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(71)申請人：比利時商ＵＣＢ生物製藥公司 (比利時) UCB BIOPHARMA SRL (BE)
比利時

(72)發明人：戴維斯 蓋瑞斯 查理斯 格林德沃 DAVIES, GARETH CHARLES GLYNDWR (GB)；達迪 妮莎 DEDI, NEESHA (GB)；麥克米蘭 大衛 詹姆士 MCMILLAN, DAVID JAMES (GB)；特梅 布雷達 TWOMEY, BREDA (IE)；萊特 麥克 約翰 WRIGHT, MICHAEL JOHN (GB)

(74)代理人：陳長文

(56)參考文獻：

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審查人員：吳思嫻

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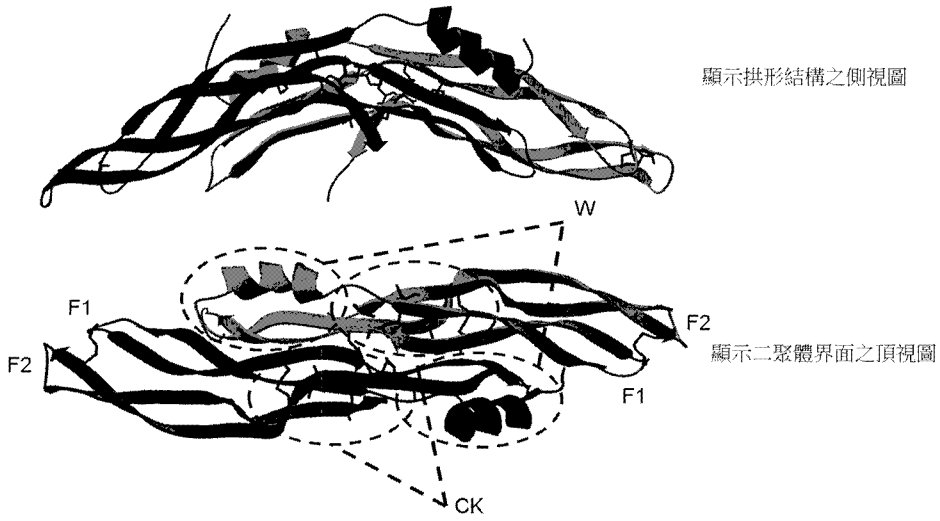
GREMLIN-1 結晶結構及抑制抗體

(57)摘要

本發明係關於人類 Gremlin-1 蛋白及與抑制抗體複合之人類 Gremlin-1 蛋白之結晶。本發明亦關於人類 Gremlin-1 (獨自，或與抗體複合)之結構及此等結構在篩檢調節 Gremlin-1 活性之藥劑中的用途。本發明另外提供結合 Gremlin-1 上之異位抑制位點之抗體，以及此類抗體之醫藥組合物及醫學用途及藉由篩檢方法鑑別之藥劑。

This invention relates to crystals of the human Gremlin-1 protein, and the human Gremlin-1 protein in complex with an inhibitory antibody. The invention also relates to the structure of human Gremlin-1 (on its own, or in complex with the antibody) and uses of these structures in screening for agents which modulate Gremlin-1 activity. The invention further provides antibodies which bind an allosteric inhibitory site on Gremlin-1, together with pharmaceutical compositions and medical uses of such antibodies and agents identified by the screening methods.

指定代表圖：



顯示拱形結構之側視圖

顯示二聚體界面之頂視圖

【圖2】

符號簡單說明：

CK・・・胱胺酸結點

F1・・・指型區 1

F2・・・指型區 2

W・・・腕型區

公告本

I787223

【發明摘要】

【中文發明名稱】

GREMLIN-1結晶結構及抑制抗體

【英文發明名稱】

GREMLIN-1 CRYSTAL STRUCTURE AND INHIBITORY ANTIBODY

【中文】

本發明係關於人類Gremlin-1蛋白及與抑制抗體複合之人類Gremlin-1蛋白之結晶。本發明亦關於人類Gremlin-1 (獨自，或與抗體複合)之結構及此等結構在篩檢調節Gremlin-1活性之藥劑中的用途。本發明另外提供結合Gremlin-1上之異位抑制位點之抗體，以及此類抗體之醫藥組合物及醫學用途及藉由篩檢方法鑑別之藥劑。

【英文】

This invention relates to crystals of the human Gremlin-1 protein, and the human Gremlin-1 protein in complex with an inhibitory antibody. The invention also relates to the structure of human Gremlin-1 (on its own, or in complex with the antibody) and uses of these structures in screening for agents which modulate Gremlin-1 activity. The invention further provides antibodies which bind an allosteric inhibitory site on Gremlin-1, together with pharmaceutical compositions and medical uses of such antibodies and agents identified by the screening methods.

【指定代表圖】

圖2

【代表圖之符號簡單說明】

CK　　胱胺酸結點

F1　　指型區1

F2　　指型區2

W　　腕型區

【發明說明書】

【中文發明名稱】

GREMLIN-1結晶結構及抑制抗體

【英文發明名稱】

GREMLIN-1 CRYSTAL STRUCTURE AND INHIBITORY ANTIBODY

【技術領域】

本發明係關於人類Gremlin-1蛋白及與抑制抗體複合之人類Gremlin-1蛋白之結晶。本發明亦關於人類Gremlin-1 (獨自，或與抗體複合)之結構及此等結構在篩檢調節Gremlin-1活性之藥劑中之用途。本發明另外提供結合Gremlin-1上之異位抑制位點之抗體，以及此類抗體之醫藥組合物及醫學用途及藉由篩檢方法鑑別之藥劑。

【先前技術】

Gremlin-1 (亦稱為Drm及CKTSF1B1)係為184個胺基酸的醣蛋白，其形成胱胺酸結分泌蛋白之DAN家族之部分(與Cerberus及Dan及其他一起)。Gremlin結合BMP-2、4及7且抑制BMP-2、4及7之傳信能力以及已證明的可能經由促效VEGFR2達成之促血管生成作用。Gremlin-1之主要作用係在發展期間，其中其在腎臟形成期間及肢芽形成期間至關重要。此等至關重要的作用使gremlin同型組合基因剔除在胚胎小鼠中為致死性的。

在成人期，gremlin之升高水準與特發性肺纖維化及肺動脈高壓相關聯，其中BMP-2、4及7傳信降低，與之相關聯地，TGF-β水準升高。在糖尿病及慢性同種移植腎病中，Gremlin-1表現與纖維化程度相關。

gremlin之升高水準亦與硬皮病、糖尿病腎病及結腸直腸癌相關。已顯示Gremlin-1活化癌細胞侵入及增殖，且被認為在子宮頸癌、肺癌、卵巢癌、腎臟癌、乳癌、結腸癌、胰臟癌及肉瘤癌中起作用。

迄今，存在若干與Gremlin-1研究相關聯之難題且缺乏關於Gremlin-1 (及其搭配物Gremlin-2)之一般理解。BMP生物學複雜且物種之間存在高同源性。對Gremlin-1之研究相當棘手，且缺乏適合工具及試劑來研究其生物學。製備Gremlin-1亦非一個簡單的過程；半胱胺酸結蛋白以難以產生著稱且Gremlin-1之游離半胱胺酸增加了問題的難度。Gremlin-1難以表現更不必說純化。迄今為止，尚未能獲得結構資訊，且文獻中鮮見關於此蛋白之資訊。

【發明內容】

如本發明中所用之術語Gremlin-1通常具有如UniProt條目O60565 (SEQ ID NO:1)中所闡述之序列。術語Gremlin-1亦可指Gremlin-1多肽，其

(a) 包含具有或不具有N端信號肽之SEQ ID NO:1之胺基酸序列或由其組成，亦即可包含如SEQ ID NO:21中所示之成熟肽序列或由其組成；或

(b) 係具有一或多種相對於具有或不具有N端信號肽之SEQ ID NO:1之胺基酸序列(如SEQ ID NO:21中所示)之胺基酸取代、修飾、缺失或插入的衍生物，其保留有Gremlin-1之活性，如SEQ ID NO:20之胺基酸序列。

(c) 其變異體，此類變異體通常保留有與SEQ ID NO:1 (或SEQ ID NO:20或21)之至少約60%、70%、80%、90%、91%、92%、93%、94%

或95%一致性(或甚至約96%、97%、98%或99%一致性)。換言之，此類變異體可以保留與SEQ ID NO:1之約60%至約99%一致性，適合地與SEQ ID NO:1之約80%至約99%一致性，更適合地與SEQ ID NO:1之約90%至約99%一致性且最適合地與SEQ ID NO:1之約95%至約99%一致性。變異體進一步描述如下。

如以下進一步論述，殘基數目通常基於SEQ ID NO:1之序列引述。然而，殘基編號可以由熟習此項技術者容易地外推至如上文所論述之衍生或變異序列。其中，在本發明中殘基數目之引述亦涵蓋變異或衍生序列上之殘基。

本發明人已結晶化了單獨及以與名為Ab 7326 (Fab片段)之抗體複合的人類Gremlin-1。Gremlin-1之結晶使得BMP結合位點中之推定殘基得以測定。此外，與異位抑制抗體Ab 7326之結晶使得抗體抗原決定基中之殘基得以測定。結合此抗原決定基之抗體具有作為與Gremlin-1相關之疾病之治療中之治療劑的潛能。

相應地，本發明提供Gremlin-1之結晶。

本發明亦提供藉由如表1中之座標所界定之人類Gremlin-1之結構。

另外，本發明提供：

- 可機讀資料儲存媒體，其包含編碼有由表1中之Gremlin-1之結構座標或界定該結構之同系物之座標界定之可機讀資料的資料儲存材料。
- 如表1中之座標所界定之Gremlin-1之結構結構作為模型之用途。
- 藉由使用結構模型鑑別之藥劑。
- 篩檢Gremlin-1活性之調節劑之方法，其包含以下步驟：

(a) 自表1中之結構座標中鑑別配位體結合位點；

(b) 鑑別與至少一部分配位體結合位點相互作用之候選藥劑；且

(c) 獲得或合成該藥劑。

- 藉由篩檢方法鑑別之Gremlin-1調節劑。
- 結合於Gremlin-1上之抗原決定基之抗體，該抗原決定基包含至少一個選自以下之殘基：Ile131、Lys147、Lys148、Phe149、Thr150、Thr151、Arg169、Lys174及Gln175，其中殘基編號係基於SEQ ID NO:1。
- 抗Gremlin-1抗體，其包含SEQ ID NO:10或12之重鏈可變區(heavy chain variable region，HCVR)內所含有之重鏈互補決定區(heavy chain complementarity determining region，HCDR)序列及/或SEQ ID NO:11或13之輕鏈可變區(light chain variable region，LCVR)內所含有之輕鏈互補決定區(light chain complementarity determining region，LCDR)序列。
- 抗Gremlin-1抗體，其包含至少一個選自SEQ ID NO:3、4、5及6之HCDR序列及/或至少一個選自SEQ ID NO:7、8及9之LCDR序列。
- 經分離之編碼該等抗體之多核苷酸。
- 帶有該多核苷酸之表現載體。
- 包含該載體之宿主細胞。
- 製備該抗體之方法，其包含在允許產生該抗體之條件下培養該宿主細胞及回收所產生之抗體。
- 包含抗體之醫藥組合物。
- 抗體或醫藥組合物，其用於藉由療法治療人類或動物體之方法中。

• 治療或預防諸如糖尿病腎病之腎纖維化、特發性肺纖維化、肺動脈高壓、血管生成及/或癌症之方法，其包含向有需要之患者投與治療有效量之抗體或醫藥組合物。

【圖式簡單說明】

圖1 (表1)展示Gremlin-1結晶學之結構資料。

圖2顯示人類Gremlin-1之結構。各個單體之帶狀圖像以不同灰度級顯示，標記出指型區1及2 (F1及F2)以及「腕型」區(w)及胱胺酸結點(CK)。形成二硫鍵之半胱胺酸顯示為黑色棒。

圖3顯示人類Gremlin-1與鼠Gremlin-2 (PRDC)之序列比對。用星號標記的殘基在BMP結合中很重要，在二聚體界面中形成關鍵接觸之殘基經加框標記出。

圖4顯示突出顯示疏水性BMP結合殘基之表面繪製。單體以兩個灰度級顯示，且參與BMP結合之六個關鍵殘基以白色顯示。

圖5展示人類Gremlin-1及鼠Gremlin-2之覆蓋圖。上部圖像係比對兩種蛋白的帶狀圖像。下部圖像將參與BMP結合之胺基酸詳細地顯示為棒(鼠Gremlin-2呈白色且人類Gremlin-1呈黑色)。

圖6(A)顯示在Hek Id1報導基因分析中全長Gremlin-1之抑制效果之圖像。

圖6(B)顯示在Hek Id1報導基因分析中截短Gremlin-1之抑制效果之圖像。

圖7顯示在Hek-Id1報導基因分析中免疫衍生抗體之傳信之復原百分比。

圖8顯示在Hek-Id1報導基因分析中庫衍生抗體之傳信之復原百分

比。

圖9顯示Hek-Id1報導基因分析之結果，具有人類Gremlin (圖9A)及鼠Gremlin (圖9B)之滴定及抗體7326 (顯示為抗體PB376)在復原BMP之傳信中之作用。

圖10顯示Gremlin-Fab複合物之模型結構，突出顯示了可能的BMP結合區及Fab抗原決定基。

圖11顯示表面繪製，其描繪呈兩個灰度級之各個Gremlin-1單體，呈黑色之藉由誘變鑑別之待參與BMP結合之六個關鍵殘基及表面上距該等六個關鍵殘基6 Å以內之所有殘基。

圖12右心室收縮壓(right ventricular systolic pressure，RVSP)之評估。

在經常氧及低氧/SU5416處理之C57Bl/6小鼠中評估抗Gremlin 1抗體對RVSP之影響。在經每三天用SU5416 (20 mg/kg)皮下注射隨後暴露於長期常壓性低氧(10% O2)或常氧中21天之雌性C57Bl/6小鼠中測定抗Gremlin 1 (n=8)、IgG1抗體對照(n=6)、PBS (n=2)、伊馬替尼(Imatinib)(n=8)對肺動脈高壓(pulmonary arterial hypertension，PAH)進展之影響。測定RVSP且繪製平均RVSP±SEM圖。

*P<0.05；**P<0.01；***P<0.005；****P<0.001，藉由單因素變異數分析(one-way ANOVA)。

圖13平均動脈系統壓(mean arterial systemic pressure，MABP)之評估。

在經抗Gremlin 1 (n=4)、IgG1抗體對照(n=4)、伊馬替尼(n=4)處理之低氧/SU5416 C57Bl/6小鼠及經抗Gremlin 1 (n=4)、IgG1抗體對照

(n=4)處理之常氧/SU5416 C57Bl/6小鼠中評估抗Gremlin 1抗體對MABP之影響，且在21天之後繪製MABP±SEM圖。

*P<0.05；**P<0.01；***P<0.005；****P<0.001，藉由單因素變異數分析。

圖14右心室肥大之評估。

在低氧/SU5416 C57Bl/6小鼠中評估抗Gremlin 1抗體對右心臟肥大(RV/LV+S)之影響。在經每三天用SU5416 (20 mg/kg)皮下注射隨後暴露於長期常壓性低氧(10% 02)或常氧中21天之雌性C57Bl/6小鼠中測定抗Gremlin 1 (n=8)、IgG抗體對照(n=6)、PBS (n=2)、伊馬替尼(n=8)對肺動脈高壓(PAH)進展之影響。測定RVSP且繪製平均RVSP±SEM圖。

*P<0.05；**P<0.01；***P<0.005；****P<0.001，藉由單因素變異數分析。

圖15肺血管肌化之組織學評估。

評估抗Gremlin 1抗體之影響。將自抗Gremlin 1 (n=6)、IgG抗體對照(n=6)、伊馬替尼(n=6)中任一者分離之肺切片嵌入石蠟，針對平滑肌肌動蛋白(smooth muscle actin，αSMA)染色以評估肌化之程度，且針對馮威里氏因子(Von Willebrand factor，vWF)染色以藉由免疫組織化學鑑別內皮細胞。肺切片藉由Nanozoomer虛擬顯微鏡(Hamamatsu, Welwyn Garden City, UK)數位化，以每組>40血管藉由獨立盲法觀測者評分為無肌化、部分肌化或完全肌化。繪製每組各個血管之模態分數之平均分數±SEM圖。常氧IgG1；低氧/SU5416 IgG1；低氧/SU5416伊馬替尼；低氧/SU5416抗Gremlin1之針對αSMA及vWF染色之嵌入石蠟之肺切片的代表性圖像。

*P<0.05；**P<0.01；***P<0.005；****P<0.001，藉由單因素變異數分析。

序列表簡單說明

SEQ ID NO:1顯示包括24胺基酸N端信號序列(Uniprot ID O60565)之人類Gremlin-1之序列。

SEQ ID NO:2顯示用於結晶學中之包括N端標籤之截短人類Gremlin-1之序列。

SEQ ID NO:3顯示Ab 7326 HCDR1 (Chothia)。

SEQ ID NO:4顯示Ab 7326 HCDR1 (Kabat)。

SEQ ID NO:5顯示Ab 7326 HCDR2 (Kabat)。

SEQ ID NO:6顯示Ab 7326 HCDR3 (Kabat)。

SEQ ID NO:7顯示Ab 7326 LCDR1 (Kabat)。

SEQ ID NO:8顯示Ab 7326 LCDR2 (Kabat)。

SEQ ID NO:9顯示Ab 7326 LCDR3 (Kabat)。

SEQ ID NO:10顯示Ab 7326重鏈可變區(變異體1)。

SEQ ID NO:11顯示Ab 7326輕鏈可變區(變異體1)。

SEQ ID NO:12顯示Ab 7326重鏈可變區(變異體2)。

SEQ ID NO:13顯示Ab 7326輕鏈可變區(變異體2)。

SEQ ID NO:14顯示鼠Ab 7326全長IgG1重鏈。

SEQ ID NO:15顯示鼠Ab 7326全長IgG1輕鏈。

SEQ ID NO:16顯示人類Ab 7326全長IgG1重鏈(變異體2)。

SEQ ID NO:17顯示人類Ab 7326全長IgG1輕鏈(變異體2)。

SEQ ID NO:18顯示Ab 7326 Fab重鏈(變異體1)。

SEQ ID NO:19顯示Ab 7326 Fab輕鏈(變異體1)。

SEQ ID NO:20顯示用於結晶學中之不含N端標籤之截短人類Gremlin-1之序列。

SEQ ID NO:21顯示成熟Gremlin-1之序列(不含信號肽之SEQ ID NO:1)。

SEQ ID NO: 22顯示人類IgG4P重鏈。

SEQ ID NO:23顯示人類IgG4P輕鏈。

SEQ ID NO:24顯示人類IgG1重鏈DNA (變異體1)。

SEQ ID NO:25顯示人類IgG1輕鏈DNA (變異體1)。

SEQ ID NO:26顯示人類IgG4P重鏈DNA。

SEQ ID NO:27顯示人類IgG4P輕鏈DNA。

SEQ ID NO:28顯示鼠全長IgG1重鏈(變異體2)。

SEQ ID NO:29顯示鼠全長IgG1輕鏈(變異體2)。

SEQ ID NO:30顯示人類全長IgG1重鏈(變異體1)。

SEQ ID NO:31顯示人類全長IgG1輕鏈(變異體1)。

SEQ ID NO:32顯示Fab重鏈(變異體2)。

SEQ ID NO:33顯示Fab輕鏈(變異體2)。

SEQ ID NO:34顯示人類IgG4P重鏈(變異體2)。

SEQ ID NO:35顯示人類IgG4P輕鏈(變異體2)。

【實施方式】

Gremlin-1晶體結構

本發明提供人類Gremlin-1之結構座標。完整座標列出於圖1中(表1)。

本發明亦提供人類Gremlin-1之結晶，其由單位晶胞尺寸為a=84.55 Å，b=107.22 Å且c=77.09 Å之C2空間群組成。

本發明另外提供與抗體，更具體言之，具有SEQ ID NO:18之重鏈及SEQ ID NO:19之輕鏈之Fab複合的Gremlin-1之結晶。

本發明另外提供可機讀資料儲存媒體，其包含編碼有由表1中之Gremlin-1之結構座標或界定該結構之同系物之座標界定之可機讀資料的資料儲存材料。

本發明提供表1中之結構資料及可機讀資料儲存媒體之用途，其作為Gremlin-1之結構模型。此類結構模型可用於篩檢與Gremlin-1相互作用之藥劑。篩檢可為高通量篩檢。

與Gremlin-1相互作用之藥劑通常係結合Gremlin-1之藥劑。與Gremlin-1相互作用之藥劑可以調節Gremlin-1。抑制調節劑可能影響Gremlin-1之任何功能，但通常降低Gremlin-1與BMP (BMP 2/4/7)之結合。Gremlin-1係BMP之負調節劑，因此降低的結合增加經由BMP之傳信。活化調節劑可以增加Gremlin-1與BMP之結合。

BMP結合及傳信可以藉由此項技術中已知之任何方法偵測。舉例而言，本申請案之實例描述SMAD磷酸化分析。SMAD1、5及8在BMP傳信時經磷酸化。SMAD磷酸化之增加可因此用於測定增加的BMP傳信，其可以反映出與Gremlin-1之結合之減少。

實例亦描述Id1報導基因分析，其中Id1基因係BMP傳信之目標基因。在此分析中傳信之復原之增加可因此亦用於確定藥劑是否抑制Gremlin-1結合於BMP。

如本文中所提及之藥劑可以係可以潛在地與Gremlin-1相互作用之任

何分子，但較佳為小分子或抗體。

本發明亦提供Gremlin-1活性之調節劑之篩檢方法，其包含以下步驟：

(a) 自表1中之結構座標中鑑別配位體結合位點；

(b) 鑑別與至少一部分配位體結合位點相互作用之候選藥劑；且

(c) 獲得或合成該藥劑。

配位體結合位點可以係Gremlin-1上與蛋白(配位體)相互作用之任何推定位點。配位體結合位點通常係BMP結合位點。如實例中所示，本發明人已鑑別基於Gremlin-1晶體結構之推定BMP結合位點。此結合位點包含以下胺基酸：Trp93、Phe117、Tyr119、Phe125、Tyr126及Phe138，其中殘基編號係基於SEQ ID NO:1。

本發明之篩檢方法可因此包含鑑別與此等殘基中之一或多種，較佳此等殘基中之至少2、3、4種或全部6種相互作用之藥劑。

藥劑與蛋白殘基之相互作用可以藉由此項技術中已知之任何適當方法測定，諸如殘基與藥劑之間之距離係藉由x射線結晶學測定(通常小於6 Å或小於4 Å)。如以下實例中所論述，可由治療劑標靶之Gremlin-1之區域可包括胺基酸Asp92-Leu99、Arg116-His130、Ser137-Ser142、Cys176-Cys178。此等距Gremlin-1之表面上之突變胺基酸6 Å以內。

篩檢方法之步驟(a)及步驟(b)通常電腦模擬進行，且藥劑可以藉由此項技術中已知之任何方法獲得及合成。

在一個實施例中，本發明提供一種與Gremlin-1上之抗原決定基結合之抗體，該抗原決定基包含至少一個選自以下之殘基：Trp93、Phe117、Tyr119、Phe125、Tyr126及Phe138，其中殘基編號係根據SEQ ID

NO:1。本發明亦提供一種抗體，其結合包含以下全部之抗原決定基：Trp93、Phe117、Tyr119、Phe125、Tyr126及Phe138。

本發明亦提供Gremlin-1之此BMP結合區用於生成(潛在抑制)抗體之用途。舉例而言，本發明提供包含至少一個(較佳全部)以上列出之殘基的抗原，其可用於抗體生成。

藥劑可異位地作用，而非與Gremlin-1之BMP結合位點相互作用。在此，藥劑相距於正常結合位點地結合但仍能夠調節Gremlin-1之活性，例如經由誘導蛋白中之構形變化。本發明之結構模型及篩檢方法可因此亦用於鑑別Gremlin-1之異位調節劑。

已發現本發明之Ab 7326抗體異位地作用。此抗體之抗原決定基包含以下殘基：Ile131、Lys147、Lys148、Phe149、Thr150、Thr151、Arg169、Lys174及Gln175，其中殘基編號係基於SEQ ID NO:1。相應地，本發明之篩檢方法可涉及鑑別與此等殘基中之至少1、2、3、4、5種或全部9種相互作用之藥劑。此類藥劑可隨後例如使用抑制BMP結合之實例中所描述之分析測試。較佳，Lys147、Lys148、Phe149、Thr150、Thr151、Arg169、Lys174及Gln175位於Gremlin-1之一個單體上，且Ile131位於Gremlin-1之另一個單體上(Gremlin-1二聚物結合於BMP二聚物)。

同樣，本發明亦涵蓋包含用於產生抗Gremlin-1抗體之此等殘基中之至少一個(較佳全部)之抗原。

另外，藥劑可以藉由此項技術中已知之任何適當方法鑑別為與此等殘基相互作用。藥劑較佳為小分子或抗體。

抗體

本發明提供結合Gremlin-1之抗體。

如本文中所提及之術語「抗體」包括整個抗體及其任何抗原結合片段(亦即，「抗原結合部分」)或單鏈。抗體係指包含藉由二硫鍵連接之至少兩個重(H)鏈及兩個輕(L)鏈之糖蛋白，或其抗原結合部分。各個重鏈包含重鏈可變區(本文中縮寫為HCVR或V_H)及重鏈恆定區。各個輕鏈包含輕鏈可變區(本文中縮寫為LCVR或V_L)及輕鏈恆定區。重鏈及輕鏈之可變區含有與抗原相互作用之結合域。V_H及V_L區可進一步再分為高變區，稱為互補決定區(complementarity determining region，CDR)，穿插有稱為框架區(framework region，FR)之更保守的區域。

抗體之恆定區可介導免疫球蛋白結合於宿主組織或因子，包括免疫系統之多種細胞(例如效應細胞)及經典補體系統之第一組分(C1q)。

本發明之抗體可為單株抗體或多株抗體，且通常為單株抗體。本發明之抗體可為嵌合抗體、CDR-移植抗體、奈米抗體、人類或人類化抗體或任何其抗原結合部分。對於單株及多株抗體之產生，實驗動物通常係非人類哺乳動物，諸如山羊、兔、大鼠或鼠，但抗體亦在其他物種中產生。

多株抗體可藉由常規方法(諸如適合動物之免疫)使用所關注之抗原產生。可隨後自動物中移除血液且純化IgG部分。

可得到抗Gremlin-1抗體，其中動物之免疫係必需的，其藉由使用熟知且常規方案(參見例如《實驗免疫學手冊(Handbook of Experimental Immunology)》D. M. Weir (編)，第4卷, Blackwell Scientific Publishers, Oxford, England, 1986))向動物，例如非人類動物，投與多肽。可對許多恆溫動物進行免疫，諸如兔、小鼠、大鼠、羊、牛、駱駝或豬。然而，小鼠、兔、豬及大鼠通常最適合。

單株抗體可藉由此項技術中已知之任何方法製備，諸如融合瘤技術(Kohler及Milstein, 1975, Nature, 256:495-497)、三源融合瘤(trioma)技術、人類B細胞融合瘤技術(Kozbor等人，1983, Immunology Today, 4:72)及EBV融合瘤技術(Cole等人, Monoclonal Antibodies and Cancer Therapy，第77-96頁，Alan R Liss, Inc., 1985)。

本發明之抗體亦可使用單淋巴球抗體方法，藉由例如由Babcook, J.等人, 1996, Proc. Natl. Acad. Sci. USA 93(15): 7843-78481；WO92/02551；WO2004/051268及WO2004/106377所描述之方法藉由選殖及表現自經選擇用於產生特異性抗體之單淋巴球產生之免疫球蛋白可變區cDNA來產生。

本發明之抗體亦可使用此項技術中已知之各種噬菌體呈現方法來產生，且該等方法包括由Brinkman等人(J. Immunol. Methods, 1995, 182: 41-50中)、Ames等人(J. Immunol. Methods, 1995, 184:177-186)、Kettleborough等人(Eur. J. Immunol. 1994, 24:952-958)、Persic等人(Gene, 1997 187 9-18)、Burton等人(Advances in Immunology, 1994, 57:191-280)及WO 90/02809；WO 91/10737；WO 92/01047；WO 92/18619；WO 93/11236；WO 95/15982；WO 95/20401；及US 5,698,426；5,223,409；5,403,484；5,580,717；5,427,908；5,750,753；5,821,047；5,571,698；5,427,908；5,516,637；5,780,225；5,658,727；5,733,743及5,969,108揭示之方法。

全人類抗體係其中重鏈及輕鏈之可變區及恆定區(當存在時)為全人源的或與人源序列基本上一致但未必來自相同抗體的彼等抗體。全人類抗體之實例可包括，例如藉由上文所述之噬菌體呈現方法產生的抗體，及藉由

其中鼠免疫球蛋白可變且視情況恆定區基因已經其人類對應物置換之小鼠產生的抗體，例如如 EP 0546073、U5,545,806、US 5,569,825、US 5,625,126、US 5,633,425、US 5,661,016、US 5,770,429、EP 0438474及EP 0463151中所概括地描述。

替代地，根據本發明抗體可藉由包含：用Gremlin-1免疫原將非人類哺乳動物免疫；獲得自該哺乳動物產生之抗體；自其導出識別Gremlin-1之單株抗體之方法產生。

本發明之抗體分子可包含具有全長重鏈及輕鏈之完整抗體分子或其片段或抗原結合部分。術語抗體之「抗原結合部分」係指抗體之一或多種片段，其保留有選擇性結合於抗原之能力。已顯示抗體之抗原結合功能可由全長抗體之片段來進行。抗體及其片段及抗原結合部分可以係但不限於：Fab、經修飾Fab、Fab'、經修飾Fab'、$F(ab')_2$、Fv、單域抗體(例如VH或VL或VHH)、scFv、二三或四價抗體、雙scFv、雙功能抗體、三功能抗體、四功能抗體及以上中任一者之抗原決定基結合片段(參見例如Holliger及Hudson, 2005, Nature Biotech. 23(9):1126-1136；Adair及Lawson, 2005, Drug Design Reviews - Online 2(3), 209-217)。用於產生及製造此等抗體片段之方法為此項技術中所熟知(參見例如Verma等人, 1998, Journal of Immunological Methods, 216, 165-181)。用於本發明之其他抗體片段包括國際專利申請案WO 2005/003169、WO 2005/003170及WO 2005/003171中所描述之Fab及Fab'片段及國際專利申請案WO 2009/040562中所描述之Fab-dAb片段。多價抗體可包含多個特異性或可為單特異性(參見例如WO 92/22853及WO 05/113605)。此等抗體片段可使用熟習此項技術者已知之習知技術獲得，且該等片段可經篩檢而以與完

整抗體相同之方式進行應用。

本發明抗體分子之恆定區域若存在，則可根據抗體分子之建議功能及尤其是可能需要的效應功能來選擇。舉例而言，恆定區域可為人類IgA、IgD、IgE、IgG或IgM域。特定言之，當抗體分子意圖用於治療用途且需要抗體效應功能時，可使用人類IgG恆定區域，尤其是IgG1及IgG3同型。或者，當抗體分子意圖用於達成治療目的且不需要抗體效應功能時，則可使用IgG2及IgG4同型。

本發明之抗體可藉由重組手段製備、表現、產生或分離，諸如(a)為得到所關注之免疫球蛋白基因而自轉殖基因或轉殖染色體的動物(例如鼠)或自其製備之融合瘤分離之抗體；(b)自經轉型以表現所關注之抗體之宿主細胞(例如自轉染瘤)分離之抗體；(c)自重組、組合抗體庫分離之抗體；及(d)藉由任何其他涉及編接免疫球蛋白基因序列至其他DNA序列之手段製備、表現、產生或分離之抗體。

本發明之抗體可為人類抗體或人類化抗體。術語「人類抗體」，如本文中所使用，意欲包括具有其中框架區及CDR區皆來源於人類生殖系免疫球蛋白序列之可變區的抗體。另外，若抗體含有恆定區，則恆定區亦來源於人類生殖系免疫球蛋白序列。本發明之人類抗體可包括非由人類生殖系免疫球蛋白序列編碼之胺基酸殘基(例如藉由活體外隨機或定點誘變或藉由活體內體細胞突變引入之突變)。然而，如本文中所使用，術語「人類抗體」不意欲包括來源於另一種哺乳動物物種(諸如小鼠)之生殖系的CDR序列已移植於人類框架序列上的抗體。

此類人類抗體可為人類單株抗體。此類人類單株抗體可藉由融合瘤產生，該融合瘤包括與永生化細胞融合之獲自轉殖基因非人類動物(例如

轉殖基因小鼠)的B細胞，該轉殖基因非人類動物具有包含人類重鏈轉殖基因及人類輕鏈轉殖基因之基因組。

人類抗體可藉由活體外免疫人類淋巴細胞，繼而用艾伯斯坦-巴爾病毒(Epstein-Barr virus)將淋巴細胞轉型來製備。

術語「人類抗體衍生物」係指人類抗體之任何經修飾形式，諸如抗體與另一種藥劑或抗體之結合物。

術語「人類化抗體」意欲指其中來源於另一哺乳動物物種(諸如鼠)之生殖系之CDR序列已經移植在人類框架序列上的CDR-移植抗體分子。在人類框架序列中可作出其他框架區修飾。

如本文中所使用，術語『CDR-移植抗體分子』係指其中重鏈及/或輕鏈含有一或多種來自供體抗體(例如鼠或大鼠單株抗體)之移植至受體抗體(例如人類抗體)之重鏈及/或輕鏈可變區框架的CDR(包括，必要時，一或多種經修飾CDR)的抗體分子。關於綜述，參見Vaughan等人，Nature Biotechnology, **16**, 535-539, 1998。在一個實施例中，僅將來自上文所描述之CDR中之任一者的決定特異性的殘基中之一或多個轉移至人類抗體框架而非轉移整個CDR (參見例如，Kashmiri等人，2005, Methods, 36, 25-34)。在一個實施例中，僅將來自上文所描述之CDR中之一或多個的決定特異性的殘基轉移至人類抗體框架。在另一實施例中，僅將來自上文所描述之各CDR的決定特異性的殘基轉移至人類抗體框架。

當移植CDR或決定特異性的殘基時，根據CDR的供體抗體的類別/類型，可使用任何適當受體可變區框架序列，包括小鼠、靈長類及人類框架區。適合地，根據本發明之CDR-移植抗體具有包含人類受體框架區以及上文所描述之CDR或決定特異性的殘基中之一或多個的可變域。因此，在

一個實施例中提供中和性CDR-移植抗體，其中可變域包含人類受體框架區及非人類供體CDR。

可用於本發明之人類框架之實例為KOL、NEWM、REI、EU、TUR、TEI、LAY及POM (Kabat等人，同前文獻)。舉例而言，KOL及NEWM可用於重鏈，REI可用於輕鏈且EU、LAY及POM可用於重鏈及輕鏈二者。替代地，可使用人類生殖系序列；此等可獲自，例如http://www.vbase2.org/ (參見Retter等人, Nucl. Acids Res. (2005) 33 (增刊1), D671-D674)。.

在本發明之CDR-移植抗體中，受體重鏈及輕鏈不一定需要來源於同一抗體且必要時可包含具有來源於不同鏈之框架區的複合鏈。

在本發明之CDR-移植抗體中，框架區無需具有與受體抗體之序列完全相同的序列。舉例而言，可將不尋常殘基改為用於該受體鏈類別或類型的更常出現的殘基。替代地，可改變在受體框架區中所選擇的殘基以使其對應於在供體抗體中之相同位置出現的殘基(參見Reichmann等人，1998, Nature, 332, 323-324)。此類改變應保持在恢復供體抗體之親和力所必需的最小程度。用於選擇受體框架區中之可能需要改變的殘基的的方案闡述於WO 91/09967中。

熟習此項技術者亦將瞭解抗體可經歷各種轉譯後修飾。此等修飾之類型及程度常常視用於表現抗體的宿主細胞株以及培養條件而定。此類修飾可包括在糖基化、甲硫胺酸氧化、二酮哌嗪形成、天冬胺酸鹽異構化及天冬醯胺脫醯胺方面之變化。常見修飾為由於羧基肽酶作用而損失羧基端鹼性殘基(諸如離胺酸或精胺酸)(如Harris, RJ. Journal of Chromatography 705:129-134, 1995中所描述)。

在一個實施例中，抗體重鏈包含CH1域且抗體輕鏈包含CL域，κ或λ。

生物分子，諸如抗體或片段，含有酸性及/或鹼性官能基，由此給予分子淨正或負電荷。總體上「觀測到」的電荷之量將視實體之絕對胺基酸序列、3D結構中帶電基團之局部環境及分子之環境條件而定。等電點(pI)係特定分子或表面不帶有淨電荷時的pH。在一個實施例中，根據本發明之抗體或片段之等電點(pI)至少為7。在一個實施例中，抗體或片段之等電點至少為8，諸如8.5、8.6、8.7、8.8或9。在一個實施例中，抗體之pI為8。可使用諸如**ExPASY http://www.expasy.ch/tools/pi_tool.html_(參見Walker, The Proteomics Protocols Handbook, Humana Press (2005), 571-607) 之程式預測抗體或片段之等電點。

結合於本文中所揭示之抗原決定基的抗體可包含SEQ ID NO:4至6之重鏈CDR序列中之至少一種、至少兩種或全部三種(分別為HCDR1/HCDR2/HCDR3)。此等為如使用Kabat方法論測定之實例之Ab 7326抗體之HCDR1/HCDR2/HCDR3序列。

用於測定CDR序列之Kabat方法及Chothia方法為此項技術(以及其他技術)中熟知的。CDR序列可使用任何適當方法測定，且在本發明中，儘管通常採用Kabat方法，但亦可以使用其他技術。在本發明實例中，SEQ ID NO:3展示如使用組合的Chothia及Kabat定義所測定之Ab 7326 HCDR1序列。

本發明之抗體可包含SEQ ID NO:7至9之輕鏈CDR序列中之至少一種、至少兩種或全部三種(分別為LCDR1/LCDR2/LCDR3)。此等為使用Kabat方法論之Ab 7326之LCDR1/LCDR2/LCDR3序列。

抗體較佳至少包含SEQ ID NO:6之HCDR3序列。

典型地，抗體包含選自SEQ ID NO:3至5之至少一種重鏈CDR序列及選自SEQ ID NO 7至9之至少一種輕鏈CDR序列。抗體可包含選自SEQ ID NO:3至5之至少兩種重鏈CDR序列及選自SEQ ID NO:7至9之至少兩種輕鏈CDR序列。抗體典型地包含SEQ ID NO:3至5之全部三種重鏈CDR序列(分別為HCDR1/HCDR2/HCDR3)及SEQ ID NO:7至9之全部三種輕鏈CDR序列(分別為LCDR1/LCDR2/LCDR3)。抗體可為嵌合抗體、人類抗體或人類化抗體。

抗體可包含SEQ ID NO:10或12之重鏈可變區(HCVR)序列(Ab 7326變異體1及變異體2之HCVR)。抗體可包含SEQ ID NO:11或13之輕鏈可變區(LCVR)序列(Ab 7326變異體1及變異體2之LCVR)。抗體較佳包含SEQ ID NO:10或12之重鏈可變區序列及SEQ ID NO:11或13之輕鏈可變區序列(尤其SEQ ID NO:10/11或12/13之HCVR/LVCR對)。

抗體可包含以下之重鏈(H鏈)序列：

SEQ ID NO:14鼠全長IgG1重鏈變異體1，或

SEQ ID NO:28鼠全長IgG1重鏈變異體2，或

SEQ ID NO:30人類全長IgG1重鏈變異體1，或

SEQ ID NO:16人類全長IgG1重鏈變異體2，或

SEQ ID NO: 22人類全長IgG4P重鏈變異體1，或

SEQ ID NO:34人類全長IgG4P重鏈變異體2，或

SEQ ID NO:18 Fab重鏈變異體1，或

SEQ ID NO:32 Fab重鏈變異體2。

抗體可包含以下之輕鏈(L鏈)序列：

SEQ ID NO:15鼠全長IgG1輕鏈變異體1，或

SEQ ID NO: 29鼠全長IgG1輕鏈變異體2，或

SEQ ID NO:31人類全長IgG1輕鏈變異體1，或

SEQ ID NO:17人類全長IgG1輕鏈變異體2，或

SEQ ID NO:23人類全長IgG4P輕鏈變異體1，或

SEQ ID NO:35人類全長IgG4P輕鏈變異體2，或

SEQ ID NO:19 Fab輕鏈變異體1，或

SEQ ID NO:33 Fab輕鏈變異體2。

在一個實例中，抗體包含以下之重鏈/輕鏈序列對：

SEQ ID NO:14/15鼠全長IgG1變異體1，或

SEQ ID NO:28/29鼠全長IgG1變異體2，或

SEQ ID NO:30/31人類全長IgG1變異體1，或

SEQ ID NO:16/17人類全長IgG1變異體2，或

SEQ ID NO:22/23人類全長IgG4P變異體1，或

SEQ ID NO:34/35人類全長IgG4P變異體2，或

SEQ ID NO:18/19 Fab輕鏈變異體1，或

SEQ ID NO:32/33 Fab輕鏈變異體2。

對應序列之變異體形式可互換。舉例而言，抗體可包含以下之重鏈/輕鏈序列對：

SEQ ID NO:14/29鼠全長IgG1重鏈變異體1/輕鏈變異體2，或

SEQ ID NO:28/15鼠全長IgG1重鏈變異體2/輕鏈變異體1，或

SEQ ID NO:30/17人類全長IgG1重鏈變異體1/輕鏈變異體2，或

SEQ ID NO:16/31人類全長IgG1重鏈變異體2/輕鏈變異體1，或

SEQ ID NO:22/35人類全長IgG4P重鏈變異體1/輕鏈變異體2，或

SEQ ID NO:34/23人類全長IgG4P重鏈變異體2/輕鏈變異體1，或

SEQ ID NO:18/33 Fab輕鏈重鏈變異體1/輕鏈變異體2，或

SEQ ID NO:32/19 Fab輕鏈重鏈變異體2/輕鏈變異體1。

抗體可為嵌合抗體、人類抗體或人類化抗體。

抗體可替代地為或可包含以上所述之特定序列中之一者之變異體。舉例而言，變異體可為以上胺基酸序列中之任一者之取代、缺失或添加變異體。

變異體抗體可包含1、2、3、4、5、至多10、至多20或更多種(典型地，至多最大值50種)自上文所論述之特定序列之胺基酸取代及/或缺失。「缺失」變異體可包含缺失個別胺基酸；缺失較小胺基酸組，諸如2、3、4或5個胺基酸；或缺失較大胺基酸區，諸如缺失特定胺基酸域或其他特徵。「取代」變異體通常涉及用相同數目之胺基酸置換一或多個胺基酸及進行保守胺基酸取代。舉例而言，胺基酸可經具有類似特性之替代胺基酸取代，例如另一鹼性胺基酸、另一酸性胺基酸、另一中性胺基酸、另一帶電荷胺基酸、另一親水性胺基酸、另一疏水性胺基酸、另一極性胺基酸、另一芳族胺基酸或另一脂族胺基酸。可用於選擇適合取代基之20種主要胺基酸之一些特性如下：

Ala	脂族，疏水性，中性	Met	疏水性，中性
Cys	極性，親水性，中性	Asn	極性，親水性，中性
Asp	極性，親水性，帶電(-)	Pro	疏水性，中性
Glu	極性，親水性，帶電(-)	Gln	極性，親水性，中性
Phe	芳族，疏水性，中性	Arg	極性，親水性，帶電(+)

Gly	脂族，中性	Ser	極性，親水性，中性
His	芳族，極性，親水性，帶電(+)	Thr	極性，親水性，中性
Ile	脂族，疏水性，中性	Val	脂族，疏水性，中性
Lys	極性，親水性，帶電(+)	Trp	芳族，疏水性，中性
Leu	脂族，疏水性，中性	Tyr	芳族，極性，疏水性

較佳「衍生物」或「變異體」一般包括其中序列中所呈現之胺基酸並非天然產生之胺基酸而係其結構類似物的彼等衍生物或變異體。用於序列中之胺基酸亦可為經衍生或修飾的(例如經標記)，其限制條件為抗體之功能不受顯著不利影響。

如上文所描述之衍生物及變異體可在抗體合成期間或藉由產生後修飾來製備，或在抗體為重組形式時使用定點誘變、隨機誘變、或酶促裂解及/或核酸接合來製備。

變異體抗體可具有與本文中所揭示之胺基酸序列(尤其HCVR/LCVR序列及H鏈及L鏈序列)具有大於約60%、或大於約70%，例如75%或80%，典型地大於約85%，例如大於約90%或95%之胺基酸一致性的胺基酸序列。另外，抗體可為與本文中所揭示之HCVR/LCVR序列及H鏈及L鏈序列具有大於約60%、或大於約70%，例如75%或80%，典型地大於約85%，例如大於約90%或95%之胺基酸一致性的變異體，同時保留針對此等序列揭示之確切CDR。同時變異體可保留與本文中所揭示之HCVR/LCVR序列及H鏈及L鏈序列之至少約90%、91%、92%、93%、94%、95%、96%、97%、98%或99%一致性(在一些情況下同時保留確切CDR)。

變異體典型地保留約60%至約99%一致性、約80%至約99%一致性、

約90%至約99%一致性或約95%至約99%一致性。此水準之胺基酸一致性跨相關SEQ ID NO序列之全長可見或遍及該序列之一部分可見，諸如跨約20、30、50、75、100、150、200或更多個胺基酸，視全長多肽之大小而定。

與胺基酸序列相關，「序列一致性」係指當用以下參數使用ClustalW (Thompson等人, 1994，前述)評估時具有所陳述之值的序列：

雙序列比對參數-方法：精確，矩陣：PAM，空位開放罰分：10.00，空位延伸罰分：0.10；

多序列對準參數-矩陣：PAM，空位開放罰分：10.00，延遲之一致性%：30，罰分端空位：開啟，空位分隔距離：0，負矩陣：無，空位延伸罰分：0.20，殘基特異性空位罰分：開啟，親水性空位罰分：開啟，親水性殘基：GPSNDQEKR。在特定殘基上之序列一致性意欲包括僅經衍生出之相同殘基。

因此提供具有特異性序列之抗體及保持此等鏈之功能或活性之變異體。

抗體可以與與上文關於H鏈/L鏈、HCVR/LCVR或CDR序列所定義之抗體相同之抗原決定基競爭結合於Gremlin-1或結合於該抗原決定基。特定言之，抗體可以與與包含SEQ ID NO:4/5/6/7/8/9之HCDR1/HCDR2/HCDR3/LCDR1/LCDR2/LCDR3序列組合之抗體相同之抗原決定基競爭結合於Gremlin-1或結合於該抗原決定基。抗體可以與與包含SEQ ID NO:10/11或12/13之HCVR及LCVR序列對或SEQ ID NO:14/15或16/17之全長鏈的抗體相同之抗原決定基競爭結合於Gremlin-1或結合於該抗原決定基。

術語「抗原決定基」為由抗體所結合之抗原之區域。抗原決定基可定義為結構性或功能性的。功能性抗原決定基通常為結構性抗原決定基之子集且具有彼等直接貢獻於相互作用之親和力的殘基。抗原決定基亦可為構形的，亦即由非線性胺基酸組成。在某些實施例中，抗原決定基可包括作為分子之化學活性表面分組的決定子，諸如胺基酸、糖側鏈、磷醯基、或磺醯基，且在某些實施例中，可具有特定三維結構特徵及/或荷質比特徵。

藉由使用此項技術中已知之常規方法，可以容易地確定抗體是否結合於與參考抗體相同之抗原決定基或與相同抗原決定基競爭結合。舉例而言，為確定測試抗體是否結合於與本發明之參考抗體相同之抗原決定基，將參考抗體在飽和條件下與蛋白或肽結合。然後，評估測試抗體結合於蛋白或肽之能力。若在飽和結合參考抗體之後測試抗體能夠結合於蛋白或肽，則可以得出結論，測試抗體結合於與參考抗體不同之抗原決定基。另一方面，若在飽和結合參考抗體之後測試抗體不能夠結合於蛋白或肽，則測試抗體可以結合於與本發明之參考抗體所結合之抗原決定基相同之抗原決定基。

為確定抗體是否與參考抗體競爭結合，以兩個定向實施上述結合方法論。在第一定向中，將參考抗體在飽和條件下與蛋白/肽結合，隨後評估測試抗體與蛋白/肽分子之結合。在第二定向中，將測試抗體在飽和條件下與蛋白/肽結合，隨後評估參考抗體與蛋白/肽之結合。在兩個定向中，若僅第一(飽和)抗體能夠結合於蛋白/肽，則得出結論，測試抗體及參考抗體競爭結合於蛋白/肽。如熟習此項技術者將瞭解，與參考抗體競爭結合之抗體未必結合於與參考抗體相同之抗原決定基，但可藉由結合重疊

或相鄰抗原決定基而在空間上阻礙參考抗體之結合。

兩種抗體結合於相同或重疊抗原決定基，則各自競爭性地抑制(阻斷)另一個結合於抗原。亦即，1、5、10、20或100倍過量之一種抗體抑制另一個之結合達至少50%、75%、90%或甚至99%，如在競爭性結合分析中所量測(參見例如，Junghans等人, Cancer Res, 1990:50:1495-1502)。替代地，若抗原中減少或消除一種抗體之結合的基本上全部胺基酸突變減少或消除了另一抗體之結合，則兩種抗體具有相同抗原決定基。若減少或消除一種抗體之結合的一些胺基酸突變減少或消除另一抗體之結合，則兩種抗體具有重疊抗原決定基。

可隨後進行其他常規實驗(例如肽突變及結合分析)，以確認所觀測到之測試抗體之結合缺失事實上是否係由於結合於與參考抗體相同之抗原決定基，或所觀測到之缺乏係空間阻礙(或另一現象)引起的。此種實驗可以使用ELISA、RIA、表面電漿子共振、流式細胞測量術或在此項技術中可用之任何其他定量或定性抗體結合分析進行。

可以藉由，例如標準ELISA或西方墨點法(Western blotting)，針對與Gremlin-1之結合對抗體進行測試。ELISA分析亦可用於針對顯示與目標蛋白之正反應性之融合瘤之篩檢。抗體之結合選擇性亦可藉由監測抗體與表現目標蛋白之細胞之結合，例如藉由流式細胞測量術測定。因此，篩檢方法可包含藉由進行ELISA或西方墨點法或藉由流式細胞測量術來鑑別能夠結合Gremlin-1抗體之步驟。

抗體可選擇性地(或特異性地)識別Gremlin-1。當抗體或其他化合物以較佳或較高親和力與其所選擇之蛋白結合時，其「選擇性地結合」或「選擇性地識別」蛋白，但不實質上結合其他蛋白，或以低親和力結合其

他蛋白。抗體之選擇性可藉由確定抗體是否結合於如上文所論述之其他相關蛋白或其是否對如上文所論述之其他相關蛋白進行區別來進一步研究。本發明之抗體通常識別人類Gremlin-1。

抗體亦可具有針對相關蛋白或人類Gremlin-1及來自其他物種之Gremlin-1之交叉反應性。

應理解，藉由特異性(或選擇性)，抗體結合於所關注之蛋白而對任何其他分子無顯著交叉反應性。交叉反應性可藉由本文中所描述之任何適合方法評估。若抗體與另一分子之結合係其與所關注之蛋白之結合強度之至少約5%、10%、15%、20%、25%、30%、35%、40%、45%、50%、55%、60%、65%、70%、75%、80%、85%、90%或100%，則可認為抗體之交叉反應性顯著。特異性(或選擇性)抗體可以小於其結合於所關注之蛋白之強度之約90%、85%、80%、75%、70%、65%、60%、55%、50%、45%、40%、35%、30%、25%或20%的強度結合於另一分子。抗體可以其結合於所關注之蛋白之強度之小於約20%、小於約15%、小於約10%或小於約5%、小於約2%或小於約1%的強度結合於另一分子。

適合與本發明一起使用之抗體可具有對(人類) Gremlin-1之高親和力結合。抗體之解離常數(K_D)可小於<1 nM，且較佳<500 pM。在一個實例中抗體之解離常數(K_D)小於200 pM。在一個實例中抗體之解離常數(K_D)小於100 pM。如熟習此項技術者已熟知，可使用各種方法測定抗體對其目標抗原之結合親和力，諸如表面電漿子共振分析、飽和分析或諸如ELISA或RIA之免疫分析。用於測定結合親和力之例示性方法為藉由在BIAcore™ 2000儀器(Biacore AB, Freiburg, Germany)上使用CM5感測器晶片之表面電漿子共振分析，如由Krinner等人, (2007) Mol. Immunol.

February; 44 (5):916-25 (2006年5月11日電子版發表)所描述。

本發明之抗體通常為抑制抗體。Gremlin-1負調節BMP-2、4及7，因此抑制Gremlin-1引起經由BMP之傳信增加。

如上文所提及，本申請案之實例描述兩個用於篩檢抗體是否能夠抑制Gremlin 1之功能性分析，即SMAD磷酸化分析及Hek Id1報導基因分析。通常，在Hek Id1報導基因分析中，抑制抗體復原SMAD磷酸化及/或復原BMP之傳信。相比於BMP對照，SMAD磷酸化可復原至至少80%、90%或100%。在Hek Id1報導基因分析中，抑制抗體之IC_{50}可小於10 nM，較佳小於5 nM。

一旦已鑑別及選擇適合抗體，便可藉由此項技術中已知之方法鑑別抗體之胺基酸序列。編碼抗體之基因可以使用簡併引子選殖。抗體可藉由常規方法重組產生。

本發明亦提供編碼本發明之抗體分子之重鏈及/或輕鏈可變區(或全長H鏈及L鏈)之經分離DNA序列。

變異體多核苷酸可包含序列表中所給定之序列之1、2、3、4、5、至多10、至多20、至多30、至多40、至多50、至多75或更多種核酸取代及/或缺失。通常，變異體具有1至20、1至50、1至75或1至100種取代及/或缺失。

適合變異體可與本文中所揭示之核酸序列中之任一者之多核苷酸至少約70%同源，典型地與其至少約80%或90%且更適合地至少約95%、97%或99%同源。變異體可保留至少約90%、91%、92%、93%、94%、95%、96%、97%、98%或99%一致性。變異體典型地保留約60%至約99%一致性、約80%至約99%一致性、約90%至約99%一致性或約95%至

約99%一致性。通常至少關於多核苷酸之編碼區存在此等水準之同源性及一致性。量測同源性之方法為此項技術中熟知，且熟習此項技術者應理解，在本上下文中，基於核酸一致性計算同源性。如此同源性遍及至少約15、至少約30，例如至少約40、60、100、200或更多個連續核苷酸之區域(視長度而定)存在。如此同源性可遍及未經修飾之多核苷酸序列之全部長度存在。

量測多核苷酸同源性或一致性之方法在此項技術中已知。例如UWGCG程式包提供可用於計算同源性之BESTFIT程式(例如以其預設設置使用)(Devereux等人(1984) Nucleic Acids Research 12, 第387-395頁)。

亦可使用PILEUP算法及BLAST算法計算同源性或排列序列(通常以其預設設置)，例如如Altschul S.F. (1993) J Mol Evol 36:290-300；Altschul, S, F等人(1990) J Mol Biol 215:403-10中所描述。

用於實施BLAST分析之軟體可由國家生物技術資訊中心(National Centre for Biotechnology Information)公開獲得(http://www.ncbi.nlm.nih.gov/)。此算法涉及藉由鑑別查詢序列中之長度W之短字來首先鑑別得高分序列對(high scoring sequence pair，HSP)，該等短字在與資料庫序列中相同長度之字比對時匹配或滿足某些正值臨限值分數T。T稱作鄰域字得分臨限值(Altschul等人，前述)。此等初始鄰域字命中充當用於啟動搜尋之種子以發現含有其之較長HSP。字命中沿各序列以兩個方向延伸，只要累積比對得分可增加即可。在以下情況中字命中在各個方向上之延伸中止：由於一或多個得負分殘基比對之積累，累積比對得分達至零或低於零；或達到任一序列之末端。BLAST算法參數W、T

及X決定比對之靈敏度及速度。BLAST程式使用以下作為預設：字長度(w)為11，BLOSUM62計分矩陣(參見Henikoff 及Henikoff (1992) Proc. Natl. Acad. Sci. USA 89:10915-10919)比對(B)為50，期望值(E)為10，M=5，N=4，及兩股之比較。

BLAST算法進行兩個序列之間相似性之統計分析；參見例如，Karlin及Altschul (1993) Proc. Natl. Acad. Sci. USA 90:5873-5787。藉由BLAST算法提供之一種相似性量測係最小總和概率(P(N))，其提供兩個核苷酸或胺基酸序列之間之匹配將偶然發生之概率的指示。舉例而言，若第一序列與第二序列相比之最小總和概率為小於約1，典型地小於約0.1，適合地小於約0.01，且最適合地小於約0.001，則認為一序列相似於另一序列。舉例而言，最小總和概率可在約1至約0.001，通常約0.01至約0.001範圍內。

同源物可與相關多核苷酸中之序列在小於約3、5、10、15、20或更多種突變上存在不同(其中各者可為取代、缺失或插入)。舉例而言，同源物可相差3至50種突變，通常3至20種突變。此等突變可遍及同源物之至少30，例如至少約40、60或100或更多個連續核苷酸之區域量測。

在一個實施例中，變異體序列可借助基因密碼中之冗餘由序列表中所給定之特定序列而變化。DNA編碼具有4種主要核酸殘基(A、T、C及G) 且使用此等來「拼寫」表示編碼在生物體基因中之胺基酸蛋白的三字母密碼子。沿DNA分子之密碼子之線性序列經轉譯成由彼等基因編碼之蛋白中之胺基酸之線性序列。密碼高度簡併，61個密碼子編碼20種天然胺基酸且3個密碼子表示「終止」信號。因此，大多數胺基酸係由多於一個密碼子編碼，事實上有幾種係由四個或更多個不同密碼子編碼。本

發明之變異體多核苷酸可因此編碼與本發明之另一多核苷酸相同之多肽序列，但由於使用不同密碼子編碼相同胺基酸而可能具有不同核酸序列。

本發明之DNA序列可包含合成DNA (例如藉由化學處理產生的)、cDNA、基因體DNA或其任何組合。

編碼本發明之抗體分子的DNA序列可藉由熟習此項技術者所熟知的方法獲得。舉例而言，編碼抗體重鏈及輕鏈之一部分或全部的DNA序列可按需要自確定的DNA序列或根據相應胺基酸序列來合成。

可構築載體之一般方法、轉染方法及培養方法為熟習此項技術者所熟知。就此而言，參考「Current Protocols in Molecular Biology」, 1999, F. M. Ausubel (編), Wiley Interscience, New York及由Cold Spring Harbor Publishing出版之Maniatis Manual。

亦提供一種宿主細胞，其包含一或多個選殖或表現載體，該一或多個選殖或表現載體包含編碼本發明之抗體的一或多個DNA序列。可使用任何適合宿主細胞/載體系統來表現編碼本發明之抗體分子的DNA序列。可使用細菌，例如大腸桿菌及其他微生物系統，或亦可使用真核(例如哺乳動物的)宿主細胞表現系統。適合哺乳動物宿主細胞包括CHO、骨髓瘤或融合瘤細胞。

本發明亦提供一種用於製造根據本發明之抗體分子的方法，其包含在適合於自編碼本發明之抗體分子的DNA表現蛋白質的條件下培養含有本發明之載體的宿主細胞，且分離抗體分子。

已鑑別本發明之Ab 7326抗體結合Gremlin-1之以下殘基：Ile110 (131)、Lys126 (147)、Lys127 (148)、Phe128 (149)、Thr129 (150)、Thr130 (151)、Arg148 (169)、Lys153 (174)及Gln154 (175)，其中

Lys126 (147)、Lys127 (148)、Phe128 (149)、Thr129 (150)、Thr130 (151)、Arg148 (169)、Lys153 (174)及Gln154 (175)存在於一種Gremlin-1單體上且Ile110 (131)存在於第二Gremlin-1單體上。不在括號中之編號係基於結構檔案(且其與基於結構比對之鼠Gremlin-2之編號相相符)。括號中之數目表示基於SEQ ID NO:1之UniProt條目O60565之殘基。如在實例部分中所論述，此等抗原決定基殘基係使用NCONT分析法以距離Gremlin-1-Ab 7326 Fab複合物4 Å加以鑑別。

本發明之抗體可因此結合於包含至少一個選自以下之殘基的抗原決定基：Ile131、Lys147、Lys148、Phe149、Thr150、Thr151、Arg169、Lys174及Gln175(殘基編號基於SEQ ID NO:1)。本發明之抗體可結合包含此等殘基中之2、3、4、5、6、7、8或全部9種(較佳至少5種殘基)的抗原決定基。

本發明之抗體亦可識別其中Ile131存在於與其他殘基不同之Gremlin-1單體上的抗原決定基。

雖然提供此等殘基用於人類Gremlin-1之特定序列，熟習此項技術者能輕易地使用常規技術推知此等殘基對於其他對應Gremlin序列(例如鼠)之位置。因此亦藉由本發明提供結合於包含此等其他Gremlin序列中之對應殘基的抗原決定基的抗體。

為篩檢結合於特定抗原決定基之抗體，可以進行常規交叉阻斷分析，諸如Antibodies, Harlow and Lane (Cold Spring Harbor Press, Cold Spring Harb., NY)中所描述。其他方法包括丙胺酸掃描突變體、肽墨點法(Reineke (2004) Methods Mol Biol 248:443-63)或肽裂解分析。另外，可以採用諸如抗原決定基切除、抗原決定基提取及化學修飾抗原之方法

(Tomer (2000) Protein Science 9: 487-496)。此類方法為此項技術中所熟知。

抗體抗原決定基亦可藉由x射線結晶學分析來測定。可因此經由抗體結合於Gremlin-1之x射線結晶學分析來評估本發明之抗體。抗原決定基尤其可以此方式藉由測定Gremlin-1上距抗體互補位殘基4Å以內之殘基來鑑別。

醫藥組合物、劑量及劑量方案

可在醫藥組合物中提供本發明之抗體或藉由篩檢方法鑑別之調節Gremlin-1之藥劑。醫藥組合物通常係經滅菌且通常包括醫藥學上可接受之載劑及/或佐劑。本發明之醫藥組合物可另外包含醫藥學上可接受之佐劑及/或載劑。

如本文所用，「醫藥學上可接受之載劑」包括生理學上可相容之任何及全部溶劑、分散介質、包衣、抗細菌劑及抗真菌劑、等張劑及吸收延遲劑及其類似者。載劑可適用於非經腸，例如靜脈內、肌內、皮內、眼內、腹膜內、皮下、脊椎或其他非經腸投與途徑，例如藉由注射或輸注。替代地，載劑可適用於非非經腸投與，諸如局部、表皮或黏膜投與途徑。載劑可適用於經口投與。視投藥途徑而定，調節劑可包覆在材料中以保護化合物不受酸及可能使該化合物失活之其他天然條件的作用。

本發明之醫藥組合物可包括一或多種醫藥學上可接受之鹽。「醫藥學上可接受之鹽」係指保留母體化合物之所需生物活性且不賦予任何非所需毒理學作用之鹽。此類鹽之實例包括酸加成鹽及鹼加成鹽。

醫藥學上可接受之載劑包含水性載劑或稀釋劑。可用於本發明之醫藥組合物之適合之水性載劑的實例包括水、緩衝水及生理鹽水。其他載劑

之實例包括乙醇、多元醇(諸如甘油、丙二醇、聚乙二醇及其類似者)及其適合之混合物、植物油(諸如橄欖油)以及可注射之有機酯(諸如油酸乙酯)。在諸多情況下，組合物中會需要包括等張劑，例如糖、多元醇(諸如甘露醇、山梨糖醇)或氯化鈉。

治療組合物在製造及儲存條件下通常必須為無菌且穩定的。組合物可調配為溶液、微乳液、脂質體或適合於較高藥物濃度之其他有序結構。

本發明之醫藥組合物可包含其他活性成分。

包含本發明之抗體或調節劑及使用說明書的套組亦處於本發明之範疇內。套組可另外含有一或多種其他試劑，諸如如上文所論述之其他治療劑或預防劑。

可投與本發明之調節劑及/或抗體或其調配物或組合物用於預防性及/或治療性治療。

在治療性應用中，已患有如上文所描述之病症或病況之個體以足以治癒、減輕或部分遏止病況或其症狀中之一或多者的量投與化合物。此類治療性治療可導致疾病症狀之嚴重程度降低，或無症狀時期之頻率或持續時間增加。足以實現此之量定義為「*治療有效量*」。

在預防性應用中，向處於如上文所描述之病症或病況風險下之個體以足以預防或降低病況或其症狀中之一或多者之後續作用的量投與調配物。足以實現此之量定義為「*預防有效量*」。用於各目的之有效量將視疾病或損傷之嚴重程度以及個體之重量及一般狀態而定。

經投藥個體可為人類或非人類動物。術語「*非人類動物*」包括所有脊椎動物，例如哺乳動物及非哺乳動物，諸如非人類靈長類動物、綿羊、狗、貓、馬、牛、雞、兩棲動物、爬行動物等。典型的為投與人類。

本發明之抗體/調節劑或醫藥組合物可使用此項技術中已知之多種方法中之一或多者經由一或多種投藥途徑投與。如熟習此項技術者應瞭解，投藥途徑及/或模式應視所需結果而變化。本發明之化合物或醫藥組合物之投與途徑的實例包括靜脈內、肌內、皮內、眼內、腹膜內、皮下、脊椎或其他非經腸投與途徑，例如藉由注射或輸注。如本文中所使用之片語「*非經腸投與*」意謂除腸內及局部投與之外的投與模式，通常藉由注射。替代地，本發明之抗體/調節劑或醫藥組合物可以透過非非經腸途徑投與，諸如局部、表皮或黏膜投與途徑。本發明之抗體/調節劑或醫藥組合物可用於經口投與。

本發明之抗體/調節劑或醫藥組合物之適合劑量可由熟練的醫學從業者來確定。本發明之醫藥組合物中活性成分之實際劑量含量可變化，以獲得針對特定患者、組合物及投藥模式有效地達成所需治療響應而對患者無毒性的活性成分之量。所選劑量含量將視多種藥物動力學因素而定，該等因素包括所採用之本發明之特定組合物的活性；投與途徑；投與時間；待採用之特定化合物之排泄速率；治療持續時間；與所採用之特定組合物組合使用的其他藥物、化合物及/或材料；待治療之患者之年齡、性別、體重、病狀、一般健康狀況及先前病史；及醫學技術中熟知之類似因素。

適合劑量可例如在待治療之患者之每公斤體重約0.01 μg至約1000 mg、通常每公斤體重約0.1 μg至約100 mg範圍內。舉例而言，適合劑量可為每天每公斤體重約1 μg至約10 mg或約10 μg至約5 mg。

可調整劑量方案以提供最優的所需響應(例如治療響應)。舉例而言，可投與單一劑量，可隨時間投與若干分次劑量，或可依治療情況之緊急性所指示按比例減少或增加劑量。如本文所使用之單位劑型係指適合作為單

個劑量用於待治療之個體的實體上離散之單位；各單位含有與所需醫藥載劑結合之經計算以產生所需治療效果的預定量之活性化合物。

投與可按單個或多個劑量。多個劑量可經由相同或不同途徑且向相同或不同位置投與。替代地，可經由持續釋放調配物給藥，在此情況下需要較不頻繁之投與。劑量及頻率可視拮抗劑在患者中之半衰期及所需治療持續時間而變化。

如上文所提及，本發明之調節劑/抗體或醫藥組合物可與一或多種其他治療劑共同投與。

兩種或更多種試劑之組合投與可以多種不同方式達成。其均可以單個組合物形式一起投與，或其可以獨立組合物形式作為組合療法之部分來投與。舉例而言，一者可在另一者之前、之後或同時投與。

治療性指示

本發明之抗體或藉由本發明之篩檢方法鑑別之調節劑可用於治療、預防或改善與Gremlin-1活性相關之任何病況。例如，全部或部分地由Gremlin-1之傳信引起的任何病況。換言之，本發明係關於由Gremlin介導或影響之病況之治療、預防或改善。此類病況包括纖維化疾病，其包括腎纖維化(例如糖尿病腎病及慢性同種移植腎病)及特發性肺纖維化、肺動脈高壓、血管生成及癌症(例如結腸直腸癌)。

以下實例說明本發明。

實例1-蛋白表現、純化、再摺疊及結構測定。

蛋白表現及包涵體製備

將經優化用於在大腸桿菌中表現之編碼序列(SEQ ID NO:20)之截短人類Gremlin-1使用BamHI/XhoI選殖至經修飾pET32a載體(Merck

Millipore)，生成編碼具有N端6His-TEV標籤之Gremlin序列(pET-hGremlin1)之載體。

表現序列：*MGSSHHHHHHSSGENLYFQGS*AMPGEEVLESSQEALHVTERKYLKRDWCKTQPLKQTIHEEGCNSRTIINRFCYGQCNSFYIPRHIRKEEGSFQSCSFCKPKKFTTMMVTLNCPELQPPTKKKRVTRVKQCRCISIDLD；SEQ ID NO:2 (6His-TEV標籤之非Gremlin殘基以斜體顯示)。序列編號基於UniProt O60565及SEQ ID NO:1。

pET-hGremlin1 質體DNA用於轉型BL21(DE3)細胞。自LB/Amp瓊脂板選取單個耐安比西林群落且用於接種100 ml之LB/Amp之起子培養物。在37℃下振盪(200 rpm) 16小時之後，將25 ml起子培養物用於接種500 mL之2xTY/Amp培養基。在37℃振盪(250 rpm)培養物直至達到OD_{600}為3。隨後，向培養物補充20 mL之MOPS+丙三醇饋料混合物(1M MOPS pH 7.4、40 %丙三醇、0.5 % $MgSO_4$、0.42 % $MgCl_2$)，用300 μM IPTG誘導且在17℃ 180 rpm下另外培育16小時。在離心機(4℃下，4,000 g，20分鐘)中收集細胞。

將細胞集結粒在4℃下再懸浮於溶胞緩衝液(PBS pH 7.4、0.35 mg/ml溶菌酶、10 μg/ml DNA水解酶及3 mM $MgCl_2$)，且藉由在4℃下以3,500 g離心30分鐘來收集不可溶部分。將集結粒化包涵體藉由在洗滌緩衝液(50 mM Tris、500 mM NaCl、0.5 %曲拉通(Triton) X-100，pH 8.0)中再懸浮來洗滌三次，隨後以21,000 g離心15分鐘。使用不含曲拉通X-100之洗滌緩衝液進行另外兩次洗滌。

溶解作用

將包涵體再懸浮於變性緩衝液(8 M脲、100 mM Tris、1 mM

EDTA、10 mM $Na_2S_4O_6$及100 mM Na_2SO_3，pH 8.5)中，在室溫下攪拌16小時且藉由以21,000 g離心15分鐘來澄清。

預再摺疊純化

將經溶解包涵體裝載在於8 M脲、50 mM MES、200 mM NaCl、1 mM EDTA (pH 6.0)中平衡之丙烯葡聚糖凝膠(Sephacryl) S-200 26/60管柱(120 mL) 上。將含有Gremlin-1蛋白之溶離份用6 M脲、20 mM MES (pH 6.0)稀釋且裝載在HiTrap Sp HP陽離子交換管柱上及用1 M NaCl梯度以10倍管柱體積(10 CV)溶離。彙集含有經純化、變性hGremlin-1蛋白之溶離份。

再摺疊

將經變性純化Gremlin-1蛋白逐滴添加至再摺疊緩衝液(50 mM Tris，pH 8.5、150 mM NaCl、5 mM GSH及5 mM GSSG、0.5 mM半胱胺酸、5 mM EDTA、0.5 M精胺酸)至最終濃度0.1 mg/ml，且在4℃下在恆定攪拌下培育5天。5天之後，將Gremlin-1蛋白針對20 mM HEPES、100 mM NaCl (pH 7.5)透析。

在透析之後將蛋白施加於肝素HiTrap管柱且用0至100%肝素溶離緩衝液(20 mM HEPES、1 M NaCl，pH 7.5)之梯度以20 CV溶析。經恰當摺疊之蛋白以1 M NaCl 溶離而任何摺疊異常之蛋白以更低鹽濃度溶離。

將以1 M NaCl溶離之蛋白濃縮且在經20 mM Hepes，pH 7.5、1 M NaCl平衡至S75 26/60管柱上進一步純化。

將蛋白藉由SDS PAGE (在膠凝中偏移)特徵化，使用液相色譜質譜(LC-MS)展示具有預期分子量及二硫鍵之恰當配置，且在細胞分析中展示活性(ID1報導分析)。

Gremlin 1結構測定

使用懸掛滴入法藉由以1:1比率混合6.6 mg/ml之Gremlin 1溶液與0.1 M檸檬酸(pH 4)、1 M氯化鋰及27%聚乙二醇(PEG) 6000來生長Gremlin 1蛋白結晶。在收集資料之前，藉由向結晶緩衝液中添加20%丙三醇來對結晶進行低溫保護。收集金剛石光源(Diamond Light Source)下之繞射資料且使用XDS (Kabsch, Wolfgang (2010) Acta Crystallographica Section D 66, 125-132)處理。繞射資料統計概述在下表中：

表2：繞射資料統計

繞射統計	
波長(Å)	0.97949
空間群	C2
細胞尺寸	a= 84.55 Å，b=107.22 Å，c=77.09 Å；α=90.00°，β=120.43°，γ=90.00°
解析度範圍* (Å)	26.19-2.72 (2.79-2.72)
完整度(%)	98.5 (99.0)
多重度	3.4 (3.4)
I/δ	9.6 (2.0)
R合併	0.095 (0.622)
細化統計	
解析度範圍(Å)	26.19-2.72
$R_{結晶}$	0.24
$R_{自由}$	0.29
R.m.s.d.鍵(Å)**	0.013
R.m.s.d.角(°)	1.782

*括號中之值對應於最高解析度層

**r.m.s.d均方根偏差

使用Phaser (McCoy等人, J Appl Cryst (2007), 40, 658-674)藉由分子替代來解決Gremlin-1結構，且Gremlin-1模型可獲自專用Gremlin-1/Fab複合物座標。所得Gremlin-1模型含有組織成兩個二聚物之四個Gremlin 1單體複本。使用Coot (Emsley等人Acta Crystallographica Section D: Biological Crystallography 66 (4), 486-501)作出模型校正，且使用Refmac (Murshudov等人REFMAC5 for the refinement of macromolecular crystal structures. Acta Crystallographica Section D: Biological Crystallography. 2011;67(第4部分):355-367)細化座標。使用Molprobity (Chen等人(2010) MolProbity: all-atom structure validation for macromolecular crystallography. Acta Crystallographica D66:12-21)驗證最終座標。模型細化統計之概述顯示於上表2中。

實例2-Gremlin-1上之BMP結合殘基

如上文所論述，Gremlin-1屬於骨形態形成蛋白(bone morphogenic protein，BMP)拮抗劑蛋白家族之稱為DAN家族之子群內。在DAN家族中，Gremlin-1與Gremlin-2 (PRDC)享有最大同源性。

描述於實例1中之2.7 Å人類Gremlin-1結構與發表之鼠Gremlin-2結構 (Nolan等人(2013), Structure, 21, 1417-1429)享有許多共同特徵。總摺疊極相似，形成反平行非共價二聚體之Gremlin-1之兩個複本以拱形配置。各個單體採用特徵性的手指型-腕型-手指型配置，以胱胺酸結基元朝向腕型末端且對著手指型(圖2)。在兩個結構中之可見序列內，蛋白之間之序列一致性為52%至67%。最高度保守之區域處於延伸的二聚體界面

中，其中所有關鍵接觸殘基均為100%保守(圖3)。

參與BMP之2、4及7與鼠Gremlin-2 (PRDC)及DAN (NBL1)結合之殘基已使用誘變鑑別(Nolan等人(2013), Structure, 21, 1417-1429及Nolan等人(2014) J. Biol. Chem. 290, 4759-4771)。預測的BMP結合抗原決定基涵蓋二聚體之凸表面上橫跨兩個單體之疏水性區片(圖4及5)。藉由誘變鑑別六種殘基：Trp72、Phe96、Tyr98、Phe104、Tyr105及Phe117 ，且其在人類Gremlin-1中100%保守(編號基於鼠Gremlin-2序列)。同源性程度延伸至在蛋白中採用相同構形之側鏈之定位(圖5)。

用於Gremlin PDB檔案中之胺基酸編號與發表之基於結構比對之鼠Gremlin-2結構中之編號相匹配。此實現在描述結構時之胺基酸之同類比較。然而，出於明晰之目的，鑑別為在BMP結合中起作用之關鍵殘基展示如下，其中基於SEQ ID NO:1之PDB檔案及UniProt檔案之編號在括號中：

Trp72(93)、Phe96(117)、Tyr98(119)、Phe104(125)、Tyr105(126)及Phe117(138)。

在鼠Gremlin -2及人類Gremlin-1中，疏水性BMP結合抗原決定基由各個蛋白之N端殘基形成之α螺旋部分掩埋。已提出BMP結合之模型，其中N端可撓曲，暴露完整BMP結合界面(Nolan等人(2013), Structure, 21, 1417-1429)。在圖4中，在繪製揭示各個蛋白上之BMP結合面之相似性的表面之前已將N端殘基自人類Gremlin-1及鼠Gremlin-2結構中移除。

文獻僅描述影響BMP結合之六種殘基之誘變。很可能，實際BMP抗原決定基覆蓋更大表面積，包涵鄰近胺基酸。藉由突出顯示全部殘基，在該等突變之6Å以內，在Gremlin-1之表面上揭示出Gremlin-1之較大區域

可以潛在地被治療劑標靶(圖11)。此更大面積的區域涵蓋人類Gremlin-1之以下胺基酸：

Asp92-Leu99

Arg116-His130

Ser137-Ser142

Cys176-Cys178

(編號基於SEQ ID NO:1)

藉由組合發表的資訊與人類Gremlin-1之晶體結構資訊，已鑑別出提供自身作為用於治療性干預阻斷其與BMP之相互作用之潛在途徑的人類Gremlin-1之區。

實例3-Hek Id1報導基因分析

背景

Hek Id1報導基因分析使用殖株(Clone) 12 Hek293-Id1報導細胞。此細胞株經Id1轉錄因子穩定轉染。Id1係BMP傳信路徑中之轉錄因子。已知Gremlin結合BMP防止結合於其受體而降低來自報導基因之螢光素酶傳信。因此，使用此報導分析，有可能篩檢抗Gremlin抗體且看是否存在任何阻斷Gremlin與BMP之相互作用的抗Gremlin抗體。若存在此相互作用之阻斷，則將在此等細胞中發現螢光素酶傳信之復原。

方法

在含有10% FCS、1×L-麩醯胺酸及1×NEAA之DMEM中培養殖株12細胞。亦在潮黴素(Hygromycin) B (200 μg/ml) 存在下生長細胞以確保細胞不失去Id1基因表現。在含有0.5% FCS、1×L-麩醯胺酸及1×NEAA之DMEM中分析細胞。細胞在分析中之短時間內不需要潮黴素B。

將細胞在PBS中洗滌，使用細胞解離緩衝液移起，旋轉且統計之後以5×104/孔以70 μl接種(密度7.14×10^5/ml)。所用板為白色不透明經聚D-離胺酸塗佈之96孔無菌板。細胞放入培育箱中約3至4小時來沈澱下來。將BMP雜二聚體在4 mM HCL中復原至200 μg/ml。使用玻璃瓶將BMP在分析培養基中稀釋至10 μg/ml，得到新處理原料。

在聚丙烯板中，將Gremlin-1以1:2稀釋用於8點劑量響應曲線，其中頂部最終劑量為1 μg/ml。

每孔添加20 μl培養基之其他體積，且將板在37℃培育45分鐘。

將以100倍製備之BMP添加至除僅含有細胞之孔之外的所有孔中。所有孔使用分析培養基組成60 μl且在37℃下另外培育45分鐘。

培育後，分析板之每孔轉移30 μl樣品，且在量測發光傳信之前培育20至24小時。

預先在室溫下解凍Cell Steady Glo。在添加試劑之前，將分析板冷卻至室溫約10至15分鐘。藉由在室溫下在振盪器上添加cell steady glo試劑(100 μl) 20分鐘偵測到螢光素酶傳信，且在Synergy 2上使用cell titre glo方案量測發光。

自含有BMP之孔產生最大值傳信，且自僅含有細胞之孔產生最小傳信。

結果

在Hek-Id1報導基因分析中測試Gremlin-1全長及截短形式以確認針對BMP4/7之阻斷活性。全長蛋白之結果顯示於圖6A中，且截短蛋白之結果顯示於圖6B中。

基於分析中之最大及最小信號計算來自劑量響應分析的抑制百分比

且使用4參數邏輯擬合法擬合資料。基於曲線之拐折點計算IC_{50}。

表3：在Hek-Id1報導基因分析中全長Gremlin-1及截短Gremlin-1之效力結果。

Hek-Id1報導基因分析	**N**	**幾何平均值 (nM)**	**95% CI (或範圍 其中N=<4)**
Gremlin 1全長	2	1.6	1.3-1.9
Gremlin 1截段	2	1.7	1.1-2.5

結論

在Hek-Id1報導基因分析中Gremlin 1能夠抑制BMP 4/7傳信。

實例4-抗Gremlin-1抗體之產生

藉由免疫及庫平移衍生抗Gremlin-1抗體。該庫係未處理人類庫經V區由獻血擴增來內部產生。

免疫由第一輪免疫產生26種結合Gremlin-1之相異抗體。將此等抗體按比例擴大及純化用於在篩檢分析中測試。

使用來自R&D Systems之重組人類Gremlin自庫中淘選25種人類及鼠交叉反應抗體。選擇10種抗體作為scFv按比例擴大及純化用於在篩檢分析中測試。

實例5-抗Gremlin-1抗體之篩檢

使用實例3中所描述之Hek-Id1報導基因分析且藉由量測SMAD磷酸化來篩檢抗體。SMAD1、5及8在BMP傳信時經磷酸化。因此Gremlin-1之抑制劑增加SMAD磷酸化。

在A549細胞上或人類肺纖維母細胞上進行SMAD磷酸化分析。使用MSD測定磷酸化水準。

結果

在Hek-Id1報導基因分析中，無明顯與免疫衍生抗體之命中(10倍過量之抗體針對BMP4/7雜二聚體測試)。結果顯示於圖7中。

相比之下，在Hek-Id1報導基因分析中(50倍過量之抗體與50% gremlin劑量)若干庫衍生抗體能夠復原傳信(圖8)。其中，Ab2416及Ab2417含有高水準之內毒素。在10倍過量下Ab7326保持阻斷能力且80%抑制Gremlin-1濃度。

其他結果展示於圖9A (人類gremlin)及圖9B (鼠Gremlin)中。此等圖顯示Ab7326 (標記為PB376)至多15 nM之滴定。顯示當由人類(IC_{50}為1.3nM)或鼠(IC_{50}為0.2nM) Gremlin阻斷時Ab7326復原BMP之傳信。該抗體起到人類及鼠IgG1之作用。

鼠及人類IgG1之序列展示如下：

因為Ab7326來自未處理人類庫，其中Ab選殖為scFv，為將7326可變區再選殖為全長Ab或Fab，有必要使用引子/簡併引子池進行PCR擴增VH及VK。隨後分解經擴增PCR產物且同時選殖至鼠載體及人類載體中。隨著VH及VK經引子/簡併引子池擴增，得到產物之兩個變異體形式，其不同之處在於在PCR方法期間由細微差別的引子黏著產生之單個胺基酸殘基。

重鏈可變區之兩個變異體形式在位置6處之單個胺基酸上不同，且輕鏈可變區之兩個變異體形式在位置7處之單個胺基酸上不同，如下文所示：

- 重鏈可變區變異體1在位置6處具有麩胺酸(E)。
- 重鏈可變區變異體2在位置6處具有麩醯胺酸(Q)。

- 輕鏈可變區變異體1在位置7處具有絲胺酸(S)。
- 輕鏈可變區變異體2在位置7處具有蘇胺酸(T)。

鼠全長IgG1-重鏈變異體1 (SEQ ID NO:14)

QVQLVESGAE VKKPGATVKI SCKVS*GYTFT* **DYYMH**WVQQA PGKGLEWMGL
VDPEDGETIY AEKFQGRVTI TADTSTDTAY MELSSLRSED TAVYYCAT**DA**
RGSGSYYPNH FDYWGQGTLV TVSSAKTTPP SVYPLAPGSA AQTNSMVTLG
CLVKGYFPEP VTVTWNSGSL SSGVHTFPAV LQSDLYTLSS SVTVPSSTWP
SETVTCNVAH PASSTKVDKK IVPRDCGCKP CICTVPEVSS VFIFPPKPKD
VLTITLTPKV TCVVVDISKD DPEVQFSWFV DDVEVHTAQT QPREEQFNST
FRSVSELPIM HQDWLNGKEF KCRVNSAAFP APIEKTISKT KGRPKAPQVY
TIPPPKEQMA KDKVSLTCMI TDFFPEDITV EWQWNGQPAE NYKNTQPIMD
TDGSYFVYSK LNVQKSNWEA GNTFTCSVLH EGLHNHHTEK SLSHSPGK

鼠全長IgG1-輕鏈變異體1 (SEQ ID NO:15)

DIVMTQSPDS LAVSLGERAT INC**KSSQSVL YSSNNKNYLA** WYQQKPGQPP
KLLIY**WASTR ES**GVPDRFSG SGSGTDFTLT INSLQAEDVA VYFC**QQYYDT**
PTFGQGTRLE IKRTDAAPTV SIFPPSSEQL TSGGASVVCF LNNFYPKDIN
VKWKIDGSER QNGVLNSWTD QDSKDSTYSM SSTLTLTKDE YERHNSYTCE
ATHKTSTSPI VKSFNRNEC

鼠全長IgG1-重鏈變異體2 (SEQ ID NO:28)

QVQLVQSGAE VKKPGATVKI SCKVS*GYTFT* **DYYMH**WVQQA PGKGLEWMGL
VDPEDGETIY AEKFQGRVTI TADTSTDTAY MELSSLRSED TAVYYCAT**DA**
RGSGSYYPNH FDYWGQGTLV TVSSAKTTPP SVYPLAPGSA AQTNSMVTLG
CLVKGYFPEP VTVTWNSGSL SSGVHTFPAV LQSDLYTLSS SVTVPSSTWP
SETVTCNVAH PASSTKVDKK IVPRDCGCKP CICTVPEVSS VFIFPPKPKD
VLTITLTPKV TCVVVDISKD DPEVQFSWFV DDVEVHTAQT QPREEQFNST
FRSVSELPIM HQDWLNGKEF KCRVNSAAFP APIEKTISKT KGRPKAPQVY
TIPPPKEQMA KDKVSLTCMI TDFFPEDITV EWQWNGQPAE NYKNTQPIMD
TDGSYFVYSK LNVQKSNWEA GNTFTCSVLH EGLHNHHTEK SLSHSPGK

鼠全長IgG1-輕鏈變異體2 (SEQ ID NO:29)

DIVMTQTPDS LAVSLGERAT INC**KSSQSVL YSSNNKNYLA** WYQQKPGQPP
KLLIY**WASTR ES**GVPDRFSG SGSGTDFTLT INSLQAEDVA VYFC**QQYYDT**
PTFGQGTRLE IKRTDAAPTV SIFPPSSEQL TSGGASVVCF LNNFYPKDIN
VKWKIDGSER QNGVLNSWTD QDSKDSTYSM SSTLTLTKDE YERHNSYTCE
ATHKTSTSPI VKSFNRNEC

人類全長IgG1-重鏈變異體1 (SEQ ID NO:30)

QVQLVESGAE VKKPGATVKI SCKVS*GYTFT* **DYYMH**WVQQA PGKGLEWMGL
VDPEDGETIY AEKFQGRVTI TADTSTDTAY MELSSLRSED TAVYYCAT**DA**
RGSGSYYPNH FDYWGQGTLV TVSSASTKGP SVFPLAPSSK STSGGTAALG
CLVKDYFPEP VTVSWNSGAL TSGVHTFPAV LQSSGLYSLS SVVTVPSSSL
GTQTYICNVN HKPSNTKVDK KVEPKSCDKT HTCPPCPAPE LLGGPSVFLF
PPKPKDTLMI SRTPEVTCVV VDVSHEDPEV KFNWYVDGVE VHNAKTKPRE
EQYNSTYRVV SVLTVLHQDW LNGKEYKCKV SNKALPAPIE KTISKAKGQP
REPQVYTLPP SRDELTKNQV SLTCLVKGFY PSDIAVEWES NGQPENNYKT
TPPVLDSDGS FFLYSKLTVD KSRWQQGNVF SCSVMHEALH NHYTQKSLSL
SPGK

人類全長IgG1-輕鏈變異體1 (SEQ ID NO:31)

DIVMTQSPDS LAVSLGERAT INC**KSSQSVL YSSNNKNYLA** WYQQKPGQPP
KLLIY**WASTR ES**GVPDRFSG SGSGTDFTLT INSLQAEDVA VYFC**QQYYDT**
PTFGQGTRLE IKRTVAAPSV FIFPPSDEQL KSGTASVVCL LNNFYPREAK
VQWKVDNALQ SGNSQESVTE QDSKDSTYSL SSTLTLSKAD YEKHKVYACE
VTHQGLSSPV TKSFNRGEC

人類全長IgG1-重鏈變異體2 (SEQ ID NO:16)

QVQLVQSGAE VKKPGATVKI SCKVS*GYTFT* **DYYMH**WVQQA PGKGLEWMG**L**
VDPEDGETIY AEKFQGRVTI TADTSTDTAY MELSSLRSED TAVYYCAT**DA**
RGSGSYYPNH FDYWGQGTLV TVSSASTKGP SVFPLAPSSK STSGGTAALG
CLVKDYFPEP VTVSWNSGAL TSGVHTFPAV LQSSGLYSLS SVVTVPSSSL
GTQTYICNVN HKPSNTKVDK KVEPKSCDKT HTCPPCPAPE LLGGPSVFLF
PPKPKDTLMI SRTPEVTCVV VDVSHEDPEV KFNWYVDGVE VHNAKTKPRE
EQYNSTYRVV SVLTVLHQDW LNGKEYKCKV SNKALPAPIE KTISKAKGQP
REPQVYTLPP SRDELTKNQV SLTCLVKGFY PSDIAVEWES NGQPENNYKT
TPPVLDSDGS FFLYSKLTVD KSRWQQGNVF SCSVMHEALH NHYTQKSLSL
SPGK

人類全長IgG1-輕鏈變異體2 (SEQ ID NO:17)

DIVMTQTPDS LAVSLGERAT INC**KSSQSVL YSSNNKNYLA** WYQQKPGQPP
KLLIY**WASTR ES**GVPDRFSG SGSGTDFTLT INSLQAEDVA VYFC**QQYYDT**
PTFGQGTRLE IKRTVAAPSV FIFPPSDEQL KSGTASVVCL LNNFYPREAK
VQWKVDNALQ SGNSQESVTE QDSKDSTYSL SSTLTLSKAD YEKHKVYACE
VTHQGLSSPV TKSFNRGEC

使用Kabat方法測定抗體CDR (在以上序列中以粗體突出顯示)。使用Chothia定義之其他HCDR1殘基呈斜體。恆定區序列亦加下劃線。

使用抗Gremlin 1抗體之p-SMAD傳信之復原顯示於下表4中。

表4：p-SMAD傳信之復原

	2417	2418	2419	2481	2482	2483	**2484**	**7326**	8427
BMP 2 50ng/ml	**109.1% +/-2.8%**	58.2% +/-1.9%	32.6% +/-1.4%	40.4% +/-0.6%	35.3% +/-0.8%	43.1% +/-2.1%	**104.0% +/-2.7%**	**107.2% +/-3.5%**	51.3% +/-1.4%
BMP 4 25ng/ml	**109.6% +/-3.0%**	71.3% +/-3.1%	31.7% +/-1.2%	60.1% +/-2.2%	54.4% +/-1.3%	72.5% +/-2.1%	**105.2% +/-3.3%**	**110.0% +/-3.8%**	78.2% +/-2.5%
BMP 7 200 ng/ml	**111.5% +/-3.8%**	**99.5% +/-3.2%**	53.8% +/-3.4%	64.4% +/-1.3%	52.3% +/-1.1%	66.2% +/-1.2%	**105.2% +/-4.3%**	**108.0% +/-3.2%**	72.6% +/-2.5%
BMP-2/7 50ng/ml	**119.3% +/-2.6%**	78.6% +/-3.6%	50.8% +/-2.7%	53.7% +/-3.1%	47.6% +/-1.5%	56.1% +/-2.5%	**120.4% +/-4.4%**	**128.5% +/-2.9%**	62.8% +/-2.5%
BMP4/7 50ng/ml	**113.7% +/-3.1%**	78.0% +/-4.0%	61.4% +/-4.0%	48.3% +/-2.1%	41.7% +/-1.7%	50.8% +/-1.7%	**112.4% +/-2.5%**	**127.0% +/-3.1%**	63.3% +/-2.1%

結果顯示為藉由BMP單獨之SMAD磷酸化之百分比(對照BMP)。使用來自特發性肺纖維化患者之肺纖維母細胞進行實驗。將rhGremlin -1及抗Gremlin-1抗體在室溫下預培育45分鐘。隨後將rhGremlin -1及抗Gremlin-1抗體與BMP添加至細胞中保持30分鐘。

表5則顯示SMAD磷酸化分析中之其他結果，其中研究由抗Gremlin-1抗體自Gremlin1-BMP複合物中置換BMP-2或BMP4/7。另外使用來自特發性肺纖維化患者之肺纖維母細胞進行實驗。在室溫下將rhBMP-2或rhBMP 4/7使用rhGremlin-1預培育1小時。將BMP-2-或BMP4/7-Gremlin-1複合物使用不同濃度之抗Gremlin-1抗體在4℃下培育隔夜。抗體濃度表示板上之最終濃度。

表5：由抗Gremlin-1抗體自Gremlin 1-BMP複合物中置換BMP-2或BMP4/7

		81.3 μg/ml	40.6 μg/ml	20.3 μg/ml	10.2 μg/ml	5.1 μg/ml	2.55 μg/ml	1.27 μg/ml	0.63 μg/ml
2484	**BMP 2 50ng/ml**	100.3% +/- 3.5%	98.8% +/- 2.7%	97.0% +/- 2.9%	93.5% +/- 2.6%	86.4% +/- 2.0%	79.9% +/- 1.9%	66.5% +/- 2.8%	54.8% +/- 0.3%
2484	**BMP4/7 50ng/ml**	136.4% +/- 4.2%	133.2% +/- 1.0%	121.4% +/- 1.4%	108.1% +/- 4.9%	86.6% +/- 4.4%	74.7% +/- 2.2%	65.8% +/- 0.6%	60.7% +/- 1.5%
7326	**BMP 2 50ng/ml**	103.7% +/- 1.1%	101.5% +/- 2.4%	99.4% +/- 3.8%	103.8% +/- 2.4%	100.3% +/- 2.2%	103.2% +/- 4.3%	102.8% +/- 2.8%	97.0% +/- 2.9%
7326	**BMP4/7 50ng/ml**	133.7% +/- 0.8%	132.3% +/- 1.8%	130.3% +/- 4.2%	125.6% +/- 10.0%	121.4% +/- 4.2%	120.9% +/- 3.3%	111.1% +/- 2.3%	102.0% +/- 4.5%

顯示於表5中之結果表明Ab7326可自Gremlin 1-BMP複合物中置換已複合的BMP-2或BMP4/7。相比於抗體2484，Ab7326可以低得多的濃度實現此置換。此提供證據，Ab7326可能以異位方式起作用，與吾人關於Ab7326之結合位點遠離gremlin-1上之已知BMP結合區的發現一致。由此即使當BMP已複合於gremlin-1時Ab7326亦能夠獲得異位結合位點，引起對gremlin活性之抑制顯著提高。

實例6-獲得與7326 Fab複合之Gremlin-1之晶體結構

與Ab 7326 Fab複合之人類Gremlin-1之晶體結構以2.1 Å之解析度解析。Fab序列展示如下：

重鏈：SEQ ID NO:18

QVQLVESGAEVKKPGATVKISCKVSGYTFTDYYMHWVQQAPGKGLEWMGLVD
PEDGETIYAEKFQGRVTITADTSTDTAYMELSSLRSEDTAVYYCATDARGSGSYYP
NHFDYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTV
SWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVD
KKVEPKSC

輕鏈：SEQ ID NO:19

DIVMTQSPDSLAVSLGERATINCKSSQSVLYSSNNKNYLAWYQQKPGQPPKLLIY
WASTRESGVPDRFSGSGSGTDFTLTINSLQAEDVAVYFCQQYYDTPTFGQGTRLEI
KRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQE
SVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

隨後使用CCP4軟體NCONT鑑別距Gremlin-1與Fab之間4Å之所有接觸點。鑑別出以下殘基：Ile131、Lys147、Lys148、Phe149、Thr150、Thr151、Arg169、Lys174及Gln175(編號基於SEQ ID NO:1之UniProt序列(在鼠Gremlin-2之編號相匹配之結構檔案中編號為Ile110、Lys126、Lys127、Phe128、Thr129、Thr130、Arg148、Lys153及Gln154))。

圖10顯示Gremlin-Fab複合物之結構模型，Fab抗原決定基殘基相對於BMP結合區顯示。

Ab 7326為異位地起作用之抑制抗體，亦即其相距於BMP結合區地結合。

實例7-抗Gremlin-1抗體Ab7326與Gremlin-1之結合之親和力量測。

使用表面電漿子共振進行抗Gremlin-1抗體Ab 7326與Gremlin-1之結合之親和力量測。

分析格式：在抗鼠Fc表面上採集抗gremlin mIgG，隨後1至5 nM滴定Gremlin。

緩衝液對照：將緩衝液在抗mFc表面上經過，隨後將Gremlin-1在抗mFc表面上經過，以檢查背景結合。

緩衝液：HBS-EP，pH 7.4且最終NaCl濃度0.3至1.0 M。

結果：發現結合親和力(處理為5次測定之平均K_D值)低於100 pM。

實例8-在小鼠中抗Gremlin-1抗體對長期低氧/SU5416-誘導之肺動脈高壓之作用之活體內評估

概述

TGFβ超家族不平衡已與若干肺病變顯著相關，包括肺動脈高壓(PAH)(Budd及Holmes Pharm Ther 2012)。Gremlin-1已涉及PAH之進展及進程(Thomas等人AJP 2009；Ciuclan等人AJP 2013)。近期研究已表明，在PAH之臨床前低氧/SU5416模型中，抗gremlin-1抗體可以抑制肺動脈高壓之進展(Ciuclan等人AJP 2013)。在此吾人評估在PAH之臨床前低氧/SU5416小鼠模型中抗Gremlin1抗體對血液動力學及血管重構之影響。

低氧/SU5416引起右心室收縮壓(RVSP)顯著增加及右心臟肥大(圖12及圖15)。相比於IgG1及PBS對照組，投與抗Gremlin-1引起RVSP顯著減少($P<0.005$)。觀測到抗Gremlin-1對保持在常氧中之動物之RVSP無顯著影響(圖12)。觀測到對系統壓(平均動脈血壓或MABP；圖13)或右心臟肥大(圖14)無影響。總體而言此研究支持gremlin-1在PAH之長期低氧/SU5416模型中肺血管重構之進展及升高的RVSP的作用及抗gremlin-1抗體在其治療中之用途。

背景

肺高血壓(Pulmonary hypertension，PH)係肺動脈中所量測之壓力升高的血液動力學狀態。臨床上此由平均靜息肺動脈壓(mean resting pulmonary arterial pressure，mPAP) >25 mmHg，肺血管阻力(pulmonary vascular resistance，PVR)≥3個Wood單位且肺楔壓≤15 mmHg界定(Badesch等人2009)。PH之病理性特徵為多層面的且包括肺動脈壓、小至中等動脈之血管重構、右心室肥大及最終右心臟衰竭(Faber及Loscalzo 2004)。PH由WHC歸類成五個主要分類，包括組I。第I組代表肺動脈高壓，其包括特發性PAH及可遺傳PAH以及引起與其他併發症(諸如系統性硬化症)結合之關聯PAH (Simonneau等人2009)。已將若干預置

突變與可遺傳及特發性PAH患者之PAH之進展聯繫起來，最主要的係向骨成形性蛋白受體BMPR2之突變(Budd及Holmes Pharm Ther 2012)。除BMP中之突變以外，亦報導了患有PAH之患者中之活化下游傳信組分Smad (Budd及Holmes Pharm Ther 2012)。最近，研究已鑑別出在患有之PAH患者中BMP抑制劑gremlin (gremlin-1及2)之水準增加(Cahill等人Circ 2012)。與gremlin-1在PAH之進展中之功能性作用一致，在低氧鼠肺中gremlin-1之單倍體缺失(haplodeficiency)強化BMP傳信且藉由緩解血管重構引起肺血管阻力降低(Cahill等人Circ 2012)。此等觀測結果由Ciuclan及同事(AJP 2013)進一步支持，他們展示在小鼠中抗gremlin-1抗體改善長期低氧/SU5416誘導之肺動脈高壓。近期研究表明，無基因機制可以貢獻於系統性硬化症患者之降低的BMPR2表現且可以貢獻於PAH之進展(Gilbane等人AJRCCM)。總體而言，BMP超家族軸不平衡可以導致諸如PAH之肺病變之進展。

本研究之目的係評估在長期低氧/SU5416小鼠模型中抗Gremlin-1對PAH之進展之活體內影響。

材料及方法

試劑

伊馬替尼： Science Warehouse 1625-1000。

SU5416：R & D Systems 3037。

αSMA抗體：Dako M085129-2。

VWF抗體：Dako A008202-2。

經生物素標記之山羊抗兔IgG抗體：Vector Labs BA-1000。

經生物素標記之馬抗鼠IgG抗體，大鼠吸附：Vector Labs BA-

2001。

羧基甲基纖維素：Sigma C5678 419273。

吐溫(TWEEN) 80：Sigma P1754。

苯甲醇：Sigma 305197；402834。

氯化鈉：Sigma S7653；VWR 10241。

VECTASTAIN ABC-AP套組：Vector Labs AK-5000。

VECTASTAIN Elite ABC套組：Vector Labs PK-6100。

正常馬血清：Vector Labs，目錄參考S-2000。

聚山梨醇酯：Sigma 59924。

實驗方案

動物

將C57Bl/6小鼠圈養在無特定病原體設施中，其可以隨意獲取食品及水且暴露於12小時亮/暗週期。此動物研究經英國內政部動物(科學程序)法 1986 (UK Home Office Animals (Scientific Procedures) Act 1986)許可。

肺動脈高壓之低氧/SU5416小鼠模型

將8至10週齡C57Bl/6雌性小鼠分組(表6)。將所有組稱重且以每公斤20 mg皮下(s.c.)投與100 µl之媒劑(0.5%羧基甲基纖維素(CMC)；0.9%氯化鈉(NaCl)；0.4%聚山梨醇酯80；0.9%苯甲醇/去離子水)中之SU5416，如Ciuclan等人AJRCCM 2013中所描述。視需要，投與第二次皮下注射，如表6中所概述，其含有PBS，30 mg/kg IgG1，或30 mg/kg抗Gremlin-1中任一者。同時對低氧+伊馬替尼組中之小鼠用伊馬替尼進行顎輸注以提供100 mg/kg/天。隨後將低氧鼠組置於常壓性低氧(10% O_2)室中，同時常

氧組中之小鼠在與室相同之房間中在常氧(21% O_2)條件中圈養。

表6：處理組：

將C57Bl/6小鼠如所指示地分成處理組。

組	小鼠數目
常氧+ PBS	2
常氧+ IgG1	6
常氧+抗GREMLIN1	8
低氧+ PBS	2
低氧+ IgG	6
低氧+抗GREMLIN1	8
低氧+伊馬替尼	8

在第7天及第14天將所有小鼠經稱重且接受皮下另外劑量之20 mg/kg SU5416。視需要，以另外皮下注射PBS，30 mg/kg IgG1；或30 mg/kg抗Gremlin-1來向小鼠投藥(如表6中所概述)。在第21天獲取右心室收縮壓(RVSP)及平均動脈血壓(MABP)且收集組織。

右心室收縮壓及組織收集

在三週低氧暴露及如表6中所概述之相關藥物處理之後自動物獲得RVSP及MABP之血液動力學量測值。將動物用1.5%異氟醚麻醉且仰臥置於恆溫控制在37℃下之加熱毯上。首先，分離右頸靜脈且引入壓力導管(具有1.4F之直徑的Millar鼠SPR-671NR壓力導管，Millar Instruments，UK)且伸進右心室來測定RVSP。其次，藉由分離左共用頸動脈來量測MABP且引入壓力導管。RVSP及MABP均記錄在預校PowerLab系統(ADInstruments，Australia)上。

藉由異氟醚過度劑量麻醉來將動物安樂死且收集全血。將全血離心

(220×g；2分鐘)，且移除血清且於-80℃下儲存。移除心臟且記錄右心室及左心室重量。用2.5 ml鹽水經由右心室灌注肺。左肺藉由用10%福馬林充氣固定，之後嵌入石蠟且切片。將右肺在液氮中速凍且於-80℃下儲存。

組織學

將載片脫蠟且用二甲苯及濃度梯度之乙醇來再含水。將載片浸沒在0.3% H_2O_2/甲醇中30分鐘以取回抗原，在PBS中洗滌3次且在1:30之正常馬血清/PBS中阻斷1小時。將濃度為1:100之抗αSMA初級抗體添加至各個載片中且在4℃下培育隔夜，隨後在PBS中沖洗三次，持續5分鐘。將經生物素標記之馬抗鼠IgG抗體，大鼠吸附之二級抗體1:200稀釋且吸取在各個載片上且培育45分鐘；隨後在PBS中洗滌3次持續5分鐘。按照製造商之說明書，提前30分鐘製備抗生物素蛋白生物素複合鹼性磷酸酶(ABC-AP)且置於各個載片上30分鐘；隨後洗滌3次持續5分鐘。按照套組說明書製備AP受質且吸取在各個載片上且使其發展；隨後洗滌3次持續5分鐘。將濃度為1:100之抗vWF初級抗體添加至各個載片中且在4℃下培育隔夜，隨後在PBS中沖洗三次持續5分鐘。將經生物素標記之山羊抗兔IgG二級抗體1:200稀釋且放置在各個載片上45分鐘；隨後在PBS中洗滌3次持續5分鐘。按照套組說明書提前30分鐘製備ABC且放在各個載片上30分鐘；隨後洗滌3次持續5分鐘。按照套組說明書製備DAB受質且吸取在各個載片上且使其發展約5至10分鐘；隨後洗滌3次持續5分鐘。將載片用蘇木精複染約40秒，脫水且使用pertex安放蓋玻片。使用Hamamatsu NanoZoomer 2.0-HT載片掃描儀(Hamamatsu，Welwyn Garden City，UK)對所有載片進行數位掃描。

資料及統計分析

自各個低氧組隨機採集大於40血管進行肌化程度之評估。由至少四個獨立觀測者來對血管評分：0=無肌化；1=部分肌化；2=完全肌化；且針對各個血管測定模態值。測定血管完全、部分或無肌化之百分比且繪製平均±SEM曲線。進行單因素變異數分析以確定顯著性*P<0.05；**P<0.01；***P<0.005；****P<0.001。

結果

相比於在PBS單獨或IgG1對照組中之21天常氧/SU5416單獨，在暴露於長期常壓性低氧(10% O_2)之後，投與SU5416 (20mg/kg)引起RVSP顯著(P<0.01)增加(圖12)。IgG1與PBS處理組之間未觀測到顯著差異。藥物處理對經投與SU5416保持在低氧中之小鼠之升高RVSP之影響：相比於對照組，伊馬替尼引起RVSP顯著(P<0.001)降低。相比於IgG1及PBS對照組，抗Gremlin 1引起RVSP顯著(P<0.005)降低。觀測到抗Gremlin 1對保持在常氧中之動物之RVSP無顯著影響(圖12)。

在低氧及常氧下評估抗Gremlin 1 (n=4)或IgG1媒劑對照(n=4)對MABP之影響(圖13)。觀測到處理對MABP無顯著影響。

測定右心臟肥大(右心室/左心室+隔膜重量)(圖14)。相比於在PBS單獨或IgG1對照組中之21天常氧/SU5416單獨，在暴露於長期常壓性低氧(10% O_2)之後，投與SU5416 (20 mg/kg)引起右心臟肥大(RV/LV+S)顯著(P<0.01)增加(圖14)。觀測到藥物處理(伊馬替尼或抗Gremlin 1)對經投與SU5416保持在低氧中之小鼠之升高的RVSP無顯著影響。

藉由將嵌入石蠟之肺切片染色來評估血管重構之程度。將血管進行馮威里氏因子(vWF)染色以鑑別內皮細胞及平滑肌肌動蛋白(αSMA)染色

以評估肌化程度。藉由Hamamatsu NanoZoomer 2.0-HT載片掃描儀將圖像數位化，且對自常氧IgG1及各個低氧組隨機採集之至少40個血管進行肌化程度之評估。由至少四個獨立觀測者來對血管評分：0=無肌化；1=部分肌化；2=完全肌化；且針對各個血管測定模態值，繪製完全、部分或無肌化血管之百分比曲線(圖15)。在暴露於長期常壓性低氧(10% O_2)之後投與SU5416 (20 mg/kg)引起完全肌化($P<0.001$)及部分肌化($P<0.01$)之顯著增加，且無肌化($P<0.001$)血管顯著降低。藥物處理對經投與SU5416保持在低氧中之小鼠之升高的RVSP之影響：伊馬替尼引起完全肌化($P<0.01$)血管之顯著($P<0.001$)降低。而且，相比於低氧SU5416 IgG1對照組，抗Gremlin 1引起顯著(分別$P<0.001$與$P<0.05$)(圖15)。相比於低氧SU5416 IgG1對照組，觀測到藥物處理(伊馬替尼或抗Gremlin1)對部分肌化血管之百分比無顯著影響。相比於低氧SU5416 IgG1對照組，藥物處理(伊馬替尼或抗Gremlin 1)引起無肌化血管之百分比增加，然而此未能達到顯著。

討論

吾人吾人評估在長期低氧/SU5416模型中抗gremlin-1抗體對PAH之進展之影響。在PAH之低氧/SU5416小鼠模型中抗gremlin-1抗體顯著抑制RVSP (圖12)及血管重構(圖15)，同時展現對系統壓(MABP)(圖13)無影響。吾人觀測到抗gremlin-1抗體對常氧/SU5416處理之小鼠之RVSP無顯著影響。抗gremlin1抗體之影響與由Ciuclan及同事(AJP 2013)所作出之觀測結果一致，在其中他們展示在PAH之長期低氧/SU5416-小鼠模型中與抗gremlin-1抗體之拮抗作用改善升高的RVSP及血管重構(圖12及圖15)。與Ciuclan及同事相反，在此研究中吾人注意到抗gremlin-1抗體對右

心臟肥大無顯著影響(圖14)。然而在此研究中吾人注意到對照藥物伊馬替尼對低氧/SU5416小鼠之右心臟肥大之進展無顯著影響。總體而言，此研究支持gremlin-1在PAH之長期低氧/SU5416模型中肺血管重構之進展及升高的RVSP的作用及抗Gremlin-1抗體在其治療中之用途。

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19555858.

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序列表

SEQ ID NO:1 (人類Gremlin-1；Uniprot ID：O60565)

MSRTAYTVGALLLLLGTLLPAAEGKKKGSQGAIPPPDKAQHNDSEQTQSPQQPGSRNRGR
GQGRGTAMPGEEVLESSQEALHVTERKYLKRDWCKTQPLKQTIHEEGCNSRTIINRFCYG
QCNSFYIPRHIRKEEGSFQSCSFCKPKKFTTMMVTLNCPELQPPTKKKRV
TRVKQCRCISIDLD

SEQ ID NO:2 (用於結晶學中之具有N端標籤之人類截短Gremlin-1)

MGSSHHHHHHSSGENLYFQGSAMPGEEVLESSQEALHVTERKYLKRDWCKTQPLKQTIHE
EGCNSRTIINRFCYGQCNSFYIPRHIRKEEGSFQSCSFCKPKKFTTMMVTLNCPELQPPT
KKKRVTRVKQCRCISIDLD

SEQ ID NO:3 (組合有Kabat及Chothia之Ab 7326 HCDR1)

GYTFTDYYMH

SEQ ID NO:4 (Ab 7326 HCDR1 Kabat)

DYYMH

SEQ ID NO:5 (Ab 7326 HCDR2 Kabat)

LVDPEDGETIYAEKFQG

SEQ ID NO:6 (Ab 7326 HCDR3 Kabat)

DARGSGSYYPNHFDY

SEQ ID NO:7 (Ab 7326 LCDR1 Kabat)

KSSQSVLYSSNNKNYLA

SEQ ID NO:8 (Ab 7326 LCDR2 Kabat)

WASTRES

SEQ ID NO:9 (Ab 7326 LCDR3 Kabat)

QQYYDTPT

SEQ ID NO:10 (Ab 7326重鏈可變區變異體1)

QVQLVESGAEVKKPGATVKISCKVSGYTFTDYYMHWVQQAPGKGLEWMGLVDPEDGETIY
AEKFQGRVTITADTSTDTAYMELSSLRSEDTAVYYCATDARGSGSYYPNH
FDYWGQGTLVTVSS

SEQ ID NO:11 (Ab 7326輕鏈可變區變異體1)

DIVMTQSPDSLAVSLGERATINCKSSQSVLYSSNNKNYLAWYQQKPGQPPKLLIYWASTR
ESGVPDRFSGSGSGTDFTLTINSLQAEDVAVYFCQQYYDTPTFGQGTRLEIK

SEQ ID NO:12 (Ab 7326重鏈可變區變異體2)

QVQLVQSGAEVKKPGATVKISCKVSGYTFTDYYMHWVQQAPGKGLEWMGLVDPEDGETIY
AEKFQGRVTITADTSTDTAYMELSSLRSEDTAVYYCATDARGSGSYYPNHFDYWGQGTLV
TVSS

SEQ ID NO:13 (Ab 7326輕鏈可變區變異體2)

DIVMTQTPDSLAVSLGERATINCKSSQSVLYSSNNKNYLAWYQQKPGQPPKLLIYWASTR
ESGVPDRFSGSGSGTDFTLTINSLQAEDVAVYFCQQYYDTPTFGQGTRLEIK

SEQ ID NO:14 (鼠全長IgG1重鏈變異體1)

QVQLVESGAEVKKPGATVKISCKVSGYTFTDYYMHWVQQAPGKGLEWMGLVDPEDGETIY
AEKFQGRVTITADTSTDTAYMELSSLRSEDTAVYYCATDARGSGSYYPNHFDYWGQGTLV
TVSSAKTTPPSVYPLAPGSAAQTNSMVTLGCLVKGYFPEPVTVTWNSGSLSSGVHTFPAV
LQSDLYTLSSSVTVPSSTWPSETVTCNVAHPASSTKVDKKIVPRDCGCKPCICTVPEVSS
VFIFPPKPKDVLTITLTPKVTCVVVDISKDDPEVQFSWFVDDVEVHTAQTQPREEQFNST
FRSVSELPIMHQDWLNGKEFKCRVNSAAFPAPIEKTISKTKGRPKAPQVYTIPPPKEQMA
KDKVSLTCMITDFFPEDITVEWQWNGQPAENYKNTQPIMDTDGSYFVYSKLNVQKSNWEA
GNTFTCSVLHEGLHNHHTEKSLSHSPGK

SEQ ID NO:15 (鼠全長IgG1輕鏈變異體1)

DIVMTQSPDSLAVSLGERATINCKSSQSVLYSSNNKNYLAWYQQKPGQPPKLLIYWASTR
ESGVPDRFSGSGSGTDFTLTINSLQAEDVAVYFCQQYYDTPTFGQGTRLEIKRTDAAPTV
SIFPPSSEQLTSGGASVVCFLNNFYPKDINVKWKIDGSERQNGVLNSWTDQDSKDSTYSM
SSTLTLTKDEYERHNSYTCEATHKTSTSPIVKSFNRNEC

SEQ ID NO:16 (人類全長IgG1重鏈變異體2)

QVQLVQSGAEVKKPGATVKISCKVSGYTFTDYYMHWVQQAPGKGLEWMGLVDPEDGETIY
AEKFQGRVTITADTSTDTAYMELSSLRSEDTAVYYCATDARGSGSYYPNHFDYWGQGTLV
TVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAV
LQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPE
LLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPRE
EQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPP
SRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVD
KSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

SEQ ID NO:17 (人類全長IgG1輕鏈變異體2)

DIVMTQTPDSLAVSLGERATINCKSSQSVLYSSNNKNYLAWYQQKPGQPPKLLIYWASTR
ESGVPDRFSGSGSGTDFTLTINSLQAEDVAVYFCQQYYDTPTFGQGTRLEIKRTVAAPSV
FIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSL
SSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

SEQ ID NO:18 (Fab重鏈變異體1)

QVQLVESGAEVKKPGATVKISCKVSGYTFTDYYMHWVQQAPGKGLEWMGLVDPEDGETIY
AEKFQGRVTITADTSTDTAYMELSSLRSEDTAVYYCATDARGSGSYYPNHFDYWGQGTLV
TVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAV
LQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSC

SEQ ID NO:19 (Fab輕鏈變異體1)

DIVMTQSPDSLAVSLGERATINCKSSQSVLYSSNNKNYLAWYQQKPGQPPKLLIYWASTR
ESGVPDRFSGSGSGTDFTLTINSLQAEDVAVYFCQQYYDTPTFGQGTRLEIKRTVAAPSV
FIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSL
SSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

SEQ ID NO:20 (用於結晶學中之不含N端標籤之人類截短Gremlin-1)

AMPGEEVLESSQEALHVTERKYLKRDWCKTQPLKQTIHEEGCNSRTIINRFCYGQCNSFY
IPRHIRKEEGSFQSCSFCKPKKFTTMMVTLNCPELQPPTKKKRVTRVKQCRCISIDLD

SEQ ID NO:21 (SEQ ID NO:1之缺少胺基酸1-21之信號肽的成熟Gremlin-1序列)

KKKGSQGAIPPPDKAQHNDSEQTQSPQQPGSRNRGRGQGRGTAMPGEEVLESSQEALHVT
ERKYLKRDWCKTQPLKQTIHEEGCNSRTIINRFCYGQCNSFYIPRHIRKEEGSFQSCSFC
KPKKFTTMMVTLNCPELQPPTKKKRVTRVKQCRCISIDLD

SEQ ID NO:22 (人類IgG4P重鏈變異體1)

QVQLVESGAEVKKPGATVKISCKVSGYTFTDYYMHWVQQAPGKGLEWMGLVDPEDGETIY
AEKFQGRVTITADTSTDTAYMELSSLRSEDTAVYYCATDARGSGSYYPNHFDYWGQGTLV
TVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAV
LQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLG
GPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQF
NSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQE
EMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSR
WQEGNVFSCSVMHEALHNHYTQKSLSLSLGK

SEQ ID NO:23 (人類IgG4P輕鏈變異體1)

DIVMTQSPDSLAVSLGERATINCKSSQSVLYSSNNKNYLAWYQQKPGQPPKLLIYWASTR
ESGVPDRFSGSGSGTDFTLTINSLQAEDVAVYFCQQYYDTPTFGQGTRLEIKRTVAAPSV
FIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSL
SSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

SEQ ID NO:24 (人類IgG1重鏈 DNA變異體1)

caagtgcaactggtggaatccggggccgaagtgaaaaagcccggagccactgtgaagatc
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SEQ ID NO:25 (人類IgG1輕鏈DNA變異體1)

gacattgtgatgacccagtcccccgattcgcttgcggtgtccctgggagaacgggccacc
attaactgcaagagctcacagtccgtcctgtattcatcgaacaacaagaattacctcgca
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SEQ ID NO:26 (人類IgG4P重鏈DNA)

caagtgcaactggtggaatccggggccgaagtgaaaaagcccggagccactgtgaagatc
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acccagaagtccctgtccctgagcctgggcaag

SEQ ID NO:27 (人類IgG4P輕鏈 DNA)

gacattgtgatgacccagtcccccgattcgcttgcggtgtccctgggagaacgggccacc
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SEQ ID NO:28 (鼠全長IgG1重鏈變異體2)

QVQLVQSGAEVKKPGATVKISCKVSGYTFTDYYMHWVQQAPGKGLEWMGLVDPEDGETIY
AEKFQGRVTITADTSTDTAYMELSSLRSEDTAVYYCATDARGSGSYYPNHFDYWGQGTLV
TVSSAKTTPPSVYPLAPGSAAQTNSMVTLGCLVKGYFPEPVTVTWNSGSLSSGVHTFPAV
LQSDLYTLSSSVTVPSSTWPSETVTCNVAHPASSTKVDKKIVPRDCGCKPCICTVPEVSS
VFIFPPKPKDVLTITLTPKVTCVVVDISKDDPEVQFSWFVDDVEVHTAQTQPREEQFNST
FRSVSELPIMHQDWLNGKEFKCRVNSAAFPAPIEKTISKTKGRPKAPQVYTIPPPKEQMA
KDKVSLTCMITDFFPEDITVEWQWNGQPAENYKNTQPIMDTDGSYFVYSKLNVQKSNWEA
GNTFTCSVLHEGLHNHHTEKSLSHSPGK

SEQ ID NO:29 (鼠全長IgG1輕鏈變異體2)

DIVMTQTPDSLAVSLGERATINCKSSQSVLYSSNNKNYLAWYQQKPGQPPKLLIYWASTR
ESGVPDRFSGSGSGTDFTLTINSLQAEDVAVYFCQQYYDTPTFGQGTRLEIKRTDAAPTV
SIFPPSSEQLTSGGASVVCFLNNFYPKDINVKWKIDGSERQNGVLNSWTDQDSKDSTYSM
SSTLTLTKDEYERHNSYTCEATHKTSTSPIVKSFNRNEC

SEQ ID NO:30 (人類全長IgG1重鏈變異體1)

QVQLVESGAEVKKPGATVKISCKVSGYTFTDYYMHWVQQAPGKGLEWMGLVDPEDGETIY
AEKFQGRVTITADTSTDTAYMELSSLRSEDTAVYYCATDARGSGSYYPNHFDYWGQGTLV
TVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAV
LQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPE
LLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPRE
EQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPP
SRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVD
KSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

SEQ ID NO:31 (人類全長IgG1輕鏈變異體1)

DIVMTQSPDSLAVSLGERATINCKSSQSVLYSSNNKNYLAWYQQKPGQPPKLLIYWASTR
ESGVPDRFSGSGSGTDFTLTINSLQAEDVAVYFCQQYYDTPTFGQGTRLEIKRTVAAPSV
FIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSL
SSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

SEQ ID NO:32 (Fab重鏈變異體2)

QVQLVQSGAEVKKPGATVKISCKVSGYTFTDYYMHWVQQAPGKGLEWMGLVDPEDGETIY
AEKFQGRVTITADTSTDTAYMELSSLRSEDTAVYYCATDARGSGSYYPNHFDYWGQGTLV
TVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAV
LQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSC

SEQ ID NO:33 (Fab輕鏈變異體2)

DIVMTQTPDSLAVSLGERATINCKSSQSVLYSSNNKNYLAWYQQKPGQPPKLLIYWASTR
ESGVPDRFSGSGSGTDFTLTINSLQAEDVAVYFCQQYYDTPTFGQGTRLEIKRTVAAPSV
FIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSL
SSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

SEQ ID NO:34 (人類IgG4P重鏈變異體2)

QVQLVQSGAEVKKPGATVKISCKVSGYTFTDYYMHWVQQAPGKGLEWMGLVDPEDGETIY
AEKFQGRVTITADTSTDTAYMELSSLRSEDTAVYYCATDARGSGSYYPNHFDYWGQGTLV
TVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAV
LQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLG
GPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQF
NSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQE
EMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSR
WQEGNVFSCSVMHEALHNHYTQKSLSLSLGK

SEQ ID NO:35 (人類IgG4P輕鏈變異體2)

DIVMTQTPDSLAVSLGERATINCKSSQSVLYSSNNKNYLAWYQQKPGQPPKLLIYWASTR
ESGVPDRFSGSGSGTDFTLTINSLQAEDVAVYFCQQYYDTPTFGQGTRLEIKRTVAAPSV
FIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSL
SSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

【符號說明】

CK　胱胺酸結點

F1　指型區1

F2　指型區2

W　腕型區

【序列表】

<110> 比利時商UCB生物製藥公司 (UCB Biopharma SPRL)

<120> GREMLIN-1結晶結構及抑制抗體

<130> PF0045-WO-PCT

<140> 106144629
<141> 2017-12-19

<150> GB 1621635.0
<151> 2016-12-19

<160> 35

<170> PatentIn version 3.5

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1               5                  10                  15

Thr Leu Leu Pro Ala Ala Glu Gly Lys Lys Lys Gly Ser Gln Gly Ala
            20                  25                  30

Ile Pro Pro Pro Asp Lys Ala Gln His Asn Asp Ser Glu Gln Thr Gln
        35                  40                  45

Ser Pro Gln Gln Pro Gly Ser Arg Asn Arg Gly Arg Gly Gln Gly Arg
    50                  55                  60

Gly Thr Ala Met Pro Gly Glu Glu Val Leu Glu Ser Ser Gln Glu Ala
65                  70                  75                  80

Leu His Val Thr Glu Arg Lys Tyr Leu Lys Arg Asp Trp Cys Lys Thr
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85 90 95

Gln Pro Leu Lys Gln Thr Ile His Glu Glu Gly Cys Asn Ser Arg Thr
100 105 110

Ile Ile Asn Arg Phe Cys Tyr Gly Gln Cys Asn Ser Phe Tyr Ile Pro
115 120 125

Arg His Ile Arg Lys Glu Glu Gly Ser Phe Gln Ser Cys Ser Phe Cys
130 135 140

Lys Pro Lys Lys Phe Thr Thr Met Met Val Thr Leu Asn Cys Pro Glu
145 150 155 160

Leu Gln Pro Pro Thr Lys Lys Lys Arg Val Thr Arg Val Lys Gln Cys
165 170 175

Arg Cys Ile Ser Ile Asp Leu Asp
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Met Gly Ser Ser His His His His His His Ser Ser Gly Glu Asn Leu
1 5 10 15

Tyr Phe Gln Gly Ser Ala Met Pro Gly Glu Glu Val Leu Glu Ser Ser
20 25 30

Gln Glu Ala Leu His Val Thr Glu Arg Lys Tyr Leu Lys Arg Asp Trp
35 40 45

Cys Lys Thr Gln Pro Leu Lys Gln Thr Ile His Glu Glu Gly Cys Asn

50 55 60

Ser Arg Thr Ile Ile Asn Arg Phe Cys Tyr Gly Gln Cys Asn Ser Phe
65 70 75 80

Tyr Ile Pro Arg His Ile Arg Lys Glu Glu Gly Ser Phe Gln Ser Cys
85 90 95

Ser Phe Cys Lys Pro Lys Lys Phe Thr Thr Met Met Val Thr Leu Asn
100 105 110

Cys Pro Glu Leu Gln Pro Pro Thr Lys Lys Lys Arg Val Thr Arg Val
115 120 125

Lys Gln Cys Arg Cys Ile Ser Ile Asp Leu Asp
130 135

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Gly Tyr Thr Phe Thr Asp Tyr Tyr Met His
1 5 10

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Asp Tyr Tyr Met His
1 5

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Leu Val Asp Pro Glu Asp Gly Glu Thr Ile Tyr Ala Glu Lys Phe Gln
1 5 10 15

Gly

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Asp Ala Arg Gly Ser Gly Ser Tyr Tyr Pro Asn His Phe Asp Tyr
1 5 10 15

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Lys Ser Ser Gln Ser Val Leu Tyr Ser Ser Asn Asn Lys Asn Tyr Leu
1 5 10 15

Ala

<210> 8
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Trp Ala Ser Thr Arg Glu Ser
1 5

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Gln Gln Tyr Tyr Asp Thr Pro Thr
1 5

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Gln Val Gln Leu Val Glu Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Thr Val Lys Ile Ser Cys Lys Val Ser Gly Tyr Thr Phe Thr Asp Tyr
20 25 30

Tyr Met His Trp Val Gln Gln Ala Pro Gly Lys Gly Leu Glu Trp Met
35 40 45

Gly Leu Val Asp Pro Glu Asp Gly Glu Thr Ile Tyr Ala Glu Lys Phe
50 55 60

Gln Gly Arg Val Thr Ile Thr Ala Asp Thr Ser Thr Asp Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Thr Asp Ala Arg Gly Ser Gly Ser Tyr Tyr Pro Asn His Phe Asp
100 105 110

Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

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Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly
1 5 10 15

Glu Arg Ala Thr Ile Asn Cys Lys Ser Ser Gln Ser Val Leu Tyr Ser
20 25 30

Ser Asn Asn Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
35 40 45

Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val
50 55 60

Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65 70 75 80

Ile Asn Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Phe Cys Gln Gln
85 90 95

Tyr Tyr Asp Thr Pro Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys
100 105 110

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<400> 12

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Thr Val Lys Ile Ser Cys Lys Val Ser Gly Tyr Thr Phe Thr Asp Tyr
20 25 30

Tyr Met His Trp Val Gln Gln Ala Pro Gly Lys Gly Leu Glu Trp Met
35 40 45

Gly Leu Val Asp Pro Glu Asp Gly Glu Thr Ile Tyr Ala Glu Lys Phe
50 55 60

Gln Gly Arg Val Thr Ile Thr Ala Asp Thr Ser Thr Asp Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Thr Asp Ala Arg Gly Ser Gly Ser Tyr Tyr Pro Asn His Phe Asp
100 105 110

Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 13
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<400> 13

Asp Ile Val Met Thr Gln Thr Pro Asp Ser Leu Ala Val Ser Leu Gly
1 5 10 15

Glu Arg Ala Thr Ile Asn Cys Lys Ser Ser Gln Ser Val Leu Tyr Ser
20 25 30

Ser Asn Asn Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
35 40 45

Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val
50 55 60

Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65 70 75 80

Ile Asn Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Phe Cys Gln Gln
85 90 95

Tyr Tyr Asp Thr Pro Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys
100 105 110

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<400> 14

Gln Val Gln Leu Val Glu Ser Gly Ala Glu Val Lys Lys Pro Gly Ala

1 5 10 15

Thr Val Lys Ile Ser Cys Lys Val Ser Gly Tyr Thr Phe Thr Asp Tyr
20 25 30

Tyr Met His Trp Val Gln Gln Ala Pro Gly Lys Gly Leu Glu Trp Met
35 40 45

Gly Leu Val Asp Pro Glu Asp Gly Glu Thr Ile Tyr Ala Glu Lys Phe
50 55 60

Gln Gly Arg Val Thr Ile Thr Ala Asp Thr Ser Thr Asp Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Thr Asp Ala Arg Gly Ser Gly Ser Tyr Tyr Pro Asn His Phe Asp
100 105 110

Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Lys Thr Thr
115 120 125

Pro Pro Ser Val Tyr Pro Leu Ala Pro Gly Ser Ala Ala Gln Thr Asn
130 135 140

Ser Met Val Thr Leu Gly Cys Leu Val Lys Gly Tyr Phe Pro Glu Pro
145 150 155 160

Val Thr Val Thr Trp Asn Ser Gly Ser Leu Ser Ser Gly Val His Thr
165 170 175

Phe Pro Ala Val Leu Gln Ser Asp Leu Tyr Thr Leu Ser Ser Ser Val
180 185 190

Thr Val Pro Ser Ser Thr Trp Pro Ser Glu Thr Val Thr Cys Asn Val
195 200 205

Ala His Pro Ala Ser Ser Thr Lys Val Asp Lys Lys Ile Val Pro Arg
210 215 220

Asp Cys Gly Cys Lys Pro Cys Ile Cys Thr Val Pro Glu Val Ser Ser
225 230 235 240

Val Phe Ile Phe Pro Pro Lys Pro Lys Asp Val Leu Thr Ile Thr Leu
245 250 255

Thr Pro Lys Val Thr Cys Val Val Val Asp Ile Ser Lys Asp Asp Pro
260 265 270

Glu Val Gln Phe Ser Trp Phe Val Asp Asp Val Glu Val His Thr Ala
275 280 285

Gln Thr Gln Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Ser Val
290 295 300

Ser Glu Leu Pro Ile Met His Gln Asp Trp Leu Asn Gly Lys Glu Phe
305 310 315 320

Lys Cys Arg Val Asn Ser Ala Ala Phe Pro Ala Pro Ile Glu Lys Thr
325 330 335

Ile Ser Lys Thr Lys Gly Arg Pro Lys Ala Pro Gln Val Tyr Thr Ile
340 345 350

Pro Pro Pro Lys Glu Gln Met Ala Lys Asp Lys Val Ser Leu Thr Cys
355 360 365

Met Ile Thr Asp Phe Phe Pro Glu Asp Ile Thr Val Glu Trp Gln Trp
370 375 380

Asn Gly Gln Pro Ala Glu Asn Tyr Lys Asn Thr Gln Pro Ile Met Asp
385 390 395 400

Thr Asp Gly Ser Tyr Phe Val Tyr Ser Lys Leu Asn Val Gln Lys Ser

405 410 415

Asn Trp Glu Ala Gly Asn Thr Phe Thr Cys Ser Val Leu His Glu Gly
420 425 430

Leu His Asn His His Thr Glu Lys Ser Leu Ser His Ser Pro Gly Lys
435 440 445

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Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly
1 5 10 15

Glu Arg Ala Thr Ile Asn Cys Lys Ser Ser Gln Ser Val Leu Tyr Ser
20 25 30

Ser Asn Asn Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
35 40 45

Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val
50 55 60

Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65 70 75 80

Ile Asn Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Phe Cys Gln Gln
85 90 95

Tyr Tyr Asp Thr Pro Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys
100 105 110

Arg Thr Asp Ala Ala Pro Thr Val Ser Ile Phe Pro Pro Ser Ser Glu

115 120 125

Gln Leu Thr Ser Gly Gly Ala Ser Val Val Cys Phe Leu Asn Asn Phe
130 135 140

Tyr Pro Lys Asp Ile Asn Val Lys Trp Lys Ile Asp Gly Ser Glu Arg
145 150 155 160

Gln Asn Gly Val Leu Asn Ser Trp Thr Asp Gln Asp Ser Lys Asp Ser
165 170 175

Thr Tyr Ser Met Ser Ser Thr Leu Thr Leu Thr Lys Asp Glu Tyr Glu
180 185 190

Arg His Asn Ser Tyr Thr Cys Glu Ala Thr His Lys Thr Ser Thr Ser
195 200 205

Pro Ile Val Lys Ser Phe Asn Arg Asn Glu Cys
210 215

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<400> 16

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Thr Val Lys Ile Ser Cys Lys Val Ser Gly Tyr Thr Phe Thr Asp Tyr
20 25 30

Tyr Met His Trp Val Gln Gln Ala Pro Gly Lys Gly Leu Glu Trp Met
35 40 45

Gly Leu Val Asp Pro Glu Asp Gly Glu Thr Ile Tyr Ala Glu Lys Phe

```
     50                  55                  60

Gln Gly Arg Val Thr Ile Thr Ala Asp Thr Ser Thr Asp Thr Ala Tyr
65                  70                  75                  80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Thr Asp Ala Arg Gly Ser Gly Ser Tyr Tyr Pro Asn His Phe Asp
            100                 105                 110

Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys
        115                 120                 125

Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly
    130                 135                 140

Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro
145                 150                 155                 160

Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr
                165                 170                 175

Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val
            180                 185                 190

Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn
        195                 200                 205

Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro
    210                 215                 220

Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu
225                 230                 235                 240

Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp
                245                 250                 255
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Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp
260 265 270

Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly
275 280 285

Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn
290 295 300

Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp
305 310 315 320

Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro
325 330 335

Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu
340 345 350

Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn
355 360 365

Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile
370 375 380

Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr
385 390 395 400

Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys
405 410 415

Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys
420 425 430

Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu
435 440 445

Ser Leu Ser Pro Gly Lys

450

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Asp Ile Val Met Thr Gln Thr Pro Asp Ser Leu Ala Val Ser Leu Gly
1 5 10 15

Glu Arg Ala Thr Ile Asn Cys Lys Ser Ser Gln Ser Val Leu Tyr Ser
20 25 30

Ser Asn Asn Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
35 40 45

Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val
50 55 60

Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65 70 75 80

Ile Asn Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Phe Cys Gln Gln
85 90 95

Tyr Tyr Asp Thr Pro Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys
100 105 110

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
115 120 125

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
130 135 140

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln

145 150 155 160

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
165 170 175

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
180 185 190

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
195 200 205

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
210 215

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<400> 18

Gln Val Gln Leu Val Glu Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Thr Val Lys Ile Ser Cys Lys Val Ser Gly Tyr Thr Phe Thr Asp Tyr
20 25 30

Tyr Met His Trp Val Gln Gln Ala Pro Gly Lys Gly Leu Glu Trp Met
35 40 45

Gly Leu Val Asp Pro Glu Asp Gly Glu Thr Ile Tyr Ala Glu Lys Phe
50 55 60

Gln Gly Arg Val Thr Ile Thr Ala Asp Thr Ser Thr Asp Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys

85 90 95

Ala Thr Asp Ala Arg Gly Ser Gly Ser Tyr Tyr Pro Asn His Phe Asp
100 105 110

Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys
115 120 125

Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly
130 135 140

Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro
145 150 155 160

Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr
165 170 175

Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val
180 185 190

Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn
195 200 205

Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro
210 215 220

Lys Ser Cys
225

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<400> 19

Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly

1 5 10 15

Glu Arg Ala Thr Ile Asn Cys Lys Ser Ser Gln Ser Val Leu Tyr Ser
20 25 30

Ser Asn Asn Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
35 40 45

Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val
50 55 60

Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65 70 75 80

Ile Asn Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Phe Cys Gln Gln
85 90 95

Tyr Tyr Asp Thr Pro Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys
100 105 110

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
115 120 125

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
130 135 140

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
145 150 155 160

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
165 170 175

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
180 185 190

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
195 200 205

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
210 215

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Ala Met Pro Gly Glu Glu Val Leu Glu Ser Ser Gln Glu Ala Leu His
1 5 10 15

Val Thr Glu Arg Lys Tyr Leu Lys Arg Asp Trp Cys Lys Thr Gln Pro
20 25 30

Leu Lys Gln Thr Ile His Glu Glu Gly Cys Asn Ser Arg Thr Ile Ile
35 40 45

Asn Arg Phe Cys Tyr Gly Gln Cys Asn Ser Phe Tyr Ile Pro Arg His
50 55 60

Ile Arg Lys Glu Glu Gly Ser Phe Gln Ser Cys Ser Phe Cys Lys Pro
65 70 75 80

Lys Lys Phe Thr Thr Met Met Val Thr Leu Asn Cys Pro Glu Leu Gln
85 90 95

Pro Pro Thr Lys Lys Lys Arg Val Thr Arg Val Lys Gln Cys Arg Cys
100 105 110

Ile Ser Ile Asp Leu Asp
115

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<400> 21

Lys Lys Lys Gly Ser Gln Gly Ala Ile Pro Pro Pro Asp Lys Ala Gln
1 5 10 15

His Asn Asp Ser Glu Gln Thr Gln Ser Pro Gln Gln Pro Gly Ser Arg
20 25 30

Asn Arg Gly Arg Gly Gln Gly Arg Gly Thr Ala Met Pro Gly Glu Glu
35 40 45

Val Leu Glu Ser Ser Gln Glu Ala Leu His Val Thr Glu Arg Lys Tyr
50 55 60

Leu Lys Arg Asp Trp Cys Lys Thr Gln Pro Leu Lys Gln Thr Ile His
65 70 75 80

Glu Glu Gly Cys Asn Ser Arg Thr Ile Ile Asn Arg Phe Cys Tyr Gly
85 90 95

Gln Cys Asn Ser Phe Tyr Ile Pro Arg His Ile Arg Lys Glu Glu Gly
100 105 110

Ser Phe Gln Ser Cys Ser Phe Cys Lys Pro Lys Lys Phe Thr Thr Met
115 120 125

Met Val Thr Leu Asn Cys Pro Glu Leu Gln Pro Pro Thr Lys Lys Lys
130 135 140

Arg Val Thr Arg Val Lys Gln Cys Arg Cys Ile Ser Ile Asp Leu Asp
145 150 155 160

<210> 22
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<400> 22

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Gln Val Gln Leu Val Glu Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1               5                  10                  15

Thr Val Lys Ile Ser Cys Lys Val Ser Gly Tyr Thr Phe Thr Asp Tyr
            20                  25                  30

Tyr Met His Trp Val Gln Gln Ala Pro Gly Lys Gly Leu Glu Trp Met
        35                  40                  45

Gly Leu Val Asp Pro Glu Asp Gly Glu Thr Ile Tyr Ala Glu Lys Phe
    50                  55                  60

Gln Gly Arg Val Thr Ile Thr Ala Asp Thr Ser Thr Asp Thr Ala Tyr
65                  70                  75                  80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Thr Asp Ala Arg Gly Ser Gly Ser Tyr Tyr Pro Asn His Phe Asp
            100                 105                 110

Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys
        115                 120                 125

Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu
    130                 135                 140

Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro
145                 150                 155                 160

Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr
                165                 170                 175
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Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val
180 185 190

Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn
195 200 205

Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser
210 215 220

Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe Leu Gly
225 230 235 240

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
245 250 255

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln
260 265 270

Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val
275 280 285

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr
290 295 300

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
305 310 315 320

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile
325 330 335

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
340 345 350

Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser
355 360 365

Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu

370 375 380

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
385 390 395 400

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val
405 410 415

Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met
420 425 430

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
435 440 445

Leu Gly Lys
450

<210> 23
<211> 219
<212> PRT
<213> 人工序列

<220>
<223> 重組序列

<400> 23

Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly
1 5 10 15

Glu Arg Ala Thr Ile Asn Cys Lys Ser Ser Gln Ser Val Leu Tyr Ser
20 25 30

Ser Asn Asn Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
35 40 45

Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val
50 55 60

Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr

65 70 75 80

Ile Asn Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Phe Cys Gln Gln
85 90 95

Tyr Tyr Asp Thr Pro Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys
100 105 110

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
115 120 125

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
130 135 140

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
145 150 155 160

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
165 170 175

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
180 185 190

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
195 200 205

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
210 215

<210> 24
<211> 1362
<212> DNA
<213> 人工序列

<220>
<223> 重組序列

<400> 24
caagtgcaac tggtggaatc cggggccgaa gtgaaaaagc ccggagccac tgtgaagatc 60

tcttgcaaag tgtccggcta caccttcacc gactattaca tgcactgggt ccagcaggca 120

cctgggaagg gccttgagtg gatgggtctg gtcgatcccg aggacggcga aactatctac 180

gccgagaagt tccagggtcg cgtcaccatc accgccgaca cttccaccga caccgcgtac 240

atggagctgt ccagcttgag gtccgaggac acagccgtgt actactgcgc cacggatgct 300

cggggaagcg gcagctacta cccgaaccac ttcgactact ggggacaggg cactctcgtg 360

actgtctcga gcgcttctac aaagggcccc tccgtgttcc cgctcgctcc atcatcgaag 420

tctaccagcg gaggcactgc ggctctcggt tgcctcgtga aggactactt cccggagccg 480

gtgaccgtgt cgtggaacag cggagccctg accagcgggg tgcacacctt tccggccgtc 540

ttgcagtcaa gcggccttta ctccctgtca tcagtggtga ctgtcccgtc cagctcattg 600

ggaacccaaa cctacatctg caatgtgaat cacaaaccta gcaacaccaa ggttgacaag 660

aaagtcgagc ccaaatcgtg tgacaagact cacacttgtc cgccgtgccc ggcacccgaa 720

ctgctgggag gtcccagcgt ctttctgttc cctccaaagc cgaaagacac gctgatgatc 780

tcccgcaccc cggaggtcac ttgcgtggtc gtggacgtgt cacatgagga cccagaggtg 840

aagttcaatt ggtacgtgga tggcgtcgaa gtccacaatg ccaaaactaa gcccagagaa 900

gaacagtaca attcgaccta ccgcgtcgtg tccgtgctca cggtgttgca tcaggattgg 960

ctgaacggga aggaatacaa gtgcaaagtg tccaacaagg cgctgccggc accgatcgag 1020

aaaactatct ccaaagcgaa gggacagcct agggaacctc aagtctacac gctgccacca 1080

tcacgggatg aactgactaa gaatcaagtc tcactgactt gtctggtgaa ggggttttac 1140

cctagcgaca ttgccgtgga gtgggaatcc aacggccagc cagagaacaa ctacaagact 1200

acccctccag tgctcgactc ggatggatcg ttcttccttt actcgaagct caccgtggat 1260

aagtcccggt ggcagcaggg aaacgtgttc tcctgctcgg tgatgcatga agccctccat 1320

aaccactata cccaaaagtc gctgtccctg tcgccgggaa ag 1362

<210> 25
<211> 657
<212> DNA
<213> 人工序列

<220>
<223> 重組序列

<400> 25
gacattgtga tgacccagtc ccccgattcg cttgcggtgt ccctgggaga acgggccacc 60

attaactgca agagctcaca gtccgtcctg tattcatcga acaacaagaa ttacctcgca 120

tggtatcagc agaagcctgg acagcctccc aagctgctca tctactgggc tagcacccgc 180

gaatccgggg tgccggatag attctccgga tcgggttcgg gcactgactt cactctgact 240

atcaactcac tgcaagccga ggatgtcgcg gtgtacttct gtcagcagta ctacgacacc 300

ccgacctttg gacaaggcac cagactggag attaagcgta cggtggccgc tccctccgtg 360

ttcatcttcc caccctccga cgagcagctg aagtccggca ccgcctccgt cgtgtgcctg 420

ctgaacaact tctaccccccg cgaggccaag gtgcagtgga aggtggacaa cgccctgcag 480

tccggcaact cccaggaatc cgtcaccgag caggactcca aggacagcac ctactccctg 540

tcctccaccc tgaccctgtc caaggccgac tacgagaagc acaaggtgta cgcctgcgaa 600

gtgacccacc agggcctgtc cagccccgtg accaagtcct tcaaccgggg cgagtgc 657

<210> 26
<211> 1353
<212> DNA
<213> 人工序列

<220>
<223> 重組序列

<400> 26
caagtgcaac tggtggaatc cggggccgaa gtgaaaaagc ccggagccac tgtgaagatc 60

tcttgcaaag tgtccggcta caccttcacc gactattaca tgcactgggt ccagcaggca 120

cctgggaagg gccttgagtg gatgggtctg gtcgatcccg aggacggcga aactatctac 180

gccgagaagt tccagggtcg cgtcaccatc accgccgaca cttccaccga caccgcgtac 240

atggagctgt ccagcttgag gtccgaggac acagccgtgt actactgcgc cacggatgct 300

cggggaagcg gcagctacta cccgaaccac ttcgactact ggggacaggg cactctcgtg 360

actgtctcga gcgcttctac aaagggcccc tccgtgttcc ctctggcccc ttgctcccgg 420

tccacctccg agtctaccgc cgctctgggc tgcctggtca aggactactt ccccgagccc 480

gtgacagtgt cctggaactc tggcgccctg acctccggcg tgcacacctt ccctgccgtg 540

ctgcagtcct ccggcctgta ctccctgtcc tccgtcgtga ccgtgccctc ctccagcctg 600

ggcaccaaga cctacacctg taacgtggac cacaagccct ccaacaccaa ggtggacaag 660

cgggtggaat ctaagtacgg ccctccctgc ccccccctgcc ctgcccctga atttctgggc 720

ggaccttccg tgttcctgtt ccccccaaag cccaaggaca ccctgatgat ctcccggacc 780

cccgaagtga cctgcgtggt ggtggacgtg tcccaggaag atcccgaggt ccagttcaat 840

tggtacgtgg acggcgtgga agtgcacaat gccaagacca agcccagaga ggaacagttc 900

aactccacct accgggtggt gtccgtgctg accgtgctgc accaggactg gctgaacggc 960

aaagagtaca agtgcaaggt gtccaacaag ggcctgccct ccagcatcga aaagaccatc 1020

tccaaggcca agggccagcc ccgcgagccc caggtgtaca ccctgccccc tagccaggaa 1080

gagatgacca agaaccaggt gtccctgacc tgtctggtca agggcttcta ccctccgac 1140

attgccgtgg aatgggagtc caacggccag cccgagaaca actacaagac cacccccct 1200

gtgctggaca gcgacggctc cttcttcctg tactctcggc tgaccgtgga caagtcccgg 1260

tggcaggaag gcaacgtctt ctcctgctcc gtgatgcacg aggccctgca caaccactac 1320

acccagaagt ccctgtccct gagcctgggc aag 1353

<210> 27
<211> 657
<212> DNA
<213> 人工序列

<220>
<223> 重組序列

<400> 27
gacattgtga tgacccagtc ccccgattcg cttgcggtgt ccctgggaga acgggccacc 60

attaactgca agagctcaca gtccgtcctg tattcatcga acaacaagaa ttacctcgca 120

tggtatcagc agaagcctgg acagcctccc aagctgctca tctactgggc tagcacccgc 180

gaatccgggg tgccggatag attctccgga tcgggttcgg gcactgactt cactctgact 240

atcaactcac tgcaagccga ggatgtcgcg gtgtacttct gtcagcagta ctacgacacc 300

ccgacctttg gacaaggcac cagactggag attaagcgta cggtggccgc tccctccgtg 360

ttcatcttcc caccctccga cgagcagctg aagtccggca ccgcctccgt cgtgtgcctg 420

ctgaacaact tctacccccg cgaggccaag gtgcagtgga aggtggacaa cgccctgcag 480

tccggcaact cccaggaatc cgtcaccgag caggactcca aggacagcac ctactccctg 540

tcctccaccc tgaccctgtc caaggccgac tacgagaagc acaaggtgta cgcctgcgaa 600

gtgacccacc agggcctgtc cagccccgtg accaagtcct tcaaccgggg cgagtgc 657

<210> 28
<211> 448
<212> PRT
<213> 人工序列

<220>
<223> 重組序列

<400> 28

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Thr Val Lys Ile Ser Cys Lys Val Ser Gly Tyr Thr Phe Thr Asp Tyr
20 25 30

Tyr Met His Trp Val Gln Gln Ala Pro Gly Lys Gly Leu Glu Trp Met
35 40 45

Gly Leu Val Asp Pro Glu Asp Gly Glu Thr Ile Tyr Ala Glu Lys Phe
50 55 60

Gln Gly Arg Val Thr Ile Thr Ala Asp Thr Ser Thr Asp Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Thr Asp Ala Arg Gly Ser Gly Ser Tyr Tyr Pro Asn His Phe Asp

100 105 110

Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Lys Thr Thr
115 120 125

Pro Pro Ser Val Tyr Pro Leu Ala Pro Gly Ser Ala Ala Gln Thr Asn
130 135 140

Ser Met Val Thr Leu Gly Cys Leu Val Lys Gly Tyr Phe Pro Glu Pro
145 150 155 160

Val Thr Val Thr Trp Asn Ser Gly Ser Leu Ser Ser Gly Val His Thr
165 170 175

Phe Pro Ala Val Leu Gln Ser Asp Leu Tyr Thr Leu Ser Ser Ser Val
180 185 190

Thr Val Pro Ser Ser Thr Trp Pro Ser Glu Thr Val Thr Cys Asn Val
195 200 205

Ala His Pro Ala Ser Ser Thr Lys Val Asp Lys Lys Ile Val Pro Arg
210 215 220

Asp Cys Gly Cys Lys Pro Cys Ile Cys Thr Val Pro Glu Val Ser Ser
225 230 235 240

Val Phe Ile Phe Pro Pro Lys Pro Lys Asp Val Leu Thr Ile Thr Leu
245 250 255

Thr Pro Lys Val Thr Cys Val Val Val Asp Ile Ser Lys Asp Asp Pro
260 265 270

Glu Val Gln Phe Ser Trp Phe Val Asp Asp Val Glu Val His Thr Ala
275 280 285

Gln Thr Gln Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Ser Val
290 295 300

Ser Glu Leu Pro Ile Met His Gln Asp Trp Leu Asn Gly Lys Glu Phe
305 310 315 320

Lys Cys Arg Val Asn Ser Ala Ala Phe Pro Ala Pro Ile Glu Lys Thr
325 330 335

Ile Ser Lys Thr Lys Gly Arg Pro Lys Ala Pro Gln Val Tyr Thr Ile
340 345 350

Pro Pro Pro Lys Glu Gln Met Ala Lys Asp Lys Val Ser Leu Thr Cys
355 360 365

Met Ile Thr Asp Phe Phe Pro Glu Asp Ile Thr Val Glu Trp Gln Trp
370 375 380

Asn Gly Gln Pro Ala Glu Asn Tyr Lys Asn Thr Gln Pro Ile Met Asp
385 390 395 400

Thr Asp Gly Ser Tyr Phe Val Tyr Ser Lys Leu Asn Val Gln Lys Ser
405 410 415

Asn Trp Glu Ala Gly Asn Thr Phe Thr Cys Ser Val Leu His Glu Gly
420 425 430

Leu His Asn His His Thr Glu Lys Ser Leu Ser His Ser Pro Gly Lys
435 440 445

<210> 29
<211> 219
<212> PRT
<213> 人工序列

<220>
<223> 重組序列

<400> 29

Asp Ile Val Met Thr Gln Thr Pro Asp Ser Leu Ala Val Ser Leu Gly
1 5 10 15

Glu Arg Ala Thr Ile Asn Cys Lys Ser Ser Gln Ser Val Leu Tyr Ser
20 25 30

Ser Asn Asn Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
35 40 45

Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val
50 55 60

Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65 70 75 80

Ile Asn Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Phe Cys Gln Gln
85 90 95

Tyr Tyr Asp Thr Pro Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys
100 105 110

Arg Thr Asp Ala Ala Pro Thr Val Ser Ile Phe Pro Pro Ser Ser Glu
115 120 125

Gln Leu Thr Ser Gly Gly Ala Ser Val Val Cys Phe Leu Asn Asn Phe
130 135 140

Tyr Pro Lys Asp Ile Asn Val Lys Trp Lys Ile Asp Gly Ser Glu Arg
145 150 155 160

Gln Asn Gly Val Leu Asn Ser Trp Thr Asp Gln Asp Ser Lys Asp Ser
165 170 175

Thr Tyr Ser Met Ser Ser Thr Leu Thr Leu Thr Lys Asp Glu Tyr Glu
180 185 190

Arg His Asn Ser Tyr Thr Cys Glu Ala Thr His Lys Thr Ser Thr Ser
195 200 205

Pro Ile Val Lys Ser Phe Asn Arg Asn Glu Cys

210 215

<210> 30
<211> 454
<212> PRT
<213> 人工序列

<220>
<223> 重組序列

<400> 30

Gln Val Gln Leu Val Glu Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Thr Val Lys Ile Ser Cys Lys Val Ser Gly Tyr Thr Phe Thr Asp Tyr
20 25 30

Tyr Met His Trp Val Gln Gln Ala Pro Gly Lys Gly Leu Glu Trp Met
35 40 45

Gly Leu Val Asp Pro Glu Asp Gly Glu Thr Ile Tyr Ala Glu Lys Phe
50 55 60

Gln Gly Arg Val Thr Ile Thr Ala Asp Thr Ser Thr Asp Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Thr Asp Ala Arg Gly Ser Gly Ser Tyr Tyr Pro Asn His Phe Asp
100 105 110

Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys
115 120 125

Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly
130 135 140

Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro

145 150 155 160

Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr
165 170 175

Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val
180 185 190

Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn
195 200 205

Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro
210 215 220

Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu
225 230 235 240

Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp
245 250 255

Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp
260 265 270

Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly
275 280 285

Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn
290 295 300

Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp
305 310 315 320

Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro
325 330 335

Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu
340 345 350

Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn
355 360 365

Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile
370 375 380

Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr
385 390 395 400

Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys
405 410 415

Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys
420 425 430

Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu
435 440 445

Ser Leu Ser Pro Gly Lys
450

<210> 31
<211> 219
<212> PRT
<213> 人工序列

<220>
<223> 重組序列

<400> 31

Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly
1 5 10 15

Glu Arg Ala Thr Ile Asn Cys Lys Ser Ser Gln Ser Val Leu Tyr Ser
20 25 30

Ser Asn Asn Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
35 40 45

Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val
50 55 60

Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65 70 75 80

Ile Asn Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Phe Cys Gln Gln
85 90 95

Tyr Tyr Asp Thr Pro Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys
100 105 110

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
115 120 125

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
130 135 140

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
145 150 155 160

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
165 170 175

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
180 185 190

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
195 200 205

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
210 215

<210> 32
<211> 227
<212> PRT
<213> 人工序列

<220>
<223> 重組序列

<400> 32

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Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1               5                  10                  15

Thr Val Lys Ile Ser Cys Lys Val Ser Gly Tyr Thr Phe Thr Asp Tyr
            20                  25                  30

Tyr Met His Trp Val Gln Gln Ala Pro Gly Lys Gly Leu Glu Trp Met
        35                  40                  45

Gly Leu Val Asp Pro Glu Asp Gly Glu Thr Ile Tyr Ala Glu Lys Phe
    50                  55                  60

Gln Gly Arg Val Thr Ile Thr Ala Asp Thr Ser Thr Asp Thr Ala Tyr
65                  70                  75                  80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Thr Asp Ala Arg Gly Ser Gly Ser Tyr Tyr Pro Asn His Phe Asp
            100                 105                 110

Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys
        115                 120                 125

Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly
    130                 135                 140

Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro
145                 150                 155                 160

Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr
                165                 170                 175

Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val
```

180 185 190

Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn
195 200 205

Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro
210 215 220

Lys Ser Cys
225

<210> 33
<211> 219
<212> PRT
<213> 人工序列

<220>
<223> 重組序列

<400> 33

Asp Ile Val Met Thr Gln Thr Pro Asp Ser Leu Ala Val Ser Leu Gly
1 5 10 15

Glu Arg Ala Thr Ile Asn Cys Lys Ser Ser Gln Ser Val Leu Tyr Ser
20 25 30

Ser Asn Asn Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
35 40 45

Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val
50 55 60

Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65 70 75 80

Ile Asn Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Phe Cys Gln Gln
85 90 95

Tyr Tyr Asp Thr Pro Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys

100 105 110

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
115 120 125

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
130 135 140

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
145 150 155 160

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
165 170 175

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
180 185 190

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
195 200 205

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
210 215

<210> 34
<211> 451
<212> PRT
<213> 人工序列

<220>
<223> 重組序列

<400> 34

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Thr Val Lys Ile Ser Cys Lys Val Ser Gly Tyr Thr Phe Thr Asp Tyr
20 25 30

Tyr Met His Trp Val Gln Gln Ala Pro Gly Lys Gly Leu Glu Trp Met

35 40 45

Gly Leu Val Asp Pro Glu Asp Gly Glu Thr Ile Tyr Ala Glu Lys Phe
50 55 60

Gln Gly Arg Val Thr Ile Thr Ala Asp Thr Ser Thr Asp Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Thr Asp Ala Arg Gly Ser Gly Ser Tyr Tyr Pro Asn His Phe Asp
100 105 110

Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys
115 120 125

Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu
130 135 140

Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro
145 150 155 160

Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr
165 170 175

Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val
180 185 190

Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn
195 200 205

Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser
210 215 220

Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe Leu Gly
225 230 235 240

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
245 250 255

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln
260 265 270

Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val
275 280 285

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr
290 295 300

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
305 310 315 320

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile
325 330 335

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
340 345 350

Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser
355 360 365

Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
370 375 380

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
385 390 395 400

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val
405 410 415

Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met
420 425 430

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser

435 440 445

Leu Gly Lys
450

<210> 35
<211> 219
<212> PRT
<213> 人工序列

<220>
<223> 重組序列

<400> 35

Asp Ile Val Met Thr Gln Thr Pro Asp Ser Leu Ala Val Ser Leu Gly
1 5 10 15

Glu Arg Ala Thr Ile Asn Cys Lys Ser Ser Gln Ser Val Leu Tyr Ser
20 25 30

Ser Asn Asn Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
35 40 45

Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val
50 55 60

Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65 70 75 80

Ile Asn Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Phe Cys Gln Gln
85 90 95

Tyr Tyr Asp Thr Pro Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys
100 105 110

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
115 120 125

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe

130 135 140

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
145 150 155 160

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
165 170 175

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
180 185 190

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
195 200 205

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
210 215

【發明申請專利範圍】

【第1項】

一種抗Gremlin-1抗體，其包含SEQ ID NO:4/5/6/7/8/9或SEQ ID NO:3/5/6/7/8/9之HCDR1/HCDR2/HCDR3/LCDR1/LCDR2/LCDR3序列組合。

【第2項】

如請求項1之抗體，其包含SEQ ID NO:10或12之重鏈可變區(HCVR)序列及/或SEQ ID NO:11或13之輕鏈可變區(LCVR)序列。

【第3項】

如請求項2之抗體，其包含SEQ ID NO:10/11或12/13之HCVR及LCVR序列對。

【第4項】

如請求項3之抗體，其中HCDR1/HCDR2/HCDR3/LCDR1/LCDR2/LCDR3序列係由SEQ ID NO:4/5/6/7/8/9或SEQ ID NO:3/5/6/7/8/9組成，且該HCVR及LCVR之其餘部分包含分別與SEQ ID NO:10、11、12及/或13之至少95%一致性。

【第5項】

如請求項2之抗體，其包含SEQ ID NO:14、16、18、22、28、30、32或34之重鏈及SEQ ID NO:15、17、19、23、29、31、33或35之輕鏈。

【第6項】

如請求項5之抗體，其包含SEQ ID NO:14/15、16/17、18/19、22/23、28/29或30/31、32/33、34/35之重鏈及輕鏈對。

【第7項】

如請求項6之抗體，其中HCDR1/HCDR2/HCDR3/LCDR1/LCDR2/LCDR3序列係由SEQ ID NO:4/5/6/7/8/9或SEQ ID NO:3/5/6/7/8/9組成，且該等重鏈及輕鏈之其餘部分包含分別與SEQ ID NO:14、15、16及/或17之至少95%一致性。

【第8項】

如請求項1之抗體，其為嵌合、人類或人類化抗體。

【第9項】

如請求項1至8中任一項之抗體，其為Fab、經修飾Fab、Fab'、經修飾Fab'、$F(ab')_2$、Fv、單域抗體或scFv。

【第10項】

一種經分離之多核苷酸，其編碼如請求項1至9中任一項所定義之抗體。

【第11項】

一種表現載體，其帶有如請求項10之多核苷酸。

【第12項】

一種宿主細胞，其包含如請求項11所定義之載體。

【第13項】

一種產生如請求項1至9中任一項所定義之抗體之方法，其包含在允許產生該抗體之條件下培養如請求項12之宿主細胞且回收所產生之該抗體。

【第14項】

一種醫藥組合物，其包含如請求項1至9中任一項所定義之抗體及醫

藥學上可接受之佐劑及/或載劑。

【第15項】

如請求項14之醫藥組合物，其係用於藉由療法治療人類或動物體之方法中。

【第16項】

如請求項15之醫藥組合物，其中糖尿病腎病之腎纖維化、特發性肺纖維化、肺動脈高壓、血管生成及/或癌症係經治療/預防。

【第17項】

如請求項1至8中任一項之抗體，其係用於藉由療法治療人類或動物體之方法中。

【第18項】

如請求項17之抗體，其中糖尿病腎病之腎纖維化、特發性肺纖維化、肺動脈高壓、血管生成及/或癌症係經治療/預防。

【第19項】

一種如請求項1至9之抗體或如請求項14之醫藥組合物之用途，其用於製造用於治療或預防糖尿病腎病之腎纖維化、特發性肺纖維化、肺動脈高壓、血管生成及/或癌症之藥劑。

【發明圖式】

表1－Gremlin-1結構座標

```
標頭          ----                                          XX-XXX-XX    xxxx
化合物        ---
備註        3
備註        3      細化。
備註        3           程式       : REFMAC 5.8.0049
備註        3           作者       : MURSHUDOV,SKUBAK,LEBEDEV,PANNU,
備註        3                        STEINER,NICHOLLS,WINN,LONG,VAGIN
備註        3
備註        3      細化目標：最大似然
備註        3
備註        3   用於細化之資料。
備註        3     高解析度範圍                          (埃)  :    2.72
備註        3     低解析度範圍                          (埃)  :   26.19
備註        3     資料截止                          (δ (F))  :    無
備註        3     範圍完整度                            (%)  :   98.44
備註        3     反射次數                                   :    14964
備註        3
備註        3   擬合至用於細化之資料。
備註        3     交叉驗證法                                 : 整個
備註        3     自由R值測試集選擇                          : 隨機
備註        3     R值(工作+測試集)                           : 0.23756
備註        3     R值(工作集)                                :  0.23451
備註        3     自由R值                                    :  0.29736
備註        3     自由R值測試集大小                     (%)  :  4.9
備註        3     自由R值測試集計數                          :   773
備註        3
備註        3   適配最高解析度BIN。
備註        3     所使用BIN之總數目                          :      20
備註        3     高BIN解析度範圍                            :   2.720
備註        3     低BIN解析度範圍                            :   2.790
備註        3     BIN之反射(工作集)                          :    1079
備註        3     BIN完整度(工作+測試)                  (%)  :   98.87
備註        3     BIN R值(工作集)                            :   0.341
備註        3     BIN自由R值集計數                           :      57
備註        3     BIN自由R值                                 :   0.392
備註        3
備註        3   用於細化之非氫原子之數目。
備註        3     全部原子                        :     3560
備註        3
備註        3   B值。
備註        3     來自WILSON曲線                 (A**2)  : 空
備註        3     平均B值                  (總計，A**2)  :  53.076
備註        3     總各向異性B值。
備註        3       B11  (A**2)  :     0.43
備註        3       B22  (A**2)  :    -0.60
備註        3       B33  (A**2)  :     0.16
備註        3       B12  (A**2)  :    -0.00
備註        3       B13  (A**2)  :    -0.09
備註        3       B23  (A**2)  :     0.00
備註        3
備註        3   估計之總座標誤差。
備註        3     基於R值之ESU                                          (A):   1.446
備註        3     基於自由R值之ESU                                      (A):   0.403
備註        3     基於最大似然之ESU                                     (A):   0.357
備註        3     用於基於最大似然之B值之ESU                          (A**2):  17.961
備註        3
備註        3   相關係數。
備註        3     相關係數FO-FC                          :   0.911
備註        3     相關係數自由FO-FC                      :   0.836
備註        3
備註        3   距理想值之RMS偏差                                 計數      RMS       權重
備註        3     鍵長，經細化原子                        (A):  3642 ; 0.013 ; 0.019
備註        3     鍵長，其他                              (A):  3547 ; 0.007 ; 0.020
```

【圖1】

```
備註      3   鍵角，經細化原子                          (度):  4886 ; 1.782 ; 1.958
備註      3   鍵角，其他                                (度):  8200 ; 1.654 ; 3.000
備註      3   扭轉角，週期1                             (度):   427 ; 8.651 ; 5.000
備註      3   扭轉角，週期2                             (度):   164 ;38.669 ;22.683
備註      3   扭轉角，週期3                             (度):   736 ;22.228 ;15.000
備註      3   扭轉角，週期4                             (度):    36 ;17.287 ;15.000
備註      3   對掌性中心約束                        (A**3):   530 ; 0.108 ; 0.200
備註      3   一般平面，經細化原子                      (A):  3942 ; 0.008 ; 0.021
備註      3   一般平面，其他                            (A):   854 ; 0.004 ; 0.020
備註      3
備註      3   各向同性熱因素約束。                          計數     RMS      權重
備註      3   主鏈鍵，經細化原子(A**2)                  :  1726 ; 3.529 ; 4.962
備註      3   主鏈鍵，其他原子(A**2)                    :  1725 ; 3.527 ; 4.962
備註      3   主鏈角，經細化原子 (A**2)                 :  2147 ; 5.858 ; 7.435
備註      3   主鏈角，經細化原子(A**2)                  :  2148 ; 5.857 ; 7.434
備註      3   側鏈鍵，經細化原子(A**2)                  :  1916 ; 3.552 ; 5.470
備註      3   側鏈鍵，其他原子(A**2)                    :  1917 ; 3.551 ; 5.469
備註      3   側鏈角，其他原子(A**2)                    :  2740 ; 5.862 ; 7.995
備註      3   長範圍B，經細化原子(A**2)                 :  3832 ; 9.862 ;38.248
備註      3   長範圍B，其他原子(A**2)                   :  3833 ; 9.861 ;38.250
備註      3
備註      3  NCS約束統計
備註      3   NCS類型    : 局部
備註      3   不同NCS對之數目                          :    6
備註      3     組    鏈1          範圍          鏈2          範圍        計數   RMS    權重
備註      3     1      A     53    160        B     53    160     5128  0.19  0.05
備註      3     2      A     52    162        C     52    162     5290  0.21  0.05
備註      3     3      A     52    162        D     52    162     4611  0.21  0.05
備註      3     4      B     53    160        C     53    160     5263  0.18  0.05
備註      3     5      B     53    161        D     53    161     4735  0.19  0.05
備註      3     6      C     52    162        D     52    162     4896  0.18  0.05
備註      3
備註      3  成對細節
備註      3   成對域之數目：空
備註      3
備註      3
備註      3  TLS細節
備註      3   TLS組之數目：空
備註      3
備註      3
備註      3  大型溶劑模擬。
備註      3   所用方法：屏蔽法
備註      3   用於屏蔽計算之參數
備註      3   VDW探針半徑              :   1.20
備註      3   離子探針半徑              :   0.80
備註      3   收縮半徑                  :   0.80
備註      3
備註      3  其他細化備註：
備註      3  已向安放位置加氫
備註      3  U值：個別地細化
備註      3
SS鍵      1 CYS A  123    CYS A   73
SS鍵      2 CYS A  137    CYS A   87
SS鍵      3 CYS A  155    CYS A   97
SS鍵      4 CYS A  157    CYS A  101
SS鍵      5 CYS B  123    CYS B   73
SS鍵      6 CYS B  137    CYS B   87
SS鍵      7 CYS B  155    CYS B   97
SS鍵      8 CYS B  157    CYS B  101
SS鍵      9 CYS C  123    CYS C   73
SS鍵     10 CYS C  137    CYS C   87
SS鍵     11 CYS C  155    CYS C   97
SS鍵     12 CYS C  157    CYS C  101
SS鍵     13 CYS D  123    CYS D   73
SS鍵     14 CYS D  155    CYS D   97
SS鍵     15 CYS D  157    CYS D  101
連接子           HIS D  83                  CYS D  87                空位
連接子           LEU D 135                  LYS D 145                空位
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【圖1】(續)

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連接子             PRO C 138                    GLN C 141                空位
CISPEP   1 GLN A  141    PRO A  142                    0.00
CISPEP   2 GLN B  141    PRO B  142                    0.00
CISPEP   3 ARG C  111    LYS C  112                    0.00
CISPEP   4 GLN C  141    PRO C  142                    0.00
CISPEP   5 VAL D  133    THR D  134                    0.00
CRYST1   84.550  107.220   77.090  90.00 120.43  90.00 C 1 2 1
SCALE1      0.011827  0.000000  0.006947        0.00000
SCALE2     -0.000000  0.009327  0.000000        0.00000
SCALE3      0.000000 -0.000000  0.015044        0.00000
ATOM      1  N   VAL A  52      63.902 -36.852  66.449  1.00 85.32       A    N
ATOM      2  CA  VAL A  52      65.116 -37.732  66.303  1.00 84.10       A    C
ATOM      3  CB  VAL A  52      66.190 -37.499  67.416  1.00 84.08       A    C
ATOM      4  CG1 VAL A  52      66.993 -36.226  67.129  1.00 79.47       A    C
ATOM      5  CG2 VAL A  52      65.566 -37.441  68.805  1.00 82.47       A    C
ATOM      6  C   VAL A  52      64.771 -39.226  66.169  1.00 78.63       A    C
ATOM      7  O   VAL A  52      63.832 -39.736  66.786  1.00 83.52       A    O
ATOM      8  N   LEU A  53      65.543 -39.905  65.328  1.00 75.19       A    N
ATOM      9  CA  LEU A  53      65.447 -41.356  65.106  1.00 74.92       A    C
ATOM     10  CB  LEU A  53      65.227 -42.105  66.409  1.00 78.67       A    C
ATOM     11  CG  LEU A  53      65.169 -43.630  66.314  1.00 86.26       A    C
ATOM     12  CD1 LEU A  53      63.719 -44.106  66.394  1.00 90.10       A    C
ATOM     13  CD2 LEU A  53      65.880 -44.245  65.106  1.00 85.38       A    C
ATOM     14  C   LEU A  53      64.353 -41.740  64.124  1.00 67.49       A    C
ATOM     15  O   LEU A  53      63.238 -42.083  64.531  1.00 57.52       A    O
ATOM     16  N   GLU A  54      64.696 -41.764  62.835  1.00 58.62       A    N
ATOM     17  CA  GLU A  54      63.671 -41.743  61.820  1.00 54.38       A    C
ATOM     18  CB  GLU A  54      64.198 -41.147  60.519  1.00 57.18       A    C
ATOM     19  CG  GLU A  54      64.837 -39.776  60.652  1.00 56.22       A    C
ATOM     20  CD  GLU A  54      63.796 -38.771  60.918  1.00 54.86       A    C
ATOM     21  OE1 GLU A  54      63.255 -38.207  59.951  1.00 54.03       A    O
ATOM     22  OE2 GLU A  54      63.488 -38.615  62.102  1.00 61.76       A    O
ATOM     23  C   GLU A  54      63.148 -43.116  61.638  1.00 50.88       A    C
ATOM     24  O   GLU A  54      62.587 -43.640  62.579  1.00 62.43       A    O
ATOM     25  N   SER A  55      63.287 -43.733  60.477  1.00 49.07       A    N
ATOM     26  CA  SER A  55      62.667 -45.047  60.315  1.00 51.27       A    C
ATOM     27  CB  SER A  55      61.159 -44.964  60.326  1.00 53.55       A    C
ATOM     28  OG  SER A  55      60.551 -46.190  60.735  1.00 60.97       A    O
ATOM     29  C   SER A  55      63.103 -45.712  59.044  1.00 48.81       A    C
ATOM     30  O   SER A  55      63.275 -46.928  59.006  1.00 43.40       A    O
ATOM     31  N   SER A  56      63.215 -44.900  57.998  1.00 48.75       A    N
ATOM     32  CA  SER A  56      63.832 -45.294  56.758  1.00 51.43       A    C
ATOM     33  CB  SER A  56      62.782 -45.750  55.738  1.00 49.64       A    C
ATOM     34  OG  SER A  56      61.723 -44.785  55.733  1.00 55.81       A    O
ATOM     35  C   SER A  56      64.565 -44.117  56.180  1.00 51.53       A    C
ATOM     36  O   SER A  56      64.352 -42.944  56.548  1.00 55.19       A    O
ATOM     37  N   GLN A  57      65.412 -44.481  55.236  1.00 52.31       A    N
ATOM     38  CA  GLN A  57      66.079 -43.566  54.356  1.00 52.66       A    C
ATOM     39  CB  GLN A  57      66.854 -44.372  53.331  1.00 54.15       A    C
ATOM     40  CG  GLN A  57      67.938 -45.238  53.957  1.00 62.25       A    C
ATOM     41  CD  GLN A  57      67.508 -46.698  54.247  1.00 71.48       A    C
ATOM     42  OE1 GLN A  57      66.349 -47.067  54.050  1.00 76.83       A    O
ATOM     43  NE2 GLN A  57      68.448 -47.527  54.717  1.00 74.09       A    N
ATOM     44  C   GLN A  57      65.093 -42.601  53.685  1.00 52.63       A    C
ATOM     45  O   GLN A  57      65.328 -41.395  53.655  1.00 55.99       A    O
ATOM     46  N   GLU A  58      63.959 -43.114  53.225  1.00 54.42       A    N
ATOM     47  CA  GLU A  58      62.990 -42.301  52.518  1.00 55.43       A    C
ATOM     48  CB  GLU A  58      62.006 -43.229  51.767  1.00 59.07       A    C
ATOM     49  CG  GLU A  58      62.692 -44.113  50.732  1.00 64.32       A    C
ATOM     50  CD  GLU A  58      61.712 -44.714  49.733  1.00 71.69       A    C
ATOM     51  OE1 GLU A  58      60.508 -44.808  50.060  1.00 77.17       A    O
ATOM     52  OE2 GLU A  58      62.136 -45.101  48.621  1.00 72.86       A    O
ATOM     53  C   GLU A  58      62.309 -41.332  53.496  1.00 55.42       A    C
ATOM     54  O   GLU A  58      62.189 -40.147  53.218  1.00 52.68       A    O
ATOM     55  N   ALA A  59      61.930 -41.804  54.676  1.00 55.43       A    N
ATOM     56  CA  ALA A  59      61.206 -40.947  55.612  1.00 57.55       A    C
ATOM     57  CB  ALA A  59      60.931 -41.707  56.888  1.00 56.65       A    C
ATOM     58  C   ALA A  59      61.938 -39.656  55.930  1.00 59.38       A    C
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【圖1】(續)

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ATOM     59  O   ALA A  59      61.349 -38.562  56.037  1.00 63.21      A    O
ATOM     60  N   LEU A  60      63.233 -39.773  56.093  1.00 60.14      A    N
ATOM     61  CA  LEU A  60      63.993 -38.664  56.612  1.00 65.84      A    C
ATOM     62  CB  LEU A  60      65.083 -39.213  57.446  1.00 76.50      A    C
ATOM     63  CG  LEU A  60      66.145 -39.911  56.648  1.00 84.66      A    C
ATOM     64  CD1 LEU A  60      67.296 -38.963  56.363  1.00 91.47      A    C
ATOM     65  CD2 LEU A  60      66.617 -41.120  57.415  1.00 92.46      A    C
ATOM     66  C   LEU A  60      64.479 -37.843  55.473  1.00 60.07      A    C
ATOM     67  O   LEU A  60      64.634 -36.645  55.589  1.00 64.13      A    O
ATOM     68  N   HIS A  61      64.699 -38.511  54.357  1.00 55.81      A    N
ATOM     69  CA  HIS A  61      64.897 -37.832  53.111  1.00 52.43      A    C
ATOM     70  CB  HIS A  61      64.948 -38.845  52.001  1.00 53.54      A    C
ATOM     71  CG  HIS A  61      65.058 -38.227  50.662  1.00 60.17      A    C
ATOM     72  ND1 HIS A  61      66.160 -37.494  50.298  1.00 64.46      A    N
ATOM     73  CE1 HIS A  61      66.001 -37.052  49.066  1.00 74.00      A    C
ATOM     74  NE2 HIS A  61      64.827 -37.467  48.623  1.00 77.65      A    N
ATOM     75  CD2 HIS A  61      64.213 -38.204  49.605  1.00 66.40      A    C
ATOM     76  C   HIS A  61      63.758 -36.849  52.848  1.00 50.86      A    C
ATOM     77  O   HIS A  61      63.979 -35.708  52.506  1.00 49.17      A    O
ATOM     78  N   VAL A  62      62.532 -37.320  53.010  1.00 49.20      A    N
ATOM     79  CA  VAL A  62      61.356 -36.499  52.866  1.00 47.00      A    C
ATOM     80  CB  VAL A  62      60.079 -37.396  52.881  1.00 49.55      A    C
ATOM     81  CG1 VAL A  62      58.804 -36.578  53.064  1.00 51.74      A    C
ATOM     82  CG2 VAL A  62      59.996 -38.221  51.594  1.00 47.72      A    C
ATOM     83  C   VAL A  62      61.354 -35.447  53.979  1.00 46.88      A    C
ATOM     84  O   VAL A  62      61.002 -34.308  53.746  1.00 51.42      A    O
ATOM     85  N   THR A  63      61.756 -35.828  55.183  1.00 45.44      A    N
ATOM     86  CA  THR A  63      61.790 -34.903  56.339  1.00 42.08      A    C
ATOM     87  CB  THR A  63      61.943 -35.714  57.662  1.00 39.72      A    C
ATOM     88  OG1 THR A  63      60.810 -36.582  57.793  1.00 38.93      A    O
ATOM     89  CG2 THR A  63      62.005 -34.832  58.902  1.00 36.49      A    C
ATOM     90  C   THR A  63      62.793 -33.744  56.209  1.00 40.71      A    C
ATOM     91  O   THR A  63      62.585 -32.679  56.772  1.00 41.30      A    O
ATOM     92  N   GLU A  64      63.838 -33.916  55.418  1.00 45.87      A    N
ATOM     93  CA  GLU A  64      64.729 -32.798  55.007  1.00 51.53      A    C
ATOM     94  CB  GLU A  64      65.445 -33.192  53.757  1.00 53.77      A    C
ATOM     95  CG  GLU A  64      66.400 -34.308  53.934  1.00 56.10      A    C
ATOM     96  CD  GLU A  64      66.930 -34.283  55.342  1.00 55.54      A    C
ATOM     97  OE1 GLU A  64      66.347 -34.986  56.172  1.00 53.14      A    O
ATOM     98  OE2 GLU A  64      67.847 -33.495  55.654  1.00 62.00      A    O
ATOM     99  C   GLU A  64      64.030 -31.558  54.556  1.00 55.96      A    C
ATOM    100  O   GLU A  64      64.641 -30.503  54.493  1.00 56.87      A    O
ATOM    101  N   ARG A  65      62.774 -31.737  54.156  1.00 59.80      A    N
ATOM    102  CA  ARG A  65      61.849 -30.666  53.781  1.00 53.47      A    C
ATOM    103  CB  ARG A  65      60.734 -31.260  52.968  1.00 58.93      A    C
ATOM    104  CG  ARG A  65      61.213 -32.185  51.848  1.00 68.79      A    C
ATOM    105  CD  ARG A  65      61.977 -31.516  50.707  1.00 73.04      A    C
ATOM    106  NE  ARG A  65      62.738 -32.507  49.922  1.00 71.19      A    N
ATOM    107  CZ  ARG A  65      63.975 -32.929  50.195  1.00 58.16      A    C
ATOM    108  NH1 ARG A  65      64.634 -32.463  51.244  1.00 53.71      A    N
ATOM    109  NH2 ARG A  65      64.553 -33.824  49.396  1.00 52.45      A    N
ATOM    110  C   ARG A  65      61.194 -29.943  54.950  1.00 51.77      A    C
ATOM    111  O   ARG A  65      60.642 -28.876  54.758  1.00 58.01      A    O
ATOM    112  N   LYS A  66      61.183 -30.547  56.131  1.00 48.97      A    N
ATOM    113  CA  LYS A  66      61.078 -29.773  57.361  1.00 48.79      A    C
ATOM    114  CB  LYS A  66      60.700 -30.613  58.607  1.00 51.70      A    C
ATOM    115  CG  LYS A  66      59.207 -30.945  58.737  1.00 56.11      A    C
ATOM    116  CD  LYS A  66      58.679 -31.865  57.625  1.00 60.10      A    C
ATOM    117  CE  LYS A  66      57.785 -32.973  58.194  1.00 64.07      A    C
ATOM    118  NZ  LYS A  66      57.033 -33.713  57.137  1.00 63.72      A    N
ATOM    119  C   LYS A  66      62.423 -29.139  57.615  1.00 46.55      A    C
ATOM    120  O   LYS A  66      62.498 -27.943  57.793  1.00 44.88      A    O
ATOM    121  N   TYR A  67      63.482 -29.943  57.660  1.00 45.72      A    N
ATOM    122  CA  TYR A  67      64.740 -29.474  58.249  1.00 46.30      A    C
ATOM    123  CB  TYR A  67      65.698 -30.631  58.559  1.00 50.14      A    C
ATOM    124  CG  TYR A  67      65.204 -31.652  59.544  1.00 52.44      A    C
ATOM    125  CD1 TYR A  67      64.347 -31.304  60.585  1.00 51.52      A    C
ATOM    126  CE1 TYR A  67      63.901 -32.256  61.471  1.00 50.75      A    C
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ATOM    127  CZ  TYR A  67      64.331 -33.559  61.343  1.00 51.48      A    C
ATOM    128  OH  TYR A  67      63.898 -34.517  62.219  1.00 59.59      A    O
ATOM    129  CE2 TYR A  67      65.195 -33.921  60.344  1.00 52.16      A    C
ATOM    130  CD2 TYR A  67      65.632 -32.969  59.454  1.00 52.15      A    C
ATOM    131  C   TYR A  67      65.503 -28.498  57.403  1.00 46.61      A    C
ATOM    132  O   TYR A  67      66.203 -27.639  57.938  1.00 50.12      A    O
ATOM    133  N   LEU A  68      65.431 -28.665  56.087  1.00 45.60      A    N
ATOM    134  CA  LEU A  68      66.189 -27.847  55.172  1.00 42.79      A    C
ATOM    135  CB  LEU A  68      66.978 -28.724  54.222  1.00 42.94      A    C
ATOM    136  CG  LEU A  68      68.135 -29.514  54.816  1.00 45.32      A    C
ATOM    137  CD1 LEU A  68      68.818 -30.286  53.699  1.00 47.47      A    C
ATOM    138  CD2 LEU A  68      69.139 -28.643  55.549  1.00 47.01      A    C
ATOM    139  C   LEU A  68      65.195 -27.038  54.347  1.00 38.36      A    C
ATOM    140  O   LEU A  68      65.242 -27.023  53.134  1.00 37.94      A    O
ATOM    141  N   LYS A  69      64.262 -26.386  54.999  1.00 38.41      A    N
ATOM    142  CA  LYS A  69      63.213 -25.693  54.261  1.00 38.91      A    C
ATOM    143  CB  LYS A  69      62.063 -25.367  55.222  1.00 41.09      A    C
ATOM    144  CG  LYS A  69      60.674 -25.506  54.638  1.00 41.79      A    C
ATOM    145  CD  LYS A  69      59.612 -25.205  55.678  1.00 42.71      A    C
ATOM    146  CE  LYS A  69      59.528 -23.725  55.968  1.00 42.81      A    C
ATOM    147  NZ  LYS A  69      58.404 -23.452  56.899  1.00 47.17      A    N
ATOM    148  C   LYS A  69      63.731 -24.383  53.703  1.00 36.90      A    C
ATOM    149  O   LYS A  69      63.274 -23.898  52.678  1.00 35.61      A    O
ATOM    150  N   ARG A  70      64.693 -23.802  54.402  1.00 36.90      A    N
ATOM    151  CA  ARG A  70      65.125 -22.448  54.062  1.00 36.20      A    C
ATOM    152  CB  ARG A  70      64.246 -21.427  54.784  1.00 39.86      A    C
ATOM    153  CG  ARG A  70      63.301 -21.995  55.801  1.00 41.47      A    C
ATOM    154  CD  ARG A  70      63.051 -20.924  56.809  1.00 45.37      A    C
ATOM    155  NE  ARG A  70      62.230 -19.864  56.264  1.00 49.35      A    N
ATOM    156  CZ  ARG A  70      61.829 -18.836  56.996  1.00 56.53      A    C
ATOM    157  NH1 ARG A  70      62.155 -18.781  58.282  1.00 63.73      A    N
ATOM    158  NH2 ARG A  70      61.103 -17.866  56.458  1.00 56.00      A    N
ATOM    159  C   ARG A  70      66.619 -22.103  54.124  1.00 35.61      A    C
ATOM    160  O   ARG A  70      67.203 -21.572  55.057  1.00 39.22      A    O
ATOM    161  N   ASP A  71      67.178 -22.326  52.975  1.00 37.26      A    N
ATOM    162  CA  ASP A  71      68.529 -21.885  52.619  1.00 38.60      A    C
ATOM    163  CB  ASP A  71      69.009 -22.760  51.458  1.00 42.18      A    C
ATOM    164  CG  ASP A  71      68.120 -22.683  50.222  1.00 49.01      A    C
ATOM    165  OD1 ASP A  71      66.945 -22.292  50.369  1.00 56.89      A    O
ATOM    166  OD2 ASP A  71      68.571 -23.037  49.094  1.00 55.13      A    O
ATOM    167  C   ASP A  71      68.523 -20.396  52.257  1.00 36.32      A    C
ATOM    168  O   ASP A  71      67.458 -19.773  52.173  1.00 32.62      A    O
ATOM    169  N   TRP A  72      69.708 -19.816  52.068  1.00 34.64      A    N
ATOM    170  CA  TRP A  72      69.802 -18.457  51.519  1.00 33.15      A    C
ATOM    171  CB  TRP A  72      69.778 -17.441  52.629  1.00 30.00      A    C
ATOM    172  CG  TRP A  72      70.916 -17.489  53.549  1.00 29.10      A    C
ATOM    173  CD1 TRP A  72      71.063 -18.311  54.648  1.00 29.32      A    C
ATOM    174  NE1 TRP A  72      72.252 -18.019  55.300  1.00 28.82      A    N
ATOM    175  CE2 TRP A  72      72.867 -16.979  54.647  1.00 27.71      A    C
ATOM    176  CD2 TRP A  72      72.058 -16.626  53.530  1.00 27.68      A    C
ATOM    177  CE3 TRP A  72      72.479 -15.591  52.679  1.00 27.02      A    C
ATOM    178  CZ3 TRP A  72      73.670 -14.959  52.951  1.00 26.66      A    C
ATOM    179  CH2 TRP A  72      74.459 -15.353  54.057  1.00 27.59      A    C
ATOM    180  CZ2 TRP A  72      74.065 -16.354  54.914  1.00 26.76      A    C
ATOM    181  C   TRP A  72      71.043 -18.231  50.653  1.00 33.14      A    C
ATOM    182  O   TRP A  72      72.065 -18.892  50.842  1.00 34.49      A    O
ATOM    183  N   CYS A  73      70.930 -17.311  49.698  1.00 30.97      A    N
ATOM    184  CA  CYS A  73      72.036 -16.958  48.797  1.00 31.56      A    C
ATOM    185  CB  CYS A  73      72.075 -17.924  47.613  1.00 30.97      A    C
ATOM    186  SG  CYS A  73      73.316 -17.618  46.354  1.00 32.57      A    S
ATOM    187  C   CYS A  73      71.871 -15.521  48.309  1.00 31.32      A    C
ATOM    188  O   CYS A  73      70.903 -15.217  47.628  1.00 30.33      A    O
ATOM    189  N   LYS A  74      72.814 -14.656  48.679  1.00 30.37      A    N
ATOM    190  CA  LYS A  74      72.758 -13.254  48.354  1.00 32.45      A    C
ATOM    191  CB  LYS A  74      73.167 -12.422  49.573  1.00 33.68      A    C
ATOM    192  CG  LYS A  74      72.094 -11.801  50.463  1.00 34.53      A    C
ATOM    193  CD  LYS A  74      70.720 -12.435  50.410  1.00 36.12      A    C
ATOM    194  CE  LYS A  74      69.705 -11.664  51.228  1.00 36.03      A    C
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ATOM    195  NZ  LYS A  74      68.315 -11.919  50.749  1.00 36.20      A    N
ATOM    196  C   LYS A  74      73.670 -12.902  47.179  1.00 35.93      A    C
ATOM    197  O   LYS A  74      74.789 -13.426  47.047  1.00 39.59      A    O
ATOM    198  N   THR A  75      73.192 -11.975  46.353  1.00 35.55      A    N
ATOM    199  CA  THR A  75      73.983 -11.340  45.315  1.00 34.19      A    C
ATOM    200  CB  THR A  75      73.198 -11.247  43.999  1.00 32.96      A    C
ATOM    201  OG1 THR A  75      72.674 -12.531  43.646  1.00 33.48      A    O
ATOM    202  CG2 THR A  75      74.086 -10.750  42.874  1.00 32.20      A    C
ATOM    203  C   THR A  75      74.273  -9.929  45.806  1.00 35.52      A    C
ATOM    204  O   THR A  75      73.385  -9.263  46.289  1.00 36.72      A    O
ATOM    205  N   GLN A  76      75.496  -9.454  45.641  1.00 36.01      A    N
ATOM    206  CA  GLN A  76      75.835  -8.136  46.117  1.00 39.15      A    C
ATOM    207  CB  GLN A  76      76.385  -8.251  47.520  1.00 43.80      A    C
ATOM    208  CG  GLN A  76      76.701  -6.917  48.159  1.00 45.97      A    C
ATOM    209  CD  GLN A  76      76.998  -7.040  49.625  1.00 51.40      A    C
ATOM    210  OE1 GLN A  76      76.408  -7.869  50.321  1.00 58.10      A    O
ATOM    211  NE2 GLN A  76      77.904  -6.191  50.121  1.00 52.67      A    N
ATOM    212  C   GLN A  76      76.848  -7.451  45.210  1.00 38.30      A    C
ATOM    213  O   GLN A  76      77.735  -8.103  44.681  1.00 38.19      A    O
ATOM    214  N   PRO A  77      76.722  -6.121  45.033  1.00 38.80      A    N
ATOM    215  CA  PRO A  77      77.604  -5.451  44.081  1.00 38.04      A    C
ATOM    216  CB  PRO A  77      76.896  -4.120  43.843  1.00 34.66      A    C
ATOM    217  CG  PRO A  77      76.173  -3.861  45.110  1.00 33.98      A    C
ATOM    218  CD  PRO A  77      75.659  -5.207  45.498  1.00 36.17      A    C
ATOM    219  C   PRO A  77      78.993  -5.206  44.617  1.00 39.81      A    C
ATOM    220  O   PRO A  77      79.173  -5.029  45.824  1.00 46.95      A    O
ATOM    221  N   LEU A  78      79.957  -5.157  43.713  1.00 40.62      A    N
ATOM    222  CA  LEU A  78      81.297  -4.727  44.052  1.00 45.63      A    C
ATOM    223  CB  LEU A  78      82.141  -5.910  44.513  1.00 47.23      A    C
ATOM    224  CG  LEU A  78      83.023  -6.604  43.482  1.00 49.43      A    C
ATOM    225  CD1 LEU A  78      84.043  -7.503  44.141  1.00 48.73      A    C
ATOM    226  CD2 LEU A  78      82.214  -7.380  42.478  1.00 51.89      A    C
ATOM    227  C   LEU A  78      81.916  -3.994  42.847  1.00 45.78      A    C
ATOM    228  O   LEU A  78      81.498  -4.207  41.716  1.00 39.80      A    O
ATOM    229  N   LYS A  79      82.875  -3.108  43.112  1.00 46.76      A    N
ATOM    230  CA  LYS A  79      83.501  -2.324  42.057  1.00 46.86      A    C
ATOM    231  CB  LYS A  79      84.041  -0.994  42.587  1.00 54.58      A    C
ATOM    232  CG  LYS A  79      82.986  -0.009  43.045  1.00 60.97      A    C
ATOM    233  CD  LYS A  79      83.617   1.102  43.856  1.00 67.31      A    C
ATOM    234  CE  LYS A  79      82.588   2.111  44.339  1.00 73.20      A    C
ATOM    235  NZ  LYS A  79      83.213   3.089  45.279  1.00 78.49      A    N
ATOM    236  C   LYS A  79      84.651  -3.096  41.467  1.00 41.74      A    C
ATOM    237  O   LYS A  79      85.331  -3.849  42.156  1.00 40.67      A    O
ATOM    238  N   GLN A  80      84.859  -2.875  40.182  1.00 40.78      A    N
ATOM    239  CA  GLN A  80      85.970  -3.433  39.431  1.00 43.40      A    C
ATOM    240  CB  GLN A  80      85.553  -4.641  38.618  1.00 45.81      A    C
ATOM    241  CG  GLN A  80      85.520  -5.910  39.449  1.00 49.45      A    C
ATOM    242  CD  GLN A  80      85.658  -7.170  38.616  1.00 51.51      A    C
ATOM    243  OE1 GLN A  80      85.085  -7.268  37.530  1.00 44.18      A    O
ATOM    244  NE2 GLN A  80      86.435  -8.142  39.122  1.00 51.33      A    N
ATOM    245  C   GLN A  80      86.368  -2.366  38.473  1.00 44.55      A    C
ATOM    246  O   GLN A  80      85.504  -1.676  37.927  1.00 44.72      A    O
ATOM    247  N   THR A  81      87.659  -2.215  38.261  1.00 42.36      A    N
ATOM    248  CA  THR A  81      88.112  -1.189  37.351  1.00 43.77      A    C
ATOM    249  CB  THR A  81      89.060  -0.186  38.041  1.00 46.04      A    C
ATOM    250  OG1 THR A  81      89.873   0.442  37.043  1.00 51.74      A    O
ATOM    251  CG2 THR A  81      89.957  -0.857  39.071  1.00 49.28      A    C
ATOM    252  C   THR A  81      88.728  -1.815  36.104  1.00 43.38      A    C
ATOM    253  O   THR A  81      89.417  -2.822  36.205  1.00 46.37      A    O
ATOM    254  N   ILE A  82      88.453  -1.224  34.938  1.00 45.72      A    N
ATOM    255  CA  ILE A  82      89.009  -1.668  33.642  1.00 51.64      A    C
ATOM    256  CB  ILE A  82      88.003  -1.584  32.502  1.00 48.69      A    C
ATOM    257  CG1 ILE A  82      86.883  -2.614  32.595  1.00 49.76      A    C
ATOM    258  CD1 ILE A  82      86.472  -3.067  33.959  1.00 52.74      A    C
ATOM    259  CG2 ILE A  82      88.638  -1.981  31.199  1.00 52.20      A    C
ATOM    260  C   ILE A  82      90.122  -0.699  33.251  1.00 60.82      A    C
ATOM    261  O   ILE A  82      89.876   0.504  33.213  1.00 64.18      A    O
ATOM    262  N   HIS A  83      91.315  -1.212  32.947  1.00 68.49      A    N
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ATOM    263  CA  HIS A  83      92.490  -0.355  32.667  1.00 76.67      A    C
ATOM    264  CB  HIS A  83      93.385  -0.239  33.921  1.00 79.17      A    C
ATOM    265  CG  HIS A  83      93.105  -1.290  34.948  1.00 86.03      A    C
ATOM    266  ND1 HIS A  83      92.438  -1.033  36.128  1.00 88.62      A    N
ATOM    267  CE1 HIS A  83      92.327  -2.155  36.818  1.00 89.28      A    C
ATOM    268  NE2 HIS A  83      92.882  -3.130  36.123  1.00 92.66      A    N
ATOM    269  CD2 HIS A  83      93.373  -2.617  34.948  1.00 89.93      A    C
ATOM    270  C   HIS A  83      93.298  -0.832  31.477  1.00 78.47      A    C
ATOM    271  O   HIS A  83      94.168  -1.681  31.634  1.00 78.83      A    O
ATOM    272  N   GLU A  84      93.055  -0.264  30.296  1.00 81.05      A    N
ATOM    273  CA  GLU A  84      93.744  -0.718  29.107  1.00 81.26      A    C
ATOM    274  CB  GLU A  84      92.771  -1.254  28.042  1.00 85.05      A    C
ATOM    275  CG  GLU A  84      93.322  -2.496  27.376  1.00 89.92      A    C
ATOM    276  CD  GLU A  84      92.354  -3.128  26.402  1.00 95.02      A    C
ATOM    277  OE1 GLU A  84      92.280  -2.613  25.269  1.00 97.56      A    O
ATOM    278  OE2 GLU A  84      91.687  -4.139  26.749  1.00100.30      A    O
ATOM    279  C   GLU A  84      94.621   0.387  28.544  1.00 83.59      A    C
ATOM    280  O   GLU A  84      94.245   1.557  28.578  1.00 84.51      A    O
ATOM    281  N   GLU A  85      95.751  -0.034  27.962  1.00 88.78      A    N
ATOM    282  CA  GLU A  85      96.987   0.788  27.785  1.00 83.78      A    C
ATOM    283  CB  GLU A  85      97.794   0.274  26.583  1.00 86.02      A    C
ATOM    284  CG  GLU A  85      98.412  -1.136  26.689  1.00 90.64      A    C
ATOM    285  CD  GLU A  85      97.789  -2.128  25.713  1.00 99.32      A    C
ATOM    286  OE1 GLU A  85      97.339  -1.703  24.620  1.00102.48      A    O
ATOM    287  OE2 GLU A  85      97.760  -3.345  26.030  1.00108.08      A    O
ATOM    288  C   GLU A  85      96.795   2.293  27.600  1.00 76.44      A    C
ATOM    289  O   GLU A  85      97.206   3.090  28.450  1.00 82.89      A    O
ATOM    290  N   GLY A  86      96.211   2.678  26.474  1.00 65.41      A    N
ATOM    291  CA  GLY A  86      96.105   4.098  26.107  1.00 59.99      A    C
ATOM    292  C   GLY A  86      94.843   4.804  26.568  1.00 58.20      A    C
ATOM    293  O   GLY A  86      94.583   5.954  26.184  1.00 59.35      A    O
ATOM    294  N   CYS A  87      94.060   4.126  27.408  1.00 59.17      A    N
ATOM    295  CA  CYS A  87      92.706   4.561  27.743  1.00 58.03      A    C
ATOM    296  CB  CYS A  87      91.727   3.424  27.442  1.00 59.04      A    C
ATOM    297  SG  CYS A  87      91.770   2.828  25.732  1.00 57.91      A    S
ATOM    298  C   CYS A  87      92.543   4.982  29.194  1.00 52.74      A    C
ATOM    299  O   CYS A  87      93.166   4.422  30.088  1.00 51.83      A    O
ATOM    300  N   ASN A  88      91.683   5.965  29.416  1.00 50.02      A    N
ATOM    301  CA  ASN A  88      91.286   6.313  30.758  1.00 48.55      A    C
ATOM    302  CB  ASN A  88      90.269   7.475  30.772  1.00 48.81      A    C
ATOM    303  CG  ASN A  88      90.887   8.827  30.407  1.00 51.24      A    C
ATOM    304  OD1 ASN A  88      90.166   9.815  30.255  1.00 46.34      A    O
ATOM    305  ND2 ASN A  88      92.216   8.880  30.269  1.00 52.00      A    N
ATOM    306  C   ASN A  88      90.668   5.053  31.351  1.00 51.33      A    C
ATOM    307  O   ASN A  88      89.831   4.382  30.729  1.00 56.17      A    O
ATOM    308  N   SER A  89      91.068   4.753  32.572  1.00 53.63      A    N
ATOM    309  CA  SER A  89      90.492   3.668  33.339  1.00 50.31      A    C
ATOM    310  CB  SER A  89      91.278   3.522  34.616  1.00 54.22      A    C
ATOM    311  OG  SER A  89      90.685   2.622  35.519  1.00 62.37      A    O
ATOM    312  C   SER A  89      89.047   3.972  33.662  1.00 45.00      A    C
ATOM    313  O   SER A  89      88.681   5.124  33.798  1.00 44.21      A    O
ATOM    314  N   ARG A  90      88.224   2.932  33.736  1.00 44.70      A    N
ATOM    315  CA  ARG A  90      86.789   3.075  34.000  1.00 40.64      A    C
ATOM    316  CB  ARG A  90      86.009   2.947  32.693  1.00 37.90      A    C
ATOM    317  CG  ARG A  90      84.507   2.949  32.851  1.00 37.42      A    C
ATOM    318  CD  ARG A  90      83.812   3.149  31.510  1.00 36.35      A    C
ATOM    319  NE  ARG A  90      82.352   3.191  31.692  1.00 38.43      A    N
ATOM    320  CZ  ARG A  90      81.439   3.049  30.723  1.00 39.02      A    C
ATOM    321  NH1 ARG A  90      81.810   2.859  29.460  1.00 41.94      A    N
ATOM    322  NH2 ARG A  90      80.142   3.100  31.014  1.00 35.29      A    N
ATOM    323  C   ARG A  90      86.327   2.010  35.003  1.00 40.08      A    C
ATOM    324  O   ARG A  90      86.773   0.874  34.970  1.00 38.01      A    O
ATOM    325  N   THR A  91      85.432   2.389  35.894  1.00 40.30      A    N
ATOM    326  CA  THR A  91      84.990   1.494  36.939  1.00 41.76      A    C
ATOM    327  CB  THR A  91      85.048   2.193  38.325  1.00 42.78      A    C
ATOM    328  OG1 THR A  91      86.419   2.457  38.667  1.00 47.03      A    O
ATOM    329  CG2 THR A  91      84.412   1.342  39.429  1.00 43.34      A    C
ATOM    330  C   THR A  91      83.585   1.027  36.627  1.00 41.58      A    C
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ATOM    331  O   THR A  91      82.726   1.825  36.271  1.00 43.20      A    O
ATOM    332  N   ILE A  92      83.376  -0.277  36.773  1.00 39.62      A    N
ATOM    333  CA  ILE A  92      82.091  -0.886  36.537  1.00 39.18      A    C
ATOM    334  CB  ILE A  92      82.079  -1.809  35.296  1.00 40.51      A    C
ATOM    335  CG1 ILE A  92      83.209  -2.852  35.336  1.00 41.03      A    C
ATOM    336  CD1 ILE A  92      82.719  -4.267  35.490  1.00 41.14      A    C
ATOM    337  CG2 ILE A  92      82.195  -0.978  34.034  1.00 41.88      A    C
ATOM    338  C   ILE A  92      81.708  -1.678  37.758  1.00 39.47      A    C
ATOM    339  O   ILE A  92      82.521  -1.897  38.651  1.00 39.18      A    O
ATOM    340  N   ILE A  93      80.449  -2.086  37.781  1.00 39.61      A    N
ATOM    341  CA  ILE A  93      79.878  -2.818  38.882  1.00 40.90      A    C
ATOM    342  CB  ILE A  93      78.504  -2.227  39.284  1.00 43.09      A    C
ATOM    343  CG1 ILE A  93      78.660  -0.899  40.091  1.00 43.79      A    C
ATOM    344  CD1 ILE A  93      79.985  -0.152  39.986  1.00 46.79      A    C
ATOM    345  CG2 ILE A  93      77.739  -3.194  40.173  1.00 44.47      A    C
ATOM    346  C   ILE A  93      79.706  -4.269  38.453  1.00 41.58      A    C
ATOM    347  O   ILE A  93      78.949  -4.540  37.515  1.00 41.60      A    O
ATOM    348  N   ASN A  94      80.419  -5.182  39.128  1.00 38.38      A    N
ATOM    349  CA  ASN A  94      80.142  -6.610  39.053  1.00 34.28      A    C
ATOM    350  CB  ASN A  94      81.424  -7.415  38.990  1.00 33.51      A    C
ATOM    351  CG  ASN A  94      81.293  -8.688  38.173  1.00 33.49      A    C
ATOM    352  OD1 ASN A  94      80.212  -9.272  38.038  1.00 31.82      A    O
ATOM    353  ND2 ASN A  94      82.415  -9.142  37.645  1.00 33.13      A    N
ATOM    354  C   ASN A  94      79.365  -7.000  40.294  1.00 34.48      A    C
ATOM    355  O   ASN A  94      78.916  -6.142  41.054  1.00 34.34      A    O
ATOM    356  N   ARG A  95      79.152  -8.298  40.477  1.00 38.10      A    N
ATOM    357  CA  ARG A  95      78.475  -8.814  41.666  1.00 35.94      A    C
ATOM    358  CB  ARG A  95      77.031  -9.162  41.323  1.00 38.60      A    C
ATOM    359  CG  ARG A  95      76.296  -7.978  40.760  1.00 42.74      A    C
ATOM    360  CD  ARG A  95      74.861  -8.243  40.418  1.00 49.54      A    C
ATOM    361  NE  ARG A  95      74.299  -7.061  39.759  1.00 57.68      A    N
ATOM    362  CZ  ARG A  95      74.363  -6.780  38.450  1.00 60.82      A    C
ATOM    363  NH1 ARG A  95      74.997  -7.566  37.575  1.00 60.41      A    N
ATOM    364  NH2 ARG A  95      73.782  -5.666  38.009  1.00 64.61      A    N
ATOM    365  C   ARG A  95      79.188 -10.031  42.197  1.00 32.53      A    C
ATOM    366  O   ARG A  95      79.908 -10.691  41.475  1.00 29.01      A    O
ATOM    367  N   PHE A  96      78.974 -10.314  43.473  1.00 33.61      A    N
ATOM    368  CA  PHE A  96      79.437 -11.557  44.069  1.00 32.57      A    C
ATOM    369  CB  PHE A  96      80.668 -11.321  44.927  1.00 32.96      A    C
ATOM    370  CG  PHE A  96      80.440 -10.487  46.148  1.00 32.04      A    C
ATOM    371  CD1 PHE A  96      80.356  -9.113  46.055  1.00 32.54      A    C
ATOM    372  CE1 PHE A  96      80.169  -8.339  47.186  1.00 32.51      A    C
ATOM    373  CZ  PHE A  96      80.097  -8.939  48.429  1.00 33.50      A    C
ATOM    374  CE2 PHE A  96      80.224 -10.310  48.542  1.00 32.61      A    C
ATOM    375  CD2 PHE A  96      80.410 -11.073  47.405  1.00 32.53      A    C
ATOM    376  C   PHE A  96      78.344 -12.283  44.834  1.00 31.83      A    C
ATOM    377  O   PHE A  96      77.306 -11.725  45.171  1.00 34.07      A    O
ATOM    378  N   CYS A  97      78.575 -13.555  45.057  1.00 32.17      A    N
ATOM    379  CA  CYS A  97      77.592 -14.431  45.673  1.00 34.11      A    C
ATOM    380  CB  CYS A  97      77.438 -15.686  44.811  1.00 35.95      A    C
ATOM    381  SG  CYS A  97      77.182 -15.365  43.059  1.00 38.11      A    S
ATOM    382  C   CYS A  97      78.089 -14.856  47.032  1.00 30.93      A    C
ATOM    383  O   CYS A  97      79.269 -15.135  47.191  1.00 29.55      A    O
ATOM    384  N   TYR A  98      77.200 -14.951  48.001  1.00 29.65      A    N
ATOM    385  CA  TYR A  98      77.539 -15.651  49.255  1.00 29.24      A    C
ATOM    386  CB  TYR A  98      78.341 -14.775  50.205  1.00 28.70      A    C
ATOM    387  CG  TYR A  98      77.627 -13.535  50.580  1.00 30.40      A    C
ATOM    388  CD1 TYR A  98      77.712 -12.406  49.781  1.00 31.69      A    C
ATOM    389  CE1 TYR A  98      77.038 -11.250  50.108  1.00 32.92      A    C
ATOM    390  CZ  TYR A  98      76.273 -11.216  51.253  1.00 34.29      A    C
ATOM    391  OH  TYR A  98      75.591 -10.066  51.551  1.00 35.12      A    O
ATOM    392  CE2 TYR A  98      76.173 -12.327  52.068  1.00 33.54      A    C
ATOM    393  CD2 TYR A  98      76.850 -13.481  51.721  1.00 32.63      A    C
ATOM    394  C   TYR A  98      76.280 -16.142  49.936  1.00 27.25      A    C
ATOM    395  O   TYR A  98      75.229 -15.523  49.824  1.00 28.27      A    O
ATOM    396  N   GLY A  99      76.381 -17.293  50.572  1.00 25.49      A    N
ATOM    397  CA  GLY A  99      75.242 -17.878  51.209  1.00 25.62      A    C
ATOM    398  C   GLY A  99      75.525 -19.198  51.883  1.00 25.51      A    C
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ATOM    399  O   GLY A  99      76.655 -19.651  51.998  1.00 24.28      A    O
ATOM    400  N   GLN A 100      74.451 -19.810  52.339  1.00 28.05      A    N
ATOM    401  CA  GLN A 100      74.505 -21.086  53.015  1.00 28.07      A    C
ATOM    402  CB  GLN A 100      74.344 -20.877  54.511  1.00 29.37      A    C
ATOM    403  CG  GLN A 100      75.362 -19.864  55.054  1.00 31.89      A    C
ATOM    404  CD  GLN A 100      75.222 -19.627  56.547  1.00 30.82      A    C
ATOM    405  OE1 GLN A 100      74.134 -19.770  57.088  1.00 32.80      A    O
ATOM    406  NE2 GLN A 100      76.313 -19.263  57.216  1.00 30.42      A    N
ATOM    407  C   GLN A 100      73.398 -21.933  52.434  1.00 28.33      A    C
ATOM    408  O   GLN A 100      72.197 -21.709  52.726  1.00 30.31      A    O
ATOM    409  N   CYS A 101      73.801 -22.857  51.566  1.00 26.41      A    N
ATOM    410  CA  CYS A 101      72.853 -23.636  50.826  1.00 28.26      A    C
ATOM    411  CB  CYS A 101      73.323 -23.810  49.388  1.00 29.41      A    C
ATOM    412  SG  CYS A 101      73.461 -22.241  48.520  1.00 34.57      A    S
ATOM    413  C   CYS A 101      72.683 -24.962  51.506  1.00 27.40      A    C
ATOM    414  O   CYS A 101      73.415 -25.283  52.410  1.00 28.72      A    O
ATOM    415  N   ASN A 102      71.725 -25.742  51.048  1.00 28.47      A    N
ATOM    416  CA  ASN A 102      71.454 -27.025  51.624  1.00 27.55      A    C
ATOM    417  CB  ASN A 102      70.051 -27.462  51.289  1.00 26.85      A    C
ATOM    418  CG  ASN A 102      69.012 -26.541  51.850  1.00 29.69      A    C
ATOM    419  OD1 ASN A 102      69.175 -25.937  52.906  1.00 32.21      A    O
ATOM    420  ND2 ASN A 102      67.927 -26.442  51.150  1.00 32.26      A    N
ATOM    421  C   ASN A 102      72.368 -28.088  51.108  1.00 29.06      A    C
ATOM    422  O   ASN A 102      72.688 -28.125  49.927  1.00 31.94      A    O
ATOM    423  N   SER A 103      72.772 -28.976  51.999  1.00 29.17      A    N
ATOM    424  CA  SER A 103      73.439 -30.195  51.599  1.00 28.46      A    C
ATOM    425  CB  SER A 103      74.944 -29.997  51.580  1.00 28.34      A    C
ATOM    426  OG  SER A 103      75.388 -29.569  52.848  1.00 30.40      A    O
ATOM    427  C   SER A 103      73.054 -31.252  52.597  1.00 28.74      A    C
ATOM    428  O   SER A 103      72.700 -30.938  53.742  1.00 29.19      A    O
ATOM    429  N   PHE A 104      73.107 -32.496  52.165  1.00 28.85      A    N
ATOM    430  CA  PHE A 104      72.833 -33.602  53.051  1.00 30.40      A    C
ATOM    431  CB  PHE A 104      71.333 -33.767  53.288  1.00 31.54      A    C
ATOM    432  CG  PHE A 104      70.519 -34.053  52.029  1.00 33.21      A    C
ATOM    433  CD1 PHE A 104      70.493 -35.295  51.464  1.00 33.65      A    C
ATOM    434  CE1 PHE A 104      69.731 -35.541  50.334  1.00 34.82      A    C
ATOM    435  CZ  PHE A 104      68.974 -34.544  49.763  1.00 33.74      A    C
ATOM    436  CE2 PHE A 104      68.973 -33.301  50.329  1.00 34.15      A    C
ATOM    437  CD2 PHE A 104      69.735 -33.065  51.454  1.00 35.51      A    C
ATOM    438  C   PHE A 104      73.409 -34.888  52.497  1.00 33.55      A    C
ATOM    439  O   PHE A 104      73.828 -34.970  51.333  1.00 32.74      A    O
ATOM    440  N   TYR A 105      73.437 -35.896  53.358  1.00 34.02      A    N
ATOM    441  CA  TYR A 105      73.939 -37.203  52.987  1.00 32.62      A    C
ATOM    442  CB  TYR A 105      75.421 -37.288  53.274  1.00 30.89      A    C
ATOM    443  CG  TYR A 105      75.985 -38.614  52.916  1.00 31.58      A    C
ATOM    444  CD1 TYR A 105      75.832 -39.713  53.762  1.00 33.78      A    C
ATOM    445  CE1 TYR A 105      76.362 -40.947  53.439  1.00 32.36      A    C
ATOM    446  CZ  TYR A 105      77.039 -41.091  52.257  1.00 30.64      A    C
ATOM    447  OH  TYR A 105      77.588 -42.280  51.917  1.00 33.60      A    O
ATOM    448  CE2 TYR A 105      77.194 -40.032  51.409  1.00 31.88      A    C
ATOM    449  CD2 TYR A 105      76.673 -38.794  51.740  1.00 32.05      A    C
ATOM    450  C   TYR A 105      73.192 -38.218  53.812  1.00 34.08      A    C
ATOM    451  O   TYR A 105      73.205 -38.158  55.041  1.00 35.01      A    O
ATOM    452  N   ILE A 106      72.540 -39.155  53.138  1.00 35.19      A    N
ATOM    453  CA  ILE A 106      71.662 -40.112  53.806  1.00 33.62      A    C
ATOM    454  CB  ILE A 106      70.196 -39.784  53.539  1.00 32.11      A    C
ATOM    455  CG1 ILE A 106      69.837 -38.428  54.142  1.00 31.60      A    C
ATOM    456  CD1 ILE A 106      68.598 -37.816  53.538  1.00 31.50      A    C
ATOM    457  CG2 ILE A 106      69.301 -40.855  54.127  1.00 33.13      A    C
ATOM    458  C   ILE A 106      71.948 -41.497  53.257  1.00 35.24      A    C
ATOM    459  O   ILE A 106      71.697 -41.739  52.077  1.00 35.15      A    O
ATOM    460  N   PRO A 107      72.506 -42.391  54.093  1.00 35.71      A    N
ATOM    461  CA  PRO A 107      72.836 -43.727  53.637  1.00 36.21      A    C
ATOM    462  CB  PRO A 107      73.485 -44.394  54.836  1.00 35.69      A    C
ATOM    463  CG  PRO A 107      73.503 -43.399  55.924  1.00 36.86      A    C
ATOM    464  CD  PRO A 107      72.659 -42.233  55.542  1.00 36.77      A    C
ATOM    465  C   PRO A 107      71.565 -44.430  53.235  1.00 39.81      A    C
ATOM    466  O   PRO A 107      70.554 -44.329  53.904  1.00 38.66      A    O
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ATOM    467  N   ARG A 108      71.640 -45.145  52.129  1.00 47.91      A    N
ATOM    468  CA  ARG A 108      70.458 -45.385  51.323  1.00 54.83      A    C
ATOM    469  CB  ARG A 108      70.682 -44.962  49.868  1.00 57.65      A    C
ATOM    470  CG  ARG A 108      69.722 -45.571  48.852  1.00 58.78      A    C
ATOM    471  CD  ARG A 108      68.671 -44.589  48.510  1.00 59.30      A    C
ATOM    472  NE  ARG A 108      68.082 -45.018  47.273  1.00 62.75      A    N
ATOM    473  CZ  ARG A 108      68.484 -44.689  46.049  1.00 64.27      A    C
ATOM    474  NH1 ARG A 108      69.502 -43.855  45.808  1.00 58.97      A    N
ATOM    475  NH2 ARG A 108      67.812 -45.204  45.034  1.00 74.19      A    N
ATOM    476  C   ARG A 108      70.151 -46.812  51.382  1.00 60.29      A    C
ATOM    477  O   ARG A 108      71.073 -47.623  51.291  1.00 52.82      A    O
ATOM    478  N   HIS A 109      68.842 -47.093  51.475  1.00 78.23      A    N
ATOM    479  CA  HIS A 109      68.315 -48.466  51.551  1.00 87.51      A    C
ATOM    480  CB  HIS A 109      66.737 -48.597  51.324  1.00 89.41      A    C
ATOM    481  CG  HIS A 109      66.111 -47.517  50.473  1.00 92.22      A    C
ATOM    482  ND1 HIS A 109      66.069 -47.599  49.098  1.00 95.93      A    N
ATOM    483  CE1 HIS A 109      65.435 -46.549  48.608  1.00 88.42      A    C
ATOM    484  NE2 HIS A 109      65.043 -45.794  49.617  1.00 85.15      A    N
ATOM    485  CD2 HIS A 109      65.433 -46.384  50.797  1.00 88.03      A    C
ATOM    486  C   HIS A 109      69.094 -49.222  50.505  1.00 89.49      A    C
ATOM    487  O   HIS A 109      68.759 -49.217  49.316  1.00 90.22      A    O
ATOM    488  N   ILE A 110      70.240 -49.705  50.969  1.00 88.72      A    N
ATOM    489  CA  ILE A 110      70.834 -50.910  50.505  1.00 91.31      A    C
ATOM    490  CB  ILE A 110      70.296 -52.114  51.346  1.00 84.46      A    C
ATOM    491  CG1 ILE A 110      69.925 -51.693  52.788  1.00 75.07      A    C
ATOM    492  CD1 ILE A 110      71.056 -51.718  53.783  1.00 70.15      A    C
ATOM    493  CG2 ILE A 110      71.241 -53.320  51.283  1.00 82.84      A    C
ATOM    494  C   ILE A 110      70.464 -51.085  49.034  1.00101.03      A    C
ATOM    495  O   ILE A 110      69.640 -51.948  48.703  1.00125.66      A    O
ATOM    496  N   ARG A 111      71.063 -50.270  48.159  1.00 91.88      A    N
ATOM    497  CA  ARG A 111      70.734 -50.266  46.705  1.00 86.41      A    C
ATOM    498  CB  ARG A 111      71.564 -49.211  45.991  1.00 89.22      A    C
ATOM    499  CG  ARG A 111      71.092 -48.948  44.565  1.00 94.69      A    C
ATOM    500  CD  ARG A 111      72.205 -48.652  43.529  1.00 96.79      A    C
ATOM    501  NE  ARG A 111      72.374 -49.776  42.592  1.00 99.25      A    N
ATOM    502  CZ  ARG A 111      71.552 -50.054  41.576  1.00 96.22      A    C
ATOM    503  NH1 ARG A 111      70.487 -49.292  41.345  1.00 98.15      A    N
ATOM    504  NH2 ARG A 111      71.787 -51.100  40.791  1.00 87.48      A    N
ATOM    505  C   ARG A 111      70.934 -51.661  46.048  1.00 79.51      A    C
ATOM    506  O   ARG A 111      71.710 -51.853  45.100  1.00 80.72      A    O
ATOM    507  N   LYS A 112      70.201 -52.628  46.583  1.00 76.45      A    N
ATOM    508  CA  LYS A 112      70.603 -54.032  46.582  1.00 80.62      A    C
ATOM    509  CB  LYS A 112      70.275 -54.682  45.245  1.00 88.65      A    C
ATOM    510  CG  LYS A 112      69.932 -56.180  45.452  1.00 94.22      A    C
ATOM    511  CD  LYS A 112      68.449 -56.473  45.305  1.00 94.84      A    C
ATOM    512  CE  LYS A 112      68.038 -57.586  46.244  1.00 93.67      A    C
ATOM    513  NZ  LYS A 112      66.759 -58.175  45.797  1.00 95.40      A    N
ATOM    514  C   LYS A 112      72.078 -54.227  46.937  1.00 79.13      A    C
ATOM    515  O   LYS A 112      72.692 -55.214  46.558  1.00 72.19      A    O
ATOM    516  N   GLU A 113      72.610 -53.294  47.727  1.00 87.06      A    N
ATOM    517  CA  GLU A 113      74.047 -53.003  47.771  1.00 86.61      A    C
ATOM    518  CB  GLU A 113      74.489 -52.440  46.419  1.00 85.09      A    C
ATOM    519  CG  GLU A 113      75.991 -52.410  46.229  1.00 80.73      A    C
ATOM    520  CD  GLU A 113      76.484 -53.655  45.545  1.00 79.23      A    C
ATOM    521  OE1 GLU A 113      76.324 -54.735  46.146  1.00 81.24      A    O
ATOM    522  OE2 GLU A 113      77.008 -53.554  44.418  1.00 74.12      A    O
ATOM    523  C   GLU A 113      74.308 -51.972  48.918  1.00 86.09      A    C
ATOM    524  O   GLU A 113      73.882 -52.199  50.050  1.00 91.56      A    O
ATOM    525  N   GLU A 114      74.971 -50.841  48.636  1.00 81.30      A    N
ATOM    526  CA  GLU A 114      75.098 -49.737  49.616  1.00 78.79      A    C
ATOM    527  CB  GLU A 114      76.105 -50.056  50.736  1.00 82.00      A    C
ATOM    528  CG  GLU A 114      76.037 -49.079  51.911  1.00 88.87      A    C
ATOM    529  CD  GLU A 114      74.711 -49.128  52.667  1.00 93.88      A    C
ATOM    530  OE1 GLU A 114      74.199 -50.242  52.908  1.00 99.73      A    O
ATOM    531  OE2 GLU A 114      74.188 -48.053  53.037  1.00 83.56      A    O
ATOM    532  C   GLU A 114      75.486 -48.401  48.950  1.00 68.37      A    C
ATOM    533  O   GLU A 114      76.573 -48.272  48.400  1.00 65.80      A    O
ATOM    534  N   GLY A 115      74.594 -47.414  49.017  1.00 59.08      A    N
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ATOM    535  CA  GLY A 115      74.853 -46.066  48.504  1.00 54.50      A    C
ATOM    536  C   GLY A 115      74.134 -45.047  49.354  1.00 51.70      A    C
ATOM    537  O   GLY A 115      73.887 -45.297  50.526  1.00 57.40      A    O
ATOM    538  N   SER A 116      73.750 -43.922  48.763  1.00 49.37      A    N
ATOM    539  CA  SER A 116      73.201 -42.815  49.541  1.00 48.35      A    C
ATOM    540  CB  SER A 116      74.363 -42.016  50.117  1.00 51.52      A    C
ATOM    541  OG  SER A 116      75.148 -41.451  49.082  1.00 49.54      A    O
ATOM    542  C   SER A 116      72.317 -41.879  48.727  1.00 44.59      A    C
ATOM    543  O   SER A 116      72.428 -41.841  47.509  1.00 44.26      A    O
ATOM    544  N   PHE A 117      71.425 -41.155  49.405  1.00 41.14      A    N
ATOM    545  CA  PHE A 117      70.767 -39.976  48.836  1.00 39.76      A    C
ATOM    546  CB  PHE A 117      69.383 -39.725  49.433  1.00 39.91      A    C
ATOM    547  CG  PHE A 117      68.350 -40.745  49.082  1.00 42.89      A    C
ATOM    548  CD1 PHE A 117      67.994 -40.973  47.762  1.00 43.87      A    C
ATOM    549  CE1 PHE A 117      67.018 -41.906  47.437  1.00 43.53      A    C
ATOM    550  CZ  PHE A 117      66.373 -42.611  48.442  1.00 43.10      A    C
ATOM    551  CE2 PHE A 117      66.700 -42.386  49.768  1.00 42.64      A    C
ATOM    552  CD2 PHE A 117      67.674 -41.451  50.089  1.00 44.61      A    C
ATOM    553  C   PHE A 117      71.623 -38.790  49.242  1.00 37.99      A    C
ATOM    554  O   PHE A 117      71.829 -38.583  50.424  1.00 36.61      A    O
ATOM    555  N   GLN A 118      72.134 -38.017  48.292  1.00 37.40      A    N
ATOM    556  CA  GLN A 118      72.935 -36.860  48.666  1.00 37.81      A    C
ATOM    557  CB  GLN A 118      74.407 -37.231  48.783  1.00 39.01      A    C
ATOM    558  CG  GLN A 118      75.002 -37.791  47.518  1.00 40.21      A    C
ATOM    559  CD  GLN A 118      76.417 -38.236  47.784  1.00 42.99      A    C
ATOM    560  OE1 GLN A 118      76.654 -39.395  48.072  1.00 47.39      A    O
ATOM    561  NE2 GLN A 118      77.357 -37.303  47.754  1.00 45.99      A    N
ATOM    562  C   GLN A 118      72.797 -35.690  47.736  1.00 37.37      A    C
ATOM    563  O   GLN A 118      72.400 -35.822  46.590  1.00 39.59      A    O
ATOM    564  N   SER A 119      73.140 -34.525  48.262  1.00 36.95      A    N
ATOM    565  CA  SER A 119      72.921 -33.286  47.578  1.00 33.24      A    C
ATOM    566  CB  SER A 119      71.475 -32.873  47.707  1.00 33.89      A    C
ATOM    567  OG  SER A 119      71.277 -31.625  47.104  1.00 37.49      A    O
ATOM    568  C   SER A 119      73.793 -32.239  48.206  1.00 32.27      A    C
ATOM    569  O   SER A 119      74.048 -32.258  49.384  1.00 32.39      A    O
ATOM    570  N   CYS A 120      74.279 -31.343  47.380  1.00 34.02      A    N
ATOM    571  CA  CYS A 120      75.069 -30.222  47.812  1.00 33.94      A    C
ATOM    572  CB  CYS A 120      76.550 -30.568  47.870  1.00 34.89      A    C
ATOM    573  SG  CYS A 120      77.566 -29.243  48.611  1.00 40.95      A    S
ATOM    574  C   CYS A 120      74.810 -29.104  46.818  1.00 32.94      A    C
ATOM    575  O   CYS A 120      74.894 -29.312  45.624  1.00 34.19      A    O
ATOM    576  N   SER A 121      74.433 -27.936  47.319  1.00 32.93      A    N
ATOM    577  CA  SER A 121      74.217 -26.795  46.483  1.00 31.93      A    C
ATOM    578  CB  SER A 121      72.822 -26.265  46.670  1.00 33.02      A    C
ATOM    579  OG  SER A 121      71.901 -27.168  46.095  1.00 34.68      A    O
ATOM    580  C   SER A 121      75.249 -25.750  46.806  1.00 31.45      A    C
ATOM    581  O   SER A 121      75.886 -25.782  47.853  1.00 32.91      A    O
ATOM    582  N   PHE A 122      75.426 -24.846  45.864  1.00 30.96      A    N
ATOM    583  CA  PHE A 122      76.559 -23.952  45.838  1.00 32.93      A    C
ATOM    584  CB  PHE A 122      77.484 -24.430  44.720  1.00 33.29      A    C
ATOM    585  CG  PHE A 122      78.774 -23.665  44.584  1.00 34.35      A    C
ATOM    586  CD1 PHE A 122      79.043 -22.515  45.314  1.00 33.74      A    C
ATOM    587  CE1 PHE A 122      80.248 -21.842  45.151  1.00 33.97      A    C
ATOM    588  CZ  PHE A 122      81.196 -22.300  44.251  1.00 33.96      A    C
ATOM    589  CE2 PHE A 122      80.942 -23.444  43.513  1.00 34.41      A    C
ATOM    590  CD2 PHE A 122      79.737 -24.115  43.679  1.00 34.87      A    C
ATOM    591  C   PHE A 122      75.977 -22.578  45.539  1.00 32.00      A    C
ATOM    592  O   PHE A 122      75.358 -22.408  44.494  1.00 34.58      A    O
ATOM    593  N   CYS A 123      76.133 -21.622  46.456  1.00 31.50      A    N
ATOM    594  CA  CYS A 123      75.642 -20.267  46.211  1.00 34.21      A    C
ATOM    595  CB  CYS A 123      75.533 -19.455  47.504  1.00 33.79      A    C
ATOM    596  SG  CYS A 123      75.144 -17.703  47.266  1.00 31.89      A    S
ATOM    597  C   CYS A 123      76.592 -19.607  45.213  1.00 35.86      A    C
ATOM    598  O   CYS A 123      77.744 -19.324  45.547  1.00 33.04      A    O
ATOM    599  N   LYS A 124      76.119 -19.434  43.976  1.00 36.05      A    N
ATOM    600  CA  LYS A 124      76.984 -19.058  42.862  1.00 37.18      A    C
ATOM    601  CB  LYS A 124      77.725 -20.295  42.335  1.00 39.54      A    C
ATOM    602  CG  LYS A 124      76.806 -21.189  41.534  1.00 42.47      A    C
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ATOM    603  CD  LYS A 124      77.421 -22.529  41.237  1.00 48.85      A    C
ATOM    604  CE  LYS A 124      78.531 -22.426  40.203  1.00 51.64      A    C
ATOM    605  NZ  LYS A 124      78.499 -23.646  39.353  1.00 56.45      A    N
ATOM    606  C   LYS A 124      76.159 -18.469  41.731  1.00 35.21      A    C
ATOM    607  O   LYS A 124      74.940 -18.461  41.798  1.00 34.34      A    O
ATOM    608  N   PRO A 125      76.827 -17.985  40.673  1.00 37.40      A    N
ATOM    609  CA  PRO A 125      76.083 -17.360  39.594  1.00 37.50      A    C
ATOM    610  CB  PRO A 125      77.190 -16.854  38.663  1.00 37.31      A    C
ATOM    611  CG  PRO A 125      78.328 -16.581  39.575  1.00 37.66      A    C
ATOM    612  CD  PRO A 125      78.278 -17.717  40.545  1.00 38.15      A    C
ATOM    613  C   PRO A 125      75.178 -18.310  38.853  1.00 36.37      A    C
ATOM    614  O   PRO A 125      75.591 -19.383  38.473  1.00 30.75      A    O
ATOM    615  N   LYS A 126      73.949 -17.872  38.623  1.00 42.73      A    N
ATOM    616  CA  LYS A 126      73.029 -18.566  37.737  1.00 46.02      A    C
ATOM    617  CB  LYS A 126      71.611 -18.377  38.223  1.00 53.04      A    C
ATOM    618  CG  LYS A 126      70.591 -19.160  37.429  1.00 59.92      A    C
ATOM    619  CD  LYS A 126      69.419 -19.537  38.318  1.00 68.50      A    C
ATOM    620  CE  LYS A 126      68.074 -19.373  37.621  1.00 72.15      A    C
ATOM    621  NZ  LYS A 126      67.582 -20.713  37.187  1.00 74.53      A    N
ATOM    622  C   LYS A 126      73.132 -18.039  36.323  1.00 44.93      A    C
ATOM    623  O   LYS A 126      73.158 -18.813  35.378  1.00 42.75      A    O
ATOM    624  N   LYS A 127      73.173 -16.715  36.186  1.00 49.66      A    N
ATOM    625  CA  LYS A 127      73.296 -16.054  34.871  1.00 51.43      A    C
ATOM    626  CB  LYS A 127      71.980 -15.327  34.438  1.00 56.95      A    C
ATOM    627  CG  LYS A 127      70.968 -15.092  35.561  1.00 64.84      A    C
ATOM    628  CD  LYS A 127      69.621 -14.552  35.057  1.00 69.23      A    C
ATOM    629  CE  LYS A 127      68.565 -15.640  34.985  1.00 69.04      A    C
ATOM    630  NZ  LYS A 127      68.008 -15.931  36.339  1.00 70.51      A    N
ATOM    631  C   LYS A 127      74.477 -15.088  34.917  1.00 47.57      A    C
ATOM    632  O   LYS A 127      74.682 -14.379  35.913  1.00 43.73      A    O
ATOM    633  N   PHE A 128      75.299 -15.133  33.872  1.00 45.23      A    N
ATOM    634  CA  PHE A 128      76.296 -14.091  33.626  1.00 43.64      A    C
ATOM    635  CB  PHE A 128      77.594 -14.703  33.156  1.00 42.33      A    C
ATOM    636  CG  PHE A 128      78.271 -15.549  34.185  1.00 40.94      A    C
ATOM    637  CD1 PHE A 128      77.897 -16.864  34.367  1.00 42.68      A    C
ATOM    638  CE1 PHE A 128      78.541 -17.656  35.301  1.00 42.56      A    C
ATOM    639  CZ  PHE A 128      79.565 -17.127  36.065  1.00 42.82      A    C
ATOM    640  CE2 PHE A 128      79.946 -15.806  35.889  1.00 42.45      A    C
ATOM    641  CD2 PHE A 128      79.305 -15.029  34.952  1.00 40.96      A    C
ATOM    642  C   PHE A 128      75.802 -13.131  32.552  1.00 43.33      A    C
ATOM    643  O   PHE A 128      74.943 -13.484  31.763  1.00 47.14      A    O
ATOM    644  N   THR A 129      76.316 -11.908  32.552  1.00 41.30      A    N
ATOM    645  CA  THR A 129      75.982 -10.911  31.533  1.00 35.65      A    C
ATOM    646  CB  THR A 129      75.434  -9.638  32.167  1.00 36.52      A    C
ATOM    647  OG1 THR A 129      74.109  -9.884  32.643  1.00 37.37      A    O
ATOM    648  CG2 THR A 129      75.384  -8.506  31.181  1.00 36.25      A    C
ATOM    649  C   THR A 129      77.252 -10.599  30.809  1.00 33.26      A    C
ATOM    650  O   THR A 129      78.323 -10.634  31.383  1.00 34.28      A    O
ATOM    651  N   THR A 130      77.157 -10.400  29.509  1.00 35.45      A    N
ATOM    652  CA  THR A 130      78.320  -9.982  28.714  1.00 33.88      A    C
ATOM    653  CB  THR A 130      78.613 -10.942  27.566  1.00 31.58      A    C
ATOM    654  OG1 THR A 130      79.249 -12.104  28.105  1.00 34.50      A    O
ATOM    655  CG2 THR A 130      79.544 -10.322  26.562  1.00 33.45      A    C
ATOM    656  C   THR A 130      78.019  -8.606  28.206  1.00 33.47      A    C
ATOM    657  O   THR A 130      76.948  -8.368  27.657  1.00 30.77      A    O
ATOM    658  N   MET A 131      78.968  -7.710  28.403  1.00 35.90      A    N
ATOM    659  CA  MET A 131      78.783  -6.319  28.108  1.00 40.66      A    C
ATOM    660  CB  MET A 131      78.519  -5.472  29.368  1.00 46.80      A    C
ATOM    661  CG  MET A 131      79.369  -5.737  30.593  1.00 52.77      A    C
ATOM    662  SD  MET A 131      79.113  -4.563  31.995  1.00 65.12      A    S
ATOM    663  CE  MET A 131      77.870  -3.369  31.437  1.00 59.85      A    C
ATOM    664  C   MET A 131      80.001  -5.868  27.345  1.00 38.26      A    C
ATOM    665  O   MET A 131      81.117  -6.253  27.659  1.00 36.69      A    O
ATOM    666  N   MET A 132      79.771  -5.146  26.258  1.00 38.83      A    N
ATOM    667  CA  MET A 132      80.847  -4.388  25.610  1.00 36.18      A    C
ATOM    668  CB  MET A 132      80.553  -4.119  24.129  1.00 36.68      A    C
ATOM    669  CG  MET A 132      80.984  -5.177  23.131  1.00 38.25      A    C
ATOM    670  SD  MET A 132      82.047  -6.497  23.750  1.00 42.89      A    S
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ATOM    671  CE  MET A 132      83.711  -6.115  23.227  1.00 42.11      A    C
ATOM    672  C   MET A 132      80.884  -3.079  26.380  1.00 33.94      A    C
ATOM    673  O   MET A 132      79.886  -2.379  26.451  1.00 33.48      A    O
ATOM    674  N   VAL A 133      82.018  -2.770  26.982  1.00 31.14      A    N
ATOM    675  CA  VAL A 133      82.178  -1.534  27.698  1.00 32.10      A    C
ATOM    676  CB  VAL A 133      82.788  -1.779  29.076  1.00 31.79      A    C
ATOM    677  CG1 VAL A 133      83.064  -0.451  29.763  1.00 32.17      A    C
ATOM    678  CG2 VAL A 133      81.842  -2.636  29.895  1.00 32.31      A    C
ATOM    679  C   VAL A 133      83.076  -0.633  26.898  1.00 34.17      A    C
ATOM    680  O   VAL A 133      84.151  -1.041  26.494  1.00 35.41      A    O
ATOM    681  N   THR A 134      82.628   0.591  26.657  1.00 37.93      A    N
ATOM    682  CA  THR A 134      83.426   1.507  25.854  1.00 39.67      A    C
ATOM    683  CB  THR A 134      82.617   2.349  24.826  1.00 39.61      A    C
ATOM    684  OG1 THR A 134      82.435   3.677  25.302  1.00 40.54      A    O
ATOM    685  CG2 THR A 134      81.263   1.729  24.546  1.00 39.68      A    C
ATOM    686  C   THR A 134      84.244   2.369  26.804  1.00 39.24      A    C
ATOM    687  O   THR A 134      83.726   2.927  27.766  1.00 37.08      A    O
ATOM    688  N   LEU A 135      85.544   2.403  26.544  1.00 41.66      A    N
ATOM    689  CA  LEU A 135      86.485   3.220  27.271  1.00 42.61      A    C
ATOM    690  CB  LEU A 135      87.762   2.423  27.506  1.00 42.44      A    C
ATOM    691  CG  LEU A 135      87.605   1.126  28.298  1.00 41.68      A    C
ATOM    692  CD1 LEU A 135      88.920   0.359  28.322  1.00 40.41      A    C
ATOM    693  CD2 LEU A 135      87.114   1.439  29.705  1.00 42.57      A    C
ATOM    694  C   LEU A 135      86.823   4.410  26.413  1.00 44.30      A    C
ATOM    695  O   LEU A 135      86.801   4.326  25.189  1.00 43.69      A    O
ATOM    696  N   ASN A 136      87.149   5.529  27.031  1.00 48.58      A    N
ATOM    697  CA  ASN A 136      87.718   6.583  26.220  1.00 52.89      A    C
ATOM    698  CB  ASN A 136      86.966   7.911  26.351  1.00 58.52      A    C
ATOM    699  CG  ASN A 136      87.493   8.792  27.444  1.00 61.38      A    C
ATOM    700  OD1 ASN A 136      87.965   8.321  28.481  1.00 69.27      A    O
ATOM    701  ND2 ASN A 136      87.401  10.100  27.225  1.00 61.43      A    N
ATOM    702  C   ASN A 136      89.238   6.694  26.338  1.00 52.17      A    C
ATOM    703  O   ASN A 136      89.848   6.596  27.418  1.00 45.77      A    O
ATOM    704  N   CYS A 137      89.824   6.890  25.167  1.00 54.07      A    N
ATOM    705  CA  CYS A 137      91.254   6.835  24.972  1.00 56.98      A    C
ATOM    706  CB  CYS A 137      91.594   5.519  24.251  1.00 60.40      A    C
ATOM    707  SG  CYS A 137      90.532   4.122  24.757  1.00 58.77      A    S
ATOM    708  C   CYS A 137      91.624   8.079  24.164  1.00 53.97      A    C
ATOM    709  O   CYS A 137      91.710   8.022  22.942  1.00 58.20      A    O
ATOM    710  N   PRO A 138      91.788   9.229  24.848  1.00 54.13      A    N
ATOM    711  CA  PRO A 138      91.950  10.534  24.175  1.00 54.05      A    C
ATOM    712  CB  PRO A 138      92.054  11.517  25.344  1.00 53.89      A    C
ATOM    713  CG  PRO A 138      91.390  10.830  26.482  1.00 52.18      A    C
ATOM    714  CD  PRO A 138      91.750   9.387  26.313  1.00 53.31      A    C
ATOM    715  C   PRO A 138      93.190  10.650  23.322  1.00 52.87      A    C
ATOM    716  O   PRO A 138      93.185  11.333  22.299  1.00 50.67      A    O
ATOM    717  N   GLU A 139      94.237   9.957  23.731  1.00 57.62      A    N
ATOM    718  CA  GLU A 139      95.516  10.069  23.093  1.00 65.84      A    C
ATOM    719  CB  GLU A 139      96.672   9.833  24.098  1.00 73.41      A    C
ATOM    720  CG  GLU A 139      96.490  10.438  25.473  1.00 81.67      A    C
ATOM    721  CD  GLU A 139      95.936   9.477  26.531  1.00 88.60      A    C
ATOM    722  OE1 GLU A 139      95.393   8.401  26.177  1.00 92.67      A    O
ATOM    723  OE2 GLU A 139      96.039   9.811  27.734  1.00 85.00      A    O
ATOM    724  C   GLU A 139      95.473   9.003  22.028  1.00 64.64      A    C
ATOM    725  O   GLU A 139      96.286   8.100  22.039  1.00 71.95      A    O
ATOM    726  N   LEU A 140      94.505   9.055  21.124  1.00 56.33      A    N
ATOM    727  CA  LEU A 140      94.333   7.854  20.279  1.00 54.53      A    C
ATOM    728  CB  LEU A 140      93.901   6.663  21.174  1.00 56.07      A    C
ATOM    729  CG  LEU A 140      94.337   5.231  20.872  1.00 60.00      A    C
ATOM    730  CD1 LEU A 140      95.753   5.071  21.386  1.00 60.59      A    C
ATOM    731  CD2 LEU A 140      93.447   4.142  21.485  1.00 63.09      A    C
ATOM    732  C   LEU A 140      93.322   7.967  19.172  1.00 52.39      A    C
ATOM    733  O   LEU A 140      92.352   8.666  19.335  1.00 58.74      A    O
ATOM    734  N   GLN A 141      93.552   7.254  18.065  1.00 47.92      A    N
ATOM    735  CA  GLN A 141      92.640   7.212  16.935  1.00 46.63      A    C
ATOM    736  CB  GLN A 141      93.274   7.873  15.707  1.00 52.10      A    C
ATOM    737  CG  GLN A 141      92.283   8.184  14.580  1.00 57.27      A    C
ATOM    738  CD  GLN A 141      91.206   9.184  15.007  1.00 60.27      A    C
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ATOM	739	OE1	GLN	A	141	91.496	10.164	15.704	1.00	68.13	A	O
ATOM	740	NE2	GLN	A	141	89.965	8.944	14.592	1.00	60.04	A	N
ATOM	741	C	GLN	A	141	92.333	5.757	16.611	1.00	46.44	A	C
ATOM	742	O	GLN	A	141	93.245	4.999	16.273	1.00	47.45	A	O
ATOM	743	N	PRO	A	142	91.055	5.338	16.736	1.00	44.73	A	N
ATOM	744	CA	PRO	A	142	89.924	6.135	17.190	1.00	42.37	A	C
ATOM	745	CB	PRO	A	142	88.716	5.293	16.800	1.00	41.07	A	C
ATOM	746	CG	PRO	A	142	89.224	3.888	16.716	1.00	41.72	A	C
ATOM	747	CD	PRO	A	142	90.723	3.904	16.700	1.00	42.33	A	C
ATOM	748	C	PRO	A	142	89.997	6.297	18.687	1.00	43.09	A	C
ATOM	749	O	PRO	A	142	90.653	5.487	19.362	1.00	42.20	A	O
ATOM	750	N	PRO	A	143	89.316	7.320	19.224	1.00	46.72	A	N
ATOM	751	CA	PRO	A	143	89.476	7.658	20.654	1.00	48.69	A	C
ATOM	752	CB	PRO	A	143	89.064	9.139	20.712	1.00	45.97	A	C
ATOM	753	CG	PRO	A	143	88.227	9.368	19.477	1.00	45.57	A	C
ATOM	754	CD	PRO	A	143	88.294	8.160	18.580	1.00	45.17	A	C
ATOM	755	C	PRO	A	143	88.619	6.814	21.624	1.00	48.13	A	C
ATOM	756	O	PRO	A	143	88.332	7.254	22.739	1.00	50.89	A	O
ATOM	757	N	THR	A	144	88.222	5.624	21.186	1.00	49.28	A	N
ATOM	758	CA	THR	A	144	87.366	4.729	21.943	1.00	50.32	A	C
ATOM	759	CB	THR	A	144	85.899	4.905	21.553	1.00	51.98	A	C
ATOM	760	OG1	THR	A	144	85.794	4.814	20.137	1.00	56.43	A	O
ATOM	761	CG2	THR	A	144	85.381	6.262	22.005	1.00	52.56	A	C
ATOM	762	C	THR	A	144	87.796	3.288	21.684	1.00	49.21	A	C
ATOM	763	O	THR	A	144	88.143	2.929	20.571	1.00	50.98	A	O
ATOM	764	N	LYS	A	145	87.837	2.491	22.737	1.00	50.31	A	N
ATOM	765	CA	LYS	A	145	87.981	1.059	22.638	1.00	48.70	A	C
ATOM	766	CB	LYS	A	145	89.275	0.648	23.302	1.00	54.16	A	C
ATOM	767	CG	LYS	A	145	90.439	1.253	22.554	1.00	61.67	A	C
ATOM	768	CD	LYS	A	145	91.110	0.262	21.609	1.00	61.98	A	C
ATOM	769	CE	LYS	A	145	92.392	0.840	21.027	1.00	62.42	A	C
ATOM	770	NZ	LYS	A	145	92.781	0.216	19.732	1.00	62.60	A	N
ATOM	771	C	LYS	A	145	86.836	0.469	23.376	1.00	45.71	A	C
ATOM	772	O	LYS	A	145	86.461	0.977	24.414	1.00	46.01	A	O
ATOM	773	N	LYS	A	146	86.283	-0.604	22.844	1.00	45.81	A	N
ATOM	774	CA	LYS	A	146	85.282	-1.386	23.537	1.00	45.56	A	C
ATOM	775	CB	LYS	A	146	84.166	-1.768	22.555	1.00	47.83	A	C
ATOM	776	CG	LYS	A	146	83.636	-0.556	21.742	1.00	52.68	A	C
ATOM	777	CD	LYS	A	146	82.141	-0.286	21.743	1.00	57.37	A	C
ATOM	778	CE	LYS	A	146	81.808	0.749	20.666	1.00	61.46	A	C
ATOM	779	NZ	LYS	A	146	80.513	1.449	20.913	1.00	63.96	A	N
ATOM	780	C	LYS	A	146	86.015	-2.601	24.148	1.00	43.85	A	C
ATOM	781	O	LYS	A	146	86.820	-3.265	23.483	1.00	41.00	A	O
ATOM	782	N	LYS	A	147	85.778	-2.846	25.430	1.00	41.56	A	N
ATOM	783	CA	LYS	A	147	86.377	-3.974	26.138	1.00	45.71	A	C
ATOM	784	CB	LYS	A	147	87.135	-3.513	27.371	1.00	48.92	A	C
ATOM	785	CG	LYS	A	147	87.643	-4.665	28.209	1.00	54.66	A	C
ATOM	786	CD	LYS	A	147	88.935	-5.288	27.717	1.00	55.50	A	C
ATOM	787	CE	LYS	A	147	89.251	-6.560	28.493	1.00	57.87	A	C
ATOM	788	NZ	LYS	A	147	88.730	-7.777	27.794	1.00	60.18	A	N
ATOM	789	C	LYS	A	147	85.275	-4.934	26.542	1.00	44.02	A	C
ATOM	790	O	LYS	A	147	84.247	-4.525	27.057	1.00	43.49	A	O
ATOM	791	N	ARG	A	148	85.479	-6.214	26.273	1.00	46.97	A	N
ATOM	792	CA	ARG	A	148	84.487	-7.237	26.652	1.00	45.15	A	C
ATOM	793	CB	ARG	A	148	84.463	-8.416	25.690	1.00	46.80	A	C
ATOM	794	CG	ARG	A	148	84.795	-9.731	26.363	1.00	49.81	A	C
ATOM	795	CD	ARG	A	148	83.649	-10.166	27.225	1.00	52.05	A	C
ATOM	796	NE	ARG	A	148	84.125	-11.295	27.983	1.00	57.96	A	N
ATOM	797	CZ	ARG	A	148	84.285	-12.519	27.505	1.00	65.37	A	C
ATOM	798	NH1	ARG	A	148	83.934	-12.816	26.257	1.00	64.74	A	N
ATOM	799	NH2	ARG	A	148	84.778	-13.467	28.298	1.00	75.10	A	N
ATOM	800	C	ARG	A	148	84.657	-7.606	28.135	1.00	41.49	A	C
ATOM	801	O	ARG	A	148	85.766	-7.861	28.632	1.00	37.80	A	O
ATOM	802	N	VAL	A	149	83.554	-7.565	28.861	1.00	39.33	A	N
ATOM	803	CA	VAL	A	149	83.557	-7.976	30.260	1.00	41.03	A	C
ATOM	804	CB	VAL	A	149	83.655	-6.769	31.209	1.00	42.33	A	C
ATOM	805	CG1	VAL	A	149	82.851	-5.615	30.667	1.00	46.28	A	C
ATOM	806	CG2	VAL	A	149	83.179	-7.130	32.606	1.00	44.45	A	C

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ATOM    807  C   VAL A 149      82.318  -8.802  30.560  1.00 42.24      A    C
ATOM    808  O   VAL A 149      81.203  -8.435  30.206  1.00 45.07      A    O
ATOM    809  N   THR A 150      82.528  -9.939  31.204  1.00 44.05      A    N
ATOM    810  CA  THR A 150      81.447 -10.816  31.597  1.00 44.25      A    C
ATOM    811  CB  THR A 150      81.767 -12.289  31.254  1.00 46.81      A    C
ATOM    812  OG1 THR A 150      81.642 -12.480  29.836  1.00 47.80      A    O
ATOM    813  CG2 THR A 150      80.804 -13.237  31.937  1.00 46.89      A    C
ATOM    814  C   THR A 150      81.264 -10.604  33.083  1.00 39.93      A    C
ATOM    815  O   THR A 150      82.220 -10.658  33.825  1.00 43.86      A    O
ATOM    816  N   ARG A 151      80.049 -10.309  33.518  1.00 37.99      A    N
ATOM    817  CA  ARG A 151      79.807 -10.019  34.920  1.00 38.91      A    C
ATOM    818  CB  ARG A 151      79.442  -8.556  35.104  1.00 39.74      A    C
ATOM    819  CG  ARG A 151      78.018  -8.292  34.697  1.00 43.32      A    C
ATOM    820  CD  ARG A 151      77.232  -7.170  35.350  1.00 45.74      A    C
ATOM    821  NE  ARG A 151      77.704  -5.802  35.149  1.00 47.69      A    N
ATOM    822  CZ  ARG A 151      76.915  -4.744  34.922  1.00 50.19      A    C
ATOM    823  NH1 ARG A 151      75.594  -4.862  34.799  1.00 49.45      A    N
ATOM    824  NH2 ARG A 151      77.460  -3.540  34.792  1.00 53.93      A    N
ATOM    825  C   ARG A 151      78.689 -10.918  35.430  1.00 40.19      A    C
ATOM    826  O   ARG A 151      77.897 -11.460  34.641  1.00 40.00      A    O
ATOM    827  N   VAL A 152      78.619 -11.062  36.744  1.00 37.13      A    N
ATOM    828  CA  VAL A 152      77.615 -11.899  37.357  1.00 37.14      A    C
ATOM    829  CB  VAL A 152      78.013 -12.257  38.802  1.00 38.41      A    C
ATOM    830  CG1 VAL A 152      76.871 -12.929  39.539  1.00 39.81      A    C
ATOM    831  CG2 VAL A 152      79.240 -13.145  38.809  1.00 38.57      A    C
ATOM    832  C   VAL A 152      76.311 -11.124  37.343  1.00 37.67      A    C
ATOM    833  O   VAL A 152      76.307  -9.934  37.588  1.00 35.29      A    O
ATOM    834  N   LYS A 153      75.208 -11.798  37.035  1.00 40.11      A    N
ATOM    835  CA  LYS A 153      73.884 -11.161  37.020  1.00 41.30      A    C
ATOM    836  CB  LYS A 153      73.084 -11.631  35.798  1.00 43.14      A    C
ATOM    837  CG  LYS A 153      71.768 -10.942  35.475  1.00 46.14      A    C
ATOM    838  CD  LYS A 153      71.467 -10.996  33.977  1.00 49.60      A    C
ATOM    839  CE  LYS A 153      70.025 -11.377  33.598  1.00 51.18      A    C
ATOM    840  NZ  LYS A 153      69.013 -10.315  33.854  1.00 53.43      A    N
ATOM    841  C   LYS A 153      73.144 -11.536  38.285  1.00 41.69      A    C
ATOM    842  O   LYS A 153      72.749 -10.673  39.058  1.00 43.07      A    O
ATOM    843  N   GLN A 154      72.969 -12.834  38.496  1.00 41.88      A    N
ATOM    844  CA  GLN A 154      72.144 -13.334  39.590  1.00 44.68      A    C
ATOM    845  CB  GLN A 154      70.746 -13.688  39.063  1.00 48.28      A    C
ATOM    846  CG  GLN A 154      69.744 -14.059  40.163  1.00 52.77      A    C
ATOM    847  CD  GLN A 154      69.316 -12.849  40.977  1.00 59.47      A    C
ATOM    848  OE1 GLN A 154      70.128 -12.310  41.723  1.00 63.25      A    O
ATOM    849  NE2 GLN A 154      68.041 -12.436  40.882  1.00 63.57      A    N
ATOM    850  C   GLN A 154      72.791 -14.558  40.239  1.00 40.54      A    C
ATOM    851  O   GLN A 154      73.195 -15.487  39.534  1.00 38.94      A    O
ATOM    852  N   CYS A 155      72.894 -14.542  41.564  1.00 35.89      A    N
ATOM    853  CA  CYS A 155      73.335 -15.711  42.307  1.00 35.93      A    C
ATOM    854  CB  CYS A 155      74.191 -15.313  43.503  1.00 35.47      A    C
ATOM    855  SG  CYS A 155      75.519 -14.202  43.064  1.00 36.10      A    S
ATOM    856  C   CYS A 155      72.166 -16.532  42.812  1.00 34.79      A    C
ATOM    857  O   CYS A 155      71.079 -16.032  43.038  1.00 34.66      A    O
ATOM    858  N   ARG A 156      72.413 -17.811  43.013  1.00 37.51      A    N
ATOM    859  CA  ARG A 156      71.413 -18.683  43.581  1.00 39.64      A    C
ATOM    860  CB  ARG A 156      70.346 -19.005  42.533  1.00 44.44      A    C
ATOM    861  CG  ARG A 156      69.072 -18.185  42.632  1.00 50.28      A    C
ATOM    862  CD  ARG A 156      68.054 -18.722  41.630  1.00 63.22      A    C
ATOM    863  NE  ARG A 156      68.274 -20.163  41.306  1.00 75.49      A    N
ATOM    864  CZ  ARG A 156      67.330 -21.056  40.992  1.00 72.51      A    C
ATOM    865  NH1 ARG A 156      66.048 -20.699  40.946  1.00 75.07      A    N
ATOM    866  NH2 ARG A 156      67.681 -22.322  40.718  1.00 66.61      A    N
ATOM    867  C   ARG A 156      72.060 -19.942  44.111  1.00 37.30      A    C
ATOM    868  O   ARG A 156      73.205 -20.273  43.764  1.00 41.15      A    O
ATOM    869  N   CYS A 157      71.342 -20.624  44.992  1.00 35.77      A    N
ATOM    870  CA  CYS A 157      71.753 -21.948  45.457  1.00 33.28      A    C
ATOM    871  CB  CYS A 157      70.957 -22.368  46.676  1.00 30.58      A    C
ATOM    872  SG  CYS A 157      71.509 -21.578  48.199  1.00 31.82      A    S
ATOM    873  C   CYS A 157      71.501 -22.929  44.340  1.00 33.95      A    C
ATOM    874  O   CYS A 157      70.356 -23.276  44.090  1.00 39.33      A    O
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ATOM    875  N   ILE A 158      72.569 -23.365  43.679  1.00 32.27      A    N
ATOM    876  CA  ILE A 158      72.487 -24.278  42.552  1.00 32.61      A    C
ATOM    877  CB  ILE A 158      73.209 -23.675  41.339  1.00 36.06      A    C
ATOM    878  CG1 ILE A 158      72.398 -22.486  40.818  1.00 39.76      A    C
ATOM    879  CD1 ILE A 158      73.213 -21.513  39.993  1.00 41.39      A    C
ATOM    880  CG2 ILE A 158      73.431 -24.715  40.242  1.00 33.32      A    C
ATOM    881  C   ILE A 158      73.128 -25.613  42.909  1.00 29.41      A    C
ATOM    882  O   ILE A 158      74.240 -25.648  43.415  1.00 27.01      A    O
ATOM    883  N   SER A 159      72.419 -26.702  42.638  1.00 28.71      A    N
ATOM    884  CA  SER A 159      72.857 -28.009  43.084  1.00 29.40      A    C
ATOM    885  CB  SER A 159      71.685 -28.982  43.165  1.00 30.03      A    C
ATOM    886  OG  SER A 159      71.650 -29.805  42.046  1.00 31.08      A    O
ATOM    887  C   SER A 159      73.936 -28.555  42.186  1.00 31.08      A    C
ATOM    888  O   SER A 159      73.966 -28.313  41.001  1.00 34.51      A    O
ATOM    889  N   ILE A 160      74.857 -29.269  42.791  1.00 34.61      A    N
ATOM    890  CA  ILE A 160      76.032 -29.749  42.134  1.00 37.05      A    C
ATOM    891  CB  ILE A 160      77.241 -29.756  43.102  1.00 36.26      A    C
ATOM    892  CG1 ILE A 160      77.672 -28.321  43.335  1.00 36.92      A    C
ATOM    893  CD1 ILE A 160      78.803 -28.199  44.318  1.00 38.37      A    C
ATOM    894  CG2 ILE A 160      78.428 -30.546  42.565  1.00 35.36      A    C
ATOM    895  C   ILE A 160      75.695 -31.143  41.695  1.00 40.64      A    C
ATOM    896  O   ILE A 160      74.961 -31.867  42.373  1.00 45.46      A    O
ATOM    897  N   ASP A 161      76.297 -31.526  40.582  1.00 44.53      A    N
ATOM    898  CA  ASP A 161      76.122 -32.823  40.007  1.00 45.42      A    C
ATOM    899  CB  ASP A 161      76.214 -32.727  38.487  1.00 48.72      A    C
ATOM    900  CG  ASP A 161      75.795 -33.992  37.783  1.00 52.42      A    C
ATOM    901  OD1 ASP A 161      74.580 -34.147  37.636  1.00 59.67      A    O
ATOM    902  OD2 ASP A 161      76.652 -34.797  37.327  1.00 54.62      A    O
ATOM    903  C   ASP A 161      77.235 -33.663  40.617  1.00 44.02      A    C
ATOM    904  O   ASP A 161      78.402 -33.554  40.245  1.00 40.35      A    O
ATOM    905  N   LEU A 162      76.872 -34.436  41.633  1.00 44.52      A    N
ATOM    906  CA  LEU A 162      77.765 -35.447  42.179  1.00 42.69      A    C
ATOM    907  CB  LEU A 162      77.304 -35.841  43.573  1.00 41.17      A    C
ATOM    908  CG  LEU A 162      77.448 -34.941  44.796  1.00 42.67      A    C
ATOM    909  CD1 LEU A 162      78.204 -33.649  44.575  1.00 43.14      A    C
ATOM    910  CD2 LEU A 162      76.091 -34.636  45.402  1.00 42.89      A    C
ATOM    911  C   LEU A 162      77.728 -36.629  41.196  1.00 43.16      A    C
ATOM    912  O   LEU A 162      76.928 -37.550  41.330  1.00 42.79      A    O
ATOM    913  N   ASP A 163      78.582 -36.580  40.184  1.00 45.44      A    N
ATOM    914  CA  ASP A 163      78.403 -37.406  38.993  1.00 52.08      A    C
ATOM    915  CB  ASP A 163      78.951 -38.793  39.235  1.00 55.18      A    C
ATOM    916  CG  ASP A 163      80.433 -38.797  39.267  1.00 55.99      A    C
ATOM    917  OD1 ASP A 163      81.026 -38.781  38.165  1.00 59.24      A    O
ATOM    918  OD2 ASP A 163      80.987 -38.785  40.382  1.00 49.29      A    O
ATOM    919  C   ASP A 163      76.944 -37.499  38.554  1.00 56.36      A    C
ATOM    920  O   ASP A 163      76.651 -37.858  37.416  1.00 62.49      A    O
ATOM    921  N   LEU B  53      81.614  -1.347  47.644  1.00 50.78      B    N
ATOM    922  CA  LEU B  53      82.939  -1.915  48.082  1.00 54.23      B    C
ATOM    923  CB  LEU B  53      82.773  -3.191  48.958  1.00 56.50      B    C
ATOM    924  CG  LEU B  53      81.955  -4.417  48.568  1.00 57.39      B    C
ATOM    925  CD1 LEU B  53      82.041  -5.422  49.716  1.00 55.31      B    C
ATOM    926  CD2 LEU B  53      80.505  -4.091  48.226  1.00 59.46      B    C
ATOM    927  C   LEU B  53      83.811  -2.221  46.892  1.00 53.97      B    C
ATOM    928  O   LEU B  53      83.428  -3.052  46.098  1.00 52.55      B    O
ATOM    929  N   GLU B  54      84.955  -1.535  46.737  1.00 58.38      B    N
ATOM    930  CA  GLU B  54      85.867  -1.831  45.630  1.00 62.52      B    C
ATOM    931  CB  GLU B  54      86.722  -0.645  45.142  1.00 70.46      B    C
ATOM    932  CG  GLU B  54      87.479   0.112  46.190  1.00 72.13      B    C
ATOM    933  CD  GLU B  54      86.746   1.351  46.652  1.00 76.55      B    C
ATOM    934  OE1 GLU B  54      85.623   1.209  47.190  1.00 77.64      B    O
ATOM    935  OE2 GLU B  54      87.293   2.464  46.460  1.00 82.79      B    O
ATOM    936  C   GLU B  54      86.759  -2.867  46.148  1.00 59.60      B    C
ATOM    937  O   GLU B  54      87.121  -2.815  47.313  1.00 69.09      B    O
ATOM    938  N   SER B  55      87.100  -3.811  45.289  1.00 56.12      B    N
ATOM    939  CA  SER B  55      88.029  -4.868  45.628  1.00 55.63      B    C
ATOM    940  CB  SER B  55      88.885  -4.407  46.767  1.00 54.74      B    C
ATOM    941  OG  SER B  55      89.803  -5.395  47.071  1.00 58.49      B    O
ATOM    942  C   SER B  55      87.467  -6.270  45.920  1.00 57.20      B    C
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【圖1】(續)

ATOM	943	O	SER	B	55	86.618	-6.474	46.776	1.00	61.53	B	O
ATOM	944	N	SER	B	56	88.007	-7.248	45.198	1.00	57.55	B	N
ATOM	945	CA	SER	B	56	87.684	-8.649	45.412	1.00	53.44	B	C
ATOM	946	CB	SER	B	56	88.274	-9.507	44.300	1.00	51.92	B	C
ATOM	947	OG	SER	B	56	87.776	-9.104	43.046	1.00	51.65	B	O
ATOM	948	C	SER	B	56	88.255	-9.107	46.725	1.00	56.87	B	C
ATOM	949	O	SER	B	56	87.604	-9.841	47.453	1.00	59.77	B	O
ATOM	950	N	GLN	B	57	89.493	-8.703	46.996	1.00	58.93	B	N
ATOM	951	CA	GLN	B	57	90.126	-8.911	48.294	1.00	62.02	B	C
ATOM	952	CB	GLN	B	57	91.395	-8.080	48.384	1.00	70.90	B	C
ATOM	953	CG	GLN	B	57	92.157	-8.192	49.735	1.00	82.79	B	C
ATOM	954	CD	GLN	B	57	91.695	-7.268	50.873	1.00	88.94	B	C
ATOM	955	OE1	GLN	B	57	90.988	-7.690	51.808	1.00	93.22	B	O
ATOM	956	NE2	GLN	B	57	92.129	-6.015	50.820	1.00	86.97	B	N
ATOM	957	C	GLN	B	57	89.235	-8.470	49.432	1.00	57.84	B	C
ATOM	958	O	GLN	B	57	89.114	-9.156	50.432	1.00	54.85	B	O
ATOM	959	N	GLU	B	58	88.650	-7.297	49.296	1.00	54.62	B	N
ATOM	960	CA	GLU	B	58	87.838	-6.767	50.362	1.00	59.53	B	C
ATOM	961	CB	GLU	B	58	87.458	-5.332	50.082	1.00	65.71	B	C
ATOM	962	CG	GLU	B	58	87.027	-4.561	51.312	1.00	71.48	B	C
ATOM	963	CD	GLU	B	58	86.181	-3.353	50.947	1.00	76.58	B	C
ATOM	964	OE1	GLU	B	58	86.243	-2.906	49.787	1.00	82.82	B	O
ATOM	965	OE2	GLU	B	58	85.443	-2.848	51.804	1.00	80.06	B	O
ATOM	966	C	GLU	B	58	86.588	-7.616	50.488	1.00	54.29	B	C
ATOM	967	O	GLU	B	58	86.212	-8.011	51.585	1.00	53.12	B	O
ATOM	968	N	ALA	B	59	85.966	-7.909	49.356	1.00	48.56	B	N
ATOM	969	CA	ALA	B	59	84.780	-8.740	49.346	1.00	44.94	B	C
ATOM	970	CB	ALA	B	59	84.246	-8.881	47.932	1.00	42.09	B	C
ATOM	971	C	ALA	B	59	85.052	-10.105	49.973	1.00	43.85	B	C
ATOM	972	O	ALA	B	59	84.233	-10.621	50.701	1.00	42.52	B	O
ATOM	973	N	LEU	B	60	86.217	-10.682	49.709	1.00	47.84	B	N
ATOM	974	CA	LEU	B	60	86.570	-11.977	50.297	1.00	48.50	B	C
ATOM	975	CB	LEU	B	60	87.824	-12.543	49.621	1.00	48.85	B	C
ATOM	976	CG	LEU	B	60	88.414	-13.847	50.161	1.00	49.60	B	C
ATOM	977	CD1	LEU	B	60	87.450	-14.975	49.862	1.00	49.56	B	C
ATOM	978	CD2	LEU	B	60	89.776	-14.131	49.540	1.00	52.02	B	C
ATOM	979	C	LEU	B	60	86.732	-11.909	51.823	1.00	53.48	B	C
ATOM	980	O	LEU	B	60	86.161	-12.718	52.554	1.00	55.92	B	O
ATOM	981	N	HIS	B	61	87.475	-10.922	52.301	1.00	55.59	B	N
ATOM	982	CA	HIS	B	61	87.654	-10.713	53.731	1.00	58.19	B	C
ATOM	983	CB	HIS	B	61	88.569	-9.525	53.944	1.00	67.88	B	C
ATOM	984	CG	HIS	B	61	88.781	-9.165	55.381	1.00	81.82	B	C
ATOM	985	ND1	HIS	B	61	89.436	-10.005	56.254	1.00	85.51	B	N
ATOM	986	CE1	HIS	B	61	89.500	-9.435	57.443	1.00	84.19	B	C
ATOM	987	NE2	HIS	B	61	88.902	-8.257	57.374	1.00	84.90	B	N
ATOM	988	CD2	HIS	B	61	88.448	-8.059	56.094	1.00	83.80	B	C
ATOM	989	C	HIS	B	61	86.342	-10.487	54.445	1.00	50.94	B	C
ATOM	990	O	HIS	B	61	86.060	-11.133	55.430	1.00	50.71	B	O
ATOM	991	N	VAL	B	62	85.528	-9.582	53.929	1.00	49.76	B	N
ATOM	992	CA	VAL	B	62	84.244	-9.269	54.561	1.00	47.16	B	C
ATOM	993	CB	VAL	B	62	83.600	-8.024	53.889	1.00	46.60	B	C
ATOM	994	CG1	VAL	B	62	82.154	-7.808	54.332	1.00	46.48	B	C
ATOM	995	CG2	VAL	B	62	84.433	-6.788	54.175	1.00	45.11	B	C
ATOM	996	C	VAL	B	62	83.291	-10.479	54.515	1.00	45.32	B	C
ATOM	997	O	VAL	B	62	82.599	-10.789	55.485	1.00	44.08	B	O
ATOM	998	N	THR	B	63	83.274	-11.170	53.387	1.00	42.02	B	N
ATOM	999	CA	THR	B	63	82.461	-12.355	53.256	1.00	41.62	B	C
ATOM	1000	CB	THR	B	63	82.568	-12.950	51.850	1.00	38.54	B	C
ATOM	1001	OG1	THR	B	63	81.963	-12.046	50.935	1.00	36.43	B	O
ATOM	1002	CG2	THR	B	63	81.844	-14.268	51.751	1.00	40.55	B	C
ATOM	1003	C	THR	B	63	82.839	-13.411	54.295	1.00	42.40	B	C
ATOM	1004	O	THR	B	63	81.965	-14.052	54.854	1.00	44.50	B	O
ATOM	1005	N	GLU	B	64	84.123	-13.609	54.528	1.00	42.91	B	N
ATOM	1006	CA	GLU	B	64	84.551	-14.599	55.516	1.00	46.67	B	C
ATOM	1007	CB	GLU	B	64	86.013	-15.006	55.322	1.00	47.40	B	C
ATOM	1008	CG	GLU	B	64	86.286	-15.740	54.013	1.00	49.57	B	C
ATOM	1009	CD	GLU	B	64	87.769	-15.857	53.708	1.00	52.06	B	C
ATOM	1010	OE1	GLU	B	64	88.189	-16.911	53.187	1.00	54.68	B	O

【圖1】(續)

ATOM	1011	OE2	GLU	B	64	88.506	-14.877	53.973	1.00	49.72	B	O
ATOM	1012	C	GLU	B	64	84.333	-14.133	56.954	1.00	49.13	B	C
ATOM	1013	O	GLU	B	64	83.787	-14.864	57.766	1.00	48.04	B	O
ATOM	1014	N	ARG	B	65	84.750	-12.912	57.264	1.00	52.61	B	N
ATOM	1015	CA	ARG	B	65	84.685	-12.397	58.626	1.00	52.95	B	C
ATOM	1016	CB	ARG	B	65	85.662	-11.194	58.760	1.00	57.56	B	C
ATOM	1017	CG	ARG	B	65	87.089	-11.475	58.275	1.00	64.08	B	C
ATOM	1018	CD	ARG	B	65	87.919	-12.303	59.231	1.00	71.32	B	C
ATOM	1019	NE	ARG	B	65	87.155	-13.147	60.153	1.00	73.28	B	N
ATOM	1020	CZ	ARG	B	65	86.691	-12.786	61.357	1.00	70.13	B	C
ATOM	1021	NH1	ARG	B	65	86.889	-11.563	61.841	1.00	66.46	B	N
ATOM	1022	NH2	ARG	B	65	86.001	-13.666	62.077	1.00	71.39	B	N
ATOM	1023	C	ARG	B	65	83.222	-12.093	59.024	1.00	50.44	B	C
ATOM	1024	O	ARG	B	65	82.707	-12.621	60.018	1.00	50.03	B	O
ATOM	1025	N	LYS	B	66	82.525	-11.315	58.210	1.00	49.51	B	N
ATOM	1026	CA	LYS	B	66	81.213	-10.829	58.579	1.00	48.59	B	C
ATOM	1027	CB	LYS	B	66	81.068	-9.380	58.140	1.00	50.57	B	C
ATOM	1028	CG	LYS	B	66	80.089	-8.578	58.972	1.00	52.95	B	C
ATOM	1029	CD	LYS	B	66	79.908	-7.171	58.413	1.00	55.61	B	C
ATOM	1030	CE	LYS	B	66	78.438	-6.760	58.446	1.00	58.04	B	C
ATOM	1031	NZ	LYS	B	66	78.265	-5.303	58.209	1.00	62.60	B	N
ATOM	1032	C	LYS	B	66	80.023	-11.640	58.062	1.00	48.09	B	C
ATOM	1033	O	LYS	B	66	79.191	-12.053	58.860	1.00	48.35	B	O
ATOM	1034	N	TYR	B	67	79.916	-11.848	56.747	1.00	47.65	B	N
ATOM	1035	CA	TYR	B	67	78.650	-12.333	56.151	1.00	45.53	B	C
ATOM	1036	CB	TYR	B	67	78.615	-12.107	54.640	1.00	46.29	B	C
ATOM	1037	CG	TYR	B	67	78.700	-10.668	54.186	1.00	46.08	B	C
ATOM	1038	CD1	TYR	B	67	78.180	-9.634	54.952	1.00	45.09	B	C
ATOM	1039	CE1	TYR	B	67	78.273	-8.327	54.527	1.00	46.50	B	C
ATOM	1040	CZ	TYR	B	67	78.853	-8.040	53.306	1.00	46.52	B	C
ATOM	1041	OH	TYR	B	67	78.935	-6.732	52.880	1.00	45.13	B	O
ATOM	1042	CE2	TYR	B	67	79.366	-9.051	52.526	1.00	44.70	B	C
ATOM	1043	CD2	TYR	B	67	79.287	-10.352	52.970	1.00	44.72	B	C
ATOM	1044	C	TYR	B	67	78.351	-13.794	56.394	1.00	44.82	B	C
ATOM	1045	O	TYR	B	67	77.198	-14.177	56.466	1.00	45.72	B	O
ATOM	1046	N	LEU	B	68	79.385	-14.610	56.482	1.00	46.55	B	N
ATOM	1047	CA	LEU	B	68	79.211	-16.047	56.587	1.00	49.20	B	C
ATOM	1048	CB	LEU	B	68	80.050	-16.747	55.508	1.00	48.49	B	C
ATOM	1049	CG	LEU	B	68	79.549	-16.562	54.071	1.00	46.03	B	C
ATOM	1050	CD1	LEU	B	68	80.464	-17.311	53.119	1.00	45.48	B	C
ATOM	1051	CD2	LEU	B	68	78.106	-17.021	53.929	1.00	45.11	B	C
ATOM	1052	C	LEU	B	68	79.582	-16.548	57.963	1.00	53.25	B	C
ATOM	1053	O	LEU	B	68	80.708	-16.970	58.189	1.00	58.18	B	O
ATOM	1054	N	LYS	B	69	78.611	-16.524	58.865	1.00	56.48	B	N
ATOM	1055	CA	LYS	B	69	78.784	-17.037	60.222	1.00	59.99	B	C
ATOM	1056	CB	LYS	B	69	78.858	-15.936	61.299	1.00	62.47	B	C
ATOM	1057	CG	LYS	B	69	79.112	-14.517	60.826	1.00	65.06	B	C
ATOM	1058	CD	LYS	B	69	79.242	-13.556	61.997	1.00	62.25	B	C
ATOM	1059	CE	LYS	B	69	80.560	-13.751	62.715	1.00	63.04	B	C
ATOM	1060	NZ	LYS	B	69	80.715	-12.725	63.774	1.00	66.70	B	N
ATOM	1061	C	LYS	B	69	77.621	-17.947	60.528	1.00	58.25	B	C
ATOM	1062	O	LYS	B	69	76.581	-17.865	59.882	1.00	50.57	B	O
ATOM	1063	N	ARG	B	70	77.806	-18.824	61.508	1.00	58.72	B	N
ATOM	1064	CA	ARG	B	70	76.730	-19.632	61.981	1.00	59.40	B	C
ATOM	1065	CB	ARG	B	70	75.565	-18.668	62.332	1.00	68.75	B	C
ATOM	1066	CG	ARG	B	70	74.817	-18.942	63.648	1.00	77.02	B	C
ATOM	1067	CD	ARG	B	70	73.731	-20.000	63.453	1.00	88.15	B	C
ATOM	1068	NE	ARG	B	70	74.215	-21.356	63.689	1.00	96.12	B	N
ATOM	1069	CZ	ARG	B	70	73.415	-22.415	63.732	1.00	99.62	B	C
ATOM	1070	NH1	ARG	B	70	72.105	-22.273	63.541	1.00	101.30	B	N
ATOM	1071	NH2	ARG	B	70	73.923	-23.615	63.963	1.00	99.82	B	N
ATOM	1072	C	ARG	B	70	76.345	-20.717	60.937	1.00	54.48	B	C
ATOM	1073	O	ARG	B	70	75.176	-21.108	60.860	1.00	51.67	B	O
ATOM	1074	N	ASP	B	71	77.309	-21.238	60.152	1.00	49.61	B	N
ATOM	1075	CA	ASP	B	71	77.027	-22.425	59.320	1.00	47.79	B	C
ATOM	1076	CB	ASP	B	71	78.160	-22.789	58.338	1.00	48.61	B	C
ATOM	1077	CG	ASP	B	71	79.471	-23.045	59.034	1.00	50.94	B	C
ATOM	1078	OD1	ASP	B	71	79.754	-22.336	60.011	1.00	55.45	B	O

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ATOM   1079  OD2 ASP B  71      80.224 -23.940  58.605  1.00 54.93      B    O
ATOM   1080  C   ASP B  71      76.755 -23.594  60.278  1.00 43.66      B    C
ATOM   1081  O   ASP B  71      77.180 -23.574  61.429  1.00 43.97      B    O
ATOM   1082  N   TRP B  72      76.038 -24.600  59.809  1.00 39.69      B    N
ATOM   1083  CA  TRP B  72      75.701 -25.727  60.651  1.00 36.06      B    C
ATOM   1084  CB  TRP B  72      74.394 -25.435  61.378  1.00 33.68      B    C
ATOM   1085  CG  TRP B  72      73.182 -25.288  60.510  1.00 31.17      B    C
ATOM   1086  CD1 TRP B  72      72.767 -24.168  59.861  1.00 28.92      B    C
ATOM   1087  NE1 TRP B  72      71.591 -24.414  59.194  1.00 28.41      B    N
ATOM   1088  CE2 TRP B  72      71.216 -25.710  59.415  1.00 28.61      B    C
ATOM   1089  CD2 TRP B  72      72.200 -26.292  60.248  1.00 29.62      B    C
ATOM   1090  CE3 TRP B  72      72.058 -27.625  60.626  1.00 28.39      B    C
ATOM   1091  CZ3 TRP B  72      70.957 -28.339  60.145  1.00 28.53      B    C
ATOM   1092  CH2 TRP B  72      70.000 -27.734  59.308  1.00 27.84      B    C
ATOM   1093  CZ2 TRP B  72      70.103 -26.423  58.943  1.00 27.38      B    C
ATOM   1094  C   TRP B  72      75.591 -27.028  59.876  1.00 37.02      B    C
ATOM   1095  O   TRP B  72      75.267 -27.022  58.697  1.00 41.55      B    O
ATOM   1096  N   CYS B  73      75.827 -28.135  60.572  1.00 36.95      B    N
ATOM   1097  CA  CYS B  73      75.720 -29.461  60.007  1.00 37.95      B    C
ATOM   1098  CB  CYS B  73      77.037 -29.807  59.330  1.00 37.81      B    C
ATOM   1099  SG  CYS B  73      77.163 -31.460  58.616  1.00 39.65      B    S
ATOM   1100  C   CYS B  73      75.360 -30.480  61.104  1.00 38.75      B    C
ATOM   1101  O   CYS B  73      76.138 -30.692  62.009  1.00 41.59      B    O
ATOM   1102  N   LYS B  74      74.188 -31.108  60.986  1.00 38.46      B    N
ATOM   1103  CA  LYS B  74      73.679 -32.058  61.962  1.00 38.96      B    C
ATOM   1104  CB  LYS B  74      72.197 -31.799  62.207  1.00 42.24      B    C
ATOM   1105  CG  LYS B  74      71.942 -30.678  63.190  1.00 44.07      B    C
ATOM   1106  CD  LYS B  74      72.036 -31.271  64.624  1.00 50.33      B    C
ATOM   1107  CE  LYS B  74      73.514 -31.249  65.191  1.00 48.08      B    C
ATOM   1108  NZ  LYS B  74      74.285 -32.537  65.419  1.00 40.69      B    N
ATOM   1109  C   LYS B  74      73.847 -33.514  61.547  1.00 38.20      B    C
ATOM   1110  O   LYS B  74      73.714 -33.858  60.373  1.00 41.55      B    O
ATOM   1111  N   THR B  75      74.179 -34.349  62.532  1.00 37.31      B    N
ATOM   1112  CA  THR B  75      74.214 -35.798  62.406  1.00 35.71      B    C
ATOM   1113  CB  THR B  75      75.475 -36.395  63.047  1.00 37.24      B    C
ATOM   1114  OG1 THR B  75      76.647 -35.730  62.542  1.00 40.64      B    O
ATOM   1115  CG2 THR B  75      75.570 -37.888  62.736  1.00 36.99      B    C
ATOM   1116  C   THR B  75      73.026 -36.336  63.174  1.00 35.00      B    C
ATOM   1117  O   THR B  75      72.761 -35.878  64.273  1.00 34.60      B    O
ATOM   1118  N   GLN B  76      72.298 -37.286  62.601  1.00 35.28      B    N
ATOM   1119  CA  GLN B  76      71.088 -37.793  63.243  1.00 36.43      B    C
ATOM   1120  CB  GLN B  76      69.915 -36.957  62.788  1.00 39.58      B    C
ATOM   1121  CG  GLN B  76      68.608 -37.340  63.442  1.00 43.18      B    C
ATOM   1122  CD  GLN B  76      67.517 -36.337  63.193  1.00 46.39      B    C
ATOM   1123  OE1 GLN B  76      67.764 -35.131  63.111  1.00 46.79      B    O
ATOM   1124  NE2 GLN B  76      66.291 -36.825  63.091  1.00 50.10      B    N
ATOM   1125  C   GLN B  76      70.828 -39.260  62.908  1.00 34.89      B    C
ATOM   1126  O   GLN B  76      71.127 -39.685  61.802  1.00 38.03      B    O
ATOM   1127  N   PRO B  77      70.285 -40.037  63.861  1.00 32.22      B    N
ATOM   1128  CA  PRO B  77      70.174 -41.466  63.624  1.00 31.04      B    C
ATOM   1129  CB  PRO B  77      69.978 -42.037  65.039  1.00 31.41      B    C
ATOM   1130  CG  PRO B  77      69.343 -40.922  65.800  1.00 31.04      B    C
ATOM   1131  CD  PRO B  77      70.045 -39.712  65.286  1.00 31.94      B    C
ATOM   1132  C   PRO B  77      68.982 -41.831  62.771  1.00 32.94      B    C
ATOM   1133  O   PRO B  77      67.974 -41.115  62.770  1.00 34.41      B    O
ATOM   1134  N   LEU B  78      69.093 -42.954  62.072  1.00 33.61      B    N
ATOM   1135  CA  LEU B  78      67.993 -43.489  61.296  1.00 36.62      B    C
ATOM   1136  CB  LEU B  78      67.983 -42.862  59.877  1.00 36.85      B    C
ATOM   1137  CG  LEU B  78      69.052 -43.063  58.762  1.00 36.23      B    C
ATOM   1138  CD1 LEU B  78      70.250 -43.930  59.105  1.00 37.46      B    C
ATOM   1139  CD2 LEU B  78      68.411 -43.576  57.505  1.00 37.26      B    C
ATOM   1140  C   LEU B  78      68.109 -45.000  61.238  1.00 39.63      B    C
ATOM   1141  O   LEU B  78      69.211 -45.536  61.353  1.00 39.46      B    O
ATOM   1142  N   LYS B  79      66.975 -45.682  61.067  1.00 46.56      B    N
ATOM   1143  CA  LYS B  79      66.945 -47.138  60.994  1.00 47.02      B    C
ATOM   1144  CB  LYS B  79      65.609 -47.708  61.405  1.00 49.23      B    C
ATOM   1145  CG  LYS B  79      65.271 -47.526  62.864  1.00 53.56      B    C
ATOM   1146  CD  LYS B  79      63.797 -47.804  63.089  1.00 58.13      B    C
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ATOM   1147  CE  LYS B  79      63.399 -47.620  64.542  1.00 64.46      B    C
ATOM   1148  NZ  LYS B  79      61.924 -47.729  64.700  1.00 68.58      B    N
ATOM   1149  C   LYS B  79      67.189 -47.586  59.586  1.00 49.88      B    C
ATOM   1150  O   LYS B  79      66.843 -46.917  58.610  1.00 56.25      B    O
ATOM   1151  N   GLN B  80      67.825 -48.734  59.498  1.00 51.43      B    N
ATOM   1152  CA  GLN B  80      68.190 -49.305  58.255  1.00 49.62      B    C
ATOM   1153  CB  GLN B  80      69.549 -48.704  57.940  1.00 50.32      B    C
ATOM   1154  CG  GLN B  80      70.362 -49.373  56.865  1.00 50.50      B    C
ATOM   1155  CD  GLN B  80      71.075 -48.323  56.083  1.00 50.15      B    C
ATOM   1156  OE1 GLN B  80      70.699 -47.949  54.957  1.00 50.85      B    O
ATOM   1157  NE2 GLN B  80      72.075 -47.789  56.711  1.00 47.69      B    N
ATOM   1158  C   GLN B  80      68.191 -50.808  58.500  1.00 50.71      B    C
ATOM   1159  O   GLN B  80      68.558 -51.282  59.584  1.00 44.30      B    O
ATOM   1160  N   THR B  81      67.703 -51.560  57.531  1.00 55.42      B    N
ATOM   1161  CA  THR B  81      67.596 -53.004  57.720  1.00 63.87      B    C
ATOM   1162  CB  THR B  81      66.148 -53.534  57.527  1.00 64.39      B    C
ATOM   1163  OG1 THR B  81      66.194 -54.927  57.191  1.00 63.53      B    O
ATOM   1164  CG2 THR B  81      65.406 -52.785  56.414  1.00 66.68      B    C
ATOM   1165  C   THR B  81      68.594 -53.723  56.818  1.00 66.86      B    C
ATOM   1166  O   THR B  81      68.775 -53.329  55.671  1.00 67.18      B    O
ATOM   1167  N   ILE B  82      69.237 -54.769  57.345  1.00 73.75      B    N
ATOM   1168  CA  ILE B  82      70.167 -55.578  56.536  1.00 83.82      B    C
ATOM   1169  CB  ILE B  82      71.592 -55.766  57.197  1.00 86.13      B    C
ATOM   1170  CG1 ILE B  82      71.517 -55.749  58.734  1.00 88.36      B    C
ATOM   1171  CD1 ILE B  82      72.779 -56.055  59.515  1.00 88.36      B    C
ATOM   1172  CG2 ILE B  82      72.559 -54.702  56.682  1.00 86.43      B    C
ATOM   1173  C   ILE B  82      69.415 -56.883  56.222  1.00 89.51      B    C
ATOM   1174  O   ILE B  82      68.996 -57.588  57.145  1.00 87.05      B    O
ATOM   1175  N   HIS B  83      69.203 -57.177  54.926  1.00 98.90      B    N
ATOM   1176  CA  HIS B  83      68.138 -58.148  54.522  1.00102.40      B    C
ATOM   1177  CB  HIS B  83      67.132 -57.626  53.429  1.00 99.49      B    C
ATOM   1178  CG  HIS B  83      67.594 -56.434  52.658  1.00100.69      B    C
ATOM   1179  ND1 HIS B  83      67.007 -55.188  52.770  1.00107.59      B    N
ATOM   1180  CE1 HIS B  83      67.604 -54.351  51.937  1.00111.12      B    C
ATOM   1181  NE2 HIS B  83      68.541 -55.012  51.282  1.00112.09      B    N
ATOM   1182  CD2 HIS B  83      68.546 -56.317  51.705  1.00107.77      B    C
ATOM   1183  C   HIS B  83      68.634 -59.582  54.190  1.00107.69      B    C
ATOM   1184  O   HIS B  83      69.840 -59.867  54.119  1.00 99.31      B    O
ATOM   1185  N   GLU B  84      67.633 -60.447  54.000  1.00120.55      B    N
ATOM   1186  CA  GLU B  84      67.748 -61.939  53.845  1.00123.08      B    C
ATOM   1187  CB  GLU B  84      66.353 -62.554  53.650  1.00123.41      B    C
ATOM   1188  CG  GLU B  84      65.441 -62.363  54.870  1.00124.59      B    C
ATOM   1189  CD  GLU B  84      64.005 -61.936  54.567  1.00116.30      B    C
ATOM   1190  OE1 GLU B  84      63.127 -62.820  54.455  1.00113.42      B    O
ATOM   1191  OE2 GLU B  84      63.734 -60.715  54.510  1.00104.58      B    O
ATOM   1192  C   GLU B  84      68.666 -62.539  52.759  1.00115.01      B    C
ATOM   1193  O   GLU B  84      68.375 -62.444  51.573  1.00107.07      B    O
ATOM   1194  N   GLU B  85      69.746 -63.189  53.188  1.00107.12      B    N
ATOM   1195  CA  GLU B  85      70.528 -64.085  52.363  1.00 98.96      B    C
ATOM   1196  CB  GLU B  85      71.999 -63.683  52.459  1.00 99.31      B    C
ATOM   1197  CG  GLU B  85      72.174 -62.160  52.441  1.00 99.77      B    C
ATOM   1198  CD  GLU B  85      72.645 -61.594  53.771  1.00101.28      B    C
ATOM   1199  OE1 GLU B  85      73.374 -62.303  54.501  1.00102.73      B    O
ATOM   1200  OE2 GLU B  85      72.306 -60.428  54.078  1.00 98.98      B    O
ATOM   1201  C   GLU B  85      70.327 -65.516  52.892  1.00 94.57      B    C
ATOM   1202  O   GLU B  85      71.291 -66.209  53.219  1.00 91.97      B    O
ATOM   1203  N   GLY B  86      69.068 -65.941  53.013  1.00 93.19      B    N
ATOM   1204  CA  GLY B  86      68.714 -67.088  53.854  1.00 90.24      B    C
ATOM   1205  C   GLY B  86      68.781 -66.762  55.344  1.00 92.83      B    C
ATOM   1206  O   GLY B  86      68.516 -67.619  56.181  1.00 91.24      B    O
ATOM   1207  N   CYS B  87      69.144 -65.524  55.680  1.00 90.65      B    N
ATOM   1208  CA  CYS B  87      69.232 -65.080  57.064  1.00 83.95      B    C
ATOM   1209  CB  CYS B  87      70.518 -64.295  57.296  1.00 88.79      B    C
ATOM   1210  SG  CYS B  87      72.040 -65.228  57.001  1.00 92.29      B    S
ATOM   1211  C   CYS B  87      68.052 -64.192  57.395  1.00 79.04      B    C
ATOM   1212  O   CYS B  87      67.554 -63.459  56.540  1.00 69.91      B    O
ATOM   1213  N   ASN B  88      67.607 -64.252  58.643  1.00 78.99      B    N
ATOM   1214  CA  ASN B  88      66.613 -63.311  59.126  1.00 80.47      B    C
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ATOM	1215	CB	ASN	B	88	66.229	-63.594	60.586	1.00	76.73	B	C
ATOM	1216	CG	ASN	B	88	65.396	-64.857	60.753	1.00	74.39	B	C
ATOM	1217	OD1	ASN	B	88	65.117	-65.266	61.885	1.00	68.81	B	O
ATOM	1218	ND2	ASN	B	88	64.983	-65.475	59.641	1.00	69.89	B	N
ATOM	1219	C	ASN	B	88	67.210	-61.910	58.992	1.00	82.89	B	C
ATOM	1220	O	ASN	B	88	68.372	-61.683	59.339	1.00	84.97	B	O
ATOM	1221	N	SER	B	89	66.415	-60.993	58.448	1.00	82.23	B	N
ATOM	1222	CA	SER	B	89	66.803	-59.609	58.294	1.00	77.61	B	C
ATOM	1223	CB	SER	B	89	65.751	-58.839	57.449	1.00	75.09	B	C
ATOM	1224	OG	SER	B	89	64.892	-58.142	58.312	1.00	77.21	B	O
ATOM	1225	C	SER	B	89	66.936	-59.015	59.704	1.00	73.65	B	C
ATOM	1226	O	SER	B	89	66.276	-59.461	60.646	1.00	70.62	B	O
ATOM	1227	N	ARG	B	90	67.818	-58.031	59.845	1.00	70.16	B	N
ATOM	1228	CA	ARG	B	90	68.074	-57.371	61.131	1.00	64.25	B	C
ATOM	1229	CB	ARG	B	90	69.383	-57.909	61.717	1.00	60.59	B	C
ATOM	1230	CG	ARG	B	90	69.858	-57.190	62.965	1.00	56.28	B	C
ATOM	1231	CD	ARG	B	90	70.958	-57.969	63.657	1.00	57.29	B	C
ATOM	1232	NE	ARG	B	90	71.408	-57.236	64.836	1.00	57.22	B	N
ATOM	1233	CZ	ARG	B	90	72.506	-57.509	65.536	1.00	57.05	B	C
ATOM	1234	NH1	ARG	B	90	73.319	-58.503	65.192	1.00	59.81	B	N
ATOM	1235	NH2	ARG	B	90	72.799	-56.775	66.604	1.00	56.51	B	N
ATOM	1236	C	ARG	B	90	68.142	-55.857	60.946	1.00	59.89	B	C
ATOM	1237	O	ARG	B	90	68.651	-55.383	59.943	1.00	59.85	B	O
ATOM	1238	N	THR	B	91	67.649	-55.099	61.916	1.00	57.22	B	N
ATOM	1239	CA	THR	B	91	67.641	-53.649	61.804	1.00	58.17	B	C
ATOM	1240	CB	THR	B	91	66.263	-53.073	62.194	1.00	59.34	B	C
ATOM	1241	OG1	THR	B	91	65.291	-53.498	61.233	1.00	61.50	B	O
ATOM	1242	CG2	THR	B	91	66.270	-51.523	62.255	1.00	60.41	B	C
ATOM	1243	C	THR	B	91	68.729	-53.047	62.669	1.00	57.08	B	C
ATOM	1244	O	THR	B	91	68.878	-53.416	63.830	1.00	58.35	B	O
ATOM	1245	N	ILE	B	92	69.479	-52.112	62.085	1.00	54.73	B	N
ATOM	1246	CA	ILE	B	92	70.557	-51.417	62.775	1.00	53.15	B	C
ATOM	1247	CB	ILE	B	92	71.946	-51.798	62.220	1.00	62.76	B	C
ATOM	1248	CG1	ILE	B	92	72.032	-51.635	60.698	1.00	67.31	B	C
ATOM	1249	CD1	ILE	B	92	72.989	-50.555	60.256	1.00	71.08	B	C
ATOM	1250	CG2	ILE	B	92	72.295	-53.233	62.601	1.00	66.73	B	C
ATOM	1251	C	ILE	B	92	70.356	-49.926	62.655	1.00	47.15	B	C
ATOM	1252	O	ILE	B	92	69.504	-49.474	61.903	1.00	48.49	B	O
ATOM	1253	N	ILE	B	93	71.150	-49.173	63.406	1.00	43.16	B	N
ATOM	1254	CA	ILE	B	93	71.106	-47.719	63.407	1.00	41.44	B	C
ATOM	1255	CB	ILE	B	93	71.154	-47.163	64.852	1.00	43.75	B	C
ATOM	1256	CG1	ILE	B	93	69.895	-47.551	65.621	1.00	44.41	B	C
ATOM	1257	CD1	ILE	B	93	68.600	-47.042	65.050	1.00	45.44	B	C
ATOM	1258	CG2	ILE	B	93	71.414	-45.658	64.882	1.00	43.30	B	C
ATOM	1259	C	ILE	B	93	72.300	-47.167	62.647	1.00	39.02	B	C
ATOM	1260	O	ILE	B	93	73.432	-47.392	63.054	1.00	38.06	B	O
ATOM	1261	N	ASN	B	94	72.034	-46.458	61.547	1.00	38.19	B	N
ATOM	1262	CA	ASN	B	94	73.040	-45.628	60.881	1.00	38.79	B	C
ATOM	1263	CB	ASN	B	94	72.937	-45.776	59.366	1.00	39.00	B	C
ATOM	1264	CG	ASN	B	94	74.277	-45.612	58.663	1.00	38.97	B	C
ATOM	1265	OD1	ASN	B	94	75.183	-44.961	59.158	1.00	37.07	B	O
ATOM	1266	ND2	ASN	B	94	74.391	-46.200	57.489	1.00	40.71	B	N
ATOM	1267	C	ASN	B	94	72.808	-44.166	61.274	1.00	39.83	B	C
ATOM	1268	O	ASN	B	94	71.991	-43.897	62.152	1.00	41.58	B	O
ATOM	1269	N	ARG	B	95	73.505	-43.238	60.614	1.00	37.34	B	N
ATOM	1270	CA	ARG	B	95	73.270	-41.825	60.780	1.00	36.90	B	C
ATOM	1271	CB	ARG	B	95	74.371	-41.219	61.624	1.00	38.67	B	C
ATOM	1272	CG	ARG	B	95	74.467	-41.901	62.961	1.00	40.96	B	C
ATOM	1273	CD	ARG	B	95	75.532	-41.317	63.863	1.00	44.66	B	C
ATOM	1274	NE	ARG	B	95	75.671	-42.067	65.118	1.00	50.83	B	N
ATOM	1275	CZ	ARG	B	95	76.622	-41.829	66.024	1.00	58.48	B	C
ATOM	1276	NH1	ARG	B	95	77.524	-40.871	65.821	1.00	63.89	B	N
ATOM	1277	NH2	ARG	B	95	76.674	-42.541	67.143	1.00	61.94	B	N
ATOM	1278	C	ARG	B	95	73.212	-41.116	59.444	1.00	36.56	B	C
ATOM	1279	O	ARG	B	95	73.709	-41.616	58.451	1.00	32.50	B	O
ATOM	1280	N	PHE	B	96	72.579	-39.947	59.429	1.00	37.33	B	N
ATOM	1281	CA	PHE	B	96	72.589	-39.104	58.245	1.00	39.94	B	C
ATOM	1282	CB	PHE	B	96	71.254	-39.178	57.484	1.00	43.53	B	C

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ATOM   1283  CG  PHE B  96      70.075 -38.607  58.222  1.00 43.39      B    C
ATOM   1284  CD1 PHE B  96      69.446 -39.339  59.222  1.00 45.73      B    C
ATOM   1285  CE1 PHE B  96      68.356 -38.826  59.903  1.00 46.06      B    C
ATOM   1286  CZ  PHE B  96      67.856 -37.576  59.567  1.00 46.94      B    C
ATOM   1287  CE2 PHE B  96      68.465 -36.847  58.554  1.00 44.36      B    C
ATOM   1288  CD2 PHE B  96      69.566 -37.367  57.887  1.00 42.63      B    C
ATOM   1289  C   PHE B  96      72.971 -37.677  58.555  1.00 38.38      B    C
ATOM   1290  O   PHE B  96      72.918 -37.242  59.702  1.00 40.31      B    O
ATOM   1291  N   CYS B  97      73.387 -36.971  57.510  1.00 38.84      B    N
ATOM   1292  CA  CYS B  97      73.899 -35.617  57.621  1.00 37.93      B    C
ATOM   1293  CB  CYS B  97      75.227 -35.515  56.890  1.00 39.69      B    C
ATOM   1294  SG  CYS B  97      76.399 -36.819  57.295  1.00 42.37      B    S
ATOM   1295  C   CYS B  97      72.960 -34.663  56.943  1.00 35.54      B    C
ATOM   1296  O   CYS B  97      72.416 -34.967  55.897  1.00 36.20      B    O
ATOM   1297  N   TYR B  98      72.768 -33.499  57.523  1.00 36.04      B    N
ATOM   1298  CA  TYR B  98      72.114 -32.418  56.803  1.00 37.70      B    C
ATOM   1299  CB  TYR B  98      70.592 -32.570  56.811  1.00 38.63      B    C
ATOM   1300  CG  TYR B  98      70.021 -32.646  58.180  1.00 39.89      B    C
ATOM   1301  CD1 TYR B  98      69.752 -31.501  58.900  1.00 42.52      B    C
ATOM   1302  CE1 TYR B  98      69.221 -31.571  60.179  1.00 44.18      B    C
ATOM   1303  CZ  TYR B  98      68.963 -32.799  60.740  1.00 41.16      B    C
ATOM   1304  OH  TYR B  98      68.442 -32.845  61.991  1.00 41.89      B    O
ATOM   1305  CE2 TYR B  98      69.227 -33.956  60.045  1.00 41.31      B    C
ATOM   1306  CD2 TYR B  98      69.756 -33.873  58.769  1.00 41.94      B    C
ATOM   1307  C   TYR B  98      72.498 -31.095  57.406  1.00 37.91      B    C
ATOM   1308  O   TYR B  98      72.711 -30.991  58.621  1.00 36.97      B    O
ATOM   1309  N   GLY B  99      72.573 -30.081  56.560  1.00 35.29      B    N
ATOM   1310  CA  GLY B  99      72.958 -28.777  57.030  1.00 34.83      B    C
ATOM   1311  C   GLY B  99      73.028 -27.731  55.939  1.00 34.72      B    C
ATOM   1312  O   GLY B  99      72.649 -27.962  54.781  1.00 32.92      B    O
ATOM   1313  N   GLN B 100      73.528 -26.571  56.337  1.00 32.10      B    N
ATOM   1314  CA  GLN B 100      73.692 -25.458  55.445  1.00 30.94      B    C
ATOM   1315  CB  GLN B 100      72.584 -24.443  55.688  1.00 31.34      B    C
ATOM   1316  CG  GLN B 100      71.210 -25.125  55.600  1.00 32.74      B    C
ATOM   1317  CD  GLN B 100      70.008 -24.231  55.763  1.00 33.31      B    C
ATOM   1318  OE1 GLN B 100      68.921 -24.523  55.239  1.00 31.17      B    O
ATOM   1319  NE2 GLN B 100      70.177 -23.149  56.496  1.00 34.91      B    N
ATOM   1320  C   GLN B 100      75.076 -24.906  55.703  1.00 30.87      B    C
ATOM   1321  O   GLN B 100      75.319 -24.278  56.716  1.00 30.96      B    O
ATOM   1322  N   CYS B 101      75.994 -25.214  54.795  1.00 32.62      B    N
ATOM   1323  CA  CYS B 101      77.387 -24.866  54.954  1.00 33.06      B    C
ATOM   1324  CB  CYS B 101      78.275 -26.012  54.486  1.00 35.51      B    C
ATOM   1325  SG  CYS B 101      77.994 -27.528  55.412  1.00 41.49      B    S
ATOM   1326  C   CYS B 101      77.649 -23.633  54.134  1.00 30.73      B    C
ATOM   1327  O   CYS B 101      76.793 -23.203  53.387  1.00 30.58      B    O
ATOM   1328  N   ASN B 102      78.823 -23.042  54.293  1.00 30.48      B    N
ATOM   1329  CA  ASN B 102      79.131 -21.820  53.582  1.00 29.55      B    C
ATOM   1330  CB  ASN B 102      80.208 -21.052  54.292  1.00 30.25      B    C
ATOM   1331  CG  ASN B 102      79.775 -20.577  55.639  1.00 31.72      B    C
ATOM   1332  OD1 ASN B 102      78.613 -20.247  55.883  1.00 34.37      B    O
ATOM   1333  ND2 ASN B 102      80.711 -20.538  56.529  1.00 33.34      B    N
ATOM   1334  C   ASN B 102      79.608 -22.087  52.207  1.00 29.04      B    C
ATOM   1335  O   ASN B 102      80.358 -23.036  51.979  1.00 32.68      B    O
ATOM   1336  N   SER B 103      79.188 -21.231  51.292  1.00 28.19      B    N
ATOM   1337  CA  SER B 103      79.752 -21.202  49.967  1.00 29.39      B    C
ATOM   1338  CB  SER B 103      78.954 -22.103  49.040  1.00 28.26      B    C
ATOM   1339  OG  SER B 103      77.606 -21.679  48.996  1.00 27.39      B    O
ATOM   1340  C   SER B 103      79.726 -19.763  49.473  1.00 30.45      B    C
ATOM   1341  O   SER B 103      78.908 -18.970  49.921  1.00 31.28      B    O
ATOM   1342  N   PHE B 104      80.605 -19.444  48.543  1.00 29.30      B    N
ATOM   1343  CA  PHE B 104      80.593 -18.141  47.943  1.00 31.33      B    C
ATOM   1344  CB  PHE B 104      81.216 -17.097  48.885  1.00 34.69      B    C
ATOM   1345  CG  PHE B 104      82.659 -17.366  49.241  1.00 38.41      B    C
ATOM   1346  CD1 PHE B 104      83.691 -17.095  48.334  1.00 38.92      B    C
ATOM   1347  CE1 PHE B 104      85.016 -17.351  48.673  1.00 41.07      B    C
ATOM   1348  CZ  PHE B 104      85.330 -17.872  49.923  1.00 38.01      B    C
ATOM   1349  CE2 PHE B 104      84.325 -18.118  50.822  1.00 38.22      B    C
ATOM   1350  CD2 PHE B 104      82.998 -17.868  50.484  1.00 39.15      B    C
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ATOM   1351  C   PHE B 104      81.303 -18.174  46.600  1.00 29.75      B    C
ATOM   1352  O   PHE B 104      81.989 -19.134  46.251  1.00 28.47      B    O
ATOM   1353  N   TYR B 105      81.136 -17.099  45.857  1.00 30.99      B    N
ATOM   1354  CA  TYR B 105      81.765 -16.959  44.560  1.00 33.87      B    C
ATOM   1355  CB  TYR B 105      80.872 -17.501  43.480  1.00 36.40      B    C
ATOM   1356  CG  TYR B 105      81.470 -17.369  42.116  1.00 41.71      B    C
ATOM   1357  CD1 TYR B 105      81.446 -16.159  41.431  1.00 42.93      B    C
ATOM   1358  CE1 TYR B 105      82.010 -16.037  40.174  1.00 44.45      B    C
ATOM   1359  CZ  TYR B 105      82.605 -17.134  39.582  1.00 46.37      B    C
ATOM   1360  OH  TYR B 105      83.157 -17.046  38.330  1.00 45.98      B    O
ATOM   1361  CE2 TYR B 105      82.639 -18.342  40.239  1.00 47.39      B    C
ATOM   1362  CD2 TYR B 105      82.072 -18.454  41.500  1.00 47.03      B    C
ATOM   1363  C   TYR B 105      82.009 -15.476  44.337  1.00 35.48      B    C
ATOM   1364  O   TYR B 105      81.080 -14.671  44.367  1.00 36.09      B    O
ATOM   1365  N   ILE B 106      83.261 -15.113  44.111  1.00 35.43      B    N
ATOM   1366  CA  ILE B 106      83.637 -13.721  43.994  1.00 35.76      B    C
ATOM   1367  CB  ILE B 106      84.418 -13.265  45.242  1.00 36.18      B    C
ATOM   1368  CG1 ILE B 106      83.530 -13.335  46.470  1.00 36.58      B    C
ATOM   1369  CD1 ILE B 106      84.302 -13.366  47.760  1.00 38.66      B    C
ATOM   1370  CG2 ILE B 106      84.929 -11.836  45.065  1.00 36.08      B    C
ATOM   1371  C   ILE B 106      84.521 -13.580  42.761  1.00 35.56      B    C
ATOM   1372  O   ILE B 106      85.647 -14.082  42.775  1.00 35.14      B    O
ATOM   1373  N   PRO B 107      84.037 -12.887  41.716  1.00 34.68      B    N
ATOM   1374  CA  PRO B 107      84.860 -12.651  40.542  1.00 36.49      B    C
ATOM   1375  CB  PRO B 107      83.978 -11.842  39.607  1.00 35.65      B    C
ATOM   1376  CG  PRO B 107      82.710 -11.624  40.307  1.00 36.82      B    C
ATOM   1377  CD  PRO B 107      82.868 -12.015  41.743  1.00 35.95      B    C
ATOM   1378  C   PRO B 107      86.095 -11.871  40.904  1.00 40.87      B    C
ATOM   1379  O   PRO B 107      86.047 -10.887  41.662  1.00 43.07      B    O
ATOM   1380  N   ARG B 108      87.204 -12.315  40.351  1.00 44.94      B    N
ATOM   1381  CA  ARG B 108      88.464 -12.038  40.967  1.00 49.41      B    C
ATOM   1382  CB  ARG B 108      89.277 -13.294  41.158  1.00 51.56      B    C
ATOM   1383  CG  ARG B 108      90.552 -13.075  41.920  1.00 51.75      B    C
ATOM   1384  CD  ARG B 108      91.384 -14.305  42.013  1.00 57.45      B    C
ATOM   1385  NE  ARG B 108      92.598 -14.038  42.784  1.00 59.69      B    N
ATOM   1386  CZ  ARG B 108      93.625 -14.878  42.851  1.00 69.37      B    C
ATOM   1387  NH1 ARG B 108      93.570 -16.049  42.225  1.00 73.31      B    N
ATOM   1388  NH2 ARG B 108      94.713 -14.557  43.544  1.00 75.02      B    N
ATOM   1389  C   ARG B 108      89.095 -11.035  40.097  1.00 56.92      B    C
ATOM   1390  O   ARG B 108      89.067 -11.151  38.868  1.00 53.86      B    O
ATOM   1391  N   HIS B 109      89.625 -10.020  40.768  1.00 75.35      B    N
ATOM   1392  CA  HIS B 109      89.920  -8.749  40.134  1.00 96.51      B    C
ATOM   1393  CB  HIS B 109      90.720  -7.803  41.050  1.00102.32      B    C
ATOM   1394  CG  HIS B 109      90.219  -6.395  41.025  1.00110.32      B    C
ATOM   1395  ND1 HIS B 109      89.154  -6.003  41.802  1.00110.73      B    N
ATOM   1396  CE1 HIS B 109      88.904  -4.725  41.589  1.00117.97      B    C
ATOM   1397  NE2 HIS B 109      89.764  -4.274  40.689  1.00117.90      B    N
ATOM   1398  CD2 HIS B 109      90.597  -5.301  40.314  1.00112.77      B    C
ATOM   1399  C   HIS B 109      90.689  -9.107  38.893  1.00106.83      B    C
ATOM   1400  O   HIS B 109      91.918  -9.221  38.915  1.00113.28      B    O
ATOM   1401  N   ILE B 110      89.940  -9.401  37.835  1.00108.35      B    N
ATOM   1402  CA  ILE B 110      90.516  -9.568  36.553  1.00110.52      B    C
ATOM   1403  CB  ILE B 110      90.573  -8.195  35.825  1.00111.09      B    C
ATOM   1404  CG1 ILE B 110      89.341  -7.321  36.148  1.00107.24      B    C
ATOM   1405  CD1 ILE B 110      88.120  -7.598  35.306  1.00106.16      B    C
ATOM   1406  CG2 ILE B 110      90.820  -8.381  34.332  1.00111.14      B    C
ATOM   1407  C   ILE B 110      91.922 -10.064  36.866  1.00117.16      B    C
ATOM   1408  O   ILE B 110      92.879  -9.291  36.805  1.00138.26      B    O
ATOM   1409  N   ARG B 111      92.030 -11.337  37.255  1.00112.29      B    N
ATOM   1410  CA  ARG B 111      93.305 -11.975  37.681  1.00111.10      B    C
ATOM   1411  CB  ARG B 111      93.041 -13.431  38.024  1.00106.43      B    C
ATOM   1412  CG  ARG B 111      94.201 -14.117  38.708  1.00102.95      B    C
ATOM   1413  CD  ARG B 111      94.149 -15.612  38.403  1.00103.24      B    C
ATOM   1414  NE  ARG B 111      94.573 -15.877  37.035  1.00100.89      B    N
ATOM   1415  CZ  ARG B 111      95.839 -16.018  36.647  1.00 97.95      B    C
ATOM   1416  NH1 ARG B 111      96.843 -15.935  37.520  1.00 95.15      B    N
ATOM   1417  NH2 ARG B 111      96.102 -16.247  35.368  1.00 97.20      B    N
ATOM   1418  C   ARG B 111      94.407 -11.834  36.597  1.00117.72      B    C
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ATOM   1419  O   ARG B 111      94.999 -12.811  36.103  1.00113.44      B    O
ATOM   1420  N   LYS B 112      94.692 -10.571  36.286  1.00118.27      B    N
ATOM   1421  CA  LYS B 112      95.270 -10.140  35.011  1.00107.01      B    C
ATOM   1422  CB  LYS B 112      96.792 -10.343  35.040  1.00105.03      B    C
ATOM   1423  CG  LYS B 112      97.665  -9.244  34.427  1.00106.51      B    C
ATOM   1424  CD  LYS B 112      98.906  -9.828  33.778  1.00106.61      B    C
ATOM   1425  CE  LYS B 112      99.737  -8.710  33.158  1.00105.62      B    C
ATOM   1426  NZ  LYS B 112      99.291  -8.187  31.831  1.00104.21      B    N
ATOM   1427  C   LYS B 112      94.568 -10.864  33.847  1.00100.99      B    C
ATOM   1428  O   LYS B 112      95.124 -10.997  32.768  1.00 93.56      B    O
ATOM   1429  N   GLU B 113      93.302 -11.243  34.067  1.00 99.14      B    N
ATOM   1430  CA  GLU B 113      92.659 -12.333  33.327  1.00 96.82      B    C
ATOM   1431  CB  GLU B 113      93.420 -13.640  33.619  1.00 95.99      B    C
ATOM   1432  CG  GLU B 113      93.202 -14.801  32.647  1.00 93.48      B    C
ATOM   1433  CD  GLU B 113      94.509 -15.382  32.155  1.00 95.19      B    C
ATOM   1434  OE1 GLU B 113      95.161 -14.749  31.294  1.00 95.77      B    O
ATOM   1435  OE2 GLU B 113      94.880 -16.475  32.621  1.00 95.47      B    O
ATOM   1436  C   GLU B 113      91.137 -12.451  33.724  1.00 93.65      B    C
ATOM   1437  O   GLU B 113      90.376 -11.460  33.707  1.00 91.96      B    O
ATOM   1438  N   GLU B 114      90.699 -13.641  34.141  1.00 91.26      B    N
ATOM   1439  CA  GLU B 114      89.288 -13.891  34.425  1.00 84.54      B    C
ATOM   1440  CB  GLU B 114      88.478 -14.000  33.125  1.00 84.57      B    C
ATOM   1441  CG  GLU B 114      86.970 -14.011  33.336  1.00 84.04      B    C
ATOM   1442  CD  GLU B 114      86.429 -12.700  33.888  1.00 82.58      B    C
ATOM   1443  OE1 GLU B 114      86.876 -11.616  33.450  1.00 84.72      B    O
ATOM   1444  OE2 GLU B 114      85.551 -12.747  34.774  1.00 84.22      B    O
ATOM   1445  C   GLU B 114      89.208 -15.158  35.279  1.00 79.96      B    C
ATOM   1446  O   GLU B 114      89.363 -16.281  34.783  1.00 82.33      B    O
ATOM   1447  N   GLY B 115      89.050 -14.949  36.585  1.00 69.85      B    N
ATOM   1448  CA  GLY B 115      88.789 -16.036  37.510  1.00 63.07      B    C
ATOM   1449  C   GLY B 115      88.040 -15.558  38.738  1.00 59.17      B    C
ATOM   1450  O   GLY B 115      87.417 -14.498  38.721  1.00 62.79      B    O
ATOM   1451  N   SER B 116      88.126 -16.314  39.824  1.00 49.97      B    N
ATOM   1452  CA  SER B 116      87.289 -16.059  40.986  1.00 44.97      B    C
ATOM   1453  CB  SER B 116      85.940 -16.696  40.744  1.00 44.24      B    C
ATOM   1454  OG  SER B 116      86.071 -18.096  40.613  1.00 44.94      B    O
ATOM   1455  C   SER B 116      87.871 -16.613  42.287  1.00 42.99      B    C
ATOM   1456  O   SER B 116      88.703 -17.505  42.264  1.00 45.15      B    O
ATOM   1457  N   PHE B 117      87.477 -16.032  43.414  1.00 40.89      B    N
ATOM   1458  CA  PHE B 117      87.667 -16.664  44.714  1.00 40.70      B    C
ATOM   1459  CB  PHE B 117      87.801 -15.642  45.838  1.00 41.27      B    C
ATOM   1460  CG  PHE B 117      89.055 -14.820  45.783  1.00 45.45      B    C
ATOM   1461  CD1 PHE B 117      90.308 -15.425  45.861  1.00 46.26      B    C
ATOM   1462  CE1 PHE B 117      91.463 -14.678  45.834  1.00 45.37      B    C
ATOM   1463  CZ  PHE B 117      91.377 -13.307  45.761  1.00 48.26      B    C
ATOM   1464  CE2 PHE B 117      90.135 -12.682  45.697  1.00 48.93      B    C
ATOM   1465  CD2 PHE B 117      88.983 -13.435  45.711  1.00 47.28      B    C
ATOM   1466  C   PHE B 117      86.408 -17.447  44.978  1.00 39.79      B    C
ATOM   1467  O   PHE B 117      85.337 -16.857  44.996  1.00 40.42      B    O
ATOM   1468  N   GLN B 118      86.499 -18.749  45.201  1.00 38.26      B    N
ATOM   1469  CA  GLN B 118      85.285 -19.500  45.502  1.00 39.37      B    C
ATOM   1470  CB  GLN B 118      84.640 -20.020  44.219  1.00 38.66      B    C
ATOM   1471  CG  GLN B 118      85.534 -20.922  43.409  1.00 38.84      B    C
ATOM   1472  CD  GLN B 118      84.860 -21.274  42.105  1.00 39.49      B    C
ATOM   1473  OE1 GLN B 118      85.086 -20.620  41.101  1.00 39.43      B    O
ATOM   1474  NE2 GLN B 118      83.974 -22.262  42.130  1.00 39.11      B    N
ATOM   1475  C   GLN B 118      85.487 -20.643  46.474  1.00 37.02      B    C
ATOM   1476  O   GLN B 118      86.578 -21.166  46.628  1.00 35.97      B    O
ATOM   1477  N   SER B 119      84.391 -21.045  47.092  1.00 34.99      B    N
ATOM   1478  CA  SER B 119      84.435 -22.033  48.130  1.00 34.06      B    C
ATOM   1479  CB  SER B 119      84.847 -21.387  49.440  1.00 34.89      B    C
ATOM   1480  OG  SER B 119      84.805 -22.345  50.474  1.00 36.74      B    O
ATOM   1481  C   SER B 119      83.081 -22.627  48.282  1.00 32.49      B    C
ATOM   1482  O   SER B 119      82.092 -21.954  48.079  1.00 31.02      B    O
ATOM   1483  N   CYS B 120      83.055 -23.910  48.607  1.00 35.13      B    N
ATOM   1484  CA  CYS B 120      81.823 -24.608  48.835  1.00 36.15      B    C
ATOM   1485  CB  CYS B 120      81.245 -25.135  47.526  1.00 35.69      B    C
ATOM   1486  SG  CYS B 120      79.573 -25.814  47.688  1.00 38.85      B    S
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ATOM	1487	C	CYS	B	120	82.121	-25.753	49.787	1.00	37.91	B	C
ATOM	1488	O	CYS	B	120	83.017	-26.547	49.548	1.00	40.36	B	O
ATOM	1489	N	SER	B	121	81.350	-25.836	50.865	1.00	39.01	B	N
ATOM	1490	CA	SER	B	121	81.439	-26.944	51.770	1.00	35.52	B	C
ATOM	1491	CB	SER	B	121	81.695	-26.429	53.154	1.00	37.45	B	C
ATOM	1492	OG	SER	B	121	83.001	-25.917	53.195	1.00	39.75	B	O
ATOM	1493	C	SER	B	121	80.171	-27.767	51.704	1.00	35.27	B	C
ATOM	1494	O	SER	B	121	79.141	-27.311	51.252	1.00	38.32	B	O
ATOM	1495	N	PHE	B	122	80.273	-28.992	52.173	1.00	35.59	B	N
ATOM	1496	CA	PHE	B	122	79.283	-30.010	51.954	1.00	37.04	B	C
ATOM	1497	CB	PHE	B	122	79.873	-30.999	50.932	1.00	35.74	B	C
ATOM	1498	CG	PHE	B	122	78.943	-32.100	50.484	1.00	33.17	B	C
ATOM	1499	CD1	PHE	B	122	77.713	-32.322	51.081	1.00	33.00	B	C
ATOM	1500	CE1	PHE	B	122	76.902	-33.366	50.658	1.00	33.91	B	C
ATOM	1501	CZ	PHE	B	122	77.332	-34.214	49.652	1.00	33.36	B	C
ATOM	1502	CE2	PHE	B	122	78.560	-34.007	49.061	1.00	32.10	B	C
ATOM	1503	CD2	PHE	B	122	79.357	-32.962	49.488	1.00	32.20	B	C
ATOM	1504	C	PHE	B	122	79.059	-30.678	53.314	1.00	38.65	B	C
ATOM	1505	O	PHE	B	122	79.999	-31.232	53.880	1.00	35.68	B	O
ATOM	1506	N	CYS	B	123	77.837	-30.601	53.847	1.00	39.33	B	N
ATOM	1507	CA	CYS	B	123	77.529	-31.262	55.115	1.00	38.08	B	C
ATOM	1508	CB	CYS	B	123	76.256	-30.706	55.750	1.00	38.45	B	C
ATOM	1509	SG	CYS	B	123	75.677	-31.615	57.208	1.00	40.71	B	S
ATOM	1510	C	CYS	B	123	77.428	-32.756	54.838	1.00	36.42	B	C
ATOM	1511	O	CYS	B	123	76.494	-33.212	54.206	1.00	33.78	B	O
ATOM	1512	N	LYS	B	124	78.429	-33.503	55.289	1.00	38.77	B	N
ATOM	1513	CA	LYS	B	124	78.588	-34.914	54.919	1.00	39.60	B	C
ATOM	1514	CB	LYS	B	124	79.256	-35.002	53.548	1.00	40.70	B	C
ATOM	1515	CG	LYS	B	124	80.730	-34.672	53.624	1.00	45.13	B	C
ATOM	1516	CD	LYS	B	124	81.346	-34.453	52.259	1.00	49.22	B	C
ATOM	1517	CE	LYS	B	124	81.487	-35.761	51.508	1.00	53.75	B	C
ATOM	1518	NZ	LYS	B	124	82.735	-35.709	50.699	1.00	54.44	B	N
ATOM	1519	C	LYS	B	124	79.453	-35.647	55.951	1.00	39.19	B	C
ATOM	1520	O	LYS	B	124	79.999	-35.015	56.860	1.00	37.81	B	O
ATOM	1521	N	PRO	B	125	79.593	-36.982	55.814	1.00	38.46	B	N
ATOM	1522	CA	PRO	B	125	80.396	-37.738	56.778	1.00	39.12	B	C
ATOM	1523	CB	PRO	B	125	80.246	-39.177	56.300	1.00	37.18	B	C
ATOM	1524	CG	PRO	B	125	78.918	-39.192	55.640	1.00	37.43	B	C
ATOM	1525	CD	PRO	B	125	78.876	-37.890	54.907	1.00	37.32	B	C
ATOM	1526	C	PRO	B	125	81.853	-37.350	56.810	1.00	39.65	B	C
ATOM	1527	O	PRO	B	125	82.485	-37.220	55.770	1.00	44.72	B	O
ATOM	1528	N	LYS	B	126	82.364	-37.140	58.006	1.00	42.71	B	N
ATOM	1529	CA	LYS	B	126	83.783	-36.950	58.216	1.00	48.61	B	C
ATOM	1530	CB	LYS	B	126	84.019	-36.025	59.384	1.00	50.56	B	C
ATOM	1531	CG	LYS	B	126	85.479	-35.708	59.614	1.00	57.68	B	C
ATOM	1532	CD	LYS	B	126	85.617	-34.322	60.218	1.00	65.92	B	C
ATOM	1533	CE	LYS	B	126	86.643	-34.259	61.338	1.00	74.51	B	C
ATOM	1534	NZ	LYS	B	126	87.903	-33.655	60.810	1.00	80.39	B	N
ATOM	1535	C	LYS	B	126	84.441	-38.288	58.505	1.00	50.60	B	C
ATOM	1536	O	LYS	B	126	85.513	-38.579	57.981	1.00	55.29	B	O
ATOM	1537	N	LYS	B	127	83.800	-39.099	59.340	1.00	51.47	B	N
ATOM	1538	CA	LYS	B	127	84.276	-40.445	59.622	1.00	54.86	B	C
ATOM	1539	CB	LYS	B	127	84.795	-40.545	61.049	1.00	58.61	B	C
ATOM	1540	CG	LYS	B	127	85.506	-39.297	61.546	1.00	66.55	B	C
ATOM	1541	CD	LYS	B	127	86.145	-39.509	62.909	1.00	66.51	B	C
ATOM	1542	CE	LYS	B	127	87.645	-39.744	62.797	1.00	63.77	B	C
ATOM	1543	NZ	LYS	B	127	88.377	-38.468	62.577	1.00	63.96	B	N
ATOM	1544	C	LYS	B	127	83.168	-41.467	59.438	1.00	50.92	B	C
ATOM	1545	O	LYS	B	127	82.036	-41.236	59.852	1.00	46.98	B	O
ATOM	1546	N	PHE	B	128	83.518	-42.599	58.834	1.00	47.21	B	N
ATOM	1547	CA	PHE	B	128	82.668	-43.790	58.834	1.00	44.58	B	C
ATOM	1548	CB	PHE	B	128	82.691	-44.436	57.472	1.00	39.94	B	C
ATOM	1549	CG	PHE	B	128	82.096	-43.589	56.399	1.00	39.77	B	C
ATOM	1550	CD1	PHE	B	128	82.857	-42.604	55.773	1.00	39.98	B	C
ATOM	1551	CE1	PHE	B	128	82.325	-41.837	54.752	1.00	37.39	B	C
ATOM	1552	CZ	PHE	B	128	81.013	-42.037	54.351	1.00	36.05	B	C
ATOM	1553	CE2	PHE	B	128	80.247	-43.010	54.966	1.00	36.72	B	C
ATOM	1554	CD2	PHE	B	128	80.790	-43.779	55.988	1.00	37.94	B	C

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ATOM   1555  C   PHE B 128      83.143 -44.805  59.878  1.00 45.58      B    C
ATOM   1556  O   PHE B 128      84.296 -44.790  60.270  1.00 46.02      B    O
ATOM   1557  N   THR B 129      82.251 -45.689  60.310  1.00 47.04      B    N
ATOM   1558  CA  THR B 129      82.604 -46.809  61.180  1.00 45.11      B    C
ATOM   1559  CB  THR B 129      81.752 -46.802  62.450  1.00 43.77      B    C
ATOM   1560  OG1 THR B 129      82.186 -45.733  63.285  1.00 44.72      B    O
ATOM   1561  CG2 THR B 129      81.867 -48.091  63.216  1.00 46.31      B    C
ATOM   1562  C   THR B 129      82.368 -48.091  60.398  1.00 47.17      B    C
ATOM   1563  O   THR B 129      81.445 -48.168  59.616  1.00 43.04      B    O
ATOM   1564  N   THR B 130      83.223 -49.084  60.604  1.00 52.27      B    N
ATOM   1565  CA  THR B 130      83.009 -50.405  60.047  1.00 57.38      B    C
ATOM   1566  CB  THR B 130      84.178 -50.841  59.164  1.00 61.37      B    C
ATOM   1567  OG1 THR B 130      84.102 -50.135  57.924  1.00 63.80      B    O
ATOM   1568  CG2 THR B 130      84.118 -52.336  58.872  1.00 63.77      B    C
ATOM   1569  C   THR B 130      82.841 -51.384  61.187  1.00 57.28      B    C
ATOM   1570  O   THR B 130      83.609 -51.366  62.137  1.00 57.73      B    O
ATOM   1571  N   MET B 131      81.833 -52.239  61.078  1.00 61.33      B    N
ATOM   1572  CA  MET B 131      81.528 -53.210  62.133  1.00 62.81      B    C
ATOM   1573  CB  MET B 131      80.423 -52.697  63.060  1.00 67.37      B    C
ATOM   1574  CG  MET B 131      80.229 -53.489  64.354  1.00 70.38      B    C
ATOM   1575  SD  MET B 131      79.088 -52.712  65.540  1.00 71.23      B    S
ATOM   1576  CE  MET B 131      78.136 -54.085  66.228  1.00 74.12      B    C
ATOM   1577  C   MET B 131      81.058 -54.506  61.515  1.00 64.78      B    C
ATOM   1578  O   MET B 131      80.454 -54.505  60.433  1.00 67.07      B    O
ATOM   1579  N   MET B 132      81.328 -55.597  62.229  1.00 69.46      B    N
ATOM   1580  CA  MET B 132      80.816 -56.924  61.890  1.00 67.30      B    C
ATOM   1581  CB  MET B 132      81.791 -58.042  62.315  1.00 68.53      B    C
ATOM   1582  CG  MET B 132      82.910 -58.431  61.353  1.00 68.89      B    C
ATOM   1583  SD  MET B 132      82.728 -57.935  59.629  1.00 74.84      B    S
ATOM   1584  CE  MET B 132      83.374 -56.276  59.728  1.00 75.98      B    C
ATOM   1585  C   MET B 132      79.493 -57.119  62.626  1.00 60.27      B    C
ATOM   1586  O   MET B 132      79.432 -57.062  63.845  1.00 58.16      B    O
ATOM   1587  N   VAL B 133      78.430 -57.328  61.877  1.00 56.55      B    N
ATOM   1588  CA  VAL B 133      77.118 -57.558  62.461  1.00 58.40      B    C
ATOM   1589  CB  VAL B 133      76.057 -56.649  61.808  1.00 59.64      B    C
ATOM   1590  CG1 VAL B 133      74.650 -56.980  62.298  1.00 59.33      B    C
ATOM   1591  CG2 VAL B 133      76.401 -55.198  62.089  1.00 58.53      B    C
ATOM   1592  C   VAL B 133      76.766 -59.002  62.262  1.00 55.56      B    C
ATOM   1593  O   VAL B 133      76.852 -59.500  61.156  1.00 49.82      B    O
ATOM   1594  N   THR B 134      76.338 -59.660  63.334  1.00 58.85      B    N
ATOM   1595  CA  THR B 134      75.981 -61.067  63.219  1.00 61.90      B    C
ATOM   1596  CB  THR B 134      76.480 -61.952  64.395  1.00 62.09      B    C
ATOM   1597  OG1 THR B 134      75.414 -62.244  65.295  1.00 60.20      B    O
ATOM   1598  CG2 THR B 134      77.599 -61.277  65.160  1.00 63.82      B    C
ATOM   1599  C   THR B 134      74.471 -61.169  63.000  1.00 61.34      B    C
ATOM   1600  O   THR B 134      73.684 -60.561  63.713  1.00 57.34      B    O
ATOM   1601  N   LEU B 135      74.107 -61.907  61.963  1.00 65.17      B    N
ATOM   1602  CA  LEU B 135      72.731 -62.221  61.629  1.00 66.49      B    C
ATOM   1603  CB  LEU B 135      72.559 -62.119  60.114  1.00 66.43      B    C
ATOM   1604  CG  LEU B 135      72.881 -60.757  59.499  1.00 66.86      B    C
ATOM   1605  CD1 LEU B 135      72.833 -60.844  57.982  1.00 69.16      B    C
ATOM   1606  CD2 LEU B 135      71.918 -59.702  60.028  1.00 64.54      B    C
ATOM   1607  C   LEU B 135      72.430 -63.652  62.032  1.00 64.78      B    C
ATOM   1608  O   LEU B 135      73.328 -64.502  62.043  1.00 58.47      B    O
ATOM   1609  N   ASN B 136      71.172 -63.962  62.327  1.00 71.66      B    N
ATOM   1610  CA  ASN B 136      70.827 -65.377  62.425  1.00 80.09      B    C
ATOM   1611  CB  ASN B 136      70.163 -65.752  63.758  1.00 78.69      B    C
ATOM   1612  CG  ASN B 136      68.660 -65.690  63.719  1.00 81.33      B    C
ATOM   1613  OD1 ASN B 136      68.075 -64.845  63.047  1.00 89.94      B    O
ATOM   1614  ND2 ASN B 136      68.020 -66.595  64.450  1.00 80.34      B    N
ATOM   1615  C   ASN B 136      70.113 -65.964  61.190  1.00 90.15      B    C
ATOM   1616  O   ASN B 136      69.218 -65.364  60.574  1.00 85.34      B    O
ATOM   1617  N   CYS B 137      70.573 -67.159  60.844  1.00 99.88      B    N
ATOM   1618  CA  CYS B 137      70.221 -67.824  59.607  1.00104.74      B    C
ATOM   1619  CB  CYS B 137      71.415 -67.750  58.646  1.00105.37      B    C
ATOM   1620  SG  CYS B 137      72.356 -66.193  58.784  1.00110.37      B    S
ATOM   1621  C   CYS B 137      69.852 -69.261  59.985  1.00108.35      B    C
ATOM   1622  O   CYS B 137      70.700 -70.149  59.959  1.00114.91      B    O
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ATOM   1623  N   PRO B 138      68.584 -69.484  60.391  1.00106.23      B    N
ATOM   1624  CA  PRO B 138      68.133 -70.798  60.877  1.00105.33      B    C
ATOM   1625  CB  PRO B 138      66.656 -70.556  61.227  1.00105.78      B    C
ATOM   1626  CG  PRO B 138      66.566 -69.081  61.458  1.00106.65      B    C
ATOM   1627  CD  PRO B 138      67.494 -68.494  60.442  1.00105.19      B    C
ATOM   1628  C   PRO B 138      68.306 -71.929  59.856  1.00102.55      B    C
ATOM   1629  O   PRO B 138      68.470 -73.080  60.252  1.00 92.96      B    O
ATOM   1630  N   GLU B 139      68.282 -71.591  58.566  1.00104.97      B    N
ATOM   1631  CA  GLU B 139      68.586 -72.548  57.480  1.00106.53      B    C
ATOM   1632  CB  GLU B 139      67.766 -72.222  56.202  1.00105.57      B    C
ATOM   1633  CG  GLU B 139      66.282 -71.816  56.359  1.00100.30      B    C
ATOM   1634  CD  GLU B 139      65.300 -72.952  56.694  1.00 95.00      B    C
ATOM   1635  OE1 GLU B 139      65.648 -74.147  56.595  1.00 88.56      B    O
ATOM   1636  OE2 GLU B 139      64.141 -72.639  57.057  1.00 90.31      B    O
ATOM   1637  C   GLU B 139      70.101 -72.662  57.085  1.00104.99      B    C
ATOM   1638  O   GLU B 139      70.394 -73.025  55.942  1.00101.13      B    O
ATOM   1639  N   LEU B 140      71.045 -72.322  57.978  1.00104.82      B    N
ATOM   1640  CA  LEU B 140      72.482 -72.638  57.807  1.00103.04      B    C
ATOM   1641  CB  LEU B 140      73.297 -71.412  57.329  1.00101.26      B    C
ATOM   1642  CG  LEU B 140      73.777 -71.415  55.867  1.00103.52      B    C
ATOM   1643  CD1 LEU B 140      74.431 -72.705  55.353  1.00 99.38      B    C
ATOM   1644  CD2 LEU B 140      72.622 -71.038  54.966  1.00109.65      B    C
ATOM   1645  C   LEU B 140      73.140 -73.257  59.052  1.00106.97      B    C
ATOM   1646  O   LEU B 140      72.579 -73.294  60.165  1.00107.19      B    O
ATOM   1647  N   GLN B 141      74.332 -73.792  58.802  1.00109.94      B    N
ATOM   1648  CA  GLN B 141      75.222 -74.325  59.821  1.00108.79      B    C
ATOM   1649  CB  GLN B 141      75.435 -75.833  59.633  1.00104.59      B    C
ATOM   1650  CG  GLN B 141      76.084 -76.525  60.829  1.00100.38      B    C
ATOM   1651  CD  GLN B 141      75.218 -76.454  62.082  1.00 99.67      B    C
ATOM   1652  OE1 GLN B 141      73.995 -76.598  62.013  1.00104.83      B    O
ATOM   1653  NE2 GLN B 141      75.843 -76.207  63.228  1.00 95.38      B    N
ATOM   1654  C   GLN B 141      76.556 -73.591  59.673  1.00113.16      B    C
ATOM   1655  O   GLN B 141      77.191 -73.693  58.626  1.00116.80      B    O
ATOM   1656  N   PRO B 142      76.976 -72.829  60.699  1.00113.61      B    N
ATOM   1657  CA  PRO B 142      76.265 -72.606  61.946  1.00116.04      B    C
ATOM   1658  CB  PRO B 142      77.332 -72.007  62.864  1.00112.60      B    C
ATOM   1659  CG  PRO B 142      78.336 -71.390  61.949  1.00112.75      B    C
ATOM   1660  CD  PRO B 142      78.110 -71.903  60.552  1.00111.15      B    C
ATOM   1661  C   PRO B 142      75.142 -71.619  61.706  1.00117.35      B    C
ATOM   1662  O   PRO B 142      75.185 -70.864  60.727  1.00121.67      B    O
ATOM   1663  N   PRO B 143      74.147 -71.594  62.598  1.00114.12      B    N
ATOM   1664  CA  PRO B 143      72.991 -70.735  62.337  1.00111.69      B    C
ATOM   1665  CB  PRO B 143      71.932 -71.267  63.316  1.00110.09      B    C
ATOM   1666  CG  PRO B 143      72.661 -72.148  64.297  1.00109.29      B    C
ATOM   1667  CD  PRO B 143      74.113 -72.202  63.938  1.00107.71      B    C
ATOM   1668  C   PRO B 143      73.309 -69.237  62.519  1.00107.33      B    C
ATOM   1669  O   PRO B 143      72.489 -68.486  63.035  1.00 96.93      B    O
ATOM   1670  N   THR B 144      74.473 -68.814  62.017  1.00102.41      B    N
ATOM   1671  CA  THR B 144      74.966 -67.447  62.200  1.00 94.19      B    C
ATOM   1672  CB  THR B 144      75.705 -67.208  63.546  1.00 90.28      B    C
ATOM   1673  OG1 THR B 144      76.376 -65.940  63.499  1.00 94.91      B    O
ATOM   1674  CG2 THR B 144      76.744 -68.282  63.815  1.00 89.54      B    C
ATOM   1675  C   THR B 144      75.928 -67.050  61.098  1.00 91.80      B    C
ATOM   1676  O   THR B 144      76.622 -67.862  60.477  1.00 99.82      B    O
ATOM   1677  N   LYS B 145      75.995 -65.753  60.904  1.00 85.19      B    N
ATOM   1678  CA  LYS B 145      76.663 -65.223  59.720  1.00 82.98      B    C
ATOM   1679  CB  LYS B 145      75.751 -65.347  58.460  1.00 84.82      B    C
ATOM   1680  CG  LYS B 145      76.391 -65.944  57.189  1.00 89.35      B    C
ATOM   1681  CD  LYS B 145      76.082 -65.142  55.916  1.00 93.75      B    C
ATOM   1682  CE  LYS B 145      76.299 -65.974  54.647  1.00 96.22      B    C
ATOM   1683  NZ  LYS B 145      76.542 -65.153  53.420  1.00 96.94      B    N
ATOM   1684  C   LYS B 145      76.947 -63.770  60.007  1.00 79.01      B    C
ATOM   1685  O   LYS B 145      76.068 -63.058  60.460  1.00 80.03      B    O
ATOM   1686  N   LYS B 146      78.172 -63.331  59.760  1.00 74.17      B    N
ATOM   1687  CA  LYS B 146      78.531 -61.951  59.977  1.00 68.56      B    C
ATOM   1688  CB  LYS B 146      80.013 -61.860  60.308  1.00 66.34      B    C
ATOM   1689  CG  LYS B 146      80.493 -62.919  61.258  1.00 69.38      B    C
ATOM   1690  CD  LYS B 146      79.910 -62.710  62.639  1.00 68.18      B    C
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ATOM	1691	CE	LYS	B	146	80.898	-61.855	63.401	1.00	69.99	B	C
ATOM	1692	NZ	LYS	B	146	80.631	-61.833	64.858	1.00	72.80	B	N
ATOM	1693	C	LYS	B	146	78.252	-61.255	58.667	1.00	69.47	B	C
ATOM	1694	O	LYS	B	146	78.293	-61.880	57.596	1.00	62.27	B	O
ATOM	1695	N	LYS	B	147	77.893	-59.982	58.769	1.00	72.08	B	N
ATOM	1696	CA	LYS	B	147	77.916	-59.074	57.630	1.00	72.48	B	C
ATOM	1697	CB	LYS	B	147	76.498	-58.660	57.233	1.00	77.76	B	C
ATOM	1698	CG	LYS	B	147	76.340	-57.570	56.153	1.00	79.89	B	C
ATOM	1699	CD	LYS	B	147	75.053	-57.777	55.376	1.00	83.08	B	C
ATOM	1700	CE	LYS	B	147	74.872	-56.732	54.286	1.00	86.35	B	C
ATOM	1701	NZ	LYS	B	147	75.372	-57.220	52.970	1.00	90.51	B	N
ATOM	1702	C	LYS	B	147	78.695	-57.829	57.979	1.00	71.37	B	C
ATOM	1703	O	LYS	B	147	78.555	-57.266	59.070	1.00	67.01	B	O
ATOM	1704	N	ARG	B	148	79.503	-57.397	57.026	1.00	74.50	B	N
ATOM	1705	CA	ARG	B	148	80.172	-56.120	57.095	1.00	74.66	B	C
ATOM	1706	CB	ARG	B	148	81.200	-56.047	55.937	1.00	83.26	B	C
ATOM	1707	CG	ARG	B	148	82.120	-57.226	55.724	1.00	89.19	B	C
ATOM	1708	CD	ARG	B	148	82.858	-57.168	54.358	1.00	93.24	B	C
ATOM	1709	NE	ARG	B	148	84.252	-57.594	54.457	1.00	92.67	B	N
ATOM	1710	CZ	ARG	B	148	85.188	-56.946	55.145	1.00	96.46	B	C
ATOM	1711	NH1	ARG	B	148	84.883	-55.842	55.821	1.00	104.15	B	N
ATOM	1712	NH2	ARG	B	148	86.431	-57.409	55.174	1.00	96.62	B	N
ATOM	1713	C	ARG	B	148	79.161	-55.016	56.841	1.00	68.44	B	C
ATOM	1714	O	ARG	B	148	78.434	-55.036	55.836	1.00	64.06	B	O
ATOM	1715	N	VAL	B	149	79.140	-54.029	57.726	1.00	65.21	B	N
ATOM	1716	CA	VAL	B	149	78.393	-52.811	57.460	1.00	64.23	B	C
ATOM	1717	CB	VAL	B	149	77.037	-52.823	58.158	1.00	62.57	B	C
ATOM	1718	CG1	VAL	B	149	77.173	-53.454	59.517	1.00	63.45	B	C
ATOM	1719	CG2	VAL	B	149	76.474	-51.411	58.275	1.00	65.82	B	C
ATOM	1720	C	VAL	B	149	79.198	-51.579	57.865	1.00	60.90	B	C
ATOM	1721	O	VAL	B	149	79.777	-51.521	58.957	1.00	55.87	B	O
ATOM	1722	N	THR	B	150	79.238	-50.610	56.954	1.00	56.95	B	N
ATOM	1723	CA	THR	B	150	79.921	-49.368	57.191	1.00	57.76	B	C
ATOM	1724	CB	THR	B	150	80.787	-48.981	55.970	1.00	61.60	B	C
ATOM	1725	OG1	THR	B	150	81.939	-49.834	55.915	1.00	69.99	B	O
ATOM	1726	CG2	THR	B	150	81.266	-47.552	56.063	1.00	61.57	B	C
ATOM	1727	C	THR	B	150	78.827	-48.346	57.480	1.00	52.14	B	C
ATOM	1728	O	THR	B	150	77.890	-48.220	56.722	1.00	50.88	B	O
ATOM	1729	N	ARG	B	151	78.948	-47.615	58.574	1.00	49.96	B	N
ATOM	1730	CA	ARG	B	151	77.946	-46.635	58.942	1.00	47.85	B	C
ATOM	1731	CB	ARG	B	151	77.176	-47.112	60.167	1.00	50.45	B	C
ATOM	1732	CG	ARG	B	151	77.818	-46.763	61.477	1.00	56.48	B	C
ATOM	1733	CD	ARG	B	151	77.328	-47.708	62.530	1.00	59.76	B	C
ATOM	1734	NE	ARG	B	151	77.544	-49.107	62.200	1.00	61.66	B	N
ATOM	1735	CZ	ARG	B	151	76.816	-50.090	62.716	1.00	61.77	B	C
ATOM	1736	NH1	ARG	B	151	75.805	-49.832	63.542	1.00	55.81	B	N
ATOM	1737	NH2	ARG	B	151	77.090	-51.341	62.387	1.00	61.06	B	N
ATOM	1738	C	ARG	B	151	78.616	-45.280	59.192	1.00	45.25	B	C
ATOM	1739	O	ARG	B	151	79.815	-45.200	59.430	1.00	39.24	B	O
ATOM	1740	N	VAL	B	152	77.822	-44.221	59.134	1.00	42.31	B	N
ATOM	1741	CA	VAL	B	152	78.321	-42.881	59.329	1.00	40.45	B	C
ATOM	1742	CB	VAL	B	152	77.308	-41.845	58.793	1.00	42.20	B	C
ATOM	1743	CG1	VAL	B	152	77.709	-40.428	59.190	1.00	44.26	B	C
ATOM	1744	CG2	VAL	B	152	77.175	-41.947	57.282	1.00	41.41	B	C
ATOM	1745	C	VAL	B	152	78.553	-42.686	60.812	1.00	40.84	B	C
ATOM	1746	O	VAL	B	152	77.733	-43.111	61.613	1.00	45.41	B	O
ATOM	1747	N	LYS	B	153	79.653	-42.042	61.180	1.00	43.32	B	N
ATOM	1748	CA	LYS	B	153	79.946	-41.744	62.586	1.00	47.45	B	C
ATOM	1749	CB	LYS	B	153	81.418	-42.023	62.898	1.00	51.70	B	C
ATOM	1750	CG	LYS	B	153	81.743	-42.427	64.352	1.00	56.65	B	C
ATOM	1751	CD	LYS	B	153	82.227	-41.328	65.259	1.00	64.78	B	C
ATOM	1752	CE	LYS	B	153	81.969	-41.702	66.714	1.00	72.57	B	C
ATOM	1753	NZ	LYS	B	153	80.555	-41.484	67.137	1.00	75.65	B	N
ATOM	1754	C	LYS	B	153	79.628	-40.287	62.883	1.00	49.15	B	C
ATOM	1755	O	LYS	B	153	78.825	-39.990	63.757	1.00	48.70	B	O
ATOM	1756	N	GLN	B	154	80.256	-39.380	62.135	1.00	53.41	B	N
ATOM	1757	CA	GLN	B	154	80.156	-37.947	62.390	1.00	51.92	B	C
ATOM	1758	CB	GLN	B	154	81.386	-37.468	63.169	1.00	54.29	B	C

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ATOM   1759  CG  GLN B 154      81.274 -36.020  63.654  1.00 59.03      B    C
ATOM   1760  CD  GLN B 154      80.290 -35.960  64.792  1.00 62.29      B    C
ATOM   1761  OE1 GLN B 154      79.083 -35.919  64.563  1.00 63.76      B    O
ATOM   1762  NE2 GLN B 154      80.782 -36.124  66.009  1.00 65.67      B    N
ATOM   1763  C   GLN B 154      80.040 -37.165  61.090  1.00 47.64      B    C
ATOM   1764  O   GLN B 154      80.827 -37.371  60.177  1.00 46.43      B    O
ATOM   1765  N   CYS B 155      79.059 -36.263  61.017  1.00 45.89      B    N
ATOM   1766  CA  CYS B 155      78.947 -35.334  59.888  1.00 44.00      B    C
ATOM   1767  CB  CYS B 155      77.492 -35.114  59.531  1.00 45.22      B    C
ATOM   1768  SG  CYS B 155      76.562 -36.647  59.315  1.00 43.72      B    S
ATOM   1769  C   CYS B 155      79.582 -33.980  60.183  1.00 45.13      B    C
ATOM   1770  O   CYS B 155      79.676 -33.562  61.329  1.00 47.04      B    O
ATOM   1771  N   ARG B 156      80.018 -33.293  59.137  1.00 46.50      B    N
ATOM   1772  CA  ARG B 156      80.576 -31.949  59.277  1.00 43.88      B    C
ATOM   1773  CB  ARG B 156      81.974 -31.999  59.907  1.00 48.53      B    C
ATOM   1774  CG  ARG B 156      81.916 -31.635  61.422  1.00 55.44      B    C
ATOM   1775  CD  ARG B 156      82.962 -32.223  62.403  1.00 63.30      B    C
ATOM   1776  NE  ARG B 156      83.281 -31.330  63.535  1.00 73.16      B    N
ATOM   1777  CZ  ARG B 156      84.178 -30.318  63.599  1.00 78.22      B    C
ATOM   1778  NH1 ARG B 156      85.040 -29.975  62.616  1.00 78.96      B    N
ATOM   1779  NH2 ARG B 156      84.238 -29.644  64.753  1.00 77.76      B    N
ATOM   1780  C   ARG B 156      80.576 -31.221  57.937  1.00 39.59      B    C
ATOM   1781  O   ARG B 156      80.421 -31.844  56.891  1.00 35.96      B    O
ATOM   1782  N   CYS B 157      80.658 -29.892  58.002  1.00 37.07      B    N
ATOM   1783  CA  CYS B 157      80.813 -29.052  56.831  1.00 35.33      B    C
ATOM   1784  CB  CYS B 157      80.551 -27.586  57.153  1.00 35.67      B    C
ATOM   1785  SG  CYS B 157      78.804 -27.159  57.297  1.00 41.27      B    S
ATOM   1786  C   CYS B 157      82.233 -29.210  56.366  1.00 35.22      B    C
ATOM   1787  O   CYS B 157      83.142 -28.685  56.987  1.00 32.12      B    O
ATOM   1788  N   ILE B 158      82.407 -29.966  55.287  1.00 35.32      B    N
ATOM   1789  CA  ILE B 158      83.706 -30.262  54.734  1.00 36.47      B    C
ATOM   1790  CB  ILE B 158      83.889 -31.792  54.612  1.00 39.05      B    C
ATOM   1791  CG1 ILE B 158      84.030 -32.412  56.011  1.00 38.44      B    C
ATOM   1792  CD1 ILE B 158      83.710 -33.888  56.058  1.00 39.02      B    C
ATOM   1793  CG2 ILE B 158      85.097 -32.135  53.751  1.00 38.57      B    C
ATOM   1794  C   ILE B 158      83.825 -29.588  53.367  1.00 38.07      B    C
ATOM   1795  O   ILE B 158      82.968 -29.747  52.513  1.00 36.68      B    O
ATOM   1796  N   SER B 159      84.914 -28.859  53.148  1.00 40.72      B    N
ATOM   1797  CA  SER B 159      85.074 -28.085  51.918  1.00 39.96      B    C
ATOM   1798  CB  SER B 159      86.106 -26.975  52.121  1.00 42.03      B    C
ATOM   1799  OG  SER B 159      87.346 -27.361  51.578  1.00 44.79      B    O
ATOM   1800  C   SER B 159      85.452 -28.968  50.724  1.00 38.45      B    C
ATOM   1801  O   SER B 159      86.157 -29.955  50.879  1.00 39.35      B    O
ATOM   1802  N   ILE B 160      85.000 -28.575  49.540  1.00 37.65      B    N
ATOM   1803  CA  ILE B 160      85.197 -29.319  48.290  1.00 39.01      B    C
ATOM   1804  CB  ILE B 160      83.901 -29.236  47.483  1.00 42.96      B    C
ATOM   1805  CG1 ILE B 160      82.801 -30.027  48.168  1.00 45.08      B    C
ATOM   1806  CD1 ILE B 160      81.484 -29.940  47.424  1.00 50.02      B    C
ATOM   1807  CG2 ILE B 160      84.092 -29.759  46.068  1.00 43.13      B    C
ATOM   1808  C   ILE B 160      86.303 -28.639  47.422  1.00 39.38      B    C
ATOM   1809  O   ILE B 160      86.585 -27.496  47.699  1.00 42.11      B    O
ATOM   1810  N   ASP B 161      86.895 -29.317  46.408  1.00 41.73      B    N
ATOM   1811  CA  ASP B 161      87.765 -28.752  45.244  1.00 42.26      B    C
ATOM   1812  CB  ASP B 161      87.294 -27.396  44.551  1.00 41.71      B    C
ATOM   1813  CG  ASP B 161      88.251 -26.909  43.337  1.00 45.05      B    C
ATOM   1814  OD1 ASP B 161      89.502 -27.036  43.406  1.00 45.65      B    O
ATOM   1815  OD2 ASP B 161      87.761 -26.361  42.298  1.00 34.98      B    O
ATOM   1816  C   ASP B 161      89.225 -28.681  45.691  1.00 43.71      B    C
ATOM   1817  O   ASP B 161      89.978 -29.645  45.541  1.00 39.94      B    O
ATOM   1818  N   GLU C  51      60.843   0.105  -0.467  1.00 73.79      C    N
ATOM   1819  CA  GLU C  51      60.571   0.115   1.003  1.00 71.92      C    C
ATOM   1820  CB  GLU C  51      60.636  -1.310   1.610  1.00 73.77      C    C
ATOM   1821  CG  GLU C  51      61.703  -2.256   1.022  1.00 81.04      C    C
ATOM   1822  CD  GLU C  51      61.327  -3.750   1.086  1.00 83.38      C    C
ATOM   1823  OE1 GLU C  51      61.047  -4.355   0.020  1.00 73.50      C    O
ATOM   1824  OE2 GLU C  51      61.317  -4.333   2.197  1.00 84.24      C    O
ATOM   1825  C   GLU C  51      61.500   1.121   1.706  1.00 71.03      C    C
ATOM   1826  O   GLU C  51      62.646   0.808   2.051  1.00 70.74      C    O
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ATOM	1827	N	VAL	C	52	60.993	2.348	1.874	1.00	66.81	C	N
ATOM	1828	CA	VAL	C	52	61.697	3.408	2.600	1.00	58.20	C	C
ATOM	1829	CB	VAL	C	52	61.948	4.661	1.737	1.00	57.65	C	C
ATOM	1830	CG1	VAL	C	52	62.621	5.762	2.559	1.00	57.78	C	C
ATOM	1831	CG2	VAL	C	52	62.798	4.324	0.518	1.00	59.63	C	C
ATOM	1832	C	VAL	C	52	60.872	3.811	3.807	1.00	51.77	C	C
ATOM	1833	O	VAL	C	52	59.864	4.489	3.677	1.00	51.87	C	O
ATOM	1834	N	LEU	C	53	61.361	3.453	4.984	1.00	47.85	C	N
ATOM	1835	CA	LEU	C	53	60.611	3.596	6.218	1.00	46.62	C	C
ATOM	1836	CB	LEU	C	53	61.254	2.757	7.303	1.00	47.55	C	C
ATOM	1837	CG	LEU	C	53	61.104	1.245	7.043	1.00	48.27	C	C
ATOM	1838	CD1	LEU	C	53	61.818	0.737	5.784	1.00	50.48	C	C
ATOM	1839	CD2	LEU	C	53	61.579	0.502	8.267	1.00	45.63	C	C
ATOM	1840	C	LEU	C	53	60.617	5.040	6.621	1.00	48.44	C	C
ATOM	1841	O	LEU	C	53	61.526	5.781	6.251	1.00	52.63	C	O
ATOM	1842	N	GLU	C	54	59.619	5.436	7.399	1.00	48.96	C	N
ATOM	1843	CA	GLU	C	54	59.434	6.847	7.706	1.00	48.02	C	C
ATOM	1844	CB	GLU	C	54	57.957	7.281	7.730	1.00	52.08	C	C
ATOM	1845	CG	GLU	C	54	57.488	7.860	6.380	1.00	59.23	C	C
ATOM	1846	CD	GLU	C	54	57.084	6.833	5.317	1.00	64.32	C	C
ATOM	1847	OE1	GLU	C	54	56.121	6.075	5.579	1.00	69.47	C	O
ATOM	1848	OE2	GLU	C	54	57.704	6.810	4.208	1.00	60.16	C	O
ATOM	1849	C	GLU	C	54	60.219	7.368	8.895	1.00	46.16	C	C
ATOM	1850	O	GLU	C	54	60.596	8.535	8.901	1.00	50.59	C	O
ATOM	1851	N	SER	C	55	60.522	6.531	9.873	1.00	44.71	C	N
ATOM	1852	CA	SER	C	55	61.215	7.010	11.077	1.00	42.70	C	C
ATOM	1853	CB	SER	C	55	60.201	7.571	12.110	1.00	40.66	C	C
ATOM	1854	OG	SER	C	55	59.637	6.532	12.896	1.00	42.46	C	O
ATOM	1855	C	SER	C	55	62.036	5.875	11.686	1.00	44.97	C	C
ATOM	1856	O	SER	C	55	61.930	4.716	11.263	1.00	44.53	C	O
ATOM	1857	N	SER	C	56	62.819	6.205	12.712	1.00	46.89	C	N
ATOM	1858	CA	SER	C	56	63.600	5.206	13.422	1.00	46.78	C	C
ATOM	1859	CB	SER	C	56	64.550	5.870	14.415	1.00	43.77	C	C
ATOM	1860	OG	SER	C	56	65.393	6.789	13.794	1.00	42.17	C	O
ATOM	1861	C	SER	C	56	62.701	4.244	14.190	1.00	47.96	C	C
ATOM	1862	O	SER	C	56	62.973	3.045	14.213	1.00	51.10	C	O
ATOM	1863	N	GLN	C	57	61.699	4.799	14.883	1.00	52.09	C	N
ATOM	1864	CA	GLN	C	57	60.660	4.013	15.577	1.00	52.67	C	C
ATOM	1865	CB	GLN	C	57	59.440	4.874	16.006	1.00	57.04	C	C
ATOM	1866	CG	GLN	C	57	58.977	4.657	17.431	1.00	62.85	C	C
ATOM	1867	CD	GLN	C	57	59.255	5.868	18.296	1.00	64.86	C	C
ATOM	1868	OE1	GLN	C	57	58.355	6.423	18.957	1.00	66.32	C	O
ATOM	1869	NE2	GLN	C	57	60.504	6.318	18.266	1.00	66.61	C	N
ATOM	1870	C	GLN	C	57	60.114	2.964	14.648	1.00	50.35	C	C
ATOM	1871	O	GLN	C	57	59.908	1.817	15.038	1.00	47.08	C	O
ATOM	1872	N	GLU	C	58	59.810	3.383	13.430	1.00	46.74	C	N
ATOM	1873	CA	GLU	C	58	59.154	2.479	12.519	1.00	47.59	C	C
ATOM	1874	CB	GLU	C	58	58.655	3.211	11.299	1.00	50.87	C	C
ATOM	1875	CG	GLU	C	58	57.560	2.462	10.562	1.00	54.51	C	C
ATOM	1876	CD	GLU	C	58	57.426	2.852	9.111	1.00	59.61	C	C
ATOM	1877	OE1	GLU	C	58	57.243	1.938	8.284	1.00	63.33	C	O
ATOM	1878	OE2	GLU	C	58	57.515	4.058	8.791	1.00	67.62	C	O
ATOM	1879	C	GLU	C	58	60.139	1.406	12.130	1.00	44.65	C	C
ATOM	1880	O	GLU	C	58	59.819	0.229	12.124	1.00	47.11	C	O
ATOM	1881	N	ALA	C	59	61.351	1.826	11.813	1.00	43.61	C	N
ATOM	1882	CA	ALA	C	59	62.401	0.893	11.427	1.00	39.46	C	C
ATOM	1883	CB	ALA	C	59	63.674	1.649	11.058	1.00	40.86	C	C
ATOM	1884	C	ALA	C	59	62.668	-0.124	12.530	1.00	35.23	C	C
ATOM	1885	O	ALA	C	59	62.872	-1.284	12.260	1.00	28.96	C	O
ATOM	1886	N	LEU	C	60	62.620	0.317	13.777	1.00	34.62	C	N
ATOM	1887	CA	LEU	C	60	62.828	-0.603	14.892	1.00	34.78	C	C
ATOM	1888	CB	LEU	C	60	63.018	0.189	16.205	1.00	31.60	C	C
ATOM	1889	CG	LEU	C	60	63.149	-0.598	17.508	1.00	30.83	C	C
ATOM	1890	CD1	LEU	C	60	64.455	-1.372	17.479	1.00	30.44	C	C
ATOM	1891	CD2	LEU	C	60	63.097	0.321	18.706	1.00	29.34	C	C
ATOM	1892	C	LEU	C	60	61.710	-1.658	14.995	1.00	37.02	C	C
ATOM	1893	O	LEU	C	60	61.984	-2.849	15.103	1.00	34.46	C	O
ATOM	1894	N	HIS	C	61	60.463	-1.202	14.958	1.00	39.07	C	N

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ATOM   1895  CA  HIS C  61      59.317  -2.082  15.012  1.00 40.32      C    C
ATOM   1896  CB  HIS C  61      58.013  -1.279  15.038  1.00 44.04      C    C
ATOM   1897  CG  HIS C  61      57.865  -0.443  16.271  1.00 48.50      C    C
ATOM   1898  ND1 HIS C  61      57.034   0.657  16.348  1.00 52.02      C    N
ATOM   1899  CE1 HIS C  61      57.140   1.196  17.552  1.00 53.46      C    C
ATOM   1900  NE2 HIS C  61      58.025   0.501  18.244  1.00 50.62      C    N
ATOM   1901  CD2 HIS C  61      58.492  -0.529  17.467  1.00 47.13      C    C
ATOM   1902  C   HIS C  61      59.340  -3.075  13.874  1.00 39.47      C    C
ATOM   1903  O   HIS C  61      59.196  -4.266  14.097  1.00 42.75      C    O
ATOM   1904  N   VAL C  62      59.545  -2.597  12.658  1.00 39.11      C    N
ATOM   1905  CA  VAL C  62      59.530  -3.474  11.483  1.00 38.43      C    C
ATOM   1906  CB  VAL C  62      59.526  -2.633  10.174  1.00 36.50      C    C
ATOM   1907  CG1 VAL C  62      59.763  -3.492   8.940  1.00 36.95      C    C
ATOM   1908  CG2 VAL C  62      58.218  -1.880  10.045  1.00 35.20      C    C
ATOM   1909  C   VAL C  62      60.706  -4.459  11.513  1.00 36.90      C    C
ATOM   1910  O   VAL C  62      60.563  -5.640  11.222  1.00 36.95      C    O
ATOM   1911  N   THR C  63      61.863  -3.969  11.899  1.00 38.10      C    N
ATOM   1912  CA  THR C  63      63.019  -4.826  12.028  1.00 39.23      C    C
ATOM   1913  CB  THR C  63      64.256  -4.018  12.463  1.00 40.02      C    C
ATOM   1914  OG1 THR C  63      64.620  -3.134  11.409  1.00 39.59      C    O
ATOM   1915  CG2 THR C  63      65.433  -4.918  12.740  1.00 41.32      C    C
ATOM   1916  C   THR C  63      62.777  -5.952  13.019  1.00 39.28      C    C
ATOM   1917  O   THR C  63      63.196  -7.073  12.781  1.00 39.39      C    O
ATOM   1918  N   GLU C  64      62.144  -5.652  14.146  1.00 40.92      C    N
ATOM   1919  CA  GLU C  64      61.862  -6.686  15.144  1.00 43.89      C    C
ATOM   1920  CB  GLU C  64      61.563  -6.095  16.525  1.00 41.67      C    C
ATOM   1921  CG  GLU C  64      62.737  -5.371  17.165  1.00 41.48      C    C
ATOM   1922  CD  GLU C  64      62.331  -4.554  18.365  1.00 46.16      C    C
ATOM   1923  OE1 GLU C  64      63.096  -4.513  19.357  1.00 49.44      C    O
ATOM   1924  OE2 GLU C  64      61.231  -3.951  18.323  1.00 49.89      C    O
ATOM   1925  C   GLU C  64      60.732  -7.627  14.722  1.00 46.06      C    C
ATOM   1926  O   GLU C  64      60.890  -8.841  14.782  1.00 50.40      C    O
ATOM   1927  N   ARG C  65      59.609  -7.082  14.274  1.00 48.47      C    N
ATOM   1928  CA  ARG C  65      58.472  -7.922  13.906  1.00 52.32      C    C
ATOM   1929  CB  ARG C  65      57.156  -7.130  13.824  1.00 60.01      C    C
ATOM   1930  CG  ARG C  65      56.089  -7.841  12.997  1.00 69.70      C    C
ATOM   1931  CD  ARG C  65      54.929  -7.028  12.483  1.00 70.81      C    C
ATOM   1932  NE  ARG C  65      54.572  -5.908  13.333  1.00 74.39      C    N
ATOM   1933  CZ  ARG C  65      55.048  -4.675  13.193  1.00 82.97      C    C
ATOM   1934  NH1 ARG C  65      55.931  -4.392  12.237  1.00 84.94      C    N
ATOM   1935  NH2 ARG C  65      54.650  -3.720  14.024  1.00 83.69      C    N
ATOM   1936  C   ARG C  65      58.729  -8.693  12.603  1.00 47.07      C    C
ATOM   1937  O   ARG C  65      58.581  -9.906  12.584  1.00 39.65      C    O
ATOM   1938  N   LYS C  66      59.095  -7.976  11.531  1.00 48.06      C    N
ATOM   1939  CA  LYS C  66      59.144  -8.545  10.166  1.00 48.46      C    C
ATOM   1940  CB  LYS C  66      58.734  -7.532   9.077  1.00 57.11      C    C
ATOM   1941  CG  LYS C  66      57.259  -7.098   9.087  1.00 65.27      C    C
ATOM   1942  CD  LYS C  66      56.364  -8.069   8.314  1.00 72.53      C    C
ATOM   1943  CE  LYS C  66      55.063  -8.375   9.069  1.00 75.36      C    C
ATOM   1944  NZ  LYS C  66      54.055  -9.064   8.211  1.00 76.87      C    N
ATOM   1945  C   LYS C  66      60.493  -9.100   9.780  1.00 43.70      C    C
ATOM   1946  O   LYS C  66      60.594 -10.276   9.457  1.00 44.06      C    O
ATOM   1947  N   TYR C  67      61.537  -8.276   9.827  1.00 40.43      C    N
ATOM   1948  CA  TYR C  67      62.801  -8.649   9.175  1.00 41.49      C    C
ATOM   1949  CB  TYR C  67      63.693  -7.426   8.962  1.00 43.27      C    C
ATOM   1950  CG  TYR C  67      63.107  -6.326   8.115  1.00 44.23      C    C
ATOM   1951  CD1 TYR C  67      62.239  -6.600   7.062  1.00 45.69      C    C
ATOM   1952  CE1 TYR C  67      61.722  -5.591   6.276  1.00 46.36      C    C
ATOM   1953  CZ  TYR C  67      62.089  -4.291   6.530  1.00 47.62      C    C
ATOM   1954  OH  TYR C  67      61.590  -3.274   5.762  1.00 48.86      C    O
ATOM   1955  CE2 TYR C  67      62.970  -3.999   7.552  1.00 47.81      C    C
ATOM   1956  CD2 TYR C  67      63.475  -5.012   8.331  1.00 45.93      C    C
ATOM   1957  C   TYR C  67      63.647  -9.703   9.891  1.00 40.37      C    C
ATOM   1958  O   TYR C  67      64.361 -10.456   9.244  1.00 41.39      C    O
ATOM   1959  N   LEU C  68      63.626  -9.704  11.220  1.00 38.04      C    N
ATOM   1960  CA  LEU C  68      64.491 -10.570  12.009  1.00 36.49      C    C
ATOM   1961  CB  LEU C  68      65.223  -9.742  13.074  1.00 34.73      C    C
ATOM   1962  CG  LEU C  68      66.293  -8.802  12.531  1.00 33.84      C    C
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ATOM	1963	CD1	LEU	C	68	66.945	-8.052	13.668	1.00	33.52	C	C
ATOM	1964	CD2	LEU	C	68	67.335	-9.565	11.714	1.00	35.36	C	C
ATOM	1965	C	LEU	C	68	63.713	-11.710	12.637	1.00	37.96	C	C
ATOM	1966	O	LEU	C	68	63.244	-11.588	13.748	1.00	42.62	C	O
ATOM	1967	N	LYS	C	69	63.587	-12.810	11.902	1.00	38.12	C	N
ATOM	1968	CA	LYS	C	69	62.890	-14.012	12.341	1.00	37.22	C	C
ATOM	1969	CB	LYS	C	69	61.615	-14.231	11.529	1.00	37.86	C	C
ATOM	1970	CG	LYS	C	69	60.782	-12.975	11.415	1.00	41.50	C	C
ATOM	1971	CD	LYS	C	69	59.724	-13.107	10.335	1.00	43.74	C	C
ATOM	1972	CE	LYS	C	69	58.587	-13.996	10.767	1.00	44.87	C	C
ATOM	1973	NZ	LYS	C	69	57.528	-13.992	9.728	1.00	47.18	C	N
ATOM	1974	C	LYS	C	69	63.832	-15.159	12.105	1.00	36.86	C	C
ATOM	1975	O	LYS	C	69	64.758	-15.063	11.311	1.00	39.18	C	O
ATOM	1976	N	ARG	C	70	63.602	-16.234	12.825	1.00	37.52	C	N
ATOM	1977	CA	ARG	C	70	64.307	-17.464	12.648	1.00	39.20	C	C
ATOM	1978	CB	ARG	C	70	64.285	-17.981	11.203	1.00	42.12	C	C
ATOM	1979	CG	ARG	C	70	62.977	-17.962	10.466	1.00	44.67	C	C
ATOM	1980	CD	ARG	C	70	62.935	-19.036	9.355	1.00	47.85	C	C
ATOM	1981	NE	ARG	C	70	61.708	-19.844	9.469	1.00	48.55	C	N
ATOM	1982	CZ	ARG	C	70	60.530	-19.500	8.939	1.00	51.08	C	C
ATOM	1983	NH1	ARG	C	70	60.379	-18.362	8.255	1.00	51.01	C	N
ATOM	1984	NH2	ARG	C	70	59.474	-20.289	9.103	1.00	52.64	C	N
ATOM	1985	C	ARG	C	70	65.738	-17.338	13.075	1.00	35.49	C	C
ATOM	1986	O	ARG	C	70	66.572	-17.972	12.461	1.00	36.11	C	O
ATOM	1987	N	ASP	C	71	66.045	-16.566	14.111	1.00	34.75	C	N
ATOM	1988	CA	ASP	C	71	67.386	-16.667	14.680	1.00	37.46	C	C
ATOM	1989	CB	ASP	C	71	67.705	-15.578	15.710	1.00	37.00	C	C
ATOM	1990	CG	ASP	C	71	66.737	-15.559	16.859	1.00	38.74	C	C
ATOM	1991	OD1	ASP	C	71	65.556	-15.816	16.635	1.00	44.04	C	O
ATOM	1992	OD2	ASP	C	71	67.149	-15.282	17.991	1.00	42.17	C	O
ATOM	1993	C	ASP	C	71	67.515	-18.057	15.308	1.00	38.65	C	C
ATOM	1994	O	ASP	C	71	66.511	-18.684	15.656	1.00	43.60	C	O
ATOM	1995	N	TRP	C	72	68.735	-18.560	15.410	1.00	37.21	C	N
ATOM	1996	CA	TRP	C	72	68.933	-19.899	15.908	1.00	33.84	C	C
ATOM	1997	CB	TRP	C	72	68.868	-20.898	14.765	1.00	32.06	C	C
ATOM	1998	CG	TRP	C	72	69.954	-20.776	13.746	1.00	32.81	C	C
ATOM	1999	CD1	TRP	C	72	69.970	-19.959	12.660	1.00	32.86	C	C
ATOM	2000	NE1	TRP	C	72	71.115	-20.159	11.921	1.00	31.97	C	N
ATOM	2001	CE2	TRP	C	72	71.855	-21.142	12.519	1.00	33.15	C	C
ATOM	2002	CD2	TRP	C	72	71.150	-21.561	13.670	1.00	34.44	C	C
ATOM	2003	CE3	TRP	C	72	71.701	-22.565	14.477	1.00	37.33	C	C
ATOM	2004	CZ3	TRP	C	72	72.916	-23.112	14.116	1.00	38.77	C	C
ATOM	2005	CH2	TRP	C	72	73.598	-22.664	12.957	1.00	36.60	C	C
ATOM	2006	CZ2	TRP	C	72	73.080	-21.684	12.156	1.00	34.00	C	C
ATOM	2007	C	TRP	C	72	70.233	-20.035	16.651	1.00	33.73	C	C
ATOM	2008	O	TRP	C	72	71.185	-19.327	16.370	1.00	35.28	C	O
ATOM	2009	N	CYS	C	73	70.254	-20.972	17.594	1.00	35.01	C	N
ATOM	2010	CA	CYS	C	73	71.429	-21.239	18.416	1.00	34.84	C	C
ATOM	2011	CB	CYS	C	73	71.439	-20.263	19.570	1.00	36.02	C	C
ATOM	2012	SG	CYS	C	73	72.763	-20.481	20.755	1.00	37.00	C	S
ATOM	2013	C	CYS	C	73	71.402	-22.682	18.930	1.00	34.57	C	C
ATOM	2014	O	CYS	C	73	70.492	-23.074	19.643	1.00	32.05	C	O
ATOM	2015	N	LYS	C	74	72.374	-23.471	18.491	1.00	35.83	C	N
ATOM	2016	CA	LYS	C	74	72.422	-24.877	18.773	1.00	38.35	C	C
ATOM	2017	CB	LYS	C	74	72.793	-25.660	17.496	1.00	43.79	C	C
ATOM	2018	CG	LYS	C	74	71.674	-25.896	16.482	1.00	46.99	C	C
ATOM	2019	CD	LYS	C	74	70.318	-25.345	16.911	1.00	52.02	C	C
ATOM	2020	CE	LYS	C	74	69.274	-25.489	15.821	1.00	53.54	C	C
ATOM	2021	NZ	LYS	C	74	67.898	-25.462	16.376	1.00	55.76	C	N
ATOM	2022	C	LYS	C	74	73.419	-25.187	19.876	1.00	39.02	C	C
ATOM	2023	O	LYS	C	74	74.490	-24.591	19.944	1.00	38.24	C	O
ATOM	2024	N	THR	C	75	73.043	-26.146	20.722	1.00	38.78	C	N
ATOM	2025	CA	THR	C	75	73.915	-26.728	21.716	1.00	38.17	C	C
ATOM	2026	CB	THR	C	75	73.194	-26.888	23.055	1.00	35.80	C	C
ATOM	2027	OG1	THR	C	75	72.601	-25.635	23.427	1.00	37.90	C	O
ATOM	2028	CG2	THR	C	75	74.160	-27.332	24.131	1.00	34.29	C	C
ATOM	2029	C	THR	C	75	74.280	-28.108	21.212	1.00	40.81	C	C
ATOM	2030	O	THR	C	75	73.421	-28.826	20.737	1.00	44.46	C	O

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ATOM   2031  N   GLN C  76      75.541 -28.493  21.320  1.00 41.47      C    N
ATOM   2032  CA  GLN C  76      75.955 -29.770  20.797  1.00 42.94      C    C
ATOM   2033  CB  GLN C  76      76.431 -29.604  19.369  1.00 45.56      C    C
ATOM   2034  CG  GLN C  76      76.804 -30.908  18.691  1.00 45.15      C    C
ATOM   2035  CD  GLN C  76      77.016 -30.755  17.199  1.00 44.23      C    C
ATOM   2036  OE1 GLN C  76      76.360 -29.948  16.547  1.00 42.67      C    O
ATOM   2037  NE2 GLN C  76      77.910 -31.556  16.652  1.00 43.91      C    N
ATOM   2038  C   GLN C  76      77.050 -30.386  21.645  1.00 44.38      C    C
ATOM   2039  O   GLN C  76      77.924 -29.678  22.123  1.00 47.28      C    O
ATOM   2040  N   PRO C  77      77.005 -31.719  21.836  1.00 42.38      C    N
ATOM   2041  CA  PRO C  77      77.948 -32.334  22.729  1.00 40.80      C    C
ATOM   2042  CB  PRO C  77      77.303 -33.684  23.010  1.00 39.70      C    C
ATOM   2043  CG  PRO C  77      76.541 -33.989  21.785  1.00 39.78      C    C
ATOM   2044  CD  PRO C  77      75.961 -32.675  21.415  1.00 41.54      C    C
ATOM   2045  C   PRO C  77      79.333 -32.527  22.126  1.00 43.08      C    C
ATOM   2046  O   PRO C  77      79.468 -32.669  20.909  1.00 48.18      C    O
ATOM   2047  N   LEU C  78      80.344 -32.530  22.988  1.00 42.76      C    N
ATOM   2048  CA  LEU C  78      81.693 -32.864  22.592  1.00 44.23      C    C
ATOM   2049  CB  LEU C  78      82.435 -31.623  22.099  1.00 44.34      C    C
ATOM   2050  CG  LEU C  78      83.323 -30.878  23.097  1.00 44.63      C    C
ATOM   2051  CD1 LEU C  78      84.254 -29.910  22.391  1.00 45.75      C    C
ATOM   2052  CD2 LEU C  78      82.515 -30.142  24.133  1.00 46.01      C    C
ATOM   2053  C   LEU C  78      82.414 -33.535  23.770  1.00 44.93      C    C
ATOM   2054  O   LEU C  78      82.038 -33.350  24.914  1.00 39.73      C    O
ATOM   2055  N   LYS C  79      83.412 -34.356  23.465  1.00 47.49      C    N
ATOM   2056  CA  LYS C  79      84.131 -35.107  24.490  1.00 50.28      C    C
ATOM   2057  CB  LYS C  79      84.706 -36.410  23.932  1.00 55.83      C    C
ATOM   2058  CG  LYS C  79      83.675 -37.448  23.536  1.00 60.03      C    C
ATOM   2059  CD  LYS C  79      84.309 -38.528  22.680  1.00 64.20      C    C
ATOM   2060  CE  LYS C  79      83.298 -39.587  22.266  1.00 65.48      C    C
ATOM   2061  NZ  LYS C  79      83.906 -40.522  21.287  1.00 68.25      C    N
ATOM   2062  C   LYS C  79      85.271 -34.279  25.030  1.00 48.02      C    C
ATOM   2063  O   LYS C  79      85.878 -33.499  24.305  1.00 50.39      C    O
ATOM   2064  N   GLN C  80      85.555 -34.491  26.306  1.00 45.90      C    N
ATOM   2065  CA  GLN C  80      86.669 -33.875  27.012  1.00 44.37      C    C
ATOM   2066  CB  GLN C  80      86.210 -32.689  27.830  1.00 45.33      C    C
ATOM   2067  CG  GLN C  80      86.063 -31.435  26.995  1.00 48.18      C    C
ATOM   2068  CD  GLN C  80      86.144 -30.176  27.815  1.00 52.77      C    C
ATOM   2069  OE1 GLN C  80      85.611 -30.112  28.924  1.00 56.43      C    O
ATOM   2070  NE2 GLN C  80      86.836 -29.163  27.290  1.00 55.08      C    N
ATOM   2071  C   GLN C  80      87.166 -34.927  27.965  1.00 44.45      C    C
ATOM   2072  O   GLN C  80      86.363 -35.668  28.533  1.00 45.99      C    O
ATOM   2073  N   THR C  81      88.469 -35.015  28.132  1.00 42.84      C    N
ATOM   2074  CA  THR C  81      89.015 -36.030  29.001  1.00 47.49      C    C
ATOM   2075  CB  THR C  81      89.969 -36.986  28.250  1.00 51.57      C    C
ATOM   2076  OG1 THR C  81      90.843 -37.618  29.189  1.00 55.19      C    O
ATOM   2077  CG2 THR C  81      90.797 -36.265  27.187  1.00 53.38      C    C
ATOM   2078  C   THR C  81      89.686 -35.411  30.215  1.00 48.22      C    C
ATOM   2079  O   THR C  81      90.360 -34.389  30.102  1.00 55.31      C    O
ATOM   2080  N   ILE C  82      89.472 -36.027  31.377  1.00 50.25      C    N
ATOM   2081  CA  ILE C  82      90.052 -35.584  32.639  1.00 55.45      C    C
ATOM   2082  CB  ILE C  82      89.094 -35.774  33.829  1.00 57.28      C    C
ATOM   2083  CG1 ILE C  82      87.643 -35.314  33.588  1.00 59.26      C    C
ATOM   2084  CD1 ILE C  82      87.395 -33.934  33.061  1.00 65.30      C    C
ATOM   2085  CG2 ILE C  82      89.772 -35.315  35.111  1.00 59.27      C    C
ATOM   2086  C   ILE C  82      91.223 -36.506  32.968  1.00 61.11      C    C
ATOM   2087  O   ILE C  82      91.049 -37.737  33.008  1.00 61.90      C    O
ATOM   2088  N   HIS C  83      92.392 -35.925  33.248  1.00 65.54      C    N
ATOM   2089  CA  HIS C  83      93.575 -36.700  33.604  1.00 67.92      C    C
ATOM   2090  CB  HIS C  83      94.764 -36.438  32.708  1.00 66.48      C    C
ATOM   2091  CG  HIS C  83      94.431 -36.088  31.295  1.00 70.49      C    C
ATOM   2092  ND1 HIS C  83      94.407 -37.034  30.294  1.00 69.18      C    N
ATOM   2093  CE1 HIS C  83      94.120 -36.448  29.146  1.00 71.88      C    C
ATOM   2094  NE2 HIS C  83      93.976 -35.151  29.365  1.00 77.07      C    N
ATOM   2095  CD2 HIS C  83      94.180 -34.895  30.700  1.00 70.55      C    C
ATOM   2096  C   HIS C  83      94.020 -36.288  34.974  1.00 68.69      C    C
ATOM   2097  O   HIS C  83      93.765 -35.174  35.394  1.00 71.87      C    O
ATOM   2098  N   GLU C  84      94.740 -37.176  35.646  1.00 69.04      C    N
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ATOM   2099  CA  GLU C  84      95.278 -36.879  36.956  1.00 68.97      C    C
ATOM   2100  CB  GLU C  84      94.172 -36.893  37.999  1.00 67.14      C    C
ATOM   2101  CG  GLU C  84      94.534 -36.178  39.291  1.00 67.42      C    C
ATOM   2102  CD  GLU C  84      93.483 -35.166  39.659  1.00 68.94      C    C
ATOM   2103  OE1 GLU C  84      92.912 -35.239  40.776  1.00 66.16      C    O
ATOM   2104  OE2 GLU C  84      93.237 -34.302  38.793  1.00 63.99      C    O
ATOM   2105  C   GLU C  84      96.345 -37.881  37.341  1.00 69.80      C    C
ATOM   2106  O   GLU C  84      96.253 -39.044  36.971  1.00 67.35      C    O
ATOM   2107  N   GLU C  85      97.348 -37.423  38.090  1.00 72.04      C    N
ATOM   2108  CA  GLU C  85      98.464 -38.292  38.481  1.00 66.30      C    C
ATOM   2109  CB  GLU C  85      99.567 -37.534  39.227  1.00 71.50      C    C
ATOM   2110  CG  GLU C  85     100.362 -36.618  38.347  1.00 77.34      C    C
ATOM   2111  CD  GLU C  85     101.583 -36.048  39.033  1.00 83.45      C    C
ATOM   2112  OE1 GLU C  85     102.135 -36.705  39.949  1.00 90.02      C    O
ATOM   2113  OE2 GLU C  85     101.996 -34.936  38.648  1.00 85.58      C    O
ATOM   2114  C   GLU C  85      97.962 -39.472  39.291  1.00 56.39      C    C
ATOM   2115  O   GLU C  85      97.275 -39.301  40.292  1.00 54.98      C    O
ATOM   2116  N   GLY C  86      98.239 -40.666  38.792  1.00 49.25      C    N
ATOM   2117  CA  GLY C  86      97.851 -41.906  39.449  1.00 51.84      C    C
ATOM   2118  C   GLY C  86      96.440 -42.434  39.212  1.00 52.54      C    C
ATOM   2119  O   GLY C  86      96.103 -43.533  39.692  1.00 55.46      C    O
ATOM   2120  N   CYS C  87      95.614 -41.671  38.490  1.00 50.75      C    N
ATOM   2121  CA  CYS C  87      94.219 -42.038  38.245  1.00 51.10      C    C
ATOM   2122  CB  CYS C  87      93.289 -40.879  38.615  1.00 52.49      C    C
ATOM   2123  SG  CYS C  87      93.424 -40.327  40.320  1.00 52.16      C    S
ATOM   2124  C   CYS C  87      93.974 -42.421  36.798  1.00 49.11      C    C
ATOM   2125  O   CYS C  87      94.576 -41.854  35.896  1.00 46.43      C    O
ATOM   2126  N   ASN C  88      93.072 -43.374  36.585  1.00 50.29      C    N
ATOM   2127  CA  ASN C  88      92.605 -43.686  35.248  1.00 50.62      C    C
ATOM   2128  CB  ASN C  88      91.582 -44.830  35.255  1.00 53.17      C    C
ATOM   2129  CG  ASN C  88      92.197 -46.192  35.558  1.00 55.98      C    C
ATOM   2130  OD1 ASN C  88      91.471 -47.178  35.697  1.00 54.75      C    O
ATOM   2131  ND2 ASN C  88      93.527 -46.259  35.649  1.00 56.01      C    N
ATOM   2132  C   ASN C  88      91.955 -42.418  34.711  1.00 53.28      C    C
ATOM   2133  O   ASN C  88      91.199 -41.732  35.408  1.00 55.44      C    O
ATOM   2134  N   SER C  89      92.309 -42.068  33.488  1.00 52.74      C    N
ATOM   2135  CA  SER C  89      91.726 -40.925  32.817  1.00 50.50      C    C
ATOM   2136  CB  SER C  89      92.462 -40.720  31.500  1.00 54.36      C    C
ATOM   2137  OG  SER C  89      91.820 -39.805  30.634  1.00 59.45      C    O
ATOM   2138  C   SER C  89      90.275 -41.247  32.581  1.00 44.57      C    C
ATOM   2139  O   SER C  89      89.935 -42.392  32.395  1.00 44.43      C    O
ATOM   2140  N   ARG C  90      89.430 -40.227  32.569  1.00 45.83      C    N
ATOM   2141  CA  ARG C  90      88.002 -40.410  32.353  1.00 44.20      C    C
ATOM   2142  CB  ARG C  90      87.277 -40.318  33.684  1.00 44.07      C    C
ATOM   2143  CG  ARG C  90      85.765 -40.380  33.595  1.00 43.98      C    C
ATOM   2144  CD  ARG C  90      85.148 -40.630  34.969  1.00 42.64      C    C
ATOM   2145  NE  ARG C  90      83.695 -40.724  34.864  1.00 42.26      C    N
ATOM   2146  CZ  ARG C  90      82.840 -40.607  35.877  1.00 43.28      C    C
ATOM   2147  NH1 ARG C  90      83.265 -40.431  37.122  1.00 44.47      C    N
ATOM   2148  NH2 ARG C  90      81.533 -40.680  35.647  1.00 42.73      C    N
ATOM   2149  C   ARG C  90      87.473 -39.357  31.382  1.00 46.23      C    C
ATOM   2150  O   ARG C  90      87.871 -38.189  31.413  1.00 45.41      C    O
ATOM   2151  N   THR C  91      86.567 -39.772  30.513  1.00 45.83      C    N
ATOM   2152  CA  THR C  91      86.047 -38.884  29.507  1.00 45.83      C    C
ATOM   2153  CB  THR C  91      86.085 -39.566  28.123  1.00 46.41      C    C
ATOM   2154  OG1 THR C  91      87.450 -39.752  27.729  1.00 44.85      C    O
ATOM   2155  CG2 THR C  91      85.361 -38.732  27.050  1.00 48.28      C    C
ATOM   2156  C   THR C  91      84.629 -38.479  29.895  1.00 45.37      C    C
ATOM   2157  O   THR C  91      83.806 -39.313  30.272  1.00 41.79      C    O
ATOM   2158  N   ILE C  92      84.364 -37.183  29.778  1.00 45.60      C    N
ATOM   2159  CA  ILE C  92      83.055 -36.633  30.068  1.00 46.79      C    C
ATOM   2160  CB  ILE C  92      83.054 -35.716  31.310  1.00 49.01      C    C
ATOM   2161  CG1 ILE C  92      84.131 -34.621  31.225  1.00 48.98      C    C
ATOM   2162  CD1 ILE C  92      83.549 -33.239  31.086  1.00 50.76      C    C
ATOM   2163  CG2 ILE C  92      83.261 -36.549  32.562  1.00 52.37      C    C
ATOM   2164  C   ILE C  92      82.567 -35.871  28.866  1.00 44.67      C    C
ATOM   2165  O   ILE C  92      83.331 -35.603  27.936  1.00 46.33      C    O
ATOM   2166  N   ILE C  93      81.281 -35.550  28.896  1.00 42.88      C    N
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ATOM   2167  CA  ILE C  93      80.625 -34.843  27.823  1.00 42.06      C    C
ATOM   2168  CB  ILE C  93      79.273 -35.497  27.502  1.00 42.48      C    C
ATOM   2169  CG1 ILE C  93      79.472 -36.887  26.893  1.00 42.61      C    C
ATOM   2170  CD1 ILE C  93      80.271 -36.932  25.617  1.00 44.22      C    C
ATOM   2171  CG2 ILE C  93      78.425 -34.600  26.615  1.00 44.31      C    C
ATOM   2172  C   ILE C  93      80.388 -33.415  28.247  1.00 41.60      C    C
ATOM   2173  O   ILE C  93      79.675 -33.189  29.217  1.00 44.24      C    O
ATOM   2174  N   ASN C  94      81.011 -32.466  27.540  1.00 40.31      C    N
ATOM   2175  CA  ASN C  94      80.659 -31.054  27.637  1.00 39.92      C    C
ATOM   2176  CB  ASN C  94      81.902 -30.167  27.643  1.00 38.03      C    C
ATOM   2177  CG  ASN C  94      81.729 -28.905  28.465  1.00 38.00      C    C
ATOM   2178  OD1 ASN C  94      80.615 -28.402  28.664  1.00 37.84      C    O
ATOM   2179  ND2 ASN C  94      82.837 -28.390  28.963  1.00 38.98      C    N
ATOM   2180  C   ASN C  94      79.779 -30.700  26.447  1.00 39.67      C    C
ATOM   2181  O   ASN C  94      79.364 -31.576  25.699  1.00 39.68      C    O
ATOM   2182  N   ARG C  95      79.461 -29.423  26.293  1.00 40.75      C    N
ATOM   2183  CA  ARG C  95      78.698 -28.971  25.142  1.00 40.67      C    C
ATOM   2184  CB  ARG C  95      77.213 -28.733  25.501  1.00 42.09      C    C
ATOM   2185  CG  ARG C  95      76.285 -29.944  25.835  1.00 44.79      C    C
ATOM   2186  CD  ARG C  95      76.310 -30.140  27.339  1.00 52.15      C    C
ATOM   2187  NE  ARG C  95      75.241 -30.961  27.919  1.00 54.01      C    N
ATOM   2188  CZ  ARG C  95      75.174 -31.296  29.202  1.00 57.75      C    C
ATOM   2189  NH1 ARG C  95      76.128 -30.906  30.046  1.00 64.24      C    N
ATOM   2190  NH2 ARG C  95      74.164 -32.038  29.651  1.00 60.65      C    N
ATOM   2191  C   ARG C  95      79.328 -27.682  24.574  1.00 36.06      C    C
ATOM   2192  O   ARG C  95      80.071 -26.982  25.261  1.00 32.40      C    O
ATOM   2193  N   PHE C  96      79.023 -27.397  23.311  1.00 34.15      C    N
ATOM   2194  CA  PHE C  96      79.374 -26.133  22.704  1.00 34.80      C    C
ATOM   2195  CB  PHE C  96      80.594 -26.281  21.784  1.00 38.26      C    C
ATOM   2196  CG  PHE C  96      80.370 -27.127  20.567  1.00 40.09      C    C
ATOM   2197  CD1 PHE C  96      80.389 -28.506  20.653  1.00 39.45      C    C
ATOM   2198  CE1 PHE C  96      80.204 -29.280  19.526  1.00 43.32      C    C
ATOM   2199  CZ  PHE C  96      80.027 -28.675  18.285  1.00 45.24      C    C
ATOM   2200  CE2 PHE C  96      80.029 -27.292  18.177  1.00 44.20      C    C
ATOM   2201  CD2 PHE C  96      80.207 -26.526  19.313  1.00 43.66      C    C
ATOM   2202  C   PHE C  96      78.193 -25.469  21.996  1.00 32.33      C    C
ATOM   2203  O   PHE C  96      77.195 -26.096  21.702  1.00 30.57      C    O
ATOM   2204  N   CYS C  97      78.332 -24.176  21.751  1.00 30.62      C    N
ATOM   2205  CA  CYS C  97      77.268 -23.361  21.198  1.00 29.86      C    C
ATOM   2206  CB  CYS C  97      77.077 -22.128  22.078  1.00 30.35      C    C
ATOM   2207  SG  CYS C  97      76.935 -22.487  23.840  1.00 32.66      C    S
ATOM   2208  C   CYS C  97      77.657 -22.893  19.820  1.00 29.27      C    C
ATOM   2209  O   CYS C  97      78.810 -22.548  19.610  1.00 29.91      C    O
ATOM   2210  N   TYR C  98      76.715 -22.870  18.882  1.00 27.76      C    N
ATOM   2211  CA  TYR C  98      76.937 -22.155  17.633  1.00 27.88      C    C
ATOM   2212  CB  TYR C  98      77.764 -22.969  16.639  1.00 27.91      C    C
ATOM   2213  CG  TYR C  98      77.115 -24.236  16.284  1.00 29.65      C    C
ATOM   2214  CD1 TYR C  98      77.305 -25.353  17.062  1.00 32.89      C    C
ATOM   2215  CE1 TYR C  98      76.688 -26.554  16.749  1.00 32.89      C    C
ATOM   2216  CZ  TYR C  98      75.865 -26.631  15.654  1.00 31.70      C    C
ATOM   2217  OH  TYR C  98      75.266 -27.821  15.378  1.00 34.71      C    O
ATOM   2218  CE2 TYR C  98      75.654 -25.531  14.856  1.00 31.29      C    C
ATOM   2219  CD2 TYR C  98      76.276 -24.336  15.178  1.00 31.69      C    C
ATOM   2220  C   TYR C  98      75.632 -21.760  17.013  1.00 26.32      C    C
ATOM   2221  O   TYR C  98      74.638 -22.451  17.159  1.00 28.62      C    O
ATOM   2222  N   GLY C  99      75.624 -20.615  16.353  1.00 25.88      C    N
ATOM   2223  CA  GLY C  99      74.399 -20.114  15.767  1.00 26.49      C    C
ATOM   2224  C   GLY C  99      74.542 -18.769  15.072  1.00 26.67      C    C
ATOM   2225  O   GLY C  99      75.634 -18.234  14.894  1.00 23.69      C    O
ATOM   2226  N   GLN C 100      73.392 -18.223  14.713  1.00 27.46      C    N
ATOM   2227  CA  GLN C 100      73.307 -16.948  14.063  1.00 29.08      C    C
ATOM   2228  CB  GLN C 100      73.072 -17.149  12.564  1.00 31.64      C    C
ATOM   2229  CG  GLN C 100      74.127 -18.074  11.955  1.00 32.55      C    C
ATOM   2230  CD  GLN C 100      74.032 -18.293  10.462  1.00 33.07      C    C
ATOM   2231  OE1 GLN C 100      75.045 -18.561   9.797  1.00 35.34      C    O
ATOM   2232  NE2 GLN C 100      72.843 -18.230   9.933  1.00 33.48      C    N
ATOM   2233  C   GLN C 100      72.174 -16.205  14.727  1.00 30.29      C    C
ATOM   2234  O   GLN C 100      70.993 -16.518  14.524  1.00 30.87      C    O
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ATOM   2235  N   CYS C 101      72.531 -15.236  15.560  1.00 29.85      C    N
ATOM   2236  CA  CYS C 101      71.553 -14.514  16.344  1.00 30.24      C    C
ATOM   2237  CB  CYS C 101      72.088 -14.308  17.748  1.00 32.71      C    C
ATOM   2238  SG  CYS C 101      72.392 -15.857  18.615  1.00 40.00      C    S
ATOM   2239  C   CYS C 101      71.240 -13.186  15.669  1.00 29.48      C    C
ATOM   2240  O   CYS C 101      71.894 -12.829  14.719  1.00 30.13      C    O
ATOM   2241  N   ASN C 102      70.258 -12.450  16.181  1.00 29.02      C    N
ATOM   2242  CA  ASN C 102      69.894 -11.180  15.604  1.00 28.60      C    C
ATOM   2243  CB  ASN C 102      68.482 -10.859  15.960  1.00 28.26      C    C
ATOM   2244  CG  ASN C 102      67.530 -11.846  15.372  1.00 31.20      C    C
ATOM   2245  OD1 ASN C 102      66.517 -12.142  15.947  1.00 33.45      C    O
ATOM   2246  ND2 ASN C 102      67.850 -12.362  14.187  1.00 34.96      C    N
ATOM   2247  C   ASN C 102      70.754 -10.058  16.090  1.00 29.15      C    C
ATOM   2248  O   ASN C 102      71.129 -10.023  17.246  1.00 31.56      C    O
ATOM   2249  N   SER C 103      71.067  -9.143  15.189  1.00 28.99      C    N
ATOM   2250  CA  SER C 103      71.691  -7.900  15.559  1.00 28.54      C    C
ATOM   2251  CB  SER C 103      73.191  -8.020  15.506  1.00 28.87      C    C
ATOM   2252  OG  SER C 103      73.595  -8.423  14.230  1.00 29.49      C    O
ATOM   2253  C   SER C 103      71.233  -6.853  14.584  1.00 28.18      C    C
ATOM   2254  O   SER C 103      70.801  -7.172  13.473  1.00 28.89      C    O
ATOM   2255  N   PHE C 104      71.248  -5.609  15.022  1.00 28.19      C    N
ATOM   2256  CA  PHE C 104      70.840  -4.502  14.174  1.00 31.61      C    C
ATOM   2257  CB  PHE C 104      69.292  -4.416  14.014  1.00 32.51      C    C
ATOM   2258  CG  PHE C 104      68.541  -4.188  15.295  1.00 31.86      C    C
ATOM   2259  CD1 PHE C 104      68.490  -2.943  15.877  1.00 32.60      C    C
ATOM   2260  CE1 PHE C 104      67.802  -2.747  17.073  1.00 33.71      C    C
ATOM   2261  CZ  PHE C 104      67.135  -3.798  17.672  1.00 31.75      C    C
ATOM   2262  CE2 PHE C 104      67.170  -5.041  17.088  1.00 32.00      C    C
ATOM   2263  CD2 PHE C 104      67.865  -5.234  15.908  1.00 32.31      C    C
ATOM   2264  C   PHE C 104      71.385  -3.194  14.697  1.00 32.81      C    C
ATOM   2265  O   PHE C 104      71.855  -3.108  15.832  1.00 32.32      C    O
ATOM   2266  N   TYR C 105      71.304  -2.178  13.853  1.00 32.81      C    N
ATOM   2267  CA  TYR C 105      71.784  -0.856  14.214  1.00 32.42      C    C
ATOM   2268  CB  TYR C 105      73.244  -0.719  13.840  1.00 32.74      C    C
ATOM   2269  CG  TYR C 105      73.796   0.617  14.175  1.00 33.32      C    C
ATOM   2270  CD1 TYR C 105      73.572   1.710  13.351  1.00 34.77      C    C
ATOM   2271  CE1 TYR C 105      74.092   2.956  13.661  1.00 36.37      C    C
ATOM   2272  CZ  TYR C 105      74.839   3.103  14.816  1.00 35.70      C    C
ATOM   2273  OH  TYR C 105      75.353   4.315  15.161  1.00 37.08      C    O
ATOM   2274  CE2 TYR C 105      75.057   2.034  15.643  1.00 34.82      C    C
ATOM   2275  CD2 TYR C 105      74.545   0.798  15.318  1.00 34.21      C    C
ATOM   2276  C   TYR C 105      70.963   0.160  13.458  1.00 31.04      C    C
ATOM   2277  O   TYR C 105      70.895   0.117  12.238  1.00 29.57      C    O
ATOM   2278  N   ILE C 106      70.321   1.058  14.191  1.00 31.12      C    N
ATOM   2279  CA  ILE C 106      69.393   1.991  13.605  1.00 30.30      C    C
ATOM   2280  CB  ILE C 106      67.948   1.611  13.950  1.00 30.68      C    C
ATOM   2281  CG1 ILE C 106      67.579   0.266  13.327  1.00 30.71      C    C
ATOM   2282  CD1 ILE C 106      66.387  -0.389  13.973  1.00 30.95      C    C
ATOM   2283  CG2 ILE C 106      66.975   2.662  13.436  1.00 33.07      C    C
ATOM   2284  C   ILE C 106      69.679   3.357  14.161  1.00 30.29      C    C
ATOM   2285  O   ILE C 106      69.475   3.577  15.338  1.00 27.61      C    O
ATOM   2286  N   PRO C 107      70.128   4.294  13.307  1.00 33.43      C    N
ATOM   2287  CA  PRO C 107      70.443   5.652  13.760  1.00 35.14      C    C
ATOM   2288  CB  PRO C 107      71.004   6.346  12.523  1.00 35.19      C    C
ATOM   2289  CG  PRO C 107      70.983   5.362  11.421  1.00 36.47      C    C
ATOM   2290  CD  PRO C 107      70.193   4.164  11.847  1.00 36.53      C    C
ATOM   2291  C   PRO C 107      69.206   6.375  14.245  1.00 37.50      C    C
ATOM   2292  O   PRO C 107      68.150   6.201  13.670  1.00 42.57      C    O
ATOM   2293  N   ARG C 108      69.372   7.170  15.294  1.00 40.56      C    N
ATOM   2294  CA  ARG C 108      68.312   7.656  16.158  1.00 43.85      C    C
ATOM   2295  CB  ARG C 108      68.380   6.825  17.435  1.00 47.95      C    C
ATOM   2296  CG  ARG C 108      67.226   6.872  18.419  1.00 48.96      C    C
ATOM   2297  CD  ARG C 108      67.643   6.307  19.775  1.00 54.78      C    C
ATOM   2298  NE  ARG C 108      66.615   6.015  20.790  1.00 58.29      C    N
ATOM   2299  CZ  ARG C 108      65.943   6.949  21.455  1.00 63.95      C    C
ATOM   2300  NH1 ARG C 108      66.159   8.238  21.211  1.00 69.93      C    N
ATOM   2301  NH2 ARG C 108      65.032   6.597  22.355  1.00 66.84      C    N
ATOM   2302  C   ARG C 108      68.634   9.082  16.547  1.00 47.03      C    C
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【圖1】(續)

ATOM	2303	O	ARG	C	108	69.738	9.555	16.352	1.00	45.46	C	O
ATOM	2304	N	HIS	C	109	67.696	9.752	17.181	1.00	59.39	C	N
ATOM	2305	CA	HIS	C	109	67.938	11.061	17.749	1.00	63.62	C	C
ATOM	2306	CB	HIS	C	109	66.952	12.067	17.191	1.00	64.44	C	C
ATOM	2307	CG	HIS	C	109	67.392	12.716	15.919	1.00	65.61	C	C
ATOM	2308	ND1	HIS	C	109	66.842	12.439	14.683	1.00	65.99	C	N
ATOM	2309	CE1	HIS	C	109	67.438	13.179	13.766	1.00	62.97	C	C
ATOM	2310	NE2	HIS	C	109	68.348	13.925	14.360	1.00	62.95	C	N
ATOM	2311	CD2	HIS	C	109	68.333	13.659	15.706	1.00	67.46	C	C
ATOM	2312	C	HIS	C	109	67.731	10.962	19.246	1.00	66.14	C	C
ATOM	2313	O	HIS	C	109	66.604	10.768	19.674	1.00	67.21	C	O
ATOM	2314	N	ILE	C	110	68.815	11.022	20.017	1.00	71.63	C	N
ATOM	2315	CA	ILE	C	110	68.762	11.321	21.468	1.00	72.24	C	C
ATOM	2316	CB	ILE	C	110	69.832	10.553	22.309	1.00	70.52	C	C
ATOM	2317	CG1	ILE	C	110	69.964	9.070	21.909	1.00	70.76	C	C
ATOM	2318	CD1	ILE	C	110	69.011	8.121	22.597	1.00	73.76	C	C
ATOM	2319	CG2	ILE	C	110	69.611	10.764	23.813	1.00	67.17	C	C
ATOM	2320	C	ILE	C	110	69.102	12.810	21.494	1.00	72.73	C	C
ATOM	2321	O	ILE	C	110	70.272	13.176	21.626	1.00	69.14	C	O
ATOM	2322	N	ARG	C	111	68.111	13.673	21.302	1.00	75.87	C	N
ATOM	2323	CA	ARG	C	111	68.449	15.058	20.970	1.00	79.41	C	C
ATOM	2324	CB	ARG	C	111	67.353	15.761	20.095	1.00	83.58	C	C
ATOM	2325	CG	ARG	C	111	67.686	15.825	18.601	1.00	87.57	C	C
ATOM	2326	CD	ARG	C	111	66.742	16.748	17.800	1.00	95.94	C	C
ATOM	2327	NE	ARG	C	111	67.474	17.732	16.987	1.00	102.55	C	N
ATOM	2328	CZ	ARG	C	111	68.112	18.811	17.450	1.00	100.80	C	C
ATOM	2329	NH1	ARG	C	111	68.144	19.078	18.749	1.00	98.59	C	N
ATOM	2330	NH2	ARG	C	111	68.734	19.630	16.601	1.00	100.22	C	N
ATOM	2331	C	ARG	C	111	68.835	15.838	22.241	1.00	76.36	C	C
ATOM	2332	O	ARG	C	111	68.415	15.469	23.338	1.00	70.95	C	O
ATOM	2333	N	LYS	C	112	69.681	16.867	22.128	1.00	76.98	C	N
ATOM	2334	CA	LYS	C	112	70.182	17.399	20.819	1.00	78.13	C	C
ATOM	2335	CB	LYS	C	112	70.644	18.879	20.905	1.00	84.18	C	C
ATOM	2336	CG	LYS	C	112	69.727	19.817	21.676	1.00	86.47	C	C
ATOM	2337	CD	LYS	C	112	70.331	21.181	22.068	1.00	91.33	C	C
ATOM	2338	CE	LYS	C	112	71.464	21.724	21.161	1.00	92.55	C	C
ATOM	2339	NZ	LYS	C	112	70.984	22.186	19.825	1.00	93.20	C	N
ATOM	2340	C	LYS	C	112	71.309	16.579	20.119	1.00	70.16	C	C
ATOM	2341	O	LYS	C	112	71.859	17.036	19.108	1.00	68.67	C	O
ATOM	2342	N	GLU	C	113	71.633	15.397	20.652	1.00	65.37	C	N
ATOM	2343	CA	GLU	C	113	72.688	14.501	20.143	1.00	62.33	C	C
ATOM	2344	CB	GLU	C	113	73.436	13.844	21.323	1.00	60.52	C	C
ATOM	2345	C	GLU	C	113	72.179	13.435	19.165	1.00	59.14	C	C
ATOM	2346	O	GLU	C	113	70.987	13.383	18.873	1.00	53.76	C	O
ATOM	2347	N	GLU	C	114	73.125	12.651	18.633	1.00	59.38	C	N
ATOM	2348	CA	GLU	C	114	72.902	11.534	17.710	1.00	59.96	C	C
ATOM	2349	CB	GLU	C	114	73.807	11.676	16.468	1.00	65.55	C	C
ATOM	2350	CG	GLU	C	114	73.125	11.972	15.136	1.00	73.06	C	C
ATOM	2351	CD	GLU	C	114	72.196	13.168	15.222	1.00	82.87	C	C
ATOM	2352	OE1	GLU	C	114	72.573	14.176	15.866	1.00	86.07	C	O
ATOM	2353	OE2	GLU	C	114	71.090	13.099	14.643	1.00	93.14	C	O
ATOM	2354	C	GLU	C	114	73.288	10.228	18.381	1.00	52.35	C	C
ATOM	2355	O	GLU	C	114	74.395	10.110	18.900	1.00	43.54	C	O
ATOM	2356	N	GLY	C	115	72.389	9.247	18.330	1.00	47.49	C	N
ATOM	2357	CA	GLY	C	115	72.669	7.907	18.829	1.00	45.36	C	C
ATOM	2358	C	GLY	C	115	71.951	6.897	17.983	1.00	42.67	C	C
ATOM	2359	O	GLY	C	115	71.672	7.163	16.827	1.00	45.52	C	O
ATOM	2360	N	SER	C	116	71.611	5.758	18.568	1.00	39.95	C	N
ATOM	2361	CA	SER	C	116	71.053	4.665	17.793	1.00	39.66	C	C
ATOM	2362	CB	SER	C	116	72.216	3.906	17.141	1.00	41.96	C	C
ATOM	2363	OG	SER	C	116	73.079	3.342	18.108	1.00	39.16	C	O
ATOM	2364	C	SER	C	116	70.235	3.692	18.643	1.00	38.29	C	C
ATOM	2365	O	SER	C	116	70.425	3.625	19.837	1.00	37.08	C	O
ATOM	2366	N	PHE	C	117	69.317	2.961	18.016	1.00	37.88	C	N
ATOM	2367	CA	PHE	C	117	68.741	1.733	18.588	1.00	36.25	C	C
ATOM	2368	CB	PHE	C	117	67.338	1.439	18.058	1.00	35.80	C	C
ATOM	2369	CG	PHE	C	117	66.298	2.427	18.479	1.00	38.70	C	C
ATOM	2370	CD1	PHE	C	117	66.025	2.638	19.827	1.00	39.63	C	C

【圖1】(續)

ATOM	2371	CE1	PHE	C	117	65.059	3.557	20.220	1.00	37.78	C	C
ATOM	2372	CZ	PHE	C	117	64.351	4.277	19.276	1.00	37.38	C	C
ATOM	2373	CE2	PHE	C	117	64.603	4.075	17.925	1.00	37.94	C	C
ATOM	2374	CD2	PHE	C	117	65.561	3.143	17.532	1.00	38.85	C	C
ATOM	2375	C	PHE	C	117	69.623	0.591	18.108	1.00	36.84	C	C
ATOM	2376	O	PHE	C	117	69.770	0.401	16.917	1.00	37.40	C	O
ATOM	2377	N	GLN	C	118	70.216	-0.175	19.007	1.00	38.62	C	N
ATOM	2378	CA	GLN	C	118	71.026	-1.295	18.569	1.00	38.52	C	C
ATOM	2379	CB	GLN	C	118	72.476	-0.876	18.392	1.00	39.55	C	C
ATOM	2380	CG	GLN	C	118	73.105	-0.308	19.638	1.00	41.07	C	C
ATOM	2381	CD	GLN	C	118	74.461	0.286	19.340	1.00	45.64	C	C
ATOM	2382	OE1	GLN	C	118	75.431	-0.435	19.105	1.00	49.52	C	O
ATOM	2383	NE2	GLN	C	118	74.531	1.606	19.282	1.00	48.97	C	N
ATOM	2384	C	GLN	C	118	70.946	-2.498	19.490	1.00	37.65	C	C
ATOM	2385	O	GLN	C	118	70.614	-2.396	20.654	1.00	36.37	C	O
ATOM	2386	N	SER	C	119	71.308	-3.641	18.933	1.00	35.58	C	N
ATOM	2387	CA	SER	C	119	71.187	-4.874	19.619	1.00	32.80	C	C
ATOM	2388	CB	SER	C	119	69.753	-5.376	19.555	1.00	36.60	C	C
ATOM	2389	OG	SER	C	119	69.664	-6.662	20.140	1.00	40.08	C	O
ATOM	2390	C	SER	C	119	72.085	-5.840	18.943	1.00	30.54	C	C
ATOM	2391	O	SER	C	119	72.278	-5.811	17.754	1.00	28.15	C	O
ATOM	2392	N	CYS	C	120	72.645	-6.718	19.740	1.00	34.51	C	N
ATOM	2393	CA	CYS	C	120	73.492	-7.791	19.242	1.00	34.48	C	C
ATOM	2394	CB	CYS	C	120	74.943	-7.341	19.101	1.00	33.25	C	C
ATOM	2395	SG	CYS	C	120	75.986	-8.591	18.301	1.00	37.97	C	S
ATOM	2396	C	CYS	C	120	73.377	-8.922	20.242	1.00	32.36	C	C
ATOM	2397	O	CYS	C	120	73.511	-8.710	21.445	1.00	30.81	C	O
ATOM	2398	N	SER	C	121	73.072	-10.109	19.750	1.00	30.66	C	N
ATOM	2399	CA	SER	C	121	72.986	-11.259	20.604	1.00	30.91	C	C
ATOM	2400	CB	SER	C	121	71.604	-11.892	20.503	1.00	30.74	C	C
ATOM	2401	OG	SER	C	121	70.659	-11.060	21.147	1.00	30.70	C	O
ATOM	2402	C	SER	C	121	74.079	-12.214	20.225	1.00	30.09	C	C
ATOM	2403	O	SER	C	121	74.623	-12.154	19.138	1.00	29.21	C	O
ATOM	2404	N	PHE	C	122	74.362	-13.116	21.141	1.00	31.05	C	N
ATOM	2405	CA	PHE	C	122	75.539	-13.955	21.088	1.00	32.52	C	C
ATOM	2406	CB	PHE	C	122	76.495	-13.427	22.166	1.00	34.27	C	C
ATOM	2407	CG	PHE	C	122	77.837	-14.108	22.227	1.00	33.28	C	C
ATOM	2408	CD1	PHE	C	122	78.138	-15.234	21.485	1.00	30.83	C	C
ATOM	2409	CE1	PHE	C	122	79.385	-15.831	21.576	1.00	30.95	C	C
ATOM	2410	CZ	PHE	C	122	80.329	-15.330	22.445	1.00	32.27	C	C
ATOM	2411	CE2	PHE	C	122	80.040	-14.209	23.202	1.00	34.67	C	C
ATOM	2412	CD2	PHE	C	122	78.802	-13.600	23.089	1.00	34.66	C	C
ATOM	2413	C	PHE	C	122	75.066	-15.357	21.421	1.00	31.07	C	C
ATOM	2414	O	PHE	C	122	74.533	-15.582	22.522	1.00	29.37	C	O
ATOM	2415	N	CYS	C	123	75.228	-16.290	20.486	1.00	30.51	C	N
ATOM	2416	CA	CYS	C	123	74.872	-17.681	20.760	1.00	32.99	C	C
ATOM	2417	CB	CYS	C	123	74.744	-18.491	19.464	1.00	34.40	C	C
ATOM	2418	SG	CYS	C	123	74.504	-20.273	19.722	1.00	38.45	C	S
ATOM	2419	C	CYS	C	123	75.920	-18.265	21.718	1.00	31.15	C	C
ATOM	2420	O	CYS	C	123	77.049	-18.487	21.328	1.00	31.38	C	O
ATOM	2421	N	LYS	C	124	75.541	-18.466	22.977	1.00	31.07	C	N
ATOM	2422	CA	LYS	C	124	76.487	-18.817	24.037	1.00	32.23	C	C
ATOM	2423	CB	LYS	C	124	77.160	-17.551	24.542	1.00	35.69	C	C
ATOM	2424	CG	LYS	C	124	76.215	-16.723	25.402	1.00	41.22	C	C
ATOM	2425	CD	LYS	C	124	76.744	-15.341	25.670	1.00	45.71	C	C
ATOM	2426	CE	LYS	C	124	77.895	-15.379	26.658	1.00	49.55	C	C
ATOM	2427	NZ	LYS	C	124	77.819	-14.170	27.518	1.00	56.21	C	N
ATOM	2428	C	LYS	C	124	75.755	-19.504	25.206	1.00	30.55	C	C
ATOM	2429	O	LYS	C	124	74.525	-19.573	25.210	1.00	29.56	C	O
ATOM	2430	N	PRO	C	125	76.497	-19.950	26.236	1.00	30.15	C	N
ATOM	2431	CA	PRO	C	125	75.850	-20.619	27.371	1.00	31.77	C	C
ATOM	2432	CB	PRO	C	125	77.031	-21.037	28.240	1.00	30.98	C	C
ATOM	2433	CG	PRO	C	125	78.136	-21.219	27.273	1.00	31.08	C	C
ATOM	2434	CD	PRO	C	125	77.961	-20.085	26.312	1.00	30.45	C	C
ATOM	2435	C	PRO	C	125	74.907	-19.740	28.184	1.00	32.55	C	C
ATOM	2436	O	PRO	C	125	75.249	-18.623	28.523	1.00	30.12	C	O
ATOM	2437	N	LYS	C	126	73.713	-20.250	28.442	1.00	35.95	C	N
ATOM	2438	CA	LYS	C	126	72.768	-19.606	29.339	1.00	42.00	C	C

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ATOM   2439  CB  LYS C 126      71.340 -19.899  28.912  1.00 45.69      C    C
ATOM   2440  CG  LYS C 126      70.289 -19.219  29.772  1.00 52.92      C    C
ATOM   2441  CD  LYS C 126      68.950 -19.044  29.040  1.00 61.15      C    C
ATOM   2442  CE  LYS C 126      67.791 -19.842  29.655  1.00 64.45      C    C
ATOM   2443  NZ  LYS C 126      66.825 -18.933  30.341  1.00 67.74      C    N
ATOM   2444  C   LYS C 126      72.985 -20.129  30.754  1.00 43.96      C    C
ATOM   2445  O   LYS C 126      72.966 -19.367  31.716  1.00 35.89      C    O
ATOM   2446  N   LYS C 127      73.166 -21.441  30.869  1.00 47.35      C    N
ATOM   2447  CA  LYS C 127      73.450 -22.059  32.143  1.00 50.62      C    C
ATOM   2448  CB  LYS C 127      72.266 -22.897  32.614  1.00 57.05      C    C
ATOM   2449  CG  LYS C 127      70.892 -22.340  32.285  1.00 62.11      C    C
ATOM   2450  CD  LYS C 127      69.773 -23.188  32.885  1.00 67.54      C    C
ATOM   2451  CE  LYS C 127      69.211 -22.558  34.153  1.00 72.56      C    C
ATOM   2452  NZ  LYS C 127      68.273 -21.447  33.835  1.00 73.42      C    N
ATOM   2453  C   LYS C 127      74.669 -22.955  32.044  1.00 47.46      C    C
ATOM   2454  O   LYS C 127      74.827 -23.698  31.066  1.00 49.77      C    O
ATOM   2455  N   PHE C 128      75.511 -22.890  33.069  1.00 42.92      C    N
ATOM   2456  CA  PHE C 128      76.558 -23.871  33.279  1.00 43.19      C    C
ATOM   2457  CB  PHE C 128      77.840 -23.180  33.703  1.00 44.31      C    C
ATOM   2458  CG  PHE C 128      78.420 -22.283  32.654  1.00 45.36      C    C
ATOM   2459  CD1 PHE C 128      77.947 -20.992  32.492  1.00 47.77      C    C
ATOM   2460  CE1 PHE C 128      78.494 -20.151  31.533  1.00 46.98      C    C
ATOM   2461  CZ  PHE C 128      79.523 -20.602  30.729  1.00 45.22      C    C
ATOM   2462  CE2 PHE C 128      80.003 -21.892  30.878  1.00 44.18      C    C
ATOM   2463  CD2 PHE C 128      79.452 -22.726  31.832  1.00 45.27      C    C
ATOM   2464  C   PHE C 128      76.156 -24.879  34.358  1.00 39.76      C    C
ATOM   2465  O   PHE C 128      75.324 -24.590  35.178  1.00 41.15      C    O
ATOM   2466  N   THR C 129      76.759 -26.062  34.335  1.00 39.09      C    N
ATOM   2467  CA  THR C 129      76.569 -27.067  35.374  1.00 41.44      C    C
ATOM   2468  CB  THR C 129      76.074 -28.382  34.768  1.00 46.12      C    C
ATOM   2469  OG1 THR C 129      74.705 -28.231  34.370  1.00 48.16      C    O
ATOM   2470  CG2 THR C 129      76.163 -29.529  35.756  1.00 46.41      C    C
ATOM   2471  C   THR C 129      77.896 -27.288  36.069  1.00 40.47      C    C
ATOM   2472  O   THR C 129      78.944 -27.215  35.440  1.00 42.66      C    O
ATOM   2473  N   THR C 130      77.863 -27.509  37.375  1.00 39.94      C    N
ATOM   2474  CA  THR C 130      79.081 -27.840  38.113  1.00 40.87      C    C
ATOM   2475  CB  THR C 130      79.328 -26.867  39.261  1.00 41.03      C    C
ATOM   2476  OG1 THR C 130      79.796 -25.645  38.713  1.00 44.45      C    O
ATOM   2477  CG2 THR C 130      80.383 -27.384  40.218  1.00 43.81      C    C
ATOM   2478  C   THR C 130      78.948 -29.246  38.638  1.00 39.90      C    C
ATOM   2479  O   THR C 130      77.930 -29.615  39.196  1.00 34.68      C    O
ATOM   2480  N   MET C 131      80.005 -30.018  38.456  1.00 41.64      C    N
ATOM   2481  CA  MET C 131      79.967 -31.421  38.677  1.00 43.28      C    C
ATOM   2482  CB  MET C 131      79.847 -32.005  37.280  1.00 48.76      C    C
ATOM   2483  CG  MET C 131      79.511 -33.478  37.176  1.00 57.26      C    C
ATOM   2484  SD  MET C 131      79.073 -34.029  35.492  1.00 71.78      C    S
ATOM   2485  CE  MET C 131      80.127 -32.980  34.503  1.00 59.43      C    C
ATOM   2486  C   MET C 131      81.242 -31.796  39.440  1.00 38.06      C    C
ATOM   2487  O   MET C 131      82.322 -31.307  39.122  1.00 33.78      C    O
ATOM   2488  N   MET C 132      81.096 -32.543  40.534  1.00 37.55      C    N
ATOM   2489  CA  MET C 132      82.232 -33.273  41.095  1.00 38.31      C    C
ATOM   2490  CB  MET C 132      82.084 -33.592  42.591  1.00 41.39      C    C
ATOM   2491  CG  MET C 132      82.630 -32.574  43.595  1.00 46.57      C    C
ATOM   2492  SD  MET C 132      83.822 -31.345  42.968  1.00 51.79      C    S
ATOM   2493  CE  MET C 132      82.602 -30.163  42.355  1.00 52.94      C    C
ATOM   2494  C   MET C 132      82.263 -34.558  40.318  1.00 33.99      C    C
ATOM   2495  O   MET C 132      81.303 -35.304  40.310  1.00 31.04      C    O
ATOM   2496  N   VAL C 133      83.369 -34.811  39.654  1.00 34.89      C    N
ATOM   2497  CA  VAL C 133      83.538 -36.058  38.929  1.00 37.54      C    C
ATOM   2498  CB  VAL C 133      84.051 -35.783  37.505  1.00 39.05      C    C
ATOM   2499  CG1 VAL C 133      84.357 -37.087  36.795  1.00 40.26      C    C
ATOM   2500  CG2 VAL C 133      83.015 -34.972  36.749  1.00 39.81      C    C
ATOM   2501  C   VAL C 133      84.512 -36.924  39.685  1.00 36.80      C    C
ATOM   2502  O   VAL C 133      85.610 -36.478  40.012  1.00 36.37      C    O
ATOM   2503  N   THR C 134      84.130 -38.167  39.938  1.00 38.85      C    N
ATOM   2504  CA  THR C 134      85.029 -39.060  40.663  1.00 42.18      C    C
ATOM   2505  CB  THR C 134      84.332 -39.936  41.735  1.00 42.31      C    C
ATOM   2506  OG1 THR C 134      84.149 -41.258  41.249  1.00 46.29      C    O
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ATOM   2507  CG2 THR C 134      82.988 -39.357  42.131  1.00 43.79      C    C
ATOM   2508  C   THR C 134      85.819 -39.879  39.647  1.00 41.07      C    C
ATOM   2509  O   THR C 134      85.264 -40.449  38.720  1.00 40.23      C    O
ATOM   2510  N   LEU C 135      87.134 -39.859  39.812  1.00 44.10      C    N
ATOM   2511  CA  LEU C 135      88.061 -40.650  39.029  1.00 44.18      C    C
ATOM   2512  CB  LEU C 135      89.312 -39.836  38.750  1.00 43.81      C    C
ATOM   2513  CG  LEU C 135      89.065 -38.537  38.005  1.00 45.34      C    C
ATOM   2514  CD1 LEU C 135      90.354 -37.739  37.916  1.00 46.51      C    C
ATOM   2515  CD2 LEU C 135      88.505 -38.831  36.629  1.00 47.25      C    C
ATOM   2516  C   LEU C 135      88.442 -41.868  39.849  1.00 45.24      C    C
ATOM   2517  O   LEU C 135      88.473 -41.797  41.072  1.00 42.08      C    O
ATOM   2518  N   ASN C 136      88.671 -42.985  39.165  1.00 49.38      C    N
ATOM   2519  CA  ASN C 136      89.227 -44.201  39.755  1.00 53.22      C    C
ATOM   2520  CB  ASN C 136      88.740 -45.433  38.956  1.00 54.84      C    C
ATOM   2521  CG  ASN C 136      88.947 -46.734  39.696  1.00 57.21      C    C
ATOM   2522  OD1 ASN C 136      89.293 -46.752  40.880  1.00 64.44      C    O
ATOM   2523  ND2 ASN C 136      88.797 -47.837  38.977  1.00 54.51      C    N
ATOM   2524  C   ASN C 136      90.743 -44.161  39.721  1.00 49.94      C    C
ATOM   2525  O   ASN C 136      91.339 -44.001  38.651  1.00 49.40      C    O
ATOM   2526  N   CYS C 137      91.356 -44.355  40.882  1.00 50.53      C    N
ATOM   2527  CA  CYS C 137      92.809 -44.335  41.018  1.00 57.86      C    C
ATOM   2528  CB  CYS C 137      93.245 -43.050  41.752  1.00 59.27      C    C
ATOM   2529  SG  CYS C 137      92.210 -41.618  41.353  1.00 62.11      C    S
ATOM   2530  C   CYS C 137      93.201 -45.618  41.773  1.00 55.70      C    C
ATOM   2531  O   CYS C 137      93.372 -45.590  42.987  1.00 46.84      C    O
ATOM   2532  N   PRO C 138      93.303 -46.759  41.049  1.00 57.24      C    N
ATOM   2533  CA  PRO C 138      93.467 -48.078  41.679  1.00 57.64      C    C
ATOM   2534  CB  PRO C 138      93.494 -49.032  40.485  1.00 58.84      C    C
ATOM   2535  CG  PRO C 138      92.795 -48.304  39.394  1.00 55.35      C    C
ATOM   2536  CD  PRO C 138      93.190 -46.879  39.585  1.00 56.37      C    C
ATOM   2537  C   PRO C 138      94.746 -48.223  42.487  1.00 58.32      C    C
ATOM   2538  O   PRO C 138      94.789 -48.971  43.472  1.00 51.06      C    O
ATOM   2539  N   GLU C 139      95.775 -47.484  42.096  1.00 64.44      C    N
ATOM   2540  CA  GLU C 139      97.032 -47.551  42.832  1.00 76.31      C    C
ATOM   2541  CB  GLU C 139      98.173 -46.870  42.045  1.00 85.94      C    C
ATOM   2542  CG  GLU C 139      98.241 -47.164  40.523  1.00 92.59      C    C
ATOM   2543  CD  GLU C 139      98.209 -48.661  40.205  1.00 95.81      C    C
ATOM   2544  OE1 GLU C 139      98.447 -49.494  41.116  1.00 99.16      C    O
ATOM   2545  OE2 GLU C 139      97.944 -49.013  39.036  1.00 89.83      C    O
ATOM   2546  C   GLU C 139      96.939 -46.942  44.244  1.00 69.71      C    C
ATOM   2547  O   GLU C 139      97.664 -47.352  45.165  1.00 68.84      C    O
ATOM   2548  N   LEU C 140      96.002 -46.019  44.416  1.00 58.69      C    N
ATOM   2549  CA  LEU C 140      96.054 -45.083  45.495  1.00 52.30      C    C
ATOM   2550  CB  LEU C 140      95.688 -43.711  44.968  1.00 54.59      C    C
ATOM   2551  CG  LEU C 140      96.638 -43.115  43.903  1.00 57.60      C    C
ATOM   2552  CD1 LEU C 140      96.154 -41.730  43.476  1.00 59.66      C    C
ATOM   2553  CD2 LEU C 140      98.082 -43.023  44.374  1.00 57.17      C    C
ATOM   2554  C   LEU C 140      95.164 -45.442  46.660  1.00 48.59      C    C
ATOM   2555  O   LEU C 140      94.258 -46.257  46.527  1.00 43.71      C    O
ATOM   2556  N   GLN C 141      95.496 -44.847  47.809  1.00 47.32      C    N
ATOM   2557  CA  GLN C 141      94.668 -44.858  48.992  1.00 47.62      C    C
ATOM   2558  CB  GLN C 141      95.371 -45.567  50.150  1.00 51.12      C    C
ATOM   2559  CG  GLN C 141      94.445 -45.915  51.313  1.00 53.24      C    C
ATOM   2560  CD  GLN C 141      93.349 -46.904  50.901  1.00 57.83      C    C
ATOM   2561  OE1 GLN C 141      93.599 -47.852  50.145  1.00 56.51      C    O
ATOM   2562  NE2 GLN C 141      92.128 -46.680  51.391  1.00 54.21      C    N
ATOM   2563  C   GLN C 141      94.391 -43.399  49.368  1.00 46.10      C    C
ATOM   2564  O   GLN C 141      95.320 -42.665  49.660  1.00 44.68      C    O
ATOM   2565  N   PRO C 142      93.120 -42.955  49.297  1.00 48.52      C    N
ATOM   2566  CA  PRO C 142      91.955 -43.731  48.867  1.00 48.89      C    C
ATOM   2567  CB  PRO C 142      90.777 -42.885  49.328  1.00 48.00      C    C
ATOM   2568  CG  PRO C 142      91.303 -41.489  49.399  1.00 48.21      C    C
ATOM   2569  CD  PRO C 142      92.807 -41.517  49.354  1.00 47.86      C    C
ATOM   2570  C   PRO C 142      91.943 -43.860  47.352  1.00 49.67      C    C
ATOM   2571  O   PRO C 142      92.589 -43.061  46.665  1.00 46.11      C    O
ATOM   2572  N   PRO C 143      91.207 -44.846  46.828  1.00 54.52      C    N
ATOM   2573  CA  PRO C 143      91.295 -45.184  45.395  1.00 58.89      C    C
ATOM   2574  CB  PRO C 143      90.854 -46.664  45.345  1.00 60.33      C    C
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ATOM   2575  CG  PRO C 143      90.102 -46.906  46.629  1.00 61.21      C    C
ATOM   2576  CD  PRO C 143      90.238 -45.701  47.537  1.00 58.17      C    C
ATOM   2577  C   PRO C 143      90.404 -44.326  44.487  1.00 59.72      C    C
ATOM   2578  O   PRO C 143      90.027 -44.758  43.383  1.00 60.29      C    O
ATOM   2579  N   THR C 144      90.070 -43.132  44.973  1.00 61.16      C    N
ATOM   2580  CA  THR C 144      89.148 -42.211  44.335  1.00 56.51      C    C
ATOM   2581  CB  THR C 144      87.772 -42.297  45.027  1.00 56.21      C    C
ATOM   2582  OG1 THR C 144      87.302 -43.648  45.044  1.00 57.95      C    O
ATOM   2583  CG2 THR C 144      86.742 -41.434  44.342  1.00 61.44      C    C
ATOM   2584  C   THR C 144      89.646 -40.793  44.541  1.00 52.92      C    C
ATOM   2585  O   THR C 144      90.014 -40.444  45.644  1.00 53.50      C    O
ATOM   2586  N   LYS C 145      89.670 -39.992  43.484  1.00 53.69      C    N
ATOM   2587  CA  LYS C 145      89.831 -38.551  43.580  1.00 56.03      C    C
ATOM   2588  CB  LYS C 145      91.079 -38.087  42.842  1.00 57.20      C    C
ATOM   2589  CG  LYS C 145      92.387 -38.552  43.484  1.00 65.94      C    C
ATOM   2590  CD  LYS C 145      93.421 -37.437  43.643  1.00 73.66      C    C
ATOM   2591  CE  LYS C 145      94.832 -37.992  43.852  1.00 76.93      C    C
ATOM   2592  NZ  LYS C 145      95.755 -37.045  44.543  1.00 77.90      C    N
ATOM   2593  C   LYS C 145      88.607 -37.943  42.931  1.00 53.74      C    C
ATOM   2594  O   LYS C 145      88.143 -38.447  41.922  1.00 54.45      C    O
ATOM   2595  N   LYS C 146      88.072 -36.882  43.514  1.00 52.35      C    N
ATOM   2596  CA  LYS C 146      86.995 -36.134  42.871  1.00 50.86      C    C
ATOM   2597  CB  LYS C 146      85.906 -35.752  43.859  1.00 54.41      C    C
ATOM   2598  CG  LYS C 146      84.932 -36.884  44.173  1.00 60.26      C    C
ATOM   2599  CD  LYS C 146      84.345 -36.747  45.584  1.00 65.56      C    C
ATOM   2600  CE  LYS C 146      82.997 -36.013  45.587  1.00 69.80      C    C
ATOM   2601  NZ  LYS C 146      82.669 -35.386  46.911  1.00 71.67      C    N
ATOM   2602  C   LYS C 146      87.611 -34.905  42.243  1.00 46.23      C    C
ATOM   2603  O   LYS C 146      88.384 -34.226  42.892  1.00 44.64      C    O
ATOM   2604  N   LYS C 147      87.254 -34.627  40.992  1.00 44.36      C    N
ATOM   2605  CA  LYS C 147      87.750 -33.462  40.270  1.00 44.88      C    C
ATOM   2606  CB  LYS C 147      88.471 -33.871  38.981  1.00 48.86      C    C
ATOM   2607  CG  LYS C 147      89.089 -32.719  38.159  1.00 49.98      C    C
ATOM   2608  CD  LYS C 147      90.590 -32.564  38.379  1.00 54.73      C    C
ATOM   2609  CE  LYS C 147      91.137 -31.274  37.776  1.00 61.06      C    C
ATOM   2610  NZ  LYS C 147      91.183 -30.169  38.777  1.00 63.03      C    N
ATOM   2611  C   LYS C 147      86.587 -32.552  39.927  1.00 44.64      C    C
ATOM   2612  O   LYS C 147      85.530 -32.989  39.475  1.00 43.34      C    O
ATOM   2613  N   ARG C 148      86.788 -31.264  40.124  1.00 44.93      C    N
ATOM   2614  CA  ARG C 148      85.794 -30.287  39.713  1.00 45.93      C    C
ATOM   2615  CB  ARG C 148      86.003 -28.968  40.395  1.00 49.81      C    C
ATOM   2616  CG  ARG C 148      84.698 -28.395  40.770  1.00 52.29      C    C
ATOM   2617  CD  ARG C 148      84.740 -26.925  40.784  1.00 56.18      C    C
ATOM   2618  NE  ARG C 148      84.936 -26.427  39.441  1.00 58.80      C    N
ATOM   2619  CZ  ARG C 148      84.702 -25.166  39.120  1.00 70.18      C    C
ATOM   2620  NH1 ARG C 148      84.215 -24.310  40.027  1.00 62.17      C    N
ATOM   2621  NH2 ARG C 148      84.932 -24.761  37.881  1.00 78.81      C    N
ATOM   2622  C   ARG C 148      85.810 -29.995  38.221  1.00 43.64      C    C
ATOM   2623  O   ARG C 148      86.874 -29.734  37.653  1.00 40.88      C    O
ATOM   2624  N   VAL C 149      84.616 -29.983  37.632  1.00 41.35      C    N
ATOM   2625  CA  VAL C 149      84.434 -29.542  36.279  1.00 40.58      C    C
ATOM   2626  CB  VAL C 149      84.492 -30.742  35.331  1.00 43.60      C    C
ATOM   2627  CG1 VAL C 149      83.781 -31.928  35.939  1.00 45.71      C    C
ATOM   2628  CG2 VAL C 149      83.892 -30.398  33.977  1.00 43.96      C    C
ATOM   2629  C   VAL C 149      83.117 -28.757  36.092  1.00 40.38      C    C
ATOM   2630  O   VAL C 149      82.060 -29.169  36.528  1.00 39.01      C    O
ATOM   2631  N   THR C 150      83.207 -27.618  35.418  1.00 43.25      C    N
ATOM   2632  CA  THR C 150      82.034 -26.812  35.068  1.00 44.59      C    C
ATOM   2633  CB  THR C 150      82.285 -25.286  35.170  1.00 46.58      C    C
ATOM   2634  OG1 THR C 150      83.537 -25.005  34.553  1.00 49.11      C    O
ATOM   2635  CG2 THR C 150      82.333 -24.816  36.608  1.00 44.40      C    C
ATOM   2636  C   THR C 150      81.789 -27.065  33.605  1.00 42.14      C    C
ATOM   2637  O   THR C 150      82.696 -26.919  32.824  1.00 40.73      C    O
ATOM   2638  N   ARG C 151      80.574 -27.426  33.220  1.00 42.32      C    N
ATOM   2639  CA  ARG C 151      80.280 -27.710  31.824  1.00 40.40      C    C
ATOM   2640  CB  ARG C 151      79.992 -29.200  31.645  1.00 41.94      C    C
ATOM   2641  CG  ARG C 151      78.554 -29.578  31.910  1.00 43.69      C    C
ATOM   2642  CD  ARG C 151      78.279 -30.880  32.603  1.00 47.67      C    C
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ATOM   2643  NE  ARG C 151      78.711 -32.083  31.941  1.00 49.34      C    N
ATOM   2644  CZ  ARG C 151      78.014 -33.218  31.983  1.00 53.84      C    C
ATOM   2645  NH1 ARG C 151      76.827 -33.283  32.591  1.00 52.86      C    N
ATOM   2646  NH2 ARG C 151      78.495 -34.295  31.393  1.00 56.75      C    N
ATOM   2647  C   ARG C 151      79.096 -26.882  31.371  1.00 38.48      C    C
ATOM   2648  O   ARG C 151      78.309 -26.386  32.191  1.00 36.13      C    O
ATOM   2649  N   VAL C 152      78.972 -26.734  30.060  1.00 38.20      C    N
ATOM   2650  CA  VAL C 152      77.883 -25.966  29.486  1.00 40.21      C    C
ATOM   2651  CB  VAL C 152      78.183 -25.571  28.024  1.00 38.83      C    C
ATOM   2652  CG1 VAL C 152      76.955 -24.970  27.349  1.00 41.71      C    C
ATOM   2653  CG2 VAL C 152      79.338 -24.589  27.970  1.00 37.90      C    C
ATOM   2654  C   VAL C 152      76.638 -26.818  29.546  1.00 40.68      C    C
ATOM   2655  O   VAL C 152      76.696 -27.999  29.275  1.00 35.76      C    O
ATOM   2656  N   LYS C 153      75.512 -26.212  29.907  1.00 45.21      C    N
ATOM   2657  CA  LYS C 153      74.258 -26.934  29.931  1.00 49.59      C    C
ATOM   2658  CB  LYS C 153      73.445 -26.565  31.156  1.00 52.91      C    C
ATOM   2659  CG  LYS C 153      72.185 -27.422  31.264  1.00 54.33      C    C
ATOM   2660  CD  LYS C 153      72.234 -28.219  32.522  1.00 57.77      C    C
ATOM   2661  CE  LYS C 153      70.836 -28.479  33.002  1.00 59.11      C    C
ATOM   2662  NZ  LYS C 153      70.241 -27.295  33.684  1.00 63.43      C    N
ATOM   2663  C   LYS C 153      73.437 -26.614  28.707  1.00 48.20      C    C
ATOM   2664  O   LYS C 153      73.039 -27.507  27.983  1.00 50.72      C    O
ATOM   2665  N   GLN C 154      73.139 -25.337  28.523  1.00 48.78      C    N
ATOM   2666  CA  GLN C 154      72.200 -24.912  27.499  1.00 51.31      C    C
ATOM   2667  CB  GLN C 154      70.817 -24.691  28.143  1.00 57.15      C    C
ATOM   2668  CG  GLN C 154      69.651 -24.586  27.206  1.00 64.35      C    C
ATOM   2669  CD  GLN C 154      68.478 -23.646  27.651  1.00 72.48      C    C
ATOM   2670  OE1 GLN C 154      68.272 -23.313  28.840  1.00 74.29      C    O
ATOM   2671  NE2 GLN C 154      67.698 -23.221  26.660  1.00 73.71      C    N
ATOM   2672  C   GLN C 154      72.718 -23.632  26.839  1.00 49.04      C    C
ATOM   2673  O   GLN C 154      73.090 -22.676  27.529  1.00 46.97      C    O
ATOM   2674  N   CYS C 155      72.759 -23.627  25.508  1.00 44.58      C    N
ATOM   2675  CA  CYS C 155      73.091 -22.419  24.757  1.00 42.04      C    C
ATOM   2676  CB  CYS C 155      73.917 -22.760  23.528  1.00 39.02      C    C
ATOM   2677  SG  CYS C 155      75.343 -23.768  23.909  1.00 42.03      C    S
ATOM   2678  C   CYS C 155      71.848 -21.667  24.298  1.00 39.97      C    C
ATOM   2679  O   CYS C 155      70.789 -22.236  24.095  1.00 36.50      C    O
ATOM   2680  N   ARG C 156      71.999 -20.370  24.119  1.00 40.84      C    N
ATOM   2681  CA  ARG C 156      70.924 -19.563  23.602  1.00 42.52      C    C
ATOM   2682  CB  ARG C 156      69.872 -19.322  24.687  1.00 47.28      C    C
ATOM   2683  CG  ARG C 156      68.640 -20.206  24.613  1.00 53.28      C    C
ATOM   2684  CD  ARG C 156      67.630 -19.723  25.651  1.00 65.60      C    C
ATOM   2685  NE  ARG C 156      67.786 -18.279  25.974  1.00 75.90      C    N
ATOM   2686  CZ  ARG C 156      66.807 -17.484  26.404  1.00 80.55      C    C
ATOM   2687  NH1 ARG C 156      65.586 -17.978  26.604  1.00 80.97      C    N
ATOM   2688  NH2 ARG C 156      67.064 -16.194  26.653  1.00 74.58      C    N
ATOM   2689  C   ARG C 156      71.459 -18.249  23.061  1.00 37.65      C    C
ATOM   2690  O   ARG C 156      72.585 -17.857  23.347  1.00 32.73      C    O
ATOM   2691  N   CYS C 157      70.642 -17.607  22.233  1.00 36.20      C    N
ATOM   2692  CA  CYS C 157      70.921 -16.257  21.751  1.00 33.80      C    C
ATOM   2693  CB  CYS C 157      70.020 -15.895  20.573  1.00 33.39      C    C
ATOM   2694  SG  CYS C 157      70.525 -16.651  19.020  1.00 33.33      C    S
ATOM   2695  C   CYS C 157      70.657 -15.305  22.872  1.00 31.67      C    C
ATOM   2696  O   CYS C 157      69.508 -15.050  23.189  1.00 33.05      C    O
ATOM   2697  N   ILE C 158      71.725 -14.799  23.473  1.00 30.60      C    N
ATOM   2698  CA  ILE C 158      71.638 -13.921  24.608  1.00 30.25      C    C
ATOM   2699  CB  ILE C 158      72.465 -14.488  25.780  1.00 32.29      C    C
ATOM   2700  CG1 ILE C 158      71.756 -15.725  26.340  1.00 33.36      C    C
ATOM   2701  CD1 ILE C 158      72.675 -16.650  27.121  1.00 34.33      C    C
ATOM   2702  CG2 ILE C 158      72.688 -13.450  26.883  1.00 32.46      C    C
ATOM   2703  C   ILE C 158      72.146 -12.560  24.202  1.00 30.08      C    C
ATOM   2704  O   ILE C 158      73.242 -12.437  23.658  1.00 34.33      C    O
ATOM   2705  N   SER C 159      71.386 -11.528  24.522  1.00 29.96      C    N
ATOM   2706  CA  SER C 159      71.732 -10.184  24.087  1.00 31.83      C    C
ATOM   2707  CB  SER C 159      70.498  -9.284  24.106  1.00 32.51      C    C
ATOM   2708  OG  SER C 159      70.488  -8.495  25.268  1.00 32.61      C    O
ATOM   2709  C   SER C 159      72.857  -9.561  24.920  1.00 31.44      C    C
ATOM   2710  O   SER C 159      72.992  -9.833  26.091  1.00 33.02      C    O
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ATOM   2711  N   ILE C 160      73.641  -8.703  24.290  1.00 33.93      C    N
ATOM   2712  CA  ILE C 160      74.845  -8.169  24.885  1.00 36.74      C    C
ATOM   2713  CB  ILE C 160      75.967  -8.101  23.812  1.00 39.07      C    C
ATOM   2714  CG1 ILE C 160      76.481  -9.512  23.533  1.00 41.83      C    C
ATOM   2715  CD1 ILE C 160      77.566  -9.572  22.474  1.00 44.33      C    C
ATOM   2716  CG2 ILE C 160      77.150  -7.242  24.256  1.00 40.04      C    C
ATOM   2717  C   ILE C 160      74.864  -6.977  25.819  1.00 39.00      C    C
ATOM   2718  O   ILE C 160      75.741  -6.980  26.654  1.00 46.50      C    O
ATOM   2719  N   ASP C 161      73.994  -5.991  25.842  1.00 40.81      C    N
ATOM   2720  CA  ASP C 161      74.284  -4.924  26.849  1.00 44.96      C    C
ATOM   2721  CB  ASP C 161      74.512  -5.489  28.273  1.00 45.94      C    C
ATOM   2722  CG  ASP C 161      74.844  -4.383  29.309  1.00 51.49      C    C
ATOM   2723  OD1 ASP C 161      75.340  -3.291  28.933  1.00 51.06      C    O
ATOM   2724  OD2 ASP C 161      74.596  -4.604  30.515  1.00 56.26      C    O
ATOM   2725  C   ASP C 161      75.532  -4.173  26.377  1.00 41.31      C    C
ATOM   2726  O   ASP C 161      76.676  -4.450  26.777  1.00 34.03      C    O
ATOM   2727  N   LEU C 162      75.290  -3.215  25.505  1.00 45.13      C    N
ATOM   2728  CA  LEU C 162      76.362  -2.609  24.754  1.00 47.54      C    C
ATOM   2729  CB  LEU C 162      75.873  -2.208  23.364  1.00 46.62      C    C
ATOM   2730  CG  LEU C 162      75.611  -3.471  22.466  1.00 45.77      C    C
ATOM   2731  CD1 LEU C 162      74.693  -3.172  21.290  1.00 44.99      C    C
ATOM   2732  CD2 LEU C 162      76.859  -4.167  21.927  1.00 46.82      C    C
ATOM   2733  C   LEU C 162      76.946  -1.461  25.565  1.00 49.32      C    C
ATOM   2734  O   LEU C 162      77.662  -1.710  26.503  1.00 52.60      C    O
ATOM   2735  N   ASP C 163      76.596  -0.227  25.266  1.00 53.34      C    N
ATOM   2736  CA  ASP C 163      77.539   0.925  25.428  1.00 58.37      C    C
ATOM   2737  CB  ASP C 163      78.669   0.708  26.478  1.00 53.44      C    C
ATOM   2738  CG  ASP C 163      78.135   0.416  27.882  1.00 57.30      C    C
ATOM   2739  OD1 ASP C 163      77.116  -0.306  28.024  1.00 51.55      C    O
ATOM   2740  OD2 ASP C 163      78.733   0.920  28.854  1.00 59.99      C    O
ATOM   2741  C   ASP C 163      78.161   1.226  24.046  1.00 55.74      C    C
ATOM   2742  O   ASP C 163      77.457   1.386  23.034  1.00 47.23      C    O
ATOM   2743  N   VAL D  52      79.024 -36.545  18.210  1.00 52.25      D    N
ATOM   2744  CA  VAL D  52      79.800 -36.073  19.371  1.00 50.19      D    C
ATOM   2745  CB  VAL D  52      79.715 -37.060  20.545  1.00 48.08      D    C
ATOM   2746  CG1 VAL D  52      80.547 -36.552  21.716  1.00 48.57      D    C
ATOM   2747  CG2 VAL D  52      78.269 -37.265  20.960  1.00 47.24      D    C
ATOM   2748  C   VAL D  52      81.260 -35.903  18.992  1.00 50.80      D    C
ATOM   2749  O   VAL D  52      81.972 -36.871  18.826  1.00 51.57      D    O
ATOM   2750  N   LEU D  53      81.700 -34.657  18.901  1.00 51.72      D    N
ATOM   2751  CA  LEU D  53      83.015 -34.325  18.381  1.00 50.14      D    C
ATOM   2752  CB  LEU D  53      83.088 -32.849  18.058  1.00 50.33      D    C
ATOM   2753  CG  LEU D  53      82.216 -32.477  16.845  1.00 48.43      D    C
ATOM   2754  CD1 LEU D  53      80.719 -32.675  17.049  1.00 47.82      D    C
ATOM   2755  CD2 LEU D  53      82.529 -31.037  16.489  1.00 49.70      D    C
ATOM   2756  C   LEU D  53      84.035 -34.652  19.421  1.00 49.78      D    C
ATOM   2757  O   LEU D  53      83.722 -34.704  20.603  1.00 56.48      D    O
ATOM   2758  N   GLU D  54      85.259 -34.865  18.981  1.00 48.77      D    N
ATOM   2759  CA  GLU D  54      86.266 -35.402  19.862  1.00 51.63      D    C
ATOM   2760  CB  GLU D  54      87.307 -36.180  19.059  1.00 57.04      D    C
ATOM   2761  CG  GLU D  54      86.728 -37.281  18.149  1.00 62.49      D    C
ATOM   2762  CD  GLU D  54      85.800 -38.253  18.890  1.00 67.06      D    C
ATOM   2763  OE1 GLU D  54      86.171 -38.752  19.971  1.00 68.26      D    O
ATOM   2764  OE2 GLU D  54      84.674 -38.513  18.399  1.00 71.87      D    O
ATOM   2765  C   GLU D  54      86.999 -34.379  20.673  1.00 48.48      D    C
ATOM   2766  O   GLU D  54      87.445 -34.691  21.757  1.00 51.05      D    O
ATOM   2767  N   SER D  55      87.186 -33.187  20.137  1.00 46.15      D    N
ATOM   2768  CA  SER D  55      87.998 -32.196  20.817  1.00 47.46      D    C
ATOM   2769  CB  SER D  55      89.501 -32.353  20.446  1.00 45.97      D    C
ATOM   2770  OG  SER D  55      89.816 -31.655  19.255  1.00 45.44      D    O
ATOM   2771  C   SER D  55      87.496 -30.796  20.462  1.00 48.18      D    C
ATOM   2772  O   SER D  55      86.654 -30.631  19.582  1.00 50.35      D    O
ATOM   2773  N   SER D  56      88.041 -29.794  21.143  1.00 47.21      D    N
ATOM   2774  CA  SER D  56      87.665 -28.416  20.905  1.00 45.51      D    C
ATOM   2775  CB  SER D  56      88.246 -27.528  21.983  1.00 45.06      D    C
ATOM   2776  OG  SER D  56      87.821 -27.965  23.254  1.00 44.29      D    O
ATOM   2777  C   SER D  56      88.168 -27.920  19.573  1.00 48.69      D    C
ATOM   2778  O   SER D  56      87.437 -27.247  18.854  1.00 52.47      D    O
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ATOM   2779  N   GLN D  57      89.425 -28.243  19.269  1.00 51.31      D    N
ATOM   2780  CA  GLN D  57      90.041 -27.980  17.961  1.00 52.05      D    C
ATOM   2781  CB  GLN D  57      91.508 -28.458  17.957  1.00 54.69      D    C
ATOM   2782  CG  GLN D  57      92.458 -27.545  18.763  1.00 58.16      D    C
ATOM   2783  CD  GLN D  57      92.491 -27.872  20.270  1.00 63.53      D    C
ATOM   2784  OE1 GLN D  57      92.189 -28.995  20.685  1.00 64.80      D    O
ATOM   2785  NE2 GLN D  57      92.853 -26.880  21.090  1.00 64.91      D    N
ATOM   2786  C   GLN D  57      89.168 -28.536  16.813  1.00 49.83      D    C
ATOM   2787  O   GLN D  57      88.891 -27.847  15.828  1.00 48.32      D    O
ATOM   2788  N   GLU D  58      88.625 -29.727  16.991  1.00 48.08      D    N
ATOM   2789  CA  GLU D  58      87.779 -30.298  15.965  1.00 51.71      D    C
ATOM   2790  CB  GLU D  58      87.486 -31.762  16.267  1.00 54.16      D    C
ATOM   2791  CG  GLU D  58      87.081 -32.576  15.058  1.00 52.09      D    C
ATOM   2792  CD  GLU D  58      86.384 -33.855  15.473  1.00 53.37      D    C
ATOM   2793  OE1 GLU D  58      86.565 -34.287  16.635  1.00 51.66      D    O
ATOM   2794  OE2 GLU D  58      85.670 -34.449  14.643  1.00 58.39      D    O
ATOM   2795  C   GLU D  58      86.481 -29.526  15.878  1.00 51.55      D    C
ATOM   2796  O   GLU D  58      86.033 -29.179  14.789  1.00 54.36      D    O
ATOM   2797  N   ALA D  59      85.869 -29.274  17.028  1.00 50.81      D    N
ATOM   2798  CA  ALA D  59      84.618 -28.531  17.080  1.00 49.73      D    C
ATOM   2799  CB  ALA D  59      84.125 -28.417  18.510  1.00 51.68      D    C
ATOM   2800  C   ALA D  59      84.778 -27.148  16.452  1.00 46.09      D    C
ATOM   2801  O   ALA D  59      83.902 -26.692  15.741  1.00 46.81      D    O
ATOM   2802  N   LEU D  60      85.911 -26.504  16.670  1.00 43.08      D    N
ATOM   2803  CA  LEU D  60      86.151 -25.197  16.053  1.00 44.09      D    C
ATOM   2804  CB  LEU D  60      87.392 -24.536  16.672  1.00 43.72      D    C
ATOM   2805  CG  LEU D  60      87.866 -23.194  16.111  1.00 42.00      D    C
ATOM   2806  CD1 LEU D  60      86.832 -22.133  16.446  1.00 41.74      D    C
ATOM   2807  CD2 LEU D  60      89.225 -22.818  16.686  1.00 41.12      D    C
ATOM   2808  C   LEU D  60      86.258 -25.252  14.524  1.00 43.38      D    C
ATOM   2809  O   LEU D  60      85.594 -24.483  13.824  1.00 45.35      D    O
ATOM   2810  N   HIS D  61      87.057 -26.182  14.014  1.00 47.12      D    N
ATOM   2811  CA  HIS D  61      87.194 -26.385  12.572  1.00 48.04      D    C
ATOM   2812  CB  HIS D  61      88.239 -27.466  12.282  1.00 50.66      D    C
ATOM   2813  CG  HIS D  61      89.609 -27.101  12.764  1.00 56.28      D    C
ATOM   2814  ND1 HIS D  61      90.598 -28.027  13.046  1.00 59.20      D    N
ATOM   2815  CE1 HIS D  61      91.682 -27.392  13.461  1.00 59.10      D    C
ATOM   2816  NE2 HIS D  61      91.426 -26.093  13.472  1.00 59.32      D    N
ATOM   2817  CD2 HIS D  61      90.139 -25.886  13.045  1.00 57.19      D    C
ATOM   2818  C   HIS D  61      85.854 -26.709  11.917  1.00 48.39      D    C
ATOM   2819  O   HIS D  61      85.462 -26.050  10.952  1.00 49.90      D    O
ATOM   2820  N   VAL D  62      85.119 -27.673  12.460  1.00 46.25      D    N
ATOM   2821  CA  VAL D  62      83.836 -28.033  11.834  1.00 48.23      D    C
ATOM   2822  CB  VAL D  62      83.250 -29.375  12.304  1.00 50.26      D    C
ATOM   2823  CG1 VAL D  62      83.562 -29.607  13.752  1.00 52.39      D    C
ATOM   2824  CG2 VAL D  62      81.742 -29.486  12.054  1.00 52.82      D    C
ATOM   2825  C   VAL D  62      82.817 -26.900  11.953  1.00 49.26      D    C
ATOM   2826  O   VAL D  62      82.044 -26.666  11.035  1.00 53.03      D    O
ATOM   2827  N   THR D  63      82.797 -26.211  13.089  1.00 49.82      D    N
ATOM   2828  CA  THR D  63      81.881 -25.083  13.277  1.00 46.05      D    C
ATOM   2829  CB  THR D  63      82.012 -24.482  14.670  1.00 44.49      D    C
ATOM   2830  OG1 THR D  63      81.529 -25.429  15.620  1.00 45.97      D    O
ATOM   2831  CG2 THR D  63      81.192 -23.229  14.801  1.00 45.49      D    C
ATOM   2832  C   THR D  63      82.118 -23.998  12.258  1.00 47.54      D    C
ATOM   2833  O   THR D  63      81.176 -23.445  11.713  1.00 47.68      D    O
ATOM   2834  N   GLU D  64      83.378 -23.710  11.970  1.00 50.97      D    N
ATOM   2835  CA  GLU D  64      83.695 -22.713  10.952  1.00 50.41      D    C
ATOM   2836  CB  GLU D  64      85.135 -22.208  11.084  1.00 54.22      D    C
ATOM   2837  CG  GLU D  64      85.421 -21.459  12.379  1.00 53.88      D    C
ATOM   2838  CD  GLU D  64      86.902 -21.236  12.601  1.00 58.63      D    C
ATOM   2839  OE1 GLU D  64      87.275 -20.154  13.101  1.00 61.98      D    O
ATOM   2840  OE2 GLU D  64      87.690 -22.161  12.294  1.00 63.12      D    O
ATOM   2841  C   GLU D  64      83.441 -23.213   9.517  1.00 49.15      D    C
ATOM   2842  O   GLU D  64      82.805 -22.516   8.732  1.00 48.19      D    O
ATOM   2843  N   ARG D  65      83.922 -24.404   9.177  1.00 49.97      D    N
ATOM   2844  CA  ARG D  65      83.782 -24.906   7.803  1.00 57.19      D    C
ATOM   2845  CB  ARG D  65      84.710 -26.086   7.488  1.00 59.70      D    C
ATOM   2846  CG  ARG D  65      86.118 -25.645   7.054  1.00 65.96      D    C
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ATOM   2847  CD  ARG D  65      86.922 -24.909   8.169  1.00 70.74      D    C
ATOM   2848  NE  ARG D  65      87.407 -23.586   7.727  1.00 76.13      D    N
ATOM   2849  CZ  ARG D  65      88.293 -22.838   8.388  1.00 76.49      D    C
ATOM   2850  NH1 ARG D  65      88.824 -23.265   9.530  1.00 79.99      D    N
ATOM   2851  NH2 ARG D  65      88.656 -21.656   7.901  1.00 75.24      D    N
ATOM   2852  C   ARG D  65      82.344 -25.300   7.483  1.00 60.50      D    C
ATOM   2853  O   ARG D  65      81.777 -24.814   6.518  1.00 66.58      D    O
ATOM   2854  N   LYS D  66      81.762 -26.166   8.307  1.00 60.72      D    N
ATOM   2855  CA  LYS D  66      80.457 -26.761   8.008  1.00 58.42      D    C
ATOM   2856  CB  LYS D  66      80.376 -28.209   8.493  1.00 63.03      D    C
ATOM   2857  CG  LYS D  66      81.260 -29.111   7.661  1.00 69.57      D    C
ATOM   2858  CD  LYS D  66      81.753 -30.378   8.280  1.00 74.04      D    C
ATOM   2859  CE  LYS D  66      80.612 -31.325   8.598  1.00 75.92      D    C
ATOM   2860  NZ  LYS D  66      81.120 -32.674   8.964  1.00 76.26      D    N
ATOM   2861  C   LYS D  66      79.266 -26.012   8.578  1.00 56.01      D    C
ATOM   2862  O   LYS D  66      78.392 -25.633   7.823  1.00 56.29      D    O
ATOM   2863  N   TYR D  67      79.218 -25.818   9.895  1.00 53.97      D    N
ATOM   2864  CA  TYR D  67      77.967 -25.415  10.551  1.00 56.56      D    C
ATOM   2865  CB  TYR D  67      78.024 -25.641  12.055  1.00 61.39      D    C
ATOM   2866  CG  TYR D  67      78.260 -27.057  12.504  1.00 65.08      D    C
ATOM   2867  CD1 TYR D  67      77.807 -28.144  11.757  1.00 63.36      D    C
ATOM   2868  CE1 TYR D  67      78.014 -29.441  12.191  1.00 65.08      D    C
ATOM   2869  CZ  TYR D  67      78.666 -29.666  13.395  1.00 65.81      D    C
ATOM   2870  OH  TYR D  67      78.877 -30.948  13.838  1.00 62.09      D    O
ATOM   2871  CE2 TYR D  67      79.114 -28.601  14.158  1.00 68.02      D    C
ATOM   2872  CD2 TYR D  67      78.906 -27.309  13.713  1.00 65.92      D    C
ATOM   2873  C   TYR D  67      77.540 -23.969  10.353  1.00 55.42      D    C
ATOM   2874  O   TYR D  67      76.353 -23.682  10.305  1.00 57.93      D    O
ATOM   2875  N   LEU D  68      78.502 -23.063  10.238  1.00 57.18      D    N
ATOM   2876  CA  LEU D  68      78.209 -21.636  10.148  1.00 54.49      D    C
ATOM   2877  CB  LEU D  68      79.033 -20.881  11.173  1.00 52.68      D    C
ATOM   2878  CG  LEU D  68      78.601 -21.118  12.618  1.00 49.65      D    C
ATOM   2879  CD1 LEU D  68      79.499 -20.303  13.524  1.00 49.95      D    C
ATOM   2880  CD2 LEU D  68      77.137 -20.768  12.823  1.00 49.59      D    C
ATOM   2881  C   LEU D  68      78.464 -21.073   8.776  1.00 58.48      D    C
ATOM   2882  O   LEU D  68      79.564 -20.639   8.463  1.00 60.76      D    O
ATOM   2883  N   LYS D  69      77.431 -21.089   7.948  1.00 59.94      D    N
ATOM   2884  CA  LYS D  69      77.503 -20.483   6.631  1.00 58.77      D    C
ATOM   2885  CB  LYS D  69      77.640 -21.558   5.575  1.00 58.62      D    C
ATOM   2886  CG  LYS D  69      78.558 -22.711   5.959  1.00 60.09      D    C
ATOM   2887  CD  LYS D  69      78.558 -23.766   4.870  1.00 60.31      D    C
ATOM   2888  CE  LYS D  69      79.333 -23.303   3.656  1.00 60.98      D    C
ATOM   2889  NZ  LYS D  69      79.405 -24.386   2.643  1.00 63.69      D    N
ATOM   2890  C   LYS D  69      76.259 -19.654   6.417  1.00 56.15      D    C
ATOM   2891  O   LYS D  69      75.321 -19.725   7.202  1.00 56.24      D    O
ATOM   2892  N   ARG D  70      76.272 -18.844   5.371  1.00 58.51      D    N
ATOM   2893  CA  ARG D  70      75.112 -18.075   4.952  1.00 57.79      D    C
ATOM   2894  CB  ARG D  70      73.930 -18.982   4.570  1.00 64.35      D    C
ATOM   2895  CG  ARG D  70      72.954 -19.357   5.724  1.00 75.04      D    C
ATOM   2896  CD  ARG D  70      72.995 -20.807   6.189  1.00 84.29      D    C
ATOM   2897  NE  ARG D  70      71.906 -21.094   7.149  1.00 88.66      D    N
ATOM   2898  CZ  ARG D  70      70.742 -21.704   6.866  1.00 89.45      D    C
ATOM   2899  NH1 ARG D  70      70.455 -22.136   5.637  1.00 88.94      D    N
ATOM   2900  NH2 ARG D  70      69.836 -21.881   7.831  1.00 84.82      D    N
ATOM   2901  C   ARG D  70      74.716 -17.023   5.982  1.00 49.72      D    C
ATOM   2902  O   ARG D  70      73.531 -16.714   6.095  1.00 46.98      D    O
ATOM   2903  N   ASP D  71      75.688 -16.455   6.711  1.00 43.72      D    N
ATOM   2904  CA  ASP D  71      75.383 -15.305   7.557  1.00 44.06      D    C
ATOM   2905  CB  ASP D  71      76.533 -14.913   8.497  1.00 43.83      D    C
ATOM   2906  CG  ASP D  71      77.789 -14.584   7.758  1.00 47.54      D    C
ATOM   2907  OD1 ASP D  71      78.071 -15.264   6.753  1.00 52.10      D    O
ATOM   2908  OD2 ASP D  71      78.509 -13.645   8.155  1.00 53.31      D    O
ATOM   2909  C   ASP D  71      75.008 -14.139   6.625  1.00 41.39      D    C
ATOM   2910  O   ASP D  71      75.370 -14.129   5.455  1.00 46.69      D    O
ATOM   2911  N   TRP D  72      74.244 -13.184   7.130  1.00 38.69      D    N
ATOM   2912  CA  TRP D  72      73.777 -12.074   6.312  1.00 33.39      D    C
ATOM   2913  CB  TRP D  72      72.448 -12.438   5.642  1.00 30.77      D    C
ATOM   2914  CG  TRP D  72      71.281 -12.659   6.563  1.00 29.62      D    C
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ATOM   2915  CD1 TRP D  72      70.966 -13.812   7.213  1.00 29.00      D    C
ATOM   2916  NE1 TRP D  72      69.819 -13.634   7.958  1.00 27.88      D    N
ATOM   2917  CE2 TRP D  72      69.371 -12.351   7.787  1.00 28.07      D    C
ATOM   2918  CD2 TRP D  72      70.264 -11.708   6.919  1.00 28.25      D    C
ATOM   2919  CE3 TRP D  72      70.035 -10.367   6.595  1.00 29.09      D    C
ATOM   2920  CZ3 TRP D  72      68.922  -9.718   7.130  1.00 26.55      D    C
ATOM   2921  CH2 TRP D  72      68.052 -10.384   7.993  1.00 26.45      D    C
ATOM   2922  CZ2 TRP D  72      68.253 -11.697   8.331  1.00 27.71      D    C
ATOM   2923  C   TRP D  72      73.616 -10.806   7.096  1.00 31.89      D    C
ATOM   2924  O   TRP D  72      73.370 -10.837   8.298  1.00 36.22      D    O
ATOM   2925  N   CYS D  73      73.732  -9.687   6.398  1.00 32.23      D    N
ATOM   2926  CA  CYS D  73      73.595  -8.369   7.002  1.00 34.19      D    C
ATOM   2927  CB  CYS D  73      74.936  -7.956   7.628  1.00 33.76      D    C
ATOM   2928  SG  CYS D  73      75.021  -6.314   8.352  1.00 36.36      D    S
ATOM   2929  C   CYS D  73      73.132  -7.377   5.932  1.00 33.90      D    C
ATOM   2930  O   CYS D  73      73.861  -7.120   4.989  1.00 37.03      D    O
ATOM   2931  N   LYS D  74      71.938  -6.814   6.113  1.00 34.26      D    N
ATOM   2932  CA  LYS D  74      71.315  -5.888   5.167  1.00 34.39      D    C
ATOM   2933  CB  LYS D  74      69.833  -6.213   4.983  1.00 36.20      D    C
ATOM   2934  CG  LYS D  74      69.545  -7.361   4.000  1.00 39.63      D    C
ATOM   2935  CD  LYS D  74      68.079  -7.602   3.603  1.00 42.21      D    C
ATOM   2936  CE  LYS D  74      67.956  -8.683   2.529  1.00 43.60      D    C
ATOM   2937  NZ  LYS D  74      66.596  -9.285   2.510  1.00 44.46      D    N
ATOM   2938  C   LYS D  74      71.436  -4.412   5.601  1.00 34.26      D    C
ATOM   2939  O   LYS D  74      71.389  -4.092   6.795  1.00 32.27      D    O
ATOM   2940  N   THR D  75      71.679  -3.550   4.604  1.00 34.18      D    N
ATOM   2941  CA  THR D  75      71.680  -2.107   4.752  1.00 33.19      D    C
ATOM   2942  CB  THR D  75      72.886  -1.447   4.065  1.00 31.73      D    C
ATOM   2943  OG1 THR D  75      74.108  -2.059   4.498  1.00 33.42      D    O
ATOM   2944  CG2 THR D  75      72.930   0.040   4.399  1.00 31.73      D    C
ATOM   2945  C   THR D  75      70.436  -1.617   4.059  1.00 32.30      D    C
ATOM   2946  O   THR D  75      70.143  -2.072   2.973  1.00 31.19      D    O
ATOM   2947  N   GLN D  76      69.699  -0.703   4.680  1.00 31.34      D    N
ATOM   2948  CA  GLN D  76      68.440  -0.250   4.115  1.00 31.39      D    C
ATOM   2949  CB  GLN D  76      67.326  -1.138   4.633  1.00 34.34      D    C
ATOM   2950  CG  GLN D  76      65.960  -0.810   4.055  1.00 37.27      D    C
ATOM   2951  CD  GLN D  76      64.896  -1.816   4.391  1.00 36.68      D    C
ATOM   2952  OE1 GLN D  76      63.734  -1.460   4.537  1.00 37.17      D    O
ATOM   2953  NE2 GLN D  76      65.286  -3.069   4.548  1.00 37.25      D    N
ATOM   2954  C   GLN D  76      68.142   1.202   4.473  1.00 30.71      D    C
ATOM   2955  O   GLN D  76      68.458   1.634   5.572  1.00 31.17      D    O
ATOM   2956  N   PRO D  77      67.547   1.966   3.540  1.00 29.17      D    N
ATOM   2957  CA  PRO D  77      67.337   3.380   3.816  1.00 30.46      D    C
ATOM   2958  CB  PRO D  77      67.042   3.960   2.430  1.00 29.10      D    C
ATOM   2959  CG  PRO D  77      66.425   2.825   1.705  1.00 29.10      D    C
ATOM   2960  CD  PRO D  77      67.215   1.639   2.146  1.00 27.70      D    C
ATOM   2961  C   PRO D  77      66.162   3.681   4.743  1.00 31.81      D    C
ATOM   2962  O   PRO D  77      65.195   2.931   4.785  1.00 31.58      D    O
ATOM   2963  N   LEU D  78      66.258   4.804   5.455  1.00 33.85      D    N
ATOM   2964  CA  LEU D  78      65.165   5.298   6.274  1.00 34.69      D    C
ATOM   2965  CB  LEU D  78      65.211   4.667   7.679  1.00 35.32      D    C
ATOM   2966  CG  LEU D  78      65.921   5.428   8.799  1.00 34.04      D    C
ATOM   2967  CD1 LEU D  78      65.574   4.858  10.161  1.00 35.70      D    C
ATOM   2968  CD2 LEU D  78      67.427   5.484   8.629  1.00 34.56      D    C
ATOM   2969  C   LEU D  78      65.243   6.816   6.352  1.00 36.82      D    C
ATOM   2970  O   LEU D  78      66.311   7.401   6.167  1.00 34.09      D    O
ATOM   2971  N   LYS D  79      64.111   7.451   6.635  1.00 42.10      D    N
ATOM   2972  CA  LYS D  79      64.039   8.902   6.693  1.00 44.22      D    C
ATOM   2973  CB  LYS D  79      62.639   9.397   6.335  1.00 47.74      D    C
ATOM   2974  CG  LYS D  79      62.195   9.144   4.896  1.00 51.60      D    C
ATOM   2975  CD  LYS D  79      60.652   9.236   4.802  1.00 56.49      D    C
ATOM   2976  CE  LYS D  79      60.174  10.403   3.930  1.00 60.70      D    C
ATOM   2977  NZ  LYS D  79      58.683  10.419   3.819  1.00 60.71      D    N
ATOM   2978  C   LYS D  79      64.387   9.388   8.078  1.00 46.43      D    C
ATOM   2979  O   LYS D  79      64.089   8.744   9.062  1.00 51.49      D    O
ATOM   2980  N   GLN D  80      64.996  10.563   8.131  1.00 48.71      D    N
ATOM   2981  CA  GLN D  80      65.342  11.248   9.369  1.00 46.32      D    C
ATOM   2982  CB  GLN D  80      66.805  11.066   9.716  1.00 45.38      D    C
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ATOM	2983	CG	GLN	D	80	67.065	9.766	10.439	1.00	47.91	D	C
ATOM	2984	CD	GLN	D	80	68.327	9.795	11.285	1.00	46.65	D	C
ATOM	2985	OE1	GLN	D	80	69.338	10.346	10.875	1.00	44.49	D	O
ATOM	2986	NE2	GLN	D	80	68.259	9.212	12.477	1.00	47.64	D	N
ATOM	2987	C	GLN	D	80	65.150	12.697	9.107	1.00	50.45	D	C
ATOM	2988	O	GLN	D	80	65.453	13.163	7.998	1.00	45.81	D	O
ATOM	2989	N	THR	D	81	64.703	13.422	10.127	1.00	54.35	D	N
ATOM	2990	CA	THR	D	81	64.548	14.855	9.981	1.00	56.15	D	C
ATOM	2991	CB	THR	D	81	63.103	15.328	10.252	1.00	57.55	D	C
ATOM	2992	OG1	THR	D	81	63.113	16.717	10.580	1.00	56.44	D	O
ATOM	2993	CG2	THR	D	81	62.437	14.545	11.391	1.00	57.94	D	C
ATOM	2994	C	THR	D	81	65.564	15.582	10.842	1.00	59.44	D	C
ATOM	2995	O	THR	D	81	65.823	15.201	11.977	1.00	61.16	D	O
ATOM	2996	N	ILE	D	82	66.151	16.627	10.271	1.00	67.08	D	N
ATOM	2997	CA	ILE	D	82	67.180	17.419	10.919	1.00	71.09	D	C
ATOM	2998	CB	ILE	D	82	68.263	17.850	9.917	1.00	70.90	D	C
ATOM	2999	CG1	ILE	D	82	68.746	16.675	9.059	1.00	73.88	D	C
ATOM	3000	CD1	ILE	D	82	69.610	17.051	7.885	1.00	73.17	D	C
ATOM	3001	CG2	ILE	D	82	69.393	18.550	10.643	1.00	72.43	D	C
ATOM	3002	C	ILE	D	82	66.563	18.724	11.392	1.00	75.03	D	C
ATOM	3003	O	ILE	D	82	65.877	19.391	10.606	1.00	70.34	D	O
ATOM	3004	N	HIS	D	83	66.841	19.100	12.644	1.00	77.44	D	N
ATOM	3005	CA	HIS	D	83	66.436	20.384	13.182	1.00	76.58	D	C
ATOM	3006	CB	HIS	D	83	65.439	20.206	14.318	1.00	76.40	D	C
ATOM	3007	CG	HIS	D	83	64.638	18.941	14.256	1.00	78.12	D	C
ATOM	3008	ND1	HIS	D	83	63.413	18.883	13.633	1.00	77.58	D	N
ATOM	3009	CE1	HIS	D	83	62.916	17.662	13.748	1.00	78.38	D	C
ATOM	3010	NE2	HIS	D	83	63.777	16.925	14.425	1.00	79.32	D	N
ATOM	3011	CD2	HIS	D	83	64.861	17.701	14.763	1.00	80.64	D	C
ATOM	3012	C	HIS	D	83	67.688	21.078	13.718	1.00	72.07	D	C
ATOM	3013	O	HIS	D	83	68.171	22.051	13.147	1.00	70.11	D	O
ATOM	3014	N	CYS	D	87	68.478	26.689	9.901	1.00	60.72	D	N
ATOM	3015	CA	CYS	D	87	67.329	27.502	10.273	1.00	66.42	D	C
ATOM	3016	CB	CYS	D	87	67.220	28.767	9.362	1.00	72.03	D	C
ATOM	3017	SG	CYS	D	87	67.321	28.571	7.540	1.00	66.98	D	S
ATOM	3018	C	CYS	D	87	66.027	26.680	10.261	1.00	70.48	D	C
ATOM	3019	O	CYS	D	87	65.478	26.355	11.313	1.00	67.88	D	O
ATOM	3020	N	ASN	D	88	65.515	26.354	9.078	1.00	75.00	D	N
ATOM	3021	CA	ASN	D	88	64.208	25.683	8.990	1.00	75.70	D	C
ATOM	3022	CB	ASN	D	88	63.830	25.380	7.540	1.00	79.32	D	C
ATOM	3023	CG	ASN	D	88	63.389	26.593	6.772	1.00	81.34	D	C
ATOM	3024	OD1	ASN	D	88	62.355	27.196	7.058	1.00	78.82	D	O
ATOM	3025	ND2	ASN	D	88	64.173	26.943	5.761	1.00	84.86	D	N
ATOM	3026	C	ASN	D	88	64.083	24.360	9.722	1.00	74.35	D	C
ATOM	3027	O	ASN	D	88	63.660	24.343	10.866	1.00	73.01	D	O
ATOM	3028	N	SER	D	89	64.452	23.277	9.019	1.00	66.53	D	N
ATOM	3029	CA	SER	D	89	64.092	21.869	9.333	1.00	64.20	D	C
ATOM	3030	CB	SER	D	89	62.869	21.696	10.235	1.00	63.10	D	C
ATOM	3031	OG	SER	D	89	62.401	20.361	10.084	1.00	59.28	D	O
ATOM	3032	C	SER	D	89	63.855	21.017	8.061	1.00	64.07	D	C
ATOM	3033	O	SER	D	89	62.953	21.286	7.268	1.00	58.02	D	O
ATOM	3034	N	ARG	D	90	64.625	19.940	7.921	1.00	63.84	D	N
ATOM	3035	CA	ARG	D	90	64.753	19.235	6.641	1.00	58.07	D	C
ATOM	3036	CB	ARG	D	90	65.991	19.804	5.952	1.00	57.81	D	C
ATOM	3037	CG	ARG	D	90	66.382	19.114	4.653	1.00	55.96	D	C
ATOM	3038	CD	ARG	D	90	67.390	19.948	3.886	1.00	56.77	D	C
ATOM	3039	NE	ARG	D	90	67.771	19.279	2.644	1.00	59.48	D	N
ATOM	3040	CZ	ARG	D	90	68.813	19.604	1.879	1.00	58.21	D	C
ATOM	3041	NH1	ARG	D	90	69.629	20.601	2.208	1.00	60.34	D	N
ATOM	3042	NH2	ARG	D	90	69.044	18.919	0.771	1.00	58.61	D	N
ATOM	3043	C	ARG	D	90	64.888	17.718	6.800	1.00	52.36	D	C
ATOM	3044	O	ARG	D	90	65.492	17.255	7.754	1.00	54.18	D	O
ATOM	3045	N	THR	D	91	64.355	16.945	5.860	1.00	48.54	D	N
ATOM	3046	CA	THR	D	91	64.448	15.504	5.979	1.00	49.64	D	C
ATOM	3047	CB	THR	D	91	63.117	14.746	5.918	1.00	51.39	D	C
ATOM	3048	OG1	THR	D	91	62.926	14.242	4.601	1.00	54.64	D	O
ATOM	3049	CG2	THR	D	91	61.976	15.643	6.342	1.00	51.63	D	C
ATOM	3050	C	THR	D	91	65.444	14.939	4.990	1.00	50.96	D	C

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ATOM   3051  O   THR D  91      65.469  15.321   3.831  1.00 50.96      D    O
ATOM   3052  N   ILE D  92      66.255  14.011   5.489  1.00 55.28      D    N
ATOM   3053  CA  ILE D  92      67.332  13.350   4.736  1.00 55.24      D    C
ATOM   3054  CB  ILE D  92      68.733  13.792   5.221  1.00 59.66      D    C
ATOM   3055  CG1 ILE D  92      68.893  13.630   6.743  1.00 60.50      D    C
ATOM   3056  CD1 ILE D  92      69.897  12.585   7.154  1.00 62.49      D    C
ATOM   3057  CG2 ILE D  92      69.003  15.235   4.813  1.00 63.32      D    C
ATOM   3058  C   ILE D  92      67.217  11.837   4.867  1.00 50.40      D    C
ATOM   3059  O   ILE D  92      66.424  11.350   5.659  1.00 47.12      D    O
ATOM   3060  N   ILE D  93      68.006  11.125   4.071  1.00 44.39      D    N
ATOM   3061  CA  ILE D  93      68.017   9.687   4.056  1.00 42.64      D    C
ATOM   3062  CB  ILE D  93      68.023   9.144   2.608  1.00 46.11      D    C
ATOM   3063  CG1 ILE D  93      66.711   9.482   1.908  1.00 47.21      D    C
ATOM   3064  CD1 ILE D  93      65.470   8.909   2.533  1.00 47.21      D    C
ATOM   3065  CG2 ILE D  93      68.349   7.649   2.549  1.00 46.11      D    C
ATOM   3066  C   ILE D  93      69.271   9.188   4.745  1.00 40.48      D    C
ATOM   3067  O   ILE D  93      70.376   9.459   4.281  1.00 38.88      D    O
ATOM   3068  N   ASN D  94      69.085   8.446   5.840  1.00 36.41      D    N
ATOM   3069  CA  ASN D  94      70.148   7.659   6.443  1.00 32.75      D    C
ATOM   3070  CB  ASN D  94      70.107   7.807   7.959  1.00 33.55      D    C
ATOM   3071  CG  ASN D  94      71.483   7.743   8.591  1.00 34.02      D    C
ATOM   3072  OD1 ASN D  94      72.402   7.086   8.077  1.00 35.30      D    O
ATOM   3073  ND2 ASN D  94      71.609   8.343   9.756  1.00 33.97      D    N
ATOM   3074  C   ASN D  94      69.953   6.189   6.056  1.00 31.89      D    C
ATOM   3075  O   ASN D  94      69.108   5.884   5.229  1.00 29.80      D    O
ATOM   3076  N   ARG D  95      70.732   5.290   6.659  1.00 31.83      D    N
ATOM   3077  CA  ARG D  95      70.554   3.856   6.495  1.00 32.58      D    C
ATOM   3078  CB  ARG D  95      71.629   3.305   5.598  1.00 33.96      D    C
ATOM   3079  CG  ARG D  95      71.620   4.004   4.265  1.00 36.16      D    C
ATOM   3080  CD  ARG D  95      72.666   3.473   3.308  1.00 40.06      D    C
ATOM   3081  NE  ARG D  95      72.721   4.236   2.057  1.00 44.64      D    N
ATOM   3082  CZ  ARG D  95      73.657   4.063   1.121  1.00 46.31      D    C
ATOM   3083  NH1 ARG D  95      74.616   3.157   1.278  1.00 47.27      D    N
ATOM   3084  NH2 ARG D  95      73.632   4.795   0.016  1.00 49.47      D    N
ATOM   3085  C   ARG D  95      70.597   3.135   7.829  1.00 32.11      D    C
ATOM   3086  O   ARG D  95      71.113   3.657   8.815  1.00 27.34      D    O
ATOM   3087  N   PHE D  96      70.016   1.938   7.858  1.00 34.06      D    N
ATOM   3088  CA  PHE D  96      70.123   1.082   9.033  1.00 37.24      D    C
ATOM   3089  CB  PHE D  96      68.834   1.076   9.869  1.00 40.32      D    C
ATOM   3090  CG  PHE D  96      67.646   0.462   9.189  1.00 42.81      D    C
ATOM   3091  CD1 PHE D  96      66.943   1.165   8.231  1.00 44.60      D    C
ATOM   3092  CE1 PHE D  96      65.835   0.618   7.610  1.00 47.54      D    C
ATOM   3093  CZ  PHE D  96      65.401  -0.651   7.964  1.00 50.93      D    C
ATOM   3094  CE2 PHE D  96      66.079  -1.358   8.945  1.00 48.06      D    C
ATOM   3095  CD2 PHE D  96      67.191  -0.796   9.558  1.00 46.08      D    C
ATOM   3096  C   PHE D  96      70.563  -0.324   8.674  1.00 35.56      D    C
ATOM   3097  O   PHE D  96      70.456  -0.756   7.533  1.00 34.10      D    O
ATOM   3098  N   CYS D  97      71.067  -1.018   9.685  1.00 34.36      D    N
ATOM   3099  CA  CYS D  97      71.608  -2.336   9.542  1.00 31.62      D    C
ATOM   3100  CB  CYS D  97      72.978  -2.374  10.203  1.00 32.81      D    C
ATOM   3101  SG  CYS D  97      74.057  -1.002   9.754  1.00 36.03      D    S
ATOM   3102  C   CYS D  97      70.714  -3.326  10.256  1.00 29.38      D    C
ATOM   3103  O   CYS D  97      70.249  -3.074  11.346  1.00 26.46      D    O
ATOM   3104  N   TYR D  98      70.544  -4.494   9.679  1.00 30.07      D    N
ATOM   3105  CA  TYR D  98      70.009  -5.617  10.446  1.00 30.31      D    C
ATOM   3106  CB  TYR D  98      68.485  -5.553  10.536  1.00 31.70      D    C
ATOM   3107  CG  TYR D  98      67.824  -5.490   9.202  1.00 33.58      D    C
ATOM   3108  CD1 TYR D  98      67.590  -6.648   8.474  1.00 36.58      D    C
ATOM   3109  CE1 TYR D  98      67.011  -6.591   7.216  1.00 38.79      D    C
ATOM   3110  CZ  TYR D  98      66.652  -5.362   6.691  1.00 37.11      D    C
ATOM   3111  OH  TYR D  98      66.078  -5.326   5.472  1.00 33.30      D    O
ATOM   3112  CE2 TYR D  98      66.884  -4.193   7.394  1.00 35.59      D    C
ATOM   3113  CD2 TYR D  98      67.482  -4.267   8.636  1.00 34.67      D    C
ATOM   3114  C   TYR D  98      70.453  -6.918   9.813  1.00 28.76      D    C
ATOM   3115  O   TYR D  98      70.606  -7.005   8.583  1.00 27.80      D    O
ATOM   3116  N   GLY D  99      70.636  -7.932  10.643  1.00 26.07      D    N
ATOM   3117  CA  GLY D  99      71.073  -9.208  10.132  1.00 27.10      D    C
ATOM   3118  C   GLY D  99      71.263 -10.273  11.173  1.00 26.01      D    C
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ATOM   3119  O   GLY D  99      70.880 -10.113  12.339  1.00 26.66      D    O
ATOM   3120  N   GLN D 100      71.795 -11.393  10.716  1.00 24.64      D    N
ATOM   3121  CA  GLN D 100      72.054 -12.504  11.570  1.00 27.07      D    C
ATOM   3122  CB  GLN D 100      71.002 -13.597  11.370  1.00 27.49      D    C
ATOM   3123  CG  GLN D 100      69.575 -13.072  11.525  1.00 28.04      D    C
ATOM   3124  CD  GLN D 100      68.520 -14.141  11.249  1.00 27.72      D    C
ATOM   3125  OE1 GLN D 100      68.767 -15.071  10.501  1.00 28.84      D    O
ATOM   3126  NE2 GLN D 100      67.351 -14.013  11.851  1.00 27.77      D    N
ATOM   3127  C   GLN D 100      73.455 -12.973  11.251  1.00 28.27      D    C
ATOM   3128  O   GLN D 100      73.682 -13.590  10.221  1.00 27.26      D    O
ATOM   3129  N   CYS D 101      74.387 -12.643  12.137  1.00 29.64      D    N
ATOM   3130  CA  CYS D 101      75.779 -12.925  11.915  1.00 32.11      D    C
ATOM   3131  CB  CYS D 101      76.617 -11.733  12.349  1.00 34.20      D    C
ATOM   3132  SG  CYS D 101      76.200 -10.223  11.438  1.00 36.82      D    S
ATOM   3133  C   CYS D 101      76.158 -14.167  12.686  1.00 32.88      D    C
ATOM   3134  O   CYS D 101      75.362 -14.655  13.462  1.00 36.54      D    O
ATOM   3135  N   ASN D 102      77.362 -14.692  12.466  1.00 32.68      D    N
ATOM   3136  CA  ASN D 102      77.798 -15.901  13.143  1.00 31.82      D    C
ATOM   3137  CB  ASN D 102      78.895 -16.583  12.379  1.00 32.44      D    C
ATOM   3138  CG  ASN D 102      78.442 -17.079  11.044  1.00 34.87      D    C
ATOM   3139  OD1 ASN D 102      77.300 -17.488  10.840  1.00 38.60      D    O
ATOM   3140  ND2 ASN D 102      79.338 -17.044  10.120  1.00 37.13      D    N
ATOM   3141  C   ASN D 102      78.335 -15.611  14.505  1.00 32.82      D    C
ATOM   3142  O   ASN D 102      79.009 -14.602  14.712  1.00 38.29      D    O
ATOM   3143  N   SER D 103      78.032 -16.504  15.433  1.00 32.00      D    N
ATOM   3144  CA  SER D 103      78.652 -16.494  16.735  1.00 32.99      D    C
ATOM   3145  CB  SER D 103      77.841 -15.657  17.713  1.00 32.84      D    C
ATOM   3146  OG  SER D 103      76.530 -16.169  17.815  1.00 34.75      D    O
ATOM   3147  C   SER D 103      78.736 -17.921  17.222  1.00 32.04      D    C
ATOM   3148  O   SER D 103      77.967 -18.771  16.802  1.00 30.92      D    O
ATOM   3149  N   PHE D 104      79.693 -18.181  18.095  1.00 32.04      D    N
ATOM   3150  CA  PHE D 104      79.830 -19.496  18.685  1.00 30.57      D    C
ATOM   3151  CB  PHE D 104      80.480 -20.478  17.713  1.00 31.57      D    C
ATOM   3152  CG  PHE D 104      81.879 -20.105  17.284  1.00 34.55      D    C
ATOM   3153  CD1 PHE D 104      82.971 -20.318  18.125  1.00 36.23      D    C
ATOM   3154  CE1 PHE D 104      84.259 -19.960  17.733  1.00 37.21      D    C
ATOM   3155  CZ  PHE D 104      84.471 -19.425  16.482  1.00 35.79      D    C
ATOM   3156  CE2 PHE D 104      83.402 -19.242  15.625  1.00 36.02      D    C
ATOM   3157  CD2 PHE D 104      82.119 -19.578  16.020  1.00 35.92      D    C
ATOM   3158  C   PHE D 104      80.608 -19.414  19.981  1.00 28.53      D    C
ATOM   3159  O   PHE D 104      81.221 -18.399  20.309  1.00 25.49      D    O
ATOM   3160  N   TYR D 105      80.558 -20.505  20.722  1.00 29.76      D    N
ATOM   3161  CA  TYR D 105      81.239 -20.597  22.003  1.00 30.79      D    C
ATOM   3162  CB  TYR D 105      80.324 -20.115  23.122  1.00 30.84      D    C
ATOM   3163  CG  TYR D 105      80.984 -20.198  24.454  1.00 32.75      D    C
ATOM   3164  CD1 TYR D 105      81.094 -21.403  25.131  1.00 33.29      D    C
ATOM   3165  CE1 TYR D 105      81.724 -21.475  26.356  1.00 35.15      D    C
ATOM   3166  CZ  TYR D 105      82.256 -20.343  26.917  1.00 34.61      D    C
ATOM   3167  OH  TYR D 105      82.892 -20.383  28.140  1.00 38.66      D    O
ATOM   3168  CE2 TYR D 105      82.163 -19.145  26.268  1.00 35.69      D    C
ATOM   3169  CD2 TYR D 105      81.533 -19.075  25.037  1.00 34.75      D    C
ATOM   3170  C   TYR D 105      81.612 -22.040  22.226  1.00 30.10      D    C
ATOM   3171  O   TYR D 105      80.741 -22.913  22.223  1.00 29.72      D    O
ATOM   3172  N   ILE D 106      82.896 -22.297  22.408  1.00 31.01      D    N
ATOM   3173  CA  ILE D 106      83.384 -23.658  22.494  1.00 34.86      D    C
ATOM   3174  CB  ILE D 106      84.132 -24.050  21.209  1.00 37.67      D    C
ATOM   3175  CG1 ILE D 106      83.187 -24.053  20.007  1.00 39.12      D    C
ATOM   3176  CD1 ILE D 106      83.901 -23.959  18.679  1.00 40.54      D    C
ATOM   3177  CG2 ILE D 106      84.750 -25.427  21.349  1.00 38.84      D    C
ATOM   3178  C   ILE D 106      84.336 -23.743  23.657  1.00 37.21      D    C
ATOM   3179  O   ILE D 106      85.401 -23.136  23.606  1.00 38.41      D    O
ATOM   3180  N   PRO D 107      83.973 -24.492  24.711  1.00 41.40      D    N
ATOM   3181  CA  PRO D 107      84.858 -24.635  25.876  1.00 44.41      D    C
ATOM   3182  CB  PRO D 107      84.055 -25.495  26.849  1.00 43.10      D    C
ATOM   3183  CG  PRO D 107      82.779 -25.837  26.190  1.00 42.35      D    C
ATOM   3184  CD  PRO D 107      82.845 -25.432  24.754  1.00 41.78      D    C
ATOM   3185  C   PRO D 107      86.150 -25.396  25.562  1.00 51.30      D    C
ATOM   3186  O   PRO D 107      86.146 -26.247  24.694  1.00 53.01      D    O
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ATOM   3187  N   ARG D 108      87.218 -25.095  26.301  1.00 57.97      D    N
ATOM   3188  CA  ARG D 108      88.481 -25.839  26.292  1.00 57.33      D    C
ATOM   3189  CB  ARG D 108      89.550 -24.859  25.787  1.00 56.67      D    C
ATOM   3190  CG  ARG D 108      89.520 -24.551  24.326  1.00 55.94      D    C
ATOM   3191  CD  ARG D 108      90.352 -23.262  24.071  1.00 56.06      D    C
ATOM   3192  NE  ARG D 108      91.724 -23.544  23.628  1.00 58.22      D    N
ATOM   3193  CZ  ARG D 108      92.662 -22.617  23.460  1.00 57.72      D    C
ATOM   3194  NH1 ARG D 108      92.406 -21.333  23.713  1.00 58.79      D    N
ATOM   3195  NH2 ARG D 108      93.871 -22.976  23.049  1.00 54.71      D    N
ATOM   3196  C   ARG D 108      88.869 -26.247  27.723  1.00 61.74      D    C
ATOM   3197  O   ARG D 108      88.228 -25.852  28.705  1.00 63.14      D    O
ATOM   3198  N   HIS D 109      89.921 -27.038  27.856  1.00 72.66      D    N
ATOM   3199  CA  HIS D 109      90.603 -27.139  29.154  1.00 86.11      D    C
ATOM   3200  CB  HIS D 109      90.969 -28.593  29.493  1.00 88.78      D    C
ATOM   3201  CG  HIS D 109      89.973 -29.286  30.382  1.00 92.39      D    C
ATOM   3202  ND1 HIS D 109      88.701 -28.803  30.640  1.00 98.38      D    N
ATOM   3203  CE1 HIS D 109      88.068 -29.635  31.451  1.00 95.86      D    C
ATOM   3204  NE2 HIS D 109      88.875 -30.645  31.717  1.00 97.93      D    N
ATOM   3205  CD2 HIS D 109      90.068 -30.453  31.060  1.00 95.18      D    C
ATOM   3206  C   HIS D 109      91.765 -26.127  29.156  1.00 94.83      D    C
ATOM   3207  O   HIS D 109      91.494 -24.928  29.176  1.00 95.59      D    O
ATOM   3208  N   ILE D 110      93.026 -26.565  29.191  1.00105.05      D    N
ATOM   3209  CA  ILE D 110      94.149 -25.780  28.632  1.00109.23      D    C
ATOM   3210  CB  ILE D 110      94.172 -25.884  27.082  1.00107.61      D    C
ATOM   3211  CG1 ILE D 110      94.406 -27.354  26.581  1.00106.13      D    C
ATOM   3212  CD1 ILE D 110      93.488 -28.467  27.078  1.00101.08      D    C
ATOM   3213  CG2 ILE D 110      95.321 -25.044  26.553  1.00107.08      D    C
ATOM   3214  C   ILE D 110      94.255 -24.279  29.043  1.00115.33      D    C
ATOM   3215  O   ILE D 110      93.279 -23.539  28.927  1.00110.81      D    O
ATOM   3216  N   ARG D 111      95.464 -23.812  29.406  1.00121.65      D    N
ATOM   3217  CA  ARG D 111      95.674 -22.472  30.013  1.00125.06      D    C
ATOM   3218  CB  ARG D 111      95.185 -21.390  29.030  1.00121.63      D    C
ATOM   3219  CG  ARG D 111      95.192 -19.960  29.534  1.00117.54      D    C
ATOM   3220  CD  ARG D 111      94.541 -19.078  28.521  1.00116.02      D    C
ATOM   3221  NE  ARG D 111      94.686 -17.647  28.846  1.00118.15      D    N
ATOM   3222  CZ  ARG D 111      95.603 -16.809  28.337  1.00113.16      D    C
ATOM   3223  NH1 ARG D 111      96.489 -17.192  27.416  1.00109.82      D    N
ATOM   3224  NH2 ARG D 111      95.620 -15.542  28.748  1.00110.79      D    N
ATOM   3225  C   ARG D 111      94.980 -22.283  31.370  1.00133.48      D    C
ATOM   3226  O   ARG D 111      93.789 -22.038  31.349  1.00147.76      D    O
ATOM   3227  N   LYS D 112      95.691 -22.344  32.519  1.00132.66      D    N
ATOM   3228  CA  LYS D 112      95.065 -22.238  33.852  1.00132.99      D    C
ATOM   3229  CB  LYS D 112      94.401 -20.851  34.008  1.00130.80      D    C
ATOM   3230  CG  LYS D 112      94.227 -20.439  35.457  1.00126.33      D    C
ATOM   3231  CD  LYS D 112      93.875 -18.969  35.706  1.00124.61      D    C
ATOM   3232  CE  LYS D 112      93.142 -18.232  34.560  1.00126.38      D    C
ATOM   3233  NZ  LYS D 112      91.723 -18.667  34.382  1.00126.02      D    N
ATOM   3234  C   LYS D 112      94.108 -23.461  34.025  1.00132.32      D    C
ATOM   3235  O   LYS D 112      94.542 -24.630  34.016  1.00129.72      D    O
ATOM   3236  N   GLU D 113      92.817 -23.202  34.181  1.00128.88      D    N
ATOM   3237  CA  GLU D 113      91.796 -24.225  34.010  1.00120.28      D    C
ATOM   3238  CB  GLU D 113      91.590 -25.019  35.302  1.00115.82      D    C
ATOM   3239  C   GLU D 113      90.529 -23.546  33.545  1.00111.48      D    C
ATOM   3240  O   GLU D 113      89.450 -23.774  34.079  1.00119.55      D    O
ATOM   3241  N   GLU D 114      90.688 -22.704  32.528  1.00 95.17      D    N
ATOM   3242  CA  GLU D 114      89.578 -21.916  32.009  1.00 81.62      D    C
ATOM   3243  CB  GLU D 114      89.216 -20.773  32.969  1.00 73.37      D    C
ATOM   3244  CG  GLU D 114      87.895 -20.097  32.629  1.00 69.67      D    C
ATOM   3245  CD  GLU D 114      86.691 -21.010  32.807  1.00 66.37      D    C
ATOM   3246  OE1 GLU D 114      86.629 -21.737  33.817  1.00 73.36      D    O
ATOM   3247  OE2 GLU D 114      85.800 -21.008  31.935  1.00 57.25      D    O
ATOM   3248  C   GLU D 114      89.897 -21.366  30.614  1.00 74.32      D    C
ATOM   3249  O   GLU D 114      90.800 -20.553  30.450  1.00 74.11      D    O
ATOM   3250  N   GLY D 115      89.144 -21.818  29.618  1.00 68.42      D    N
ATOM   3251  CA  GLY D 115      89.323 -21.356  28.245  1.00 61.93      D    C
ATOM   3252  C   GLY D 115      88.127 -21.616  27.345  1.00 53.62      D    C
ATOM   3253  O   GLY D 115      87.340 -22.547  27.558  1.00 54.76      D    O
ATOM   3254  N   SER D 116      87.966 -20.771  26.347  1.00 45.06      D    N
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ATOM   3255  CA  SER D 116      87.017 -21.058  25.290  1.00 44.39      D    C
ATOM   3256  CB  SER D 116      85.618 -20.505  25.614  1.00 47.28      D    C
ATOM   3257  OG  SER D 116      85.623 -19.089  25.748  1.00 47.43      D    O
ATOM   3258  C   SER D 116      87.500 -20.475  23.985  1.00 41.86      D    C
ATOM   3259  O   SER D 116      88.243 -19.517  23.982  1.00 42.76      D    O
ATOM   3260  N   PHE D 117      87.083 -21.072  22.880  1.00 39.39      D    N
ATOM   3261  CA  PHE D 117      87.135 -20.419  21.581  1.00 39.13      D    C
ATOM   3262  CB  PHE D 117      87.295 -21.439  20.448  1.00 40.26      D    C
ATOM   3263  CG  PHE D 117      88.601 -22.181  20.459  1.00 40.68      D    C
ATOM   3264  CD1 PHE D 117      89.806 -21.495  20.338  1.00 39.75      D    C
ATOM   3265  CE1 PHE D 117      91.009 -22.167  20.327  1.00 39.78      D    C
ATOM   3266  CZ  PHE D 117      91.021 -23.545  20.403  1.00 42.65      D    C
ATOM   3267  CE2 PHE D 117      89.826 -24.249  20.509  1.00 43.41      D    C
ATOM   3268  CD2 PHE D 117      88.626 -23.569  20.536  1.00 41.85      D    C
ATOM   3269  C   PHE D 117      85.798 -19.745  21.388  1.00 37.00      D    C
ATOM   3270  O   PHE D 117      84.780 -20.407  21.394  1.00 38.42      D    O
ATOM   3271  N   GLN D 118      85.771 -18.443  21.191  1.00 40.33      D    N
ATOM   3272  CA  GLN D 118      84.484 -17.777  20.951  1.00 39.45      D    C
ATOM   3273  CB  GLN D 118      83.870 -17.310  22.251  1.00 38.07      D    C
ATOM   3274  CG  GLN D 118      84.763 -16.370  22.997  1.00 42.01      D    C
ATOM   3275  CD  GLN D 118      84.361 -16.097  24.428  1.00 47.31      D    C
ATOM   3276  OE1 GLN D 118      83.378 -16.602  24.971  1.00 44.74      D    O
ATOM   3277  NE2 GLN D 118      85.186 -15.298  25.059  1.00 50.91      D    N
ATOM   3278  C   GLN D 118      84.570 -16.617  19.985  1.00 36.79      D    C
ATOM   3279  O   GLN D 118      85.627 -16.030  19.755  1.00 35.95      D    O
ATOM   3280  N   SER D 119      83.429 -16.306  19.403  1.00 35.10      D    N
ATOM   3281  CA  SER D 119      83.362 -15.319  18.351  1.00 34.52      D    C
ATOM   3282  CB  SER D 119      83.768 -15.938  17.020  1.00 34.63      D    C
ATOM   3283  OG  SER D 119      83.635 -14.984  16.000  1.00 35.23      D    O
ATOM   3284  C   SER D 119      81.955 -14.836  18.254  1.00 31.33      D    C
ATOM   3285  O   SER D 119      81.030 -15.588  18.493  1.00 29.40      D    O
ATOM   3286  N   CYS D 120      81.814 -13.567  17.933  1.00 29.95      D    N
ATOM   3287  CA  CYS D 120      80.525 -12.964  17.796  1.00 32.52      D    C
ATOM   3288  CB  CYS D 120      79.986 -12.491  19.148  1.00 32.31      D    C
ATOM   3289  SG  CYS D 120      78.255 -11.934  19.086  1.00 34.83      D    S
ATOM   3290  C   CYS D 120      80.674 -11.783  16.865  1.00 34.62      D    C
ATOM   3291  O   CYS D 120      81.555 -10.954  17.049  1.00 35.67      D    O
ATOM   3292  N   SER D 121      79.827 -11.727  15.850  1.00 34.19      D    N
ATOM   3293  CA  SER D 121      79.838 -10.627  14.938  1.00 34.08      D    C
ATOM   3294  CB  SER D 121      80.063 -11.128  13.517  1.00 36.11      D    C
ATOM   3295  OG  SER D 121      81.398 -11.556  13.392  1.00 38.29      D    O
ATOM   3296  C   SER D 121      78.532  -9.892  15.060  1.00 33.72      D    C
ATOM   3297  O   SER D 121      77.556 -10.422  15.560  1.00 33.95      D    O
ATOM   3298  N   PHE D 122      78.540  -8.660  14.583  1.00 33.68      D    N
ATOM   3299  CA  PHE D 122      77.516  -7.686  14.878  1.00 33.08      D    C
ATOM   3300  CB  PHE D 122      78.109  -6.686  15.882  1.00 31.39      D    C
ATOM   3301  CG  PHE D 122      77.153  -5.640  16.388  1.00 29.33      D    C
ATOM   3302  CD1 PHE D 122      75.880  -5.483  15.860  1.00 28.81      D    C
ATOM   3303  CE1 PHE D 122      75.044  -4.487  16.321  1.00 29.09      D    C
ATOM   3304  CZ  PHE D 122      75.471  -3.633  17.315  1.00 29.20      D    C
ATOM   3305  CE2 PHE D 122      76.739  -3.778  17.835  1.00 28.60      D    C
ATOM   3306  CD2 PHE D 122      77.565  -4.776  17.377  1.00 27.50      D    C
ATOM   3307  C   PHE D 122      77.202  -7.019  13.559  1.00 34.75      D    C
ATOM   3308  O   PHE D 122      78.087  -6.420  12.952  1.00 34.94      D    O
ATOM   3309  N   CYS D 123      75.966  -7.174  13.077  1.00 36.28      D    N
ATOM   3310  CA  CYS D 123      75.566  -6.521  11.832  1.00 35.86      D    C
ATOM   3311  CB  CYS D 123      74.291  -7.133  11.250  1.00 35.73      D    C
ATOM   3312  SG  CYS D 123      73.603  -6.239   9.827  1.00 36.73      D    S
ATOM   3313  C   CYS D 123      75.414  -5.036  12.147  1.00 34.58      D    C
ATOM   3314  O   CYS D 123      74.472  -4.629  12.805  1.00 34.73      D    O
ATOM   3315  N   LYS D 124      76.364  -4.238  11.675  1.00 35.50      D    N
ATOM   3316  CA  LYS D 124      76.458  -2.816  12.032  1.00 35.11      D    C
ATOM   3317  CB  LYS D 124      77.181  -2.700  13.351  1.00 37.02      D    C
ATOM   3318  CG  LYS D 124      78.659  -2.957  13.195  1.00 40.93      D    C
ATOM   3319  CD  LYS D 124      79.348  -3.152  14.528  1.00 45.38      D    C
ATOM   3320  CE  LYS D 124      79.463  -1.847  15.286  1.00 48.65      D    C
ATOM   3321  NZ  LYS D 124      80.757  -1.839  16.028  1.00 50.10      D    N
ATOM   3322  C   LYS D 124      77.233  -2.025  10.947  1.00 35.45      D    C
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ATOM	3323	O	LYS	D	124	77.765	-2.623	10.000	1.00	33.28	D	O
ATOM	3324	N	PRO	D	125	77.308	-0.687	11.081	1.00	34.95	D	N
ATOM	3325	CA	PRO	D	125	78.031	0.107	10.098	1.00	35.05	D	C
ATOM	3326	CB	PRO	D	125	77.848	1.531	10.607	1.00	34.24	D	C
ATOM	3327	CG	PRO	D	125	76.561	1.482	11.325	1.00	35.29	D	C
ATOM	3328	CD	PRO	D	125	76.603	0.173	12.041	1.00	35.77	D	C
ATOM	3329	C	PRO	D	125	79.516	-0.222	9.988	1.00	35.74	D	C
ATOM	3330	O	PRO	D	125	80.207	-0.308	10.997	1.00	35.60	D	O
ATOM	3331	N	LYS	D	126	79.980	-0.408	8.762	1.00	36.80	D	N
ATOM	3332	CA	LYS	D	126	81.391	-0.510	8.486	1.00	43.57	D	C
ATOM	3333	CB	LYS	D	126	81.638	-1.416	7.297	1.00	49.54	D	C
ATOM	3334	CG	LYS	D	126	83.132	-1.599	7.012	1.00	57.67	D	C
ATOM	3335	CD	LYS	D	126	83.503	-3.078	6.704	1.00	65.41	D	C
ATOM	3336	CE	LYS	D	126	84.252	-3.273	5.381	1.00	71.15	D	C
ATOM	3337	NZ	LYS	D	126	85.511	-4.106	5.519	1.00	75.89	D	N
ATOM	3338	C	LYS	D	126	81.976	0.876	8.188	1.00	43.02	D	C
ATOM	3339	O	LYS	D	126	83.058	1.207	8.640	1.00	37.77	D	O
ATOM	3340	N	LYS	D	127	81.257	1.661	7.402	1.00	49.82	D	N
ATOM	3341	CA	LYS	D	127	81.654	3.022	7.101	1.00	56.92	D	C
ATOM	3342	CB	LYS	D	127	82.066	3.168	5.634	1.00	62.32	D	C
ATOM	3343	CG	LYS	D	127	82.764	1.963	5.013	1.00	68.03	D	C
ATOM	3344	CD	LYS	D	127	83.293	2.283	3.616	1.00	69.75	D	C
ATOM	3345	CE	LYS	D	127	84.793	2.557	3.633	1.00	70.28	D	C
ATOM	3346	NZ	LYS	D	127	85.574	1.284	3.710	1.00	70.47	D	N
ATOM	3347	C	LYS	D	127	80.512	3.982	7.363	1.00	55.15	D	C
ATOM	3348	O	LYS	D	127	79.367	3.700	7.007	1.00	53.83	D	O
ATOM	3349	N	PHE	D	128	80.846	5.121	7.963	1.00	53.29	D	N
ATOM	3350	CA	PHE	D	128	79.942	6.269	8.036	1.00	52.87	D	C
ATOM	3351	CB	PHE	D	128	80.012	6.904	9.408	1.00	47.30	D	C
ATOM	3352	CG	PHE	D	128	79.527	6.023	10.498	1.00	45.74	D	C
ATOM	3353	CD1	PHE	D	128	80.363	5.070	11.063	1.00	45.53	D	C
ATOM	3354	CE1	PHE	D	128	79.914	4.252	12.085	1.00	45.14	D	C
ATOM	3355	CZ	PHE	D	128	78.612	4.389	12.550	1.00	46.02	D	C
ATOM	3356	CE2	PHE	D	128	77.770	5.344	11.999	1.00	44.37	D	C
ATOM	3357	CD2	PHE	D	128	78.230	6.151	10.976	1.00	45.09	D	C
ATOM	3358	C	PHE	D	128	80.317	7.314	6.993	1.00	53.16	D	C
ATOM	3359	O	PHE	D	128	81.442	7.336	6.529	1.00	58.63	D	O
ATOM	3360	N	THR	D	129	79.368	8.166	6.622	1.00	52.58	D	N
ATOM	3361	CA	THR	D	129	79.628	9.291	5.745	1.00	51.95	D	C
ATOM	3362	CB	THR	D	129	78.718	9.248	4.517	1.00	54.62	D	C
ATOM	3363	OG1	THR	D	129	79.161	8.204	3.641	1.00	60.68	D	O
ATOM	3364	CG2	THR	D	129	78.738	10.547	3.748	1.00	59.27	D	C
ATOM	3365	C	THR	D	129	79.370	10.547	6.538	1.00	57.00	D	C
ATOM	3366	O	THR	D	129	78.476	10.584	7.359	1.00	55.31	D	O
ATOM	3367	N	THR	D	130	80.172	11.575	6.306	1.00	63.72	D	N
ATOM	3368	CA	THR	D	130	79.920	12.889	6.891	1.00	66.91	D	C
ATOM	3369	CB	THR	D	130	81.102	13.371	7.733	1.00	73.33	D	C
ATOM	3370	OG1	THR	D	130	81.110	12.653	8.966	1.00	74.44	D	O
ATOM	3371	CG2	THR	D	130	80.998	14.857	8.033	1.00	73.66	D	C
ATOM	3372	C	THR	D	130	79.667	13.869	5.772	1.00	61.56	D	C
ATOM	3373	O	THR	D	130	80.387	13.876	4.778	1.00	63.68	D	O
ATOM	3374	N	MET	D	131	78.633	14.682	5.932	1.00	59.03	D	N
ATOM	3375	CA	MET	D	131	78.237	15.629	4.892	1.00	58.22	D	C
ATOM	3376	CB	MET	D	131	77.106	15.063	4.021	1.00	62.74	D	C
ATOM	3377	CG	MET	D	131	76.811	15.839	2.740	1.00	65.66	D	C
ATOM	3378	SD	MET	D	131	75.699	15.013	1.570	1.00	70.86	D	S
ATOM	3379	CE	MET	D	131	74.113	15.830	1.828	1.00	68.27	D	C
ATOM	3380	C	MET	D	131	77.748	16.901	5.529	1.00	59.97	D	C
ATOM	3381	O	MET	D	131	77.193	16.877	6.635	1.00	57.29	D	O
ATOM	3382	N	MET	D	132	77.931	17.996	4.800	1.00	66.74	D	N
ATOM	3383	CA	MET	D	132	77.383	19.298	5.162	1.00	72.45	D	C
ATOM	3384	CB	MET	D	132	78.301	20.441	4.666	1.00	81.24	D	C
ATOM	3385	CG	MET	D	132	79.460	20.878	5.565	1.00	88.33	D	C
ATOM	3386	SD	MET	D	132	79.360	20.418	7.311	1.00	98.34	D	S
ATOM	3387	CE	MET	D	132	80.065	18.770	7.178	1.00	103.55	D	C
ATOM	3388	C	MET	D	132	76.009	19.452	4.503	1.00	68.45	D	C
ATOM	3389	O	MET	D	132	75.907	19.392	3.285	1.00	65.89	D	O
ATOM	3390	N	VAL	D	133	74.973	19.655	5.318	1.00	65.75	D	N

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ATOM   3391  CA  VAL D 133      73.588  19.923   4.882  1.00 63.85      D    C
ATOM   3392  CB  VAL D 133      72.640  18.864   5.466  1.00 65.19      D    C
ATOM   3393  CG1 VAL D 133      71.195  19.086   5.000  1.00 68.34      D    C
ATOM   3394  CG2 VAL D 133      73.075  17.446   5.151  1.00 62.45      D    C
ATOM   3395  C   VAL D 133      73.137  21.209   5.669  1.00 64.69      D    C
ATOM   3396  O   VAL D 133      73.065  21.066   6.885  1.00 62.40      D    O
ATOM   3397  N   THR D 134      72.770  22.428   5.232  1.00 72.08      D    N
ATOM   3398  CA  THR D 134      72.339  23.033   3.972  1.00 78.27      D    C
ATOM   3399  CB  THR D 134      72.593  22.167   2.733  1.00 84.64      D    C
ATOM   3400  OG1 THR D 134      73.954  21.748   2.705  1.00 92.16      D    O
ATOM   3401  CG2 THR D 134      72.293  22.910   1.430  1.00 85.23      D    C
ATOM   3402  C   THR D 134      70.825  23.345   4.181  1.00 72.08      D    C
ATOM   3403  O   THR D 134      69.975  22.629   3.715  1.00 68.03      D    O
ATOM   3404  N   LEU D 135      70.492  24.394   4.929  1.00 71.06      D    N
ATOM   3405  CA  LEU D 135      69.129  24.628   5.393  1.00 71.27      D    C
ATOM   3406  CB  LEU D 135      69.178  24.593   6.914  1.00 73.30      D    C
ATOM   3407  CG  LEU D 135      69.733  23.293   7.539  1.00 73.76      D    C
ATOM   3408  CD1 LEU D 135      69.767  23.398   9.057  1.00 75.34      D    C
ATOM   3409  CD2 LEU D 135      68.942  22.055   7.129  1.00 73.08      D    C
ATOM   3410  C   LEU D 135      68.527  25.971   4.895  1.00 68.82      D    C
ATOM   3411  O   LEU D 135      67.402  26.380   5.252  1.00 64.59      D    O
ATOM   3412  N   LYS D 145      72.019  27.845   6.735  1.00 72.03      D    N
ATOM   3413  CA  LYS D 145      72.982  27.176   7.583  1.00 70.41      D    C
ATOM   3414  CB  LYS D 145      72.354  26.837   8.925  1.00 71.07      D    C
ATOM   3415  CG  LYS D 145      72.328  27.989   9.904  1.00 73.78      D    C
ATOM   3416  CD  LYS D 145      73.621  28.091  10.684  1.00 77.64      D    C
ATOM   3417  CE  LYS D 145      73.642  27.060  11.785  1.00 78.32      D    C
ATOM   3418  NZ  LYS D 145      74.983  27.059  12.410  1.00 81.66      D    N
ATOM   3419  C   LYS D 145      73.453  25.906   6.911  1.00 70.31      D    C
ATOM   3420  O   LYS D 145      72.710  25.275   6.158  1.00 71.64      D    O
ATOM   3421  N   LYS D 146      74.703  25.543   7.176  1.00 74.49      D    N
ATOM   3422  CA  LYS D 146      75.197  24.206   6.877  1.00 73.38      D    C
ATOM   3423  CB  LYS D 146      76.484  24.249   6.087  1.00 69.80      D    C
ATOM   3424  CG  LYS D 146      76.277  24.569   4.619  1.00 70.43      D    C
ATOM   3425  CD  LYS D 146      77.479  25.343   4.111  1.00 74.35      D    C
ATOM   3426  CE  LYS D 146      77.098  26.757   3.672  1.00 76.82      D    C
ATOM   3427  NZ  LYS D 146      78.220  27.462   2.985  1.00 78.39      D    N
ATOM   3428  C   LYS D 146      75.395  23.453   8.180  1.00 73.23      D    C
ATOM   3429  O   LYS D 146      76.083  23.922   9.074  1.00 78.97      D    O
ATOM   3430  N   LYS D 147      74.764  22.293   8.284  1.00 76.18      D    N
ATOM   3431  CA  LYS D 147      74.830  21.468   9.484  1.00 79.01      D    C
ATOM   3432  CB  LYS D 147      73.447  21.170  10.033  1.00 79.19      D    C
ATOM   3433  CG  LYS D 147      73.555  20.438  11.363  1.00 79.89      D    C
ATOM   3434  CD  LYS D 147      72.538  19.333  11.522  1.00 84.87      D    C
ATOM   3435  CE  LYS D 147      72.434  18.858  12.964  1.00 84.56      D    C
ATOM   3436  NZ  LYS D 147      71.346  19.567  13.695  1.00 86.85      D    N
ATOM   3437  C   LYS D 147      75.512  20.149   9.169  1.00 81.61      D    C
ATOM   3438  O   LYS D 147      75.245  19.549   8.120  1.00 84.78      D    O
ATOM   3439  N   ARG D 148      76.384  19.713  10.081  1.00 84.12      D    N
ATOM   3440  CA  ARG D 148      77.036  18.413   9.977  1.00 85.04      D    C
ATOM   3441  CB  ARG D 148      78.217  18.271  10.976  1.00 89.93      D    C
ATOM   3442  CG  ARG D 148      79.538  18.888  10.486  1.00 95.95      D    C
ATOM   3443  CD  ARG D 148      79.701  20.365  10.837  1.00 94.63      D    C
ATOM   3444  NE  ARG D 148      80.411  20.598  12.101  1.00 90.44      D    N
ATOM   3445  CZ  ARG D 148      81.727  20.465  12.256  1.00 87.47      D    C
ATOM   3446  NH1 ARG D 148      82.479  20.072  11.234  1.00 79.96      D    N
ATOM   3447  NH2 ARG D 148      82.288  20.708  13.439  1.00 88.21      D    N
ATOM   3448  C   ARG D 148      76.068  17.296  10.294  1.00 80.95      D    C
ATOM   3449  O   ARG D 148      75.379  17.314  11.327  1.00 69.68      D    O
ATOM   3450  N   VAL D 149      76.044  16.311   9.408  1.00 71.38      D    N
ATOM   3451  CA  VAL D 149      75.346  15.073   9.697  1.00 69.11      D    C
ATOM   3452  CB  VAL D 149      73.956  15.041   9.051  1.00 71.04      D    C
ATOM   3453  CG1 VAL D 149      73.998  15.688   7.685  1.00 75.13      D    C
ATOM   3454  CG2 VAL D 149      73.433  13.615   8.947  1.00 73.80      D    C
ATOM   3455  C   VAL D 149      76.178  13.880   9.248  1.00 63.37      D    C
ATOM   3456  O   VAL D 149      76.703  13.856   8.128  1.00 57.97      D    O
ATOM   3457  N   THR D 150      76.289  12.903  10.146  1.00 56.44      D    N
ATOM   3458  CA  THR D 150      77.014  11.689   9.876  1.00 55.11      D    C
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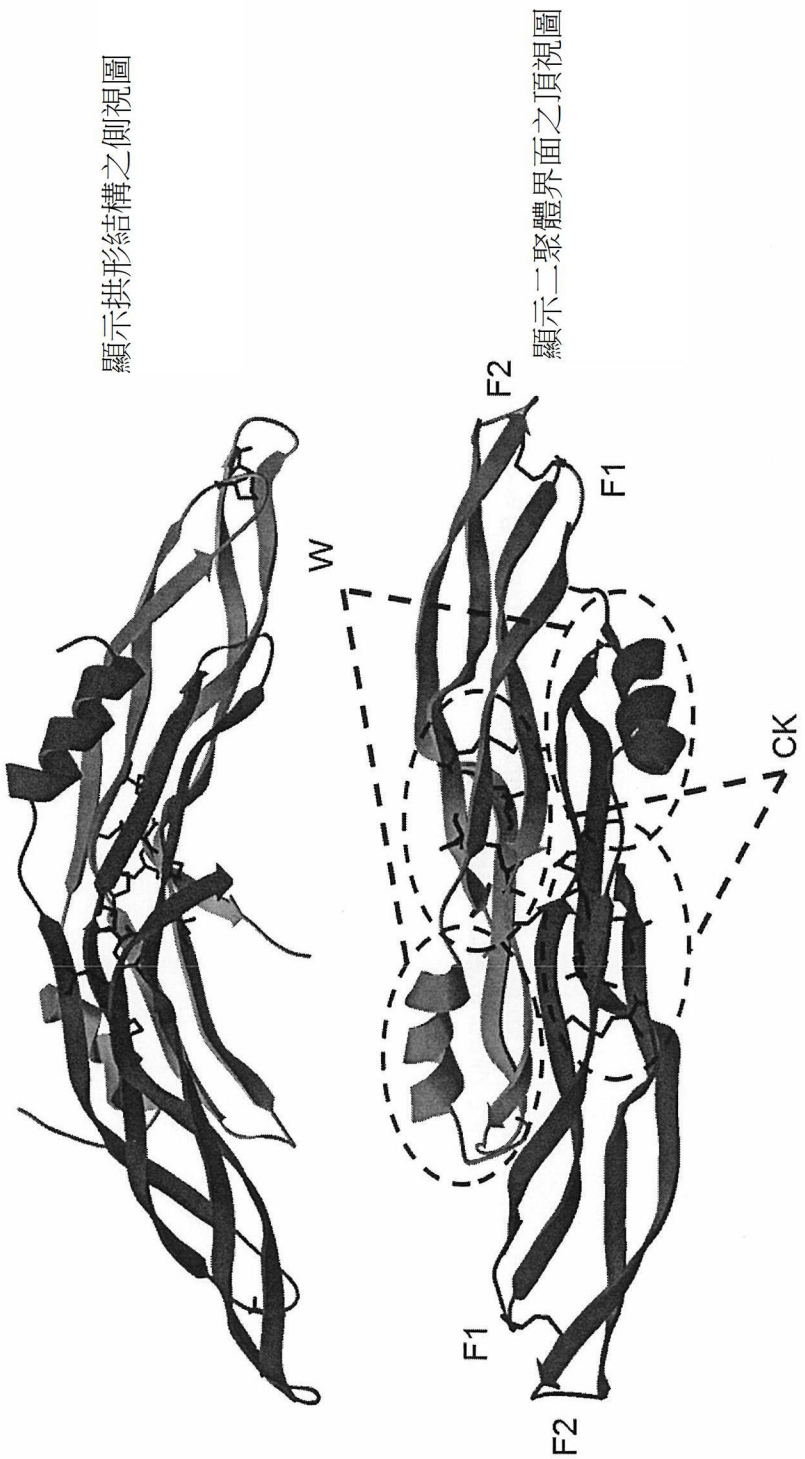
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ATOM   3459  CB  THR D 150      77.953  11.336  11.052  1.00 55.05      D    C
ATOM   3460  OG1 THR D 150      79.061  12.245  11.061  1.00 58.15      D    O
ATOM   3461  CG2 THR D 150      78.494   9.932  10.918  1.00 54.91      D    C
ATOM   3462  C   THR D 150      75.963  10.613   9.630  1.00 49.64      D    C
ATOM   3463  O   THR D 150      75.058  10.463  10.415  1.00 52.19      D    O
ATOM   3464  N   ARG D 151      76.069   9.897   8.524  1.00 46.71      D    N
ATOM   3465  CA  ARG D 151      75.089   8.900   8.172  1.00 46.60      D    C
ATOM   3466  CB  ARG D 151      74.248   9.377   6.984  1.00 47.36      D    C
ATOM   3467  CG  ARG D 151      74.872   9.123   5.634  1.00 51.71      D    C
ATOM   3468  CD  ARG D 151      74.690  10.253   4.621  1.00 57.59      D    C
ATOM   3469  NE  ARG D 151      73.314  10.741   4.458  1.00 55.78      D    N
ATOM   3470  CZ  ARG D 151      72.968  11.998   4.159  1.00 57.51      D    C
ATOM   3471  NH1 ARG D 151      73.877  12.951   3.999  1.00 56.63      D    N
ATOM   3472  NH2 ARG D 151      71.688  12.317   4.028  1.00 61.12      D    N
ATOM   3473  C   ARG D 151      75.794   7.579   7.862  1.00 45.50      D    C
ATOM   3474  O   ARG D 151      76.987   7.546   7.585  1.00 44.47      D    O
ATOM   3475  N   VAL D 152      75.050   6.485   7.945  1.00 43.35      D    N
ATOM   3476  CA  VAL D 152      75.606   5.159   7.724  1.00 41.20      D    C
ATOM   3477  CB  VAL D 152      74.679   4.065   8.306  1.00 39.62      D    C
ATOM   3478  CG1 VAL D 152      75.116   2.678   7.867  1.00 39.30      D    C
ATOM   3479  CG2 VAL D 152      74.620   4.153   9.815  1.00 38.25      D    C
ATOM   3480  C   VAL D 152      75.755   4.978   6.220  1.00 42.44      D    C
ATOM   3481  O   VAL D 152      74.884   5.382   5.463  1.00 37.85      D    O
ATOM   3482  N   LYS D 153      76.860   4.376   5.800  1.00 45.95      D    N
ATOM   3483  CA  LYS D 153      77.094   4.102   4.394  1.00 50.20      D    C
ATOM   3484  CB  LYS D 153      78.542   4.447   4.020  1.00 57.18      D    C
ATOM   3485  CG  LYS D 153      78.844   4.422   2.533  1.00 59.94      D    C
ATOM   3486  CD  LYS D 153      80.191   5.041   2.139  1.00 67.24      D    C
ATOM   3487  CE  LYS D 153      80.973   4.276   1.046  1.00 70.37      D    C
ATOM   3488  NZ  LYS D 153      80.393   4.368  -0.335  1.00 68.90      D    N
ATOM   3489  C   LYS D 153      76.846   2.644   4.097  1.00 48.69      D    C
ATOM   3490  O   LYS D 153      76.019   2.325   3.255  1.00 49.79      D    O
ATOM   3491  N   GLN D 154      77.574   1.764   4.788  1.00 47.08      D    N
ATOM   3492  CA  GLN D 154      77.536   0.336   4.499  1.00 46.80      D    C
ATOM   3493  CB  GLN D 154      78.731  -0.067   3.639  1.00 52.03      D    C
ATOM   3494  CG  GLN D 154      78.736  -1.546   3.174  1.00 61.17      D    C
ATOM   3495  CD  GLN D 154      77.945  -1.853   1.924  1.00 69.11      D    C
ATOM   3496  OE1 GLN D 154      78.518  -1.917   0.837  1.00 78.44      D    O
ATOM   3497  NE2 GLN D 154      76.652  -2.139   2.073  1.00 73.54      D    N
ATOM   3498  C   GLN D 154      77.534  -0.460   5.790  1.00 43.76      D    C
ATOM   3499  O   GLN D 154      78.343  -0.211   6.679  1.00 39.71      D    O
ATOM   3500  N   CYS D 155      76.599  -1.408   5.901  1.00 42.50      D    N
ATOM   3501  CA  CYS D 155      76.573  -2.346   7.033  1.00 41.07      D    C
ATOM   3502  CB  CYS D 155      75.141  -2.646   7.456  1.00 39.83      D    C
ATOM   3503  SG  CYS D 155      74.151  -1.162   7.738  1.00 40.54      D    S
ATOM   3504  C   CYS D 155      77.267  -3.651   6.686  1.00 41.42      D    C
ATOM   3505  O   CYS D 155      77.317  -4.051   5.531  1.00 42.79      D    O
ATOM   3506  N   ARG D 156      77.776  -4.323   7.701  1.00 42.61      D    N
ATOM   3507  CA  ARG D 156      78.373  -5.633   7.516  1.00 43.60      D    C
ATOM   3508  CB  ARG D 156      79.749  -5.508   6.848  1.00 48.29      D    C
ATOM   3509  CG  ARG D 156      79.712  -5.742   5.335  1.00 56.48      D    C
ATOM   3510  CD  ARG D 156      80.989  -5.685   4.547  1.00 66.09      D    C
ATOM   3511  NE  ARG D 156      81.911  -6.734   4.965  1.00 74.77      D    N
ATOM   3512  CZ  ARG D 156      82.856  -7.259   4.194  1.00 83.38      D    C
ATOM   3513  NH1 ARG D 156      83.015  -6.841   2.938  1.00 91.50      D    N
ATOM   3514  NH2 ARG D 156      83.640  -8.211   4.687  1.00 82.71      D    N
ATOM   3515  C   ARG D 156      78.454  -6.377   8.855  1.00 40.62      D    C
ATOM   3516  O   ARG D 156      78.332  -5.772   9.919  1.00 35.08      D    O
ATOM   3517  N   CYS D 157      78.592  -7.696   8.772  1.00 37.15      D    N
ATOM   3518  CA  CYS D 157      78.854  -8.523   9.928  1.00 34.59      D    C
ATOM   3519  CB  CYS D 157      78.667 -10.002   9.607  1.00 33.67      D    C
ATOM   3520  SG  CYS D 157      76.938 -10.514   9.529  1.00 36.35      D    S
ATOM   3521  C   CYS D 157      80.288  -8.288  10.323  1.00 35.68      D    C
ATOM   3522  O   CYS D 157      81.199  -8.776   9.655  1.00 34.15      D    O
ATOM   3523  N   ILE D 158      80.478  -7.551  11.411  1.00 35.59      D    N
ATOM   3524  CA  ILE D 158      81.797  -7.189  11.904  1.00 37.74      D    C
ATOM   3525  CB  ILE D 158      81.916  -5.653  12.034  1.00 38.99      D    C
ATOM   3526  CG1 ILE D 158      81.958  -5.027  10.635  1.00 42.76      D    C
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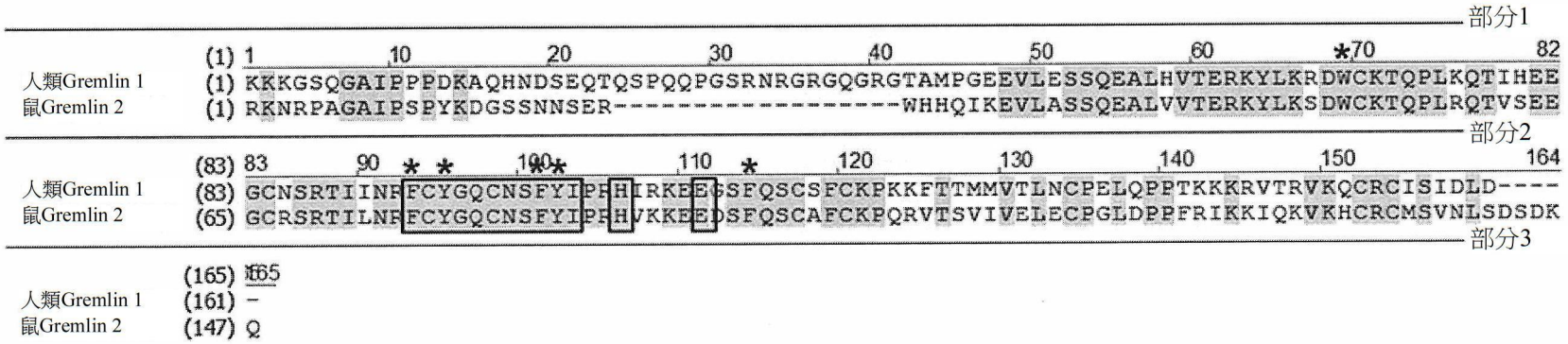
【圖1】(續)

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ATOM   3527  CD1 ILE D 158      81.562  -3.565  10.609  1.00 45.23      D    C
ATOM   3528  CG2 ILE D 158      83.143  -5.262  12.820  1.00 37.02      D    C
ATOM   3529  C   ILE D 158      82.023  -7.855  13.251  1.00 37.86      D    C
ATOM   3530  O   ILE D 158      81.196  -7.752  14.141  1.00 37.43      D    O
ATOM   3531  N   SER D 159      83.160  -8.523  13.399  1.00 39.55      D    N
ATOM   3532  CA  SER D 159      83.421  -9.300  14.590  1.00 39.84      D    C
ATOM   3533  CB  SER D 159      84.502 -10.346  14.330  1.00 39.50      D    C
ATOM   3534  OG  SER D 159      85.740  -9.884  14.814  1.00 40.74      D    O
ATOM   3535  C   SER D 159      83.797  -8.406  15.766  1.00 39.53      D    C
ATOM   3536  O   SER D 159      84.430  -7.378  15.606  1.00 44.63      D    O
ATOM   3537  N   ILE D 160      83.413  -8.835  16.956  1.00 38.89      D    N
ATOM   3538  CA  ILE D 160      83.593  -8.072  18.162  1.00 38.73      D    C
ATOM   3539  CB  ILE D 160      82.388  -8.245  19.085  1.00 39.99      D    C
ATOM   3540  CG1 ILE D 160      81.202  -7.511  18.491  1.00 41.71      D    C
ATOM   3541  CD1 ILE D 160      79.937  -7.693  19.294  1.00 44.39      D    C
ATOM   3542  CG2 ILE D 160      82.648  -7.712  20.486  1.00 41.37      D    C
ATOM   3543  C   ILE D 160      84.829  -8.620  18.826  1.00 42.65      D    C
ATOM   3544  O   ILE D 160      85.153  -9.801  18.695  1.00 48.72      D    O
ATOM   3545  N   ASP D 161      85.530  -7.759  19.542  1.00 45.71      D    N
ATOM   3546  CA  ASP D 161      86.757  -8.160  20.212  1.00 45.52      D    C
ATOM   3547  CB  ASP D 161      87.639  -6.940  20.477  1.00 47.83      D    C
ATOM   3548  CG  ASP D 161      89.081  -7.308  20.921  1.00 52.56      D    C
ATOM   3549  OD1 ASP D 161      89.301  -8.367  21.570  1.00 53.19      D    O
ATOM   3550  OD2 ASP D 161      90.009  -6.513  20.628  1.00 53.87      D    O
ATOM   3551  C   ASP D 161      86.397  -8.909  21.503  1.00 47.82      D    C
ATOM   3552  O   ASP D 161      86.011  -8.300  22.492  1.00 48.70      D    O
ATOM   3553  N   LEU D 162      86.498 -10.236  21.455  1.00 47.09      D    N
ATOM   3554  CA  LEU D 162      86.106 -11.142  22.542  1.00 44.91      D    C
ATOM   3555  CB  LEU D 162      86.773 -10.798  23.899  1.00 43.07      D    C
ATOM   3556  CG  LEU D 162      88.273 -10.945  24.159  1.00 45.95      D    C
ATOM   3557  CD1 LEU D 162      89.091 -11.430  22.975  1.00 47.72      D    C
ATOM   3558  CD2 LEU D 162      88.863  -9.648  24.688  1.00 48.85      D    C
ATOM   3559  C   LEU D 162      84.568 -11.220  22.627  1.00 42.09      D    C
ATOM   3560  O   LEU D 162      83.931 -12.066  21.966  1.00 36.05      D    O
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【圖1】(續)

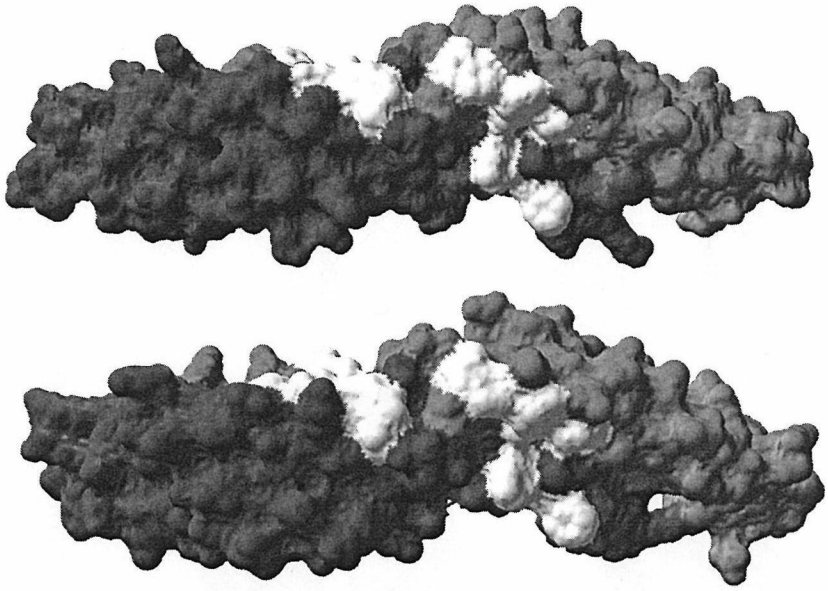


【圖2】



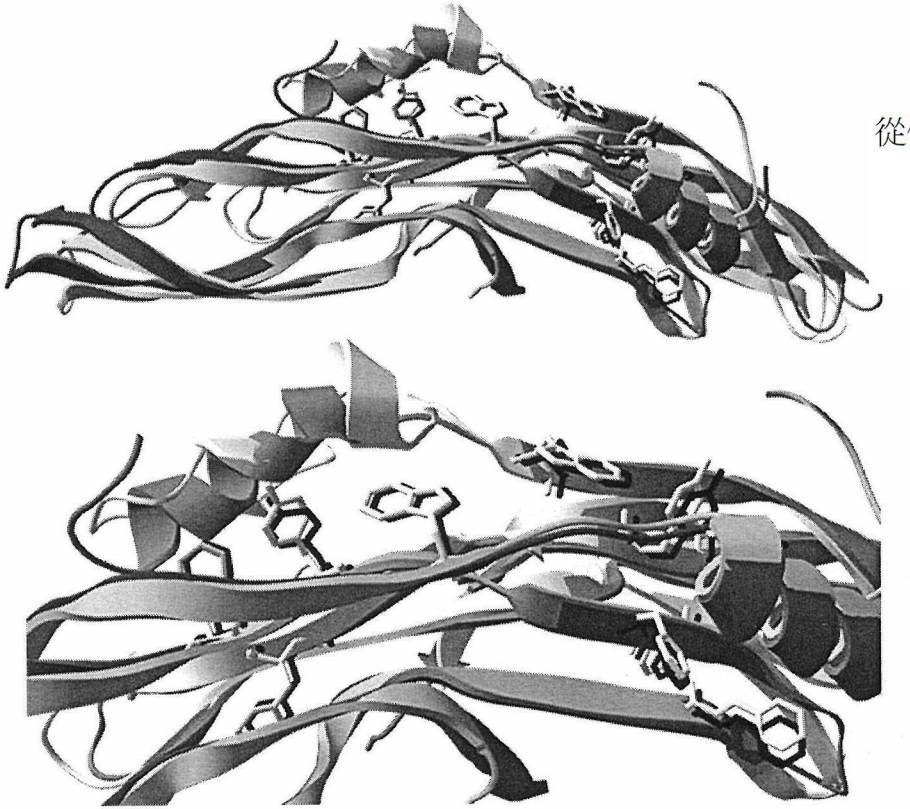
用星號標記的殘基在BMP結合中很重要，且在二聚體界面中形成關鍵接觸之殘基經加框標記。

【圖3】



以兩個灰度級表面渲染描繪各單體且以白色表面渲染描繪參與BMP結合之六個關鍵殘基。

【圖4】

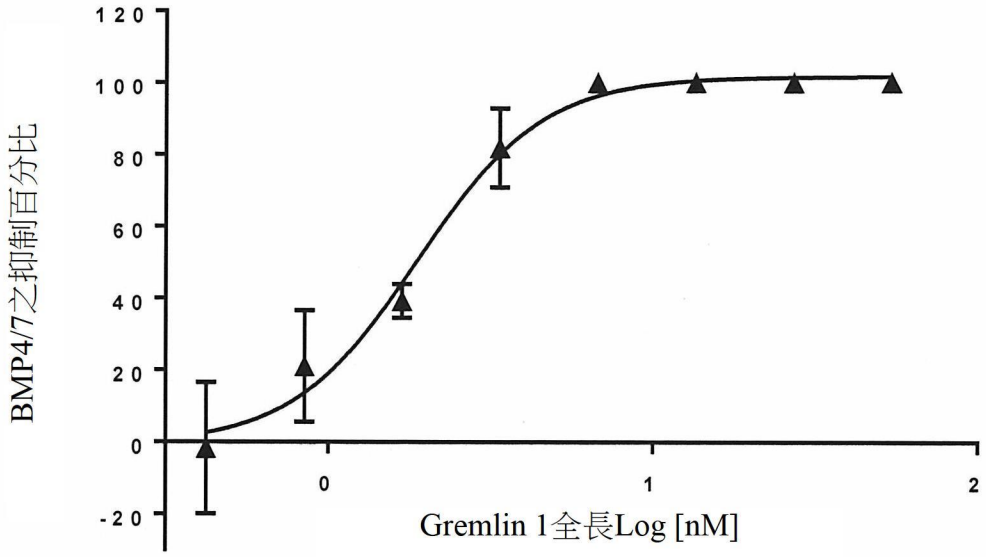


從側面觀測之顯示總摺疊相似性之比對。

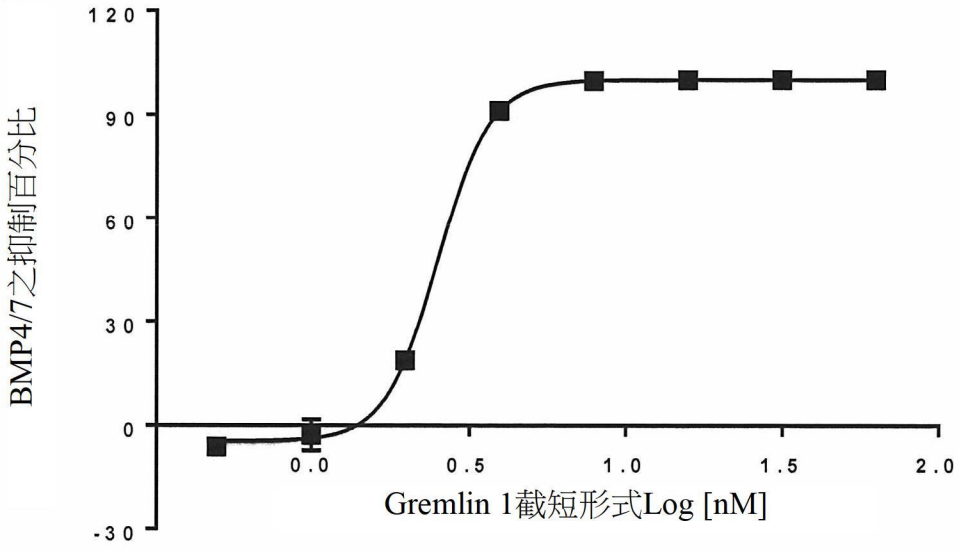
顯示參與BMP結合之殘基之細節視圖

上部圖像：比對兩種蛋白的帶狀圖像。
下部圖像：參與BMP結合之胺基酸詳細地顯示為棒(鼠Gremlin-2呈白色且人類Gremlin-1呈黑色)

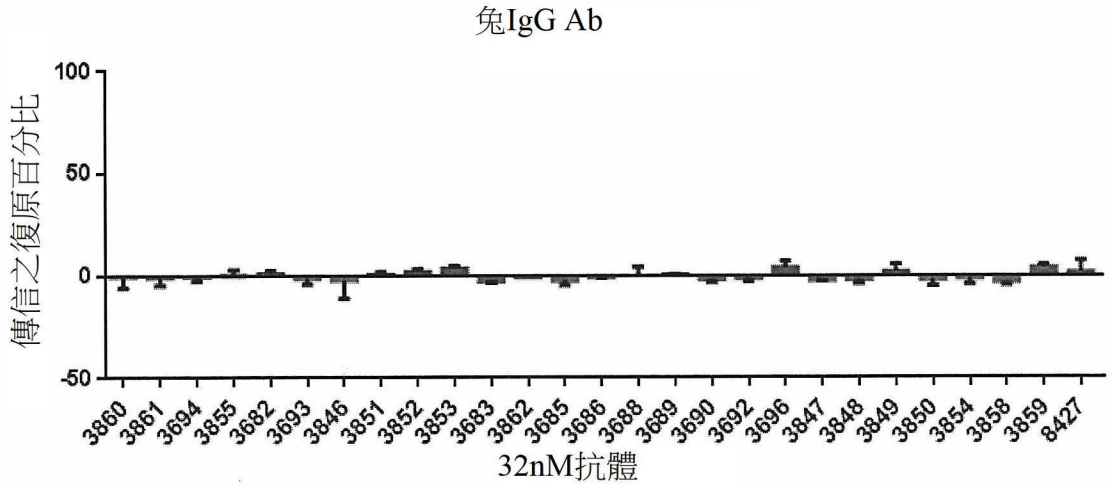
【圖5】


120
100
80
60
40
20
0
-20
BMP4/7之抑制百分比
0
1
2
Gremlin 1全長Log [nM]

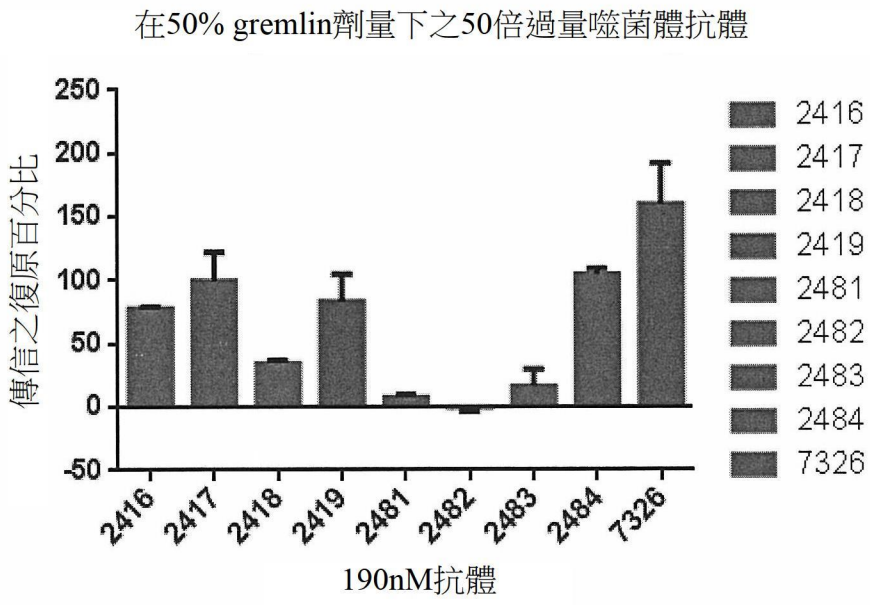
【圖6A】


120
90
60
30
0
-30
BMP4/7之抑制百分比
0.0
0.5
1.0
1.5
2.0
Gremlin 1截短形式Log [nM]

【圖6B】

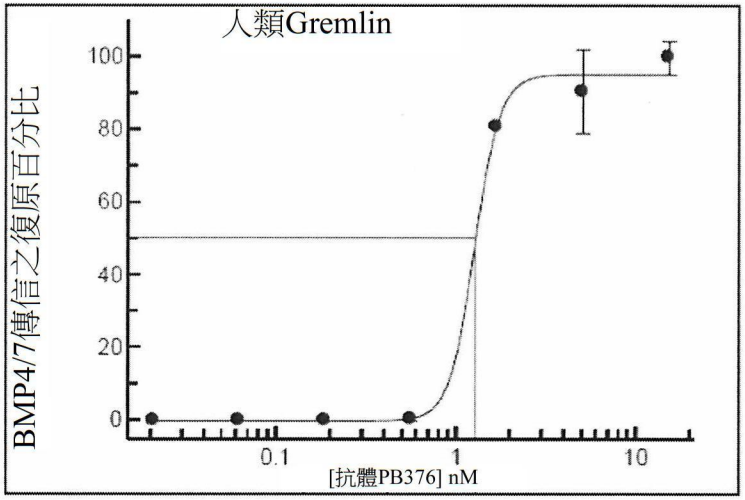

兔IgG Ab
傳信之復原百分比
100
50
0
-50
3860
3861
3694
3855
3682
3693
3846
3851
3852
3853
3683
3862
3685
3686
3688
3689
3690
3692
3696
3847
3848
3849
3850
3854
3858
3859
8427
32nM抗體

【圖7】

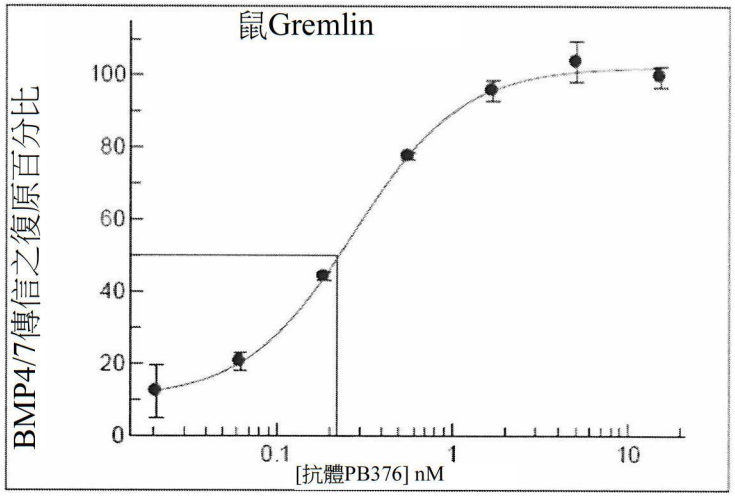

在50% gremlin劑量下之50倍過量噬菌體抗體
傳信之復原百分比
250
200
150
100
50
0
-50
2416
2417
2418
2419
2481
2482
2483
2484
7326
190nM抗體

【圖8】

跨板的7個點之3倍滴定-最高濃度15 nM (10次100% Gremlin劑量)

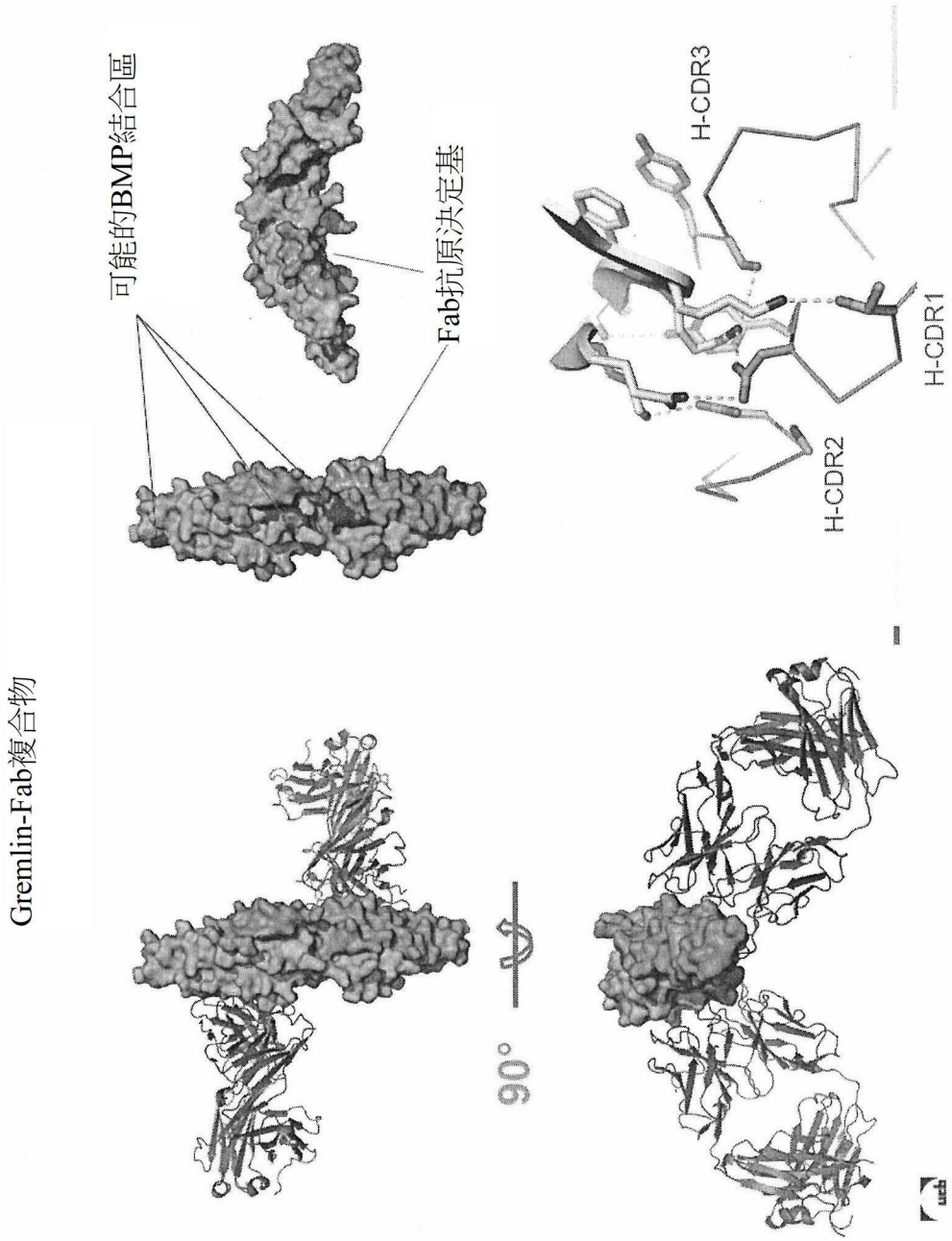


人類Gremlin	IC50(nM)	IC80(nM)
PB376	1.3	1.6

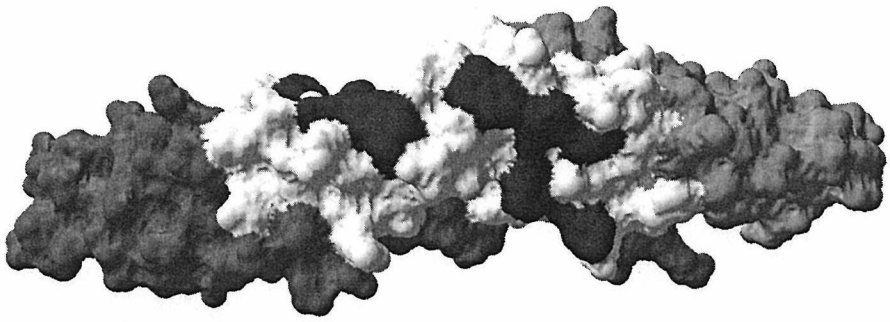


鼠Gremlin	IC50(nM)	IC80(nM)
2898	0.7	1.9
PB376	0.2	0.6

【圖9】



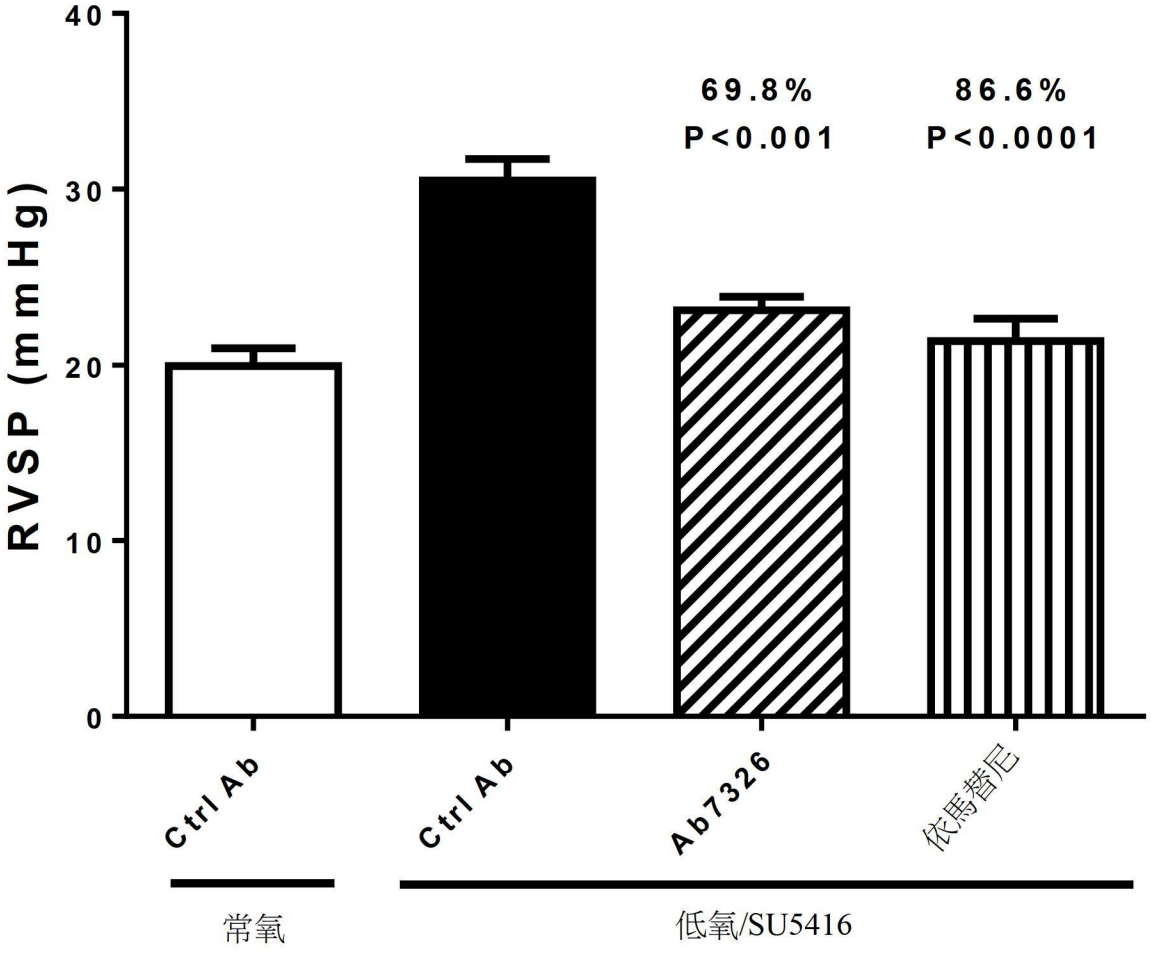
【圖10】



人類Gremlin 1

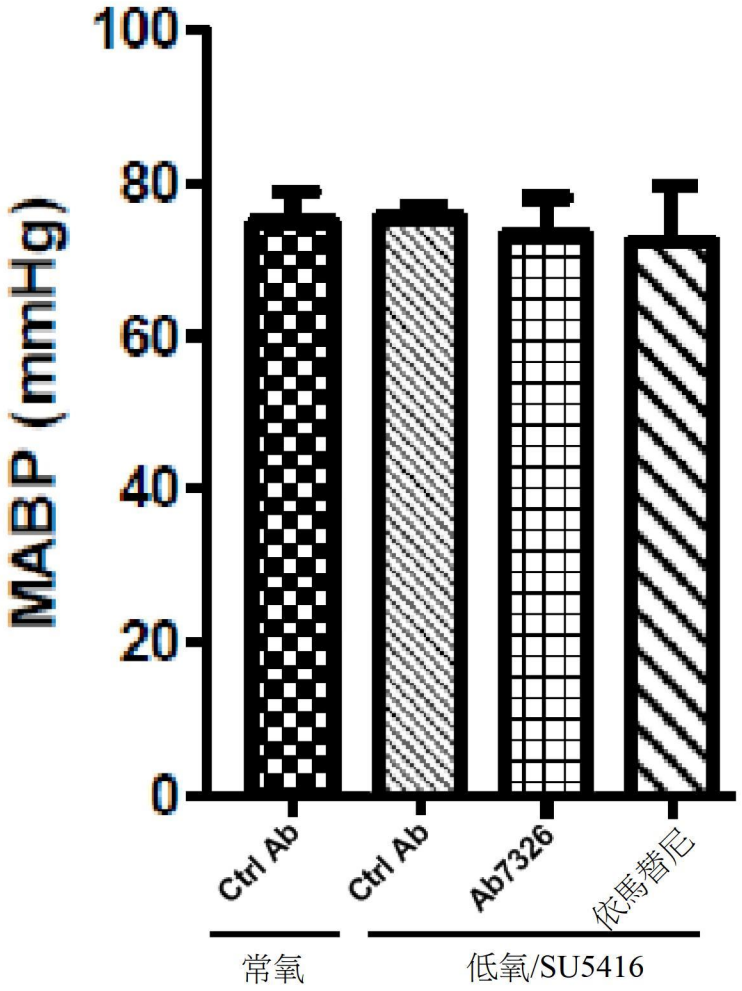
【圖11】

右心室收縮壓(RVSP)之評估



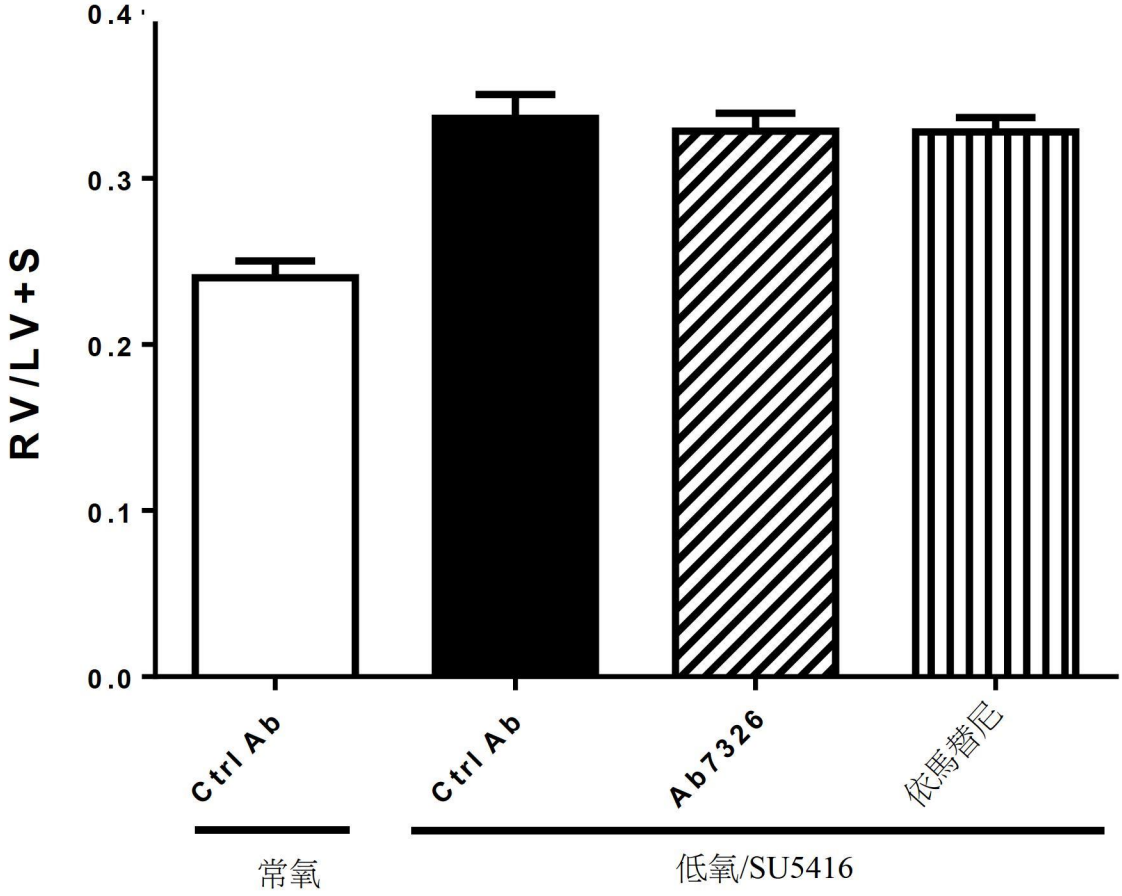
【圖12】

平均動脈系統壓(MABP)之評估

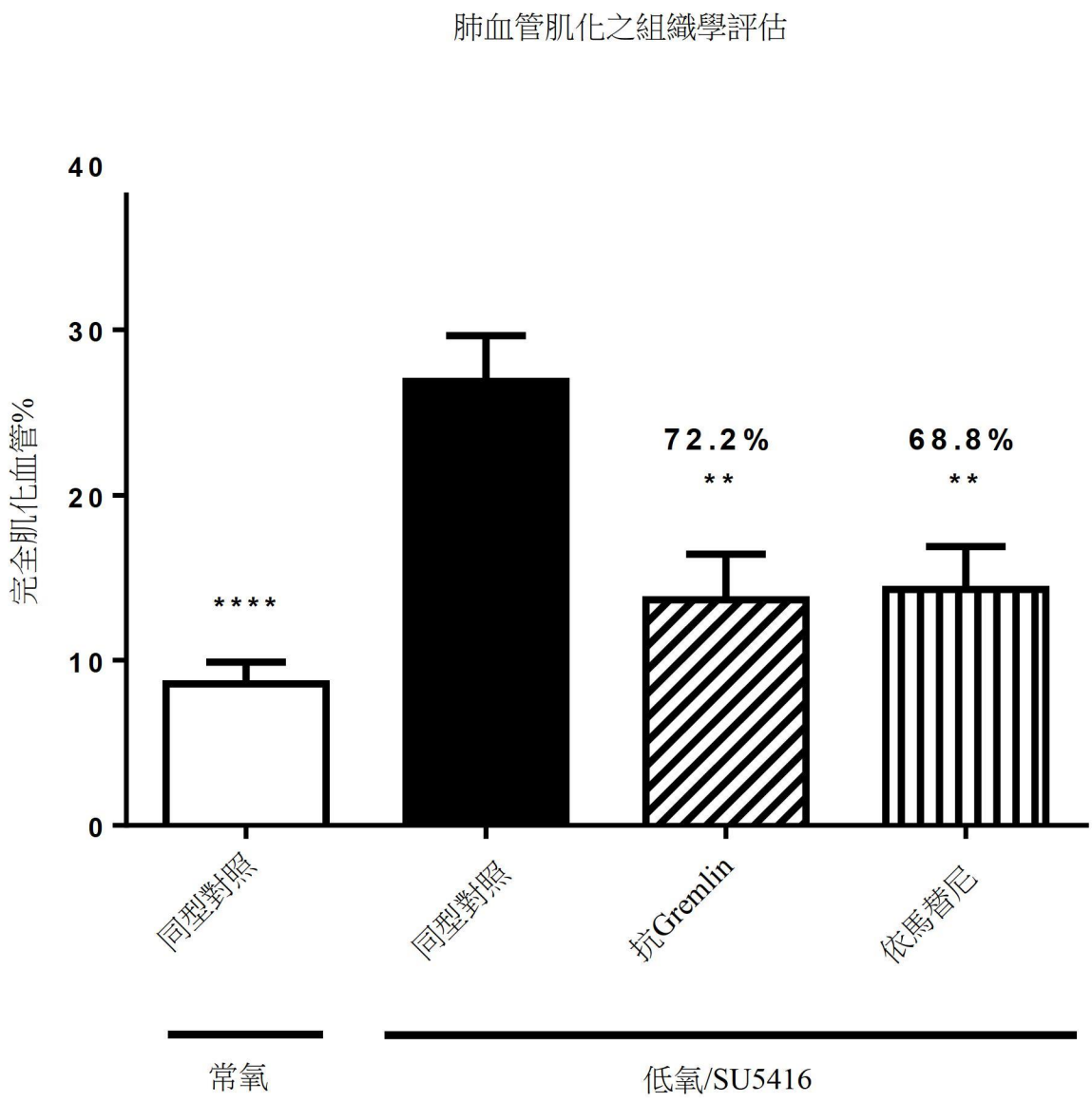


【圖13】

右心室肥大之評估(RV/LV + S)



【圖14】


肺血管肌化之組織學評估
完全肌化血管%
40
30
20
10
0
****
72.2%
**
68.8%
**
同型對照
同型對照
抗Gremlin
依馬替尼
常氧
低氧/SU5416

【圖15】