50 forms the substrate binding cavity of CcMan5. As a minimal requirement, G71, G72, D355, R405, Q536, N588, Q589, T626, D660, D662 form the catalytic center, where N588, Q589 and D660 are involved in coordinating the catalytic Ca2+ ion, D662 and D660 are involved in activating the nucleophilic water, Q536 stabilizes the anomeric oxygen during the transition state and G71, G71, D355, R405 and T626 are involved in substrate binding at

the -1 site. See FIG. 30 for a representation of this minimal catalytic center. As such, a mannosidase can be selected as a candidate mannosidase capable of hydrolyzing terminal mannose-1-phospho-6-mannose linkages when the three dimensional protein coordinates of the atoms in the amino acid side chains located in the minimal catalytic center (e.g., as set forth in FIG. 30) fall within 1.5 Å deviation of the coordinates of the equivalent atoms in FIG. 33.

A conserved motif also can be a GDXGN motif in the N-terminal domain of the protein, where X can be any amino acid except P. This motif is found at residues 21-25 of SEQ ID NO:50 and forms part of the substrate binding pocket of the enzyme as shown in FIG. 24. In particular, the side chains of the D and N line the substrate binding cavity and may shape an alternative subpocket to bind the +1 mannose.

As set forth in Example 14, performing a query on a database of polypeptide sequences identified homologs of CcMan5 in the following organisms: *Streptomyces coelicolor* (GenBank Accession No. NP_630514), *Streptomyces lividans* (GenBank Accession No. ZP_05522540); *Streptomyces lividans* (GenBank Accession No. ZP_06527366); *Clostridium spiroforme* (GenBank Accession No. ZP_02866543), *Bacteroides thetaiotaomicron* (GenBank Accession No. NP_812442), *Zunongwangia profunda* (GenBank Accession No. YP_003584502); *Chitinophaga pinensis* (GenBank Accession No. YP_003120664); *Paenibacillus sp* (GenBank Accession No. YP_003013376); *Bacteroides sp.* (GenBank Accession No. ZP_04848482); *Bacteroides cellulosilyticus* (GenBank Accession No. ZP_03677957); *Leeuwenhoekiella blandensis* (GenBank Accession No. ZP_01061975); *Sphingobacterium spiritivorum* (GenBank Accession No. ZP_07083984); and *Pedobacter sp.* (GenBank Accession No. ZP_01885202). The mannosidases from *Streptomyces coelicolor* and *Streptomyces lividans* are similar (66% sequence identity to the CcMan5 GH92 domain, with 501 identities over 765 aligned residues by BLASTP), not only in the above motifs but also in many the loops of the three dimensional structure.

Isolated nucleic acid molecules encoding mannosidase polypeptides can be produced by standard techniques. For example, polymerase chain reaction (PCR) techniques can be used to obtain an isolated nucleic acid containing a nucleotide sequence described herein. PCR can be used to amplify specific sequences from DNA as

well as RNA, including sequences from total genomic DNA or total cellular RNA. Generally, sequence information from the ends of the region of interest or beyond is employed to design oligonucleotide primers that are identical or similar in sequence to opposite strands of the template to be amplified. Various PCR strategies also are available by which site-specific nucleotide sequence modifications can be introduced into a template nucleic acid. Isolated nucleic acids also can be chemically synthesized, either as a single nucleic acid molecule (e.g., using automated DNA synthesis in the 3' to 5' direction using phosphoramidite technology) or as a series of oligonucleotides. For example, one or more pairs of long oligonucleotides (e.g., >100 nucleotides) can be synthesized that contain the desired sequence, with each pair containing a short segment of complementarity (e.g., about 15 nucleotides) such that a duplex is formed when the oligonucleotide pair is annealed. DNA polymerase is used to extend the oligonucleotides, resulting in a single, double-stranded nucleic acid molecule per oligonucleotide pair, which then can be ligated into a vector. Isolated nucleic acids of the invention also can be obtained by mutagenesis of, e.g., a naturally occurring DNA.

This document also provides (i) biologically active variants and (ii) biologically active fragments or biologically active variants thereof, of the mannosidases described herein. Biologically active variants of mannosidases can contain additions, deletions, or substitutions relative to the sequences set forth in SEQ ID NOs: 7, 9, 11, 13, 15, or 50. Proteins with substitutions will generally have not more than 50 (e.g., not more than one, two, three, four, five, six, seven, eight, nine, ten, 12, 15, 20, 25, 30, 35, 40, or 50) conservative amino acid substitutions. A conservative substitution is the substitution of one amino acid for another with similar characteristics. Conservative substitutions include substitutions within the following groups: valine, alanine and glycine; leucine, valine, and isoleucine; aspartic acid and glutamic acid; asparagine and glutamine; serine, cysteine, and threonine; lysine and arginine; and phenylalanine and tyrosine. The non-polar hydrophobic amino acids include alanine, leucine, isoleucine, valine, proline, phenylalanine, tryptophan and methionine. The polar neutral amino acids include glycine, serine, threonine, cysteine, tyrosine, asparagine and glutamine. The positively charged (basic) amino acids include arginine, lysine and histidine. The negatively charged (acidic) amino acids include aspartic acid and glutamic acid. Any substitution of

one member of the above-mentioned polar, basic or acidic groups by another member of the same group can be deemed a conservative substitution. By contrast, a non-conservative substitution is a substitution of one amino acid for another with dissimilar characteristics. The sequence alignments set forth in FIGs. 31 and 32 provide numerous examples of amino acid substitutions that can be made.

Deletion variants can lack one, two, three, four, five, six, seven, eight, nine, ten, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 amino acid segments (of two or more amino acids) or non-contiguous single amino acids.

Additions (addition variants) include fusion proteins containing: (a) a mannosidase set forth in SEQ ID NOs: 7, 9, 11, 13, or 15, or a fragment thereof; and (b) internal or terminal (C or N) irrelevant or heterologous amino acid sequences. In the context of such fusion proteins, the term "heterologous amino acid sequences" refers to an amino acid sequence other than (a). A heterologous sequence can be, for example a sequence used for purification of the recombinant protein (e.g., FLAG, polyhistidine (e.g., hexahistidine), hemagluttanin (HA), glutathione-S-transferase (GST), or maltose-binding protein (MBP)). Heterologous sequences also can be proteins useful as diagnostic or detectable markers, for example, luciferase, green fluorescent protein (GFP), or chloramphenicol acetyl transferase (CAT). In some embodiments, the fusion protein contains a signal sequence from another protein. In certain host cells (e.g., yeast host cells), expression and/or secretion of the target protein can be increased through use of a heterologous signal sequence. In some embodiments, the fusion protein can contain a carrier (e.g., KLH) useful, e.g., in eliciting an immune response for antibody generation) or endoplasmic reticulum or Golgi apparatus retention signals. Heterologous sequences can be of varying length and in some cases can be a longer sequences than the full-length target proteins to which the heterologous sequences are attached.

Biologically active fragments or biologically active variants of the mannosidases have at least 40% (e.g., at least: 50%; 60%; 70%; 75%; 80%; 85%; 90%; 95%; 97%; 98%; 99%; 99.5%, or 100% or even greater) of the mannosidase activity (e.g., uncapping of M6P residues) of the wild-type, full-length, mature protein. For example, a biologically active fragment of a mannosidase can contain residues 1 to 774 of SEQ ID NO:50.

The mannosidases described herein can be used to produce molecules (e.g., target proteins) having uncapped terminal phospho-6-mannose (M6P) residues. The methods can be performed *in vitro* or *in vivo*.

In Vitro Methods of Uncapping M6P Residues

A mannosidase described herein can be recombinantly produced and used *in vitro* to uncap terminal M6P residues on oligosaccharides. To recombinantly produce a mannosidase, a vector is used that contains a promoter operably linked to nucleic acid encoding a mannosidase polypeptide. As used herein, a "promoter" refers to a DNA sequence that enables a gene to be transcribed. The promoter is recognized by RNA polymerase, which then initiates transcription. Thus, a promoter contains a DNA sequence that is either bound directly by, or is involved in the recruitment, of RNA polymerase. A promoter sequence can also include "enhancer regions," which are one or more regions of DNA that can be bound with proteins (namely, the trans-acting factors, much like a set of transcription factors) to enhance transcription levels of genes (hence the name) in a gene-cluster. The enhancer, while typically at the 5' end of a coding region, can also be separate from a promoter sequence and can be, e.g., within an intronic region of a gene or 3' to the coding region of the gene.

As used herein, "operably linked" means incorporated into a genetic construct (e.g., vector) so that expression control sequences effectively control expression of a coding sequence of interest.

Expression vectors can be introduced into host cells (e.g., by transformation or transfection) for expression of the encoded polypeptide, which then can be purified. Expression systems that can be used for small or large scale production of mannosidase polypeptides include, without limitation, microorganisms such as bacteria (e.g., *E. coli*) transformed with recombinant bacteriophage DNA, plasmid DNA, or cosmid DNA expression vectors containing the nucleic acid molecules, and fungal (e.g., *S. cerevisiae*, *Yarrowia lipolytica*, *Arxula adeninivorans*, *Pichia pastoris*, *Hansenula polymorpha*, or *Aspergillus*) transformed with recombinant fungal expression vectors containing the nucleic acid molecules. Useful expression systems also include insect cell systems infected with recombinant virus expression vectors (e.g., baculovirus) containing the

nucleic acid molecules, and plant cell systems infected with recombinant virus expression vectors (e.g., tobacco mosaic virus) or transformed with recombinant plasmid expression vectors (e.g., Ti plasmid) containing the nucleic acid molecules. Mannosidase polypeptides also can be produced using mammalian expression systems, which include cells (e.g., immortalized cell lines such as COS cells, Chinese hamster ovary cells, HeLa cells, human embryonic kidney 293 cells, and 3T3 L1 cells) harboring recombinant expression constructs containing promoters derived from the genome of mammalian cells (e.g., the metallothionein promoter) or from mammalian viruses (e.g., the adenovirus late promoter and the cytomegalovirus promoter), along with the nucleic acids described herein.

Typically, recombinant mannosidase polypeptides are tagged with a heterologous amino acid sequence such FLAG, polyhistidine (e.g., hexahistidine), hemagluttanin (HA), glutathione-S-transferase (GST), or maltose-binding protein (MBP) to aid in purifying the protein. Other methods for purifying proteins include chromatographic techniques such as ion exchange, hydrophobic and reverse phase, size exclusion, affinity, hydrophobic charge-induction chromatography, and the like (see, e.g., Scopes, Protein Purification: Principles and Practice, third edition, Springer-Verlag, New York (1993); Burton and Harding, *J. Chromatogr. A* 814:71-81 (1998)).

To produce molecules having uncapped terminal M6P residues *in vitro*, a target molecule containing a mannose-1-phospho-6 mannose linkage is contacted under suitable conditions with a purified mannosidase or a cell lysate containing a recombinantly produced mannosidase. The cell lysate can be from any genetically engineered cell, including a fungal cell, a plant cell, or animal cell. Non-limiting examples of animal cells include nematode, insect, plant, bird, reptile, and mammals such as a mouse, rat, rabbit, hamster, gerbil, dog, cat, goat, pig, cow, horse, whale, monkey, or human. Upon contacting the target molecule (e.g., an oligosaccharide or glycoprotein) with the purified mannosidase or cell lysate, the mannosidase hydrolyzes the mannose-1-phospho-6 mannose linkage and produces a target molecule having one or more uncapped terminal M6P residues. The methods described in Example 2 can be used to determine if the terminal M6P residues have been uncapped. Following processing by the mannosidase, the target molecule having uncapped terminal M6P residues can be isolated.

Suitable methods for obtaining cell lysates that preserve the activity or integrity of the mannosidase activity in the lysate can include the use of appropriate buffers and/or inhibitors, including nuclease, protease and phosphatase inhibitors that preserve or minimize changes in N-glycosylation activities in the cell lysate. Such inhibitors include, for example, chelators such as ethylenediamine tetraacetic acid (EDTA), ethylene glycol bis(P-aminoethyl ether) N,N,N1,Nl-tetraacetic acid (EGTA), protease inhibitors such as phenylmethylsulfonyl fluoride (PMSF), aprotinin, leupeptin, antipain and the like, and phosphatase inhibitors such as phosphate, sodium fluoride, vanadate and the like. Appropriate buffers and conditions for obtaining lysates containing enzymatic activities are described in, e.g., Ausubel et al. Current Protocols in Molecular Biology (Supplement 47), John Wiley & Sons, New York (1999); Harlow and Lane, Antibodies: A Laboratory Manual Cold Spring Harbor Laboratory Press (1988); Harlow and Lane, Using Antibodies: A Laboratory Manual, Cold Spring Harbor Press (1999); Tietz Textbook of Clinical Chemistry, 3rd ed. Burtis and Ashwood, eds. W.B. Saunders, Philadelphia, (1999).

A cell lysate can be further processed to eliminate or minimize the presence of interfering substances, as appropriate. If desired, a cell lysate can be fractionated by a variety of methods well known to those skilled in the art, including subcellular fractionation, and chromatographic techniques such as ion exchange, hydrophobic and reverse phase, size exclusion, affinity, hydrophobic charge-induction chromatography, and the like.

In some embodiments, a cell lysate can be prepared in which whole cellular organelles remain intact and/or functional. For example, a lysate can contain one or more of intact rough endoplasmic reticulum, intact smooth endoplasmic reticulum, or intact Golgi apparatus. Suitable methods for preparing lysates containing intact cellular organelles and testing for the functionality of the organelles are described in, e.g., Moreau *et al.* (1991) *J. Biol. Chem.* 266(7):4329-4333; Moreau *et al.* (1991) *J. Biol. Chem.* 266(7):4322-4328; Rexach *et al.* (1991) *J. Cell Biol.* 114(2):219-229; and Paulik *et al.* (1999) *Arch. Biochem. Biophys.* 367(2):265-273.

Target molecules, as used herein, refer to any molecule containing terminal mannose-1-phospho-6 mannose linkages or any molecule, when expressed in a cell of

fungal origin, that contains mannose-1-phospho-6 mannose linkages. Suitable target proteins include pathogen proteins such as tetanus toxoid or diptheria toxoid; viral surface proteins such as cytomegalovirus (CMV) glycoproteins B, H and gCIII, human immunodeficiency virus 1 (HIV-1) envelope glycoproteins, Rous sarcoma virus (RSV) envelope glycoproteins, herpes simplex virus (HSV) envelope glycoproteins, Epstein Barr virus (EBV) envelope glycoproteins, varicella-zoster virus (VZV) envelope glycoproteins, human papilloma virus (HPV) envelope glycoproteins, Influenza virus glycoproteins, and Hepatitis family surface antigen; lysosomal proteins (e.g., acid alpha glucosidase, alpha galatosidase, glucocerebrosidase, cerebrosidase, or galactocerebrosidase); insulin; glucagons; growth factors; cytokines; chemokines; and antibodies or fragments thereof. Growth factors include, e.g., vascular endothelial growth factor (VEGF), Insulin-like growth factor (IGF), bone morphogenic protein (BMP), Granulocyte-colony stimulating factor (G-CSF), Granulocyte-macrophage colony stimulating factor (GM-CSF), Nerve growth factor (NGF); a Neurotrophin, Platelet-derived growth factor (PDGF), Erythropoietin (EPO), Thrombopoietin (TPO), Myostatin (GDF-8), Growth Differentiation factor-9 (GDF9), basic fibroblast growth factor (bFGF or FGF2), Epidermal growth factor (EGF), Hepatocyte growth factor (HGF). Cytokines include, for example, interleukins such as IL-1 to IL-33 (e.g., IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-12, IL-13, or IL-15)). Chemokines include, e.g., I-309, TCA-3, MCP-1, MIP-1α, MIP-1β, RANTES, C10, MRP-2, MARC, MCP-3, MCP-2, MRP-2, CCF18, MIP-1γ, Eotaxin, MCP-5, MCP-4, NCC-1, Ckβ10, HCC-1, Leukotactin-1, LEC, NCC-4, TARC, PARC, or Eotaxin-2. Also included are tumor glycoproteins (e.g., tumor-associated antigens), for example, carcinoembryonic antigen (CEA), human mucins, HER-2/neu, and prostate-specific antigen (PSA) [Henderson and Finn, *Advances in Immunology*, 62, pp. 217-56 (1996)].

In some embodiments, the target protein can be one associated with a lysosomal storage disorder, which target proteins include, e.g., acid alpha glucosidase, alpha galactosidase, alpha-L-iduronidase, beta-D-galactosidase, beta-glucosidase, beta-hexosaminidase, beta-D-mannosidase, alpha-L-fucosidase, arylsulfatase B, arylsulfatase A, alpha-N-acetylgalactosaminidase, aspartylglucosaminidase, iduronate-2-sulfatase, alpha-glucosaminide-N-acetyltransferase, beta-D-glucoronidase, hyaluronidase, alpha-L-

mannosidase, alpha-neuraminidase, phosphotransferase, acid lipase, acid ceramidase, sphingomyelinase, thioesterase, cathepsin K, and lipoprotein lipase.

In some embodiments, the target proteins are fusion proteins in which the target protein is fused to another polypeptide sequence, or to a polymer, a carrier, an adjuvant, an immunotoxin, or a detectable (e.g., fluorescent, luminescent, or radioactive) moiety. For example, a target protein can be joined to a polymer such as polyethyleneglycol to increase the molecular weight of small proteins and/or increase circulation residence time.

In Vivo Methods of Uncapping M6P Residues

Genetically engineered cells described herein can be used to produce target molecules containing uncapped M6P residues. For example, a cell based method can include the steps of introducing into a fungal cell genetically engineered to include a nucleic acid encoding a mannosidase, a nucleic acid encoding a target molecule, wherein the cell produces the target molecule containing uncapped terminal M6P residues. In some embodiments, the nucleic acids encoding the mannosidase and target molecule contain a secretion sequence such that the mannosidase and target molecule are co-secreted.

Genetically engineered cells described herein contain a nucleic acid encoding a mannosidase and are useful for producing one or more target molecules having uncapped terminal M6P residues. Cells suitable for *in vivo* production of uncapped M6P residues can be of fungal origin, including *Yarrowia lipolytica*, *Arxula adeninivorans*, methylotrophic yeast (such as a methylotrophic yeast of the genus *Candida*, *Hansenula*, *Oogataea*, *Pichia* or *Torulopsis*) or filamentous fungi of the genus *Aspergillus*, *Trichoderma*, *Neurospora*, *Fusarium*, or *Chrysosporium*. Exemplary fungal species include, without limitation, *Pichia anomala, Pichia bovis, Pichia canadensis, Pichia carsonii, Pichia farinose, Pichia fermentans, Pichia fluxuum, Pichia membranaefaciens, Pichia membranaefaciens, Candida valida, Candida albicans, Candida ascalaphidarum, Candida amphixiae, Candida Antarctica, Candida atlantica, Candida atmosphaerica, Candida blattae, Candida carpophila, Candida cerambycidarum, Candida chauliodes, Candida corydalis, Candida dosseyi, Candida dubliniensis, Candida ergatensis, Candida*

fructus, Candida glabrata, Candida fermentati, Candida guilliermondii, Candida haemulonii, Candida insectamens, Candida insectorum, Candida intermedia, Candida jeffresii, Candida kefyr, Candida krusei, Candida lusitaniae, Candida lyxosophila, Candida maltosa, Candida membranifaciens, Candida milleri, Candida oleophila, Candida oregonensis, Candida parapsilosis, Candida quercitrusa, Candida shehatea, Candida temnochilae, Candida tenuis, Candida tropicalis, Candida tsuchiyae, Candida sinolaborantium, Candida sojae, Candida viswanathii, Candida utilis, Oogataea minuta, Pichia membranaefaciens, Pichia silvestris, Pichia membranaefaciens, Pichia chodati, Pichia membranaefaciens, Pichia menbranaefaciens, Pichia minuscule, Pichia pastoris, Pichia pseudopolymorpha, Pichia quercuum, Pichia robertsii, Pichia saitoi, Pichia silvestrisi, Pichia strasburgensis, Pichia terricola, Pichia vanriji, Pseudozyma Antarctica, Rhodosporidium toruloides, Rhodotorula glutinis, Saccharomyces bayanus, Saccharomyces bayanus, Saccharomyces momdshuricus, Saccharomyces uvarum, Saccharomyces bayanus, Saccharomyces cerevisiae, Saccharomyces bisporus, Saccharomyces chevalieri, Saccharomyces delbrueckii, Saccharomyces exiguous, Saccharomyces fermentati, Saccharomyces fragilis, Saccharomyces marxianus, Saccharomyces mellis, Saccharomyces rosei, Saccharomyces rouxii, Saccharomyces uvarum, Saccharomyces willianus, Saccharomycodes ludwigii, Saccharomycopsis capsularis, Saccharomycopsis fibuligera, Saccharomycopsis fibuligera, Endomyces hordei, Endomycopsis fobuligera. Saturnispora saitoi, Schizosaccharomyces octosporus, Schizosaccharomyces pombe, Schwanniomyces occidentalis, Torulaspora delbrueckii, Torulaspora delbrueckii, Saccharomyces dairensis, Torulaspora delbrueckii, Torulaspora fermentati, Saccharomyces fermentati, Torulaspora delbrueckii, Torulaspora rosei, Saccharomyces rosei,Torulaspora delbrueckii, Saccharomyces rosei, Torulaspora delbrueckii, Saccharomyces delbrueckii, Torulaspora delbrueckii, Saccharomyces delbrueckii, Zygosaccharomyces mongolicus, Dorulaspora globosa, Debaryomyces globosus, Torulopsis globosa, Trichosporon cutaneum, Trigonopsis variabilis, Williopsis californica, Williopsis saturnus, Zygosaccharomyces bisporus, Zygosaccharomyces bisporus, Debaryomyces disporua. Saccharomyces bisporas, Zygosaccharomyces bisporus, Saccharomyces bisporus, Zygosaccharomyces mellis, Zygosaccharomyces priorianus, Zygosaccharomyces rouxiim, Zygosaccharomyces rouxii, Zygosaccharomyces

barkeri, Saccharomyces rouxii, Zygosaccharomyces rouxii, Zygosaccharomyces major, Saccharomyces rousii, Pichia anomala, Pichia bovis, Pichia Canadensis, Pichia carsonii, Pichia farinose, Pichia fermentans, Pichia fluxuum, Pichia membranaefaciens, Pichia pseudopolymorpha, Pichia quercuum, Pichia robertsii, Pseudozyma Antarctica, Rhodosporidium toruloides, Rhodosporidium toruloides, Rhodotorula glutinis, Saccharomyces bayanus, Saccharomyces bayanus, Saccharomyces bisporus, Saccharomyces cerevisiae, Saccharomyces chevalieri, Saccharomyces delbrueckii, Saccharomyces fermentati, Saccharomyces fragilis, Saccharomycodes ludwigii, Schizosaccharomyces pombe, Schwanniomyces occidentalis, Torulaspora delbrueckii, Torulaspora globosa, Trigonopsis variabilis, Williopsis californica, Williopsis saturnus, Zygosaccharomyces bisporus, Zygosaccharomyces mellis, or *Zygosaccharomyces rouxii*. Exemplary filamentous fungi include various species of *Aspergillus* including, but not limited to, *Aspergillus caesiellus, Aspergillus candidus, Aspergillus carneus, Aspergillus clavatus, Aspergillus deflectus, Aspergillus flavus, Aspergillus fumigatus, Aspergillus glaucus, Aspergillus nidulans, Aspergillus niger, Aspergillus ochraceus, Aspergillus oryzae, Aspergillus parasiticus, Aspergillus penicilloides, Aspergillus restrictus, Aspergillus sojae, Aspergillus sydowi, Aspergillus tamari, Aspergillus terreus, Aspergillus ustus,* or *Aspergillus versicolor*. Such cells, prior to the genetic engineering as specified herein, can be obtained from a variety of commercial sources and research resource facilities, such as, for example, the American Type Culture Collection (Rockville, MD). Target molecules include proteins such as any of the target proteins described herein (see above).

Genetic engineering of a cell can include, in addition to an exogenous nucleic acid encoding a mannosidase, one or more genetic modifications such as: (i) deletion of an endogenous gene encoding an Outer CHain elongation (OCH1) protein; (ii) introduction of a recombinant nucleic acid encoding a polypeptide capable of promoting mannosyl phosphorylation (e.g, a MNN4 polypeptide from *Yarrowia lipolytica*, *S. cerevisiae*, *Ogataea minuta*, *Pichia pastoris*, or *C. albicans*, or PNO1 polypeptide from *P. pastoris*) to increasing phosphorylation of mannose residues; (iii) introduction or expression of an RNA molecule that interferes with the functional expression of an OCH1 protein; (iv) introduction of a recombinant nucleic acid encoding a wild-type (e.g., endogenous or

exogenous) protein having a N-glycosylation activity (i.e., expressing a protein having an N-glycosylation activity); (v) introduction of a recombinant nucleic acid encoding a target molecule described above; or (v) altering the promoter or enhancer elements of one or more endogenous genes encoding proteins having N-glycosylation activity to thus alter the expression of their encoded proteins. RNA molecules include, e.g., small-interfering RNA (siRNA), short hairpin RNA (shRNA), anti-sense RNA, or micro RNA (miRNA). Genetic engineering also includes altering an endogenous gene encoding a protein having an N-glycosylation activity to produce a protein having additions (e.g., a heterologous sequence), deletions, or substitutions (e.g., mutations such as point mutations; conservative or non-conservative mutations). Mutations can be introduced specifically (e.g., by site-directed mutagenesis or homologous recombination) or can be introduced randomly (for example, cells can be chemically mutagenized as described in, e.g., Newman and Ferro-Novick (1987) *J. Cell Biol.* 105(4):1587.

Genetic modifications described herein can result in one or more of (i) an increase in one or more activities in the genetically modified cell, (ii) a decrease in one or more activities in the genetically modified cell, or (iii) a change in the localization or intracellular distribution of one or more activities in the genetically modified cell. It is understood that an increase in the amount of a particular activity (e.g., promoting mannosyl phosphorylation) can be due to overexpressing one or more proteins capable of promoting mannosyl phosphorylation, an increase in copy number of an endogenous gene (e.g., gene duplication), or an alteration in the promoter or enhancer of an endogenous gene that stimulates an increase in expression of the protein encoded by the gene. A decrease in one or more particular activities can be due to overexpression of a mutant form (e.g., a dominant negative form), introduction or expression of one or more interfering RNA molecules that reduce the expression of one or more proteins having a particular activity, or deletion of one or more endogenous genes that encode a protein having the particular activity.

To disrupt a gene by homologous recombination, a "gene replacement" vector can be constructed in such a way to include a selectable marker gene. The selectable marker gene can be operably linked, at both 5' and 3' end, to portions of the gene of sufficient length to mediate homologous recombination. The selectable marker can be one of any

number of genes which either complement host cell auxotrophy or provide antibiotic resistance, including URA3, LEU2 and HIS3 genes. Other suitable selectable markers include the CAT gene, which confers chloramphenicol resistance to yeast cells, or the lacZ gene, which results in blue colonies due to the expression of β-galactosidase. Linearized DNA fragments of the gene replacement vector are then introduced into the cells using methods well known in the art (see below). Integration of the linear fragments into the genome and the disruption of the gene can be determined based on the selection marker and can be verified by, for example, Southern blot analysis. A selectable marker can be removed from the genome of the host cell by, e.g., Cre-loxP systems (see below).

Alternatively, a gene replacement vector can be constructed in such a way as to include a portion of the gene to be disrupted, which portion is devoid of any endogenous gene promoter sequence and encodes none or an inactive fragment of the coding sequence of the gene. An “inactive fragment" is a fragment of the gene that encodes a protein having, e.g., less than about 10% (e.g., less than about 9%, less than about 8%, less than about 7%, less than about 6%, less than about 5%, less than about 4%, less than about 3%, less than about 2%, less than about 1%, or 0%) of the activity of the protein produced from the full-length coding sequence of the gene. Such a portion of the gene is inserted in a vector in such a way that no known promoter sequence is operably linked to the gene sequence, but that a stop codon and a transcription termination sequence are operably linked to the portion of the gene sequence. This vector can be subsequently linearized in the portion of the gene sequence and transformed into a cell. By way of single homologous recombination, this linearized vector is then integrated in the endogenous counterpart of the gene.

Expression vectors can be autonomous or integrative. A recombinant nucleic acid (e.g., one encoding a mannosidase) can be in introduced into the cell in the form of an expression vector such as a plasmid, phage, transposon, cosmid or virus particle. The recombinant nucleic acid can be maintained extrachromosomally or it can be integrated into the yeast cell chromosomal DNA. Expression vectors can contain selection marker genes encoding proteins required for cell viability under selected conditions (e.g., URA3, which encodes an enzyme necessary for uracil biosynthesis or TRP1, which encodes an enzyme required for tryptophan biosynthesis) to permit detection and/or selection of

those cells transformed with the desired nucleic acids (see, e.g., U.S. Pat. No. 4,704,362). Expression vectors can also include an autonomous replication sequence (ARS). For example, U.S. Pat. No. 4,837,148 describes autonomous replication sequences which provide a suitable means for maintaining plasmids in *Pichia pastoris*.

Integrative vectors are disclosed, e.g., in U.S. Pat. No. 4,882,279. Integrative vectors generally include a serially arranged sequence of at least a first insertable DNA fragment, a selectable marker gene, and a second insertable DNA fragment. The first and second insertable DNA fragments are each about 200 (e.g., about 250, about 300, about 350, about 400, about 450, about 500, or about 1000 or more) nucleotides in length and have nucleotide sequences which are homologous to portions of the genomic DNA of the species to be transformed. A nucleotide sequence containing a gene of interest (e.g., a gene encoding a protein having N-glycosylation activity) for expression is inserted in this vector between the first and second insertable DNA fragments whether before or after the marker gene. Integrative vectors can be linearized prior to yeast transformation to facilitate the integration of the nucleotide sequence of interest into the host cell genome.

An expression vector can feature a recombinant nucleic acid under the control of a yeast (e.g., *Yarrowia lipolytica, Arxula adeninivorans, P. pastoris,* or other suitable fungal species) promoter, which enables them to be expressed in fungal cells. Suitable yeast promoters include, e.g., ADC1, TPI1, ADH2, hp4d, POX, and Gal10 (see, e.g., Guarente *et al.* (1982) *Proc. Natl. Acad. Sci. USA* 79(23):7410) promoters. Additional suitable promoters are described in, e.g., Zhu and Zhang (1999) *Bioinformatics* 15(7-8):608-611 and U.S. Patent No. 6,265,185.

A promoter can be constitutive or inducible (conditional). A constitutive promoter is understood to be a promoter whose expression is constant under the standard culturing conditions. Inducible promoters are promoters that are responsive to one or more induction cues. For example, an inducible promoter can be chemically regulated (e.g., a promoter whose transcriptional activity is regulated by the presence or absence of a chemical inducing agent such as an alcohol, tetracycline, a steroid, a metal, or other small molecule) or physically regulated (e.g., a promoter whose transcriptional activity is regulated by the presence or absence of a physical inducer such as light or high or low

temperatures). An inducible promoter can also be indirectly regulated by one or more transcription factors that are themselves directly regulated by chemical or physical cues.

It is understood that other genetically engineered modifications can also be conditional. For example, a gene can be conditionally deleted using, e.g., a site-specific DNA recombinase such as the Cre-loxP system (see, e.g., Gossen *et al.* (2002) *Ann. Rev. Genetics* 36:153-173 and U.S. Application Publication No. 20060014264).

A recombinant nucleic acid can be introduced into a cell described herein using a variety of methods such as the spheroplast technique or the whole-cell lithium chloride yeast transformation method. Other methods useful for transformation of plasmids or linear nucleic acid vectors into cells are described in, for example, U.S. Patent No. 4,929,555; Hinnen *et al.* (1978) *Proc. Nat. Acad. Sci. USA* 75:1929; Ito *et al.* (1983) *J. Bacteriol.* 153:163; U.S. Patent No. 4,879,231; and Sreekrishna *et al.* (1987) *Gene* 59:115, the disclosures of each of which are incorporated herein by reference in their entirety. Electroporation and PEG1000 whole cell transformation procedures may also be used, as described by Cregg and Russel, Methods in Molecular Biology: Pichia Protocols, Chapter 3, Humana Press, Totowa, N.J., pp. 27-39 (1998).

Transformed fungal cells can be selected for by using appropriate techniques including, but not limited to, culturing auxotrophic cells after transformation in the absence of the biochemical product required (due to the cell's auxotrophy), selection for and detection of a new phenotype, or culturing in the presence of an antibiotic which is toxic to the yeast in the absence of a resistance gene contained in the transformants. Transformants can also be selected and/or verified by integration of the expression cassette into the genome, which can be assessed by, e.g., Southern blot or PCR analysis.

Prior to introducing the vectors into a target cell of interest, the vectors can be grown (e.g., amplified) in bacterial cells such as *Escherichia coli* (*E. coli*) as described above. The vector DNA can be isolated from bacterial cells by any of the methods known in the art which result in the purification of vector DNA from the bacterial milieu. The purified vector DNA can be extracted extensively with phenol, chloroform, and ether, to ensure that no *E. coli* proteins are present in the plasmid DNA preparation, since these proteins can be toxic to mammalian cells.

In some embodiments, the genetically engineered fungal cell lacks the OCH1 gene or gene products (e.g., mRNA or protein) thereof, and is deficient in OCH1 activity. In some embodiments, the genetically engineered cell expresses a polypeptide capable of promoting mannosyl phosphorylation (e.g., a MNN4 polypeptide from *Yarrowia lipolytica*, *S. cerevisiae*, *Ogataea minuta*, *Pichia pastoris*, or *C. albicans*, or a PNO1 polypeptide from *P. pastoris*). For example, the fungal cell can express a MNN4 polypeptide from *Y. lipolytica* (Genbank® Acccession Nos: XM_503217, Genolevures Ref: YALI0D24101g). In some embodiments, the genetically engineered cell is deficient in OCH1 activity and expresses a polypeptide capable of promoting mannosyl phosphorylation.

Following uncapping of the M6P residues, the target molecule can be isolated. In some embodiments, the target molecule is maintained within the yeast cell and released upon cell lysis. In some embodiments, the target molecule is secreted into the culture medium via a mechanism provided by a coding sequence (either native to the exogenous nucleic acid or engineered into the expression vector), which directs secretion of the molecule from the cell. The presence of the uncapped target molecule in the cell lysate or culture medium can be verified by a variety of standard protocols for detecting the presence of the molecule. For example, where the altered target molecule is a protein, such protocols can include, but are not limited to, immunoblotting or radioimmunoprecipitation with an antibody specific for the altered target protein (or the target protein itself), binding of a ligand specific for the altered target protein (or the target protein itself), or testing for a specific enzyme activity of the altered target protein (or the target protein itself).

In the target molecules produced using the methods described herein, at least 47% (e.g., at least 50, 55, 60, 65, 70, 75, 80, 85, or 90%) of the N-glycans on the glycoprotein have terminal phospho-6-mannose residues. The percentage of N-glycans having terminal phospho-6-mannose residues can be estimated from the peak areas in the DSA-FACE electropherograms. See Example 13.

In some embodiments, following isolation, the uncapped target molecule can be attached to a heterologous moiety, e.g., using enzymatic or chemical means. A "heterologous moiety" refers to any constituent that is joined (e.g., covalently or non-

covalently) to the altered target molecule, which constituent is different from a constituent originally present on the altered target molecule. Heterologous moieties include, e.g., polymers, carriers, adjuvants, immunotoxins, or detectable (e.g., fluorescent, luminescent, or radioactive) moieties. In some embodiments, an additional N-glycan can be added to the altered target molecule.

Methods for detecting glycosylation of a target molecule include DNA sequencer-assisted (DSA), fluorophore-assisted carbohydrate electrophoresis (FACE) or surface-enhanced laser desorption/ionization time-of-flight mass spectrometry (SELDI-TOF MS). For example, an analysis can utilize DSA-FACE in which, for example, glycoproteins are denatured followed by immobilization on, e.g., a membrane. The glycoproteins can then be reduced with a suitable reducing agent such as dithiothreitol (DTT) or β-mercaptoethanol. The sulfhydryl groups of the proteins can be carboxylated using an acid such as iodoacetic acid. Next, the N-glycans can be released from the protein using an enzyme such as N-glycosidase F. N-glycans, optionally, can be reconstituted and derivatized by reductive amination. The derivatized N-glycans can then be concentrated. Instrumentation suitable for N-glycan analysis includes, e.g., the ABI PRISM® 377 DNA sequencer (Applied Biosystems). Data analysis can be performed using, e.g., GENESCAN® 3.1 software (Applied Biosystems). Optionally, isolated mannoproteins can be further treated with one or more enzymes to confirm their N-glycan status. Additional methods of N-glycan analysis include, e.g., mass spectrometry (e.g., MALDI-TOF-MS), high-pressure liquid chromatography (HPLC) on normal phase, reversed phase and ion exchange chromatography (e.g., with pulsed amperometric detection when glycans are not labeled and with UV absorbance or fluorescence if glycans are appropriately labeled). See also Callewaert *et al.* (2001) *Glycobiology* 11(4):275-281 and Freire *et al.* (2006) *Bioconjug. Chem.* 17(2):559-564.

Cultures of Engineered Cells

This document also provides a substantially pure culture of any of the genetically engineered cells described herein. As used herein, a "substantially pure culture" of a genetically engineered cell is a culture of that cell in which less than about 40% (i.e., less than about : 35%; 30%; 25%; 20%; 15%; 10%; 5%; 2%; 1%; 0.5%; 0.25%; 0.1%; 0.01%;

0.001%; 0.0001%; or even less) of the total number of viable cells in the culture are viable cells other than the genetically engineered cell, e.g., bacterial, fungal (including yeast), mycoplasmal, or protozoan cells. The term "about" in this context means that the relevant percentage can be 15% percent of the specified percentage above or below the specified percentage. Thus, for example, about 20% can be 17% to 23%. Such a culture of genetically engineered cells includes the cells and a growth, storage, or transport medium. Media can be liquid, semi-solid (e.g., gelatinous media), or frozen. The culture includes the cells growing in the liquid or in/on the semi-solid medium or being stored or transported in a storage or transport medium, including a frozen storage or transport medium. The cultures are in a culture vessel or storage vessel or substrate (e.g., a culture dish, flask, or tube or a storage vial or tube).

The genetically engineered cells described herein can be stored, for example, as frozen cell suspensions, e.g., in buffer containing a cryoprotectant such as glycerol or sucrose, as lyophilized cells. Alternatively, they can be stored, for example, as dried cell preparations obtained, e.g., by fluidized bed drying or spray drying, or any other suitable drying method.

Metabolic Disorders

Molecules having uncapped terminal M6P residues can be used to treat a variety of metabolic disorders. A metabolic disorder is one that affects the production of energy within individual human (or animal) cells. Most metabolic disorders are genetic, though some can be "acquired" as a result of diet, toxins, infections, etc. Genetic metabolic disorders are also known as inborn errors of metabolism. In general, the genetic metabolic disorders are caused by genetic defects that result in missing or improperly constructed enzymes necessary for some step in the metabolic process of the cell. The largest classes of metabolic disorders are disorders of carbohydrate metabolism, disorders of amino acid metabolism, disorders of organic acid metabolism (organic acidurias), disorders of fatty acid oxidation and mitochondrial metabolism, disorders of porphyrin metabolism, disorders of purine or pyrimidine metabolism, disorders of steroid metabolism disorders of mitochondrial function, disorders of peroxisomal function, and lysosomal storage disorders (LSDs).

Examples of metabolic disorders that can be treated through the administration of one or more molecules having uncapped terminal M6P residues (or pharmaceutical compositions of the same) can include hereditary hemochromatosis, oculocutaneous albinism, protein C deficiency, type I hereditary angioedema, congenital sucrase-isomaltase deficiency, Crigler-Najjar type II, Laron syndrome, hereditary Myeloperoxidase, primary hypothyroidism, congenital long QT syndrome, tyroxine binding globulin deficiency, familial hypercholesterolemia, familial chylomicronemia, abeta-lipoproteinema, low plasma lipoprotein A levels, hereditary emphysema with liver injury, congenital hypothyroidism, osteogenesis imperfecta, hereditary hypofibrinogenemia, alpha-1antichymotrypsin deficiency, nephrogenic diabetes insipidus, neurohypophyseal diabetes insipidus, adenosine deaminase deficiency, Pelizaeus Merzbacher disease, von Willebrand disease type IIA, combined factors V and VIII deficiency, spondylo-epiphyseal dysplasia tarda, choroideremia, I cell disease, Batten disease, ataxia telangiectasias, ADPKD-autosomal dominant polycystic kidney disease, microvillus inclusion disease, tuberous sclerosis, oculocerebro-renal syndrome of Lowe, amyotrophic lateral sclerosis, myelodysplastic syndrome, Bare lymphocyte syndrome, Tangier disease, familial intrahepatic cholestasis, X-linked adreno-leukodystrophy, Scott syndrome, Hermansky-Pudlak syndrome types 1 and 2, Zellweger syndrome, rhizomelic chondrodysplasia puncta, autosomal recessive primary hyperoxaluria, Mohr Tranebjaerg syndrome, spinal and bullar muscular atrophy, primary ciliary diskenesia (Kartagener's syndrome), giantism and acromegaly, galactorrhea, Addison's disease, adrenal virilism, Cushing's syndrome, ketoacidosis, primary or secondary aldosteronism, Miller Dieker syndrome, lissencephaly, motor neuron disease, Usher's syndrome, Wiskott-Aldrich syndrome, Optiz syndrome, Huntington's disease, hereditary pancreatitis, anti-phospholipid syndrome, overlap connective tissue disease, Sjögren's syndrome, stiff-man syndrome, Brugada syndrome, congenital nephritic syndrome of the Finnish type, Dubin-Johnson syndrome, X-linked hypophosphosphatemia, Pendred syndrome, persistent hyperinsulinemic hypoglycemia of infancy, hereditary spherocytosis, aceruloplasminemia, infantile neuronal ceroid lipofuscinosis, pseudoachondroplasia and multiple epiphyseal, Stargardt-like macular dystrophy, X-linked Charcot-Marie-Tooth disease, autosomal dominant retinitis

pigmentosa, Wolcott-Rallison syndrome, Cushing's disease, limb-girdle muscular dystrophy, mucoploy-saccharidosis type IV, hereditary familial amyloidosis of Finish, Anderson disease, sarcoma, chronic myelomonocytic leukemia, cardiomyopathy, faciogenital dysplasia, Torsion disease, Huntington and spinocerebellar ataxias, hereditary hyperhomosyteinemia, polyneuropathy, lower motor neuron disease, pigmented retinitis, seronegative polyarthritis, interstitial pulmonary fibrosis, Raynaud's phenomenon, Wegner's granulomatosis, preoteinuria, CDG-Ia, CDG-Ib, CDG-Ic, CDG-Id, CDG-Ie, CDG-If, CDG-IIa, CDG-IIb, CDG-IIc, CDG-IId, Ehlers-Danlos syndrome, multiple exostoses, Griscelli syndrome (type 1 or type 2), or X-linked non-specific mental retardation. In addition, metabolic disorders can also include lysosomal storage disorders such as, but not limited to, Fabry disease, mucopolysaccharidosis I, Farber disease, Gaucher disease, GM_1-gangliosidosis, Tay-Sachs disease, Sandhoff disease, GM_2 activator disease, Krabbe disease, metachromatic leukodystrophy, Niemann-Pick disease (types A, B, and C), Scheie disease, Hunter disease, Sanfilippo disease, Morquio disease, Maroteaux-Lamy disease, hyaluronidase deficiency, aspartylglucosaminuria, fucosidosis, mannosidosis, Schindler disease, sialidosis type 1, Pompe disease, Pycnodysostosis, ceroid lipofuscinosis, cholesterol ester storage disease, Wolman disease, Multiple sulfatase deficiency, galactosialidosis, mucolipidosis (types II ,III, and IV), cystinosis, sialic acid storage disorder, chylomicron retention disease with Marinesco-Sjögren syndrome, Hermansky-Pudlak syndrome, Chediak-Higashi syndrome, Danon disease, or Geleophysic dysplasia.

Symptoms of a metabolic disorder are numerous and diverse and can include one or more of, e.g., anemia, fatigue, bruising easily, low blood platelets, liver enlargement, spleen enlargement, skeletal weakening, lung impairment, infections (e.g., chest infections or pneumonias), kidney impairment, progressive brain damage, seizures, extra thick meconium, coughing, wheezing, excess saliva or mucous production, shortness of breath, abdominal pain, occluded bowel or gut, fertility problems, polyps in the nose, clubbing of the finger/toe nails and skin, pain in the hands or feet, angiokeratoma, decreased perspiration, corneal and lenticular opacities, cataracts, mitral valve prolapse and/or regurgitation, cardiomegaly, temperature intolerance, difficulty walking, difficulty swallowing, progressive vision loss, progressive hearing loss, hypotonia, macroglossia,

areflexia, lower back pain, sleep apnea, orthopnea, somnolence, lordosis, or scoliosis. It is understood that due to the diverse nature of the defective or absent proteins and the resulting disease phenotypes (e.g., symptomatic presentation of a metabolic disorder), a given disorder will generally present only symptoms characteristic to that particular disorder. For example, a patient with Fabry disease can present a particular subset of the above-mentioned symptoms such as, but not limited to, temperature intolerance, corneal whirling, pain, skin rashes, nausea, or dirarrhea. A patient with Gaucher syndrome can present with splenomegaly, cirrhosis, convulsions, hypertonia, apnea, osteoporosis, or skin discoloration.

In addition to the administration of one or more uncapped molecules described herein, a metabolic disorder can also be treated by proper nutrition and vitamins (e.g., cofactor therapy), physical therapy, and pain medications.

Depending on the specific nature of a given metabolic disorder, a patient can present these symptoms at any age. In many cases, symptoms can present in childhood or in early adulthood. For example, symptoms of Fabry disease can present at an early age, e.g., at 10 or 11 years of age.

As used herein, a subject "at risk of developing a metabolic disorder" is a subject that has a predisposition to develop a disorder, i.e., a genetic predisposition to develop metabolic disorder as a result of a mutation in a enzyme such as acid alpha glucosidase, alpha galactosidase, alpha-L-iduronidase, beta-D-galactosidase, beta-glucosidase, beta-hexosaminidase, beta-D-mannosidase, alpha-L-fucosidase, arylsulfatase B, arylsulfatase A, alpha-N-acteylgalactosaminidase, aspartylglucosaminidase, iduronate-2-sulfatase, alpha-glucosaminide-N-acetyltransferase, beta-D-glucoronidase, hyaluronidase, alpha-L-mannosidase, alpha-neurominidase, phosphotransferase, acid lipase, acid ceramidase, sphinogmyelinase, thioesterase, cathepsin K, or lipoprotein lipase. Clearly, subjects "at risk of developing a metabolic disorder" are not all the subjects within a species of interest.

A subject "suspected of having a disorder" is one having one or more symptoms of a metabolic disorder such as any of those described herein.

Pharmaceutical Compositions and Methods of Treatment

A target molecule having uncapped M6P residues can be incorporated into a pharmaceutical composition containing a therapeutically effective amount of the molecule and one or more adjuvants, excipients, carriers, and/or diluents. Acceptable diluents, carriers and excipients typically do not adversely affect a recipient's homeostasis (e.g., electrolyte balance). Acceptable carriers include biocompatible, inert or bioabsorbable salts, buffering agents, oligo- or polysaccharides, polymers, viscosity-improving agents, preservatives and the like. One exemplary carrier is physiologic saline (0.15 M NaCl, pH 7.0 to 7.4). Another exemplary carrier is 50 mM sodium phosphate, 100 mM sodium chloride. Further details on techniques for formulation and administration of pharmaceutical compositions can be found in, e.g., Remington's Pharmaceutical Sciences (Maack Publishing Co., Easton, Pa.). Supplementary active compounds can also be incorporated into the compositions.

Administration of a pharmaceutical composition containing molecules with uncapped M6P residues can be systemic or local. Pharmaceutical compositions can be formulated such that they are suitable for parenteral and/or non-parenteral administration. Specific administration modalities include subcutaneous, intravenous, intramuscular, intraperitoneal, transdermal, intrathecal, oral, rectal, buccal, topical, nasal, ophthalmic, intra-articular, intra-arterial, sub-arachnoid, bronchial, lymphatic, vaginal, and intra-uterine administration.

Administration can be by periodic injections of a bolus of the pharmaceutical composition or can be uninterrupted or continuous by intravenous or intraperitoneal administration from a reservoir which is external (e.g., an IV bag) or internal (e.g., a bioerodable implant, a bioartificial organ, or a colony of implanted altered N-glycosylation molecule production cells). See, e.g., U.S. Pat. Nos. 4,407,957, 5,798,113, and 5,800,828. Administration of a pharmaceutical composition can be achieved using suitable delivery means such as: a pump (see, e.g., Annals of Pharmacotherapy, 27:912 (1993); Cancer, 41:1270 (1993); Cancer Research, 44:1698 (1984); microencapsulation (see, e.g., U.S. Pat. Nos. 4,352,883; 4,353,888; and 5,084,350); continuous release polymer implants (see, e.g., Sabel, U.S. Pat. No. 4,883,666); macroencapsulation (see, e.g., U.S. Pat. Nos. 5,284,761, 5,158,881, 4,976,859 and 4,968,733 and published PCT patent applications WO92/19195, WO 95/05452); injection, either subcutaneously,

intravenously, intra-arterially, intramuscularly, or to other suitable site; or oral administration, in capsule, liquid, tablet, pill, or prolonged release formulation.

Examples of parenteral delivery systems include ethylene-vinyl acetate copolymer particles, osmotic pumps, implantable infusion systems, pump delivery, encapsulated cell delivery, liposomal delivery, needle-delivered injection, needle-less injection, nebulizer, aerosolizer, electroporation, and transdermal patch.

Formulations suitable for parenteral administration conveniently contain a sterile aqueous preparation of the altered N-glycosylation molecule, which preferably is isotonic with the blood of the recipient (*e.g.*, physiological saline solution). Formulations can be presented in unit-dose or multi-dose form.

Formulations suitable for oral administration can be presented as discrete units such as capsules, cachets, tablets, or lozenges, each containing a predetermined amount of the altered N-glycosylation molecule; or a suspension in an aqueous liquor or a non-aqueous liquid, such as a syrup, an elixir, an emulsion, or a draught.

A molecule having uncapped M6P residues suitable for topical administration can be administered to a mammal (e.g., a human patient) as, e.g., a cream, a spray, a foam, a gel, an ointment, a salve, or a dry rub. A dry rub can be rehydrated at the site of administration. Such molecules can also be infused directly into (e.g., soaked into and dried) a bandage, gauze, or patch, which can then be applied topically. Such molecules can also be maintained in a semi-liquid, gelled, or fully-liquid state in a bandage, gauze, or patch for topical administration (see, e.g., U.S. Patent No. 4,307,717).

Therapeutically effective amounts of a pharmaceutical composition can be administered to a subject in need thereof in a dosage regimen ascertainable by one of skill in the art. For example, a composition can be administered to the subject, e.g., systemically at a dosage from 0.01μg/kg to 10,000 μg/kg body weight of the subject, per dose. In another example, the dosage is from 1 μg/kg to 100 μg/kg body weight of the subject, per dose. In another example, the dosage is from 1 μg/kg to 30 μg/kg body weight of the subject, per dose, e.g., from 3 μg/kg to 10 μg/kg body weight of the subject, per dose.

In order to optimize therapeutic efficacy, a molecule having uncapped M6P residues can be first administered at different dosing regimens. The unit dose and

regimen depend on factors that include, *e.g.*, the species of mammal, its immune status, the body weight of the mammal. Typically, levels of a such a molecule in a tissue can be monitored using appropriate screening assays as part of a clinical testing procedure, *e.g.*, to determine the efficacy of a given treatment regimen.

The frequency of dosing for a molecule having uncapped M6P residues is within the skills and clinical judgement of medical practitioners (e.g., doctors or nurses). Typically, the administration regime is established by clinical trials which may establish optimal administration parameters. However, the practitioner may vary such administration regimes according to the subject's age, health, weight, sex and medical status. The frequency of dosing can be varied depending on whether the treatment is prophylactic or therapeutic.

Toxicity and therapeutic efficacy of such molecules or pharmaceutical compositions thereof can be determined by known pharmaceutical procedures in, for example, cell cultures or experimental animals. These procedures can be used, e.g., for determining the LD50 (the dose lethal to 50% of the population) and the ED50 (the dose therapeutically effective in 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index and it can be expressed as the ratio LD50/ED50. Pharmaceutical compositions that exhibit high therapeutic indices are preferred. While pharmaceutical compositions that exhibit toxic side effects can be used, care should be taken to design a delivery system that targets such compounds to the site of affected tissue in order to minimize potential damage to normal cells (e.g., non-target cells) and, thereby, reduce side effects.

The data obtained from the cell culture assays and animal studies can be used in formulating a range of dosage for use in appropriate subjects (e.g., human patients). The dosage of such pharmaceutical compositions lies generally within a range of circulating concentrations that include the ED50 with little or no toxicity. The dosage may vary within this range depending upon the dosage form employed and the route of administration utilized. For a pharmaceutical composition used as described herein (e.g., for treating a metabolic disorder in a subject), the therapeutically effective dose can be estimated initially from cell culture assays. A dose can be formulated in animal models to achieve a circulating plasma concentration range that includes the IC50 (i.e., the

concentration of the pharmaceutical composition which achieves a half-maximal inhibition of symptoms) as determined in cell culture. Such information can be used to more accurately determine useful doses in humans. Levels in plasma can be measured, for example, by high performance liquid chromatography.

As defined herein, a "therapeutically effective amount" of a molecule having uncapped M6P residues is an amount of the molecule that is capable of producing a medically desirable result (e.g., amelioration of one or more symptoms of a metabolic disorder) in a treated subject. A therapeutically effective amount (i.e., an effective dosage) can includes milligram or microgram amounts of the compound per kilogram of subject or sample weight (e.g., about 1 microgram per kilogram to about 500 milligrams per kilogram, about 100 micrograms per kilogram to about 5 milligrams per kilogram, or about 1 microgram per kilogram to about 50 micrograms per kilogram).

The subject can be any mammal, e.g., a human (e.g., a human patient) or a non-human primate (e.g., chimpanzee, baboon, or monkey), a mouse, a rat, a rabbit, a guinea pig, a gerbil, a hamster, a horse, a type of livestock (e.g., cow, pig, sheep, or goat), a dog, a cat, or a whale.

A molecule or pharmaceutical composition thereof described herein can be administered to a subject as a combination therapy with another treatment, e.g., a treatment for a metabolic disorder (e.g., a lysosomal storage disorder). For example, the combination therapy can include administering to the subject (e.g., a human patient) one or more additional agents that provide a therapeutic benefit to the subject who has, or is at risk of developing, (or suspected of having) a metabolic disorder (e.g., a lysosomal storage disorder). Thus, the compound or pharmaceutical composition and the one or more additional agents can be administered at the same time. Alternatively, the molecule can be administered first and the one or more additional agents administered second, or vice versa.

It will be appreciated that in instances where a previous therapy is particularly toxic (e.g., a treatment for a metabolic disorder with significant side-effect profiles), administration of a molecule described herein can be used to offset and/or lessen the amount of the previously therapy to a level sufficient to give the same or improved therapeutic benefit, but without the toxicity.

Any of the pharmaceutical compositions described herein can be included in a container, pack, or dispenser together with instructions for administration.

The following are examples of the practice of the invention. They are not to be construed as limiting the scope of the invention in any way.

EXAMPLES

EXAMPLE 1

Creation of a *Yarrowia lipolytica* strain with a higher degree of phosphorylated N-glycans

To upregulate the phosphorylation of glycans in *Y. lipolytica*, strain MTLY60 was transformed with 2 extra copies of the MNN4 gene, each in a separate expression vector. The MNN4 gene is involved in increasing glycan phosphorylation in yeast. FIG. 1 contains a schematic of the pYLTmAX plasmid into which the MNN4 gene was cloned to produce pYLTmAXMnn4, which contains the MNN4 open reading frame under control of the TEF promoter. A strain was made that contains two extra copies of the MNN4 gene, one under control of the hp4d promoter and one under control of the TEF1 promoter. N-glycans were prepared from strain MTLY60Δoch1 (1 wild type copy of MNN4), strain MTLY60Δoch1+Hp4dMNN4 (1WT +1 extra copy of MNN4) and strain MTLY60Δoch1+Hp4dMNN4+TEFMNN4 (1WT +2 extra copies of Mnn4) and assayed by DNA sequencer-assisted (DSA), fluorophore-assisted carbohydrate electrophoresis (FACE). See, Callewaert *et al.*, *Glycobiology* 11(4):275-281 (2001). Based on the results in FIG. 2, it can be deduced that the mono phosphorylated peak is upregulated in the strain with 1 extra copy and that a peak of double phosphorylation appears. In the strain with 2 extra copies, the double phosphorylated peak was much higher and the peak of neutral $Man_8GlcNAc_2$ sugars was much lower.

EXAMPLE 2

Identification of a mannosidase activity that can uncap the capping mannose residue present on phosphorylated glycans of fungal origin.

The phosphorylation of sugars by yeast and filamentous fungi results in a mannose-phospho-mannose di-ester linkage (FIG. 3). To obtain a structure where the

phosphate is in a mono-ester linkage, a mannosidase is required that is able to hydrolyze the mannose-phosphate linkage, leaving the phosphate attached to the 6 position of a mannose of the high mannose glycan structure. Chiba *et al.*, *Glycobiology*, 12(12):821-8 (2002) indicate that a mannosidase from a *Cellulomonas* species is capable of decapping the mannose. However, Chiba *et al.* only partially purified the mannosidase protein and could not identify the gene encoding the protein.

A *Cellulosimicrobium cellulans* (also known as *Oerskovia xanthineolytica* and *Arthrobacter luteus*) isolate was obtained from the LMG bacteria collection and tested for production of mannosidase activity. The bacteria were grown at 30°C and in mannan containing medium to secrete the mannosidase in the medium. Bacterial supernatants (SN) were obtained from the cultures and tested for the desired mannosidase activity by incubating the SN with isolated N-glycans derived from the MNN4 overexpressing strain described in Example 1. After incubation, the glycans were assayed by DSA-FACE (FIG. 4).

After treatment with the SN, glycans gain an additional charge and migrate faster in the electric field and shift to the left hand side of the electroferogram. If these fast-running structures are indeed phosphomonoester-substituted high mannose glycans, they would be larger in size than the neutral products running at the same position. Treatment of such glycans with a phosphatase would result in neutral oligosaccharides that run much slower. As shown in FIG. 5, treatment with calf intestine phosphatase (CIP) resulted in the peaks displaying lower electrophoretic mobility, proving that the phosphates are terminal and that the mannose was decapped.

EXAMPLE 3

Partial purification and further identification of a mannosidase

To purify the mannosidase, *C. cellulans* was grown in 1L of medium B (Bagiyan *et al.*, *Eur. J. Biochem.* 249(1):286-92 (1997)) or medium A (Chiba et al., 2002, *supra*). See Table 1. Thereafter, the medium was precipitated with 40% and 80% ammonium sulphate and the samples were analysed by SDS-PAGE. The ammonium sulphate fractions were dialyzed against 20mM Na-phosphate buffer pH 6.5 with 1 mM $CaCl_2$, and then tested for activity on oligosaccharides derived from a MNN4 overexpressing strain (Example 1).

TABLE 1

Medium components

Medium A (1 liter)	**Medium B (1 liter)**
2 g mannan	2 g mannan
0.5 g $(NH_4)_2SO_4$	2 g $(NH_4)_2SO_4$
0.4 g $MgSO_4 .7H_2O$	0.02 g $MgSO_4 .7H_2O$
20 mg $FeSO_4 .7H_2O$	1 mg $FeSO_4 .7H_2O$
60 mg $CaCl_2.2H_2O$	1 g yeast extract
1 g yeast extract	4.2 g KOH
7.54 g K_2HPO_4	14 g $KH_2 PO_4$
2.32 g $KH_2 PO_4$	

Both cultivation conditions resulted in the production of the uncapping activity. Only the 40% ammonium sulphate fraction derived from medium B showed activity, whereas all fractions of the medium A supernatant displayed activity.

The 40% ammonium sulphate sample derived from the medium A cultivation was further purified over a silica-based gel filtration column (FIG. 6). This resulted in a peak with a shoulder around 670 kDa.

All elution fractions were incubated with oligosaccharides derived from a MNN4 overexpressing *Yarrowia lipolytica* strain (described in Example 1) (with or without a following CIP-digest) to test for the phosphate uncapping activity. The decapping and mannosidase activity was observed in all of the samples. Samples were also analyzed on SDS-PAGE (FIG. 7), which showed not just one protein band, but several protein bands. Several bands were cut out from the gel and portions of their sequence analyzed by de novo peptide sequencing using Mass Spectrometry.

The de novo sequencing results revealed several peptide sequences, whichwere compared against the sequences in the non redundant database using BLAST. Peptides with homology to the following proteins were identified: a phosphodiesterase, a hypothetical protein, a putative alpha-1,2 mannosidase (identified peptides shown in Table 2) (homology to a mannosidase from *Magnetospirillum*), and an aminopeptidase Y. The phosphodiesterase was a possible candidate, but here only 2 of the 6 peptides gave a hit. The mannosidase also was a candidate with 3/5 and 5/5 hits for 2 different mannosidases.

TABLE 2

Peptide Sequences

Peptide Sequence	SEQ ID NO
SAYQSFTTR	1
VWGFSHR	2
VEGGWLPR	3
TQGNNFALLLPER	4
DVHAELTAMAR	5

EXAMPLE 4

Identification of mannosidases with the desired sequence based on whole genome sequencing

To identify the mannosidase gene coding for the desired activity, the genome of *C. cellulans* was sequenced using a Titanium 454 sequencing (Eurofins MWG Operon). Due to the high GC content, the sequencing was only partial (1.96 Mbases) and of poor quality (with only a low average contig size). The high GC content of the genome that causes loop formation during the emulsion PCR (emPCR), resulting in deletions and very short sequences.

This problem was overcome using new sequencing chemistry for the emPCR that was made available in beta testing by Roche. This gave a much improved sequence (4.7 Mbases), allowing the identification of 5 mannosidase genes belonging to glycosyl hydrolase family 92, one of which (CcMan1, SEQ ID NO:6) corresponds to the sequence from which the peptides described in Example 3 were obtained. No mannosidases from family 38 or 47 were found. The start codon of each of CcMan1-CcMan4 was predicted by MetaGeneAnnotator (see the world wide web at metagene.cb.k.u-tokyo.ac.jp/metagene/) and compared to Blast results with known genes. The start codon of CcMan5 could not be predicted since it is missing from the sequence. The signal sequence of each gene was predicted with signal P (see the world wide web at cbs.dtu.dk/services/SignalP/) by two methods (neural networks and hidden markov models).

FIGs. 8-12 contain the nucleotide and encoded amino acid sequences of the 5 mannosidase genes from *C. cellulans*.

EXAMPLE 5

Heterologous expression of mannosidase for *in vitro* or *in vivo* mannose decapping.

In order to allow decapping of the yeast type phosphorylation by the mannosidase, it has to be expressed either heterologously in a different host or in the same fungal host from which the protein for therapeutic use is expressed. In the latter case it can be co-secreted or targeted to an intracellular compartment (e.g., Golgi apparatus or endoplasmic reticulum). This can be accomplished by cloning the gene (be it codon optimised for the target host or not) operably linked after a promoter in an expression vector. The mannosidase can be tagged with an epitope tag to allow easy detection and purification or expressed as such. It can be secreted in the periplasm of a bacterial cell or expressed intracellularly. In case of expression in the fungal host, the sequence can contain a secretion signal or a targeting signal to target the protein to an intracellular compartment or both. Table 3 contains a list of secretion and targeting signals for expression in fungal organisms. Examples of such expression vectors are presented in FIG. 13.

TABLE 3

Secretion and targeting signals for expression in fungal organisms

Secretion signals	**Golgi targeting signal**	
	N-terminal	**C-terminal**
LIP2 prepro	*MNN2*	*KEX2*
LIP2 pre	*MNN4*	
S.c. α mating factor	*MNN6*	
XPR2 prepro	*MNN1*	
XPR2 pre	*MNN9*	
	OCH1	
	SEC12	
	KRE2	

The CcMan1-Man5 genes were codon optimized for expression in *E. coli*. See FIGs. 14-18 for the codon optimized sequences. Table 4 contains the length of each

codon optimized nucleotide sequence and the predicted molecular weight of each polypeptide without the signal sequence.

TABLE 4

Codon Optimized Genes

	Length (bp)	**SEQ ID NO**	**Size (kDa) of encoded product**
CcMan1	2613	16	92.6
CcMan2	3483	17	121.6
CcMan3	3363	18	116
CcMan4	5283	19	184
CcMan5	4956	20	173

EXAMPLE 6

Cloning and Activity of *C. cellulans* Glycosyl Hydrolase (GH) Family 92 Enzymes

The CcMan1-CcMan5 codon optimized nucleic acids were cloned into *E. coli* vectors pLSH36, which contains a Spy signal sequence, and/or pLSAH36, which contains a DsbA signal sequence for periplasmic expression. Both pLSH36 and pLSAH36 result in the encoded polypeptide having a polyhistidine tag and a murine caspase-3 site, which can be used for the removal of the His6-tag during purification. FIG. 19 contains a schematic of the pLSH36 and pLSAH36 vectors as well as the cloning strategy for introducing the *C. cellulans* GH92 genes into the vectors. After cloning, the different mannosidases were transformed into *E. coli* BL21 + pICa2 expression strain. The transformed strains were grown to an optical density (OD) of 0.5 to 1 and induced with 1 mM isopropyl β-D-1-thiogalactopyranoside (IPTG). Different cell fractions (medium, periplasm, soluble and insoluble fraction) were isolated and analyzed by SDS PAGE and Western blotting with an anti-His6 antibody. For CcMan1, CcMan2, and CcMan3, expression was detected in all fractions. For CcMan4 and CcMan5, expression was the highest in the soluble fraction, but some expression also was detected in the other fractions.

To determine the activity of the CcMan1-CcMan5 proteins, activity tests were performed using methylumbelliferyl alpha mannoside (MUM) as set forth in Chiba *et al.*, 2002, *supra*. For CcMan1 and CcMan2, the medium and periplasm samples were able to hydrolyze MUM weakly, whereas CcMan3 and CcMan5 were not able to hydrolyze

MUM. The soluble fraction of CcMan4 gave the highest fluorescent signal, indicating that CcMan4 is the only mannosidase with α1,2-mannosidase activity.

All medium and periplasmic samples of the 5 different *C. cellulans* mannosidases also were tested on sugars derived from the MNN4 overexpressing strain of Example 1 (referred to herein as MNN4 sugars) to see if they were able to degrade the sugars and uncap the mannose of the mannose-6-phosphate. The sugars were incubated overnight and analysed by DNA sequencer-assisted, fluorophore-assisted carbohydrate electrophoresis (DSA-FACE). The sugar profiles of the medium samples could not be analyzed due to fluorophoric molecules in the medium presentation resulting in irrelevant peaks in the electroferogram. The sugar profiles of the periplasm of CcMan1, CcMan2 and CcMan3 showed neither degradation nor decapping, CcMan4 showed degradation, and CcMan5 showed decapping activity (FIG. 20). A CIP-digest on the decapped sugars confirmed the decapping activity of CcMan5 as the dephosphorylated peaks moved to neutral Man8.

The active mannosidases CcMan4 and CcMan5 were aligned with Bt3990 (744 AA) and Bt2199 (739 AA), family 92 mannosidases with known structure (see Zhu *et al.*, *Nat. Chem. Biol.*, 6(2):125-32. Epub 2009 Dec 27 (2010)). See FIG. 21. Since only the first part of CcMan4 and CcMan5 aligned with Bt3990 and Bt2199, and because they are large proteins, it was decided to clone the first domain of each protein separately and test the activity. CcMan4domain (1-3357 bp, i.e., nucleotides 1-3357 of SEQ ID NO:20) and CcMan5domain (1-2322 bp, i.e., nucleotides 1-2322 of SEQ ID NO:20) were cloned into the pLSAH36 *E. coli* expression vector. See, FIG. 19 for a schematic of the pLSAH36 cloning vector. The expression vectors were transformed into the *E. coli* BL21 + pICa2 expression strain, which was grown to an OD of 0.5 to 1, and induced with 1 mM IPTG. Different cell fractions (medium, periplasm, soluble and insoluble fraction) were isolated and analyzed by SDS PAGE and Western blotting with an anti-His6 antibody. Expression was detected in all 4 cell fractions.

The activity of the domains was tested on Mnn4 sugars. Hereto, the periplasmic fraction of each of the CcMan4domain and CcMan5domain was incubated in the presence of Mnn4 sugars (FIG. 22) and analyzed by DSA-FACE. This experiment showed that the CcMan4domain lost its mannosidase activity since no degradation could

be detected (FIG. 22, panel 4). In contrast, the CcMan5domain kept its uncapping activity (FIG. 22, panel 6).

EXAMPLE 7

Production and Purification of CcMan5 and its family 92 homologous domain

The recombinant CCman5 (nucleotides 1-4995 of SEQ ID NO:20 and CCMan5 domain (nucleotides 1-2322 of SEQ ID NO:20)were expressed in *E. coli* strain BL21codon + pICA2 that were transformed with the expression vectors pLSAHCcMan5 and pLSAHCcMan5domain. Expression was induced by IPTG under control of a λpL-promotor (see WO 98/48025 and WO 04/074488). See Example 6 and FIG. 19 for a descriptionof pLSAH. The transformed bacteria were grown in Luria Bertani (LB) medium supplemented with ampicillin (100 µg/ml) and kanamycin (50 µg/ml) overnight at 28 °C before 1/100 inoculation in a 20 liter fermenter provided with LB medium supplemented with ampicillin (100 µg/ml) and 1 % glycerol. The initial stirring and airflow was 200 rpm and 1.5 l/min., respectively, and was automatically adapted to keep the pO_2 at 30 %. The temperature was kept at 28°C. The cells were grown to an optical density of $A_{600\ nm}$ = 1.0, transferred at 20°C, and expression was induced by addition of 1 mM IPTG overnight. Cells were then harvested and frozen at -20 °C. After thawing, the cells were gently resuspended at a concentration of 3 ml/g in 50 mM NaH_2PO_4 pH 8.0, 300 mM NaCl, 1 mM PMSF and 10 µg/ml DNaseI. The periplasmic fraction was prepared by stirring the cell suspension for 1 h at 4 °C and was isolated by centrifugation at 18,000 x g for 30 min. All steps were conducted at 4 °C. The clear supernatant was applied to a 20 ml Ni-Sepharose 6 FF column (GE Healthcare), equilibrated with 20 mM NaH_2PO_4 pH 7.4, 300 mM NaCl, 20 mM imidazole, 0.1 % CHAPS. The column was eluted with 20 mM NaH_2PO_4 pH 7.4, 20 mM NaCl, 400 mM imidazole, 0.1 % CHAPS after an extra wash step with 50 mM of imidazole in the same buffer. The elution fraction was diluted 1/10 with 20 mM Tris pH 8.0, 0.1 % CHAPS and loaded on an 14 ml Source 15Q column (GE Healthcare) to remove contaminants. After equilibration, the protein of interest was eluted by a linear gradient over 10 column volumes of NaCl from 0 to 1 M in 20 mM Tris, 0.1 % CHAPS. The CcMan5 and CcMan5 domain containing fractions were further injected on a HiLoad 26/60 Superdex 200 prep grade with PBS as running

solution. The obtained fractions were analyzed by SDS-PAGE and western blotting with an anti-His6 antibody. Finally, the concentration was determined using the BCA assay (Pierce). The purified yield for the full-length CcMan5 protein was 5.7 mg, and for the CcMan5 family 92 domain, it was 110 mg from these 20 L fermentations, showing that the family 92 domain alone can be produced and purified in higher yield. The activity of the purified CcMan5 domain was tested on the Mnn4 isolated sugars as set forth in Example 6. A decapped sugar profile was obtained.

EXAMPLE 8

Structure of CcMan5domain

$CcMan5_{1-774}$ (residues 1 to 774 of SEQ ID NO:50, encoded by nucleotides 1-2322 of SEQ ID NO:20; corresponding to the mature protein after removal its natural leader sequence) was expressed in *E. coli* BL21 (DE3) periplasm as a fusion product starting with an N-terminal 6xHis tag followed by a 9 amino acid linker (VGPGSDEVD, SEQ ID NO:21) after the DsbA leader sequence. Cells were cultured in M9 medium containing 100 µg/ml of kanamycin and 100 µg/ml ampicillin at 28 C. At an OD_{600} of 0.4, $CcMan5_{1-774}$ expression was induced by addition of 1mM IPTG and the culture was further grown overnight at 18°C. Cells from the overnight culture were harvested by centrifugation, washed and incubated for 20 min at 4°C with buffer containing 20 mM Tris/HCl pH 8.0, 20% sucrose, 5 mM EDTA, and 0.1 mg/ml lysozyme to make spheroplasts. Periplasmic proteins were isolated from spheroplasts by centrifugation at 20,000x*g* for 20 min. $CcMan5_{1-774}$ was purified from the periplasmic extract by metal ion affinity chromatography (HisTrap HP, GE Healthcare, loading under a buffer containing 50 mM Tris-HCl pH 8.0, 150 mM NaCl, and eluted using an imidazole gradient up to 400 mM), ion exchange chromatography (HiTrap Q FF, GE Healthcare, buffer: 20 mM Tris-HCl pH 8.0, 40 mM NaCl and a NaCl gradient up to 1 M) and hydrophobic interaction chromatography (HiTrap Phenyl HP, GE Healthcare, loading buffer: 20 mM Tris-HCl pH 8.0, 10 mM NaCl, 1 M $(NH_4)_2SO_4$ and eluted using a $(NH_4)_2SO_4$ gradient up to 0 mM).

Purified $CcMan5_{1-774}$ was concentrated to 130 mg/ml in 10 mM Tris– HCl pH 8.0, 10mM NaCl and plate-like crystals (0.2x0.07x0.01 mm^3) were grown by vapor diffusion using a crystallization solution containing 0.2 M Na fluoride, 0.1 M Bis-Tris propane pH

7.5 and 20% PEG 3350. Crystals were briefly transferred into a cryoprotecting solution containing the crystallization solution supplemented with 10%(v/v) glycerol and flash-cooled in liquid nitrogen. Single crystal diffraction data were collected at 100 K at the PXIII beamline at the Swiss Light Source (SLS, Villigen, Swiss) and beamline BM30A at the European Synchrotron Radiation Facility (ESRF, Grenoble, France). The structure of $CcMan5_{1-774}$ was solved using a KAuCl4-soaked crystal for the calculation of experimental phases from a SAD experiment at 11.958 keV, corresponding to the Au L-III absorption edge. FIG. 33 contains the structural coordinates of the catalytic center. The CcMan5 model built from the experimental phases was refined by maximum likelihood methods against 2Å resolution data collected on a native crystal to a final R- and freeR-factor of 19.3 and 23.9 %, respectively. The final model contains 2 $CcMan5_{1-774}$ molecules per asymmetric unit (residues 8 to 771), comprising 11.513 protein atoms, 860 solvent atoms, 2 Ca^{2+} ions and 1 bis-tris-propane and glycerol molecule each.

Based on sequence similarity, CcMan5 falls within family 92 of glycosyl hydrolases (GH92), which are defined as exo-acting alpha-mannosidases. The X-ray structures for two GH92 family members with α1, 2-mannosidase activity are available: Bt3990 and Bt2199 (PDB access codes 2WVX and 2WVY, respectively). The overall fold seen from the $CcMan5_{1-774}$ structure solved here, and deposited as PDB entry 2xsg, corresponds well with that seen in both Bt3990 and Bt2199, with r.m.s.d (root mean standard deviation) values of 1.99 Å and 2.12 Å over 624 and 621 matched Cα atoms, respectively. $CcMan5_{1-774}$ consists of two domains, an N-terminal β-sandwich domain (residues 8 to 271) and a C-terminal (αα)6 barrel domain (residues 291 to 771), connected via an α-helical linker (residues 272 to 290). The interface between both domains gives shape to a shallow cavity that harbors a conserved catalytic Ca^{2+} ion and gives shape to the -1 substrate binding site (nomenclature: Davies *et al.*, *Biochem. J.* 321:557-9 (1997)) and the catalytic center (FIGs. 23 and 24).

GH92 family glycosyl hydrolases are Ca^{2+}-dependent alpha-mannosidases that catalyse glycosidic bond hydrolysis through a single displacement mechanism, leading to inversion of the anomeric configuration in the released mannose (Zhu *et. al.*, 2010, *supra*). In $CcMan5_{1-774}$, the catalytic Ca^{2+} is octahedrally coordinated via the carbonyl oxygen of Asn 588, a carboxyl oxygen of Glu589 and Asp662 each, and three water

molecules (W1, W2, W3 – see FIG. 23) that lie in the equatorial coordination plane. An additional water molecule (W4) is present near the catalytic center, bound to the carboxyl groups of the conserved pair Asp 660 and Asp 662. The substrate binding cavity surrounding the catalytic Ca^{2+} is lined by the residues Asn 588, Gln 589, Thr 626, Thr 658, Asp 22, Asn 25, Gly 71, Gly 72, Phe 195, Tyr 196, Arg 405, Trp 354, Tyr 535, and and Gln536 (FIG. 23).

CcMan5 sets itself apart from other alpha-mannosidases in the GH92 family because of its unique ability to accept mannose-alpha-1-phospho-6-mannose (Man-P-Man) as a substrate and a lack of alpha-1,2-, alpha-1,3-, alpha-1,4- or alpha-1,6-mannosidase activity. In order to obtain insight in the discriminating residues in the CcMan5 active site that give rise to this unique substrate specificity, Man-P-Man was modeled into the $CcMan5_{1-774}$ active site of molecule B of the asymmetric unit (FIG. 25). Positioning of the -1 mannose was based on the gross binding conformation observed in Bt3990 and guided by the positions of two water molecules (W2 and W3) and a glycerol molecule present in the apo active site. In this way, the O2, O3, O4 and O6 hydroxyl groups of the -1 mannose take equivalent positions to those observed for the water molecules W2, W3 and the O1 and O3 hydroxyl groups of the glycerol molecule, respectively. Thus, the mannose -1 O2 and O3 hydroxyl group position in the equatorial plane of the actohedral Ca^{2+} coordination sphere. O3 makes an additional hydrogen bond to the Asp 355 carboxyl group. The latter is further provides a H-bond to the O4 hydroxyl, which also comes within H-bonding distance of the Arg 405 guanidinium group. The O6 hydoxyl and O5 oxygen can be involved in H-bonding with the Gly 71 amide. For modeling, the -1 mannose was retained in its ground state chair conformation. As observed for Bt3990, positioning of the O2 hydroxyl group to come into idealized coordination with Ca^{2+} will lead to a distortion of the sugar ring to a half chair conformation (see FIG. 25). This is in line with the general acceptance that a distortion of the sugar ring during catalysis is required for the nucleophilic substitution at the acetal center in α-mannosides in order to break the 1,2-diaxial interaction of the incoming nucleophile with the O2 hydroxyl (Vocadlo *et al.*, *Curr. Opin. Chem. Biol.* 12:539-55 (2008)). The obtained model for substrate binding in the -1 site further shows that water molecule W4 lies in a good position to act as nucleophile for in line attack on the acetal

carbon. W4 is in H-bond interaction with the carboxyl groups of Asp 660 and Asp 662, which are conserved throughout GH92 enzymes and are proposed to form the base catalyst(s) for activation of the nucleophile. Therefore, the modeled substrate binding at the -1 site and the position of catalytic residues and nucleophile are consistent with the mechanistic requirements for nucleophilic substitution with inversion of the anomeric center in the released mannose. As discussed above, CcMan5 distinguishes itself by the ability to bind and hydrolyse Man-P-Man. The obtained model for Man-P-Man binding to the CcMan5 active site now provides a rationale for these observations. In known GH92 family members, the anomeric oxygen making the glycosidic bond, is in electrostatic interaction with the carboxyl group of a conserved glutamic acid residue (Glu 533 in Bt3990). The glutamic acid residue has been shown to serve as catalytic acid, stabilizing the transition intermediate by binding the anomeric oxygen and protonating the leaving group (Zhu *et. al.*, 2010, *supra*). In CcMan5, the equivalent residue to Bt3990 Glu 533 is mutated to glutamine, which is not able to serve as a proton donor and therefore explains the loss-of-function in CcMan5 for hydrolysis of mannobiosides. In Man-P-Man substrates, however, the phosphate bound to the anomeric oxygen constitutes a much stronger leaving group that would not require an acid catalyst to protonate the anomeric oxygen, explaining why enzymes like CcMan5 can retain catalytic activity for Man-P-Man substrates. Concomitant with substitution of the catalytic acid, the equivalent of Glu 585 in Bt3990 is replaced by Thr in CcMan5 (Thr 626). In Bt3990, Glu 585 interacts with Glu 533 and has been suggested to regulate the latter's pK_a and/or play a role in binding the leaving group in 2-linked mannosides (Zhu *et. al.*, 2010, *supra*).

It appears that mutation to non-acidic residues in the Gln 536 and Thr 626 pair alleviates part of the negative electrostatic potential in the binding site, thereby tolerating the phosphate linkage to the anomeric oxygen in Man-P-Man substrates. In CcMan5, the modeled phosphate binding site (P in FIG. 25) is shaped by Thr 626 and the amide of Gly 72, both of which appear able to donate a H-bond to the non-glycosidic oxygens in the phosphate.

Finally, based on the modeled binding of Man-p-Man in the $CcMan5_{1-774}$ active site, the reducing end mannose comes in the vicinity of two tyrosine residues, Tyr 535 and Tyr 196, suggesting the latter to residues form part of the +1 mannose binding site.

Both residues lay at the edge of a shallow cleft that could be involved in further interactions with glycans at the reducing end of the glycan tree.

EXAMPLE 9

Expression of αGalactosidaseA in *Y. lipolytica*

A nucleic acid encoding human α-GalactosidaseA , without pre and pro sequence, was synthesized with codon optimization for *Y. lipolytica* and addition of a Myc-His tag. The obtained sequence was cloned in frame after the pre sequence of the lip2 gene. The nucleotide sequence of the codon optimized nucleotide sequence (SEQ ID NO:22) is set forth in FIG. 26A; amino acid sequence (SEQ ID NO:23) is presented in FIG. 26B.

Y. lipolytica MTLY60 with 2 extra copies of MNN4 and one copy of α-GalactosidaseA was induced in a larger culture to purify over a Ni-NTA column. Thus, they were grown in YTG and induced in oleic acid medium in 2 x 225 ml (2L shake flask) during 48 hours. The culture was centrifuged, followed by filtration of the medium over a 0.22 µm filter. The filtered medium was desalted on a sephadex G25 XK50/100 column (GE Healthcare) to 20 mM NaH_2PO_4 pH 7.4, 0.5 M NaCl, 20 mM imidazole to remove non-protein disturbing contaminants before purification on Ni-sepharose 6 FF. The desalted protein fraction was loaded on a 4.3 ml Ni-sepharose 6 FF column (GE Healthcare), equilibrated with 20 mM NaH_2PO_4 pH 7.4, 0.5 M NaCl, 20 mM imidazole, washed with 50 mM imidazole in the same buffer and eluted with 20 mM NaH_2PO_4 pH 7.4, 20 mM NaCl, 400 mM imidazole. Samples 3-10 and 36-49 after the Ni-sepharose column were analysed on SDS-PAGE and Western blotting using an anti-His6 antibody. A protein band of around 50 kDa and of 65 kDa was present on coomassie in samples 40 and 41 was revealed by Coomassie blue staining of the SDS-PAGE gel. In the western blot, only a band of 50 kDa was detected and is most likely the α-GalactosidaseA. The estimated yield of the purified α-GalactosidaseA was 100-125 µg/L culture medium.

The purified sample was used to determine the type of sugars on the recombinant α-GalactosidaseA. The sugars were removed in solution and afterwards labelled with APTS. After cleaning the sample by gel filtration, the sugars were analyzed on DSA-FACE. The expected sugars, the mono mannophosphorylated $Man_8GlcNAc_2$ peak (P)

and the double mannophosphorylated $Man_8GlcNAc_2$ peak (PP) were present as major peaks.

EXAMPLE 10

Expression of human alpha glucosidase in *Y. lipolytica*

Y. lipolytica strain OXYY1589 was constructed that contained three copies of the human alpha glucosidase (also known as acid alpha glucosidase (GAA) or acid maltase EC3.2.1.3) and two copies of the *Y. lipolytica* MNN4 gene. The genotype of strain OXYY1589 is as follows:

MatA, leu2-958, ura3-302, xpr2-322,
gut2-744, ade2-844

POX2-Lip2pre-huGAA:URA3Ex::zeta
POX2-Lip2pre-huGAA:LEU2Ex::zeta
POX2-Lip2pre-hGM-CSF:GUTEx::zeta
YlMNN4-POX2-hp4d-YLMNN4 :ADE2*::PT targeted*

All transformations were carried out according to well established protocols with modifications for the different selective markers. In all cases (unless otherwise specified), a huGAA integration fragment has been obtained by NotI restriction digestion in order to remove the kanamycin resistance gene from the expression plasmids. The resulting fragments were all separated by agarose gel electrophoresis followed by Qiagen column purification of the correct huGAA fragment. Strain OXYY1589 was constructed by first cloning human GAA (huGAA) into a *Y. lipolytica* expression vector and constructing a *Y. lipolytica* MNN4 tandem expression vector. Three stable integrative transformations then were performed in order to obtain the final huGAA production strain OXYY1589.

Y. lipolytica codon optimized huGAA expression vector: The nucleotide sequence encoding the 110 kDA human GAA (huGAA) precursor was chemically synthesized and codon optimized for *Y. lipolytica* expression. In the synthetic construct, the pre- and the pro- huGAA signal peptides were eliminated such that the protein starts at amino acid 57. The synthetic ORF of huGAA (FIG. 27A) is fused in frame at the 5' end to the 3'end of the *Y. lipolytica* LIP2 signal sequence (pre), followed by the coding sequence of two Xxx-Ala cleavage sites and flanked by BamHI and AvrII restriction sites

for cloning in expression vector. The construct is under the control of the inducible POX2 promoter. The complete amino acid sequence of the fusion construct is shown on FIG. 27B.

A general scheme of an expression vector is presented in FIG. 28. The bacterial moiety is derived from the plasmid pHSS6, and comprises a bacterial origin of replication (ori) and the kanamycin-resistant gene conferring resistance to kanamycin (KanR). The integration cassette comprises a) the selection marker for transformation to *Yarrowia lipolytica* (URA3; LEU2; GUT2), b) the expression cassette composed of a promoter, c) a multiple cloning site (MCS) to insert huGAA in frame with signal sequence and d) the terminator of the LIP2 gene. The integration cassette is flanked by zeta sequences for stable non-homologous integration into the *Y. lipolytica* genome. Two NotI restriction sites enable the isolation of the expression cassette before transformation. Plasmids pRAN034, pRAN036 and OXYP183 have been used to generate huGAA expression vectors pRAN058, pRAN059 and pRAN060, respectively, containing URA3, LEU2 and GUT2 transformation markers, respectively.

Tandem YlMNN4 expression vector: The YlMNN4 gene was cloned under control of the inducible pPOX2 promoter and the (semi)constitutive hp4d promoter. These two expression cassettes of YlMNN4 were subcloned in one vector as a tandem construct carrying flanking regions (PT) of the ADE2 gene for targeted integration into the *ADE2* locus of the genome and the ADE2 gene as a selection marker.

Intermediate Strain OXYY1569: The first transformation was a co-transformation of the expression cassette purified from pRAN058 and pRAN059 vectors using URA3 and LEU2 marker to produce intermediate recombinant strain OXYY1569. OXYY1569 carries two expression constructs of huGAA under control of the pPOX2 promoter randomly integrated in the genome of strain G014.

OXYY1569 was selected as follows. PCR screening of genomic DNA was performed in order to confirm the integration of the foreign huGAA DNA into the genome of *Y. lipolytica*. Primers were designed to amplify a fragment of 2552bp from huGAA nucleotide sequence. Southern blot analysis of the genomic DNA also was performed in order to confirm the integration of at least 2 copies of huGAA DNA. In

particular, genomic DNA from OXYY1569 clones were digested with Hind III and probed with huGAA DIG labeled specific probe.

In order to select a clone secreting high levels of huGAA, several randomly selected clones that were identified as positive in the PCR screening and Southern blot were grown in shake flasks under POX2 inducing conditions according to a standard procedure. In all cases, the culture supernatant was collected 72h post-induction and screened in a standard Western blot and enzyme activity assay analysis. N-Glycan analysis of OXYY1569 indicated the predominant structure in OXYY1569 is $Man_8GlcNAc_2$.

Intermediate Strain OXYY1584: Recombinant strain OXYY1569 was transformed in order to integrate two copies of the *Y. lipolytica* MNN4 gene into its genome to produce OXYY1584. The transformation was performed with a SacII/XmaI derived expression cassette excised from plasmid OXYP1479B. The expression cassette was designed for targeted integration into the ADE2 locus of *Y.lipolytica* genome. The recombinant strain was selected after Southern blotting and glycan analysis to evaluate the strain behavior with respect to the increased phosphorylation. Genomic DNA of several arbitrary chosen transformants was SpeI digested and probed with MNN4 specific DIG labeled probe. Correct targeted integration of MNN4 expression cassette into the ADE2 locus of *Y. lipolytica* genome should give 4207bp and 5683bp bands. Southern blot positive clones were grown in a standard shake flask procedure. N-glycan analysis of secreted proteins was performed in order to select the intermediate clone OXYY1584. Compared to the parent stain OXXY1569, the predominant structures after MNN4 over-expression are $Man_8GlcNAc_2(PMan)_1$ and $Man_8GlcNAc_2$ $(PMan)_2$.

Production strain OXYY1589: To generate the final prototrophic production strain OXYY1589, a third copy of huGAA was integrated into the genome of recombinant OXYY1584 strain. The transformation was performed with Not I excised expression cassette from pRAN069. Transformants were first screened by PCR on gDNA for presence of the additional copy of huGAA. To evaluate huGAA production arbitrary selected PCR positive clones were further analyzed for expression after a standard shake flask cultivation. The clone expressing the highest level of huGAA (OXYY1589) was chosen after Western blot analysis and enzymatic activity assay. It also was reconfirmed

that the conversion levels of M8 to MP2-M8 and MP-M8 N-glycans was not influenced by the presence of the additional huGAA expression cassette.

EXAMPLE 11

Fed Batch Cultivation of Strain OXYY1589

To produce huGAA from strain OXYY1589 (Example 10), a fed batch process was established using a 10 L stirred tank, with a working volume of 6-8 liters. The process was divided in two phases:

1) Batch growth on glucose for biomass formation
2) Product formation by induction with help of a limited oleic acid feed.

Typically the batch phase was about 20 hours (h) and the production phase approximately 72 hours. At the end of the process, the culture broth was centrifuged and the supernatant was collected. The supernatant was used as starting material for the purification of the GAA (see Example 12).

The following parameters were controlled during the fermentation. Aeration was maintained at a constant value of 1.5 vvm air (volume per volume per minute). Dissolved oxygen (DO) was initially kept at 30%. The stirring was increased from 600 to 1200rpm depending on the DO levels. Once it reached the maximum of 1200 rpm, this speed was kept constant and the DO-setpoint was set to 10%. To maintain 10% DO, oxygen was spiked into the reactor with a maximal percentage of 50%. Foam evolution was controlled by a foam probe. In case of foam detection, antifoam was added to the bioreactor. The pH was controlled by adding 14% (v/v) ammonia (base) or 10% phosphoric acid to maintain a constant value of pH 6.8. The temperature was kept constant at 28°C throughout the whole process.

Biomass was monitored by measurement of optical density at 600 nm (OD600). The samples were diluted 2 – 1000 times in distilled water to obtain values in the linear range of the spectrophotometer. Product formation was detected by Western blot analysis and specific enzymatic activity tests.

EXAMPLE 12

Purification of recombinant huGAA (rhGAA)

The supernatant after cultivation (see Example 11) was clarified via depth filtration. The resulting material was then concentrated 20 times via TFF and diafiltered against 20 mM sodium phosphate pH 6 and 100 mM NaCl on a 10kDa MWCO membrane (Millipore).

Purification of rhGAA was start by adding ammonium sulphate up to a concentration of 1 M. After centrifugation, the supernatant was loaded on a Toyopearl-Phenyl 650M (Tosoh Biosciences) packed XK16/40 column. A linear gradient from 1 to 0 M ammonium sulphate was applied for elution. Those fractions that contain rhGAA were then pooled and subjected to a buffer exchange into 10 mM BIS-TRIS pH 6. Further purification was achieved via anion exchange chromatography on a source 30Q packed Tricorn 10/50 or XK25/20 column (GE Healthcare) using a linear salt gradient from 0 to 1 M NaCl. The resulting GAA-containing fractions were then concentrated before loading onto a final Hiload 16/60 superdex 200 gel filtration column (GE Healthcare) that was pre-equilibrated with 50 mM sodium phosphate pH 6 and 200 mM NaCl. Fractions were selected on the basis of specific activity and purity on Coomassie-stained SDS-PAGE gels and then combined and concentrated to a final concentration of 5-10 mg/ml. Protein concentration was done on 15 ml Amicon Ultra centrifugal devices (Millipore) with a MWCO of 10 kDa.

The reactions for the qualitative screening for rhGAA were started by adding the reaction buffer consisting of 0.35 mM 4-MUG, 0.1% BSA and 100 mM sodium acetate pH 4 in a 10:1 or 20:1 volume proportion to 10 or 5 µl of elution fraction. All reactions were done in 96-well flat-bottom microtiter plates. After an incubation period of 30 minutes to 1 hour at 37°C, an equal volume of 100 mM glycine pH11 was added to stop the reaction and the release of the fluorogenic reaction product 4-methylumbelliferone was observed under UV-light. Specific activities (units/mg protein) were determined using a colorimetric assay with the synthetic substrate p-nitrophenyl-α-D-glucopyranoside (PNPG) that measures the enzymatic release of the yellow coloured p-nitrophenolate reaction product. The reactions were started by mixing 10 µl of enzyme solution and 90 µl of substrate reaction buffer (2 mM PNPG in 150mM citrate-phosphate buffer pH4, 1% BSA) in reaction wells of a microtiterplate and were subsequently incubated at 37°C. After 1 to 2 hours an equal volume of stop buffer, 10% sodium

carbonate pH 12, was added to quench the reaction and bring the released p-nitrophenol (PNP) in its ionized state. Background-corrected absorbances and p-nitrophenolate standards were measured at a wavelength of 405 nm and specific activities were calculated. Protein concentrations were determined with the bicinchoninic acid (BCA) method. One unit was defined as the amount of enzyme that catalyzes the conversion of 1 nmol of PNPG to 1 nmol PNP and D-glucose per min at 37°C at a final substrate concentration of 2 mM in a citrate-phosphate buffer, pH 4.0.

EXAMPLE 13

Phosphate uncapping activity of heterologously expressed CcMan5 on glycoproteins expressed in a *Y. lipolytica* strain with a higher degree of phosphorylated N-glycans

The huGAA was expressed in *Y. lipolytica* strain OXYY1589 to yield a glycoprotein with a high degree of phosphorylated N-glycan structures (see Example 10). The huGAA was purified as described in Example 12.

CcMan5 (1 and 5 µl respectively at a concentration of 70 µg/ml) was added to a solution of 4 µg huGAA in 100 mM HEPES buffer pH 7.0 with 2 mM $CaCl_2$. The 20 µl reaction mixture was incubated overnight at room temperature. The N-glycans were released with PNGaseF, labelled with APTS and subsequently analysed on DSA-FACE, essentially as described in Laroy W. *et al.*, *Nature Protocols*, 1: 397-405 (2006). The N-glycan profiles before and after CcMan5 treatment are shown in Figure 29. The N-glycan mixture released from purified huGAA is mainly composed of ManP-Man8GlcNAc$_2$ and (ManP)2-Man8GlcNAc$_2$ (FIG. 29, panel B). A peak running slightly faster than ManP-Man8GlcNAc$_2$ can be assigned to ManP-Man7GlcNAc$_2$. Only very minor amounts of Man$_8$GlcNAc$_2$ and Man$_7$GlcNAc$_2$ are present. After incubation of huGAA with CcMan5 the conversion of ManP-Man8GlcNAc$_2$ and (ManP)2-Man8GlcNAc$_2$ to P-Man8GlcNAc$_2$ and P2-Man8GlcNAc$_2$ respectively is observed (FIG. 29, panel C and D). The peak in the electropherogram running between P-Man8GlcNAc$_2$ and P2-Man8GlcNAc$_2$ corresponds to the partially uncapped bi-phosphorylated (ManP)2-Man8GlcNAc$_2$ with a phosphodiester- and a phosphomonoester-linkage present ((MP)-M8-P in FIG. 29, panel

C and D). This product is further hydrolyzed to the fully uncapped P2-Man8GlcNAc$_2$ when using a higher concentration of CcMan5 or a longer incubation time.

The percentage of phosphorylated N-glycans versus neutral N-glycans was estimated from measuring the peak areas in the DSA-FACE electropherograms (FIG. 29). The figures related to the area under the curve are presented for the different N-glycans present on huGAA before (Panel B) and after CcMan5 treatment (Panel D). In huGAA (Panel B), (ManP)2-Man8GlcNAc$_2$ (11597), ManP-Man6GlcNAc$_2$ (1261), ManP-Man7GlcNAc$_2$ (5901), ManP-Man8GlcNAc$_2$ (15576), Man6GlcNAc$_2$ (680), Man7GlcNAc$_2$ (1716), Man8GlcNAc$_2$ (1572) were present. Approximately 90 % of the N-glycans on recombinant huGAA were composed of mannose-phosphate containing structures.

After an overnight treatment of recombinant huGAA with CcMan5 (Panel D), P2-Man8GlcNAc$_2$ (16182), (ManP)P-Man8GlcNAc$_2$ (1997), P-Man7GlcNAc$_2$ (8254), P-Man8GlcNAc$_2$ (17893), ManP-Man6GlcNAc$_2$ (500), ManP-Man7GlcNAc$_2$ (2495), ManP-Man8GlcNAc$_2$ (1326), Man6GlcNAc$_2$ (1097), Man7GlcNAc$_2$ (2143), Man8GlcNAc$_2$ (1599) were present. The N-glycans released from huGAA were composed of 83 % uncapped phosphorylated structures, 8 % is still mannose-phosphate capped and 9 % neutral N-glycans are present. The percentage of uncapped phosphorylated structures can be increased when using a higher concentration of CcMan5 or a longer incubation time.

EXAMPLE 14

Identification of Homologs Likely to Have Uncapping Activity

To identify other GH92 family members with similar predicted catalytic site topology and functionality, curated GH92 family members, as mined from the world wide web at cazy.org/GH92_all.html, were analyzed as were the top 500 hits obtained by Blastp search with the CcMan5 domain sequence on the Non Redundant Protein Sequences database at NCBI. Subsequently, these 392 sequences were used as the input for the multiple sequence alignment package MUSCLE (MUltiple Sequence Comparison by Log-Expectation), which also ranks the sequences in order of 'phylogenetic' distance (from closest related to furthest related).

Based on the curated GH92 family members from the Cazy database, MUSCLE alignment of all GH92 protein sequences (392) and the CcMan5 domain sequence identified the following as the closest homologs of CcMan5:

Streptomyces coelicolor CAA18915 (GenBank Accession No. NP_630514)

Clostridium spiroforme (GenBank Accession No. ZP_02866543)

Bacteroides thetaiotaomicron AAO78636 (GenBank Accession No. NP_812442)

Zunongwangia profunda ADF52306 (GenBank Accession No. YP_003584502)

Chitinophaga pinensis ACU58463 (GenBank Accession No. YP_003120664)

Their sequences and those of the next 5 closest homologs are aligned in FIG. 31.

Based on MUSCLE alignment of the 500 best scoring blastp protein hits versus the CcMan5 domain, the following were considered the closest homologs of CcMan5

Streptomyces coelicolor (GenBank Accession No. NP_630514)

Streptomyces lividans (GenBank Accession No. ZP_05522540)

Streptomyces lividans (GenBank Accession No. ZP_06527366)

Paenibacillus sp (GenBank Accession No. YP_003013376)

Bacteroides thetaiotaomicron (GenBank Accession No. NP_812442)

Bacteroides sp. (GenBank Accession No. ZP_04848482)

Bacteroides cellulosilyticus (GenBank Accession No. ZP_03677957)

Zunongwangia profunda (GenBank Accession No. YP_003584502)

Leeuwenhoekiella blandensis (GenBank Accession No. ZP_01061975)

Sphingobacterium spiritivorum (GenBank Accession No. ZP_07083984)

Chitinophaga pinensis (GenBank Accession No. YP_003120664)

Pedobacter sp. (GenBank Accession No. ZP_01885202)

Clostridium spiroforme (GenBank Accession No. ZP_02866543)

Alignment of these and the 5 next-best homologs can be found in FIG. 32. All 5 best hits from the annotated GH92 database are also found in these 13 best hits from the Blast search on the entire sequence database.

The top 5 hits in FIG. 31 and the top 13 hits in FIG. 32 uniquely share the following three motifs, which were shown in the crystal structure of Example 8 to be different from the alpha-1,2-mannosidase GH92 family members of which the structure was reported in Zhu *et. al.*, 2010, *supra*.

1) a glycine-rich motif GVGxxGxGG, with each X being G, S, T, V, A, C or Q (small side chains), numbering of crystal structure residues of CcMan5 domain: 69-77. This region makes a loop that provides essential hydrogen bonds to the -1 and phosphate--binding subsite in the active site of the enzyme.

2) a VRxE motif. The R makes a hydrogen bond to the -1 ring and possibly the +1 ring. E is in a salt bridge to this R residue, probably shaping this motif. x is W in the closest-related subfamily (top 3 homologs to CcMan5), or could be any of the 20 amino acids except P. This motif is found at residues 404-407 of SEQ ID NO:50.

3) a LYQGT motif, containing the Q which is an E in the mannosidases (proton donor), and which contains Y535, which is important for the +1 site formation. In some of the sequences, the L is A or Y and could reasonably be expected to also be I, V, A, F or M, and in some of them the T is N and can be expected to also tolerate S. Two *Caulobacter* sequences have an E instead of Q and would thus be predicted not to work on phosphorylated glycans.

4) a GDXGN motif. The D and N make part of the substrate binding cavity and may shape an alternative subpocket to bind the +1 mannose. X can be any amino acid other than P. This motif is found at residues 21-25 of SEQ ID NO:50.

Based on the above bioinformatics workflow and motif search based on the structure, it is thus possible to filter the GH92 sequences present in the non-redundant proteins sequence database (currently containing over 1220 sequences) for those rare family members that are good candidates for having the same substrate specificity to CcMan5, i.e., to be capable of uncapping Man-6-Pi-Man structures. In particular, the 3 sequences from *Streptomyces coelicolor* and *Streptomyces lividans* are similar to CcMan5, not only in the above motifs but also in many of the loops of the structure.

A search with Hidden Markov Models based on the sequence elements unique to CcMan5 and its closest homologs, reveals no further GH92 sequences which contain all of these elements, strongly indicating that no such GH92 members have obtained these elements through convergent evolution (these are the ones that would not be top-ranked in multiple-sequence alignments).

EXAMPLE 15

The presence of phosphate uncapping activity in GH92 glycosidases from *Bacteroides thetaiotaomicron*

An enzymatic analysis of 23 family GH92 α-mannosidases from *Bacteroides thetaiotaomicron* has been reported by Zhu, Y. *et al*, 2010, *supra*. Enzymes with α1,2-, α1,4-, α1,3- or α1,6-mannosidase activity are present in this group of enzymes, although some variants display very low activity. The three-dimensional structure of two α-1,2 mannosidases (Bt3990 and Bt2199) allowed to identify key amino-acid residues which seem to be a signature motif for α-1,2-mannosidase activity, i.e. His584-Glu585 and Trp99 in Bt3990. The activity on phosphorylated N-glycans (MNN4 sugars described in Example 1) of three GH92 enzymes from *B. thetaiotaomicron*, Bt3530 (Genbank nr AAO78636.1), Bt3965 (Genbank nr AAO79070.1) and Bt3994 (Genbank nr AAO79099.1) was tested. These enzymes display low α1,4-mannosidase activity and lack the His-Glu and Pro-Trp motif.

Bt3530, Bt3965 and Bt3994 were expressed in *E.coli* and purified as described in Zhu *et al*, 2010, *supra*. Samples (1 µl enzyme at a concentration of 0.1 mg/ml) were incubated with 7 µl APTS-labeled MNN4 sugars dissolved in 10 mM HEPES buffer pH 7.0 with 2 mM $CaCl_2$ in an overnight assay at room temperature. A control assay with CcMan5 was included. To confirm the presence of a terminal phosphate the reaction mixture was incubated with CIP. An N-glycan preparation containing $Man8GlcNAc_2$ (M8) and the monophosphorylated $ManP\text{-}Man8GlcNAc_2$ (MP-M8) was used as substrate. No uncapping activity for Bt3530, Bt3965 and Bt3994 was detected under the above assay conditions. No shift in electrophoretic mobility of the peaks was observed compared to the CcMan5 control reaction (appearance of fast running P-M8 peak), followed by CIP treatment (disappearance of P-M8).

In an additional experiment, 1 µl of enzyme, i.e. Bt3530 (0.1 mg/ml), Bt3965 (4.75 mg/ml) and Bt3994 (1.37 mg/ml) respectively, was incubated with MNN4 N-glycans at pH 7.0 (10 mM HEPES buffer pH 7.0 with 2 mM $CaCl_2$) and at pH 5.0 (10 mM Ammonium Acetate pH 5.0 with 2 mM $CaCl_2$) during 60 hours at room temperature. Very minor α1,2-mannosidase activity was observed with Bt3530 at pH 7.0, as a small $Man5GlcNAc_2$ (M5) peak appears in the electropherogram. At pH 5.0, on

the other hand, no α1,2-mannosidase activity is present, but a fast running peak at the left hand side of the electropherogram appears . This peak has the same electrophoretic mobility as P-Man8GlcNAc$_2$ (P-M8) and the terminal phosphate is hydrolyzed after incubation with CIP. CcMan5 (used at same concentration as Bt3530) is fully uncapping ManP-Man8GlcNAc$_2$ within 20 hours incubation at room temperature and at pH 7.0; therefore the observed activity of Bt3530 is rather low. After purification, the Bt3530 sample slowly precipitates when stored at 4 ˚C in 20 mM TRIS buffer, pH 8.0 with 300 mM NaCl. Therefore it is possible that instability of the Bt3530 protein influences the activity under the assay conditions used. Bt3965, which was used at a 40 times higher concentration, gave a similar result as Bt3530 at pH 7.0 (Panel G and H) and pH 5.0 (Panel I and J). No activity at all was observed with Bt3994 under the same reaction conditions (Panel K till N).

From these experiments can be concluded that phosphate uncapping activity is only a minor side activity of two of the three *B. thetaiotaomicron* GH 92 enzymes tested on MNN4 sugars.

OTHER EMBODIMENTS

While the invention has been described in conjunction with the detailed description thereof, the foregoing description is intended to illustrate and not limit the scope of the invention, which is defined by the scope of the appended claims. Other aspects, advantages, and modifications are within the scope of the following claims.

What is claimed is:

1. A method for uncapping a mannose-6-phosphate residue on an oligosaccharide, said method comprising

a) providing said oligosaccharide having a mannose-1-phospho-6-mannose linkage; and

b) contacting said oligosaccharide with a mannosidase capable of hydrolyzing said mannose-1-phospho-6-mannose linkage to phospho-6-mannose.

2. The method of claim 1, wherein said mannosidase comprises an amino acid sequence having at least 90% identity to the amino acid sequence set forth in residues 1 to 774 of SEQ ID NO:50 or to the amino acid sequence set forth in SEQ ID NO:50.

3. The method of claim 1, wherein said mannosidase comprises an amino acid sequence having at least 95% identity to the amino acid sequence set forth in residues 1 to 774 of SEQ ID NO:50 or to the amino acid sequence set forth in SEQ ID NO:50.

4. The method of claim 1, wherein said mannosidase comprises an amino acid sequence having at least 98% identity to the amino acid sequence set forth in residues 1 to 774 of SEQ ID NO:50 or to the amino acid sequence set forth in SEQ ID NO:50.

5. The method of claim 1, wherein for said mannosidase, the three dimensional protein coordinates of the atoms in the amino acid side chains located in the minimal catalytic center fall within 1.5 Å deviation of the coordinates of the equivalent atoms in FIG. 33.

6. The method of claim 1, wherein said mannosidase comprises an amino acid sequence having (i) a GVGXXGXGG motif, where X is Gly, Ala, Ser, Thr, or Cys; (ii) a VRXE motif, where X is any amino acid other than Pro; (iii) an X_1YQGX_2 motif, where X_1 is Leu, Ile, Val, Ala, Phe, Tyr or Met, and X_2 is Thr, Ser, or Asn; or (iv) GDXGN, where X can be any amino acid other than Pro.

7. The method of any one of claim 1-6, wherein said contacting step is performed using a purified mannosidase, a recombinant mannosidase, a cell lysate containing said recombinant mannosidase, or a fungal cell containing said recombinant mannosidase.

8. The method of any one of claims 1-7, wherein said oligosaccharide is attached to a protein.

9. The method of claim 7, wherein said protein is a human protein expressed in a fungal organism.

10. The method of claim 9, wherein said fungal organism is *Yarrowia lipolytica* or *Arxula adeninivorans*.

11. The method of claim 9, wherein said fungal organism is a methylotrophic yeast.

12. The method of claim 11, wherein said methylotrophic yeast is *Pichia pastoris*, *Pichia methanolica*, *Oogataea minuta*, or *Hansenula polymorpha*.

13. The method of claim 9, wherein said fungal organism is a filamentous fungus.

14. The method of claim 13, wherein said filamentous fungus is selected from the group consisting of *Aspergillus caesiellus, Aspergillus candidus, Aspergillus carneus, Aspergillus clavatus, Aspergillus deflectus, Aspergillus flavus, Aspergillus fumigatus, Aspergillus glaucus, Aspergillus nidulans, Aspergillus niger, Aspergillus ochraceus, Aspergillus oryzae, Aspergillus parasiticus, Aspergillus penicilloides, Aspergillus restrictus, Aspergillus sojae, Aspergillus sydowi, Aspergillus tamari, Aspergillus terreus, Aspergillus ustus,* and *Aspergillus versicolor.*

15. The method of claim 8, wherein said protein is a pathogen protein, a lysosomal protein, a growth factor, a cytokine, a chemokine, an antibody or antigen-binding fragment thereof, or a fusion protein.

16. The method of claim 15, wherein said lysosomal protein is a lysosomal enzyme.

17. The method of claim 16, wherein said lysosomal enzyme is associated with a lysosomal storage disorder (LSD).

18. The method of claim 17, wherein said LSD is Fabry's disease, mucopolysaccharidosis I, Farber disease, Gaucher disease, GM1-gangliosidosis, Tay-Sachs disease, Sandhoff disease, GM2 activator disease, Krabbe disease, metachromatic leukodystrophy, Niemann-Pick disease, Scheie disease, Hunter disease, Sanfilippo disease, Morquio disease, Maroteaux-Lamy disease, hyaluronidase deficiency, aspartylglucosaminuria, fucosidosis, mannosidosis, Schindler disease, sialidosis type 1, Pompe disease, Pycnodysostosis, ceroid lipofuscinosis, cholesterol ester storage disease, Wolman disease, Multiple sulfatase deficiency, galactosialidosis, mucolipidosis, cystinosis, sialic acid storage disorder, chylomicron retention disease with Marinesco-Sjögren syndrome, Hermansky-Pudlak syndrome, Chediak-Higashi syndrome, Danon disease, or Geleophysic dysplasia.

19. The method of claim 18, wherein said LSD is Pompe disease or Fabry's disease.

20. The method of any one of claims 1-6, wherein said mannosidase comprises a targeting sequence.

21. A method of producing a target protein having terminal phospho-6-mannose residues, said method comprising:

providing a fungal cell genetically engineered to comprise a nucleic acid encoding a mannosidase, said mannosidase capable of hydrolyzing a mannose-1-phospho-6-mannose linkage to phospho-6-mannose; and

introducing into said cell a nucleic acid encoding a target protein, wherein said cell produces said target protein comprising said terminal phospho-6-mannose residues.

22. The method of claim 21, wherein for said mannosidase, the three dimensional protein coordinates of the atoms in the amino acid side chains located in the minimal catalytic center fall within 1.5 Å deviation of the coordinates of the equivalent atoms in FIG. 33.

23. The method of claim 21, wherein said mannosidase comprises a) an amino acid sequence having at least 90% sequence identity to amino acids 1 to 774 of SEQ ID NO:50 or to the amino acid sequence of SEQ ID NO:50; or (b) an amino acid sequence having (i) a GVGXXGXGG motif, where X is Gly, Ala, Ser, Thr, or Cys; (ii) a VRXE motif, where X is any amino acid other than Pro; (iii) an X_1YQGX_2 motif, where X_1 is Leu, Ile, Val, Ala, Phe, Tyr or Met, and X_2 is Thr, Ser, or Asn; or (iv) GDXGN, where X can be any amino acid other than Pro.

24. The method of any one of claims 21-23, wherein said fungal cell further comprises a nucleic acid encoding a polypeptide capable of promoting mannosyl phosphorylation.

25. The method of any one of claims 21-24, wherein said fungal cell is genetically engineered to be deficient in OCH1 activity.

26. The method of any one of claims 21-25, wherein said mannosidase is a *C. cellulans*, *Streptomyces coelicolor*, or *Streptomyces lividans* mannosidase.

27. A method of producing a target protein having terminal phospho-6-mannose residues in a fungal organism, said method comprising

a) providing a fungal cell genetically engineered to comprise a nucleic acid encoding a mannosidase capable of hydrolyzing a mannose-1-phospho-6-mannose linkage to phospho-6-mannose, and said fungal cell further comprising a nucleic acid encoding a target protein; and

b) isolating said target protein having said terminal phospho-6-mannose residues.

28. The method of claim 27, wherein for said mannosidase, the three dimensional protein coordinates of the atoms in the amino acid side chains located in the minimal catalytic center fall within 1.5 Å deviation of the coordinates of the equivalent atoms in FIG. 33.

29. The method of claim 27, wherein said mannosidase comprises (i) an amino acid sequence having at least 90% sequence identity to amino acids 1 to 774 of SEQ ID NO:50 or to the amino acid sequence set forth in SEQ ID NO:50; or (ii) an amino acid sequence having (i) a GVGXXGXGG motif, where X is Gly, Ala, Ser, Thr, or Cys; (ii) a VRXE motif, where X is any amino acid other than Pro; (iii) an X_1YQGX_2 motif, where X_1 is Leu, Ile, Val, Ala, Phe, Tyr or Met, and X_2 is Thr, Ser, or Asn; or (iv) GDXGN, where X can be any amino acid other than Pro.

30. The method of any one of claims 27-29, wherein said target protein and said mannosidase are co-secreted.

31. An isolated fungal cell genetically engineered to produce glycoproteins comprising terminal phospho-6-mannose residues, said fungal cell comprising a nucleic acid encoding a mannosidase, wherein expression of said mannosidase in said fungal cell produces glycoproteins comprising said terminal phospho-6-mannose residues.

32. The fungal cell of claim 31, wherein for said mannosidase, the three dimensional protein coordinates of the atoms in the amino acid side chains located in the minimal catalytic center fall within 1.5 Å deviation of the coordinates of the equivalent atoms in FIG. 33.

33. The fungal cell of claim 31, wherein said mannosidase comprises a) an amino acid sequence having at least 90% sequence identity to amino acids 1 to 774 of SEQ ID NO:50 or to the amino acid sequence of SEQ ID NO:50; or b) an amino acid sequence having (i) a GVGXXGXGG motif, where X is Gly, Ala, Ser, Thr, or Cys; (ii) a VRXE motif, where X is any amino acid other than Pro; (iii) an X_1YQGX_2 motif, where X_1 is

Leu, Ile, Val, Ala, Phe, Tyr or Met, and X_2 is Thr, Ser, or Asn; or (iv) GDXGN, where X can be any amino acid other than Pro.

34. The fungal cell of any one of claims 31-33, said fungal cell further comprising a nucleic acid encoding a polypeptide capable of promoting mannosyl phosphorylation.

35. The fungal cell of any one of claims 31-33, wherein said fungal cell is genetically engineered to be deficient in OCH1 activity.

36. The fungal cell of any one of claims 31-33, said fungal cell further comprising a nucleic acid encoding a polypeptide capable of promoting mannosyl phosphorylation, and wherein said fungal cell is genetically engineered to be deficient in OCH1 activity.

37. The fungal cell of any one of claims 31 to 36, said fungal cell further comprising a nucleic acid encoding a target protein, wherein said target protein is a glycoprotein.

38. The fungal cell of any one of claims 31 to 36, wherein said target protein is a human protein.

39. The fungal cell of claim 38, wherein said target protein is a pathogen protein, a lysosomal protein, a growth factor, a cytokine, a chemokine, an antibody or antigen-binding fragment thereof, or a fusion protein.

40. The fungal cell of claim 39, wherein said lysosomal protein is a lysosomal enzyme.

41. The fungal cell of claim 40, wherein said lysosomal enzyme is acid alpha glucosidase or alpha galactosidase.

42. The fungal cell of claim 38, wherein said target protein is a protein associated with a LSD.

43. The fungal cell of claim 42, wherein said LSD is Fabry's disease, mucopolysaccharidosis I, Farber disease, Gaucher disease, GM1-gangliosidosis, Tay-Sachs disease, Sandhoff disease, GM2 activator disease, Krabbe disease, metachromatic leukodystrophy, Niemann-Pick disease, Scheie disease, Hunter disease, Sanfilippo disease, Morquio disease, Maroteaux-Lamy disease, hyaluronidase deficiency, aspartylglucosaminuria, fucosidosis, mannosidosis, Schindler disease, sialidosis type 1, Pompe disease, Pycnodysostosis, ceroid lipofuscinosis, cholesterol ester storage disease, Wolman disease, Multiple sulfatase deficiency, galactosialidosis, mucolipidosis, cystinosis, sialic acid storage disorder, chylomicron retention disease with Marinesco-Sjögren syndrome, Hermansky-Pudlak syndrome, Chediak-Higashi syndrome, Danon disease, or Geleophysic dysplasia.

44. The fungal cell of any one of claims 31 to 43, wherein said fungal cell is a *Yarrowia lipolytica* or *Arxula adeninivorans* cell.

45. The fungal cell of claim 32, wherein said polypeptide capable of promoting mannosyl phosphorylation is a MNN4 polypeptide.

46. The fungal cell of claim 45, wherein said MNN4 polypeptide is a *Yarrowia lipolytica*, *S. cerevisiae*, *Ogataea minuta*, *Pichia pastoris*, or *C. albicans* polypeptide.

47. The fungal cell of claim 46, wherein said polypeptide capable of promoting mannosyl phosphorylation is a *P. pastoris* PNO1 polypeptide.

48. The fungal cell of any one of claims 31 to 47, wherein said mannosidase is a *C. cellulans*, *Streptomyces coelicolor*, or *Streptomyces lividans* mannosidase.

49. The fungal cell of any one of claims 31 to 47, wherein said mannosidase comprises a secretion signal.

50. The fungal cell of any one of claims 31 to 47, wherein said mannosidase comprises a targeting signal to target said mannosidase to an intracellular compartment.

51. The fungal cell of any one of claims 31 to 47, wherein said mannosidase comprises a secretion signal and a targeting signal to target said mannosidase to an intracellular compartment.

52. A substantially pure culture of *Yarrowia lipolytica*, *Pichia pastoris*, *Hansenula polymorpha*, *Arxula adeninivorans*, *Pichia methanolica*, *Oogataea minuta*, or *Aspergillus niger* cells, a substantial number of which are genetically engineered to produce glycoproteins comprising a terminal phospho-6-mannose residue, said cells comprising a nucleic acid encoding a mannosidase capable of hydrolyzing a mannose-1-phospho-6-mannose linkage to phospho-6-mannose.

53. The culture of claim 52, wherein for said mannosidase, the three dimensional protein coordinates of the atoms in the amino acid side chains located in the minimal catalytic center fall within 1.5 Å deviation of the coordinates of the equivalent atoms in FIG. 33.

54. The culture of claim 52, wherein said mannosidase comprises a) an amino acid sequence having at least 90% sequence identity to amino acids 1 to 774 of SEQ ID NO:50 or to the amino acid sequence of SEQ ID NO:50; or b) an amino acid sequence having (i) a GVGXXGXGG motif, where X is Gly, Ala, Ser, Thr, or Cys; (ii) a VRXE motif, where X is any amino acid other than Pro; (iii) an X_1YQGX_2 motif, where X_1 is Leu, Ile, Val, Ala, Phe, Tyr or Met, and X_2 is Thr, Ser, or Asn; or (iv) GDXGN, where X can be any amino acid other than Pro.

55. The culture of any one of claims 52-54, wherein said cells further comprise a nucleic acid encoding a polypeptide capable of promoting mannosyl phosphorylation.

56. The culture of claim 55, wherein said cells are genetically engineered to be deficient in OCH1 activity.

57. An isolated glycoprotein comprising terminal phospho-6-mannose residues, wherein the protein is produced by the method of any one of claims 1-30.

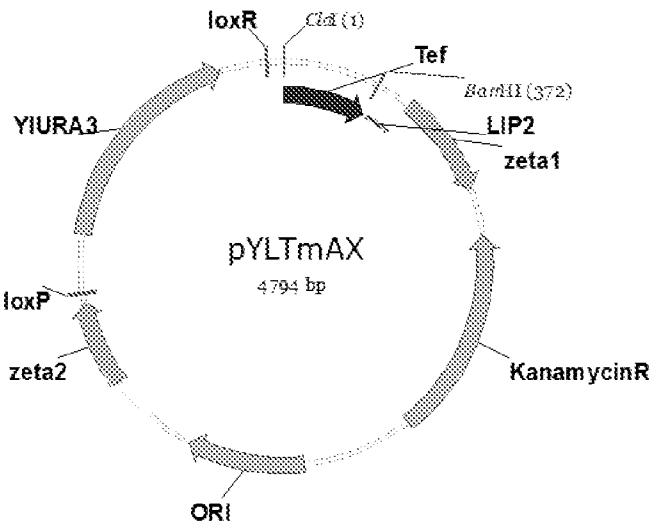
58. A composition comprising a glycoprotein, wherein at least 47% of the N-glycans on said glycoprotein have terminal phospho-6-mannose residues.

59. The composition of claim 58, wherein at least 50% of the N-glycans on said glycoprotein have terminal phospho-6-mannose residues.

60. The composition of claim 58, wherein at least 75% of the N-glycans on said glycoprotein have terminal phospho-6-mannose residues.

61. The composition of claim 58, wherein at least 90% of the N-glycans on said glycoprotein have terminal phospho-6-mannose residues.

FIG. 1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Tef
BamHI (372)
YlURA3
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zeta1
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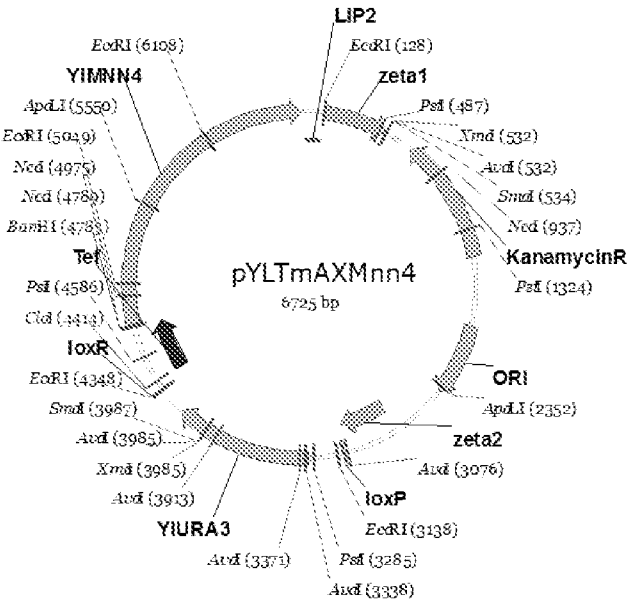
zeta2
KanamycinR
ORI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EcoRI (6108)
EcoRI (128)
YlMNN4
zeta1
ApaLI (5550)
PstI (487)
EcoRI (5049)
XmaI (532)
NcoI (4975)
AvaI (532)
NcoI (4789)
SmaI (534)
BamHI (4783)
NcoI (937)
Tef
KanamycinR
pYLTmAXMnn4
PstI (4586)
8725 bp
PstI (1324)
ClaI (4414)
loxR
ORI
EcoRI (4348)
ApaLI (2352)
SmaI (3987)
zeta2
AvaI (3985)
AvaI (3076)
XmaI (3985)
loxP
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FIG. 2

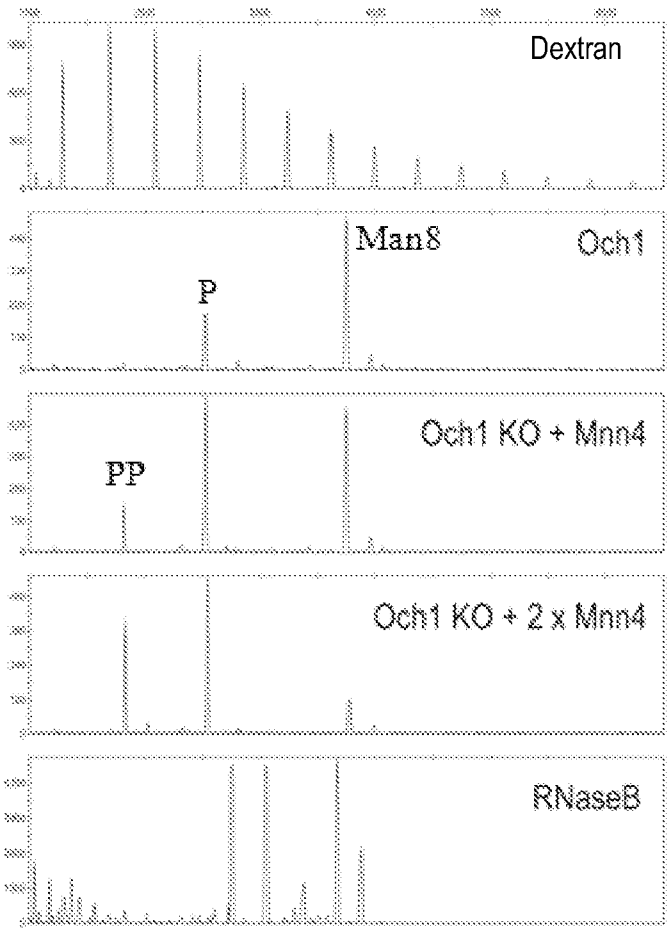

FIG. 3

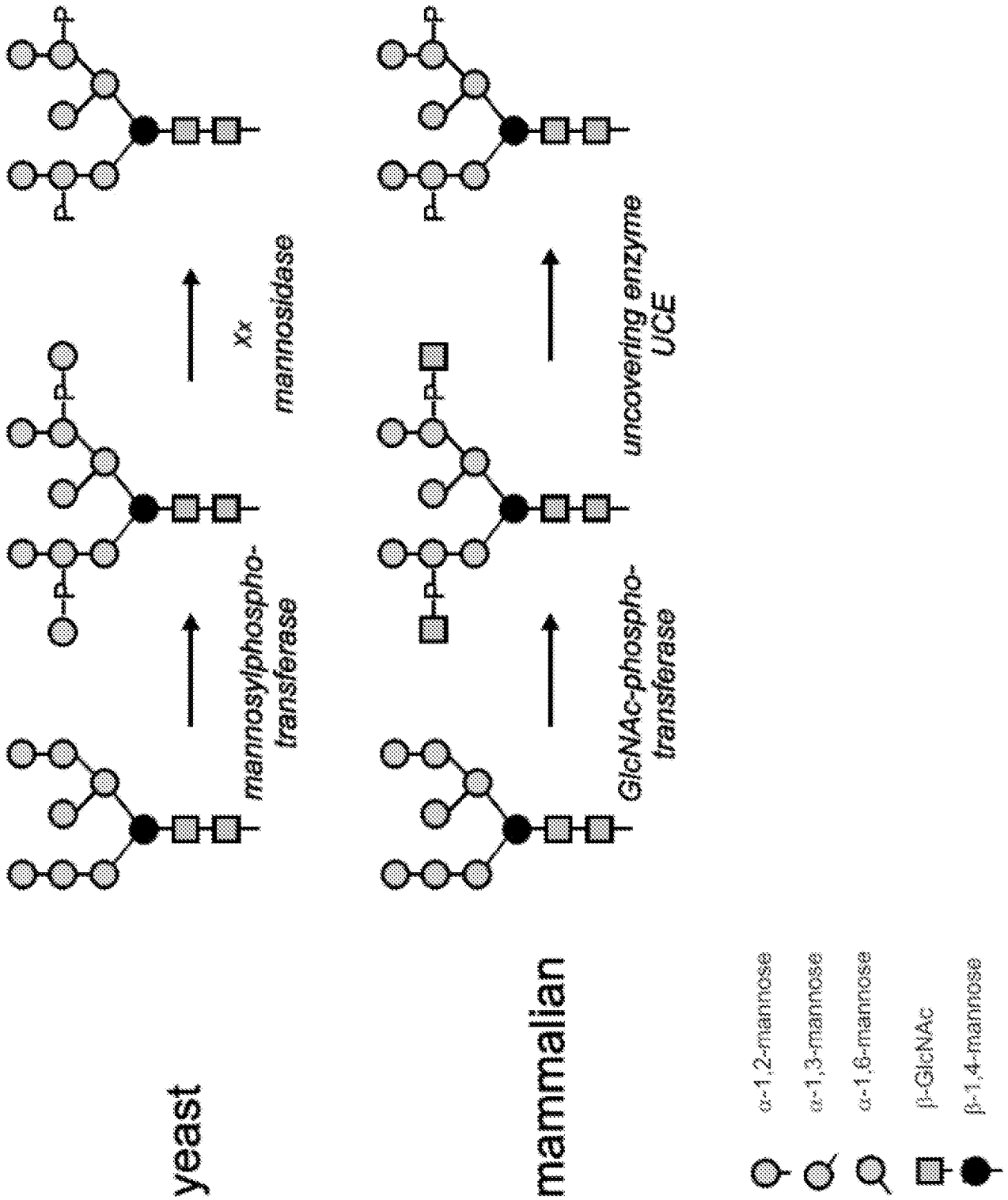
yeast
mammalian
mannosylphospho-transferase
Xx mannosidase
GlcNAc-phospho-transferase
uncovering enzyme UCE
α-1,2-mannose
α-1,3-mannose
α-1,6-mannose
β-GlcNAc
β-1,4-mannose

FIG. 4

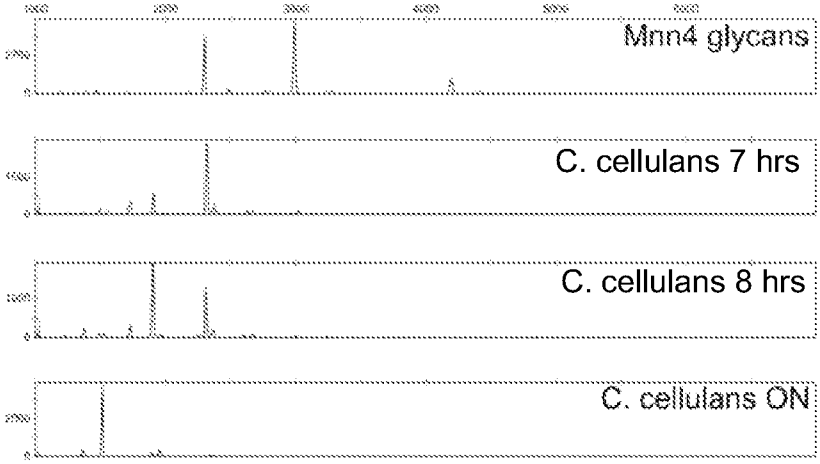
Mnn4 glycans
C. cellulans 7 hrs
C. cellulans 8 hrs
C. cellulans ON

FIG. 5

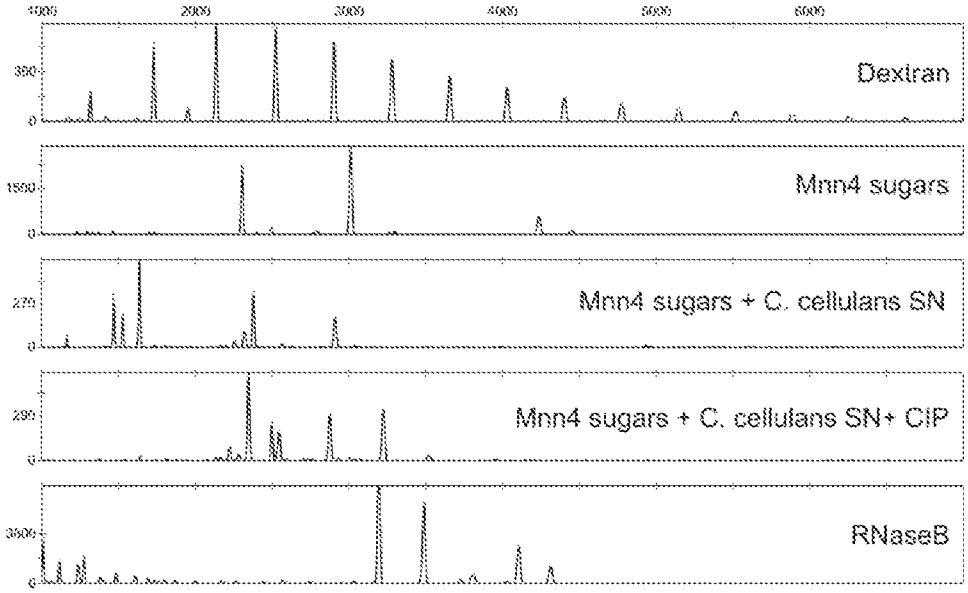
Dextran
Mnn4 sugars
Mnn4 sugars + C. cellulans SN
Mnn4 sugars + C. cellulans SN+ CIP
RNaseB

FIG. 6

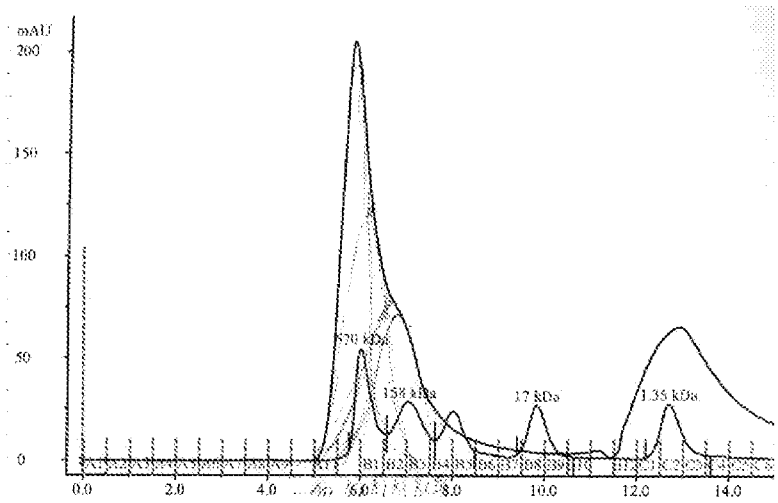

FIG. 7

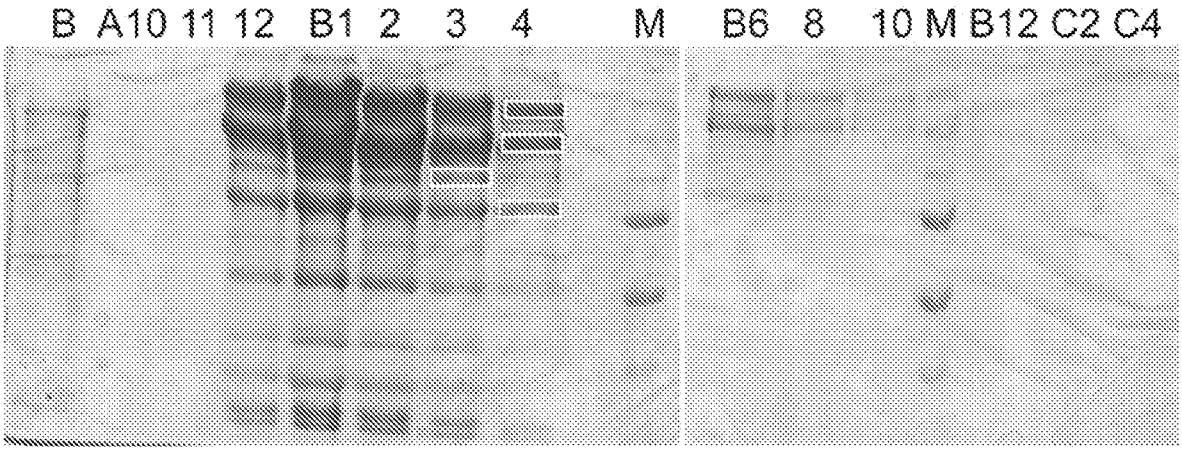

FIGURE 8A

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GAACTCCTACGCCTCGACGTCGTACAGCACGAACGCGGGGCGCGTGTGGGGCTTCAGCC
ACCGGCACGTGAACAGCGCGGGCTGCCCCGCGGCGGGCGAGCTGCTCGTCACGCCGGAC
ACGAGCGCGACCCCGCGCACGTCGCGCTCCTTCATCGCCATCAAGGACCAGAAGAGCAC
CGAGCGCGCGTCGGCCGGGTTCTACGAGGTGACCCTCGCGAACGACGTGCACGCCGAGC
TCACCGCGACCACGCGCGTCGGCGCGCACCGCTACACGTTCCCCGCCTCGACGACGTCG
CACCTGTCGTTCAACGTGGGCCAGACCCTGCGCGACGCCGGCGCGAGCTCGGTGACGTG
GGTCGACGACCGCACGCTCGAGGGCTGGGTCGACAACGGCGGCTTCTGCGGCGGCACGC
CGGACAAGCAGCGGTACTTCTTCAGCGCGACGTTCGACCGCCCGGTCGCGTCGAGCGGC
ACGTGGGGGACCGATGCGCGCTACGTCGCGGGCTCCACGACGAGCGAGGTCGCGGGCGG
CAACAACGGCGCCGTCGCGGTGTTCGACACCACGACCGACCGCGACGTCGAGGTGAGCG
TGGGCGTGTCCTTCGTGAGCGTCGACGGCGCGCGCGCCAACCGCGAGGCCGAGGCCACC
GACGAGGGCGGGCAGGTCGCGTTCGACACCGTGCGTGAGGAGGCCCGCGACGCGTGGAA
CGCGGAGCTGGGCCGTGCCGCGATCGACGCGTCGCCCGACCAGCGCCGGATCTTCTACA
CCCAGCTCTACAAGACGCTGCTGTCCCCGACGATCGGCAGCGACGTCGACGGCCGGTAC
CGCGGCATGGACCTCGAGGTCCACCAGGCCGACGGCTGGGACTACTACCAGAACTTCTC
GCTCTGGGACACGTACCGCACGCAGGCGACGCTGCACGCCCTCCTGCTGCCCGAGCGCG
CGCAGGACATCGTGCGCTCGATGTACCAGCACCGCGTCGAGGGCGGCTGGCTGCCGCGC
TGGTCCCTCGGTGCACTGGAGACCAACATCATGGCGGGCGACCCCGTCACGCCGTGGCT
CGCGGAGAACTTCGCGCTCGGCACCGTCCCCGACGACATCGCGGACGAGCTGTGGGACT
ACCTCGTCGAGAACGCCACGACGACCCCGCCGGACGACGTCGCGTCCGTCGGGCGGCGC
AGCACCGAGTTCTACGCCGAGCACGGCCACGTGCCGTTCTACCCCGAGAACGAGGGCGG
CCTCGGCGGCCAGTTCGAGGAGTACCGCCACGGCGGCTCGGCGACGCTCGAGCTCGCGC
TCGCCGACGCGAGCCTCGGCGCTGCGGCCGAGCGCACGGGTCGCGAGGGCGGCCAGGCG
TTCCTCGACAAGGGTCGCAACTGGCGCAACCTCTGGAACCCGGACGTCGAGCTCTCGGG
TGGCTTCCAGGGCATGGTCAACGCGAAGCGCCCGACGGGCGAGTTCGTCACGCTGCCCG
AGCTGACGGACGTCACGCGCTCCGGCTTCCACGAGGGCGTGCCGTGGCAGTACCAGTGG
ATGGTGCCGCAGGACGTCACGGGCCTCCAGGAGGTCATGGGCGGCGAGGACGGCTTCGT
CGAGCGTCTCGACTACTACTTCGACCAGCCGGCGCTCGCCGCGAACCCCGGCGTCTCGC
CGAGCACGTGGGCCAAGGGCGGCAGCTCGTACTACACGACCATCCGCTACAACCCGGGC
AACGAGCCGACGATCATGAACGCGTGGCTCTACGGCTACGTGGGCCAGCCGTGGAAGAC
GAACGACGTCCTCGCCGCGAACCTCAACCGCTTCCCGGACACCCCGGGCGGCGGCGTCG
GGAACGACGACCTCGGCACGCTTGCCGCCTGGTACGTCATGGCGTCGCTCGGGTTCGAG
CCCGTCATGCCGGGCTCGGGGATCCTCGCGCTCAACGCGCCGAAGGTGCAGGCCGCGAC
GCTCACGACCGATGCCGGGGCGACGCTGCGCATCGACGCGGCGGGCGCGAACGAGAAGC
TCCCGAGCTACGTCGCCGGCCTGGAGGTCGACGGCGTCGCGCACACCGCCGCGTGGCTC
GACGTCGCGGCGCTGCAGGACGGCGGCACGCTCGACTTCGACCTGTCCGGCACGAGCGC
GGGCCTCACGTGGGGCACCGGCGCGGCCGACCGCATCCCGTCGGTCTCCGCCGTCGCCC
CGCCCGCGCCGGTCGAGGTCGAGGCGAGCGCGCGCTGCCTCGGCGGCCGGGCGTTCGTC
GCGGTCCGCGCGACCAGCACGGCCGACGCGCCGGTGGACGTGACTCTCACGACGCCGTT

CGGCGAGCGGACGGTCCGGCACGTGCAGCCGGGCAGGAGCGCCTACCAGTCGTTCACGA
CGCGCACGACGTCCGTCGAGGCCGGGACGGCGACCGTCACGGTCGTCGCCGCGGACGGC
ACGACGTCGACGGTCGACGCGGCGTACGAGGCGCTGGCCTGCGGC (SEQ ID NO:6)

FIGURE 8B

MRRPRLALLAAGLALAVAPGTLLPVAAGAAPADEGTVTAAAGDDLTLEVNPFVGTESEG
NAYPGATVPFGMVQLSPDNTNSYASTSYSTNAGRVWGFSHRHVNSAGCPAAGELLVTPD
TSATPRTSRSFIAIKDQKSTERASAGFYEVTLANDVHAELTATTRVGAHRYTFPASTTS
HLSFNVGQTLRDAGASSVTWVDDRTLEGWVDNGGFCGGTPDKQRYFFSATFDRPVASSG
TWGTDARYVAGSTTSEVAGGNNGAVAVFDTTTDRDVEVSVGVSFVSVDGARANREAEAT
DEGGQVAFDTVREEARDAWNAELGRAAIDASPDQRRIFYTQLYKTLLSPTIGSDVDGRY
RGMDLEVHQADGWDYYQNFSLWDTYRTQATLHALLLPERAQDIVRSMYQHRVEGGWLPR
WSLGALETNIMAGDPVTPWLAENFALGTVPDDIADELWDYLVENATTTPPDDVASVGRR
STEFYAEHGHVPFYPENEGGLGGQFEEYRHGGSATLELALADASLGAAAERTGREGGQA
FLDKGRNWRNLWNPDVELSGGFQGMVNAKRPTGEFVTLPELTDVTRSGFHEGVPWQYQW
MVPQDVTGLQEVMGGEDGFVERLDYYFDQPALAANPGVSPSTWAKGGSSYYTTIRYNPG
NEPTIMNAWLYGYVGQPWKTNDVLAANLNRFPDTPGGGVGNDDLGTLAAWYVMASLGFE
PVMPGSGILALNAPKVQAATLTTDAGATLRIDAAGANEKLPSYVAGLEVDGVAHTAAWL
DVAALQDGGTLDFDLSGTSAGLTWGTGAADRIPSVSAVAPPAPVEVEASARCLGGRAFV
AVRATSTADAPVDVTLTTPFGERTVRHVQPGRSAYQSFTTRTTSVEAGTATVTVVAADG
TTSTVDAAYEALACG (SEQ ID NO:7)

FIGURE 9A

GTGAGCCTCGCGCTCCCGCTGGCGGCGTACGCGGCGCCCGGGATCGGGGCGTCGCCCGC
GACCGCCGCCGGGACGGAGGCAGCGACGGGGTCCGATGCCGCCGCCGTCGACGGCCCGC
TGGTCGACTACGTCAACCCGTTCATCGGGACCAAGGACGACGGCAACACCTACCCGGGC
GCTGCCGTGCCGTTCGGCATGGTGCAACTCTCGCCGGACAACGGCCACAACGTCGGGTA
CGACTACGACCGCACGTCGGTGCGCGGGTTCTCGCTCGTGCACCTGTCCGGCGTCGGCT
GCGGCCTCGGCGGTCCGCTCCCGACCCTGCCGACGACGGGCGCGATCACCTCGACCGAC
TACGGCCAGTACGCGCTCGGTTTCTCGCACGACGACGAGGAGGCCTCGCCGGGGTACTA
CCGCGTGGGTCTCCAGGCGCCGGCGGGCACGATCGAGGCCGAGCTCACCGCGACCGAGC
GCACGGGCGTCCAGCGGTACACGTTCCCCGCGACGGCGCAGGCCAACGTCCTGCTCAAC
GCCGGCCAGGCGCTCAACCGGGTGACGGAGTCCGACGTGCGCGTCGTGGACGACCGCAC
GGTCGAGACGCGCATCACCGTCCGCGGCTTCTGCCAGGACACCGAGCCGCAGACGATCT
GGACCCGCACGACCTTCGACCGGCCGTTCGTCGCGCACGGCACGTGGGACGGCCAGGTC
GTCACCGCGGGCGCGGACGCCGCGTCCGGCGGCGAGGGCCGTCGCGGCGCGTACGTCAC
GTTCGACACGACCGGCGGCGACCTCGACGTCGAGGCCGTCACCGCGATGAGCTACGTGG
GCGCCGACGGCGCCGCGGCGAACCTCGCCGCGGAGGCCGGCACGTTCGACGCCGTGCAC
GACGCCGCGCGCTCGGCCTGGGAGGAGCGGCTCGGCCTCGTGCGGGTCGCGCAGGGCGA
CCCGGACGACCTGCGCACCTTCTACTCCTCGCTCTACCGCAGCTTCCTCGCGCCGAACG
TCGGCTCCGACGTCGACGGGCGCTACCGCGGCTGGGACCAGGAGGTCCACGCCGCGGAA
CCGGACTTCACCTACTACCAGAACTACTCGCTCTGGGACACGTACCGCACCCAGCAGCA
GCTCCTGTACCTGCTCGCGCCCGACGAGTCGGCCGACATGGCGCTCTCGCTCGTGCGCC
AGGGCCAGCAGGGCGGGTGGCTCCCGCGCTGGGGCTACGGCACGGTCGAGACGAACATC
ATGACCGGCGACCCGGCGACGCCGTTCCTCGTCAGCGCCTGGCGCCAGGGCCTGCTCGC
GGGCCACGAGGAGGAGGCGTACGCGGTCCTGAGGGAGAACGCCGACGGCGTCCCGCCCG
CCGACTCGCCCTTCAACGGGCGCGCGGCGAACGTCGAGTACCTGCGCGACGGGTTCGTC
CCGCACGAGCCGGCGCGCTCGGGCAAGCCCGGCGACTACGACCTCCAGCACGGCGCCTC
GGCGACCATGGAGTACGCCCTCGCCGACGCGATGCTCTCGACCATGGCGCGCGGCCTCG
GCCACGACGAGGACGCCGACCGGTACGCCGCCCGCGGCCAGAGCTACCGCAACGTGTTC
GACCCGCGCACGGGCAACTTCCGGGCGCGTAACGCGGACGGCTTCTTCGTGGGCGACGC
GGACCCCGCGCACTCCGACGGGTTCCACGAGGGCACGGCGGTGCAGTACCAGTGGCTCG
TGCCCCAGGACGTGCCGGGCCTGTTCGACCTCATGGGCGGCACCGACGCCGCGGTCGAC
CGCCTCGATGCGTTCTTCGCGTACGACGAGCTCGTCGCCGACCCCCCGCACGTCGCGAG
CGAGGTGTGGGTCAACGGCACGTACGACTACTACGGCTGGGAGACCTACAACCCGAACA
ACGAGCCCAACCTCCATGCGCCGTACGTCTACCTGTGGACCGGGCAGCCCTGGAAGACG
ACGGACGTCGTGCGCGCCGCGTCGACCCTCTTCACCGACGGCCCCGACGGCGTCACGGG
CAACGACGACCTCGGCACGATGTCCGCGTGGCACGTGCTGTCGTCGATCGGCGTGTACC
CGATCGTGCCGGGCGCCGATCTGTGGGGCCTGACGACGCCGCTCTTCGACGACGTGACG
ATCACGCTCGACCCGGAGGTCTTCGGTCGGGACTCCCTGCGCCTCACGGCGGACGGCGT
CGCGCCCGACACGCACTACACGCAGTCCGTGTCGCTCGGCGGCGAGCCGCTCGATCGCG
CCTGGGTCACGGGCGACGAGCTCACCGCGGCCGGCACGCTCGACGTGACCGTCGGCACC
GAGCCGTCCGCGTGGGCGACCGACCCCGCGGCCTCGCCGGGCGCCGTCGTGCCTGCGGA
CGGCACGGTCGAGCGCCTGTTCGTCGGCGCGACGCCGCGGCAGCCGGTCCTCGCCCCGG
GCGGGCGGACCGAGGTCGCAGTCCAGGTCGTCGCCCAGGGCGCGGGGACGTCCAGCGGG
ACGCTCGAGGTGACGTCCGACGGCGCGGTCACCGCGACGACCGACCTCGCCGAGTGGAC
CGCCGAGTCCGACGGCCTGCCGGCCACGGTCGAGGGCACGGTGACGATCGAGGCTCCCG
CCGACGCCGAGCCGGGTCTGCACACGGTGCGGCTCGTCGTGCGCGACGCCGCGGGGACC

GAGGCGGTCCGCGAGGTCTCGGTCGTCGTGTCCGGGGAGTCGTGGATCGCCGACGCGTT
CGACAACGTCGGCATCGGCGACGCCGGGGCGGCCAACGCGAACCTCGACGGCTCGGGCG
CCTACCTCCTGCGCGACCTGCTCGCGGACCTCGGCGCCGTCCAGGGCCTGGAGCTCACC
GTGCCGGGCACGGACCTCACCTACACGCTCGGGGCCCCGCGGGCGGGCGCGCCCGACAA
CGTCGCCGCGAGCGGCGAGGTCCTCGAGGTGCCCGAGCACCTGCGCTCGGCCCGCCACC
TCTCGGTGGTCGGGACGAGCACGCACGGCACGCACGGGGGCGGCCTCGTCCTCGGGTTC
GCCGACGGCTCGTCGCAGACCGTCGACGTGCGCCTCAGCGACTGGTGCACGGGCTCGCC
CGAGCCCGGCAACATCACGGTCGCGAAGGCCGGGGCGCGCGGCGACCGCGAGAACGTGC
AGAAGATCGGCTGCGGCCTCTACGCCACCGCGCCCGTCGCGATCCCCGAGGGCAAGGTC
CTGACGTCGGTCACGCTGCCGAGCGACGAGCGGTTCCACGTGTTCGCGATCGCGACCGA
CGCGACGGGGGACGTCCCCGCGCCGCAGGTCGAGGTCACGGCGCAGGCCCGCTGCCTCG
GCGGCAAGGCGTTCGTCGCGGTGCGCGCGCTCAACACGGGCGAGCAGCCCGCCGCGATC
GAGCTCGCGACCCCGTACGGCTCCAAGCTCTTCGGTGACGTCGCTCCCGGGGCGAACGC
GTACCAGTCGTTCGCCACCCGCGCCGCCGCCGTCGAGGCGGGCGAGGTCACGGTGACCG
TGACGACGCCCGACGGCGAGCCCCAGCAGGTCACGGCCGCGTACGACGCCGCCGCCTGC
TCC (SEQ ID NO:8)

FIGURE 9B

VSLALPLAAYAAPGIGASPATAAGTEAATGSDAAAVDGPLVDYVNPFIGTKDDGNTYPG
AAVPFGMVQLSPDNGHNVGYDYDRTSVRGFSLVHLSGVGCGLGGPLPTLPTTGAITSTD
YGQYALGFSHDDEEASPGYYRVGLQAPAGTIEAELTATERTGVQRYTFPATAQANVLLN
AGQALNRVTESDVRVVDDRTVETRITVRGFCQDTEPQTIWTRTTFDRPFVAHGTWDGQV
VTAGADAASGGEGRRGAYVTFDTTGGDLDVEAVTAMSYVGADGAAANLAAEAGTFDAVH
DAARSAWEERLGLVRVAQGDPDDLRTFYSSLYRSFLAPNVGSDVDGRYRGWDQEVHAAE
PDFTYYQNYSLWDTYRTQQQLLYLLAPDESADMALSLVRQGQQGGWLPRWGYGTVETNI
MTGDPATPFLVSAWRQGLLAGHEEEAYAVLRENADGVPPADSPFNGRAANVEYLRDGFV
PHEPARSGKPGDYDLQHGASATMEYALADAMLSTMARGLGHDEDADRYAARGQSYRNVF
DPRTGNFRARNADGFFVGDADPAHSDGFHEGTAVQYQWLVPQDVPGLFDLMGGTDAAVD
RLDAFFAYDELVADPPHVASEVWVNGTYDYYGWETYNPNNEPNLHAPYVYLWTGQPWKT
TDVVRAASTLFTDGPDGVTGNDDLGTMSAWHVLSSIGVYPIVPGADLWGLTTPLFDDVT
ITLDPEVFGRDSLRLTADGVAPDTHYTQSVSLGGEPLDRAWVTGDELTAAGTLDVTVGT
EPSAWATDPAASPGAVVPADGTVERLFVGATPRQPVLAPGGRTEVAVQVVAQGAGTSSG
TLEVTSDGAVTATTDLAEWTAESDGLPATVEGTVTIEAPADAEPGLHTVRLVVRDAAGT
EAVREVSVVVSGESWIADAFDNVGIGDAGAANANLDGSGAYLLRDLLADLGAVQGLELT
VPGTDLTYTLGAPRAGAPDNVAASGEVLEVPEHLRSARHLSVVGTSTHGTHGGGLVLGF
ADGSSQTVDVRLSDWCTGSPEPGNITVAKAGARGDRENVQKIGCGLYATAPVAIPEGKV
LTSVTLPSDERFHVFAIATDATGDVPAPQVEVTAQARCLGGKAFVAVRALNTGEQPAAI
ELATPYGSKLFGDVAPGANAYQSFATRAAAVEAGEVTVTVTTPDGEPQQVTAAYDAAAC
S

FIGURE 10A

GTGCGGCGCTCCGTCGCGGCGCTCTCTGCCACGGCGGTCCTGGCCGCCGGACTCTCGAT
CGCGCCCGCCGTCGGGCTCGCGGTCCCGGCGGTCGCGGCCGCACCCGACCTCGTTGAGG
ACCCCGTCTCCTTCGTCGACCCGTTCGTCGGGACCGGCCAGGCGACGGGCGTCGTCGGG
GAGATCAACAACTTCCCCGGGCCGTCGATGCCGTTCGGCATGATGCAGCTCTCGCCCGA
CACCCAGGTCTCCGTGGGCAACGGCGACAAGGCGTACGCGGGCTACCGCTACTCGCACC
AGGCGATCCGCGGCTTCTCCATGACGCACGCGGCCGCCGGGTGCTGGATCTTCGGCGAC
GTCCCGATCCTCCCCGTGACGGGCGACGTCGGGCAGTACCCGTGGGACCGCAAGGAGGC
GTTCAGCCACGACGCGGAGAGCGCCGAGGTCGGCCGGTACGCGGTCACGCTCCAGTCGT
CGGGGATCGATGCGGAGGTGTCGGCCGCGACCCGCTCGGGCGGACTGACGTTCGACTAC
CCCGAGGGCGGTGCCGCGTCGCAGGTGATCGTCAACGCCGCGGGCTCGCTCGCGAGCGT
GCGCAACGCGACGGTCGAGGTCGAGGACGCGCGCACGGTCACCGGCTCGGTGACGAGCG
GCGGGTTCTGCGGCAAGAACAACACGCACACGACGTACTTCGCGATCGAGCTCGACCAG
GACGCGCAGGCGTTCGGCACGTGGCAGGGCTCGACCGTCTCGCCCGGCGACCCGTCGGC
CGACGGCAACGGCGCGGGCGCGTGGCTCACCTTCGCGCCCGGCGCGACGGTGCACGCGA
AGGTCGGCATGTCCTACGTGAGCGTCGAGGGCGCGCGCGCCAACCTCGCGGCCGAGATC
CCGGGCTTCGACTTCGACGCCGTCCGGGACGCCAACCGCGCCGCCTGGTCCGACCTGCT
CGGCAAGGTCCGCGTCGCGGGGCAGGACGCCGACGACCTCACCATGTTCTACACGTCGC
TCTACCACTCGCTGCTGCACCCGAACACGTTCACCGACGTGGACGGCCGGTACGTCGGG
TTCGACGGGGAGATCCACCAGGCCCCCGAGGGGCACGAGCGGTACGCGAACTTCTCCGA
CTGGGACACGTACCGGTCGCTCGGCGCGCTCCAGGCGCTGCTGGCGCCCGACCAGGCGT
CGGACATGGCGCAGTCGCTCGTCGAGGTCGCCGACCAGTCCGGCTGGCTGCCGCGCTGG
CCCGTCGCGAACCAGCACACGGGCCAGATGACCGGTGACTCCTCGGTGCCGCTCATCGC
GAGCATGTACGCGTTCGGGGCGCGCGACTTCGACGCGGAGTCGGCGCTCGCGCACATGG
TCAAGGGTGCGACGAGCGCCGCCCCGACCGCGAACGGCTACGTGCAGCGGCGCGGGATC
GAGACGTACCTCGAGCGCGGCTACGCGCCCCAGACCGAGGAGTTCCGGGGCGACCACCG
CGTCGTCGGCGCGTCGATCACGCTCGAGTGGTCGATCGCCGACTTCGCGATCGGGCAGC
TCGCGGCCGCGCTCGGCCAGGACGACGTCGCCACCGAGTACGCCGCCCGCGGCCAGTGG
TGGCAGAACGTCCACGACCCCGTGACCCGCACGGCGGGCGCCCGGAACGACGACGGCAC
GTTCGTGCGGTCGCAGGGCGGCGGCGGGTTCGGGCAGGAGGGCTTCGACGAGGGCAACG
CCGAGCAGTACACGTGGCTCGTGCCGCAGAACGTCGCGGGGCTCACCGACGCGCTCGGC
GGGCGTGAGGCCGTCGCGGAGCGGCTCGATGCCTTCACGGTGCAGCACAACGCCGGCCC
GAACGAGCCGTACCTGTGGATCGGCAACGAGCCGAACTTCGGCGTCCCGTGGCTGTACG
ACTACGTGGGCCAGCCGTGGCGGACGAGCGAGCTCGTGGACGAGCTTACGTCCACGCTG
TTCCGGCCCGAGCCGAACGGCAAGCCCGGCAACGACGACCTCGGCGCCCAGGCCGGCTG
GTACGTGTGGGCCGCGATGGGCCTGTACCCCACCACGCCGGGCACGGACGTGCTCGCGC
TCAACGCGCCGCGCTTCGACCGCGTCGTGGTCGACCTCGGCGAGGGCGACACCCTCGAC
CTGCGCGCCCCCGGCGCCTCGACCGGCGCCCGCTACATCAGCGGCGTCACCATCGACGG
CGCAGCCTGGGACGGGACCTCCCTGCCGCGCCACGTCGCGCACGACGGCGGCGTCGTCG
AGCTCGCGATGTCGACCGCACGCGACACGACGTGGGGGACCGCAGCCGAGGACGCCCCG
CCGTCGTGGCGCGACGGCGAGTCCGCCGTGGTCGCCGCCGCGGACCCGGGCCTCGTGAC
GGTCGCCCCCGGCGGGACCGCCGACGCGTCGGTGGCCGTGCAGCTCTTCGGCGCCGACG
CCGCCGACGTGCGCGTCGCGGTCGACGCGCCCGGGGGCATCGGGGTCGGTGAGCCCGCG
CTCGTCGACGACGGCTCGGGCCACCTCACCGGGACGGTCCCCGTCCAGGTGGGTGCCGG
CGTCGCGTCCGGCTACCACGACGCGCGCCTCGTGCTCTCGGCCGGGGACGACGACGTCG
AGGTGCCCCTCACCGTCCTCGTCGCCGCGCCCGGGTCGCTCGTTGCGGCCTACGACACG

GTCGGCACTGCGCCCGAGGCGAACCGCGGCGTCGGGAACTTCGACGCGGCCGGCAACTC
GTTCTCGCGCGAGGCGCTCGCCGACGCGGGTCTCACGCCCGGGTCGGCGCACGACGTCG
ACGGCCTGGCGTTCACGTGGCCGTCCTCACCCGTGGGGCGCCCGGACTCGGTCACGCTC
ACCGGCGAGACCGTGCGGCTCGACGCGCCGACGAGCCGGCTCGCGTTCGTGGGCGCCGC
GACCGACGGGACCCATCGCGGGACCGCGGTCGTGACGTTCGACGACGGCAGCACCGCGA
CCACGACGATCGGCTTCGGCGACTGGGTGCTGCCGAGCGCGGACGGCTCGCCGGTCGAG
GGCAACTCGGTCGTCGCGCAGATGAACCGGCGCAACGGCGACAAGGACAGCGCGTTCGT
GTTCGCCACCGCCCCGTACACCGCGCCCGAGGACCGCCGCGTGGTCGCGGTGAGGTTCC
CCGACGTCGACGACCTGCACGTCTTTGCGATCGCGACCGAGCCGGCCGCGGACGTGCAC
CTCGTGGACGTGACGGTCTCCCTGCGCTGCCTCGCCGGGACCCCGTACGTGGCGGTGCG
CGCGGCGAACGTCTCCGCCGGGGCCGTCGACGTCGACCTCACGACGGGCGTGGGCTCGC
GGTCCTTCACGGCCGTCGCCCCCGGCGCCAACGCCTACCAGTCGTTCGCCGCCCGCGGC
GCGACCGGGAACGTCGACGTCACCGTCACGGCCACGGGGGAGGAGGGGACGCAGACGGT
CGCGCGGACCGTCGTCGTCCCGCGCTGCTCC (SEQ ID NO:10)

FIGURE 10B

VRRSVAALSATAVLAAGLSIAPAVGLAVPAVAAAPDLVEDPVSFVDPFVGTGQATGVVG
EINNFPGPSMPFGMMQLSPDTQVSVGNGDKAYAGYRYSHQAIRGFSMTHAAAGCWIFGD
VPILPVTGDVGQYPWDRKEAFSHDAESAEVGRYAVTLQSSGIDAEVSAATRSGGLTFDY
PEGGAASQVIVNAAGSLASVRNATVEVEDARTVTGSVTSGGFCGKNNTHTTYFAIELDQ
DAQAFGTWQGSTVSPGDPSADGNGAGAWLTFAPGATVHAKVGMSYVSVEGARANLAAEI
PGFDFDAVRDANRAAWSDLLGKVRVAGQDADDLTMFYTSLYHSLLHPNTFTDVDGRYVG
FDGEIHQAPEGHERYANFSDWDTYRSLGALQALLAPDQASDMAQSLVEVADQSGWLPRW
PVANQHTGQMTGDSSVPLIASMYAFGARDFDAESALAHMVKGATSAAPTANGYVQRRGI
ETYLERGYAPQTEEFRGDHRVVGASITLEWSIADFAIGQLAAALGQDDVATEYAARGQW
WQNVHDPVTRTAGARNDDGTFVRSQGGGGFGQEGFDEGNAEQYTWLVPQNVAGLTDALG
GREAVAERLDAFTVQHNAGPNEPYLWIGNEPNFGVPWLYDYVGQPWRTSELVDELTSTL
FRPEPNGKPGNDDLGAQAGWYVWAAMGLYPTTPGTDVLALNAPRFDRVVVDLGEGDTLD
LRAPGASTGARYISGVTIDGAAWDGTSLPRHVAHDGGVVELAMSTARDTTWGTAAEDAP
PSWRDGESAVVAAADPGLVTVAPGGTADASVAVQLFGADAADVRVAVDAPGGIGVGEPA
LVDDGSGHLTGTVPVQVGAGVASGYHDARLVLSAGDDDVEVPLTVLVAAPGSLVAAYDT
VGTAPEANRGVGNFDAAGNSFSREALADAGLTPGSAHDVDGLAFTWPSSPVGRPDSVTL
TGETVRLDAPTSRLAFVGAATDGTHRGTAVVTFDDGSTATTTIGFGDWVLPSADGSPVE
GNSVVAQMNRRNGDKDSAFVFATAPYTAPEDRRVVAVRFPDVDDLHVFAIATEPAADVH
LVDVTVSLRCLAGTPYVAVRAANVSAGAVDVDLTTGVGSRSFTAVAPGANAYQSFAARG
ATGNVDVTVTATGEEGTQTVARTVVVPRCS (SEQ ID NO:11)

FIGURE 11A

ATGACCAGACCACTCCCGCCCGGACGCGCGGTCGCGCGGTCCGGCAGCGGCCGCGCCCG
GCCCCTCGGCCTCGTGCTCGCCGCCGCACTCGCCGTCCCGCTCGGGGTGCCTCTCGCGG
CCCCCGCGGGAGCCCTCGCTGCCGCGCCCGCCGCGGCCGCCGAGCCCGGCGACTTCTCG
TCCTCGTTCGAGTCCGGCGACCCGGCCGCGCTGCCCACCACCGTGGCGGAGCGCGACGG
CGCGCCCTGGCAGGCGAACGTCGGCTCGTTCACGGCCGGCCTGCCCGGGAGCGTCCTCG
GGCAGCTGAAGGGCGTCACGGCGAGCGCGCAGAACCTGCCCAACGAGGGCGCGGCGAAC
CTCGCCGACGGCAGCTCGGGCACCAAGTGGCTCGCGTTCGCGTCGACCGGCTGGGTCCG
GTACGAGTTCGCCGAGCCCGTCTCGTTCGTCGCGTACACGATGACCTCCGGCGACGACG
CCGCCGGTCGCGACCCGAAGACCTGGACGGTCGAGGGGTCGAACGACGGGTCCACGTGG
GCCGCGCTCGACCGCCGGACGGACGAGGACTTCCCGAACCGCCAGCAGACGCGCACGTT
CGAGCTCGAGGCGCCCACCGCGGCGTACACGTACCTGCGCCTCAACGTCACGGCGAACT
CGGGCGACTCCATCGTCCAGCTCGCCGGGTGGGACCTCTCGGCCGACCTGAGCGCCGGC
CCGTCCGCGGCCCCCATGACGACGAAGGTCGGCACCGGGCCGCGCGTCAGCTTCACCAA
CAAGGCGGGCGTCGGGTTCTCCGGCCTGCACTCGCTCCGGTACGACGGCTCGCACCTCG
CCGACGGCGAGACGTACGCGACGAACGTGCTCTACGACGACGTGGACGTCGTCGTCGGC
GAGGACACGCGCCTGAGCTACACGATCTTCCCCGAGCTGCTCGACGATCTGCAGTACCC
GTCGACGTACGCGGCGGTGGACGTCCTGTTCACCGACGGGACCTACCTGTCCGACCTCG
GCGCGCGCGACGCGCACGAGACGGTCGCGACCGCGCAGGCGCAGGGCGAGGGCAAGATC
CTCTACGCCGACCAGTGGAACTCGGTGCGGGTCGACCTCGGCGACGTCGCCGAGGGCAA
GACCGTGGACCAGGTGCTGCTCGGGTACGACAACCCGGGCGGTCACGCCGGGACGAAGT
TCGCGGGCTGGCTCGACGACGTCGAGATCACGGCGGAGCCGGCCACGATCGACGGGTCG
AGCCTCGCCAACTACGTGGACACGCGCCGCGGCACGCTCGCGTCGGGCAGCTTCTCGCG
CGGGAACAACATCCCCGCGACGGCGACGCCGAACGGGTTCAACTTCTGGACGCCGTACA
CGAACGCCTCCTCGCAGAGCTGGCTGTACGAGTACCACAAGGCCAACAACGCCAACAAC
AAGCCCGTCCTCCAGGGCTTCGGGATCTCGCACGAGCCGAGCCCGTGGATGGGCGACCG
CAACCAGCTGACGTTCCTCCCGTCGACGGCGTCGGGGACGCCCGACGCCACGCTCTCGA
CGCGCGGCCTCGAGTTCGACCACGCGGACGAGACGGCGCGGCCGGACTACTACGGGGTC
ACGTTCACCAACGGGTCCGCGATCGAGGCGACGCCCACCGACCACGGCGCGGTGCTCCG
CTTCAGCTACCCCGGAGCCAAGGGCCACGTGCTCGTGGACAAGGTGGACGGCTCCTCCA
AGCTCACGTACGACCAGGCCACGGGCACGATCTCCGGCTGGGTCGAGAACGGCTCGGGC
CTGTCCGTGGGCCGCACGCGCATGTTCGTCGCCGGCACCTTCGACCGTAGTCCGACGGC
GGTCGGGACGGCGGCGGGCAACCGTGCGGACGCGCGCTTCGCGACGTTCGAGACGTCGT
CCGACAAGACGGTCGAGCTGCGCGTCGCGACGTCGTTCATCAGCCTCGACCAGGCGCGC
AAGAACCTCGACCTGGAGGTGACGGGCAAGACCTTCACGGAGGTCAAGGCCGCCGCCGC
GCAGGCGTGGAACGACCGCCTGGGGGTCATCGAGGTCGAGGGCGCGAGCGAGGACCAGC
TCGTCACGCTGTACTCGAACCTCTACCGCCTCAACCTGTACCCGAACTCGCAGTTCGAG
AACACGGGCACGGCGCAGGAGCCGGTGTACAGGTACGCGAGCCCGGTCTCCGCGACCAC
GGGCTCCGCGACGGACACGCAGACCAACGCGAAGATCGTCGACGGCAAGATCTACGTGA
ACAACGGGTTCTGGGACACGTACCGCACGGCCTGGCCGGCGTACTCGCTCCTCTACCCG
GAGCTCGCGGCCGAGCTGGTCGACGGGTTCGTCCAGCAGTACCGCGACGGCGGCTGGAT
CGCGCGCTGGTCCTCGCCGGGCTACGCCGACCTCATGACGGGCACGAGCTCCGACGTGG
CGTTCGCCGACGCGTACCTCAAGGGCTCGCTCCCCACGGGCACGGCGCTCGAGGCGTAC
GACGCCGCGCTGCGCAACGCGACCGTCGCGCCGCCGAGCAACGCCGTGGGCCGCAAGGG
CCTGCAGACCTCGCCGTTCCTCGGGTTCACGCCGGAGTCCACGCACGAGTCCGTGTCGT

GGGGCCTGGAGGGCCTGGTCAACGACTTCGGCATCGGCAACATGGCCGCCGCCCTCGCG
GAGGACCCGGCGACGCCGGAGGAGCGCCGCGAGACGCTGCGCGAGGAGTCCGCGTACTT
CCTCGAGCGGGCCACGCACTACGTCGAGCTGTTCGACCCCGAGGTCGACTTCTTCGTGC
CGCGGCACGAGGACGGCACGTGGGCCGTCGACCCCGAGACGTACGACCCGGAGGCCTGG
GGCGGCGGGTACACCGAGACGAACGGCTGGAACTTCGCGTTCCACGCCCCGCAGGACGG
CCAGGGCCTCGCCAACCTCTACGGCGGCAAGCAGGGCCTCGAGGACAAGCTCGACGAGT
TCTTCTCCACGCCGGAGAAGGGCGCCGGCAACGGCGGCATCCACGAGCAGCGCGAGGCG
CGCGACGTCCGCATGGGCCAGTGGGGCATGAGCAACCAGGTGTCGCACCACATCCCGTG
GCTCTACGACGCCGCGGGCGCGCCGTCGAAGGCGCAGGAGAAGGTCCGCGAGGTCACCC
GCCGCCTGTTCGTGGGCAGCGAGATCGGCCAGGGCTACCCGGGCGACGAGGACAACGGC
GAGATGTCGTCGTGGTGGATCTTCGCCTCGCTCGGCTTCTACCCGCTCCAGGTCGGCTC
GGACCAGTACGCGGTCGGTTCGCCGCTGTTCGACAAGGCGACCGTGCACCTGCCGGACG
GCGACCTCGTCGTCAACGCCGAGAACAACTCGGTCGACAACGTCTACGTGCAGTCCCTC
GCGGTGGACGGCGAGGCCCGCACCTCGACGTCACTCTCCCAGGCGGACCTCTCGGGCGG
CACGACTCTGGACTTCGTCATGGGTCCGGAGCCGTCGGACTGGGGCACGGGCGAGGACG
ACGCGCCGCCGTCGCTCACCGAGGGCGACGAGCCCCCGACGCCGGTGCAGGACGCGACG
ACCGCGGGCCTCGGCACCACCACCGTCGCCGACGGCGACGCCACCACGAGCGCCGCGGC
GCTCACGGACAACACGTCCGGGACGCGCACGACGTTCGCCACCACGACGCCGTCGATCA
CGTGGGCGGGCAACGGCATCCGCCCGACCGTCGGGTCGTACACGCTGACCTCCGGGGCG
AGCGGGACGGCGTCACCGTCCGCATGGACTCTCGAGGGTTCCGACGACGGCGAGACGTG
GACGACGCTCGACGAGCGGTCCGGCGAGCAGTTCCGCTGGGCCCTGCAGACGCGGCCGT
TCACGGTCGCGGAGCCGACGGCGTTCGCGCGGTACCGGGTCACGGTCACCGCGACGTCG
GGCTCCGGCGCGCTGTCGCTCGCCGAGGTCGAGCTCCTCGCCGACCCGAAGGAGTCGGG
GGCCGAGGAGCTCACCCTCTCGGCCGCGCCGGACCGTGACGGCGTCACGGGCCGCGAGG
TCTCGGGCTCGTTCGCGACCCTCACCGGGGTCGAGGGCGACGTCGCGGCGCTCGACGTG
CAGGTCGCGTTCGGCGACGGCTCCGAGCCGGTCGCCGGGACGCTGCGGGCGGGCGCGTT
CGGCGGGTACGCGGTGGACGCCGCGCACACGTGGACCGCACCCGGCGTCTACCCCGTGA
CCGTCACGGTCTCGGGCGAGGGGATCGAGACCGTCTCGGCCTCCTCGTACGTCAGCGTC
TCGCTCCTGCGCGAGGGCTCGCTGCTCGCCGCGTACGACAACGTCTGCATCGGCGACGC
CGGGACGACGGTCGGCTCGTGCGACGGCCAGGGCGTGTTCTTCGACCGGGCGCAGCTCG
CGGCGAAGGGCTTCGTCCAGGGCGAGCGCGCGACGGTGCCGGGCACGGACCTCGCGTTC
GACGTCCCGGCGGTCCCCGCCGGGCAGCCGGACAACGCCACGGGCGACGGGCAGACCAT
CGAGCTCGACGTCCCCGCGGACGCGGAGCAGCTCTCGGTGATCGGCACGGGCACGGAGA
AGAACCAGCAGGCCACCGGCACGCTGACCTTCGACGACGGCTCGACCCAGCCGATCGAC
CTGAGCTTCGGCGACTGGTCGGGCGCGGCCCGCAACCCCGTGTTCGGCAACATCCCCGT
CGCGGTGACGGACAGCCGCCTCCGCGGCGGCAGCCCGCAGACCGGCACCCCCGCCGCGT
TCTTCGCGACGGCGCCGATCACCCTCCCCGAGGGCAAGCGGCCCGTGAGCCTCACGCTC
CCGGACCAGCCGGGCGAGCTCTCGCGCGACGGCCGCATCCACGTGGTCGCGGTCGCGCA
CGACGGCACGTTCGCCGAGCACCCCGCGCTCGAGGTCACGGCCGCGGAGGGCGTGACGC
TCGCCGTCGGGCAGACCTCGGACGTGGCGCTCGCCCAGGTGGCGGGCGGCCGCGAGGGC
GCCGACCTCCGGGCGGCGGTCACGTGGGGCGACGGCTCCGACGTCGCGGCCGGCGCGGT
GACCGACGGGTCGGTCTCCGGCTCGCACGCCTACACGGCGGCCGGGACGTACACGGCGT
ACGTCGTGGTCGACGACGGCTGGACCAGCCAGGTGGTCGAGGTCCCCGTGACCGTGACC
GAGGCGGAGCCGGCCCTCGCCGTCGACGTCACGGTGAGCACACGCTGCCTCGCCGGCAA
GGCGTACGTCGCGGTCCGCGCCGAGAACGGCGAGGACGTGCCGCTCGCGATCCGGCTCG
TCACGCCGTTCGGCACCAAGGAGGTCGCGGCCGTCGCGCCGGGCGCCAACGCCTACCAG
TCGTTCGCGACGCGGGTCACGGCGGTCGAGGCCGGCACCGTCACCGTCGAGGCGACGCG

CGGCACCGGCGACGAGGAGGTGACGGCGTCGATCCAGGCCGACTACGCCGCCGTGACCT
GCGGC (SEQ ID NO:12)

FIGURE 11B

MTRPLPPGRAVARSGSGRARPLGLVLAAALAVPLGVPLAAPAGALAAAPAAAAEPGDFS
SSFESGDPAALPTTVAERDGAPWQANVGSFTAGLPGSVLGQLKGVTASAQNLPNEGAAN
LADGSSGTKWLAFASTGWVRYEFAEPVSFVAYTMTSGDDAAGRDPKTWTVEGSNDGSTW
AALDRRTDEDFPNRQQTRTFELEAPTAAYTYLRLNVTANSGDSIVQLAGWDLSADLSAG
PSAAPMTTKVGTGPRVSFTNKAGVGFSGLHSLRYDGSHLADGETYATNVLYDDVDVVVG
EDTRLSYTIFPELLDDLQYPSTYAAVDVLFTDGTYLSDLGARDAHETVATAQAQGEGKI
LYADQWNSVRVDLGDVAEGKTVDQVLLGYDNPGGHAGTKFAGWLDDVEITAEPATIDGS
SLANYVDTRRGTLASGSFSRGNNIPATATPNGFNFWTPYTNASSQSWLYEYHKANNANN
KPVLQGFGISHEPSPWMGDRNQLTFLPSTASGTPDATLSTRGLEFDHADETARPDYYGV
TFTNGSAIEATPTDHGAVLRFSYPGAKGHVLVDKVDGSSKLTYDQATGTISGWVENGSG
LSVGRTRMFVAGTFDRSPTAVGTAAGNRADARFATFETSSDKTVELRVATSFISLDQAR
KNLDLEVTGKTFTEVKAAAAQAWNDRLGVIEVEGASEDQLVTLYSNLYRLNLYPNSQFE
NTGTAQEPVYRYASPVSATTGSATDTQTNAKIVDGKIYVNNGFWDTYRTAWPAYSLLYP
ELAAELVDGFVQQYRDGGWIARWSSPGYADLMTGTSSDVAFADAYLKGSLPTGTALEAY
DAALRNATVAPPSNAVGRKGLQTSPFLGFTPESTHESVSWGLEGLVNDFGIGNMAAALA
EDPATPEERRETLREESAYFLERATHYVELFDPEVDFFVPRHEDGTWAVDPETYDPEAW
GGGYTETNGWNFAFHAPQDGQGLANLYGGKQGLEDKLDEFFSTPEKGAGNGGIHEQREA
RDVRMGQWGMSNQVSHHIPWLYDAAGAPSKAQEKVREVTRRLFVGSEIGQGYPGDEDNG
EMSSWWIFASLGFYPLQVGSDQYAVGSPLFDKATVHLPDGDLVVNAENNSVDNVYVQSL
AVDGEARTSTSLSQADLSGGTTLDFVMGPEPSDWGTGEDDAPPSLTEGDEPPTPVQDAT
TAGLGTTTVADGDATTSAAALTDNTSGTRTTFATTTPSITWAGNGIRPTVGSYTLTSGA
SGTASPSAWTLEGSDDGETWTTLDERSGEQFRWALQTRPFTVAEPTAFARYRVTVTATS
GSGALSLAEVELLADPKESGAEELTLSAAPDRDGVTGREVSGSFATLTGVEGDVAALDV
QVAFGDGSEPVAGTLRAGAFGGYAVDAAHTWTAPGVYPVTVTVSGEGIETVSASSYVSV
SLLREGSLLAAYDNVCIGDAGTTVGSCDGQGVFFDRAQLAAKGFVQGERATVPGTDLAF
DVPAVPAGQPDNATGDGQTIELDVPADAEQLSVIGTGTEKNQQATGTLTFDDGSTQPID
LSFGDWSGAARNPVFGNIPVAVTDSRLRGGSPQTGTPAAFFATAPITLPEGKRPVSLTL
PDQPGELSRDGRIHVVAVAHDGTFAEHPALEVTAAEGVTLAVGQTSDVALAQVAGGREG
ADLRAAVTWGDGSDVAAGAVTDGSVSGSHAYTAAGTYTAYVVVDDGWTSQVVEVPVTVT
EAEPALAVDVTVSTRCLAGKAYVAVRAENGEDVPLAIRLVTPFGTKEVAAVAPGANAYQ
SFATRVTAVEAGTVTVEATRGTGDEEVTASIQADYAAVTCG (SEQ ID NO:13)

FIGURE 12A

GCGCTCGCCGTCGTCGGCCTCGCGCCCGCGACCGCCGCGAGCGCCGCCCCCGAGCCGCC
GTCGGCCGACTACGCGTCCCTGGTCGACGTCTTCGTCGGCACCGAGGGCGACTTCGGCA
ACGACATGCCCGCCGCGCAGGCGCCGAACGGCCTCGCGAAGGTCAACCCGCGCACGACC
CCGGGCCGCAACAACACCGGGTACGACTACGCGCAGTCGAAGATCTCGGGCTTCACGCA
CACCAACCTCGACGGGGTCGGGGGCTCCGGCGGCGGTGGTGACCTCCTCGTGGTGCCGA
CGTCCGGGTCGTACACGGCGCGCCCCGGCACGGGCACGTACGCGCACCCGTTCTCGCAC
GACGACGAGGACGCCGGACCGGGCTTCTACTCCGTCGGGCTCGGCAACGTCGCGGGCAC
GGACGGCGCGATCACCGGCGCGCCGGGCACGATCGAGGCCGAGGTCGCGGCGGCCACGC
GCTCGGGCGTGCACCGCTACGCGTTCCCCGCGGGCTCGACGCCGAGCCTCGTCGTGGAC
CTCGAGACGAACAACACGAGCCGCCGGTCGTCCTCGGTGCAGGTCGAGACGCGCGCGGA
CGGCACCGTGGAGCTGTCCGGACAGGTCACGGGCTACTTCTACAACGCGGCCTACACGC
TGTACTACACCGCGCGCACGCTCCAGCCCGCGACGGTGCAGACGTGGGGCGACGACGAC
CGGCTCGTCGACGCCACGGCCCAGGACGGCGTCGACACCGGCGCGATCCTCACGTTCGA
CCCGGCGGACGCCGGGGAGATCGGGCTCCAGGTCACCCTGTCGCCGGTGAGCGTCGAGC
AGGCGCGGATCGACCAGCAGGTCGAGCTCGGCGACCTGTCGTTCGACGCGATCCGTGAC
CGCACCCGCGCGGAGTGGAACGCGACGCTCGGGCGGGTCGCGATCGACGCCTCGACGGC
GACGGACCCGACGGGCGAGCTCCAGCGGCTCTTCTACACGCACCTCTACCGCATGTTCG
CGATGCCGATGAACGCGACGAGCACCTCGGGCACGTACCGCGGCGTCGACGGGGCGGTG
CACGCCGCGCAGGGCTTCACGTACTACGACTCGTGGGCCACGTGGGACGACTTCCGCAA
GTTCTCCGTCATCGCGTACATCGACCCGGCGCTGTACCGGGACATGGTGCAGTCGCTGG
TCTACCTGTTCGCGGACGCCGAGGCGACGGGCACCGGCGGCGGCCTCGGCGGGTTCGTG
CACTCGGTCCCGACGGTGCGCTGGGAGCGGTCGTCGGTCGTGGTCGCGGACGCGATCGC
CAAGGGCTTCGACGGGTTCGACCGCCTCGACGAGGCGTACCCGGCGCTCCAGCGGCTCG
TCGGGCAGTACAGCGCGGACGAGCTCCGGCGCGGCTACGTGGCGGGCAACCCCGGCGCG
TCCGTGCAGCGCGGCTACGACCAGTACGGCCTGTCCGTGATCGCGGACGAGCTCGGCCT
GACCGAGGAGGCCGAGACGCTGCGCGAGCAGGCGTCGTGGCCGATCGAGAAGCTCACCA
AGCCGGGCGCGTGGACCGCCGCCGACGGCACGCAGGTCGGCCTCCTCACCCCGCGCGCC
GCGGACGGGTCGTGGCAGAGCGCCGACCACGCGAAGTTCGAGGCCGCCGGCCTCTACCA
GGGCACGCTCTGGCAGTACCACTGGTACGACGCGTACGACATGGACGCGCTCGTCGAGG
CGATGGGCGGCCACGAGGCGGCGCGCCTCGGCATGCGCCACATGTTCGGTGAGCACGCG
CCGGACGACGGCAAGGCCATGCTCCACTCGAACGCCAACGAGATCGACCTCCAGGCGCC
GTACCTCTTCAACTACACGGGCGAGCCGAGCCTCACGCAGAAGTGGGCGCGCGCGATCT
ACACGAAGGAGACCTGGAACCGGTACATCGCGACCGGCTCCTCCAGCGCCGTGCCGAGC
GGCGGCGGCGAGTTCACGCCGCCCTTGAAGACGAAGGTGTACCGGCTCGACCCCCGCGG
GATGCTCCCCACGATGGACAACGACGCGGGCACGATGTCGACGATGTTCGTCGCCGCGG
CCGTCGGGCTGTTCCCGGTGACCGCGGGCTCGTCCCAGTTCCAGGTCGGGTCGCCGTTC
TTCGACTCGACGACCATCACCTACGACGACGGCAGCGCCTTCACGGTCACGGCCGACGG
CGTCTCCGAGGACGCGTTCTACGTCCAGTCCGCGACGCTCGACGGCGCGACGTTCGGCA
ACACGTGGGTCGACTACGCCACCGTGGTCGGGGGAGCCGACCTCGCGTTCCGCATGGGC
GAGCAGCCGAGCGACTGGGGCACGGACACCGCGCCCGCGTTCTCGATGAGTACCGCGAC
CGACGAGCCGGCCGAGGGACCGCGCGTCAGCGCCGAACCGACCACCGTGCAGACCGGCG
ACGGCGGCGCGCTCGACGCGACCGTGACGCTCACGCTCGACGGCGCCCGCCTCGCCGCG
CCCGCCGGCACGGACCTCGTCACGAGCGGGGCGGCGAGCGTCGTCGGGCTGCCCGACGG
CGTCACGGCGGCCGTGACGGTCGCGTCGCCGACCGCGCTGACCGTCTCCCTGACGGGGA
CGGCGTCCGCCGACGCGCGCTTCTTCGTGCACCTGCGCGACGCCGCGCTCGCCGACGGC

GTCGCCGCGGCGTCGCTCCAGGGACAGGGCGTCTCGGTGCGCTCGCCCCTGCGGCTGTC
CGTGGCGTCCGCCGAGCGCGACGCGCTCGCCGCGCTCGTCGACGACGCCGTGCTCGTGC
GGCACGGGAACTACTCCTCGGTGACGTTCGACCGGTTCTCCACCGCGCTGACGAAGGCG
CAGGAGGCCCTCGGTGACGAGGCCGCGACGAGCATCGCGCTGCGGTTCGCGGCCGACCG
GCTCGGTGCGGCGGCCGACGCGCTCGACCTCACGGGCGGCGGGTACCGCACGCTCGAGG
CCGAGCAGTCCGAGGCGTGGTCGGGCGGGGAGCTGAAGAACGAGGCGAACAGCTCGTCC
GGCAACCTCGGCGGCGTGCGCTCCGGGTCGTGGGTGCAGTACCGCGACATGACCTTCGA
GACCGCCGCCGGGGACACCCCGCCGCGCTTCCTCACGGTCCGGTACGACACGAGCTTCG
CCCCGACGGACACGCCGAGCACCGTGCGCGTGCACGCGGGCGACGTGAGCGGCCCTGTG
GTCGCGACCGTCGACCTGAAGGGCACGAGCGGCTGGGGCAAGTACACCGAGGTCACGGC
GGAGCTCGGCGACGTGCAGGCGCTCGTCGACGCGCAGGTCGTCACGTTCGAGCTGCTCG
CGCCGTCCGGGCGGAGCTGGGTCGGCAACTTCGACTGGTTCCGGTTCAGCGCCGAGGAC
CCGGCTGCCCCAGGTCAGCCGGGCGAGTCCCCGACGGTGACGATCGAGGCCGAGGACTG
GACCGCGAGCTCCGGTCGCGGGCTCAAGAAGGAGTCCTCGACGTGGACGAGCGGTCCGG
TGACGAACGTCGGCGGCACCGCGGACGGCGACTGGATCGCCTACGGCGAGGTCGACCTG
GGTGAGCTCCCGCTCGGCGAGCTGTCGGTCCACTACGTGCACAACTCCAACCGGTCCGG
GAACAACTCCGCGCTGTCGGTGTACCTCGACGCGTTCGACCCGGCGAACCCGGGCGAGC
CGTTCGTCACCGTGCCGCTGCCGACGACCGGGTCGAGCTGGACCGCGGACGGGACCGCG
ACCGTCGTCCTGCCCGAGACGGTGCAGGGGACGCACGAGGTGTTCGTGCGCCTGTCGAC
CGAGCCGTACGCCGACCACCCGTACGTCGCGAACCTCGACAGCCTGACGTTCGCGCCGG
GCGGCCCGACGTCGGTCGTCGTCGAGTCCGAGGCCTGGACGTCGAACTCCGGCCGCGGG
CTGAAGAACGAGAGCTCGACGTGGACGAGCGGTCCGGTGACGAACGTCGGCGGCACCGC
GGACGGCGACTGGCTCGCCTACGGCGAGATCGACCTCGGCTCCGCCGCGCTCGACCAGC
TCTCGGTCCACTACGTGCACAACTCCAACCGGTCCGGGCGGAACTCCGCGCTGTCGGTG
TACCTCGACGCGTTCGACCCGGCGAACCCGGGCGAGCCGTTCGTCACCGTCCCGCTGGC
CAACACCGGGTCGAGCTGGACGACGGACGGGACCGCCGTCGTCGACCTGCCGAGCACGG
TGCGCGGCAAGCACCAGGTGTGGGTGCGCCTGTCCACCGAGGCGTACGCCGACCACCCG
TACGTCGCCAACCTCGACAGCATGCGCTTCTTCACCGACGCGTACGACGTCGAGGTCCC
GCCGACCGACACCGCGGCGCTCGCGGCGGTGGTCGACGCGGCCGGGACGCCCGAGGCGG
AGATCGCGCGGTACGGCCGGATCGACGCGCGCGTCTTCACACGCGAGCTCGCGGCGGCA
CGGTCCGTGCTCGCCGACGCCGGCGCCACCCAGGCGCAGGCCGACGAGCGGGCGCGGCG
CCTCGGCCTGGCGACCGACCAGCTCGTGCCCGCCGAGCGCCGTCGGCTCGAGAACCTCG
TGGCGAGCGCCGAGGCCCTGACCGACGAGGGGTACAGCCCCGAGTCCTGGCAGGCCTTC
CGCACGGCTCTCGCCGCGGCGACCGGGACGCTCGACGACGCGGCGGCGTCCGACGAGGC
GCTGCACGACGCGCGGCTCGCGCTCCAGGGCGCCGTCGACGCCCTGGAGGAGCCGGCCG
ACGTCGTGCTCGTCGAGGTCGAGGTCAGCCCGCGCTGCCTCGCCGGCAAGCCCTACGTC
GCGGTCCGCGCGGTGAACGTCTCCGACGCGGCCGTCGACGTCGAGCTGGCGTCGTCACT
GGGCACGAGGTCGTTCGTCGGCGTCGCGCCGGGGGCGAGCGCGTACCAGTCGTTCGCCG
CGCGGTCCGCGACGGGCGACCTGGACGTCACCGTCACGGCGACGGGGGCGGACGGCACC
CAGACGGTCGAGCAGGTCGTCACCGTCCCGTCCTGCTCC (SEQ ID NO:14)

FIGURE 12B

ALAVVGLAPATAASAAPEPPSADYASLVDVFVGTEGDFGNDMPAAQAPNGLAKVNPRTT
PGRNNTGYDYAQSKISGFTHTNLDGVGGSGGGGDLLVVPTSGSYTARPGTGTYAHPFSH
DDEDAGPGFYSVGLGNVAGTDGAITGAPGTIEAEVAAATRSGVHRYAFPAGSTPSLVVD
LETNNTSRRSSSVQVETRADGTVELSGQVTGYFYNAAYTLYYTARTLQPATVQTWGDDD
RLVDATAQDGVDTGAILTFDPADAGEIGLQVTLSPVSVEQARIDQQVELGDLSFDAIRD
RTRAEWNATLGRVAIDASTATDPTGELQRLFYTHLYRMFAMPMNATSTSGTYRGVDGAV
HAAQGFTYYDSWATWDDFRKFSVIAYIDPALYRDMVQSLVYLFADAEATGTGGGLGGFV
HSVPTVRWERSSVVVADAIAKGFDGFDRLDEAYPALQRLVGQYSADELRRGYVAGNPGA
SVQRGYDQYGLSVIADELGLTEEAETLREQASWPIEKLTKPGAWTAADGTQVGLLTPRA
ADGSWQSADHAKFEAAGLYQGTLWQYHWYDAYDMDALVEAMGGHEAARLGMRHMFGEHA
PDDGKAMLHSNANEIDLQAPYLFNYTGEPSLTQKWARAIYTKETWNRYIATGSSSAVPS
GGGEFTPPLKTKVYRLDPRGMLPTMDNDAGTMSTMFVAAAVGLFPVTAGSSQFQVGSPF
FDSTTITYDDGSAFTVTADGVSEDAFYVQSATLDGATFGNTWVDYATVVGGADLAFRMG
EQPSDWGTDTAPAFSMSTATDEPAEGPRVSAEPTTVQTGDGGALDATVTLTLDGARLAA
PAGTDLVTSGAASVVGLPDGVTAAVTVASPTALTVSLTGTASADARFFVHLRDAALADG
VAAASLQGQGVSVRSPLRLSVASAERDALAALVDDAVLVRHGNYSSVTFDRFSTALTKA
QEALGDEAATSIALRFAADRLGAAADALDLTGGGYRTLEAEQSEAWSGGELKNEANSSS
GNLGGVRSGSWVQYRDMTFETAAGDTPPRFLTVRYDTSFAPTDTPSTVRVHAGDVSGPV
VATVDLKGTSGWGKYTEVTAELGDVQALVDAQVVTFELLAPSGRSWVGNFDWFRFSAED
PAAPGQPGESPTVTIEAEDWTASSGRGLKKESSTWTSGPVTNVGGTADGDWIAYGEVDL
GELPLGELSVHYVHNSNRSGNNSALSVYLDAFDPANPGEPFVTVPLPTTGSSWTADGTA
TVVLPETVQGTHEVFVRLSTEPYADHPYVANLDSLTFAPGGPTSVVVESEAWTSNSGRG
LKNESSTWTSGPVTNVGGTADGDWLAYGEIDLGSAALDQLSVHYVHNSNRSGRNSALSV
YLDAFDPANPGEPFVTVPLANTGSSWTTDGTAVVDLPSTVRGKHQVWVRLSTEAYADHP
YVANLDSMRFFTDAYDVEVPPTDTAALAAVVDAAGTPEAEIARYGRIDARVFTRELAAA
RSVLADAGATQAQADERARRLGLATDQLVPAERRRLENLVASAEALTDEGYSPESWQAF
RTALAAATGTLDDAAASDEALHDARLALQGAVDALEEPADVVLVEVEVSPRCLAGKPYV
AVRAVNVSDAAVDVELASSLGTRSFVGVAPGASAYQSFAARSATGDLDVTVTATGADGT
QTVEQVVTVPSCS (SEQ ID NO:15)

FIGURE 12C

APEPPSADYASLVDVFVGTEGDFGNDMPAAQAPNGLAKVNPRTTPGRNNTGYDYAQSKISGF
THTNLDGVGGSGGGGDLLVVPTSGSYTARPGTGTYAHPFSHDDEDAGPGFYSVGLGNVAGTD
GAITGAPGTIEAEVAAATRSGVHRYAFPAGSTPSLVVDLETNNTSRRSSSVQVETRADGTVE
LSGQVTGYFYNAAYTLYYTARTLQPATVQTWGDDDRLVDATAQDGVDTGAILTFDPADAGEI
GLQVTLSPVSVEQARIDQQVELGDLSFDAIRDRTRAEWNATLGRVAIDASTATDPTGELQRL
FYTHLYRMFAMPMNATSTSGTYRGVDGAVHAAQGFTYYDSWATWDDFRKFSVIAYIDPALYR
DMVQSLVYLFADAEATGTGGGLGGFVHSVPTVRWERSSVVVADAIAKGFDGFDRLDEAYPAL
QRLVGQYSADELRRGYVAGNPGASVQRGYDQYGLSVIADELGLTEEAETLREQASWPIEKLT
KPGAWTAADGTQVGLLTPRAADGSWQSADHAKFEAAGLYQGTLWQYHWYDAYDMDALVEAMG
GHEAARLGMRHMFGEHAPDDGKAMLHSNANEIDLQAPYLFNYTGEPSLTQKWARAIYTKETW
NRYIATGSSSAVPSGGGEFTPPLKTKVYRLDPRGMLPTMDNDAGTMSTMFVAAAVGLFPVTA
GSSQFQVGSPFFDSTTITYDDGSAFTVTADGVSEDAFYVQSATLDGATFGNTWVDYATVVGG
ADLAFRMGEQPSDWGTDTAPAFSMSTATDEPAEGPRVSAEPTTVQTGDGGALDATVTLTLDG
ARLAAPAGTDLVTSGAASVVGLPDGVTAAVTVASPTALTVSLTGTASADARFFVHLRDAALA
DGVAAASLQGQGVSVRSPLRLSVASAERDALAALVDDAVLVRHGNYSSVTFDRFSTALTKAQ
EALGDEAATSIALRFAADRLGAAADALDLTGGGYRTLEAEQSEAWSGGELKNEANSSSGNLG
GVRSGSWVQYRDMTFETAAGDTPPRFLTVRYDTSFAPTDTPSTVRVHAGDVSGPVVATVDLK
GTSGWGKYTEVTAELGDVQALVDAQVVTFELLAPSGRSWVGNFDWFRFSAEDPAAPGQPGES
PTVTIEAEDWTASSGRGLKKESSTWTSGPVTNVGGTADGDWIAYGEVDLGELPLGELSVHYV
HNSNRSGNNSALSVYLDAFDPANPGEPFVTVPLPTTGSSWTADGTATVVLPETVQGTHEVFV
RLSTEPYADHPYVANLDSLTFAPGGPTSVVVESEAWTSNSGRGLKNESSTWTSGPVTNVGGT
ADGDWLAYGEIDLGSAALDQLSVHYVHNSNRSGRNSALSVYLDAFDPANPGEPFVTVPLANT
GSSWTTDGTAVVDLPSTVRGKHQVWVRLSTEAYADHPYVANLDSMRFFTDAYDVEVPPTDTA
ALAAVVDAAGTPEAEIARYGRIDARVFTRELAAARSVLADAGATQAQADERARRLGLATDQL
VPAERRRLENLVASAEALTDEGYSPESWQAFRTALAAATGTLDDAAASDEALHDARLALQGA
VDALEEPADVVLVEVEVSPRCLAGKPYVAVRAVNVSDAAVDVELASSLGTRSFVGVAPGASA
YQSFAARSATGDLDVTVTATGADGTQTVEQVVTVPSCS (SEQ ID NO:50)

FIG. 13

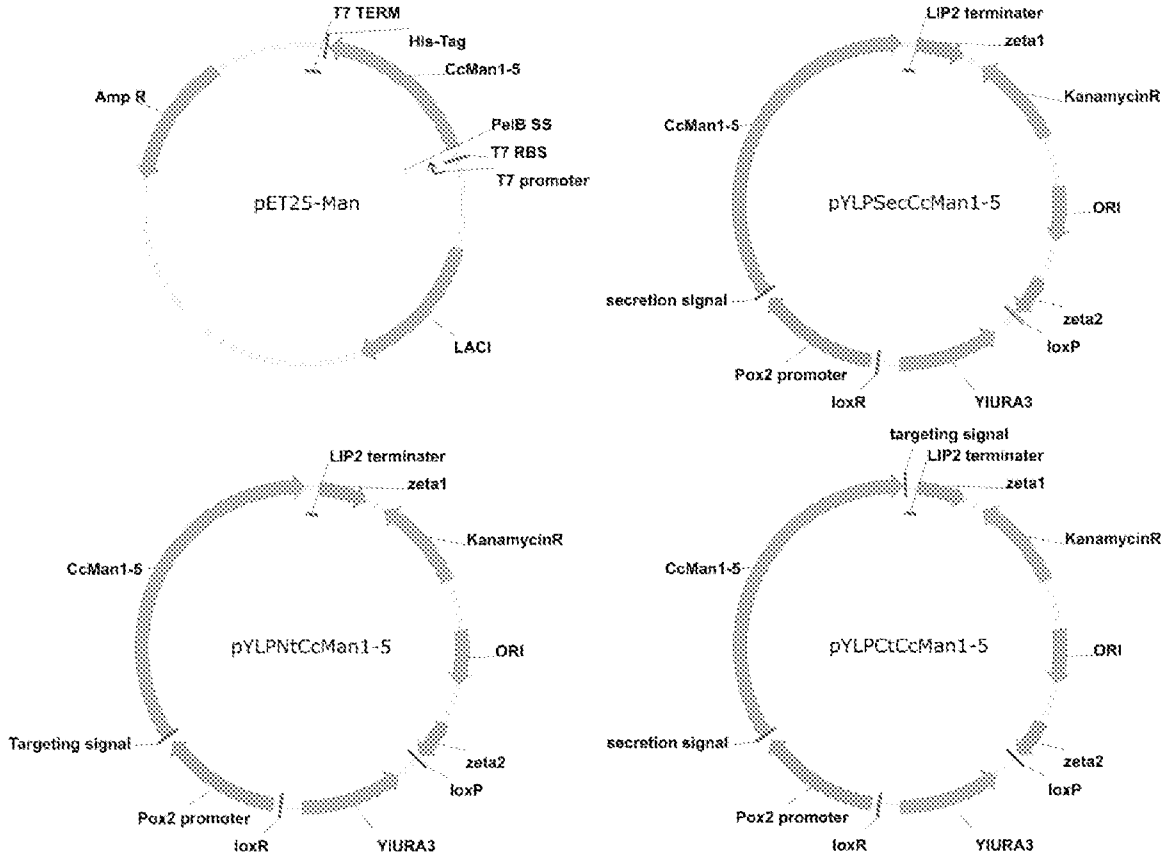

T7 TERM
His-Tag
CcMan1-5
Amp R
PelB SS
T7 RBS
T7 promoter
pET25-Man
LACI
LIP2 terminater
zeta1
KanamycinR
CcMan1-5
pYLPSecCcMan1-5
ORI
secretion signal
zeta2
loxP
Pox2 promoter
loxR
YlURA3
LIP2 terminater
zeta1
KanamycinR
CcMan1-5
pYLPNtCcMan1-5
ORI
Targeting signal
zeta2
loxP
Pox2 promoter
loxR
YlURA3
targeting signal
LIP2 terminater
zeta1
KanamycinR
CcMan1-5
pYLPCtCcMan1-5
ORI
secretion signal
zeta2
loxP
Pox2 promoter
loxR
YlURA3

FIGURE 14

GCACCGGCAGATGAAGGCACCGTTACCGCAGCAGCCGGTGATGATCTGACCCTGGAAGTTAATCCGTTTGT
TGGCACCGAAAGCGAAGGTAATGCATATCCGGGTGCAACCGTTCCGTTTGGTATGGTTCAGCTGTCTCCGG
ATAATACCAATAGCTATGCCAGCACCAGCTATAGCACCAATGCAGGTCGTGTTTGGGGTTTTAGCCATCGT
CATGTTAATAGCGCAGGTTGTCCGGCAGCCGGTGAACTGCTGGTTACACCGGATACCAGCGCAACACCGCG
TACCAGCCGTAGCTTTATTGCCATCAAAGATCAGAAAAGCACCGAACGTGCAAGCGCAGGTTTTTATGAAG
TTACCCTGGCAAATGATGTTCATGCAGAACTGACCGCAACCACCCGTGTTGGTGCACATCGTTATACCTTT
CCGGCAAGCACCACCTCTCATCTGAGCTTTAATGTTGGTCAGACCCTGCGTGATGCCGGTGCAAGCAGCGT
TACCTGGGTTGATGATCGTACACTGGAAGGTTGGGTTGATAATGGTGGTTTTTGTGGTGGTACACCGGATA
AACAGCGCTATTTTTTTAGCGCAACCTTTGATCGTCCGGTTGCCAGCAGCGGTACATGGGGCACCGATGCA
CGTTATGTTGCAGGTAGCACCACCAGTGAAGTTGCCGGTGGTAATAATGGTGCAGTTGCCGTTTTTGATAC
CACCACCGATCGTGATGTTGAAGTTAGCGTTGGTGTTAGCTTTGTTAGCGTTGATGGTGCACGTGCAAATC
GTGAAGCCGAAGCAACCGATGAAGGTGGTCAGGTTGCATTTGATACCGTTCGTGAAGAAGCACGCGACGCC
TGGAATGCAGAACTGGGTCGTGCAGCAATTGATGCATCTCCGGATCAGCGTCGTATCTTTTATACCCAGCT
GTATAAAACCCTGCTGAGCCCGACCATTGGTTCTGATGTTGATGGTCGTTATCGTGGTATGGATCTGGAAG
TTCATCAGGCAGATGGCTGGGATTATTATCAGAACTTTAGCCTGTGGGATACCTATCGTACCCAGGCAACC
CTGCATGCACTGCTGCTGCCGGAACGTGCACAGGATATTGTTCGTAGCATGTATCAGCATCGTGTTGAAGG
TGGTTGGCTGCCTCGTTGGTCTCTGGGTGCACTGGAAACCAATATCATGGCAGGCGATCCGGTTACCCCGT
GGCTGGCAGAAAATTTTGCACTGGGCACCGTTCCGGATGATATTGCAGATGAACTGTGGGATTATCTGGTT
GAAAATGCAACCACCACCCCTCCGGATGATGTTGCCAGCGTTGGTCGTCGTAGCACCGAATTTTATGCCGA
ACATGGTCATGTTCCGTTTTATCCGGAAAACGAAGGTGGCCTGGGTGGTCAGTTTGAAGAATATCGTCATG
GTGGTAGCGCAACCCTGGAACTGGCACTGGCAGATGCAAGCCTGGGTGCCGCAGCAGAACGTACCGGTCGT
GAAGGTGGCCAGGCATTTCTGGATAAAGGTCGCAATTGGCGTAATCTGTGGAATCCGGATGTTGAACTGAG
CGGTGGTTTTCAGGGTATGGTTAATGCAAAACGTCCGACCGGTGAATTTGTTACCCTGCCGGAACTGACCG
ATGTTACCCGTAGCGGTTTTCATGAAGGTGTTCCGTGGCAGTATCAGTGGATGGTTCCGCAGGATGTTACC
GGTCTGCAAGAAGTTATGGGAGGCGAAGATGGTTTTGTGGAACGCCTGGATTATTATTTTGATCAGCCTGC
ACTGGCAGCAAATCCGGGTGTTAGCCCGAGCACCTGGGCAAAAGGTGGTAGCAGCTATTATACCACCATTC
GCTATAATCCGGGTAATGAACCGACCATTATGAATGCATGGCTGTATGGTTATGTTGGTCAGCCGTGGAAA
ACCAATGATGTTCTGGCAGCCAATCTGAATCGTTTTCCGGATACACCGGGTGGTGGTGTTGGTAATGATGA
TCTGGGCACCCTGGCAGCATGGTATGTTATGGCCAGCCTGGGTTTTGAACCGGTTATGCCTGGTAGCGGTA
TTCTGGCACTGAATGCACCGAAAGTTCAGGCAGCAACCCTGACCACCGATGCCGGTGCCACCCTGCGTATT
GATGCAGCCGGTGCAAATGAAAAACTGCCGAGCTATGTTGCCGGTCTGGAAGTTGATGGTGTTGCACATAC
CGCAGCATGGCTGGATGTTGCAGCACTGCAGGATGGTGGCACCCTGGATTTTGATCTGAGCGGTACAAGCG
CAGGTCTGACATGGGGTACAGGTGCAGCAGATCGTATTCCGAGCGTTAGCGCAGTTGCACCGCCTGCACCG
GTTGAAGTGGAAGCAAGCGCACGTTGTCTGGGTGGTCGTGCATTTGTTGCAGTTCGTGCAACCAGCACCGC
AGATGCACCGGTGGATGTTACACTGACCACACCGTTTGGTGAACGTACCGTTCGTCATGTTCAGCCTGGTC
GTAGCGCATATCAGAGCTTTACCACCCGTACCACCTCTGTTGAAGCAGGCACCGCAACCGTTACCGTTGTT
GCAGCAGATGGCACCACCTCAACCGTTGATGCAGCATATGAAGCACTGGCATGTGGTTAATAA (SEQ ID
NO:16)

FIGURE 15

GCAGGCACCGAAGCAGCAACCGGTTCTGATGCAGCAGCAGTTGATGGTCCGCTGGTTGATTATGTGAATCC
GTTTATTGGCACCAAAGATGATGGTAATACCTATCCGGGTGCAGCAGTTCCGTTTGGTATGGTTCAGCTGT
CTCCGGATAATGGTCATAATGTGGGCTATGATTATGATCGTACCAGCGTTCGTGGTTTTAGCCTGGTTCAT
CTGAGCGGTGTTGGTTGTGGTCTGGGTGGTCCGCTGCCGACACTGCCGACCACCGGTGCAATTACCAGCAC
CGATTATGGTCAGTATGCACTGGGTTTTAGCCATGATGATGAAGAAGCATCTCCGGGTTATTATCGTGTTG
GTCTGCAGGCACCTGCAGGAACCATTGAAGCAGAACTGACCGCAACCGAACGTACCGGTGTTCAGCGTTAT
ACCTTTCCGGCAACCGCACAGGCAAATGTTCTGCTGAATGCAGGTCAGGCACTGAATCGTGTTACCGAATC
TGATGTTCGTGTTGTTGATGATCGTACCGTTGAAACCCGTATTACCGTGCGTGGTTTTTGTCAGGATACCG
AACCGCAGACCATTTGGACCCGTACCACCTTTGATCGTCCGTTTGTTGCACATGGCACCTGGGATGGTCAG
GTTGTTACCGCAGGCGCAGATGCAGCAAGCGGTGGTGAAGGTCGTCGTGGTGCATATGTTACCTTTGATAC
AACCGGTGGTGATCTGGATGTTGAAGCAGTTACCGCAATGAGCTATGTTGGTGCAGATGGTGCAGCAGCAA
ATCTGGCAGCAGAAGCAGGCACCTTTGACGCAGTTCATGATGCAGCACGTAGCGCATGGGAAGAACGTCTG
GGTCTGGTTCGTGTTGCACAGGGTGATCCGGATGATCTGCGTACCTTTTATAGCAGCCTGTATCGTAGCTT
TCTGGCACCGAATGTTGGTTCTGATGTGGATGGTCGTTATCGTGGTTGGGATCAGGAAGTTCACGCAGCAG
AACCGGATTTTACCTATTATCAGAATTATAGCCTGTGGGATACCTATCGTACCCAACAGCAACTGCTGTAT
CTGCTGGCACCGGATGAAAGCGCAGATATGGCACTGAGCCTGGTTCGTCAGGGTCAGCAGGGTGGTTGGCT
GCCTCGTTGGGGTTATGGTACAGTGGAAACCAATATTATGACCGGTGATCCGGCAACCCCGTTTCTGGTTA
GCGCATGGCGTCAGGGTCTGCTGGCAGGTCATGAAGAAGAAGCATACGCAGTCCTGCGTGAAAATGCAGAT
GGTGTTCCTCCGGCAGATAGCCCGTTTAATGGTCGTGCAGCCAATGTTGAATATCTGCGTGATGGTTTTGT
TCCGCATGAACCGGCACGTAGCGGTAAACCGGGTGATTATGATCTGCAGCATGGTGCAAGCGCAACCATGG
AATATGCACTGGCAGATGCAATGCTGAGCACCATGGCACGTGGTCTGGGTCATGATGAAGATGCAGATCGT
TATGCAGCCCGTGGTCAGAGCTATCGTAATGTTTTTGATCCGCGTACCGGTAATTTTCGTGCACGTAATGC
CGATGGTTTTTTTGTTGGTGATGCAGATCCGGCACATTCTGATGGTTTTCATGAAGGCACCGCAGTTCAGT
ATCAGTGGCTGGTTCCGCAGGATGTTCCGGGTCTGTTTGATCTGATGGGTGGCACCGATGCAGCCGTTGAT
CGTCTGGATGCATTTTTTGCCTATGATGAACTGGTTGCAGATCCTCCGCATGTTGCAAGCGAAGTTTGGGT
TAATGGCACCTATGATTATTATGGCTGGGAAACCTATAATCCGAATAATGAACCGAATCTGCATGCACCGT
ATGTTTATCTGTGGACCGGTCAGCCGTGGAAAACCACCGATGTTGTTCGTGCAGCAAGCACCCTGTTTACC
GATGGTCCGGATGGTGTTACCGGTAATGATGATCTGGGCACCATGAGCGCATGGCATGTTCTGAGCAGCAT
TGGTGTTTATCCGATTGTTCCGGGTGCCGATCTGTGGGGTCTGACCACACCGCTGTTTGATGATGTTACCA
TTACCCTGGACCCGGAAGTTTTTGGTCGTGATAGCCTGCGTCTGACCGCAGATGGTGTGGCACCGGATACC
CATTATACCCAGAGCGTTAGCCTGGGTGGTGAACCGCTGGATCGTGCATGGGTTACAGGTGATGAACTGAC
CGCTGCAGGCACCCTGGATGTTACCGTTGGCACCGAACCGAGCGCATGGGCAACCGATCCGGCAGCATCAC
CGGGTGCAGTTGTTCCGGCTGATGGCACCGTTGAACGTCTGTTTGTTGGTGCAACACCGCGTCAGCCGGTT
CTGGCACCGGGTGGTCGTACCGAAGTTGCAGTTCAGGTTGTTGCCCAGGGTGCAGGCACCTCTAGCGGCAC
CCTGGAAGTGACCTCTGATGGTGCAGTTACCGCCACCACCGATCTGGCAGAATGGACCGCAGAATCTGATG
GTCTGCCTGCCACCGTTGAAGGAACCGTTACCATTGAAGCTCCGGCAGATGCCGAACCGGGTCTGCATACC
GTTCGTCTGGTTGTTCGTGATGCAGCCGGTACAGAAGCAGTTCGCGAAGTTAGCGTTGTTGTTAGCGGTGA
AAGCTGGATTGCAGATGCCTTTGATAATGTGGGTATTGGTGATGCCGGTGCAGCAAATGCAAATCTGGATG
GTAGCGGTGCCTATCTGCTGCGTGATCTGCTGGCCGATCTGGGTGCAGTTCAGGGTCTGGAACTGACCGTT
CCGGGTACTGATCTGACCTATACCCTGGGTGCACCGCGTGCTGGTGCACCGGATAATGTTGCAGCCAGCGG
TGAAGTTCTGGAAGTTCCGGAACATCTGCGTAGCGCACGTCATCTGAGCGTTGTGGGCACCAGCACCCATG
GTACACATGGTGGTGGTCTGGTTCTGGGTTTTGCCGATGGTAGCAGCCAGACCGTTGATGTTCGTCTGAGC
GATTGGTGTACCGGTTCTCCGGAACCGGGTAATATTACCGTTGCAAAAGCCGGTGCACGTGGTGATCGTGA
AAATGTGCAGAAAATTGGCTGTGGTCTGTATGCAACCGCACCGGTGGCAATTCCGGAAGGTAAAGTTCTGA
CCAGCGTTACCCTGCCGTCTGATGAACGTTTTCATGTGTTTGCAATTGCAACCGATGCAACCGGTGATGTT
CCGGCACCGCAGGTTGAAGTTACCGCACAGGCTCGTTGTCTGGGTGGTAAAGCATTTGTTGCAGTTCGTGC
ACTGAATACCGGTGAACAGCCTGCAGCAATTGAACTGGCAACCCCGTATGGTAGCAAACTGTTTGGTGATG
TTGCTCCGGGTGCAAATGCATATCAGAGCTTTGCAACCCGTGCAGCAGCCGTTGAAGCCGGTGAAGTTACC
GTTACCGTGACCACACCGGATGGTGAACCGCAGCAGGTTACCGCAGCATATGATGCAGCGGCATGTAGCTA
ATAA (SEQ ID NO:17)

FIGURE 16

GCAGGCACCGAAGCAGCAACCGGTTCTGATGCAGCAGCAGTTGATGGTCCGCTGGTTGATTATGTGAATCC
GTTTATTGGCACCAAAGATGATGGTAATACCTATCCGGGTGCAGCAGTTCCGTTTGGTATGGTTCAGCTGT
CTCCGGATAATGGTCATAATGTGGGCTATGATTATGATCGTACCAGCGTTCGTGGTTTTAGCCTGGTTCAT
CTGAGCGGTGTTGGTTGTGGTCTGGGTGGTCCGCTGCCGACACTGCCGACCACCGGTGCAATTACCAGCAC
CGATTATGGTCAGTATGCACTGGGTTTTAGCCATGATGATGAAGAAGCATCTCCGGGTTATTATCGTGTTG
GTCTGCAGGCACCTGCAGGAACCATTGAAGCAGAACTGACCGCAACCGAACGTACCGGTGTTCAGCGTTAT
ACCTTTCCGGCAACCGCACAGGCAAATGTTCTGCTGAATGCAGGTCAGGCACTGAATCGTGTTACCGAATC
TGATGTTCGTGTTGTTGATGATCGTACCGTTGAAACCCGTATTACCGTGCGTGGTTTTTGTCAGGATACCG
AACCGCAGACCATTTGGACCCGTACCACCTTTGATCGTCCGTTTGTTGCACATGGCACCTGGGATGGTCAG
GTTGTTACCGCAGGCGCAGATGCAGCAAGCGGTGGTGAAGGTCGTCGTGGTGCATATGTTACCTTTGATAC
AACCGGTGGTGATCTGGATGTTGAAGCAGTTACCGCAATGAGCTATGTTGGTGCAGATGGTGCAGCAGCAA
ATCTGGCAGCAGAAGCAGGCACCTTTGACGCAGTTCATGATGCAGCACGTAGCGCATGGGAAGAACGTCTG
GGTCTGGTTCGTGTTGCACAGGGTGATCCGGATGATCTGCGTACCTTTTATAGCAGCCTGTATCGTAGCTT
TCTGGCACCGAATGTTGGTTCTGATGTGGATGGTCGTTATCGTGGTTGGGATCAGGAAGTTCACGCAGCAG
AACCGGATTTTACCTATTATCAGAATTATAGCCTGTGGGATACCTATCGTACCCAACAGCAACTGCTGTAT
CTGCTGGCACCGGATGAAAGCGCAGATATGGCACTGAGCCTGGTTCGTCAGGGTCAGCAGGGTGGTTGGCT
GCCTCGTTGGGGTTATGGTACAGTGGAAACCAATATTATGACCGGTGATCCGGCAACCCCGTTTCTGGTTA
GCGCATGGCGTCAGGGTCTGCTGGCAGGTCATGAAGAAGAAGCATACGCAGTCCTGCGTGAAAATGCAGAT
GGTGTTCCTCCGGCAGATAGCCCGTTTAATGGTCGTGCAGCCAATGTTGAATATCTGCGTGATGGTTTTGT
TCCGCATGAACCGGCACGTAGCGGTAAACCGGGTGATTATGATCTGCAGCATGGTGCAAGCGCAACCATGG
AATATGCACTGGCAGATGCAATGCTGAGCACCATGGCACGTGGTCTGGGTCATGATGAAGATGCAGATCGT
TATGCAGCCCGTGGTCAGAGCTATCGTAATGTTTTTGATCCGCGTACCGGTAATTTTCGTGCACGTAATGC
CGATGGTTTTTTTGTTGGTGATGCAGATCCGGCACATTCTGATGGTTTTCATGAAGGCACCGCAGTTCAGT
ATCAGTGGCTGGTTCCGCAGGATGTTCCGGGTCTGTTTGATCTGATGGGTGGCACCGATGCAGCCGTTGAT
CGTCTGGATGCATTTTTTGCCTATGATGAACTGGTTGCAGATCCTCCGCATGTTGCAAGCGAAGTTTGGGT
TAATGGCACCTATGATTATTATGGCTGGGAAACCTATAATCCGAATAATGAACCGAATCTGCATGCACCGT
ATGTTTATCTGTGGACCGGTCAGCCGTGGAAAACCACCGATGTTGTTCGTGCAGCAAGCACCCTGTTTACC
GATGGTCCGGATGGTGTTACCGGTAATGATGATCTGGGCACCATGAGCGCATGGCATGTTCTGAGCAGCAT
TGGTGTTTATCCGATTGTTCCGGGTGCCGATCTGTGGGGTCTGACCACACCGCTGTTTGATGATGTTACCA
TTACCCTGGACCCGGAAGTTTTTGGTCGTGATAGCCTGCGTCTGACCGCAGATGGTGTGGCACCGGATACC
CATTATACCCAGAGCGTTAGCCTGGGTGGTGAACCGCTGGATCGTGCATGGGTTACAGGTGATGAACTGAC
CGCTGCAGGCACCCTGGATGTTACCGTTGGCACCGAACCGAGCGCATGGGCAACCGATCCGGCAGCATCAC
CGGGTGCAGTTGTTCCGGCTGATGGCACCGTTGAACGTCTGTTTGTTGGTGCAACACCGCGTCAGCCGGTT
CTGGCACCGGGTGGTCGTACCGAAGTTGCAGTTCAGGTTGTTGCCCAGGGTGCAGGCACCTCTAGCGGCAC
CCTGGAAGTGACCTCTGATGGTGCAGTTACCGCCACCACCGATCTGGCAGAATGGACCGCAGAATCTGATG
GTCTGCCTGCCACCGTTGAAGGAACCGTTACCATTGAAGCTCCGGCAGATGCCGAACCGGGTCTGCATACC
GTTCGTCTGGTTGTTCGTGATGCAGCCGGTACAGAAGCAGTTCGCGAAGTTAGCGTTGTTGTTAGCGGTGA
AAGCTGGATTGCAGATGCCTTTGATAATGTGGGTATTGGTGATGCCGGTGCAGCAAATGCAAATCTGGATG
GTAGCGGTGCCTATCTGCTGCGTGATCTGCTGGCCGATCTGGGTGCAGTTCAGGGTCTGGAACTGACCGTT
CCGGGTACTGATCTGACCTATACCCTGGGTGCACCGCGTGCTGGTGCACCGGATAATGTTGCAGCCAGCGG
TGAAGTTCTGGAAGTTCCGGAACATCTGCGTAGCGCACGTCATCTGAGCGTTGTGGGCACCAGCACCCATG
GTACACATGGTGGTGGTCTGGTTCTGGGTTTTGCCGATGGTAGCAGCCAGACCGTTGATGTTCGTCTGAGC
GATTGGTGTACCGGTTCTCCGGAACCGGGTAATATTACCGTTGCAAAAGCCGGTGCACGTGGTGATCGTGA
AAATGTGCAGAAAATTGGCTGTGGTCTGTATGCAACCGCACCGGTGGCAATTCCGGAAGGTAAAGTTCTGA
CCAGCGTTACCCTGCCGTCTGATGAACGTTTTCATGTGTTTGCAATTGCAACCGATGCAACCGGTGATGTT
CCGGCACCGCAGGTTGAAGTTACCGCACAGGCTCGTTGTCTGGGTGGTAAAGCATTTGTTGCAGTTCGTGC
ACTGAATACCGGTGAACAGCCTGCAGCAATTGAACTGGCAACCCCGTATGGTAGCAAACTGTTTGGTGATG
TTGCTCCGGGTGCAAATGCATATCAGAGCTTTGCAACCCGTGCAGCAGCCGTTGAAGCCGGTGAAGTTACC
GTTACCGTGACCACACCGGATGGTGAACCGCAGCAGGTTACCGCAGCATATGATGCAGCGGCATGTAGCTA
ATAA (SEQ ID NO:18)

FIGURE 17

GCAGAACCGGGTGATTTTAGCAGCAGCTTTGAATCTGGCGATCCGGCAGCACTGCCGACCACCGTTGCAGA
ACGTGATGGTGCACCGTGGCAGGCAAATGTTGGTAGCTTTACCGCAGGTCTGCCTGGTAGCGTTCTGGGTC
AGCTGAAAGGTGTTACCGCAAGCGCACAGAATCTGCCGAATGAAGGTGCAGCAAATCTGGCAGATGGTAGC
AGCGGCACCAAATGGCTGGCATTTGCAAGCACCGGTTGGGTTCGTTATGAATTTGCAGAACCGGTTAGCTT
TGTTGCATATACCATGACCAGCGGTGATGATGCCGCAGGTCGTGATCCGAAAACCTGGACCGTTGAAGGTA
GCAATGATGGTTCTACCTGGGCAGCACTGGATCGTCGTACCGATGAAGATTTTCCGAATCGTCAGCAGACC
CGTACCTTTGAACTGGAAGCACCGACCGCAGCATATACCTATCTGCGTCTGAATGTTACCGCAAATAGCGG
TGATAGCATTGTTCAGCTGGCAGGTTGGGATCTGAGCGCAGATCTGTCTGCAGGTCCGAGCGCAGCACCGA
TGACCACCAAAGTTGGCACCGGTCCGCGTGTTAGCTTTACCAATAAAGCCGGTGTTGGTTTTAGCGGTCTG
CATAGCCTGCGTTATGATGGTAGCCATCTGGCCGATGGTGAAACCTATGCAACCAATGTGCTGTATGATGA
TGTTGATGTTGTGGTTGGTGAAGATACCCGTCTGAGCTATACCATTTTTCCGGAACTGCTGGATGATCTGC
AGTATCCGAGCACCTATGCAGCAGTTGATGTTCTGTTTACCGATGGCACCTATCTGAGCGATCTGGGTGCA
CGTGATGCACATGAAACCGTTGCAACCGCACAGGCACAGGGTGAAGGTAAAATTCTGTATGCCGATCAGTG
GAATAGCGTTCGTGTTGATCTGGGTGATGTTGCAGAAGGTAAAACCGTTGATCAGGTTCTGCTGGGTTATG
ATAATCCGGGTGGTCATGCAGGCACCAAATTTGCAGGTTGGCTGGATGATGTTGAAATTACCGCAGAACCG
GCAACCATTGATGGTAGCTCACTGGCAAATTATGTTGATACCCGTCGTGGCACCCTGGCAAGCGGTAGCTT
TAGCCGTGGTAATAATATTCCGGCAACCGCAACCCCGAATGGTTTTAATTTTTGGACCCCGTATACCAATG
CAAGCAGCCAGAGCTGGCTGTATGAATATCATAAAGCCAATAATGCGAATAATAAACCGGTTCTGCAGGGT
TTTGGTATTAGCCATGAACCGAGCCCGTGGATGGGTGATCGTAATCAGCTGACCTTTCTGCCGAGCACCGC
AAGCGGTACACCGGATGCAACCCTGAGCACCCGTGGTCTGGAATTTGATCATGCAGATGAAACCGCACGTC
CGGATTATTATGGTGTGACCTTTACCAATGGTAGCGCAATTGAAGCAACCCCGACCGATCATGGTGCAGTT
CTGCGTTTTAGCTATCCGGGTGCAAAAGGTCATGTTCTGGTGGATAAAGTTGATGGTAGCAGTAAACTGAC
CTATGATCAGGCAACCGGCACCATTAGCGGTTGGGTTGAAAATGGTAGCGGTCTGAGCGTTGGTCGTACCC
GTATGTTTGTTGCAGGCACCTTTGATCGTAGCCCGACCGCAGTTGGCACAGCAGCAGGTAATCGTGCAGAT
GCACGTTTTGCAACCTTTGAAACCAGCAGCGATAAAACCGTGGAACTGCGTGTTGCAACCAGCTTTATTAG
CCTGGATCAGGCACGTAAAAATCTGGATCTGGAAGTTACCGGTAAAACCTTTACCGAAGTTAAAGCAGCAG
CAGCACAGGCATGGAATGATCGTCTGGGTGTTATTGAAGTTGAAGGTGCAAGCGAAGATCAGCTGGTTACC
CTGTATAGCAATCTGTATCGCCTGAATCTGTATCCGAATAGCCAGTTTGAAAATACCGGCACCGCACAGGA
ACCGGTTTATCGTTACGCATCTCCGGTTAGCGCAACCACCGGTAGCGCAACCGATACCCAGACCAATGCCA
AAATTGTGGATGGCAAAATTTATGTGAATAATGGCTTTTGGGATACCTATCGTACCGCATGGCCTGCATAT
AGCCTGCTGTATCCGGAACTGGCAGCAGAACTGGTTGATGGTTTTGTTCAGCAGTATCGTGATGGTGGTTG
GATTGCACGTTGGAGCAGTCCGGGTTATGCAGATCTGATGACCGGTACAAGCTCTGATGTTGCATTTGCAG
ATGCCTATCTGAAAGGTAGCCTGCCGACCGGTACAGCACTGGAAGCATATGATGCAGCACTGCGTAATGCA
ACCGTTGCACCTCCGAGCAATGCAGTTGGTCGTAAAGGTCTGCAGACAAGCCCGTTTCTGGGTTTTACACC
GGAAAGCACCCATGAAAGCGTTAGCTGGGGTCTGGAAGGTCTGGTTAATGATTTTGGCATTGGCAATATGG
CTGCAGCACTGGCAGAAGATCCGGCAACACCGGAAGAACGTCGTGAAACCCTGCGTGAAGAAAGCGCATAT
TTTCTGGAACGTGCCACCCATTATGTTGAACTGTTTGATCCGGAAGTGGATTTTTTTGTTCCGCGTCATGA
AGATGGTACATGGGCAGTTGATCCGGAAACCTATGATCCGGAAGCATGGGGTGGTGGTTATACCGAAACCA
ATGGCTGGAATTTTGCATTTCATGCACCGCAGGATGGTCAGGGTCTGGCAAATCTGTATGGTGGTAAACAG
GGTCTGGAAGATAAACTGGATGAATTTTTTAGCACACCGGAAAAAGGTGCAGGTAATGGTGGTATTCATGA
ACAGCGTGAAGCACGTGATGTTCGTATGGGTCAGTGGGGTATGAGCAATCAGGTTAGCCATCATATTCCGT
GGCTGTATGATGCAGCCGGTGCTCCGAGCAAAGCACAGGAAAAAGTTCGCGAAGTTACCCGTCGTCTGTTT
GTTGGTAGCGAAATTGGTCAGGGTTATCCGGGTGATGAAGATAATGGTGAAATGTCCTCCTGGTGGATTTT
TGCAAGCCTGGGTTTTTATCCGCTGCAGGTTGGTAGCGATCAGTATGCAGTTGGTTCTCCGCTGTTTGATA
AAGCAACCGTTCATCTGCCGGATGGTGATCTGGTTGTTAATGCCGAAAATAATAGCGTGGATAATGTGTAT
GTTCAGAGCCTGGCAGTTGATGGTGAAGCACGTACCAGCACCAGCCTGAGCCAGGCAGATCTGAGCGGTGG
CACCACCCTGGATTTTGTTATGGGTCCGGAACCGAGCGATTGGGGCACCGGTGAAGATGATGCACCTCCGT
CACTGACCGAAGGTGATGAACCTCCGACACCGGTTCAGGATGCAACCACCGCAGGCCTGGGCACCACCACC
GTTGCCGATGGTGATGCCACCACCTCTGCAGCAGCCCTGACCGATAATACCAGCGGCACCCGTACCACCTT
TGCAACCACCACCCCGAGCATTACATGGGCAGGTAATGGCATTCGTCCGACCGTTGGTAGCTATACCCTGA
CCTCTGGTGCAAGCGGCACCGCAAGCCCGTCTGCATGGACCCTGGAAGGTTCTGATGATGGCGAAACCTGG
ACCACACTGGATGAACGTAGCGGTGAACAGTTTCGTTGGGCACTGCAGACCCGTCCGTTTACCGTTGCCGA
ACCGACCGCATTTGCACGTTATCGTGTTACCGTTACCGCAACCAGCGGTTCTGGTGCACTGAGCCTGGCAG
AAGTTGAACTGCTGGCAGATCCGAAAGAAAGCGGTGCAGAAGAACTGACCCTGTCTGCAGCACCGGATCGT

GATGGCGTTACCGGTCGTGAAGTTAGCGGTTCTTTTGCAACCCTGACCGGTGTTGAAGGTGATGTTGCCGC
ACTGGATGTTCAGGTTGCATTTGGTGATGGTAGCGAACCGGTTGCAGGTACACTGCGTGCCGGTGCATTTG
GTGGTTATGCAGTTGATGCAGCACATACCTGGACCGCACCGGGTGTTTATCCGGTTACCGTGACCGTTAGC
GGTGAAGGTATTGAAACCGTTAGCGCAAGCAGCTATGTTAGCGTTAGCCTGCTGCGTGAAGGTTCTCTGCT
GGCAGCATATGATAATGTGTGCATTGGTGATGCAGGTACAACCGTTGGTTCTTGTGATGGTCAGGGCGTTT
TTTTTGATCGTGCACAGCTGGCAGCAAAAGGTTTTGTGCAGGGTGAACGTGCAACCGTTCCGGGTACAGAT
CTGGCATTTGATGTTCCGGCAGTTCCGGCTGGTCAGCCTGATAATGCAACCGGTGATGGTCAGACCATTGA
ACTGGATGTTCCGGCTGATGCAGAACAGCTGAGCGTTATTGGCACCGGCACCGAAAAAAATCAGCAGGCAA
CCGGTACACTGACCTTTGATGATGGTTCTACCCAGCCGATTGATCTGAGCTTTGGTGATTGGAGCGGTGCA
GCACGTAATCCGGTGTTTGGTAATATTCCGGTTGCAGTTACCGATAGCCGTCTGCGTGGTGGTTCTCCGCA
GACCGGTACACCGGCAGCATTTTTTGCCACCGCACCGATTACCCTGCCGGAAGGTAAACGTCCGGTTAGCC
TGACCCTGCCGGATCAGCCTGGTGAACTGAGCCGTGATGGTCGTATTCATGTTGTTGCAGTTGCACATGAT
GGCACCTTTGCAGAACATCCTGCACTGGAAGTGACCGCAGCAGAAGGTGTTACCCTGGCAGTTGGTCAGAC
CTCAGATGTTGCACTGGCACAGGTTGCCGGTGGTCGTGAAGGTGCAGATCTGCGTGCCGCAGTTACCTGGG
GTGATGGTTCTGATGTGGCAGCCGGTGCCGTTACCGATGGTAGCGTTAGCGGTAGCCATGCATATACCGCA
GCAGGCACCTATACCGCATATGTTGTTGTGGATGATGGTTGGACCAGCCAGGTTGTTGAAGTTCCGGTGAC
CGTTACAGAAGCCGAACCGGCACTGGCCGTTGATGTCACCGTTAGCACCCGTTGCCTGGCAGGTAAAGCAT
ATGTTGCAGTGCGTGCAGAAAATGGTGAAGATGTTCCGCTGGCAATTCGTCTGGTTACCCCGTTTGGCACC
AAAGAAGTTGCAGCAGTTGCTCCGGGAGCCAATGCATATCAGAGCTTTGCAACCCGTGTTACCGCAGTTGA
AGCAGGCACCGTTACCGTTGAAGCCACCCGTGGCACCGGTGATGAAGAAGTTACCGCCAGCATTCAGGCAG
ATTATGCAGCCGTTACCTGCGGTTAATAA (SEQ ID NO:19)

FIGURE 18

GATATGCCTGCAGCACAGGCACCGAATGGTCTGGCAAAAGTTAATCCGCGTACCACACCGGGTCGTAATAA
TACCGGTTATGATTATGCCCAGAGCAAAATTAGCGGTTTTACCCATACCAATCTGGATGGTGTTGGTGGTA
GCGGTGGTGGTGGTGATCTGCTGGTTGTTCCGACCAGCGGTAGCTATACCGCACGTCCGGGTACAGGCACC
TATGCACATCCGTTTAGCCATGATGATGAAGATGCAGGTCCGGGTTTTTATAGCGTTGGTCTGGGTAATGT
TGCAGGCACCGATGGTGCAATTACCGGTGCTCCGGGTACAATTGAAGCAGAAGTTGCAGCAGCAACCCGTA
GCGGTGTTCATCGTTATGCATTTCCGGCAGGTAGCACCCCGAGCCTGGTTGTTGATCTGGAAACCAATAAT
ACCAGCCGTCGTAGCAGCAGCGTTCAGGTTGAAACCCGTGCAGATGGCACCGTTGAACTGAGCGGTCAGGT
TACCGGCTATTTTTATAATGCAGCCTATACCCTGTATTATACCGCACGCACCCTGCAGCCTGCAACCGTTC
AGACCTGGGGTGATGATGATCGTCTGGTTGATGCAACCGCACAGGATGGTGTTGATACCGGTGCAATTCTG
ACCTTTGATCCGGCAGATGCCGGTGAAATTGGTCTGCAGGTTACCCTGTCTCCGGTTAGCGTTGAACAGGC
ACGTATTGATCAGCAGGTTGAACTGGGTGATCTGAGCTTTGATGCAATTCGTGATCGTACCCGTGCAGAAT
GGAATGCAACCCTGGGTCGTGTTGCAATTGATGCAAGCACCGCAACCGATCCGACCGGTGAACTGCAGCGT
CTGTTTTATACCCATCTGTATCGCATGTTTGCAATGCCGATGAATGCAACCAGCACCAGCGGCACCTATCG
TGGTGTTGATGGTGCAGTTCATGCAGCACAGGGCTTTACCTATTATGATAGCTGGGCAACCTGGGATGATT
TTCGCAAATTTAGCGTGATTGCCTATATTGATCCGGCACTGTATCGTGATATGGTTCAGAGCCTGGTTTAC
CTGTTTGCAGATGCAGAAGCAACCGGTACAGGCGGTGGTCTGGGTGGTTTTGTTCATAGCGTTCCGACCGT
TCGTTGGGAACGTAGCAGCGTTGTTGTTGCAGATGCAATTGCCAAAGGCTTTGATGGTTTTGATCGTCTGG
ATGAAGCATATCCGGCACTGCAGCGCCTGGTTGGTCAGTATAGCGCAGATGAACTGCGTCGTGGTTATGTT
GCAGGTAATCCGGGTGCAAGCGTTCAGCGTGGTTATGATCAGTATGGTCTGAGCGTTATTGCCGATGAACT
GGGTCTGACCGAAGAAGCAGAAACCCTGCGCGAACAGGCAAGCTGGCCGATTGAAAAACTGACCAAACCGG
GTGCATGGACCGCAGCAGATGGTACACAGGTTGGTCTGCTGACACCGCGTGCAGCCGATGGTAGCTGGCAG
AGCGCAGATCATGCCAAATTTGAAGCAGCAGGTCTGTATCAGGGCACCCTGTGGCAGTATCATTGGTATGA
TGCCTATGATATGGATGCACTGGTTGAAGCAATGGGTGGTCATGAAGCAGCCCGTCTGGGTATGCGTCATA
TGTTTGGTGAACATGCACCGGATGATGGTAAAGCAATGCTGCATAGCAATGCCAATGAAATTGATCTGCAG
GCACCGTACCTGTTTAATTATACCGGTGAACCGAGCCTGACCCAGAAATGGGCACGTGCAATTTATACCAA
AGAAACCTGGAATCGCTATATTGCAACCGGTAGCAGCTCTGCAGTTCCGTCAGGTGGTGGTGAATTTACAC
CTCCGCTGAAAACCAAAGTTTATCGTCTGGACCCTCGTGGTATGCTGCCGACCATGGATAATGATGCAGGT
ACAATGAGCACCATGTTTGTTGCAGCAGCCGTTGGTCTGTTTCCGGTTACCGCAGGTAGCAGCCAGTTTCA
GGTTGGTAGCCCGTTTTTTGATAGCACCACCATTACCTATGATGATGGTAGCGCATTTACCGTTACCGCAG
ATGGTGTTAGCGAAGATGCCTTTTATGTTCAGAGCGCAACCCTGGATGGTGCAACCTTTGGTAATACCTGG
GTTGATTATGCAACCGTTGTTGGTGGTGCAGATCTGGCATTTCGTATGGGTGAACAGCCGAGCGATTGGGG
CACCGATACCGCACCGGCATTTAGCATGAGCACCGCCACCGATGAACCGGCAGAAGGTCCTCGCGTTAGCG
CAGAACCGACCACCGTGCAGACCGGTGATGGTGGTGCACTGGATGCAACCGTTACCCTGACACTGGATGGC
GCACGTCTGGCAGCACCGGCAGGTACAGATCTGGTTACCAGCGGTGCAGCAAGCGTTGTTGGTCTGCCGGA
TGGTGTTACCGCAGCAGTTACCGTTGCAAGCCCGACCGCACTGACCGTTAGCCTGACCGGCACCGCATCAG
CAGATGCACGTTTTTTTGTGCATCTGCGTGATGCAGCACTGGCCGATGGTGTTGCAGCCGCAAGCCTGCAG
GGTCAGGGTGTTAGCGTTCGTTCTCCGCTGCGTCTGAGCGTTGCAAGCGCAGAACGTGATGCACTGGCAGC
ACTGGTTGATGATGCCGTTCTGGTTCGTCATGGTAATTATAGCAGCGTTACCTTTGATCGTTTTAGCACCG
CTCTGACAAAAGCACAGGAAGCACTGGGCGACGAAGCAGCAACCAGCATTGCACTGCGTTTTGCAGCAGAT
CGTCTGGGTGCAGCAGCAGATGCACTGGATCTGACCGGTGGTGGTTATCGTACCCTGGAAGCAGAACAGAG
CGAAGCATGGTCTGGTGGTGAACTGAAAAATGAAGCCAATAGCAGCAGCGGTAATCTGGGTGGTGTTCGTA
GCGGTAGCTGGGTTCAGTATCGCGATATGACCTTTGAAACCGCAGCCGGTGATACACCTCCGCGTTTTCTG
ACCGTTCGTTATGATACCAGCTTTGCACCGACCGATACCCCGAGCACCGTTCGTGTTCATGCCGGTGATGT
TTCTGGTCCGGTTGTTGCAACCGTTGATCTGAAAGGCACCAGCGGTTGGGGTAAATATACCGAAGTTACCG
CAGAACTGGGTGATGTTCAGGCCCTGGTTGATGCCCAGGTTGTTACCTTTGAACTGCTGGCACCGAGCGGT
CGTAGCTGGGTTGGTAATTTTGATTGGTTTCGCTTTAGCGCAGAAGATCCGGCAGCACCGGGTCAGCCTGG
TGAAAGCCCGACCGTTACCATTGAAGCCGAAGATTGGACCGCAAGCAGCGGTCGTGGTCTGAAAAAAGAAA
GCAGCACCTGGACCAGCGGTCCGGTGACCAATGTTGGTGGTACAGCAGATGGTGATTGGATTGCCTATGGT
GAAGTTGATCTGGGTGAACTGCCGCTGGGCGAACTGAGCGTTCATTATGTGCATAATAGCAATCGCAGCGG
TAATAATAGCGCACTGAGCGTTTATCTGGATGCATTTGATCCGGCTAATCCGGGTGAACCGTTTGTTACCG
TTCCGCTGCCGACCACCGGTAGCAGTTGGACCGCAGATGGCACAGCCACCGTTGTTCTGCCGGAAACCGTG
CAGGGCACCCATGAAGTTTTTGTTCGTCTGAGCACCGAACCGTATGCAGATCATCCGTATGTTGCAAATCT
GGATAGCCTGACCTTTGCACCGGGTGGTCCGACCAGCGTTGTGGTTGAAAGCGAAGCCTGGACCAGCAATT
CTGGTCGTGGCCTGAAAAATGAATCTTCTACCTGGACCTCTGGTCCGGTTACAAATGTGGGTGGCACCGCT

GATGGCGATTGGCTGGCATATGGCGAAATTGATCTGGGCAGCGCAGCACTGGATCAGCTGTCTGTGCATTA
TGTTCATAATTCTAATCGCTCTGGTCGTAATTCTGCACTGTCTGTGTATCTGGATGCCTTTGATCCGGCAA
ATCCGGGTGAACCGTTTGTGACAGTGCCGCTGGCAAATACCGGTAGCTCTTGGACCACCGATGGTACTGCA
GTTGTGGATCTGCCGTCTACCGTTCGTGGTAAACATCAGGTTTGGGTTCGTCTGTCTACCGAAGCATATGC
CGATCATCCGTATGTGGCCAATCTGGATTCTATGCGCTTTTTTACCGATGCATATGATGTTGAAGTTCCTC
CGACCGATACAGCAGCACTGGCAGCCGTTGTTGATGCAGCAGGTACACCGGAAGCAGAAATTGCACGTTAT
GGTCGTATTGATGCCCGTGTTTTTACCCGTGAACTGGCAGCAGCACGTAGCGTTCTGGCCGATGCCGGTGC
AACACAGGCACAGGCAGATGAACGTGCTCGTCGTCTGGGTCTGGCAACCGATCAGCTGGTTCCGGCAGAAC
GTCGTCGTCTGGAAAATCTGGTTGCCAGCGCAGAAGCACTGACCGACGAAGGTTATTCTCCGGAAAGCTGG
CAGGCATTTCGTACCGCACTGGCTGCTGCAACCGGCACCCTGGATGATGCAGCAGCATCTGATGAAGCACT
GCATGATGCACGTCTGGCGCTGCAGGGTGCAGTTGATGCACTGGAAGAACCGGCAGATGTTGTTCTGGTTG
AAGTTGAAGTTTCTCCGCGTTGTCTGGCAGGTAAACCGTATGTTGCCGTTCGTGCAGTTAATGTTTCTGAT
GCAGCCGTTGATGTTGAACTGGCAAGCTCTCTGGGCACCCGTAGCTTTGTTGGTGTGGCACCGGGTGCGAG
CGCATATCAGAGCTTTGCAGCCCGTAGCGCAACCGGTGATCTGGATGTTACCGTGACCGCAACCGGTGCAG
ATGGTACTCAGACCGTTGAACAGGTTGTGACCGTTCCGAGCTGTAGCTAATAA (SEQ ID NO:20)

FIGURE 19

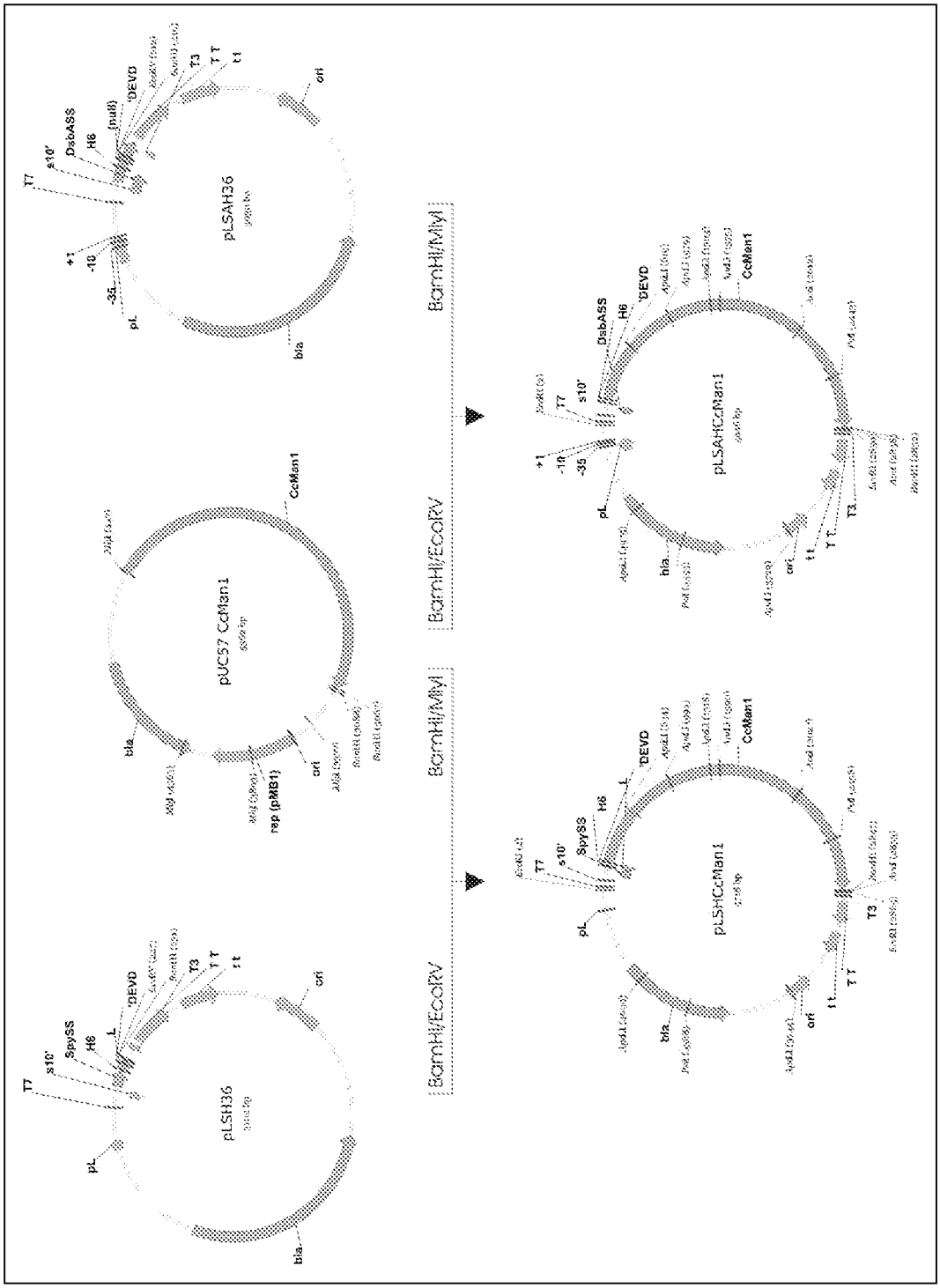

pLSH36
pLSAH36
pUC57 CcMan1
pLSHCcMan1
pLSAHCcMan1
BamHI/MlyI
EcoRV
CcMan1
DEVD
SpySS
DsbASS
H6
T7
s10'
pL
bla
ori
rep (pMB1)

FIGURE 20

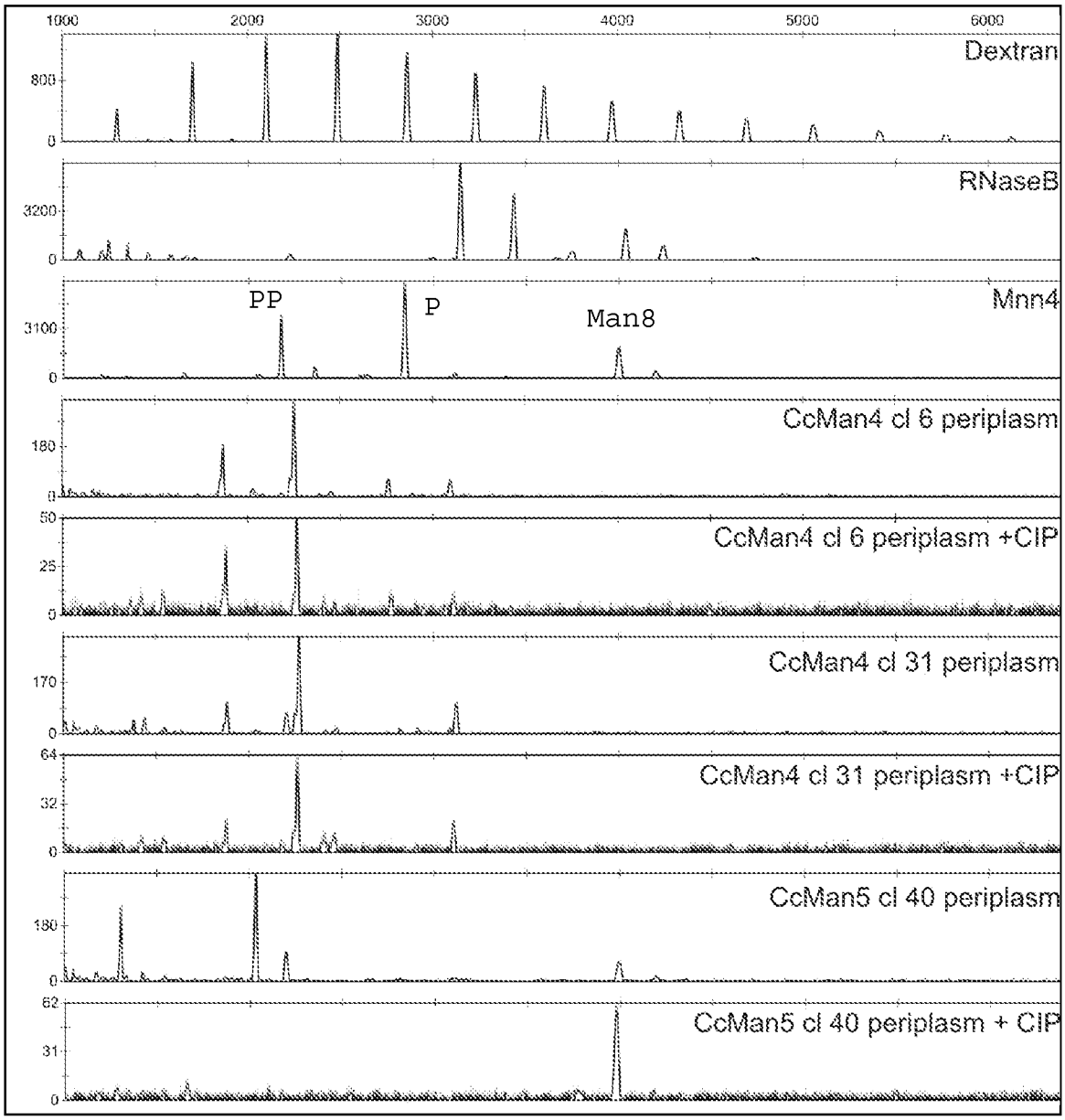

1000
2000
3000
4000
5000
6000
Dextran
800
0
RNaseB
3200
0
PP
P
Man8
Mnn4
3100
0
CcMan4 cl 6 periplasm
180
0
50
25
0
CcMan4 cl 6 periplasm +CIP
CcMan4 cl 31 periplasm
170
0
64
32
0
CcMan4 cl 31 periplasm +CIP
CcMan5 cl 40 periplasm
180
0
62
31
0
CcMan5 cl 40 periplasm + CIP

FIGURE 21

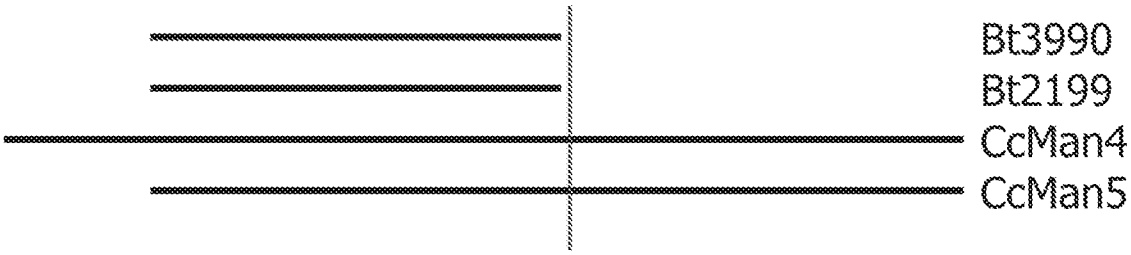


FIGURE 22

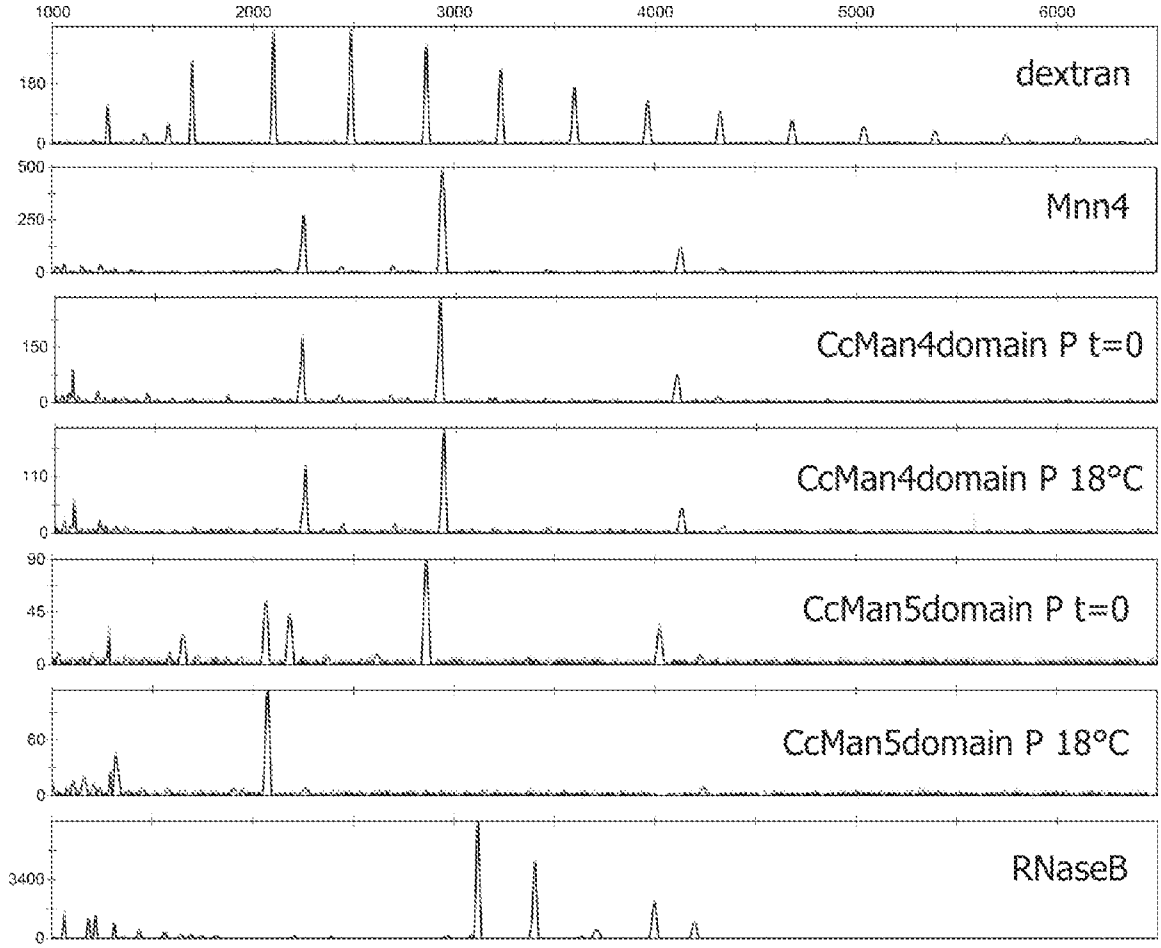

1000
2000
3000
4000
5000
6000
180
0
dextran
500
250
0
Mnn4
150
0
CcMan4domain P t=0
110
0
CcMan4domain P 18°C
90
45
0
CcMan5domain P t=0
60
0
CcMan5domain P 18°C
3400
0
RNaseB

FIG. 23

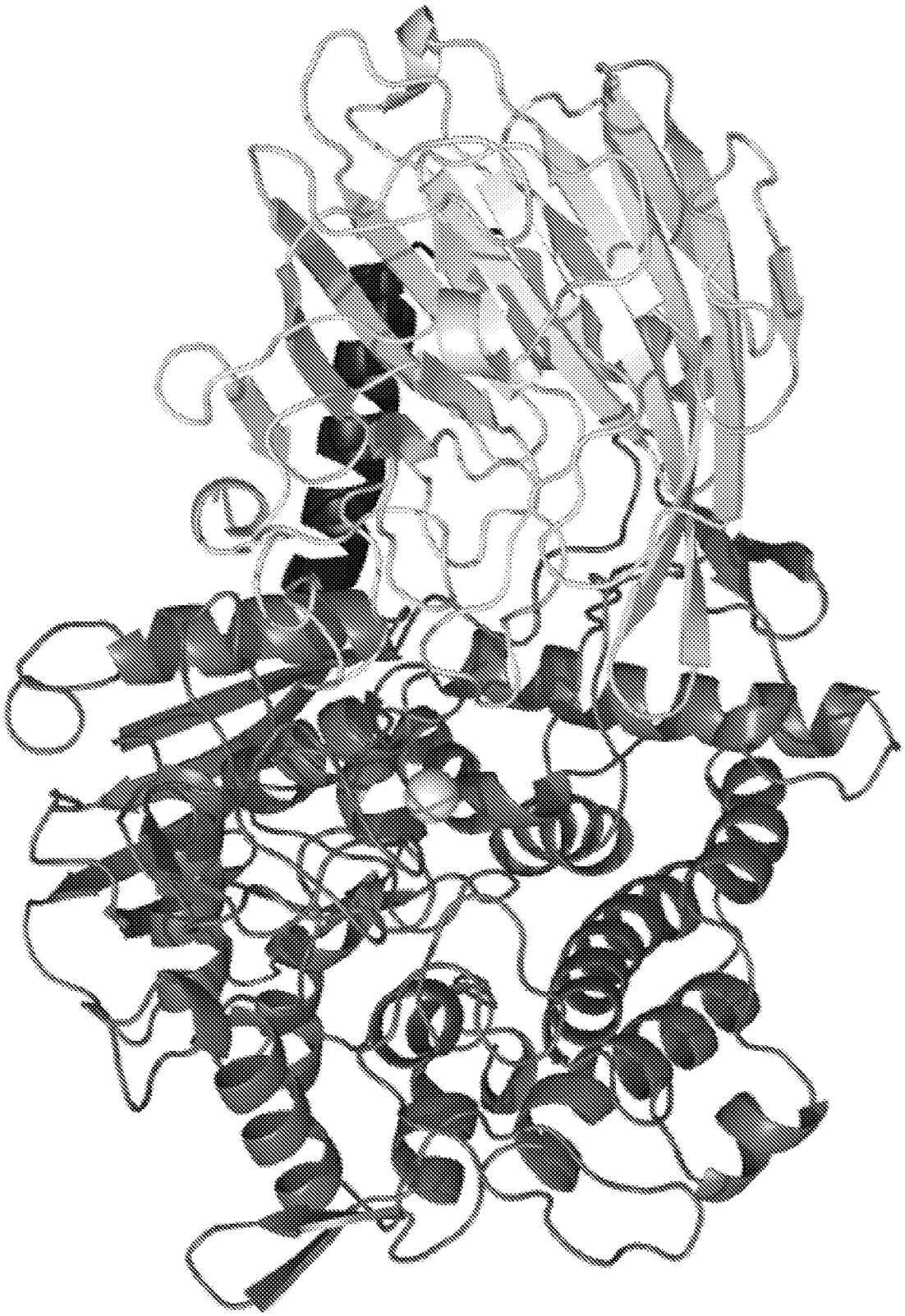


FIG. 24

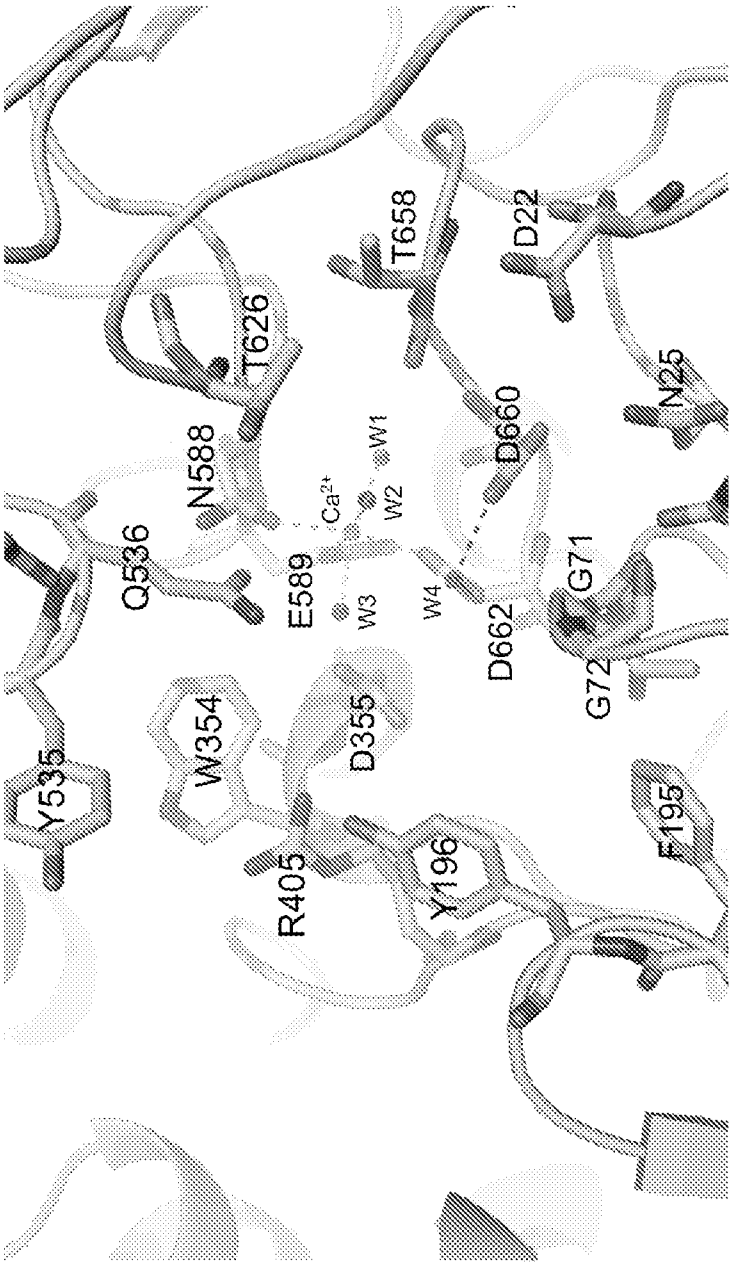

T658
D22
T626
N25
N588
D660
W1
W2
Ca2+
Q536
E589
W3
W4
G71
D662
G72
W354
D355
Y535
F195
R405
Y196

FIG. 25

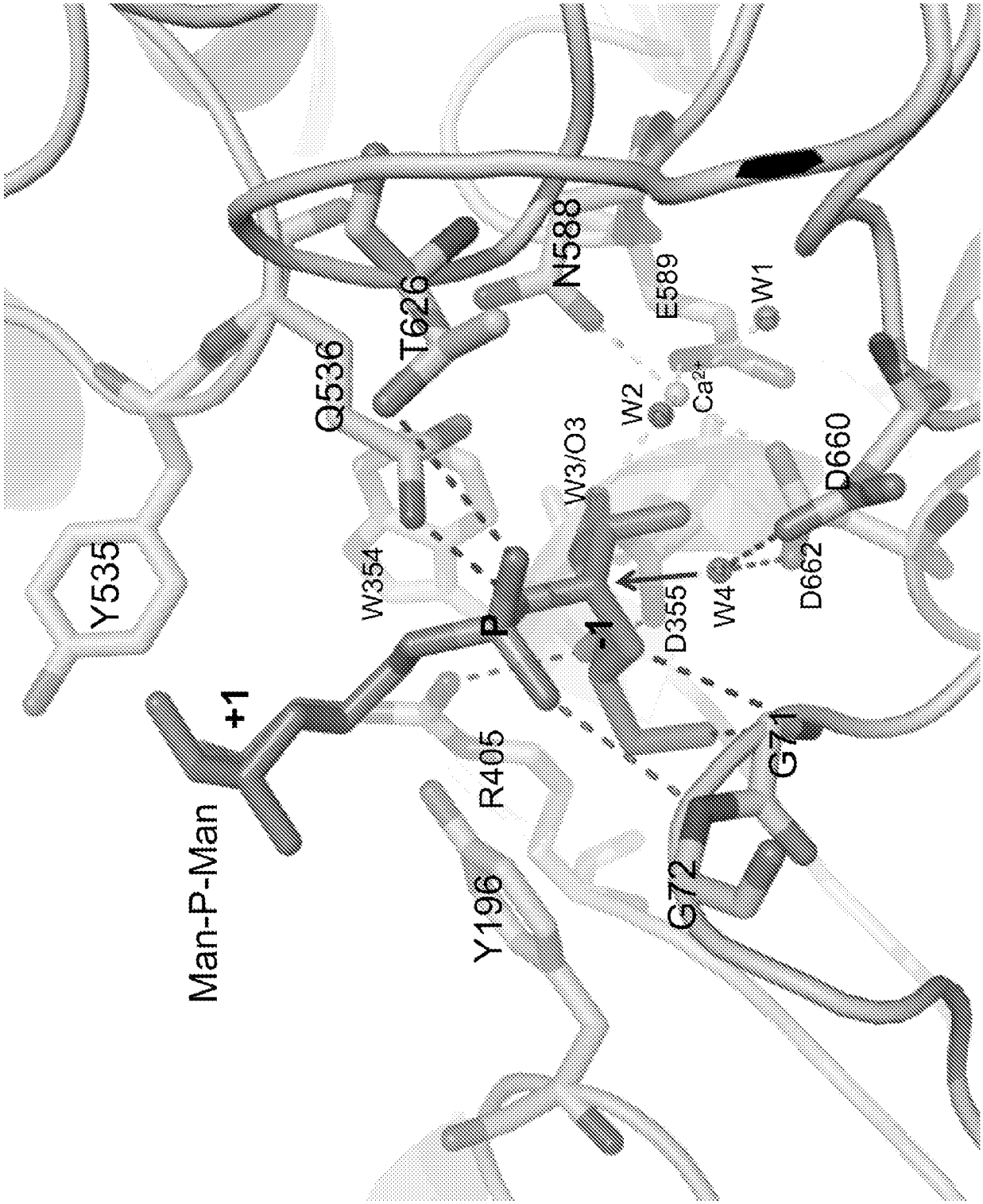

Man-P-Man
+1
Y535
Q536
T626
N588
E589
W1
W2
Ca2+
W3/O3
W354
P
-1
D355
W4
D662
D660
R405
G71
G72
Y196

FIGURE 26A

ATGAAGCTTTCCACCATCCTCTTCACAGCCTGCGCTACCCTGGCCCTGGACAACGGCCTGGCCCGAACCCC
CACCATGGGCTGGCTGCACTGGGAGCGATTCATGTGTAACCTGGACTGTCAGGAAGAGCCCGACTCTTGTA
TCTCTGAGAAGCTGTTCATGGAAATGGCCGAGCTGATGGTGTCTGAGGGCTGGAAGGACGCCGGCTACGAG
TACCTGTGTATCGACGACTGTTGGATGGCCCCCCAGCGAGACTCTGAGGGCCGACTCCAGGCCGACCCCCA
GCGATTCCCCCACGGCATCCGACAGCTCGCCAACTACGTGCACTCTAAGGGCCTGAAGCTGGGCATCTACG
CCGACGTGGGCAACAAGACCTGTGCCGGCTTCCCCGGCTCTTTCGGCTACTACGACATCGACGCCCAGACC
TTCGCCGACTGGGGCGTGGACCTGCTGAAGTTCGACGGCTGTTACTGTGACTCTCTCGAGAACCTGGCCGA
CGGCTACAAGCACATGTCTCTGGCCCTGAACCGAACCGGCCGATCTATCGTGTACTCTTGTGAGTGGCCCC
TGTACATGTGGCCCTTCCAGAAGCCCAACTACACCGAGATCCGACAGTACTGTAACCACTGGCGAAACTTC
GCCGACATCGACGACTCGTGGAAGTCTATCAAGTCTATTCTGGACTGGACCTCTTTCAACCAGGAGCGAAT
CGTCGACGTCGCCGGACCCGGCGGATGGAACGACCCCGACATGCTGGTGATCGGCAACTTCGGCCTGTCTT
GGAACCAGCAGGTGACCCAGATGGCCCTGTGGGCTATCATGGCTGCCCCCCTGTTCATGTCTAACGACCTG
CGACACATCTCTCCCCAGGCCAAGGCCCTGCTCCAGGACAAGGACGTGATCGCCATCAACCAGGACCCCCT
GGGCAAGCAGGGCTACCAGCTCCGACAGGGCGACAACTTCGAGGTGTGGGAGCGACCCCTGTCTGGCCTGG
CCTGGGCCGTGGCCATGATCAACCGACAGGAGATCGGCGGACCCCGATCTTACACCATCGCCGTGGCCTCC
CTGGGAAAGGGCGTGGCCTGTAACCCCGCCTGTTTCATCACCCAGCTCCTGCCCGTGAAGCGAAAGCTGGG
ATTCTACGAGTGGACCTCTCGACTGCGATCTCACATCAACCCCACCGGCACCGTGCTGCTCCAGCTCGAGA
ACACCATGCAGATGTCTCTGAAGGACCTGCTGACGCGTGAACAAAAACTCATCTCAGAAGAGGATCTGAAT
AGCGCCGTCGACCATCATCATCATCATCAT (SEQ ID NO:22)

FIGURE 26B

MKLSTILFTACATLALDNGLARTPTMGWLHWERFMCNLDCQEEPDSCISEKLFMEMAELMVSEGWKDAGYE
YLCIDDCWMAPQRDSEGRLQADPQRFPHGIRQLANYVHSKGLKLGIYADVGNKTCAGFPGSFGYYDIDAQT
FADWGVDLLKFDGCYCDSLENLADGYKHMSLALNRTGRSIVYSCEWPLYMWPFQKPNYTEIRQYCNHWRNF
ADIDDSWKSIKSILDWTSFNQERIVDVAGPGGWNDPDMLVIGNFGLSWNQQVTQMALWAIMAAPLFMSNDL
RHISPQAKALLQDKDVIAINQDPLGKQGYQLRQGDNFEVWERPLSGLAWAVAMINRQEIGGPRSYTIAVAS
LGKGVACNPACFITQLLPVKRKLGFYEWTSRLRSHINPTGTVLLQLENTMQMSLKDLLTREQKLISEEDLN
SAVDHHHHHH (SEQ ID NO:23)

FIGURE 27A

ATGAAGCTTTCCACCATCCTCTTCACAGCCTGCGCTACCCTGGCTGCCGCCCAGCAGGGAGCCT
CTCGACCCGGACCCCGAGATGCCCAGGCTCACCCCGGACGACCTCGAGCTGTGCCCACCCAGTGTG
ACGTGCCCCCCAACTCTCGATTCGACTGTGCCCCCGACAAGGCCATCACCCAGGAGCAGTGCGAGG
CCCGAGGCTGTTGTTACATCCCCGCTAAGCAGGGCCTGCAGGGCGCTCAGATGGGCCAGCCCTGGT
GTTTCTTCCCCCCCTCTTACCCCTCCTACAAGCTGGAGAACCTGTCCTCTTCGGAGATGGGCTACAC
CGCCACCCTGACCCGAACCACCCCCACCTTTTTCCCCAAGGACATCCTGACCCTGCGACTGGACGTG
ATGATGGAGACCGAGAACCGACTGCACTTCACCATCAAGGACCCCGCCAACCGACGATACGAGGT
GCCCCTGGAGACCCCCCACGTGCACTCTCGAGCCCCTTCCCCCCTGTACTCTGTGGAGTTCTCTGAG
GAGCCCTTCGGCGTGATCGTGCGACGACAGCTGGACGGCCGAGTGCTGCTGAACACCACCGTGGCC
CCCCTGTTCTTCGCCGACCAGTTCCTGCAGCTGTCTACCTCTCTGCCCTCTCAGTACATCACCGGCCT
GGCCGAGCACCTGTCCCCCCTGATGCTGTCCACCTCTTGGACTCGAATCACCCTGTGGAACCGAGA
CCTGGCCCCCACCCCCGGTGCCAACCTGTACGGCTCTCACCCCTTCTACCTGGCCCTGGAGGACGGC
GGCTCTGCCCACGGCGTGTTTCTGCTGAACTCTAACGCCATGGACGTGGTGCTGCAGCCCTCTCCCG
CCCTGTCTTGGCGATCTACCGGCGGCATCCTGGACGTGTACATCTTCCTGGGCCCTGAGCCCAAGTC
TGTGGTCCAGCAGTACCTGGACGTGGTCGGATACCCCTTCATGCCCCCCTACTGGGGCCTGGGCTTC
CACCTGTGTCGATGGGGCTACTCTTCTACCGCCATCACCCGACAGGTGGTGGAGAACATGACCCGA
GCCCACTTCCCCCTGGACGTGCAATGGAACGACCTGGACTACATGGACTCTCGACGAGACTTCACC
TTCAACAAGGACGGCTTCCGAGACTTCCCCGCCATGGTCCAGGAGCTGCACCAGGGAGGACGACG
ATACATGATGATCGTGGACCCCGCCATCTCTTCTTCCGGACCCGCCGGATCTTACCGACCCTACGAC
GAGGGCCTGCGACGAGGCGTGTTCATCACCAACGAGACCGGCCAGCCCCTGATCGGCAAGGTGTG
GCCCGGCTCTACCGCCTTCCCCGACTTCACCAACCCCACCGCCCTGGCTTGGTGGGAGGACATGGT
GGCCGAGTTCCACGACCAGGTGCCCTTCGACGGCATGTGGATCGACATGAACGAGCCCTCTAACTT
CATCCGAGGCTCTGAGGACGGCTGTCCCAACAACGAGCTGGAGAACCCCCCCTACGTGCCCGGCGT
GGTGGGCGGAACCCTGCAGGCCGCCACCATCTGTGCCTCTTCGCACCAGTTTCTGTCTACCCACTAC
AACCTGCACAACCTGTACGGACTGACCGAGGCCATTGCCTCTCACCGAGCCCTGGTGAAGGCCCGA
GGCACCCGACCCTTCGTGATCTCTCGATCTACCTTCGCCGGCCACGGCCGATACGCCGGACACTGG
ACCGGCGATGTGTGGTCCTCTTGGGAGCAGCTGGCCTCTTCTGTGCCCGAGATCCTGCAGTTCAACC
TGCTGGGCGTGCCCCTGGTGGGCGCCGACGTGTGTGGCTTCCTGGGCAACACCTCTGAGGAGCTGT
GTGTTCGATGGACCCAGCTCGGCGCCTTCTACCCTTTCATGCGAAACCACAACTCCCTGCTGTCTCT
GCCCCAGGAGCCCTACTCGTTCTCTGAGCCCGCTCAGCAGGCCATGCGAAAGGCTCTGACCCTGCG
ATACGCCCTGCTGCCCCACCTGTACACCCTGTTCCACCAGGCCCACGTGGCTGGAGAGACCGTGGC
CCGACCCCTGTTCCTGGAGTTCCCTAAGGACTCTTCTACCTGGACCGTGGACCATCAGCTGCTGTGG
GGCGAGGCCCTCCTGATCACCCCCGTGCTGCAGGCCGGCAAGGCTGAGGTGACCGGCTACTTCCCT
CTGGGCACCTGGTACGACCTGCAGACCGTGCCTGTGGAGGCCCTGGGATCTCTGCCCCCTCCTCCCG
CCGCTCCCCGAGAGCCCGCCATCCACTCTGAGGGCCAGTGGGTGACCCTGCCCGCTCCCCTGGACA
CCATCAACGTGCACCTGCGAGCCGGCTACATCATCCCTCTGCAGGGACCCGGCCTGACCACCACCG
AGTCTCGACAGCAGCCCATGGCCCTGGCCGTGGCTCTGACCAAGGGCGGAGAGGCCCGAGGCGAG
CTGTTCTGGGACGATGGCGAGTCTCTGGAGGTGCTGGAGCGAGGCGCCTACACCCAGGTGATCTTT
CTGGCCCGAAACAACACCATCGTGAACGAGCTGGTGCGAGTGACCTCTGAGGGCGCTGGTCTGCAG
CTCCAGAAGGTGACCGTCCTGGGCGTGGCCACCGCTCCCCAGCAGGTCCTGTCTAACGGCGTGCCC
GTGTCTAACTTCACCTACTCTCCCGACACCAAGGTGCTGGACATCTGTGTGTCTCTGCTGATGGGCG
AGCAGTTCCTGGTGTCTTGGTGTTAAC (SEQ ID NO:24)

FIGURE 27B

MKLSTILFTACATLAAAQQGASRPGPRDAQAHPGRPRAVPTQCDVPPNSRFDCAPDK
AITQEQCEARGCCYIPAKQGLQGAQMGQPWCFFPPSYPSYKLENLSSSEMGYTATLTRT
TPTFFPKDILTLRLDVMMETENRLHFTIKDPANRRYEVPLETPHVHSRAPSPLYSVEFSE
EPFGVIVRRQLDGRVLLNTTVAPLFFADQFLQLSTSLPSQYITGLAEHLSPLMLSTSWTR
ITLWNRDLAPTPGANLYGSHPFYLALEDGGSAHGVFLLNSNAMDVVLQPSPALSWRST
GGILDVYIFLGPEPKSVVQQYLDVVGYPFMPPYWGLGFHLCRWGYSSTAITRQVVENM
TRAHFPLDVQWNDLDYMDSRRDFTFNKDGFRDFPAMVQELHQGGRRYMMIVDPAISS
SGPAGSYRPYDEGLRRGVFITNETGQPLIGKVWPGSTAFPDFTNPTALAWWEDMVAEF
HDQVPFDGMWIDMNEPSNFIRGSEDGCPNNELENPPYVPGVVGGTLQAATICASSHQF
LSTHYNLHNLYGLTEAIASHRALVKARGTRPFVISRSTFAGHGRYAGHWTGDVWSSWE
QLASSVPEILQFNLLGVPLVGADVCGFLGNTSEELCVRWTQLGAFYPFMRNHNSLLSLP
QEPYSFSEPAQQAMRKALTLRYALLPHLYTLFHQAHVAGETVARPLFLEFPKDSSTWT
VDHQLLWGEALLITPVLQAGKAEVTGYFPLGTWYDLQTVPVEALGSLPPPPAAPREPAI
HSEGQWVTLPAPLDTINVHLRAGYIIPLQGPGLTTTESRQQPMALAVALTKGGEARGEL
FWDDGESLEVLERGAYTQVIFLARNNTIVNELVRVTSEGAGLQLQKVTVLGVATAPQQ
VLSNGVPVSNFTYSPDTKVLDICVSLLMGEQFLVSWC* (SEQ ID NO:25)

FIGURE 28

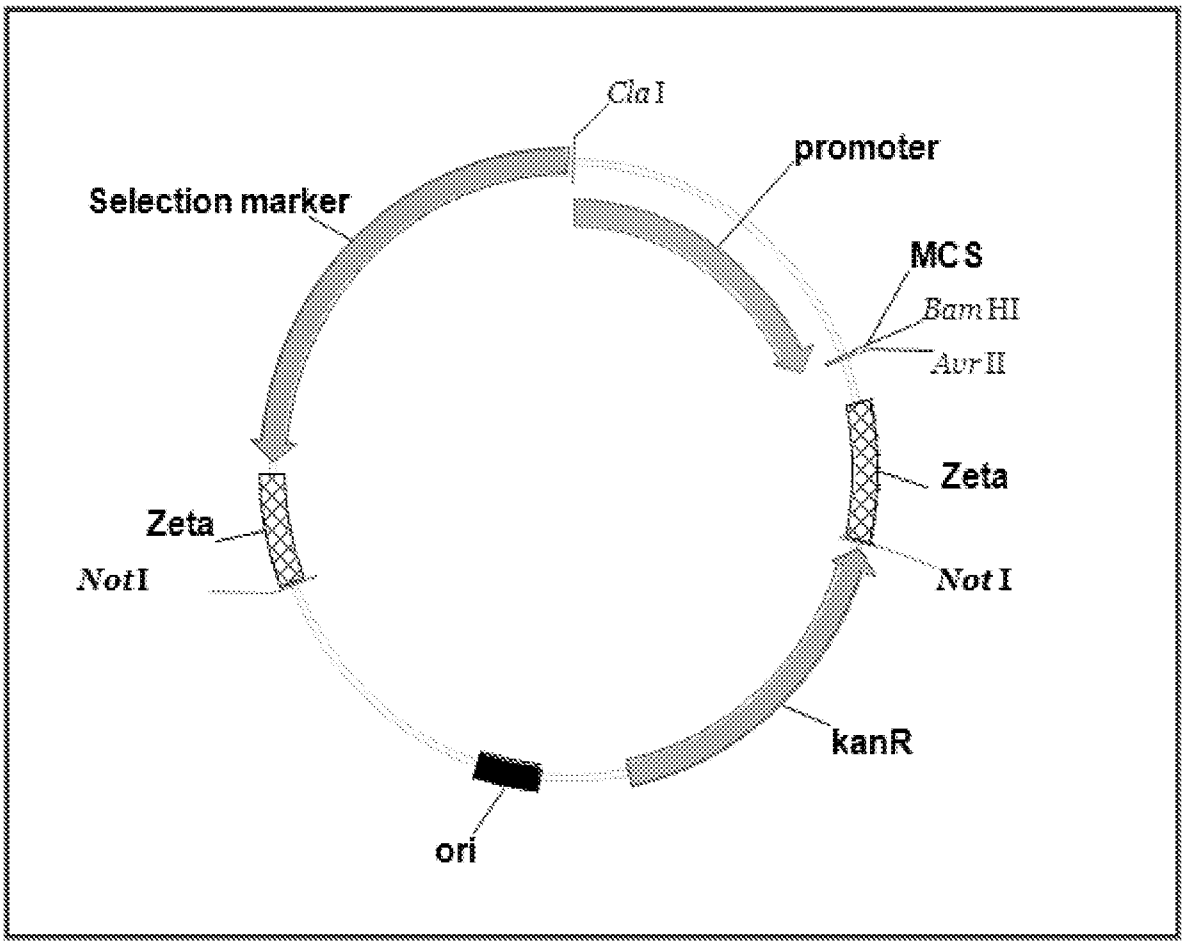

ClaI
promoter
Selection marker
MCS
BamHI
AvrII
Zeta
Zeta
NotI
NotI
kanR
ori

FIGURE 29

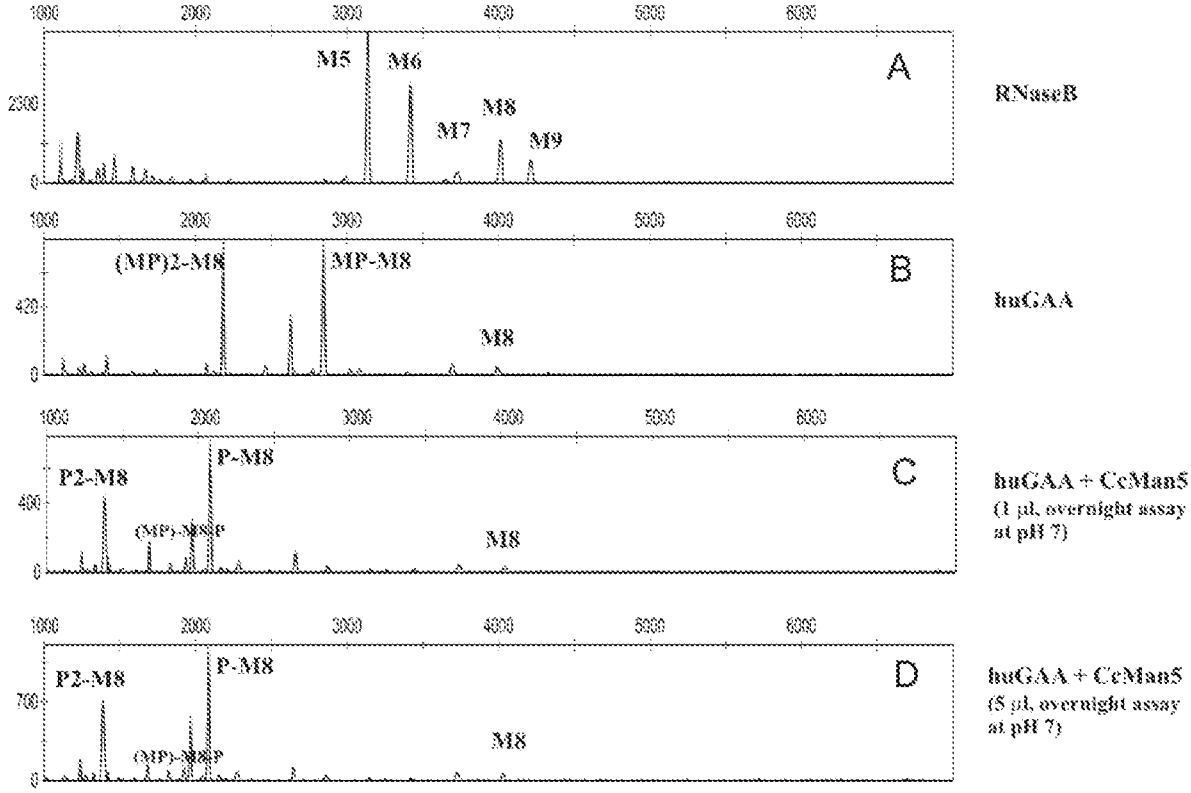
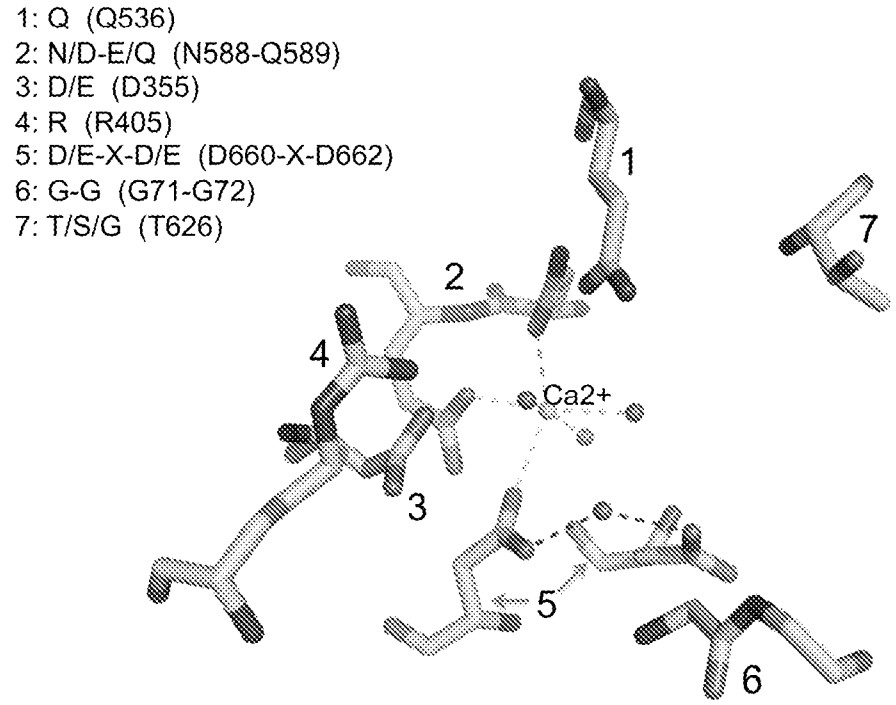

1000
2000
3000
4000
5000
6000
M5
M6
M8
M7
M9
A
RNaseB
(MP)2-M8
MP-M8
M8
B
huGAA
P2-M8
P-M8
(MP)-M8P
M8
C
huGAA + CcMan5
(1 µl, overnight assay at pH 7)
P2-M8
P-M8
(MP)-M8P
M8
D
huGAA + CcMan5
(5 µl, overnight assay at pH 7)

FIGURE 30



Numbering for equivalent residues in SEC ID NO:50 is given in parenthesis

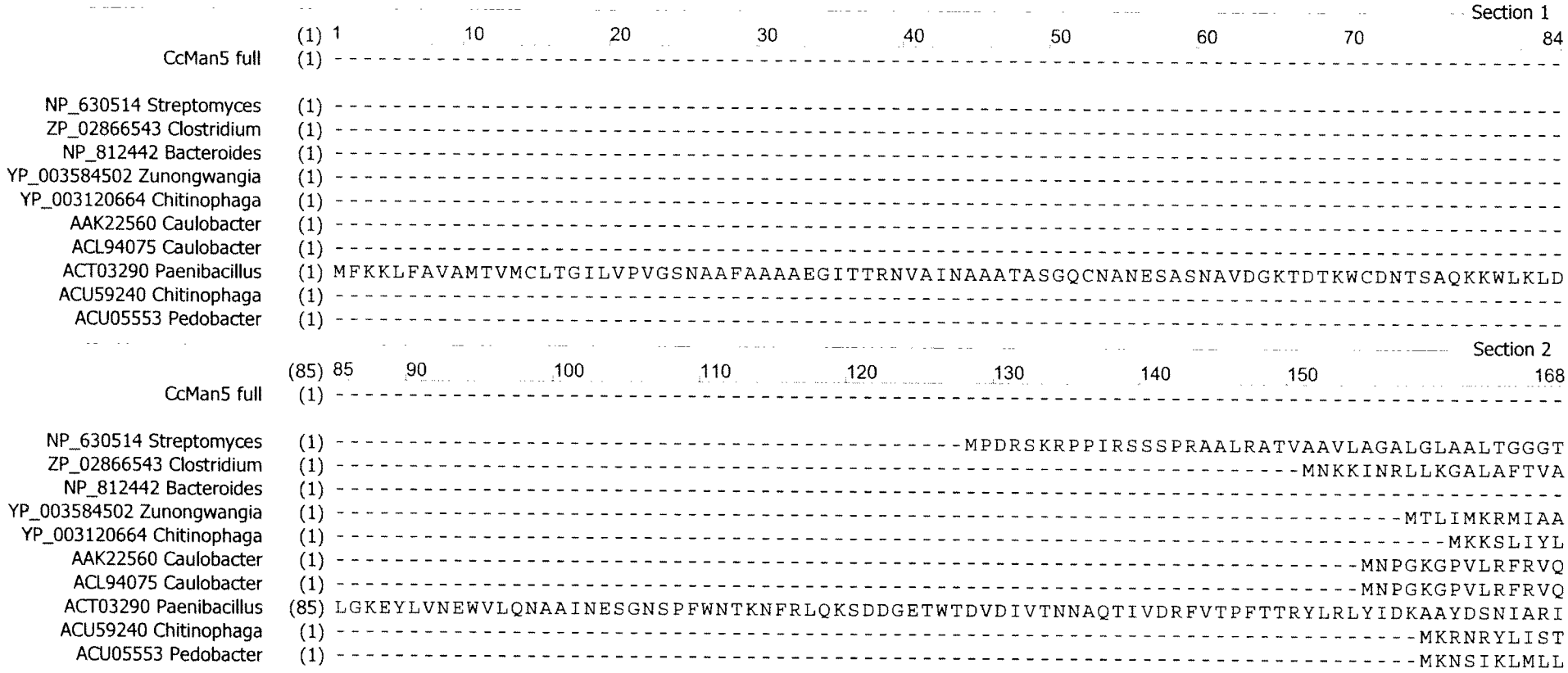
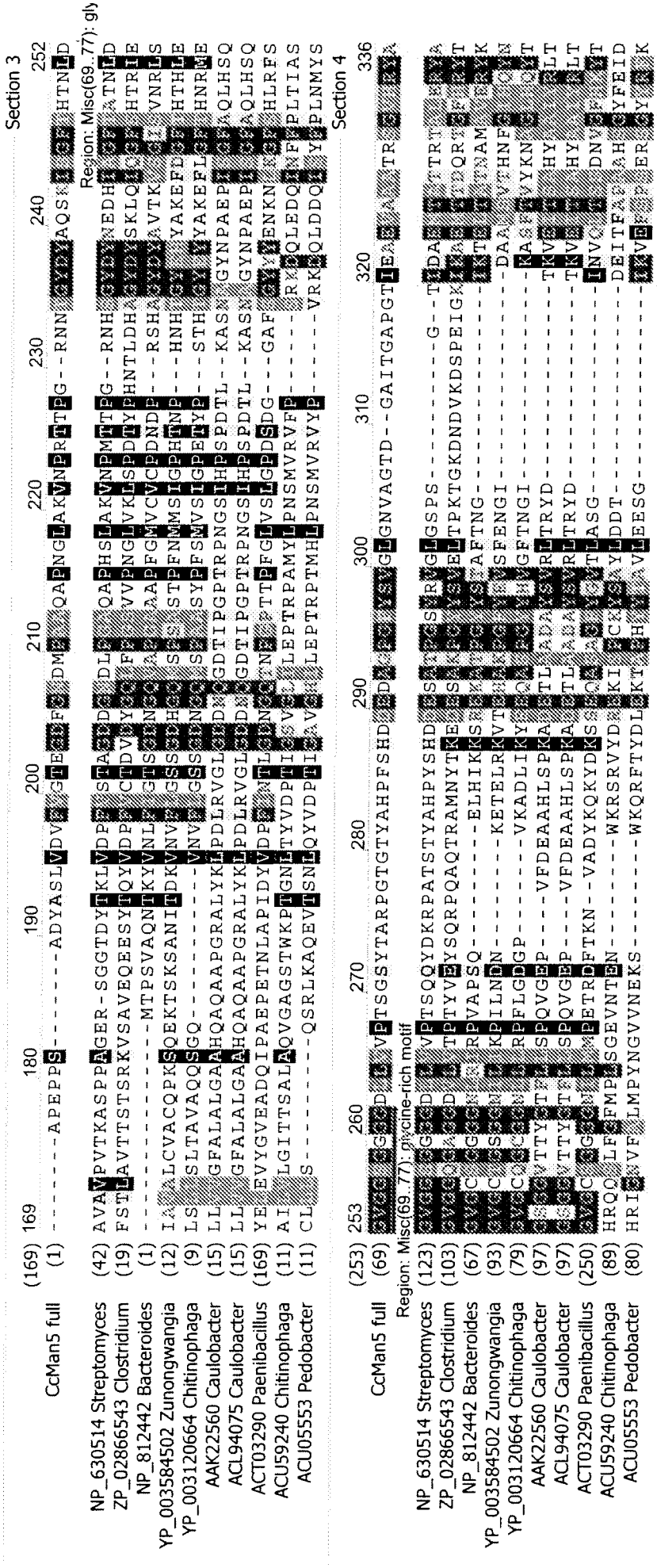

Section 1
(1) 1 10 20 30 40 50 60 70 84
CcMan5 full (1) ----------
NP_630514 Streptomyces (1) ----------
ZP_02866543 Clostridium (1) ----------
NP_812442 Bacteroides (1) ----------
YP_003584502 Zunongwangia (1) ----------
YP_003120664 Chitinophaga (1) ----------
AAK22560 Caulobacter (1) ----------
ACL94075 Caulobacter (1) ----------
ACT03290 Paenibacillus (1) MFKKLFAVAMTVMCLTGILVPVGSNAAFAAAAEGITTRNVAINAAATASGQCNANESASNAVDGKTDTKWCDNTSAQKKWLKLD
ACU59240 Chitinophaga (1) ----------
ACU05553 Pedobacter (1) ----------
Section 2
(85) 85 90 100 110 120 130 140 150 168
CcMan5 full (1) ----------
NP_630514 Streptomyces (1) ----------MPDRSKRPPIRSSSPRAALRATVAAVLAGALGLAALTGGGT
ZP_02866543 Clostridium (1) ----------MNKKINRLLKGALAFTVA
NP_812442 Bacteroides (1) ----------
YP_003584502 Zunongwangia (1) ----------MTLIMKRMIAA
YP_003120664 Chitinophaga (1) ----------MKKSLIYL
AAK22560 Caulobacter (1) ----------MNPGKGPVLRFRVQ
ACL94075 Caulobacter (1) ----------MNPGKGPVLRFRVQ
ACT03290 Paenibacillus (85) LGKEYLVNEWVLQNAAINESGNSPFWNTKNFRLQKSDDGETWTDVDIVTNNAQTIVDRFVTPFTTRYLRLYIDKAAYDSNIARI
ACU59240 Chitinophaga (1) ----------MKRNRYLIST
ACU05553 Pedobacter (1) ----------MKNSIKLMLL

FIG. 31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Section 4
Region: Misc(69..77): glycine-rich motif
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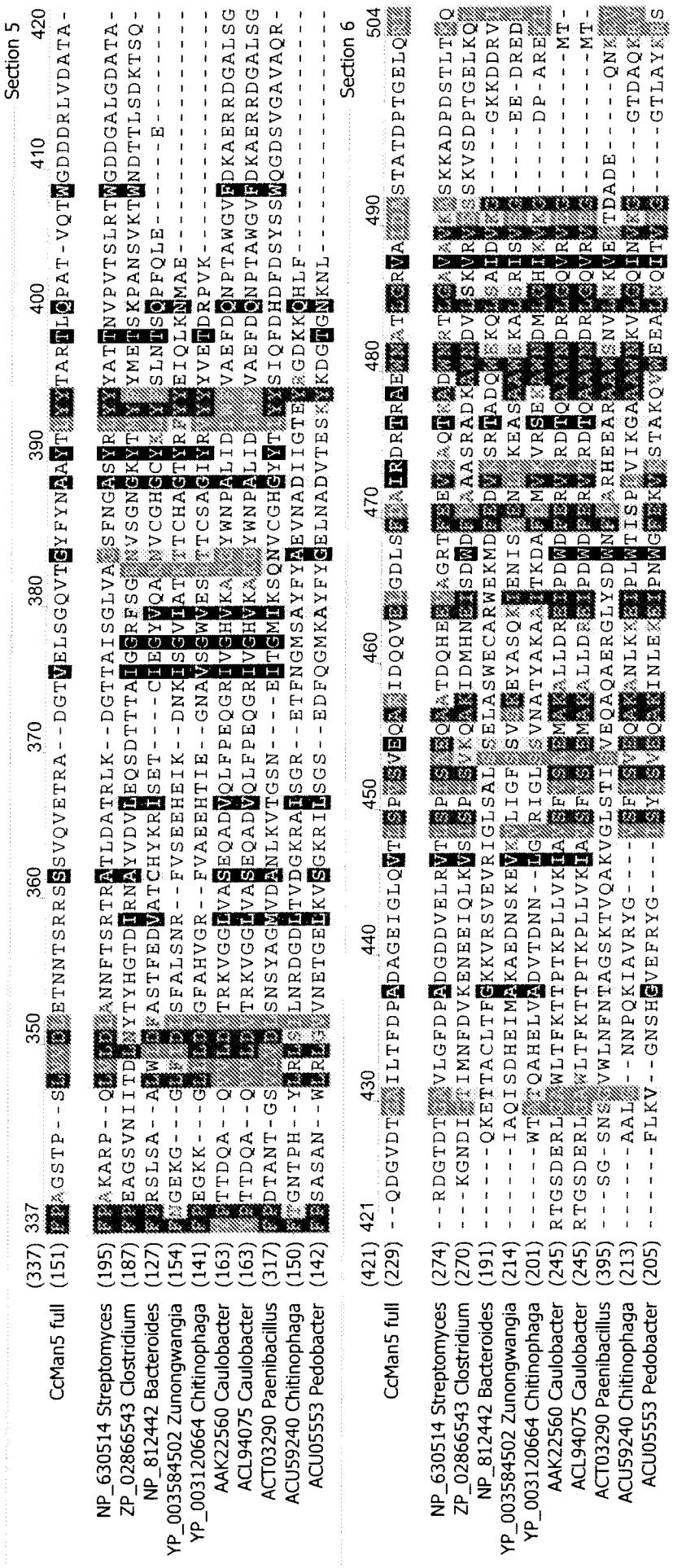
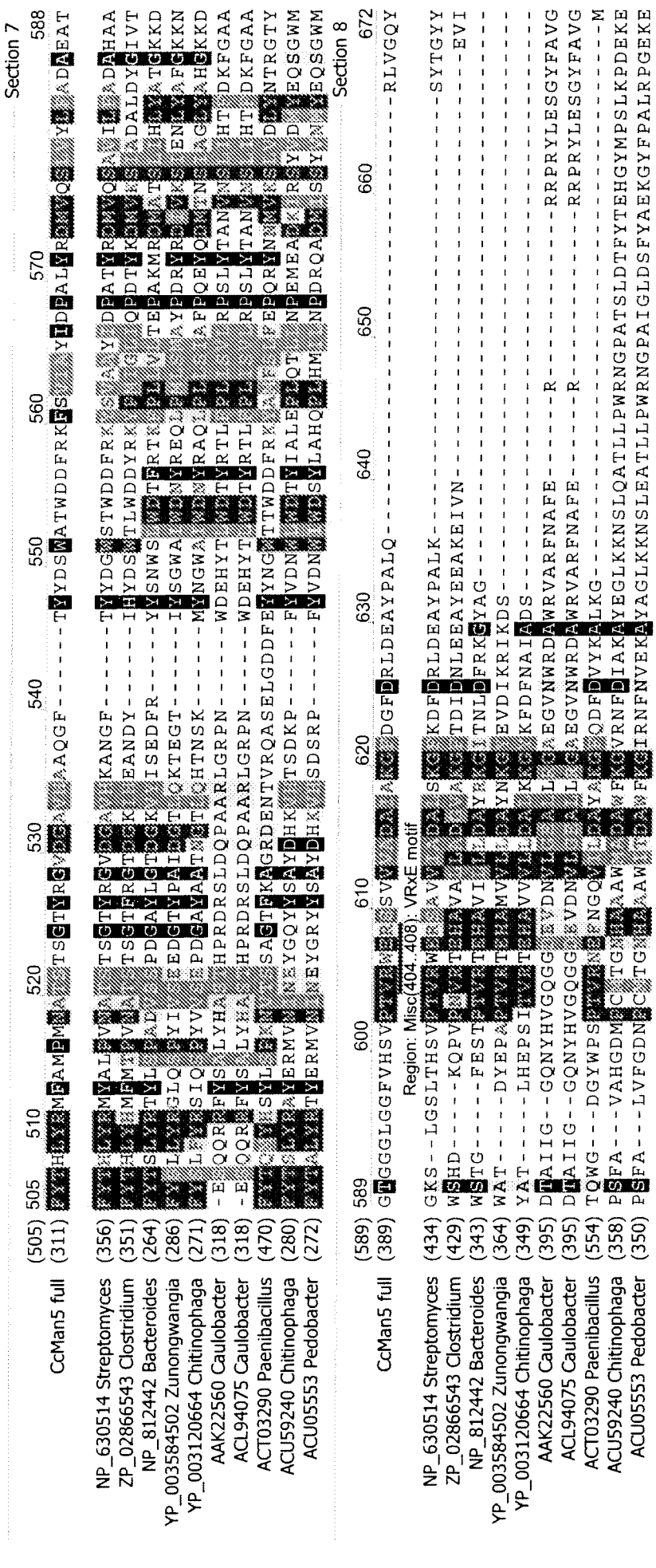
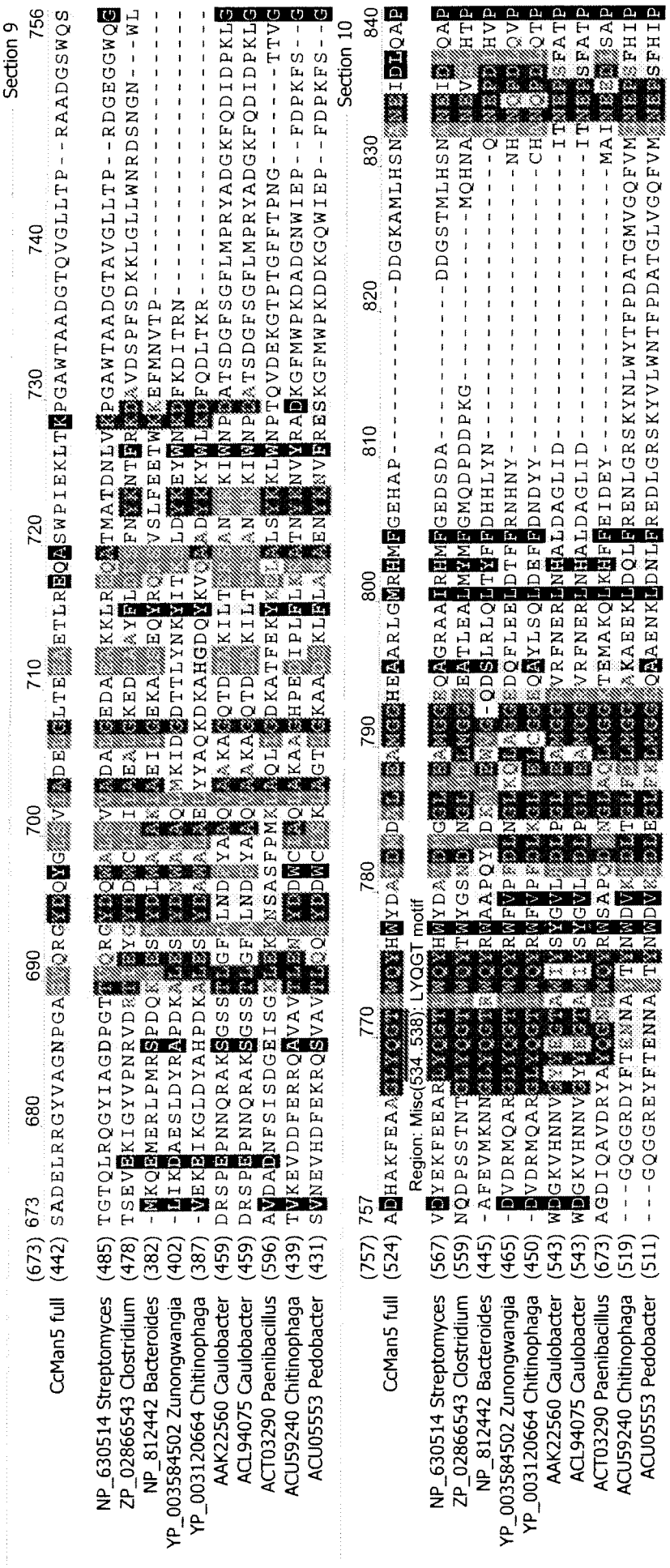
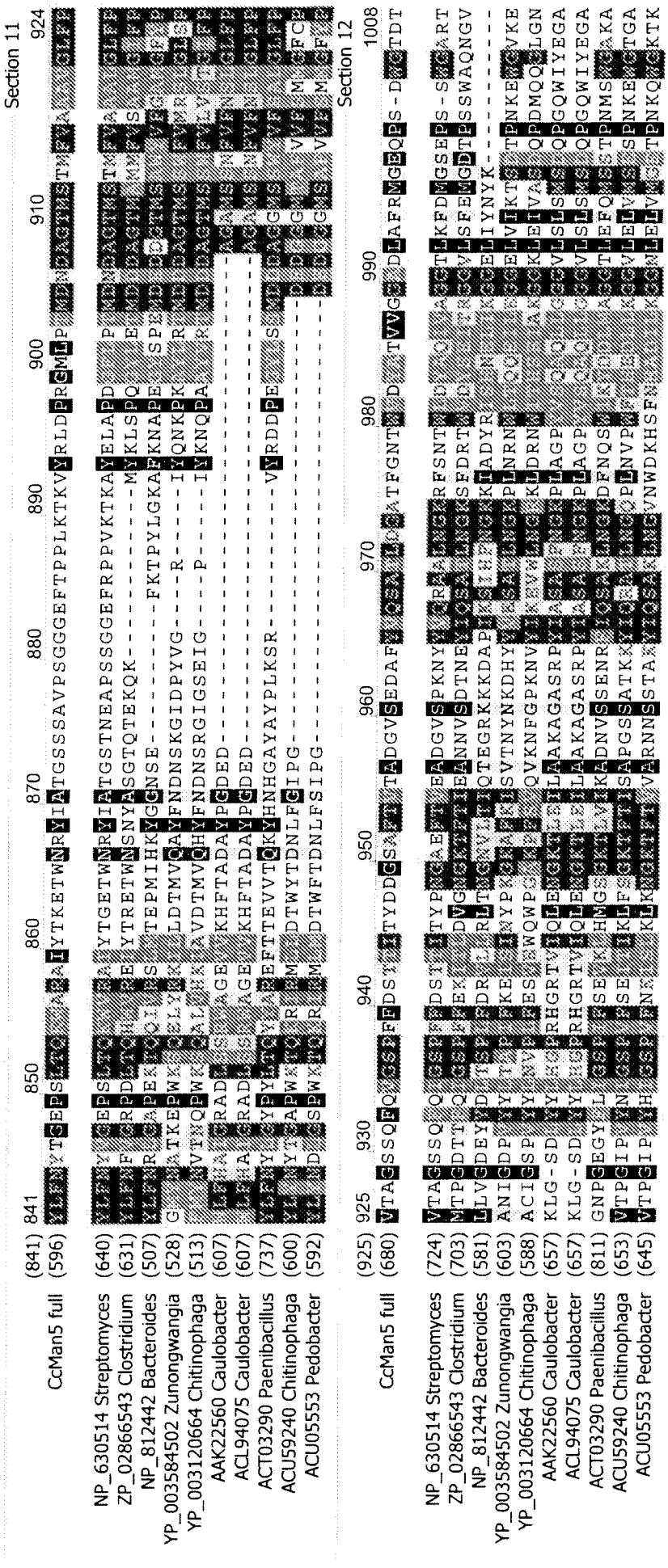
ZP_02866543 Clostridium
NP_812442 Bacteroides
YP_003584502 Zunongwangia
YP_003120664 Chitinophaga
AAK22560 Caulobacter
ACL94075 Caulobacter
ACT03290 Paenibacillus
ACU59240 Chitinophaga
ACU05553 Pedobacter


Section 5
Section 6
CcMan5 full
NP_630514 Streptomyces
ZP_02866543 Clostridium
NP_812442 Bacteroides
YP_003584502 Zunongwangia
YP_003120664 Chitinophaga
AAK22560 Caulobacter
ACL94075 Caulobacter
ACT03290 Paenibacillus
ACU59240 Chitinophaga
ACU05553 Pedobacter


Section 7
Section 8
CcMan5 full
NP_630514 Streptomyces
ZP_02866543 Clostridium
NP_812442 Bacteroides
YP_003584502 Zunongwangia
YP_003120664 Chitinophaga
AAK22560 Caulobacter
ACL94075 Caulobacter
ACT03290 Paenibacillus
ACU59240 Chitinophaga
ACU05553 Pedobacter
Region: Misc(404..408): VRxE motif


Section 9
Section 10
CcMan5 full
NP_630514 Streptomyces
ZP_02866543 Clostridium
NP_812442 Bacteroides
YP_003584502 Zunongwangia
YP_003120664 Chitinophaga
AAK22560 Caulobacter
ACL94075 Caulobacter
ACT03290 Paenibacillus
ACU59240 Chitinophaga
ACU05553 Pedobacter
Region: Misc(534..538) LYQGT motif

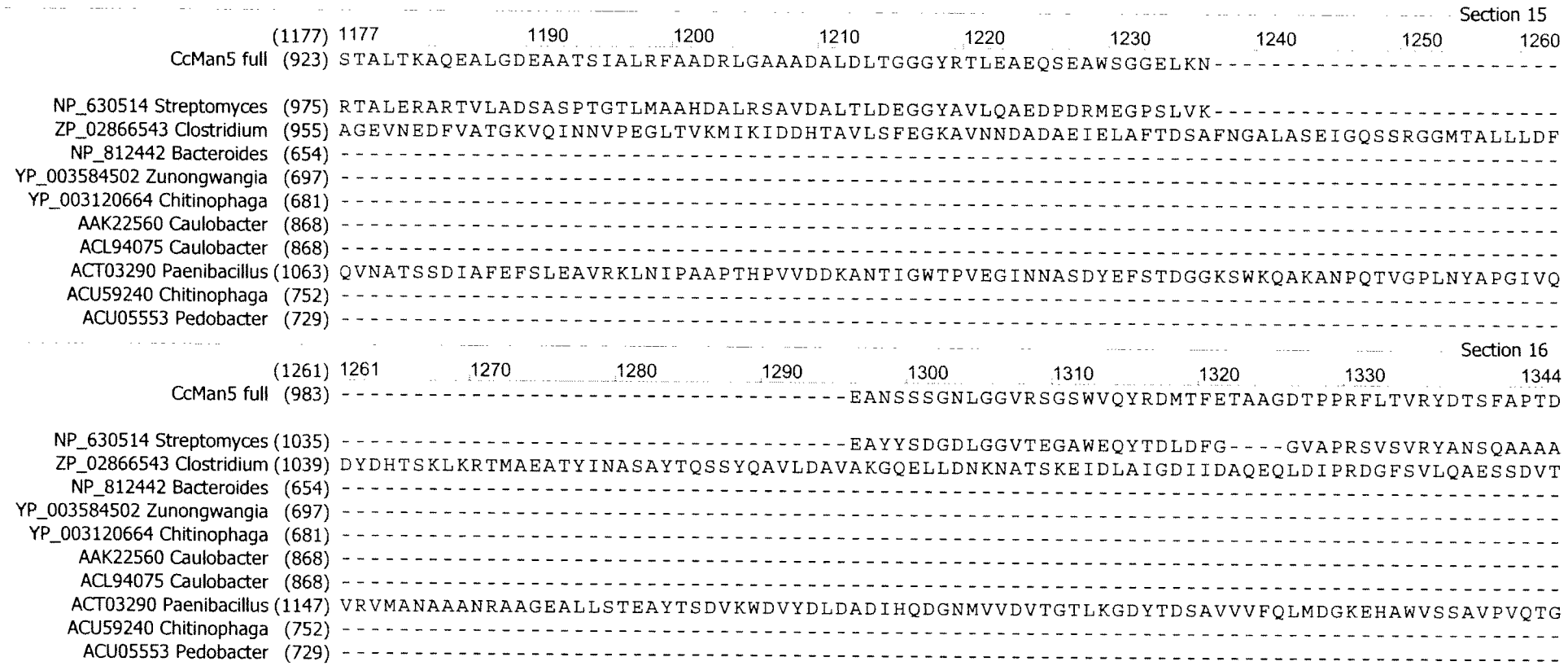

Section 11
Section 12
CcMan5 full
NP_630514 Streptomyces
ZP_02866543 Clostridium
NP_812442 Bacteroides
YP_003584502 Zunongwangia
YP_003120664 Chitinophaga
AAK22560 Caulobacter
ACL94075 Caulobacter
ACT03290 Paenibacillus
ACU59240 Chitinophaga
ACU05553 Pedobacter

```
                                                                                  Section 13
                                (1009) 1009      1020       1030       1040       1050       1060       1070       1080       1092
CcMan5 full                     (763)  APAFSMSTATDEPAEGPR-------VSAEPTTVQTGDGGALDATVTLTLDG-ARLAAPAGTDLVTSGAASVVGLPDGVTAAVTV

NP_630514 Streptomyces          (807)  EPAYSLNTDSGDGDDEHAPGRGTTVVSARPETVRTAADGTVDASVELRLSGRASFAARKGTSLTRTGAASVTGLPDGVTADLRV
ZP_02866543 Clostridium         (787)  TAKSSSDNADTSTYDDDEIAYSSAMFEESKANDGSFDQKITITLKTKEFAGEIGEDLVATGKINITNIPEGLEASAIKTEANKV
NP_812442 Bacteroides           (654)  ------------------------------------------------------------------------------------
YP_003584502 Zunongwangia       (687)  AWVSSIRQYL--------------------------------------------------------------------------
YP_003120664 Chitinophaga       (672)  KWIADITRQ---------------------------------------------------------------------------
AAK22560 Caulobacter            (740)  VLTVRADQPSLVDGKTSTGWRAASGQSVTFSLKAPACIAAYSVSVGPDQADPSHWTLQAYDGRAWVSVDQQSNVVFDHRHATRT
ACL94075 Caulobacter            (740)  VLTVRADQPSLVDGKTSTGWRAASGQSVTFSLKAPACIAAYSVSVGPDQADPSHWTLQAYDGRAWVSVDQQSNVVFDHRHATRT
ACT03290 Paenibacillus          (895)  SAAPPTVDYNADMDNDFNHEQLIPEKSTWKYDDKGKEAGEGWTQVDFDDSSWSSGKAMLGYDSYGKPATTVSYGPNANNKYVTT
ACU59240 Chitinophaga           (737)  QAAPPSSLNYSPAGK---------------------------------------------------------------------
ACU05553 Pedobacter             (729)  ------------------------------------------------------------------------------------

                                                                                  Section 14
                                (1093) 1093 1100      1110       1120       1130       1140       1150       1160       1176
CcMan5 full                     (839)  ASPTALTVSLTGTASADARFFVHLRDAALADGVAAASLQGQGVSVRSPLRLSVASAERDALAALVDDAVLVRHGNYSSVTFDRF

NP_630514 Streptomyces          (891)  TGKRTASLRLTGTTRTDARFGITFRDRAFPHGIPASTVTGTGVSVTDPLIVSAAAVHRGSLAALVDEASLVREGNYSDGSYGIF
ZP_02866543 Clostridium         (871)  EVSLNGKAKNHTLNDSISNLTIEITDGATNEPIKDSIRKTKDNVKVMFIDNQLTYSQSEFKESESDDGAILETSTITLTGDTTF
NP_812442 Bacteroides           (654)  ------------------------------------------------------------------------------------
YP_003584502 Zunongwangia       (697)  ------------------------------------------------------------------------------------
YP_003120664 Chitinophaga       (681)  ------------------------------------------------------------------------------------
AAK22560 Caulobacter            (824)  FPLAPGRYARLRWVLDGGSEASVSEVELIAGASCAAPTSGAPLL----------------------------------------
ACL94075 Caulobacter            (824)  FPLAPGRYARLRWVLDGGSEASVSEVELIAGASCAAPTSGAPLL----------------------------------------
ACT03290 Paenibacillus          (979)  YFRKTFDAKDLDGILELDGSLIRDDGAIVYLNGHEIFRTNMPTGAVNYSTFANATVGDERDKNGFIIDPSYLVEGKNVLTAEVH
ACU59240 Chitinophaga           (752)  ------------------------------------------------------------------------------------
ACU05553 Pedobacter             (729)  ------------------------------------------------------------------------------------
```


Section 15
(1177) 1177 1190 1200 1210 1220 1230 1240 1250 1260
CcMan5 full (923) STALTKAQEALGDEAATSIALRFAADRLGAAADALDLTGGGYRTLEAEQSEAWSGGELKN----------
NP_630514 Streptomyces (975) RTALERARTVLADSASPTGTLMAAHDALRSAVDALTLDEGGYAVLQAEDPDRMEGPSLVK----------
ZP_02866543 Clostridium (955) AGEVNEDFVATGKVQINNVPEGLTVKMIKIDDHTAVLSFEGKAVNNDADAEIELAFTDSAFNGALASEIGQSSRGGMTALLLDF
NP_812442 Bacteroides (654) ----------
YP_003584502 Zunongwangia (697) ----------
YP_003120664 Chitinophaga (681) ----------
AAK22560 Caulobacter (868) ----------
ACL94075 Caulobacter (868) ----------
ACT03290 Paenibacillus (1063) QVNATSSDIAFEFSLEAVRKLNIPAAPTHPVVDDKANTIGWTPVEGINNASDYEFSTDGGKSWKQAKANPQTVGPLNYAPGIVQ
ACU59240 Chitinophaga (752) ----------
ACU05553 Pedobacter (729) ----------
Section 16
(1261) 1261 1270 1280 1290 1300 1310 1320 1330 1344
CcMan5 full (983) ----------EANSSSGNLGGVRSGSWVQYRDMTFETAAGDTPPRFLTVRYDTSFAPTD
NP_630514 Streptomyces (1035) ----------EAYYSDGDLGGVTEGAWEQYTDLDFG----GVAPRSVSVRYANSQAAAA
ZP_02866543 Clostridium (1039) DYDHTSKLKRTMAEATYINASAYTQSSYQAVLDAVAKGQELLDNKNATSKEIDLAIGDIIDAQEQLDIPRDGFSVLQAESSDVT
NP_812442 Bacteroides (654) ----------
YP_003584502 Zunongwangia (697) ----------
YP_003120664 Chitinophaga (681) ----------
AAK22560 Caulobacter (868) ----------
ACL94075 Caulobacter (868) ----------
ACT03290 Paenibacillus (1147) VRVMANAAANRAAGEALLSTEAYTSDVKWDVYDLDADIHQDGNMVVDVTGTLKGDYTDSAVVVFQLMDGKEHAWVSSAVPVQTG
ACU59240 Chitinophaga (752) ----------
ACU05553 Pedobacter (729) ----------

```
                                                                                   Section 17
                          (1345) 1345 1350      1360      1370      1380      1390      1400      1410            1428
                 CcMan5 full (1032) TPS-----------------------------------TVRVHAGDVSGPVVATVDLKGTSGWGKYTEVTAELGDVQALVDAQV

    NP_630514 Streptomyces (1080) EPS-----------------------------------SVDIHAGDADGPVVATVSLPGTGGWQYYTTVRAAVSDPQALLKASS
   ZP_02866543 Clostridium (1123) SGGSLRVEGSVLHGTYDGAWIRYDALDFNGLSPKYLELRYDNASNRCASDSHLEVRLDGVDGTLIGDIQLPATGTAWGSYETLQ
     NP_812442 Bacteroides  (654) ------------------------------------------------------------------------------------
YP_003584502 Zunongwangia  (697) ------------------------------------------------------------------------------------
YP_003120664 Chitinophaga  (681) ------------------------------------------------------------------------------------
      AAK22560 Caulobacter  (868) ------------------------------------------------------------------------------------
      ACL94075 Caulobacter  (868) ------------------------------------------------------------------------------------
  ACT03290 Paenibacillus (1231) SFD-----------------------------------ISQIYNVDASKYKVNVYLVNEFNGDIYESPLWLADPIVQQSEPGSL
    ACU59240 Chitinophaga  (752) ------------------------------------------------------------------------------------
     ACU05553 Pedobacter  (729) ------------------------------------------------------------------------------------

                                                                                   Section 18
                          (1429) 1429      1440      1450      1460      1470      1480      1490      1500          1512
                 CcMan5 full (1081) VTFELLAPSGRSWVGNFDWFRFSAEDPAAPGQPGESPTVTIEAEDWTASSGRGLKKESSTWTSGPVTNVGGTADGDWIAYGEVD

    NP_630514 Streptomyces (1129) ATFVFHAPSGRQWVSNFDWYQFSPEAAPSSSPITTLATLTTANTTSTGDGSLPLKVSGGVFEN--------VTNGAWAEWRDTD
   ZP_02866543 Clostridium (1207) FEISNPELLDGKHDVYFVFKGTTEDSKPYVAKVDYLQFKETADIDSVKLEAEKSDENSGNGLKNESINLGGTYDGAWIKYNNVN
     NP_812442 Bacteroides  (654) ------------------------------------------------------------------------------------
YP_003584502 Zunongwangia  (697) ------------------------------------------------------------------------------------
YP_003120664 Chitinophaga  (681) ------------------------------------------------------------------------------------
      AAK22560 Caulobacter  (868) ------------------------------------------------------------------------------------
      ACL94075 Caulobacter  (868) ------------------------------------------------------------------------------------
  ACT03290 Paenibacillus (1280) PDPEGPPVTEEPLPEPIPLPDPKPDEPEEPEVPETGMKIQFEDRAEWTSAAHPNGGGGLSTEAGNGGTVVAHTFGGAWLAYNVD
    ACU59240 Chitinophaga  (752) ------------------------------------------------------------------------------------
     ACU05553 Pedobacter  (729) ------------------------------------------------------------------------------------
```

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                                                                                                      Section 21
                            (1681) 1681     1690      1700      1710      1720      1730      1740      1750          1764
                   CcMan5 full (1329) HNSNRSGRNSALSVY-------------------------------------------------LDAFDPANPGEPFVTVPLAN

      NP_630514 Streptomyces (1367) NNSARCGTGSAVQLY-------------------------------------------------LDSFDPDAPGTPYATVPLPV
     ZP_02866543 Clostridium (1449) PGTAGTNSRIDVYLDNMDGNPIGTINLPTTNGWANYTVIREVFDQEITGSHDVYLKLHTDGSGWVANFDWFEFGEPIADVDKSQ
        NP_812442 Bacteroides  (654) ------------------------------------------------------------------------------------
  YP_003584502 Zunongwangia  (697) ------------------------------------------------------------------------------------
  YP_003120664 Chitinophaga  (681) ------------------------------------------------------------------------------------
        AAK22560 Caulobacter  (868) ------------------------------------------------------------------------------------
        ACL94075 Caulobacter  (868) ------------------------------------------------------------------------------------
     ACT03290 Paenibacillus (1532) GNSTNTFNNSAVEVR-------------------------------------------------LGSPTGTLVGTVATPPTAAA
      ACU59240 Chitinophaga  (752) ------------------------------------------------------------------------------------
        ACU05553 Pedobacter  (729) ------------------------------------------------------------------------------------
                                                                                                      Section 22
                            (1765) 1765 1770      1780      1790      1800      1810      1820      1830          1848
                   CcMan5 full (1364) TGSSWTTDGTAVVDLPSTVRGKHQVWVRLSTEAYADHPYVANLDSMRFFTDAYDVEVPPTDTAALAAVVDAAGTPEAEIARYGR

      NP_630514 Streptomyces (1402) TGSSWSSGGTTSLTLPEAITGTHAVHLRLTTNADSSHPYVANLGQVAFDRVEAPAQT---DLSALRKAIEQYEGLSEDADRYGT
     ZP_02866543 Clostridium (1533) LQAKYDENVALLQEYDKYHYVGFNIFKDRLLTGSAVIDNQNATANDVRIAIKDIDNALAALQYKIAFDLNDYVVQLENINEADY
        NP_812442 Bacteroides  (654) ------------------------------------------------------------------------------------
  YP_003584502 Zunongwangia  (697) ------------------------------------------------------------------------------------
  YP_003120664 Chitinophaga  (681) ------------------------------------------------------------------------------------
        AAK22560 Caulobacter  (868) ------------------------------------------------------------------------------------
        ACL94075 Caulobacter  (868) ------------------------------------------------------------------------------------
     ACT03290 Paenibacillus (1567) WGTYATVSGSLTQKLTGLQDVYLVFTGSAANGETGKKYIGNFDNASFSLSVQEPEEPEQPQQPEQEQITVQFESKTEWNTALNT
      ACU59240 Chitinophaga  (752) ------------------------------------------------------------------------------------
        ACU05553 Pedobacter  (729) ------------------------------------------------------------------------------------
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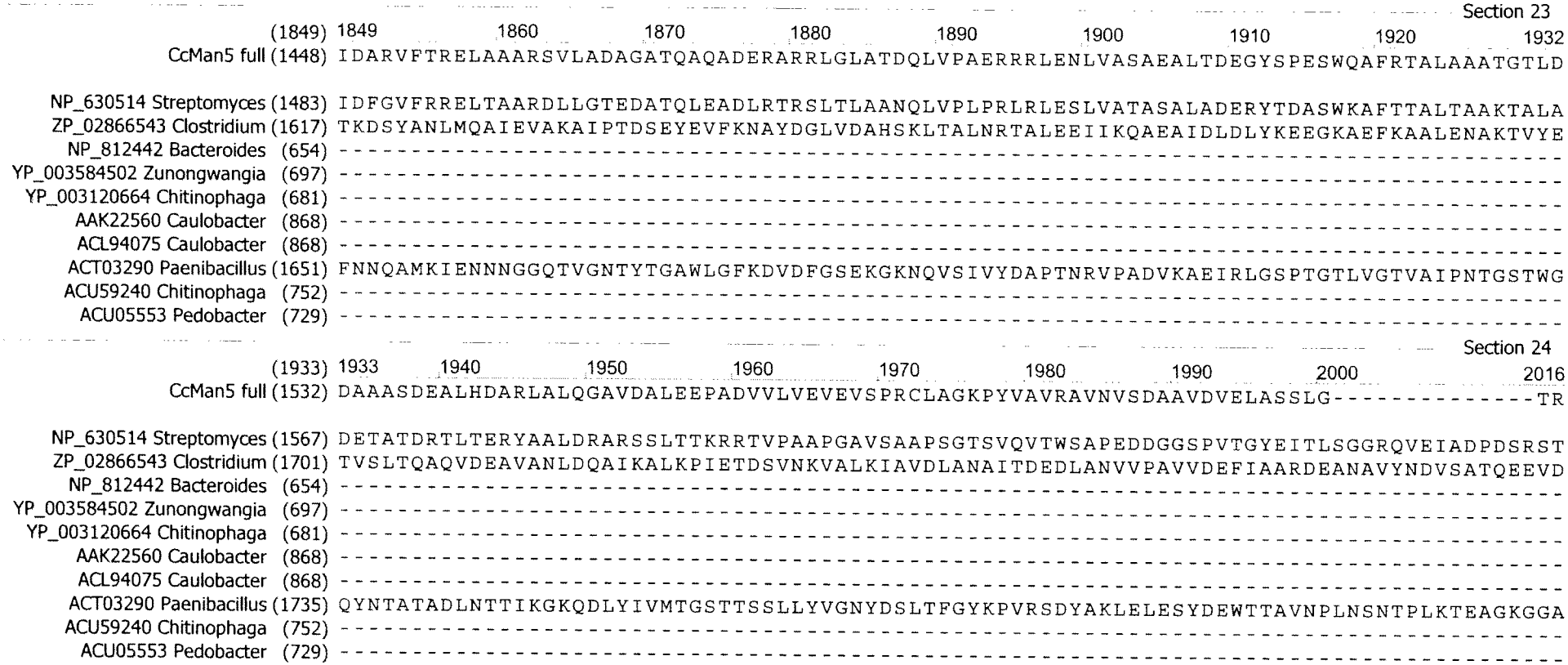
Section 23
(1849) 1849 1860 1870 1880 1890 1900 1910 1920 1932
CcMan5 full (1448) IDARVFTRELAAARSVLADAGATQAQADERARRLGLATDQLVPAERRRLENLVASAEALTDEGYSPESWQAFRTALAAAATGTLD
NP_630514 Streptomyces (1483) IDFGVFRRELTAARDLLGTEDATQLEADLRTRSLTLAANQLVPLPRLRLESLVATASALADERYTDASWKAFTTALTAAKTALA
ZP_02866543 Clostridium (1617) TKDSYANLMQAIEVAKAIPTDSEYEVFKNAYDGLVDAHSKLTALNRTALEEIIKQAEAIDLDLYKEEGKAEFKAALENAKTVYE
NP_812442 Bacteroides (654)
YP_003584502 Zunongwangia (697)
YP_003120664 Chitinophaga (681)
AAK22560 Caulobacter (868)
ACL94075 Caulobacter (868)
ACT03290 Paenibacillus (1651) FNNQAMKIENNNGGQTVGNTYTGAWLGFKDVDFGSEKGKNQVSIVYDAPTNRVPADVKAEIRLGSPTGTLVGTVAIPNTGSTWG
ACU59240 Chitinophaga (752)
ACU05553 Pedobacter (729)
Section 24
(1933) 1933 1940 1950 1960 1970 1980 1990 2000 2016
CcMan5 full (1532) DAAASDEALHDARLALQGAVDALEEPADVVLVEVEVSPRCLAGKPYVAVRAVNVSDAAVDVELASSLG----------TR
NP_630514 Streptomyces (1567) DETATDRTLTERYAALDRARSSLTTKRRTVPAAPGAVSAAPSGTSVQVTWSAPEDDGGSPVTGYEITLSGGRQVEIADPDSRST
ZP_02866543 Clostridium (1701) TVSLTQAQVDEAVANLDQAIKALKPIETDSVNKVALKIAVDLANAITDEDLANVVPAVVDEFIAARDEANAVYNDVSATQEEVD
NP_812442 Bacteroides (654)
YP_003584502 Zunongwangia (697)
YP_003120664 Chitinophaga (681)
AAK22560 Caulobacter (868)
ACL94075 Caulobacter (868)
ACT03290 Paenibacillus (1735) QYNTATADLNTTIKGKQDLYIVMTGSTTSSLLYVGNYDSLTFGYKPVRSDYAKLELESYDEWTTAVNPLNSNTPLKTEAGKGGA
ACU59240 Chitinophaga (752)
ACU05553 Pedobacter (729)

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                                                                                     Section 25
                        (2017) 2017        2030      2040      2050      2060      2070      2080      2090     2100
            CcMan5 full (1602) SFVGVAPGASAYQSFAARSATGDLDVTVTATGADGTQTVEQVVTVPSCS-----------------------------------

 NP_630514 Streptomyces (1651) VFTRLKDGTSYTARVRAVNALGDSPWSARTQPAVTGDNRPQTPTVTGVVTDGERVRVNWRPAGDGGFPVVGYTVALDDGTTAHV
ZP_02866543 Clostridium (1785) NAFDRLASVMQKLEFFKGDKKALKAFIDKVTGLDSSKYTQTTWTAFDKELTEAIAVYNDENAMQEEVNTAYSELVTAFLNLRLI
  NP_812442 Bacteroides  (654) ------------------------------------------------------------------------------------
YP_003584502 Zunongwangia (697) ------------------------------------------------------------------------------------
YP_003120664 Chitinophaga (681) ------------------------------------------------------------------------------------
   AAK22560 Caulobacter  (868) ------------------------------------------------------------------------------------
   ACL94075 Caulobacter  (868) ------------------------------------------------------------------------------------
ACT03290 Paenibacillus (1819) GKQVANTFNGAWLAYKRMDFGTEGVNTFAVEYAGNTTNCFTNSAVEIRLGSPTGTLVGKISTPPKAGNWTTYDTVSGTLTQKLT
  ACU59240 Chitinophaga  (752) ------------------------------------------------------------------------------------
   ACU05553 Pedobacter  (729) ------------------------------------------------------------------------------------

                                                                                     Section 26
                        (2101) 2101     2110      2120      2130      2140      2150      2160      2170          2184
            CcMan5 full (1651) ------------------------------------------------------------------------------------

 NP_630514 Streptomyces (1735) PGTTSTAVLTAAGGAKAHTATVTAVTRAGSSDGSGATVSTAPATSTTSATSATSTGDPAEYEPSPFPGDTLDATYASDAWPETG
ZP_02866543 Clostridium (1869) PDKSLLEDLINQANGLNGANYTKATFDGLTKALDEAKAVYENPDATQKEVDNAKDVLAKAIAGLQTVTTDNTVSTPVNNGDTTA
  NP_812442 Bacteroides  (654) ------------------------------------------------------------------------------------
YP_003584502 Zunongwangia (697) ------------------------------------------------------------------------------------
YP_003120664 Chitinophaga (681) ------------------------------------------------------------------------------------
   AAK22560 Caulobacter  (868) ------------------------------------------------------------------------------------
   ACL94075 Caulobacter  (868) ------------------------------------------------------------------------------------
ACT03290 Paenibacillus (1903) GIQDVYLVLTGSAGNGETGKKYIGNFDNAAFSLKV-------------------------------------------------
  ACU59240 Chitinophaga  (752) ------------------------------------------------------------------------------------
   ACU05553 Pedobacter  (729) ------------------------------------------------------------------------------------
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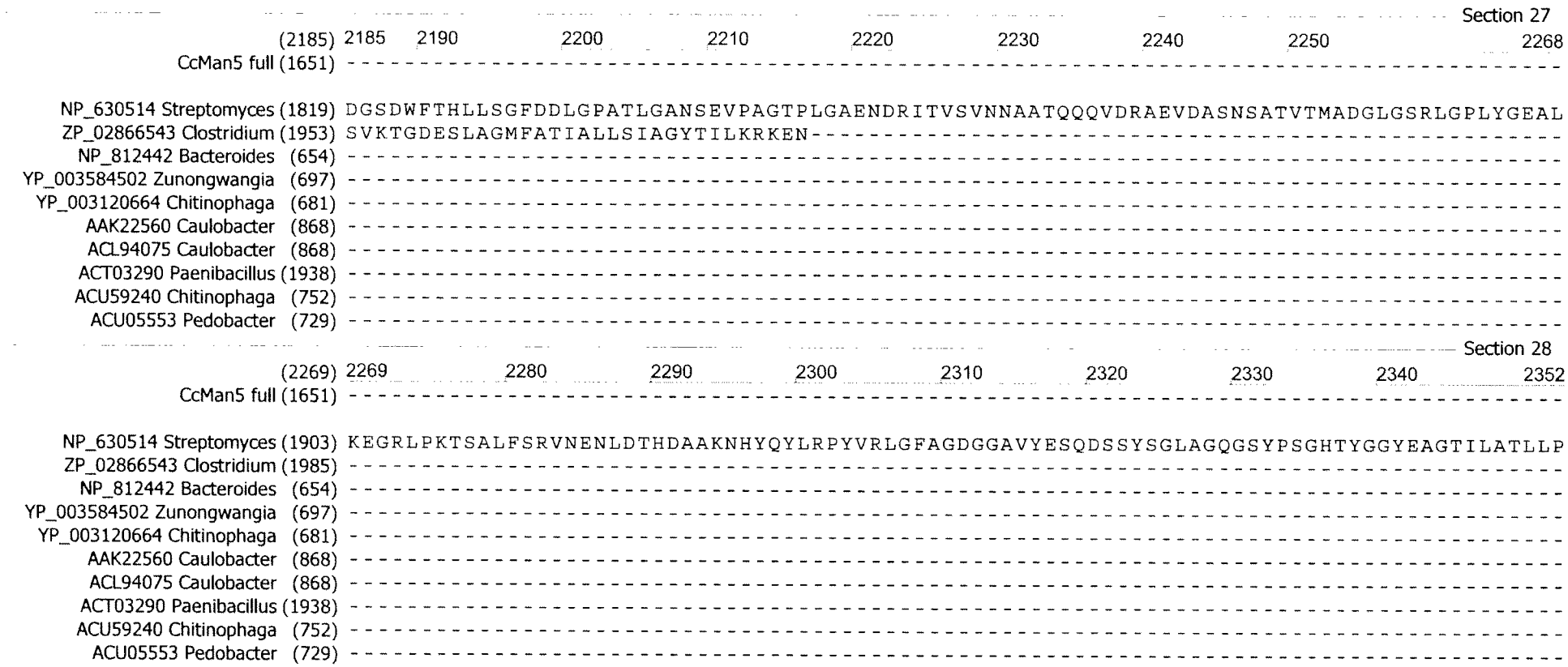
Section 27
(2185) 2185 2190 2200 2210 2220 2230 2240 2250 2268
CcMan5 full (1651) ----------
NP_630514 Streptomyces (1819) DGSDWFTHLLSGFDDLGPATLGANSEVPAGTPLGAENDRITVSVNNAATQQQVDRAEVDASNSATVTMADGLGSRLGPLYGEAL
ZP_02866543 Clostridium (1953) SVKTGDESLAGMFATIALLSIAGYTILKRKEN----------
NP_812442 Bacteroides (654) ----------
YP_003584502 Zunongwangia (697) ----------
YP_003120664 Chitinophaga (681) ----------
AAK22560 Caulobacter (868) ----------
ACL94075 Caulobacter (868) ----------
ACT03290 Paenibacillus (1938) ----------
ACU59240 Chitinophaga (752) ----------
ACU05553 Pedobacter (729) ----------
Section 28
(2269) 2269 2280 2290 2300 2310 2320 2330 2340 2352
CcMan5 full (1651) ----------
NP_630514 Streptomyces (1903) KEGRLPKTSALFSRVNENLDTHDAAKNHYQYLRPYVRLGFAGDGGAVYESQDSSYSGLAGQGSYPSGHTYGGYEAGTILATLLP
ZP_02866543 Clostridium (1985) ----------
NP_812442 Bacteroides (654) ----------
YP_003584502 Zunongwangia (697) ----------
YP_003120664 Chitinophaga (681) ----------
AAK22560 Caulobacter (868) ----------
ACL94075 Caulobacter (868) ----------
ACT03290 Paenibacillus (1938) ----------
ACU59240 Chitinophaga (752) ----------
ACU05553 Pedobacter (729) ----------

Section 29
(2353) 2353 2360 2370 2380 2390 2400 2410 2420 2436
CcMan5 full (1651) ----------
NP_630514 Streptomyces (1987) DLAPSILARTSEYGDNRIVLGFHYPLDVMGGRITAQATVAHRWADPEFAKLLGQAHTEIENVLLARCEEEGYGDTLTACAGDPY
ZP_02866543 Clostridium (1985) ----------
NP_812442 Bacteroides (654) ----------
YP_003584502 Zunongwangia (697) ----------
YP_003120664 Chitinophaga (681) ----------
AAK22560 Caulobacter (868) ----------
ACL94075 Caulobacter (868) ----------
ACT03290 Paenibacillus (1938) ----------
ACU59240 Chitinophaga (752) ----------
ACU05553 Pedobacter (729) ----------
Section 30
(2437) 2437 2450 2460 2470 2480 2490 2500 2510 2520
CcMan5 full (1651) ----------
NP_630514 Streptomyces (2071) AGLSTAQQVDRYTQRLTYGFSRTGEAGQALDAPSDAAALLITAFPDLTAEQRAQVLEQTATDSGYPLDLTGSGGPGWQRINLAA
ZP_02866543 Clostridium (1985) ----------
NP_812442 Bacteroides (654) ----------
YP_003584502 Zunongwangia (697) ----------
YP_003120664 Chitinophaga (681) ----------
AAK22560 Caulobacter (868) ----------
ACL94075 Caulobacter (868) ----------
ACT03290 Paenibacillus (1938) ----------
ACU59240 Chitinophaga (752) ----------
ACU05553 Pedobacter (729) ----------

```
                                                                                                        Section 31
                              (2521) 2521     2530      2540      2550      2560      2570      2580      2590          2604
                     CcMan5 full (1651) ------------------------------------------------------------------------------------

     NP_630514 Streptomyces (2155) AMAADVVVNADGSVTVTNFPDPTAASAAEAVAITVGGVALDGFDPDVSTYVVDWPRNGGRIPAVGAVTAASGARVKVTSGSSTV
      ZP_02866543 Clostridium (1985) ------------------------------------------------------------------------------------
        NP_812442 Bacteroides  (654) ------------------------------------------------------------------------------------
YP_003584502 Zunongwangia  (697) ------------------------------------------------------------------------------------
  YP_003120664 Chitinophaga  (681) ------------------------------------------------------------------------------------
       AAK22560 Caulobacter  (868) ------------------------------------------------------------------------------------
       ACL94075 Caulobacter  (868) ------------------------------------------------------------------------------------
    ACT03290 Paenibacillus (1938) ------------------------------------------------------------------------------------
      ACU59240 Chitinophaga  (752) ------------------------------------------------------------------------------------
       ACU05553 Pedobacter  (729) ------------------------------------------------------------------------------------
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                                                                                                 Section 32
                              (2605) 2605 2610      2620      2630      2640      2650      2660      2670      2680
                     CcMan5 full (1651) ----------------------------------------------------------------------------

     NP_630514 Streptomyces (2239) SSSQRGFSTRTLTVTSADGEFTRTYTVGFRPVEQHPHRPGALRDTGGGGTAGGSAGGGDVGGGLWSPAREWELTVN
      ZP_02866543 Clostridium (1985) ----------------------------------------------------------------------------
        NP_812442 Bacteroides  (654) ----------------------------------------------------------------------------
YP_003584502 Zunongwangia  (697) ----------------------------------------------------------------------------
  YP_003120664 Chitinophaga  (681) ----------------------------------------------------------------------------
       AAK22560 Caulobacter  (868) ----------------------------------------------------------------------------
       ACL94075 Caulobacter  (868) ----------------------------------------------------------------------------
    ACT03290 Paenibacillus (1938) ----------------------------------------------------------------------------
      ACU59240 Chitinophaga  (752) ----------------------------------------------------------------------------
       ACU05553 Pedobacter  (729) ----------------------------------------------------------------------------
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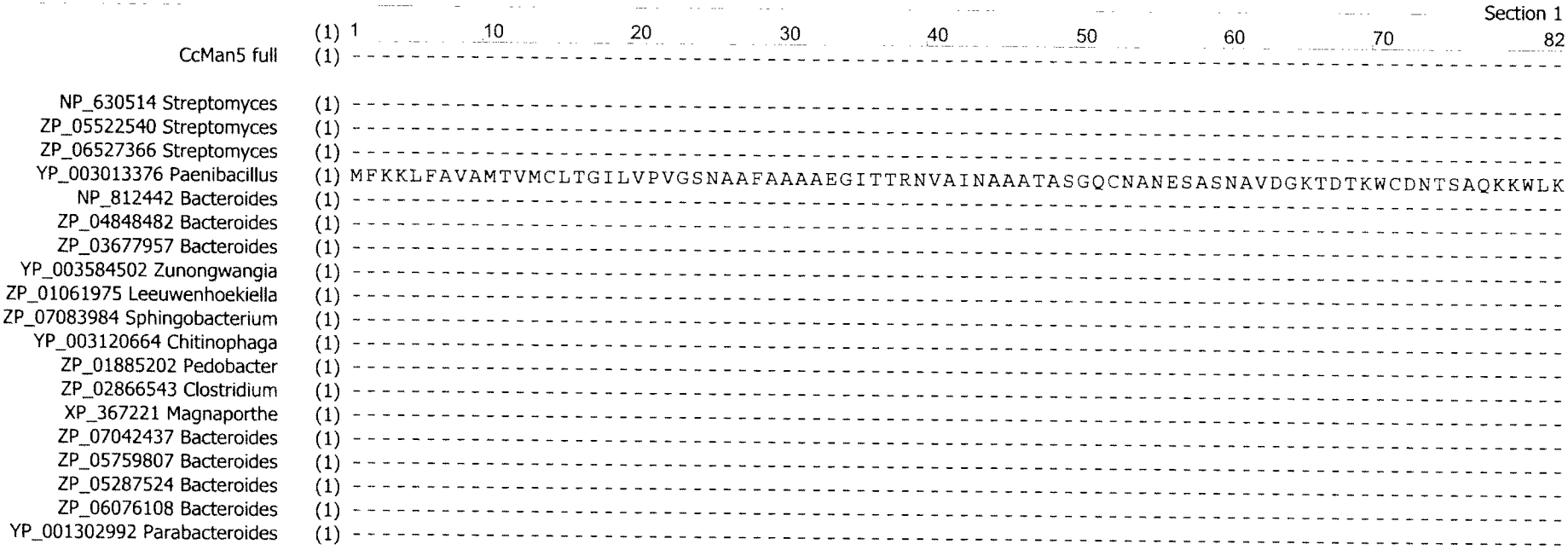
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(1) 1 10 20 30 40 50 60 70 82
CcMan5 full (1)
NP_630514 Streptomyces (1)
ZP_05522540 Streptomyces (1)
ZP_06527366 Streptomyces (1)
YP_003013376 Paenibacillus (1) MFKKLFAVAMTVMCLTGILVPVGSNAAFAAAAEGITTRNVAINAAATASGQCNANESASNAVDGKTDTKWCDNTSAQKKWLK
NP_812442 Bacteroides (1)
ZP_04848482 Bacteroides (1)
ZP_03677957 Bacteroides (1)
YP_003584502 Zunongwangia (1)
ZP_01061975 Leeuwenhoekiella (1)
ZP_07083984 Sphingobacterium (1)
YP_003120664 Chitinophaga (1)
ZP_01885202 Pedobacter (1)
ZP_02866543 Clostridium (1)
XP_367221 Magnaporthe (1)
ZP_07042437 Bacteroides (1)
ZP_05759807 Bacteroides (1)
ZP_05287524 Bacteroides (1)
ZP_06076108 Bacteroides (1)
YP_001302992 Parabacteroides (1)

FIG. 32

```
                                                                                        Section 2
                                  (83) 83     90        100       110       120       130       140       150           164
CcMan5 full                        (1) ----------------------------------------------------------------------------------

NP_630514 Streptomyces             (1) ----------------------------------------------MPDRSKRPPIRSSSPRAALRATVAAVLAGALGLAAL
ZP_05522540 Streptomyces           (1) -------------------------------------------MLVMPDRSKRPPIRSSSPRAALRATVAAVLAGALGLAAL
ZP_06527366 Streptomyces           (1) -----------------------------------------------------------------------MLAGALGLAAL
YP_003013376 Paenibacillus        (83) LDLGKEYLVNEWVLQNAAINESGNSPFWNTKNFRLQKSDDGETWTDVDIVTNNAQTIVDRFVTPFTTRYLRLYIDKAAYDSN
NP_812442 Bacteroides              (1) ----------------------------------------------------------------------------------
ZP_04848482 Bacteroides            (1) ----------------------------------------------------------------------------------
ZP_03677957 Bacteroides            (1) -------------------------------------------------------------------------------MKN
YP_003584502 Zunongwangia          (1) ----------------------------------------------------------------------------------
ZP_01061975 Leeuwenhoekiella       (1) ---------------------------------------------------------------------------MTLIMKR
ZP_07083984 Sphingobacterium       (1) -------------------------------------------------------------------------------MKN
YP_003120664 Chitinophaga          (1) --------------------------------------------------------------------MQVLTDLLLVSMKN
ZP_01885202 Pedobacter             (1) ----------------------------------------------------------------------------------
ZP_02866543 Clostridium            (1) ---------------------------------------------------------------------------MFFMLKM
XP_367221 Magnaporthe              (1) --------------------------------------------------------------------MNKKINRLLKGALA
ZP_07042437 Bacteroides            (1) ----------------------------------------------------------------------------------
ZP_05759807 Bacteroides            (1) ----------------------------------------------------------------------------------
ZP_05287524 Bacteroides            (1) ----------------------------------------------------------------------------------
ZP_06076108 Bacteroides            (1) ---------------------------------------------------------------------------------M
YP_001302992 Parabacteroides       (1) ---------------------------------------------------------------------------------M
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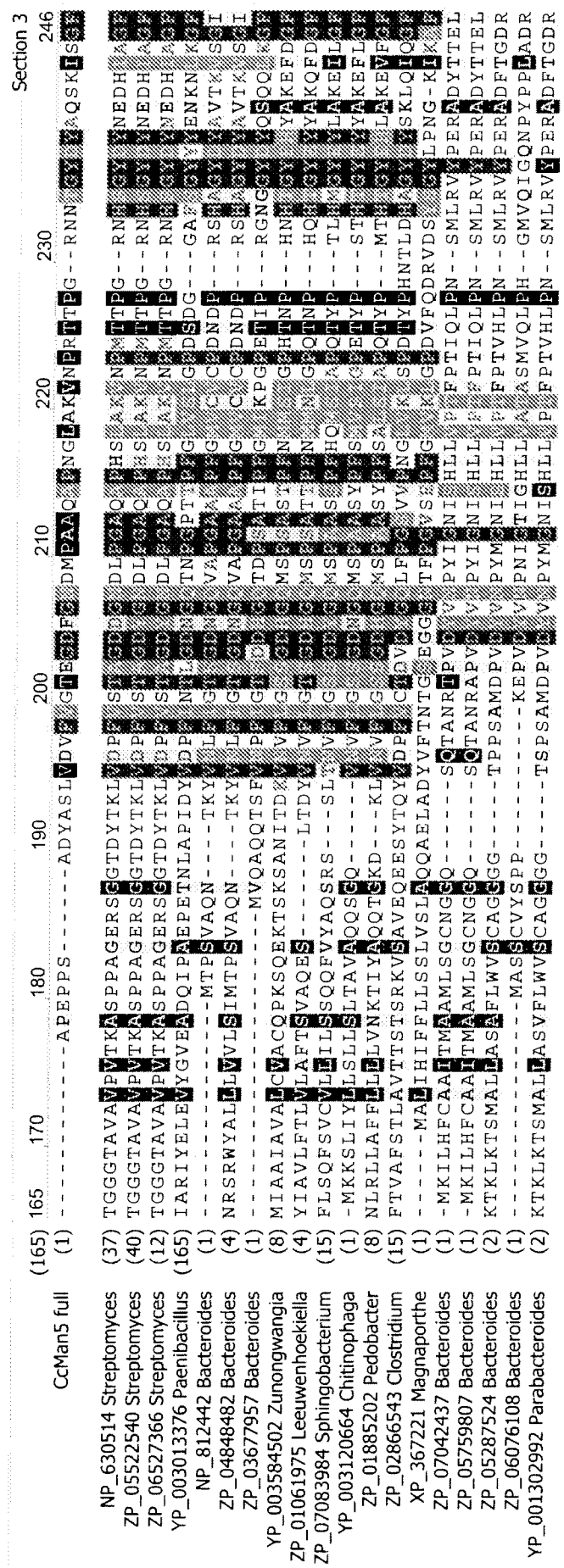
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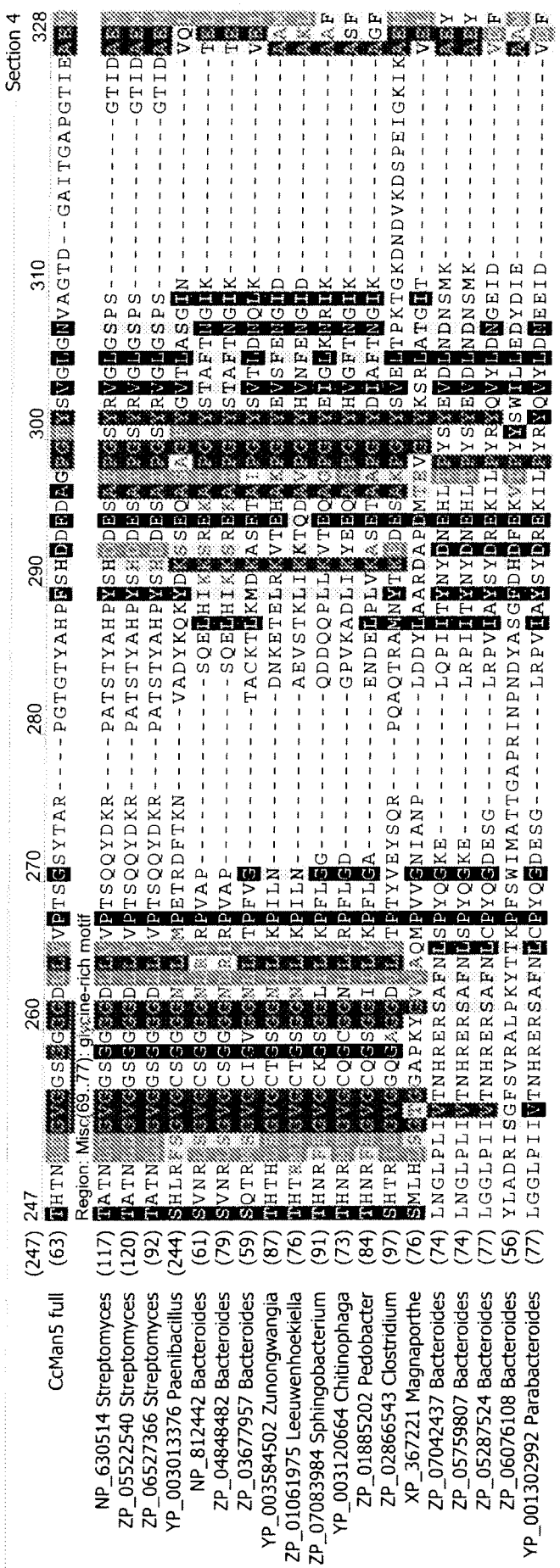
CcMan5 full
NP_630514 Streptomyces
ZP_05522540 Streptomyces
ZP_06527366 Streptomyces
YP_003013376 Paenibacillus
NP_812442 Bacteroides
ZP_04848482 Bacteroides
ZP_03677957 Bacteroides
YP_003584502 Zunongwangia
ZP_01061975 Leeuwenhoekiella
ZP_07083984 Sphingobacterium
YP_003120664 Chitinophaga
ZP_01885202 Pedobacter
ZP_02866543 Clostridium
XP_367221 Magnaporthe
ZP_07042437 Bacteroides
ZP_05759807 Bacteroides
ZP_05287524 Bacteroides
ZP_06076108 Bacteroides
YP_001302992 Parabacteroides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CcMan5 full
NP_630514 Streptomyces
ZP_05522540 Streptomyces
ZP_06527366 Streptomyces
YP_003013376 Paenibacillus
NP_812442 Bacteroides
ZP_04848482 Bacteroides
ZP_03677957 Bacteroides
YP_003584502 Zunongwangia
ZP_01061975 Leeuwenhoekiella
ZP_07083984 Sphingobacterium
YP_003120664 Chitinophaga
ZP_01885202 Pedobacter
ZP_02866543 Clostridium
XP_367221 Magnaporthe
ZP_07042437 Bacteroides
ZP_05759807 Bacteroides
ZP_05287524 Bacteroides
ZP_06076108 Bacteroides
YP_001302992 Parabacteroides
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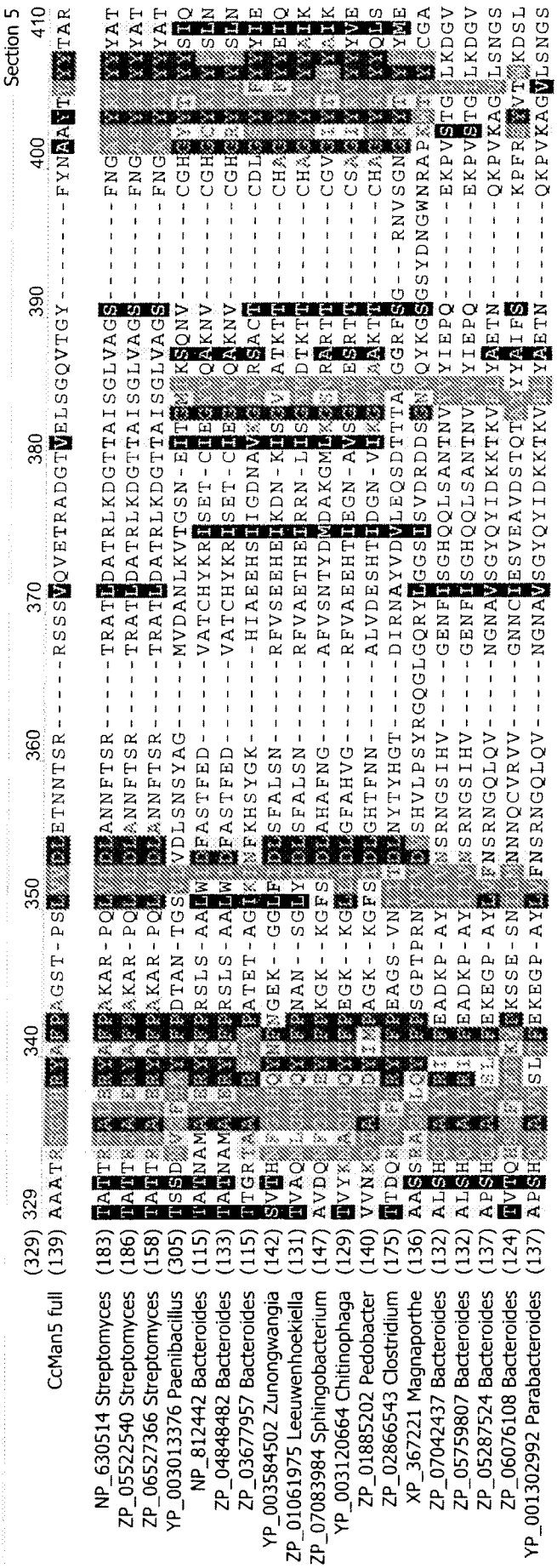
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CcMan5 full
NP_630514 Streptomyces
ZP_05522540 Streptomyces
ZP_06527366 Streptomyces
YP_003013376 Paenibacillus
NP_812442 Bacteroides
ZP_04848482 Bacteroides
ZP_03677957 Bacteroides
YP_003584502 Zunongwangia
ZP_01061975 Leeuwenhoekiella
ZP_07083984 Sphingobacterium
YP_003120664 Chitinophaga
ZP_01885202 Pedobacter
ZP_02866543 Clostridium
XP_367221 Magnaporthe
ZP_07042437 Bacteroides
ZP_05759807 Bacteroides
ZP_05287524 Bacteroides
ZP_06076108 Bacteroides
YP_001302992 Parabacteroides

```
                                                                                                      Section 6
                                    (411) 411       420       430       440       450       460       470       480      492
                     CcMan5 full    (208) TLQPAT-VQTWGD----DDRLVDATAQDGVDTGA TFDPADAGEIGLQVT SP SVEQARIDQQVE GD-LSF A DRTR

          NP_630514 Streptomyces    (252) TNVPVTSLRTWGD----DGALGDATARDGTDT A GFDPADGDDVE R T SPISAEQAATDQHEE AG-RTF EV AQT
        ZP_05522540 Streptomyces    (255) TNVPVTSLRTWGD----DGALGDATARDGTDT A GFDPADGDDVE R T SPISAEQAATDQHEE AG-RTF EV AQT
        ZP_06527366 Streptomyces    (227) TNVPVTSLRTWGD----DGALGDATARDGTDT A GFDPADGDDVE R T SPISAEQAATDQHEE AG-RTF EV AQT
     YP_003013376 Paenibacillus    (373) FDHDFDSYSSWQG----DSVGAVAQ-RSGSNS VW NFNTAGSKTVQA G STISVEQAQAERGLYS-D-WNF ARHEE
            NP_812442 Bacteroides   (182) TSQPFQ-------------------LEEQKETTACLTFGKKVRSVE R G SA SS LASWECARWEK--MDF DV SRTA
          ZP_04848482 Bacteroides   (200) TSHPFQ-------------------LEEQKETTACLTFGKKVRSVE R G SA SS LASWECARWEK--MDF DV SRTA
          ZP_03677957 Bacteroides   (182) KDKSTYEP------------------EDNDSEL WKFQTEPNEQII G SS SAEEAEANLKKECSN-QSF Q TN
       YP_003584502 Zunongwangia  (208) LKNMAE-------------------IAQISDHE AKAEDNSKEVK L GFSS SKEYASQKIEN-----IS N KE S
  ZP_01061975 Leeuwenhoekiella    (197) LPEEAQ-------------------IQNVGEHQ VKGLG--DAAE Q GFSS NEGYAKKRITS-----DDF T GK S
  ZP_07083984 Sphingobacterium    (214) VSSSHV-------------------WEGKGNQ- TLHLEENSEKVT Q FSA SVQKAVETLLHNAD--RS SEV NA Q
     YP_003120664 Chitinophaga    (195) TDRPVK-------------------WTATQAHE ADVTDNN--LG R G SS NATYAKAAITKD-----AF MV VR K
         ZP_01885202 Pedobacter    (206) FNQSVK-------------------WKDLGEHR AVPADDATAVQ R D SA STEYAVKASKK--K--LSF EA KN A
        ZP_02866543 Clostridium    (248) TSKPANSVKTWND----TTLSDKTS-QKGNDIGT NFDVKENEEIQ S SPISVKQAKIDMHNE SD-WDF AAASR D
        XP_367221 Magnaporthe     (218) FNSSATFKTFVGTNATANTLSKFSNDNKVESLSR GAVFTFDAANVVSR E SFISE QACTNLDQQ PESTSISQ QKT
          ZP_07042437 Bacteroides   (201) IEASKDN-------------------AEGIN CAAWRFADGTTTVS RYG SFISEEQAEKNMRNE KD-YNIKN AKTG
          ZP_05759807 Bacteroides   (201) IEASKDN-------------------AEGIN CAAWRFADGTTTVS RYE SFISEEQAEKNMRNE KD-YNIKN AKAG
          ZP_05287524 Bacteroides   (206) VKYDETS-------------------VEGTN A ALSFGEDVKKLG RYG SFISEEQAKKNLEKE AA-YDV VV AKI
          ZP_06076108 Bacteroides   (193) ISQDVKQ-------------------EGLDI A TFDTSQDEEIM E SFIDMEQAKRNLEME PA-WDF KV ND
   YP_001302992 Parabacteroides    (206) VNYNETS-------------------VEGIN A ALSFGEDVKKLG RYG SFISEEQAKKNLEKE AA-YDV VV AKI
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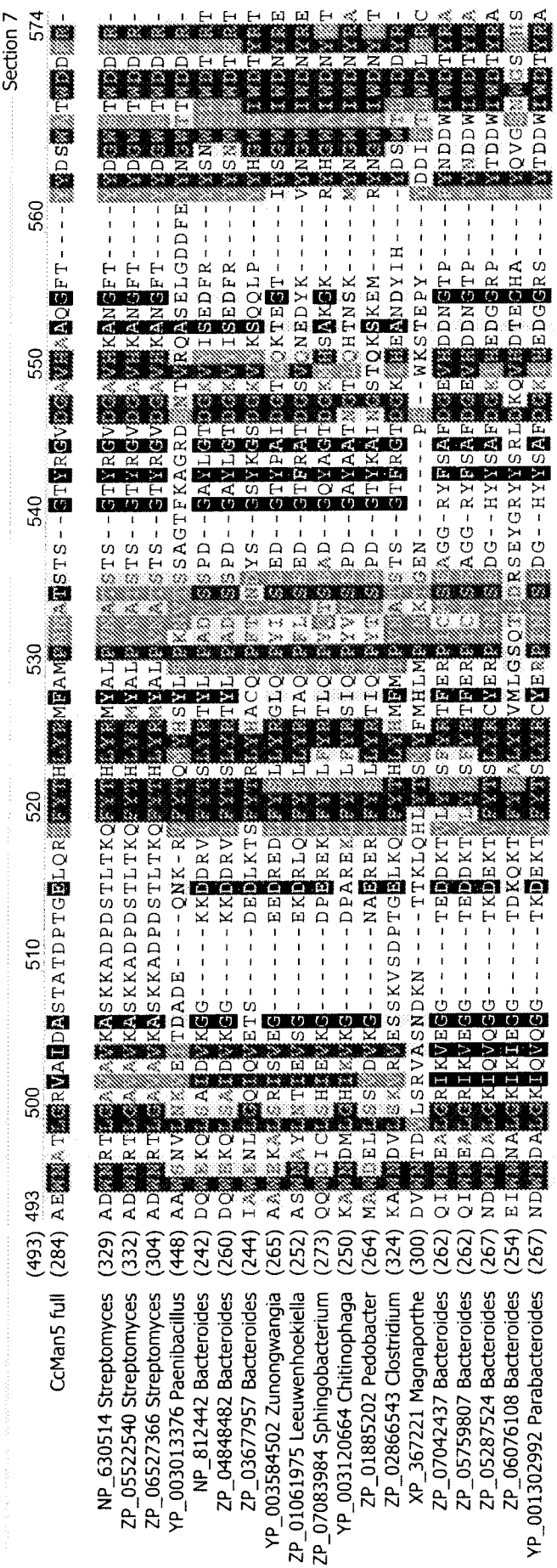
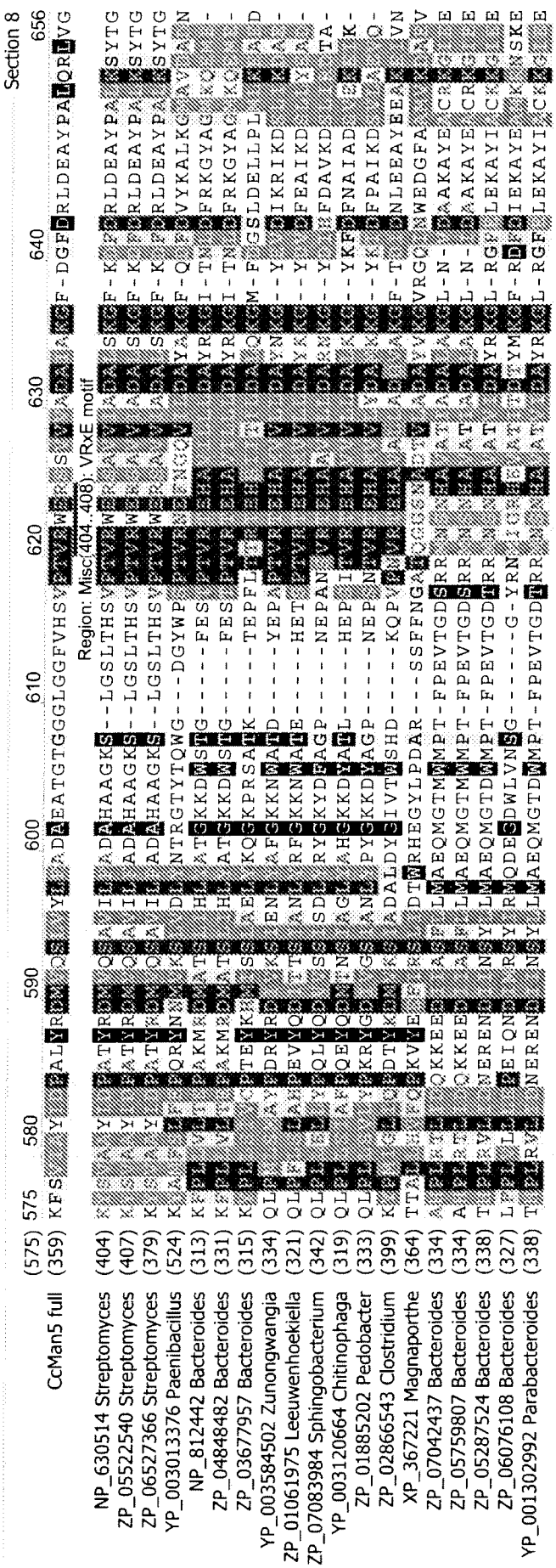
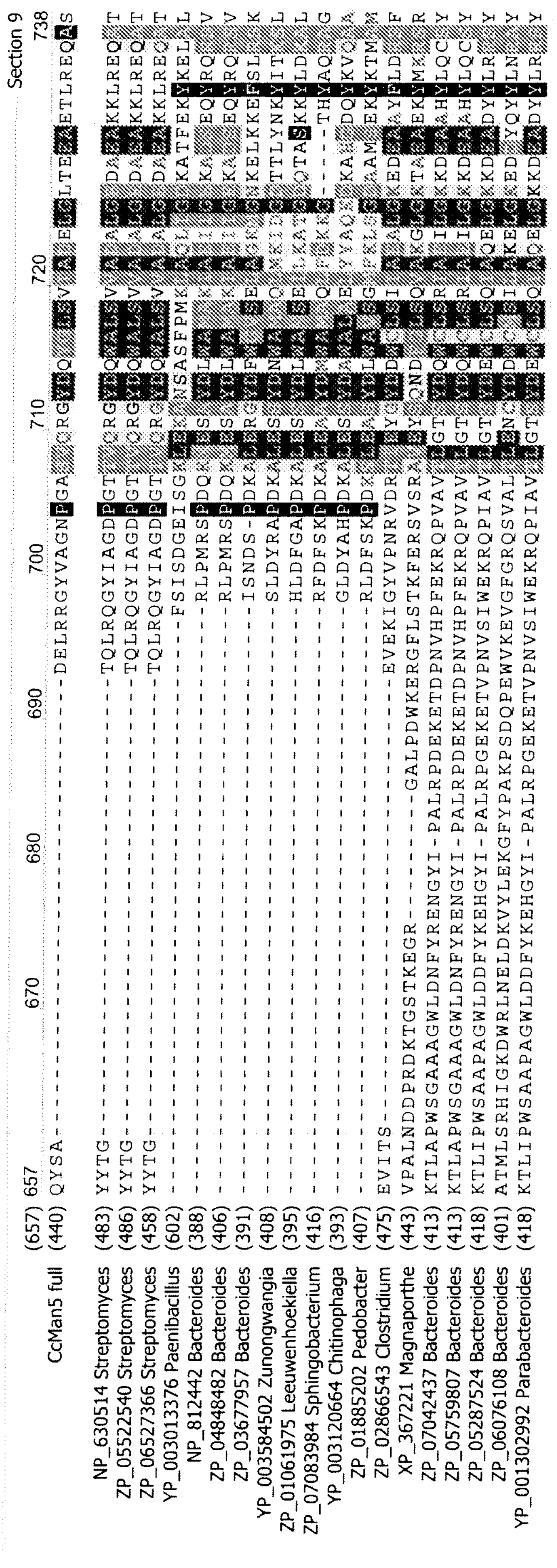
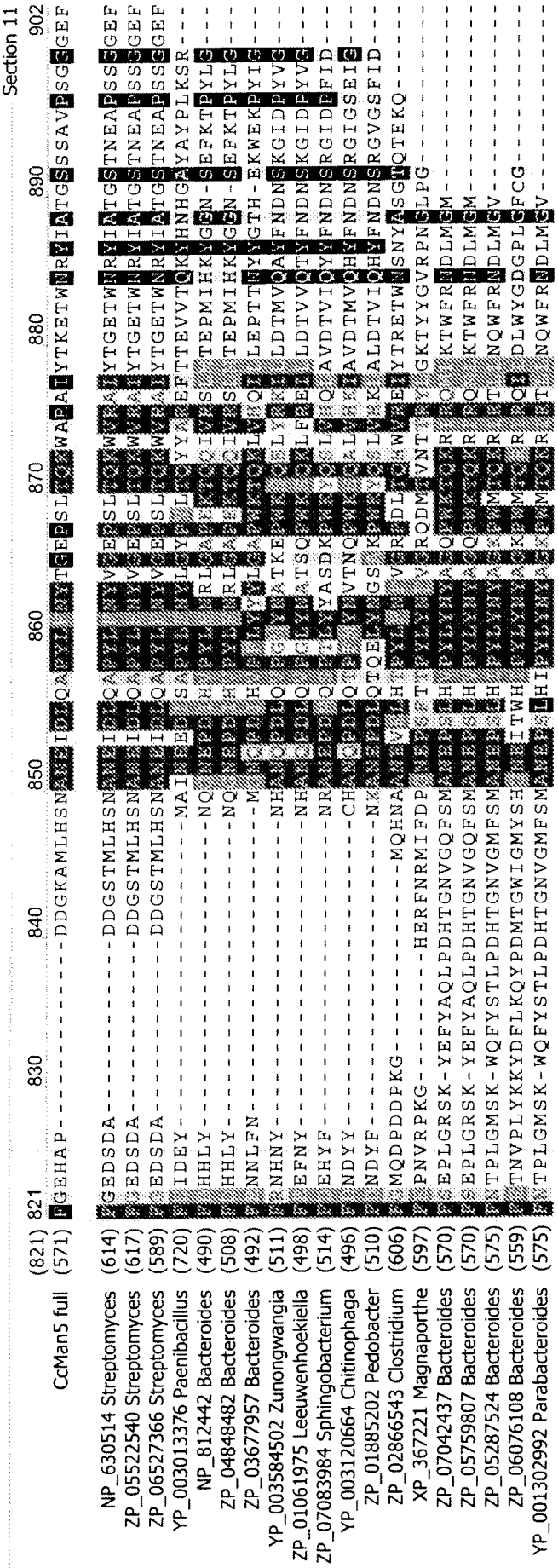
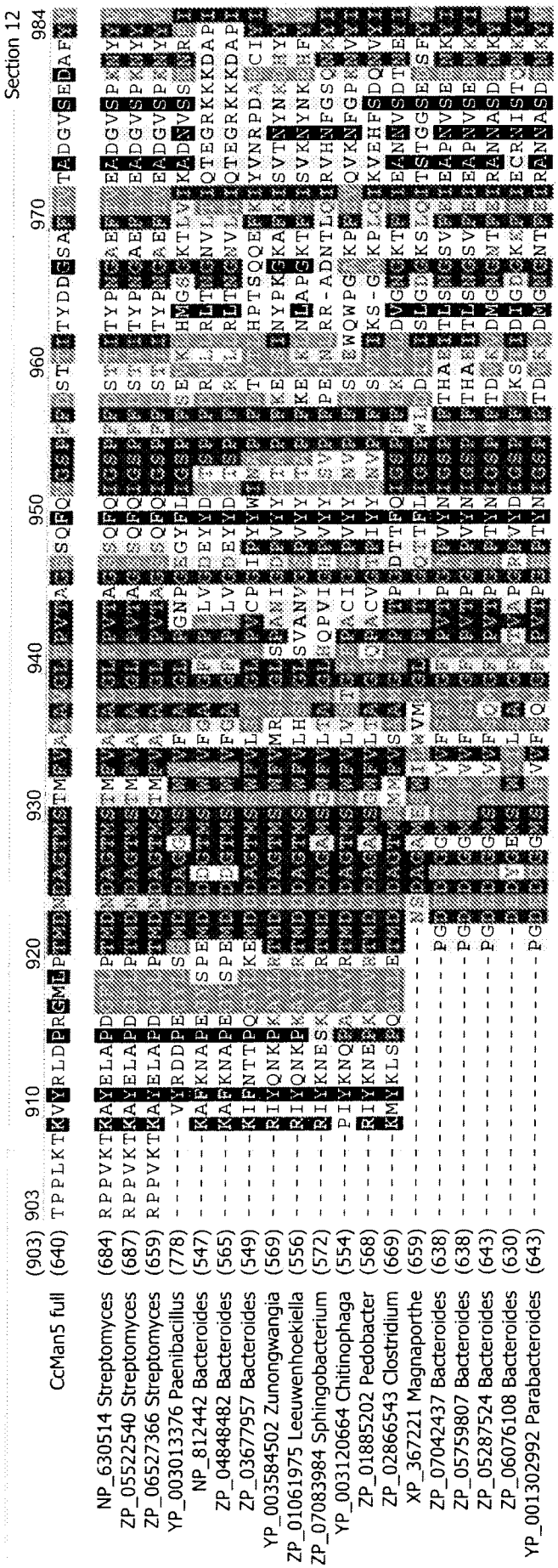

Section 7
CcMan5 full
NP_630514 Streptomyces
ZP_05522540 Streptomyces
ZP_06527366 Streptomyces
YP_003013376 Paenibacillus
NP_812442 Bacteroides
ZP_04848482 Bacteroides
ZP_03677957 Bacteroides
YP_003584502 Zunongwangia
ZP_01061975 Leeuwenhoekiella
ZP_07083984 Sphingobacterium
YP_003120664 Chitinophaga
ZP_01885202 Pedobacter
ZP_02866543 Clostridium
XP_367221 Magnaporthe
ZP_07042437 Bacteroides
ZP_05759807 Bacteroides
ZP_05287524 Bacteroides
ZP_06076108 Bacteroides
YP_001302992 Parabacteroides

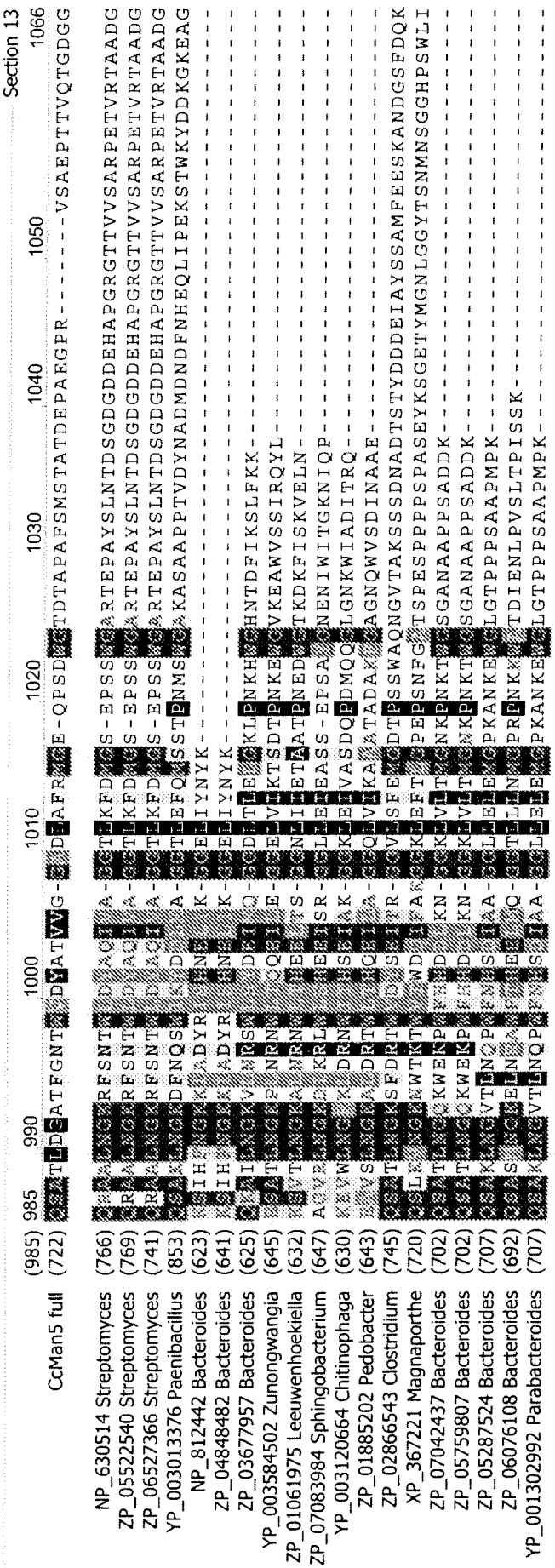

Section 8
575
580
590
600
610
620
630
640
656
Region: Misc(404..408): VRxE motif
CcMan5 full
NP_630514 Streptomyces
ZP_05522540 Streptomyces
ZP_06527366 Streptomyces
YP_003013376 Paenibacillus
NP_812442 Bacteroides
ZP_04848482 Bacteroides
ZP_03677957 Bacteroides
YP_003584502 Zunongwangia
ZP_01061975 Leeuwenhoekiella
ZP_07083984 Sphingobacterium
YP_003120664 Chitinophaga
ZP_01885202 Pedobacter
ZP_02866543 Clostridium
XP_367221 Magnaporthe
ZP_07042437 Bacteroides
ZP_05759807 Bacteroides
ZP_05287524 Bacteroides
ZP_06076108 Bacteroides
YP_001302992 Parabacteroides


Section 9
(657) 657 670 680 690 700 710 720 738
CcMan5 full (440)
NP_630514 Streptomyces (483)
ZP_05522540 Streptomyces (486)
ZP_06527366 Streptomyces (458)
YP_003013376 Paenibacillus (602)
NP_812442 Bacteroides (388)
ZP_04848482 Bacteroides (406)
ZP_03677957 Bacteroides (391)
YP_003584502 Zunongwangia (408)
ZP_01061975 Leeuwenhoekiella (395)
ZP_07083984 Sphingobacterium (416)
YP_003120664 Chitinophaga (393)
ZP_01885202 Pedobacter (407)
ZP_02866543 Clostridium (475)
XP_367221 Magnaporthe (443)
ZP_07042437 Bacteroides (413)
ZP_05759807 Bacteroides (413)
ZP_05287524 Bacteroides (418)
ZP_06076108 Bacteroides (401)
YP_001302992 Parabacteroides (418)

Section 10
Region: Misc(534..538): LYQGT motif
CcMan5 full
NP_630514 Streptomyces
ZP_05522540 Streptomyces
ZP_06527366 Streptomyces
YP_003013376 Paenibacillus
NP_812442 Bacteroides
ZP_04848482 Bacteroides
ZP_03677957 Bacteroides
YP_003584502 Zunongwangia
ZP_01061975 Leeuwenhoekiella
ZP_07083984 Sphingobacterium
YP_003120664 Chitinophaga
ZP_01885202 Pedobacter
ZP_02866543 Clostridium
XP_367221 Magnaporthe
ZP_07042437 Bacteroides
ZP_05759807 Bacteroides
ZP_05287524 Bacteroides
ZP_06076108 Bacteroides
YP_001302992 Parabacteroides


Section 11
821
830
840
850
860
870
880
890
902
CcMan5 full (821) (571)
NP_630514 Streptomyces (614)
ZP_05522540 Streptomyces (617)
ZP_06527366 Streptomyces (589)
YP_003013376 Paenibacillus (720)
NP_812442 Bacteroides (490)
ZP_04848482 Bacteroides (508)
ZP_03677957 Bacteroides (492)
YP_003584502 Zunongwangia (511)
ZP_01061975 Leeuwenhoekiella (498)
ZP_07083984 Sphingobacterium (514)
YP_003120664 Chitinophaga (496)
ZP_01885202 Pedobacter (510)
ZP_02866543 Clostridium (606)
XP_3672221 Magnaporthe (597)
ZP_07042437 Bacteroides (570)
ZP_05759807 Bacteroides (570)
ZP_05287524 Bacteroides (575)
ZP_06076108 Bacteroides (559)
YP_001302992 Parabacteroides (575)


Section 12
CcMan5 full
NP_630514 Streptomyces
ZP_05522540 Streptomyces
ZP_06527366 Streptomyces
YP_003013376 Paenibacillus
NP_812442 Bacteroides
ZP_04848482 Bacteroides
ZP_03677957 Bacteroides
YP_003584502 Zunongwangia
ZP_01061975 Leeuwenhoekiella
ZP_07083984 Sphingobacterium
YP_003120664 Chitinophaga
ZP_01885202 Pedobacter
ZP_02866543 Clostridium
XP_367221 Magnaporthe
ZP_07042437 Bacteroides
ZP_05759807 Bacteroides
ZP_05287524 Bacteroides
ZP_06076108 Bacteroides
YP_001302992 Parabacteroides


Section 13
CcMan5 full
NP_630514 Streptomyces
ZP_05522540 Streptomyces
ZP_06527366 Streptomyces
YP_003013376 Paenibacillus
NP_812442 Bacteroides
ZP_04848482 Bacteroides
ZP_03677957 Bacteroides
YP_003584502 Zunongwangia
ZP_01061975 Leeuwenhoekiella
ZP_07083984 Sphingobacterium
YP_003120664 Chitinophaga
ZP_01885202 Pedobacter
ZP_02866543 Clostridium
XP_367221 Magnaporthe
ZP_07042437 Bacteroides
ZP_05759807 Bacteroides
ZP_05287524 Bacteroides
ZP_06076108 Bacteroides
YP_001302992 Parabacteroides

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                                                                                          Section 14
                          (1067) 1067        1080      1090      1100      1110      1120      1130                1148
                CcMan5 full (795) ALDATVTLTLDG-ARLAAPAGTDLVTSGAASVVGLPDGVTAAVTVASPTALTVSLTGTASADARFFVHLRDAALADGVAAAS

     NP_630514 Streptomyces (846) TVDASVELRLSGRASFAARKGTSLTRTGAASVTGLPDGVTADLRVTGKRTASLRLTGTTRTDARFGITFRDRAFPHGIPAST
   ZP_05522540 Streptomyces (849) TVDASVELRLSGRASFAARKGTSLTRTGAASVTGLPDGVTADLRVTGKRTASLRLTGTTRTDARFGITFRDRAFPHGIPAST
   ZP_06527366 Streptomyces (821) TVDASVELRLSGRASFAARKGTSLTRTGAASVTGLPDGVTADLRVTGKRTASLRLTGTTRTDARFGITFRDRAFPHGIPAST
 YP_003013376 Paenibacillus (934) EGWTQVDFDDSSWSSGKAMLGYDSYGKPATTVSYGPNANNKYVTTYFRKTFDAKDLDGILELDGSLIRDDGAIVYLNGHEIF
       NP_812442 Bacteroides (654) ----------------------------------------------------------------------------------
    ZP_04848482 Bacteroides (672) ----------------------------------------------------------------------------------
    ZP_03677957 Bacteroides (676) ----------------------------------------------------------------------------------
  YP_003584502 Zunongwangia (697) ----------------------------------------------------------------------------------
ZP_01061975 Leeuwenhoekiella (683) ----------------------------------------------------------------------------------
ZP_07083984 Sphingobacterium (698) ----------------------------------------------------------------------------------
  YP_003120664 Chitinophaga (681) ----------------------------------------------------------------------------------
     ZP_01885202 Pedobacter (695) ----------------------------------------------------------------------------------
    ZP_02866543 Clostridium (826) ITITLKTKEFAGEIGEDLVATGKINITNIPEGLEASAIKTEANKVEVSLNGKAKNHTLNDSISNLTIEITDGATNEPIKDSI
     XP_367221 Magnaporthe (802) PVAVTVPIVVVAAFAICVTFFFIRRRAAAAQKALSSGSGTPESGIETLTPTSQPVDTSKTNVQVEIVGAPPLDSTQGANIA
    ZP_07042437 Bacteroides (754) ----------------------------------------------------------------------------------
    ZP_05759807 Bacteroides (754) ----------------------------------------------------------------------------------
    ZP_05287524 Bacteroides (759) ----------------------------------------------------------------------------------
    ZP_06076108 Bacteroides (747) ----------------------------------------------------------------------------------
YP_001302992 Parabacteroides (759) ----------------------------------------------------------------------------------
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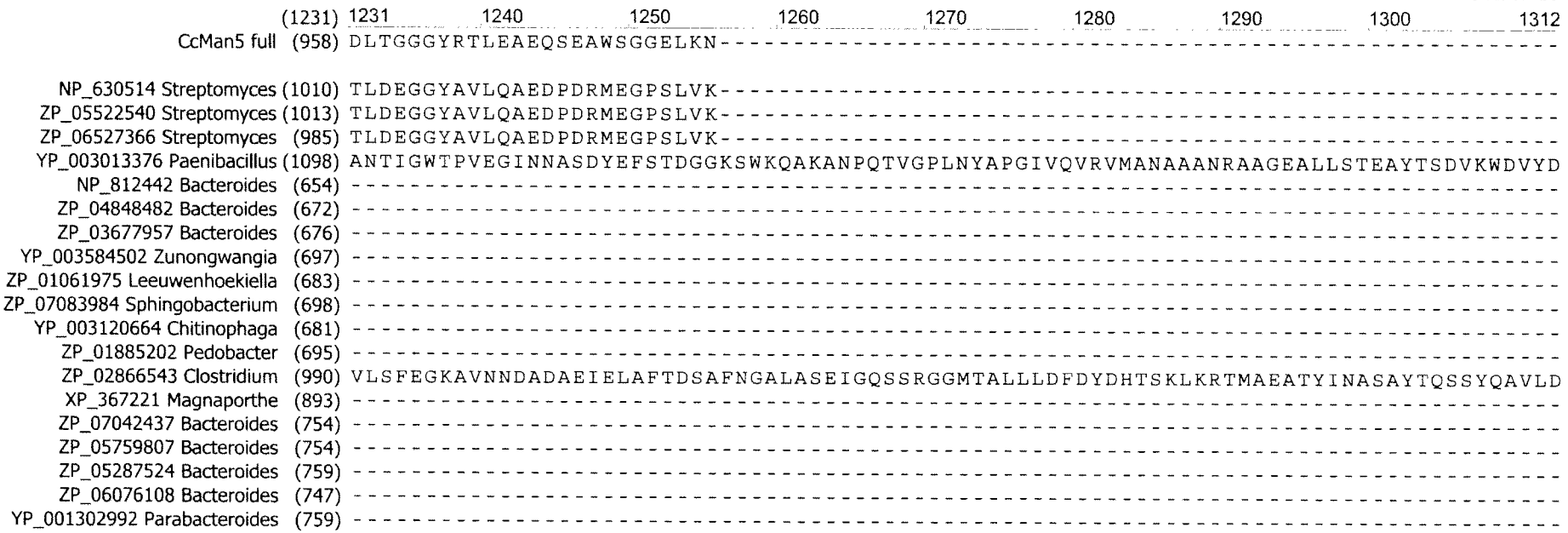
Section 15

		1149	1160	1170	1180	1190	1200	1210	1220	1230
	(1149)									
CcMan5 full	(876)	LQGQGVSVRSPLRLSVASAERDALAALVDDAVLVRHGNYSSVTFDRFSTALTKAQEALGDEAATSIALRFAADRLGAAADAL								
NP_630514 Streptomyces	(928)	VTGTGVSVTDPLIVSAAAVHRGSLAALVDEASLVREGNYSDGSYGIFRTALERARTVLADSASPTGTLMAAHDALRSAVDAL								
ZP_05522540 Streptomyces	(931)	VTGTGVSVTDPLIVSAAAVHRGSLAALVDEASLVREGNYSDGSYGIFRTALERARTVLADSASPTGTLMAAHDALRSAVDAL								
ZP_06527366 Streptomyces	(903)	VTGTGVSVTDPLIVSAAAVHRGSLAALVDEASLVREGNYSDGSYGIFRTALERARTVLADSASPTGTLMAAHDALRSAVDAL								
YP_003013376 Paenibacillus	(1016)	RTNMPTGAVNYSTFANATVGDERDKNGFIIDPSYLVEGKNVLTAEVHQVNATSSDIAFEFSLEAVRKLNIPAAPTHPVVDDK								
NP_812442 Bacteroides	(654)	----------								
ZP_04848482 Bacteroides	(672)	----------								
ZP_03677957 Bacteroides	(676)	----------								
YP_003584502 Zunongwangia	(697)	----------								
ZP_01061975 Leeuwenhoekiella	(683)	----------								
ZP_07083984 Sphingobacterium	(698)	----------								
YP_003120664 Chitinophaga	(681)	----------								
ZP_01885202 Pedobacter	(695)	----------								
ZP_02866543 Clostridium	(908)	RKTKDNVKVMFIDNQLTYSQSEFKESESDDGAILETSTITLTGDTTFAGEVNEDFVATGKVQINNVPEGLTVKMIKIDDHTA								
XP_367221 Magnaporthe	(884)	QLPPPVANR----------								
ZP_07042437 Bacteroides	(754)	----------								
ZP_05759807 Bacteroides	(754)	----------								
ZP_05287524 Bacteroides	(759)	----------								
ZP_06076108 Bacteroides	(747)	----------								
YP_001302992 Parabacteroides	(759)	----------								


Section 16
(1231) 1231 1240 1250 1260 1270 1280 1290 1300 1312
CcMan5 full (958) DLTGGGYRTLEAEQSEAWSGGELKN
NP_630514 Streptomyces (1010) TLDEGGYAVLQAEDPDRMEGPSLVK
ZP_05522540 Streptomyces (1013) TLDEGGYAVLQAEDPDRMEGPSLVK
ZP_06527366 Streptomyces (985) TLDEGGYAVLQAEDPDRMEGPSLVK
YP_003013376 Paenibacillus (1098) ANTIGWTPVEGINNASDYEFSTDGGKSWKQAKANPQTVGPLNYAPGIVQVRVMANAAANRAAGEALLSTEAYTSDVKWDVYD
NP_812442 Bacteroides (654)
ZP_04848482 Bacteroides (672)
ZP_03677957 Bacteroides (676)
YP_003584502 Zunongwangia (697)
ZP_01061975 Leeuwenhoekiella (683)
ZP_07083984 Sphingobacterium (698)
YP_003120664 Chitinophaga (681)
ZP_01885202 Pedobacter (695)
ZP_02866543 Clostridium (990) VLSFEGKAVNNDADAEIELAFTDSAFNGALASEIGQSSRGGMTALLLDFDYDHTSKLKRTMAEATYINASAYTQSSYQAVLD
XP_367221 Magnaporthe (893)
ZP_07042437 Bacteroides (754)
ZP_05759807 Bacteroides (754)
ZP_05287524 Bacteroides (759)
ZP_06076108 Bacteroides (747)
YP_001302992 Parabacteroides (759)

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                                                                                                    Section 17
                              (1313) 1313      1320      1330      1340      1350      1360      1370      1380         1394
                   CcMan5 full (983) ---EANSSSGNLGGVRSGSWVQYRDMTFETAAGDTPPRFLTVRYDTSFAPTD------------------------------

     NP_630514 Streptomyces (1035) ---EAYYSDGDLGGVTEGAWEQYTDLDFGGVA----PRSVSVRYANSQAAAA------------------------------
   ZP_05522540 Streptomyces (1038) ---EAYYSDGDLGGVTEGAWEQYTDLDFGGVP----PRSVSVRYANSQAAAA------------------------------
   ZP_06527366 Streptomyces (1010) ---EAYYSDGDLGGVTEGAWEQYTDLDFGGVP----PRSVSVRYANSQAAAA------------------------------
YP_003013376 Paenibacillus (1180) LDADIHQDGNMVVDVTGTLKGDYTDSAVVVFQLMDGKEHAWVSSAVPVQTGS------------------------------
        NP_812442 Bacteroides (654) ----------------------------------------------------------------------------------
     ZP_04848482 Bacteroides (672) ----------------------------------------------------------------------------------
     ZP_03677957 Bacteroides (676) ----------------------------------------------------------------------------------
    YP_003584502 Zunongwangia (697) ----------------------------------------------------------------------------------
 ZP_01061975 Leeuwenhoekiella (683) ----------------------------------------------------------------------------------
ZP_07083984 Sphingobacterium (698) ----------------------------------------------------------------------------------
   YP_003120664 Chitinophaga (681) ----------------------------------------------------------------------------------
      ZP_01885202 Pedobacter (695) ----------------------------------------------------------------------------------
    ZP_02866543 Clostridium (1072) AVAKGQELLDNKNATSKEIDLAIGDIIDAQEQLDIPRDGFSVLQAESSDVTSGGSLRVEGSVLHGTYDGAWIRYDALDFNGL
      XP_367221 Magnaporthe (893) ----------------------------------------------------------------------------------
     ZP_07042437 Bacteroides (754) ----------------------------------------------------------------------------------
     ZP_05759807 Bacteroides (754) ----------------------------------------------------------------------------------
     ZP_05287524 Bacteroides (759) ----------------------------------------------------------------------------------
     ZP_06076108 Bacteroides (747) ----------------------------------------------------------------------------------
YP_001302992 Parabacteroides (759) ----------------------------------------------------------------------------------
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                                                                                          Section 18
                              (1395) 1395 1400      1410      1420      1430      1440      1450      1460           1476
                    CcMan5 full (1032) ----TPSTVRVHAGDVSGPVVATVDLKGTSGWGKYTEVTAELGDVQALVDAQVVTFELLAPSGRSWVGNFDWFRFSAEDPAA

          NP_630514 Streptomyces (1080) ----EPSSVDIHAGDADGPVVATVSLPGTGGWQYYTTVRAAVSDPQALLKASSATFVFHAPSGRQWVSNFDWYQFSPEAAPS
        ZP_05522540 Streptomyces (1083) ----EPSSVDIHAGDADGPVVATVSLPGTGGWQYYTTVRAAVSDPQALLKASSATFVFHAPSGRQWVSNFDWYQFSPEAAPS
        ZP_06527366 Streptomyces (1055) ----EPSSVDIHAGDADGPVVATVSLPGTGGWQYYTTVRAAVSDPQALLKASSATFVFHAPSGRQWVSNFDWYQFSPEAAPS
      YP_003013376 Paenibacillus (1232) ----FDISQIYNVDASKYKVNVYLVNEFNGDIYESPLWLADPIVQQSEPGSLPDPEGPPVTEEPLPEPIPLPDPKPDEPEEP
            NP_812442 Bacteroides  (654) ----------------------------------------------------------------------------------
          ZP_04848482 Bacteroides  (672) ----------------------------------------------------------------------------------
          ZP_03677957 Bacteroides  (676) ----------------------------------------------------------------------------------
         YP_003584502 Zunongwangia (697) ----------------------------------------------------------------------------------
     ZP_01061975 Leeuwenhoekiella  (683) ----------------------------------------------------------------------------------
    ZP_07083984 Sphingobacterium  (698) ----------------------------------------------------------------------------------
        YP_003120664 Chitinophaga  (681) ----------------------------------------------------------------------------------
           ZP_01885202 Pedobacter  (695) ----------------------------------------------------------------------------------
        ZP_02866543 Clostridium (1154) SPKYLELRYDNASNRCASDSHLEVRLDGVDGTLIGDIQLPATGTAWGSYETLQFEISNPELLDGKHDVYFVFKGTTEDSKPY
            XP_367221 Magnaporthe  (893) ----------------------------------------------------------------------------------
          ZP_07042437 Bacteroides  (754) ----------------------------------------------------------------------------------
          ZP_05759807 Bacteroides  (754) ----------------------------------------------------------------------------------
          ZP_05287524 Bacteroides  (759) ----------------------------------------------------------------------------------
          ZP_06076108 Bacteroides  (747) ----------------------------------------------------------------------------------
    YP_001302992 Parabacteroides  (759) ----------------------------------------------------------------------------------
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Section 19

	(1477)	1477 1490 1500 1510 1520 1530 1540 1558
CcMan5 full	(1110)	PGQPGESPTVTIEAEDWTASSGRGLKKESSTWTSGPVTNVGGTADGDWIAYGEVDLGELPLGELSVHYVHNSNRSGNNSALS
NP_630514 Streptomyces	(1158)	SSPITTLATLTTANTTSTGDGSLPLKVSGGVFEN--------VTNGAWAEWRDTDLGDGADTVTVSYDKPRSR-----AASD
ZP_05522540 Streptomyces	(1161)	SSPITTLATLTTANTTSTGDGALPLKVSGGVFEN--------VTNGAWAEWRDTDLGDGADTVTVSYDKPRSR-----AASD
ZP_06527366 Streptomyces	(1133)	SSPITTLATLTTANTTSTGDGALPLKVSGGVFEN--------VTNGAWAEWRDTDLGDGADTVTVSYDKPRSR-----AASD
YP_003013376 Paenibacillus	(1310)	EVPETGMKIQFEDRAEWTSAAHPNGGGGLSTEAGNGGTVVAHTFGGAWLAYNVDFGTTGYNNVTVQYDAPTDKVPAGSKLEF
NP_812442 Bacteroides	(654)	--
ZP_04848482 Bacteroides	(672)	--
ZP_03677957 Bacteroides	(676)	--
YP_003584502 Zunongwangia	(697)	--
ZP_01061975 Leeuwenhoekiella	(683)	--
ZP_07083984 Sphingobacterium	(698)	--
YP_003120664 Chitinophaga	(681)	--
ZP_01885202 Pedobacter	(695)	--
ZP_02866543 Clostridium	(1236)	VAKVDYLQFKETADIDSVKLEAEKSDENSGNGLKNESINLGGTYDGAWIKYNNVNFNNLEADTINVHYSTRVDACALDARIE
XP_367221 Magnaporthe	(893)	--
ZP_07042437 Bacteroides	(754)	--
ZP_05759807 Bacteroides	(754)	--
ZP_05287524 Bacteroides	(759)	--
ZP_06076108 Bacteroides	(747)	--
YP_001302992 Parabacteroides	(759)	--

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                                                                                            Section 20
                                 (1559) 1559       1570       1580       1590       1600       1610       1620       1630       1640
                        CcMan5 full (1192) VYLDAFDPANPGEPFVTVPLPTTGSSWTADGTATVVLPETVQG--THEVFVRLSTEPYADHPYVANLDSLTFAPGGPTSVVV

          NP_630514 Streptomyces (1227) SHIELRPGAKDGPTAVTVPLDYTGSGWGTVASTSVRLDPDVFEGTQDVYAVFVSSTQTDAQPYVANVHSLTLTRQADAPVVF
         ZP_05522540 Streptomyces (1230) SHIELRPGAKDGPTAVTVPLDYTGSGWGTVASTSVRLDPDVFEGTQDVYAVFVSSTQTDAQPYVANVHSLTLTRQADAPVVF
         ZP_06527366 Streptomyces (1202) SHIELRPGAKDGPTAVTVPLDYTGSGWGTVASTSVRLDPDVFEGTQDVYAVFVSSTQTDAQPYVANVHSLTLTRQADAPVVF
       YP_003013376 Paenibacillus (1392) RLGSVSGELVGTVNMEDKNAGWGSYITTKANLTRTLTGQQKLYVVMVAGTPNNLPYIGNFDWFKFDYEKIRSDYAKLELESY
             NP_812442 Bacteroides (654) ----------------------------------------------------------------------------------
           ZP_04848482 Bacteroides (672) ----------------------------------------------------------------------------------
           ZP_03677957 Bacteroides (676) ----------------------------------------------------------------------------------
        YP_003584502 Zunongwangia (697) ----------------------------------------------------------------------------------
     ZP_01061975 Leeuwenhoekiella (683) ----------------------------------------------------------------------------------
    ZP_07083984 Sphingobacterium (698) ----------------------------------------------------------------------------------
        YP_003120664 Chitinophaga (681) ----------------------------------------------------------------------------------
            ZP_01885202 Pedobacter (695) ----------------------------------------------------------------------------------
          ZP_02866543 Clostridium (1318) IRKDNKDGELLGTIMLPLTGGWSDYQTVSTKLDTSVTGVQDICFVLRGTNDGGRPYVANIDYMEFVNSGVNHIEAENKDDWS
            XP_367221 Magnaporthe (893) ----------------------------------------------------------------------------------
           ZP_07042437 Bacteroides (754) ----------------------------------------------------------------------------------
           ZP_05759807 Bacteroides (754) ----------------------------------------------------------------------------------
           ZP_05287524 Bacteroides (759) ----------------------------------------------------------------------------------
           ZP_06076108 Bacteroides (747) ----------------------------------------------------------------------------------
    YP_001302992 Parabacteroides (759) ----------------------------------------------------------------------------------
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                                                                                                      Section 21
                               (1641) 1641     1650      1660      1670      1680      1690      1700      1710       1722
                      CcMan5 full (1272) ESEAWTSNSGRGLKNESSTWT-SGPVTNVGG----------------------------------------TADGDWLAYGE

        NP_630514 Streptomyces (1309) DATAFEGSSGGGLKSEPATWSGAGSATSLGG----------------------------------------TYDGAWLDYGD
      ZP_05522540 Streptomyces (1312) DATAFEGSSGGGLKSEPATWSGAGSATSLGG----------------------------------------TYDGAWLDYGD
      ZP_06527366 Streptomyces (1284) DATAFEGSSGGGLKSEPATWSGAGSATSLGG----------------------------------------TYDGAWLDYGD
     YP_003013376 Paenibacillus (1474) DEWTTDVNTGNNNTPLKTEAGKGGVGQQVAN----------------------------------------TFNGAWLAYKR
          NP_812442 Bacteroides (654) ----------------------------------------------------------------------------------
        ZP_04848482 Bacteroides (672) ----------------------------------------------------------------------------------
        ZP_03677957 Bacteroides (676) ----------------------------------------------------------------------------------
      YP_003584502 Zunongwangia (697) ----------------------------------------------------------------------------------
   ZP_01061975 Leeuwenhoekiella (683) ----------------------------------------------------------------------------------
  ZP_07083984 Sphingobacterium (698) ----------------------------------------------------------------------------------
      YP_003120664 Chitinophaga (681) ----------------------------------------------------------------------------------
         ZP_01885202 Pedobacter (695) ----------------------------------------------------------------------------------
      ZP_02866543 Clostridium (1400) GAELKVENSTDNTGKSLTNIGGARNDAWLRYNGVEFNGKTEMTVRYSHNPGTAGTNSRIDVYLDNMDGNPIGTINLPTTNGW
         XP_367221 Magnaporthe (893) ----------------------------------------------------------------------------------
        ZP_07042437 Bacteroides (754) ----------------------------------------------------------------------------------
        ZP_05759807 Bacteroides (754) ----------------------------------------------------------------------------------
        ZP_05287524 Bacteroides (759) ----------------------------------------------------------------------------------
        ZP_06076108 Bacteroides (747) ----------------------------------------------------------------------------------
 YP_001302992 Parabacteroides (759) ----------------------------------------------------------------------------------
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                                                                                                        Section 22
                                        (1723) 1723      1730      1740      1750      1760      1770      1780      1790          1804
                         CcMan5 full    (1313) IDLGSAALDQLSVHYVHNSNRSGRNSALSVYLDAFDPANPGEPFVTVPLANTGSSWTTDGTAVVDLPSTVRGKHQVWVRLST

        NP_630514 Streptomyces          (1351) VDFGDSPKNTVTLTYVNNSARCGTGSAVQLYLDSFDPDAPGTPYATVPLPVTGSSWSSGGTTSLTLPEAITGTHAVHLRLTT
       ZP_05522540 Streptomyces         (1354) VDFGDSPKNTVTLTYVNNSARCGTGSAVQLYLDSFDPDAPGTPYATVPLPVTGSSWSSGGTTSLTLPEAITGTHAVHLRLTT
       ZP_06527366 Streptomyces         (1326) VDFGDSPKNTVTLTYVNNSARCGTGSAVQLYLDSFDPDAPGTPYATVPLPVTGSSWSSGGTTSLTLPEAITGTHAVHLRLTT
       YP_003013376 Paenibacillus       (1516) MDFGSEGVDKFSIEYAGNSTNTFNNSAVEVRLGSPTGTLVGTVATPPTAAAWGTYATVSGSLTQKLTGLQDVYLVFTGSAAN
        NP_812442 Bacteroides           (654)  ----------------------------------------------------------------------------------
       ZP_04848482 Bacteroides          (672)  ----------------------------------------------------------------------------------
       ZP_03677957 Bacteroides          (676)  ----------------------------------------------------------------------------------
      YP_003584502 Zunongwangia         (697)  ----------------------------------------------------------------------------------
     ZP_01061975 Leeuwenhoekiella       (683)  ----------------------------------------------------------------------------------
     ZP_07083984 Sphingobacterium       (698)  ----------------------------------------------------------------------------------
      YP_003120664 Chitinophaga         (681)  ----------------------------------------------------------------------------------
       ZP_01885202 Pedobacter           (695)  ----------------------------------------------------------------------------------
       ZP_02866543 Clostridium          (1482) ANYTVIREVFDQEITGSHDVYLKLHTDGSGWVANFDWFEFGEPIADVDKSQLQAKYDENVALLQEYDKYHYVGFNIFKDRLL
        XP_367221 Magnaporthe           (893)  ----------------------------------------------------------------------------------
       ZP_07042437 Bacteroides          (754)  ----------------------------------------------------------------------------------
       ZP_05759807 Bacteroides          (754)  ----------------------------------------------------------------------------------
       ZP_05287524 Bacteroides          (759)  ----------------------------------------------------------------------------------
       ZP_06076108 Bacteroides          (747)  ----------------------------------------------------------------------------------
     YP_001302992 Parabacteroides       (759)  ----------------------------------------------------------------------------------
```

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                                                                            Section 23
                                 (1805) 1805  1810      1820      1830      1840      1850      1860      1870           1886
                      CcMan5 full (1395) EAYADHPYVANLDSMRFFTDAYDVEVPPTDTAALAAVVDAAGTPEAEIARYGRIDARVFTRELAAARSVLADAGATQAQADE

      NP_630514 Streptomyces (1433) NADSSHPYVANLGQVAFDRVEAPAQT---DLSALRKAIEQYEGLSEDADRYGTIDFGVFRRELTAARDLLGTEDATQLEADL
    ZP_05522540 Streptomyces (1436) DADSSHPYVANLGQVTFDRVEAPAQT---DLSALRKAIEQYEGLSEDADRYGTIDFGVFRRELTAARDLLGTEDATQLEADL
    ZP_06527366 Streptomyces (1408) DADSSHPYVANLGQVTFDRVEAPAQT---DLSALRKAIEQYEGLSEDADRYGTIDFGVFRRELTAARDLLGTEDATQLEADL
 YP_003013376 Paenibacillus (1598) GETGKKYIGNFDNASFSLSVQEPEEPEQPQQPEQEQITVQFESKTEWNTALNTFNNQAMKIENNNGGQTVGNTYTGAWLGFK
         NP_812442 Bacteroides (654) ----------------------------------------------------------------------------------
       ZP_04848482 Bacteroides (672) ----------------------------------------------------------------------------------
       ZP_03677957 Bacteroides (676) ----------------------------------------------------------------------------------
     YP_003584502 Zunongwangia (697) ----------------------------------------------------------------------------------
 ZP_01061975 Leeuwenhoekiella (683) ----------------------------------------------------------------------------------
ZP_07083984 Sphingobacterium (698) ----------------------------------------------------------------------------------
     YP_003120664 Chitinophaga (681) ----------------------------------------------------------------------------------
        ZP_01885202 Pedobacter (695) ----------------------------------------------------------------------------------
      ZP_02866543 Clostridium (1564) TGSAVIDNQNATANDVRIAIKDIDNALAALQYKIAFDLNDYVVQLENINEADYTKDSYANLMQAIEVAKAIPTDSEYEVFKN
        XP_367221 Magnaporthe (893) ----------------------------------------------------------------------------------
       ZP_07042437 Bacteroides (754) ----------------------------------------------------------------------------------
       ZP_05759807 Bacteroides (754) ----------------------------------------------------------------------------------
       ZP_05287524 Bacteroides (759) ----------------------------------------------------------------------------------
       ZP_06076108 Bacteroides (747) ----------------------------------------------------------------------------------
YP_001302992 Parabacteroides (759) ----------------------------------------------------------------------------------
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                                         Section 24
                          (1887) 1887   1900   1910   1920   1930   1940   1950   1968
CcMan5 full              (1477) RARRLGLATDQLVPAERRRLENLVASAEALTDEGYSPESWQAFRTALAAATGTLDDAAASDEALHDARLALQGAVDALEEPA

NP_630514 Streptomyces   (1512) RTRSLTLAANQLVPLPRLRLESLVATASALADERYTDASWKAFTTALTAAKTALADETATDRTLTERYAALDRARSSLTTKR
ZP_05522540 Streptomyces (1515) RTRSLTLAANQLVPLPRLRLESLVATASALADERYTDASWKAFTTALTAAKTAVADETATDRTLTERYAALDRARSSLTTKR
ZP_06527366 Streptomyces (1487) RTRSLTLAANQLVPLPRLRLESLVATASALADERYTDASWKAFTTALTAAKTAVADETATDRTLTERYAALDRARSSLTTKR
YP_003013376 Paenibacillus (1680) DVDFGSEKGKNQVSIVYDAPTNRVPADVKAEIRLGSPTGTLVGTVAIPNTGSTWGQYNTATADLNTTIKGKQDLYIVMTGST
NP_812442 Bacteroides     (654) ----------------------------------------------------------------------------------
ZP_04848482 Bacteroides   (672) ----------------------------------------------------------------------------------
ZP_03677957 Bacteroides   (676) ----------------------------------------------------------------------------------
YP_003584502 Zunongwangia (697) ----------------------------------------------------------------------------------
ZP_01061975 Leeuwenhoekiella (683) ----------------------------------------------------------------------------------
ZP_07083984 Sphingobacterium (698) ----------------------------------------------------------------------------------
YP_003120664 Chitinophaga (681) ----------------------------------------------------------------------------------
ZP_01885202 Pedobacter    (695) ----------------------------------------------------------------------------------
ZP_02866543 Clostridium  (1646) AYDGLVDAHSKLTALNRTALEEIIKQAEAIDLDLYKEEGKAEFKAALENAKTVYETVSLTQAQVDEAVANLDQAIKALKPIE
XP_367221 Magnaporthe     (893) ----------------------------------------------------------------------------------
ZP_07042437 Bacteroides   (754) ----------------------------------------------------------------------------------
ZP_05759807 Bacteroides   (754) ----------------------------------------------------------------------------------
ZP_05287524 Bacteroides   (759) ----------------------------------------------------------------------------------
ZP_06076108 Bacteroides   (747) ----------------------------------------------------------------------------------
YP_001302992 Parabacteroides (759) ----------------------------------------------------------------------------------
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                                                                                   Section 25
                                (1969) 1969       1980      1990      2000      2010      2020      2030      2040      2050
                       CcMan5 full (1559) DVVLVEVEVSPRCLAGKPYYVAVRAVNVSDAAVDVELASSLG---------TRS----FVGVAPGASAYQSFAARSATGDLD

          NP_630514 Streptomyces (1594) RTVPAAPGAVSAAPSGTSVQVTWSAPEDDGGSPVTGYEITLSGGRQVEIADPDSRSTVFTRLKDGTSYTARVRAVNALGDSP
        ZP_05522540 Streptomyces (1597) RTVPAAPGAVSAAPSGTSVQVTWSAPEDDGGSPVTGYEITLSGGRQVEIADPDSRSTVFTRLKDGTSYTARVRAVNALGDSP
        ZP_06527366 Streptomyces (1569) RTVPAAPGAVSAAPSGTSVQVTWSAPEDDGGSPVTGYEITLSGGRQVEIADPDSRSTVFTRLKDGTSYTARVRAVNALGDSP
      YP_003013376 Paenibacillus (1762) TSSLLYVGNYDSLTFGYKPVRSDYAKLELESYDEWTTAVNPLNSNTPLKTEAGKGGAGKQVANTFNGAWLAYKRMDFGTEGV
            NP_812442 Bacteroides  (654) ----------------------------------------------------------------------------------
          ZP_04848482 Bacteroides  (672) ----------------------------------------------------------------------------------
          ZP_03677957 Bacteroides  (676) ----------------------------------------------------------------------------------
        YP_003584502 Zunongwangia  (697) ----------------------------------------------------------------------------------
     ZP_01061975 Leeuwenhoekiella  (683) ----------------------------------------------------------------------------------
    ZP_07083984 Sphingobacterium  (698) ----------------------------------------------------------------------------------
        YP_003120664 Chitinophaga  (681) ----------------------------------------------------------------------------------
           ZP_01885202 Pedobacter  (695) ----------------------------------------------------------------------------------
         ZP_02866543 Clostridium (1728) TDSVNKVALKIAVDLANAITDEDLANVVPAVVDEFIAARDEANAVYNDVSATQEEVDNAFDRLASVMQKLEFFKGDKKALKA
           XP_367221 Magnaporthe  (893) ----------------------------------------------------------------------------------
          ZP_07042437 Bacteroides  (754) ----------------------------------------------------------------------------------
          ZP_05759807 Bacteroides  (754) ----------------------------------------------------------------------------------
          ZP_05287524 Bacteroides  (759) ----------------------------------------------------------------------------------
          ZP_06076108 Bacteroides  (747) ----------------------------------------------------------------------------------
    YP_001302992 Parabacteroides  (759) ----------------------------------------------------------------------------------
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                                                                                                    Section 26
                                   (2051) 2051     2060      2070      2080      2090      2100      2110      2120        2132
                          CcMan5 full (1627) VTVTATGADGTQTVEQVVTVPSCS----------------------------------------------------------

          NP_630514 Streptomyces (1676) WSARTQPAVTGDNRPQTPTVTGVVTDGERVRVNWRPAGDGGFPVVGYTVALDDGTTAHVPGTTSTAVLTAAGGAKAHTATVT
        ZP_05522540 Streptomyces (1679) WSARTQPAVTGDNRPQAPTVTGVVTDGERVRVNWRPAGDGGFPVVGYTVALDDGTTAHVPGTTSTAVLTAAGGAKAHTATVT
        ZP_06527366 Streptomyces (1651) WSARTQPAVTGDNRPQAPTVTGVVTDGERVRVNWRPAGDGGFPVVGYTVALDDGTTAHVPGTTSTAVLTAAGGAKAHTATVT
       YP_003013376 Paenibacillus (1844) NTFAVEYAGNTTNCFTNSAVEIRLGSPTGTLVGKISTPPKAGNWTTYDTVSGTLTQKLTGIQDVYLVLTGSAGNGETGKKYI
            NP_812442 Bacteroides  (654) ----------------------------------------------------------------------------------
          ZP_04848482 Bacteroides  (672) ----------------------------------------------------------------------------------
          ZP_03677957 Bacteroides  (676) ----------------------------------------------------------------------------------
        YP_003584502 Zunongwangia  (697) ----------------------------------------------------------------------------------
    ZP_01061975 Leeuwenhoekiella  (683) ----------------------------------------------------------------------------------
    ZP_07083984 Sphingobacterium  (698) ----------------------------------------------------------------------------------
        YP_003120664 Chitinophaga  (681) ----------------------------------------------------------------------------------
           ZP_01885202 Pedobacter  (695) ----------------------------------------------------------------------------------
          ZP_02866543 Clostridium (1810) FIDKVTGLDSSKYTQTTWTAFDKELTEAIAVYNDENAMQEEVNTAYSELVTAFLNLRLIPDKSLLEDLINQANGLNGANYTK
           XP_367221 Magnaporthe  (893) ----------------------------------------------------------------------------------
          ZP_07042437 Bacteroides  (754) ----------------------------------------------------------------------------------
          ZP_05759807 Bacteroides  (754) ----------------------------------------------------------------------------------
          ZP_05287524 Bacteroides  (759) ----------------------------------------------------------------------------------
          ZP_06076108 Bacteroides  (747) ----------------------------------------------------------------------------------
   YP_001302992 Parabacteroides  (759) ----------------------------------------------------------------------------------
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                                                                                      Section 27
                              (2133) 2133   2140      2150      2160      2170      2180      2190      2200          2214
                     CcMan5 full (1651) ----------------------------------------------------------------------------------

        NP_630514 Streptomyces (1758) AVTRAGSSDGSGATVSTAPATSTTSATSATSTGDPAEYEPSPFPGDTLDATYASDAWPETGDGSDWFTHLLSGFDDLGPATL
       ZP_05522540 Streptomyces (1761) AVTRAGSSDGSGATVSTAPATSTTSATSAG---DPAEYEPSPFPGDTLDATYASDAWPETGDGSDWFTHLLSGFDDLGPATL
       ZP_06527366 Streptomyces (1733) AVTRAGSSDGSGATVSTAPATSTTSATSAG---DPAEYEPSPFPGDTLDATYASDAWPETGDGSDWFTHLLSGFDDLGPATL
     YP_003013376 Paenibacillus (1926) GNFDNAAFSLKV----------------------------------------------------------------------
          NP_812442 Bacteroides (654) ----------------------------------------------------------------------------------
        ZP_04848482 Bacteroides (672) ----------------------------------------------------------------------------------
        ZP_03677957 Bacteroides (676) ----------------------------------------------------------------------------------
      YP_003584502 Zunongwangia (697) ----------------------------------------------------------------------------------
  ZP_01061975 Leeuwenhoekiella (683) ----------------------------------------------------------------------------------
  ZP_07083984 Sphingobacterium (698) ----------------------------------------------------------------------------------
      YP_003120664 Chitinophaga (681) ----------------------------------------------------------------------------------
         ZP_01885202 Pedobacter (695) ----------------------------------------------------------------------------------
      ZP_02866543 Clostridium (1892) ATFDGLTKALDEAKAVYENPDATQKEVDNAKDVLAKAIAGLQTVTTDNTVSTPVNNGDTTASVKTGDESLAGMFATIALLSI
        XP_367221 Magnaporthe (893) ----------------------------------------------------------------------------------
        ZP_07042437 Bacteroides (754) ----------------------------------------------------------------------------------
        ZP_05759807 Bacteroides (754) ----------------------------------------------------------------------------------
        ZP_05287524 Bacteroides (759) ----------------------------------------------------------------------------------
        ZP_06076108 Bacteroides (747) ----------------------------------------------------------------------------------
  YP_001302992 Parabacteroides (759) ----------------------------------------------------------------------------------
```

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                                                                                       Section 28
                                   (2215) 2215 2220      2230      2240      2250      2260      2270      2280            2296
                     CcMan5 full (1651) ----------------------------------------------------------------------------------

       NP_630514 Streptomyces (1840) GANSEVPAGTPLGAENDRITVSVNNAATQQQVDRAEVDASNSATVTMADGLGSRLGPLYGEALKEGRLPKTSALFSRVNENL
     ZP_05522540 Streptomyces (1840) GANSEVPAGTPLGAENDRITVRVNNAATQQQVDRAEVDASNSATVTMADGLGSRLGPLYGEALKEGRLPKTSALFSRVNENL
     ZP_06527366 Streptomyces (1812) GANSEVPAGTPLGAENDRITVRVNNAATQQQVDRAEVDASNSATVTMADGLGSRLGPLYGEALKEGRLPKTSALFSRVNENL
   YP_003013376 Paenibacillus (1938) ----------------------------------------------------------------------------------
        NP_812442 Bacteroides  (654) ----------------------------------------------------------------------------------
      ZP_04848482 Bacteroides  (672) ----------------------------------------------------------------------------------
      ZP_03677957 Bacteroides  (676) ----------------------------------------------------------------------------------
    YP_003584502 Zunongwangia  (697) ----------------------------------------------------------------------------------
 ZP_01061975 Leeuwenhoekiella  (683) ----------------------------------------------------------------------------------
ZP_07083984 Sphingobacterium  (698) ----------------------------------------------------------------------------------
   YP_003120664 Chitinophaga  (681) ----------------------------------------------------------------------------------
       ZP_01885202 Pedobacter  (695) ----------------------------------------------------------------------------------
     ZP_02866543 Clostridium (1974) AGYTILKRKEN-----------------------------------------------------------------------
      XP_367221 Magnaporthe  (893) ----------------------------------------------------------------------------------
      ZP_07042437 Bacteroides  (754) ----------------------------------------------------------------------------------
      ZP_05759807 Bacteroides  (754) ----------------------------------------------------------------------------------
      ZP_05287524 Bacteroides  (759) ----------------------------------------------------------------------------------
      ZP_06076108 Bacteroides  (747) ----------------------------------------------------------------------------------
YP_001302992 Parabacteroides  (759) ----------------------------------------------------------------------------------
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Section 29
(2297) 2297 2310 2320 2330 2340 2350 2360 2378
CcMan5 full (1651) ----------
NP_630514 Streptomyces (1922) DTHDAAKNHYQYLRPYVRLGFAGDGGAVYESQDSSYSGLAGQGSYPSGHTYGGYEAGTILATLLPDLAPSILARTSEYGDNR
ZP_05522540 Streptomyces (1922) DTHDAAKNHYQYLRPYVRLGFAGDGGAVYESQDSSYSGLAGQGSYPSGHTYGGYEAGTILATLLPDLAPSILARTSEYGDNR
ZP_06527366 Streptomyces (1894) DTHDAAKNHYQYLRPYVRLGFAGDGGAVYESQDSSYSGLAGQGSYPSGHTYGGYEAGTILATLLPDLAPSILARTSEYGDNR
YP_003013376 Paenibacillus (1938) ----------
NP_812442 Bacteroides (654) ----------
ZP_04848482 Bacteroides (672) ----------
ZP_03677957 Bacteroides (676) ----------
YP_003584502 Zunongwangia (697) ----------
ZP_01061975 Leeuwenhoekiella (683) ----------
ZP_07083984 Sphingobacterium (698) ----------
YP_003120664 Chitinophaga (681) ----------
ZP_01885202 Pedobacter (695) ----------
ZP_02866543 Clostridium (1985) ----------
XP_367221 Magnaporthe (893) ----------
ZP_07042437 Bacteroides (754) ----------
ZP_05759807 Bacteroides (754) ----------
ZP_05287524 Bacteroides (759) ----------
ZP_06076108 Bacteroides (747) ----------
YP_001302992 Parabacteroides (759) ----------

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                                                                                              Section 30
                           (2379) 2379      2390      2400      2410      2420      2430      2440      2450      2460
                 CcMan5 full (1651) ----------------------------------------------------------------------------------

  NP_630514 Streptomyces (2004) IVLGFHYPLDVMGGRITAQATVAHRWADPEFAKLLGQAHTEIENVLLARCEEEGYGDTLTACAGDPYAGLSTAQQVDRYTQR
 ZP_05522540 Streptomyces (2004) IVLGFHYPLDVMGGRITAQATVAHRWADPEFAKLLGQAHTEIENVLLARCEEEGYGDTLTACAGDPYAGLSTAQQVDRYTQR
 ZP_06527366 Streptomyces (1976) IVLGFHYPLDVMGGRITAQATVAHRWADPEFAKLLGQAHTEIENVLLARCEEEGYGDTLTACAGDPYAGLSTAQQVDRYTQR
YP_003013376 Paenibacillus (1938) ----------------------------------------------------------------------------------
      NP_812442 Bacteroides (654) ----------------------------------------------------------------------------------
    ZP_04848482 Bacteroides (672) ----------------------------------------------------------------------------------
    ZP_03677957 Bacteroides (676) ----------------------------------------------------------------------------------
   YP_003584502 Zunongwangia (697) ----------------------------------------------------------------------------------
ZP_01061975 Leeuwenhoekiella (683) ----------------------------------------------------------------------------------
ZP_07083984 Sphingobacterium (698) ----------------------------------------------------------------------------------
   YP_003120664 Chitinophaga (681) ----------------------------------------------------------------------------------
      ZP_01885202 Pedobacter (695) ----------------------------------------------------------------------------------
     ZP_02866543 Clostridium (1985) ----------------------------------------------------------------------------------
      XP_367221 Magnaporthe (893) ----------------------------------------------------------------------------------
    ZP_07042437 Bacteroides (754) ----------------------------------------------------------------------------------
    ZP_05759807 Bacteroides (754) ----------------------------------------------------------------------------------
    ZP_05287524 Bacteroides (759) ----------------------------------------------------------------------------------
    ZP_06076108 Bacteroides (747) ----------------------------------------------------------------------------------
YP_001302992 Parabacteroides (759) ----------------------------------------------------------------------------------
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Section 31

		2461	2470	2480	2490	2500	2510	2520	2530	2542
	(2461)									
CcMan5 full	(1651)	----------	----------	----------	----------	----------	----------	----------	----------	----------
NP_630514 Streptomyces	(2086)	LTYGFSRTGEAGQALDAPSDAAALLITAFPDLTAEQRAQVLEQTATDSGYPLDLTGSGGPGWQRINLAAAMAADVVVNADGS
ZP_05522540 Streptomyces	(2086)	LTYGFSRTGEAGQALDAPSDAAALLITAFPDLTAEQRTQVLEQTATDSGYPLDLTGSGGPGWQRINLAAAMAADVVVNADGS
ZP_06527366 Streptomyces	(2058)	LTYGFSRTGEAGQALDAPSDAAALLITAFPDLTAEQRTQVLEQTATDSGYPLDLTGSGGPGWQRINLAAAMAADVVVNADGS
YP_003013376 Paenibacillus	(1938)	----------	----------	----------	----------	----------	----------	----------	----------	----------
NP_812442 Bacteroides	(654)	----------	----------	----------	----------	----------	----------	----------	----------	----------
ZP_04848482 Bacteroides	(672)	----------	----------	----------	----------	----------	----------	----------	----------	----------
ZP_03677957 Bacteroides	(676)	----------	----------	----------	----------	----------	----------	----------	----------	----------
YP_003584502 Zunongwangia	(697)	----------	----------	----------	----------	----------	----------	----------	----------	----------
ZP_01061975 Leeuwenhoekiella	(683)	----------	----------	----------	----------	----------	----------	----------	----------	----------
ZP_07083984 Sphingobacterium	(698)	----------	----------	----------	----------	----------	----------	----------	----------	----------
YP_003120664 Chitinophaga	(681)	----------	----------	----------	----------	----------	----------	----------	----------	----------
ZP_01885202 Pedobacter	(695)	----------	----------	----------	----------	----------	----------	----------	----------	----------
ZP_02866543 Clostridium	(1985)	----------	----------	----------	----------	----------	----------	----------	----------	----------
XP_367221 Magnaporthe	(893)	----------	----------	----------	----------	----------	----------	----------	----------	----------
ZP_07042437 Bacteroides	(754)	----------	----------	----------	----------	----------	----------	----------	----------	----------
ZP_05759807 Bacteroides	(754)	----------	----------	----------	----------	----------	----------	----------	----------	----------
ZP_05287524 Bacteroides	(759)	----------	----------	----------	----------	----------	----------	----------	----------	----------
ZP_06076108 Bacteroides	(747)	----------	----------	----------	----------	----------	----------	----------	----------	----------
YP_001302992 Parabacteroides	(759)	----------	----------	----------	----------	----------	----------	----------	----------	----------

Section 32
(2543) 2543 2550 2560 2570 2580 2590 2600 2610 2624
CcMan5 full (1651)
NP_630514 Streptomyces (2168)
ZP_05522540 Streptomyces (2168)
ZP_06527366 Streptomyces (2140)
YP_003013376 Paenibacillus (1938)
NP_812442 Bacteroides (654)
ZP_04848482 Bacteroides (672)
ZP_03677957 Bacteroides (676)
YP_003584502 Zunongwangia (697)
ZP_01061975 Leeuwenhoekiella (683)
ZP_07083984 Sphingobacterium (698)
YP_003120664 Chitinophaga (681)
ZP_01885202 Pedobacter (695)
ZP_02866543 Clostridium (1985)
XP_367221 Magnaporthe (893)
ZP_07042437 Bacteroides (754)
ZP_05759807 Bacteroides (754)
ZP_05287524 Bacteroides (759)
ZP_06076108 Bacteroides (747)
YP_001302992 Parabacteroides (759)

Section 33

```
                         (2625) 2625 2630      2640      2650      2660      2670              2689
                 CcMan5 full (1651) -----------------------------------------------------------------

     NP_630514 Streptomyces (2250) LTVTSADGEFTRTYTVGFRPVEQHPHRPGALRDTGGGGTAGGSAGGGDVGGGLWSPAREWELTVN
   ZP_05522540 Streptomyces (2250) LTVTSADGEFTRTYTVGFRPVEQHPHRPGALRDTGGGGTAGGSGGGGDVGGGLWSPAREWEQTVN
   ZP_06527366 Streptomyces (2222) LTVTSADGEFTRTYTVGFRPVEQHPHRPGALRDTGGGGTAGGSGGGGDVGGGLWSPAREWEQTVN
  YP_003013376 Paenibacillus (1938) -----------------------------------------------------------------
       NP_812442 Bacteroides  (654) -----------------------------------------------------------------
     ZP_04848482 Bacteroides  (672) -----------------------------------------------------------------
     ZP_03677957 Bacteroides  (676) -----------------------------------------------------------------
   YP_003584502 Zunongwangia  (697) -----------------------------------------------------------------
ZP_01061975 Leeuwenhoekiella  (683) -----------------------------------------------------------------
ZP_07083984 Sphingobacterium  (698) -----------------------------------------------------------------
   YP_003120664 Chitinophaga  (681) -----------------------------------------------------------------
      ZP_01885202 Pedobacter  (695) -----------------------------------------------------------------
     ZP_02866543 Clostridium (1985) -----------------------------------------------------------------
      XP_367221 Magnaporthe   (893) -----------------------------------------------------------------
     ZP_07042437 Bacteroides  (754) -----------------------------------------------------------------
     ZP_05759807 Bacteroides  (754) -----------------------------------------------------------------
     ZP_05287524 Bacteroides  (759) -----------------------------------------------------------------
     ZP_06076108 Bacteroides  (747) -----------------------------------------------------------------
YP_001302992 Parabacteroides  (759) -----------------------------------------------------------------
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FIG. 33

```
ATOM   5859  N   GLY B  21       8.798  41.888 151.532  1.00  6.14       B    N
ATOM   5860  CA  GLY B  21       7.349  41.901 151.577  1.00  6.87       B    C
ATOM   5861  C   GLY B  21       6.718  40.662 150.976  1.00  7.36       B    C
ATOM   5862  O   GLY B  21       7.111  39.526 151.272  1.00  7.83       B    O
ATOM   5863  N   ASP B  22       5.749  40.896 150.115  1.00  6.97       B    N
ATOM   5864  CA  ASP B  22       5.019  39.846 149.439  1.00  6.61       B    C
ATOM   5865  CB  ASP B  22       3.516  40.156 149.545  1.00  6.75       B    C
ATOM   5866  CG  ASP B  22       2.645  38.964 149.165  1.00  8.00       B    C
ATOM   5867  OD1 ASP B  22       3.121  37.817 149.252  1.00  8.66       B    O
ATOM   5868  OD2 ASP B  22       1.479  39.168 148.781  1.00 10.69       B    O
ATOM   5869  C   ASP B  22       5.471  39.814 147.976  1.00  6.58       B    C
ATOM   5870  O   ASP B  22       4.647  39.889 147.070  1.00  6.88       B    O
ATOM   5871  N   PHE B  23       6.785  39.719 147.753  1.00  5.72       B    N
ATOM   5872  CA  PHE B  23       7.350  39.730 146.400  1.00  5.51       B    C
ATOM   5873  CB  PHE B  23       8.139  41.020 146.136  1.00  5.56       B    C
ATOM   5874  CG  PHE B  23       7.315  42.266 146.256  1.00  6.28       B    C
ATOM   5875  CD1 PHE B  23       7.127  42.875 147.497  1.00  7.33       B    C
ATOM   5876  CE1 PHE B  23       6.344  44.032 147.621  1.00  6.32       B    C
ATOM   5877  CZ  PHE B  23       5.755  44.584 146.490  1.00  7.38       B    C
ATOM   5878  CE2 PHE B  23       5.941  43.979 145.235  1.00  7.39       B    C
ATOM   5879  CD2 PHE B  23       6.713  42.824 145.132  1.00  7.45       B    C
ATOM   5880  C   PHE B  23       8.243  38.517 146.175  1.00  5.47       B    C
ATOM   5881  O   PHE B  23       9.345  38.640 145.612  1.00  5.14       B    O
ATOM   5882  N   GLY B  24       7.750  37.349 146.600  1.00  4.56       B    N
ATOM   5883  CA  GLY B  24       8.458  36.090 146.362  1.00  4.07       B    C
ATOM   5884  C   GLY B  24       8.397  35.090 147.499  1.00  3.76       B    C
ATOM   5885  O   GLY B  24       8.310  33.871 147.263  1.00  4.04       B    O
ATOM   5886  N   ASN B  25       8.467  35.594 148.734  1.00  2.92       B    N
ATOM   5887  CA  ASN B  25       8.571  34.746 149.915  1.00  2.81       B    C
ATOM   5888  CB  ASN B  25       7.253  34.007 150.179  1.00  3.39       B    C
ATOM   5889  CG  ASN B  25       6.227  34.911 150.842  1.00  3.67       B    C
ATOM   5890  OD1 ASN B  25       6.478  35.461 151.917  1.00  6.16       B    O
ATOM   5891  ND2 ASN B  25       5.090  35.098 150.199  1.00  5.91       B    N
ATOM   5892  C   ASN B  25       9.804  33.822 149.943  1.00  2.73       B    C
ATOM   5893  O   ASN B  25       9.747  32.691 150.423  1.00  2.49       B    O
ATOM   5894  N   ASP B  26      10.924  34.343 149.450  1.00  3.00       B    N
ATOM   5895  CA  ASP B  26      12.206  33.663 149.535  1.00  3.13       B    C
ATOM   5896  CB  ASP B  26      12.975  33.829 148.235  1.00  3.67       B    C
ATOM   5897  CG  ASP B  26      12.481  32.904 147.140  1.00  4.56       B    C
ATOM   5898  OD1 ASP B  26      12.308  31.693 147.408  1.00  6.75       B    O
ATOM   5899  OD2 ASP B  26      12.281  33.385 146.007  1.00  5.43       B    O
ATOM   5900  C   ASP B  26      13.041  34.166 150.702  1.00  3.37       B    C
ATOM   5901  O   ASP B  26      12.747  35.212 151.278  1.00  3.44       B    O
ATOM   6036  N   GLY B  46       7.869  42.799 161.557  1.00  5.19       B    N
ATOM   6037  CA  GLY B  46       7.346  42.212 160.323  1.00  4.86       B    C
ATOM   6038  C   GLY B  46       8.311  41.184 159.770  1.00  5.18       B    C
ATOM   6039  O   GLY B  46       9.481  41.143 160.175  1.00  5.13       B    O
ATOM   6040  N   ARG B  47       7.818  40.352 158.848  1.00  5.25       B    N
ATOM   6041  CA  ARG B  47       8.581  39.247 158.248  1.00  4.58       B    C
ATOM   6042  CB  ARG B  47       8.650  38.046 159.210  1.00  4.70       B    C
ATOM   6043  CG  ARG B  47       7.282  37.403 159.599  1.00  5.20       B    C
ATOM   6044  CD  ARG B  47       7.495  36.267 160.596  1.00  6.03       B    C
ATOM   6045  NE  ARG B  47       6.339  35.388 160.817  1.00  5.27       B    N
ATOM   6046  CZ  ARG B  47       5.957  34.374 160.030  1.00  7.87       B    C
ATOM   6047  NH1 ARG B  47       6.586  34.104 158.889  1.00  6.65       B    N
ATOM   6048  NH2 ARG B  47       4.910  33.627 160.378  1.00  6.18       B    N
ATOM   6049  C   ARG B  47       7.861  38.854 156.975  1.00  4.46       B    C
ATOM   6050  O   ARG B  47       6.656  39.124 156.837  1.00  3.68       B    O
ATOM   6051  N   ASN B  48       8.584  38.257 156.029  1.00  4.25       B    N
ATOM   6052  CA  ASN B  48       7.898  37.485 154.983  1.00  4.09       B    C
ATOM   6053  CB  ASN B  48       8.627  37.525 153.605  1.00  3.81       B    C
ATOM   6054  CG  ASN B  48       9.824  36.572 153.502  1.00  3.63       B    C
ATOM   6055  OD1 ASN B  48      10.191  35.864 154.455  1.00  4.51       B    O
ATOM   6056  ND2 ASN B  48      10.441  36.556 152.325  1.00  2.00       B    N
ATOM   6057  C   ASN B  48       7.626  36.082 155.535  1.00  4.15       B    C
ATOM   6058  O   ASN B  48       7.928  35.813 156.710  1.00  4.08       B    O
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ATOM   6059  N   ASN B  49       7.049  35.200 154.730  1.00  3.96       B    N
ATOM   6060  CA  ASN B  49       6.685  33.858 155.217  1.00  4.78       B    C
ATOM   6061  CB  ASN B  49       5.892  33.072 154.155  1.00  4.58       B    C
ATOM   6062  CG  ASN B  49       4.528  33.683 153.864  1.00  6.22       B    C
ATOM   6063  OD1 ASN B  49       3.827  33.270 152.922  1.00  8.25       B    O
ATOM   6064  ND2 ASN B  49       4.151  34.685 154.655  1.00  4.90       B    N
ATOM   6065  C   ASN B  49       7.840  33.013 155.763  1.00  4.50       B    C
ATOM   6066  O   ASN B  49       7.632  32.168 156.622  1.00  5.46       B    O
ATOM   6067  N   THR B  50       9.054  33.243 155.273  1.00  5.02       B    N
ATOM   6068  CA  THR B  50      10.246  32.518 155.744  1.00  4.39       B    C
ATOM   6069  CB  THR B  50      11.413  32.651 154.748  1.00  4.34       B    C
ATOM   6070  OG1 THR B  50      11.882  34.011 154.742  1.00  3.44       B    O
ATOM   6071  CG2 THR B  50      10.950  32.254 153.325  1.00  4.57       B    C
ATOM   6072  C   THR B  50      10.745  33.031 157.096  1.00  4.84       B    C
ATOM   6073  O   THR B  50      11.450  32.306 157.804  1.00  4.54       B    O
ATOM   6074  N   GLY B  51      10.432  34.293 157.416  1.00  4.48       B    N
ATOM   6075  CA  GLY B  51      10.802  34.910 158.707  1.00  4.48       B    C
ATOM   6076  C   GLY B  51      11.560  36.232 158.553  1.00  5.18       B    C
ATOM   6077  O   GLY B  51      11.862  36.918 159.542  1.00  5.14       B    O
ATOM   6200  N   LEU B  67      10.876  26.584 154.563  1.00  4.27       B    N
ATOM   6201  CA  LEU B  67      10.335  26.228 153.272  1.00  4.24       B    C
ATOM   6202  CB  LEU B  67       8.858  25.822 153.413  1.00  3.74       B    C
ATOM   6203  CG  LEU B  67       8.558  24.462 154.063  1.00  2.90       B    C
ATOM   6204  CD1 LEU B  67       7.076  24.167 154.019  1.00  2.92       B    C
ATOM   6205  CD2 LEU B  67       9.361  23.328 153.400  1.00  2.00       B    C
ATOM   6206  C   LEU B  67      10.436  27.457 152.371  1.00  4.38       B    C
ATOM   6207  O   LEU B  67       9.926  28.517 152.720  1.00  4.30       B    O
ATOM   6208  N   ASP B  68      11.070  27.282 151.216  1.00  4.40       B    N
ATOM   6209  CA  ASP B  68      11.312  28.351 150.252  1.00  4.81       B    C
ATOM   6210  CB  ASP B  68      12.398  27.937 149.254  1.00  4.70       B    C
ATOM   6211  CG  ASP B  68      13.677  27.502 149.932  1.00  5.37       B    C
ATOM   6212  OD1 ASP B  68      13.702  26.364 150.444  1.00  4.55       B    O
ATOM   6213  OD2 ASP B  68      14.636  28.300 149.964  1.00  5.37       B    O
ATOM   6214  C   ASP B  68      10.079  28.727 149.459  1.00  4.93       B    C
ATOM   6215  O   ASP B  68       9.469  27.878 148.818  1.00  5.94       B    O
ATOM   6216  N   GLY B  69       9.723  30.005 149.507  1.00  5.17       B    N
ATOM   6217  CA  GLY B  69       8.769  30.598 148.558  1.00  4.56       B    C
ATOM   6218  C   GLY B  69       7.327  30.161 148.689  1.00  4.60       B    C
ATOM   6219  O   GLY B  69       6.573  30.236 147.713  1.00  4.30       B    O
ATOM   6220  N   VAL B  70       6.932  29.725 149.887  1.00  3.48       B    N
ATOM   6221  CA  VAL B  70       5.589  29.149 150.102  1.00  3.51       B    C
ATOM   6222  CB  VAL B  70       5.627  27.927 151.063  1.00  3.54       B    C
ATOM   6223  CG1 VAL B  70       6.419  26.772 150.442  1.00  3.34       B    C
ATOM   6224  CG2 VAL B  70       6.209  28.314 152.422  1.00  2.91       B    C
ATOM   6225  C   VAL B  70       4.609  30.183 150.644  1.00  3.44       B    C
ATOM   6226  O   VAL B  70       5.033  31.257 151.119  1.00  3.41       B    O
ATOM   6227  N   GLY B  71       3.317  29.856 150.590  1.00  3.21       B    N
ATOM   6228  CA  GLY B  71       2.243  30.766 151.033  1.00  4.39       B    C
ATOM   6229  C   GLY B  71       1.896  30.610 152.517  1.00  5.23       B    C
ATOM   6230  O   GLY B  71       2.732  30.168 153.313  1.00  5.01       B    O
ATOM   6231  N   GLY B  72       0.653  30.950 152.869  1.00  5.67       B    N
ATOM   6232  CA  GLY B  72       0.165  30.889 154.256  1.00  5.93       B    C
ATOM   6233  C   GLY B  72       0.949  31.862 155.107  1.00  6.07       B    C
ATOM   6234  O   GLY B  72       1.165  33.016 154.692  1.00  6.64       B    O
ATOM   6235  N   SER B  73       1.390  31.404 156.282  1.00  5.79       B    N
ATOM   6236  CA  SER B  73       2.360  32.159 157.086  1.00  5.71       B    C
ATOM   6237  CB  SER B  73       1.884  32.320 158.534  1.00  5.72       B    C
ATOM   6238  OG  SER B  73       1.572  31.062 159.111  1.00  5.04       B    O
ATOM   6239  C   SER B  73       3.751  31.512 157.055  1.00  5.79       B    C
ATOM   6240  O   SER B  73       4.621  31.864 157.855  1.00  5.53       B    O
ATOM   6241  N   GLY B  74       3.943  30.560 156.136  1.00  5.50       B    N
ATOM   6242  CA  GLY B  74       5.232  29.886 155.962  1.00  4.98       B    C
ATOM   6243  C   GLY B  74       5.389  28.660 156.834  1.00  4.36       B    C
ATOM   6244  O   GLY B  74       4.702  28.512 157.834  1.00  4.36       B    O
ATOM   6245  N   GLY B  75       6.284  27.765 156.443  1.00  4.59       B    N
ATOM   6246  CA  GLY B  75       6.527  26.565 157.216  1.00  4.40       B    C
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ATOM   6247  C   GLY B  75       7.889  26.594 157.880  1.00  4.18       B    C
ATOM   6248  O   GLY B  75       8.717  27.435 157.575  1.00  4.41       B    O
ATOM   6249  N   GLY B  76       8.116  25.653 158.788  1.00  4.82       B    N
ATOM   6250  CA  GLY B  76       9.371  25.580 159.508  1.00  4.57       B    C
ATOM   6251  C   GLY B  76       9.475  26.759 160.434  1.00  4.29       B    C
ATOM   6252  O   GLY B  76       8.504  27.108 161.114  1.00  4.51       B    O
ATOM   6253  N   GLY B  77      10.647  27.390 160.433  1.00  3.80       B    N
ATOM   6254  CA  GLY B  77      10.953  28.443 161.386  1.00  3.39       B    C
ATOM   6255  C   GLY B  77      11.241  27.958 162.792  1.00  3.21       B    C
ATOM   6256  O   GLY B  77      11.099  28.729 163.743  1.00  3.66       B    O
ATOM   7082  N   TYR B 194       3.643  22.233 162.238  1.00  3.12       B    N
ATOM   7083  CA  TYR B 194       2.613  21.951 161.250  1.00  3.30       B    C
ATOM   7084  CB  TYR B 194       1.229  21.842 161.911  1.00  3.34       B    C
ATOM   7085  CG  TYR B 194       0.110  21.512 160.940  1.00  3.71       B    C
ATOM   7086  CD1 TYR B 194      -0.461  22.504 160.135  1.00  4.84       B    C
ATOM   7087  CE1 TYR B 194      -1.490  22.204 159.240  1.00  6.19       B    C
ATOM   7088  CZ  TYR B 194      -1.954  20.908 159.146  1.00  4.77       B    C
ATOM   7089  OH  TYR B 194      -2.964  20.602 158.255  1.00  6.66       B    O
ATOM   7090  CE2 TYR B 194      -1.400  19.908 159.936  1.00  5.56       B    C
ATOM   7091  CD2 TYR B 194      -0.370  20.213 160.817  1.00  2.00       B    C
ATOM   7092  C   TYR B 194       2.618  23.039 160.183  1.00  3.39       B    C
ATOM   7093  O   TYR B 194       2.833  24.217 160.484  1.00  2.89       B    O
ATOM   7094  N   PHE B 195       2.402  22.634 158.934  1.00  3.57       B    N
ATOM   7095  CA  PHE B 195       2.176  23.583 157.852  1.00  4.28       B    C
ATOM   7096  CB  PHE B 195       3.495  24.128 157.273  1.00  3.41       B    C
ATOM   7097  CG  PHE B 195       3.307  25.061 156.101  1.00  2.84       B    C
ATOM   7098  CD1 PHE B 195       2.857  26.368 156.296  1.00  2.00       B    C
ATOM   7099  CE1 PHE B 195       2.688  27.240 155.214  1.00  2.78       B    C
ATOM   7100  CZ  PHE B 195       2.970  26.810 153.920  1.00  2.01       B    C
ATOM   7101  CE2 PHE B 195       3.431  25.487 153.713  1.00  3.28       B    C
ATOM   7102  CD2 PHE B 195       3.588  24.636 154.801  1.00  2.14       B    C
ATOM   7103  C   PHE B 195       1.340  22.977 156.739  1.00  4.75       B    C
ATOM   7104  O   PHE B 195       1.700  21.949 156.158  1.00  4.94       B    O
ATOM   7105  N   TYR B 196       0.234  23.655 156.460  1.00  6.22       B    N
ATOM   7106  CA  TYR B 196      -0.598  23.421 155.296  1.00  7.19       B    C
ATOM   7107  CB  TYR B 196       0.228  23.437 153.995  1.00  7.83       B    C
ATOM   7108  CG  TYR B 196      -0.616  23.795 152.800  1.00 10.54       B    C
ATOM   7109  CD1 TYR B 196      -1.022  25.116 152.596  1.00 12.24       B    C
ATOM   7110  CE1 TYR B 196      -1.824  25.468 151.513  1.00 15.08       B    C
ATOM   7111  CZ  TYR B 196      -2.227  24.487 150.619  1.00 16.10       B    C
ATOM   7112  OH  TYR B 196      -3.015  24.861 149.550  1.00 19.44       B    O
ATOM   7113  CE2 TYR B 196      -1.840  23.147 150.800  1.00 15.05       B    C
ATOM   7114  CD2 TYR B 196      -1.038  22.812 151.890  1.00 11.35       B    C
ATOM   7115  C   TYR B 196      -1.432  22.161 155.434  1.00  7.32       B    C
ATOM   7116  O   TYR B 196      -2.592  22.244 155.848  1.00  8.08       B    O
ATOM   7117  N   ASN B 197      -0.848  21.010 155.111  1.00  6.91       B    N
ATOM   7118  CA  ASN B 197      -1.557  19.737 155.149  1.00  7.00       B    C
ATOM   7119  CB  ASN B 197      -1.448  19.010 153.804  1.00  6.93       B    C
ATOM   7120  CG  ASN B 197      -2.381  19.573 152.756  1.00  8.25       B    C
ATOM   7121  OD1 ASN B 197      -3.492  19.991 153.063  1.00  6.81       B    O
ATOM   7122  ND2 ASN B 197      -1.932  19.577 151.499  1.00  9.68       B    N
ATOM   7123  C   ASN B 197      -1.097  18.779 156.242  1.00  6.55       B    C
ATOM   7124  O   ASN B 197      -1.841  17.875 156.589  1.00  6.69       B    O
ATOM   7125  N   ALA B 198       0.104  18.977 156.793  1.00  5.68       B    N
ATOM   7126  CA  ALA B 198       0.738  17.907 157.606  1.00  5.17       B    C
ATOM   7127  CB  ALA B 198       1.519  16.952 156.715  1.00  3.99       B    C
ATOM   7128  C   ALA B 198       1.644  18.391 158.727  1.00  4.90       B    C
ATOM   7129  O   ALA B 198       2.316  19.416 158.594  1.00  5.24       B    O
ATOM   8311  N   ALA B 352       5.634  20.319 147.023  1.00  5.44       B    N
ATOM   8312  CA  ALA B 352       4.594  21.317 146.769  1.00  6.09       B    C
ATOM   8313  CB  ALA B 352       5.135  22.730 146.962  1.00  5.99       B    C
ATOM   8314  C   ALA B 352       4.223  21.089 145.329  1.00  6.35       B    C
ATOM   8315  O   ALA B 352       4.288  21.990 144.503  1.00  6.13       B    O
ATOM   8316  N   THR B 353       3.821  19.855 145.044  1.00  7.15       B    N
ATOM   8317  CA  THR B 353       3.818  19.352 143.690  1.00  7.57       B    C
ATOM   8318  CB  THR B 353       3.887  17.837 143.696  1.00  7.65       B    C
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ATOM   8319  OG1 THR B 353       4.943  17.447 144.580  1.00  8.17       B     O
ATOM   8320  CG2 THR B 353       4.184  17.295 142.296  1.00  6.93       B     C
ATOM   8321  C   THR B 353       2.656  19.914 142.859  1.00  8.28       B     C
ATOM   8322  O   THR B 353       2.750  19.992 141.631  1.00  8.21       B     O
ATOM   8323  N   TRP B 354       1.581  20.325 143.531  1.00  8.91       B     N
ATOM   8324  CA  TRP B 354       0.511  21.060 142.861  1.00 10.28       B     C
ATOM   8325  CB  TRP B 354      -0.559  21.535 143.859  1.00 10.88       B     C
ATOM   8326  CG  TRP B 354      -1.795  22.053 143.189  1.00 13.77       B     C
ATOM   8327  CD1 TRP B 354      -2.904  21.331 142.861  1.00 15.75       B     C
ATOM   8328  NE1 TRP B 354      -3.829  22.131 142.242  1.00 18.84       B     N
ATOM   8329  CE2 TRP B 354      -3.338  23.407 142.172  1.00 19.33       B     C
ATOM   8330  CD2 TRP B 354      -2.050  23.396 142.759  1.00 17.76       B     C
ATOM   8331  CE3 TRP B 354      -1.317  24.588 142.806  1.00 19.35       B     C
ATOM   8332  CZ3 TRP B 354      -1.887  25.751 142.273  1.00 22.00       B     C
ATOM   8333  CH2 TRP B 354      -3.175  25.730 141.696  1.00 22.73       B     C
ATOM   8334  CZ2 TRP B 354      -3.914  24.569 141.634  1.00 22.09       B     C
ATOM   8335  C   TRP B 354       1.082  22.248 142.090  1.00  9.94       B     C
ATOM   8336  O   TRP B 354       0.679  22.498 140.957  1.00 10.17       B     O
ATOM   8337  N   ASP B 355       2.027  22.961 142.708  1.00  9.68       B     N
ATOM   8338  CA  ASP B 355       2.607  24.171 142.126  1.00  9.25       B     C
ATOM   8339  CB  ASP B 355       3.020  25.161 143.224  1.00  9.39       B     C
ATOM   8340  CG  ASP B 355       1.920  25.410 144.250  1.00 11.18       B     C
ATOM   8341  OD1 ASP B 355       2.026  24.884 145.380  1.00 12.17       B     O
ATOM   8342  OD2 ASP B 355       0.957  26.138 143.927  1.00 14.96       B     O
ATOM   8343  C   ASP B 355       3.832  23.883 141.261  1.00  8.63       B     C
ATOM   8344  O   ASP B 355       4.010  24.505 140.198  1.00  8.49       B     O
ATOM   8345  N   ASP B 356       4.679  22.961 141.721  1.00  7.73       B     N
ATOM   8346  CA  ASP B 356       6.027  22.821 141.162  1.00  7.97       B     C
ATOM   8347  CB  ASP B 356       7.084  22.835 142.282  1.00  8.30       B     C
ATOM   8348  CG  ASP B 356       7.193  21.517 143.028  1.00 10.67       B     C
ATOM   8349  OD1 ASP B 356       6.378  20.590 142.800  1.00 12.81       B     O
ATOM   8350  OD2 ASP B 356       8.130  21.405 143.856  1.00 13.11       B     O
ATOM   8351  C   ASP B 356       6.290  21.648 140.225  1.00  6.85       B     C
ATOM   8352  O   ASP B 356       7.432  21.434 139.843  1.00  6.23       B     O
ATOM   8702  N   THR B 403       6.656  20.211 154.931  1.00  2.24       B     N
ATOM   8703  CA  THR B 403       6.223  19.841 153.605  1.00  2.00       B     C
ATOM   8704  CB  THR B 403       6.095  18.282 153.520  1.00  2.05       B     C
ATOM   8705  OG1 THR B 403       5.760  17.892 152.198  1.00  3.15       B     O
ATOM   8706  CG2 THR B 403       5.030  17.770 154.453  1.00  2.00       B     C
ATOM   8707  C   THR B 403       4.913  20.578 153.289  1.00  2.00       B     C
ATOM   8708  O   THR B 403       4.316  21.193 154.178  1.00  2.00       B     O
ATOM   8709  N   VAL B 404       4.491  20.536 152.026  1.00  2.00       B     N
ATOM   8710  CA  VAL B 404       3.295  21.247 151.582  1.00  2.02       B     C
ATOM   8711  CB  VAL B 404       3.633  22.358 150.571  1.00  2.00       B     C
ATOM   8712  CG1 VAL B 404       2.406  23.239 150.320  1.00  2.00       B     C
ATOM   8713  CG2 VAL B 404       4.800  23.187 151.064  1.00  2.00       B     C
ATOM   8714  C   VAL B 404       2.175  20.345 151.023  1.00  2.65       B     C
ATOM   8715  O   VAL B 404       1.183  20.118 151.702  1.00  2.92       B     O
ATOM   8716  N   ARG B 405       2.332  19.834 149.803  1.00  3.29       B     N
ATOM   8717  CA  ARG B 405       1.236  19.105 149.134  1.00  3.66       B     C
ATOM   8718  CB  ARG B 405       0.170  20.101 148.633  1.00  3.90       B     C
ATOM   8719  CG  ARG B 405       0.641  20.982 147.480  1.00  3.00       B     C
ATOM   8720  CD  ARG B 405      -0.271  22.201 147.301  1.00  2.02       B     C
ATOM   8721  NE  ARG B 405      -1.643  21.828 146.974  1.00  3.88       B     N
ATOM   8722  CZ  ARG B 405      -2.594  22.700 146.644  1.00  5.53       B     C
ATOM   8723  NH1 ARG B 405      -2.324  24.001 146.580  1.00  5.29       B     N
ATOM   8724  NH2 ARG B 405      -3.812  22.271 146.379  1.00  6.56       B     N
ATOM   8725  C   ARG B 405       1.717  18.221 147.981  1.00  3.69       B     C
ATOM   8726  O   ARG B 405       2.837  18.353 147.494  1.00  3.54       B     O
ATOM   8727  N   TRP B 406       0.861  17.315 147.540  1.00  4.26       B     N
ATOM   8728  CA  TRP B 406       1.343  16.193 146.726  1.00  4.40       B     C
ATOM   8729  CB  TRP B 406       1.380  14.920 147.575  1.00  4.23       B     C
ATOM   8730  CG  TRP B 406       2.088  15.094 148.872  1.00  4.31       B     C
ATOM   8731  CD1 TRP B 406       3.417  14.922 149.110  1.00  4.94       B     C
ATOM   8732  NE1 TRP B 406       3.696  15.167 150.429  1.00  5.82       B     N
ATOM   8733  CE2 TRP B 406       2.537  15.516 151.067  1.00  4.54       B     C
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ATOM   8734  CD2 TRP B 406       1.500  15.472 150.112  1.00  4.03       B     C
ATOM   8735  CE3 TRP B 406       0.192  15.805 150.507  1.00  2.57       B     C
ATOM   8736  CZ3 TRP B 406      -0.024  16.148 151.840  1.00  4.33       B     C
ATOM   8737  CH2 TRP B 406       1.032  16.167 152.764  1.00  4.13       B     C
ATOM   8738  CZ2 TRP B 406       2.316  15.859 152.397  1.00  3.80       B     C
ATOM   8739  C   TRP B 406       0.565  15.933 145.433  1.00  4.65       B     C
ATOM   9696  N   GLY B 533     -15.847  27.725 140.342  1.00  9.53       B     N
ATOM   9697  CA  GLY B 533     -15.211  26.855 141.335  1.00  9.25       B     C
ATOM   9698  C   GLY B 533     -13.705  26.691 141.187  1.00  8.71       B     C
ATOM   9699  O   GLY B 533     -13.098  25.875 141.883  1.00  8.16       B     O
ATOM   9700  N   LEU B 534     -13.099  27.477 140.293  1.00  8.58       B     N
ATOM   9701  CA  LEU B 534     -11.653  27.388 140.006  1.00  8.07       B     C
ATOM   9702  CB  LEU B 534     -11.286  28.145 138.734  1.00  7.63       B     C
ATOM   9703  CG  LEU B 534     -11.866  27.619 137.420  1.00  6.93       B     C
ATOM   9704  CD1 LEU B 534     -11.597  28.602 136.307  1.00  3.89       B     C
ATOM   9705  CD2 LEU B 534     -11.303  26.245 137.079  1.00  7.25       B     C
ATOM   9706  C   LEU B 534     -10.747  27.869 141.134  1.00  8.88       B     C
ATOM   9707  O   LEU B 534     -11.033  28.870 141.822  1.00  7.62       B     O
ATOM   9708  N   TYR B 535      -9.637  27.152 141.288  1.00  9.49       B     N
ATOM   9709  CA  TYR B 535      -8.638  27.486 142.280  1.00 10.81       B     C
ATOM   9710  CB  TYR B 535      -8.010  26.197 142.861  1.00 11.89       B     C
ATOM   9711  CG  TYR B 535      -8.753  25.749 144.106  1.00 16.97       B     C
ATOM   9712  CD1 TYR B 535      -8.130  25.772 145.361  1.00 20.37       B     C
ATOM   9713  CE1 TYR B 535      -8.832  25.389 146.520  1.00 23.75       B     C
ATOM   9714  CZ  TYR B 535     -10.184  25.009 146.424  1.00 23.62       B     C
ATOM   9715  OH  TYR B 535     -10.865  24.649 147.562  1.00 24.62       B     O
ATOM   9716  CE2 TYR B 535     -10.827  24.987 145.193  1.00 22.59       B     C
ATOM   9717  CD2 TYR B 535     -10.111  25.365 144.038  1.00 20.68       B     C
ATOM   9718  C   TYR B 535      -7.604  28.447 141.703  1.00 10.16       B     C
ATOM   9719  O   TYR B 535      -6.865  28.094 140.801  1.00 10.24       B     O
ATOM   9720  N   GLN B 536      -7.600  29.677 142.211  1.00  9.98       B     N
ATOM   9721  CA  GLN B 536      -6.568  30.681 141.905  1.00 10.33       B     C
ATOM   9722  CB  GLN B 536      -5.234  30.334 142.598  1.00 10.30       B     C
ATOM   9723  CG  GLN B 536      -5.313  30.141 144.128  1.00 13.24       B     C
ATOM   9724  CD  GLN B 536      -3.939  29.900 144.772  1.00 16.30       B     C
ATOM   9725  OE1 GLN B 536      -2.909  29.886 144.095  1.00 17.97       B     O
ATOM   9726  NE2 GLN B 536      -3.929  29.725 146.091  1.00 18.13       B     N
ATOM   9727  C   GLN B 536      -6.337  30.936 140.402  1.00 10.03       B     C
ATOM   9728  O   GLN B 536      -5.217  31.217 139.967  1.00 10.11       B     O
ATOM   9729  N   GLY B 537      -7.397  30.850 139.608  1.00 10.06       B     N
ATOM   9730  CA  GLY B 537      -7.264  31.159 138.187  1.00  8.79       B     C
ATOM   9731  C   GLY B 537      -8.584  31.268 137.454  1.00  8.30       B     C
ATOM   9732  O   GLY B 537      -9.659  31.075 138.037  1.00  7.71       B     O
ATOM  10119  N   ASN B 586       1.158  35.774 134.842  1.00  4.61       B     N
ATOM  10120  CA  ASN B 586       2.561  35.487 135.130  1.00  4.87       B     C
ATOM  10121  CB  ASN B 586       3.446  36.671 134.695  1.00  4.94       B     C
ATOM  10122  CG  ASN B 586       3.354  36.964 133.194  1.00  4.99       B     C
ATOM  10123  OD1 ASN B 586       2.930  38.041 132.796  1.00  8.76       B     O
ATOM  10124  ND2 ASN B 586       3.754  36.017 132.371  1.00  4.46       B     N
ATOM  10125  C   ASN B 586       2.791  35.182 136.618  1.00  5.09       B     C
ATOM  10126  O   ASN B 586       3.852  34.691 136.997  1.00  3.71       B     O
ATOM  10127  N   ALA B 587       1.777  35.465 137.446  1.00  5.34       B     N
ATOM  10128  CA  ALA B 587       1.917  35.442 138.923  1.00  6.16       B     C
ATOM  10129  CB  ALA B 587       1.006  36.491 139.546  1.00  5.10       B     C
ATOM  10130  C   ALA B 587       1.688  34.108 139.635  1.00  6.83       B     C
ATOM  10131  O   ALA B 587       2.084  33.957 140.784  1.00  6.45       B     O
ATOM  10132  N   ASN B 588       0.997  33.179 138.977  1.00  8.41       B     N
ATOM  10133  CA  ASN B 588       0.684  31.857 139.540  1.00  9.70       B     C
ATOM  10134  CB  ASN B 588      -0.790  31.765 139.954  1.00 10.13       B     C
ATOM  10135  CG  ASN B 588      -1.026  30.752 141.077  1.00 12.26       B     C
ATOM  10136  OD1 ASN B 588      -0.090  30.198 141.622  1.00 15.20       B     O
ATOM  10137  ND2 ASN B 588      -2.286  30.513 141.418  1.00 15.01       B     N
ATOM  10138  C   ASN B 588       1.027  30.786 138.509  1.00 10.25       B     C
ATOM  10139  O   ASN B 588       1.296  31.109 137.356  1.00 10.70       B     O
ATOM  10140  N   GLU B 589       1.014  29.523 138.913  1.00 10.86       B     N
ATOM  10141  CA  GLU B 589       1.574  28.445 138.079  1.00 11.52       B     C
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ATOM  10142  CB  GLU B 589       2.198  27.370 138.976  1.00 11.45       B     C
ATOM  10143  CG  GLU B 589       3.501  27.805 139.630  1.00  9.96       B     C
ATOM  10144  CD  GLU B 589       3.311  28.386 141.028  1.00 10.68       B     C
ATOM  10145  OE1 GLU B 589       2.146  28.629 141.434  1.00 10.43       B     O
ATOM  10146  OE2 GLU B 589       4.335  28.606 141.722  1.00  8.00       B     O
ATOM  10147  C   GLU B 589       0.608  27.804 137.071  1.00 11.76       B     C
ATOM  10148  O   GLU B 589       1.027  27.008 136.207  1.00 11.79       B     O
ATOM  10149  N   ILE B 590      -0.670  28.170 137.171  1.00 11.86       B     N
ATOM  10150  CA  ILE B 590      -1.724  27.523 136.394  1.00 11.76       B     C
ATOM  10151  CB  ILE B 590      -3.097  28.106 136.760  1.00 11.88       B     C
ATOM  10152  CG1 ILE B 590      -3.531  27.471 138.085  1.00 12.53       B     C
ATOM  10153  CD1 ILE B 590      -4.228  28.396 138.985  1.00 13.66       B     C
ATOM  10154  CG2 ILE B 590      -4.143  27.847 135.665  1.00 12.30       B     C
ATOM  10155  C   ILE B 590      -1.461  27.444 134.877  1.00 11.77       B     C
ATOM  10156  O   ILE B 590      -1.563  26.362 134.286  1.00 11.66       B     O
ATOM  10444  CA  ILE B 624      -2.166  38.601 140.777  1.00  6.95       B     C
ATOM  10445  CB  ILE B 624      -2.394  39.529 142.009  1.00  7.43       B     C
ATOM  10446  CG1 ILE B 624      -3.881  39.873 142.189  1.00  6.21       B     C
ATOM  10447  CD1 ILE B 624      -4.256  40.384 143.612  1.00  6.93       B     C
ATOM  10448  CG2 ILE B 624      -1.589  40.820 141.848  1.00  5.38       B     C
ATOM  10449  C   ILE B 624      -2.529  37.158 141.097  1.00  8.00       B     C
ATOM  10450  O   ILE B 624      -3.395  36.597 140.423  1.00  7.71       B     O
ATOM  10451  N   ALA B 625      -1.876  36.566 142.107  1.00  8.28       B     N
ATOM  10452  CA  ALA B 625      -2.036  35.146 142.429  1.00  9.17       B     C
ATOM  10453  CB  ALA B 625      -0.672  34.532 142.890  1.00  8.73       B     C
ATOM  10454  C   ALA B 625      -3.121  34.848 143.476  1.00  9.67       B     C
ATOM  10455  O   ALA B 625      -3.305  33.688 143.871  1.00  9.55       B     O
ATOM  10456  N   THR B 626      -3.813  35.889 143.941  1.00 10.19       B     N
ATOM  10457  CA  THR B 626      -4.883  35.743 144.940  1.00  9.61       B     C
ATOM  10458  CB  THR B 626      -4.311  35.718 146.381  1.00 10.06       B     C
ATOM  10459  OG1 THR B 626      -5.328  35.322 147.300  1.00  9.01       B     O
ATOM  10460  CG2 THR B 626      -3.722  37.088 146.791  1.00 10.40       B     C
ATOM  10461  C   THR B 626      -5.890  36.882 144.760  1.00  9.89       B     C
ATOM  10462  O   THR B 626      -5.682  37.753 143.914  1.00  9.41       B     O
ATOM  10463  N   GLY B 627      -6.954  36.880 145.563  1.00 10.02       B     N
ATOM  10464  CA  GLY B 627      -8.057  37.828 145.428  1.00 11.00       B     C
ATOM  10465  C   GLY B 627      -7.684  39.294 145.557  1.00 12.06       B     C
ATOM  10466  O   GLY B 627      -8.185  40.135 144.815  1.00 12.64       B     O
ATOM  10467  N   SER B 628      -6.793  39.604 146.489  1.00 13.03       B     N
ATOM  10468  CA  SER B 628      -6.410  40.988 146.753  1.00 14.00       B     C
ATOM  10469  CB  SER B 628      -7.482  41.650 147.614  1.00 14.26       B     C
ATOM  10470  OG  SER B 628      -7.266  43.039 147.649  1.00 15.26       B     O
ATOM  10471  C   SER B 628      -5.047  41.111 147.452  1.00 14.28       B     C
ATOM  10472  O   SER B 628      -4.640  40.217 148.191  1.00 14.61       B     O
ATOM  10473  N   SER B 629      -4.362  42.229 147.219  1.00 14.43       B     N
ATOM  10474  CA  SER B 629      -3.055  42.511 147.827  1.00 14.96       B     C
ATOM  10475  CB  SER B 629      -1.950  42.366 146.779  1.00 14.81       B     C
ATOM  10476  OG  SER B 629      -0.708  42.826 147.280  1.00 15.07       B     O
ATOM  10477  C   SER B 629      -2.997  43.923 148.390  1.00 15.25       B     C
ATOM  10478  O   SER B 629      -3.433  44.866 147.747  1.00 15.02       B     O
ATOM  10680  N   PRO B 657       4.050  41.388 143.073  1.00  6.53       B     N
ATOM  10681  CA  PRO B 657       3.402  41.236 144.385  1.00  6.71       B     C
ATOM  10682  CB  PRO B 657       2.633  42.551 144.560  1.00  6.75       B     C
ATOM  10683  CG  PRO B 657       2.497  43.125 143.179  1.00  6.81       B     C
ATOM  10684  CD  PRO B 657       3.695  42.650 142.401  1.00  6.65       B     C
ATOM  10685  C   PRO B 657       2.446  40.037 144.343  1.00  7.09       B     C
ATOM  10686  O   PRO B 657       1.785  39.823 143.317  1.00  7.31       B     O
ATOM  10687  N   THR B 658       2.382  39.270 145.438  1.00  6.82       B     N
ATOM  10688  CA  THR B 658       1.659  37.972 145.528  1.00  7.41       B     C
ATOM  10689  CB  THR B 658       0.160  38.025 145.092  1.00  7.22       B     C
ATOM  10690  OG1 THR B 658       0.091  38.108 143.663  1.00  8.46       B     O
ATOM  10691  CG2 THR B 658      -0.562  39.183 145.720  1.00  7.56       B     C
ATOM  10692  C   THR B 658       2.281  36.761 144.802  1.00  6.95       B     C
ATOM  10693  O   THR B 658       1.850  35.614 145.012  1.00  7.00       B     O
ATOM  10694  N   MET B 659       3.266  37.002 143.944  1.00  6.43       B     N
ATOM  10695  CA  MET B 659       3.892  35.925 143.184  1.00  5.95       B     C
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ATOM  10696  CB  MET B 659       4.588  36.511 141.944  1.00  5.41       B    C
ATOM  10697  CG  MET B 659       5.187  35.490 140.977  1.00  5.34       B    C
ATOM  10698  SD  MET B 659       5.754  36.339 139.483  1.00  5.63       B    S
ATOM  10699  CE  MET B 659       6.973  35.196 138.813  1.00  4.33       B    C
ATOM  10700  C   MET B 659       4.865  35.073 144.034  1.00  5.78       B    C
ATOM  10701  O   MET B 659       6.092  35.284 144.006  1.00  6.02       B    O
ATOM  10702  N   ASP B 660       4.327  34.118 144.791  1.00  4.92       B    N
ATOM  10703  CA  ASP B 660       5.190  33.199 145.543  1.00  4.96       B    C
ATOM  10704  CB  ASP B 660       4.357  32.285 146.424  1.00  5.01       B    C
ATOM  10705  CG  ASP B 660       3.584  33.032 147.473  1.00  6.04       B    C
ATOM  10706  OD1 ASP B 660       4.035  34.111 147.913  1.00  7.34       B    O
ATOM  10707  OD2 ASP B 660       2.522  32.524 147.864  1.00  7.88       B    O
ATOM  10708  C   ASP B 660       6.037  32.337 144.596  1.00  4.93       B    C
ATOM  10709  O   ASP B 660       5.508  31.791 143.621  1.00  4.69       B    O
ATOM  10710  N   ASN B 661       7.340  32.240 144.873  1.00  4.84       B    N
ATOM  10711  CA  ASN B 661       8.255  31.368 144.118  1.00  5.08       B    C
ATOM  10712  CB  ASN B 661       9.694  31.455 144.681  1.00  5.10       B    C
ATOM  10713  CG  ASN B 661      10.780  31.140 143.629  1.00  6.08       B    C
ATOM  10714  OD1 ASN B 661      10.526  30.495 142.608  1.00  5.96       B    O
ATOM  10715  ND2 ASN B 661      11.992  31.636 143.872  1.00  6.67       B    N
ATOM  10716  C   ASN B 661       7.761  29.903 144.132  1.00  5.04       B    C
ATOM  10717  O   ASN B 661       7.831  29.211 143.113  1.00  4.57       B    O
ATOM  10718  N   ASP B 662       7.240  29.473 145.287  1.00  4.48       B    N
ATOM  10719  CA  ASP B 662       6.702  28.114 145.513  1.00  4.85       B    C
ATOM  10720  CB  ASP B 662       5.483  27.819 144.630  1.00  5.02       B    C
ATOM  10721  CG  ASP B 662       4.285  28.656 144.989  1.00  5.82       B    C
ATOM  10722  OD1 ASP B 662       3.900  28.697 146.173  1.00  7.25       B    O
ATOM  10723  OD2 ASP B 662       3.725  29.259 144.068  1.00  5.44       B    O
ATOM  10724  C   ASP B 662       7.733  27.009 145.308  1.00  4.49       B    C
ATOM  10725  O   ASP B 662       7.726  26.335 144.268  1.00  4.33       B    O
ATOM  10726  N   ALA B 663       8.587  26.804 146.304  1.00  4.58       B    N
ATOM  10727  CA  ALA B 663       9.647  25.783 146.215  1.00  5.19       B    C
ATOM  10728  CB  ALA B 663       9.032  24.354 146.294  1.00  4.88       B    C
ATOM  10729  C   ALA B 663      10.523  25.941 144.958  1.00  5.61       B    C
ATOM  10730  O   ALA B 663      10.951  24.953 144.355  1.00  6.58       B    O
ATOM  10731  N   GLY B 664      10.798  27.191 144.580  1.00  6.10       B    N
ATOM  10732  CA  GLY B 664      11.674  27.503 143.453  1.00  5.63       B    C
ATOM  10733  C   GLY B 664      11.067  27.352 142.068  1.00  5.88       B    C
ATOM  10734  O   GLY B 664      11.783  27.416 141.077  1.00  6.30       B    O
ATOM  12383 CA    CA C   6       1.503  30.134 143.317  1.00 32.32       C   CA
ATOM  11905  O   HOH C   7       2.949  31.974 142.705  1.00  3.45       C    O
ATOM  12345  O   HOH C   8       1.937  29.983 147.278  1.00 20.75       C    O
ATOM  12381  O   HOH C   9       0.607  31.785 144.943  1.00 23.64       C    O
ATOM  12380  O   HOH C  10       0.075  28.500 144.774  1.00 23.09       C    O
ATOM  12403  O3  GOL E   1       2.366  27.082 149.806  1.00 23.71       E    O
ATOM  12404  C3  GOL E   1       0.966  27.273 149.833  1.00 24.21       E    C
ATOM  12405  C2  GOL E   1       0.495  27.587 148.416  1.00 22.96       E    C
ATOM  12406  O2  GOL E   1      -0.173  28.816 148.396  1.00 22.95       E    O
ATOM  12407  C1  GOL E   1      -0.470  26.521 147.940  1.00 23.83       E    C
ATOM  12408  O1  GOL E   1       0.108  25.826 146.867  1.00 22.02       E    O
END
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FIG. 34

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CRYST1   82.202   91.158  224.523  90.00  90.00  90.00 P 2 2 21
SCALE1      0.012165  0.000000  0.000000        0.00000
SCALE2     -0.000000  0.010970  0.000000        0.00000
SCALE3      0.000000 -0.000000  0.004454        0.00000
ATOM      2  CA  ALA A   7      74.405  12.350  86.541  1.00 19.71       A    C
ATOM      7  CA  ASP A   8      72.571  11.287  83.330  1.00 16.72       A    C
ATOM     15  CA  TYR A   9      68.912  11.738  84.261  1.00 12.13       A    C
ATOM     27  CA  ALA A  10      68.003  12.081  80.575  1.00  8.97       A    C
ATOM     32  CA  SER A  11      68.548   8.297  80.172  1.00  8.34       A    C
ATOM     38  CA  LEU A  12      65.749   7.661  82.703  1.00  6.43       A    C
ATOM     46  CA  VAL A  13      63.113   9.628  80.736  1.00  5.75       A    C
ATOM     53  CA  ASP A  14      60.886   7.538  78.450  1.00  6.27       A    C
ATOM     61  CA  VAL A  15      59.534  10.004  75.843  1.00  4.66       A    C
ATOM     68  CA  PHE A  16      57.177   7.311  74.498  1.00  3.87       A    C
ATOM     79  CA  VAL A  17      55.121   7.160  77.667  1.00  3.47       A    C
ATOM     86  CA  GLY A  18      51.656   8.454  76.810  1.00  3.67       A    C
ATOM     90  CA  THR A  19      52.191   8.387  72.991  1.00  3.13       A    C
ATOM     97  CA  GLU A  20      49.720   5.556  72.200  1.00  4.27       A    C
ATOM    106  CA  GLY A  21      46.188   6.265  70.980  1.00  5.40       A    C
ATOM    110  CA  ASP A  22      43.990   8.104  73.483  1.00  5.27       A    C
ATOM    118  CA  PHE A  23      46.225   7.338  76.520  1.00  4.39       A    C
ATOM    129  CA  GLY A  24      47.673  10.774  77.312  1.00  3.08       A    C
ATOM    133  CA  ASN A  25      48.095  12.630  73.991  1.00  2.47       A    C
ATOM    141  CA  ASP A  26      51.797  13.270  74.588  1.00  3.20       A    C
ATOM    149  CA  MET A  27      54.547  13.334  71.981  1.00  3.36       A    C
ATOM    157  CA  PRO A  28      57.941  11.662  71.502  1.00  3.20       A    C
ATOM    164  CA  ALA A  29      59.066  14.935  69.784  1.00  3.06       A    C
ATOM    169  CA  ALA A  30      62.625  16.198  70.105  1.00  3.69       A    C
ATOM    174  CA  GLN A  31      62.423  19.283  72.321  1.00  5.14       A    C
ATOM    183  CA  ALA A  32      64.432  21.430  74.735  1.00  4.55       A    C
ATOM    188  CA  PRO A  33      63.094  22.317  78.204  1.00  4.64       A    C
ATOM    195  CA  ASN A  34      60.021  24.568  77.625  1.00  4.19       A    C
ATOM    203  CA  GLY A  35      60.994  24.689  73.959  1.00  3.44       A    C
ATOM    207  CA  LEU A  36      59.041  26.309  71.169  1.00  3.34       A    C
ATOM    215  CA  ALA A  37      60.477  23.938  68.541  1.00  3.52       A    C
ATOM    220  CA  LYS A  38      58.932  20.498  68.910  1.00  3.01       A    C
ATOM    229  CA  VAL A  39      60.209  18.174  66.213  1.00  2.00       A    C
ATOM    236  CA  ASN A  40      57.543  15.463  66.213  1.00  2.24       A    C
ATOM    244  CA  PRO A  41      57.420  12.468  63.910  1.00  3.24       A    C
ATOM    251  CA  ARG A  42      53.989  12.144  62.244  1.00  4.43       A    C
ATOM    262  CA  THR A  43      52.366   8.720  62.032  1.00  5.82       A    C
ATOM    269  CA  THR A  44      49.941   7.692  59.271  1.00  7.54       A    C
ATOM    276  CA  PRO A  45      47.070   6.985  58.732  1.00  7.64       A    C
ATOM    283  CA  GLY A  46      46.363   7.283  62.482  1.00  5.22       A    C
ATOM    287  CA  ARG A  47      47.876   9.677  65.005  1.00  4.33       A    C
ATOM    298  CA  ASN A  48      47.297  10.971  68.487  1.00  2.87       A    C
ATOM    306  CA  ASN A  49      46.469  14.686  68.971  1.00  3.59       A    C
ATOM    314  CA  THR A  50      50.174  15.553  68.695  1.00  2.96       A    C
ATOM    321  CA  GLY A  51      50.582  13.739  65.384  1.00  2.16       A    C
ATOM    325  CA  TYR A  52      52.147  10.463  66.622  1.00  2.75       A    C
ATOM    337  CA  ASP A  53      50.289   7.308  67.663  1.00  3.03       A    C
ATOM    345  CA  TYR A  54      52.612   4.563  69.034  1.00  3.42       A    C
ATOM    357  CA  ALA A  55      50.295   1.835  67.698  1.00  3.80       A    C
ATOM    362  CA  GLN A  56      50.932   2.905  64.064  1.00  4.22       A    C
ATOM    371  CA  SER A  57      53.533   1.527  61.658  1.00  6.71       A    C
ATOM    377  CA  LYS A  58      54.051   4.328  59.145  1.00  6.64       A    C
ATOM    386  CA  ILE A  59      55.576   7.777  59.431  1.00  5.57       A    C
ATOM    394  CA  SER A  60      55.344  10.584  56.904  1.00  4.00       A    C
ATOM    400  CA  GLY A  61      57.749  13.214  58.346  1.00  3.12       A    C
ATOM    404  CA  PHE A  62      58.483  15.778  61.088  1.00  4.01       A    C
ATOM    415  CA  THR A  63      56.355  18.741  62.206  1.00  3.06       A    C
ATOM    422  CA  HIS A  64      57.952  21.581  64.185  1.00  2.46       A    C
ATOM    432  CA  THR A  65      55.187  23.059  66.366  1.00  2.07       A    C
ATOM    439  CA  ASN A  66      52.932  21.418  68.894  1.00  2.86       A    C
ATOM    447  CA  LEU A  67      51.019  21.341  72.178  1.00  3.42       A    C
ATOM    455  CA  ASP A  68      51.501  18.692  74.851  1.00  2.88       A    C
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ATOM	463	CA	GLY	A	69	48.598	16.584	76.017	1.00	3.16	A	C
ATOM	467	CA	VAL	A	70	45.743	18.719	74.687	1.00	2.95	A	C
ATOM	474	CA	GLY	A	71	42.319	17.506	73.447	1.00	4.24	A	C
ATOM	478	CA	GLY	A	72	40.310	18.076	70.238	1.00	5.07	A	C
ATOM	482	CA	SER	A	73	42.497	16.981	67.319	1.00	5.30	A	C
ATOM	488	CA	GLY	A	74	45.570	18.647	68.860	1.00	4.44	A	C
ATOM	492	CA	GLY	A	75	47.211	22.012	68.196	1.00	4.03	A	C
ATOM	496	CA	GLY	A	76	50.230	23.149	66.192	1.00	3.47	A	C
ATOM	500	CA	GLY	A	77	51.645	20.417	63.910	1.00	2.77	A	C
ATOM	504	CA	ASP	A	78	53.003	23.083	61.502	1.00	3.19	A	C
ATOM	512	CA	LEU	A	79	55.816	22.729	58.975	1.00	3.46	A	C
ATOM	520	CA	LEU	A	80	55.960	19.099	57.867	1.00	3.19	A	C
ATOM	528	CA	VAL	A	81	59.330	17.935	56.541	1.00	2.38	A	C
ATOM	535	CA	VAL	A	82	59.151	14.633	54.633	1.00	2.66	A	C
ATOM	542	CA	PRO	A	83	62.241	12.791	53.307	1.00	3.10	A	C
ATOM	549	CA	THR	A	84	61.709	10.950	50.007	1.00	3.64	A	C
ATOM	556	CA	SER	A	85	63.546	9.484	47.006	1.00	3.93	A	C
ATOM	562	CA	GLY	A	86	60.474	10.171	44.894	1.00	4.58	A	C
ATOM	566	CA	SER	A	87	59.775	13.000	42.432	1.00	6.80	A	C
ATOM	572	CA	TYR	A	88	56.783	15.353	42.023	1.00	6.34	A	C
ATOM	584	CA	THR	A	89	55.158	17.278	39.133	1.00	6.35	A	C
ATOM	591	CA	ALA	A	90	52.313	18.731	41.257	1.00	5.37	A	C
ATOM	596	CA	ARG	A	91	51.505	19.377	44.932	1.00	5.13	A	C
ATOM	607	CA	PRO	A	92	52.147	16.058	46.755	1.00	5.88	A	C
ATOM	614	CA	GLY	A	93	49.327	13.739	47.757	1.00	6.88	A	C
ATOM	618	CA	THR	A	94	49.802	13.201	51.509	1.00	7.19	A	C
ATOM	625	CA	GLY	A	95	49.477	9.410	51.104	1.00	6.49	A	C
ATOM	629	CA	THR	A	96	52.770	9.459	49.173	1.00	4.50	A	C
ATOM	636	CA	TYR	A	97	54.650	10.619	52.300	1.00	3.46	A	C
ATOM	648	CA	ALA	A	98	54.035	7.311	54.100	1.00	3.39	A	C
ATOM	653	CA	HIS	A	99	57.136	5.240	55.089	1.00	4.47	A	C
ATOM	663	CA	PRO	A	100	57.203	1.916	56.975	1.00	5.44	A	C
ATOM	670	CA	PHE	A	101	58.803	2.128	60.401	1.00	5.59	A	C
ATOM	681	CA	SER	A	102	59.416	-0.191	63.342	1.00	7.19	A	C
ATOM	687	CA	HIS	A	103	59.895	0.563	67.048	1.00	6.56	A	C
ATOM	697	CA	ASP	A	104	62.859	-1.852	66.789	1.00	10.20	A	C
ATOM	705	CA	ASP	A	105	64.517	0.789	64.587	1.00	10.01	A	C
ATOM	713	CA	GLU	A	106	63.589	3.886	66.611	1.00	9.26	A	C
ATOM	722	CA	ASP	A	107	65.354	5.697	69.473	1.00	9.20	A	C
ATOM	730	CA	ALA	A	108	64.518	8.899	71.371	1.00	5.45	A	C
ATOM	735	CA	GLY	A	109	65.127	10.798	74.597	1.00	4.60	A	C
ATOM	739	CA	PRO	A	110	65.502	14.365	75.895	1.00	3.95	A	C
ATOM	746	CA	GLY	A	111	66.404	16.609	72.933	1.00	4.26	A	C
ATOM	750	CA	PHE	A	112	66.407	13.997	70.163	1.00	4.28	A	C
ATOM	761	CA	TYR	A	113	64.446	11.529	68.079	1.00	5.36	A	C
ATOM	773	CA	SER	A	114	65.729	8.957	65.540	1.00	5.75	A	C
ATOM	779	CA	VAL	A	115	64.016	6.387	63.260	1.00	4.53	A	C
ATOM	786	CA	GLY	A	116	64.781	4.199	60.259	1.00	5.51	A	C
ATOM	790	CA	LEU	A	117	62.194	4.893	57.576	1.00	5.77	A	C
ATOM	798	CA	GLY	A	118	61.496	2.539	54.687	1.00	6.00	A	C
ATOM	802	CA	ASN	A	119	62.614	4.169	51.445	1.00	5.77	A	C
ATOM	810	CA	VAL	A	120	59.965	5.458	49.014	1.00	5.26	A	C
ATOM	817	CA	ALA	A	121	60.384	6.350	45.306	1.00	6.56	A	C
ATOM	822	CA	GLY	A	122	58.455	6.925	42.071	1.00	6.12	A	C
ATOM	826	CA	THR	A	123	56.572	9.913	40.635	1.00	7.50	A	C
ATOM	833	CA	ASP	A	124	53.544	11.573	42.245	1.00	7.71	A	C
ATOM	841	CA	GLY	A	125	50.654	9.176	43.087	1.00	7.97	A	C
ATOM	845	CA	ALA	A	126	52.803	6.284	41.903	1.00	8.07	A	C
ATOM	850	CA	ILE	A	127	55.283	6.769	44.795	1.00	8.60	A	C
ATOM	858	CA	THR	A	128	55.591	3.528	46.766	1.00	9.40	A	C
ATOM	865	CA	GLY	A	129	58.010	1.444	48.876	1.00	9.09	A	C
ATOM	869	CA	ALA	A	130	61.528	1.221	47.442	1.00	8.74	A	C
ATOM	874	CA	PRO	A	131	64.650	-0.773	48.532	1.00	9.45	A	C
ATOM	881	CA	GLY	A	132	66.719	0.579	51.405	1.00	9.13	A	C
ATOM	885	CA	THR	A	133	66.380	2.820	54.435	1.00	8.85	A	C
ATOM	892	CA	ILE	A	134	66.150	6.548	55.020	1.00	7.14	A	C

ATOM	900	CA	GLU	A	135	67.868	6.967	58.400	1.00	7.03	A	C
ATOM	909	CA	ALA	A	136	66.326	10.008	60.046	1.00	5.25	A	C
ATOM	914	CA	GLU	A	137	67.736	11.833	63.043	1.00	3.46	A	C
ATOM	923	CA	VAL	A	138	66.270	15.029	64.552	1.00	2.00	A	C
ATOM	930	CA	ALA	A	139	67.283	17.116	67.586	1.00	2.00	A	C
ATOM	935	CA	ALA	A	140	66.021	20.401	69.089	1.00	3.29	A	C
ATOM	940	CA	ALA	A	141	67.192	23.587	70.725	1.00	5.41	A	C
ATOM	945	CA	THR	A	142	64.774	26.112	72.324	1.00	3.98	A	C
ATOM	952	CA	ARG	A	143	63.747	27.685	69.007	1.00	3.05	A	C
ATOM	963	CA	SER	A	144	65.230	25.253	66.475	1.00	3.15	A	C
ATOM	969	CA	GLY	A	145	64.814	21.822	64.969	1.00	3.61	A	C
ATOM	973	CA	VAL	A	146	67.745	20.138	63.259	1.00	3.66	A	C
ATOM	980	CA	HIS	A	147	67.601	17.212	60.859	1.00	4.27	A	C
ATOM	990	CA	ARG	A	148	70.193	14.697	59.628	1.00	5.28	A	C
ATOM	1001	CA	TYR	A	149	69.133	12.182	56.930	1.00	5.88	A	C
ATOM	1013	CA	ALA	A	150	70.978	9.286	55.295	1.00	6.54	A	C
ATOM	1018	CA	PHE	A	151	69.444	8.138	51.980	1.00	6.34	A	C
ATOM	1029	CA	PRO	A	152	70.329	4.881	50.196	1.00	8.11	A	C
ATOM	1036	CA	ALA	A	153	73.284	5.138	47.799	1.00	9.27	A	C
ATOM	1041	CA	GLY	A	154	72.114	6.052	44.300	1.00	9.43	A	C
ATOM	1045	CA	SER	A	155	69.016	7.860	45.553	1.00	8.94	A	C
ATOM	1051	CA	THR	A	156	68.111	11.379	44.480	1.00	5.81	A	C
ATOM	1058	CA	PRO	A	157	67.363	12.771	47.997	1.00	5.54	A	C
ATOM	1065	CA	SER	A	158	64.501	15.181	48.463	1.00	5.58	A	C
ATOM	1071	CA	LEU	A	159	62.757	16.902	51.348	1.00	4.75	A	C
ATOM	1079	CA	VAL	A	160	59.189	18.092	50.985	1.00	3.15	A	C
ATOM	1086	CA	VAL	A	161	58.408	21.099	53.170	1.00	2.91	A	C
ATOM	1093	CA	ASP	A	162	54.597	21.001	53.529	1.00	2.92	A	C
ATOM	1101	CA	LEU	A	163	53.165	24.242	54.913	1.00	4.33	A	C
ATOM	1109	CA	GLU	A	164	49.518	23.198	54.922	1.00	4.22	A	C
ATOM	1118	CA	THR	A	165	49.840	20.473	57.636	1.00	3.08	A	C
ATOM	1125	CA	ASN	A	166	48.201	21.399	60.948	1.00	3.13	A	C
ATOM	1133	CA	ASN	A	167	46.701	19.356	63.804	1.00	3.44	A	C
ATOM	1141	CA	THR	A	168	43.479	21.366	63.648	1.00	4.11	A	C
ATOM	1148	CA	SER	A	169	43.334	24.170	61.080	1.00	2.77	A	C
ATOM	1154	CA	ARG	A	170	45.644	25.892	58.648	1.00	3.20	A	C
ATOM	1165	CA	ARG	A	171	44.592	29.537	58.189	1.00	2.85	A	C
ATOM	1176	CA	SER	A	172	47.387	30.959	56.027	1.00	2.36	A	C
ATOM	1182	CA	SER	A	173	50.992	30.215	55.065	1.00	3.42	A	C
ATOM	1188	CA	SER	A	174	53.845	31.585	52.935	1.00	4.21	A	C
ATOM	1194	CA	VAL	A	175	57.213	30.528	51.618	1.00	4.87	A	C
ATOM	1201	CA	GLN	A	176	60.036	32.533	50.050	1.00	7.10	A	C
ATOM	1210	CA	VAL	A	177	63.000	30.700	48.499	1.00	8.23	A	C
ATOM	1217	CA	GLU	A	178	66.645	31.960	48.440	1.00	10.90	A	C
ATOM	1226	CA	THR	A	179	69.583	30.187	46.804	1.00	9.85	A	C
ATOM	1233	CA	ARG	A	180	72.927	31.368	48.203	1.00	10.39	A	C
ATOM	1244	CA	ALA	A	181	76.419	31.485	46.632	1.00	11.40	A	C
ATOM	1249	CA	ASP	A	182	77.367	28.014	47.948	1.00	11.35	A	C
ATOM	1257	CA	GLY	A	183	74.201	26.531	46.431	1.00	9.02	A	C
ATOM	1261	CA	THR	A	184	72.333	25.942	49.723	1.00	6.71	A	C
ATOM	1268	CA	VAL	A	185	68.670	26.993	50.031	1.00	5.35	A	C
ATOM	1275	CA	GLU	A	186	66.959	29.077	52.696	1.00	5.35	A	C
ATOM	1284	CA	LEU	A	187	63.146	29.005	52.987	1.00	3.46	A	C
ATOM	1292	CA	SER	A	188	61.169	31.481	55.086	1.00	2.87	A	C
ATOM	1298	CA	GLY	A	189	57.690	32.795	55.787	1.00	2.92	A	C
ATOM	1302	CA	GLN	A	190	54.805	32.417	58.222	1.00	2.71	A	C
ATOM	1311	CA	VAL	A	191	52.276	29.832	59.268	1.00	2.84	A	C
ATOM	1318	CA	THR	A	192	48.954	30.792	60.850	1.00	3.69	A	C
ATOM	1325	CA	GLY	A	193	46.998	28.051	62.583	1.00	3.21	A	C
ATOM	1329	CA	TYR	A	194	44.116	27.757	64.995	1.00	3.16	A	C
ATOM	1341	CA	PHE	A	195	43.413	25.739	68.120	1.00	3.26	A	C
ATOM	1352	CA	TYR	A	196	40.408	25.930	70.460	1.00	3.84	A	C
ATOM	1364	CA	ASN	A	197	39.874	29.693	71.045	1.00	4.26	A	C
ATOM	1372	CA	ALA	A	198	42.510	31.491	69.033	1.00	3.45	A	C
ATOM	1377	CA	ALA	A	199	44.567	31.753	65.914	1.00	3.47	A	C
ATOM	1382	CA	TYR	A	200	48.369	32.096	66.243	1.00	2.36	A	C

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ATOM   1394  CA  THR A 201      51.191  33.045  63.858  1.00  2.69       A    C
ATOM   1401  CA  LEU A 202      54.816  31.843  63.819  1.00  2.11       A    C
ATOM   1409  CA  TYR A 203      57.621  32.892  61.467  1.00  2.45       A    C
ATOM   1421  CA  TYR A 204      60.210  30.396  60.264  1.00  2.82       A    C
ATOM   1433  CA  THR A 205      63.573  30.086  58.500  1.00  2.58       A    C
ATOM   1440  CA  ALA A 206      64.904  26.723  57.213  1.00  4.47       A    C
ATOM   1445  CA  ARG A 207      68.253  26.305  55.508  1.00  5.09       A    C
ATOM   1456  CA  THR A 208      69.773  23.209  53.912  1.00  4.88       A    C
ATOM   1463  CA  LEU A 209      73.404  22.419  54.654  1.00  5.26       A    C
ATOM   1471  CA  GLN A 210      73.983  20.900  51.175  1.00  6.01       A    C
ATOM   1480  CA  PRO A 211      73.274  22.391  47.732  1.00  6.91       A    C
ATOM   1487  CA  ALA A 212      69.689  21.962  46.560  1.00  7.18       A    C
ATOM   1492  CA  THR A 213      67.307  23.100  43.847  1.00  5.83       A    C
ATOM   1499  CA  VAL A 214      63.724  23.957  44.710  1.00  5.43       A    C
ATOM   1506  CA  GLN A 215      60.145  24.166  43.470  1.00  5.10       A    C
ATOM   1515  CA  THR A 216      57.130  25.576  45.286  1.00  4.16       A    C
ATOM   1522  CA  TRP A 217      53.372  25.146  45.243  1.00  3.72       A    C
ATOM   1536  CA  GLY A 218      50.356  27.288  46.105  1.00  3.16       A    C
ATOM   1540  CA  ASP A 219      46.606  26.736  46.322  1.00  3.69       A    C
ATOM   1548  CA  ASP A 220      46.180  25.735  42.659  1.00  3.99       A    C
ATOM   1556  CA  ASP A 221      48.330  22.647  43.374  1.00  5.99       A    C
ATOM   1564  CA  ARG A 222      50.800  23.609  40.598  1.00  6.95       A    C
ATOM   1575  CA  LEU A 223      54.426  22.727  41.314  1.00  6.51       A    C
ATOM   1583  CA  VAL A 224      56.418  25.552  39.779  1.00  7.29       A    C
ATOM   1590  CA  ASP A 225      59.828  27.203  39.638  1.00  8.47       A    C
ATOM   1598  CA  ALA A 226      58.537  30.421  41.281  1.00  8.13       A    C
ATOM   1603  CA  THR A 227      60.445  31.382  44.417  1.00  7.82       A    C
ATOM   1610  CA  ALA A 228      57.480  32.859  46.386  1.00  7.30       A    C
ATOM   1615  CA  GLN A 229      54.054  31.642  47.513  1.00  5.21       A    C
ATOM   1624  CA  ASP A 230      51.457  33.169  49.802  1.00  5.36       A    C
ATOM   1632  CA  GLY A 231      48.063  31.590  50.521  1.00  3.52       A    C
ATOM   1636  CA  VAL A 232      46.718  28.704  52.595  1.00  2.62       A    C
ATOM   1643  CA  ASP A 233      48.105  25.470  51.111  1.00  3.49       A    C
ATOM   1651  CA  THR A 234      51.701  26.281  50.149  1.00  3.46       A    C
ATOM   1658  CA  GLY A 235      54.937  24.312  50.148  1.00  3.13       A    C
ATOM   1662  CA  ALA A 236      58.416  23.735  48.763  1.00  3.15       A    C
ATOM   1667  CA  ILE A 237      60.286  20.673  47.495  1.00  3.80       A    C
ATOM   1675  CA  LEU A 238      64.059  20.549  47.934  1.00  4.57       A    C
ATOM   1683  CA  THR A 239      66.059  18.244  45.649  1.00  6.16       A    C
ATOM   1690  CA  PHE A 240      69.681  17.295  46.371  1.00  8.00       A    C
ATOM   1701  CA  ASP A 241      72.537  15.737  44.401  1.00 10.79       A    C
ATOM   1709  CA  PRO A 242      72.834  11.907  44.637  1.00 10.26       A    C
ATOM   1716  CA  ALA A 243      76.443  12.489  45.768  1.00  9.54       A    C
ATOM   1721  CA  ASP A 244      75.082  13.939  49.047  1.00  9.68       A    C
ATOM   1729  CA  ALA A 245      72.792  10.984  49.778  1.00  9.01       A    C
ATOM   1734  CA  GLY A 246      75.008   9.953  52.749  1.00  8.32       A    C
ATOM   1738  CA  GLU A 247      74.244  13.241  54.603  1.00  8.02       A    C
ATOM   1747  CA  ILE A 248      71.325  15.626  54.100  1.00  6.42       A    C
ATOM   1755  CA  GLY A 249      71.023  18.320  56.806  1.00  5.33       A    C
ATOM   1759  CA  LEU A 250      68.338  20.892  57.577  1.00  3.68       A    C
ATOM   1767  CA  GLN A 251      67.982  23.542  60.272  1.00  3.91       A    C
ATOM   1776  CA  VAL A 252      64.613  25.109  61.086  1.00  4.45       A    C
ATOM   1783  CA  THR A 253      64.148  28.007  63.522  1.00  4.13       A    C
ATOM   1790  CA  LEU A 254      60.850  29.555  64.744  1.00  3.15       A    C
ATOM   1798  CA  SER A 255      60.066  33.075  65.957  1.00  3.13       A    C
ATOM   1804  CA  PRO A 256      56.835  34.755  67.030  1.00  2.32       A    C
ATOM   1811  CA  VAL A 257      58.462  38.034  65.945  1.00  2.47       A    C
ATOM   1818  CA  SER A 258      59.667  37.831  62.318  1.00  3.37       A    C
ATOM   1824  CA  VAL A 259      61.516  35.892  59.699  1.00  3.32       A    C
ATOM   1831  CA  GLU A 260      64.595  38.024  60.217  1.00  4.54       A    C
ATOM   1840  CA  GLN A 261      64.385  37.533  63.976  1.00  2.88       A    C
ATOM   1849  CA  ALA A 262      64.235  33.748  63.289  1.00  3.15       A    C
ATOM   1854  CA  ARG A 263      67.445  34.085  61.196  1.00  4.21       A    C
ATOM   1865  CA  ILE A 264      69.210  35.928  64.012  1.00  4.33       A    C
ATOM   1873  CA  ASP A 265      67.932  33.358  66.544  1.00  4.14       A    C
ATOM   1881  CA  GLN A 266      69.289  30.623  64.311  1.00  6.08       A    C
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ATOM   1890  CA  GLN A 267      72.772  32.164  64.108  1.00  9.62      A    C
ATOM   1899  CA  VAL A 268      72.748  32.711  67.907  1.00  8.96      A    C
ATOM   1906  CA  GLU A 269      71.365  29.282  68.815  1.00  8.04      A    C
ATOM   1915  CA  LEU A 270      73.089  27.042  66.271  1.00  8.55      A    C
ATOM   1923  CA  GLY A 271      76.001  29.052  64.802  1.00 10.23      A    C
ATOM   1927  CA  ASP A 272      78.321  26.600  63.009  1.00 10.69      A    C
ATOM   1935  CA  LEU A 273      77.764  23.840  65.566  1.00  8.02      A    C
ATOM   1943  CA  SER A 274      77.383  20.316  64.224  1.00  5.99      A    C
ATOM   1949  CA  PHE A 275      74.219  18.210  64.582  1.00  4.80      A    C
ATOM   1960  CA  ASP A 276      75.912  16.069  67.289  1.00  5.78      A    C
ATOM   1968  CA  ALA A 277      76.925  19.139  69.337  1.00  5.08      A    C
ATOM   1973  CA  ILE A 278      73.442  20.669  69.150  1.00  5.84      A    C
ATOM   1981  CA  ARG A 279      71.924  17.315  70.206  1.00  6.83      A    C
ATOM   1992  CA  ASP A 280      74.549  16.902  72.944  1.00  7.77      A    C
ATOM   2000  CA  ARG A 281      74.023  20.429  74.293  1.00  7.74      A    C
ATOM   2011  CA  THR A 282      70.270  19.953  74.599  1.00  6.38      A    C
ATOM   2018  CA  ARG A 283      70.839  16.638  76.431  1.00  5.81      A    C
ATOM   2029  CA  ALA A 284      73.047  18.504  78.940  1.00  5.99      A    C
ATOM   2034  CA  GLU A 285      70.461  21.247  79.310  1.00  6.57      A    C
ATOM   2043  CA  TRP A 286      67.904  18.490  80.139  1.00  5.67      A    C
ATOM   2057  CA  ASN A 287      70.291  16.909  82.648  1.00  8.00      A    C
ATOM   2065  CA  ALA A 288      70.657  20.275  84.422  1.00  8.86      A    C
ATOM   2070  CA  THR A 289      66.862  20.740  84.464  1.00  7.09      A    C
ATOM   2077  CA  LEU A 290      66.138  17.180  85.630  1.00  6.19      A    C
ATOM   2085  CA  GLY A 291      69.085  17.378  88.069  1.00  6.65      A    C
ATOM   2089  CA  ARG A 292      67.121  19.931  90.104  1.00  6.77      A    C
ATOM   2100  CA  VAL A 293      65.530  16.844  91.707  1.00  8.09      A    C
ATOM   2107  CA  ALA A 294      67.845  14.070  92.912  1.00 10.40      A    C
ATOM   2112  CA  ILE A 295      66.318  10.811  94.046  1.00 13.23      A    C
ATOM   2120  CA  ASP A 296      67.534   7.879  96.121  1.00 14.69      A    C
ATOM   2128  CA  ALA A 297      65.001   5.043  95.685  1.00 12.88      A    C
ATOM   2133  CA  SER A 298      65.612   1.701  97.466  1.00 11.58      A    C
ATOM   2139  CA  THR A 299      64.657  -1.726  96.152  1.00  9.13      A    C
ATOM   2146  CA  ALA A 300      61.955  -1.728  98.846  1.00  7.00      A    C
ATOM   2151  CA  THR A 301      59.955   1.150  97.314  1.00  6.08      A    C
ATOM   2158  CA  ASP A 302      61.022   0.632  93.655  1.00  6.93      A    C
ATOM   2166  CA  PRO A 303      62.048  -3.016  93.116  1.00  7.98      A    C
ATOM   2173  CA  THR A 304      62.107  -2.745  89.277  1.00  8.90      A    C
ATOM   2180  CA  GLY A 305      63.438   0.816  88.893  1.00  8.26      A    C
ATOM   2184  CA  GLU A 306      60.285   1.808  86.935  1.00  8.98      A    C
ATOM   2193  CA  LEU A 307      59.007   4.206  89.571  1.00  6.57      A    C
ATOM   2201  CA  GLN A 308      62.236   6.260  89.308  1.00  7.75      A    C
ATOM   2210  CA  ARG A 309      61.928   6.228  85.486  1.00  7.83      A    C
ATOM   2221  CA  LEU A 310      58.276   7.252  85.828  1.00  6.95      A    C
ATOM   2229  CA  PHE A 311      59.288  10.140  88.071  1.00  5.21      A    C
ATOM   2240  CA  TYR A 312      61.933  11.475  85.641  1.00  4.28      A    C
ATOM   2252  CA  THR A 313      59.676  10.962  82.611  1.00  3.87      A    C
ATOM   2259  CA  HIS A 314      56.982  13.080  84.288  1.00  4.29      A    C
ATOM   2269  CA  LEU A 315      59.509  15.636  85.519  1.00  3.00      A    C
ATOM   2277  CA  TYR A 316      60.512  15.912  81.827  1.00  2.15      A    C
ATOM   2289  CA  ARG A 317      56.827  16.467  80.909  1.00  3.71      A    C
ATOM   2300  CA  MET A 318      56.497  19.172  83.611  1.00  6.35      A    C
ATOM   2308  CA  PHE A 319      58.967  21.419  81.712  1.00  7.83      A    C
ATOM   2319  CA  ALA A 320      57.045  21.807  78.404  1.00  7.53      A    C
ATOM   2324  CA  MET A 321      54.323  24.487  78.650  1.00  6.18      A    C
ATOM   2332  CA  PRO A 322      54.063  27.434  78.638  1.00  5.02      A    C
ATOM   2339  CA  MET A 323      56.762  27.568  75.935  1.00  4.44      A    C
ATOM   2347  CA  ASN A 324      59.593  30.069  75.619  1.00  3.49      A    C
ATOM   2355  CA  ALA A 325      57.989  32.716  73.341  1.00  2.49      A    C
ATOM   2360  CA  THR A 326      61.012  35.098  73.515  1.00  2.79      A    C
ATOM   2367  CA  SER A 327      63.597  35.861  70.819  1.00  3.68      A    C
ATOM   2373  CA  THR A 328      67.381  35.744  71.383  1.00  4.17      A    C
ATOM   2380  CA  SER A 329      67.191  39.550  71.284  1.00  4.95      A    C
ATOM   2386  CA  GLY A 330      64.860  39.602  74.327  1.00  4.52      A    C
ATOM   2390  CA  THR A 331      61.681  40.533  72.420  1.00  2.64      A    C
ATOM   2397  CA  TYR A 332      58.212  38.956  72.097  1.00  2.99      A    C
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ATOM   2409  CA  ARG A 333      55.039  39.623  70.103  1.00  4.36       A    C
ATOM   2420  CA  GLY A 334      52.050  40.974  71.967  1.00  4.85       A    C
ATOM   2424  CA  VAL A 335      48.352  40.362  71.328  1.00  5.79       A    C
ATOM   2431  CA  ASP A 336      48.362  43.923  69.904  1.00  8.91       A    C
ATOM   2439  CA  GLY A 337      50.391  42.488  67.010  1.00  8.05       A    C
ATOM   2443  CA  ALA A 338      53.464  44.524  67.878  1.00  7.17       A    C
ATOM   2448  CA  VAL A 339      56.967  43.729  69.093  1.00  6.49       A    C
ATOM   2455  CA  HIS A 340      57.792  44.405  72.780  1.00  8.62       A    C
ATOM   2465  CA  ALA A 341      60.735  44.008  75.137  1.00  9.13       A    C
ATOM   2470  CA  ALA A 342      60.679  41.217  77.711  1.00 11.07       A    C
ATOM   2475  CA  GLN A 343      62.952  43.339  79.907  1.00 14.61       A    C
ATOM   2484  CA  GLY A 344      64.997  41.352  82.439  1.00 14.36       A    C
ATOM   2488  CA  PHE A 345      62.907  38.172  82.163  1.00 11.18       A    C
ATOM   2499  CA  THR A 346      61.913  35.493  79.671  1.00  8.35       A    C
ATOM   2506  CA  TYR A 347      58.429  35.786  78.204  1.00  5.52       A    C
ATOM   2518  CA  TYR A 348      56.503  32.511  78.127  1.00  4.55       A    C
ATOM   2530  CA  ASP A 349      53.244  31.880  76.254  1.00  3.32       A    C
ATOM   2538  CA  SER A 350      50.780  29.020  75.499  1.00  3.95       A    C
ATOM   2544  CA  TRP A 351      48.175  28.588  78.184  1.00  3.88       A    C
ATOM   2558  CA  ALA A 352      45.515  26.000  79.064  1.00  3.39       A    C
ATOM   2563  CA  THR A 353      44.865  27.385  82.495  1.00  3.82       A    C
ATOM   2570  CA  TRP A 354      41.278  26.050  82.947  1.00  4.26       A    C
ATOM   2584  CA  ASP A 355      42.871  22.556  82.994  1.00  4.99       A    C
ATOM   2592  CA  ASP A 356      46.325  23.205  84.330  1.00  5.97       A    C
ATOM   2600  CA  PHE A 357      46.209  25.899  87.012  1.00  5.02       A    C
ATOM   2611  CA  ARG A 358      47.423  23.675  89.886  1.00  4.11       A    C
ATOM   2622  CA  LYS A 359      50.623  22.752  87.999  1.00  2.82       A    C
ATOM   2631  CA  PHE A 360      52.171  26.201  88.467  1.00  2.32       A    C
ATOM   2642  CA  SER A 361      52.008  25.888  92.261  1.00  2.68       A    C
ATOM   2648  CA  VAL A 362      54.293  22.814  91.937  1.00  3.61       A    C
ATOM   2655  CA  ILE A 363      56.639  24.444  89.399  1.00  3.43       A    C
ATOM   2663  CA  ALA A 364      57.066  27.142  92.096  1.00  3.80       A    C
ATOM   2668  CA  TYR A 365      58.855  24.692  94.414  1.00  4.70       A    C
ATOM   2680  CA  ILE A 366      60.869  22.863  91.729  1.00  6.01       A    C
ATOM   2688  CA  ASP A 367      62.106  25.826  89.627  1.00  5.57       A    C
ATOM   2696  CA  PRO A 368      61.194  29.124  91.362  1.00  3.96       A    C
ATOM   2703  CA  ALA A 369      62.922  31.367  88.734  1.00  3.74       A    C
ATOM   2708  CA  LEU A 370      61.088  29.740  85.833  1.00  3.88       A    C
ATOM   2716  CA  TYR A 371      57.804  30.009  87.729  1.00  4.80       A    C
ATOM   2728  CA  ARG A 372      58.430  33.689  88.384  1.00  5.45       A    C
ATOM   2739  CA  ASP A 373      59.035  34.310  84.651  1.00  6.19       A    C
ATOM   2747  CA  MET A 374      55.843  32.441  83.776  1.00  3.88       A    C
ATOM   2755  CA  VAL A 375      53.730  34.523  86.171  1.00  2.79       A    C
ATOM   2762  CA  GLN A 376      55.358  37.744  84.962  1.00  3.18       A    C
ATOM   2771  CA  SER A 377      54.574  36.606  81.413  1.00  3.14       A    C
ATOM   2777  CA  LEU A 378      50.953  35.908  82.336  1.00  3.14       A    C
ATOM   2785  CA  VAL A 379      50.799  39.454  83.766  1.00  3.57       A    C
ATOM   2792  CA  TYR A 380      52.193  40.950  80.508  1.00  4.06       A    C
ATOM   2804  CA  LEU A 381      49.694  38.961  78.456  1.00  4.18       A    C
ATOM   2812  CA  PHE A 382      46.697  40.475  80.286  1.00  4.57       A    C
ATOM   2823  CA  ALA A 383      48.397  43.881  80.475  1.00  6.03       A    C
ATOM   2828  CA  ASP A 384      48.684  43.708  76.664  1.00  7.44       A    C
ATOM   2836  CA  ALA A 385      44.974  42.882  76.223  1.00  9.01       A    C
ATOM   2841  CA  GLU A 386      44.199  45.935  78.362  1.00 10.91       A    C
ATOM   2850  CA  ALA A 387      46.670  48.106  76.365  1.00 12.41       A    C
ATOM   2855  CA  THR A 388      44.776  47.471  73.087  1.00 13.68       A    C
ATOM   2862  CA  GLY A 389      41.944  49.514  74.624  1.00 14.39       A    C
ATOM   2866  CA  THR A 390      39.452  47.191  72.889  1.00 15.63       A    C
ATOM   2873  CA  GLY A 391      38.019  45.522  76.019  1.00 14.99       A    C
ATOM   2877  CA  GLY A 392      37.896  42.282  73.993  1.00 13.79       A    C
ATOM   2881  CA  GLY A 393      38.759  38.874  75.470  1.00 11.07       A    C
ATOM   2885  CA  LEU A 394      42.017  37.084  74.740  1.00  7.81       A    C
ATOM   2893  CA  GLY A 395      40.142  34.863  72.238  1.00  7.24       A    C
ATOM   2897  CA  GLY A 396      39.767  37.812  69.847  1.00  7.80       A    C
ATOM   2901  CA  PHE A 397      43.479  38.330  69.213  1.00  7.11       A    C
ATOM   2912  CA  VAL A 398      46.038  36.458  67.145  1.00  5.79       A    C
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ATOM   2919  CA  HIS A 399      48.445  34.799  69.624  1.00  3.71       A    C
ATOM   2929  CA  SER A 400      52.295  34.534  69.502  1.00  3.42       A    C
ATOM   2935  CA  VAL A 401      52.383  30.703  69.819  1.00  2.51       A    C
ATOM   2942  CA  PRO A 402      49.744  27.945  69.645  1.00  3.03       A    C
ATOM   2949  CA  THR A 403      47.621  28.327  72.753  1.00  2.63       A    C
ATOM   2956  CA  VAL A 404      44.423  27.083  74.389  1.00  2.59       A    C
ATOM   2963  CA  ARG A 405      42.502  28.941  77.121  1.00  2.87       A    C
ATOM   2974  CA  TRP A 406      43.027  31.341  80.033  1.00  3.31       A    C
ATOM   2988  CA  GLU A 407      40.430  30.754  82.763  1.00  4.40       A    C
ATOM   2997  CA  ARG A 408      41.810  30.579  86.344  1.00  3.53       A    C
ATOM   3008  CA  SER A 409      44.708  32.938  85.445  1.00  3.56       A    C
ATOM   3014  CA  SER A 410      43.670  35.101  88.462  1.00  4.17       A    C
ATOM   3020  CA  VAL A 411      44.366  32.099  90.707  1.00  3.23       A    C
ATOM   3027  CA  VAL A 412      47.816  31.532  89.197  1.00  2.11       A    C
ATOM   3034  CA  VAL A 413      48.819  35.209  89.648  1.00  2.29       A    C
ATOM   3041  CA  ALA A 414      47.478  35.051  93.214  1.00  2.19       A    C
ATOM   3046  CA  ASP A 415      49.593  31.906  93.728  1.00  3.52       A    C
ATOM   3054  CA  ALA A 416      52.816  33.913  93.216  1.00  3.54       A    C
ATOM   3059  CA  ILE A 417      51.560  36.792  95.351  1.00  4.96       A    C
ATOM   3067  CA  ALA A 418      50.526  34.493  98.238  1.00  7.10       A    C
ATOM   3072  CA  LYS A 419      53.976  32.864  97.904  1.00  7.37       A    C
ATOM   3081  CA  GLY A 420      55.694  36.259  98.483  1.00  8.91       A    C
ATOM   3085  CA  PHE A 421      56.789  37.036  94.914  1.00  9.86       A    C
ATOM   3096  CA  ASP A 422      56.741  40.741  94.170  1.00 13.61       A    C
ATOM   3104  CA  GLY A 423      57.809  43.423  91.676  1.00 13.34       A    C
ATOM   3108  CA  PHE A 424      55.491  42.086  88.966  1.00 11.76       A    C
ATOM   3119  CA  ASP A 425      55.749  44.833  86.387  1.00 12.47       A    C
ATOM   3127  CA  ARG A 426      52.408  45.949  84.848  1.00 10.18       A    C
ATOM   3138  CA  LEU A 427      50.173  44.147  87.370  1.00  9.19       A    C
ATOM   3146  CA  ASP A 428      48.058  47.323  87.662  1.00 10.66       A    C
ATOM   3154  CA  GLU A 429      47.378  47.038  83.880  1.00 10.07       A    C
ATOM   3163  CA  ALA A 430      46.738  43.286  83.995  1.00  8.16       A    C
ATOM   3168  CA  TYR A 431      44.091  43.690  86.747  1.00  8.25       A    C
ATOM   3180  CA  PRO A 432      41.138  45.159  84.775  1.00  8.05       A    C
ATOM   3187  CA  ALA A 433      41.670  42.554  82.030  1.00  7.78       A    C
ATOM   3192  CA  LEU A 434      41.696  39.872  84.724  1.00  7.30       A    C
ATOM   3200  CA  GLN A 435      38.424  41.359  86.060  1.00  9.52       A    C
ATOM   3209  CA  ARG A 436      36.760  41.034  82.610  1.00  8.83       A    C
ATOM   3220  CA  LEU A 437      38.067  37.458  82.349  1.00  8.34       A    C
ATOM   3228  CA  VAL A 438      36.448  36.553  85.664  1.00  9.83       A    C
ATOM   3235  CA  GLY A 439      33.227  38.399  84.746  1.00  9.87       A    C
ATOM   3239  CA  GLN A 440      30.557  39.769  87.076  1.00 11.48       A    C
ATOM   3248  CA  TYR A 441      27.387  38.162  88.403  1.00  9.32       A    C
ATOM   3260  CA  SER A 442      24.326  39.771  86.747  1.00  9.01       A    C
ATOM   3266  CA  ALA A 443      21.930  41.944  88.804  1.00 10.00       A    C
ATOM   3271  CA  ASP A 444      19.645  38.962  89.504  1.00 11.36       A    C
ATOM   3279  CA  GLU A 445      22.683  36.814  90.345  1.00 10.65       A    C
ATOM   3288  CA  LEU A 446      24.057  39.420  92.752  1.00 12.13       A    C
ATOM   3296  CA  ARG A 447      20.688  39.484  94.519  1.00 14.84       A    C
ATOM   3307  CA  ARG A 448      20.411  35.689  94.956  1.00 13.37       A    C
ATOM   3318  CA  GLY A 449      24.148  34.933  95.289  1.00 11.12       A    C
ATOM   3322  CA  TYR A 450      24.570  32.356  92.478  1.00 11.01       A    C
ATOM   3334  CA  VAL A 451      24.024  31.514  88.794  1.00 10.44       A    C
ATOM   3341  CA  ALA A 452      20.597  29.813  88.469  1.00 11.06       A    C
ATOM   3346  CA  GLY A 453      20.832  26.118  87.493  1.00 10.92       A    C
ATOM   3350  CA  ASN A 454      24.597  26.415  86.920  1.00  9.68       A    C
ATOM   3358  CA  PRO A 455      26.517  25.184  90.002  1.00  9.01       A    C
ATOM   3365  CA  GLY A 456      29.710  24.813  87.923  1.00  7.30       A    C
ATOM   3369  CA  ALA A 457      29.902  28.429  86.804  1.00  5.98       A    C
ATOM   3374  CA  SER A 458      29.216  29.530  90.428  1.00  5.00       A    C
ATOM   3380  CA  VAL A 459      32.021  27.538  92.097  1.00  3.77       A    C
ATOM   3387  CA  GLN A 460      34.377  28.579  89.287  1.00  3.69       A    C
ATOM   3396  CA  ARG A 461      33.738  32.298  89.725  1.00  3.05       A    C
ATOM   3407  CA  GLY A 462      34.143  31.742  93.464  1.00  2.45       A    C
ATOM   3411  CA  TYR A 463      37.707  30.519  92.994  1.00  3.51       A    C
ATOM   3423  CA  ASP A 464      38.419  33.243  90.372  1.00  3.80       A    C
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ATOM   3431  CA  GLN A 465      37.202  35.909  92.790  1.00  4.82       A    C
ATOM   3440  CA  TYR A 466      39.300  34.526  95.621  1.00  5.23       A    C
ATOM   3452  CA  GLY A 467      42.325  34.871  93.265  1.00  5.67       A    C
ATOM   3456  CA  LEU A 468      41.385  38.365  92.150  1.00  6.17       A    C
ATOM   3464  CA  SER A 469      40.991  39.304  95.828  1.00  5.97       A    C
ATOM   3470  CA  VAL A 470      44.682  38.455  96.482  1.00  6.48       A    C
ATOM   3477  CA  ILE A 471      45.705  40.579  93.461  1.00  6.17       A    C
ATOM   3485  CA  ALA A 472      43.411  43.420  94.600  1.00  8.07       A    C
ATOM   3490  CA  ASP A 473      45.060  43.606  98.080  1.00 10.08       A    C
ATOM   3498  CA  GLU A 474      48.496  43.569  96.443  1.00 10.69       A    C
ATOM   3507  CA  LEU A 475      47.508  46.603  94.342  1.00 11.15       A    C
ATOM   3515  CA  GLY A 476      46.177  48.346  97.453  1.00 13.34       A    C
ATOM   3519  CA  LEU A 477      42.538  48.006  96.344  1.00 15.39       A    C
ATOM   3527  CA  THR A 478      41.434  47.034  99.867  1.00 17.62       A    C
ATOM   3534  CA  GLU A 479      37.723  47.742  99.394  1.00 18.74       A    C
ATOM   3543  CA  GLU A 480      37.595  45.763  96.110  1.00 16.33       A    C
ATOM   3552  CA  ALA A 481      39.372  42.864  97.813  1.00 13.75       A    C
ATOM   3557  CA  GLU A 482      36.715  42.720 100.595  1.00 14.63       A    C
ATOM   3566  CA  THR A 483      33.842  42.673  98.101  1.00 12.95       A    C
ATOM   3573  CA  LEU A 484      35.614  39.932  96.121  1.00 11.73       A    C
ATOM   3581  CA  ARG A 485      36.127  37.758  99.233  1.00 11.05       A    C
ATOM   3592  CA  GLU A 486      32.458  38.265 100.146  1.00 10.61       A    C
ATOM   3601  CA  GLN A 487      31.331  37.147  96.664  1.00  8.60       A    C
ATOM   3610  CA  ALA A 488      33.786  34.225  96.759  1.00  6.52       A    C
ATOM   3615  CA  SER A 489      32.029  32.893  99.875  1.00  7.12       A    C
ATOM   3621  CA  TRP A 490      28.661  32.726  98.010  1.00  7.33       A    C
ATOM   3635  CA  PRO A 491      28.980  29.421  96.072  1.00  6.73       A    C
ATOM   3642  CA  ILE A 492      29.748  27.439  99.257  1.00  8.58       A    C
ATOM   3650  CA  GLU A 493      27.034  29.091 101.368  1.00 11.10       A    C
ATOM   3659  CA  LYS A 494      24.283  29.217  98.744  1.00 10.38       A    C
ATOM   3668  CA  LEU A 495      24.772  25.992  96.727  1.00  8.08       A    C
ATOM   3676  CA  THR A 496      25.642  23.390  99.397  1.00  9.94       A    C
ATOM   3683  CA  LYS A 497      22.269  21.696  99.874  1.00 10.32       A    C
ATOM   3692  CA  PRO A 498      21.844  20.282 103.387  1.00  9.82       A    C
ATOM   3699  CA  GLY A 499      21.074  16.559 103.567  1.00 10.14       A    C
ATOM   3703  CA  ALA A 500      21.838  16.042  99.846  1.00 10.82       A    C
ATOM   3708  CA  TRP A 501      23.386  12.728 100.863  1.00 11.71       A    C
ATOM   3722  CA  THR A 502      22.581  10.696 104.006  1.00 12.62       A    C
ATOM   3729  CA  ALA A 503      25.365   8.647 105.597  1.00 13.78       A    C
ATOM   3734  CA  ALA A 504      24.951   4.994 106.737  1.00 15.02       A    C
ATOM   3739  CA  ASP A 505      24.357   6.130 110.325  1.00 14.83       A    C
ATOM   3747  CA  GLY A 506      21.856   8.861 109.305  1.00 12.52       A    C
ATOM   3751  CA  THR A 507      24.298  11.810 109.343  1.00 10.12       A    C
ATOM   3758  CA  GLN A 508      23.119  14.588 106.989  1.00  8.56       A    C
ATOM   3767  CA  VAL A 509      25.765  15.604 104.451  1.00  6.31       A    C
ATOM   3774  CA  GLY A 510      25.468  18.758 102.362  1.00  5.03       A    C
ATOM   3778  CA  LEU A 511      26.594  18.750  98.722  1.00  4.48       A    C
ATOM   3786  CA  LEU A 512      26.884  21.120  95.793  1.00  5.45       A    C
ATOM   3794  CA  THR A 513      23.470  21.012  94.071  1.00  7.09       A    C
ATOM   3801  CA  PRO A 514      21.941  23.109  91.250  1.00  7.88       A    C
ATOM   3808  CA  ARG A 515      19.517  25.737  92.573  1.00  9.63       A    C
ATOM   3819  CA  ALA A 516      16.670  27.438  90.743  1.00 11.40       A    C
ATOM   3824  CA  ALA A 517      16.201  31.213  90.509  1.00 13.83       A    C
ATOM   3829  CA  ASP A 518      13.518  31.125  93.261  1.00 16.58       A    C
ATOM   3837  CA  GLY A 519      15.865  29.277  95.648  1.00 16.47       A    C
ATOM   3841  CA  SER A 520      14.202  25.852  95.069  1.00 15.99       A    C
ATOM   3847  CA  TRP A 521      16.785  23.089  94.870  1.00 13.14       A    C
ATOM   3861  CA  GLN A 522      16.878  21.329  91.494  1.00 12.01       A    C
ATOM   3870  CA  SER A 523      16.780  17.550  91.127  1.00 12.74       A    C
ATOM   3876  CA  ALA A 524      20.170  15.972  90.267  1.00 11.18       A    C
ATOM   3881  CA  ASP A 525      22.087  12.671  90.488  1.00  8.84       A    C
ATOM   3889  CA  HIS A 526      25.271  13.887  92.225  1.00  6.57       A    C
ATOM   3899  CA  ALA A 527      27.293  11.003  90.717  1.00  6.14       A    C
ATOM   3904  CA  LYS A 528      26.151  11.481  87.106  1.00  7.50       A    C
ATOM   3913  CA  PHE A 529      28.818  12.767  84.690  1.00  7.13       A    C
ATOM   3924  CA  GLU A 530      27.867  16.202  83.304  1.00  7.91       A    C
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ATOM   3933  CA  ALA A 531      24.533  16.513  85.106  1.00  8.44      A    C
ATOM   3938  CA  ALA A 532      23.397  20.032  86.170  1.00  7.77      A    C
ATOM   3943  CA  GLY A 533      25.194  21.889  83.332  1.00  6.76      A    C
ATOM   3947  CA  LEU A 534      28.619  20.734  84.578  1.00  5.97      A    C
ATOM   3955  CA  TYR A 535      31.682  20.411  82.372  1.00  8.46      A    C
ATOM   3967  CA  GLN A 536      33.627  17.123  82.410  1.00  6.34      A    C
ATOM   3976  CA  GLY A 537      32.521  16.050  85.901  1.00  4.04      A    C
ATOM   3980  CA  THR A 538      29.936  15.281  88.564  1.00  3.50      A    C
ATOM   3987  CA  LEU A 539      28.500  17.232  91.498  1.00  3.71      A    C
ATOM   3995  CA  TRP A 540      30.500  15.072  93.986  1.00  3.80      A    C
ATOM   4009  CA  GLN A 541      33.680  16.012  92.073  1.00  3.42      A    C
ATOM   4018  CA  TYR A 542      32.808  19.714  91.708  1.00  4.03      A    C
ATOM   4030  CA  HIS A 543      31.606  19.795  95.352  1.00  4.44      A    C
ATOM   4040  CA  TRP A 544      35.221  20.315  96.537  1.00  4.40      A    C
ATOM   4054  CA  TYR A 545      36.045  23.019  93.950  1.00  4.18      A    C
ATOM   4066  CA  ASP A 546      36.276  26.024  96.237  1.00  5.25      A    C
ATOM   4074  CA  ALA A 547      39.546  24.793  97.671  1.00  5.51      A    C
ATOM   4079  CA  TYR A 548      40.358  28.217  99.183  1.00  6.10      A    C
ATOM   4091  CA  ASP A 549      37.753  27.586 101.917  1.00  6.22      A    C
ATOM   4099  CA  MET A 550      37.554  24.017 103.177  1.00  6.61      A    C
ATOM   4107  CA  ASP A 551      36.549  25.382 106.586  1.00  8.26      A    C
ATOM   4115  CA  ALA A 552      33.422  27.067 105.225  1.00  7.80      A    C
ATOM   4120  CA  LEU A 553      32.800  24.021 103.028  1.00  7.77      A    C
ATOM   4128  CA  VAL A 554      32.983  21.675 106.066  1.00  8.48      A    C
ATOM   4135  CA  GLU A 555      30.421  23.906 107.886  1.00 10.05      A    C
ATOM   4144  CA  ALA A 556      28.101  24.172 104.869  1.00  8.14      A    C
ATOM   4149  CA  MET A 557      28.262  20.355 104.586  1.00  7.75      A    C
ATOM   4157  CA  GLY A 558      26.833  20.080 108.112  1.00  7.77      A    C
ATOM   4161  CA  GLY A 559      29.995  19.989 110.230  1.00  8.36      A    C
ATOM   4165  CA  HIS A 560      33.086  17.891 110.775  1.00 10.24      A    C
ATOM   4175  CA  GLU A 561      31.496  14.448 111.036  1.00 10.61      A    C
ATOM   4184  CA  ALA A 562      29.420  15.118 107.900  1.00  9.17      A    C
ATOM   4189  CA  ALA A 563      32.594  16.099 105.943  1.00  7.47      A    C
ATOM   4194  CA  ARG A 564      34.534  13.129 107.304  1.00  6.15      A    C
ATOM   4205  CA  LEU A 565      31.813  10.683 106.236  1.00  5.27      A    C
ATOM   4213  CA  GLY A 566      31.408  12.469 102.857  1.00  4.45      A    C
ATOM   4217  CA  MET A 567      35.136  12.086 102.137  1.00  5.05      A    C
ATOM   4225  CA  ARG A 568      35.000   8.412 103.020  1.00  6.55      A    C
ATOM   4236  CA  HIS A 569      31.985   7.943 100.689  1.00  7.31      A    C
ATOM   4246  CA  MET A 570      33.786   9.924  97.906  1.00  7.92      A    C
ATOM   4254  CA  PHE A 571      36.388   7.150  97.840  1.00  7.04      A    C
ATOM   4265  CA  GLY A 572      34.058   4.168  98.426  1.00  8.17      A    C
ATOM   4269  CA  GLU A 573      35.790   3.316 101.736  1.00 10.14      A    C
ATOM   4278  CA  HIS A 574      32.693   1.377 102.888  1.00 11.27      A    C
ATOM   4288  CA  ALA A 575      32.914  -0.845  99.770  1.00 11.91      A    C
ATOM   4293  CA  PRO A 576      36.615  -1.198  98.736  1.00 13.14      A    C
ATOM   4300  CA  ASP A 577      35.923  -3.909  96.131  1.00 13.69      A    C
ATOM   4308  CA  ASP A 578      32.994  -2.108  94.404  1.00 12.41      A    C
ATOM   4316  CA  GLY A 579      34.247  -0.097  91.423  1.00 11.12      A    C
ATOM   4320  CA  LYS A 580      30.905   1.748  91.259  1.00 11.21      A    C
ATOM   4329  CA  ALA A 581      31.370   3.276  94.757  1.00  8.19      A    C
ATOM   4334  CA  MET A 582      34.358   5.303  93.506  1.00  5.86      A    C
ATOM   4342  CA  LEU A 583      33.022   8.889  93.198  1.00  4.23      A    C
ATOM   4350  CA  HIS A 584      36.434  10.466  92.671  1.00  3.37      A    C
ATOM   4360  CA  SER A 585      37.816  10.665  89.125  1.00  3.12      A    C
ATOM   4366  CA  ASN A 586      41.508  10.091  88.359  1.00  3.90      A    C
ATOM   4374  CA  ALA A 587      41.103  10.824  84.638  1.00  5.72      A    C
ATOM   4379  CA  ASN A 588      40.425  14.577  84.853  1.00  7.03      A    C
ATOM   4387  CA  GLU A 589      41.649  17.614  86.824  1.00  7.17      A    C
ATOM   4396  CA  ILE A 590      38.295  18.647  88.338  1.00  7.24      A    C
ATOM   4404  CA  ASP A 591      38.863  16.848  91.650  1.00  7.24      A    C
ATOM   4412  CA  LEU A 592      42.668  16.421  91.471  1.00  6.70      A    C
ATOM   4420  CA  GLN A 593      42.981  17.626  95.053  1.00  4.59      A    C
ATOM   4429  CA  ALA A 594      40.356  15.206  96.428  1.00  4.71      A    C
ATOM   4434  CA  PRO A 595      42.784  12.503  97.633  1.00  5.03      A    C
ATOM   4441  CA  TYR A 596      44.506  15.069  99.845  1.00  6.02      A    C
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ATOM   4453  CA  LEU A 597      41.304  16.226 101.591  1.00  4.94       A     C
ATOM   4461  CA  PHE A 598      41.417  13.474 104.213  1.00  5.47       A     C
ATOM   4472  CA  ASN A 599      44.037  15.684 105.929  1.00  6.53       A     C
ATOM   4480  CA  TYR A 600      41.176  18.148 106.491  1.00  7.92       A     C
ATOM   4492  CA  THR A 601      38.801  15.556 107.938  1.00  9.25       A     C
ATOM   4499  CA  GLY A 602      41.334  14.393 110.555  1.00  9.27       A     C
ATOM   4503  CA  GLU A 603      42.259  11.247 108.634  1.00  8.63       A     C
ATOM   4512  CA  PRO A 604      45.684  11.982 107.132  1.00  7.11       A     C
ATOM   4519  CA  SER A 605      46.475   8.224 106.915  1.00  5.46       A     C
ATOM   4525  CA  LEU A 606      43.781   7.928 104.201  1.00  4.96       A     C
ATOM   4533  CA  THR A 607      45.390  10.729 102.175  1.00  4.57       A     C
ATOM   4540  CA  GLN A 608      48.682   8.824 102.399  1.00  5.02       A     C
ATOM   4549  CA  LYS A 609      47.008   5.602 101.265  1.00  5.44       A     C
ATOM   4558  CA  TRP A 610      45.214   7.208  98.331  1.00  5.42       A     C
ATOM   4572  CA  ALA A 611      48.211   9.266  97.205  1.00  6.31       A     C
ATOM   4577  CA  ARG A 612      50.436   6.184  97.099  1.00  5.71       A     C
ATOM   4588  CA  ALA A 613      47.643   4.074  95.492  1.00  4.20       A     C
ATOM   4593  CA  ILE A 614      46.445   6.379  92.691  1.00  4.67       A     C
ATOM   4601  CA  TYR A 615      49.973   7.212  91.557  1.00  4.85       A     C
ATOM   4613  CA  THR A 616      51.897   3.953  92.071  1.00  4.62       A     C
ATOM   4620  CA  LYS A 617      49.365   1.088  92.368  1.00  6.36       A     C
ATOM   4629  CA  GLU A 618      46.132  -0.236  90.829  1.00  7.91       A     C
ATOM   4638  CA  THR A 619      42.939   1.583  91.795  1.00  6.88       A     C
ATOM   4645  CA  TRP A 620      39.227   1.357  91.008  1.00  7.46       A     C
ATOM   4659  CA  ASN A 621      38.296   3.692  88.170  1.00  6.73       A     C
ATOM   4667  CA  ARG A 622      34.663   4.574  87.576  1.00  4.87       A     C
ATOM   4678  CA  TYR A 623      35.087   7.709  85.473  1.00  5.03       A     C
ATOM   4690  CA  ILE A 624      36.716   8.661  82.149  1.00  5.64       A     C
ATOM   4698  CA  ALA A 625      37.316  12.291  81.127  1.00  6.35       A     C
ATOM   4703  CA  THR A 626      34.590  12.516  78.472  1.00  6.19       A     C
ATOM   4710  CA  GLY A 627      31.208  10.937  77.589  1.00  5.93       A     C
ATOM   4714  CA  SER A 628      32.592   7.840  75.913  1.00  7.00       A     C
ATOM   4720  CA  SER A 629      35.720   6.302  74.355  1.00  9.77       A     C
ATOM   4726  CA  SER A 630      36.292   3.632  71.688  1.00 11.33       A     C
ATOM   4732  CA  ALA A 631      39.492   2.767  73.559  1.00 10.90       A     C
ATOM   4737  CA  VAL A 632      37.659   1.102  76.492  1.00  8.53       A     C
ATOM   4744  CA  PRO A 633      34.094  -0.107  77.097  1.00  7.28       A     C
ATOM   4751  CA  SER A 634      32.472   3.099  78.345  1.00  5.04       A     C
ATOM   4757  CA  GLY A 635      29.414   5.345  78.326  1.00  4.96       A     C
ATOM   4761  CA  GLY A 636      27.832   8.244  80.176  1.00  6.17       A     C
ATOM   4765  CA  GLY A 637      31.304   9.416  81.298  1.00  5.99       A     C
ATOM   4769  CA  GLU A 638      32.099   6.071  82.923  1.00  5.01       A     C
ATOM   4778  CA  PHE A 639      34.109   2.868  82.500  1.00  4.24       A     C
ATOM   4789  CA  THR A 640      31.342   0.261  81.956  1.00  5.80       A     C
ATOM   4796  CA  PRO A 641      32.109  -1.741  83.969  1.00  6.76       A     C
ATOM   4803  CA  PRO A 642      34.393   0.103  86.417  1.00  8.12       A     C
ATOM   4810  CA  LEU A 643      38.016  -0.971  85.969  1.00  9.82       A     C
ATOM   4818  CA  LYS A 644      40.825  -1.805  88.435  1.00 11.06       A     C
ATOM   4827  CA  THR A 645      43.998  -0.565  86.793  1.00  8.37       A     C
ATOM   4834  CA  LYS A 646      47.067   1.637  87.273  1.00  7.54       A     C
ATOM   4843  CA  VAL A 647      46.307   5.272  86.488  1.00  5.75       A     C
ATOM   4850  CA  TYR A 648      49.922   5.925  85.527  1.00  5.56       A     C
ATOM   4862  CA  ARG A 649      51.964   3.328  83.533  1.00  7.76       A     C
ATOM   4873  CA  LEU A 650      55.512   3.322  82.177  1.00  6.76       A     C
ATOM   4881  CA  ASP A 651      54.026   2.407  78.809  1.00  6.42       A     C
ATOM   4889  CA  PRO A 652      53.043   4.126  75.570  1.00  5.92       A     C
ATOM   4896  CA  ARG A 653      49.549   3.680  77.020  1.00  4.60       A     C
ATOM   4907  CA  GLY A 654      50.724   6.058  79.774  1.00  4.89       A     C
ATOM   4911  CA  MET A 655      47.517   7.356  81.356  1.00  4.93       A     C
ATOM   4919  CA  LEU A 656      43.963   6.075  81.567  1.00  3.04       A     C
ATOM   4927  CA  PRO A 657      42.105   6.134  78.251  1.00  3.10       A     C
ATOM   4934  CA  THR A 658      40.754   9.734  77.676  1.00  3.53       A     C
ATOM   4941  CA  MET A 659      43.088  11.046  80.398  1.00  3.65       A     C
ATOM   4949  CA  ASP A 660      44.895  13.859  78.555  1.00  3.95       A     C
ATOM   4957  CA  ASN A 661      48.031  15.161  80.276  1.00  3.15       A     C
ATOM   4965  CA  ASP A 662      46.843  18.761  79.522  1.00  2.87       A     C
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ATOM	4973	CA	ALA	A	663	50.075	20.739	79.098	1.00	3.12	A	C
ATOM	4978	CA	GLY	A	664	51.894	18.459	81.548	1.00	2.70	A	C
ATOM	4982	CA	THR	A	665	49.328	18.721	84.376	1.00	2.81	A	C
ATOM	4989	CA	MET	A	666	48.910	14.993	85.026	1.00	2.55	A	C
ATOM	4997	CA	SER	A	667	52.753	14.620	84.897	1.00	2.87	A	C
ATOM	5003	CA	THR	A	668	53.193	17.564	87.294	1.00	3.50	A	C
ATOM	5010	CA	MET	A	669	50.719	16.032	89.771	1.00	2.90	A	C
ATOM	5018	CA	PHE	A	670	52.751	12.810	89.639	1.00	2.90	A	C
ATOM	5029	CA	VAL	A	671	55.921	14.716	90.519	1.00	3.29	A	C
ATOM	5036	CA	ALA	A	672	54.049	16.446	93.385	1.00	3.04	A	C
ATOM	5041	CA	ALA	A	673	52.740	13.126	94.733	1.00	3.21	A	C
ATOM	5046	CA	ALA	A	674	56.289	11.665	94.548	1.00	4.16	A	C
ATOM	5051	CA	VAL	A	675	57.770	14.572	96.510	1.00	3.68	A	C
ATOM	5058	CA	GLY	A	676	54.729	14.329	98.773	1.00	3.81	A	C
ATOM	5062	CA	LEU	A	677	53.628	17.976	98.689	1.00	3.63	A	C
ATOM	5070	CA	PHE	A	678	50.401	18.865	96.910	1.00	4.98	A	C
ATOM	5081	CA	PRO	A	679	48.736	22.236	96.308	1.00	4.89	A	C
ATOM	5088	CA	VAL	A	680	45.131	21.802	97.449	1.00	3.54	A	C
ATOM	5095	CA	THR	A	681	44.815	25.594	97.517	1.00	3.01	A	C
ATOM	5102	CA	ALA	A	682	46.410	27.062	94.421	1.00	2.78	A	C
ATOM	5107	CA	GLY	A	683	46.558	30.790	95.067	1.00	4.10	A	C
ATOM	5111	CA	SER	A	684	47.895	30.234	98.585	1.00	5.30	A	C
ATOM	5117	CA	SER	A	685	51.390	29.528	99.913	1.00	6.30	A	C
ATOM	5123	CA	GLN	A	686	50.476	26.083	101.310	1.00	5.66	A	C
ATOM	5132	CA	PHE	A	687	51.101	22.447	100.320	1.00	5.37	A	C
ATOM	5143	CA	GLN	A	688	49.438	19.356	101.748	1.00	4.94	A	C
ATOM	5152	CA	VAL	A	689	51.517	16.390	102.936	1.00	5.79	A	C
ATOM	5159	CA	GLY	A	690	50.928	13.088	101.117	1.00	6.69	A	C
ATOM	5163	CA	SER	A	691	52.974	9.889	100.906	1.00	7.27	A	C
ATOM	5169	CA	PRO	A	692	56.528	10.626	99.669	1.00	6.85	A	C
ATOM	5176	CA	PHE	A	693	57.581	7.765	97.347	1.00	6.34	A	C
ATOM	5187	CA	PHE	A	694	61.346	7.747	97.796	1.00	6.87	A	C
ATOM	5198	CA	ASP	A	695	63.891	7.202	100.575	1.00	7.56	A	C
ATOM	5206	CA	SER	A	696	65.365	10.632	99.830	1.00	6.91	A	C
ATOM	5212	CA	THR	A	697	64.278	13.400	97.424	1.00	7.09	A	C
ATOM	5219	CA	THR	A	698	66.465	16.572	97.123	1.00	7.46	A	C
ATOM	5226	CA	ILE	A	699	65.459	19.752	95.308	1.00	6.95	A	C
ATOM	5234	CA	THR	A	700	68.553	21.914	94.670	1.00	8.40	A	C
ATOM	5241	CA	TYR	A	701	67.913	25.630	94.091	1.00	9.41	A	C
ATOM	5253	CA	ASP	A	702	69.971	28.028	91.946	1.00	11.48	A	C
ATOM	5261	CA	ASP	A	703	72.068	29.199	94.915	1.00	13.97	A	C
ATOM	5269	CA	GLY	A	704	73.018	25.617	95.847	1.00	13.70	A	C
ATOM	5273	CA	SER	A	705	70.765	25.419	98.907	1.00	12.46	A	C
ATOM	5279	CA	ALA	A	706	68.419	22.383	98.854	1.00	10.18	A	C
ATOM	5284	CA	PHE	A	707	65.052	21.131	100.137	1.00	7.55	A	C
ATOM	5295	CA	THR	A	708	65.351	17.581	101.387	1.00	7.30	A	C
ATOM	5302	CA	VAL	A	709	62.397	15.352	102.091	1.00	7.65	A	C
ATOM	5309	CA	THR	A	710	63.206	11.874	103.424	1.00	8.06	A	C
ATOM	5316	CA	ALA	A	711	60.926	8.889	103.973	1.00	8.76	A	C
ATOM	5321	CA	ASP	A	712	62.785	6.541	106.270	1.00	10.03	A	C
ATOM	5329	CA	GLY	A	713	61.790	2.931	105.687	1.00	7.18	A	C
ATOM	5333	CA	VAL	A	714	59.420	3.754	102.770	1.00	5.21	A	C
ATOM	5340	CA	SER	A	715	58.461	0.754	100.621	1.00	5.75	A	C
ATOM	5346	CA	GLU	A	716	55.621	-0.434	98.399	1.00	7.40	A	C
ATOM	5355	CA	ASP	A	717	53.911	-1.492	101.619	1.00	7.77	A	C
ATOM	5363	CA	ALA	A	718	55.257	1.143	103.999	1.00	5.28	A	C
ATOM	5368	CA	PHE	A	719	53.472	4.224	102.665	1.00	3.86	A	C
ATOM	5379	CA	TYR	A	720	51.935	5.573	105.926	1.00	5.07	A	C
ATOM	5391	CA	VAL	A	721	53.647	8.305	107.943	1.00	6.16	A	C
ATOM	5398	CA	GLN	A	722	54.378	7.196	111.544	1.00	8.68	A	C
ATOM	5407	CA	SER	A	723	56.107	10.362	112.750	1.00	9.44	A	C
ATOM	5413	CA	ALA	A	724	57.936	13.385	111.311	1.00	8.65	A	C
ATOM	5418	CA	THR	A	725	60.561	16.054	112.006	1.00	8.30	A	C
ATOM	5425	CA	LEU	A	726	61.170	19.486	110.467	1.00	8.74	A	C
ATOM	5433	CA	ASP	A	727	64.804	20.662	110.723	1.00	9.93	A	C
ATOM	5441	CA	GLY	A	728	65.330	18.182	113.597	1.00	11.60	A	C

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ATOM   5445  CA  ALA A 729      62.241  19.122 115.635  1.00 11.25      A    C
ATOM   5450  CA  THR A 730      58.993  17.157 116.102  1.00 10.67      A    C
ATOM   5457  CA  PHE A 731      56.579  18.068 113.320  1.00  9.05      A    C
ATOM   5468  CA  GLY A 732      52.846  17.319 113.474  1.00  8.76      A    C
ATOM   5472  CA  ASN A 733      51.196  19.402 110.742  1.00  8.99      A    C
ATOM   5480  CA  THR A 734      49.869  17.843 107.528  1.00  9.35      A    C
ATOM   5487  CA  TRP A 735      50.725  20.969 105.477  1.00  8.91      A    C
ATOM   5501  CA  VAL A 736      53.901  22.986 104.955  1.00  8.70      A    C
ATOM   5508  CA  ASP A 737      54.483  26.555 103.781  1.00  8.20      A    C
ATOM   5516  CA  TYR A 738      56.186  27.338 100.476  1.00  6.61      A    C
ATOM   5528  CA  ALA A 739      58.753  29.427 102.391  1.00  6.41      A    C
ATOM   5533  CA  THR A 740      59.787  26.356 104.396  1.00  7.06      A    C
ATOM   5540  CA  VAL A 741      60.397  24.354 101.242  1.00  6.62      A    C
ATOM   5547  CA  VAL A 742      62.422  26.857  99.172  1.00  7.73      A    C
ATOM   5554  CA  GLY A 743      64.172  27.894 102.414  1.00  9.90      A    C
ATOM   5558  CA  GLY A 744      65.997  24.543 102.207  1.00  9.66      A    C
ATOM   5562  CA  ALA A 745      64.348  22.686 105.078  1.00  9.46      A    C
ATOM   5567  CA  ASP A 746      64.950  19.052 106.107  1.00  9.46      A    C
ATOM   5575  CA  LEU A 747      61.574  17.315 106.252  1.00  7.98      A    C
ATOM   5583  CA  ALA A 748      62.092  13.775 107.535  1.00  8.59      A    C
ATOM   5588  CA  PHE A 749      59.312  11.203 107.659  1.00  9.99      A    C
ATOM   5599  CA  ARG A 750      59.298   7.807 109.398  1.00 11.09      A    C
ATOM   5610  CA  MET A 751      57.231   5.392 107.265  1.00  8.36      A    C
ATOM   5618  CA  GLY A 752      55.426   2.175 108.214  1.00  8.95      A    C
ATOM   5622  CA  GLU A 753      53.025  -0.439 106.937  1.00 10.36      A    C
ATOM   5631  CA  GLN A 754      50.077   0.533 109.170  1.00 10.20      A    C
ATOM   5640  CA  PRO A 755      48.009   3.743 109.500  1.00  9.59      A    C
ATOM   5647  CA  SER A 756      49.021   5.965 112.430  1.00 10.96      A    C
ATOM   5653  CA  ASP A 757      47.455   8.970 114.180  1.00 12.99      A    C
ATOM   5661  CA  TRP A 758      50.369  11.238 113.073  1.00 11.54      A    C
ATOM   5675  CA  GLY A 759      49.073  14.673 112.067  1.00 12.17      A    C
ATOM   5679  CA  THR A 760      45.608  14.275 113.614  1.00 12.83      A    C
ATOM   5686  CA  ASP A 761      46.374  17.270 115.851  1.00 13.13      A    C
ATOM   5694  CA  THR A 762      47.486  19.473 112.939  1.00 10.45      A    C
ATOM   5701  CA  ALA A 763      47.395  23.279 113.167  1.00  9.30      A    C
ATOM   5706  CA  PRO A 764      44.545  24.274 110.760  1.00  8.86      A    C
ATOM   5713  CA  ALA A 765      45.404  24.788 107.092  1.00  8.11      A    C
ATOM   5718  CA  PHE A 766      44.495  27.881 105.084  1.00  9.09      A    C
ATOM   5729  CA  SER A 767      40.845  28.777 104.561  1.00  9.56      A    C
ATOM   5735  CA  MET A 768      39.792  32.266 103.433  1.00 11.12      A    C
ATOM   5743  CA  SER A 769      37.000  32.501 106.061  1.00 14.28      A    C
ATOM   5749  CA  THR A 770      39.217  31.636 109.046  1.00 17.50      A    C
ATOM   5756  CA  ALA A 771      42.527  33.224 107.955  1.00 19.68      A    C
ATOM   5761  CA  ASP B   8      33.160  32.500 141.172  1.00 18.72      B    C
ATOM   5769  CA  TYR B   9      29.570  31.506 140.304  1.00 14.20      B    C
ATOM   5781  CA  ALA B  10      28.422  31.895 143.925  1.00 10.68      B    C
ATOM   5786  CA  SER B  11      29.320  35.614 143.693  1.00 10.07      B    C
ATOM   5792  CA  LEU B  12      26.696  36.062 140.938  1.00  8.36      B    C
ATOM   5800  CA  VAL B  13      23.923  34.801 143.242  1.00  6.94      B    C
ATOM   5807  CA  ASP B  14      21.880  37.475 145.012  1.00  6.81      B    C
ATOM   5815  CA  VAL B  15      20.179  35.726 147.955  1.00  4.17      B    C
ATOM   5822  CA  PHE B  16      18.230  38.889 148.802  1.00  3.40      B    C
ATOM   5833  CA  VAL B  17      16.289  38.686 145.547  1.00  3.53      B    C
ATOM   5840  CA  GLY B  18      12.666  38.026 146.520  1.00  4.03      B    C
ATOM   5844  CA  THR B  19      13.196  38.689 150.262  1.00  5.26      B    C
ATOM   5851  CA  GLU B  20      10.979  41.797 150.516  1.00  5.53      B    C
ATOM   5860  CA  GLY B  21       7.349  41.901 151.577  1.00  6.87      B    C
ATOM   5864  CA  ASP B  22       5.019  39.846 149.439  1.00  6.61      B    C
ATOM   5872  CA  PHE B  23       7.350  39.730 146.400  1.00  5.51      B    C
ATOM   5883  CA  GLY B  24       8.458  36.090 146.362  1.00  4.07      B    C
ATOM   5887  CA  ASN B  25       8.571  34.746 149.915  1.00  2.81      B    C
ATOM   5895  CA  ASP B  26      12.206  33.663 149.535  1.00  3.13      B    C
ATOM   5903  CA  MET B  27      14.936  33.714 152.197  1.00  4.16      B    C
ATOM   5911  CA  PRO B  28      18.521  35.051 152.473  1.00  3.52      B    C
ATOM   5918  CA  ALA B  29      19.101  32.077 154.801  1.00  2.82      B    C
ATOM   5923  CA  ALA B  30      22.436  30.302 154.790  1.00  2.98      B    C
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ATOM   5928  CA  GLN B  31      21.896  26.852 153.161  1.00  4.61       B     C
ATOM   5937  CA  ALA B  32      23.671  24.106 151.121  1.00  5.14       B     C
ATOM   5942  CA  PRO B  33      22.280  22.821 147.805  1.00  6.54       B     C
ATOM   5949  CA  ASN B  34      18.900  21.202 148.694  1.00  5.61       B     C
ATOM   5957  CA  GLY B  35      19.876  21.616 152.349  1.00  4.62       B     C
ATOM   5961  CA  LEU B  36      17.780  20.633 155.336  1.00  5.14       B     C
ATOM   5969  CA  ALA B  37      19.361  23.299 157.533  1.00  3.87       B     C
ATOM   5974  CA  LYS B  38      18.219  26.746 156.507  1.00  3.49       B     C
ATOM   5983  CA  VAL B  39      19.767  29.259 158.889  1.00  3.32       B     C
ATOM   5990  CA  ASN B  40      17.444  32.228 158.346  1.00  3.22       B     C
ATOM   5998  CA  PRO B  41      17.676  35.552 160.107  1.00  3.73       B     C
ATOM   6005  CA  ARG B  42      14.314  36.534 161.600  1.00  3.05       B     C
ATOM   6016  CA  THR B  43      13.161  40.161 161.230  1.00  2.90       B     C
ATOM   6023  CA  THR B  44      10.738  41.938 163.588  1.00  5.21       B     C
ATOM   6030  CA  PRO B  45       8.030  43.161 163.977  1.00  6.45       B     C
ATOM   6037  CA  GLY B  46       7.346  42.212 160.323  1.00  4.86       B     C
ATOM   6041  CA  ARG B  47       8.581  39.247 158.248  1.00  4.58       B     C
ATOM   6052  CA  ASN B  48       7.898  37.485 154.983  1.00  4.09       B     C
ATOM   6060  CA  ASN B  49       6.685  33.858 155.217  1.00  4.78       B     C
ATOM   6068  CA  THR B  50      10.246  32.518 155.744  1.00  4.39       B     C
ATOM   6075  CA  GLY B  51      10.802  34.910 158.707  1.00  4.48       B     C
ATOM   6079  CA  TYR B  52      12.692  37.754 157.012  1.00  5.15       B     C
ATOM   6091  CA  ASP B  53      11.399  40.842 155.301  1.00  5.15       B     C
ATOM   6099  CA  TYR B  54      14.064  43.028 153.656  1.00  5.43       B     C
ATOM   6111  CA  ALA B  55      11.984  46.169 154.374  1.00  5.97       B     C
ATOM   6116  CA  GLN B  56      12.446  45.769 158.155  1.00  6.73       B     C
ATOM   6125  CA  SER B  57      15.268  47.086 160.349  1.00  7.18       B     C
ATOM   6131  CA  LYS B  58      15.306  44.770 163.351  1.00  4.81       B     C
ATOM   6140  CA  ILE B  59      16.408  41.138 163.680  1.00  4.41       B     C
ATOM   6148  CA  SER B  60      15.847  38.827 166.673  1.00  4.63       B     C
ATOM   6154  CA  GLY B  61      17.915  35.758 165.791  1.00  3.36       B     C
ATOM   6158  CA  PHE B  62      18.275  32.810 163.426  1.00  3.48       B     C
ATOM   6169  CA  THR B  63      15.870  29.935 162.748  1.00  3.46       B     C
ATOM   6176  CA  HIS B  64      17.063  26.576 161.377  1.00  3.52       B     C
ATOM   6186  CA  THR B  65      14.187  25.010 159.402  1.00  4.13       B     C
ATOM   6193  CA  ASN B  66      12.141  26.467 156.576  1.00  4.29       B     C
ATOM   6201  CA  LEU B  67      10.335  26.228 153.272  1.00  4.24       B     C
ATOM   6209  CA  ASP B  68      11.312  28.351 150.252  1.00  4.81       B     C
ATOM   6217  CA  GLY B  69       8.769  30.598 148.558  1.00  4.56       B     C
ATOM   6221  CA  VAL B  70       5.589  29.149 150.102  1.00  3.51       B     C
ATOM   6228  CA  GLY B  71       2.243  30.766 151.033  1.00  4.39       B     C
ATOM   6232  CA  GLY B  72       0.165  30.889 154.256  1.00  5.93       B     C
ATOM   6236  CA  SER B  73       2.360  32.159 157.086  1.00  5.71       B     C
ATOM   6242  CA  GLY B  74       5.232  29.886 155.962  1.00  4.98       B     C
ATOM   6246  CA  GLY B  75       6.527  26.565 157.216  1.00  4.40       B     C
ATOM   6250  CA  GLY B  76       9.371  25.580 159.508  1.00  4.57       B     C
ATOM   6254  CA  GLY B  77      10.953  28.443 161.386  1.00  3.39       B     C
ATOM   6258  CA  ASP B  78      11.986  26.048 164.188  1.00  3.33       B     C
ATOM   6266  CA  LEU B  79      14.888  26.547 166.612  1.00  5.32       B     C
ATOM   6274  CA  LEU B  80      15.348  30.284 167.110  1.00  5.08       B     C
ATOM   6282  CA  VAL B  81      18.851  31.213 168.309  1.00  4.86       B     C
ATOM   6289  CA  VAL B  82      19.084  34.745 169.745  1.00  5.18       B     C
ATOM   6296  CA  PRO B  83      22.375  36.414 170.798  1.00  5.18       B     C
ATOM   6303  CA  THR B  84      22.055  38.823 173.750  1.00  4.92       B     C
ATOM   6310  CA  SER B  85      24.059  40.445 176.538  1.00  3.51       B     C
ATOM   6316  CA  GLY B  86      20.865  40.604 178.572  1.00  3.93       B     C
ATOM   6320  CA  SER B  87      19.752  38.579 181.582  1.00  5.35       B     C
ATOM   6326  CA  TYR B  88      16.498  36.652 182.221  1.00  5.05       B     C
ATOM   6338  CA  THR B  89      14.650  35.335 185.336  1.00  5.80       B     C
ATOM   6345  CA  ALA B  90      11.608  33.987 183.442  1.00  4.94       B     C
ATOM   6350  CA  ARG B  91      10.687  32.820 179.933  1.00  5.95       B     C
ATOM   6361  CA  PRO B  92      11.913  35.587 177.603  1.00  5.93       B     C
ATOM   6368  CA  GLY B  93       9.414  38.047 176.166  1.00  5.97       B     C
ATOM   6372  CA  THR B  94       9.767  37.813 172.371  1.00  6.48       B     C
ATOM   6379  CA  GLY B  95      10.124  41.588 172.055  1.00  4.67       B     C
ATOM   6383  CA  THR B  96      13.359  41.564 174.059  1.00  4.62       B     C
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ATOM   6390  CA  TYR B  97      15.098  39.627 171.228  1.00  4.32       B     C
ATOM   6402  CA  ALA B  98      15.015  42.620 168.846  1.00  4.26       B     C
ATOM   6407  CA  HIS B  99      18.311  44.130 167.648  1.00  4.45       B     C
ATOM   6417  CA  PRO B 100      18.684  47.027 165.199  1.00  4.56       B     C
ATOM   6424  CA  PHE B 101      20.304  46.145 161.878  1.00  5.62       B     C
ATOM   6435  CA  SER B 102      21.236  47.834 158.588  1.00  6.73       B     C
ATOM   6441  CA  HIS B 103      21.603  46.324 155.111  1.00  7.29       B     C
ATOM   6451  CA  ASP B 104      24.879  48.336 155.037  1.00  9.91       B     C
ATOM   6459  CA  ASP B 105      26.290  45.946 157.703  1.00 10.20       B     C
ATOM   6467  CA  GLU B 106      24.917  42.703 156.229  1.00  9.23       B     C
ATOM   6476  CA  ASP B 107      26.499  40.286 153.765  1.00  9.46       B     C
ATOM   6484  CA  ALA B 108      25.242  36.970 152.370  1.00  6.84       B     C
ATOM   6489  CA  GLY B 109      25.559  34.488 149.524  1.00  4.80       B     C
ATOM   6493  CA  PRO B 110      25.491  30.714 148.861  1.00  4.09       B     C
ATOM   6500  CA  GLY B 111      26.276  29.034 152.198  1.00  4.03       B     C
ATOM   6504  CA  PHE B 112      26.451  32.010 154.507  1.00  4.63       B     C
ATOM   6515  CA  TYR B 113      24.841  35.051 156.062  1.00  4.43       B     C
ATOM   6527  CA  SER B 114      26.381  37.783 158.200  1.00  5.09       B     C
ATOM   6533  CA  VAL B 115      24.962  40.865 159.954  1.00  4.89       B     C
ATOM   6540  CA  GLY B 116      25.874  43.467 162.573  1.00  6.35       B     C
ATOM   6544  CA  LEU B 117      23.215  43.427 165.294  1.00  6.43       B     C
ATOM   6552  CA  GLY B 118      22.939  46.299 167.802  1.00  6.20       B     C
ATOM   6556  CA  ASN B 119      23.960  44.928 171.238  1.00  5.86       B     C
ATOM   6564  CA  VAL B 120      21.162  44.472 173.803  1.00  4.83       B     C
ATOM   6571  CA  ALA B 121      21.260  44.132 177.613  1.00  4.23       B     C
ATOM   6576  CA  GLY B 122      19.365  44.559 180.892  1.00  4.26       B     C
ATOM   6580  CA  THR B 123      16.919  42.174 182.582  1.00  5.43       B     C
ATOM   6587  CA  ASP B 124      13.711  40.546 181.298  1.00  5.91       B     C
ATOM   6595  CA  GLY B 125      11.132  43.006 179.823  1.00  6.02       B     C
ATOM   6599  CA  ALA B 126      13.463  45.973 180.415  1.00  5.90       B     C
ATOM   6604  CA  ILE B 127      16.092  44.620 177.976  1.00  5.52       B     C
ATOM   6612  CA  THR B 128      17.063  47.192 175.369  1.00  4.75       B     C
ATOM   6619  CA  GLY B 129      19.991  48.703 173.407  1.00  4.79       B     C
ATOM   6623  CA  ALA B 130      23.437  48.378 175.037  1.00  5.28       B     C
ATOM   6628  CA  PRO B 131      26.932  49.536 173.894  1.00  5.84       B     C
ATOM   6635  CA  GLY B 132      28.389  48.225 170.633  1.00  5.70       B     C
ATOM   6639  CA  THR B 133      27.548  45.592 168.062  1.00  6.06       B     C
ATOM   6646  CA  ILE B 134      27.013  41.848 168.174  1.00  7.11       B     C
ATOM   6654  CA  GLU B 135      28.833  40.654 165.045  1.00  8.84       B     C
ATOM   6663  CA  ALA B 136      26.820  37.651 163.802  1.00  6.10       B     C
ATOM   6668  CA  GLU B 137      27.966  35.088 161.226  1.00  4.63       B     C
ATOM   6677  CA  VAL B 138      26.200  31.897 160.196  1.00  3.25       B     C
ATOM   6684  CA  ALA B 139      26.905  29.212 157.622  1.00  3.25       B     C
ATOM   6689  CA  ALA B 140      25.244  25.933 156.657  1.00  4.37       B     C
ATOM   6694  CA  ALA B 141      26.177  22.444 155.558  1.00  5.98       B     C
ATOM   6699  CA  THR B 142      23.483  19.964 154.381  1.00  4.34       B     C
ATOM   6706  CA  ARG B 143      22.140  19.123 157.865  1.00  4.38       B     C
ATOM   6717  CA  SER B 144      23.954  21.728 159.957  1.00  4.49       B     C
ATOM   6723  CA  GLY B 145      23.839  25.419 160.895  1.00  5.05       B     C
ATOM   6727  CA  VAL B 146      26.994  26.868 162.414  1.00  4.62       B     C
ATOM   6734  CA  HIS B 147      27.242  30.186 164.272  1.00  4.38       B     C
ATOM   6744  CA  ARG B 148      30.103  32.540 165.208  1.00  4.25       B     C
ATOM   6755  CA  TYR B 149      29.335  35.704 167.264  1.00  4.46       B     C
ATOM   6767  CA  ALA B 150      31.522  38.561 168.553  1.00  5.60       B     C
ATOM   6772  CA  PHE B 151      30.094  40.472 171.553  1.00  6.42       B     C
ATOM   6783  CA  PRO B 152      31.380  43.820 172.738  1.00  8.35       B     C
ATOM   6790  CA  ALA B 153      34.133  43.586 175.369  1.00  8.99       B     C
ATOM   6795  CA  GLY B 154      32.667  43.385 178.865  1.00  8.42       B     C
ATOM   6799  CA  SER B 155      29.390  41.759 177.743  1.00  8.54       B     C
ATOM   6805  CA  THR B 156      28.171  38.643 179.484  1.00  7.06       B     C
ATOM   6812  CA  PRO B 157      27.319  36.804 176.247  1.00  7.08       B     C
ATOM   6819  CA  SER B 158      24.232  34.650 176.044  1.00  6.71       B     C
ATOM   6825  CA  LEU B 159      22.370  32.582 173.502  1.00  4.87       B     C
ATOM   6833  CA  VAL B 160      18.646  31.941 173.847  1.00  3.09       B     C
ATOM   6840  CA  VAL B 161      17.419  28.777 172.147  1.00  3.34       B     C
ATOM   6847  CA  ASP B 162      13.682  29.337 171.720  1.00  4.07       B     C
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ATOM   6855  CA  LEU B 163      11.876  26.065 170.870  1.00  3.79       B     C
ATOM   6863  CA  GLU B 164       8.402  27.636 170.688  1.00  4.18       B     C
ATOM   6872  CA  THR B 165       9.046  29.648 167.474  1.00  2.64       B     C
ATOM   6879  CA  ASN B 166       7.417  28.351 164.312  1.00  2.42       B     C
ATOM   6887  CA  ASN B 167       6.159  30.090 161.193  1.00  2.44       B     C
ATOM   6895  CA  THR B 168       2.700  28.469 161.520  1.00  2.77       B     C
ATOM   6902  CA  SER B 169       2.191  26.088 164.470  1.00  3.44       B     C
ATOM   6908  CA  ARG B 170       4.367  24.663 167.209  1.00  3.61       B     C
ATOM   6919  CA  ARG B 171       2.777  21.329 168.092  1.00  4.09       B     C
ATOM   6930  CA  SER B 172       5.367  20.136 170.618  1.00  3.92       B     C
ATOM   6936  CA  SER B 173       9.026  20.436 171.605  1.00  4.52       B     C
ATOM   6942  CA  SER B 174      11.644  19.095 174.010  1.00  5.26       B     C
ATOM   6948  CA  VAL B 175      15.144  19.964 175.194  1.00  7.61       B     C
ATOM   6955  CA  GLN B 176      17.707  17.942 177.116  1.00  9.87       B     C
ATOM   6964  CA  VAL B 177      20.827  19.575 178.479  1.00 10.75       B     C
ATOM   6971  CA  GLU B 178      24.266  17.972 178.853  1.00 11.75       B     C
ATOM   6980  CA  THR B 179      27.408  19.621 180.271  1.00 10.76       B     C
ATOM   6987  CA  ARG B 180      30.637  17.869 179.161  1.00 11.07       B     C
ATOM   6998  CA  ALA B 181      34.052  17.533 180.867  1.00 12.22       B     C
ATOM   7003  CA  ASP B 182      35.476  20.584 179.033  1.00 11.74       B     C
ATOM   7011  CA  GLY B 183      32.508  22.707 180.228  1.00  9.15       B     C
ATOM   7015  CA  THR B 184      30.755  22.961 176.837  1.00  5.80       B     C
ATOM   7022  CA  VAL B 185      27.013  22.306 176.541  1.00  5.32       B     C
ATOM   7029  CA  GLU B 186      24.991  20.053 174.245  1.00  6.37       B     C
ATOM   7038  CA  LEU B 187      21.225  20.551 173.801  1.00  5.44       B     C
ATOM   7046  CA  SER B 188      19.138  17.900 172.108  1.00  4.09       B     C
ATOM   7052  CA  GLY B 189      15.468  17.073 171.486  1.00  3.12       B     C
ATOM   7056  CA  GLN B 190      12.682  17.282 168.938  1.00  2.37       B     C
ATOM   7065  CA  VAL B 191      10.502  19.973 167.357  1.00  2.26       B     C
ATOM   7072  CA  THR B 192       7.128  19.112 165.863  1.00  2.53       B     C
ATOM   7079  CA  GLY B 193       5.491  21.715 163.683  1.00  2.57       B     C
ATOM   7083  CA  TYR B 194       2.613  21.951 161.250  1.00  3.30       B     C
ATOM   7095  CA  PHE B 195       2.176  23.583 157.852  1.00  4.28       B     C
ATOM   7106  CA  TYR B 196      -0.598  23.421 155.296  1.00  7.19       B     C
ATOM   7118  CA  ASN B 197      -1.557  19.737 155.149  1.00  7.00       B     C
ATOM   7126  CA  ALA B 198       0.738  17.907 157.606  1.00  5.17       B     C
ATOM   7131  CA  ALA B 199       2.648  17.834 160.876  1.00  4.90       B     C
ATOM   7136  CA  TYR B 200       6.409  17.069 160.789  1.00  4.22       B     C
ATOM   7148  CA  THR B 201       9.101  16.185 163.362  1.00  5.31       B     C
ATOM   7155  CA  LEU B 202      12.799  16.977 163.328  1.00  3.48       B     C
ATOM   7163  CA  TYR B 203      15.415  15.973 165.896  1.00  3.48       B     C
ATOM   7175  CA  TYR B 204      18.277  18.294 166.724  1.00  4.54       B     C
ATOM   7187  CA  THR B 205      21.584  18.490 168.504  1.00  5.64       B     C
ATOM   7194  CA  ALA B 206      23.308  21.765 169.341  1.00  5.72       B     C
ATOM   7199  CA  ARG B 207      26.654  22.253 170.998  1.00  5.49       B     C
ATOM   7210  CA  THR B 208      28.601  25.232 172.226  1.00  4.80       B     C
ATOM   7217  CA  LEU B 209      32.264  25.598 171.305  1.00  4.71       B     C
ATOM   7225  CA  GLN B 210      33.041  27.516 174.554  1.00  6.35       B     C
ATOM   7234  CA  PRO B 211      32.110  26.663 178.148  1.00  7.67       B     C
ATOM   7241  CA  ALA B 212      28.543  27.611 179.143  1.00  7.25       B     C
ATOM   7246  CA  THR B 213      26.099  27.434 182.004  1.00  7.17       B     C
ATOM   7253  CA  VAL B 214      22.470  26.720 181.121  1.00  6.69       B     C
ATOM   7260  CA  GLN B 215      18.911  27.268 182.283  1.00  6.38       B     C
ATOM   7269  CA  THR B 216      15.794  25.836 180.631  1.00  4.98       B     C
ATOM   7276  CA  TRP B 217      12.111  26.702 180.466  1.00  3.64       B     C
ATOM   7290  CA  GLY B 218       8.884  24.866 180.016  1.00  5.63       B     C
ATOM   7294  CA  ASP B 219       5.244  25.649 179.622  1.00  8.12       B     C
ATOM   7302  CA  ASP B 220       4.977  27.146 183.127  1.00 12.50       B     C
ATOM   7310  CA  ASP B 221       7.168  30.093 181.953  1.00 12.91       B     C
ATOM   7318  CA  ARG B 222       9.634  29.500 184.787  1.00 11.75       B     C
ATOM   7329  CA  LEU B 223      13.374  29.633 184.047  1.00  9.26       B     C
ATOM   7337  CA  VAL B 224      15.093  26.886 186.002  1.00  9.70       B     C
ATOM   7344  CA  ASP B 225      18.254  24.870 186.542  1.00  9.71       B     C
ATOM   7352  CA  ALA B 226      16.446  21.645 185.479  1.00  8.94       B     C
ATOM   7357  CA  THR B 227      18.172  19.922 182.585  1.00  8.94       B     C
ATOM   7364  CA  ALA B 228      15.027  18.498 180.872  1.00  8.41       B     C
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ATOM   7369  CA  GLN B 229      11.887  19.991 179.343  1.00  7.11       B     C
ATOM   7378  CA  ASP B 230       9.154  18.361 177.262  1.00  7.62       B     C
ATOM   7386  CA  GLY B 231       5.982  20.180 176.272  1.00  5.49       B     C
ATOM   7390  CA  VAL B 232       5.019  22.814 173.687  1.00  3.91       B     C
ATOM   7397  CA  ASP B 233       6.717  26.124 174.666  1.00  3.59       B     C
ATOM   7405  CA  THR B 234      10.207  25.219 175.870  1.00  3.22       B     C
ATOM   7412  CA  GLY B 235      13.760  26.456 175.485  1.00  2.52       B     C
ATOM   7416  CA  ALA B 236      17.165  27.054 176.932  1.00  2.01       B     C
ATOM   7421  CA  ILE B 237      19.409  30.014 177.730  1.00  2.62       B     C
ATOM   7429  CA  LEU B 238      23.188  29.544 177.393  1.00  3.80       B     C
ATOM   7437  CA  THR B 239      25.439  31.941 179.352  1.00  5.81       B     C
ATOM   7444  CA  PHE B 240      29.137  32.391 178.663  1.00  7.71       B     C
ATOM   7455  CA  ASP B 241      32.053  34.026 180.461  1.00 10.49       B     C
ATOM   7463  CA  PRO B 242      32.976  37.585 179.419  1.00 10.21       B     C
ATOM   7470  CA  ALA B 243      36.482  36.270 178.652  1.00 10.56       B     C
ATOM   7475  CA  ASP B 244      34.898  34.545 175.608  1.00 10.22       B     C
ATOM   7483  CA  ALA B 245      32.993  37.584 174.265  1.00  9.19       B     C
ATOM   7488  CA  GLY B 246      35.260  37.861 171.199  1.00  9.07       B     C
ATOM   7492  CA  GLU B 247      34.117  34.471 169.883  1.00  8.40       B     C
ATOM   7501  CA  ILE B 248      30.976  32.504 170.743  1.00  6.26       B     C
ATOM   7509  CA  GLY B 249      30.419  29.317 168.700  1.00  5.26       B     C
ATOM   7513  CA  LEU B 250      27.365  27.148 168.128  1.00  4.75       B     C
ATOM   7521  CA  GLN B 251      26.729  24.080 165.940  1.00  4.54       B     C
ATOM   7530  CA  VAL B 252      23.221  22.815 165.229  1.00  4.09       B     C
ATOM   7537  CA  THR B 253      22.517  19.573 163.382  1.00  3.14       B     C
ATOM   7544  CA  LEU B 254      19.085  18.325 162.254  1.00  3.66       B     C
ATOM   7552  CA  SER B 255      17.710  14.818 161.568  1.00  3.72       B     C
ATOM   7558  CA  PRO B 256      14.350  13.322 160.581  1.00  3.90       B     C
ATOM   7565  CA  VAL B 257      15.675  10.122 162.247  1.00  4.49       B     C
ATOM   7572  CA  SER B 258      16.553  10.685 165.919  1.00  5.09       B     C
ATOM   7578  CA  VAL B 259      18.811  12.681 168.270  1.00  6.85       B     C
ATOM   7585  CA  GLU B 260      21.309   9.841 168.225  1.00  8.56       B     C
ATOM   7594  CA  GLN B 261      21.425  10.162 164.416  1.00  7.14       B     C
ATOM   7603  CA  ALA B 262      21.764  13.965 164.573  1.00  6.00       B     C
ATOM   7608  CA  ARG B 263      24.840  13.567 166.780  1.00  6.59       B     C
ATOM   7619  CA  ILE B 264      26.315  11.008 164.363  1.00  7.36       B     C
ATOM   7627  CA  ASP B 265      25.571  13.292 161.370  1.00  6.50       B     C
ATOM   7635  CA  GLN B 266      27.201  16.188 163.205  1.00  7.37       B     C
ATOM   7644  CA  GLN B 267      30.403  14.178 163.786  1.00 11.20       B     C
ATOM   7653  CA  VAL B 268      30.481  13.075 160.124  1.00 10.88       B     C
ATOM   7660  CA  GLU B 269      29.430  16.369 158.505  1.00 11.16       B     C
ATOM   7669  CA  LEU B 270      31.314  18.882 160.704  1.00 10.96       B     C
ATOM   7677  CA  GLY B 271      33.869  16.943 162.740  1.00 11.80       B     C
ATOM   7681  CA  ASP B 272      36.639  19.186 164.002  1.00 11.87       B     C
ATOM   7689  CA  LEU B 273      36.374  21.606 161.059  1.00  9.30       B     C
ATOM   7697  CA  SER B 274      36.585  25.316 161.684  1.00  8.10       B     C
ATOM   7703  CA  PHE B 275      33.692  27.729 161.001  1.00  7.57       B     C
ATOM   7714  CA  ASP B 276      35.633  29.179 158.049  1.00  9.11       B     C
ATOM   7722  CA  ALA B 277      36.288  25.679 156.588  1.00  8.17       B     C
ATOM   7727  CA  ILE B 278      32.607  24.690 156.805  1.00  6.31       B     C
ATOM   7735  CA  ARG B 279      31.510  27.935 155.180  1.00  7.50       B     C
ATOM   7746  CA  ASP B 280      34.193  27.585 152.447  1.00  8.14       B     C
ATOM   7754  CA  ARG B 281      33.248  23.952 151.718  1.00  7.53       B     C
ATOM   7765  CA  THR B 282      29.590  24.914 151.207  1.00  7.03       B     C
ATOM   7772  CA  ARG B 283      30.749  27.741 148.908  1.00  8.06       B     C
ATOM   7783  CA  ALA B 284      32.685  25.192 146.809  1.00  7.18       B     C
ATOM   7788  CA  GLU B 285      29.647  22.838 146.826  1.00  8.04       B     C
ATOM   7797  CA  TRP B 286      27.513  25.684 145.409  1.00  6.44       B     C
ATOM   7811  CA  ASN B 287      30.194  26.541 142.822  1.00  7.77       B     C
ATOM   7819  CA  ALA B 288      30.163  22.844 141.765  1.00  8.01       B     C
ATOM   7824  CA  THR B 289      26.340  22.924 141.481  1.00  7.57       B     C
ATOM   7831  CA  LEU B 290      25.928  26.258 139.687  1.00  6.68       B     C
ATOM   7839  CA  GLY B 291      28.902  25.412 137.486  1.00  8.30       B     C
ATOM   7843  CA  ARG B 292      26.832  22.721 135.807  1.00  8.97       B     C
ATOM   7854  CA  VAL B 293      25.594  25.636 133.725  1.00 10.54       B     C
ATOM   7861  CA  ALA B 294      28.121  27.918 132.046  1.00 12.46       B     C
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ATOM   7866  CA  ILE B 295      26.911  31.025 130.202  1.00 15.01       B     C
ATOM   7874  CA  ASP B 296      28.503  33.444 127.742  1.00 16.68       B     C
ATOM   7882  CA  ALA B 297      26.492  36.686 127.506  1.00 16.02       B     C
ATOM   7887  CA  SER B 298      27.400  39.653 125.271  1.00 15.25       B     C
ATOM   7893  CA  THR B 299      26.635  43.276 126.121  1.00 14.42       B     C
ATOM   7900  CA  ALA B 300      24.046  43.110 123.326  1.00 11.48       B     C
ATOM   7905  CA  THR B 301      21.783  40.582 125.103  1.00  9.84       B     C
ATOM   7912  CA  ASP B 302      22.704  41.528 128.706  1.00  9.77       B     C
ATOM   7920  CA  PRO B 303      23.868  45.197 128.715  1.00 10.54       B     C
ATOM   7927  CA  THR B 304      23.489  45.589 132.512  1.00 11.07       B     C
ATOM   7934  CA  GLY B 305      24.761  42.154 133.524  1.00 11.11       B     C
ATOM   7938  CA  GLU B 306      21.483  41.714 135.432  1.00 10.64       B     C
ATOM   7947  CA  LEU B 307      20.268  38.736 133.293  1.00 10.30       B     C
ATOM   7955  CA  GLN B 308      23.365  36.685 134.127  1.00 10.19       B     C
ATOM   7964  CA  ARG B 309      22.914  37.468 137.835  1.00  8.46       B     C
ATOM   7975  CA  LEU B 310      19.207  36.600 137.644  1.00  6.90       B     C
ATOM   7983  CA  PHE B 311      20.109  33.341 135.894  1.00  5.42       B     C
ATOM   7994  CA  TYR B 312      22.509  32.208 138.679  1.00  4.65       B     C
ATOM   8006  CA  THR B 313      20.288  33.567 141.446  1.00  3.72       B     C
ATOM   8013  CA  HIS B 314      17.411  31.465 140.078  1.00  3.77       B     C
ATOM   8023  CA  LEU B 315      19.597  28.424 139.419  1.00  4.98       B     C
ATOM   8031  CA  TYR B 316      20.467  28.753 143.144  1.00  4.55       B     C
ATOM   8043  CA  ARG B 317      16.731  28.839 144.007  1.00  5.20       B     C
ATOM   8054  CA  MET B 318      16.085  25.817 141.789  1.00  7.54       B     C
ATOM   8062  CA  PHE B 319      18.175  23.558 144.063  1.00  8.02       B     C
ATOM   8073  CA  ALA B 320      16.316  24.249 147.345  1.00  7.25       B     C
ATOM   8078  CA  MET B 321      13.403  21.781 147.467  1.00  5.88       B     C
ATOM   8086  CA  PRO B 322      12.863  18.952 147.903  1.00  4.25       B     C
ATOM   8093  CA  MET B 323      15.380  18.850 150.760  1.00  3.69       B     C
ATOM   8101  CA  ASN B 324      17.944  16.177 151.447  1.00  3.38       B     C
ATOM   8109  CA  ALA B 325      16.107  14.123 154.077  1.00  3.72       B     C
ATOM   8114  CA  THR B 326      18.714  11.357 154.443  1.00  3.39       B     C
ATOM   8121  CA  SER B 327      21.071  10.805 157.383  1.00  4.75       B     C
ATOM   8127  CA  THR B 328      24.861  10.478 156.953  1.00  5.56       B     C
ATOM   8134  CA  SER B 329      24.175   6.783 157.673  1.00  5.03       B     C
ATOM   8140  CA  GLY B 330      21.990   6.586 154.509  1.00  5.56       B     C
ATOM   8144  CA  THR B 331      18.681   6.308 156.385  1.00  4.67       B     C
ATOM   8151  CA  TYR B 332      15.380   8.194 156.221  1.00  4.08       B     C
ATOM   8163  CA  ARG B 333      12.110   8.234 158.156  1.00  5.90       B     C
ATOM   8174  CA  GLY B 334       8.940   7.045 156.393  1.00  7.33       B     C
ATOM   8178  CA  VAL B 335       5.362   8.276 156.776  1.00  9.86       B     C
ATOM   8185  CA  ASP B 336       4.715   4.745 158.108  1.00 11.83       B     C
ATOM   8193  CA  GLY B 337       6.472   5.889 161.292  1.00 12.67       B     C
ATOM   8197  CA  ALA B 338       9.546   3.712 160.784  1.00 10.29       B     C
ATOM   8202  CA  VAL B 339      13.181   4.400 159.827  1.00  8.36       B     C
ATOM   8209  CA  HIS B 340      14.277   2.783 156.523  1.00  8.22       B     C
ATOM   8219  CA  ALA B 341      17.345   2.468 154.295  1.00  9.30       B     C
ATOM   8224  CA  ALA B 342      17.738   4.699 151.232  1.00 10.96       B     C
ATOM   8229  CA  GLN B 343      19.736   1.973 149.549  1.00 14.92       B     C
ATOM   8238  CA  GLY B 344      22.061   3.243 146.798  1.00 14.18       B     C
ATOM   8242  CA  PHE B 345      20.330   6.658 146.470  1.00  9.94       B     C
ATOM   8253  CA  THR B 346      19.663   9.851 148.454  1.00  5.70       B     C
ATOM   8260  CA  TYR B 347      16.132  10.341 149.769  1.00  3.08       B     C
ATOM   8272  CA  TYR B 348      14.568  13.786 149.336  1.00  2.49       B     C
ATOM   8284  CA  ASP B 349      11.394  15.091 150.938  1.00  2.40       B     C
ATOM   8292  CA  SER B 350       9.337  18.340 151.066  1.00  3.13       B     C
ATOM   8298  CA  TRP B 351       6.904  18.658 148.223  1.00  3.44       B     C
ATOM   8312  CA  ALA B 352       4.594  21.317 146.769  1.00  6.09       B     C
ATOM   8317  CA  THR B 353       3.818  19.352 143.690  1.00  7.57       B     C
ATOM   8324  CA  TRP B 354       0.511  21.060 142.861  1.00 10.28       B     C
ATOM   8338  CA  ASP B 355       2.607  24.171 142.126  1.00  9.25       B     C
ATOM   8346  CA  ASP B 356       6.027  22.821 141.162  1.00  7.97       B     C
ATOM   8354  CA  PHE B 357       5.476  19.675 139.069  1.00  5.45       B     C
ATOM   8365  CA  ARG B 358       7.086  21.219 135.922  1.00  4.54       B     C
ATOM   8376  CA  LYS B 359      10.204  22.174 137.907  1.00  3.86       B     C
ATOM   8385  CA  PHE B 360      11.251  18.513 137.948  1.00  3.85       B     C
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ATOM   8396  CA  SER B 361      11.230  18.254 134.132  1.00  4.19       B     C
ATOM   8402  CA  VAL B 362      13.848  21.051 134.057  1.00  4.66       B     C
ATOM   8409  CA  ILE B 363      15.981  19.656 136.859  1.00  3.60       B     C
ATOM   8417  CA  ALA B 364      15.986  16.487 134.724  1.00  4.12       B     C
ATOM   8422  CA  TYR B 365      18.152  18.190 132.040  1.00  5.46       B     C
ATOM   8434  CA  ILE B 366      20.412  20.182 134.397  1.00  6.51       B     C
ATOM   8442  CA  ASP B 367      21.232  17.592 137.055  1.00  6.76       B     C
ATOM   8450  CA  PRO B 368      19.936  14.178 135.858  1.00  6.15       B     C
ATOM   8457  CA  ALA B 369      21.272  12.238 138.895  1.00  5.16       B     C
ATOM   8462  CA  LEU B 370      19.595  14.581 141.391  1.00  5.66       B     C
ATOM   8470  CA  TYR B 371      16.368  14.351 139.411  1.00  5.00       B     C
ATOM   8482  CA  ARG B 372      16.537  10.538 139.507  1.00  6.13       B     C
ATOM   8493  CA  ASP B 373      16.991  10.482 143.321  1.00  4.65       B     C
ATOM   8501  CA  MET B 374      14.069  12.884 143.690  1.00  3.74       B     C
ATOM   8509  CA  VAL B 375      11.706  10.681 141.648  1.00  3.94       B     C
ATOM   8516  CA  GLN B 376      12.853   7.548 143.481  1.00  3.66       B     C
ATOM   8525  CA  SER B 377      12.139   9.421 146.732  1.00  3.93       B     C
ATOM   8531  CA  LEU B 378       8.564  10.288 145.559  1.00  4.51       B     C
ATOM   8539  CA  VAL B 379       8.064   6.634 144.704  1.00  3.56       B     C
ATOM   8546  CA  TYR B 380       9.204   5.663 148.259  1.00  4.32       B     C
ATOM   8558  CA  LEU B 381       6.959   8.247 149.897  1.00  3.49       B     C
ATOM   8566  CA  PHE B 382       3.838   6.774 148.265  1.00  3.82       B     C
ATOM   8577  CA  ALA B 383       5.141   3.221 148.777  1.00  4.94       B     C
ATOM   8582  CA  ASP B 384       5.471   3.995 152.503  1.00  6.79       B     C
ATOM   8590  CA  ALA B 385       1.923   5.413 152.611  1.00  9.08       B     C
ATOM   8595  CA  GLU B 386       0.765   2.141 150.976  1.00 10.89       B     C
ATOM   8604  CA  ALA B 387       2.810   0.119 153.498  1.00 13.19       B     C
ATOM   8609  CA  THR B 388       0.740   1.552 156.445  1.00 15.38       B     C
ATOM   8616  CA  GLY B 389      -2.271  -0.495 155.224  1.00 15.84       B     C
ATOM   8620  CA  THR B 390      -4.587   2.321 156.337  1.00 14.91       B     C
ATOM   8627  CA  GLY B 391      -5.415   3.542 152.829  1.00 12.96       B     C
ATOM   8631  CA  GLY B 392      -5.069   7.090 154.245  1.00 10.55       B     C
ATOM   8635  CA  GLY B 393      -3.986  10.168 152.254  1.00  8.29       B     C
ATOM   8639  CA  LEU B 394      -0.516  11.679 152.818  1.00  6.39       B     C
ATOM   8647  CA  GLY B 395      -1.926  14.514 154.938  1.00  6.61       B     C
ATOM   8651  CA  GLY B 396      -2.978  12.076 157.705  1.00  7.77       B     C
ATOM   8655  CA  PHE B 397       0.603  11.030 158.585  1.00  7.05       B     C
ATOM   8666  CA  VAL B 398       3.457  12.825 160.317  1.00  6.28       B     C
ATOM   8673  CA  HIS B 399       6.082  13.832 157.779  1.00  4.37       B     C
ATOM   8683  CA  SER B 400       9.868  13.714 158.080  1.00  4.62       B     C
ATOM   8689  CA  VAL B 401      10.519  17.328 157.074  1.00  3.81       B     C
ATOM   8696  CA  PRO B 402       8.279  20.398 156.732  1.00  2.81       B     C
ATOM   8703  CA  THR B 403       6.223  19.841 153.605  1.00  2.00       B     C
ATOM   8710  CA  VAL B 404       3.295  21.247 151.582  1.00  2.02       B     C
ATOM   8717  CA  ARG B 405       1.236  19.105 149.134  1.00  3.66       B     C
ATOM   8728  CA  TRP B 406       1.343  16.193 146.726  1.00  4.40       B     C
ATOM   8742  CA  GLU B 407      -1.154  16.632 143.859  1.00  4.95       B     C
ATOM   8751  CA  ARG B 408       0.354  16.056 140.358  1.00  4.63       B     C
ATOM   8762  CA  SER B 409       2.805  13.445 141.798  1.00  4.41       B     C
ATOM   8768  CA  SER B 410       1.577  10.955 139.158  1.00  5.65       B     C
ATOM   8774  CA  VAL B 411       2.871  13.412 136.534  1.00  4.55       B     C
ATOM   8781  CA  VAL B 412       6.352  13.733 138.090  1.00  3.62       B     C
ATOM   8788  CA  VAL B 413       6.857   9.945 138.202  1.00  3.87       B     C
ATOM   8795  CA  ALA B 414       5.438   9.658 134.653  1.00  5.13       B     C
ATOM   8800  CA  ASP B 415       7.928  12.368 133.664  1.00  4.82       B     C
ATOM   8808  CA  ALA B 416      10.908  10.154 134.619  1.00  4.44       B     C
ATOM   8813  CA  ILE B 417       9.427   7.020 132.987  1.00  5.16       B     C
ATOM   8821  CA  ALA B 418       8.712   8.909 129.732  1.00  6.23       B     C
ATOM   8826  CA  LYS B 419      12.303  10.194 129.851  1.00  8.29       B     C
ATOM   8835  CA  GLY B 420      13.794   6.686 129.922  1.00 10.82       B     C
ATOM   8839  CA  PHE B 421      14.569   6.285 133.624  1.00 11.95       B     C
ATOM   8850  CA  ASP B 422      13.949   2.885 135.136  1.00 14.48       B     C
ATOM   8858  CA  GLY B 423      14.815   0.654 138.084  1.00 14.15       B     C
ATOM   8862  CA  PHE B 424      12.489   2.574 140.366  1.00 12.52       B     C
ATOM   8873  CA  ASP B 425      12.381   0.289 143.387  1.00 12.13       B     C
ATOM   8881  CA  ARG B 426       8.874  -0.058 144.898  1.00  9.62       B     C
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ATOM   8892  CA  LEU B 427       6.950   1.477 141.964  1.00  9.74       B     C
ATOM   8900  CA  ASP B 428       4.503  -1.436 142.300  1.00 11.74       B     C
ATOM   8908  CA  GLU B 429       3.837  -0.485 145.942  1.00 10.85       B     C
ATOM   8917  CA  ALA B 430       3.557   3.228 145.139  1.00  9.56       B     C
ATOM   8922  CA  TYR B 431       0.970   2.649 142.393  1.00  9.69       B     C
ATOM   8934  CA  PRO B 432      -2.178   2.019 144.553  1.00  8.88       B     C
ATOM   8941  CA  ALA B 433      -1.368   5.086 146.736  1.00  7.60       B     C
ATOM   8946  CA  LEU B 434      -0.914   7.129 143.566  1.00  7.98       B     C
ATOM   8954  CA  GLN B 435      -4.332   5.893 142.378  1.00  9.79       B     C
ATOM   8963  CA  ARG B 436      -5.876   6.985 145.714  1.00  8.63       B     C
ATOM   8974  CA  LEU B 437      -4.175  10.398 145.345  1.00  8.82       B     C
ATOM   8982  CA  VAL B 438      -5.651  10.832 141.863  1.00 10.72       B     C
ATOM   8989  CA  GLY B 439      -9.074   9.520 142.973  1.00 11.53       B     C
ATOM   8993  CA  GLN B 440     -11.952   7.945 141.034  1.00 13.71       B     C
ATOM   9002  CA  TYR B 441     -14.865   9.454 139.124  1.00 12.01       B     C
ATOM   9014  CA  SER B 442     -18.189   8.549 140.760  1.00 12.74       B     C
ATOM   9020  CA  ALA B 443     -20.666   6.339 138.839  1.00 12.68       B     C
ATOM   9025  CA  ASP B 444     -22.553   9.434 137.687  1.00 12.69       B     C
ATOM   9033  CA  GLU B 445     -19.307  11.199 136.788  1.00 10.37       B     C
ATOM   9042  CA  LEU B 446     -18.282   8.164 134.766  1.00 10.75       B     C
ATOM   9050  CA  ARG B 447     -21.517   8.211 132.730  1.00 12.18       B     C
ATOM   9061  CA  ARG B 448     -21.331  11.954 131.904  1.00 11.28       B     C
ATOM   9072  CA  GLY B 449     -17.521  12.199 131.769  1.00  9.56       B     C
ATOM   9076  CA  TYR B 450     -16.840  15.171 134.104  1.00  8.69       B     C
ATOM   9088  CA  VAL B 451     -17.362  16.664 137.586  1.00  8.42       B     C
ATOM   9095  CA  ALA B 452     -20.609  18.655 137.398  1.00  9.63       B     C
ATOM   9100  CA  GLY B 453     -19.943  22.350 137.910  1.00  9.76       B     C
ATOM   9104  CA  ASN B 454     -16.242  21.775 138.624  1.00  8.50       B     C
ATOM   9112  CA  PRO B 455     -14.156  22.194 135.439  1.00  8.32       B     C
ATOM   9119  CA  GLY B 456     -11.107  22.756 137.692  1.00  8.02       B     C
ATOM   9123  CA  ALA B 457     -11.159  19.292 139.280  1.00  6.90       B     C
ATOM   9128  CA  SER B 458     -11.963  17.688 135.889  1.00  6.05       B     C
ATOM   9134  CA  VAL B 459      -8.939  18.989 133.896  1.00  5.70       B     C
ATOM   9141  CA  GLN B 460      -6.681  18.365 136.882  1.00  5.79       B     C
ATOM   9150  CA  ARG B 461      -7.804  14.732 137.121  1.00  6.42       B     C
ATOM   9161  CA  GLY B 462      -7.221  14.406 133.370  1.00  5.35       B     C
ATOM   9165  CA  TYR B 463      -3.539  15.278 133.771  1.00  5.04       B     C
ATOM   9177  CA  ASP B 464      -3.270  13.035 136.851  1.00  5.57       B     C
ATOM   9185  CA  GLN B 465      -4.804  10.198 134.841  1.00  5.78       B     C
ATOM   9194  CA  TYR B 466      -2.483  10.769 131.919  1.00  6.49       B     C
ATOM   9206  CA  GLY B 467       0.439  10.511 134.378  1.00  5.94       B     C
ATOM   9210  CA  LEU B 468      -1.027   7.423 136.006  1.00  7.08       B     C
ATOM   9218  CA  SER B 469      -1.447   5.806 132.563  1.00  7.35       B     C
ATOM   9224  CA  VAL B 470       2.324   6.119 131.916  1.00  7.31       B     C
ATOM   9231  CA  ILE B 471       3.054   4.452 135.299  1.00  7.55       B     C
ATOM   9239  CA  ALA B 472       0.432   1.758 134.635  1.00  8.69       B     C
ATOM   9244  CA  ASP B 473       2.077   0.765 131.318  1.00 10.11       B     C
ATOM   9252  CA  GLU B 474       5.524   0.684 132.942  1.00 11.08       B     C
ATOM   9261  CA  LEU B 475       4.081  -1.770 135.471  1.00 10.77       B     C
ATOM   9269  CA  GLY B 476       2.557  -3.863 132.643  1.00 12.28       B     C
ATOM   9273  CA  LEU B 477      -1.005  -2.946 133.703  1.00 14.48       B     C
ATOM   9281  CA  THR B 478      -1.957  -2.607 130.034  1.00 17.13       B     C
ATOM   9288  CA  GLU B 479      -5.736  -2.506 130.474  1.00 18.35       B     C
ATOM   9297  CA  GLU B 480      -5.722   0.045 133.355  1.00 15.71       B     C
ATOM   9306  CA  ALA B 481      -3.447   2.289 131.256  1.00 13.30       B     C
ATOM   9311  CA  GLU B 482      -5.993   2.198 128.387  1.00 13.38       B     C
ATOM   9320  CA  THR B 483      -8.838   3.007 130.776  1.00 11.91       B     C
ATOM   9327  CA  LEU B 484      -6.802   5.857 132.279  1.00  9.11       B     C
ATOM   9335  CA  ARG B 485      -6.030   7.235 128.765  1.00  8.25       B     C
ATOM   9346  CA  GLU B 486      -9.735   7.030 127.831  1.00  8.59       B     C
ATOM   9355  CA  GLN B 487     -10.721   8.982 130.961  1.00  7.84       B     C
ATOM   9364  CA  ALA B 488      -7.917  11.568 130.491  1.00  6.89       B     C
ATOM   9369  CA  SER B 489      -9.413  12.554 127.143  1.00  6.88       B     C
ATOM   9375  CA  TRP B 490     -12.765  13.388 128.798  1.00  7.07       B     C
ATOM   9389  CA  PRO B 491     -12.065  16.904 130.180  1.00  7.75       B     C
ATOM   9396  CA  ILE B 492     -11.008  18.232 126.748  1.00 10.03       B     C
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ATOM   9404  CA  GLU B 493     -13.896  16.510 124.905  1.00 12.06       B     C
ATOM   9413  CA  LYS B 494     -16.671  17.061 127.427  1.00 10.91       B     C
ATOM   9422  CA  LEU B 495     -15.887  20.513 128.833  1.00  9.26       B     C
ATOM   9430  CA  THR B 496     -14.827  22.544 125.800  1.00  9.84       B     C
ATOM   9437  CA  LYS B 497     -17.972  24.524 124.878  1.00 10.36       B     C
ATOM   9446  CA  PRO B 498     -18.062  25.503 121.171  1.00 10.16       B     C
ATOM   9453  CA  GLY B 499     -18.441  29.251 120.587  1.00 11.73       B     C
ATOM   9457  CA  ALA B 500     -17.533  30.238 124.169  1.00 12.89       B     C
ATOM   9462  CA  TRP B 501     -15.579  33.120 122.622  1.00 13.32       B     C
ATOM   9476  CA  THR B 502     -16.087  34.739 119.196  1.00 14.82       B     C
ATOM   9483  CA  ALA B 503     -13.072  36.086 117.234  1.00 17.18       B     C
ATOM   9488  CA  ALA B 504     -12.857  39.344 115.232  1.00 19.86       B     C
ATOM   9493  CA  ASP B 505     -13.256  36.963 112.234  1.00 21.28       B     C
ATOM   9501  CA  GLY B 506     -16.585  35.755 113.609  1.00 20.03       B     C
ATOM   9505  CA  THR B 507     -14.731  32.439 114.087  1.00 18.03       B     C
ATOM   9512  CA  GLN B 508     -16.251  30.532 117.010  1.00 15.34       B     C
ATOM   9521  CA  VAL B 509     -13.708  29.336 119.570  1.00 11.34       B     C
ATOM   9528  CA  GLY B 510     -14.366  26.537 122.049  1.00  9.07       B     C
ATOM   9532  CA  LEU B 511     -13.197  27.026 125.631  1.00  7.86       B     C
ATOM   9540  CA  LEU B 512     -13.219  25.124 128.921  1.00  7.01       B     C
ATOM   9548  CA  THR B 513     -16.601  25.890 130.550  1.00  8.85       B     C
ATOM   9555  CA  PRO B 514     -18.393  24.554 133.677  1.00 10.28       B     C
ATOM   9562  CA  ARG B 515     -21.081  22.039 132.717  1.00 12.26       B     C
ATOM   9573  CA  ALA B 516     -24.111  20.973 134.766  1.00 13.16       B     C
ATOM   9578  CA  ALA B 517     -24.951  17.342 135.665  1.00 14.35       B     C
ATOM   9583  CA  ASP B 518     -27.642  17.167 132.923  1.00 16.53       B     C
ATOM   9591  CA  GLY B 519     -25.191  18.281 130.210  1.00 16.33       B     C
ATOM   9595  CA  SER B 520     -26.240  21.945 129.971  1.00 15.96       B     C
ATOM   9601  CA  TRP B 521     -23.559  24.648 130.008  1.00 15.21       B     C
ATOM   9615  CA  GLN B 522     -23.432  26.929 133.060  1.00 15.39       B     C
ATOM   9624  CA  SER B 523     -22.733  30.599 132.427  1.00 15.49       B     C
ATOM   9630  CA  ALA B 524     -19.406  32.190 133.361  1.00 13.08       B     C
ATOM   9635  CA  ASP B 525     -16.958  34.949 132.667  1.00 10.42       B     C
ATOM   9643  CA  HIS B 526     -13.996  33.026 131.216  1.00  9.11       B     C
ATOM   9653  CA  ALA B 527     -11.679  35.887 132.307  1.00  9.10       B     C
ATOM   9658  CA  LYS B 528     -12.918  36.154 135.899  1.00 10.32       B     C
ATOM   9667  CA  PHE B 529     -10.563  35.052 138.686  1.00  8.73       B     C
ATOM   9678  CA  GLU B 530     -11.981  32.026 140.571  1.00  8.70       B     C
ATOM   9687  CA  ALA B 531     -15.175  31.800 138.513  1.00  9.23       B     C
ATOM   9692  CA  ALA B 532     -16.810  28.339 138.183  1.00 10.00       B     C
ATOM   9697  CA  GLY B 533     -15.211  26.855 141.335  1.00  9.25       B     C
ATOM   9701  CA  LEU B 534     -11.653  27.388 140.006  1.00  8.07       B     C
ATOM   9709  CA  TYR B 535      -8.638  27.486 142.280  1.00 10.81       B     C
ATOM   9721  CA  GLN B 536      -6.568  30.681 141.905  1.00 10.33       B     C
ATOM   9730  CA  GLY B 537      -7.264  31.159 138.187  1.00  8.79       B     C
ATOM   9734  CA  THR B 538      -9.626  31.771 135.278  1.00  7.44       B     C
ATOM   9741  CA  LEU B 539     -11.154  29.505 132.643  1.00  8.31       B     C
ATOM   9749  CA  TRP B 540      -8.976  31.006 129.900  1.00  6.79       B     C
ATOM   9763  CA  GLN B 541      -6.001  30.062 132.087  1.00  5.72       B     C
ATOM   9772  CA  TYR B 542      -7.247  26.567 133.014  1.00  6.07       B     C
ATOM   9784  CA  HIS B 543      -8.336  25.987 129.378  1.00  6.44       B     C
ATOM   9794  CA  TRP B 544      -4.804  24.912 128.489  1.00  5.93       B     C
ATOM   9808  CA  TYR B 545      -4.279  22.715 131.546  1.00  4.79       B     C
ATOM   9820  CA  ASP B 546      -4.407  19.324 129.817  1.00  4.56       B     C
ATOM   9828  CA  ALA B 547      -0.984  19.835 128.277  1.00  5.44       B     C
ATOM   9833  CA  TYR B 548      -0.609  16.142 127.393  1.00  6.08       B     C
ATOM   9845  CA  ASP B 549      -3.092  16.487 124.510  1.00  5.83       B     C
ATOM   9853  CA  MET B 550      -2.830  19.820 122.688  1.00  7.27       B     C
ATOM   9861  CA  ASP B 551      -3.867  18.042 119.495  1.00  9.92       B     C
ATOM   9869  CA  ALA B 552      -7.181  17.034 121.101  1.00  9.29       B     C
ATOM   9874  CA  LEU B 553      -7.610  20.544 122.602  1.00  8.74       B     C
ATOM   9882  CA  VAL B 554      -6.969  22.270 119.281  1.00  9.28       B     C
ATOM   9889  CA  GLU B 555      -9.660  20.056 117.696  1.00 10.79       B     C
ATOM   9898  CA  ALA B 556     -12.151  20.721 120.539  1.00  8.98       B     C
ATOM   9903  CA  MET B 557     -11.629  24.480 120.201  1.00  9.27       B     C
ATOM   9911  CA  GLY B 558     -12.831  24.096 116.592  1.00 11.18       B     C
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ATOM   9915  CA  GLY B 559      -9.648  23.449 114.651  1.00 12.57       B     C
ATOM   9919  CA  HIS B 560      -6.240  24.925 113.907  1.00 13.76       B     C
ATOM   9929  CA  GLU B 561      -7.665  28.397 113.047  1.00 13.40       B     C
ATOM   9938  CA  ALA B 562      -9.852  28.561 116.156  1.00 11.93       B     C
ATOM   9943  CA  ALA B 563      -6.829  27.744 118.342  1.00 11.17       B     C
ATOM   9948  CA  ARG B 564      -4.548  30.202 116.523  1.00 10.14       B     C
ATOM   9959  CA  LEU B 565      -6.933  33.107 117.193  1.00  9.78       B     C
ATOM   9967  CA  GLY B 566      -7.517  31.781 120.725  1.00  8.93       B     C
ATOM   9971  CA  MET B 567      -3.792  31.948 121.520  1.00  9.45       B     C
ATOM   9979  CA  ARG B 568      -3.398  35.497 120.126  1.00  9.92       B     C
ATOM   9990  CA  HIS B 569      -6.452  36.629 122.170  1.00  9.91       B     C
ATOM  10000  CA  MET B 570      -4.961  34.969 125.270  1.00 10.22       B     C
ATOM  10008  CA  PHE B 571      -1.992  37.376 124.985  1.00  9.43       B     C
ATOM  10019  CA  GLY B 572      -3.956  40.469 123.877  1.00 11.08       B     C
ATOM  10023  CA  GLU B 573      -2.195  40.540 120.475  1.00 13.30       B     C
ATOM  10032  CA  HIS B 574      -5.029  42.598 118.931  1.00 14.86       B     C
ATOM  10042  CA  ALA B 575      -4.622  45.304 121.645  1.00 15.90       B     C
ATOM  10047  CA  PRO B 576      -0.972  45.390 122.696  1.00 17.21       B     C
ATOM  10054  CA  ASP B 577      -1.328  48.595 124.695  1.00 18.80       B     C
ATOM  10062  CA  ASP B 578      -4.343  47.440 126.680  1.00 16.37       B     C
ATOM  10070  CA  GLY B 579      -3.447  45.773 129.999  1.00 14.31       B     C
ATOM  10074  CA  LYS B 580      -6.893  44.273 130.536  1.00 14.35       B     C
ATOM  10083  CA  ALA B 581      -6.401  42.289 127.289  1.00 11.55       B     C
ATOM  10088  CA  MET B 582      -3.732  40.150 128.992  1.00  9.08       B     C
ATOM  10096  CA  LEU B 583      -5.611  36.913 129.818  1.00  6.75       B     C
ATOM  10104  CA  HIS B 584      -2.406  35.066 130.755  1.00  5.26       B     C
ATOM  10114  CA  SER B 585      -1.183  35.314 134.331  1.00  5.08       B     C
ATOM  10120  CA  ASN B 586       2.561  35.487 135.130  1.00  4.87       B     C
ATOM  10128  CA  ALA B 587       1.917  35.442 138.923  1.00  6.16       B     C
ATOM  10133  CA  ASN B 588       0.684  31.857 139.540  1.00  9.70       B     C
ATOM  10141  CA  GLU B 589       1.574  28.445 138.079  1.00 11.52       B     C
ATOM  10150  CA  ILE B 590      -1.724  27.523 136.394  1.00 11.76       B     C
ATOM  10158  CA  ASP B 591      -0.787  28.589 132.835  1.00 11.65       B     C
ATOM  10166  CA  LEU B 592       3.036  28.784 133.060  1.00 10.00       B     C
ATOM  10174  CA  GLN B 593       3.220  26.855 129.797  1.00  7.99       B     C
ATOM  10183  CA  ALA B 594       0.955  29.258 127.891  1.00  7.42       B     C
ATOM  10188  CA  PRO B 595       3.697  31.434 126.264  1.00  6.47       B     C
ATOM  10195  CA  TYR B 596       5.040  28.300 124.524  1.00  5.99       B     C
ATOM  10207  CA  LEU B 597       1.684  27.269 123.043  1.00  5.41       B     C
ATOM  10215  CA  PHE B 598       2.175  29.492 119.962  1.00  6.82       B     C
ATOM  10226  CA  ASN B 599       4.570  26.728 118.788  1.00  7.99       B     C
ATOM  10234  CA  TYR B 600       1.469  24.494 118.559  1.00  8.95       B     C
ATOM  10246  CA  THR B 601      -0.592  27.029 116.565  1.00  9.34       B     C
ATOM  10253  CA  GLY B 602       2.026  27.493 113.815  1.00  9.48       B     C
ATOM  10257  CA  GLU B 603       3.299  30.812 115.139  1.00  9.51       B     C
ATOM  10266  CA  PRO B 604       6.593  29.991 116.946  1.00  8.50       B     C
ATOM  10273  CA  SER B 605       7.845  33.578 116.478  1.00  7.57       B     C
ATOM  10279  CA  LEU B 606       5.226  34.638 119.060  1.00  7.18       B     C
ATOM  10287  CA  THR B 607       6.464  32.030 121.578  1.00  5.66       B     C
ATOM  10294  CA  GLN B 608       9.959  33.487 121.141  1.00  5.96       B     C
ATOM  10303  CA  LYS B 609       8.701  37.059 121.593  1.00  6.51       B     C
ATOM  10312  CA  TRP B 610       6.714  36.241 124.769  1.00  7.00       B     C
ATOM  10326  CA  ALA B 611       9.360  33.957 126.314  1.00  7.18       B     C
ATOM  10331  CA  ARG B 612      11.852  36.768 125.860  1.00  7.07       B     C
ATOM  10342  CA  ALA B 613       9.502  39.547 127.021  1.00  7.16       B     C
ATOM  10347  CA  ILE B 614       8.036  37.923 130.160  1.00  7.15       B     C
ATOM  10355  CA  TYR B 615      11.442  37.037 131.623  1.00  8.13       B     C
ATOM  10367  CA  THR B 616      13.573  39.966 130.409  1.00  8.81       B     C
ATOM  10374  CA  LYS B 617      11.308  42.977 129.716  1.00  9.89       B     C
ATOM  10383  CA  GLU B 618       8.250  44.801 130.976  1.00 10.62       B     C
ATOM  10392  CA  THR B 619       4.925  43.183 130.129  1.00 10.85       B     C
ATOM  10399  CA  TRP B 620       1.277  43.848 130.780  1.00 10.87       B     C
ATOM  10413  CA  ASN B 621       0.104  42.242 133.955  1.00  8.54       B     C
ATOM  10421  CA  ARG B 622      -3.614  41.858 134.675  1.00  6.42       B     C
ATOM  10432  CA  TYR B 623      -3.638  39.092 137.312  1.00  6.84       B     C
ATOM  10444  CA  ILE B 624      -2.166  38.601 140.777  1.00  6.95       B     C
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ATOM  10452  CA  ALA B 625      -2.036  35.146 142.429  1.00  9.17       B     C
ATOM  10457  CA  THR B 626      -4.883  35.743 144.940  1.00  9.61       B     C
ATOM  10464  CA  GLY B 627      -8.057  37.828 145.428  1.00 11.00       B     C
ATOM  10468  CA  SER B 628      -6.410  40.988 146.753  1.00 14.00       B     C
ATOM  10474  CA  SER B 629      -3.055  42.511 147.827  1.00 14.96       B     C
ATOM  10480  CA  SER B 630      -2.186  45.392 150.152  1.00 15.87       B     C
ATOM  10486  CA  ALA B 631       1.099  45.793 148.230  1.00 15.15       B     C
ATOM  10491  CA  VAL B 632      -0.451  46.993 144.954  1.00 12.68       B     C
ATOM  10498  CA  PRO B 633      -3.837  48.543 144.078  1.00 11.90       B     C
ATOM  10505  CA  SER B 634      -5.790  45.403 143.232  1.00 10.24       B     C
ATOM  10511  CA  GLY B 635      -9.047  43.424 143.655  1.00 10.87       B     C
ATOM  10515  CA  GLY B 636     -10.965  40.434 142.243  1.00 11.37       B     C
ATOM  10519  CA  GLY B 637      -7.618  38.717 141.514  1.00 10.74       B     C
ATOM  10523  CA  GLU B 638      -6.354  41.552 139.331  1.00 10.06       B     C
ATOM  10532  CA  PHE B 639      -4.034  44.542 139.288  1.00 10.96       B     C
ATOM  10543  CA  THR B 640      -6.497  47.479 139.174  1.00 13.37       B     C
ATOM  10550  CA  PRO B 641      -5.496  48.960 136.843  1.00 14.12       B     C
ATOM  10557  CA  PRO B 642      -3.275  46.456 134.964  1.00 13.72       B     C
ATOM  10564  CA  LEU B 643       0.396  47.404 135.238  1.00 14.65       B     C
ATOM  10572  CA  LYS B 644       3.137  47.317 132.691  1.00 13.96       B     C
ATOM  10581  CA  THR B 645       6.095  45.936 134.647  1.00 11.78       B     C
ATOM  10588  CA  LYS B 646       8.969  43.450 134.688  1.00 11.14       B     C
ATOM  10597  CA  VAL B 647       7.800  40.166 136.218  1.00  8.36       B     C
ATOM  10604  CA  TYR B 648      11.303  39.198 137.406  1.00  7.74       B     C
ATOM  10616  CA  ARG B 649      13.591  41.824 139.020  1.00  9.04       B     C
ATOM  10627  CA  LEU B 650      17.093  41.707 140.433  1.00  7.53       B     C
ATOM  10635  CA  ASP B 651      15.807  43.347 143.621  1.00  5.17       B     C
ATOM  10643  CA  PRO B 652      14.545  42.350 147.055  1.00  5.40       B     C
ATOM  10650  CA  ARG B 653      11.139  42.853 145.381  1.00  6.53       B     C
ATOM  10661  CA  GLY B 654      12.108  40.059 142.996  1.00  6.41       B     C
ATOM  10665  CA  MET B 655       8.705  38.795 141.823  1.00  6.72       B     C
ATOM  10673  CA  LEU B 656       5.334  40.460 141.196  1.00  6.70       B     C
ATOM  10681  CA  PRO B 657       3.402  41.236 144.385  1.00  6.71       B     C
ATOM  10688  CA  THR B 658       1.659  37.972 145.528  1.00  7.41       B     C
ATOM  10695  CA  MET B 659       3.892  35.925 143.184  1.00  5.95       B     C
ATOM  10703  CA  ASP B 660       5.190  33.199 145.543  1.00  4.96       B     C
ATOM  10711  CA  ASN B 661       8.255  31.368 144.118  1.00  5.08       B     C
ATOM  10719  CA  ASP B 662       6.702  28.114 145.513  1.00  4.85       B     C
ATOM  10727  CA  ALA B 663       9.647  25.783 146.215  1.00  5.19       B     C
ATOM  10732  CA  GLY B 664      11.674  27.503 143.453  1.00  5.63       B     C
ATOM  10736  CA  THR B 665       9.108  26.987 140.680  1.00  6.11       B     C
ATOM  10743  CA  MET B 666       9.161  30.568 139.404  1.00  7.32       B     C
ATOM  10751  CA  SER B 667      12.973  30.544 139.595  1.00  7.14       B     C
ATOM  10757  CA  THR B 668      13.107  27.187 137.738  1.00  8.41       B     C
ATOM  10764  CA  MET B 669      10.894  28.674 134.975  1.00  8.61       B     C
ATOM  10772  CA  PHE B 670      13.293  31.613 134.474  1.00  5.87       B     C
ATOM  10783  CA  VAL B 671      16.232  29.234 134.165  1.00  5.19       B     C
ATOM  10790  CA  ALA B 672      14.275  27.232 131.532  1.00  5.77       B     C
ATOM  10795  CA  ALA B 673      13.327  30.366 129.576  1.00  6.53       B     C
ATOM  10800  CA  ALA B 674      17.004  31.392 129.591  1.00  6.52       B     C
ATOM  10805  CA  VAL B 675      18.093  27.945 128.278  1.00  6.08       B     C
ATOM  10812  CA  GLY B 676      15.236  28.143 125.757  1.00  5.59       B     C
ATOM  10816  CA  LEU B 677      13.801  24.680 126.537  1.00  4.36       B     C
ATOM  10824  CA  PHE B 678      10.456  24.513 128.310  1.00  4.27       B     C
ATOM  10835  CA  PRO B 679       8.476  21.441 129.468  1.00  4.23       B     C
ATOM  10842  CA  VAL B 680       4.935  22.169 128.193  1.00  4.71       B     C
ATOM  10849  CA  THR B 681       4.133  18.524 128.725  1.00  4.02       B     C
ATOM  10856  CA  ALA B 682       5.534  17.401 132.028  1.00  2.99       B     C
ATOM  10861  CA  GLY B 683       5.162  13.611 132.013  1.00  4.05       B     C
ATOM  10865  CA  SER B 684       6.552  13.443 128.463  1.00  5.13       B     C
ATOM  10871  CA  SER B 685      10.143  13.369 127.150  1.00  6.66       B     C
ATOM  10877  CA  GLN B 686       9.863  16.641 125.200  1.00  6.38       B     C
ATOM  10886  CA  PHE B 687      10.738  20.344 125.639  1.00  5.59       B     C
ATOM  10897  CA  GLN B 688       9.427  23.232 123.520  1.00  6.03       B     C
ATOM  10906  CA  VAL B 689      11.793  25.796 122.043  1.00  6.55       B     C
ATOM  10913  CA  GLY B 690      11.579  29.419 123.274  1.00  7.04       B     C
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ATOM  10917  CA  SER B 691      14.106  32.286 122.899  1.00  7.79       B     C
ATOM  10923  CA  PRO B 692      17.484  31.426 124.521  1.00  7.84       B     C
ATOM  10930  CA  PHE B 693      18.864  34.550 126.227  1.00  7.82       B     C
ATOM  10941  CA  PHE B 694      22.594  34.064 125.890  1.00  7.33       B     C
ATOM  10952  CA  ASP B 695      25.205  33.655 123.125  1.00  9.43       B     C
ATOM  10960  CA  SER B 696      26.210  30.332 124.574  1.00  9.32       B     C
ATOM  10966  CA  THR B 697      24.781  28.206 127.383  1.00  8.98       B     C
ATOM  10973  CA  THR B 698      26.586  24.967 128.241  1.00  8.91       B     C
ATOM  10980  CA  ILE B 699      25.297  22.278 130.616  1.00  9.45       B     C
ATOM  10988  CA  THR B 700      28.086  19.908 131.647  1.00 10.12       B     C
ATOM  10995  CA  TYR B 701      27.061  16.493 132.887  1.00  9.88       B     C
ATOM  11007  CA  ASP B 702      28.712  14.246 135.442  1.00 11.45       B     C
ATOM  11015  CA  ASP B 703      30.657  12.267 132.819  1.00 13.40       B     C
ATOM  11023  CA  GLY B 704      32.161  15.461 131.345  1.00 11.98       B     C
ATOM  11027  CA  SER B 705      29.921  15.485 128.268  1.00 10.92       B     C
ATOM  11033  CA  ALA B 706      27.904  18.613 127.584  1.00 10.52       B     C
ATOM  11038  CA  PHE B 707      24.798  20.036 125.938  1.00  9.26       B     C
ATOM  11049  CA  THR B 708      25.464  23.375 124.241  1.00  8.88       B     C
ATOM  11056  CA  VAL B 709      22.737  25.748 123.064  1.00  9.09       B     C
ATOM  11063  CA  THR B 710      24.043  28.747 121.128  1.00 11.17       B     C
ATOM  11070  CA  ALA B 711      22.134  31.834 120.050  1.00 12.24       B     C
ATOM  11075  CA  ASP B 712      24.141  33.564 117.322  1.00 14.25       B     C
ATOM  11083  CA  GLY B 713      23.722  37.334 117.271  1.00 12.57       B     C
ATOM  11087  CA  VAL B 714      21.303  37.259 120.194  1.00 12.10       B     C
ATOM  11094  CA  SER B 715      20.477  40.687 121.622  1.00 11.79       B     C
ATOM  11100  CA  GLU B 716      17.633  42.447 123.438  1.00 13.43       B     C
ATOM  11109  CA  ASP B 717      16.112  43.108 119.987  1.00 12.74       B     C
ATOM  11117  CA  ALA B 718      17.337  39.953 118.227  1.00 11.10       B     C
ATOM  11122  CA  PHE B 719      15.169  37.456 120.135  1.00 10.51       B     C
ATOM  11133  CA  TYR B 720      13.602  35.772 117.045  1.00 10.60       B     C
ATOM  11145  CA  VAL B 721      14.971  32.509 115.687  1.00  9.51       B     C
ATOM  11152  CA  GLN B 722      15.866  32.757 111.949  1.00  9.69       B     C
ATOM  11161  CA  SER B 723      17.260  29.236 111.377  1.00 10.67       B     C
ATOM  11167  CA  ALA B 724      18.749  26.372 113.367  1.00 10.44       B     C
ATOM  11172  CA  THR B 725      21.057  23.385 113.295  1.00 10.19       B     C
ATOM  11179  CA  LEU B 726      21.285  20.299 115.497  1.00  9.79       B     C
ATOM  11187  CA  ASP B 727      24.740  18.682 115.470  1.00 10.78       B     C
ATOM  11195  CA  GLY B 728      25.486  20.479 112.168  1.00  9.59       B     C
ATOM  11199  CA  ALA B 729      22.291  19.355 110.407  1.00  9.37       B     C
ATOM  11204  CA  THR B 730      19.314  21.561 109.427  1.00  9.54       B     C
ATOM  11211  CA  PHE B 731      16.911  21.620 112.380  1.00  9.46       B     C
ATOM  11222  CA  GLY B 732      13.291  22.799 111.894  1.00 10.01       B     C
ATOM  11226  CA  ASN B 733      11.327  21.345 114.825  1.00 10.28       B     C
ATOM  11234  CA  THR B 734       9.967  23.567 117.612  1.00 10.95       B     C
ATOM  11241  CA  TRP B 735      10.620  20.889 120.262  1.00  9.83       B     C
ATOM  11255  CA  VAL B 736      13.510  18.634 121.295  1.00  9.57       B     C
ATOM  11262  CA  ASP B 737      13.581  15.277 123.044  1.00  9.41       B     C
ATOM  11270  CA  TYR B 738      15.214  14.889 126.458  1.00  7.09       B     C
ATOM  11282  CA  ALA B 739      17.644  12.232 125.051  1.00  6.73       B     C
ATOM  11287  CA  THR B 740      19.020  14.795 122.576  1.00  6.66       B     C
ATOM  11294  CA  VAL B 741      19.805  17.297 125.352  1.00  6.54       B     C
ATOM  11301  CA  VAL B 742      21.387  14.908 127.847  1.00  6.53       B     C
ATOM  11308  CA  GLY B 743      23.160  13.136 124.956  1.00  8.60       B     C
ATOM  11312  CA  GLY B 744      25.256  16.293 124.535  1.00  8.96       B     C
ATOM  11316  CA  ALA B 745      23.948  17.869 121.301  1.00  8.77       B     C
ATOM  11321  CA  ASP B 746      24.948  21.245 119.824  1.00  9.99       B     C
ATOM  11329  CA  LEU B 747      21.727  23.156 119.256  1.00  9.20       B     C
ATOM  11337  CA  ALA B 748      22.723  26.298 117.347  1.00  9.57       B     C
ATOM  11342  CA  PHE B 749      20.245  29.087 116.636  1.00  9.42       B     C
ATOM  11353  CA  ARG B 750      20.864  32.051 114.353  1.00 10.76       B     C
ATOM  11364  CA  MET B 751      18.965  35.015 115.906  1.00 10.21       B     C
ATOM  11372  CA  GLY B 752      17.572  38.240 114.387  1.00 12.06       B     C
ATOM  11376  CA  GLU B 753      15.318  41.247 114.999  1.00 14.15       B     C
ATOM  11385  CA  GLN B 754      12.309  40.094 112.922  1.00 15.06       B     C
ATOM  11394  CA  PRO B 755       9.930  37.094 113.128  1.00 14.14       B     C
ATOM  11401  CA  SER B 756      10.685  34.248 110.709  1.00 14.80       B     C
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ATOM  11407  CA  ASP B 757       8.804  31.176 109.465  1.00 14.96       B     C
ATOM  11415  CA  TRP B 758      11.407  28.912 111.150  1.00 13.21       B     C
ATOM  11429  CA  GLY B 759       9.689  25.918 112.773  1.00 13.37       B     C
ATOM  11433  CA  THR B 760       6.357  26.434 111.014  1.00 13.94       B     C
ATOM  11440  CA  ASP B 761       6.914  23.033 109.382  1.00 13.96       B     C
ATOM  11448  CA  THR B 762       7.829  21.295 112.640  1.00 10.47       B     C
ATOM  11455  CA  ALA B 763       7.173  17.563 113.052  1.00  9.77       B     C
ATOM  11460  CA  PRO B 764       4.213  17.436 115.464  1.00  9.45       B     C
ATOM  11467  CA  ALA B 765       4.950  17.568 119.216  1.00  7.60       B     C
ATOM  11472  CA  PHE B 766       3.648  14.939 121.659  1.00  7.84       B     C
ATOM  11483  CA  SER B 767      -0.100  14.561 122.179  1.00  8.05       B     C
ATOM  11489  CA  MET B 768      -1.670  11.546 123.865  1.00 10.37       B     C
ATOM  11497  CA  SER B 769      -4.411  11.138 121.212  1.00 13.56       B     C
ATOM  11503  CA  THR B 770      -1.982  11.233 118.242  1.00 17.85       B     C
ATOM  11510  CA  ALA B 771       0.792   9.094 119.762  1.00 20.44       B     C
ATOM  12382 CA    CA C   1      41.425  16.915  81.268  1.00 30.05       C    CA
ATOM  12383 CA    CA C   6       1.503  30.134 143.317  1.00 32.32       C    CA
END
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