(19) DANMARK

(10) DK/EP 2250279 T3

(12) Oversættelse af europæisk patentskrift

Patent- og Varemærkestyrelsen

(51) Int.Cl.: *C 07 K 16/28 (2006.01)* *A 61 K 39/00 (2006.01)*

(45) Oversættelsen bekendtgjort den: **2016-08-01**

(80) Dato for Den Europæiske Patentmyndigheds bekendtgørelse om meddelelse af patentet: **2016-04-13**

(86) Europæisk ansøgning nr.: **09707396.9**

(86) Europæisk indleveringsdag: **2009-02-06**

(87) Den europæiske ansøgnings publiceringsdag: **2010-11-17**

(86) International ansøgning nr.: **US2009033358**

(87) Internationalt publikationsnr.: **WO2009100309**

(30) Prioritet: **2008-02-08 US 6962 P**
2008-03-07 US 34618 P
2008-05-02 US 49970 P

(84) Designerede stater: **AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HR HU IE IS IT LI LT LU LV MC MK MT NL NO PL PT RO SE SI SK TR**

(73) Patenthaver: **MedImmune, LLC, One MedImmune Way, Gaithersburg, MD 20878, USA**

(72) Opfinder: **COYLE, Anthony, 1155 23rd Street, Washington, DC 20037, USA**
KIENER, Peter, 14017 Gorky Drive, Potomac, MD 20854, USA
WU, Herren, 14405 Havest Moon Road, Boyds, MD 20841, USA
CIBOTTI, Ricardo, 7102 Amy Lane, Bethesda, MD, USA

(74) Fuldmægtig i Danmark: **RWS Group, Europa House, Chiltern Park, Chiltern Hill, Chalfont St Peter, Bucks SL9 9FG, Storbritannien**

(54) Benævnelse: **ANTI-IFNAR1-ANTISTOFFER MED REDUCERET FC-LIGANDAFFINITET**

(56) Fremdragne publikationer:
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DESCRIPTION

1. FIELD OF THE INVENTION

[0001] The present invention relates to isolated antibodies and compositions specific for the interferon alpha receptor 1 (IFNAR1) with reduced affinity for Fc ligands. The invention also comprises nucleic acids encoding such antibodies, complementary nucleic acids, vectors, host cells, and methods of making and using thereof, including therapeutic compositions, formulations, administrations and devices.

2. BACKGROUND OF THE INVENTION

2.1 Interferons:

[0002] Type I interferons (IFN) (IFNα, IFNβ, IFNω, IFNτ) are a family of structurally related cytokines having antiviral, antitumor and immunomodulatory effects (Hardy et al. (2001) Blood 97:473; Cutrone and Langer (2001) J. Biol. Chem. 276:17140). The human IFNα locus includes two subfamilies. The first subfamily consists of 14 non-allelic genes and 4 pseudogenes having at least 80% homology. The second subfamily, αII or omega (ω), contains 5 pseudogenes and 1 functional gene which exhibits 70% homology with the IFNα genes (Weissmann and Weber (1986) Prog. Nucl. Acid Res. Mol. Biol., 33:251-300). The subtypes of IFNα have different specific activities but they possess the same biological spectrum (Streuli et al. (1981) Proc. Natl. Acad. Sci. USA 78:2848) and have the same cellular receptor (Agnet M. et al. in "Interferon 5" Ed. I. Gresser p. 1-22, Academic Press, London 1983). Interferon alpha subtypes have been identified with the following nomenclature: IFNα 1, 2a, 2b, 4, 4b, 5, 6, 7, 8, 10, 14, 16, 17, and 21.

[0003] The interferon β (IFNβ) is encoded by a single gene, which has approximately 50% homology with the IFNα genes.

[0004] Interferon γ, which is produced by activated lymphocytes, does not possess any homology with the alpha/beta interferons and it does not react with their receptor.

2.1.1 Interferon receptors:

[0005] All human type I interferons bind to a cell surface receptor (IFN alpha receptor, IFNAR) consisting of two transmembrane proteins, IFNAR1 and IFNAR2 (Uze et al. (1990) Cell 60:225; Novick et al. (1994) Cell 77:391). IFNAR1 is essential for high affinity binding and differential specificity of the IFNAR complex (Cutrone et al. (2001) J. Bio Chem 276(20):17140-8) While functional differences for each of the type I IFN subtypes have not been identified, it is thought that each may exhibit different interactions with the IFNAR receptor components leading to potentially diverse signaling outcomes (Cook et al. (1996) J. Biol. Chem. 271:13448). In particular, studies utilizing mutant forms of IFNAR1 and IFNAR2 suggested that alpha and beta interferons signal differently through the receptor by interacting differentially with respective chains (Lewerenz et al. (1998) J. Mol. Biol. 282:585).

2.1.2 Function of interferons:

[0006] Early functional studies of type I IFNs focused on innate defense against viral infections (Haller et al. (1981) J. Exp. Med. 154:199; Lindenmann et al. (1981) Methods Enzymol. 78:181). More recent studies, however, implicate type I IFNs as potent immunoregulatory cytokines in the adaptive immune response. Specifically, type I IFNs have been shown to facilitate differentiation of naive T cells along the Th1 pathway (Brinkmann et al. (1993) J. Exp. Med. 178:1655), to enhance antibody production (Finkelman et al. (1991) J. Exp. Med. 174:1179) and to support the functional activity and survival of memory T cells (Santini et al. (2000) J. Exp. Med. 191:1777; Tough et al. (1996) Science 272:1947).

[0007] Recent work by a number of groups suggests that IFNα may enhance the maturation or activation of dendritic cells (DCs) (Santini et al. (2000) J. Exp. Med. 191:1777; Luft et al. (1998) J. Immunol. 161:1947; Luft et al. (2002) Int. Immunol. 14:367; Radvanyi et al. (1999) Scand. J. Immunol. 50:499). Furthermore, increased expression of type I interferons has been described in numerous autoimmune diseases (Foulis et al. (1987) Lancet 2:1423; Hooks et al. (1982) Arthritis Rheum. 25:396; Hertzog et al.

(1988) Clin. Immunol. Immunopathol. 48:192; Hopkins and Meager (1988) Clin. Exp. Immunol. 73:88; Arvin and Miller (1984) Arthritis Rheum. 27:582). The most studied examples of this are insulin-dependent diabetes mellitus (IDDM) (Foulis (1987)) and systemic lupus erythematosus (SLE) (Hooks (1982)), which are associated with elevated levels of IFNα, and rheumatoid arthritis (RA) (Hertzog (1988), Hopkins and Meager (1988), Arvin and Miller (1984)), in which IFNβ may play a more significant role.

[0008] Moreover, administration of interferon α has been reported to exacerbate underlying disease in patients with psoriasis and multiple sclerosis and to induce an SLE-like syndrome in patients without a previous history of autoimmune disease. Interferon α has also been shown to induce glomerulonephritis in normal mice and to accelerate the onset of the spontaneous autoimmune disease of NZB/W mice. Further, IFNα therapy has been shown in some cases to lead to undesired side effects, including fever and neurological disorders. Hence there are pathological situations in which inhibition of Type I IFN activity may be beneficial to the patient and a need exists for agents effective in inhibiting Type I IFN activity.

2.1.3 Antibody Effector Functions:

[0009] The Fc region of an antibody interacts with a number of ligands (also referred herein as "Fc ligands" which include but are not limited to agents that specifically bind to the Fc region of antibodies, such as Fc receptors and C1q) including Fc receptors and C1q, imparting an array of important functional capabilities referred to as effector functions. The Fc receptors mediate communication between antibodies and the cellular arm of the immune system (Raghavan et al., 1996, Annu Rev Cell Dev Biol 12:181-220; Ravetch et al., 2001, Annu Rev Immunol 19:275-290). In humans this protein family includes FcγRI (CD64), including isoforms FcγRIA, FcγRIB, and FcγRIC; FcγRII (CD32), including isoforms FcγRIIA, FcγRIIB, and FcγRIIC; and FcγRIII (CD16), including isoforms FcγRIIIA and FcγRIIB (Jefferis et al., 2002, Immunol Lett 82:57-65). These receptors typically have an extracellular domain that mediates binding to Fc, a membrane spanning region, and an intracellular domain that may mediate some signaling event within the cell. These receptors are expressed in a variety of immune cells including monocytes, macrophages, neutrophils, dendritic cells, eosinophils, mast cells, platelets, B cells, large granular lymphocytes, Langerhans' cells, natural killer (NK) cells, and T cells. Formation of the Fc/FcγR complex recruits these effector cells to sites of bound antigen, typically resulting in signaling events within the cells and important subsequent immune responses such as release of inflammation mediators, B cell activation, endocytosis, phagocytosis, and cytotoxic attack. The ability to mediate cytotoxic and phagocytic effector functions is a potential mechanism by which antibodies destroy targeted cells. The cell-mediated reaction wherein nonspecific cytotoxic cells that express FcγRs recognize bound antibody on a target cell and subsequently cause lysis of the target cell is referred to as antibody dependent cell-mediated cytotoxicity (ADCC) (Raghavan et al., 1996, Annu Rev Cell Dev Biol 12:181-220; Ghetie et al., 2000, Annu Rev Immunol 18:739-766; Ravetch et al., 2001, Annu Rev Immunol 19:275-290). The cell-mediated reaction wherein nonspecific cytotoxic cells that express FcγRs recognize bound antibody on a target cell and subsequently cause phagocytosis of the target cell is referred to as antibody dependent cell-mediated phagocytosis (ADCP). In addition, an overlapping site on the Fc region of the molecule also controls the activation of a cell independent cytotoxic function mediated by complement, otherwise known as complement dependent cytotoxicity (CDC).

2.1.4 The different types of human FcγR:

[0010] Human FcγRs are divided into three distinct classes: FcγRI (CD64), FcγRII (CD32) and FcγRIII (CD16). FcγRI is a high affinity receptor (K_a: 10^8-10^9 M^{-1}) and binds both immune complexes and monomeric IgG molecules while the Fc receptors FcγRII and FcγRIII exhibit lower affinities (<10^7 M^{-1} and 2-3x10^7 respectively) (Gessner J.E. et al., 1998, Ann. Hematology 76:231-48). Signaling through the FcγRs is either through an immunoreceptor tyrosine-based activation motif (ITAM) or immunoreceptor tyrosine-based inhibitory motif (ITIM) for all the transmembrane receptors (Presta, 2006, Adv. Drug Deliv. Rev 58:640-656).

[0011] The 72 kDa extracellular glycoprotein FcγRI is mainly expressed on myeloid cells such as monocytes, macrophages CD4+ progenitor cells and may elicit the ADCC, endocytosis, and phagocytosis responses (Siberil et al., 2006, J. Immunol. Lett. 106:111-118).

[0012] The 40 kDa FcγRII group of receptors (A, B and C isoforms) exhibit extracellular domains but do not contain active signal transduction domains. These receptors propagate signals through phosphorylation of a cytoplasmic tail domain (Amigorena S. et al., 1992 Science. 256:1808-12). The FcγRIIA is mainly expressed on monocytes, macrophages, neutrophils, and platelets whereas the FcγRIIC receptor has only been identified on NK cells. These two receptors have been shown to initiate ADCC, endocytosis, phagocytosis and inflammatory mediator release (Cassel et al., 1993. Mol Immunol 30:451-60). By contrast, the

FcγRIIB (B1 and B2 types) receptors are expressed on B cells, Mast cells, basophils, monocytes, macrophages and dendritic cells and have been shown to downregulate the immune response triggered by the A and C isoforms.

[0013] The 50 kDa FcγRIIIA, is expressed on NK cells, monocytes, macrophages and a subset of T lymphocytes where it activates ADCC, phagocytosis, endocytosis and cytokine release (Gessner *et al.*). The FcγRIIIB isoform is a glycosyl-phosphatidylinositol (GPI) anchored peripheral membrane protein involved in the degranulation and the production of reactive oxygen intermediates (Salmon J.E. et al., 1995, J. Clin. Inves. 95:2877-85).

[0014] IgG molecules also exhibit differential isotype specificity for FcγRs. IgG3 molecules bind strongly to all FcγR isoforms. IgG1, the most prevalent isoform in the blood binds to all FcγRs albeit with a lower affinity for the FcγRIIA/B isoforms. IgG4 is an intermediate binder to FcγRI and a weak binder to FcγRIIB. Finally, IgG2 binds only weakly to one allelic form of FcγRIIA (FcγRIIA-H131) (Siberil et al., 2006, J. Immunol. Lett. 106:111-118).

2.1.5 Complement

[0015] The complement inflammatory cascade is a part of the innate immune response and is crucial to the ability for an individual to ward off infection. Another important Fc ligand is the complement protein C1q. Fc binding to C1q mediates a process called complement dependent cytotoxicity (CDC) (reviewed in Ward et al., 1995, Ther Immunol 2:77-94). C1q is capable of binding six antibodies, although binding to two IgGs is sufficient to activate the complement cascade. C1q forms a complex with the C1r and C1s serine proteases to form the C1 complex of the complement pathway.

2.1.6 Regions and amino-acid residues of IgG involved in FcγR binding

[0016] The mapping of human IgG binding sites to different FcγR has been studied extensively. These studies, based on genetically altered IgG molecules have identified a short continuous stretch of amino acid residues (234-238) of the N-terminus part of the CH2 domain as being directly involved in the binding to all FcγRs. Additionally, residues 268, 297, 327 and 329 may impact binding to a subset of FcγRs. Also, multiple residues located in the CH2 and CH3 domains also contribute to FcγR binding (Canfield SM. et al., 1991, J. Exp. Med. 173:1483-91; Chappel MS. et al., 1991, Proc Nat Acad Sci USA 888:9036-40 ; Gergely J. et al., 1990 FASEB J 4:3275-83).

2.2 Antibody therapeutic related toxicity

[0017] In many circumstances, the binding and stimulation of effector functions mediated by the Fc region of immunoglobulins is highly beneficial, however, in certain instances it may be more advantageous to decrease or eliminate effector function. This is particularly true for those antibodies designed to deliver a drug (e.g., toxins and isotopes) to the target cell where the Fc/FcγR mediated effector functions bring healthy immune cells into the proximity of the deadly payload, resulting in depletion of normal lymphoid tissue along with the target cells (Hutchins et al., 1995, PNAS USA 92:11980-11984; White et al., 2001, Annu. Rev. Med. 52:125-145). In these cases the use of antibodies that poorly recruit complement or effector cells would be of tremendous benefit (see for example, Wu et al., 2000, Cell Immunol 200:16-26; Shields et al., 2001, J. Biol. Chem 276:6591-6604; U.S. 6,194,551; U.S. 5,885,573 and PCT publication WO 04/029207).

[0018] In other instances, for example, where blocking the interaction of a widely expressed receptor with its cognate ligand is the objective, it would be advantageous to decrease or eliminate all antibody effector function to reduce unwanted toxicity. Also, in the instance where a therapeutic antibody exhibited promiscuous binding across a number of human tissues it would be prudent to limit the targeting of effector function to a diverse set of tissues to limit toxicity. Although there are certain subclasses of human immunoglobulins that lack specific effector functions, there are no known naturally-occurring immunoglobulins that lack all effector functions. An alternate approach would be to engineer or mutate the critical residues in the Fc region that are responsible for effector function. For examples see publications WO2006076594, WO1999058572 US20060134709, WO2006047350, WO2006053301, and U.S. 5,624,821.

[0019] The use of monoclonal antibodies in the treatment of many disease states has been well documented. With the myriad of effector functions that an antibody can trigger, one of the requirements of antibody therapeutics is that they are targeted specifically to a target of interest. For example, but not limited to, the specificity of a target tissue is analyzed by examining the immunohistochemistry (IHC) of a tissue of interest. It is important that the therapeutic only bind to tissues that contain a target of

interest. Failure to do so could result in higher toxicity of the antibody therapeutic due to inappropriate activation of effector function elicited at the non-targeted site. If the effector function could be diminished or ablated, the danger of the widespread binding of the therapeutic could be avoided. With all these considerations, there is an unmet need for antibodies with reduced or ablated affinity for at least one Fc ligand responsible for facilitating effector function. Such antibodies would be of particular benefit for use in the treatment of chronic inflammatory and autoimmune conditions.

[0020] US 2006/0029601 A1 describes isolated human monoclonal antibodies that bind IFNAR-1 and inhibit the biological activity of type I interferon; modification of the Fc region at specified residues to alter the effector function of the antibody is also described.

[0021] US 2005/0226876 A1 describes various modifications of the Fc region of an anti-P-selectin antibody to reduce FcR binding.

[0022] Radaev et al., (2001) J. Biol. Chem., vol. 276: 16469 - 16477 describes the structure of a human type III Fcγ receptor in complex with a human IgG Fc region.

[0023] Shields et al., (2001) J. Bio. Chem., vol 276: 6591 - 6604 describes high resolution mapping of the binding site on human IgG1 for FcγRI, FcγRII, FcγRIII and FcRn and design of IgG1 variants with improved binding to FcγR.

[0024] US 2004/0132101 A1 describes an Fc region modified to reduce binding to an Fc ligand.

[0025] WO 2006/002177 A2 describes human monoclonal antibodies that bind to IFNAR-1 and are capable of inhibiting the biological activity of Type I interferons

[0026] US 6, 194, 551 B1 describes a variant human IgG3 Fc region with altered effector function.

[0027] WO 94/029351 A2 describes modifications of Fc that alter effector function.

[0028] US 5, 624, 821 A describes modifications of Fc that alter effector function.

[0029] US 5, 648, 260 A describes alterations of Fc that affect effector function and decrease binding to the high affinity Fc receptor.

[0030] WO 2006/036291 A2 describes modifications that impair effector function of antibodies.

[0031] EP 1 707 627 A1 describes Fc modifications that decrease ADCC.

[0032] Armour et al., (2003) Molecular Immunology Vol. 40, No. 9: 585-593 describe differential binding to human FcγRIIa and FcγRIIb receptors by human IgG wildtype and mutant antibodies.

[0033] Organesyan et al., (2008) Acta Crystallographica Section D: Biological Crystallography vol. 64, no. 6: 700 - 704 describe structural characterization of a human Fc fragment engineered for lack of effector functions.

3. BRIEF DESCRIPTION OF THE FIGURES

[0034]

Figure 1A. Nucleic acid (SEQ ID No:7) and amino acid (SEQ ID No:8) sequence alignment of 3F11 VH with the CDR regions are indicated by the overline.

Figure 1B. Nucleic acid (SEQ ID No:9) and amino acid (SEQ ID No: 10) sequence alignment of 3F11 VK with the CDR regions outlined are indicated by the overline.

Figure 2A. Nucleic acid (SEQ ID No:17) and amino acid (SEQ ID No:18) sequence alignment of 4G5 VH with the CDR regions outlined are indicated by the overline.

Figure 2B. Nucleic acid (SEQ ID No:19) and amino acid (SEQ ID No:20) sequence alignment of 4G5 VK with the CDR regions

outlined are indicated by the overline.

Figure 3A. Nucleic acid (SEQ ID No:27) and amino acid (SEQ ID No:28) sequence alignment of 11E2 VH with the CDR regions outlined are indicated by the overline.

Figure 3B. Nucleic acid (SEQ ID No:29) and amino acid (SEQ ID No:30) sequence alignment of 11E2 VK with the CDR regions outlined are indicated by the overline.

Figure 4A. Nucleic acid (SEQ ID No:37) and amino acid (SEQ ID No:38) sequence alignment of 9D4 VH with the CDR regions outlined are indicated by the overline.

Figure 4B. Nucleic acid (SEQ ID No:39) and amino acid (SEQ ID No:40) sequence alignment of 9D4 VK with the CDR regions outlined are indicated by the overline.

Figure 5. Amino acid sequence alignment of heavy chain constant regions for 9D4. Arrows indicate amino acid substitutions (unmodified to modified) to increase stability and reduce affinity to at least one Fc ligand.

Figure 6A. Immunohistochemical staining profile of human cerebrum tissue treated with various anti-IFNAR1 antibodies. The 9D4 antibody exhibits a lower staining profile when incubated with human cerebrum tissue compared to 4G5 and MDX-1333 antibodies.

Figure 6B. Immunohistochemical staining profile of human monocytes treated with various anti-IFNAR1 antibodies. As a positive control, various anti-IFNAR1 antibodies were tested for reactivity to human monocytes.

Figure 7. The anti-IFNAR1 antibody 9D4 inhibits IFNα signaling in a cell based STAT activation assay. Treatment with antibody 9D4 inhibits STAT1/3/4 tyrosine phosphorylation in response to stimulation with interferon alpha as determined by Western Blot analysis with commercially available STAT antibodies.

Figure 8. Anti-IFNAR1 antibodies block signaling of various concentrations of pDC Cell derived Type IIFNs. Presented are the IC50 values for antibody 9D4 blocking IFN signaling in a luciferase reporter assay utilizing type I IFN supernatants purified from 3 independent donors. Included are the relative amounts of IFNα, IFNβ, and IFNω in each purified type I interferon supernatant.

Figure 9 A, B, C. Anti-IFNAR1 antibodies 9D4, 9D4-DM (Double Mutant), and 9D4-TM (Triple Mutant) exhibit similar binding characteristics. Presented are data representing the unmodified 9D4 antibody along with 2 modified antibodies, 9D4-DM and 9D4-TM. The modified antibodies exhibit similar IFNAR1 binding characteristics to the unmodified antibody.

Figure 10A. The anti-IFNAR1 antibody 9D4 binds soluble interferon alpha receptor (sIFNαR1). Presented are equilibrium binding data that demonstrate dose dependent binding of 9D4 to soluble interferon alpha receptor.

Figure 10B. Determination of the Kd of 9D4 on human PBMCs. Presented is the dissociation constant determination of 9D4 measured by binding to human PBMCs.

Figure 11. Anti-IFNAR1 antibodies inhibit IFNα induced signaling in a luciferase reporter assay. Anti-IFNAR1 antibodies including unmodified and modified antibodies demonstrate similar IC50 values for blocking Leukocyte IFN signaling in a luciferase reporter assay system.

Figure 12A. Determination of the isoelectric point of 9D4 (unmodified) and modified 9D4 antibodies. Presented is an IEF gel documenting the relative pI values for the 9D4 WT (unmodified), 9D4-DM, and 9D4-TM antibodies.

Figure 12B. Determination of the thermal melting temperatures of 9D4 (unmodified) and modified 9D4 antibodies. Presented here is a melt cure documenting the relative melting temperatures (Tm) for the 9D4, 9D4-DM, and 9D4-TM antibodies.

Figure 13. Prophylactic treatment with anti-IFNAR antibodies blocks Adv-IFNα induced proteinuria. Mice treated with control vector, Adv-IFNα, Adv-IFNα + isotype control pretreatment, and Adv-IFNα + anti-IFNAR pretreatment were analyzed for proteinuria over 9 weeks. Mice pretreated with anti-IFNAR did not exhibit proteinuria after IFNα challenge.

Figure 14. Prophylactic treatment with anti-IFNAR antibodies blocks the upregulation of IFNα responsive genes (IFIT1, IFI44, CXCL11, IFI202b, CXCL19, CXCL9) in blood. Mice pre-treated with anti-IFNAR antibodies did not exhibit not upregulated selected IFNα responsive genes upon challenge with adenovirus encoded IFN alpha as compared to mice pretreated with control virus, PBS, or isotype IgG controls. Presented are the relative expression of six genes known to be responsive to IFNα in blood samples taken from mice 3 weeks post IFNα induction by infection with Adv-IFNα.

Figure 15 A, B. Prophylactic treatment with anti-IFNAR antibodies blocks IFNα induced autoantibody production. Mice pre-treated with anti-IFNAR antibodies did not exhibit elevated autoantibody production upon challenge with adenovirus encoded IFNα as

compared to mice pretreated with control virus, PBS or isotype IgG controls. Presented are the concentrations of anti-dsDNA and anti-SSA/Ro in blood samples taken from mice 6 weeks post IFNα induction by infection with Adv-IFNα.

Figure 16 A, B. Prophylactic treatment with anti-IFNAR antibodies blocks the upregulation of cytokines in the kidney. Mice pretreated with anti-IFNAR antibodies did not exhibit upregulated cytokines in the kidney upon challenge with adenovirus encoded IFNα5 as compared to mice pretreated with, control virus, PBS or isotype IgG controls. Presented are the measurement of IP-10, and IL-18 levels in kidney samples taken from mice 6 weeks post IFNα induction by infection with Adv-IFNα5.

Figure 17. Prophylactic treatment with anti-IFNAR antibodies blocks IFN induced autoantibody production. Presented here are the relative titers of anti-nuclear antigen (ANA) antibodies from mouse serum. Mice pretreated with anti-IFNAR antibodies exhibited lower ANA serum titers after IFN challenge than mice pretreated with control virus, PBS, or isotype control.

Figure 18. Antibody mediated inhibition of SLE plasma mediated Dendritic cell development. Presented are the results of 5 individual experiments in which IFN derived from SLE patients was incubated in the presence of anti-IFNAR1 antibody 9D4 and subsequently added to human monocytes. The presence of anti-IFNAR1 antibody 9D4 inhibited the ability of IFN derived from SLE patients to induce the dendritic cell markers CD38 and CD 123 in differentiating monocytes.

Figure 19. Anti-IFNAR1 antibodies suppress the expression of CD38, CD123 and CD86 in monocytes stimulated with Leukocyte Interferon. As measured by percent suppression of control stimulated expression, anti-IFNAR1 antibodies 9D4, 9D4-DM and 9D4-TM exhibited similar inhibition profiles for the expression of CD38, CD123 and CD86 in differentiating monocytes.

Figure 20. Modified anti-IFNAR1 antibodies exhibit decreased binding to the Fc receptor FcγRI as compared to unmodified anti-IFNAR1 antibodies. Anti-IFNAR1 antibodies 9D4 (unmodified), 9D4-DM (modified) and 9D4-TM (modified) were analyzed for the ability to bind to plate bound FcγRI in an ELISA experiment. As a positive control for Fc receptor binding, an unrelated unmodified antibody was used (control antibody).

Figure 21, A, B, C. Modified anti-IFNAR1 antibodies exhibit decreased binding to the Fc receptor FcγRIIIA as compared to unmodified anti-IFNAR1 antibodies. Plate bound unmodified anti-IFNAR1 antibody 9D4(A) and modified anti-IFNAR1 antibodies 9D4-DM (B) and 9D4-TM(C) were analyzed for the ability to bind free FcγRIIIA in an ELISA experimental format.

Figure 22, A, B, C. Modified anti-IFNAR1 antibodies exhibit decreased binding to the Fc receptor FcγRIIIA. Free unmodified anti-IFNAR1 antibody 9D4(A) and modified anti-IFNAR1 antibodies 9D4-DM(B) and 9D4-TM(C) were analyzed for the ability to bind plate bound FcγRIIIA in an ELISA experimental format.

Figure 23 A-E. Neutralization of IFN subtypes in SLE patient serum. As measured by reporter assay, anti-IFNAR1 antibodies MDX-1333, 9D4-WT and 9D4-TM inhibited IFN mediated signaling of α10 (A), Leukocyte interferon (B), α2b (C), ω (D), and β (E).

Figure 24. Anti-IFNAR1 antibodies neutralize type I interferon from SLE patients. By reporter assay, the anti-IFNAR1 antibody, 9D4, inhibited type I interferon mediated signaling as compared to a control, unrelated antibody.

Figure 25 A-D. Anti-IFNAR antibodies suppress the IFNα induced pDC population in PBMC's. Anti-IFNAR antibodies blocked the elevation of pDC cells measured by cell surface epitope expression, induced by ectopic adenoviral induced expression of interferon alpha in spleen (A), lymph nodes (B), peripheral blood (C) and bone marrow (D).

Figure 26. Binding analysis of anti-IFNAR1 antibodies 9D4-WT, 9D4-DM, and 9D4-TM to the Fc receptor FcγRI was determined by BIACore analysis. Briefly, anti-IFNAR1 antibodies were immobilized and free FcγRI was added to measure affinity. As demonstrated by the tracing, the modified antibodies, 9D4-DM, and 9D4-TM exhibited lower affinities to the free FcγRI as compared to the unmodified 9D4-WT antibody.

Figure 27 A-C. Binding analysis of anti-IFNAR1 antibodies 9D4-WT, 9D4-DM, and 9D4-TM to the Fc receptor FcγRI was determined by BiaCore analysis. Briefly, free anti-IFNAR1 antibodies were passed over immobilized FcγRI to measure affinity. As demonstrated by the tracing, the modified antibodies 9D4-DM (B), and 9D4-TM (C) exhibited lower affinities to the bound FcγRI as compared to the unmodified 9D4-WT (A) antibody.

Figure 28. Anti-IFNAR antibodies inhibit IFNα responsive gene induction in the kidney. Briefly, in the accelerated lupus mouse model, treatment with anti-IFNAR antibodies blocks induction in the kidney of six genes (ICAM1, VCAM1, CXCL9, CXCL10, and IFIT1) mediated by the ectopically expression of IFNα compared to control mice as measured by a Taqman assay.

Figure 29. Anti-IFNAR antibodies inhibit the production of anti-ds DNA antibodies in the accelerated lupus mouse model. Briefly, mice ectopically expressing IFNα and treated with anti-IFNAR antibodies did not accumulate anti-ds DNA antibodies to the same level as mice similarly infected and treated with an IgG control antibody.

Figure 30. Anti-IFNAR antibodies are able to reduce proteinuria in a therapeutic setting of the accelerated lupus mouse model. (A) Briefly, mice ectopically expressing IFNα developed Lupus like symptoms, such as proteinuria. In a therapeutic study, anti-IFNAR antibodies were administered to mice once a threshold proteinuria score was reached. Anti-IFNAR antibodies, PBS, or control IgG were administered semi-weekly over a 5 week time course. The anti-IFNAR antibody treated group exhibited decreased severity of proteinuria during the experiment compared to PBS only or control IgG treated groups.

Figure 31. Anti-IFNAR antibodies are able to increase survival in a therapeutic setting of the accelerated lupus mouse model. (A) Briefly, mice ectopically expressing IFNα had a reduced survival rate at about 8 weeks after developing Lupus-like symptoms such as proteinuria. In the therapeutic study, anti-IFNAR antibodies were administered to mice once a threshold proteinuria score was reached. Anti-IFNAR antibodies, PBS, or control IgG were administered semi-weekly over a 5 week time course. After the five weeks, antibody treatment was stopped and the mortality tracked for all three treatment groups. The anti-IFNAR antibody treated group exhibited a much lower rate of mortality than the PBS alone, or control IgG groups, which both exhibited complete mortality by 9 weeks.

Figure 32. Representation of the asymmetric unit contents of the crystals of Fc-TM that comprises L234F/L235E/P331S mutations. The mutation P331 is indicated in red. One zinc ion is chelated by two spatially close Histidine residues. The carbohydrate residues attached to 297 were modeled according to their electron density.

Figure 33. Kinetic images demonstrate 9D4-TM internalization. THP-1 cells were stained with 1 µM CFSE in a 37°C CO_2 incubator for 10 min followed by 1 µg/ml of Alexa647-9D4-TM on ice for 1 hr. After removal of unbound the cells were incubated at 37°C for the times indicated (0, 15, 30 and 60 minutes) and the images of cells were taken.

Figure 34. The anti-IFNAR1 antibody, 9D4-TM does not exhibit CDC activity in an in vitro assay. Presented in this panel are the results from a CDC assay to determine the ability of the 9D4-TM antibody to elicit CDC activity. As presented, the 9D4-TM antibody did not exhibit any CDC activity as compared to the positive control antibody. CDC activity was also undetectable for an unrelated control antibody, R347. Briefly, cells expressing IFNAR1 antigen were incubated with either the positive control antibody, 9D4-TM, or R347. After a series of washes, freshly prepared human serum was added. Complement dependent cytotoxicity (CDC) was measured using a LDH release assay.

4. TERMINOLOGY

[0035] The terms "interferon alpha", "IFNα", "IFNa", "IFNA" and "IFN alpha" are used interchangeably and intended to refer to IFN alpha proteins encoded by a functional gene of the interferon alpha gene locus with 75% or greater sequence identity to IFN alpha 1 (GenBank accession number NP_076918 or protein encoded by GenBank accession number NM_024013). Examples of IFN alpha subtypes include IFN alpha 1, alpha 2a, alpha 2b, alpha 4, alpha 4b alpha 5, alpha 6, alpha 7, alpha 8, alpha 10, alpha 13, alpha 14, alpha 16, alpha 17 and alpha 21. The terms "interferon alpha", "IFNα", and "IFN alpha" are intended to encompass recombinant forms of the various IFN alpha subtypes, as well as naturally occurring preparations that comprise IFN alpha proteins, such as leukocyte IFN and lymphoblastoid IFN.

[0036] The terms "Interferon alpha receptor-1,", "IFNAR1" "IFNAR-1," and "IFNAR-1 antigen" are used interchangeably, and include variants, isoforms, species homologs of human IFNAR-1, and analogs having at least one common epitope with IFNAR-1. Accordingly, human antibodies described herein may cross-react with IFNAR-1 from species other than human, or other proteins which are structurally related to human IFNAR-1 (e.g., human IFNAR-1 homologs).Alternatively, the antibodies may be completely specific for human IFNAR-1 and not exhibit species or other types of cross-reactivity. The complete cDNA sequence of human IFNAR-1 has the Genbank accession number NM_000629.

[0037] As used herein, the term "conservative sequence modifications" is intended to include amino acid modifications that do not affect or alter the binding characteristics of the antibody containing the amino acid sequence. Such conservative modifications include amino acid substitutions, additions and deletions. Modifications can be introduced into an antibody described herein by standard techniques known in the art, such as site-directed mutagenesis and PCR-mediated mutagenesis. Conservative amino acid substitutions are ones in which the amino acid residue is replaced with an amino acid residue having a similar side chain. For example, one or more amino acids of a similar polarity act as functional equivalents and result in a silent alteration within the amino acid sequence of the peptide. Substitutions that are charge neutral and which replace a residue with a smaller residue may also be considered "conservative substitutions" even if the residues are in different groups (e.g., replacement of phenylalanine with the smaller isoleucine). Families of amino acid residues having similar side chains have been defined in the art. Several non-limiting examples of families of conservative amino acid substitutions are shown in Table 1.

Table 1: Families of Conservative Amino Acid Substitutions

Family	Amino Acids
non-polar	Trp, Phe, Met, Leu, Ile, Val, Ala, Pro
Uncharged polar	Gly, Ser, Thr, Asn, Gln, Tyr, Cys
acidic/negatively charged	Asp, Glu
basic/positively charged	Arg, Lys, His
Beta-branched	Thr, Val, Ile
residues that influence chain orientation	Gly, Pro
Aromatic	Tip, Tyr, Phe, His

5. DETAILED DESCRIPTION

[0038] In contrast to previous teachings, the inventors have found that anti-IFNAR1 antibodies with reduced or ablated effector function are desired for the treatment of chronic autoimmune and/or inflammatory diseases. Previously, antibodies directed against IFNAR1 were developed with the understanding that effector function would play a role in mediating treatment or at least moderation of a chronic autoimmune and/or inflammatory disease state (see, for example U.S. Publication No. 20060029601 or PCT publication No. WO06002177). With this concept, many of the previous teachings directed the artisan to identify anti-IFNAR1 antibodies with strong effector function and to further enhance the effector function by increasing the affinity of the antibody for Fc receptors *(e.g.,* FcRn, FcγRIIIa, FcγRIIb) and/or the complement protein C1q. These resultant effector function-enhanced anti-IFNAR1 antibodies were thought to be advantageous in the treatment of disease states.

[0039] In contrast to this previous understanding, the present invention describes anti-IFNAR1 antibodies with reduced or ablated effector function (such as ADCC and/or CDC). Through tissue cross-reactivitiy studies, it was surprisingly found that anti-IFNAR1 antibodies with strong or enhanced effector function displayed a propensity for unwanted toxicity due to the prevalence of staining of anti-IFNAR1 on non-target tissues. This toxicity would result from the non-specific activation of ADCC and/or CDC at inappropriate sites. To reduce of or eliminate this unwanted toxicity, the invetors recognized the need to reduce effector function of polypeptides comprising an Fc region.

[0040] The invention provides a modified IgG class monoclonal antibody specific for IFNAR1, wherein said antibody comprises in the Fc region an amino acid substitution of L234F, as numbered by the EU index as set forth in Kabat and wherein said antibody exhibits reduced affinity for at least one Fc ligand compared to an unmodified antibody. Preferably said antibody is an IgG1 or IgG4 subclass antibody.

[0041] An antibody described herein may further comprise an amino acid substitution of L235E and / or P331S.

[0042] An antibody described herein may comprise: a. a human heavy chain variable region CDR1 comprising Seq ID NO: 1, b. a human heavy chain variable region CDR2 comprising Seq ID NO: 2; c. a human heavy chain variable region CDR3 comprising Seq ID NO: 3; d. a human light chain variable region CDR1 comprising Seq ID NO: 4; e. a human light chain variable region CDR2 comprising Seq ID NO: 5; and f. a human light chain variable region CDR3 comprising Seq ID NO: 6.

[0043] An antibody described herein may comprise: a. a human heavy chain variable region CDR1 comprising Seq ID NO: 21; b. a human heavy chain variable region CDR2 comprising Seq ID NO: 22; c. a human heavy chain variable region CDR3 comprising Seq ID NO: 23; d. a human light chain variable region CDR1 comprising Seq ID NO: 24; e. a human light chain variable region CDR2 comprising Seq ID NO: 25; and f. a human light chain variable region CDR3 comprising Seq ID NO: 26.

[0044] An antibody described herein may comprise: a. a human heavy chain variable region comprising the amino acid sequence of Seq ID No: 38; and b. a human light chain variable region comprising the amino acid sequence of Seq No: 40.

[0045] An antibody described herein may comprise: a. a human heavy chain variable region comprising amino sequence of Seq ID No: 18; and b. a human light chain variable region comprising the amino acid sequence of Seq ID No: 20.

[0046] Am antibody described herein may comprise: a. a human heavy chain variable region comprising the amino acid sequence of Seq ID No: 28; and b. a human light chain variable region comprising the amino acid sequence of Seq ID No: 30.

[0047] An antibody described herein may comprise the light chain constant region sequence of Seq ID No: 41.

[0048] An antibody described herein may comprise the heavy chain constant region of Seq ID No: 42.

[0049] An antibody described herein may comprise the light chain constant region having the amino acid sequence of Seq ID No: 41 and the heavy chain constant region having the amino acid sequence of Seq ID No: 42.

[0050] An antibody described herein may comprise a heavy chain amino acid sequence comprising allelic variation, wherein said allelic variation is at least one or more positions selected from the group consisting of 214, 221, 356 and 358 as defined by the EU index numbering system.

[0051] The invention further provides an isolated nucleic acid comprising a polynucleotide sequence encoding the antibody of any of the preceding claims.

[0052] The invention yet further provides a pharmaceutical composition comprising the antibody described herein, and a pharmaceutically acceptable excipient.

[0053] The invention also provides a pharmaceutical composition described herein for use in treating a disease or disorder chosen from Grave's disease, Hashimoto's thyroiditis, Crohn's disease, psoriasis, psoriatic arthritis, sympathetic ophthalmitis, autoimmune oophoritis, autoimmune orchitis, autoimmune lymphoproliferative syndrome, antiphospholipid syndrome, Sjogren's syndrome, scleroderma, Addison's disease, polyendocrine deficiency syndrome, Guillain-Barré syndrome, immune thrombocytopenic purpura, pernicious anemia, myasthenia gravis, primary biliary cirrhosis, mixed connective tissue disease, vitiligo, autoimmune uveitis, autoimmune hemolytic anemia, autoimmune thrombocytopenia, celiac disease, dermatitis herpetiformis, autoimmune hepatitis, pemphigus, pemphigus vulgaris, pemphigus foliaceus, bullous pemphigoid, autoimmune myocarditis, autoimmune vasculitis, alopecia areata, autoimmune atherosclerosis, Behçet's disease, autoimmune myelopathy, autoimmune hemophilia, autoimmune interstitial cystitis, autoimmune diabetes insipidus, autoimmune endometriosis, relapsing polychondritis, ankylosing spondylitis, autoimmune urticaria, dermatomyositis, Miller-Fisher syndrome, IgA nephropathy, Goodpasture's syndrome, and herpes gestationis.

[0054] Accordingly, we describe modified antibodies or other polypeptides comprising the Fc region of an antibody, comprising the addition, substitution, or deletion of at least one amino acid residue to the Fc region resulting in reduced or ablated affinity for at least one Fc ligand (referred to herein as "modified antibodies"). The Fc region interacts with a number of ligands including, but not limited to, Fc Receptors *(e.g.,* FcRn, FcγRIIIa, FcγRIIb), the complement protein C1q, and other molecules, such as proteins A and G. These interactions are essential for a variety of effector functions and downstream signaling events including, but not limited to, antibody dependent cell-mediated cytotoxicity (ADCC) and complement dependent cytotoxicity (CDC). Antibodies described herein may have reduced or ablated affinity for an Fc ligand responsible for facilitating effector function compared to an antibody having the same amino acid sequence but not comprising the addition, substitution, or deletion of at least one amino acid residue to the Fc region (also referred to herein as an "unmodified antibody"). Antibodies described herein may comprise at least one or more of the following properties: reduced or ablated effector (ADCC and/or CDC) function, reduced or ablated binding to Fc receptors, or reduced or ablated toxicities. More specifically, we describe anti-IFNAR1 antibodies with reduced affinity for Fc receptors *(e.g.,* FcRn, FcγRIIIa, FcγRIIb) and/or the complement protein C1q.

[0055] Antibodies described herein may comprise an Fc region comprising at least one addition, substitution, or deletion of an amino acid residue selected from the positions consisting of: 234, 235, and 331, wherein the numbering system of the constant region is that of the EU index as set forth in Kabat et al. (1991, NIH Publication 91-3242, National Technical Information Service, Springfield, VA). Antibodies described herein may comprise an Fc region comprising at least one amino acid substitution selected from the group consisting of: L234F, L235E, and P331S, wherein the first letter and number represent the unmodified amino acid and its position and the second letter represents the substituted amino acid at said position.

[0056] Antibodies described herein may further comprise an Fc region comprising at least one addition, substitution, or deletion of an amino acid residue that is correlated with increased stability of the antibody. The addition, substitution, or deletion of an amino acid residue may be at position 228 of the Fc region, wherein the numbering system of the constant region is that of the EU index as set forth in Kabat *et al.* Antibodies described herein may comprise an Fc region comprising an amino acid substitution at position 228, wherein the substitution is a serine residue. Antibodies of the IgG4 subtype may comprise an amino acid substitution of serine at position 228 of the Fc region. Antibodies described herein may already comprise a serine residue at position 228 of the Fc region; in such antibodies, no modification is required. Alternatively, antibodies described herein may not require modification of residue 228 of the Fc region or may already comprise serine at said position.

[0057] Antibodies described herein may be any of any class (for example, but not limited to IgG, IgM, and IgE). Antibodies described herein are members of the IgG class of antibodies. In a specific embodiment, antibodies described herein are of the IgG1 subclass. In another specific embodiment, antibodies described herein are of the IgG1 subclass and comprise the following amino acid substitutions: 234F, 235E and 331S of the Fc region. In alternate embodiments, antibodies described herein are of the IgG4 subclass. Antibodies described herein of the IgG4 subclass may comprise the following amino acid substitutions: S228P and L235E of the Fc region.

[0058] Modified antibodies may be produced by combining a variable domain, or fragment thereof, with an Fc domain comprising one or more of the amino acid substitutions disclosed herein. Modified antibodies may be produced by modifying an Fc domain-containing antibody by introducing one or more of the amino acid substitutions residues into the Fc domain.

5.1 Reduced binding to Fc ligands

[0059] One skilled in the art will understand that antibodies described herein may have altered (relative to an unmodified antibody) FcγR and/or C1q binding properties (examples of binding properties include but are not limited to, binding specificity, equilibrium dissociation constant (K_D), dissociation and association rates (K_{off} and K_{on} respectively), binding affinity and/or avidity) and that certain alterations are more or less desirable. It is known in the art that the equilibrium dissociation constant (K_D) is defined as k_{off}/k_{on}. One skilled in the art can determine which kinetic parameter is most important for a given antibody application. For example, a modification that reduces binding to one or more positive regulator (e.g., FcγRIIIA) and/or enhanced binding to an inhibitory Fc receptor (e.g., FcγRIIB) would be suitable for reducing ADCC activity. Accordingly, the ratio of binding affinities *(e.g.,* equilibrium dissociation constants (K_D)) can indicate if the ADCC activity of an antibody is enhanced or decreased. Additionally, a modification that reduces binding to C1q would be suitable for reducing or eliminating CDC activity.

[0060] The affinities and binding properties of an Fc region for its ligand, may be determined by a variety of *in vitro* assay methods (biochemical or immunological based assays) known in the art for determining Fc-FcγR interactions, *i.e.*, specific binding of an Fc region to an FcγR including but not limited to, equilibrium methods (e.g., enzyme-linked immunoabsorbent assay (ELISA) or radioimmunoassay (RIA)), or kinetics (e.g., BIACORE® analysis), and other methods such as indirect binding assays, competitive inhibition assays, fluorescence resonance energy transfer (FRET), gel electrophoresis and chromatography *(e.g.,* gel filtration). These and other methods may utilize a label on one or more of the components being examined and/or employ a variety of detection methods including but not limited to chromogenic, fluorescent, luminescent, or isotopic labels. A detailed description of binding affinities and kinetics can be found in Paul, W.E., ed., Fundamental Immunology, 4th Ed., Lippincott-Raven, Philadelphia (1999).

[0061] Antibodies described herein may exhibit reduced binding affinity for one or more Fc receptors including, but not limited to FcγRI (CD64) including isoforms FcγRIA, FcγRIB, and FcγRIC; FcγRII (CD32 including isoforms FcγRIIA, FcγRIIB, and FcγRIIC); and FcγRIII (CD16, including isoforms FcγRIIIA and FcγRIIB) as compared to an unmodified antibody. Antibodies described herein may not comprise a concomitant increase in binding the FcγRIIB receptor as compared to an unmodified (for example, containing a wild type Fc region) antibody.

[0062] Antibodies described herein may exhibit decreased affinities to FcγRI relative to an unmodified antibody. Antibodies described herein may exhibit affinities for FcγRI receptor that are at least 2 fold, or at least 3 fold, or at least 5 fold, or at least 7 fold, or a least 10 fold, or at least 20 fold, or at least 30 fold, or at least 40 fold, or at least 50 fold, or at least 60 fold, or at least 70 fold, or at least 80 fold, or at least 90 fold, or at least 100 fold, or at least 200 fold less than an unmodified antibody.

[0063] Antibodies described herein may exhibit an affinity for FcγRI receptor that is at least 90%, at least 80%, at least 70%, at least 60%, at least 50%, at least 40%, at least 30%, at least 20%, at least 10%, or at least 5% less than an unmodified antibody.

[0064] Antibodies described herein may exhibit decreased affinity for the FcγRIIIA receptor relative to an unmodified antibody. Antibodies described herein may exhibit affinities for FcγRIIIA receptor that are at least 2 fold, or at least 3 fold, or at least 5 fold, or at least 7 fold, or a least 10 fold, or at least 20 fold, or at least 30 fold, or at least 40 fold, or at least 50 fold, or at least 60 fold, or at least 70 fold, or at least 80 fold, or at least 90 fold, or at least 100 fold, or at least 200 fold less than an unmodified antibody.

[0065] Antibodies described herein may exhibit affinities for FcγRIIIA receptor that are at least 90%, at least 80%, at least 70%, at least 60%, at least 50%, at least 40%, at least 30%, at least 20%, at least 10%, or at least 5% less than an unmodified antibody.

[0066] It is understood in the art that the F158V allelic variant of the FcγRIIIA receptor has altered binding characteristics to antibodies. Antibodies described herein may bind with decreased affinities to FcγRIIIA (F158V) relative to an unmodified antibody. Antibodies described herein may exhibit affinities for FcγRIIIA (F158V) receptor that are at least 2 fold, or at least 3 fold, or at least 5 fold, or at least 7 fold, or a least 10 fold, or at least 20 fold, or at least 30 fold, or at least 40 fold, or at least 50 fold, or at least 60 fold, or at least 70 fold, or at least 80 fold, or at least 90 fold, or at least 100 fold, or at least 200 fold less than that of an unmodified antibody. Antibodies described herein may exhibit affinities for the FcγRIIIA(F158V) receptor that are at least 90%, at least 80%, at least 70%, at least 60%, at least 50%, at least 40%, at least 30%, at least 20%, at least 10%, or at least 5% less than an unmodified antibody.

[0067] Antibodies described herein may exhibit increased affinities for the FcγRIIB receptor as compared to unmodified antibody. Antibodies described herein may exhibit affinities for the FcγRIIB receptor that are unchanged or increased by at least at least 2 fold, or at least 3 fold, or at least 5 fold, or at least 7 fold, or a least 10 fold, or at least 20 fold, or at least 30 fold, or at least 40 fold, or at least 50 fold, or at least 60 fold, or at least 70 fold, or at least 80 fold, or at least 90 fold, or at least 100 fold, or at least 200 fold than that of an unmodified antibody. Antibodies described herein may exhibit affinities for the FcγRIIB receptor that are increased by at least 5%, at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, or at least 95% than an unmodified antibody.

[0068] Antibodies described herein may exhibit affinities for the FcγRI, FcγRIIIA, or FcγRIIIA (F158V) receptors that are between about 100 nM to about 100 μM, or about 100 nM to about 10 μM, or about 100 nM to about 1 μM, or about 1 nM to about 100 μM, or about about 10 nM to about 100 μM, or about 1 μM to about 100 μM, or about 10 μM to about 100 μM. Antibodies described herein may exhibit affinities for the FcγRI, FcγRIIIA, or FcγRIIIA (F158V) receptors that are greater than 1 μM, greater than 5 μM, greater than 10 μM, greater than 25 μM, greater than 50 μM, or greater than 100 μM.

[0069] Antibodies described herein may exhibit affinities for the FcγRIIB receptor that are between about 100 nM to about 100 μM, or about 100 nM to about 10 μM, or about 100 nM to about 1 μM, or about 1 nM to about 100 μM, or about 10 nM to about 100 μM, or about 1 μM to about 100 μM, or about 10 μM to about 100 μM. Antibodies described herein may exhibit affinities for the FcγRI, FcγRIIIA, or FcγRIIIA (F158V) receptors that are less than 100 μM, less than 50 μM, less than 10 μM, less than 5 μM, less than 2.5 μM, less than 1 μM, or less than 100 nM, or less than 10 nM.

[0070] Antibodies described herein may exhibit affinities for the FcγRIIB receptor that are between about 100 nM to about 100 μM, or about 100 nM to about 10 μM, or about 100 nM to about 1 μM, or about 1 nM to about 100 μM, or about 10 nM to about 100 μM, or about 1 μM to about 100 μM, or about 10 μM to about 100 μM. Antibodies described herein may exhibit affinities for the FcγRI, FcγRIIIA, or FcγRIIIA (F158V) receptors that are less than 100 μM, less than 50 μM, less than 10 μM, less than 5 μM, less than 2.5 μM, less than 1 μM, or less than 100 nM, or less than 10 nM.

5.2 Reduced ADCC activity

[0071] It is well known in the art that antibodies are capable of directing the attack and destruction of targeted antigen through multiple processes collectively known in the art as antibody effector functions. One of these processes, known as "antibody-dependent cell-mediated cytotoxicity" or "ADCC" refers to a form of cytotoxicity in which secreted Ig bound onto Fc receptors (FcRs) present on certain cytotoxic cells *(e.g.,* Natural Killer (NK) cells, neutrophils, and macrophages) enables these cytotoxic effector cells to bind specifically to an antigen-bearing target cell and subsequently kill the target cell with cytotoxins. Specific high-affinity IgG antibodies directed to the surface of target cells "arm" the cytotoxic cells and are required for such killing. Lysis of the target cell is extracellular, requires direct cell-to-cell contact, and does not involve complement. Another process encompassed by the term "effector function" is complement dependent cytotoxicity (hereinafter referred to as "CDC") which refers to a biochemical event of antibody-mediated target cell destruction by the complement system. The complement system is a complex system of proteins found in normal blood plasma that combines with antibodies to destroy pathogenic bacteria and other foreign cells.

[0072] The ability of any particular antibody to mediate lysis of the target cell by ADCC can be assayed. To assess ADCC activity an antibody of interest is added to target cells in combination with immune effector cells, which may be activated by the antigen antibody complexes resulting in cytolysis of the target cell. Cytolysis is generally detected by the release of label (e.g., radioactive substrates, fluorescent dyes or natural intracellular proteins) from the lysed cells. Useful effector cells for such assays include peripheral blood mononuclear cells (PBMC) and Natural Killer (NK) cells. Specific examples of *in vitro* ADCC assays are described in Wisecarver *et al.*, 1985 79:277-282; Bruggemann et al., 1987, J Exp Med 166:1351-1361; Wilkinson et al., 2001, J Immunol

Methods 258:183-191; Patel et al., 1995 J Immunol Methods 184:29-38. Alternatively, or additionally, ADCC activity of the antibody of interest may be assessed *in vivo, e.g.,* in an animal model such as that disclosed in Clynes et al., 1998, PNAS USA 95:652-656.

[0073] It is contemplated that antibodies described herein are characterized by *in vitro* functional assays for determining one or more FcγR mediated effector cell functions. Antibodies described herein may have similar binding properties and effector cell functions in *in vivo* models (such as those described and disclosed herein) as those in *in vitro* based assays. However, antibodies described herein that do not exhibit the desired phenotype in *in vitro* based assays may exhibit the desired phenotype *in vivo*.

[0074] Antibodies described herein may exhibit decreased ADCC activities as compared to an unmodified antibody. Antibodies described herein may exhibit ADCC activities that are at least 2 fold, or at least 3 fold, or at least 5 fold, or at least 10 fold, or at least 50 fold, or at least 100 fold less than that of an unmodified antibody. In still another embodiment, antibodies described herein may exhibit ADCC activities that are reduced by at least 10%, or at least 20%, or by at least 30%, or by at least 40%, or by at least 50%, or by at least 60%, or by at least 70%, or by at least 80%, or by at least 90%, or by at least 100%, or by at least 200%, or by at least 300%, or by at least 400%, or by at least 500% relative to an unmodified antibody. Antibodies described herein may have no detectable ADCC activity. In specific embodiments, the reduction and/or ablatement of ADCC activity may be attributed to the reduced affinity that antibodies described herein may exhibit for Fc ligands and/or receptors.

5.3 Reduced CDC activity

[0075] The complement activation pathway is initiated by the binding of the first component of the complement system (C1q) to a molecule, an antibody for example, complexed with a cognate antigen. To assess complement activation, a CDC assay, *e.g.,* as described in Gazzano-Santoro et al., 1996, J. Immunol. Methods, 202:163, may be performed.

[0076] Antibodies described herein may exhibit decreased affinities to C1q relative to an unmodified antibody. Antibodies described herein may exhibit affinities for C1q receptor that are at least 2 fold, or at least 3 fold, or at least 5 fold, or at least 7 fold, or a least 10 fold, or at least 20 fold, or at least 30 fold, or at least 40 fold, or at least 50 fold, or at least 60 fold, or at least 70 fold, or at least 80 fold, or at least 90 fold, or at least 100 fold, or at least 200 fold less than an unmodified antibody.

[0077] Antibodies described herein may exhibit affinities for C1q that are at least 90%, at least 80%, at least 70%, at least 60%, at least 50%, at least 40%, at least 30%, at least 20%, at least 10%, or at least 5% less than an unmodified antibody.

[0078] Antibodies described herein may exhibit affinities for C1q that are between about 100 nM to about 100 μM, or about 100 nM to about 10 μM, or about 100 nM to about 1 μM, or about 1 nM to about 100 μM, or about 10 nM to about 100 μM, or about 1 μM to about 100 μM, or about 10 μM to about 100 μM. Antibodies described herein may exhibit affinities for C1q that are greater than 1 μM, greater than 5 μM, greater than 10 μM, greater than 25 μM, greater than 50 μM, or greater than 100 μM.

[0079] Antibodies described herein may exhibit decreased CDC activities as compared to an unmodified antibody. Antibodies described herein may exhibit CDC activities that are at least 2 fold, or at least 3 fold, or at least 5 fold, or at least 10 fold, or at least 50 fold, or at least 100 fold less than that of an unmodified antibody. In still another embodiment, antibodies described herein may exhibit CDC activities that are reduced by at least 10%, or at least 20%, or by at least 30%, or by at least 40%, or by at least 50%, or by at least 60%, or by at least 70%, or by at least 80%, or by at least 90%, or by at least 100%, or by at least 200%, or by at least 300%, or by at least 400%, or by at least 500% relative to an unmodified antibody. Antibodies described herein may exhibit no detectable CDC activities. In specific embodiments, the reduction and/or ablatement of CDC activity may be attributed to the reduced affinity antibodies described herein may exhibit for Fc ligands and/or receptors.

5.4 Reduced antibody related toxicity

[0080] It is understood in the art that biological therapies may have adverse toxicity issues associated with the complex nature of directing the immune system to recognize and attack unwanted cells and/or targets. When the recognition and/or the targeting for attack do not take place where the treatment is required, consequences such as adverse toxicity may occur. For example, antibody staining of non-targeted tissues may be indicative of potential toxicity issues.

[0081] Antibodies described herein may exhibit reduced staining of non-targeted tissues as compared to an unmodified antibody. Antibodies described herein may exhibit reduced staining of non-targeted tissues that are at least 2 fold, or at least 3 fold, or at

least 5 fold, or at least 7 fold, or at least 10 fold, or at least 20 fold, or at least 30 fold, or at least 40 fold, or at least 50 fold, or at least 60 fold, or at least 70 fold, or at least 80 fold, or at least 90 fold, or at least 100 fold, or at least 200 fold less than that of an unmodified antibody. Antibodies described herein may exhibit reduced staining of non-targeted tissues that are reduced by at least 10%, or by at least 20%, or by at least 30%, or by at least 40%, or by at least 50%, or by at least 60%, or by at least 70%, or by at least 80%, or by at least 90%, or by at least 100%, or by at least 200%, or by at least 300%, or by at least 400%, or by at least 500% relative to an unmodified antibody.

[0082] Antibodies described herein may exhibit a reduced antibody-related toxicity as compared to an unmodified antibody. Antibodies described herein may exhibit toxicities that are at least 2 fold, or at least 3 fold, or at least 5 fold, or at least 7 fold, or a least 10 fold, or at least 20 fold, or at least 30 fold, or at least 40 fold, or at least 50 fold, or at least 60 fold, or at least 70 fold, or at least 80 fold, or at least 90 fold, or at least 100 fold, or at least 200 fold less than that of an unmodified antibody. Antibodies described herein may exhibit toxicities that are reduced by at least 10%, or by at least 20%, or by at least 30%, or by at least 40%, or by at least 50%, or by at least 60%, or by at least 70%, or by at least 80%, or by at least 90%, or by at least 100%, or by at least 200%, or by at least 300%, or by at least 400%, or by at least 500% relative to an unmodified antibody.

5.5 Internalizing Antibodies

[0083] Antibodies described herein may bind to cell-surface antigens that may internalize, further carrying the antibodies into the cell. Once inside the cell, the antibodies may be released into the cytoplasm, targeted to a specific compartment, or recycled to the cell surface. Antibodies described herein may bind to a cell-surface antigen that internalizes. Antibodies described herein may be targeted to specific organelles or compartments of the cell. Antibodies described herein may be recycled to the cell surface or periphery after internalization. In a specific embodiment, the antibody described herein is specific for IFNAR1.

[0084] Internalization of antibodies may be measured by art-accepted techniques such as those presented in Example 34. The extent of internalization can be represented as a percentage of total antibody bound to cells. The extent of antibody internalization can be represented as a comparison to a non-specific control antibody. The extent of antibody internalization can be represented as a comparison to an antibody that binds a cell-surface antigen that does not internalize. The extent of antibody internalization can be correlated with the degradation of the antibody. The extent of antibody internalization can be represented as a ratio of cytoplasmic versus cell surface staining.

[0085] The antibodies described herein once bound, may internalize into cells wherein internalization is at least about 10%, at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, or at least about 90%, at least about 100%, at least about 110%, at least about 130%, at least about 140%, at least about 150%, at least about 160%, or at least about 170% more than a non-specific control antibody.

[0086] The antibodies described herein once bound, may internalize into cells wherein internalization is 1-10%, 10-20%, 20-30%, 30-40%,40-50%, 50-60%, 60-70%, 70-80%, 80-90%, 90-100%, 100-110%, 110-120%, 120-130%, 130-140%, 140-150%, 150-160%, 160-170% more than a non-specific control antibody.

[0087] The antibodies described herein once bound, may internalize into cells wherein internalization is 1-10%, 10-20%, 20-30%, 30-40%,40-50%, 50-60%, 60-70%, 70-80%, 80-90%, 90-100%, 100-110%, 110-120%, 120-130%, 130-140%, 140-150%, 150-160%, 160-170% more than control antibodies as determined by the internalization assay using a secondary antibody.

5.6 Three-Dimensional Structure of a human Fc region

[0088] Herein we describe crystalline forms of a human IgG Fc region, wherein the human Fc region, designated as Fc-TM, comprises amino acid substitutions of L234F, L235E and P331S as numbered by the EU index as set forth in Kabat and exhibits reduced or ablated effector (ADCC and/or CDC) function, reduced or ablated binding to Fc receptors, and/or reduced or ablated toxicities. The crystals may be characterized by an orthorhombic space group $C222_1$ with unit cell of a=50.18, b=147.30 and c=75.47. In certain embodiments, the crystals are of diffraction quality to permit the determination of the three-dimensional X-ray diffraction structure of the crystalline polypeptide(s) to high resolution, preferably to a resolution of greater than about 3 Å, typically in the range of about 2 Å to about 3 Å.

[0089] We describe the high-resolution three-dimensional structures and atomic structure coordinates of the Fc-TM crystals. The specific methods used to obtain crystals and structure coordinates are provided in the examples, *infra*.

[0090] The atomic structure coordinates of crystalline Fc-TM, obtained from the $C222_1$ form of the crystal to 2.3 Å resolution, are listed in Table 6. All residues at positions 236 to 445 could be traced in the electron density and no electron density was observed for hinge residues prior to position 236, including the L234F and L235E mutations. The electron density at position 331 corresponded to serine.

[0091] The overall three-dimensional structure of Fc-TM was very similar to previously reported structures of unliganded human Fc regions (Deisenhofer, (1981). Biochemistry, 20, 2361-2370 ; Krapp et al., (2003). J. Mol. Biol. 325, 979-989; Matsumiya et al., (2007). J. Mol. Biol. 368, 767-779; Oganesyan et al., (2007) Molecular Immunology, December 11, 2007, in press). When considered individually, Fc-TM C_H2 and C_H3 domains showed great structural conservation and rigidity when compared with other unliganded, unmutated human Fc structures.

[0092] The structure information can be used in a variety of computation or computer-based methods to screen, design or identify anti-IFNAR antibodies that have altered biological properties. For example, the crystals and structure coordinates obtained therefrom can be used to screen, design or identify amino acid additions, substitutions or deletions in Fc region that result in reduced or ablated binding to Fc receptors, reduced or ablated effector (ADCC and/or CDC) function, or reduced or ablated toxicities.

[0093] Once an antibody has been designed or selected by the above methods, its effector function, binding to Fc receptors, or toxicities may be tested and optimized by any methods known to those of skill in the art. Exemplary methods are described in sections 5.1-5.4 above.

[0094] We describe anti-IFNAR1 antibodies that are designed or selected by the use of the structure information of Fc-TM and that exhibit the desired biological activities. Such antibodies may comprise an Fc region with the mutations of L234F, L235E, and P331S. Such antibodies may comprise an Fc region with one or more addition, substitution, or deletion of an amino acid residue other than amino acid residues 234, 235, and 331.

5.7 Anti-IFNAR1 antibodies

[0095] Antibodies described herein are specific for (*i.e.,* specifically bind) IFNAR1. Such antibodies may also be referred to herein as "anti-IFNAR1 antibodies described herein." Antibodies described herein are specific for human IFNAR1. The anti-IFNAR1 antibodies described herein may cross-react with IFNAR1 from species other than human, or other proteins which are structurally related to human IFNAR1 (for example, human IFNAR1 homologs). Anti-IFNAR1 antibodies described herein may be specific for human IFNAR1 only and not exhibit species or other types of cross-reactivity.

[0096] Anti-IFNAR1 antibodies described herein may exhibit reduced binding affinities for Fc ligands and have at least one of the following properties: reduced or ablated effector (ADCC and/or CDC) function, reduced or ablated binding to Fc ligands, or reduced or ablated toxicities as compared to an unmodified antibody.

[0097] Anti-IFNAR1 antibodies described herein may comprise the addition, substitution or deletion of at least one amino acid residue selected from the group consisting of: L234F, L235E, and P331S. Anti-IFNAR1 antibodies described herein may comprise the amino acid substitutions: L234F, L235E, and P331S of the Fc region. An anti-IFNAR1 antibody described herein may be an IgG isotype antibody.

[0098] Anti-IFNAR1 antibodies described herein may be of the IgG4 subclass. Anti-IFNAR1 IgG4 antibodies described herein may comprise the amino acid substitution L235E of the Fc region. Anti-IFNAR1 IgG4 antibodies described herein may also comprise an amino acid change that is correlated with increased stability. Anti-IFNAR1 IgG4 antibodies described herein may further comprise the amino acid substitution S228P of the Fc region.

[0099] Anti-IFNAR1 antibodies described herein may exhibit reduced or ablated binding affinities for Fc receptors (for example, but not limited to FcγRI (CD64), including isoforms FcγRIA, FcγRIB, and FcγRIC; FcγRII (CD32), including isoforms FcγRIIA, FcγRIIB, and FcγRIIC; and FcγRIII (CD16), including isoforms FcγRIIIA and FcγRIIB) as compared to an unmodified antibody. Anti-IFNAR 1 antibodies described herein may exhibit decreased affinities to FcγRI relative to an unmodified antibody. Anti-IFNAR1 antibodies described herein exhibit may decreased affinities for the FcγRIIIA receptor relative to an unmodified antibody. Anti-IFNAR1 antibodies described herein may bind with decreased affinities to the F158V allele of FcγRIIIA relative to an unmodified antibody.

[0100] Anti-IFNAR1 antibodies described herein may exhibit reduced or ablated binding affinities for C1q as compared to an unmodified antibody. Anti-IFNAR 1 antibodies described herein may exhibit decreased affinities to FcγRI relative to an unmodified antibody.

[0101] Anti-IFNAR1 antibodies described herein may exhibit reduced or ablated effector function. Anti-IFNAR1 antibodies described herein may exhibit reduced or ablated ADCC and/or CDC activity. Anti-IFNAR1 antibodies described herein may exhibit reduced or ablated toxicity.

5.7.1 Anti-IFNAR1 antibody sequences

[0102] Amino acid sequences of the heavy chain variable regions and/or light chain variable regions of anti-IFNAR1 antibodies described herein are provided as Figures 1A, 2A, 3A, 4A and Figures 1B, 2B, 3B, 4B, respectively. The polynucleotide sequence encoding the heavy chain variable and light chain variable regions of the anti-IFNAR1 antibodies described herein are provided as Figures 1A, 2A, 3A, 4A and Figures 1B, 2B, 3B, 4B, respectively.

[0103] Selected sequences of anti-IFNAR1 antibodies described herein can be found in US Patent No. 5,919,453, US Patent Application Serial Nos: 10/831,459, 10/182,058, 11/157,494, and 11/521,102. Sequences of anti-IFNAR1 antibodies described herein may not comprise the sequences found in US Patent No. 5,919,453, US Patent Application Serial Nos: 10/831,459, 10/182,058, 11/157,494, and 11/521,102.

[0104] Antibodies described herein are disclosed in U.S. Patent Provisional Applications Serial Nos. 60/842,925, filed September 8, 2006, 60/866,917; filed November 22, 2006; 60/911,397, filed April 12, 2007; 60/915,309, filed May 22, 2007; US Patent Application Serial No. 11/852,106, filed September 7, 2007; and PCT Application Serial No. US2007/07791, filed September 7, 2007.

[0105] Anti-IFNAR1 antibodies described herein also include antibodies that comprise an amino acid sequence of a variable heavy chain and/or variable light chain that is at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% identical to the amino acid sequence of the variable heavy chain and/or light chain of the 3F11, 11E2, 4G5, and 9D4 antibodies (see Figures 1-4 for sequences).

[0106] It will be understood that the complementarity determining regions (CDRs) residue numbers referred to herein are those of Kabat *et al.*, (1991, NIH Publication 91-3242, National Technical Information Service, Springfield, VA). Specifically, residues 24-34 (CDR1), 50-56 (CDR2) and 89-97 (CDR3) in the light chain variable domain and 31-35 (CDR1), 50-65 (CDR2) and 95-102 (CDR3) in the heavy chain variable domain. Note that CDRs vary considerably from antibody to antibody (and by definition will not exhibit homology with the Kabat consensus sequences). Maximal alignment of framework residues frequently requires the insertion of "spacer" residues in the numbering system, to be used for the Fv region. It will be understood that the CDRs referred to herein are those of Kabat *et al. supra*. In addition, the identity of certain individual residues at any given Kabat site number may vary from antibody chain to antibody chain due to interspecies or allelic divergence.

[0107] Anti-IFNAR1 antibodies described herein may comprise at least one VH CDR having an amino acid sequence of any one of the VH CDRs listed in Table 2. Anti-IFNAR1 antibodies described herein may comprise at least one VL CDR having an amino acid sequence of any one of the VL CDRs listed in Table 2. Anti-IFNAR1 antibodies described herein may comprise one or more of the VH CDRs and one or more of the VL CDRs listed in Table 2. Anti-IFNAR1 antibodies described herein may comprise any combination of the VH CDRs and VL CDRs listed in Table 2. Anti-IFNAR1 antibodies described herein may comprise at least 1, or at least 2, or at least 3, or at least 4, or at least 5, or at least 6 CDRs selected from Table 2. Anti-IFNAR1 antibodies described herein may comprise a VH domain and/or a VL domain each comprising 1, 2 or 3 CDRs. The anti-IFNAR1 antibodies described herein may comprise a VH further comprising 1, 2, or 3 heavy chain CDRs (CDRH#) listed in Table 2. The anti-IFNAR1 antibodies described herein may comprise a VL further comprising 1, 2, or 3 light chain CDRs (CDRL#) listed in Table 2.

[0108] Anti-IFNAR1 antibodies described herein may comprise the CDRs of antibody 3F11 (see for example Table 2). Anti-IFNAR1 antibodies described herein may comprise the CDRs of antibody 4G5 (see for example Table 2). Anti-IFNAR1 antibodies described herein may comprise the CDRs of antibody 11E2 (see for example Table 2). Anti-IFNAR1 antibodies described herein comprise the CDRs of antibody 9D4 (see for example Table 2).

Table 2. Anti-IFNAR1 antibody CDR sequences

Antibody	CDR	Sequence	Seq ID No:
3F11	CDRL1	RASQGIYSVLA	1
3F11	CDRL2	DASRLES	2
3F11	CDRL3	QQFNSYIT	3
3F11	CDRH1	GYFWS	4
3F11	CDRH2	EIDHSGKTNYNPSLKS	5
3F11	CDRH3	ESKYYFGLDV	6
4G5	CDRL1	RATQDISIALV	11
4G5	CDRL2	DASGLGS	12
4G5	CDRL3	QQFNSYPYT	13
4G5	CDRH1	NYYWS	14
4G5	CDRH2	EIILSGSTNYNPSLKS	15
4G5	CDRH3	ESKWGYYFDS	16
11E2	CDRL1	RASQSVSSSFFA	21
11E2	CDRL2	GASSRAT	22
11E2	CDRL3	QQYYDSSAIT	23
11E2	CDRH1	NYWIA	24
11E2	CDRH2	IIYPGDSDIRYSPSFQG	25
11E2	CDRH3	HDIEGFDY	26
9D4	CDRL1	RASQSVSSSFFA	31
9D4	CDRL2	GASSRAT	32
9D4	CDRL3	QQYDSSAIT	33
9D4	CDR11	NYWIA	34
9D4	CDRH2	IIYPGDSDIRYSPSFQG	35
9D4	CDRH3	HDIEGFDY	36

[0109] Anti-IFNAR1 antibodies described herein may comprise an amino acid sequence of a variable heavy chain and/or variable light chain that comprises at least 1, at least 2, at least 3, at least 4, at least 5, at least 10, at least 15, or at least 20 amino acid substitutions, additions, or deletions as compared to the variable heavy chains and/or light chains represented in Figures 1, 2, 3, or 4. Anti-IFNAR1 antibodies described herein may comprise one or more CDRs with at least 1, at least 2, at least 3, at least 4, at least 5, or at least 10 amino acid substitutions, deletions, or additions of one or more CDRs listed in Table 2.

[0110] Anti-IFNAR1 antibodies described herein may comprise antibodies encoded by a polynucleotide sequence that hybridizes to the nucleotide sequence represented in Figures 1, 2, 3, or 4 under stringent conditions. Anti-IFNAR1 antibodies described herein may comprise one or more CDRs encoded by a nucleotide sequence that hybridizes under stringent conditions to the nucleotide sequence of one or more CDRs listed in Figures 1, 2, 3, or 4. Stringent hybridization conditions include, but are not limited to, hybridization to filter-bound DNA in 6X sodium chloride/sodium citrate (SSC) at about 45°C followed by one or more washes in 0.2X SSC/0.1% SDS at about 50-65°C, highly stringent conditions such as hybridization to filter-bound DNA in 6X SSC at about 45°C followed by one or more washes in 0.1X SSC/0.2% SDS at about 60°C, or any other stringent hybridization conditions known to those skilled in the art (see, for example, Ausubel, F.M. et al., eds. 1989 Current Protocols in Molecular Biology, vol. 1, Green Publishing Associates, Inc. and John Wiley and Sons, Inc., NY at pages 6.3.1 to 6.3.6 and 2.10.3). Anti-IFNAR1 antibodies described herein include, but are not limited to, antibodies encoded by a polynucleotide sequence that is at least 70%, at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to a polynucleotide sequence encoding antibodies 3F11, 11E2, 4G5, or 9D4 (see Figures 1-4).

5.7.2 Anti-IFNAR1 binding affinity

[0111] Anti-IFNAR1 antibodies described herein may exhibit a high binding affinity for IFNAR1. Anti-IFNAR1 antibodies described

herein may exhibit association rate (k_{on}) of at least $10^5M^{-1}s^{-1}$, at least $5\times10^5M^{-1}s^{-1}$, at least $10^6M^{-1}s^{-1}$, at least $5\times10^6M^{-1}s^{-1}$, at least $10^7M^{-1}s^{-1}$, at least $5\times10^7M^{-1}s^{-1}$, or at least $10^8M^{-1}s^{-1}$. Anti-IFNAR1 antibodies described herein may exhibit a k_{on} of at least $2\times10^5M^{-1}s^{-1}$, at least $5\times10^5M^{-1}s^{-1}$, at least $10^6M^{-1}s^{-1}$, at least $5\times10^6M^{-1}s^{-1}$, at least $10^7M^{-1}s^{-1}$, at least $5\times10^7M^{-1}s^{-1}$, or at least $10^8M^{-1}s^{-1}$.

[0112] Anti-IFNAR1 antibodies described herein may exhibit a dissociation rate (k_{off}) of less than $10^{-1}s^{-1}$, less than $5\times10^{-1}s^{-1}$, less than $10^{-2}s^{-1}$, less than $5\times10^{-2}s^{-1}$, less than $10^{-3}s^{-1}$, less than $5\times10^{-3}s^{-1}$, less than $10^{-4}s^{-1}$, less than $5\times10^{-4}s^{-1}$, less than $10^{-5}s^{-1}$, less than $5\times10^{-5}s^{-1}$, less than $10^{-6}s^{-1}$, less than $5\times10^{-6}s^{-1}$, less than $10^{-7}s^{-1}$, less than $5\times10^{-7}s^{-1}$, less than $10^{-8}s^{-1}$, less than $5\times10^{-8}s^{-1}$, less than $10^{-9}s^{-1}$, less than $5\times10^{-9}s^{-1}$, or less than $10^{-10-1}s^{-1}$. Anti-IFNAR1 antibodies described herein may exhibit a k_{off}, of less than $5\times10^{-4}s^{-1}$, less than $10^{-5}s^{-1}$, less than $5\times10^{-5}s^{-1}$, less than $10^{-6}s^{-1}$, less than $5\times10^{-6}s^{-1}$, less than $10^{-7}s^{-1}$, less than $5\times10^{-7}s^{-1}$, less than $10^{-8}s^{-1}$, less than $5\times10^{-8}s^{-1}$, less than $10^{-9}s^{-1}$, less than $5\times10^{-9}s^{-1}$, or less than $10^{-10}s^{-1}$.

[0113] Anti-IFNAR1 antibodies described herein may exhibit an affinity constant or K_a (k_{on}/k_{off}) of at least 10^2M^{-1}, at least $5\times10^2M^{-1}$, at least 10^3M^{-1}, at least $5\times10^3M^{-1}$, at least 10^4M^{-1}, at least $5\times10^4M^{-1}$, at least 10^5M^{-1}, at least $5\times10^5M^{-1}$, at least 10^6M^{-1}, at least $5\times10^6M^{-1}$, at least 10^7M^{-1}, at least $5\times10^7M^{-1}$, at least 10^8M^{-1}, at least $5\times10^8M^{-1}$, at least 10^9M^{-1}, at least $5\times10^9M^{-1}$, at least $10^{10}M^{-1}$, at least $5\times10^1M^{-1}$, at least $10^{11}M^{-1}$, at least $5\times10^{11}M^{-1}$, at least $10^{12}M^{-1}$, at least $5\times10^{12}M$, at least $10^{13}M^{-1}$, at least $5\times10^{13}M^{-1}$, at least $10^{14}M^{-1}$, at least $5\times10^{14}M^{-1}$, at least $10^{15}M^{-1}$, or at least $5\times10^{15}M^{-1}$.

[0114] Anti-IFNAR1 antibodies described herein may exhibit a dissociation constant or K_d(k_{off}/k_{on}) of less than $10^{-2}M$, less than $5\times10^{-2}M$, less than $10^{-3}M$, less than $5\times10^{-3}M$, less than $10^{-4}M$, less than $5\times10^{-4}M$, less than $10^{-5}M$, less than $5\times10^{-5}M$, less than $10^{-6}M$, less than $5\times10^{-6}M$, less than $10^{-7}M$, less than $5\times10^{-7}M$, less than $10^{-8}M$, less than $5\times10^{-8}M$, less than $10^{-9}M$, less than $5\times10^{-9}M$, less than $10^{-10}M$, less than $5\times10^{-10}M$, less than $10^{-11}M$, less than $5\times10^{-11}M$, less than $10^{-12}M$, less than $5\times10^{-12}M$, less than $10^{-13}M$, less than $5\times10^{-13}M$, less than $10^{-14}M$, less than $5\times10^{-14}M$, less than $10^{-15}M$, or less than $5\times10^{-15}M$.

5.7.3 Interferon alpha subtype specificity

[0115] Anti-IFNAR1 antibodies described herein may exhibit the ability to block binding to IFNAR1 and/or neutralize the biological activity of one or more Type I interferon (IFN) including, but not limited to, IFNα, IFNβ, and IFNω. Binding of IFNα subtypes can be determined by routine competition assays such as that described in "Antibodies: A Laboratory Manual", CSHL. The anti-IFNAR1 antibodies described herein may exhibit the ability to block binding to IFNAR1 and/or neutralize the biological activity of IFNα, IFNβ, and IFNω. The anti-IFNAR1 antibodies described herein may exhibit the ability to block binding to IFNAR1 and/or neutralize the biological activity of one or more subtypes of IFNα including, but not limited to, IFNα subtypes 1, 2a, 2b, 4, 4b, 5, 6, 7, 8, 10, 14, 16, 17, and 21. The anti-IFNAR1 antibodies described herein may exhibit the ability to block binding to IFNAR1 and/or neutralize the biological activity of all subtypes of IFNα. In this context, anti-IFNAR1 antibodies described herein may exhibit the ability to block the binding of and/or neutralize the biological activity of IFNα subtypes IFNα 1, 2a, 2b, 4, 4b, 5, 6, 7, 8, 10, 14, 16, 17, and 21. Anti-IFNAR1 antibodies described herein may not exhibit the ability to block binding to IFNAR1 and/or neutralize the biological activity of one or more subtypes of IFNα including, but not limited to, IFNα subtypes 1, 2a, 2b, 4, 4b, 5, 6, 7, 8, 10, 14, 16, 17, and 21. In a specific embodiment, anti-IFNAR1 antibodies described herein may exhibit the ability to block binding to IFNAR1 and/or neutralize the biological activity all IFNα subtypes except IFNα21.

[0116] The anti-IFNAR1 antibodies described herein may exhibit the ability to block binding to IFNAR1 and/or neutralize the biological activity of at least 1, at least 2, at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, at least 10, at least 11, at least 12, or at least 13 of the following IFNα subtypes: 1, 2a, 2b, 4, 4b, 5, 6, 7, 8, 10, 14, 16, 17, and 21. In an alternative embodiment, the anti-IFNAR1 antibodies described herein may not exhibit the ability to block binding to IFNAR1 and/or neutralize the biological activity of at least 1, at least 2, at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, at least 10, at least 11, at least 12, or at least 13 of the following IFNα subtypes: 1, 2a, 2b, 4, 4b, 5, 6, 7, 8, 10, 14, 16, 17, and 21.

[0117] Anti-IFNAR1 antibodies described herein may exhibit the ability to block binding to IFNAR1 and/or neutralize the biological activity of non-naturally-occurring type I-like interferons. Such non-naturally occurring type I-like interferons, or hybrid type I-like interferons represent molecules that have been altered from their naturallyoccurung structures by recombinant or synthetic

techniques. Hybrid interferons, as described in U.S. Patent No. 7,232,563, represent a molecular replacement of various segments of a naturally occurring interferon structure to create a molecule that has increased potency and/or reduced toxicity.

[0118] Anti-IFNAR1 antibodies described herein may exhibit the ability to block binding to IFNAR1 and/or neutralize the biological activity of mutated type I interferons. Mutated type I interferons are described in U.S. Patent Nos. 6,299,870 and 6,300,474.

[0119] Anti-IFNAR1 antibodies described herein may exhibit the ability to block binding to IFNAR1 and/or neutralize the biological activity of type I-like interferons derived from other animal species. Such type I-like interferons are isolated from chicken, cat, mouse, rat, rabbit, goat, horse or other animal species. In specific embodiments, human type I interferons are isolated from cells derived from chicken, cat, mouse, rat, rabbit, goat, horse or other animal species. In other embodiments, human type I interferons entail different glycosylation patterns when derived from chicken, cat, mouse, rat, rabbit, goat, horse or other animal species. Further discussion of interferons from other animal species can be found in WIPO publication No. WO06099451A3.

[0120] For the purpose of the present invention, the ability of anti-IFNAR1 antibodies described herein to neutralize the activity of IFNα, can be monitored, for example, in a Kinase Receptor Activation (KIRA) Assay as described in WO 95/14930, published Jun. 1, 1995, by measuring the ability of a candidate antibody to reduce tyrosine phosphorylation (resulting from ligand binding) of the IFNAR1/R2 receptor complex.

[0121] Alternatively, or optionally, the ability of anti-IFNAR1 antibodies described herein to neutralize the elicitation of a cellular response by IFNα may be tested by monitoring the neutralization of the antiviral activity of IFNα, as described by Kawade, J. Interferon Res. 1:61 70 (1980), or Kawade and Watanabe, J. Interferon Res. 4:571 584 (1984), or Yousefi, et al., Am. J. Clin. Pathol. 83: 735 740 (1985), or by testing the ability of anti-IFNAR1 antibodies described herein to neutralize the ability of IFNα to activate the binding of the signaling molecule, interferon-stimulated factor 3 (ISGF3), to an oligonucleotide derived from the interferon-stimulated response element (ISRE), in an electrophoretic mobility shift assay, as described by Kurabayashi et al., Mol. Cell Biol., 15: 6386 (1995).

[0122] Anti-IFNAR1 antibodies described herein may exhibit the ability to inhibit at least one IFNα mediated function of the IFNAR1 receptor. Anti-IFNAR1 antibodies described herein may inhibit the activity of the IFNAR1 receptor in response to IFNα or subtypes thereof by at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, or at least about 99% . The anti-IFNAR1 antibodies described herein may inhibit the activity of the IFNAR1 receptor in response to IFNα or subtypes thereof as measured by the KIRA assay described above by at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, or at least about 99%. The anti-IFNAR1 antibodies described herein may inhibit the activity of the IFNAR1 receptor in response to IFNα or subtypes thereof as measured by the binding of the signaling molecule, interferon-stimulated factor 3 (ISGF3), to an oligonucleotide derived from the interferon-stimulated response element (ISRE), in an electrophoretic mobility shift assay, as described by Kurabayashi et al., Mol. Cell Biol., 15: 6386 (1995) by at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, or at least about 99% . The anti-IFNAR1 antibodies described herein may inhibit the activity of the IFNAR1 receptor in response to IFNα or subtypes thereof as measured by an assay known in the art by at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, or at least about 99%.

[0123] Anti-IFNAR1 antibodies described herein may exhibit the ability to neutralize the anti-viral properties of IFNα or subtypes thereof. Anti-IFNAR1 antibodies described herein may neutralize at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, or at least about 99% of the anti-viral activity of IFNα or subtypes thereof, as determined by the anti-viral assay of Kawade (1980), or Yousefi (1985). In an alternative embodiment, anti-IFNAR1 antibodies described herein may not neutralize the anti-viral properties of IFNα or subtypes thereof.

[0124] The ability of anti-IFNAR1 antibodies described herein to block the binding of IFNα or subtypes thereof to IFNAR1 can be determined by a routine competition assay such as that described in "Antibodies: A Laboratory Manual", Cold Spring Harbor Laboratory, Ed Harlow and David Lane (1988). Anti-IFNAR1 antibodies described herein may exhibit the ability to block or inhibit binding of the following IFNα subtypes: 1, 2, 4, 5, 8, 10, and 21 to IFNAR1. The anti-IFNAR1 antibodies described herein may exhibit the ability to block or inhibit binding of: at least 1, at least 2, at least 3, at least 4, at least 5, at least 6, or at least 7 of the following IFNα subtypes: 1, 2, 4, 5, 8, 10, and 21 to IFNAR1.

[0125] Antibodies described herein may act on IFNAR to regulate IFN-I responsive genes. IFN-I responsive genes have been identified in US Patent Applications entitled "IFN alpha-induced Pharmacodynamic Markers" with the following serial numbers; 60/873,008, filed December 6, 2006; 60/907,762, filed April 16, 2007; 60/924, 584, filed May 21, 2007 and 60/960,187, filed September 19, 2007.

5.7.4 Antibodies

[0126] Antibodies described herein may include monoclonal antibodies, multispecific antibodies, human antibodies, humanized antibodies, camelized antibodies, chimeric antibodies, single-chain Fvs (scFv), disulfide-linked Fvs (sdFv), and anti-idiotypic (anti-Id) antibodies, and epitope-binding fragments of any of the above. In particular, antibodies include immunoglobulin molecules and immunologically active fragments of immunoglobulin molecules, *i.e.,* molecules that contain an antigen-binding site, these fragments may or may not be fused to another immunoglobulin domain including but not limited to, an Fc region or fragment thereof. As outlined herein, the terms "antibody" and "antibodies" specifically include the modified antibodies described herein. Immunoglobulin molecules can be of any type *(e.g.,* IgG, IgE, IgM, IgD, IgA and IgY), class *(e.g.,* IgG1, IgG2, IgG3, IgG4, IgA1 and IgA2) or subclass. Antibodies described herein can be of any isotype. Antibodies described hereincan be of the IgG1, IgG2, IgG3 or IgG4 isotype. Antibodies described herein can be full-length antibodies comprising variable and constant regions, or they can be antigen-binding fragments thereof, such as a single chain antibody.

[0127] The term "antigen-binding fragment" of an antibody (or simply "antibody fragment"), as used herein, refers to one or more fragments of an antibody that retain the ability to specifically bind to an antigen (*e.g.*, IFNAR1). It has been shown that the antigen-binding function of an antibody can be performed by fragments of a full-length antibody. Examples of binding fragments encompassed within the term "antigen-binding fragment" of an antibody include (i) a Fab fragment, a monovalent fragment consisting of the V_L, V_H, C_L and C_{H1} domains; (ii) a $F(ab')_2$ fragment, a bivalent fragment comprising two Fab fragments linked by a disulfide bridge at the hinge region; (iii) a Fd fragment consisting of the V_H and C_{H1} domains; (iv) a Fv fragment consisting of the V_L and V_H domains of a single arm of an antibody, (v) a dAb fragment (Ward et al., (1989) Nature 341:544-546), which consists of a V_H domain; and (vi) an isolated complementarity determining region (CDR). Furthermore, although the two domains of the Fv fragment, V_L and V_H, are coded for by separate genes, they can be joined, using recombinant methods, by a synthetic linker that enables them to be made as a single protein chain in which the V_L and V_H regions pair to form monovalent molecules (known as single chain Fv (scFv); *see e.g.,* Bird et al. (1988) Science 242:423-426; and Huston et al. (1988) Proc. Natl. Acad. Sci. USA 85:5879-5883). Such single chain antibodies are also intended to be encompassed within the term "antigen-binding fragment" of an antibody. These antibody fragments are obtained using conventional techniques known to those with skill in the art, and the fragments are screened for utility in the same manner as are intact antibodies.

[0128] We describe fusion proteins (hereinafter referred to as "fusion proteins described herein") comprising a modified Fc region with reduced or ablated affinity for an Fc ligand responsible for facilitating effector function compared to an Fc region having the same amino acid sequence as the fusion protein described herein but not comprising the addition, substitution, or deletion of at least one amino acid residue of the Fc region.

[0129] Fusion proteins described herein may comprise a peptide, polypeptide, protein scaffold, scFv, dsFv, diabody, Tandab, or an antibody mimetic fused to a modified Fc region. Fusion proteins described herein may comprise a linker region connecting the peptide, polypeptide, protein scaffold, scFv, dsFv, diabody, Tandab, or an antibody mimetic to the modified Fc region. The use of naturally occurring, as well as artificial, peptide linkers to connect polypeptides into novel, linked fusion polypeptides is well known in the literature (Hallewell et al., (1989), J. Biol. Chem. 264, 5260-5268; Alfthan et al., (1995), Protein Eng. 8, 725-731; Robinson & Sauer (1996), Biochemistry 35, 109-116; Khandekar et al., (1997), J. Biol. Chem. 272, 32190-32197; Fares et al., (1998), Endocrinology 139, 2459-2464; Smallshaw et al., (1999), Protein Eng. 12, 623-630; U.S. Pat. No. 5,856,456).

[0130] Fusion proteins described herein may comprise an Fc region comprising at least one addition, substitution, or deletion of an amino acid residue selected from the group consisting of: 234, 235, and 331, wherein the numbering system of the constant region is that of the EU index as set forth in Kabat et al. (1991, NIH Publication 91-3242, National Technical Information Service, Springfield, VA). Fusion proteins described herein may comprise an Fc region comprising at least one amino acid residue selected from the group consisting of: L234F, L235E, and P331S.

[0131] Fusion proteins described herein may further comprise an Fc region comprising at least one addition, substitution, or deletion of an amino acid residue that is correlated with increased stability of the fusion protein. The addition, substitution, or deletion of an amino acid residue may be at position 228 of the Fc region, wherein the numbering system of the constant region is that of the EU index as set forth in Kabat *et al.* (supra). Fusion proteins described herein may comprise an Fc region comprising an amino acid substitution at position 228, wherein the substitution is a serine residue.

[0132] Antibodies or fusion proteins may comprise one or more engineered glycoforms, *i.e.,* a carbohydrate composition that is

covalently attached to a molecule comprising an Fc region. Engineered glycoforms may be useful for a variety of purposes, including, but not limited to, reducing effector function. Engineered glycoforms may be generated by any method known to one skilled in the art, for example by using engineered or variant expression strains, by co-expression with one or more enzymes, for example DI N-acetylglucosaminyltransferase III (GnTI11), by expressing a molecule comprising an Fc region in various organisms or cell lines from various organisms, or by modifying carbohydrate(s) after the molecule comprising Fc region has been expressed. Methods for generating engineered glycoforms are known in the art, and include, but are not limited to, those described in Umana et al., 1999, Nat. Biotechnol 17:176-180; Davies et al., 20017 Biotechnol Bioeng 74:288-294; Shields et al., 2002, J Biol Chem 277:26733-26740; Shinkawa et al., 2003, J Biol Chem 278:3466-3473) U.S. Pat. No. 6,602,684; U.S. Ser. No. 10/277,370; U.S. Ser. No. 10/113,929; PCT WO 00/61739A1; PCT WO 01/292246A1; PCT WO 02/311140A1; PCT WO 02/30954A1; Potillegent™ technology (Biowa, Inc. Princeton, N.J.); GlycoMAb™ glycosylation engineering technology (GLYCART biotechnology AG, Zurich, Switzerland); WO 00061739; EA01229125; US 20030115614; Okazaki et al., 2004, JMB, 336: 1239-49.

5.7.5 Antibody Conjugates

[0133] We describe the use of antibodies or fragments thereof conjugated or fused to one or more moieties, including but not limited to, peptides, polypeptides, proteins, fusion proteins, nucleic acid molecules, small molecules, mimetic agents, synthetic drugs, inorganic molecules, and organic molecules.

[0134] We describe the use of antibodies or fragments thereof recombinantly fused or chemically conjugated (including both covalent and non-covalent conjugations) to a heterologous protein or polypeptide (or fragment thereof, to a polypeptide of at least 10, at least 20, at least 30, at least 40, at least 50, at least 60, at least 70, at least 80, at least 90 or at least 100 amino acids) to generate fusion proteins. The fusion does not necessarily need to be direct, but may occur through linker sequences. For example, antibodies may be used to target heterologous polypeptides to particular cell types, either *in vitro* or *in vivo,* by fusing or conjugating the antibodies to antibodies specific for particular cell surface receptors. Antibodies fused or conjugated to heterologous polypeptides may also be used in *in vitro* immunoassays and purification methods using methods known in the art. See e.g., International publication No. WO 93/21232; European Patent No. EP 439,095; Naramura et al., 1994, Immunol. Lett. 39:91-99; U.S. Pat. No. 5,474,981; Gillies et al., 1992, PNAS 89:1428-1432; and Fell et al., 1991, J. Immunol. 146:2446-2452.

[0135] Additional fusion proteins may be generated through the techniques of gene-shuffling, motif-shuffling, exon-shuffling, and/or codon-shuffling (collectively referred to as "DNA shuffling"). DNA shuffling may be employed to alter the activities of antibodies described herein or fragments thereof (*e.g.*, antibodies or fragments thereof with higher affinities and lower dissociation rates). See, generally, U.S. Pat. Nos. 5,605,793; 5,811,238; 5,830,721; 5,834,252; and 5,837,458, and Patten et al., 1997, Curr. Opinion Biotechnol. 8:724-33; Harayama, 1998, Trends Biotechnol. 16(2):76-82; Hansson, et al., 1999, J. Mol. Biol. 287:265-76; and Lorenzo and Blasco, 1998, Biotechniques 24(2):308-313. Antibodies or fragments thereof, or the encoded antibodies or fragments thereof, may be modified by being subjected to random mutagenesis by error-prone PCR, random nucleotide insertion or other methods prior to recombination. One or more portions of a polynucleotide encoding an antibody or antibody fragment, which portions specifically bind to IFNAR1 may be recombined with one or more components, motifs, sections, parts, domains, fragments, etc., of one or more heterologous molecules.

[0136] Moreover, the antibodies or fragments thereof can be fused to marker sequences, such as a peptide to facilitate purification. The marker amino acid sequence may be a hexa-histidine peptide, such as the tag provided in a pQE vector (QIAGEN, Inc., 9259 Eton Avenue, Chatsworth, Calif., 91311), among others, many of which are commercially available. As described in Gentz et al., 1989, Proc. Natl. Acad. Sci. USA 86:821-824, for instance, hexa-histidine provides for convenient purification of the fusion protein. Other peptide tags useful for purification include, but are not limited to, the hemagglutinin "HA" tag, which corresponds to an epitope derived from the influenza hemagglutinin protein (Wilson et al., 1984, Cell 37:767) and the "Flag" tag.

[0137] Antibodies or fragments, analogs or derivatives thereof may be conjugated to a diagnostic or detectable agent. Such antibodies can be useful for monitoring or prognosing the development or progression of an inflammatory disorder as part of a clinical testing procedure, such as determining the efficacy of a particular therapy. Such diagnosis and detection can be accomplished by coupling the antibody to detectable substances including, but not limited to various enzymes, such as, but not limited to, horseradish peroxidase, alkaline phosphatase, beta-galactosidase, or acetylcholinesterase; prosthetic groups, such as, but not limited to, streptavidin/biotin and avidin/biotin; fluorescent materials, such as, but not limited to, umbelliferone, fluorescein, fluorescein isothiocynate, rhodamine, dichlorotriazinylamine fluorescein, dansyl chloride or phycoerythrin; luminescent materials, such as, but not limited to, luminol; bioluminescent materials, such as, but not limited to, luciferase, luciferin, and aequorin; radioactive materials, such as, but not limited to, iodine (^{131}I, ^{125}I, ^{123}I, ^{121}I), carbon (^{14}C), sulfur (^{35}S), tritium (^{3}H), indium

(^{115}In, ^{113}In, ^{112}In, ^{111}In,), and technetium (^{99}Tc), thallium (^{201}Ti), gallium (^{68}Ga, ^{67}Ga), palladium (^{103}Pd), molybdenum (^{99}Mo), xenon (^{133}Xe), fluorine (^{18}F), ^{153}Sm, ^{177}Lu, ^{159}Gd, ^{149}Pm, ^{140}La, ^{175}Yb, ^{166}Ho, ^{90}Y, ^{47}Sc, ^{186}Re, ^{188}Re, ^{142}Pr, ^{105}Ph, ^{97}Ru, ^{68}Ge, ^{57}Co, ^{65}Zn, ^{85}Sr, ^{32}P, ^{153}Gd, ^{169}Yb, ^{51}Cr, ^{54}Mn, ^{75}Se, ^{113}Sn, and ^{117}Tin; positron emitting metals using various positron emission tomographies, non-radioactive paramagnetic metal ions, and molecules that are radiolabelled or conjugated to specific radioisotopes.

[0138] Techniques for conjugating therapeutic moieties to antibodies are well known, see, e.g., Arnon et al., "Monoclonal Antibodies For Immunotargeting Of Drugs In Cancer Therapy", in Monoclonal Antibodies And Cancer Therapy, Reisfeld et al. (eds.), pp. 243-56. (Alan R. Liss, Inc. 1985); Hellstrom et al., "Antibodies For Drug Delivery", in Controlled Drug Delivery (2nd Ed.), Robinson et al. (eds.), pp. 623-53 (Marcel Dekker, Inc. 1987); Thorpe, "Antibody Carriers Of Cytotoxic Agents In Cancer Therapy: A Review", in Monoclonal Antibodies 84: Biological And Clinical Applications, Pinchera et al. (eds.), pp. 475-506 (1985); "Analysis, Results, And Future Prospective Of The Therapeutic Use Of Radiolabeled Antibody In Cancer Therapy", in Monoclonal Antibodies For Cancer Detection And Therapy, Baldwin et al. (eds.), pp. 303-16 (Academic Press 1985), and Thorpe et al., 1982, Immunol. Rev. 62:119-58.

[0139] Alternatively, an antibody can be conjugated to a second antibody to form an antibody heteroconjugate as described by Segal in U.S. Pat. No. 4,676,980.

[0140] The therapeutic moiety or drug conjugated to an antibody or fragment thereof that specifically binds to IFNAR1 should be chosen to achieve the desired prophylactic or therapeutic effect(s) for a particular disorder in a subject. A clinician or other medical personnel should consider the following when deciding on which therapeutic moiety or drug to conjugate to an antibody or fragment thereof that specifically binds to IFNAR1: the nature of the disease, the severity of the disease, and the condition of the subject.

5.7.6 Methods of Producing Antibodies

[0141] The antibodies or fragments thereof can be produced by any method known in the art for the synthesis of antibodies, in particular, by chemical synthesis or by recombinant expression techniques.

[0142] Monoclonal antibodies can be prepared using a wide variety of techniques known in the art including the use of hybridoma, recombinant, and phage display technologies, or a combination thereof. For example, monoclonal antibodies can be produced using hybridoma techniques including those known in the art and taught, for example, in Harlow et al., "Antibodies: A Laboratory Manual", (Cold Spring Harbor Laboratory Press, 2nd ed. 1988); Hammerling, et al., in: Monoclonal Antibodies and T-Cell Hybridomas 563-681 (Elsevier, N.Y., 1981). The term "monoclonal antibody" as used herein is not limited to antibodies produced through hybridoma technology. The term "monoclonal antibody" refers to an antibody that is derived from a single clone, including any eukaryotic, prokaryotic, or phage clone, and not the method by which it is produced.

[0143] Methods for producing and screening for specific antibodies using hybridoma technology are routine and known in the art. Briefly, mice can be immunized with IFNAR1 and once an immune response is detected, *e.g.*, antibodies specific for IFNAR1 are detected in the mouse serum, the mouse spleen is harvested and splenocytes isolated. The splenocytes are then fused by well known techniques to any suitable myeloma cells, for example, cells from cell line SP20 available from the ATCC. Hybridomas are selected and cloned by limited dilution. The hybridoma clones are then assayed by methods known in the art for cells that secrete antibodies capable of binding a polypeptide described herein. Ascites fluid, which generally contains high levels of antibodies, can be generated by immunizing mice with positive hybridoma clones.

[0144] Accordingly, monoclonal antibodies can be generated by culturing a hybridoma cell secreting an antibody described herein, wherein the hybridoma is generated by fusing splenocytes isolated from a mouse immunized with IFNAR1 with myeloma cells and then screening the hybridomas resulting from the fusion for hybridoma clones that secrete an antibody able to bind IFNAR1.

[0145] Antibody fragments which recognize specific IFNAR1 epitopes may be generated by any technique known to those of skill in the art. For example, Fab and $F(ab')_2$ fragments described herein may be produced by proteolytic cleavage of immunoglobulin molecules, using enzymes such as papain (to produce Fab fragments) or pepsin (to produce $F(ab')_2$ fragments). $F(ab')_2$ fragments contain the variable region, the light chain constant region and the CH1 domain of the heavy chain. Further, antibodies can also be generated using various phage display methods known in the art.

[0146] In phage display methods, functional antibody domains are displayed on the surface of phage particles which carry the polynucleotide sequences encoding them. In particular, DNA sequences encoding VH and VL domains are amplified from animal cDNA libraries (e.g., human or murine cDNA libraries of lymphoid tissues). The DNA encoding the VH and VL domains are recombined together with an scFv linker by PCR and cloned into a phagemid vector *(e.g.,* p CANTAB 6 or pComb 3 HSS). The vector is electroporated in *E. coli* and the *E. coli* is infected with helper phage. Phage used in these methods are typically filamentous phage including fd and M13 and the VH and VL domains are usually recombinantly fused to either the phage gene III or gene VIII. Phage expressing an antigen binding domain that binds to the IFNAR1 epitope of interest can be selected or identified with antigen, *e.g.,* using labeled antigen or antigen bound or captured to a solid surface or bead. Examples of phage display methods that can be used to make the antibodies of the present invention include those disclosed in Brinkman et al., 1995, J. Immunol. Methods 182:41-50; Ames et al., 1995, J. Immunol. Methods 184:177-186; Kettleborough et al., 1994, Eur. J. Immunol. 24:952-958; Persic et al., 1997, Gene 187:9-18; Burton et al., 1994, Advances in Immunology 57:191-280; International Application No. PCT/GB91/01134; International Publication Nos. WO 90/02809, WO 91/10737, WO 92/01047, WO 92/18619, WO 93/11236, WO 95/15982, WO 95/20401, and WO97/13844; and U.S. Pat. Nos. 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 and 5,969,108.

[0147] As described in the above references, after phage selection, the antibody coding regions from the phage can be isolated and used to generate whole antibodies, including human antibodies, or any other desired antigen binding fragment, and expressed in any desired host, including mammalian cells, insect cells, plant cells, yeast, and bacteria, *e.g.,* as described below. Techniques to recombinantly produce Fab, Fab' and F(ab')2 fragments can also be employed using methods known in the art such as those disclosed in International Publication No. WO 92/22324; Mullinax et al., 1992, BioTechniques 12(6):864-869; Sawai et al., 1995, AJRI 34:26-34; and Better et al., 1988, Science 240:1041-1043.

[0148] To generate whole antibodies, PCR primers including VH or VL nucleotide sequences, a restriction site, and a flanking sequence to protect the restriction site can be used to amplify the VH or VL sequences in scFv clones. Utilizing cloning techniques known to those of skill in the art, the PCR amplified VH domains can be cloned into vectors expressing a VH constant region, *e.g.* the human gamma 4 constant region, and the PCR amplified VL domains can be cloned into vectors expressing a VL constant region, *e.g.*, human kappa or lambda constant regions. In certain embodiments, the vectors for expressing the VH or VL domains comprise an EF-lalpha promoter, a secretion signal, a cloning site for the variable domain, constant domains, and a selection marker such as neomycin. The VH and VL domains may also be cloned into one vector expressing the necessary constant regions. The heavy chain conversion vectors and light chain conversion vectors are then co-transfected into cell lines to generate stable or transient cell lines that express full-length antibodies, *e.g.*, IgG, using techniques known to those of skill in the art.

[0149] For some uses, including *in vivo* use of antibodies in humans and *in vitro* detection assays, it may be advantageous to use human or chimeric antibodies. Completely human antibodies are particularly desirable for therapeutic treatment of human subjects. Human antibodies can be made by a variety of methods known in the art including phage display methods described above using antibody libraries derived from human immunoglobulin sequences. See also U.S. Pat. Nos. 4,444,887 and 4,716,111; and International Publication Nos. WO 98/46645, WO 98/50433, WO 98/24893, WO98/16654, WO 96/34096, WO 96/33735, and WO 91/10741.

[0150] A chimeric antibody is a molecule in which different portions of the antibody are derived from different immunoglobulin molecules. Methods for producing chimeric antibodies are known in the art. See, *e.g.,* Morrison, 1985, Science 229:1202; Oi et al., 1986, BioTechniques 4:214; Gillies et al., 1989, J. Immunol. Methods 125:191-202; and U.S. Pat. Nos. 5,807,715, 4,816,567, 4,816,397, and 6,311,415.

[0151] A humanized antibody is an antibody or fragment thereof which is capable of binding to a predetermined antigen and which comprises a framework region having substantially the amino acid sequence of a human immunoglobulin and a CDR having substantially the amino acid sequence of a non-human immunoglobulin. A humanized antibody comprises substantially all of at least one, and typically two, variable domains (Fab, Fab', $F(ab')_2$, Fabc, Fv) in which all or substantially all of the CDR regions correspond to those of a non-human immunoglobulin (*i.e.,* donor antibody) and all or substantially all of the framework regions are those of a human immunoglobulin consensus sequence. In certain instances, a humanized antibody also comprises at least a portion of an immunoglobulin constant region (Fc), typically that of a human immunoglobulin. Ordinarily, the antibody will contain both the light chain as well as at least the variable domain of a heavy chain. The antibody also may include the CH1, hinge, CH2, CH3, and CH4 regions of the heavy chain. The humanized antibody can be selected from any class of immunoglobulins, including IgM, IgG, IgD; IgA and IgE, and any isotype, including IgG1, IgG2, IgG3 and IgG4. Usually the constant domain is a complement fixing constant domain where it is desired that the humanized antibody exhibit: cytotoxic activity and the class is typically IgG_1. Where such cytotoxic activity is not desirable, the constant domain may be of the IgG_2 class. The humanized antibody may

comprise sequences from more than one class or isotype, and selecting particular constant domains to optimize desired effector functions is within the ordinary skill in the art. The framework and CDR regions of a humanized antibody need not correspond precisely to the parental sequences, *e.g.,* the donor CDR or the consensus framework may be mutagenized by substitution, insertion or deletion of at least one residue so that the CDR or framework residue at that site does not correspond to either the consensus or the import antibody. Such mutations, however, will not be extensive. Usually, at least 75% of the humanized antibody residues will correspond to those of the parental framework region (FR) and CDR sequences, more often 90%, and possibly greater than 95%. Humanized antibody can be produced using variety of techniques known in the art, including but not limited to, CDR-grafting (European Patent No. EP 239,400; International Publication No. WO 91/09967; and U.S. Pat. Nos. 5,225,539, 5,530,101, and 5,585,089), veneering or resurfacing (European Patent Nos. EP 592,106 and EP 519,596; Padlan, 1991, Molecular Immunology 28(4/5):489-498; Studnicka et al., 1994, Protein Engineering 7(6):805-814; and Roguska et al., 1994, PNAS 91:969-973), chain shuffling (U.S. Pat. No. 5,565,332), and techniques disclosed in, e.g., U.S. Pat. Nos. 6,407,213, 5,766,886, WO 9317105, Tan et al., J. Immunol. 169:1119-25 (2002), Caldas et al., Protein Eng. 13(5):353-60 (2000), Morea et al., Methods 20(3):267-79 (2000), Baca et al., J. Biol. Chem. 272(16):10678-84 (1997), Roguska et al., Protein Eng. 9(10):895-904 (1996), Couto et al., Cancer Res. 55 (23 Supp):5973s-5977s (1995), Couto et al., Cancer Res. 55(8):1717-22 (1995), Sandhu J S, Gene 150(2):409-10 (1994), and Pedersen et al., J. Mol. Biol. 235(3):959-73 (1994). Often, framework residues in the framework regions will be substituted with the corresponding residue from the CDR donor antibody to alter or improve antigen binding. These framework substitutions are identified by methods known in the art, *e.g.,* by modeling of the interactions of the CDR and framework residues to identify framework residues important for antigen binding and sequence comparison to identify unusual framework residues at particular positions. (See, e.g., Queen et al., U.S. Pat. No. 5,585,089; and Riechmann et al., 1988, Nature 332:323.

5.7.7 Polynucleotides Encoding an Antibody

[0152] We describe polynucleotides that hybridize under high stringency, intermediate or lower stringency hybridization conditions, *e.g.*, as defined above, to polynucleotides that encode an antibody described herein.

[0153] The polynucleotides may be obtained, and the nucleotide sequence of the polynucleotides determined, by any method known in the art. Since the amino acid sequences of the antibodies are known, nucleotide sequences encoding these antibodies can be determined using methods known in the art, *i.e.,* nucleotide codons known to encode particular amino acids are assembled in such a way to generate a nucleic acid that encodes the antibody or fragment thereof described herein. Such a polynucleotide encoding the antibody maybe assembled from chemically synthesized oligonucleotides (*e.g.*, as described in Kutmejer et al., 1994, BioTechniques 17:242), which, briefly, involves the synthesis of overlapping oligonucleotides containing portions of the sequence encoding the antibody, annealing and ligating of those oligonucleotides, and then amplification of the ligated oligonucleotides by PCR.

[0154] Alternatively, a polynucleotide encoding an antibody may be generated from nucleic acid from a suitable source. If a clone containing a nucleic acid encoding a particular antibody is not available, but the sequence of the antibody molecule is known, a nucleic acid encoding the immunoglobulin may be chemically synthesized or obtained from a suitable source *(e.g.,* an antibody cDNA library, or a cDNA library generated from, or nucleic acid, usually poly A+RNA, isolated from, any tissue or cells expressing the antibody, such as hybridoma cells selected to express an antibody described herein) by PCR amplification using synthetic primers hybridizable to the 3' and 5' ends of the sequence or by cloning using an oligonucleotide probe specific for the particular gene sequence to identify, e.g., a cDNA clone from a cDNA library that encodes the antibody. Amplified nucleic acids generated by PCR may then be cloned into replicable cloning vectors using any method known in the art.

[0155] Once the nucleotide sequence of the antibody is determined, the nucleotide sequence of the antibody may be manipulated using methods known in the art for the manipulation of nucleotide sequences, *e.g.*, recombinant DNA techniques, site-directed mutagenesis, PCR, etc. (see, for example, the techniques described in Sambrook et al., 1990, "Molecular Cloning, A Laboratory Manual", 2d Ed., Cold Spring Harbor Laboratory, Cold Spring Harbor, N.Y. and Ausubel et al., eds., 1998, Current Protocols in Molecular Biology, John Wiley & Sons, NY, to generate antibodies having a different amino acid sequence, for example to create amino acid substitutions, deletions, and/or insertions.

[0156] In a specific embodiment, one or more of the CDRs is inserted within framework regions using routine recombinant DNA techniques. The framework regions may be naturally-occurring or consensus framework regions, and in certain instances, human framework regions (see, *e.g.,* Chothia et al., 1998, J. Mol. Biol. 278: 457-479 for a listing of human framework regions). Optionally, the polynucleotide generated by the combination of the framework regions and CDRs encodes an antibody that specifically binds to IFNAR1. Optionally, one or more amino acid substitutions may be made within the framework regions, and, in certain instances,

the amino acid substitutions improve binding of the antibody to its antigen. Additionally, such methods may be used to make amino acid substitutions or deletions of one or more variable region cysteine residues participating in an intrachain disulfide bond to generate antibody molecules lacking one or more intrachain disulfide bonds. Other alterations to the polynucleotide are encompassed by the present invention and within the skill of the art.

[0157] In specific embodiments, antibodies described herein are encoded by polynucleotide sequences exemplified in Figures 1-4. In other specific embodiments, polynucleotides described herein encode antibodies comprising light chain and heavy chain constant regions corresponding to SEQ ID Nos: 41 and 42 respectively. In yet other specifc embodiments, polynucleotides described herein encode antibodies comprising heavy chain constant regions corresponding to SEQ ID No: 42 with an allowance for allelic variation wherein the variation is at least one or more residue selected from the group consisting of positions 214, 221, 356, and 358 as defined by the EU index numbering system.

5.7.8 Recombinant Expression of an Antibody

[0158] Recombinant expression of an antibody described herein, derivative, analog or fragment thereof, *(e.g.,* a heavy or light chain of an antibody described herein or a portion thereof or a single chain antibody described herein), requires construction of an expression vector containing a polynucleotide that encodes the antibody. Once a polynucleotide encoding an antibody molecule or a heavy or light chain of an antibody, or portion thereof (but not necessarily containing the heavy or light chain variable domain), described herein has been obtained, the vector for the production of the antibody molecule may be produced by recombinant DNA technology using techniques known in the art. Thus, methods for preparing a protein by expressing a polynucleotide containing an antibody encoding nucleotide sequence are described herein. Methods which are well known to those skilled in the art can be used to construct expression vectors containing antibody coding sequences and appropriate transcriptional and translational control signals. These methods include, for example, *in vitro* recombinant DNA techniques, synthetic techniques, and *in vivo* genetic recombination. Thus we describe replicable vectors comprising a nucleotide sequence encoding an antibody molecule described herein, a heavy or light chain of an antibody, a heavy or light chain variable domain of an antibody or a portion thereof, or a heavy or light chain CDR, operably linked to a promoter. Such vectors may include the nucleotide sequence encoding the constant region of the antibody molecule (see, *e.g.*, International Publication No. WO 86/05807; International Publication No. WO 89/01036; and U.S. Pat. No. 5,122,464) and the variable domain of the antibody maybe cloned into such a vector for expression of the entire heavy, the entire light chain, or both the entire heavy and light chains.

[0159] The expression vector is transferred to a host cell by conventional techniques and the transfected cells are then cultured by conventional techniques to produce an antibody described herein. Thus, we describe host cells containing a polynucleotide encoding an antibody described herein or fragments thereof, or a heavy or light chain thereof, or portion thereof, or a single chain antibody described herein, operably linked to a heterologous promoter. For the expression of double-chained antibodies, vectors encoding both the heavy and light chains may be co-expressed in the host cell for expression of the entire immunoglobulin molecule, as detailed below.

[0160] A variety of host-expression vector systems may be utilized to express the antibody molecules described herein (see, *e.g.,* U.S. Pat. No. 5,807,715). Such host-expression systems represent vehicles by which the coding sequences of interest may be produced and subsequently purified, but also represent cells which may, when transformed or transfected with the appropriate nucleotide coding sequences, express an antibody molecule described herein *in situ*. These include but are not limited to microorganisms such as bacteria (*e.g., E. coli* and *B. subtilis*) transformed with recombinant bacteriophage DNA, plasmid DNA or cosmid DNA expression vectors containing antibody coding sequences; yeast *(e.g., Saccharomyces* and *Pichia*) transformed with recombinant yeast expression vectors containing antibody coding sequences; insect cell systems infected with recombinant virus expression vectors (e.g., baculovirus) containing antibody coding sequences; plant cell systems infected with recombinant virus expression vectors (*e.g.,* cauliflower mosaic virus, CaMV; tobacco mosaic virus, TMV) or transformed with recombinant plasmid expression vectors *(e.g.* Ti plasmid) containing antibody coding sequences; or mammalian cell systems (*e.g.,* COS, CHO, BHK, 293, NS0, and 3T3 cells) harboring recombinant expression constructs containing promoters derived from the genome of mammalian cells *(e.g.,* metallothionein promoter) or from mammalian viruses *(e.g.,* the adenovirus late promoter; the vaccinia virus 7.5K promoter). Bacterial cells such as *Escherichia coli,* and in otheralternatives, eukaryotic cells, especially for the expression of whole recombinant antibody molecule, may be used for the expression of a recombinant antibody molecule. For example, mammalian cells such as Chinese hamster ovary cells (CHO), in conjunction with a vector such as the major intermediate early gene promoter element from human cytomegalovirus is an effective expression system for antibodies (Foecking et al., 1986, Gene 45:101; and Cockett et al., 1990, Bio/Technology 8:2). In a specific embodiment, the expression of nucleotide sequences encoding antibodies or fragments thereof which specifically bind to IFNAR1 is regulated by a constitutive

promoter, inducible promoter or tissue specific promoter.

[0161] In bacterial systems, a number of expression vectors may be advantageously selected depending upon the use intended for the antibody molecule being expressed. For example, when a large quantity of such a protein is to be produced, for the generation of pharmaceutical compositions of an antibody molecule, vectors which direct the expression of high levels of fusion protein products that are readily purified may be desirable. Such vectors include, but are not limited to, the *E. coli* expression vector pUR278 (Ruther et al., 1983, EMBO 12:1791), in which the antibody coding sequence may be ligated individually into the vector in frame with the lac Z coding region so that a fusion protein is produced; pIN vectors (Inouye & Inouye, 1985, Nucleic Acids Res. 13:3101-3109; Van Heeke & Schuster, 1989, J. Biol. Chem. 24:5503-5509); and the like. pGEX vectors may also be used to express foreign polypeptides as fusion proteins with glutathione 5-transferase (GST). In general, such fusion proteins are soluble and can easily be purified from lysed cells by adsorption and binding to matrix glutathione agarose beads followed by elution in the presence of free glutathione. The pGEX vectors are designed to include thrombin or factor Xa protease cleavage sites so that the cloned target gene product can be released from the GST moiety.

[0162] In mammalian host cells, a number of viral-based expression systems may be utilized. In cases where an adenovirus is used as an expression vector, the antibody coding sequence of interest may be ligated to an adenovirus transcription/translation control complex, *e.g.,* the late promoter and tripartite leader sequence. This chimeric gene may then be inserted in the adenovirus genome by *in vitro* or *in vivo* recombination. Insertion in a non-essential region of the viral genome (*e.g.*, region E1 or E3) will result in a recombinant virus that is viable and capable of expressing the antibody molecule in infected hosts *(e.g.,* see Logan & Shenk, 1984, Proc. Natl. Acad. Sci. USA 8 1:355-359). Specific initiation signals may also be required for efficient translation of inserted antibody coding sequences. These signals include the ATG initiation codon and adjacent sequences. Furthermore, the initiation codon must be in phase with the reading frame of the desired coding sequence to ensure translation of the entire insert. These exogenous translational control signals and initiation codons can be of a variety of origins, both natural and synthetic. The efficiency of expression may be enhanced by the inclusion of appropriate transcription enhancer elements, transcription terminators, *etc.* (see, *e.g.,* Bittner et al., 1987, Methods in Enzymol. 153:516-544).

[0163] In addition, a host cell strain may be chosen which modulates the expression of the inserted sequences, or modifies and processes the gene product in the specific fashion desired. Such modifications *(e.g.,* glycosylation) and processing *(e.g.,* cleavage) of protein products may be important for the function of the protein. Different host cells have characteristic and specific mechanisms for the post-translational processing and modification of proteins and gene products. Appropriate cell lines or host systems can be chosen to ensure the correct modification and processing of the foreign protein expressed. To this end, eukaryotic host cells which possess the cellular machinery for proper processing of the primary transcript, glycosylation, and phosphorylation of the gene product may be used. Such mammalian host cells include but are not limited to CHO, VERY, BHK, HeLa, COS, MDCK, 293, 3T3, W138, BT483, Hs578T, HTB2, BT2O and T47D, NS0 (a murine myeloma cell line that does not endogenously produce any immunoglobulin chains), CRL7O3O and HsS78Bst cells.

[0164] For long-term, high-yield production of recombinant proteins, stable expression is preferred. For example, cell lines which stably express the antibody molecule may be engineered. Rather than using expression vectors which contain viral origins of replication, host cells can be transformed with DNA controlled by appropriate expression control elements (*e.g.*, promoter, enhancer, sequences, transcription terminators, polyadenylation sites, *etc.*), and a selectable marker. Following the introduction of the foreign DNA, engineered cells may be allowed to grow for 1-2 days in an enriched media, and then are switched to a selective media. The selectable marker in the recombinant plasmid confers resistance to the selection and allows cells to stably integrate the plasmid into their chromosomes and grow to form foci which in turn can be cloned and expanded into cell lines. This method may advantageously be used to engineer cell lines which express the antibody molecule. Such engineered cell lines may be particularly useful in screening and evaluation of compositions that interact directly or indirectly with the antibody molecule.

[0165] A number of selection systems may be used, including but not limited to, the herpes simplex virus thymidine kinase (Wigler et al., 1977, Cell 11:223), hypoxanthineguanine phosphoribosyltransferase (Szybalska & Szybalski, 1992, Proc.Natl. Acad. Sci. USA 48:202), and adenine phosphoribosyltransferase (Lowy et al., 1980, Cell 22:8-17) genes can be employed in tk-, hgprt- or aprt- cells, respectively. Also, antimetabolite resistance can be used as the basis of selection for the following genes: dhfr, which confers resistance to methotrexate (Wigler et al., 1980, Natl. Acad. Sci. USA 77:357 ; O'Hare et al., 1981, Proc. Natl. Acad. Sci. USA 78:1527); gpt, which confers resistance to mycophenolic acid (Mulligan & Berg, 1981, Proc. Natl. Acad. Sci. USA 78:2072); neo, which confers resistance to the aminoglycoside G-418 (Wu and Wu, 1991, Biotherapy 3:87-95; Tolstoshev, 1993, Ann. Rev. Pharmacol. Toxicol. 32:573-596 ; Mulligan, 1993, Science 260:926-932; and Morgan and Anderson, 1993, Ann. Rev. Biochem. 62: 191-217; May, 1993, TIB TECH 11(5): 155-2 15); and hygro, which confers resistance to hygromycin (Santerre et al., 1984, Gene 30:147). Methods commonly known in the art of recombinant DNA technology may be routinely applied to select the desired recombinant clone, and such methods are described, for example, in Ausubel et al. (eds.), Current Protocols in Molecular Biology, John Wiley & Sons, NY (1993); Kriegler, Gene Transfer and Expression, A Laboratory Manual, Stockton Press,

NY (1990); and in Chapters 12 and 13, Dracopoli et al. (eds), Current Protocols in Human Genetics, John Wiley & Sons, NY (1994); Colberre-Garapin et al., 1981, J. Mol. Biol. 150: 1, which are incorporated by reference herein in their entireties.

[0166] The expression levels of an antibody molecule can be increased by vector amplification (for a review, see Bebbington and Hentschel, The use of vectors based on gene amplification for the expression of cloned genes in mammalian cells in DNA cloning, Vol.3. (Academic Press, New York, 1987)). When a marker in the vector system expressing antibody is amplifiable, increase in the level of inhibitor present in culture of host cell will increase the number of copies of the marker gene. Since the amplified region is associated with the antibody gene, production of the antibody will also increase (Crouse et al., 1983, Mol. Cell. Biol. 3:257).

[0167] The host cell may be co-transfected with two expression vectors described herein, the first vector encoding a heavy chain derived polypeptide and the second vector encoding a light chain derived polypeptide. The two vectors may contain identical selectable markers which enable equal expression of heavy and light chain polypeptides. Alternatively, a single vector may be used which encodes, and is capable of expressing, both heavy and light chain polypeptides. In such situations, the light chain should be placed before the heavy chain to avoid an excess of toxic free heavy chain (Proudfoot, 1986, Nature 322:52; and Kohler, 1980, Proc. Natl. Acad. Sci. USA 77:2 197). The coding sequences for the heavy and light chains may comprise cDNA or genomic DNA.

[0168] Once an antibody molecule described herein has been produced by recombinant expression, it may be purified by any method known in the art for purification of an immunoglobulin molecule, for example, by chromatography (*e.g.*, ion exchange, affinity, particularly by affinity for the specific antigen after Protein A, and sizing column chromatography), centrifugation, differential solubility, or by any other standard technique for the purification of proteins. Further, the antibodies described herein or fragments thereof may be fused to heterologous polypeptide sequences described herein or otherwise known in the art to facilitate purification.

5.8 Scalable Production of Antibodies

[0169] In an effort to obtain large quantities, antibodies described herein may be produced by a scalable process (hereinafter referred to as "scalable process described herein"). In some embodiments, antibodies may be produced by a scalable process described herein in the research laboratory that may be scaled up to produce the antibodies described herein in analytical scale bioreactors (for example, but not limited to 5L, 10L, 15L, 30L, or 50L bioreactors). In other embodiments, the antibodies may be produced by a scalable process described herein in the research laboratory that may be scaled up to produce the antibodies described herein in production scale bioreactors (for example, but not limited to 75L, 100L, 150L, 300L, or 500L). In some embodiments, the scalable process described herein results in little or no reduction in production efficiency as compared to the production process performed in the research laboratory. In other embodiments, the scalable process described herein produces antibodies at production efficiency of about 10 mg/L, about 20 m/L, about 30 mg/L, about 50 mg/L, about 75 mg/L, about 100 mg/L, about 125 mg/L, about 150 mg/L, about 175 mg/L, about 200 mg/L, about 250 mg/L, about 300 mg/L or higher. In other embodiments, fusion proteins may be produced by scalable processes described herein.

[0170] In other embodiments, the scalable process described herein produces antibodies at production efficiency of at least about 10 mg/L, at least about 20 m/L, at least about 30 mg/L, at least about 50 mg/L, at least about 75 mg/L, at least about 100 mg/L, at least about 125 mg/L, at least about 150 mg/L, at least about 175 mg/L, at least about 200 mg/L, at least about 250 mg/L, at least about 300 mg/L or higher.

[0171] In other embodiments, the scalable process described herein produces antibodies at production efficiency from about 10 mg/L to about 300 mg/L, from about 10 mg/L to about 250 mg/L, from about 10 mg/L to about 200 mg/L, from about 10 mg/L to about 175 mg/L, from about 10 mg/L to about 150 mg/L, from about 10 mg/L to about 100 mg/L, from about 20 mg/L to about 300 mg/L, from about 20 mg/L to about 250 mg/L, from about 20 mg/L to about 200 mg/L, from 20 mg/L to about 175 mg/L, from about 20 mg/L to about 150 mg/L, from about 20 mg/L to about 125 mg/L, from about 20 mg/L to about 100 mg/L, from about 30 mg/L to about 300 mg/L, from about 30 mg/L to about 250 mg/L, from about 30 mg/L to about 200 mg/L, from about 30 mg/L to about 175 mg/L, from about 30 mg/L to about 150 mg/L, from about 30 mg/L to about 125 mg/L, from about 30 mg/L to about 100 mg/L, from about 50 mg/L to about 300 mg/L, from about 50 mg/L to about 250 mg/L, from about 50 mg/L to about 200 mg/L, from 50 mg/L to about 175 mg/L, from about 50 mg/L to about 150 mg/L, from about 50 mg/L to about 125 mg/L, or from about 50 mg/L to about 100 mg/L.

5.8.1 Further methods of engineering antibodies

[0172] An Fc hinge region of an antibody described herein may be mutated to decrease the biological half life of the antibody. More specifically, one or more amino acid mutations may be introduced into the CH2-CH3 domain interface region of the Fc-hinge fragment such that the antibody has impaired Staphylococcyl protein A (SpA) binding relative to native Fc-hinge domain SpA binding. This approach is described in further detail in U.S. Patent No. 6,165,745 by Ward et al.

[0173] An antibody may be modified to increase its biological half life. Various approaches are possible. For example, one or more of the following mutations can be introduced: T252L, T254S, T256F, as described in U.S. Patent No. 6,277,375. In another embodiment, one or more of the following mutations can be introduced: M252Y, S254T, T256E, as described in U.S. Patent No. 7,083,784. Alternatively, to increase the biological half life, the antibody can be modified within the CH1 or CL region to contain a salvage receptor binding epitope taken from two loops of a CH2 domain of an Fc region of an IgG, as described in U.S. Patent Nos. 5,869,046 and 6,121,022 by Presta et al.

[0174] An Fc region may be modified by replacing at least one amino acid residue with a different amino acid residue to reduce the effector function(s) of the antibody. For example, one or more amino acids selected from amino acid residues 234, 235, 236, 237, 297, 318, 320 and 322 can be replaced with a different amino acid residue such that the antibody has reduced affinity for an effector ligand but retains the antigen-binding ability of the parent antibody. The effector ligand to which affinity is reduced can be, for example, an Fc receptor or the C1 component of complement. This approach is described in further detail in U.S. Patent Nos. 5,624,821 and 5,648,260, both by Winter *et al.*

[0175] In another example, one or more amino acids selected from amino acid residues 329, 331 and 322 can be replaced with a different amino acid residue such that the antibody has reduced C1q binding and/or reduced or abolished complement dependent cytotoxicity (CDC). This approach is described in further detail in U.S. Patent Nos. 6,194,551 by Idusogie et al.

[0176] In another example, one or more amino acid residues within amino acid positions 231 and 239 are modified to thereby reduce the ability of the antibody to fix complement. This approach is described further in PCT Publication WO 94/29351 by Bodmer et al.

[0177] An Fc region of an antibody described herein may be further modified to decrease the ability of the antibody to mediate antibody dependent cellular cytotoxicity (ADCC) and/or to decrease the affinity of the antibody for an Fcγ receptor by modifying one or more amino acids at the following positions: 238, 239, 248, 249, 252, 254, 255, 256, 258, 265, 267, 268, 269, 270, 272, 276, 278, 280, 283, 285, 286, 289, 290, 292, 293, 294, 295, 296, 298, 301, 303, 305, 307, 309, 312, 315, 320, 322, 324, 326, 327, 329, 330, 333, 334, 335, 337, 338, 340, 360, 373, 376, 378, 382, 388, 389, 398, 414, 416, 419, 430, 434, 435, 437, 438 or 439. This approach is described further in PCT Publication WO 00/42072 by Presta.

[0178] Another modification of the antibodies herein that is contemplated is pegylation. An antibody can be pegylated to, for example, increase the biological (e.g., serum) half life of the antibody. To pegylate an antibody, the antibody, or fragment thereof, typically is reacted with polyethylene glycol (PEG), such as a reactive ester or aldehyde derivative of PEG, under conditions in which one or more PEG groups become attached to the antibody or antibody fragment. In certain instances, the pegylation is carried out via an acylation reaction or an alkylation reaction with a reactive PEG molecule (or an analogous reactive water-soluble polymer). As used herein, the term "polyethylene glycol" is intended to encompass any of the forms of PEG that have been used to derivatize other proteins, such as mono (C1-C10) alkoxy- or aryloxy-polyethylene glycol or polyethylene glycol-maleimide. In certain embodiments, the antibody to be pegylated is an aglycosylated antibody. Methods for pegylating proteins are known in the art and can be applied to antibodies described herein. See for example, EP 0 154 316 by Nishimura et al. and EP 0 401 384 by Ishikawa et al.

[0179] Thus, in another aspect described herein, the structural features of anti-IFNAR1 antibodies, for example, but not limited to 3F11, 4G5, 11E2, and 9D4, are used to create structurally related anti-IFNAR1 antibodies that retain at least one functional property of antibodies described herein, such as binding to IFNAR1. For example, one or more CDR regions of 3F11, 4G5, 11E2, or 9D4, or mutations thereof, can be combined recombinantly with known framework regions and/or other CDRs to create additional, recombinantly-engineered, anti-IFNAR1 antibodies described herein, as discussed above. Other types of modifications include those described in the previous section. The starting material for the engineering method is one or more of the V_H and/or V_L sequences provided herein, or one or more CDR regions thereof. To create the engineered antibody, it is not necessary to actually prepare (*i.e.,* express as a protein) an antibody having one or more of the V_H and/or V_L sequences provided herein, or one or more CDR regions thereof. Rather, the information contained in the sequence(s) is used as the starting material to create a "second generation" sequence(s) derived from the original sequence(s) and then the "second generation" sequence(s) is prepared and expressed as a protein.

5.9 Compositions

[0180] In another aspect, we describe compositions containing one or a combination of monoclonal antibodies, or fusion proteins comprising an Fc region thereof, as described herein, formulated together with a carrier. Such compositions may include one or a combination of *(e.g.,* two or more different) antibodies, fusion proteins, immunoconjugates or bispecific molecules described herein. In some embodiments, such compositions are physiologically tolerable and as such are suitable for administration to a subject (also referred to as a "pharmaceutical composition described herein." For example, pharmaceutical compositions described herein may comprise a combination of antibodies (or immunoconjugates or bispecifics) that bind to different epitopes on the target antigen or that have complementary activities.

[0181] In another embodiment, compositions described herein may include one or more pharmaceutically acceptable salts. Examples of such salts include acid addition salts and base addition salts. Acid addition salts include those derived from nontoxic inorganic acids, such as hydrochloric, nitric, phosphoric, sulfuric, hydrobromic, hydroiodic, phosphorous and the like, as well as from nontoxic organic acids such as aliphatic mono- and dicarboxylic acids, phenyl-substituted alkanoic acids, hydroxy alkanoic acids, aromatic acids, aliphatic and aromatic sulfonic acids and the like. Base addition salts include those derived from alkaline earth metals, such as sodium, potassium, magnesium, calcium and the like, as well as from nontoxic organic amines, such as N,N'-dibenzylethylenediamine, N-methylglucamine, chloroprocaine, choline, diethanolamine, ethylenediamine, procaine and the like.

[0182] Compositions described herein also may include a pharmaceutically acceptable anti-oxidant. Examples of pharmaceutically acceptable antioxidants include: (1) water soluble antioxidants, such as ascorbic acid, cysteine hydrochloride, sodium bisulfate, sodium metabisulfite, sodium sulfite and the like; (2) oil-soluble antioxidants, such as ascorbyl palmitate, butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), lecithin, propyl gallate, alpha-tocopherol, and the like; and (3) metal chelating agents, such as citric acid, ethylenediamine tetraacetic acid (EDTA), sorbitol, tartaric acid, phosphoric acid, and the like.

[0183] Examples of suitable aqueous and nonaqueous carriers that may be employed in contemplated compositions described herein include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the like), and suitable mixtures thereof, vegetable oils, such as olive oil, and injectable organic esters, such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of coating materials, such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

[0184] Compositions described herein may also contain adjuvants such as preservatives, wetting agents, emulsifying agents and dispersing agents. Prevention of presence of microorganisms may be ensured both by sterilization procedures and by the inclusion of various antibacterial and antifungal agents, for example, paraben, chlorobutanol, phenol sorbic acid, and the like. It may also be desirable to include isotonic agents, such as sugars, sodium chloride, and the like into the compositions. In addition, prolonged absorption of the injectable pharmaceutical form may be brought about by the inclusion of agents which delay absorption such as aluminum monostearate and gelatin.

[0185] Pharmaceutically acceptable carriers include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion. The use of such media and agents for pharmaceutically active substances is known in the art. Except insofar as any conventional media or agent is incompatible with the active compound, use thereof in the pharmaceutical compositions described herein is contemplated. Supplementary active compounds can also be incorporated into the compositions. Therapeutic compositions typically must be sterile and stable under the conditions of manufacture and storage. The composition can be formulated as a solution, microemulsion, liposome, or other ordered structure suitable to high drug concentration. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. In many cases, it will be suitable to include isotonic agents, for example, sugars, polyalcohols such as mannitol, sorbitol, or sodium chloride in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent that delays absorption, for example, monostearate salts and gelatin.

[0186] Sterile injectable solutions can be prepared by incorporating the active compound in the required amount in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by sterilization microfiltration. Generally, dispersions are prepared by incorporating the active compound into a sterile vehicle that contains a basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the

preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and freeze-drying (lyophilization) that yield a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

[0187] In one embodiment, compositions (*e.g.*, liquid formulations) described herein are pyrogen-free formulations which are substantially free of endotoxins and/or related pyrogenic substances. Endotoxins include toxins that are confined inside a microorganism and are released when the microorganisms are broken down or die. Pyrogenic substances also include fever-inducing, thermostable substances (glycoproteins) from the outer membrane of bacteria and other microorganisms. Both of these substances can cause fever, hypotension and shock if administered to humans. Due to the potential harmful effects, it is advantageous to remove even low amounts of endotoxins from intravenously administered pharmaceutical drug solutions. The Food & Drug Administration ("FDA") has set an upper limit of 5 endotoxin units (EU) per dose per kilogram body weight in a single one hour period for intravenous drug applications (The United States Pharmacopeial Convention, Pharmacopeial Forum 26 (1):223 (2000)). When therapeutic proteins are administered in amounts of several hundred or thousand milligrams per kilogram body weight, as can be the case with monoclonal antibodies, it is advantageous to remove even trace amounts of endotoxin. Endotoxin and pyrogen levels in the composition are preferably less than 10 EU/mg, or less than 5 EU/mg, or less than 1 EU/mg, or less than 0.1 EU/mg, or less than 0.01 EU/mg, or less than 0.001 EU/mg. Endotoxin and pyrogen levels in the composition may be less than about 10 EU/mg, or less than about 5 EU/mg, or less than about 1 EU/mg, or less than about 0.1 EU/mg, or less than about 0.01 EU/mg, or less than about 0.001 EU/mg.

[0188] The amount of active ingredient which can be combined with a carrier material to produce a single dosage form will vary depending upon the subject being treated, and the particular mode of administration. The amount of active ingredient which can be combined with a carrier material to produce a single dosage form will generally be that amount of the composition which produces a therapeutic effect. Generally, out of one hundred per cent, this amount will range from about 0.01 per cent to about ninety-nine percent of active ingredient, also from about 0.1 per cent to about 70 per cent, also from about 1 per cent to about 30 per cent of active ingredient in combination with a pharmaceutically acceptable carrier.

[0189] Dosage regimens are adjusted to provide the optimum desired response *(e.g.,* a therapeutic response). For example, a single bolus may be administered, several divided doses may be administered over time or the dose may be proportionally reduced or increased as indicated by the exigencies of the therapeutic situation. It is especially advantageous to formulate parenteral compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the subjects to be treated; each unit contains a predetermined quantity of active compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specification for the dosage unit forms described herein are dictated by and directly dependent on (a) the unique characteristics of the active compound and the particular therapeutic effect to be achieved, and (b) the limitations inherent in the art of compounding such an active compound for the treatment of sensitivity in individuals.

[0190] For administration of an antibody, the dosage ranges from about 0.0001 to 100 mg/kg, and more usually 0.01 to 5 mg/kg, of the host body weight. For example dosages can be 0.3 mg/kg body weight, 1 mg/kg body weight, 3 mg/kg body weight, 5 mg/kg body weight or 10 mg/kg body weight or within the range of 1-10 mg/kg. A treatment regime may entail administration once per week, once every two weeks, once every three weeks, once every four weeks, once a month, once every 3 months or once every three to 6 months. Dosage regimens for an anti-IFNAR1 antibody described herein include 1 mg/kg body weight or 3 mg/kg body weight via intravenous administration, with the antibody being given using one of the following dosing schedules: (i) every four weeks for six dosages, then every three months; (ii) every three weeks; (iii) 3 mg/kg body weight once followed by 1 mg/kg body weight every three weeks.

[0191] Alternatively, an antibody or fusion protein may be administered as a sustained release formulation, in which case less frequent administration is required. Dosage and frequency vary depending on the half-life of the antibody in the patient. In general, human antibodies show the longest half life, followed by humanized antibodies, chimeric antibodies, and non-human antibodies. The dosage and frequency of administration can vary depending on whether the treatment is prophylactic or therapeutic. In prophylactic applications, a relatively low dosage is administered at relatively infrequent intervals over a long period of time. Some patients continue to receive treatment for the rest of their lives. In therapeutic applications, a relatively high dosage at relatively short intervals is sometimes required until progression of the disease is reduced or terminated, and usually until the patient shows partial or complete amelioration of symptoms of disease. Thereafter, the patient can be administered a prophylactic regime.

[0192] Actual dosage levels of the active ingredients in the pharmaceutical compositions described herein may be varied so as to obtain an amount of the active ingredient which is effective to achieve the desired therapeutic response for a particular patient, composition, and mode of administration, without being toxic to the patient. The selected dosage level will depend upon a variety

of pharmacokinetic factors including the activity of the particular compositions employed, or the ester, salt or amide thereof, the route of administration, the time of administration, the rate of excretion of the particular compound being employed, the duration of the treatment, other drugs, compounds and/or materials used in combination with the particular compositions employed, the age, sex, weight, condition, general health and prior medical history of the patient being treated, and like factors well known in the medical arts.

[0193] A therapeutically effective dosage of an anti-IFNAR1 antibody described herein results in a decrease in severity of disease symptoms, an increase in frequency and duration of disease symptom-free periods, or a prevention of impairment or disability due to the disease affliction. In the case of, for example, Systemic Lupus Erythematosus (SLE), a therapeutically effective dose may prevent further deterioration of physical symptoms associated with SLE, such as, for example, pain, fatigue or weakness. A therapeutically effective dose may also prevent or delays onset of SLE, such as may be desired when early or preliminary signs of the disease are present. Likewise it includes delaying chronic progression associated with SLE. Laboratory tests utilized in the diagnosis of SLE include chemistries, hematology, serology and radiology. Accordingly, any clinical or biochemical assay that monitors any of the foregoing may be used to determine whether a particular treatment is a therapeutically effective dose for treating SLE. One of ordinary skill in the art would be able to determine such amounts based on such factors as the subject's size, the severity of the subject's symptoms, and the particular composition or route of administration selected.

[0194] A composition described herein can be administered via one or more routes of administration using one or more of a variety of methods known in the art. As will be appreciated by the skilled artisan, the route and/or mode of administration will vary depending upon the desired results. Selected routes of administration for antibodies described herein include intravenous, intramuscular, intradermal, intraperitoneal, subcutaneous, spinal or other parenteral routes of administration, for example by injection or infusion. Parenteral administration may represent modes of administration other than enteral and topical administration, usually by injection, and includes, without limitation, intravenous, intramuscular, intraarterial, intrathecal, intracapsular, intraorbital, intracardiac, intradermal, intraperitoneal, transtracheal, subcutaneous, subcuticular, intraarticular, subcapsular, subarachnoid, intraspinal, epidural and intrasternal injection and infusion.

[0195] Alternatively, an antibody described herein can be administered via a non-parenteral route, such as a topical, epidermal or mucosal route of administration, for example, intranasally, orally, vaginally, rectally, sublingually or topically.

[0196] The active compounds can be prepared with carriers that will protect the compound against rapid release, such as a controlled release formulation, including implants, transdermal patches, and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid. Many methods for the preparation of such formulations are patented or generally known to those skilled in the art. See, *e.g.,* Sustained and Controlled Release Drug Delivery Systems, J.R. Robinson, ed., Marcel Dekker, Inc., New York, 1978.

[0197] Therapeutic compositions can be administered with medical devices known in the art. For example, a therapeutic composition described herein can be administered with a needleless hypodermic injection device, such as the devices disclosed in U.S. Patent Nos. 5,399,163; 5,383,851; 5,312,335; 5,064,413; 4,941,880; 4,790,824; or 4,596,556. Examples of well-known implants and modules useful in the present invention include: U.S. Patent No. 4,487,603, which discloses an implantable micro-infusion pump for dispensing medication at a controlled rate; U.S. Patent No. 4,486,194, which discloses a therapeutic device for administering medicants through the skin; U.S. Patent No. 4,447,233, which discloses a medication infusion pump for delivering medication at a precise infusion rate; U.S. Patent No. 4,447,224, which discloses a variable flow implantable infusion apparatus for continuous drug delivery; U.S. Patent No. 4,439,196, which discloses an osmotic drug delivery system having multi-chamber compartments; and U.S. Patent No. 4,475,196, which discloses an osmotic drug delivery system. Many other such implants, delivery systems, and modules are known to those skilled in the art.

[0198] Antibodies described herein can be formulated to ensure proper distribution *in vivo.* For example, the blood-brain barrier (BBB) excludes many highly hydrophilic compounds. To ensure that the therapeutic compounds described herein cross the BBB (if desired), they can be formulated, for example, in liposomes. For methods of manufacturing liposomes, see, *e.g.,* U.S. Patents 4,522,811; 5,374,548; and 5,399,331. The liposomes may comprise one or more moieties which are selectively transported into specific cells or organs, thus enhance targeted drug delivery (*see, e.g.,* V.V. Ranade (1989) J. Clin. Pharmacol. 29:685). Exemplary targeting moieties include folate or biotin (see, *e.g.,* U.S. Patent 5,416,016 to Low et al.); mannosides (Umezawa et al., (1988) Biochem. Biophys. Res. Commun. 153:1038); antibodies (P.G. Bloeman et al. (1995) FEBS Lett. 357:140; M. Owais et al. (1995) Antimicrob. Agents Chemother. 39:180); surfactant protein A receptor (Briscoe et al. (1995) Am. J. Physiol. 1233:134); p120 (Schreier et al. (1994) J. Biol. Chem. 269:9090); see also K. Keinanen; M.L. Laukkanen (1994) FEBS Lett. 346:123; J.J. Killion; I.J. Fidler (1994) Immunomethods 4:273.

5.10 Diagnostic uses

[0199] In other embodiments, antibodies described herein have *in vitro* and *in vivo* diagnostic and therapeutic utilities. For example, these molecules can be administered to cells in culture, *e.g. in vitro* or *ex vivo,* or in a subject, *e.g., in vivo,* to treat, prevent or diagnose a variety of disorders.

[0200] Antibodies described herein can be used to detect levels of IFNAR1, or levels of cells that express IFNAR1. This can be achieved, for example, by contacting a sample (such as an *in vitro* sample) and a control sample with the anti-IFNAR1 antibody under conditions that allow for the formation of a complex between the antibody and IFNAR1. Any complexes formed between the antibody and IFNAR1 are detected and compared in the sample and the control. For example, standard detection methods, well-known in the art, such as ELISA and flow cytometic assays, can be performed using the compositions described herein.

[0201] Accordingly, we describe methods for detecting the presence of IFNAR1 *(e.g.,* human IFNAR1 antigen) in a sample, or measuring the amount of IFNAR1, comprising contacting the sample, and a control sample, with antibodies described herein, or an antigen binding portion thereof, which specifically binds to IFNAR1, under conditions that allow for formation of a complex between the antibody or portion thereof and IFNAR1. The formation of a complex is then detected, wherein a difference in complex formation between the sample compared to the control sample is indicative of the presence of IFNAR1 in the sample.

5.11 Therapeutic applications

[0202] IFNAR1 is part of the cellular receptor for Type I interferons, and Type I interferons are known to be immunoregulatory cytokines that are involved in T cell differentiation, antibody production and activity and survival of memory T cells. Moreover, increased expression of Type I interferons has been described in numerous autoimmune diseases, in HIV infection, in transplant rejection and in graft versus host disease (GVHD). Accordingly, the anti-IFNAR1 antibodies described herein or fragments thereof, which inhibit the functional activity of Type I interferons, can be used in a variety of clinical indications involving aberrant or undesired Type I interferon activity. We describe methods of preventing, treating, maintaining, ameliorating, or inhibiting a Type I interferon-mediated disease or disorder, wherein the methods comprise administering antibodies, or antigen-binding portions thereof, described herein.

[0203] Specific examples of autoimmune conditions in which antibodies described herein can be used include, but are not limited to, the following: systemic lupus erythematosus (SLE), insulin dependent diabetes mellitus (IDDM), inflammatory bowel disease (IBD) (including Crohn's Disease, Ulcerative Colitis and Celiac's Disease), multiple sclerosis (MS), psoriasis, autoimmune thyroiditis, rheumatoid arthritis (RA) and glomerulonephritis. Furthermore, the antibody compositions described herein can be used for inhibiting or preventing transplant rejection or in the treatment of graft versus host disease (GVHD) or in the treatment of HIV infection/AIDS.

[0204] High levels of IFNα have been observed in the serum of patients with systemic lupus erythematosus (SLE) (see *e.g.,* Kim et al. (1987) Clin. Exp. Immunol. 70:562-569). Moreover, administration of IFNα, for example in the treatment of cancer or viral infections, has been shown to induce SLE (Garcia-Porrua et al. (1998) Clin. Exp. Rheumatol. 16:107-108). Accordingly, Anti-IFNAR1 antibodies described herein can be used in the treatment of SLE by administering the antibody to a subject in need of treatment.

[0205] Other methods of treating SLE are described in U.S. Patent Applications entitled "Methods of treating SLE" with the following serial numbers; 60/907, 767, filed April 16, 07 and 60/966,174, filed November 5, 2007..

[0206] IFNα also has been implicated in the pathology of Type I diabetes. For example, the presence of immunoreactive IFNα in pancreatic beta cells of Type I diabetes patients has been reported (Foulis et al. (1987) Lancet 2:1423-1427). Prolonged use of IFNα in anti-viral therapy also has been shown to induce Type I diabetes (Waguri et al. (1994) Diabetes Res. Clin. Pract. 23:33-36). Accordingly, the anti-IFNAR1 antibodies or fragments thereof described herein can be used in the treatment of Type I diabetes by administering the antibody to a subject in need of treatment. The antibody can be used alone or in combination with other anti-diabetic agents, such as insulin.

[0207] Antibodies to IFNAR1 have been shown to be effective in an animal model of inflammatory bowel disease (see US Patent Application 60/465,155). Thus, the anti-IFNAR1 antibodies or fragments thereof described herein can be used in the treatment of inflammatory bowel disease (IBD), including ulcerative colitis and Crohn's disease, by administering the antibody to a subject in

need of treatment.

[0208] Treatment with IFNα has also been observed to induce autoimmune thyroiditis (Monzani et al. (2004) Clin. Exp. Med. 3:199-210; Prummel and Laurberg (2003) Thyroid 13:547-551). Accordingly, anti-IFNAR1 antibodies described herein can be used in the treatment of autoimmune thyroid disease, including autoimmune primary hypothyroidism, Graves Disease, Hashimoto's thyroiditis and destructive thyroiditis with hypothyroidism, by administering an antibody described herein to a subject in need of treatment. Antibodies described herein can be used alone or in combination with other agents or treatments, such as anti-thyroid drugs, radioactive iodine and subtotal thyroidectomy.

[0209] High levels of IFNα also have been observed in the circulation of patients with HIV infection and its presence is a predictive marker of AIDS progression (DeStefano et al. (1982) J. Infec. Disease 146:451; Vadhan-Raj et al. (1986) Cancer Res. 46:417). Thus, anti-IFNAR1 antibodies described herein may be used in the treatment of HIV infection or AIDS by administering the antibody described herein to a subject in need of treatment. Antibodies described herein can be used alone or in combination with other anti-HIV agents, such as nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, protease inhibitors and fusion inhibitors.

[0210] Antibodies to IFNAR1 have been demonstrated to be effective in inhibiting allograft rejection and prolonging allograft survival (see *e.g.,* Tovey et al. (1996) J. Leukoc. Biol. 59:512-517; Benizri et al. (1998) J. Interferon Cytokine Res. 18:273-284). Accordingly, the anti-IFNAR1 antibodies described herein also can be used in transplant recipients to inhibit allograft rejection and/or prolong allograft survival. We describe a method of inhibiting transplant rejection by administering anti-IFNAR1 antibodies described herein to a transplant recipient in need of treatment. Examples of tissue transplants that can be treated include, but are not limited to, liver, lung, kidney, heat, small bowel, and pancreatic islet cells, as well as the treatment of graft versus host disease (GVHD). Antibodies described herein can be used alone or in combination with other agents for inhibiting transplant rejection, such as immunosuppressive agents (*e.g.*, cyclosporine, azathioprine, methylprednisolone, prednisolone, prednisone, mycophenolate mofetil, sirilimus, rapamycin, tacrolimus), anti-infective agents (*e.g.*, acyclovir, clotrimazole, ganciclovir, nystatin, trimethoprimsulfarnethoxazole), diuretics (*e.g.*, bumetanide, furosemide, metolazone) and ulcer medications (*e.g.*, cimetidine, farnotidine, lansoprazole, omeprazole, ranitidine, sucralfate).

[0211] We describe methods of administering and using compositions and antibodies described herein to treat and prevent a wide range of inflammatory conditions including both chronic and acute conditions, such as, but not limited to, appendicitis, peptic, gastric and duodenal ulcers, peritonitis, pancreatitis, ulcerative, pseudomembranous, acute and ischemic colitis, diverticulitis, epiglottitis, achalasia, cholangitis, cholecystitis, hepatitis, Crohn's disease, enteritis, Whipple's disease, asthma, allergy, anaphylactic shock, immune complex disease, organ ischemia, reperfusion injury, organ necrosis, hay fever, sepsis, septicemia, endotoxic shock, cachexia, hyperpyrexia, eosinophilic granuloma, granulomatosis, sarcoidosis, septic abortion, epididymitis, vaginitis, prostatitis, urethritis, bronchitis, emphysema, rhinitis, cystic fibrosis, pneumonitis, pneumoultramicroscopicsilicovolcanoconiosis, alveolitis, bronchiolitis, pharyngitis, pleurisy, sinusitis, influenza, respiratory syncytial virus infection, herpes infection, HIV infection, hepatitis B virus infection, hepatitis C virus infection, disseminated bacteremia, Dengue fever, candidiasis, malaria, filariasis, amebiasis, hydatid cysts, burns, dermatitis, dermatomyositis, sunburn, urticaria, warts, wheals, vasulitis, angiitis, endocarditis, arteritis, atherosclerosis, thrombophlebitis, peucarditis, myocarditis, myocardial ischemia, periarteutis nodosa, rheumatic fever, Alzheimer's disease, celiac disease, congestive heart failure, restenosis, COPD adult respiratory distress syndrome, meningitis, encephalitis, multiple sclerosis, cerebral infarction, cerebral embolism, Guillain-Barré syndrome, neuritis, neuralgia, spinal cord injury, paralysis, uveitis, arthritides, arthralgias, osteomyelitis, fascitis, Paget's disease, gout, periodontal disease, rheumatoid arthritis, synovitis, myasthenia gravis, thryoiditis, systemic lupus erythematosus, Goodpasture's syndrome, Behçets's syndrome, allograft rejection, graft-versus-host disease, Type I diabetes, ankylosing spondylitis, Berger's disease, Retier's syndrome, and Hodgkin's disease.

[0212] In another embodiment, methods of administration and compositions of antibodies described herein may be useful in the prevention, treatment, amelioration of symptoms associated with the following conditions or disease states: Graves's disease, Hashimoto's thyroiditis, Crohn's disease, psoriasis, psoriatic arthritis, sympathetic ophthalmitis, autoimmune oophoritis, autoimmune orchitis, autoimmune lymphoproliferative syndrome, antiphospholipid syndrome. Sjögren's syndrome, scleroderma, Addison's disease, polyendocrine deficiency syndrome, Guillain-Barré syndrome, immune thrombocytopenic purpura, pernicious anemia, myasthenia gravis, primary biliary cirrhosis, mixed connective tissue disease, vitiligo, autoimmune uveitis, autoimmune hemolytic anemia, autoimmune thrombocytopenia, celiac disease, dermatitis herpetiformis, autoimmune hepatitis, pemphigus, pemphigus vulgaris, pemphigus foliaceus, bullous pemphigoid, autoimmune myocarditis, autoimmune vasculitis, alopecia areata, autoimmune artherosclerosis, Behçet's disease, autoimmune myelopathy, autoimmune hemophilia, autoimmune interstitial cystitis, autoimmune diabetes isipidus, autoimmune endometriosis, relapsing polychondritis, ankylosing spondylitis, autoimmune urticaria, dermatomyositis, Miller-Fisher syndrome, IgA nephropathy, goodpastures syndrome, and herpes gestationis.

[0213] In another embodiment, methods of administration and compositions of antibodies described herein may be useful in the prevention, treatment, amelioration of symptoms associated with Sjögren's syndrome. Sjögren's syndrome is an autoimmune disorder in which immune cells attack and destroy the exocrine glands that produce tears and saliva. It is named after Swedish ophthalmologist Henrik Sjögren (1899-1986), who first described it. Sjögren's syndrome is also associated with rheumatic disorders such as rheumatoid arthritis, and it is rheumatoid factor positive in 90 percent of cases. The hallmark symptoms of the disorder are dry mouth and dry eyes. In addition, Sjögren's syndrome may cause skin, nose, and vaginal dryness, and may affect other organs of the body, including the kidneys, blood vessels, lungs, liver, pancreas, and brain. Nine out of ten Sjögren's patients are women and the average age of onset is late 40s, although Sjögren's occurs in all age groups in both women and men. It is estimated to strike as many as 4 million people in the United States alone making it the second most common autoimmune rheumatic disease.

[0214] Myositis is general condition characterized by inflammation of skeletal muscle or voluntary muscle. Muscle inflammation may be caused by an allergic reaction, exposure to a toxic substance or medicine, another disease such as cancer or rheumatoid conditions, or a virus or other infectious agent. The chronic inflammatory myopathies are idiopathic, meaning they have no known cause. They are understood to be autoimmune disorders, in which the body's white blood cells (that normally fight disease) attack blood vessels, normal muscle fibers, and connective tissue in organs, bones, and joints.

[0215] Polymyositis affects skeletal muscles (involved with making movement) on both sides of the body. It is rarely seen in persons under age 18; most cases are in patients between the ages of 31 and 60. In addition to symptoms listed above, progressive muscle weakness leads to difficulty swallowing, speaking, rising from a sitting position, climbing stairs, lifting objects, or reaching overhead. Patients with polymyositis may also experience arthritis, shortness of breath, and heart arrhythmias.

[0216] Dermatomyositis is characterized by a skin rash that precedes or accompanies progressive muscle weakness. The rash looks patchy, with bluish-purple or red discolorations, and characteristically develops on the eyelids and on muscles used to extend or straighten joints, including knuckles, elbows, heels, and toes. Red rashes may also occur on the face, neck, shoulders, upper chest, back, and other locations, and there may be swelling in the affected areas. The rash sometimes occurs without obvious muscle involvement. Adults with dermatomyositis may experience weight loss or a low-grade fever, have inflamed lungs, and be sensitive to light. Adult dermatomyositis, unlike polymyositis, may accompany tumors of the breast, lung, female genitalia, or bowel. Children and adults with dermatomyositis may develop calcium deposits, which appear as hard bumps under the skin or in the muscle (called calcinosis). Calcinosis most often occurs 1-3 years after disease onset but may occur many years later. These deposits are seen more often in childhood dermatomyositis than in dermatomyositis that begins in adults. Dermatomyositis may be associated with collagen-vascular or autoimmune diseases.

[0217] Inclusion body myositis (IBM) is characterized by progressive muscle weakness and wasting. IBM is similar to polymyositis but has its own distinctive features. The onset of muscle weakness is generally gradual (over months or years) and affects both proximal and distal muscles. Muscle weakness may affect only one side of the body. Small holes called vacuoles are seen in the cells of affected muscle fibers. Falling and tripping are usually the first noticeable symptoms of IBM. For some patients the disorder begins with weakness in the wrists and fingers that causes difficulty with pinching, buttoning, and gripping objects. There may be weakness of the wrist and finger muscles and atrophy (thinning or loss of muscle bulk) of the forearm muscles and quadricep muscles in the legs. Difficulty swallowing occurs in approximately half of IBM cases. Symptoms of the disease usually begin after the age of 50, although the disease can occur earlier. Unlike polymyositis and dermatomyositis, IBM occurs more frequently in men than in women.

[0218] Juvenile myositis has some similarities to adult dermatomyositis and polymyositis. It typically affects children ages 2 to 15 years, with symptoms that include proximal muscle weakness and inflammation, edema (an abnormal collection of fluids within body tissues that causes swelling), muscle pain, fatigue, skin rashes, abdominal pain, fever, and contractures (chronic shortening of muscles or tendons around joints, caused by inflammation in the muscle tendons, which prevents the joints from moving freely). Children with juvenile myositis may also have difficulty swallowing and breathing, and the heart may be affected. Approximately 20 to 30 percent of children with juvenile dermatomyositis develop calcinosis. Juvenile patients may not show higher than normal levels of the muscle enzyme creatine kinase in their blood but have higher than normal levels of other muscle enzymes.

[0219] Antibodies described herein may be useful in the prevention, treatment, or amelioration of myositis, inflammatory myositis, idiopathic myositis, polymyositis, dermatomyositis, inclusion body myositis (IBM), juvenile myositis or symptoms associated with these conditions.

[0220] Antibodies described herein may be useful in the prevention, treatment, or amelioration of symptoms associated with vasculitis.

[0221] Antibodies described herein may be useful for the treatment of scleroderma. Methods of treating Scleroderma are described in a U.S. patent application entitled "Methods Of Treating Scleroderma" with an application serial number of 60/996,175, filed on November 5, 2007 and PCT Application No. PCT/US2008/82481 (WO 2009/061818).

[0222] Antibodies described herein may be useful in the prevention, treatment, or amelioration of symptoms associated with sarcoidosis. Sarcoidosis (also called sarcoid or Besnier-Boeck disease) is an immune system disorder characterized by non-necrotizing granulomas (small inflammatory nodules). Virtually any organ can be affected; however, granulomas most often appear in the lungs or the lymph nodes. Symptoms can occasionally appear suddenly but usually appear gradually. When viewing X-rays of the lungs, sarcoidosis can have the appearance of tuberculosis or lymphoma.

[0223] Also described herein are kits comprising the compositions (*e.g.*, anti-IFNAR1 antibodies) described herein and instructions for use. The kit can further contain a least one additional reagent, or one or more additional antibodies described herein *(e.g.,* an antibody having a complementary activity which binds to an epitope on the target antigen distinct from the first antibody). Kits typically include a label indicating the intended use of the contents of the kit. The term label includes any writing, or recorded material supplied on or with the kit, or which otherwise accompanies the kit.

5.12 Combinations

[0224] Compositions described herein also can be administered in combination therapy, such as, combined with other agents. For example, the combination therapy can include an anti-IFNAR1 antibody described herein combined with at least one other immunosuppressent.

[0225] In some methods, two or more monoclonal antibodies with different binding specificities are administered simultaneously, in which case the dosage of each antibody administered falls within the ranges indicated. The antibody is usually administered on multiple occasions. Intervals between single dosages can be, for example, weekly, monthly, every three months or yearly. Intervals can also be irregular as indicated by measuring blood levels of antibody to the target antigen in the patient. In some methods, dosage is adjusted to achieve a plasma antibody concentration of about 1-1000 µg /ml and in some methods about 25-300 µg /ml.

[0226] When antibodies to IFNAR1 are administered together with another agent, the two can be administered in either order or simultaneously. For example, an anti-IFNAR1 antibody described herein can be used in combination with one or more of the following agents: drugs containing mesalamine (including sulfasalazine and other agents containing 5-aminosalicylic acid (5-ASA), such as olsalazine and balsalazide), non-steroidal antiinflammatory drugs (NSAIDs), analgesics, corticosteroids (*e.g.*, predinisone, hydrocortisone), TNF-inhibitors (including adalimumab (HUMIRA®), etanercept (ENBREL®) and infliximab (REMICADE®)), immunosuppressants (such as 6-mercaptopurine, azathioprine and cyclosporine, A), and antibiotics anti-IFNα antibody, anti-IFNγ receptor antibody, and soluble IFNγ receptor. Furthermore, an anti-IFNAR1 antibody can be used in combination with a Flt3 ligand antagonist (see *e.g.,* U.S. Patent Application Publication No. 2002/0160974).

[0227] The compositions described herein may also include agents useful in the treatment of SLE. Such agents include analgesics, corticosteroids (*e.g.*, predinisone, hydrocortisone), immunosuppressants (such as cyclophosphamide, azathioprine, and methotrexate), antimalarials (such as hydroxychloroquine) and biologic drugs that inhibit the production of dsDNA antibodies (*e.g.*, LJP 394).

5.13 Equivalents

[0228] Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to features described herein.

5.14 Specific Disclosures

[0229]

1. 1. A modified IgG class monoclonal antibody specific for IFNAR1, wherein said antibody comprises in the Fc region at least

one amino acid substitution selected from the group consisting of L234F, L235E, and P331S, as numbered by the EU index as set forth in Kabat and wherein said antibody exhibits reduced affinity for at least one Fc ligand compared to an unmodified antibody.

2. 2. The antibody of clause 1, wherein, said antibody is an IgG1 or IgG4 subclass.
3. 3. The antibody of clause 2, wherein said antibody is an IgG1 class molecule.
4. 4. The antibody of clause 3, wherein said antibody comprises an amino acid substitution of P331S.
5. 5. The antibody of clause 3, wherein said antibody comprises the amino acid substitutions: L234F and L235E.
6. 6. The antibody of clause 3, wherein said antibody comprises the amino acid substitutions: L234F, L235E and P331S.
7. 7. The antibody of clause 3 wherein, said antibody is an IgG4 class molecule.
8. 8. The antibody of clause 7 wherein, said antibody comprises an amino acid substitution of L235E of the Fc region.
9. 9. The antibody of clause 7, wherein, said antibody further comprises in the Fc region amino acid substitution S228P.
10. 10. The antibody of any of clauses 1-9 wherein, said antibody comprises at least one complementarity determining region (CDR) selected from Table 2.
11. 11. The antibody of any of clauses 1-10, wherein, said antibody comprises:
    1. a. a human heavy chain variable region CDR1 comprising Seq ID NO: 31;
    2. b. a human heavy chain variable region CDR2 comprising Seq ID NO: 32;
    3. c. a human heavy chain variable region CDR3 comprising Seq ID NO: 33;
    4. d. a human light chain variable region CDR1 comprising Seq ID NO: 34;
    5. e. a human light chain variable region CDR2 comprising Seq ID NO: 35; and
    6. f. a human light chain variable region CDR3 comprising Seq ID NO: 36.
12. 12. The antibody of any of clauses 1-10, wherein, said antibody comprises:
    1. a. a human heavy chain variable region CDR1 comprising Seq ID NO: 1;
    2. b. a human heavy chain variable region CDR2 comprising Seq ID NO: 2;
    3. c. a human heavy chain variable region CDR3 comprising Seq ID NO: 3;
    4. d. a human light chain variable region CDR1 comprising Seq ID NO: 4;
    5. e. a human light chain variable region CDR2 comprising Seq ID NO: 5; and
    6. f. a human light chain variable region CDR3 comprising Seq ID NO: 6.
13. 13. The antibody of any of clauses 1-10, wherein, said antibody comprises:
    1. a. a human heavy chain variable region CDR1 comprising Seq ID NO: 11;
    2. b. a human heavy chain variable region CDR2 comprising Seq ID NO: 12;
    3. c. a human heavy chain variable region CDR3 comprising Seq ID NO: 13;
    4. d. a human light chain variable region CDR1 comprising Seq ID NO: 14;
    5. e. a human light chain variable region CDR2 comprising Seq ID NO: 15; and
    6. f. a human light chain variable region CDR3 comprising Seq ID NO: 16.
14. 14. The antibody of any of clauses 1-10, wherein, said antibody comprises:
    1. a. a human heavy chain variable region CDR1 comprising Seq ID NO: 21;
    2. b. a human heavy chain variable region CDR2 comprising Seq ID NO: 22;
    3. c. a human heavy chain variable region CDR3 comprising Seq ID NO: 23;
    4. d. a human light chain variable region CDR1 comprising Seq ID NO: 24;
    5. e. a human light chain variable region CDR2 comprising Seq ID NO: 25; and
    6. f. a human light chain variable region CDR3 comprising Seq ID NO: 26.
15. 15. The antibody of any of clauses 1-10, wherein, said antibody comprises:
    1. a. a human heavy chain variable region comprising the amino acid sequence of Seq ID No: 38; and
    2. b. a human light chain variable region comprising the amino acid sequence of Seq ID No: 40.
16. 16. The antibody of any of clauses 1-10, wherein, said antibody comprises:
    1. a. a human heavy chain variable region comprising the amino acid sequence of Seq ID No: 8; and
    2. b. a human light chain variable region comprising the amino acid sequence of Seq ID No: 10.
17. 17. The antibody of any of clauses 1-10, wherein, said antibody comprises:
    1. a. a human heavy chain variable region comprising the amino acid sequence of Seq ID No: 18; and
    2. b. a human light chain variable region comprising the amino acid sequence of Seq ID No: 20.
18. 18. The antibody of any of clauses 1-10, wherein, said antibody comprises:
    1. a. a human heavy chain variable region comprising the amino acid sequence of Seq ID No: 28; and
    2. b. a human light chain variable region comprising the amino acid sequence of Seq ID No: 30.
19. 19. The antibody of any of clauses 1-18, wherein, said antibody comprises the light chain constant region sequence of Seq ID No: 41.
20. 20. The antibody of any of clauses 1-18, wherein, said antibody comprises the heavy chain constant region of Seq ID No: 42.
21. 21. The antibody of any of clauses 1-18, wherein, said antibody comprises the light chain constant region having the amino

acid sequence of SEQ ID No:41 and the heavy chain constant region having the amino acid sequence of Seq ID No: 42.

22. 22. The antibody of any of clauses 19-21, wherein, said antibody comprises a heavy chain amino acid sequence comprising allelic variation, wherein said allelic variation is at least one or more positions selected from the group consisting of 214, 221, 356 and 358 as defined by the EU index numbering system.
23. 23. The antibody of any of the preceding clauses wherein, said antibody is selected from the group consisting of: human antibody, humanized antibody, chimeric antibody, intrabody, and a synthetic antibody.
24. 24. An isolated nucleic acid comprising a polynucleotide sequence encoding the antibody of any of the preceding clauses.
25. 25. The nucleic acid of clause 24 wherein, said nucleic acid is a replicable vector.
26. 26. The nucleic acid of clause 25 wherein, said polynucleotide sequence is operably linked to a promoter.
27. 27. A host cell comprising or transformed with the vector of clause 25 or 26.
28. 28. A transgenic mouse comprising human immunoglobulin heavy and light chain transgenes, wherein the mouse expresses the antibody of any of clauses 1-23.
29. 29. A hybridoma prepared from the mouse of clause 28 wherein the hybridoma produces said antibody.
30. 30. A pharmaceutical composition comprising the antibody of any of the clauses 1-23, and a pharmaceutically acceptable excipient.
31. 31. A method of treating a condition or a disease associated with an immune disorder, comprising administering to a subject in need thereof an effective amount of the composition of clause 30.
32. 32. The method of clause 31 wherein said disease is a type I interferon mediated disease.
33. 33. The method of clause 32 wherein said type I interferon is interferon alpha.
34. 34. The method of clause 33 wherein said type I interferon mediated disease is associated with the type I interferon receptor.
35. 35. The method of clause 31, wherein said disease or disorder is HIV infection of AIDS.
36. 36. The method of clause 31, wherein said disease or disorder is systemic lupus erythematosus.
37. 37. The method of clause 31, wherein said disease or disorder is Sjogren's syndrome.
38. 38. The method of clause 31, wherein said disease or disorder is myositis.
39. 39. The method of clause 31, wherein said disease or disorder is inflammatory myositis.
40. 40. The method of clause 31, wherein said disease or disorder is polymyositis.
41. 41. The method of clause 31, wherein said disease or disorder is dermatomyositis.
42. 42. The method of clause 31, wherein said disease or disorder is inclusion body myositis.
43. 43. The method of clause 31, wherein said disease or disorder is juvenile myositis.
44. 44. The method of clause 31, wherein said disease or disorder is idiopathic inflammatory myositis.
45. 45. The method of clause 31, wherein said disease or disorder is vasculitis.
46. 46. The method of clause 31, wherein said disease or disorder is sarcoidosis.
47. 47. The method of clause 31, wherein said disease or disorder is selected from the group consisting of: inflammatory bowel disease, multiple sclerosis, autoimmune thyroiditis, rheumatoid arthritis, insulin dependent diabetes mellitus, glomerulonephritis, and graft versus host disease.
48. 48. The method of clause 31, wherein said disease or disorder is psoriasis or conditions resulting thereof.
49. 49. The method of clause 31, wherein said disease or disorder is transplant rejection or graft versus host disease.
50. 50. The method of clause 31 wherein said disease or disorder is selected from the group consisting of: Grave's disease, Hashimoto's thyroiditis, Crohn's disease, psoriasis, psoriatic arthritis, sympathetic ophthalmitis, autoimmune oophoritis, autoimmune orchitis, autoimmune lymphoproliferative syndrome, antiphospholipid syndrome. Sjögren's syndrome, scleroderma, Addison's disease, polyendocrine deficiency syndrome, Guillain-Barré syndrome, immune thrombocytopenic purpura, pernicious anemia, myasthenia gravis, primary biliary cirrhosis, mixed connective tissue disease, vitiligo, autoimmune uveitis, autoimmune hemolytic anemia, autoimmune thrombocytopenia, celiac disease, dermatitis herpetiformis, autoimmune hepatitis, pemphigus, pemphigus vulgaris, pemphigus foliaceus, bullous pemphigoid, autoimmune myocarditis, autoimmune vasculitis, alopecia areata, autoimmune artherosclerosis, Behçet's disease, autoimmune myelopathy, autoimmune hemophelia, autoimmune interstitial cystitis, autoimmune diabetes isipidus, autoimmune endometriosis, relapsing polychondritis, ankylosing spondylitis, autoimmune urticaria, dermatomyositis, Miller-Fisher syndrome, IgA nephropathy, Goodpasture's syndrome, and herpes gestationis.
51. 51. The method of any of clauses 31-50, further comprising administering at least one agent selected from the group consisting of: phototherapy, corticosteroids, prednisone, NSAIDS, plasmapheresis, immunosuppressants, methotrexate, retinoic acid, tioguanine, mycophenolate mofetil, fumaric esters, cyclophosphamide, azathioprine, cyclosporine, and immunoglobulins.
52. 52. The method of any of clauses 31-51 further comprising administering at least one agent selected from the group consisting of: alefacept (AMEVIVE™), etanercept (ENBREL®), adalimumab (HUMIRA®), infliximab (REMICADE®), belimumab (LYMPHOSTATB™), rituxumab (RITUXAN®), and efalizumab (RAPTIVA®).
53. 53. A crystal comprising a human IgG Fc region, wherein the human IgG Fc region comprises at least one amino acid

substitution selected from the group consisting of L234F, L235E, and P331S, as numbered by the EU index as set forth in Kabat and wherein said fragment exhibits reduced affinity for at least one Fc ligand compared to an unmodified Fc region.

54. 54. The crystal of clause 53, wherein the human IgG Fc region comprises the amino acid substitutions L234F, L235E and P331S.
55. 55. The crystal of clause 53, which is diffraction quality.
56. 56. The crystal of clause 53, which is a native crystal.
57. 57. The crystal of clause 53, which is characterized by an orthorhombic unit cell of a=50.18±0.2 Å, b=147.30±0.2 Å, and c=75.47 ±0.2 Å.
58. 58. The crystal of clause 53, which has a space group of $C222_1$.
59. 59. A modified monoclonal antibody, wherein said antibody comprises in the Fc region the amino acid substitutions L234F, L235E, and P331S, as numbered by the EU index as set forth in Kabat and wherein said antibody exhibits reduced affinity for at least one Fc ligand compared to an unmodified antibody.
60. 60. A fusion protein comprising a modified Fc region, wherein said Fc region comprises the amino acid substitutions L234F, L235E, and P331S, as numbered by the EU index as set forth in Kabat and wherein said Fc region exhibits reduced affinity for at least one Fc ligand compared to an Fc region.
61. 61. A method of making the antibody of any of clauses 1-23 or 59.
62. 62. The antibody of any of clauses 1-23 or 59, wherein said antibody is an internalizing antibody.
63. 63. The fusion protein of clause 60, wherein said fusion protein is an internalizing fusion protein.
64. 64. The fusion protein of clause 63, wherein said fusion protein specifically binds IFNAR1.
65. 65. The antibody of any of clauses 1-23, 59, or 62, wherein said antibody exhibits reduced or ablated antibody dependent cell-mediated cytotoxicity (ADCC) as compared to said unmodified antibody.
66. 66. The antibody of any of clauses 1-23, 59, or 62, wherein said antibody exhibits reduced or ablated complement mediated cytotoxicity (CDC) as compared to said unmodified antibody.
67. 67. The antibody of any of clauses 1-23, 59, or 62, wherein said antibody exhibits reduced or ablated ADCC and CDC as compared to said unmodified antibody.

5.15 Sequences

[0230]

Light Chain constant region (SEQ ID No:41)
RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVT
EQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

Heavy Chain constant region (SEQ ID No:42)
ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL
QSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAP
EFEGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKT
KPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPASIEKTISKAKGQPREP
QVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGS
FFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

6. EXAMPLES

[0231] The invention is now described with reference to the following examples.

6.1 Example 1: IHC profile of multiple Anti-IFNAR1 antibodies

[0232] **Purpose:** To evaluate the IHC profile of anti-IFNAR1 antibodies on a diverse set of tissues.

[0233] **Methods:** Immunohistochemistry techniques to study antibody binding characteristics are readily known in the art and for example, could be performed by isolating the desired cells or tissues and preparing them for microscopy by standard fixation and mounting techniques.

[0234] Mouse Macrophages: A cell suspension was spun down to form a loose pellet. The pellet was frozen in OCT freezing medium to form a block. Slide sections were cut to 5 microns thickness, soaked in acetone for 10 minutes and allowed to dry with dessicant overnight. Prior to use, the slides were dipped into 10% neutral buffered formalin for 10 sec and washed 3X in buffer (1X TBS with 0.01% Tween20).

[0235] Human Monocytes: A cell suspension was smeared/spotted directly onto slides. The slides were allowed to dry overnight and then soaked in Acetone for 10 min and allowed to air dry. Prior to use, slides were dipped into 10% neutral buffered formalin for 10 secs and washed 3X in buffer (1X TBS with 0.01% Tween20).

[0236] Human Cerebrum and Cardiac Tissue: Tissue samples from donors were frozen in OCT freezing medium to form a block. Slide sections were cut to 5 micron thickness, soaked in acetone for 10 minutes and allowed to dry with dessicant overnight. Prior to use, the slides were dipped into 10% neutral buffered formalin for 10 sec and washed 3X in buffer (1XTBS with 0.01% Tween 20).

[0237] Antibody labeling: Antibodies were conjugated to biotin by the following protocol. Approximately 500 µg of antibody was mixed with a 20 fold excess of biotin and incubated for 2 hours in the dark at 4°C. After the 2 hour incubation, the antibody/biotin mix was applied to a pre-equilibrated PD10 column with 1X PBS. Subsequently, the biotin conjugated antibodies were concentrated to a desired concentration using an YM-30 Centricon concentration tube.

[0238] Slide staining: After washing in buffer, slides were treated to quench endogenous peroxidases by treatment with a solution of Glucose Oxidase (1 U/ml, Sigma G0543), B-D(+) Glucose (10 mM, Sigma G5250), Sodium Azide (1 mM, Sigma, S8032) for 1 hour at room temperature. Slides were then rinsed in wash buffer (1X TBS with 0.01% Tween 20). Slides were placed in a protein block solution (1x PBS pH7.2, 0.5% casein(N-Z amine, Sigma C0626), 1% BSA (Sigma A7906), 1.5% Normal Goat serum (Jackson Labs #005-000-001) for 30 min at room temperature. Biotinylated antibody (see above) was applied to the slides by dilution into the protein block solution. Incubation of the slides with the biotinylated antibody was performed at room temperature for 2 hours. Slides were rinsed 3X in wash buffer (1X TBS, 0.01% Tween 20). Antibody detection was performed using a Vectastain Kit (Vector Laboratories). Slides were washed and counterstained with hematoxylin. Slides were dehydrated and mounted with coverslips prior to viewing.

[0239] Results: Presented in Fig 6A are the results of an IHC analysis of Human cerebrum tissue stained with various anti-IFNAR1 and control antibodies. The antibodies MDX-1333 (75 µg/ml) and 4G5 (50 µg/ml) exhibited strong staining of the cerebrum tissue as exemplified by the brown/dark staining seen throughout the samples. Antibody 9D4 (50 µg/ml) did not stain the human cerebrum tissue sample as well as MDX-1333 and 4G5 as demonstrated by the reduced brown/dark staining throughout the sample. An IgG1 isotype control was included to demonstrate that binding specificity of the individual antibodies.

[0240] Presented in Fig 6B are the results of an IHC analysis of monocytes stained with various anti-IFNAR1 and control antibodies. The antibodies MDX-1333 (50 and 20 µg/ml), 4G5 (50 µg/ml) and 9D4 (50 and 20 µg/ml) all exhibited prominent staining on human monocytes as demonstrated by the brown/dark staining of the samples. The isotype control antibody R3-47 (50 µg/ml) did not exhibit prominent staining on human monocytes. In addition, MDX-1333(50 µg/ml) did not stain purified mouse macrophages.

[0241] **Conclusions:** In IHC study the anti-IFNAR1 antibody 9D4 exhibited a lower level of staining as compared to other anti-IFNAR1 antibodies such as MDX-1333 and 4G5.

6.2 Example 2: Generation of antibody 9D4 TM

[0242] The modified anti-IFNAR1 antibody designated "9D4-TM" was generated through the following procedure;

[0243] Human γ1 Fc was cloned and engineered from human PBLs by first isolating total RNA, transcribing cDNA, and PCR amplifying the constant regions with gene-specific primers containing restriction sites Apa I and EcoRI for cloning into the mammalian vector PEE6. The triple mutant (TM) includes three amino acid changes in human IgG to decrease ADCC effector function (L234F, L235E, and P331S). TM was engineered using human IgG1 (KOL) as a template, and utilizing site-directed mutagenesis (QuickChange XL, Stratagene) to encode three residue changes in the Fc. Sequence of the mutagenic primers used to encode the L234F/L235E/P331S changes were as follows:

MD1056 = 5' cgtgcccagcacctgaaTtcGAgggggaccgtcagtcttc 3'L234F, L235E forward (SEQ ID NO:43)

MD1057 = 5' gaagactgacggtccccccTCgaAttcaggtgctgggcacg 3' L234F, L235E reverse (SEQ ID NO:44)

MD1058 = 5' ccaacaaagccctcccagccTccatcgagaaaaccatctcc 3' P331S forward (SEQ ID NO:45)

MD1059 = 5' ggagatggttttctcgatggAggctgggagggctttgttgg 3' P331S reverse (SEQ ID NO:46)

[0244] Clones encoding the 9D4-TM antibody were sequenced to confirm the triple mutations, and resolved on the ABI3100 genetic analyzer.

6.3 Example 3: Generation of antibody 9D4 DM

[0245] The modified anti-IFNAR1 antibody designated "9D4-DM" was generated through the following procedure;

[0246] Human γ4 Fc was cloned and engineered from human PBLs by first isolating total RNA, transcribing cDNA, and PCR amplifying the constant regions with gene-specific primers containing restriction sites Apa I and EcoRI for cloning into the mammalian vector PEE6.

[0247] The double mutant (DM) consists of two mutations in human IgG4 Fc: S228P and L235E. Mutagenic primers to encode DM include:

MD1060 = 5' ggtcccccatgcccaCcatgcccagcacctg 3' hinge S228P forward (SEQ ID NO:47)

MD1061 = 5' caggtgctgggcatgGtgggcatgggggacc 3' hinge S228P reverse (SEQ ID NO:48)

MD1062 = 5' ccagcacctgagttcGAgggggggaccatcagtc 3'IgG4 L234F, L235E forward (SEQ ID NO:49)

MD1063 = 5' gactgatggtcccccTCgaactcaggtgctgg 3' IgG4 L234F, L235E reverse (SEQ ID NO:50)

[0248] Clones encoding the 9D4-DM antibody were sequenced to confirm the encoded changes, and resolved on the ABI3100 genetic analyzer.

6.4 Example 4 Anti-IFNAR1 antibodies inhibit IFN mediated STAT phosphorylation.

[0249] **Purpose:** To establish the ability of the anti-IFNAR1 antibody 9D4-TM to inhibit IFN mediated STAT phosphorylation in peripheral blood mononuclear cells.

[0250] **Methods:** Peripheral blood mononuclear cells were purified from healthy human donors using LSM media (MP Biomedical, Solon OH). PBMCs were quantified and seeded at 10^6 cell per condition per well. Antibodies were added at 10 µg/mL to appropriate well and incubated at 37°C, 5% CO_2 for 10 minutes. After pre-incubation with antibodies, recombinant human IFNα2a (PBL Biomedical, Piscataway NJ) or human plasmacytoid dendritic cell-derived IFN (see below for generation of PDCs derived type-I IFN supernatants) was added to appropriate wells at 100 or 500IU/mL for 20 minutes. Cells were spun at 1200rpm for 5 minutes and washed with sterile 1x PBS. After one additional spin, PBS was removed and cells were lysed using mammalian protein extraction reagent (Pierce, Rockford IL) supplemented with 300 µL of 1x phosphatase inhibitor cocktails 1 and 2 (Sigma, St. Louis MO) and 1x protease inhibitor (Roche Biomedical, Nutley NJ). Lysates were incubated for 10 minutes on an orbital shaker to ensure complete lysis, transferred to microfuge tubes and spun at 14000 rpm to remove cellular debris. NuPAGE sample buffer (Invitrogen, Carlsbad CA) and dTT (Sigma, St. Louis MO) were added to lysates for a final concentration of 1x and all samples were denatured in a heat block at 100°C for approximately 10 minutes. 15 µL of each sample was added to NuPage 10% Bis-tris polyacrylamide gel (Invitrogen, Carlsbad CA) in NuPAGE MES SDS running buffer supplemented with 1x NuPAGE antioxidant buffer. Samples were run at 180V for 30 minutes for separation of protein bands. Proteins were then transferred to a nitrocellulose membrane and blots were blocked with 1xPBS (Gibco BRL, Carlsbad CA) containing 5% BSA (Sigma, St. Louis MO) overnight at 4°C. Blocking media was subsequently removed and 0.2 µg/mL anti-STAT1, anti-STAT1 pY701, or 1:1000 dilution of β-Actin antibodies (Cell Signaling Technology, Danvers MA) were added to appropriate blots and incubated overnight at 4°C.

Blots were washed 3x in 1x TBS with 0.05% Tween20 (Sigma, St. Louis MO). 1:2500 diluted, HRP conjugated anti-rabbit secondary antibody was added to blots and incubated for 1hr at room temperature. Blots were washed as described before and 3mL of a 1:1 mixture of Pico Supersignal West reagent (Pierce, Rockford IL) was added to each blot for 1 minute. Blots were drained, excess reagent was removed and bands were visualized using a Kodak X-omat 1000A Processor.

[0251] Results: Presented in Fig 7. are the results of a STAT activation assay in which cells stimulated with Leukocyte IFN in the presence or absence of anti-IFNAR1 antibodies. In the absence of antibodies, leukocyte interferon stimulates the phosphorylation of STAT isoforms 1, 3 and 5. Incubation of cells with 9D4-TM antibody inhibits the phosphorylation mediated by treatment with leukocyte interferon. Cells treated with the isotype control antibody R3-47 do not exhibit inhibition of STAT phosphorylation in response to stimulation with leukocyte interferon.

[0252] Conclusions: The results in Fig 7 demonstrate that 9D4-TM is capable of inhibiting responses to IFNα such as the induction of STAT phosphorylation in peripheral blood mononuclear cells.

6.5 Example 5: Anti-IFNAR1 antibodies inhibit Type I IFN signaling.

[0253] Purpose: Using purified Type I IFN from pDC cells, a reporter assay was used to test the ability of anti-IFNAR1 antibodies to block Type I IFN signaling.

[0254] Methods: Plasmacytoid dendritic cells (PDCs) were isolated from whole blood of healthy donors using a lymphocyte separation media (MP Biomedical, Solon OH) followed by positive selection using CD304 (BDCA-4/Neuropilin-1) MicroBead Kit (Milteny Biotec, Auburn CA). Purified PDCs were then cultured at $1x10^6$ cells/mL in RPMI 1640 supplemented with 10% FBS (Gibco BRL) and 6 µg/mL CpGA (InVivogen, San Diego CA). Supernatants were harvested and clarified after 20 hours in culture and type-I IFN was quantified using a stably transfected HEK293-ISRE reporter cell line against a standard curve of human leukocyte IFN (PBL Biomedical, Piscataway NJ).

[0255] pDCs from three healthy human donors were used to generate human pDC-derived type-I interferon supernatants, as described above. HEK293 (ATCC, Manassas VA) cells were stably transfected with pHTS-ISRE reported plasmid (Biomyx Technology, San Diego CA) and were maintained in DMEM supplemented with 10% FBS, 1x NEAA, and 700 µg/mL G418 (Invitrogen, Carlsbad CA). Cells were seeded at a concentration of 80,000 cells per well in Optilix white/clear 96 well plates (VWR, West Chester PA). Appropriate concentrations of antibodies (611 - 0.00004nM) were added to each well followed by addition of appropriate concentrations of human PDC-derived type-I interferon supernatants. Cells, IFN, and antibodies were incubated overnight at 37°C, 5% CO_2 and amplification of the luciferase protein was evaluated by lysing the cells with Cell Culture Lysis reagent and visualization using the Luciferase Assay System (Promega, Madison WI). Signal was measured in cps and IC50 values were generated.

[0256] Results: Type I IFN supernatants were harvested from pDC cells derived from three individual donors. In a Luciferase reporter assay, incubation of anti-IPNAR1 antibodies inhibited the signaling ability of various concentrations of Type I IFN supernatant (Figure 8).

[0257] Conclusions: These results demonstrate that anti-IFNAR1 antibodies are capable of inhibiting Type I IFN mediated signaling as measured by reporter assay activity.

6.6 Example 6: Modified anti-IFNAR1 antibodies exhibit similar binding characteristics to the parental unmodified antibody.

[0258] Purpose: To investigate the IFNAR1 binding characteristics of modified antibodies as compared to parental unmodified versions. Represented in Figure 9 are the binding affinity curves for 9D4, 9D4DM, and 9D4TM. The binding constants (Kd) for the 9D4, 9D4DM, and 9D4TM anti-IFNAR1 antibodies were determined from the binding curves.

[0259] Methods: 200,000 HEK 293F cells were seeded in a round bottom, 96-well plate using 50 µL RPMI 1640 media supplemented with 10% FBS. Europium-labeled 9D4-TM was prepared under contract by PerkinElmer Life and Analytical Sciences. To measure non-specific Europium signal, 25 µL of 100-fold excess unlabeled, serially diluted anti-IFNARI antibodies were added to appropriate wells of the 96 well for 5-10 minutes prior to the addition of labeled 9D4-TM. 25 µL of europium conjugated, serially diluted antibody was then added to appropriate wells and cells and antibodies were agitated gently at room

temperature for 1-2 hours. After binding incubation, 150 µL of cell media was added to all wells and plates were spun at 1200rpm for 5 minutes at room temperature. Plates were quickly decanted and 250 µL cell media was added to all wells. Spins and washes were repeated for a total of 3 washes. Cells were then resuspended in 100 µL cell media. 50 µL of resuspended cells were transferred to 200 µL of DELPHIA enhancement solution (PerkinElmer) in a DELPHIA yellow microtiter plate and Europium emission was measured on a Victor2 Multilabel reader (PerkinElmer). Signal was measured in cps and K_d values and B_{max} values were generated using GraphPad Prism 4 analysis software.

[0260] Results: The data represented in Figure 9 demonstrates that the modified antibodies 9D4-TM and 9D4-DM exhibit similar binding affinities for IFNAR1 (9D4 = 0.06 +/- 0.02 nM, 9D4-DM = 0.06 +/- 0.02 nM, 9D4-TM = 0.03 +/- 0.01 nM) to the parental unmodified antibody.

[0261] Conclusions: The data presented in this example demonstrates that the modified antibodies share similar IFNAR1 binding characteristics with the parental unmodified antibodies.

6.7 Example 7: Equilibrium binding assay data for 9D4-TM vs. sIFNαRI

[0262] Purpose: To determine equilibrium binding data for 9D4-TM using soluble IFNAR1 (srIPNAR1)

[0263] Methods: srIFNAR1 ligand was coated onto UltraLink® Biosupport beads (PIERCE, Rockford, IL) at concentrations of 5 µg/mL and 50 µg/mL in coating buffer (50mM sodium carbonate buffer, pH9) for a period of 1-2 days at 4°C. Coated beads were then separated (gentle pulse spin) from unreacted ligand solution, and gently rocked in block buffer (1mL 1M Tris, pH8, containing BSA at 10mg/mL) for about 15 min at room temperature (RT). After this, the bead slurry was again spun to remove the blocking solution, and then the block step was repeated for about 2 hrs at RT using a fresh aliquot of block buffer. Following the blocking step, the coated beads were stored at 4°C until used. Prior to use, the srIPNAR1-coated beads were transferred to a bead vial, resuspended in 27mLs of instrument run buffer (PBS, pH7.4 - 0.02% NaN3), then attached to the KinExA 3000 instrument.

[0264] All equilibrium binding constants (K_D) were obtained from measurements made on a KinExA 3000 instrument (Sapidyne Instruments, Boise, ID). Briefly, 9D4-TM IgG was prepared at 1pM, 10pM and 50pM and dispensed into three series of tubes. This range of IgG concentrations was designed to permit measurements to be made at under both receptor- and K_D -controlled conditions. Two-fold serial dilutions of srIFNAR1 ligand were then titrated across these IgG solutions, at concentrations ranging from19.5fM - 1nM. Based on the vendor-supplied, theory curve simulations available through the software (Sapidyne Instruments, Boise, Idaho), these equilibration mixtures were incubated anywhere from 2-6 days at RT. At the end of this time, signal-testing experiments were conducted to determine the appropriate run conditions. Detection of free antibody was made possible using a species-specific, Cy5-labeled secondary antibody reagent (Cy5 AffiniPure F(ab')2 Fragment Goat Anti-Human IgG, Part #109-176-097, Jackson ImmunoResearch Laboratories), employed at 0.1, 1.0 or 2.0 µg/mL of PBS, pH7.4 - 0.02% NaN3 containing BSA at 1mg/mL. Data obtained from the experiments were then simultaneously fitted using the software provided n-Curve analysis feature to obtain the reported binding constant (K_D).

[0265] Results: Depicted in Fig 10A are the binding curves for three concentrations of 9D4-TM (1 pM, 10 pM, and 50 pM) with sIFNαRI. Data obtained from at least three independent experiments were fitted to a software derived binding curve to establish a relative K_D for 9D4-TM. The K_D of 9D4-TM in this binding assay was determined to be 1.1 pM with a 95% confidence interval of 0.603 pM - 1.8 pM. The percentage error of the K_D determination of 1.1 pM was 1.96%. The Kon and Koff for 9D4-TM was also determined to be 7×10^6 +/- 1.3×10^6 S^{-1} and 7.7×10^{-6} +/- 1.57×10^{-6} 1/Ms respectively (data not shown).

[0266] Conclusions: The modified anti-IFNAR1 antibody 9D4=TM exhibits a very low K_D of approximately 1.1 pM, for sIFNAR1 as determined by the KinExa assay.

6.8 Example 8: Determination of binding affinity of 9D4-TM on Human PBMCs

[0267] Purpose: To determine the binding affinity on human PBMC's

[0268] Methods: Peripheral blood mononuclear cells were purified from healthy human donors using LSM media (MP Biomedical, Solon OH). Cells were counted and 200,000 cells were seeded in a round bottom, 96-well plate using 50 µL RPMI

1640 media supplemented with 10% FBS. Europium-labeled 9D4-TM was prepared under contract by PerkinElmer Life and Analytical Sciences. To measure non-specific europium signal, 25 µL of 100-fold excess unlabeled, serially diluted 9D4-TM was added to appropriate wells of the 96 well for 5-10 minutes prior to the addition of labeled 9D4-TM. 25 µL of europium conjugated, serially diluted 9D4-TM was then added to appropriate wells and cells and antibodies were agitated gently at room temperature for 1-2 hours. After binding incubation, 150 µL of cell media was added to all wells and plates were spun at 1200rpm for 5 minutes at room temperature. Plates were quickly decanted and 250 µL cell media was added to all wells. Spins and washes were repeated for a total of 3 washes. Cells were then resuspended in 100 µL cell media. 50 µL of resuspended cells were transferred to 200 µL of DELPHIA enhancement solution (PerkinElmer) in a DELPHIA yellow microtiter plate and Europium emission was measured on a Victor2 Multilabel reader (PerkinElmer). Signal was measured in cps and Kd values and B max values were generated using GraphPad Prism 4 analysis software.

[0269] Results: Using the affinity measurements documented in Figure 10B. it was determined that the Kd for 9D4-TM binding to human PBMCs was 0.29 nM +/- 0.11 nM with the number of binding sites determined to be 1448 +/- 447. Using a similar approach, the affinity binding constant for cynomologus monkey IFNAR was determined to be 0.65 +/-0.42 nM with the number of binding sites determined to be 648 +/-204 (data not shown).

[0270] Conclusions: The results presented in Figure 10B demonstrate that 9D4-TM binds specifically and with high affinity to human PBMCs.

6.9 Example 9: The modified anti-IFNAR1 antibodies exhibit similar potency with the parental unmodified antibody.

[0271] Purpose: To demonstrate that modified anti-IFNAR2 antibodies (*i.e.* anti-IFNAR1 antibodies with reduced Fc ligand affinity) exhibit similar potency with the parental unmodified antibodies.

[0272] Methods: The Luciferase Reporter assay system used in this example has been previously described above (See Example 3). Antibodies to IFNAR1 used in this example include 9D4, 9D4-DM, 9D4-TM, MDX-1333. Included is a control antibody R3-47.

[0273] Results: Using the Luciferase reporter system, IC50 values were generated for the various anti-IFNAR1 antibodies described above (See Figure 11A). The anti-IFNAR1 antibody 9D4 (0.01 nM) and the modified antibodies, such as 9D4-DM (0.01 nM) and 9D4-TM (0.02 nM) each elicit a similar IC50 value in the reporter assay demonstrating that they exhibit a similar potency. Another anti-IFNAR1 antibody, MDX1333 (0.04 nM) also exhibits a similar potency to the unmodified 9D4 antibody. The isotype control does not inhibit Type I IFN mediated signaling in this Luciferase reporter assay.

[0274] Conclusions: Modified anti-IFNAR1 antibodies share similar potencies to the unmodified versions as demonstrated by IC50 values generated in a Luciferase Reporter assay system designed to quantify IFN signaling events.

6.10 Example 10: 9D4-TM inhibits the activity of multiple Type I interferon alpha isoforms

[0275] Purpose: To demonstrate that 9D4-TM inhibits signaling attributed to specific and multiple interferon alpha isoforms.

[0276] Methods: The Luciferase Reporter assay system used in this example has been previously described above (See Example 5).

[0277] Results: The IC50 values for the 9D4-TM mediated inhibition of Type I interferon activity are presented in Table 4.

Table 4: IC50 values for 9D4-TM mediated inhibition of Type I interferon activity

Type I Interferon	9D4-TM IC50 (nM)
IFN-α2b	0.07 +/- 0.01
IFN-α2a	0.3 +/- 0.2
IFN-α6	0.04 +/- 0.01
IFN-α16	0.02 +/- 0.03
IFN-α8	0.03 +/- 0.04
IFN-α10	0.01 +/- 0.01

Type I Interferon	9D4-TM IC50 (nM)
Leukocyte Interferon	0.01 +/- 0.01
IFN-α17	0.04 +/- 0.03
IFN-α14	0.02 +/- 0.01
IFN-α1	0.004 +/- 0.01
IFN-α21	0.01 +/- 0.002
IFN-α7	0.04 +/- 0.01
IFN-α4b	0.02 +/- 0.01
IFN-β1	6.8 +/- 9.4
IFN-ω	0.1 +/- 0

[0278] As shown, 9D4-TM exhibits IC50 values in the sub-nanomolar range for multiple interferon alpha isoforms, leukocyte interferon, and interferon omega.

[0279] **Conclusions:** The modified anti-IFNAR1 antibody 9D4-TM demonstrates the ability to inhibit the signaling attributed to multiple specific interferon alpha subtypes as well as leukocyte interferon alpha in a reporter assay

6.11 Example 11: Isoelectric point determination of 9D4, 9D4DM and 9D4TM

[0280] **Purpose:** To evaluate the biophysical characteristics of the parental unmodified antibody 9D4 in comparison to the modified antibodies 9D4-DM and 9D4-TM.

[0281] **Methods:** Native Isoelectric Focusing Polyacrylamide Gel Electrophoresis (IEF-PAGE) analysis was performed as follows: Pre-cast ampholine gels (Amersham Biosciences, pI range 3.5-9.5) were loaded with 8 µg of protein. Protein samples were dialyzed in 10 mM Histidine pH-6 before loading on the gel. Broad range pI marker standards (Amersham, pI range 3-10, 8 µL) were used to determine relative pI for the Mabs. Electrophoresis was performed at 1500 V, 50 mA for 105 minutes. The gel was fixed for 45 minutes using a Sigma fixing solution (5x) diluted with purified water to 1x. Staining was performed overnight at room temperature using Simply Blue stain (Invitrogen). Destaining was carried out with a solution that consisted of 25% ethanol, 8% acetic acid and 67% purified water. Isoelectric points were determined using a Bio-Rad GS-800 Densitometer with Quantity One Imaging Software.

[0282] **Results:** Depicted in Figure 12A is the isoelectric point (pI) determination for antibodies 9D4WT, 9D4DM, and 9D4TM. Samples of the antibodies were run according to the methods above and exhibited the following characteristics. The 9D4 WT antibody exhibited prominent protein bands corresponding to 8.2, 8.35 and 8.51. The 9D4 DM antibody exhibited a single prominent protein band corresponding to 7.13. The 9D4 TM antibody exhibited prominent protein bands corresponding to 8.09 and 8.18.

[0283] **Conclusions:** As presented in this Example, the modified antibodies 9D4-DM and 9D4-TM exhibit very similar biophysical characteristics (pI) to the parental unmodified antibody 9D4.

6.12 Example 12: Thermostability of 9D4, 9D4-DM and 9D4-TM

[0284] **Purpose:** To evaluate the biophysical characteristics of the parental unmodified antibody 9D4 in comparison to the modified antibodies 9D4-DM and 9D4-TM.

[0285] **Methods:** Differential Scanning Calorimetry was performed as follows: thermal melting temperatures (T_m) were measured with a VP-DSC (MicroCal, LLC) using a scan rate of 1.0°C/min and a temperature range of 20 -110°C. A filter period of 8 seconds was used along with a 15 minute pre-scan. Samples were prepared by dialysis into 10 mM Histidine-HCl, pH 6 using Pierce dialysis cassettes (3.5 kD). Mab concentrations were 0.14 mg/ml, 0.79 mg/ml, and 0.64 mg/ml as determined by A_{280}. Melting

temperatures were determined following manufacturer procedures using Origin software supplied with the system. Briefly, multiple baselines were run with buffer in both the sample and reference cell to establish thermal equilibrium. After the baseline was subtracted from the sample thermogram, the data were concentration normalized.

[0286] Results: The antibodies 9D4, 9D4-DM, 9D4-TM were subjected to differential scanning calorimetry as detailed above with the results presented in Figure 12B. Each of the antibodies studied exhibited similar melting temperatures in the assay. Specifically, the antibodies exhibited the following melting temperatures; 9D4 WT = 70.41°C, 9D4-DM = 70.41°C, and 9D4-TM = 70.88°C.

[0287] Conclusions: As presented in this Example, the modified antibodies 9D4-DM and 9D4-TM exhibit very similar biophysical characteristics (T_m) to the parental unmodified antibody 9D4.

6.13 Example 13: Surrogate anti-IFNAR antibodies protect mice from IFNα induced proteinuria

[0288] Purpose: To demonstrate that anti-IFNAR antibodies protect mice from induced proteinuria in a model of SLE.

[0289] Methods: Female NZB/W F1 mice were purchased from Jackson Labs and housed in pathogen-free barrier facility. The recombinant adenovirus vector containing the mouse IFNα subtype 5 cDNA under the control of the CMV promoter/enhancer (Adv-mIFNα5) was used to induce early lupus in these mice. Mice (8 mice/group) were treated at 8-11 wk of age with a single i.v. injection of $0.3x10^{10}$ Adv-mIFNα5 viral particles (vp). Controls received the same amount of control Adv particles. In some experiments, mice were injected with gradual doses of Adv-mIFNα5 ranging from $0.01\ x10^{10}$ to $1.0x10^{10}$ vp/mouse. To test the efficacy of anti-IPNAR1, mice were treated with successive 5 daily i.p. dosing of antibody at 10 mg/kg starting at the time of Adv delivery. For proteinuria, urine was tested using a dipstick (Chemstrip 2 GP; Roche Diagnostics). Proteinuria scored as 1 for levels of 30 mg/dl, 2 for 100 mg/dl, and 3 for levels ≥ 500 mg/dl. Mice were considered to have proteinuria if two consecutive urine samples scored 2 or higher.

[0290] Results: The results of the adenovirus infected mice treated with anti-IFNAR1 antibodies are presented in Figure 13. Mice infected with Adv-mIFNα5 exhibit proteinuria with an onset of about 3 weeks. Infected mice treated with control mouse IgG antibody are not protected from the onset of proteinuria over the course of the experiment as demonstrated by an onset of proteinuria of about 4 weeks. Mice treated with anti-IFNAR antibodies do not show evidence of proteinuria throughout the 8 week time course. Mice treated with an adenovirus control show no proteinuria over the experimental time course.

[0291] Conclusions: Taken together, the data in this example demonstrates that the presence of anti-IFNAR antibodies is protective against adv-IFN induced proteinuria in an *in vivo* mouse model.

6.14 Example 14: Anti-IFNAR antibodies block Type I IFN induced gene regulation

[0292] Purpose: To demonstrate that anti-IFNAR1 antibodies inhibit or reduce Type I interferon gene regulation in a mouse model of SLE.

[0293] Methods: Mice from the experimental procedures described in Example 13 also provided samples for analysis in this example. RNA was prepared from tissues using RLT lysis buffer (Qiagen). For solid tissues (kidney, spleen, skin), no more than 50 mg of tissue was used for RNA processing each time. Samples were placed in lysis buffer and lysing matrix A (Qbiogene), and processed for 30 sec at 4.5m/s using Fastprep24 homogenizer instrument (Thermo Electron Corporation, Waltham, MA). For PBMC, whole blood samples were centrifuged and the pellet was lysed in RLT buffer. Upon lysis, samples were snap frozen at -80 °C until further processed. To isolate RNA, thawed tissue lysates were first processed using Qiashredder spin columns, then equal volumes of 70% ethanol were added to the tissue lysates and RNA was purified using Rneasy mini spin column kits according to the manufacturer's instruction.

[0294] cDNA was generated from 3 µg of RNA using SuperScript III reverse transcriptase and oligo d(T) as described in the manufacturer's protocol (Invitrogen, Corp. Carlsbad, CA). Samples of cDNA were diluted in nuclease-free water and stored at -80 °C.

[0295] Expression levels of selected genes were measured by real-time PCR TaqMan® analysis using the ABI 7900HT Fast

Real-time PCR system (Applied Biosystems, Foster City, CA). Housekeeping gene β-actin was used for endogenous control. Reaction mixtures had a final volume of 20 µl consisting of 1 µl of cDNA, 2 µl of 20x primers and probes (TaqMan® Gene Expression Assays, Applied Biosystems) and 18 µl of diluted TaqMan® Fast Universal PCR Master Mix. Amplification conditions were: 20 seconds at 95 °C, 50 cycles of 1 second at 95 °C and 20 seconds at 60 °C. CT values range from 0 to 50, with the latter number assumed to represent no product formation. Quantification of gene expression was performed using the comparative CT method (Sequence Detector User Bulletin 2; Applied Biosystems) and reported as the fold difference relative to the housekeeping gene.

[0296] Results: Type I interferon ectopically expressed in mice (See example 13) leads to induction of a number of genes. Presented in Figure 14 are the fold changes of six Type I interferon responsive genes in the different populations of mice used in this experiment. Specifically, genes IFIT1, IFI44, IFI202b, CXCL9, CXCL10, and CXCL11 are all induced in the mice ectopically expressing IFNα and treated with nonspecific Mouse IgG. Mice ectopically expressing IFNα and treated with anti-IFNAR antibodies do not show any induction of the six Type I interferon responsive genes. As a control to demonstrate specificity of the adenovirally encoded IFNα, mice treated with PBS, or control adenovirus do not show any induction of these 6 genes. These results demonstrate that the administration of anti-IFNAR antibodies can block the gene induction response to IFN alpha in an *in vivo* mouse model.

[0297] Conclusions: Anti-IFNAR antibodies can block the regulation of Type I responsive genes in mouse model of SLE.

6.15 Example 15: Anti-IFNAR antibodies block the production of Anti-dsDNA and Anti-SSA/Ro (anti-nuclear antigen) antibodies induced by Type I interferon

[0298] Purpose: To demonstrate the ability of anti-IFNAR antibodies to block the production of anti-nuclear antibodies, such as anti-dsDNA and anti-SSa/Ro induced by Type I interferon in a mouse model of SLE.

[0299] Methods: Mice were prepared and treated as described in Example 13. Serum anti-dsDNA autoantibody levels were assessed by ELISA. Briefly, ELISA plates pretreated with poly (L-lysine) (100 µg/ml) were coated with calf thymus activated DNA (5 µg/ml in carbonate-bicarbonate buffer) (SIGMA). After overnight incubation at 4°C, plates were blocked with PBS/ 10% FCS. Sera (1/200 dilution) were incubated for 30 minutes at room temperature. Bound IgG was detected with peroxidase-conjugated goat anti-mouse IgG (1/4000) (KPL) added to the plates for 30 min. Binding was measured by adding TMB substrate (KPL) and stop solution (KPL), and the OD was read at 450 nm. A mouse anti-ds DNA IgG standard in serum was run in serial dilution (from 625 ng/ml) (Alpha Diagnostic) on each plate to allow standardization. Serum anti-SSA/Ro autoantibody levels were measured by ELISA (Alpha Diagnostic) following the manufacturer's instructions.

[0300] Results: Type I interferon ectopically expressed in mice (See Example 13) leads to accumulation of anti-dsDNA and anti-SSA/Ro antibodies. Presented in Fig 15 are the relative quantities of anti-dsDNA (A) and anti-SSA/Ro (B) antibodies in the different populations of mice (control adenovirus, Adv-IFNα + PBS, Adv-IFNα+MuIgG, and Adv-IFNα + Anti-IFNAR) as measured by ELISA. Control adenovirus infected mice show little accumulation of anti-dsDNA or anti-SSA/Ro antibodies in this experiment. Mice infected with adenovirus encoding IFNα and treated with PBS accumulate anti-dsDNA and anti-SSA/Ro antibodies. Adv-IFNα infected mice treated with anti-IFNAR antibodies acquire less anti-dsDNA and anti-SSA/Ro antibodies than Adv-IFNα infected mice treated with non-specific IgG. These results demonstrate that treatment with anti-IFNAR antibodies inhibits the accumulation of anti-dsDNA and anti-SSA/Ro antibodies in response to ectopically expressed Type I IFN.

6.16 Example 16: Anti-IFNAR antibodies block the production of IP-10 and IL-18 induced by Type I interferon

[0301] Purpose: To demonstrate the ability of anti-IFNAR antibodies to block the accumulation of IFNα induced cytokines in a mouse model of SLE.

[0302] Methods: Mice from the experimental procedures described in Example 13 also provided samples for analysis in this example. Serum levels of cytokines were measured by ELISA (R&D systems) following the manufacturer's instructions.

[0303] Results: Type I interferon ectopically expressed in mice (See Example 13) leads to accumulation of IP-10 and IL-18 cytokines. Presented in Figure 16 are the relative quantities of IP-10 (A) and IL-18 (B) in the different populations of mice (PBS, control adenovirus, Adv-IFNα+MuIgG, and Adv-IFNα + Anti-IFNAR) as measured by ELISA. Type I interferon ectopically expressed in mice (See Example 12) leads to accumulation of the cytokines, IP-10 and IL-18. Control adenovirus infected mice show little

accumulation of IP-10 (A) or IL-18 (B) cytokines in this experiment. Adv-IFNα infected mice treated with anti-IFNAR antibodies accumulate less IP-10 and IL-18 cytokines than Adv-IFNα infected mice treated with non-specific IgG. These results demonstrate that treatment with anti-IFNAR antibodies inhibits the accumulation of the cytokines IP-10 and IL-18 in response to ectopically expressed Type I IFN.

[0304] Conclusions: Anti-IFNAR antibodies are able to block the accumulation of IFNα induced cytokines in a mouse model of SLE.

6.17 Example 17: Anti-IFNAR antibodies block the production of ANA (Anti-nuclear antibodies) induced by Type I interferon

[0305] Purpose: To demonstrate the ability of anti-IFNAR antibodies to block the accumulation of IFNα induced anti-nuclear antibodies in a mouse model of SLE.

[0306] Methods: Mice from the experimental procedures described in Example 13 also provided samples for analysis in this example. Antinuclear antibody (ANA) levels were measured by ANA test kit (Antibodies Incorporated) with Hep-2 stabilized substrate and mitotic figures following the manufacturer's instruction. Serum was serially diluted and incubated with the Hep-2 cells on slides and the bound antinuclear antibody was detected by Hi-FITC labeled goat anti-mouse IgG (H+L) (Antibodies Incorporated). The titer of ANA is defined as the serum dilution factor where the ANA is no longer detectable.

[0307] Results: Type I interferon ectopically expressed in mice (See Example 13) leads to accumulation of anti-ANA antibodies. Presented in Figure 17 is the serum titer of anti-ANA antibodies in the different populations of mice (no virus, control adenovirus, Adv-IFNα + PBS, Adv-IFNα+MuIgG, and Adv-IFNα + Anti-IFNAR) as measured by serial dilution staining on HEP2 cells. Control adenovirus infected mice show little accumulation of anti-ANA antibodies in this experiment. Mice infected with adenovirus encoding IFNα and treated with PBS accumulate anti-ANA antibodies. Adv-IFNα infected mice treated with anti-IFNAR antibodies acquire less anti-ANA antibodies than Adv-IFNα infected mice treated with non-specific IgG. These results demonstrate that treatment with anti-IFNAR antibodies inhibits the accumulation of anti-ANA antibodies in response to ectopically expressed Type I IFN.

[0308] Conclusions: Anti-IFNAR antibodies are able to block the accumulation of anti-nuclear antibodies induced by IFNα in a mouse model of SLE.

6.18 Example 18: Antibody Inhibition of SLE Plasma Mediated Dendritic Cell Development

[0309] Purpose: SLE plasma induces dendritic cell development from normal human monocytes. In this example, the purified monoclonal antibody 9D4-TM was tested for the inhibition of dendritic cell development, as assessed by the ability of the antibodies to inhibit the induction of the cell surface markers CD38, and CD 123 by SLE plasma.

[0310] Methods: The methods have been previously described in US Patent Application Publication No. 2006/0029601. Essentially, the experiments were conducted as follows: A 25 ml buffy coat was diluted four-fold with phosphate buffered saline (PBS). The sample was separated into 4x50 ml conical tubes, and 15 ml of lymphocyte separation medium (ICN Biomedicals) was layered underneath. After a 30 minute spin at 500 *g*, the buffy layer containing the peripheral blood mononuclear cells (PBMCs) was removed and washed with PBS. Cells were resuspended in culture media containing 1% heat inactivated human serum at $4x10^6$ cells/ml. Monocytes were isolated by incubating PBMCs ($2.0x10^7$ cells/5 ml/25 cm^2 flask) for 1.5 hours at 37°C in culture media and then washing away non-adherent cells twice. For induction of monocyte maturation, the cells were incubated with medium containing 25% human plasma from healthy volunteers or from patients with SLE. Antibody blocking studies were conducted by adding 30 µg/ml of anti-IFNAR1 antibody or isotype control, IgG1, to the culture. The cells were incubated for 4 days, washed with PBS, and treated with 1:5000 Versene for 10 minutes at 37°C. When necessary, the cells were detached by gentle cell scraping before being washed and analyzed. Each culture was resuspended in staining medium (Hanks's Balanced Salt Solution with 0.2% sodium bicarbonate, 0.01% sodium azide, 0.1 mM EDTA, 20 mM HEPES, and 2% fetal calf serum) and separated equally into six wells of a V bottom 96 well plate. The cells were pulse-spun at 2100 rpm on a Sorvall RTH-750 rotor, and resuspended in 25 µl of staining media. One microgram of specific phycoerythrin conjugated antibody was added to each well and incubated on ice for 45 minutes. The cells were washed three times, resuspended in 200 µl of 2% paraformaldehyde in PBS, and analyzed by flow cytometry with the Becton Dickinson FACScalibur. Gates were drawn on the forward *v* side scatter graph to remove contaminating cells from the analysis.

[0311] Results: In this experiment, the differentiation of human monocytes to dendritic cells in response to IFN derived from the plasma of SLE patients blocked by treatment with 9D4-TM was measured by surface expression of two dendritic cell markers, CD38 and CD123. In Figure 18. multiple serum samples from SLE patients failed to increase the surface expression of CD38 and CD123 in the presence of 9D4-TM. The IC50 values for 9D4-TM varied from 0.02 nM to 0.06 nM for both CD38 and CD123.

[0312] Conclusions: The anti-IFNAR1 antibody 9D4-TM was able to block the ability of IFNα derived form SLE patients to induce pDC maturation as measured by cell surface marker expression.

6.19 Example 19: Anti-IFNAR antibodies suppress the expression of CD38, CD123 and CD86 in monocytes stimulated with Leukocyte-IFN.

[0313] Purpose: In this example, the antibodies 9D4, 9D4-DM and 9D4 TM were tested for the inhibition of dendritic cell development, as assessed by the ability of the antibodies to inhibit the induction of the cell surface markers CD38, and CD 123 by Leukocyte IFN.

[0314] Methods: Monocytes were isolated from whole blood of healthy donors using a lymphocyte separation media (MP Biomedical, Solon OH) followed by positive selection using Monocyte Isolation kit II (Milteny Biotec, Auburn CA). Purified monocytes were then cultured at $1x10^6$ cells/mL in RPMI 1640 supplemented with 10% FBS (Gibco BRL). Serially diluted antibodies were prepared at final concentrations of 3 µg/mL - 20pg/mL in media and were added to appropriate wells of cells. After pre-incubation of approximately 5 minutes, 100IU/mL of human leukocyte IFN (PBL Biomedical, Piscataway NJ) was added to appropriate wells and cultures were incubated at 37°C, 5% CO_2 for 48 hours after which surface expression of CD38 and CD123 evaluated. Briefly, cells were pelleted at 1200rpm for 5 minutes and culture media was removed from monolayers by aspiration followed by one wash 1x with sterile PBS. PBS was removed and 1mL sterile cell dissociation buffer (Gibco BRL, Carlsbad CA) or 0.05% trypsin (Invitrogen, Carlsbad CA) was added to wells to remove cells from monolayers. After 5 minutes and brief agitation, equal volumes of RPMI 1640 supplemented with 10% FBS was added to each well, followed by two series of centrifugation and washes with sterile PBS. 50 µL of 1x PBS supplemented with 5% BSA (Sigma, St. Louis MO) and 10 µg/mL whole human IgG (Jackson ImmunoResearch Laboratories, West Grove PA) was added to each well for blocking of non-specific Fc antibody binding and incubated for 10 minutes at room temperature. 50 µL of 1x PBS supplemented with 5% BSA and PE-anti human CD123 and FITC-anti human CD38 antibodies (Becton Dickinson, Franklin Lakes NJ) were added to appropriate wells and incubated for 30 minutes on ice. Cells were washed once in 1x PBS supplemented with 5% BSA and surface protein expression was measured on a BD LSRII (Becton Dickinson, Franklin Lakes NJ).

[0315] Results: Presented in Figure 19 are the suppression curves of CD38 (A), CD123 (B), and CD86(C) expression exhibited by leukocyte-IFN stimulated PBMCs incubated with anti-IFNAR antibodies 9D4, 9D4DM, and 9D4TM. For each CD molecule, the anti-IFNAR antibodies elicited similar suppression curves which were utilized to generate IC50 values. For CD38 expression on PBMCs stimulated with leukocyte-IFN (A), the anti-IFNAR antibodies elicited IC50 values as follows: 9D4=4.3 ng/ml, 9D4DM=40 ng/ml, 9D4TM=25 ng/ml. For CD123 expression on PBMCs stimulated with leukocyte-IFN (B), the anti-IFNAR antibodies elicited IC50 values as follows: 9D4=7 ng/ml, 9D4DM=21 ng/ml, 9D4TM=10 ng/ml. For CD86 expression on PBMCs stimulated with leukocyte-IFN (C), the anti-IFNAR antibodies elicited IC50 values as follows: 9D4=20 ng/ml, 9D4DM=20 ng/ml, 9D4TM=26 ng/ml.

[0316] Conclusions: The results in this Example demonstrate that antibodies 9D4-DM and 9D4-TM exhibit similar suppression curves of IFN induction of pDC cell surface markers as compared to the parental 9D4 antibody.

6.20 Example 20: Modified anti-IFNAR1 antibodies exhibit decreased binding to the Fc receptor FcγRI.

[0317] Purpose: To demonstrate the reduced binding of a specific Fc receptor to modified anti-IFNAR1 antibodies.

[0318] Methods: The binding activity of modified antibodies 9D4-DM and 9D4-TM to human FcγRI (CD64) was evaluated by ELISA. FcγRI in PBS (pH7.4) was coated at 25 µl/well in a microtiter plate (Costar cat. 3690) at the concentration of 20 µg/ml over night at 4°C. After washing and blocking with 4% milk 1hr at room temperature, the biotinylated 9D4, 9D4TM, 9D4DM and control antibodies were added into the previously blocked plate and incubated at 37°C for an hour, starting at 500 µg/ml and then in two fold serial dilution. The plate was washed with PBS (pH7.4) containing 0.05 % of Tween 20 and 25µl of HRP conjugated Avidin was added to each well. After an hour incubation at 37°C, the plates were washed again and 50 µl/well of substrate - SureBlue

TMB peroxidase (KPL cat. 52-00-03) was added. The reaction was stopped with 50 µl of 0.2M H_2SO_4 after 5-10 minutes development. The ELISA signal was read at 450nM.

[0319] Results: In an ELISA based binding assay (Figure 20), Modified anti-IFNAR1 antibodies 9D4DM and 9D4TM exhibited lower binding affinities to the FcγRI that the unmodified 9D4WT antibody as well as the control antibody.

[0320] Conclusions: These results demonstrate that the modified anti-IFNAR1 antibodies 9D4-DM and 9D4-TM elicit a lower affinity for the Fc receptor FcγRI as compared to the unmodified 9D4 antibody. The lowered affinity for the FcγRI receptor would lead to a lower induction of ADCC.

6.21 Example 21: The Fc receptor FcγRIIIA exhibits reduced binding to the modified anti-IFNAR1 antibodies.

[0321] Purpose: To demonstrate the reduced binding of a specific Fc receptor to the modified anti-IFNAR1 antibodies 9D4-DM and 9D4-TM as compared to the unmodified anti-IFNAR1 antibody 9D4.

[0322] Methods: Fifty µg/ml of 9D4, 9D4TM, and 9D4DM antibodies diluted in PBS were coated on Immunlon IV microtiter plate over night at 4°C. After washing and blocking with 4% milk 1hr at room temperature FcγRIIIA variants 158F (low affinity) and 158V(high affinity) with Flag tag were added to the wells of the blocked plate, starting at 50 µg/ml then in two-fold serial dilution. The plate was washed one hour later and incubated with biotin conjugated anti Flag antibody (Sigma) at 2 µg/ml. After washing 25µl of HRP conjugated Avidin was added to each well. The unbound materials were removed by washing one hour after incubation. The binding signal was detected with the substrate TMB.

[0323] Results: The results from an ELISA based binding assay between anti-IFNAR1 antibodies (9D4WT, 9D4DM, and 9D4TM) and the high and low affinity Fc receptor FcγRIIIA are presented in Fig 21(A, B, C). In Fig 21(A) 9D4WT antibodies coated on the ELISA plate efficiently bind the high affinity FcγRIIIA receptor at concentrations greater than 3 ng/ml while there is limited binding of the low affinity FcγRIIIA receptor at all concentrations tested. In Fig 21(B) Modified 9D4DM antibodies coated on the ELISA plate do not efficiently bind the high or low affinity FcγRIIIA receptors at any concentrations tested. Likewise, in Fig 21(C) Modified 9D4TM antibodies coated on the ELISA plate do not efficiently bind the high or low affinity FcγRIIIA receptors at any concentrations tested.

[0324] Conclusions: These results suggest that the modified anti-IFNAR1 antibodies 9D4-DM and 9D4-TM have a decreased affinity for the FcγRIIIA receptor as compared to the unmodified anti-IFNAR1 antibody 9D4. Additionally, the decreased affinity for the specific Fc receptor could lead to a decrease in ADCC effector function.

6.22 Example 22: The modified antibodies 9D4DM and 9D4TM exhibit reduced binding for the Fc receptor FcγRIIIA.

[0325] Purpose: To demonstrate the reduced binding of a specific Fc receptor to modified antibodies 9D4DM and 9D4TM.

[0326] Methods: Fifty µg/ml of FcγRIIIA variants (FcγRIIIA-10 158F and FcγRIIIA-10 158V) in PBS were coated on Immunlon IV microtiter plate over night at 4°C. After washing and blocking with 4% milk 1hr at room temperature biotinylated 9D4, 9D4TM, and 9D4DM antibodies were added to the wells of the blocked plate at 100 µg/mL. The plate was washed one hour later and incubated with HRP conjugated Avidin. The unbound materials were removed by washing one hr after incubation. The binding signal was detected with the substrate TMB.

[0327] Results: The results from an ELISA based binding assay between the high and low affinity Fc receptors FcγRIIIA and anti-IFNAR1 antibodies (9D4WT, 9D4DM, and 9D4TM) are presented in Figure 22(A, B, C). In Figure 22(A) the unmodified anti-IFNAR1 antibody 9D4, at concentrations greater than 3 ng/ml, efficiently binds the high affinity FcγRIIIA receptor immobilized on the ELISA plate, whereas the antibody demonstrates limited binding to the immobilized low affinity FcγRIIIA receptor at all concentrations tested. In Figure 22(B) the modified anti-IFNAR1 antibody 9D4DM does not efficiently bind the immobilized high or low affinity FcγRIIIA receptors at any concentrations tested compared to the unmodified 9D4WT anti-IFNAR1 antibody. Likewise, in Figure 22(C) the modified anti-IFNAR1 antibody 9D4TM does not efficiently bind the immobilized high or low affinity FcγRIIIA receptors at any concentrations tested compared to the unmodified 9D4WT anti-IFNAR1 antibody.

[0328] Conclusions: This Example demonstrates that the modified antibodies 9D4DM and 9D4TM, exhibit decreased affinity for the Fc receptor, FcγRIIIA as compared to the parental unmodified 9D4 antibody. This reduced affinity could lead to a decrease in

FcγRIIIA mediated ADCC effector function as compared to the parental antibody.

6.23 Example 23: Neutralization of IFNα subtypes by anti-IFNAR1 antibodies.

[0329] Purpose: To demonstrate the ability of the anti-IFNAR1 antibodies MDX-1333, 9D4WT, and 9D4TM to neutralize specific IFNα subtypes in a reporter assay

[0330] Methods: Reporter assays for IFNα neutralization have been well documented in the art. In this example, IFNα neutralization is measured by a HiL3 based reporter assay. An example of how a IFNα neutralization assay using HiL3 cells as a reporter is as follows: A human hepatoma cell line HiL3 was transfected with a plasmid containing an IFNα stimulated response element-luciferase (ISRE-Luc), and a neomycin resistance gene. These cells were kindly provided by Dr Michael Tovey (CNRS, Paris, France). Hil3, 30,000 cells/well, was cultured in white reflective 96 well plates (DYNEX Microlite) and grown overnight in Dulbecco's modified Eagle's medium containing 10% fetal bovine serum and 1 mg/ml G418 (+penicillin/streptomycin/L-glutamine). After this incubation, various forms of interferon were added and the plates were cultured for 18 hours. The reaction was terminated by adding 10 ml of lysis buffer to luciferase substrate vial (Luc Lite Plus kit, Perkin-Elmer); 100 µl of this substrate solution was added to each well and read on Top Count for 10 minutes (10 minutes waiting in the dark, then 1 second read/well). The counts per second (cps) at each IFN concentration were determined and the IFN concentration or cps in each sample was calculated from the IFN titration curve using Prism software (San Diego, CA) with linear regression parameters.

[0331] Results: The neutralization capacity for anti-IFNAR1 antibodies for various IFN species in a HiL3 reporter assay is presented in Figure 23 (A-E). The anti-IFNAR1 antibodies MDX-1333, 9D4WT and 9D4TM inhibit multiple Type I interferon subtypes with similar potency. The anti-IFNAR1 antibodies MDX-1333, 9D4WT and 9D4TM neutralize IFNα10 (A) with IC50 values of 0.09880 µg/ml, 0.008345 µg/ml, and 0.004287 µg/ml respectively. The anti-IFNAR1 antibodies MDX-1333, 9D4WT and 9D4TM neutralize Human Leukocyte IFN (B) with IC50 values of 1.121 µg/ml, 0.02104 µg/ml, and 0.02120 µg/ml respectively. The anti-IFNAR1 antibodies MDX-1333, 9D4WT and 9D4TM neutralize IFNα 2b (C) with IC50 values of 0.0006462 µg/ml, 0.002789 µg/ml, and 0.0008279 µg/ml respectively. The anti-IFNAR1 antibodies MDX-1333, 9D4WT and 9D4TM neutralize IFNω (D) with IC50 values of 5.323 µg/ml, 0.01015 µg/ml, and 0.01423 µg/ml respectively. The anti-IFNAR1 antibodies MDX-1333, 9D4WT and 9D4TM neutralize IFNβ (E) with IC50 values of 18.97 µg/ml, 0.7403 µg/ml, and 0.2611 µg/ml respectively.

[0332] Conclusions: These results indicate that the anti-IFNAR1 antibodies MDX-1333, 9D4WT (unmodified) and 9D4TM (modified) exhibit similar neutralization specificity and capacity for multiple Type I interferons.

6.24 Example 24: Anti-IFNAR1 antibodies neutralize Type I IFN in plasma from SLE patients

[0333] Purpose: To demonstrate the ability of anti-IFNAR1 antibodies to neutralize Type I IFN in plasma isolated from SLE patients as measured by a report assay.

[0334] Methods: Stably transfected PIL-5 ISRE cells were maintained in RPMI 1640 + 1X Pen-strep-glutamine + 10% FBS and seeded at 100,000 cells per well in Optilix white/clear 96 well plates (VWR, West Chester PA). Antibodies were titrated added to appropriate wells for a final concentration ranging from 90 µg/mL - 60pg/mL. Type-I interferon positive human SLE patient serum samples were added to each well for a final serum percentage of 50% per well. Cells, IFN, and antibodies were incubated overnight at 37°C, 5% CO_2. After overnight incubation, cells were pelleted briefly at 1200rpm for 5 minutes and amplification of the luciferase protein was evaluated by lysing the cells with Cell Culture Lysis reagent and visualization using the Luciferase Assay System (Promega, Madison WI). Signal was measured in cps and IC50 curves were generated using GraphPad Prism 4 analysis software.

[0335] Results: 9D4-TM neutralizes Type I interferons in SLE patient plasma. The results from a neutralization assay of Type I interferons in SLE patient plasma is presented in Figure 24. Neutralization of Type I interferon contained in the SLE patient plasma sample is specifically neutralized with 9D4-TM versus an Isotype control at increasing antibody concentrations. Specifically, 9D4-TM exhibits an IC50 of 0.04 nM for neutralization of Type I interferons in this plasma sample taken from an SLE patient.

[0336] Conclusions: This result suggests that the modified anti-IFNAR1 antibody 9D4-TM has the capacity to effectively neutralize Type I interferon in SLE patients.

6.25 Example 25: Anti-IFNAR antibodies suppress the IFNα induced pDC population in PBMCs

[0337] Purpose: To demonstrate the ability of anti-IFNAR antibodies to suppress the accumulation of pDC cells in the peripheral blood of mice from a model of SLE.

[0338] Methods: Mice from the experimental procedures described in Example 13 also provided samples for analysis in this example. PBMCs were isolated from Spleen, Lymph Nodes, Bone Marrow and Peripheral Blood using standard isolation techniques and stained for the B220 and Ly6C surface markers. Isolated PBMCs were analyzed by FACS and double positive (B220 and Ly6C) cells were scored as pDC cells and the relative populations are represented in Fig 25.

[0339] Results: As represented in Figure 25, ectopic expression of IFNα triggers an increase in pDC cells within the PBMCs isolated from spleen (A), lymph nodes (B), blood (C), and bone marrow (D) in the presence of PBS or mouse non-specific IgG. Mice treated with anti-IFNAR antibodies do not accumulate pDC cells in response to IFN-alpha. Mice treated with control Adenovirus do not accumulate pDCs in the PBMC population.

[0340] Conclusions: These results suggest that anti-IFNAR antibodies specifically block the IFNα induced upregulation of pDC cells.

6.26 Example 26: Modified anti-IFNAR1 antibodies exhibit lower binding affinities to Fc receptors.

[0341] Purpose: To evaluate the relative binding affinities of the modified anti-IFNAR1 antibodies 9D4-DM and 9D4-TM with the parental unmodified antibody 9D4 to various Fc receptors.

[0342] Methods: All experiments were performed on a BIAcore 3000 instrument (BIAcore, Inc., Uppsala, Sweden). In a typical experiment 1μM solutions of 9D4 IgGs were used to immobilize anywhere from ~ 7000 RUs - ~ 11,000 RUs of protein onto CM5 sensor chip surfaces using a standard amino coupling protocol (BIAcore, Inc.). Separately, a blank surface was also prepared on each chip using the identical protocol, minus the protein. This blank surface was used as a reference cell throughout the experiment, and served to correct for both non-specific binding and certain housekeeping artifacts. For the test-binding experiments, FcγRI was prepared at 20nM in HBS-EP buffer (BIAcore, Inc., consisting of the following: 10mM HEPES buffer, pH7.4, 150mM NaCl, 3mM EDTA, and 0.005% P20. Between FcγRI injections, the IgG surface was regenerated with a 1 min. injection of 5mM HCl. Sensorgram overlays were generated using the BIAevaluation 4.1 software (BIAcore, Inc, Uppsala, Sweden).

[0343] Results: The anti-IFNAR1 antibody 9D4 and modified anti-IFNAR1 antibodies 9D4-TM and 9D4-DM were tested for binding affinity to immobilized FcγRI protein in a BIAcore assay format. As depicted in Figure 26, the anti-IFNAR1 antibody 9D4 exhibits a high affinity for the immobilized FcγRI. The binding of the anti-IFNAR1 antibody 9D4 to FcγRI is specific as the similar assay run with ovalbumin exhibits very little affinity for the immobilized receptor. The modified anti-IFNAR1 antibodies 9D4-TM and 9D4-DM exhibit a lower affinity of the immobilized receptor FcγRI compared to the unmodified 9D4 anti-IFNAR1 antibody.

[0344] Conclusions: The resultant lower affinities for FcγRI exhibited by the modified anti-IFNAR1 antibodies 9D4-TM and 9D4-DM suggest that these antibodies would have a diminished capacity to activate ADCC *in vivo*.

6.27 Example 27: Fc receptors exhibit reduced binding affinities to modified anti-IFNAR1 antibodies.

[0345] Purpose: To evaluate the relative binding affinities of various Fc receptors to the modified anti-IFNAR1 antibodies 9D4-DM and 9D4-TM and the parental unmodified anti-IFNAR1 antibody 9D4.

[0346] Methods: Surface Plasmon Resonance Measurements

[0347] All experiments were performed on a BIAcore 3000 instrument (BIAcore, Inc., Uppsala, Sweden). In a typical experiment a 1μM solution of FcγRI was used to immobilize anywhere from ~ 7000 RUs - ~ 11,000 RUs of protein onto CM5 sensor chip surfaces using a standard amino coupling protocol (BIAcore, Inc.). Separately, a blank surface was also prepared on each chip using the identical protocol, minus the protein. This blank surface was used as a reference cell throughout the experiment, and served to correct for both non-specific binding and certain housekeeping artifacts. For the test-binding experiments, antibodies

were prepared at 333nM in HBS-EP buffer (BIAcore, Inc., consisting of the following: 10mM HEPES buffer, pH7.4, 150mM NaCl, 3mM EDTA, and 0.005% P20. Between antibody injections, the FcγRI surface was regenerated with a 1 min. injection of 3M MgCl2. Sensorgram overlays were generated using the BIAevaluation 4.1 software (BIAcore, Inc, Uppsala, Sweden).

[0348] Results: The anti-IFNAR1 antibodies 9D4, 9D4-TM and 9D4-DM were immobilized and incubated with soluble FcγRI. Binding affinity of the soluble FcγRI receptor to each of the anti-IFNAR1 antibodies were measured in a BIAcore assay and the resultant tracings are represented in Figure 27A, B, C. The FcγRI bound the immobilized anti-IFNAR1 antibody 9D4 with a high affinity as represented in Figure 27A. This interaction was highly specific as soluble ovalbumin did not show any binding to the immobilized anti-IFNAR1 antibody 9D4. The modified antibodies 9D4-TM and 9D4-DM do not bind the FcγRI as strongly as the wild type unmodified 9D4 antibody. In Fig 27B, the modified anti-IFNAR1 antibody 9D4-DM was immobilized and incubated with either soluble FcγRI or ovalbumin. The FcγRI exhibited a low binding affinity for the immobilized 9D4-DM antibody. This binding affinity is similar to the non-specific interaction seen with soluble ovalbumin. In Fig 27C, the modified anti-IFNAR1 antibody 9D4-TM was immobilized and incubated with either soluble FcγRI or ovalbumin. The FcγRI exhibited a low binding affinity for the immobilized 9D4-TM antibody. This binding affinity is similar to the non-specific interaction seen with soluble ovalbumin.

[0349] Conclusions: The lower affinities exhibited by the Fc receptor FcγRI for the immobilized modified anti-IFNAR1 antibodies 9D4-DM and 9D4-TM over the unmodified anti-IFNAR1 antibody 9D4 suggests that the modified antibodies would exhibit a lower capacity to elicit an ADCC response.

6.28 Example 28: Anti-IFNAR antibodies block IFNα responsive gene induction.

[0350] Purpose: To demonstrate the ability of anti-IFNAR antibodies to block the induction of IFNα responsive genes in a mouse model of SLE.

[0351] Methods: Mice from the experimental procedures described in Example 13 also provided samples for analysis in this example. After 8 weeks into the experiment the mice were sacrificed and kidney tissue was removed. No more than 50 mg of tissue was used for RNA extraction using RLT lysis buffer (Qiagen). Samples were placed in lysis buffer and lysing matrix A (Qbiogene), and processed for 30 sec at 4.5m/s using Fastprep24 homogenizer instrument (Thermo Electron Corporation, Waltham, MA). To isolate RNA, thawed tissue lysates were first processed using Qiashredder spin columns, then equal volumes of 70% ethanol were added to the tissue lysates and RNA was purified using Rneasy mini spin column kits according to the manufacturer's instruction. cDNA was generated from 3 µg of RNA using SuperScript III reverse transcriptase and oligo d(T) as described in the manufacturer's protocol (Invitrogen, Corp. Carlsbad, CA). Samples of cDNA were diluted in nuclease-free water and stored at -80 °C.

[0352] Expression levels of selected genes were measured by real-time PCR TaqMan® analysis using the ABI 7900HT Fast Real-time PCR system (Applied Biosystems, Foster City, CA). Housekeeping gene β-actin was used for endogenous control. Reaction mixtures had a final volume of 20 µl consisting of 1 µl of cDNA, 2 µl of 20x primers and probes

[0353] (TaqMan® Gene Expression Assays, Applied Biosystems) and 18 µl of diluted TaqMan® Fast Universal PCR Master Mix. Amplification conditions were: 20 seconds at 95 °C, 50 cycles of 1 second at 95 °C and 20 seconds at 60 °C. CT values range from 0 to 50, with the latter number assumed to represent no product formation. Quantification of gene expression was performed using the comparative CT method (Sequence Detector User Bulletin 2; Applied Biosystems) and reported as the fold difference relative to the housekeeping gene.

[0354] Results: Presented in Figure 28 are the results from a comparative expression analysis in the kidney of 6 genes induced by interferon alpha after 8 weeks in an accelerated lupus mouse model. Mice ectopically expressing interferon alpha were treated with mouse IgG or anti-IFNAR antibodies. After 8 weeks, the mice treated with control IgG demonstrated a high induction of IFNα responsive genes namely ICAM1, VCAM1, CXCL9, CXCL10, and IFIT1. Mice treated with anti-IFNAR antibodies did not show induction of IFNα responsive genes after 8 weeks.

[0355] Conclusions: In the accelerated lupus mouse model treatment with anti-IFNAR antibodies blocks induction in the kidney of six genes (ICAM1, VCAM1, CXCL9, CXCL10, and IFIT1) mediated by the ectopically expression of IFN-alpha compared to control mice as measured by a Taqman assay. These results demonstrate that anti-IFNAR antibodies are capable of blocking IFNα mediated signaling in a SLE mouse model.

6.29 Example 29: Anti-IFNAR antibodies inhibit accumulation of autoantibodies in serum

[0356] Purpose: To demonstrate the ability of anti-IFNAR antibodies to inhibit the accumulation of autoantibodies in serum of mice in an SLE model.

[0357] Methods: Mice from the experimental procedures described in Example 13 also provided samples for analysis in this example. Whole blood samples were taken at 1 week intervals from week 2-7 of the regimen. Serum anti-dsDNA autoantibody levels were assessed by ELISA. Briefly, ELISA plates pretreated with poly (L-lysine) (100 µg/ml) were coated with calf thymus activated DNA (5 µg/ml in carbonate-bicarbonate buffer) (SIGMA). After overnight incubation at 4°C, plates were blocked with PBS/ 10% FCS. Sera (1/200 dilution) were incubated for 30 minutes at room temperature. Bound IgG was detected with peroxidase-conjugated goat anti-mouse IgG (1/4000) (KPL) added to the plates for 30 min. Binding was measured by adding TMB substrate (KPL) and stop solution (KPL), and the OD was read at 450 nm. A mouse anti-ds DNA IgG standard in serum was run in serial dilution (from 625 ng/ml) (Alpha Diagnostic) on each plate to allow standardization.

[0358] Results: Presented in Figure 29 are the results from the ELISA based analysis of the levels of anti-ds DNA antibodies in mouse serum during an accelerated lupus mouse model time course. Mice ectopically expressing IFNα were treated with anti-IFNAR antibodies or mouse IgG control antibodies during an 7 week regimen. The mice treated with anti-IFNAR antibodies did not accumulate anti-dsDNA antibodies at the same rate or to the same extent of mice treated with control IgG antibodies. Mice infected with control adenovirus did not develop anti-ds DNA antibodies over the time course.

[0359] Conclusions: These results demonstrate that anti-IFNAR antibodies reduced the accumulation of anti-dsDNA antibodies in response to elevated levels of IFN alpha.

6.30 Example 30: Anti-IFNAR antibodies reduce proteinuria in the accelerated lupus mouse model.

[0360] Purpose: To demonstrate the ability of anti-IFNAR antibodies to reduce established proteinuria (therapeutic setting) in the SLE mouse model.

[0361] Methods: Mice from the experimental procedures described in Example 13 also provided samples for analysis in this example. However, in a therapeutic approach, mice were allowed to develop proteinuria as a symptom of Lupus before application of the antibodies. Specifically, mice were allowed to develop a proteinuria score of 2.0 - 2.5 as described previously. Once the threshold level of proteinuria was passed, a treatment regimen of semi-weekly doses of PBS, control IgG or anti-IFNAR antibodies was conducted for 5 additional weeks. At semi-weekly intervals urine samples were tested and given a proteinuria score.

[0362] Results: Presented in Figure 30A are the results from a therapeutic study of anti-IFNAR antibodies reducing the proteinuria score of mice from an accelerated lupus model Briefly, mice were allowed to develop proteinuria at which time, the cohort was either given PBS, control IgG or anti-IFNAR antibodies as treatment. As documented within the figure, the proteinuria score decreased for only the group receiving anti-IFNAR antibodies. The mice receiving PBS or control IgG as treatment continued to increase the proteinuria score over time. (B) An analysis of the area under the curve for the results over the five weeks determined that the anti-IFNAR antibody treated group differed from the PBS alone or IgG control groups, both of which were very similar.

[0363] Conclusions: These results demonstrate that anti-IFNAR antibodies could be used in a therapeutic setting of SLE.

6.31 Example 31: Anti-IFNAR antibodies reduce mortality in the accelerated lupus mouse model.

[0364] Purpose: To demonstrate the ability of anti-IFNAR antibodies to reduce mortality in a therapeutic setting of the SLE lupus mouse model.

[0365] Methods: Mice from the experimental procedures described in Example 30 also provided samples for analysis in this example.. In a therapeutic approach, mice were allowed to develop proteinuria as a symptom of Lupus before application of the antibodies. Specifically, mice were allowed to develop a proteinuria score of 2.0 - 2.5 as described previously. Once the threshold level of proteinuria was passed, a treatment regimen of semi-weekly doses of PBS, control IgG or anti-IFNAR antibodies was conducted for 5 additional weeks. Overall mortality was tracked for an additional 4 weeks.

[0366] **Results:** Presented in Figure 31 are the mortality rates from a therapeutic study of anti-IFNAR antibodies in an accelerated lupus model Briefly, mice were allowed to develop proteinuria at which time, the cohort was either given PBS, control IgG or anti-IFNAR antibodies as treatment. Mice treated with anti-IFNAR antibodies exhibited no mortality at week 5, whereas mice treated with PBS or control IgG exhibited mortality rates of 87.5% and 62.5% respectively. Additionally, over the nine week study, anti-IFNAR treated animals exhibited a high survival rate compared to PBS or control IgG treated animals.

[0367] **Conclusions:** The results in this Example demonstrate that anti-IFNAR antibodies can decrease the mortality associated with Lupus.

6.32 Example 32: Absence of 9D4-TM mediated ADCC activity.

[0368] Purpose: To verify that 9D4-TM is unable to induce ADCC activity, due to its poor binding affinity to FcγRI and FcγRIIIA a series of experiments were conducted.

[0369] Methods: 293F target cells were labeled with DiO cell label (Invitrogen, experiments I & II) and combined with unlabeled effectors PBMCs (for 4h at 37°C, in the absence or presence 10 µg/ml of 9D4-TM, human IgG1 isotype negative control R3-47, 9D4-WT or anti-EphA2 antibody used as a positive control. Lysis of target cells was evaluated by measuring DiO^+/PI^+ (propidium iodide) double positive staining. Effector-target ratio = 50-1, percent of lysis was calculated according to the formula : [(percent of double positive staining in the presence of antibodies - percent of double positive staining in media alone) / (percent of double positive staining in the presence of lysis buffer - percent of double positive staining in media alone)]. One hundred percent of lysis was achieved by adding lysis buffer (Promega).

[0370] Alternatively, 293F target cells were incubated with cells from a transgenic NK cell line stably expressing FcγRIIIA (experiment III) for 4h at 37°C, in the absence or presence 10 µg/ml of 9D4-TM, human IgG1 isotype negative control R3-47, 9D4-wt or anti-EphA2 antibody used as a positive control. Effector-target ratio =4-1 and percent of lysis was calculated according to the formula : 100 x (Experimental - Effector Spontaneous - Target Spontaneous) /(Target Maximum-Target Spontaneous).

[0371] On experiments I & II (PBMCs-293H ratio = 50-1), percent of lysis was calculated according to the formula : [(percent of double positive staining in the presence of antibodies - percent of double positive staining in media alone) / (percent of double positive staining in the presence of lysis buffer - percent of double positive staining in media alone)]. On experiment III (Transgenic NK cell line expressing FcγIIIA-293H ratio = 4-1), percent of lysis was calculated according to the formula : 100 x (Experimental - Effector Spontaneous - Target Spontaneous) /(Target Maximum-Target Spontaneous).

[0372] **Results:** The modified antibody 9D4-TM or the unmodified antibody 9D4-WT exhibited no detectable ADCC activity on 293F cells over that observed with the R3-47 antibody, (Table 4). In contrast, the positive control antibody, an anti-EphA2 antibody, caused a two-fold increase in cytotoxicity over background level. These results confirm that 9D4-TM cannot mediate ADCC on IFNAR1 expressing targets.

Table 5: Evaluation of ADCC activity of Anti-IFNAR1 antibodies.

Antibodies	Exp.I	Exp.II	Exp.III
	% of target lysis	% of target lysis	% of target lysis
Positive control: Anti-EphA2	33±4	36±1	43.4±0.5
Negative control: R3-47	14±1	18±3	18.1±1.1
9D4-WT	14±2	20±2	17.5±1.6
9D-TM	14±2	20±2	ND
Exp.I/II/III: experiments I/II/III. ND: not done.			

[0373] **Conclusions:** These results demonstrate that modified anti-IFNAR1 antibody 9D4-TM does not stimulate detectable ADCC activity directed at IFNAR1 expressing target cells.

6.33 Example 33: Three-Dimenstional Structures of Human Fc region Comprising L234F/L235E/P331S Mutations.

[0374] **Purpose:** To determine the three-dimensional structures of human IgG1 Fc region comprising L234F/L235E/P331S

mutations (Fc-TM).

Methods:

[0375] Purification of Fc-TM: The human Fc/TM fragment was obtained from the enzymatic cleavage of 9D4-TM. Digestion was carried out using immobilized ficin according to the manufacturer's instructions (Pierce). Purification was first performed on HiTrap Protein A columns according to the manufacturer's instructions (GE Healthcare, Piscataway, NJ). After dialysis in 50 mM NaOAc/pH 5.2, the protein solution was applied to a HiTrap SP HP column (GE Healthcare) and collected in the flow through. The flow through was loaded onto a HiTrap Q column (GE Healthcare) and eluted in a NaCl gradient to yield a homogenous Fc/TM preparation, as judged by reducing and non-reducing SDS-PAGE. Fc-TM SDS-PAGE profile showed the presence of only one band around 25 kDa or 50 kDa under reducing or non reducing conditions, respectively. This observation clearly demonstrated the presence of at least one interchain disulfide bond at positions C226 and/or C229. Consequently, mutated 'downstream' residues F234 and E235 were present in the polypeptide chain comprising the crystal.

[0376] Crystallization of Fc-TM: Purified Fc-TM was concentrated to about 5 mg/ml using a Centricon concentrator (Millipore, Billerica MA,30 KDa cutoff). Crystallization conditions were identified using the commercial screens from Hampton Research (Hampton Research, Aliso Viejo, CA), Emerald BioSystems (Emerald BioSystems, Inc., Bainbridge Island, WA) and Molecular Dimensions (Molecular Dimensions Inc., Apopka, FL). Each screen yielded several potentially usable crystallization conditions. Upon optimization, diffraction-quality crystals were obtained from 0.2 M Zinc acetate, 0.1 M Imidazole-Malate, pH 8.0, 5% PEG 3350, 5% glycerol at protein concentration of 2.0 mg/ml. Under these conditions, well-shaped crystals with three dimensions ranging from 0.1 to 0.2 mm grew in 2-3 days.

[0377] Data collection: Diffraction data were collected from a single crystal at the Center for Advanced Research in Biotechnology (CARB, University of Maryland Biotechnology Institute, Rockville, MD) using a Rigaku MicroMax™ 007 rotating anode generator with an R-AXIS IV++ imaging plate (Rigaku/MSC, The Woodlands, TX). Prior to cooling, the crystal was kept for a few minutes in its growth solution supplemented with 20% glycerol. The crystal was then cooled to 105 kelvins with an X-stream 2000 Cryogenic cooler (Rigaku/MSC). Diffraction of up to 2.3 Å was achieved after one round of annealing as described (Oganesyan *et al.,* 2007). Diffraction data comprising 234 images were collected using an oscillation range of 0.5°, a crystal/detector distance of 200 mm and an exposure time of 600 s. Data were integrated and scaled using the HKL 2000 software (Otwinowski & Minor, 1997).

[0378] Structure Determination: Molecular replacement, refinement, and electron density calculation were carried out using the CCP4 (Collaborative Computational Project) program suite. The C-face centered orthorhombic crystal had a 58% solvent content and V_M of 2.9, assuming one Fc polypeptide in the asymmetric unit of the cell. The crystal structure of Fc/TM was determined by molecular replacement and refined at 2.3Å resolution. The human Fc structure corresponding to PDB ID number 2DTQ (Matsumiya et al., (2007) J. Mol. Biol. 368:767-779) was used as the model because of its high resolution and unliganded state. In particular, the C_H2 and C_H3 domains were considered separately to minimize any bias in terms of the domains relative conformation. Data up to 3.0 Å were used for the molecular replacement problem using Phaser (McCoy et al., (2005) Acta Cryst. D61, 458-464). After refinement of the solutions, the final LL-gain and the Z-score were 1192 and 31, respectively. Weighted electron density calculated with FWT/PHWT at 3.0 Å showed a good match with the model with the exception of some loops in the C_H2 and C_H3 domains. Strong positive difference electron density calculated with DELFWT/PHDELWT was visible in the expected place of N-linked carbohydrate residues attached to N297. There was no density present for any hinge residue preceding that at position 236, a result presumably attributable to the high flexibility of this region. It is noted that only two previously described unliganded human Fc structures could reveal positions 234 and 235 (2DTQ/2DTS; Matsumiya et al., (2007) J. Mol. Biol. 368:767-779). Likewise, residues at positions 446 and 447 could not be visualized. The residue at position 331 was first modeled as an alanine.

[0379] Several alternating rounds of refinement with 'Refmac 5' (Murshudov et al., (1997) Acta Cryst. D53, 240-255) and manual building using the "O" graphics software (Jones et al., (1991) Acta Cryst. A47, 110-119) converged with R_{factor} of 21.6 and Free R_{factor} of 27.5 for data up to 2.3 Å resolution. After the first round of refinement, the electron density allowed placement of the carbohydrates as well as substitution by a serine residue at position 331. At later stages of refinement, the model was analyzed using the TLS Motion Determination (TLSMD) program running on its web Server (Painter et al. (2006). J. Appl. Cryst. 39, 109-111; Painter et al. (2006) Acta Cryst. D62, 439-450). Further refinement was then carried out with Refmac 5 in TLS and restrained refinement mode using five distinct groups of residues (236-324, 325-341, 342-358, 359-403 and 404-445). Zinc ions present in the crystallization buffer were detected in the electron density and modeled as such when the coordination sphere and

distance permitted. In particular, one zinc ion was found coordinated by H310 and H435. Another was coordinated by H285 and H268 of the symmetry related polypeptide. Two others were bound to E318 and E345. In all cases, water molecules completed the expected tetrahedral coordination sphere of the zinc ions. The carbohydrate moiety was modeled according to its electron density and the final model contained nine sugar residues, essentially as described by us in the context of another human Fc structure (Oganesyan et al., (2007) Molecular Immunology, December 11, 2007, in press). The final model contained 75 solvent molecules. Crystallographic data and refinement statistics are given in Table 6.

Table 6. X-Ray data collection and model refinement statistics.

Wavelength, Å	1.54
Resolution, Å	36.83 - 2.30 (2.38-2.30)[a]
Space group	$C222_1$
Cell parameters, Å	50.18, 147.30, 75.47
Total reflections	54,409
Unique reflections	12,617
Average redundancy	4.31 (2.72)[a]
Completeness, %	98.3 (90.0)[a]
R_{merge}	0.062 (0.300)[a]
I/σ(I)	13.0 (3.3)[a]
R factor/Free R factor	0.216/0.275
RMSD bonds, Å	0.012
RMSD angles, °	1.48
Residues in most favored region of {ϕ,ψ} space, %	89.9
Residues in additionally allowed region of {ϕ,ψ} space, %	10.1
Number of protein atoms	1678
Number of non-protein atoms	189
B factor (Model/Wilson), Å2	43/40

[a] Values in parentheses correspond to the highest resolution shell

[0380] **Results:** Fc-TM crystallized in space group $C222_1$ with one polypeptide in the asymmetric unit (Figure 32). The crystal diffracted to 2.3 Å resolution, and exhibited a relatively high average mosaicity of 1.26°. This high mosaicity appeared to be a property of both cooled and non-cooled crystals. All residues at positions 236 to 445 could be traced in the electron density and no electron density was observed for hinge residues prior to position 236, thus rendering the L234F and L235E mutations invisible. The electron density at position 331 corresponded to serine.

[0381] The atomic coordinates and experimental structure factors of Fc-TM have been deposited with the Protein Data Bank under accession number 3C2S.

[0382] The overall three-dimensional structure of Fc-TM was very similar to previously reported structures of unliganded human Fc regions (Deisenhofer, (1981). Biochemistry, 20: 2361-2370; Krapp et al., (2003). J. Mol. Biol. 325, 979-989; Matsumiya et al., (2007). J. Mol. Biol. 368:767-779; Oganesyan et al., (2007) Molecular Immunology, December 11, 2007, in press). More precisely, the human Fc structures corresponding to PDB ID numbers 1H3W (Krapp et al., (2003). J. Mol. Biol. 325:979-989) and 2QL1 (Oganesyan et al., (2007) Molecular Immunology, December 11, 2007, In the press) were closest to Fc-TM in terms of cell parameters, asymmetric unit content, space group and packing. When considered individually, Fc-TM C_H2 and C_H3 domains showed great structural conservation and rigidity when compared with other unliganded, unmutated human Fc structures. For instance, rms coordinate displacements of Cα atoms were 0.6 and 0.4 Å for the C_H2 and C_H3 domains, respectively, when superimposing Fc-TM with chain A of PDB ID number 2DTQ (Matsumiya et al., (2007). J. Mol. Biol. 368, 767-779).

[0383] Table 7 following below, provides the atomic structure coordinates of Fc-TM. The following abbreviations are used in Table 7

[0384] "Atom Type" refers to the element whose coordinates are provided. The first letter in the column defines the element.

[0385] "A.A." refers to amino acid.

[0386] "X, Y and Z" provide the Cartesian coordinates of the element.

[0387] "B" is a thermal factor that measures movement of the atom around its atomic center.

[0388] "OCC" refers to occupancy, and represents the percentage of time the atom type occupies the particular coordinate. OCC values range from 0 to 1, with 1 being 100%.

Table 7.: The atomic structure coordinates of Fc-TM

```
REMARK   3
REMARK   3 REFINEMENT.
REMARK   3   PROGRAM     : REFMAC 5.2.0019
REMARK   3   AUTHORS     : MURSHUDOV,VAGIN,DODSON
REMARK   3
REMARK   3    REFINEMENT TARGET : MAXIMUM LIKELIHOOD
REMARK   3
REMARK   3  DATA USED IN REFINEMENT.
REMARK   3   RESOLUTION RANGE HIGH (ANGSTROMS) :   2.30
REMARK   3   RESOLUTION RANGE LOW  (ANGSTROMS) :  30.00
REMARK   3   DATA CUTOFF            (SIGMA(F)) : NONE
REMARK   3   COMPLETENESS FOR RANGE        (%) :  98.43
REMARK   3   NUMBER OF REFLECTIONS             :   11994
REMARK   3
REMARK   3  FIT TO DATA USED IN REFINEMENT.
REMARK   3   CROSS-VALIDATION METHOD          : THROUGHOUT
REMARK   3   FREE R VALUE TEST SET SELECTION  : RANDOM
REMARK   3   R VALUE     (WORKING + TEST SET) : 0.21928
REMARK   3   R VALUE             (WORKING SET) :  0.21637
REMARK   3   FREE R VALUE                      :  0.27541
REMARK   3   FREE R VALUE TEST SET SIZE   (%) :  4.9
REMARK   3   FREE R VALUE TEST SET COUNT      :   619
REMARK   3
REMARK   3  FIT IN THE HIGHEST RESOLUTION BIN.
REMARK   3   TOTAL NUMBER OF BINS USED           :      20
REMARK   3   BIN RESOLUTION RANGE HIGH           :    2.300
REMARK   3   BIN RESOLUTION RANGE LOW            :    2.360
REMARK   3   REFLECTION IN BIN     (WORKING SET) :      794
REMARK   3   BIN COMPLETENESS (WORKING+TEST) (%) :    89.74
REMARK   3   BIN R VALUE           (WORKING SET) :    0.242
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REMARK   3   BIN FREE R VALUE SET COUNT          :       46
REMARK   3   BIN FREE R VALUE                    :    0.342
REMARK   3
REMARK   3  NUMBER OF NON-HYDROGEN ATOMS USED IN REFINEMENT.
REMARK   3   ALL ATOMS                 :     1867
REMARK   3
REMARK   3  B VALUES.
REMARK   3   FROM WILSON PLOT           (A**2) : NULL
REMARK   3   MEAN B VALUE      (OVERALL, A**2) :  43.320
REMARK   3   OVERALL ANISOTROPIC B VALUE.
REMARK   3    B11 (A**2) :    -3.83
REMARK   3    B22 (A**2) :     0.96
REMARK   3    B33 (A**2) :     2.88
REMARK   3    B12 (A**2) :     0.00
REMARK   3    B13 (A**2) :     0.00
REMARK   3    B23 (A**2) :     0.00
REMARK   3
REMARK   3  ESTIMATED OVERALL COORDINATE ERROR.
REMARK   3   ESU BASED ON R VALUE                            (A):   0.327
REMARK   3   ESU BASED ON FREE R VALUE                       (A):   0.256
REMARK   3   ESU BASED ON MAXIMUM LIKELIHOOD                 (A):   0.194
REMARK   3   ESU FOR B VALUES BASED ON MAXIMUM LIKELIHOOD (A**2):  14.024
REMARK   3
REMARK   3 CORRELATION COEFFICIENTS.
REMARK   3   CORRELATION COEFFICIENT FO-FC      :   0.941
REMARK   3   CORRELATION COEFFICIENT FO-FC FREE :   0.898
REMARK   3
REMARK   3  RMS DEVIATIONS FROM IDEAL VALUES        COUNT    RMS    WEIGHT
REMARK   3   BOND LENGTHS REFINED ATOMS         (A):  1845 ; 0.012 ; 0.022
REMARK   3   BOND ANGLES REFINED ATOMS   (DEGREES):  2527 ; 1.482 ; 2.032
REMARK   3   TORSION ANGLES, PERIOD 1    (DEGREES):   209 ; 6.172 ; 5.000
REMARK   3   TORSION ANGLES, PERIOD 2    (DEGREES):    76 ;33.844 ;25.000
REMARK   3   TORSION ANGLES, PERIOD 3    (DEGREES):   295 ;17.124 ;15.000
REMARK   3   TORSION ANGLES, PERIOD 4    (DEGREES):     6 ;20.037 ;15.000
REMARK   3   CHIRAL-CENTER RESTRAINTS       (A**3):   302 ; 0.085 ; 0.200
REMARK   3   GENERAL PLANES REFINED ATOMS       (A):  1323 ; 0.005 ; 0.020
REMARK   3   NON-BONDED CONTACTS REFINED ATOMS  (A):   714 ; 0.202 ; 0.200
REMARK   3   NON-BONDED TORSION REFINED ATOMS   (A):  1211 ; 0.311 ; 0.200
REMARK   3   H-BOND (X...Y) REFINED ATOMS       (A):    85 ; 0.168 ; 0.200
REMARK   3   POTENTIAL METAL-ION REFINED ATOMS  (A):     1 ; 0.013 ; 0.200
REMARK   3   SYMMETRY VDW REFINED ATOMS         (A):    45 ; 0.267 ; 0.200
REMARK   3   SYMMETRY H-BOND REFINED ATOMS      (A):    10 ; 0.166 ; 0.200
REMARK   3
REMARK   3  ISOTROPIC THERMAL FACTOR RESTRAINTS.     COUNT   RMS    WEIGHT
REMARK   3   MAIN-CHAIN BOND REFINED ATOMS  (A**2):  1090 ; 0.502 ; 1.500
REMARK   3   MAIN-CHAIN ANGLE REFINED ATOMS (A**2):  1737 ; 0.773 ; 2.000
REMARK   3   SIDE-CHAIN BOND REFINED ATOMS  (A**2):   850 ; 1.312 ; 3.000
REMARK   3   SIDE-CHAIN ANGLE REFINED ATOMS (A**2):   790 ; 2.117 ; 4.500
REMARK   3
REMARK   3  NCS RESTRAINTS STATISTICS
REMARK   3   NUMBER OF NCS GROUPS : NULL
REMARK   3
REMARK   3
REMARK   3  TLS DETAILS
REMARK   3   NUMBER OF TLS GROUPS  :    5
REMARK   3   ATOM RECORD CONTAINS RESIDUAL B FACTORS ONLY
REMARK   3
REMARK   3   TLS GROUP :     1
```

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REMARK   3    NUMBER OF COMPONENTS GROUP :    1
REMARK   3    COMPONENTS        C SSSEQI   TO  C SSSEQI
REMARK   3    RESIDUE RANGE :   A   236        A   324
REMARK   3    ORIGIN FOR THE GROUP (A):   8.3389  24.1913  -4.5478
REMARK   3    T TENSOR
REMARK   3      T11:   0.0215 T22:   0.0920
REMARK   3      T33:   0.3541 T12:   0.0433
REMARK   3      T13:  -0.0938 T23:  -0.3463
REMARK   3    L TENSOR
REMARK   3      L11:   5.5174 L22:   6.9851
REMARK   3      L33:   1.3110 L12:   0.6985
REMARK   3      L13:  -0.3877 L23:   1.4474
REMARK   3    S TENSOR
REMARK   3      S11:   0.0024 S12:  -0.9714 S13:   1.6061
REMARK   3      S21:   0.4006 S22:   0.0112 S23:  -0.5043
REMARK   3      S31:  -0.2230 S32:  -0.0083 S33:  -0.0136
REMARK   3
REMARK   3   TLS GROUP :     2
REMARK   3    NUMBER OF COMPONENTS GROUP :    1
REMARK   3    COMPONENTS        C SSSEQI   TO  C SSSEQI
REMARK   3    RESIDUE RANGE :   A   325        A   341
REMARK   3    ORIGIN FOR THE GROUP (A):   6.2355  28.7737 -13.4151
REMARK   3    T TENSOR
REMARK   3      T11:   0.4194 T22:   0.0438
REMARK   3      T33:   0.6367 T12:   0.0309
REMARK   3      T13:  -0.1209 T23:  -0.1743
REMARK   3    L TENSOR
REMARK   3      L11:   2.0696 L22:   7.3867
REMARK   3      L33:   3.9900 L12:   0.5828
REMARK   3      L13:  -0.3193 L23:   2.0049
REMARK   3    S TENSOR
REMARK   3      S11:  -0.3128 S12:  -0.3347 S13:   1.6116
REMARK   3      S21:  -0.6048 S22:   0.4400 S23:   0.4114
REMARK   3      S31:  -1.6055 S32:   0.0271 S33:  -0.1271
REMARK   3
REMARK   3   TLS GROUP :     3
REMARK   3    NUMBER OF COMPONENTS GROUP :    1
REMARK   3    COMPONENTS        C SSSEQI   TO  C SSSEQI
REMARK   3    RESIDUE RANGE :   A   342        A   358
REMARK   3    ORIGIN FOR THE GROUP (A):  19.6741  -9.9102 -17.8082
REMARK   3    T TENSOR
REMARK   3      T11:   0.0147 T22:  -0.0558
REMARK   3      T33:   0.2412 T12:   0.0130
REMARK   3      T13:  -0.0465 T23:   0.0419
REMARK   3    L TENSOR
REMARK   3      L11:   5.9397 L22:   3.4770
REMARK   3      L33:   1.3027 L12:  -0.2675
REMARK   3      L13:  -2.7731 L23:   0.2922
REMARK   3    S TENSOR
REMARK   3      S11:   0.1902 S12:   0.1053 S13:  -2.1005
REMARK   3      S21:  -0.2927 S22:  -0.5125 S23:  -0.3505
REMARK   3      S31:   0.2359 S32:  -0.0277 S33:   0.3223
REMARK   3
REMARK   3   TLS GROUP :     4
REMARK   3    NUMBER OF COMPONENTS GROUP :    1
REMARK   3    COMPONENTS        C SSSEQI   TO  C SSSEQI
REMARK   3    RESIDUE RANGE :   A   359        A   403
REMARK   3    ORIGIN FOR THE GROUP (A):  21.2651  -3.5914 -12.2859
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REMARK   3    T TENSOR
REMARK   3      T11:  -0.1689 T22:  -0.0639
REMARK   3      T33:  -0.1638 T12:   0.0043
REMARK   3      T13:   0.0241 T23:   0.0801
REMARK   3    L TENSOR
REMARK   3      L11:  12.4510 L22:   2.7911
REMARK   3      L33:   2.9332 L12:   0.0470
REMARK   3      L13:   0.1119 L23:  -0.2768
REMARK   3    S TENSOR
REMARK   3      S11:  -0.1346 S12:  -1.2217 S13:  -1.1281
REMARK   3      S21:   0.1580 S22:   0.0409 S23:  -0.1830
REMARK   3      S31:   0.0059 S32:   0.2154 S33:   0.0937
REMARK   3
REMARK   3   TLS GROUP :     5
REMARK   3    NUMBER OF COMPONENTS GROUP :    1
REMARK   3    COMPONENTS        C SSSEQI   TO  C SSSEQI
REMARK   3    RESIDUE RANGE :   A   404        A   445
REMARK   3    ORIGIN FOR THE GROUP (A):  19.4718  -9.7512  -9.1313
REMARK   3    T TENSOR
REMARK   3      T11:  -0.0158 T22:   0.1994
REMARK   3      T33:   0.1938 T12:   0.0293
REMARK   3      T13:   0.0582 T23:   0.3819
REMARK   3    L TENSOR
REMARK   3      L11:  13.1107 L22:   0.0678
REMARK   3      L33:   1.6932 L12:   0.9209
REMARK   3      L13:  -1.5605 L23:  -0.0412
REMARK   3    S TENSOR
REMARK   3      S11:  -0.1532 S12:  -2.3239 S13:  -2.6014
REMARK   3      S21:  -0.0410 S22:  -0.1484 S23:  -0.1293
REMARK   3      S31:   0.3788 S32:   0.2592 S33:   0.3017
REMARK   3
REMARK   3
REMARK   3  BULK SOLVENT MODELLING.
REMARK   3   METHOD USED :  MASK
REMARK   3   PARAMETERS FOR MASK CALCULATION
REMARK   3   VDW PROBE RADIUS   :   1.20
REMARK   3   ION PROBE RADIUS   :   0.80
REMARK   3   SHRINKAGE RADIUS   :   0.80
REMARK   3
REMARK   3  OTHER REFINEMENT REMARKS: NULL
REMARK   3
SSBOND   1 CYS A  321    CYS A  261
SSBOND   2 CYS A  425    CYS A  367
LINK         C1  NAG C   1        1.439    ND2 ASN A 297
NAG-ASN
CISPEP   1 TYR A  373    PRO A  374                    0.00
LINK             NAG C   1                     NAG C   2
BETA1-4
LINK             NAG C   2                     BMA C   3
BETA1-4
LINK             BMA C   3                     MAN C   4
ALPHA1-3
LINK             MAN C   4                     NAG C   5
BETA1-2
LINK             BMA C   3                     MAN C   7
ALPHA1-6
LINK             MAN C   7                     NAG C   8
BETA1-2
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LINK             NAG C   8                    GAL C   9
BETA1-4
LINK             NAG C   1                    FUC C  11
ALPHA1-6
MODRES      NAG C    1  NAG-b-D
RENAME
MODRES      NAG C    2  NAG-b-D
RENAME
MODRES      MAN C    4  MAN-a-D
RENAME
MODRES      NAG C    5  NAG-b-D
RENAME
MODRES      MAN C    7  MAN-a-D
RENAME
MODRES      NAG C    8  NAG-b-D
RENAME
MODRES      GAL C    9  GAL-b-D
RENAME
MODRES      FUC C   11  FUC-a-L
RENAME
CRYST1   50.178  147.301   75.473  90.00  90.00  90.00 C 2 2 21
SCALE1      0.019929  0.000000  0.000000        0.00000
SCALE2      0.000000  0.006789  0.000000        0.00000
SCALE3      0.000000  0.000000  0.013250        0.00000
ATOM      1  N   GLY A 236      18.122  39.286 -14.907  1.00 50.67
N
ANISOU    1  N   GLY A 236     6366   6478   6407     30     -8    -27
N
ATOM      2  CA  GLY A 236      17.938  40.336 -13.862  1.00 50.37
C
ANISOU    2  CA  GLY A 236     6370   6447   6319     23     15     16
C
ATOM      3  C   GLY A 236      17.092  39.872 -12.683  1.00 50.35
C
ANISOU    3  C   GLY A 236     6337   6451   6340      0      7     36
C
ATOM      4  O   GLY A 236      17.603  39.755 -11.559  1.00 50.77
O
ANISOU    4  O   GLY A 236     6425   6518   6346    -19    -27     64
O
ATOM      5  N   GLY A 237      15.805  39.607 -12.942  1.00 49.94
N
ANISOU    5  N   GLY A 237     6294   6360   6321     -7     22     32
N
ATOM      6  CA  GLY A 237      14.821  39.264 -11.889  1.00 48.94
C
ANISOU    6  CA  GLY A 237     6194   6188   6211     20     42     32
C
ATOM      7  C   GLY A 237      15.074  37.906 -11.254  1.00 48.37
C
ANISOU    7  C   GLY A 237     6128   6107   6142     17     76      5
C
ATOM      8  O   GLY A 237      16.078  37.256 -11.568  1.00 48.88
O
ANISOU    8  O   GLY A 237     6209   6156   6205     47     90    -11
O
ATOM      9  N   PRO A 238      14.186  37.462 -10.336  1.00 47.63
N
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ANISOU    9  N   PRO A 238     6027   5985   6082     15     57    -17
N
ATOM     10  CA  PRO A 238      14.432  36.144  -9.746  1.00 46.76
C
ANISOU   10  CA  PRO A 238     5926   5876   5964     31     25    -22
C
ATOM     11  CB  PRO A 238      13.327  36.008  -8.686  1.00 46.65
C
ANISOU   11  CB  PRO A 238     5911   5868   5945     11    -23      3
C
ATOM     12  CG  PRO A 238      12.878  37.422  -8.404  1.00 46.85
C
ANISOU   12  CG  PRO A 238     5930   5861   6007     30     38      0
C
ATOM     13  CD  PRO A 238      12.974  38.083  -9.771  1.00 47.56
C
ANISOU   13  CD  PRO A 238     6038   5947   6084     21     63    -44
C
ATOM     14  C   PRO A 238      14.308  35.056 -10.800  1.00 46.45
C
ANISOU   14  C   PRO A 238     5899   5823   5925     31      3    -16
C
ATOM     15  O   PRO A 238      13.803  35.311 -11.898  1.00 46.74
O
ANISOU   15  O   PRO A 238     5942   5884   5930     50    -21    -25
O
ATOM     16  N   SER A 239      14.806  33.868 -10.471  1.00 46.09
N
ANISOU   16  N   SER A 239     5876   5767   5868     24     12    -30
N
ATOM     17  CA  SER A 239      14.710  32.689 -11.333  1.00 45.35
C
ANISOU   17  CA  SER A 239     5783   5670   5778     -8     43     -6
C
ATOM     18  CB  SER A 239      16.093  32.273 -11.833  1.00 45.44
C
ANISOU   18  CB  SER A 239     5822   5669   5773     12     73    -51
C
ATOM     19  OG  SER A 239      16.516  33.126 -12.892  1.00 46.53
O
ANISOU   19  OG  SER A 239     6055   5754   5871     22    122      1
O
ATOM     20  C   SER A 239      14.112  31.580 -10.496  1.00 44.68
C
ANISOU   20  C   SER A 239     5695   5601   5679      8     13      0
C
ATOM     21  O   SER A 239      14.492  31.423  -9.338  1.00 44.81
O
ANISOU   21  O   SER A 239     5689   5655   5681     51     18     72
O
ATOM     22  N   VAL A 240      13.161  30.845 -11.077  1.00 43.99
N
ANISOU   22  N   VAL A 240     5587   5491   5634     -1     45      2
N
ATOM     23  CA  VAL A 240      12.474  29.760 -10.386  1.00 43.00
C
ANISOU   23  CA  VAL A 240     5453   5401   5482     -1     37    -22
C
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ATOM     24  CB  VAL A 240      10.932  29.909 -10.474  1.00 43.13
C
ANISOU   24  CB  VAL A 240     5481   5408   5496      8     59    -20
C
ATOM     25  CG1 VAL A 240      10.217  28.789  -9.696  1.00 42.84
C
ANISOU   25  CG1 VAL A 240     5433   5309   5533     54    -34    -15
C
ATOM     26  CG2 VAL A 240      10.519  31.239  -9.927  1.00 43.46
C
ANISOU   26  CG2 VAL A 240     5572   5367   5572     -2     12      0
C
ATOM     27  C   VAL A 240      12.868  28.427 -10.986  1.00 42.45
C
ANISOU   27  C   VAL A 240     5377   5353   5396    -10     11     -1
C
ATOM     28  O   VAL A 240      12.936  28.272 -12.207  1.00 42.69
O
ANISOU   28  O   VAL A 240     5376   5426   5419    -44     62    -24
O
ATOM     29  N   PHE A 241      13.128  27.468 -10.108  1.00 41.87
N
ANISOU   29  N   PHE A 241     5300   5311   5296    -10      1    -22
N
ATOM     30  CA  PHE A 241      13.405  26.097 -10.498  1.00 40.91
C
ANISOU   30  CA  PHE A 241     5188   5170   5185    -31    -20    -52
C
ATOM     31  CB  PHE A 241      14.884  25.757 -10.294  1.00 41.14
C
ANISOU   31  CB  PHE A 241     5199   5228   5204    -15    -44    -34
C
ATOM     32  CG  PHE A 241      15.799  26.534 -11.203  1.00 41.60
C
ANISOU   32  CG  PHE A 241     5289   5240   5274    -81      3     -5
C
ATOM     33  CD1 PHE A 241      16.448  27.682 -10.744  1.00 41.55
C
ANISOU   33  CD1 PHE A 241     5248   5213   5326    -52      1    -15
C
ATOM     34  CE1 PHE A 241      17.271  28.424 -11.601  1.00 40.85
C
ANISOU   34  CE1 PHE A 241     5052   5159   5308    -21    -14    -18
C
ATOM     35  CZ  PHE A 241      17.448  28.019 -12.917  1.00 40.46
C
ANISOU   35  CZ  PHE A 241     5124   5094   5154    -75     22    -43
C
ATOM     36  CE2 PHE A 241      16.792  26.872 -13.391  1.00 42.17
C
ANISOU   36  CE2 PHE A 241     5259   5419   5342     51     84    -27
C
ATOM     37  CD2 PHE A 241      15.978  26.143 -12.537  1.00 41.34
C
ANISOU   37  CD2 PHE A 241     5253   5148   5303   -103     60    -23
C
ATOM     38  C   PHE A 241      12.493  25.189  -9.716  1.00 40.07
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ANISOU   38  C   PHE A 241     5090   5072   5061    -21    -17    -53
C
ATOM     39  O   PHE A 241      12.175  25.475  -8.572  1.00 40.18
O
ANISOU   39  O   PHE A 241     5110   5045   5111    -37   -101   -113
O
ATOM     40  N   LEU A 242      12.044  24.109 -10.356  1.00 39.75
N
ANISOU   40  N   LEU A 242     5035   5028   5040      6     13    -59
N
ATOM     41  CA  LEU A 242      11.017  23.235  -9.794  1.00 38.92
C
ANISOU   41  CA  LEU A 242     4944   4899   4942      2     21    -61
C
ATOM     42  CB  LEU A 242       9.663  23.546 -10.438  1.00 38.70
C
ANISOU   42  CB  LEU A 242     4941   4864   4898    -18      4    -84
C
ATOM     43  CG  LEU A 242       8.396  22.862  -9.936  1.00 38.46
C
ANISOU   43  CG  LEU A 242     4855   4805   4951     71    -15    -74
C
ATOM     44  CD1 LEU A 242       8.085  23.234  -8.504  1.00 37.91
C
ANISOU   44  CD1 LEU A 242     4727   4827   4849     50    -49    -62
C
ATOM     45  CD2 LEU A 242       7.275  23.271 -10.825  1.00 38.22
C
ANISOU   45  CD2 LEU A 242     4846   4868   4806    137   -149   -134
C
ATOM     46  C   LEU A 242      11.409  21.793 -10.021  1.00 39.20
C
ANISOU   46  C   LEU A 242     4972   4961   4959    -11     13    -31
C
ATOM     47  O   LEU A 242      11.605  21.361 -11.149  1.00 39.40
O
ANISOU   47  O   LEU A 242     5021   4924   5024    -24     63    -55
O
ATOM     48  N   PHE A 243      11.510  21.044  -8.936  1.00 39.65
N
ANISOU   48  N   PHE A 243     4992   5044   5028     12    -12    -43
N
ATOM     49  CA  PHE A 243      12.230  19.792  -8.968  1.00 39.97
C
ANISOU   49  CA  PHE A 243     5044   5044   5099    -24     -2    -51
C
ATOM     50  CB  PHE A 243      13.404  19.823  -7.970  1.00 40.13
C
ANISOU   50  CB  PHE A 243     5022   5064   5162     -8     40    -26
C
ATOM     51  CG  PHE A 243      14.424  20.876  -8.279  1.00 41.34
C
ANISOU   51  CG  PHE A 243     5170   5154   5381    -72      6    -95
C
ATOM     52  CD1 PHE A 243      14.319  22.156  -7.719  1.00 42.25
C
ANISOU   52  CD1 PHE A 243     5360   5249   5441     34    -36    -90
C
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ATOM     53  CE1 PHE A 243      15.269  23.146  -8.016  1.00 41.11
C
ANISOU   53  CE1 PHE A 243     5158   5065   5394    -69     72    -88
C
ATOM     54  CZ  PHE A 243      16.321  22.865  -8.888  1.00 41.69
C
ANISOU   54  CZ  PHE A 243     5217   5205   5418    -88     -1    -97
C
ATOM     55  CE2 PHE A 243      16.435  21.587  -9.458  1.00 42.21
C
ANISOU   55  CE2 PHE A 243     5279   5206   5551    -93    135    -80
C
ATOM     56  CD2 PHE A 243      15.487  20.603  -9.154  1.00 42.21
C
ANISOU   56  CD2 PHE A 243     5308   5220   5508    -31     66   -136
C
ATOM     57  C   PHE A 243      11.275  18.673  -8.648  1.00 40.06
C
ANISOU   57  C   PHE A 243     5009   5104   5107    -37    -10    -64
C
ATOM     58  O   PHE A 243      10.462  18.809  -7.729  1.00 39.94
O
ANISOU   58  O   PHE A 243     4936   5131   5107    -18    -13    -92
O
ATOM     59  N   PRO A 244      11.369  17.561  -9.405  1.00 40.05
N
ANISOU   59  N   PRO A 244     5036   5044   5138    -26     19    -78
N
ATOM     60  CA  PRO A 244      10.474  16.436  -9.204  1.00 39.94
C
ANISOU   60  CA  PRO A 244     5074   5000   5099     -2     16    -66
C
ATOM     61  CB  PRO A 244      10.819  15.510 -10.373  1.00 40.24
C
ANISOU   61  CB  PRO A 244     5091   5057   5139    -22     19    -62
C
ATOM     62  CG  PRO A 244      12.252  15.834 -10.700  1.00 40.53
C
ANISOU   62  CG  PRO A 244     5047   5064   5287    -14    -26    -70
C
ATOM     63  CD  PRO A 244      12.334  17.315 -10.494  1.00 40.31
C
ANISOU   63  CD  PRO A 244     5051   5061   5203    -28    -12    -57
C
ATOM     64  C   PRO A 244      10.810  15.760  -7.881  1.00 39.34
C
ANISOU   64  C   PRO A 244     5004   4929   5012     10    -25    -82
C
ATOM     65  O   PRO A 244      11.848  16.049  -7.315  1.00 39.44
O
ANISOU   65  O   PRO A 244     5071   4916   4996     11    -14   -147
O
ATOM     66  N   PRO A 245       9.943  14.861  -7.397  1.00 38.79
N
ANISOU   66  N   PRO A 245     4967   4861   4907      1    -10    -50
N
ATOM     67  CA  PRO A 245      10.374  14.051  -6.266  1.00 38.61
C
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ANISOU   67  CA  PRO A 245     4913   4858   4895    -18    -64    -80
C
ATOM     68  CB  PRO A 245       9.108  13.286  -5.850  1.00 38.29
C
ANISOU   68  CB  PRO A 245     4913   4765   4870    -17    -31    -43
C
ATOM     69  CG  PRO A 245       7.963  13.883  -6.657  1.00 38.73
C
ANISOU   69  CG  PRO A 245     4943   4859   4914     -8    -25    -82
C
ATOM     70  CD  PRO A 245       8.576  14.533  -7.845  1.00 38.57
C
ANISOU   70  CD  PRO A 245     4919   4821   4912     41    -48    -19
C
ATOM     71  C   PRO A 245      11.490  13.073  -6.621  1.00 38.77
C
ANISOU   71  C   PRO A 245     4914   4890   4926    -38    -52    -39
C
ATOM     72  O   PRO A 245      11.863  12.917  -7.800  1.00 37.94
O
ANISOU   72  O   PRO A 245     4774   4779   4862   -114    -92     -2
O
ATOM     73  N   LYS A 246      12.028  12.430  -5.589  1.00 39.37
N
ANISOU   73  N   LYS A 246     4984   4983   4991    -16    -60    -30
N
ATOM     74  CA  LYS A 246      12.931  11.318  -5.796  1.00 39.82
C
ANISOU   74  CA  LYS A 246     5023   5058   5050     14    -26    -33
C
ATOM     75  CB  LYS A 246      13.669  10.947  -4.509  1.00 40.23
C
ANISOU   75  CB  LYS A 246     5091   5073   5120     18    -39    -40
C
ATOM     76  CG  LYS A 246      14.888  11.842  -4.290  1.00 41.46
C
ANISOU   76  CG  LYS A 246     5178   5330   5245    -27     39      8
C
ATOM     77  CD  LYS A 246      15.623  12.015  -5.627  1.00 45.52
C
ANISOU   77  CD  LYS A 246     5812   5935   5546     66    -16    -88
C
ATOM     78  CE  LYS A 246      16.445  13.285  -5.737  1.00 46.82
C
ANISOU   78  CE  LYS A 246     5686   5640   6463   -111    -80    -47
C
ATOM     79  NZ  LYS A 246      16.762  13.502  -7.165  1.00 46.41
N
ANISOU   79  NZ  LYS A 246     5883   6214   5535     18    173    183
N
ATOM     80  C   LYS A 246      12.159  10.148  -6.374  1.00 39.48
C
ANISOU   80  C   LYS A 246     4992   5034   4975     21    -27    -32
C
ATOM     81  O   LYS A 246      11.088   9.797  -5.861  1.00 39.69
O
ANISOU   81  O   LYS A 246     5028   5127   4923     65    -62   -106
O
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ATOM     82  N   PRO A 247      12.697   9.540  -7.448  1.00 39.18
N
ANISOU   82  N   PRO A 247     4951   5000   4932     33    -13    -12
N
ATOM     83  CA  PRO A 247      12.000   8.478  -8.161  1.00 38.92
C
ANISOU   83  CA  PRO A 247     4924   4959   4905     51    -17    -16
C
ATOM     84  CB  PRO A 247      13.085   7.878  -9.054  1.00 38.79
C
ANISOU   84  CB  PRO A 247     4920   4940   4877     55      8     -7
C
ATOM     85  CG  PRO A 247      14.014   8.985  -9.285  1.00 38.59
C
ANISOU   85  CG  PRO A 247     4889   4914   4858     19     11    -18
C
ATOM     86  CD  PRO A 247      14.021   9.809  -8.040  1.00 39.18
C
ANISOU   86  CD  PRO A 247     4973   4976   4934     18      3     -6
C
ATOM     87  C   PRO A 247      11.450   7.425  -7.230  1.00 38.87
C
ANISOU   87  C   PRO A 247     4936   4933   4896     54      4    -38
C
ATOM     88  O   PRO A 247      10.303   7.039  -7.385  1.00 38.56
O
ANISOU   88  O   PRO A 247     4878   4910   4862     97      6    -34
O
ATOM     89  N   LYS A 248      12.246   6.970  -6.261  1.00 38.99
N
ANISOU   89  N   LYS A 248     4950   4955   4907     43      4    -29
N
ATOM     90  CA  LYS A 248      11.781   5.891  -5.389  1.00 38.78
C
ANISOU   90  CA  LYS A 248     4934   4936   4863     41    -23    -10
C
ATOM     91  CB  LYS A 248      12.937   5.021  -4.850  1.00 39.27
C
ANISOU   91  CB  LYS A 248     5026   4978   4917      7    -18    -25
C
ATOM     92  CG  LYS A 248      13.648   5.482  -3.580  1.00 36.38
C
ANISOU   92  CG  LYS A 248     4760   4251   4810    413   -171    220
C
ATOM     93  CD  LYS A 248      14.700   4.434  -3.086  1.00 40.67
C
ANISOU   93  CD  LYS A 248     5196   5302   4953    -77     72   -121
C
ATOM     94  CE  LYS A 248      14.061   3.085  -2.711  1.00 35.80
C
ANISOU   94  CE  LYS A 248     4447   4475   4680    291   -218    261
C
ATOM     95  NZ  LYS A 248      15.004   2.044  -2.179  1.00 40.36
N
ANISOU   95  NZ  LYS A 248     5159   5539   4635   -366    221   -488
N
ATOM     96  C   LYS A 248      10.799   6.352  -4.312  1.00 38.61
C
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ANISOU   96  C   LYS A 248     4939   4906   4825     14    -19     -2
C
ATOM     97  O   LYS A 248      10.063   5.550  -3.775  1.00 38.84
O
ANISOU   97  O   LYS A 248     5003   4972   4783     16    -22    -36
O
ATOM     98  N   ASP A 249      10.750   7.655  -4.033  1.00 38.44
N
ANISOU   98  N   ASP A 249     4875   4955   4772     44      3    -16
N
ATOM     99  CA  ASP A 249       9.691   8.181  -3.171  1.00 37.92
C
ANISOU   99  CA  ASP A 249     4847   4859   4700     48    -19     22
C
ATOM    100  CB  ASP A 249       9.970   9.633  -2.774  1.00 38.25
C
ANISOU  100  CB  ASP A 249     4896   4868   4767     11      7     17
C
ATOM    101  CG  ASP A 249      10.882   9.741  -1.587  1.00 38.86
C
ANISOU  101  CG  ASP A 249     5031   4871   4860     18     23     22
C
ATOM    102  OD1 ASP A 249      11.024   8.755  -0.860  1.00 41.27
O
ANISOU  102  OD1 ASP A 249     5480   5121   5080    125     28    -54
O
ATOM    103  OD2 ASP A 249      11.457  10.815  -1.352  1.00 41.70
O
ANISOU  103  OD2 ASP A 249     5332   5260   5250    -57    123      4
O
ATOM    104  C   ASP A 249       8.325   8.043  -3.853  1.00 36.93
C
ANISOU  104  C   ASP A 249     4734   4748   4547     24     -9     14
C
ATOM    105  O   ASP A 249       7.300   7.842  -3.198  1.00 36.04
O
ANISOU  105  O   ASP A 249     4654   4626   4413     57    -57     34
O
ATOM    106  N   THR A 250       8.338   8.136  -5.182  1.00 36.24
N
ANISOU  106  N   THR A 250     4619   4672   4477     50    -15     16
N
ATOM    107  CA  THR A 250       7.131   7.982  -5.982  1.00 35.08
C
ANISOU  107  CA  THR A 250     4477   4569   4283      0      2     47
C
ATOM    108  CB  THR A 250       7.233   8.753  -7.345  1.00 35.01
C
ANISOU  108  CB  THR A 250     4440   4538   4324     26      1     31
C
ATOM    109  OG1 THR A 250       7.969   7.992  -8.287  1.00 33.57
O
ANISOU  109  OG1 THR A 250     4192   4584   3978     26    -86    100
O
ATOM    110  CG2 THR A 250       7.901  10.112  -7.157  1.00 34.29
C
ANISOU  110  CG2 THR A 250     4178   4535   4312    -61    -10    167
C
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ATOM    111  C   THR A 250       6.674   6.521  -6.163  1.00 34.51
C
ANISOU  111  C   THR A 250     4501   4473   4136     12     33     -4
C
ATOM    112  O   THR A 250       5.499   6.269  -6.443  1.00 33.70
O
ANISOU  112  O   THR A 250     4487   4349   3968    -15     94    -34
O
ATOM    113  N   LEU A 251       7.570   5.569  -5.940  1.00 34.49
N
ANISOU  113  N   LEU A 251     4464   4483   4158    -14     57    -24
N
ATOM    114  CA  LEU A 251       7.288   4.145  -6.229  1.00 35.46
C
ANISOU  114  CA  LEU A 251     4591   4519   4360    -36     56     39
C
ATOM    115  CB  LEU A 251       8.416   3.552  -7.084  1.00 34.39
C
ANISOU  115  CB  LEU A 251     4522   4286   4258    -37     43     44
C
ATOM    116  CG  LEU A 251       8.640   4.234  -8.448  1.00 32.40
C
ANISOU  116  CG  LEU A 251     4144   4197   3968    -25      0    -41
C
ATOM    117  CD1 LEU A 251       9.950   3.850  -9.025  1.00 31.29
C
ANISOU  117  CD1 LEU A 251     4008   4153   3728     70   -120     25
C
ATOM    118  CD2 LEU A 251       7.538   3.937  -9.435  1.00 30.02
C
ANISOU  118  CD2 LEU A 251     3862   3832   3709    -19    204    164
C
ATOM    119  C   LEU A 251       6.967   3.247  -4.999  1.00 36.71
C
ANISOU  119  C   LEU A 251     4788   4688   4471    -34     12     51
C
ATOM    120  O   LEU A 251       6.530   2.097  -5.126  1.00 36.26
O
ANISOU  120  O   LEU A 251     4757   4604   4414    -55     47    142
O
ATOM    121  N   MET A 252       7.187   3.791  -3.816  1.00 38.60
N
ANISOU  121  N   MET A 252     5026   4943   4698    -27     20     29
N
ATOM    122  CA  MET A 252       6.895   3.102  -2.566  1.00 40.29
C
ANISOU  122  CA  MET A 252     5241   5198   4870      1     -7     44
C
ATOM    123  CB  MET A 252       8.114   3.092  -1.677  1.00 40.45
C
ANISOU  123  CB  MET A 252     5226   5262   4879    -22    -28    -14
C
ATOM    124  CG  MET A 252       9.210   2.179  -2.138  1.00 42.62
C
ANISOU  124  CG  MET A 252     5404   5525   5262     48      6    -36
C
ATOM    125  SD  MET A 252      10.657   2.547  -1.165  1.00 43.78
S
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ANISOU  125  SD  MET A 252     5542   5849   5244     48    -85     63
S
ATOM    126  CE  MET A 252      10.140   1.837   0.396  1.00 45.33
C
ANISOU  126  CE  MET A 252     5743   5827   5653    -34    103    102
C
ATOM    127  C   MET A 252       5.829   3.879  -1.874  1.00 39.26
C
ANISOU  127  C   MET A 252     5153   5083   4681     -6    -19     52
C
ATOM    128  O   MET A 252       6.043   5.040  -1.508  1.00 39.40
O
ANISOU  128  O   MET A 252     5246   5129   4594    -46    -43     54
O
ATOM    129  N   ILE A 253       4.682   3.237  -1.700  1.00 39.08
N
ANISOU  129  N   ILE A 253     5163   5016   4667     12    -39     49
N
ATOM    130  CA  ILE A 253       3.486   3.888  -1.183  1.00 39.29
C
ANISOU  130  CA  ILE A 253     5103   5050   4775     29     12     19
C
ATOM    131  CB  ILE A 253       2.247   3.011  -1.395  1.00 38.95
C
ANISOU  131  CB  ILE A 253     5067   5028   4703     31     24     14
C
ATOM    132  CG1 ILE A 253       0.953   3.823  -1.205  1.00 39.49
C
ANISOU  132  CG1 ILE A 253     5092   5115   4795      9     -6    -38
C
ATOM    133  CD1 ILE A 253      -0.330   3.042  -1.535  1.00 38.97
C
ANISOU  133  CD1 ILE A 253     5004   5047   4756     10     47     50
C
ATOM    134  CG2 ILE A 253       2.320   1.777  -0.515  1.00 39.92
C
ANISOU  134  CG2 ILE A 253     5138   5135   4895     40    -36      1
C
ATOM    135  C   ILE A 253       3.622   4.327   0.280  1.00 39.88
C
ANISOU  135  C   ILE A 253     5183   5139   4829     56     53     44
C
ATOM    136  O   ILE A 253       2.795   5.089   0.776  1.00 40.73
O
ANISOU  136  O   ILE A 253     5278   5260   4936     23     76     42
O
ATOM    137  N   SER A 254       4.683   3.892   0.950  1.00 40.46
N
ANISOU  137  N   SER A 254     5255   5229   4888     63     59     23
N
ATOM    138  CA  SER A 254       4.863   4.181   2.364  1.00 40.63
C
ANISOU  138  CA  SER A 254     5276   5248   4914      9     50     -9
C
ATOM    139  CB  SER A 254       5.567   3.005   3.055  1.00 40.37
C
ANISOU  139  CB  SER A 254     5254   5212   4870     59     53    -23
C
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ATOM    140  OG  SER A 254       6.984   3.119   2.972  1.00 40.90
O
ANISOU  140  OG  SER A 254     5421   5224   4893    -34    108    -21
O
ATOM    141  C   SER A 254       5.628   5.488   2.550  1.00 40.97
C
ANISOU  141  C   SER A 254     5312   5271   4982    -19     76     25
C
ATOM    142  O   SER A 254       5.603   6.114   3.632  1.00 41.28
O
ANISOU  142  O   SER A 254     5346   5328   5007    -41    116     79
O
ATOM    143  N   ARG A 255       6.307   5.897   1.484  1.00 41.20
N
ANISOU  143  N   ARG A 255     5344   5362   4946    -17     73    -22
N
ATOM    144  CA  ARG A 255       7.116   7.128   1.464  1.00 40.77
C
ANISOU  144  CA  ARG A 255     5217   5295   4977    -30     15    -71
C
ATOM    145  CB  ARG A 255       8.312   6.960   0.520  1.00 41.05
C
ANISOU  145  CB  ARG A 255     5254   5318   5025    -26     19    -59
C
ATOM    146  CG  ARG A 255       9.203   5.754   0.873  1.00 41.23
C
ANISOU  146  CG  ARG A 255     5241   5314   5109    -16    -53    -75
C
ATOM    147  CD  ARG A 255      10.479   5.781   0.055  1.00 42.71
C
ANISOU  147  CD  ARG A 255     5282   5481   5463    -20    -70    -52
C
ATOM    148  NE  ARG A 255      11.486   4.874   0.595  1.00 44.95
N
ANISOU  148  NE  ARG A 255     5686   5632   5761    -23     -8      6
N
ATOM    149  CZ  ARG A 255      12.800   5.096   0.570  1.00 44.62
C
ANISOU  149  CZ  ARG A 255     5581   5638   5732    -42    -75     37
C
ATOM    150  NH1 ARG A 255      13.283   6.213   0.045  1.00 44.95
N
ANISOU  150  NH1 ARG A 255     5600   5866   5612   -153   -140     84
N
ATOM    151  NH2 ARG A 255      13.632   4.205   1.093  1.00 45.14
N
ANISOU  151  NH2 ARG A 255     5708   5780   5660      6   -107    -75
N
ATOM    152  C   ARG A 255       6.300   8.371   1.111  1.00 40.62
C
ANISOU  152  C   ARG A 255     5207   5295   4932    -38     26    -78
C
ATOM    153  O   ARG A 255       5.092   8.307   0.939  1.00 41.23
O
ANISOU  153  O   ARG A 255     5213   5455   4994      0     -1   -130
O
ATOM    154  N   THR A 256       6.959   9.512   1.013  1.00 40.48
N
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ANISOU  154  N   THR A 256     5221   5247   4910    -13     43    -73
N
ATOM    155  CA  THR A 256       6.253  10.779   0.949  1.00 40.65
C
ANISOU  155  CA  THR A 256     5233   5241   4969     29     14      6
C
ATOM    156  CB  THR A 256       6.265  11.522   2.350  1.00 40.92
C
ANISOU  156  CB  THR A 256     5291   5223   5035     40     47    -14
C
ATOM    157  OG1 THR A 256       6.218  10.571   3.438  1.00 42.34
O
ANISOU  157  OG1 THR A 256     5543   5436   5106    142     62   -151
O
ATOM    158  CG2 THR A 256       5.082  12.466   2.479  1.00 41.51
C
ANISOU  158  CG2 THR A 256     5386   5196   5190     75     11     15
C
ATOM    159  C   THR A 256       6.931  11.637  -0.116  1.00 40.11
C
ANISOU  159  C   THR A 256     5160   5179   4899      0      8     30
C
ATOM    160  O   THR A 256       7.896  12.347   0.183  1.00 40.28
O
ANISOU  160  O   THR A 256     5245   5223   4835    -24     20    133
O
ATOM    161  N   PRO A 257       6.448  11.568  -1.366  1.00 39.60
N
ANISOU  161  N   PRO A 257     5072   5102   4872    -11      3     -7
N
ATOM    162  CA  PRO A 257       7.093  12.373  -2.402  1.00 39.43
C
ANISOU  162  CA  PRO A 257     5067   5077   4836      1    -29    -23
C
ATOM    163  CB  PRO A 257       6.587  11.750  -3.707  1.00 39.18
C
ANISOU  163  CB  PRO A 257     5053   5055   4778      7     -3    -63
C
ATOM    164  CG  PRO A 257       5.294  11.091  -3.363  1.00 39.06
C
ANISOU  164  CG  PRO A 257     5063   5013   4764    -13     -1    -34
C
ATOM    165  CD  PRO A 257       5.315  10.781  -1.890  1.00 40.06
C
ANISOU  165  CD  PRO A 257     5172   5085   4963     -7     17      5
C
ATOM    166  C   PRO A 257       6.744  13.855  -2.321  1.00 39.42
C
ANISOU  166  C   PRO A 257     5113   5073   4792    -38    -37    -56
C
ATOM    167  O   PRO A 257       5.645  14.229  -1.926  1.00 38.86
O
ANISOU  167  O   PRO A 257     5152   4918   4693    -21    -22    -87
O
ATOM    168  N   GLU A 258       7.692  14.683  -2.730  1.00 40.26
N
ANISOU  168  N   GLU A 258     5231   5155   4908    -57    -80   -131
N
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ATOM    169  CA  GLU A 258       7.562  16.117  -2.647  1.00 40.63
C
ANISOU  169  CA  GLU A 258     5252   5182   5001    -31    -77    -91
C
ATOM    170  CB  GLU A 258       8.386  16.633  -1.456  1.00 41.53
C
ANISOU  170  CB  GLU A 258     5416   5269   5091    -15    -86    -96
C
ATOM    171  CG  GLU A 258       7.818  16.238  -0.078  1.00 44.60
C
ANISOU  171  CG  GLU A 258     5886   5562   5495    -57    188    -51
C
ATOM    172  CD  GLU A 258       8.897  16.116   1.007  1.00 40.88
C
ANISOU  172  CD  GLU A 258     4965   5716   4850   -392    -49    386
C
ATOM    173  OE1 GLU A 258       8.594  15.520   2.079  1.00 48.80
O
ANISOU  173  OE1 GLU A 258     6168   6166   6208     50   -119   -284
O
ATOM    174  OE2 GLU A 258      10.041  16.600   0.785  1.00 46.91
O
ANISOU  174  OE2 GLU A 258     6298   5858   5666     75   -119   -191
O
ATOM    175  C   GLU A 258       8.092  16.753  -3.903  1.00 40.29
C
ANISOU  175  C   GLU A 258     5202   5119   4985    -31    -97   -129
C
ATOM    176  O   GLU A 258       9.072  16.292  -4.477  1.00 40.44
O
ANISOU  176  O   GLU A 258     5293   5116   4956    -54    -98   -185
O
ATOM    177  N   VAL A 259       7.459  17.840  -4.303  1.00 40.01
N
ANISOU  177  N   VAL A 259     5143   5064   4994    -48    -92   -112
N
ATOM    178  CA  VAL A 259       7.948  18.670  -5.392  1.00 40.26
C
ANISOU  178  CA  VAL A 259     5155   5061   5081     18    -77    -86
C
ATOM    179  CB  VAL A 259       6.797  18.967  -6.381  1.00 40.32
C
ANISOU  179  CB  VAL A 259     5194   5086   5040      3    -70    -79
C
ATOM    180  CG1 VAL A 259       7.169  20.031  -7.349  1.00 39.85
C
ANISOU  180  CG1 VAL A 259     5102   5046   4994    -46    -49    -51
C
ATOM    181  CG2 VAL A 259       6.390  17.682  -7.103  1.00 40.01
C
ANISOU  181  CG2 VAL A 259     5111   5024   5065     55    -92   -113
C
ATOM    182  C   VAL A 259       8.529  19.942  -4.761  1.00 40.31
C
ANISOU  182  C   VAL A 259     5146   5030   5137     22    -59     -6
C
ATOM    183  O   VAL A 259       7.939  20.517  -3.840  1.00 39.93
O
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ANISOU  183  O   VAL A 259     5181   4910   5080     30    -43    -21
O
ATOM    184  N   THR A 260       9.704  20.355  -5.211  1.00 40.59
N
ANISOU  184  N   THR A 260     5198   5044   5180     37    -40      1
N
ATOM    185  CA  THR A 260      10.377  21.475  -4.556  1.00 40.90
C
ANISOU  185  CA  THR A 260     5225   5103   5210     17    -22    -52
C
ATOM    186  CB  THR A 260      11.722  21.052  -3.918  1.00 40.60
C
ANISOU  186  CB  THR A 260     5177   5055   5191      5      7    -62
C
ATOM    187  OG1 THR A 260      11.488  19.986  -2.986  1.00 40.40
O
ANISOU  187  OG1 THR A 260     5213   5077   5059     47     26   -208
O
ATOM    188  CG2 THR A 260      12.342  22.196  -3.157  1.00 40.61
C
ANISOU  188  CG2 THR A 260     5192   5102   5132    -11     38     10
C
ATOM    189  C   THR A 260      10.510  22.656  -5.512  1.00 41.22
C
ANISOU  189  C   THR A 260     5246   5148   5267    -11     -3    -54
C
ATOM    190  O   THR A 260      11.068  22.527  -6.598  1.00 41.63
O
ANISOU  190  O   THR A 260     5257   5264   5294     15     23   -122
O
ATOM    191  N   CYS A 261       9.943  23.795  -5.109  1.00 41.33
N
ANISOU  191  N   CYS A 261     5272   5136   5296    -17    -27    -88
N
ATOM    192  CA  CYS A 261      10.029  25.032  -5.889  1.00 41.26
C
ANISOU  192  CA  CYS A 261     5292   5146   5237    -26    -50    -63
C
ATOM    193  CB  CYS A 261       8.691  25.769  -5.894  1.00 40.72
C
ANISOU  193  CB  CYS A 261     5249   5103   5116     -4    -33    -99
C
ATOM    194  SG  CYS A 261       8.495  27.040  -7.213  1.00 41.29
S
ANISOU  194  SG  CYS A 261     5307   4989   5391    -25    -29   -151
S
ATOM    195  C   CYS A 261      11.104  25.928  -5.292  1.00 41.60
C
ANISOU  195  C   CYS A 261     5340   5207   5259    -19    -18    -67
C
ATOM    196  O   CYS A 261      11.014  26.324  -4.133  1.00 42.19
O
ANISOU  196  O   CYS A 261     5452   5297   5280    -24    -69    -78
O
ATOM    197  N   VAL A 262      12.121  26.234  -6.084  1.00 41.65
N
ANISOU  197  N   VAL A 262     5287   5236   5301    -27      5    -70
N
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ATOM    198  CA  VAL A 262      13.192  27.102  -5.645  1.00 41.52
C
ANISOU  198  CA  VAL A 262     5296   5172   5305    -10     -8    -79
C
ATOM    199  CB  VAL A 262      14.566  26.403  -5.736  1.00 41.57
C
ANISOU  199  CB  VAL A 262     5266   5213   5312     -4    -11    -73
C
ATOM    200  CG1 VAL A 262      15.703  27.418  -5.531  1.00 41.51
C
ANISOU  200  CG1 VAL A 262     5318   5058   5393     16     35   -129
C
ATOM    201  CG2 VAL A 262      14.667  25.238  -4.732  1.00 40.60
C
ANISOU  201  CG2 VAL A 262     5239   5053   5131    -58    -15   -107
C
ATOM    202  C   VAL A 262      13.230  28.375  -6.493  1.00 41.97
C
ANISOU  202  C   VAL A 262     5353   5249   5344     -6      1    -62
C
ATOM    203  O   VAL A 262      13.277  28.308  -7.744  1.00 41.34
O
ANISOU  203  O   VAL A 262     5297   5185   5225      3     27   -162
O
ATOM    204  N   VAL A 263      13.200  29.523  -5.795  1.00 41.79
N
ANISOU  204  N   VAL A 263     5323   5198   5357     -8     26    -81
N
ATOM    205  CA  VAL A 263      13.450  30.829  -6.399  1.00 41.87
C
ANISOU  205  CA  VAL A 263     5331   5210   5365     13     -1    -48
C
ATOM    206  CB  VAL A 263      12.381  31.882  -6.011  1.00 42.15
C
ANISOU  206  CB  VAL A 263     5365   5244   5407    -13    -13    -29
C
ATOM    207  CG1 VAL A 263      12.197  32.897  -7.151  1.00 41.64
C
ANISOU  207  CG1 VAL A 263     5414   5099   5308     -3    -61    -36
C
ATOM    208  CG2 VAL A 263      11.070  31.217  -5.688  1.00 41.69
C
ANISOU  208  CG2 VAL A 263     5219   5254   5366     28     11      9
C
ATOM    209  C   VAL A 263      14.825  31.331  -5.954  1.00 42.07
C
ANISOU  209  C   VAL A 263     5367   5246   5371    -13     24    -47
C
ATOM    210  O   VAL A 263      15.194  31.243  -4.773  1.00 42.24
O
ANISOU  210  O   VAL A 263     5419   5263   5365     -9     12    -77
O
ATOM    211  N   VAL A 264      15.594  31.819  -6.915  1.00 42.34
N
ANISOU  211  N   VAL A 264     5407   5261   5417    -40     15    -20
N
ATOM    212  CA  VAL A 264      16.912  32.371  -6.640  1.00 42.34
C
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ANISOU  212  CA  VAL A 264     5355   5321   5408    -44    -15      0
C
ATOM    213  CB  VAL A 264      18.086  31.458  -7.123  1.00 42.32
C
ANISOU  213  CB  VAL A 264     5369   5281   5427    -74    -22      5
C
ATOM    214  CG1 VAL A 264      18.307  30.333  -6.151  1.00 42.89
C
ANISOU  214  CG1 VAL A 264     5398   5442   5455     11    -96     65
C
ATOM    215  CG2 VAL A 264      17.862  30.926  -8.536  1.00 42.03
C
ANISOU  215  CG2 VAL A 264     5346   5351   5270    -55     -7     25
C
ATOM    216  C   VAL A 264      17.003  33.756  -7.271  1.00 42.94
C
ANISOU  216  C   VAL A 264     5419   5400   5493    -38    -13     22
C
ATOM    217  O   VAL A 264      16.131  34.135  -8.077  1.00 43.29
O
ANISOU  217  O   VAL A 264     5396   5527   5525    -14    -27     41
O
ATOM    218  N   ASP A 265      18.057  34.500  -6.918  1.00 42.97
N
ANISOU  218  N   ASP A 265     5466   5374   5487    -58    -15     -6
N
ATOM    219  CA  ASP A 265      18.204  35.890  -7.353  1.00 43.20
C
ANISOU  219  CA  ASP A 265     5502   5401   5511    -43     11      9
C
ATOM    220  CB  ASP A 265      18.142  36.018  -8.889  1.00 43.15
C
ANISOU  220  CB  ASP A 265     5545   5394   5456    -50    -12    -19
C
ATOM    221  CG  ASP A 265      19.371  35.453  -9.579  1.00 44.92
C
ANISOU  221  CG  ASP A 265     5679   5711   5678    -48     12     -4
C
ATOM    222  OD1 ASP A 265      19.303  35.191 -10.803  1.00 46.63
O
ANISOU  222  OD1 ASP A 265     5857   6021   5836   -140    -10    -71
O
ATOM    223  OD2 ASP A 265      20.411  35.263  -8.906  1.00 47.21
O
ANISOU  223  OD2 ASP A 265     5935   5986   6016   -141    -96    -22
O
ATOM    224  C   ASP A 265      17.117  36.728  -6.695  1.00 43.08
C
ANISOU  224  C   ASP A 265     5496   5395   5475    -37     49     -4
C
ATOM    225  O   ASP A 265      16.547  37.636  -7.313  1.00 43.22
O
ANISOU  225  O   ASP A 265     5505   5422   5495    -37    102     40
O
ATOM    226  N   VAL A 266      16.787  36.397  -5.449  1.00 43.36
N
ANISOU  226  N   VAL A 266     5544   5410   5520    -42      9    -52
N
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ATOM    227  CA  VAL A 266      15.823  37.227  -4.722  1.00 43.59
C
ANISOU  227  CA  VAL A 266     5576   5445   5541    -38     -7    -62
C
ATOM    228  CB  VAL A 266      15.117  36.476  -3.564  1.00 43.62
C
ANISOU  228  CB  VAL A 266     5567   5440   5564    -36    -10    -65
C
ATOM    229  CG1 VAL A 266      14.260  37.426  -2.730  1.00 43.27
C
ANISOU  229  CG1 VAL A 266     5518   5469   5453    -20    -46   -125
C
ATOM    230  CG2 VAL A 266      14.253  35.309  -4.109  1.00 43.36
C
ANISOU  230  CG2 VAL A 266     5463   5462   5547     25    -14    -83
C
ATOM    231  C   VAL A 266      16.653  38.421  -4.250  1.00 43.81
C
ANISOU  231  C   VAL A 266     5612   5461   5572    -40    -47    -75
C
ATOM    232  O   VAL A 266      17.678  38.243  -3.606  1.00 44.05
O
ANISOU  232  O   VAL A 266     5645   5485   5605    -62    -80    -95
O
ATOM    233  N   SER A 267      16.252  39.625  -4.629  1.00 44.16
N
ANISOU  233  N   SER A 267     5674   5467   5637    -42    -51    -55
N
ATOM    234  CA  SER A 267      17.044  40.809  -4.291  1.00 44.92
C
ANISOU  234  CA  SER A 267     5742   5605   5720    -26    -25    -27
C
ATOM    235  CB  SER A 267      16.574  42.015  -5.098  1.00 44.80
C
ANISOU  235  CB  SER A 267     5731   5551   5737    -24    -13     -6
C
ATOM    236  OG  SER A 267      15.463  42.605  -4.458  1.00 44.95
O
ANISOU  236  OG  SER A 267     5676   5584   5816      9      4    -13
O
ATOM    237  C   SER A 267      16.978  41.119  -2.789  1.00 45.15
C
ANISOU  237  C   SER A 267     5807   5630   5718    -32     -6    -55
C
ATOM    238  O   SER A 267      16.586  40.278  -1.978  1.00 45.49
O
ANISOU  238  O   SER A 267     5828   5712   5744    -51      7    -60
O
ATOM    239  N   HIS A 268      17.366  42.333  -2.428  1.00 45.94
N
ANISOU  239  N   HIS A 268     5897   5755   5801    -37     -7    -42
N
ATOM    240  CA  HIS A 268      17.252  42.793  -1.044  1.00 46.15
C
ANISOU  240  CA  HIS A 268     5932   5783   5817    -26    -11    -31
C
ATOM    241  CB  HIS A 268      18.614  43.221  -0.546  1.00 46.45
C
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ANISOU  241  CB  HIS A 268     5950   5843   5855    -51    -45    -21
C
ATOM    242  CG  HIS A 268      19.575  42.093  -0.372  1.00 47.75
C
ANISOU  242  CG  HIS A 268     6131   5941   6069     30    -23    -45
C
ATOM    243  ND1 HIS A 268      19.941  41.617   0.869  1.00 49.83
N
ANISOU  243  ND1 HIS A 268     6445   6227   6259    116      7     -9
N
ATOM    244  CE1 HIS A 268      20.804  40.628   0.722  1.00 49.57
C
ANISOU  244  CE1 HIS A 268     6470   6345   6018     34     60    -31
C
ATOM    245  NE2 HIS A 268      21.011  40.445  -0.570  1.00 49.91
N
ANISOU  245  NE2 HIS A 268     6326   6330   6306     20    -64      2
N
ATOM    246  CD2 HIS A 268      20.257  41.354  -1.276  1.00 48.94
C
ANISOU  246  CD2 HIS A 268     6300   6208   6085     12      8    -40
C
ATOM    247  C   HIS A 268      16.270  43.953  -0.932  1.00 46.31
C
ANISOU  247  C   HIS A 268     5952   5787   5855    -19      8    -26
C
ATOM    248  O   HIS A 268      15.635  44.151   0.120  1.00 46.57
O
ANISOU  248  O   HIS A 268     6023   5813   5856    -91      5    -43
O
ATOM    249  N   GLU A 269      16.140  44.701  -2.032  1.00 46.57
N
ANISOU  249  N   GLU A 269     5987   5794   5912      0     24     16
N
ATOM    250  CA  GLU A 269      15.251  45.875  -2.109  1.00 46.95
C
ANISOU  250  CA  GLU A 269     5979   5849   6010      4     29    -27
C
ATOM    251  CB  GLU A 269      15.603  46.754  -3.323  1.00 46.62
C
ANISOU  251  CB  GLU A 269     5977   5776   5960     -3     18     -3
C
ATOM    252  CG  GLU A 269      17.070  46.679  -3.764  1.00 47.69
C
ANISOU  252  CG  GLU A 269     5996   5921   6202    -64     33     27
C
ATOM    253  CD  GLU A 269      17.958  47.749  -3.127  1.00 50.37
C
ANISOU  253  CD  GLU A 269     6386   6291   6460    -14    -39    -64
C
ATOM    254  OE1 GLU A 269      17.419  48.766  -2.634  1.00 49.63
O
ANISOU  254  OE1 GLU A 269     6277   6189   6390     40     -9   -219
O
ATOM    255  OE2 GLU A 269      19.208  47.585  -3.161  1.00 51.70
O
ANISOU  255  OE2 GLU A 269     6319   6463   6858     16   -192     20
O
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ATOM    256  C   GLU A 269      13.797  45.428  -2.211  1.00 47.24
C
ANISOU  256  C   GLU A 269     6001   5892   6054      2     38    -55
C
ATOM    257  O   GLU A 269      12.901  46.013  -1.583  1.00 48.33
O
ANISOU  257  O   GLU A 269     6161   6020   6182     27     66    -84
O
ATOM    258  N   ASP A 270      13.572  44.392  -3.019  1.00 47.26
N
ANISOU  258  N   ASP A 270     6029   5892   6034     10     36    -52
N
ATOM    259  CA  ASP A 270      12.251  43.806  -3.226  1.00 46.94
C
ANISOU  259  CA  ASP A 270     5979   5862   5992     11     11    -19
C
ATOM    260  CB  ASP A 270      11.817  44.010  -4.678  1.00 47.64
C
ANISOU  260  CB  ASP A 270     6125   5924   6052    -10      2    -55
C
ATOM    261  CG  ASP A 270      12.011  45.446  -5.149  1.00 49.53
C
ANISOU  261  CG  ASP A 270     6428   6106   6283      5     83     46
C
ATOM    262  OD1 ASP A 270      11.562  46.383  -4.426  1.00 50.58
O
ANISOU  262  OD1 ASP A 270     6655   6105   6455     75    138    -47
O
ATOM    263  OD2 ASP A 270      12.620  45.632  -6.232  1.00 50.17
O
ANISOU  263  OD2 ASP A 270     6461   6333   6269     47    198   -153
O
ATOM    264  C   ASP A 270      12.379  42.331  -2.925  1.00 46.46
C
ANISOU  264  C   ASP A 270     5904   5821   5928      4      5    -41
C
ATOM    265  O   ASP A 270      12.490  41.528  -3.852  1.00 46.73
O
ANISOU  265  O   ASP A 270     5861   5902   5992     73     80     -3
O
ATOM    266  N   PRO A 271      12.383  41.970  -1.628  1.00 46.30
N
ANISOU  266  N   PRO A 271     5872   5815   5902     19      9    -39
N
ATOM    267  CA  PRO A 271      12.735  40.625  -1.182  1.00 46.38
C
ANISOU  267  CA  PRO A 271     5878   5802   5940      8      8    -53
C
ATOM    268  CB  PRO A 271      13.321  40.873   0.207  1.00 46.74
C
ANISOU  268  CB  PRO A 271     5927   5842   5990      0     20    -18
C
ATOM    269  CG  PRO A 271      12.532  42.082   0.732  1.00 46.35
C
ANISOU  269  CG  PRO A 271     5868   5817   5922     37    -13    -51
C
ATOM    270  CD  PRO A 271      12.074  42.863  -0.487  1.00 46.34
C
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ANISOU  270  CD  PRO A 271     5887   5812   5907     47     16    -33
C
ATOM    271  C   PRO A 271      11.567  39.661  -1.064  1.00 46.91
C
ANISOU  271  C   PRO A 271     5915   5843   6064     16     18    -55
C
ATOM    272  O   PRO A 271      11.751  38.464  -1.297  1.00 47.80
O
ANISOU  272  O   PRO A 271     5999   5932   6231     72     10    -41
O
ATOM    273  N   GLU A 272      10.385  40.161  -0.703  1.00 47.03
N
ANISOU  273  N   GLU A 272     5924   5834   6111     10      9    -81
N
ATOM    274  CA  GLU A 272       9.255  39.289  -0.375  1.00 46.90
C
ANISOU  274  CA  GLU A 272     5899   5861   6056    -31      2    -69
C
ATOM    275  CB  GLU A 272       8.199  40.002   0.480  1.00 47.05
C
ANISOU  275  CB  GLU A 272     5905   5909   6061    -29     -1    -57
C
ATOM    276  CG  GLU A 272       8.736  40.972   1.528  1.00 48.65
C
ANISOU  276  CG  GLU A 272     6104   6206   6174    -35    -24    -64
C
ATOM    277  CD  GLU A 272       9.674  40.329   2.566  1.00 50.71
C
ANISOU  277  CD  GLU A 272     6405   6393   6466     10    -66     39
C
ATOM    278  OE1 GLU A 272       9.577  39.104   2.812  1.00 51.33
O
ANISOU  278  OE1 GLU A 272     6528   6257   6717    -21     33    -12
O
ATOM    279  OE2 GLU A 272      10.509  41.074   3.139  1.00 50.98
O
ANISOU  279  OE2 GLU A 272     6448   6560   6361    -33   -177    -55
O
ATOM    280  C   GLU A 272       8.631  38.686  -1.633  1.00 46.54
C
ANISOU  280  C   GLU A 272     5881   5811   5989    -31    -30    -51
C
ATOM    281  O   GLU A 272       8.366  39.380  -2.630  1.00 47.00
O
ANISOU  281  O   GLU A 272     5929   5827   6100    -69    -26    -34
O
ATOM    282  N   VAL A 273       8.434  37.372  -1.573  1.00 45.97
N
ANISOU  282  N   VAL A 273     5822   5768   5875    -28    -35    -72
N
ATOM    283  CA  VAL A 273       7.935  36.586  -2.697  1.00 45.26
C
ANISOU  283  CA  VAL A 273     5738   5675   5781    -15     -4    -87
C
ATOM    284  CB  VAL A 273       9.042  35.675  -3.296  1.00 45.49
C
ANISOU  284  CB  VAL A 273     5723   5777   5781    -37      9   -110
C
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ATOM    285  CG1 VAL A 273       8.629  35.110  -4.669  1.00 45.42
C
ANISOU  285  CG1 VAL A 273     5681   5791   5783    -59      0    -59
C
ATOM    286  CG2 VAL A 273      10.363  36.439  -3.429  1.00 45.73
C
ANISOU  286  CG2 VAL A 273     5844   5761   5769   -107      2    -86
C
ATOM    287  C   VAL A 273       6.749  35.756  -2.202  1.00 44.66
C
ANISOU  287  C   VAL A 273     5681   5592   5694      0      3   -104
C
ATOM    288  O   VAL A 273       6.687  35.353  -1.029  1.00 44.72
O
ANISOU  288  O   VAL A 273     5778   5509   5704     26     36   -129
O
ATOM    289  N   LYS A 274       5.811  35.522  -3.108  1.00 43.97
N
ANISOU  289  N   LYS A 274     5556   5534   5616     10     13   -109
N
ATOM    290  CA  LYS A 274       4.568  34.833  -2.807  1.00 43.21
C
ANISOU  290  CA  LYS A 274     5485   5435   5495     -5     21    -75
C
ATOM    291  CB  LYS A 274       3.407  35.759  -3.179  1.00 42.77
C
ANISOU  291  CB  LYS A 274     5436   5394   5419      0    -19   -102
C
ATOM    292  CG  LYS A 274       2.050  35.407  -2.597  1.00 41.82
C
ANISOU  292  CG  LYS A 274     5335   5189   5365    -22    -50   -111
C
ATOM    293  CD  LYS A 274       0.997  36.393  -3.092  1.00 42.08
C
ANISOU  293  CD  LYS A 274     5342   5275   5370    -13     -1    -45
C
ATOM    294  CE  LYS A 274       0.899  36.385  -4.614  1.00 44.59
C
ANISOU  294  CE  LYS A 274     5681   5789   5470   -483    152   -326
C
ATOM    295  NZ  LYS A 274      -0.045  37.398  -5.185  1.00 40.06
N
ANISOU  295  NZ  LYS A 274     5019   4610   5590    369   -248     81
N
ATOM    296  C   LYS A 274       4.498  33.570  -3.651  1.00 43.36
C
ANISOU  296  C   LYS A 274     5514   5454   5504     -3     30    -52
C
ATOM    297  O   LYS A 274       4.678  33.627  -4.873  1.00 43.92
O
ANISOU  297  O   LYS A 274     5587   5567   5534     35     17    -66
O
ATOM    298  N   PHE A 275       4.229  32.431  -3.024  1.00 43.43
N
ANISOU  298  N   PHE A 275     5510   5465   5523     17      5    -41
N
ATOM    299  CA  PHE A 275       4.007  31.206  -3.803  1.00 43.22
C
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ANISOU  299  CA  PHE A 275     5474   5466   5480      9      9    -42
C
ATOM    300  CB  PHE A 275       4.673  30.013  -3.158  1.00 43.00
C
ANISOU  300  CB  PHE A 275     5486   5398   5452      2     15    -33
C
ATOM    301  CG  PHE A 275       6.166  30.040  -3.246  1.00 43.42
C
ANISOU  301  CG  PHE A 275     5474   5474   5547     30     -1    -25
C
ATOM    302  CD1 PHE A 275       6.929  30.554  -2.193  1.00 42.75
C
ANISOU  302  CD1 PHE A 275     5315   5360   5568      9    -25    -65
C
ATOM    303  CE1 PHE A 275       8.322  30.570  -2.263  1.00 42.60
C
ANISOU  303  CE1 PHE A 275     5337   5322   5527    -92    -56     14
C
ATOM    304  CZ  PHE A 275       8.962  30.062  -3.392  1.00 42.99
C
ANISOU  304  CZ  PHE A 275     5390   5492   5450    -41    -24    -57
C
ATOM    305  CE2 PHE A 275       8.208  29.543  -4.459  1.00 43.86
C
ANISOU  305  CE2 PHE A 275     5445   5657   5560    -71     26    -48
C
ATOM    306  CD2 PHE A 275       6.818  29.538  -4.379  1.00 43.43
C
ANISOU  306  CD2 PHE A 275     5481   5591   5428      9    -44      3
C
ATOM    307  C   PHE A 275       2.544  30.902  -4.001  1.00 43.40
C
ANISOU  307  C   PHE A 275     5526   5484   5479    -33     19    -47
C
ATOM    308  O   PHE A 275       1.750  30.906  -3.046  1.00 44.16
O
ANISOU  308  O   PHE A 275     5666   5605   5505    -26     30    -41
O
ATOM    309  N   ASN A 276       2.177  30.660  -5.252  1.00 43.24
N
ANISOU  309  N   ASN A 276     5500   5462   5466    -18     42    -22
N
ATOM    310  CA  ASN A 276       0.890  30.052  -5.539  1.00 43.32
C
ANISOU  310  CA  ASN A 276     5497   5427   5532     -7     31    -42
C
ATOM    311  CB  ASN A 276       0.089  30.864  -6.573  1.00 42.83
C
ANISOU  311  CB  ASN A 276     5423   5396   5453     32     70     -1
C
ATOM    312  CG  ASN A 276      -0.109  32.337  -6.171  1.00 43.44
C
ANISOU  312  CG  ASN A 276     5519   5499   5487      9      9    -16
C
ATOM    313  OD1 ASN A 276      -0.722  33.112  -6.918  1.00 44.20
O
ANISOU  313  OD1 ASN A 276     5682   5657   5455    -11     91     56
O
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ATOM    314  ND2 ASN A 276       0.392  32.724  -4.997  1.00 44.64
N
ANISOU  314  ND2 ASN A 276     5694   5621   5644     84    -43     23
N
ATOM    315  C   ASN A 276       1.193  28.629  -6.021  1.00 43.23
C
ANISOU  315  C   ASN A 276     5471   5387   5567     12     67    -36
C
ATOM    316  O   ASN A 276       2.271  28.381  -6.566  1.00 43.45
O
ANISOU  316  O   ASN A 276     5468   5431   5610     15     74    -38
O
ATOM    317  N   TRP A 277       0.261  27.703  -5.780  1.00 43.29
N
ANISOU  317  N   TRP A 277     5473   5373   5600     17     43    -43
N
ATOM    318  CA  TRP A 277       0.403  26.290  -6.173  1.00 42.95
C
ANISOU  318  CA  TRP A 277     5415   5377   5523     -6      0   -103
C
ATOM    319  CB  TRP A 277       0.758  25.397  -4.985  1.00 42.16
C
ANISOU  319  CB  TRP A 277     5263   5304   5451     28     -4    -65
C
ATOM    320  CG  TRP A 277       2.183  25.417  -4.469  1.00 42.99
C
ANISOU  320  CG  TRP A 277     5406   5401   5527      5     23    -87
C
ATOM    321  CD1 TRP A 277       2.657  26.129  -3.398  1.00 42.90
C
ANISOU  321  CD1 TRP A 277     5338   5415   5547     10    -15   -143
C
ATOM    322  NE1 TRP A 277       3.990  25.862  -3.194  1.00 43.36
N
ANISOU  322  NE1 TRP A 277     5319   5500   5653    -54    -62    -48
N
ATOM    323  CE2 TRP A 277       4.405  24.949  -4.125  1.00 42.25
C
ANISOU  323  CE2 TRP A 277     5236   5343   5471     68     39   -134
C
ATOM    324  CD2 TRP A 277       3.289  24.634  -4.943  1.00 42.84
C
ANISOU  324  CD2 TRP A 277     5364   5403   5509     30     27    -96
C
ATOM    325  CE3 TRP A 277       3.455  23.715  -5.991  1.00 43.02
C
ANISOU  325  CE3 TRP A 277     5359   5403   5582     49    -27   -100
C
ATOM    326  CZ3 TRP A 277       4.717  23.141  -6.186  1.00 42.65
C
ANISOU  326  CZ3 TRP A 277     5369   5373   5462    -37    -12   -164
C
ATOM    327  CH2 TRP A 277       5.801  23.471  -5.354  1.00 42.95
C
ANISOU  327  CH2 TRP A 277     5324   5462   5533      8    -25    -87
C
ATOM    328  CZ2 TRP A 277       5.668  24.376  -4.322  1.00 43.40
C
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ANISOU  328  CZ2 TRP A 277     5423   5476   5590    -13     -3    -46
C
ATOM    329  C   TRP A 277      -0.922  25.793  -6.720  1.00 42.96
C
ANISOU  329  C   TRP A 277     5381   5417   5524      9      0   -104
C
ATOM    330  O   TRP A 277      -1.978  26.129  -6.192  1.00 43.23
O
ANISOU  330  O   TRP A 277     5408   5439   5576    -15    -28   -119
O
ATOM    331  N   TYR A 278      -0.842  24.965  -7.754  1.00 42.84
N
ANISOU  331  N   TYR A 278     5366   5431   5478     38    -13   -101
N
ATOM    332  CA  TYR A 278      -1.988  24.432  -8.471  1.00 42.52
C
ANISOU  332  CA  TYR A 278     5338   5365   5451     19    -12    -52
C
ATOM    333  CB  TYR A 278      -2.247  25.265  -9.746  1.00 43.43
C
ANISOU  333  CB  TYR A 278     5419   5517   5565      0    -11    -30
C
ATOM    334  CG  TYR A 278      -2.307  26.769  -9.500  1.00 44.08
C
ANISOU  334  CG  TYR A 278     5578   5473   5695      8     54      0
C
ATOM    335  CD1 TYR A 278      -1.140  27.535  -9.452  1.00 43.87
C
ANISOU  335  CD1 TYR A 278     5454   5517   5694     19     -5    -65
C
ATOM    336  CE1 TYR A 278      -1.177  28.900  -9.228  1.00 44.77
C
ANISOU  336  CE1 TYR A 278     5712   5565   5732      0    -41    -53
C
ATOM    337  CZ  TYR A 278      -2.395  29.528  -9.019  1.00 44.46
C
ANISOU  337  CZ  TYR A 278     5561   5435   5893      3     -8    -83
C
ATOM    338  OH  TYR A 278      -2.429  30.889  -8.788  1.00 45.34
O
ANISOU  338  OH  TYR A 278     5756   5539   5929     47     81     -4
O
ATOM    339  CE2 TYR A 278      -3.575  28.797  -9.047  1.00 46.00
C
ANISOU  339  CE2 TYR A 278     5736   5868   5872      2      3     28
C
ATOM    340  CD2 TYR A 278      -3.525  27.416  -9.291  1.00 44.42
C
ANISOU  340  CD2 TYR A 278     5603   5446   5827     91     -7     -3
C
ATOM    341  C   TYR A 278      -1.705  22.978  -8.845  1.00 42.48
C
ANISOU  341  C   TYR A 278     5350   5371   5416     -2    -44    -14
C
ATOM    342  O   TYR A 278      -0.649  22.659  -9.386  1.00 42.02
O
ANISOU  342  O   TYR A 278     5346   5257   5361     43    -47    -56
O
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ATOM    343  N   VAL A 279      -2.658  22.100  -8.551  1.00 42.92
N
ANISOU  343  N   VAL A 279     5472   5419   5416     -5    -44     20
N
ATOM    344  CA  VAL A 279      -2.610  20.701  -8.983  1.00 42.90
C
ANISOU  344  CA  VAL A 279     5447   5421   5431     20    -27     -3
C
ATOM    345  CB  VAL A 279      -2.902  19.744  -7.795  1.00 42.52
C
ANISOU  345  CB  VAL A 279     5413   5380   5362     33    -38     -9
C
ATOM    346  CG1 VAL A 279      -2.993  18.320  -8.244  1.00 41.55
C
ANISOU  346  CG1 VAL A 279     5177   5298   5311     13    -94     26
C
ATOM    347  CG2 VAL A 279      -1.824  19.896  -6.731  1.00 42.94
C
ANISOU  347  CG2 VAL A 279     5406   5427   5483     79      6     17
C
ATOM    348  C   VAL A 279      -3.633  20.546 -10.115  1.00 43.47
C
ANISOU  348  C   VAL A 279     5510   5501   5503     -5    -32    -11
C
ATOM    349  O   VAL A 279      -4.840  20.532  -9.876  1.00 43.83
O
ANISOU  349  O   VAL A 279     5537   5526   5589    -14    -44    -13
O
ATOM    350  N   ASP A 280      -3.133  20.472 -11.348  1.00 43.97
N
ANISOU  350  N   ASP A 280     5575   5537   5591     11    -28    -30
N
ATOM    351  CA  ASP A 280      -3.963  20.499 -12.557  1.00 44.09
C
ANISOU  351  CA  ASP A 280     5575   5525   5649      5    -64    -42
C
ATOM    352  CB  ASP A 280      -4.869  19.252 -12.634  1.00 44.22
C
ANISOU  352  CB  ASP A 280     5608   5545   5645     17    -30      9
C
ATOM    353  CG  ASP A 280      -4.151  18.026 -13.197  1.00 43.82
C
ANISOU  353  CG  ASP A 280     5606   5434   5609    -22    -32    -26
C
ATOM    354  OD1 ASP A 280      -3.283  18.156 -14.086  1.00 43.76
O
ANISOU  354  OD1 ASP A 280     5538   5390   5698    -27     32   -141
O
ATOM    355  OD2 ASP A 280      -4.474  16.915 -12.756  1.00 43.89
O
ANISOU  355  OD2 ASP A 280     5597   5469   5609     -7      1     -1
O
ATOM    356  C   ASP A 280      -4.786  21.799 -12.756  1.00 44.61
C
ANISOU  356  C   ASP A 280     5619   5577   5751     16    -59    -63
C
ATOM    357  O   ASP A 280      -5.887  21.761 -13.314  1.00 45.34
O
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ANISOU  357  O   ASP A 280     5661   5665   5897     54    -94    -85
O
ATOM    358  N   GLY A 281      -4.254  22.941 -12.318  1.00 44.62
N
ANISOU  358  N   GLY A 281     5615   5564   5774      9    -33    -63
N
ATOM    359  CA  GLY A 281      -4.920  24.239 -12.522  1.00 43.93
C
ANISOU  359  CA  GLY A 281     5546   5506   5639     43    -15     -9
C
ATOM    360  C   GLY A 281      -5.889  24.672 -11.425  1.00 44.05
C
ANISOU  360  C   GLY A 281     5544   5513   5679     30    -12      3
C
ATOM    361  O   GLY A 281      -6.548  25.727 -11.535  1.00 44.55
O
ANISOU  361  O   GLY A 281     5577   5596   5754     17     20    -60
O
ATOM    362  N   VAL A 282      -5.968  23.871 -10.367  1.00 43.31
N
ANISOU  362  N   VAL A 282     5472   5421   5561     14     -8     19
N
ATOM    363  CA  VAL A 282      -6.851  24.121  -9.241  1.00 43.04
C
ANISOU  363  CA  VAL A 282     5464   5380   5508     26    -25    -11
C
ATOM    364  CB  VAL A 282      -7.691  22.860  -8.916  1.00 43.44
C
ANISOU  364  CB  VAL A 282     5511   5459   5536     37      4    -16
C
ATOM    365  CG1 VAL A 282      -8.661  23.101  -7.753  1.00 44.12
C
ANISOU  365  CG1 VAL A 282     5583   5557   5621     14     21    -60
C
ATOM    366  CG2 VAL A 282      -8.442  22.350 -10.169  1.00 42.54
C
ANISOU  366  CG2 VAL A 282     5348   5334   5481     10    -71     16
C
ATOM    367  C   VAL A 282      -5.948  24.480  -8.073  1.00 43.28
C
ANISOU  367  C   VAL A 282     5520   5394   5528     31     -9      0
C
ATOM    368  O   VAL A 282      -4.938  23.807  -7.830  1.00 43.32
O
ANISOU  368  O   VAL A 282     5586   5392   5480     -4     -7      0
O
ATOM    369  N   GLU A 283      -6.269  25.552  -7.361  1.00 43.39
N
ANISOU  369  N   GLU A 283     5533   5428   5524     46    -30    -15
N
ATOM    370  CA  GLU A 283      -5.332  26.039  -6.359  1.00 43.99
C
ANISOU  370  CA  GLU A 283     5588   5513   5614     39    -27    -44
C
ATOM    371  CB  GLU A 283      -5.541  27.527  -6.015  1.00 44.14
C
ANISOU  371  CB  GLU A 283     5616   5518   5637     22    -32    -77
C
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ATOM    372  CG  GLU A 283      -4.233  28.237  -5.566  1.00 45.14
C
ANISOU  372  CG  GLU A 283     5698   5626   5824      1    -30    -88
C
ATOM    373  CD  GLU A 283      -4.371  29.755  -5.272  1.00 45.52
C
ANISOU  373  CD  GLU A 283     5808   5640   5847     63    -22    -79
C
ATOM    374  OE1 GLU A 283      -5.169  30.449  -5.936  1.00 45.98
O
ANISOU  374  OE1 GLU A 283     5903   5748   5817    168   -129   -128
O
ATOM    375  OE2 GLU A 283      -3.643  30.256  -4.381  1.00 45.87
O
ANISOU  375  OE2 GLU A 283     5852   5692   5885     80    -99   -213
O
ATOM    376  C   GLU A 283      -5.379  25.129  -5.137  1.00 43.97
C
ANISOU  376  C   GLU A 283     5562   5548   5597     37     -9    -38
C
ATOM    377  O   GLU A 283      -6.407  24.499  -4.844  1.00 44.59
O
ANISOU  377  O   GLU A 283     5634   5595   5712     35     51    -49
O
ATOM    378  N   VAL A 284      -4.236  24.998  -4.479  1.00 43.75
N
ANISOU  378  N   VAL A 284     5529   5540   5552     44    -36    -57
N
ATOM    379  CA  VAL A 284      -4.120  24.176  -3.273  1.00 43.31
C
ANISOU  379  CA  VAL A 284     5511   5464   5480     32    -24    -78
C
ATOM    380  CB  VAL A 284      -3.476  22.788  -3.586  1.00 43.18
C
ANISOU  380  CB  VAL A 284     5470   5449   5488     12    -27    -98
C
ATOM    381  CG1 VAL A 284      -4.052  22.210  -4.898  1.00 43.69
C
ANISOU  381  CG1 VAL A 284     5545   5529   5525     52     -3    -77
C
ATOM    382  CG2 VAL A 284      -1.955  22.880  -3.689  1.00 42.77
C
ANISOU  382  CG2 VAL A 284     5474   5424   5350     28     -8   -121
C
ATOM    383  C   VAL A 284      -3.295  25.000  -2.284  1.00 43.29
C
ANISOU  383  C   VAL A 284     5540   5456   5451     58      2    -99
C
ATOM    384  O   VAL A 284      -2.599  25.934  -2.685  1.00 43.04
O
ANISOU  384  O   VAL A 284     5517   5406   5431     65     12   -172
O
ATOM    385  N   HIS A 285      -3.359  24.658  -1.005  1.00 43.83
N
ANISOU  385  N   HIS A 285     5611   5536   5504     66    -17    -98
N
ATOM    386  CA  HIS A 285      -2.861  25.567   0.027  1.00 44.27
C
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ANISOU  386  CA  HIS A 285     5668   5587   5565     87    -30    -55
C
ATOM    387  CB  HIS A 285      -4.050  26.282   0.698  1.00 44.73
C
ANISOU  387  CB  HIS A 285     5756   5646   5593     75    -33    -36
C
ATOM    388  CG  HIS A 285      -4.976  26.958  -0.275  1.00 44.92
C
ANISOU  388  CG  HIS A 285     5649   5723   5694     77    -25    -31
C
ATOM    389  ND1 HIS A 285      -4.656  28.136  -0.918  1.00 44.58
N
ANISOU  389  ND1 HIS A 285     5612   5609   5716     66    -65    -20
N
ATOM    390  CE1 HIS A 285      -5.646  28.483  -1.724  1.00 45.27
C
ANISOU  390  CE1 HIS A 285     5786   5744   5667     95     17   -124
C
ATOM    391  NE2 HIS A 285      -6.598  27.573  -1.625  1.00 43.43
N
ANISOU  391  NE2 HIS A 285     5469   5597   5434     28     51    -17
N
ATOM    392  CD2 HIS A 285      -6.199  26.603  -0.735  1.00 44.79
C
ANISOU  392  CD2 HIS A 285     5612   5701   5703     19     85   -129
C
ATOM    393  C   HIS A 285      -1.950  24.866   1.049  1.00 44.64
C
ANISOU  393  C   HIS A 285     5770   5605   5584     68    -24    -62
C
ATOM    394  O   HIS A 285      -1.415  25.503   1.966  1.00 44.57
O
ANISOU  394  O   HIS A 285     5789   5585   5561     88     -2    -76
O
ATOM    395  N   ASN A 286      -1.729  23.565   0.843  1.00 44.50
N
ANISOU  395  N   ASN A 286     5789   5535   5584     80     -9    -57
N
ATOM    396  CA  ASN A 286      -0.962  22.747   1.781  1.00 44.26
C
ANISOU  396  CA  ASN A 286     5730   5533   5553     67    -12    -83
C
ATOM    397  CB  ASN A 286      -1.450  21.295   1.735  1.00 44.27
C
ANISOU  397  CB  ASN A 286     5748   5527   5545     38      6    -34
C
ATOM    398  CG  ASN A 286      -1.216  20.635   0.373  1.00 44.25
C
ANISOU  398  CG  ASN A 286     5821   5469   5519     47    -24    -56
C
ATOM    399  OD1 ASN A 286      -1.410  21.255  -0.676  1.00 43.91
O
ANISOU  399  OD1 ASN A 286     5808   5508   5364      5    -68   -229
O
ATOM    400  ND2 ASN A 286      -0.803  19.376   0.391  1.00 44.62
N
ANISOU  400  ND2 ASN A 286     5770   5592   5590    125      0    -53
N
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ATOM    401  C   ASN A 286       0.568  22.816   1.625  1.00 44.26
C
ANISOU  401  C   ASN A 286     5738   5529   5547     68    -18    -77
C
ATOM    402  O   ASN A 286       1.286  22.107   2.322  1.00 45.01
O
ANISOU  402  O   ASN A 286     5800   5597   5702    141    -25     -4
O
ATOM    403  N   ALA A 287       1.077  23.681   0.750  1.00 43.66
N
ANISOU  403  N   ALA A 287     5666   5502   5421     51    -13   -117
N
ATOM    404  CA  ALA A 287       2.530  23.836   0.631  1.00 43.65
C
ANISOU  404  CA  ALA A 287     5588   5531   5464     78    -35    -99
C
ATOM    405  CB  ALA A 287       2.881  24.633  -0.594  1.00 43.62
C
ANISOU  405  CB  ALA A 287     5586   5509   5477    102    -29   -107
C
ATOM    406  C   ALA A 287       3.178  24.463   1.879  1.00 43.97
C
ANISOU  406  C   ALA A 287     5604   5597   5503     92    -43   -106
C
ATOM    407  O   ALA A 287       2.539  25.238   2.598  1.00 43.85
O
ANISOU  407  O   ALA A 287     5569   5635   5454    105    -67   -115
O
ATOM    408  N   LYS A 288       4.453  24.128   2.104  1.00 44.17
N
ANISOU  408  N   LYS A 288     5627   5595   5558     72    -23   -103
N
ATOM    409  CA  LYS A 288       5.217  24.563   3.272  1.00 44.18
C
ANISOU  409  CA  LYS A 288     5625   5588   5572     29    -45    -99
C
ATOM    410  CB  LYS A 288       5.689  23.352   4.080  1.00 44.81
C
ANISOU  410  CB  LYS A 288     5699   5701   5626     40    -42   -150
C
ATOM    411  CG  LYS A 288       4.593  22.555   4.792  1.00 46.48
C
ANISOU  411  CG  LYS A 288     5865   5903   5892    -76     11    -29
C
ATOM    412  CD  LYS A 288       4.200  23.232   6.110  1.00 49.09
C
ANISOU  412  CD  LYS A 288     6127   6301   6221   -126    134    -75
C
ATOM    413  CE  LYS A 288       2.938  22.633   6.718  1.00 52.04
C
ANISOU  413  CE  LYS A 288     6488   6709   6575     43    -23    -39
C
ATOM    414  NZ  LYS A 288       1.723  22.869   5.865  1.00 52.37
N
ANISOU  414  NZ  LYS A 288     6568   6732   6598     74    -80     19
N
ATOM    415  C   LYS A 288       6.420  25.342   2.794  1.00 44.20
C
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ANISOU  415  C   LYS A 288     5613   5591   5587     58    -50   -120
C
ATOM    416  O   LYS A 288       7.391  24.752   2.339  1.00 44.44
O
ANISOU  416  O   LYS A 288     5687   5545   5650     97   -149   -161
O
ATOM    417  N   THR A 289       6.354  26.670   2.864  1.00 44.16
N
ANISOU  417  N   THR A 289     5601   5569   5607     51    -24   -106
N
ATOM    418  CA  THR A 289       7.461  27.508   2.418  1.00 44.15
C
ANISOU  418  CA  THR A 289     5612   5539   5620     39      5    -85
C
ATOM    419  CB  THR A 289       6.970  28.884   1.928  1.00 44.07
C
ANISOU  419  CB  THR A 289     5583   5531   5628     43      0    -85
C
ATOM    420  OG1 THR A 289       5.785  28.708   1.148  1.00 44.05
O
ANISOU  420  OG1 THR A 289     5591   5462   5685     41     30   -182
O
ATOM    421  CG2 THR A 289       8.017  29.571   1.057  1.00 43.05
C
ANISOU  421  CG2 THR A 289     5481   5379   5495     32     70   -140
C
ATOM    422  C   THR A 289       8.492  27.654   3.538  1.00 44.68
C
ANISOU  422  C   THR A 289     5698   5604   5673     42      1    -63
C
ATOM    423  O   THR A 289       8.134  27.775   4.699  1.00 44.31
O
ANISOU  423  O   THR A 289     5702   5521   5612     66     10    -51
O
ATOM    424  N   LYS A 290       9.774  27.609   3.180  1.00 45.81
N
ANISOU  424  N   LYS A 290     5825   5733   5846     14    -29    -52
N
ATOM    425  CA  LYS A 290      10.851  27.684   4.165  1.00 46.81
C
ANISOU  425  CA  LYS A 290     5945   5856   5982     13    -25    -36
C
ATOM    426  CB  LYS A 290      12.115  26.942   3.676  1.00 47.41
C
ANISOU  426  CB  LYS A 290     6028   5957   6026     13      4    -53
C
ATOM    427  CG  LYS A 290      11.847  25.624   2.921  1.00 48.57
C
ANISOU  427  CG  LYS A 290     6220   6021   6211     -2     67    -25
C
ATOM    428  CD  LYS A 290      11.104  24.615   3.765  1.00 51.96
C
ANISOU  428  CD  LYS A 290     6717   6409   6614     73    185      3
C
ATOM    429  CE  LYS A 290       9.953  24.034   2.979  1.00 49.11
C
ANISOU  429  CE  LYS A 290     6138   6223   6296   -248     15     22
C
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ATOM    430  NZ  LYS A 290       9.085  23.115   3.801  1.00 53.79
N
ANISOU  430  NZ  LYS A 290     6802   6907   6729    208    -33   -113
N
ATOM    431  C   LYS A 290      11.172  29.147   4.440  1.00 46.84
C
ANISOU  431  C   LYS A 290     5963   5877   5957      0    -26    -24
C
ATOM    432  O   LYS A 290      11.011  29.996   3.549  1.00 47.40
O
ANISOU  432  O   LYS A 290     5986   5914   6109      0    -16     -3
O
ATOM    433  N   PRO A 291      11.592  29.457   5.681  1.00 46.94
N
ANISOU  433  N   PRO A 291     5985   5900   5950    -14    -59     -1
N
ATOM    434  CA  PRO A 291      12.091  30.804   5.994  1.00 46.84
C
ANISOU  434  CA  PRO A 291     5974   5891   5931    -18    -52     -2
C
ATOM    435  CB  PRO A 291      12.554  30.682   7.462  1.00 46.82
C
ANISOU  435  CB  PRO A 291     5971   5895   5921    -11    -80     -5
C
ATOM    436  CG  PRO A 291      12.624  29.199   7.753  1.00 46.92
C
ANISOU  436  CG  PRO A 291     6015   5881   5931    -28   -125      7
C
ATOM    437  CD  PRO A 291      11.585  28.578   6.870  1.00 47.19
C
ANISOU  437  CD  PRO A 291     6015   5909   6005    -25    -71     32
C
ATOM    438  C   PRO A 291      13.261  31.147   5.075  1.00 46.64
C
ANISOU  438  C   PRO A 291     5925   5886   5910      5    -30     -4
C
ATOM    439  O   PRO A 291      14.133  30.296   4.863  1.00 47.04
O
ANISOU  439  O   PRO A 291     5987   5882   6001     31    -44    -33
O
ATOM    440  N   ARG A 292      13.264  32.364   4.520  1.00 46.46
N
ANISOU  440  N   ARG A 292     5884   5850   5915     18    -40    -33
N
ATOM    441  CA  ARG A 292      14.214  32.738   3.462  1.00 46.02
C
ANISOU  441  CA  ARG A 292     5853   5808   5821     13    -28    -46
C
ATOM    442  CB  ARG A 292      13.794  34.046   2.798  1.00 46.45
C
ANISOU  442  CB  ARG A 292     5904   5847   5896      2    -27    -71
C
ATOM    443  CG  ARG A 292      13.611  35.259   3.741  1.00 47.04
C
ANISOU  443  CG  ARG A 292     6025   5960   5886      9    -27    -61
C
ATOM    444  CD  ARG A 292      13.483  36.560   2.938  1.00 47.13
C
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ANISOU  444  CD  ARG A 292     6000   5923   5984    -61    -73    -30
C
ATOM    445  NE  ARG A 292      12.698  37.551   3.667  1.00 47.83
N
ANISOU  445  NE  ARG A 292     6097   5602   6472    -52     16   -335
N
ATOM    446  CZ  ARG A 292      13.127  38.770   4.014  1.00 57.33
C
ANISOU  446  CZ  ARG A 292     7795   7019   6967     93   -377    229
C
ATOM    447  NH1 ARG A 292      14.348  39.183   3.676  1.00 49.57
N
ANISOU  447  NH1 ARG A 292     5617   6420   6794   -337    306     19
N
ATOM    448  NH2 ARG A 292      12.320  39.589   4.688  1.00 48.78
N
ANISOU  448  NH2 ARG A 292     5976   6056   6501    282    328   -326
N
ATOM    449  C   ARG A 292      15.654  32.829   3.962  1.00 46.46
C
ANISOU  449  C   ARG A 292     5866   5923   5862      7     -4    -68
C
ATOM    450  O   ARG A 292      15.881  33.227   5.111  1.00 46.71
O
ANISOU  450  O   ARG A 292     5920   5996   5831      8     24   -119
O
ATOM    451  N   GLU A 293      16.617  32.446   3.108  1.00 46.36
N
ANISOU  451  N   GLU A 293     5854   5928   5831     24     -8    -73
N
ATOM    452  CA  GLU A 293      18.053  32.436   3.465  1.00 46.15
C
ANISOU  452  CA  GLU A 293     5799   5867   5867      0     -8    -62
C
ATOM    453  CB  GLU A 293      18.639  31.019   3.384  1.00 46.12
C
ANISOU  453  CB  GLU A 293     5824   5830   5866      1    -58      0
C
ATOM    454  CG  GLU A 293      17.798  29.901   3.963  1.00 47.34
C
ANISOU  454  CG  GLU A 293     5940   5960   6085    -28    -21    -38
C
ATOM    455  CD  GLU A 293      18.535  28.556   3.942  1.00 47.14
C
ANISOU  455  CD  GLU A 293     5934   5957   6020     39   -105    -55
C
ATOM    456  OE1 GLU A 293      19.338  28.315   4.865  1.00 49.59
O
ANISOU  456  OE1 GLU A 293     6438   6317   6085     42   -160     10
O
ATOM    457  OE2 GLU A 293      18.316  27.742   3.006  1.00 48.92
O
ANISOU  457  OE2 GLU A 293     6228   6211   6148    -49    -12    -85
O
ATOM    458  C   GLU A 293      18.833  33.336   2.514  1.00 45.36
C
ANISOU  458  C   GLU A 293     5761   5721   5752    -18    -34    -35
C
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ATOM    459  O   GLU A 293      18.457  33.457   1.355  1.00 45.82
O
ANISOU  459  O   GLU A 293     5815   5803   5791    -15      0   -122
O
ATOM    460  N   GLU A 294      19.926  33.938   2.994  1.00 45.28
N
ANISOU  460  N   GLU A 294     5733   5714   5756    -18     -2    -11
N
ATOM    461  CA  GLU A 294      20.712  34.932   2.222  1.00 44.87
C
ANISOU  461  CA  GLU A 294     5685   5636   5725    -25    -11    -35
C
ATOM    462  CB  GLU A 294      21.091  36.145   3.107  1.00 44.81
C
ANISOU  462  CB  GLU A 294     5705   5615   5706    -20     -7    -42
C
ATOM    463  CG  GLU A 294      21.392  37.439   2.323  1.00 44.23
C
ANISOU  463  CG  GLU A 294     5601   5551   5653    -69    -25    -17
C
ATOM    464  CD  GLU A 294      22.111  38.531   3.140  1.00 44.89
C
ANISOU  464  CD  GLU A 294     5751   5638   5664    -73      2    -26
C
ATOM    465  OE1 GLU A 294      22.680  39.462   2.517  1.00 44.05
O
ANISOU  465  OE1 GLU A 294     5729   5440   5566   -143     73   -204
O
ATOM    466  OE2 GLU A 294      22.116  38.473   4.393  1.00 46.43
O
ANISOU  466  OE2 GLU A 294     5939   5975   5726   -261    -49     46
O
ATOM    467  C   GLU A 294      21.976  34.325   1.586  1.00 44.97
C
ANISOU  467  C   GLU A 294     5700   5636   5749    -24    -23    -39
C
ATOM    468  O   GLU A 294      22.738  33.611   2.247  1.00 45.23
O
ANISOU  468  O   GLU A 294     5722   5641   5823      4    -34    -91
O
ATOM    469  N   GLN A 295      22.211  34.628   0.315  1.00 45.12
N
ANISOU  469  N   GLN A 295     5687   5686   5771    -24      0    -36
N
ATOM    470  CA  GLN A 295      23.288  33.972  -0.424  1.00 45.81
C
ANISOU  470  CA  GLN A 295     5768   5739   5898      0    -23    -34
C
ATOM    471  CB  GLN A 295      22.770  33.466  -1.772  1.00 45.40
C
ANISOU  471  CB  GLN A 295     5746   5699   5802     14     -9    -34
C
ATOM    472  CG  GLN A 295      21.458  32.654  -1.658  1.00 45.05
C
ANISOU  472  CG  GLN A 295     5671   5623   5819     25    -48     39
C
ATOM    473  CD  GLN A 295      21.627  31.319  -0.930  1.00 50.11
C
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ANISOU  473  CD  GLN A 295     6357   6206   6473   -225   -440   -126
C
ATOM    474  OE1 GLN A 295      22.456  30.493  -1.319  1.00 46.51
O
ANISOU  474  OE1 GLN A 295     5639   5846   6183    244     39   -244
O
ATOM    475  NE2 GLN A 295      20.831  31.098   0.119  1.00 44.53
N
ANISOU  475  NE2 GLN A 295     5399   5954   5566   -128    161    -70
N
ATOM    476  C   GLN A 295      24.555  34.838  -0.580  1.00 46.43
C
ANISOU  476  C   GLN A 295     5854   5802   5984     26     12      5
C
ATOM    477  O   GLN A 295      24.486  36.076  -0.703  1.00 47.58
O
ANISOU  477  O   GLN A 295     6015   5902   6161     59     10    -25
O
ATOM    478  N   TYR A 296      25.714  34.187  -0.561  1.00 46.40
N
ANISOU  478  N   TYR A 296     5836   5823   5968     44     40     12
N
ATOM    479  CA  TYR A 296      26.988  34.887  -0.681  1.00 46.22
C
ANISOU  479  CA  TYR A 296     5850   5807   5904      6      0    -13
C
ATOM    480  CB  TYR A 296      28.136  33.947  -0.299  1.00 46.54
C
ANISOU  480  CB  TYR A 296     5879   5805   5997     11     21     -4
C
ATOM    481  CG  TYR A 296      28.369  33.809   1.199  1.00 46.10
C
ANISOU  481  CG  TYR A 296     5899   5814   5802    -12     36     13
C
ATOM    482  CD1 TYR A 296      27.454  33.149   2.015  1.00 46.85
C
ANISOU  482  CD1 TYR A 296     5952   5814   6034     41     56    -47
C
ATOM    483  CE1 TYR A 296      27.676  33.022   3.393  1.00 47.39
C
ANISOU  483  CE1 TYR A 296     6047   6058   5900      5    -74      8
C
ATOM    484  CZ  TYR A 296      28.836  33.551   3.951  1.00 46.56
C
ANISOU  484  CZ  TYR A 296     5965   5924   5799    -82      4     31
C
ATOM    485  OH  TYR A 296      29.080  33.427   5.309  1.00 47.47
O
ANISOU  485  OH  TYR A 296     6193   5903   5937    -47     -8    -40
O
ATOM    486  CE2 TYR A 296      29.756  34.202   3.145  1.00 47.62
C
ANISOU  486  CE2 TYR A 296     5995   5884   6215     36     51    -59
C
ATOM    487  CD2 TYR A 296      29.520  34.324   1.786  1.00 45.57
C
ANISOU  487  CD2 TYR A 296     5830   5826   5658      6    -68     15
C
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ATOM    488  C   TYR A 296      27.193  35.501  -2.083  1.00 46.49
C
ANISOU  488  C   TYR A 296     5907   5803   5951      6     -4      3
C
ATOM    489  O   TYR A 296      28.292  35.440  -2.666  1.00 46.50
O
ANISOU  489  O   TYR A 296     5897   5779   5989    -14    -14    -11
O
ATOM    490  N   ASN A 297      26.119  36.064  -2.631  1.00 46.88
N
ANISOU  490  N   ASN A 297     5965   5855   5991     17    -15    -17
N
ATOM    491  CA  ASN A 297      26.216  36.949  -3.792  1.00 47.71
C
ANISOU  491  CA  ASN A 297     6085   5986   6055     26    -38    -12
C
ATOM    492  CB  ASN A 297      26.142  36.169  -5.117  1.00 48.85
C
ANISOU  492  CB  ASN A 297     6260   6139   6160     64      0    -11
C
ATOM    493  CG  ASN A 297      24.947  35.221  -5.195  1.00 50.92
C
ANISOU  493  CG  ASN A 297     6460   6440   6445    -63     58     -1
C
ATOM    494  OD1 ASN A 297      24.216  35.028  -4.220  1.00 52.42
O
ANISOU  494  OD1 ASN A 297     6674   6584   6659     87     34   -103
O
ATOM    495  ND2 ASN A 297      24.768  34.605  -6.370  1.00 56.08
N
ANISOU  495  ND2 ASN A 297     7171   7114   7021    -39    -31    -25
N
ATOM    496  C   ASN A 297      25.188  38.088  -3.729  1.00 47.37
C
ANISOU  496  C   ASN A 297     6034   5962   6003      2    -36    -28
C
ATOM    497  O   ASN A 297      24.879  38.733  -4.748  1.00 47.54
O
ANISOU  497  O   ASN A 297     6064   5970   6028    -37    -68    -27
O
ATOM    498  N   SER A 298      24.679  38.332  -2.516  1.00 47.02
N
ANISOU  498  N   SER A 298     5921   5925   6017      5    -15    -17
N
ATOM    499  CA  SER A 298      23.797  39.477  -2.220  1.00 46.71
C
ANISOU  499  CA  SER A 298     5868   5873   6005    -26    -29      0
C
ATOM    500  CB  SER A 298      24.415  40.801  -2.693  1.00 46.68
C
ANISOU  500  CB  SER A 298     5861   5857   6015    -11    -30     45
C
ATOM    501  OG  SER A 298      25.715  40.961  -2.150  1.00 48.13
O
ANISOU  501  OG  SER A 298     6019   6020   6244    -95    -25    -12
O
ATOM    502  C   SER A 298      22.395  39.255   2.792  1.00 46.18
C
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ANISOU  502  C   SER A 298     5828   5812   5906    -33    -31     13
C
ATOM    503  O   SER A 298      21.852  40.082  -3.545  1.00 46.36
O
ANISOU  503  O   SER A 298     5846   5850   5918    -31    -40     43
O
ATOM    504  N   THR A 299      21.810  38.137  -2.365  1.00 45.58
N
ANISOU  504  N   THR A 299     5776   5728   5815    -47    -20      0
N
ATOM    505  CA  THR A 299      20.634  37.558  -2.982  1.00 45.03
C
ANISOU  505  CA  THR A 299     5757   5632   5719    -42    -23    -30
C
ATOM    506  CB  THR A 299      21.118  36.736  -4.229  1.00 45.29
C
ANISOU  506  CB  THR A 299     5793   5664   5749    -38    -58    -30
C
ATOM    507  OG1 THR A 299      20.498  37.203  -5.433  1.00 46.45
O
ANISOU  507  OG1 THR A 299     5934   5743   5972     21    -92     -8
O
ATOM    508  CG2 THR A 299      20.931  35.249  -4.066  1.00 45.09
C
ANISOU  508  CG2 THR A 299     5820   5677   5634    -42    -57    -34
C
ATOM    509  C   THR A 299      19.994  36.667  -1.895  1.00 44.73
C
ANISOU  509  C   THR A 299     5717   5578   5700    -68    -31    -58
C
ATOM    510  O   THR A 299      20.734  36.055  -1.103  1.00 44.52
O
ANISOU  510  O   THR A 299     5722   5570   5623    -99    -47    -90
O
ATOM    511  N   TYR A 300      18.656  36.609  -1.809  1.00 44.50
N
ANISOU  511  N   TYR A 300     5713   5554   5640    -37      1    -53
N
ATOM    512  CA  TYR A 300      18.007  35.534  -1.007  1.00 44.78
C
ANISOU  512  CA  TYR A 300     5706   5632   5674    -53     22   -106
C
ATOM    513  CB  TYR A 300      16.841  36.048  -0.117  1.00 45.79
C
ANISOU  513  CB  TYR A 300     5829   5719   5847    -42     30   -116
C
ATOM    514  CG  TYR A 300      17.195  37.233   0.822  1.00 47.96
C
ANISOU  514  CG  TYR A 300     6051   6119   6052      4     19    -11
C
ATOM    515  CD1 TYR A 300      17.216  38.547   0.337  1.00 46.79
C
ANISOU  515  CD1 TYR A 300     6033   5674   6069    -83     -3   -132
C
ATOM    516  CE1 TYR A 300      17.531  39.614   1.158  1.00 47.40
C
ANISOU  516  CE1 TYR A 300     6116   6018   5876    -35      4   -148
C
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ATOM    517  CZ  TYR A 300      17.834  39.387   2.495  1.00 47.96
C
ANISOU  517  CZ  TYR A 300     6083   6090   6048     47    -15     45
C
ATOM    518  OH  TYR A 300      18.148  40.465   3.318  1.00 46.29
O
ANISOU  518  OH  TYR A 300     6171   5754   5662    -44   -150   -180
O
ATOM    519  CE2 TYR A 300      17.804  38.096   3.006  1.00 47.39
C
ANISOU  519  CE2 TYR A 300     6071   5825   6109     49    -44    -39
C
ATOM    520  CD2 TYR A 300      17.490  37.029   2.170  1.00 46.41
C
ANISOU  520  CD2 TYR A 300     5977   5849   5807    -92   -119    -95
C
ATOM    521  C   TYR A 300      17.585  34.279  -1.817  1.00 44.23
C
ANISOU  521  C   TYR A 300     5614   5568   5621    -41     28    -39
C
ATOM    522  O   TYR A 300      17.452  34.29[illegible]  -3.056  1.00 44.14
O
ANISOU  522  O   TYR A 300     5567   5606   5598    -57     27    -81
O
ATOM    523  N   ARG A 301      17.383  33.193  -1.085  1.00 43.82
N
ANISOU  523  N   ARG A 301     5560   5519   5571     14    -13    -43
N
ATOM    524  CA  ARG A 301      16.918  31.936  -1.647  1.00 43.57
C
ANISOU  524  CA  ARG A 301     5505   5506   5542     -3     -7    -33
C
ATOM    525  CB  ARG A 301      18.004  30.864  -1.516  1.00 43.36
C
ANISOU  525  CB  ARG A 301     5504   5467   5501     15    -47    -49
C
ATOM    526  CG  ARG A 301      17.592  29.478  -2.000  1.00 44.07
C
ANISOU  526  CG  ARG A 301     5519   5525   5699    -32    -46     -8
C
ATOM    527  CD  ARG A 301      18.816  28.61[illegible]  -2.243  1.00 44.34
C
ANISOU  527  CD  ARG A 301     5415   5556   5873    -21    -27   -130
C
ATOM    528  NE  ARG A 301      18.503  27.319  -2.846  1.00 45.93
N
ANISOU  528  NE  ARG A 301     5462   6031   5957    106    -48   -104
N
ATOM    529  CZ  ARG A 301      18.153  26.232  -2.170  1.00 42.24
C
ANISOU  529  CZ  ARG A 301     5643   5431   4975   -212     61    -40
C
ATOM    530  NH1 ARG A 301      18.055  26.272  -0.844  1.00 47.72
N
ANISOU  530  NH1 ARG A 301     5737   6114   6280      8   -101    -45
N
ATOM    531  NH2 ARG A 301      17.891  25.102  -2.82[illegible]  1.00 46.14
N
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ANISOU  531  NH2 ARG A 301     5495   6132   5903    156    108     67
N
ATOM    532  C   ARG A 301      15.674  31.523  -0.876  1.00 43.64
C
ANISOU  532  C   ARG A 301     5540   5535   5503      1    -17     -7
C
ATOM    533  O   ARG A 301      15.705  31.440   0.362  1.00 44.01
O
ANISOU  533  O   ARG A 301     5675   5632   5413     52      3      7
O
ATOM    534  N   VAL A 302      14.574  31.295  -1.598  1.00 43.14
N
ANISOU  534  N   VAL A 302     5467   5424   5499    -21     -5     -6
N
ATOM    535  CA  VAL A 302      13.342  30.854  -0.956  1.00 42.72
C
ANISOU  535  CA  VAL A 302     5403   5315   5512    -37      8    -17
C
ATOM    536  CB  VAL A 302      12.244  31.957  -0.857  1.00 43.01
C
ANISOU  536  CB  VAL A 302     5439   5350   5551    -47     13    -13
C
ATOM    537  CG1 VAL A 302      11.403  31.739   0.404  1.00 42.56
C
ANISOU  537  CG1 VAL A 302     5310   5394   5466   -110     -2   -109
C
ATOM    538  CG2 VAL A 302      12.860  33.368  -0.830  1.00 43.35
C
ANISOU  538  CG2 VAL A 302     5471   5351   5646    -38     32     -2
C
ATOM    539  C   VAL A 302      12.803  29.606  -1.643  1.00 42.39
C
ANISOU  539  C   VAL A 302     5389   5308   5407    -33     -5    -28
C
ATOM    540  O   VAL A 302      12.657  29.560  -2.863  1.00 41.88
O
ANISOU  540  O   VAL A 302     5326   5264   5320     -2    -39    -30
O
ATOM    541  N   VAL A 303      12.529  28.603  -0.810  1.00 42.33
N
ANISOU  541  N   VAL A 303     5387   5251   5445    -64     -2    -41
N
ATOM    542  CA  VAL A 303      12.107  27.279  -1.230  1.00 42.18
C
ANISOU  542  CA  VAL A 303     5328   5270   5427    -26     30    -33
C
ATOM    543  CB  VAL A 303      13.036  26.184  -0.605  1.00 42.24
C
ANISOU  543  CB  VAL A 303     5310   5283   5454    -22     24    -23
C
ATOM    544  CG1 VAL A 303      12.534  24.790  -0.910  1.00 41.59
C
ANISOU  544  CG1 VAL A 303     5214   5202   5384    -38     86    -28
C
ATOM    545  CG2 VAL A 303      14.501  26.353  -1.073  1.00 42.85
C
ANISOU  545  CG2 VAL A 303     5375   5362   5542    -30     59    -55
C
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ATOM    546  C   VAL A 303      10.674  27.041  -0.748  1.00 41.94
C
ANISOU  546  C   VAL A 303     5300   5258   5377    -12     27    -38
C
ATOM    547  O   VAL A 303      10.364  27.277   0.424  1.00 42.19
O
ANISOU  547  O   VAL A 303     5391   5257   5381     11     76     22
O
ATOM    548  N   SER A 304       9.801  26.596  -1.648  1.00 41.73
N
ANISOU  548  N   SER A 304     5238   5240   5375      4     30    -44
N
ATOM    549  CA  SER A 304       8.505  26.065  -1.231  1.00 41.38
C
ANISOU  549  CA  SER A 304     5196   5202   5323    -26      5    -31
C
ATOM    550  CB  SER A 304       7.339  26.861  -1.831  1.00 41.38
C
ANISOU  550  CB  SER A 304     5184   5211   5327    -22     -8    -54
C
ATOM    551  OG  SER A 304       6.152  26.629  -1.076  1.00 40.98
O
ANISOU  551  OG  SER A 304     5221   5152   5196     20     16   -154
O
ATOM    552  C   SER A 304       8.391  24.579  -1.579  1.00 41.13
C
ANISOU  552  C   SER A 304     5166   5191   5269    -40     12    -60
C
ATOM    553  O   SER A 304       8.646  24.190  -2.718  1.00 40.85
O
ANISOU  553  O   SER A 304     5073   5198   5250    -55     -3    -38
O
ATOM    554  N   VAL A 305       7.992  23.779  -0.583  1.00 41.00
N
ANISOU  554  N   VAL A 305     5201   5158   5219    -43    -30    -25
N
ATOM    555  CA  VAL A 305       7.796  22.329  -0.709  1.00 40.98
C
ANISOU  555  CA  VAL A 305     5182   5183   5204    -45    -18    -47
C
ATOM    556  CB  VAL A 305       8.559  21.550   0.407  1.00 40.91
C
ANISOU  556  CB  VAL A 305     5162   5158   5221     31     36     13
C
ATOM    557  CG1 VAL A 305       8.340  20.053   0.282  1.00 40.60
C
ANISOU  557  CG1 VAL A 305     5114   5164   5145    -82   -121    -82
C
ATOM    558  CG2 VAL A 305      10.044  21.845   0.363  1.00 41.19
C
ANISOU  558  CG2 VAL A 305     5200   5121   5326    -85    -25    -36
C
ATOM    559  C   VAL A 305       6.306  21.921  -0.660  1.00 41.10
C
ANISOU  559  C   VAL A 305     5186   5211   5215    -36    -14    -73
C
ATOM    560  O   VAL A 305       5.573  22.260   0.293  1.00 40.73
O
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ANISOU  560  O   VAL A 305     5174   5103   5197    -37      9   -126
O
ATOM    561  N   LEU A 306       5.887  21.153  -1.666  1.00 41.07
N
ANISOU  561  N   LEU A 306     5191   5259   5153    -10    -16    -73
N
ATOM    562  CA  LEU A 306       4.535  20.592  -1.719  1.00 40.99
C
ANISOU  562  CA  LEU A 306     5188   5219   5166    -16    -40    -36
C
ATOM    563  CB  LEU A 306       3.748  21.148  -2.918  1.00 41.06
C
ANISOU  563  CB  LEU A 306     5204   5163   5234    -12    -54    -29
C
ATOM    564  CG  LEU A 306       2.268  20.728  -3.008  1.00 40.75
C
ANISOU  564  CG  LEU A 306     5172   5155   5154     53     -5    -10
C
ATOM    565  CD1 LEU A 306       1.434  21.455  -1.976  1.00 40.43
C
ANISOU  565  CD1 LEU A 306     5289   5183   4888    -31    -17     50
C
ATOM    566  CD2 LEU A 306       1.705  20.962  -4.394  1.00 40.87
C
ANISOU  566  CD2 LEU A 306     5213   5177   5135    -17    -41    -45
C
ATOM    567  C   LEU A 306       4.544  19.069  -1.779  1.00 41.08
C
ANISOU  567  C   LEU A 306     5177   5234   5197     40    -34    -43
C
ATOM    568  O   LEU A 306       5.110  18.481  -2.693  1.00 40.95
O
ANISOU  568  O   LEU A 306     5163   5223   5171     14    -57    -46
O
ATOM    569  N   THR A 307       3.895  18.438  -0.807  1.00 41.54
N
ANISOU  569  N   THR A 307     5217   5276   5288     40    -35    -55
N
ATOM    570  CA  THR A 307       3.718  17.004  -0.828  1.00 42.10
C
ANISOU  570  CA  THR A 307     5268   5362   5363     50    -25    -59
C
ATOM    571  CB  THR A 307       3.238  16.490   0.534  1.00 42.33
C
ANISOU  571  CB  THR A 307     5295   5394   5391     46    -26    -62
C
ATOM    572  OG1 THR A 307       4.261  16.717   1.510  1.00 43.20
O
ANISOU  572  OG1 THR A 307     5387   5546   5479     27    -27   -143
O
ATOM    573  CG2 THR A 307       2.943  15.007   0.486  1.00 42.37
C
ANISOU  573  CG2 THR A 307     5388   5344   5365     25    -24    -57
C
ATOM    574  C   THR A 307       2.738  16.624  -1.946  1.00 42.61
C
ANISOU  574  C   THR A 307     5343   5394   5419     60    -18    -56
C
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ATOM    575  O   THR A 307       1.695  17.279  -2.138  1.00 43.31
O
ANISOU  575  O   THR A 307     5405   5457   5593    122    -38    -50
O
ATOM    576  N   VAL A 308       3.092  15.590  -2.705  1.00 41.88
N
ANISOU  576  N   VAL A 308     5290   5285   5337     54     -5    -77
N
ATOM    577  CA  VAL A 308       2.175  15.039  -3.688  1.00 41.32
C
ANISOU  577  CA  VAL A 308     5239   5211   5250     40    -12    -42
C
ATOM    578  CB  VAL A 308       2.772  15.033  -5.136  1.00 41.12
C
ANISOU  578  CB  VAL A 308     5250   5192   5180     37    -40    -41
C
ATOM    579  CG1 VAL A 308       3.194  16.439  -5.532  1.00 40.83
C
ANISOU  579  CG1 VAL A 308     5238   5210   5064    -11    -14    -71
C
ATOM    580  CG2 VAL A 308       3.956  14.098  -5.273  1.00 40.49
C
ANISOU  580  CG2 VAL A 308     5160   5093   5131     11    -79    -30
C
ATOM    581  C   VAL A 308       1.678  13.663  -3.230  1.00 41.17
C
ANISOU  581  C   VAL A 308     5209   5209   5223     41    -23    -66
C
ATOM    582  O   VAL A 308       2.346  12.959  -2.475  1.00 40.78
O
ANISOU  582  O   VAL A 308     5262   5123   5107     24    -11    -56
O
ATOM    583  N   LEU A 309       0.480  13.302  -3.665  1.00 40.99
N
ANISOU  583  N   LEU A 309     5170   5164   5238     33     -1    -65
N
ATOM    584  CA  LEU A 309      -0.019  11.972  -3.414  1.00 40.25
C
ANISOU  584  CA  LEU A 309     5082   5101   5109     31    -12    -14
C
ATOM    585  CB  LEU A 309      -1.545  11.939  -3.388  1.00 40.44
C
ANISOU  585  CB  LEU A 309     5114   5151   5098      6    -34    -12
C
ATOM    586  CG  LEU A 309      -2.214  12.728  -2.261  1.00 41.27
C
ANISOU  586  CG  LEU A 309     5230   5236   5213     32    -21      0
C
ATOM    587  CD1 LEU A 309      -3.692  12.898  -2.547  1.00 42.21
C
ANISOU  587  CD1 LEU A 309     5289   5393   5355     41    -69     23
C
ATOM    588  CD2 LEU A 309      -2.011  12.051  -0.896  1.00 42.35
C
ANISOU  588  CD2 LEU A 309     5357   5365   5366     17    -14      3
C
ATOM    589  C   LEU A 309       0.561  10.988   4.429  1.00 39.55
C
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ANISOU  589  C   LEU A 309     4964   5033   5027     -2    -36    -27
C
ATOM    590  O   LEU A 309       0.800  11.310  -5.591  1.00 38.60
O
ANISOU  590  O   LEU A 309     4763   4962   4938     33    -16    -94
O
ATOM    591  N   HIS A 310       0.816   9.795  -3.922  1.00 39.07
N
ANISOU  591  N   HIS A 310     4906   4954   4982      4    -10    -70
N
ATOM    592  CA  HIS A 310       1.381   8.692  -4.663  1.00 38.71
C
ANISOU  592  CA  HIS A 310     4886   4959   4862     -8      4    -35
C
ATOM    593  CB  HIS A 310       1.371   7.441  -3.778  1.00 37.81
C
ANISOU  593  CB  HIS A 310     4801   4808   4757     22     -8    -14
C
ATOM    594  CG  HIS A 310       1.655   6.180  -4.519  1.00 36.41
C
ANISOU  594  CG  HIS A 310     4652   4701   4480    -32     -3     59
C
ATOM    595  ND1 HIS A 310       2.932   5.690  -4.685  1.00 34.00
N
ANISOU  595  ND1 HIS A 310     4396   4421   4101    -33    -38     -4
N
ATOM    596  CE1 HIS A 310       2.880   4.568  -5.376  1.00 34.94
C
ANISOU  596  CE1 HIS A 310     4527   4316   4434     -5     -4    140
C
ATOM    597  NE2 HIS A 310       1.614   4.314  -5.667  1.00 34.85
N
ANISOU  597  NE2 HIS A 310     4517   4245   4480     61     16    113
N
ATOM    598  CD2 HIS A 310       0.829   5.307  -5.140  1.00 35.34
C
ANISOU  598  CD2 HIS A 310     4432   4621   4373      9     62     95
C
ATOM    599  C   HIS A 310       0.644   8.427  -5.973  1.00 38.70
C
ANISOU  599  C   HIS A 310     4902   4960   4840    -15    -27    -46
C
ATOM    600  O   HIS A 310       1.277   8.305  -7.027  1.00 37.82
O
ANISOU  600  O   HIS A 310     4807   4841   4722    -36    -23    -44
O
ATOM    601  N   GLN A 311      -0.684   8.335  -5.883  1.00 39.22
N
ANISOU  601  N   GLN A 311     5005   5002   4894     -3     19    -72
N
ATOM    602  CA  GLN A 311      -1.541   8.052  -7.037  1.00 39.83
C
ANISOU  602  CA  GLN A 311     5068   5069   4997      4    -14    -53
C
ATOM    603  CB  GLN A 311       2.941   7.575   6.615  1.00 39.64
C
ANISOU  603  CB  GLN A 311     5050   5101   4910      8     -4    -67
C
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ATOM    604  CG  GLN A 311      -3.814   8.592  -5.859  1.00 41.81
C
ANISOU  604  CG  GLN A 311     5349   5334   5203     34      4      3
C
ATOM    605  CD  GLN A 311      -3.637   8.590  -4.319  1.00 44.78
C
ANISOU  605  CD  GLN A 311     5943   5685   5387    -47     37    -57
C
ATOM    606  OE1 GLN A 311      -2.590   8.195  -3.771  1.00 43.08
O
ANISOU  606  OE1 GLN A 311     5380   5867   5120     97    -37   -211
O
ATOM    607  NE2 GLN A 311      -4.681   9.036  -3.622  1.00 43.39
N
ANISOU  607  NE2 GLN A 311     5563   5667   5256    170    135    -45
N
ATOM    608  C   GLN A 311      -1.594   9.229  -7.995  1.00 39.90
C
ANISOU  608  C   GLN A 311     5049   5064   5045    -16     -7    -58
C
ATOM    609  O   GLN A 311      -1.555   9.046  -9.229  1.00 40.38
O
ANISOU  609  O   GLN A 311     5051   5083   5207    -72     45    -44
O
ATOM    610  N   ASP A 312      -1.642  10.431  -7.425  1.00 39.64
N
ANISOU  610  N   ASP A 312     5014   5048   4998    -22    -10    -70
N
ATOM    611  CA  ASP A 312      -1.723  11.662  -8.196  1.00 39.61
C
ANISOU  611  CA  ASP A 312     5003   5033   5013     -9     -1    -80
C
ATOM    612  CB  ASP A 312      -1.841  12.891  -7.276  1.00 39.79
C
ANISOU  612  CB  ASP A 312     5039   5090   4987     -8    -26   -109
C
ATOM    613  CG  ASP A 312      -3.202  13.029  -6.639  1.00 40.70
C
ANISOU  613  CG  ASP A 312     5104   5172   5286    -39     18   -131
C
ATOM    614  OD1 ASP A 312      -4.081  12.167  -6.863  1.00 42.10
O
ANISOU  614  OD1 ASP A 312     5286   5405   5303     51     91   -230
O
ATOM    615  OD2 ASP A 312      -3.389  14.010  -5.888  1.00 43.00
O
ANISOU  615  OD2 ASP A 312     5297   5347   5692    -20     69      1
O
ATOM    616  C   ASP A 312      -0.518  11.833  -9.091  1.00 38.73
C
ANISOU  616  C   ASP A 312     4902   4899   4914     11     12   -121
C
ATOM    617  O   ASP A 312      -0.655  12.241 -10.251  1.00 39.28
O
ANISOU  617  O   ASP A 312     4946   4963   5014     -3     85   -129
O
ATOM    618  N   TRP A 313       0.656  11.537  -8.543  1.00 37.61
N
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ANISOU  618  N   TRP A 313     4772   4760   4758     -8     10   -110
N
ATOM    619  CA  TRP A 313       1.907  11.678  -9.279  1.00 36.85
C
ANISOU  619  CA  TRP A 313     4619   4730   4649     -7    -60    -88
C
ATOM    620  CB  TRP A 313       3.129  11.487  -8.357  1.00 36.13
C
ANISOU  620  CB  TRP A 313     4550   4680   4494     -8    -75    -20
C
ATOM    621  CG  TRP A 313       4.441  11.751  -9.093  1.00 35.34
C
ANISOU  621  CG  TRP A 313     4466   4697   4264     43   -176   -103
C
ATOM    622  CD1 TRP A 313       5.343  10.827  -9.512  1.00 35.07
C
ANISOU  622  CD1 TRP A 313     4501   4715   4109    -17   -197    -29
C
ATOM    623  NE1 TRP A 313       6.406  11.442 -10.135  1.00 34.18
N
ANISOU  623  NE1 TRP A 313     4463   4332   4191    -11   -148     20
N
ATOM    624  CE2 TRP A 313       6.187  12.796 -10.146  1.00 35.05
C
ANISOU  624  CE2 TRP A 313     4446   4707   4162    -75   -196    -97
C
ATOM    625  CD2 TRP A 313       4.954  13.028  -9.497  1.00 33.56
C
ANISOU  625  CD2 TRP A 313     4353   4503   3893    -30   -139      4
C
ATOM    626  CE3 TRP A 313       4.501  14.348  -9.354  1.00 32.76
C
ANISOU  626  CE3 TRP A 313     4229   4481   3734      0   -202     82
C
ATOM    627  CZ3 TRP A 313       5.279  15.377  -9.862  1.00 35.07
C
ANISOU  627  CZ3 TRP A 313     4469   4665   4192     -3   -238     41
C
ATOM    628  CH2 TRP A 313       6.493  15.113 -10.532  1.00 34.15
C
ANISOU  628  CH2 TRP A 313     4324   4418   4233    -22   -142     86
C
ATOM    629  CZ2 TRP A 313       6.959  13.833 -10.685  1.00 35.30
C
ANISOU  629  CZ2 TRP A 313     4442   4682   4288    -11   -136    -64
C
ATOM    630  C   TRP A 313       1.998  10.709 -10.457  1.00 36.14
C
ANISOU  630  C   TRP A 313     4477   4717   4537      0    -78    -55
C
ATOM    631  O   TRP A 313       2.313  11.107 -11.562  1.00 35.50
O
ANISOU  631  O   TRP A 313     4328   4708   4450     45   -104    -91
O
ATOM    632  N   LEU A 314       1.765   9.438 -10.157  1.00 35.58
N
ANISOU  632  N   LEU A 314     4401   4613   4503    -13    -76    -52
N
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ATOM    633  CA  LEU A 314       1.729   8.348 -11.105  1.00 35.56
C
ANISOU  633  CA  LEU A 314     4445   4567   4497     28      5    -28
C
ATOM    634  CB  LEU A 314       1.574   7.016 -10.361  1.00 35.07
C
ANISOU  634  CB  LEU A 314     4405   4507   4410    -12     18    -47
C
ATOM    635  CG  LEU A 314       2.750   6.390  -9.621  1.00 34.91
C
ANISOU  635  CG  LEU A 314     4444   4487   4331    -14    -28    -14
C
ATOM    636  CD1 LEU A 314       2.290   5.110  -8.980  1.00 35.56
C
ANISOU  636  CD1 LEU A 314     4432   4609   4471     17   -104    -47
C
ATOM    637  CD2 LEU A 314       3.922   6.091 -10.522  1.00 34.75
C
ANISOU  637  CD2 LEU A 314     4491   4405   4306     41   -118     -7
C
ATOM    638  C   LEU A 314       0.618   8.461 -12.146  1.00 35.53
C
ANISOU  638  C   LEU A 314     4500   4504   4495    -33    -16    -32
C
ATOM    639  O   LEU A 314       0.782   7.941 -13.236  1.00 35.75
O
ANISOU  639  O   LEU A 314     4455   4563   4564    -36     -3     17
O
ATOM    640  N   ASN A 315      -0.504   9.110 -11.802  1.00 35.21
N
ANISOU  640  N   ASN A 315     4478   4419   4481    -76    -52    -36
N
ATOM    641  CA  ASN A 315      -1.580   9.402 -12.763  1.00 35.05
C
ANISOU  641  CA  ASN A 315     4531   4373   4411    -33      2    -57
C
ATOM    642  CB  ASN A 315      -2.958   9.466 -12.074  1.00 35.00
C
ANISOU  642  CB  ASN A 315     4513   4349   4433    -40    -16    -16
C
ATOM    643  CG  ASN A 315      -3.500   8.086 -11.725  1.00 35.48
C
ANISOU  643  CG  ASN A 315     4451   4447   4582   -119    -42   -126
C
ATOM    644  OD1 ASN A 315      -3.252   7.128 -12.445  1.00 33.89
O
ANISOU  644  OD1 ASN A 315     4226   4285   4363   -276   -266   -225
O
ATOM    645  ND2 ASN A 315      -4.209   7.977 -10.601  1.00 34.22
N
ANISOU  645  ND2 ASN A 315     4214   4375   4410   -223     34    -77
N
ATOM    646  C   ASN A 315      -1.379  10.647 -13.620  1.00 34.87
C
ANISOU  646  C   ASN A 315     4516   4388   4343    -23      1    -67
C
ATOM    647  O   ASN A 315      -2.321  11.112 -14.237  1.00 34.63
O
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ANISOU  647  O   ASN A 315     4549   4319   4289    -30     41    -65
O
ATOM    648  N   GLY A 316      -0.171  11.197 -13.639  1.00 35.22
N
ANISOU  648  N   GLY A 316     4517   4502   4360      6      3    -37
N
ATOM    649  CA  GLY A 316       0.165  12.331 -14.516  1.00 35.71
C
ANISOU  649  CA  GLY A 316     4494   4573   4500     -5     -1    -46
C
ATOM    650  C   GLY A 316      -0.397  13.709 -14.206  1.00 35.78
C
ANISOU  650  C   GLY A 316     4467   4612   4516    -28    -42    -50
C
ATOM    651  O   GLY A 316      -0.366  14.597 -15.058  1.00 35.56
O
ANISOU  651  O   GLY A 316     4332   4654   4522     -7    -66    -97
O
ATOM    652  N   LYS A 317      -0.902  13.890 -12.991  1.00 36.31
N
ANISOU  652  N   LYS A 317     4528   4698   4570    -30    -42    -59
N
ATOM    653  CA  LYS A 317      -1.315  15.203 -12.493  1.00 37.07
C
ANISOU  653  CA  LYS A 317     4699   4780   4606     -7    -28    -47
C
ATOM    654  CB  LYS A 317      -1.755  15.110 -11.031  1.00 37.28
C
ANISOU  654  CB  LYS A 317     4696   4803   4663    -25     -9    -80
C
ATOM    655  CG  LYS A 317      -3.033  14.325 -10.813  1.00 38.63
C
ANISOU  655  CG  LYS A 317     4886   4905   4884    -49     -2    -35
C
ATOM    656  CD  LYS A 317      -3.784  14.865  -9.616  1.00 39.92
C
ANISOU  656  CD  LYS A 317     4984   5172   5010     19     65    -11
C
ATOM    657  CE  LYS A 317      -5.138  14.188  -9.434  1.00 40.77
C
ANISOU  657  CE  LYS A 317     5161   5227   5100    116     79    -35
C
ATOM    658  NZ  LYS A 317      -6.015  15.042  -8.572  1.00 41.78
N
ANISOU  658  NZ  LYS A 317     5263   5525   5086    124     26     96
N
ATOM    659  C   LYS A 317      -0.180  16.214 -12.629  1.00 37.17
C
ANISOU  659  C   LYS A 317     4747   4823   4551    -27    -28    -80
C
ATOM    660  O   LYS A 317       0.980  15.859 -12.440  1.00 37.06
O
ANISOU  660  O   LYS A 317     4756   4804   4520    -34     84   -155
O
ATOM    661  N   GLU A 318      -0.525  17.462 -12.941  1.00 37.60
N
ANISOU  661  N   GLU A 318     4848   4817   4621    -12    -30    -99
N
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ATOM    662  CA  GLU A 318       0.452  18.519 -13.238  1.00 40.15
C
ANISOU  662  CA  GLU A 318     5164   5032   5058    -54    -30   -117
C
ATOM    663  CB  GLU A 318       0.052  19.263 -14.523  1.00 39.10
C
ANISOU  663  CB  GLU A 318     5034   4963   4859    -60    -36    -45
C
ATOM    664  CG  GLU A 318       0.271  18.492 -15.799  1.00 41.10
C
ANISOU  664  CG  GLU A 318     5181   5159   5275    -19      9   -184
C
ATOM    665  CD  GLU A 318       0.118  19.357 -17.031  1.00 38.29
C
ANISOU  665  CD  GLU A 318     4479   5157   4911    107     25    128
C
ATOM    666  OE1 GLU A 318       1.126  19.619 -17.700  1.00 46.87
O
ANISOU  666  OE1 GLU A 318     6088   5866   5854    -27    -89   -299
O
ATOM    667  OE2 GLU A 318      -0.997  19.815 -17.354  1.00 46.71
O
ANISOU  667  OE2 GLU A 318     6297   5852   5598   -240    197   -211
O
ATOM    668  C   GLU A 318       0.583  19.530 -12.092  1.00 38.57
C
ANISOU  668  C   GLU A 318     4938   4896   4818    -31    -53    -85
C
ATOM    669  O   GLU A 318      -0.425  20.012 -11.578  1.00 38.13
O
ANISOU  669  O   GLU A 318     4923   4789   4774    -39   -135   -122
O
ATOM    670  N   TYR A 319       1.821  19.851 -11.705  1.00 38.78
N
ANISOU  670  N   TYR A 319     4998   4868   4867    -48    -21    -87
N
ATOM    671  CA  TYR A 319       2.079  20.701 -10.529  1.00 39.04
C
ANISOU  671  CA  TYR A 319     5000   4916   4916    -26    -53    -60
C
ATOM    672  CB  TYR A 319       2.884  19.937  -9.476  1.00 38.84
C
ANISOU  672  CB  TYR A 319     4972   4905   4879    -26    -72    -93
C
ATOM    673  CG  TYR A 319       2.172  18.689  -8.973  1.00 37.38
C
ANISOU  673  CG  TYR A 319     4832   4650   4719    -86     32    -11
C
ATOM    674  CD1 TYR A 319       2.258  17.460  -9.673  1.00 38.12
C
ANISOU  674  CD1 TYR A 319     4829   4759   4893      7     -6    -24
C
ATOM    675  CE1 TYR A 319       1.593  16.320  -9.215  1.00 36.71
C
ANISOU  675  CE1 TYR A 319     4646   4520   4781    -18   -157   -183
C
ATOM    676  CZ  TYR A 319       0.834  16.411  -8.065  1.00 36.25
C
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ANISOU  676  CZ  TYR A 319     4621   4505   4646   -178    -20    -20
C
ATOM    677  OH  TYR A 319       0.166  15.322  -7.573  1.00 39.25
O
ANISOU  677  OH  TYR A 319     5143   5009   4759     54   -255    -66
O
ATOM    678  CE2 TYR A 319       0.725  17.612  -7.374  1.00 37.40
C
ANISOU  678  CE2 TYR A 319     4648   4766   4794     39    -30    -82
C
ATOM    679  CD2 TYR A 319       1.389  18.736  -7.836  1.00 36.44
C
ANISOU  679  CD2 TYR A 319     4701   4522   4622     68   -116   -138
C
ATOM    680  C   TYR A 319       2.745  22.028 -10.889  1.00 39.24
C
ANISOU  680  C   TYR A 319     5014   4957   4938    -40    -57    -97
C
ATOM    681  O   TYR A 319       3.918  22.071 -11.266  1.00 39.11
O
ANISOU  681  O   TYR A 319     4977   4930   4951    -22    -85   -124
O
ATOM    682  N   LYS A 320       1.961  23.101 -10.790  1.00 39.64
N
ANISOU  682  N   LYS A 320     5077   5012   4970     -1    -53   -107
N
ATOM    683  CA  LYS A 320       2.398  24.454 -11.109  1.00 40.77
C
ANISOU  683  CA  LYS A 320     5193   5147   5150    -23    -13    -85
C
ATOM    684  CB  LYS A 320       1.310  25.173 -11.921  1.00 40.27
C
ANISOU  684  CB  LYS A 320     5129   5063   5107     21    -64    -45
C
ATOM    685  CG  LYS A 320       1.704  26.535 -12.547  1.00 46.09
C
ANISOU  685  CG  LYS A 320     6665   5282   5563   -484    537   -253
C
ATOM    686  CD  LYS A 320       0.609  27.084 -13.492  1.00 38.31
C
ANISOU  686  CD  LYS A 320     4594   5097   4864    287   -177    117
C
ATOM    687  CE  LYS A 320      -0.733  27.374 -12.771  1.00 47.84
C
ANISOU  687  CE  LYS A 320     6419   5509   6250   -354    338   -151
C
ATOM    688  NZ  LYS A 320      -1.892  27.744 -13.695  1.00 37.09
N
ANISOU  688  NZ  LYS A 320     4077   5276   4737    675   -795    197
N
ATOM    689  C   LYS A 320       2.759  25.250  -9.840  1.00 40.86
C
ANISOU  689  C   LYS A 320     5229   5123   5173     18    -10    -35
C
ATOM    690  O   LYS A 320       2.030  25.259  -8.843  1.00 40.72
O
ANISOU  690  O   LYS A 320     5252   5105   5111     38    -28    -57
O
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ATOM    691  N   CYS A 321       3.915  25.888  -9.894  1.00 41.68
N
ANISOU  691  N   CYS A 321     5350   5199   5287     18     -5    -32
N
ATOM    692  CA  CYS A 321       4.373  26.788  -8.860  1.00 42.24
C
ANISOU  692  CA  CYS A 321     5408   5260   5381     31      1    -18
C
ATOM    693  CB  CYS A 321       5.763  26.361  -8.379  1.00 42.35
C
ANISOU  693  CB  CYS A 321     5400   5274   5415      9     -9    -35
C
ATOM    694  SG  CYS A 321       6.500  27.426  -7.128  1.00 42.58
S
ANISOU  694  SG  CYS A 321     5484   5270   5421     50    -14    -77
S
ATOM    695  C   CYS A 321       4.411  28.191  -9.472  1.00 42.81
C
ANISOU  695  C   CYS A 321     5475   5310   5480      8     16     -9
C
ATOM    696  O   CYS A 321       5.156  28.422 -10.460  1.00 42.92
O
ANISOU  696  O   CYS A 321     5461   5316   5528     24     61     -9
O
ATOM    697  N   LYS A 322       3.570  29.085  -8.924  1.00 42.76
N
ANISOU  697  N   LYS A 322     5459   5348   5439     17     33    -26
N
ATOM    698  CA  LYS A 322       3.565  30.511  -9.287  1.00 42.86
C
ANISOU  698  CA  LYS A 322     5437   5374   5471     56    -15      9
C
ATOM    699  CB  LYS A 322       2.147  31.078  -9.435  1.00 43.24
C
ANISOU  699  CB  LYS A 322     5551   5409   5468     25     18    -36
C
ATOM    700  CG  LYS A 322       2.064  32.254 -10.426  1.00 44.33
C
ANISOU  700  CG  LYS A 322     5694   5515   5634     14    -35    -25
C
ATOM    701  CD  LYS A 322       0.634  32.831 -10.569  1.00 45.76
C
ANISOU  701  CD  LYS A 322     5744   5672   5970    -51     35   -111
C
ATOM    702  CE  LYS A 322       0.468  33.530 -11.933  1.00 40.52
C
ANISOU  702  CE  LYS A 322     4781   4752   5862   1225   -190    243
C
ATOM    703  NZ  LYS A 322      -0.714  34.463 -12.029  1.00 52.37
N
ANISOU  703  NZ  LYS A 322     7085   6923   5891   -760     97    -81
N
ATOM    704  C   LYS A 322       4.352  31.332  -8.284  1.00 42.99
C
ANISOU  704  C   LYS A 322     5456   5381   5497      1     30      0
C
ATOM    705  O   LYS A 322       4.196  31.206  -7.065  1.00 42.73
O
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ANISOU  705  O   LYS A 322     5391   5361   5482     50     28    -24
O
ATOM    706  N   VAL A 323       5.220  32.172  -8.823  1.00 43.35
N
ANISOU  706  N   VAL A 323     5501   5422   5545    -16    -11     12
N
ATOM    707  CA  VAL A 323       6.125  32.979  -8.025  1.00 42.78
C
ANISOU  707  CA  VAL A 323     5428   5354   5472    -14    -20    -20
C
ATOM    708  CB  VAL A 323       7.586  32.528  -8.212  1.00 42.83
C
ANISOU  708  CB  VAL A 323     5397   5384   5491    -25    -20     12
C
ATOM    709  CG1 VAL A 323       8.557  33.587  -7.703  1.00 41.95
C
ANISOU  709  CG1 VAL A 323     5327   5304   5305     17    -15    -62
C
ATOM    710  CG2 VAL A 323       7.811  31.192  -7.509  1.00 43.44
C
ANISOU  710  CG2 VAL A 323     5415   5409   5681     24     -7    -27
C
ATOM    711  C   VAL A 323       5.942  34.423  -8.432  1.00 42.81
C
ANISOU  711  C   VAL A 323     5441   5360   5463    -14    -20    -44
C
ATOM    712  O   VAL A 323       6.102  34.796  -9.621  1.00 42.57
O
ANISOU  712  O   VAL A 323     5408   5357   5408    -89     29    -68
O
ATOM    713  N   SER A 324       5.597  35.219  -7.421  1.00 42.64
N
ANISOU  713  N   SER A 324     5419   5369   5414     -2     -9    -59
N
ATOM    714  CA  SER A 324       5.207  36.605  -7.584  1.00 42.51
C
ANISOU  714  CA  SER A 324     5426   5317   5408    -11     -3    -71
C
ATOM    715  CB  SER A 324       3.750  36.783  -7.154  1.00 42.22
C
ANISOU  715  CB  SER A 324     5364   5281   5394     16    -26    -72
C
ATOM    716  OG  SER A 324       2.864  36.502  -8.216  1.00 41.92
O
ANISOU  716  OG  SER A 324     5332   5206   5387     19     53   -145
O
ATOM    717  C   SER A 324       6.104  37.522  -6.760  1.00 43.07
C
ANISOU  717  C   SER A 324     5479   5404   5481    -32    -10    -59
C
ATOM    718  O   SER A 324       6.352  37.271  -5.575  1.00 42.70
O
ANISOU  718  O   SER A 324     5452   5352   5420    -41    -68    -72
O
ATOM    719  N   ASN A 325       6.571  38.596  -7.396  1.00 44.33
N
ANISOU  719  N   ASN A 325     5633   5581   5628    -43     19    -83
N
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ATOM    720  CA  ASN A 325       7.437  39.570  -6.724  1.00 45.40
C
ANISOU  720  CA  ASN A 325     5802   5719   5727    -31     13    -62
C
ATOM    721  CB  ASN A 325       8.886  39.074  -6.668  1.00 45.78
C
ANISOU  721  CB  ASN A 325     5807   5817   5767    -17     24    -48
C
ATOM    722  CG  ASN A 325       9.749  39.887  -5.724  1.00 47.87
C
ANISOU  722  CG  ASN A 325     6012   6087   6088    -56    -15    -90
C
ATOM    723  OD1 ASN A 325       9.252  40.493  -4.758  1.00 51.73
O
ANISOU  723  OD1 ASN A 325     6606   6613   6436     43     24   -165
O
ATOM    724  ND2 ASN A 325      11.055  39.898  -5.986  1.00 49.10
N
ANISOU  724  ND2 ASN A 325     6088   6256   6312     27     72     40
N
ATOM    725  C   ASN A 325       7.379  40.924  -7.396  1.00 45.82
C
ANISOU  725  C   ASN A 325     5904   5749   5757    -16     29    -60
C
ATOM    726  O   ASN A 325       7.568  41.032  -8.624  1.00 46.11
O
ANISOU  726  O   ASN A 325     5966   5817   5735      8     24    -72
O
ATOM    727  N   LYS A 326       7.106  41.945  -6.581  1.00 46.40
N
ANISOU  727  N   LYS A 326     5999   5832   5798      6     54   -106
N
ATOM    728  CA  LYS A 326       7.088  43.359  -6.999  1.00 46.62
C
ANISOU  728  CA  LYS A 326     6011   5855   5844    -28     75    -54
C
ATOM    729  CB  LYS A 326       6.596  44.250  -5.847  1.00 46.66
C
ANISOU  729  CB  LYS A 326     6026   5795   5908    -14     78    -87
C
ATOM    730  CG  LYS A 326       5.693  43.541  -4.808  1.00 46.45
C
ANISOU  730  CG  LYS A 326     6008   5829   5811      1    106    -66
C
ATOM    731  CD  LYS A 326       5.224  44.500  -3.730  1.00 46.76
C
ANISOU  731  CD  LYS A 326     6052   5871   5842    -23    128    -26
C
ATOM    732  CE  LYS A 326       4.627  43.755  -2.527  1.00 47.92
C
ANISOU  732  CE  LYS A 326     6179   6075   5951    -22     57     57
C
ATOM    733  NZ  LYS A 326       3.645  44.615  -1.795  1.00 46.79
N
ANISOU  733  NZ  LYS A 326     6086   5950   5742     84    143     63
N
ATOM    734  C   LYS A 326       8.492  43.774  -7.398  1.00 47.27
C
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ANISOU  734  C   LYS A 326     6099   5947   5913    -66     66    -56
C
ATOM    735  O   LYS A 326       9.180  44.487  -6.654  1.00 48.18
O
ANISOU  735  O   LYS A 326     6284   6034   5987    -48     39     -1
O
ATOM    736  N   ALA A 327       8.916  43.299  -8.570  1.00 48.04
N
ANISOU  736  N   ALA A 327     6153   6097   6003    -80     76    -72
N
ATOM    737  CA  ALA A 327      10.266  43.501  -9.120  1.00 48.25
C
ANISOU  737  CA  ALA A 327     6151   6154   6027    -80     65    -43
C
ATOM    738  CB  ALA A 327      11.322  42.844  -8.247  1.00 48.36
C
ANISOU  738  CB  ALA A 327     6156   6153   6064    -60     40    -40
C
ATOM    739  C   ALA A 327      10.305  42.901 -10.522  1.00 48.66
C
ANISOU  739  C   ALA A 327     6209   6190   6089    -90     89    -47
C
ATOM    740  O   ALA A 327      11.017  43.403 -11.396  1.00 49.36
O
ANISOU  740  O   ALA A 327     6216   6343   6195   -143    160    -32
O
ATOM    741  N   LEU A 328       9.531  41.834 -10.732  1.00 48.61
N
ANISOU  741  N   LEU A 328     6214   6128   6125    -66     61    -36
N
ATOM    742  CA  LEU A 328       9.411  41.216 -12.056  1.00 48.46
C
ANISOU  742  CA  LEU A 328     6198   6118   6096     -1     44     -5
C
ATOM    743  CB  LEU A 328       8.993  39.743 -11.934  1.00 48.19
C
ANISOU  743  CB  LEU A 328     6138   6070   6100     13     48      9
C
ATOM    744  CG  LEU A 328      10.002  38.667 -11.520  1.00 48.23
C
ANISOU  744  CG  LEU A 328     6153   6038   6133      9     15     36
C
ATOM    745  CD1 LEU A 328       9.283  37.550 -10.802  1.00 46.88
C
ANISOU  745  CD1 LEU A 328     5933   5924   5956     -6      2     89
C
ATOM    746  CD2 LEU A 328      10.797  38.134 -12.728  1.00 46.84
C
ANISOU  746  CD2 LEU A 328     6059   5772   5966     30    -18      8
C
ATOM    747  C   LEU A 328       8.377  41.962 -12.905  1.00 48.82
C
ANISOU  747  C   LEU A 328     6215   6170   6161     42     47      3
C
ATOM    748  O   LEU A 328       7.346  42.391 -12.370  1.00 49.39
O
ANISOU  748  O   LEU A 328     6288   6214   6264     62     78    -17
O
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ATOM    749  N   PRO A 329       8.627  42.096 -14.233  1.00 48.99
N
ANISOU  749  N   PRO A 329     6230   6210   6172     52     35     20
N
ATOM    750  CA  PRO A 329       7.583  42.691 -15.083  1.00 48.98
C
ANISOU  750  CA  PRO A 329     6183   6202   6224     38     16     11
C
ATOM    751  CB  PRO A 329       8.121  42.512 -16.512  1.00 48.81
C
ANISOU  751  CB  PRO A 329     6180   6199   6165     26      5     20
C
ATOM    752  CG  PRO A 329       9.255  41.473 -16.402  1.00 49.03
C
ANISOU  752  CG  PRO A 329     6235   6230   6164     50    -11     24
C
ATOM    753  CD  PRO A 329       9.824  41.712 -15.016  1.00 49.11
C
ANISOU  753  CD  PRO A 329     6245   6228   6184     54     26     18
C
ATOM    754  C   PRO A 329       6.275  41.925 -14.898  1.00 49.47
C
ANISOU  754  C   PRO A 329     6237   6232   6324     32     28     24
C
ATOM    755  O   PRO A 329       5.199  42.555 -14.828  1.00 50.19
O
ANISOU  755  O   PRO A 329     6307   6296   6465     82     62     20
O
ATOM    756  N   ALA A 330       6.386  40.588 -14.815  1.00 49.21
N
ANISOU  756  N   ALA A 330     6236   6180   6279     31     21     35
N
ATOM    757  CA  ALA A 330       5.267  39.685 -14.511  1.00 48.97
C
ANISOU  757  CA  ALA A 330     6221   6162   6220      0     15     46
C
ATOM    758  C   ALA A 330       5.734  38.538 -13.611  1.00 48.44
C
ANISOU  758  C   ALA A 330     6145   6082   6176     14     16     18
C
ATOM    759  O   ALA A 330       6.938  38.338 -13.433  1.00 48.63
O
ANISOU  759  O   ALA A 330     6183   6095   6196     22      6     21
O
ATOM    760  CB  ALA A 330       4.638  39.170 -15.796  1.00 49.45
C
ANISOU  760  CB  ALA A 330     6282   6264   6242     -3     41     22
C
ATOM    761  N   SER A 331       4.774  37.789 -13.057  1.00 47.86
N
ANISOU  761  N   SER A 331     6127   5988   6070     15     23     18
N
ATOM    762  CA  SER A 331       5.044  36.573 -12.279  1.00 47.47
C
ANISOU  762  CA  SER A 331     6076   5962   5998     20     52     -2
C
ATOM    763  CB  SER A 331       3.732  35.989 -11.759  1.00 47.76
C
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ANISOU  763  CB  SER A 331     6111   5968   6068    -34     62     -6
C
ATOM    764  OG  SER A 331       3.328  36.636 -10.566  1.00 49.07
O
ANISOU  764  OG  SER A 331     6264   6200   6180    -65    112    -82
O
ATOM    765  C   SER A 331       5.784  35.490 -13.063  1.00 46.93
C
ANISOU  765  C   SER A 331     6026   5870   5936     45     11     17
C
ATOM    766  O   SER A 331       5.841  35.530 -14.306  1.00 46.88
O
ANISOU  766  O   SER A 331     6028   5874   5910     64     -8     49
O
ATOM    767  N   ILE A 332       6.349  34.524 -12.326  1.00 46.46
N
ANISOU  767  N   ILE A 332     5955   5859   5838     52      8     10
N
ATOM    768  CA  ILE A 332       6.997  33.345 -12.921  1.00 45.16
C
ANISOU  768  CA  ILE A 332     5784   5664   5710     32      1    -50
C
ATOM    769  CB  ILE A 332       8.447  33.111 -12.418  1.00 45.49
C
ANISOU  769  CB  ILE A 332     5827   5705   5750     38     30    -55
C
ATOM    770  CG1 ILE A 332       9.226  34.425 -12.299  1.00 45.00
C
ANISOU  770  CG1 ILE A 332     5746   5597   5752      3      1    -96
C
ATOM    771  CD1 ILE A 332      10.603  34.263 -11.676  1.00 44.54
C
ANISOU  771  CD1 ILE A 332     5753   5514   5657     62     -2    -95
C
ATOM    772  CG2 ILE A 332       9.199  32.107 -13.353  1.00 46.08
C
ANISOU  772  CG2 ILE A 332     5899   5694   5914      5      5    -81
C
ATOM    773  C   ILE A 332       6.212  32.091 -12.614  1.00 45.22
C
ANISOU  773  C   ILE A 332     5786   5699   5695     11     19    -20
C
ATOM    774  O   ILE A 332       5.959  31.784 -11.447  1.00 45.15
O
ANISOU  774  O   ILE A 332     5742   5739   5670     47    -18    -46
O
ATOM    775  N   GLU A 333       5.846  31.365 -13.675  1.00 45.30
N
ANISOU  775  N   GLU A 333     5774   5702   5736    -22     17      4
N
ATOM    776  CA  GLU A 333       5.198  30.059 -13.561  1.00 45.04
C
ANISOU  776  CA  GLU A 333     5702   5658   5752      6     34     -3
C
ATOM    777  CB  GLU A 333       3.920  30.002 -14.403  1.00 45.11
C
ANISOU  777  CB  GLU A 333     5759   5677   5704     -3     34     16
C
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ATOM    778  CG  GLU A 333       2.743  30.808 -13.893  1.00 46.10
C
ANISOU  778  CG  GLU A 333     5802   5868   5845      9     -6     18
C
ATOM    779  CD  GLU A 333       1.567  30.734 -14.839  1.00 47.62
C
ANISOU  779  CD  GLU A 333     6049   5979   6064    -46      8     80
C
ATOM    780  OE1 GLU A 333       0.502  31.308 -14.524  1.00 49.66
O
ANISOU  780  OE1 GLU A 333     6257   6258   6355    147    141     19
O
ATOM    781  OE2 GLU A 333       1.706  30.101 -15.911  1.00 49.76
O
ANISOU  781  OE2 GLU A 333     6561   6209   6136     66     28    -65
O
ATOM    782  C   GLU A 333       6.112  28.961 -14.076  1.00 44.61
C
ANISOU  782  C   GLU A 333     5648   5599   5700     -8     55     47
C
ATOM    783  O   GLU A 333       6.661  29.064 -15.180  1.00 44.56
O
ANISOU  783  O   GLU A 333     5623   5595   5712    -41    123     71
O
ATOM    784  N   LYS A 334       6.230  27.892 -13.290  1.00 44.01
N
ANISOU  784  N   LYS A 334     5544   5539   5638     18     36     50
N
ATOM    785  CA  LYS A 334       6.873  26.659 -13.734  1.00 42.98
C
ANISOU  785  CA  LYS A 334     5422   5388   5518     15     17     31
C
ATOM    786  CB  LYS A 334       8.212  26.486 -13.006  1.00 43.19
C
ANISOU  786  CB  LYS A 334     5438   5429   5541     15     10     54
C
ATOM    787  CG  LYS A 334       9.342  27.415 -13.491  1.00 43.78
C
ANISOU  787  CG  LYS A 334     5486   5549   5597    -63     48    -57
C
ATOM    788  CD  LYS A 334       9.999  26.862 -14.756  1.00 47.27
C
ANISOU  788  CD  LYS A 334     6256   5959   5746    137   -131   -161
C
ATOM    789  CE  LYS A 334      11.210  27.670 -15.180  1.00 41.47
C
ANISOU  789  CE  LYS A 334     5573   4547   5633   -141    -13    547
C
ATOM    790  NZ  LYS A 334      10.822  28.944 -15.871  1.00 48.95
N
ANISOU  790  NZ  LYS A 334     5949   6476   6171   -108   -137   -288
N
ATOM    791  C   LYS A 334       5.942  25.479 -13.449  1.00 42.38
C
ANISOU  791  C   LYS A 334     5339   5347   5415     47     18      4
C
ATOM    792  O   LYS A 334       5.416  25.373 -12.342  1.00 41.36
O
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ANISOU  792  O   LYS A 334     5235   5235   5242     88     46     19
O
ATOM    793  N   THR A 335       5.737  24.606 -14.448  1.00 42.28
N
ANISOU  793  N   THR A 335     5315   5358   5388     22     -3      5
N
ATOM    794  CA  THR A 335       4.887  23.413 -14.297  1.00 42.27
C
ANISOU  794  CA  THR A 335     5328   5336   5394     20    -27    -22
C
ATOM    795  CB  THR A 335       3.669  23.442 -15.297  1.00 42.66
C
ANISOU  795  CB  THR A 335     5389   5366   5451     24    -40      7
C
ATOM    796  OG1 THR A 335       2.797  24.540 -14.973  1.00 43.84
O
ANISOU  796  OG1 THR A 335     5548   5558   5551     61    -31    -90
O
ATOM    797  CG2 THR A 335       2.849  22.137 -15.256  1.00 42.03
C
ANISOU  797  CG2 THR A 335     5251   5336   5381      1    -34     33
C
ATOM    798  C   THR A 335       5.691  22.094 -14.399  1.00 42.02
C
ANISOU  798  C   THR A 335     5275   5343   5344      6     -2      3
C
ATOM    799  O   THR A 335       6.591  21.962 -15.233  1.00 42.24
O
ANISOU  799  O   THR A 335     5317   5422   5307     -6     27     -4
O
ATOM    800  N   ILE A 336       5.364  21.130 -13.536  1.00 41.53
N
ANISOU  800  N   ILE A 336     5220   5253   5307    -22      0     -2
N
ATOM    801  CA  ILE A 336       6.033  19.830 -13.521  1.00 41.14
C
ANISOU  801  CA  ILE A 336     5192   5158   5280     -5     -6    -31
C
ATOM    802  CB  ILE A 336       7.112  19.767 -12.399  1.00 41.49
C
ANISOU  802  CB  ILE A 336     5260   5196   5307      8      7    -66
C
ATOM    803  CG1 ILE A 336       8.130  18.656 -12.661  1.00 41.08
C
ANISOU  803  CG1 ILE A 336     5207   5068   5332     72     -8    -97
C
ATOM    804  CD1 ILE A 336       9.561  19.137 -12.634  1.00 40.27
C
ANISOU  804  CD1 ILE A 336     5179   4874   5247     -8    -10    -97
C
ATOM    805  CG2 ILE A 336       6.480  19.580 -11.011  1.00 42.34
C
ANISOU  805  CG2 ILE A 336     5379   5259   5448    -35     90      0
C
ATOM    806  C   ILE A 336       5.046  18.664 -13.378  1.00 40.65
C
ANISOU  806  C   ILE A 336     5139   5100   5203     -7      0    -31
C
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ATOM    807  O   ILE A 336       4.003  18.801 -12.761  1.00 41.39
O
ANISOJ  807  O   ILE A 336     5205   5207   5311    -38    -23    -17
O
ATOM    808  N   SER A 337       5.387  17.522 -13.967  1.00 39.94
N
ANISOJ  808  N   SER A 337     5084   5004   5084    -68    -53    -17
N
ATOM    809  CA  SER A 337       4.678  16.250 -13.746  1.00 38.58
C
ANISOJ  809  CA  SER A 337     4946   4829   4883    -42    -91    -14
C
ATOM    810  CB  SER A 337       3.495  16.104 -14.717  1.00 38.30
C
ANISOJ  810  CB  SER A 337     4878   4805   4869    -19    -98     -9
C
ATOM    811  OG  SER A 337       3.996  15.979 -16.037  1.00 37.12
O
ANISOJ  811  OG  SER A 337     4890   4556   4658    -36   -329     74
O
ATOM    812  C   SER A 337       5.671  15.117 -13.992  1.00 37.26
C
ANISOJ  812  C   SER A 337     4761   4669   4727    -28    -55    -53
C
ATOM    813  O   SER A 337       6.763  15.356 -14.454  1.00 36.64
O
ANISOJ  813  O   SER A 337     4712   4560   4646    -72    -77   -119
O
ATOM    814  N   LYS A 338       5.259  13.888 -13.696  1.00 36.86
N
ANISOJ  814  N   LYS A 338     4689   4665   4651     34    -19    -58
N
ATOM    815  CA  LYS A 338       5.995  12.667 -14.048  1.00 36.00
C
ANISOJ  815  CA  LYS A 338     4571   4534   4570     -3    -18    -52
C
ATOM    816  CB  LYS A 338       5.191  11.468 -13.542  1.00 35.29
C
ANISOJ  816  CB  LYS A 338     4455   4494   4457      5     24    -42
C
ATOM    817  CG  LYS A 338       5.828  10.099 -13.681  1.00 33.67
C
ANISOJ  817  CG  LYS A 338     4244   4375   4173     27    -21     32
C
ATOM    818  CD  LYS A 338       4.832   8.999 -13.385  1.00 30.62
C
ANISOJ  818  CD  LYS A 338     3883   4010   3741     34    -66      1
C
ATOM    819  CE  LYS A 338       3.843   8.803 -14.522  1.00 29.42
C
ANISOJ  819  CE  LYS A 338     3949   3572   3656     25    104     81
C
ATOM    820  NZ  LYS A 338       4.576   8.396 -15.745  1.00 27.21
N
ANISOJ  820  NZ  LYS A 338     3843   3118   3374    -83   -117    132
N
ATOM    821  C   LYS A 338       6.258  12.571 -15.572  1.00 35.50
C
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ANISOU  821  C   LYS A 338     4535   4440   4512    -21    -20    -80
C
ATOM    822  O   LYS A 338       5.479  13.073 -16.374  1.00 34.30
O
ANISOU  822  O   LYS A 338     4439   4209   4381    -34      4   -116
O
ATOM    823  N   ALA A 339       7.366  11.950 -15.968  1.00 35.70
N
ANISOU  823  N   ALA A 339     4573   4471   4517    -35    -30    -65
N
ATOM    824  CA  ALA A 339       7.638  11.750 -17.393  1.00 36.15
C
ANISOU  824  CA  ALA A 339     4615   4521   4599    -15    -13    -58
C
ATOM    825  CB  ALA A 339       8.837  10.811 -17.606  1.00 36.05
C
ANISOU  825  CB  ALA A 339     4546   4589   4559    -45    -58    -37
C
ATOM    826  C   ALA A 339       6.373  11.204 -18.084  1.00 36.01
C
ANISOU  826  C   ALA A 339     4591   4506   4583    -12     -7    -66
C
ATOM    827  O   ALA A 339       5.767  10.235 -17.626  1.00 35.29
O
ANISOU  827  O   ALA A 339     4495   4403   4508     20      0    -69
O
ATOM    828  N   LYS A 340       5.957  11.871 -19.150  1.00 36.06
N
ANISOU  828  N   LYS A 340     4636   4483   4580    -50     15    -31
N
ATOM    829  CA  LYS A 340       4.776  11.478 -19.901  1.00 36.79
C
ANISOU  829  CA  LYS A 340     4727   4622   4626    -22     -2    -23
C
ATOM    830  CB  LYS A 340       4.201  12.675 -20.674  1.00 37.11
C
ANISOU  830  CB  LYS A 340     4729   4625   4746    -33     22    -34
C
ATOM    831  CG  LYS A 340       3.417  13.646 -19.808  1.00 38.15
C
ANISOU  831  CG  LYS A 340     4951   4783   4759    -17      8    -23
C
ATOM    832  CD  LYS A 340       3.035  14.930 -20.552  1.00 38.31
C
ANISOU  832  CD  LYS A 340     4857   4845   4852    -53    -56    -11
C
ATOM    833  CE  LYS A 340       2.454  15.928 -19.583  1.00 39.66
C
ANISOU  833  CE  LYS A 340     4859   5039   5171     67    -10    -26
C
ATOM    834  NZ  LYS A 340       2.557  17.333 -20.080  1.00 42.09
N
ANISOU  834  NZ  LYS A 340     5215   5411   5363    -28     21     40
N
ATOM    835  C   LYS A 340       5.120  10.297 -20.833  1.00 36.19
C
ANISOU  835  C   LYS A 340     4615   4591   4545      0      0    -14
C
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ATOM    836  O   LYS A 340       6.286   9.917 -20.940  1.00 36.01
O
ANISOU  836  O   LYS A 340     4613   4608   4461    -17     -8     -9
O
ATOM    837  N   GLY A 341       4.109   9.717 -21.486  1.00 35.13
N
ANISOU  837  N   GLY A 341     4487   4443   4417     -7      9    -27
N
ATOM    838  CA  GLY A 341       4.315   8.552 -22.351  1.00 33.53
C
ANISOU  838  CA  GLY A 341     4232   4341   4165     28    -19     20
C
ATOM    839  C   GLY A 341       3.679   7.281 -21.845  1.00 32.52
C
ANISOU  839  C   GLY A 341     4085   4155   4114     71    -32    -34
C
ATOM    840  O   GLY A 341       3.552   7.075 -20.628  1.00 31.86
O
ANISOU  840  O   GLY A 341     3925   4073   4106     82    -44    -75
O
ATOM    841  N   GLN A 342       3.276   6.427 -22.781  1.00 31.81
N
ANISOU  841  N   GLN A 342     4021   4126   3939     78    -15    -18
N
ATOM    842  CA  GLN A 342       2.697   5.123 -22.472  1.00 31.42
C
ANISOU  842  CA  GLN A 342     4041   3988   3909     45    -37    -59
C
ATOM    843  CB  GLN A 342       2.283   4.401 -23.770  1.00 31.69
C
ANISOU  843  CB  GLN A 342     4054   3993   3992     79    -26    -40
C
ATOM    844  CG  GLN A 342       1.017   4.931 -24.463  1.00 30.27
C
ANISOU  844  CG  GLN A 342     4081   3823   3597      2    -53   -130
C
ATOM    845  CD  GLN A 342      -0.282   4.551 -23.748  1.00 28.05
C
ANISOU  845  CD  GLN A 342     3804   3406   3445    149    -27     92
C
ATOM    846  OE1 GLN A 342      -0.345   3.562 -22.997  1.00 31.57
O
ANISOU  846  OE1 GLN A 342     4346   4036   3611     80    115   -150
O
ATOM    847  NE2 GLN A 342      -1.324   5.329 -23.982  1.00 27.78
N
ANISOU  847  NE2 GLN A 342     3742   3685   3128     63     86     28
N
ATOM    848  C   GLN A 342       3.699   4.278 -21.678  1.00 31.71
C
ANISOU  848  C   GLN A 342     4108   3972   3968      2    -33    -40
C
ATOM    849  O   GLN A 342       4.828   4.083 -22.128  1.00 31.42
O
ANISOU  849  O   GLN A 342     4162   3884   3891    -39   -112    -23
O
ATOM    850  N   PRO A 343       3.301   3.785 -20.489  1.00 32.23
N
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ANISOU  850  N   PRO A 343     4160   4035   4051     10    -31    -23
N
ATOM    851  CA  PRO A 343       4.181   2.960 -19.638  1.00 32.69
C
ANISOU  851  CA  PRO A 343     4213   4109   4098     -3     -4      6
C
ATOM    852  CB  PRO A 343       3.380   2.837 -18.349  1.00 32.19
C
ANISOU  852  CB  PRO A 343     4159   4011   4060     30    -13     10
C
ATOM    853  CG  PRO A 343       1.964   2.866 -18.832  1.00 32.66
C
ANISOU  853  CG  PRO A 343     4242   4047   4116      0     21    -24
C
ATOM    854  CD  PRO A 343       1.968   3.940 -19.879  1.00 32.17
C
ANISOU  854  CD  PRO A 343     4181   4052   3987     16    -21    -13
C
ATOM    855  C   PRO A 343       4.431   1.555 -20.220  1.00 33.20
C
ANISOU  855  C   PRO A 343     4284   4187   4141    -16     -2     31
C
ATOM    856  O   PRO A 343       3.523   0.944 -20.760  1.00 32.66
O
ANISOU  856  O   PRO A 343     4246   4100   4061    -46    -31     42
O
ATOM    857  N   ARG A 344       5.661   1.059 -20.113  1.00 34.11
N
ANISOU  857  N   ARG A 344     4385   4381   4194    -20    -12      7
N
ATOM    858  CA  ARG A 344       5.966  -0.318 -20.495  1.00 34.88
C
ANISOU  858  CA  ARG A 344     4443   4484   4326      4     -8    -16
C
ATOM    859  CB  ARG A 344       6.837  -0.389 -21.766  1.00 35.47
C
ANISOU  859  CB  ARG A 344     4420   4544   4511    -12    -30    -52
C
ATOM    860  CG  ARG A 344       6.369   0.413 -22.984  1.00 35.46
C
ANISOU  860  CG  ARG A 344     4558   4556   4357    -10    103    -41
C
ATOM    861  CD  ARG A 344       7.187  -0.019 -24.224  1.00 42.30
C
ANISOU  861  CD  ARG A 344     5121   5594   5357     27   -186   -291
C
ATOM    862  NE  ARG A 344       7.453   1.068 -25.179  1.00 34.97
N
ANISOU  862  NE  ARG A 344     4759   4835   3690    -15    779    214
N
ATOM    863  CZ  ARG A 344       8.223   0.943 -26.268  1.00 46.83
C
ANISOU  863  CZ  ARG A 344     5377   6384   6029   -370   -579   -303
C
ATOM    864  NH1 ARG A 344       8.798  -0.225 -26.541  1.00 36.80
N
ANISOU  864  NH1 ARG A 344     4533   4393   5057    477    227   -349
N
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ATOM    865  NH2 ARG A 344       8.406   1.976 -27.085  1.00 32.95
N
ANISOU  865  NH2 ARG A 344     4473   3988   4058   -185    138    349
N
ATOM    866  C   ARG A 344       6.652  -1.014 -19.326  1.00 35.55
C
ANISOU  866  C   ARG A 344     4503   4565   4439     -1      2    -55
C
ATOM    867  O   ARG A 344       7.600  -0.490 -18.751  1.00 35.51
O
ANISOU  867  O   ARG A 344     4476   4590   4426     24    -11    -37
O
ATOM    868  N   GLU A 345       6.144  -2.186 -18.971  1.00 35.97
N
ANISOU  868  N   GLU A 345     4588   4586   4489     -8    -41    -78
N
ATOM    869  CA  GLU A 345       6.656  -2.995 -17.880  1.00 36.16
C
ANISOU  869  CA  GLU A 345     4630   4626   4481      3    -56    -31
C
ATOM    870  CB  GLU A 345       5.668  -4.114 -17.573  1.00 36.66
C
ANISOU  870  CB  GLU A 345     4710   4666   4553      2    -39    -45
C
ATOM    871  CG  GLU A 345       5.939  -4.802 -16.249  1.00 38.92
C
ANISOU  871  CG  GLU A 345     5030   4961   4795     50    -70     23
C
ATOM    872  CD  GLU A 345       5.466  -6.244 -16.197  1.00 39.25
C
ANISOU  872  CD  GLU A 345     4949   4976   4987    -33    -88     12
C
ATOM    873  OE1 GLU A 345       6.215  -7.086 -15.680  1.00 41.62
O
ANISOU  873  OE1 GLU A 345     5509   5056   5247    -30     46    -48
O
ATOM    874  OE2 GLU A 345       4.360  -6.544 -16.660  1.00 41.29
O
ANISOU  874  OE2 GLU A 345     5302   5254   5132     24     -6    -54
O
ATOM    875  C   GLU A 345       8.014  -3.607 -18.213  1.00 36.11
C
ANISOU  875  C   GLU A 345     4648   4610   4459    -14    -51    -17
C
ATOM    876  O   GLU A 345       8.151  -4.270 -19.242  1.00 35.55
O
ANISOU  876  O   GLU A 345     4678   4510   4316    -23    -92     -1
O
ATOM    877  N   PRO A 346       9.029  -3.396 -17.338  1.00 35.96
N
ANISOU  877  N   PRO A 346     4575   4638   4446    -16    -46    -18
N
ATOM    878  CA  PRO A 346      10.320  -4.041 -17.561  1.00 35.46
C
ANISOU  878  CA  PRO A 346     4492   4581   4399      4    -42    -18
C
ATOM    879  CB  PRO A 346      11.182  -3.552 -16.380  1.00 35.73
C
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ANISOU  879  CB  PRO A 346     4524   4597   4452     12    -21      4
C
ATOM    880  CG  PRO A 346      10.228  -3.061 -15.358  1.00 35.62
C
ANISOU  880  CG  PRO A 346     4572   4580   4380     38    -12    -22
C
ATOM    881  CD  PRO A 346       9.046  -2.540 -16.136  1.00 35.89
C
ANISOU  881  CD  PRO A 346     4545   4611   4479     -7    -43    -41
C
ATOM    882  C   PRO A 346      10.299  -5.561 -17.570  1.00 35.18
C
ANISOU  882  C   PRO A 346     4416   4581   4370    -24    -79    -24
C
ATOM    883  O   PRO A 346       9.494  -6.194 -16.877  1.00 34.62
O
ANISOU  883  O   PRO A 346     4353   4580   4219    -12   -186    -66
O
ATOM    884  N   GLN A 347      11.219  -6.120 -18.349  1.00 35.18
N
ANISOU  884  N   GLN A 347     4543   4504   4317    -46    -63    -72
N
ATOM    885  CA  GLN A 347      11.631  -7.507 -18.254  1.00 35.53
C
ANISOU  885  CA  GLN A 347     4553   4530   4414      0    -45    -78
C
ATOM    886  CB  GLN A 347      11.789  -8.075 -19.670  1.00 36.10
C
ANISOU  886  CB  GLN A 347     4629   4569   4515      5    -25   -114
C
ATOM    887  CG  GLN A 347      10.539  -7.907 -20.521  1.00 37.59
C
ANISOU  887  CG  GLN A 347     4887   4687   4707     85    -90   -113
C
ATOM    888  CD  GLN A 347      10.854  -7.408 -21.902  1.00 40.93
C
ANISOU  888  CD  GLN A 347     5327   5075   5147    -59     -3      9
C
ATOM    889  OE1 GLN A 347      11.724  -7.946 -22.587  1.00 42.38
O
ANISOU  889  OE1 GLN A 347     5289   5375   5436     61     68    117
O
ATOM    890  NE2 GLN A 347      10.135  -6.381 -22.337  1.00 41.52
N
ANISOU  890  NE2 GLN A 347     5299   5090   5385     92   -137    -75
N
ATOM    891  C   GLN A 347      12.969  -7.538 -17.513  1.00 34.81
C
ANISOU  891  C   GLN A 347     4451   4436   4337    -31      7    -68
C
ATOM    892  O   GLN A 347      13.907  -6.895 -17.937  1.00 34.34
O
ANISOU  892  O   GLN A 347     4438   4322   4286    -90    -26    -42
O
ATOM    893  N   VAL A 348      13.034  -8.283 -16.409  1.00 34.50
N
ANISOU  893  N   VAL A 348     4388   4352   4366    -33     16     -8
N
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ATOM    894  CA  VAL A 348      14.195  -8.336 -15.520  1.00 34.25
C
ANISOU  894  CA  VAL A 348     4345   4345   4324    -31     17     -6
C
ATOM    895  CB  VAL A 348      13.798  -8.061 -14.027  1.00 34.35
C
ANISOU  895  CB  VAL A 348     4334   4344   4372    -35     28     27
C
ATOM    896  CG1 VAL A 348      14.988  -8.250 -13.096  1.00 33.51
C
ANISOU  896  CG1 VAL A 348     4238   4355   4138    -36     50    -12
C
ATOM    897  CG2 VAL A 348      13.222  -6.668 -13.844  1.00 33.93
C
ANISOU  897  CG2 VAL A 348     4281   4316   4294      5     17     -7
C
ATOM    898  C   VAL A 348      14.833  -9.720 -15.601  1.00 34.64
C
ANISOU  898  C   VAL A 348     4404   4383   4373    -32      6     27
C
ATOM    899  O   VAL A 348      14.156 -10.730 -15.359  1.00 34.49
O
ANISOU  899  O   VAL A 348     4366   4418   4317    -11    -34     44
O
ATOM    900  N   TYR A 349      16.126  -9.769 -15.935  1.00 34.98
N
ANISOU  900  N   TYR A 349     4437   4393   4459    -54     12     32
N
ATOM    901  CA  TYR A 349      16.835 -11.040 -16.125  1.00 35.60
C
ANISOU  901  CA  TYR A 349     4504   4476   4547    -57    -29     71
C
ATOM    902  CB  TYR A 349      17.128 -11.334 -17.612  1.00 33.85
C
ANISOU  902  CB  TYR A 349     4148   4389   4323    -53   -206     -7
C
ATOM    903  CG  TYR A 349      15.930 -11.322 -18.532  1.00 37.15
C
ANISOU  903  CG  TYR A 349     4880   4508   4724     99    192    -36
C
ATOM    904  CD1 TYR A 349      14.882 -12.237 -18.364  1.00 33.27
C
ANISOU  904  CD1 TYR A 349     4290   4016   4335    -10    -59     97
C
ATOM    905  CE1 TYR A 349      13.785 -12.242 -19.206  1.00 31.99
C
ANISOU  905  CE1 TYR A 349     4268   3911   3974     66   -115    123
C
ATOM    906  CZ  TYR A 349      13.707 -11.324 -20.253  1.00 36.97
C
ANISOU  906  CZ  TYR A 349     5013   4524   4509    156    357   -207
C
ATOM    907  OH  TYR A 349      12.592 -11.340 -21.085  1.00 32.56
O
ANISOU  907  OH  TYR A 349     3951   4398   4022    -11   -218    -91
O
ATOM    908  CE2 TYR A 349      14.726  10.404  20.457  1.00 31.78
C
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ANISOU  908  CE2 TYR A 349     4079   4051   3944   -130     10    -26
C
ATOM    909  CD2 TYR A 349      15.850 -10.416 -19.605  1.00 34.01
C
ANISOU  909  CD2 TYR A 349     4476   4272   4172     69    -61     92
C
ATOM    910  C   TYR A 349      18.143 -11.028 -15.368  1.00 36.74
C
ANISOU  910  C   TYR A 349     4676   4594   4687    -68    -58     59
C
ATOM    911  O   TYR A 349      18.887 -10.037 -15.418  1.00 37.20
O
ANISOU  911  O   TYR A 349     4797   4592   4743    -80   -156    107
O
ATOM    912  N   THR A 350      18.432 -12.130 -14.680  1.00 37.32
N
ANISOU  912  N   THR A 350     4742   4621   4817    -56    -66     36
N
ATOM    913  CA  THR A 350      19.718 -12.304 -14.026  1.00 38.14
C
ANISOU  913  CA  THR A 350     4825   4721   4943    -21    -81     20
C
ATOM    914  CB  THR A 350      19.559 -12.839 -12.597  1.00 38.40
C
ANISOU  914  CB  THR A 350     4860   4761   4966    -31    -61      7
C
ATOM    915  OG1 THR A 350      18.731 -14.018 -12.598  1.00 39.46
O
ANISOU  915  OG1 THR A 350     4927   4782   5282    -54   -167    -97
O
ATOM    916  CG2 THR A 350      18.928 -11.782 -11.709  1.00 37.43
C
ANISOU  916  CG2 THR A 350     4800   4532   4887     17   -112    -76
C
ATOM    917  C   THR A 350      20.611 -13.217 -14.868  1.00 38.74
C
ANISOU  917  C   THR A 350     4927   4769   5022      1    -79     18
C
ATOM    918  O   THR A 350      20.123 -14.185 -15.444  1.00 38.86
O
ANISOU  918  O   THR A 350     4914   4739   5112      8   -126     13
O
ATOM    919  N   LEU A 351      21.898 -12.871 -14.979  1.00 39.30
N
ANISOU  919  N   LEU A 351     4977   4875   5078      7    -62     40
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ATOM    920  CA  LEU A 351      22.867 -13.658 -15.755  1.00 40.29
C
ANISOU  920  CA  LEU A 351     5136   5014   5156      0    -38      5
C
ATOM    921  CB  LEU A 351      23.357 -12.912 -17.004  1.00 40.56
C
ANISOU  921  CB  LEU A 351     5169   5086   5156      3      7     12
C
ATOM    922  CG  LEU A 351      22.508 -11.927 -17.836  1.00 41.22
C
ANISOU  922  CG  LEU A 351     5191   5222   5247     -1     -7     19
C
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ATOM    923  CD1 LEU A 351      23.198 -11.617 -19.177  1.00 42.94
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ANISOU  923  CD1 LEU A 351     5594   5366   5355     47     57    -43
C
ATOM    924  CD2 LEU A 351      21.117 -12.418 -18.099  1.00 41.57
C
ANISOU  924  CD2 LEU A 351     5226   5213   5354     23    -32    -39
C
ATOM    925  C   LEU A 351      24.076 -14.028 -14.888  1.00 40.94
C
ANISOU  925  C   LEU A 351     5192   5092   5268      4    -33    -14
C
ATOM    926  O   LEU A 351      24.582 -13.189 -14.116  1.00 41.33
O
ANISOU  926  O   LEU A 351     5233   5217   5252      6     14      2
O
ATOM    927  N   PRO A 352      24.561 -15.277 -15.020  1.00 41.37
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ANISOU  927  N   PRO A 352     5252   5155   5309     -9    -38    -17
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C
ANISOU  928  CA  PRO A 352     5288   5166   5287      4    -22      0
C
ATOM    929  CB  PRO A 352      25.512 -17.225 -14.185  1.00 41.27
C
ANISOU  929  CB  PRO A 352     5261   5141   5277    -45    -23    -16
C
ATOM    930  CG  PRO A 352      25.003 -17.514 -15.565  1.00 41.74
C
ANISOU  930  CG  PRO A 352     5297   5231   5329    -13    -41     16
C
ATOM    931  CD  PRO A 352      24.147 -16.336 -15.966  1.00 41.31
C
ANISOU  931  CD  PRO A 352     5282   5099   5315      6      7    -17
C
ATOM    932  C   PRO A 352      27.006 -15.272 -14.759  1.00 41.59
C
ANISOU  932  C   PRO A 352     5340   5165   5297    -16      0     11
C
ATOM    933  O   PRO A 352      27.064 -14.880 -15.928  1.00 42.08
O
ANISOU  933  O   PRO A 352     5477   5215   5295     16     16    -12
O
ATOM    934  N   PRO A 353      28.089 -15.328 -13.967  1.00 41.79
N
ANISOU  934  N   PRO A 353     5347   5197   5334    -44      8     11
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ATOM    935  CA  PRO A 353      29.375 -14.972 -14.556  1.00 42.47
C
ANISOU  935  CA  PRO A 353     5405   5319   5412    -10     26    -14
C
ATOM    936  CB  PRO A 353      30.363 -15.451 -13.503  1.00 42.11
C
ANISOU  936  CB  PRO A 353     5366   5274   5359      6     19      1
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ATOM    937  CG  PRO A 353      29.616 -15.312 -12.210  1.00 41.83
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ANISOU  937  CG  PRO A 353     5318   5207   5368    -12     18     34
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ATOM    938  CD  PRO A 353      28.212 -15.662 -12.533  1.00 41.62
C
ANISOU  938  CD  PRO A 353     5287   5204   5320    -37      9     -1
C
ATOM    939  C   PRO A 353      29.664 -15.642 -15.914  1.00 43.38
C
ANISOU  939  C   PRO A 353     5539   5438   5506    -59      7      0
C
ATOM    940  O   PRO A 353      29.099 -16.686 -16.238  1.00 43.79
O
ANISOU  940  O   PRO A 353     5568   5453   5616    -92    -13      7
O
ATOM    941  N   SER A 354      30.550 -15.029 -16.692  1.00 44.02
N
ANISOU  941  N   SER A 354     5647   5507   5570    -62     32     25
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ATOM    942  CA  SER A 354      31.029 -15.600 -17.947  1.00 44.25
C
ANISOU  942  CA  SER A 354     5684   5544   5581    -36      2     16
C
ATOM    943  CB  SER A 354      31.801 -14.533 -18.728  1.00 43.63
C
ANISOU  943  CB  SER A 354     5643   5426   5508    -42      5     44
C
ATOM    944  OG  SER A 354      32.102 -14.957 -20.044  1.00 43.43
O
ANISOU  944  OG  SER A 354     5647   5312   5541    -41   -107     63
O
ATOM    945  C   SER A 354      31.932 -16.816 -17.684  1.00 44.69
C
ANISOU  945  C   SER A 354     5752   5587   5640     28      2     53
C
ATOM    946  O   SER A 354      32.576 -16.911 -16.628  1.00 45.23
O
ANISOU  946  O   SER A 354     5780   5703   5700    -78    -15     91
O
ATOM    947  N   ARG A 355      31.978 -17.740 -18.639  1.00 45.17
N
ANISOU  947  N   ARG A 355     5825   5641   5696    -10     22     54
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ATOM    948  CA  ARG A 355      32.923 -18.860 -18.570  1.00 45.90
C
ANISOU  948  CA  ARG A 355     5863   5750   5824     12     -2     65
C
ATOM    949  CB  ARG A 355      32.871 -19.735 -19.832  1.00 46.10
C
ANISOU  949  CB  ARG A 355     5934   5737   5845     20     17     36
C
ATOM    950  CG  ARG A 355      33.824 -20.954 -19.799  1.00 47.55
C
ANISOU  950  CG  ARG A 355     6059   5947   6060     67     78     50
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ATOM    951  CD  ARG A 355      33.145 -22.221 -19.262  1.00 49.46
C
ANISOU  951  CD  ARG A 355     6372   5960   6459    -34     23     14
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ANISOU  952  NE  ARG A 355     6419   6227   6849     47     33     24
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ATOM    953  CZ  ARG A 355      33.662 -24.659 -19.211  1.00 49.87
C
ANISOU  953  CZ  ARG A 355     5961   6130   6856     36     60     63
C
ATOM    954  NH1 ARG A 355      32.368 -24.974 -19.225  1.00 51.01
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ANISOU  954  NH1 ARG A 355     6530   6058   6792    -50     14     64
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ATOM    955  NH2 ARG A 355      34.566 -25.636 -19.183  1.00 51.06
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ANISOU  955  NH2 ARG A 355     6527   6353   6518   -114    122    111
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ATOM    956  C   ARG A 355      34.337 -18.338 -18.363  1.00 46.16
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ANISOU  956  C   ARG A 355     5873   5790   5874      3    -27     85
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ATOM    957  O   ARG A 355      35.002 -18.735 -17.402  1.00 46.73
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ANISOU  957  O   ARG A 355     5996   5863   5893     12    -54    137
O
ATOM    958  N   GLU A 356      34.784 -17.436 -19.244  1.00 46.08
N
ANISOU  958  N   GLU A 356     5863   5771   5872     22    -47    101
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ATOM    959  CA  GLU A 356      36.160 -16.914 -19.201  1.00 45.95
C
ANISOU  959  CA  GLU A 356     5824   5716   5915    -12    -25     83
C
ATOM    960  CB  GLU A 356      36.460 -16.024 -20.406  1.00 46.56
C
ANISOU  960  CB  GLU A 356     5923   5802   5963    -14    -29     55
C
ATOM    961  CG  GLU A 356      35.478 -16.076 -21.574  1.00 48.71
C
ANISOU  961  CG  GLU A 356     6157   6172   6178    -18    -52    -43
C
ATOM    962  CD  GLU A 356      35.388 -14.734 -22.325  1.00 44.20
C
ANISOU  962  CD  GLU A 356     5022   5601   6171   -315   -566    188
C
ATOM    963  OE1 GLU A 356      36.355 -13.927 -22.227  1.00 50.80
O
ANISOU  963  OE1 GLU A 356     6751   6418   6131    327     68     47
O
ATOM    964  OE2 GLU A 356      34.348 -14.493 -23.006  1.00 52.20
O
ANISOU  964  OE2 GLU A 356     7079   5919   6833   -107    191    -53
O
ATOM    965  C   GLU A 356      36.487 -16.133 -17.917  1.00 45.96
C
ANISOU  965  C   GLU A 356     5812   5714   5934     -1    -14     67
C
ATOM    966  O   GLU A 356      37.654 -16.022 -17.533  1.00 46.16
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ANISOU  966  O   GLU A 356     5833   5670   6036     10    -15     75
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ATOM    967  N   GLU A 357      35.465 -15.585 -17.259  1.00 46.00
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ANISOU  967  N   GLU A 357     5832   5718   5928     -5     -1     46
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ATOM    968  CA  GLU A 357      35.658 -14.822 -16.022  1.00 46.17
C
ANISOU  968  CA  GLU A 357     5858   5789   5893    -19    -29     37
C
ATOM    969  CB  GLU A 357      34.500 -13.832 -15.807  1.00 46.20
C
ANISOU  969  CB  GLU A 357     5855   5775   5922    -22    -31     25
C
ATOM    970  CG  GLU A 357      34.741 -12.830 -14.672  1.00 46.03
C
ANISOU  970  CG  GLU A 357     5890   5813   5786     -3     20      5
C
ATOM    971  CD  GLU A 357      33.511 -12.050 -14.288  1.00 45.84
C
ANISOU  971  CD  GLU A 357     5810   5736   5870     18    -15     23
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ATOM    972  OE1 GLU A 357      32.394 -12.574 -14.466  1.00 47.43
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ANISOU  972  OE1 GLU A 357     5997   5800   6223    -69     19     64
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ATOM    973  OE2 GLU A 357      33.665 -10.908 -13.793  1.00 47.18
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ANISOU  973  OE2 GLU A 357     6018   5915   5990    -47     69     47
O
ATOM    974  C   GLU A 357      35.791 -15.713 -14.789  1.00 46.48
C
ANISOU  974  C   GLU A 357     5902   5797   5962      2    -60     36
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ATOM    975  O   GLU A 357      36.116 -15.242 -13.695  1.00 46.82
O
ANISOU  975  O   GLU A 357     5954   5880   5956     12    -81     46
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ATOM    976  N   MET A 358      35.527 -17.000 -14.966  1.00 47.05
N
ANISOU  976  N   MET A 358     5945   5879   6053    -19    -52     49
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ATOM    977  CA  MET A 358      35.559 -17.963 -13.864  1.00 47.74
C
ANISOU  977  CA  MET A 358     6017   5957   6164    -17    -69     67
C
ATOM    978  CB  MET A 358      34.728 -19.192 -14.238  1.00 48.21
C
ANISOU  978  CB  MET A 358     6105   5944   6269    -34    -75     93
C
ATOM    979  CG  MET A 358      33.208 -18.945 -14.199  1.00 49.31
C
ANISOU  979  CG  MET A 358     6165   6106   6465     -8    -14     71
C
ATOM    980  SD  MET A 358      32.552 -19.075 -12.527  1.00 52.44
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ANISOU  980  SD  MET A 358     6730   6476   6717   -163     20    106
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ATOM    981  CE  MET A 358      32.822 -17.454 -11.834  1.00 51.39
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ANISOU  981  CE  MET A 358     6475   6527   6523     47    -35    165
C
ATOM    982  C   MET A 358      36.981 -18.353 -13.440  1.00 47.84
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ANISOU  982  C   MET A 358     6037   5968   6170    -13    -76     65
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ATOM    983  O   MET A 358      37.261 -19.524 -13.131  1.00 48.04
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ANISOU  983  O   MET A 358     6128   5948   6176    -23    -92     42
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ATOM    984  N   THR A 359      37.855 -17.348 -13.399  1.00 47.68
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ANISOU  984  N   THR A 359     6033   5948   6134    -20    -77     59
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ATOM    985  CA  THR A 359      39.290 -17.516 -13.163  1.00 47.64
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ANISOU  985  CA  THR A 359     6020   5995   6085      0    -63     39
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ATOM    986  CB  THR A 359      40.100 -17.070 -14.403  1.00 47.73
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ANISOU  986  CB  THR A 359     6003   6022   6108     15    -50     37
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ATOM    987  OG1 THR A 359      39.769 -17.914 -15.522  1.00 49.09
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ANISOU  987  OG1 THR A 359     6271   6170   6209     91    -41     16
O
ATOM    988  CG2 THR A 359      41.608 -17.130 -14.143  1.00 48.38
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ANISOU  988  CG2 THR A 359     6138   6071   6172     -8    -78      7
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ANISOU  989  C   THR A 359     5966   5981   6070     -5    -71     67
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ANISOU  990  O   THR A 359     6050   6064   6120      6    -66    108
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ATOM    991  N   LYS A 360      39.081 -15.545 -11.763  1.00 46.86
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ANISOU  991  N   LYS A 360     5868   5926   6009     11    -50     41
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ATOM    992  CA  LYS A 360      39.494 -14.595 -10.743  1.00 47.00
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ATOM    993  CB  LYS A 360      39.110 -13.153 -11.142  1.00 46.95
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ANISOU  993  CB  LYS A 360     5886   5968   5983     21     -5     46
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ATOM    994  CG  LYS A 360      38.907 -12.927 -12.637  1.00 47.63
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ANISOU  994  CG  LYS A 360     5963   6082   6050     61    -16    111
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ATOM    996  CE  LYS A 360      39.961 -12.875 -14.932  1.00 49.77
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ANISOU  996  CE  LYS A 360     6180   6480   6250     30    132     33
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ATOM    997  NZ  LYS A 360      41.160 -12.482 -15.751  1.00 53.54
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ANISOU  997  NZ  LYS A 360     6756   6647   6937     76      9    -32
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ATOM    998  C   LYS A 360      38.846 -15.001  -9.427  1.00 47.06
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ANISOU  998  C   LYS A 360     5905   5954   6021     12    -44     84
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ANISOU 1001  CA  ASN A 361     5932   5982   5992     48     -3     96
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ATOM   1002  CB  ASN A 361      39.554 -14.470  -5.963  1.00 47.64
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ANISOU 1002  CB  ASN A 361     5962   6070   6066     49    -24     69
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ATOM   1003  CG  ASN A 361      40.414 -13.225  -6.085  1.00 48.35
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ANISOU 1004  OD1 ASN A 361     6442   6402   6351    180     54    178
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ATOM   1005  ND2 ASN A 361      41.709 -13.426  -6.389  1.00 49.41
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ANISOU 1005  ND2 ASN A 361     6268   6360   6143     31     24     44
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ATOM   1007  O   ASN A 361      36.510 -14.058  -5.815  1.00 47.14
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ANISOU 1007  O   ASN A 361     5925   6049   5938    101    -35    168
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ATOM   1008  N   GLN A 362      37.081 -12.666  -7.503  1.00 46.36
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C
ATOM   1011  CG  GLN A 362      36.150 -10.334  -5.621  1.00 45.58
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ANISOU 1011  CG  GLN A 362     5724   5792   5802    -53     11     71
C
ATOM   1012  CD  GLN A 362      36.166  -8.891  -5.204  1.00 45.91
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ANISOU 1012  CD  GLN A 362     5751   5817   5875     17    163     20
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ATOM   1013  OE1 GLN A 362      35.381  -8.478  -4.363  1.00 47.89
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ANISOU 1013  OE1 GLN A 362     6152   5957   6085    -12     83    107
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ATOM   1014  NE2 GLN A 362      37.063   8.105   5.797  1.00 48.21
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ANISOU 1014  NE2 GLN A 362     6100   5959   6259     38      0     10
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ATOM   1015  C   GLN A 362      35.119 -12.139  -8.842  1.00 44.69
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ANISOU 1015  C   GLN A 362     5577   5712   5689     45      2     97
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ANISOU 1016  O   GLN A 362     5562   5769   5766     68     40     92
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ANISOU 1018  CA  VAL A 363     5413   5445   5488     52     -6     43
C
ATOM   1019  CB  VAL A 363      32.402 -13.912 -10.140  1.00 43.18
C
ANISOU 1019  CB  VAL A 363     5453   5459   5492     67     13     28
C
ATOM   1020  CG1 VAL A 363      33.520 -14.906 -10.390  1.00 43.95
C
ANISOU 1020  CG1 VAL A 363     5470   5624   5603     82     29     48
C
ATOM   1021  CG2 VAL A 363      31.600 -14.302  -8.882  1.00 42.30
C
ANISOU 1021  CG2 VAL A 363     5359   5266   5446     80     -4     36
C
ATOM   1022  C   VAL A 363      31.853 -11.440 -10.120  1.00 42.52
C
ANISOU 1022  C   VAL A 363     5376   5398   5380     63    -27     59
C
ATOM   1023  O   VAL A 363      31.447 -10.834  -9.104  1.00 42.81
O
ANISOU 1023  O   VAL A 363     5403   5365   5495     71    -45      3
O
ATOM   1024  N   SER A 364      31.354 -11.252 -11.343  1.00 41.31
N
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ANISOU 1024  N   SER A 364     5256   5207   5231     62     -5    118
N
ATOM   1025  CA  SER A 364      30.298 -10.280 -11.635  1.00 40.20
C
ANISOU 1025  CA  SER A 364     5150   5057   5065     36    -19    138
C
ATOM   1026  CB  SER A 364      30.652  -9.403 -12.850  1.00 39.70
C
ANISOU 1026  CB  SER A 364     5109   4974   5002     54    -65    171
C
ATOM   1027  OG  SER A 364      31.895  -8.732 -12.692  1.00 37.97
O
ANISOU 1027  OG  SER A 364     5007   4675   4744    119    -32    315
O
ATOM   1028  C   SER A 364      28.962 -10.967 -11.868  1.00 39.95
C
ANISOU 1028  C   SER A 364     5127   5016   5034     45    -31    160
C
ATOM   1029  O   SER A 364      28.831 -11.854 -12.735  1.00 39.44
O
ANISOU 1029  O   SER A 364     5142   4888   4955     54    -17    221
O
ATOM   1030  N   LEU A 365      27.981 -10.554 -11.071  1.00 39.87
N
ANISOU 1030  N   LEU A 365     5068   5037   5042     61    -21    140
N
ATOM   1031  CA  LEU A 365      26.589 -10.955 -11.269  1.00 39.99
C
ANISOU 1031  CA  LEU A 365     5074   5073   5045      9    -33     86
C
ATOM   1032  CB  LEU A 365      25.924 -11.321  -9.937  1.00 40.04
C
ANISOU 1032  CB  LEU A 365     5074   5098   5040    -11    -44     81
C
ATOM   1033  CG  LEU A 365      26.530 -12.451  -9.066  1.00 40.30
C
ANISOU 1033  CG  LEU A 365     5182   5030   5100     14    -46     30
C
ATOM   1034  CD1 LEU A 365      25.665 -12.646  -7.874  1.00 39.40
C
ANISOU 1034  CD1 LEU A 365     5149   4949   4869    -42     31    113
C
ATOM   1035  CD2 LEU A 365      26.697 -13.782  -9.784  1.00 39.06
C
ANISOU 1035  CD2 LEU A 365     5102   4928   4808     -9    -43     35
C
ATOM   1036  C   LEU A 365      25.801  -9.848 -11.985  1.00 39.79
C
ANISOU 1036  C   LEU A 365     4994   5066   5057     24     48     75
C
ATOM   1037  O   LEU A 365      25.823  -8.677 -11.582  1.00 38.88
O
ANISOU 1037  O   LEU A 365     4910   4982   4882     74    -17     36
O
ATOM   1038  N   THR A 366      25.099 -10.244 -13.044  1.00 39.92
N
ANISOU 1038  N   THR A 366     5000   5095   5069     45    -33     66
N
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ATOM   1039  CA  THR A 366      24.421  -9.292 -13.933  1.00 39.88
C
ANISOU 1039  CA  THR A 366     4988   5034   5128     11    -42     67
C
ATOM   1040  CB  THR A 366      24.903  -9.487 -15.393  1.00 39.60
C
ANISOU 1040  CB  THR A 366     4964   5029   5051     11    -16     62
C
ATOM   1041  OG1 THR A 366      26.320  -9.308 -15.459  1.00 38.90
O
ANISOU 1041  OG1 THR A 366     5015   4949   4816    -20   -181    162
O
ATOM   1042  CG2 THR A 366      24.235  -8.512 -16.335  1.00 38.62
C
ANISOU 1042  CG2 THR A 366     4770   4839   5062    -13     46     66
C
ATOM   1043  C   THR A 366      22.871  -9.311 -13.869  1.00 39.94
C
ANISOU 1043  C   THR A 366     4957   5035   5180     37    -21     65
C
ATOM   1044  O   THR A 366      22.232 -10.335 -14.103  1.00 39.93
O
ANISOU 1044  O   THR A 366     4869   5040   5262     43     12     60
O
ATOM   1045  N   CYS A 367      22.280  -8.161 -13.565  1.00 39.76
N
ANISOU 1045  N   CYS A 367     4930   5062   5115     29    -27     86
N
ATOM   1046  CA  CYS A 367      20.852  -7.960 -13.805  1.00 39.32
C
ANISOU 1046  CA  CYS A 367     4931   4985   5022     26     -8     80
C
ATOM   1047  CB  CYS A 367      20.233  -7.205 -12.634  1.00 39.39
C
ANISOU 1047  CB  CYS A 367     4944   5076   4946     21     -2    117
C
ATOM   1048  SG  CYS A 367      18.472  -7.483 -12.391  1.00 39.53
S
ANISOU 1048  SG  CYS A 367     4830   5094   5094     24   -129    170
S
ATOM   1049  C   CYS A 367      20.601  -7.210 -15.139  1.00 38.81
C
ANISOU 1049  C   CYS A 367     4865   4957   4923     15     -1     46
C
ATOM   1050  O   CYS A 367      21.014  -6.067 -15.311  1.00 38.63
O
ANISOU 1050  O   CYS A 367     4817   5047   4814      9     43    133
O
ATOM   1051  N   LEU A 368      19.929  -7.861 -16.076  1.00 38.38
N
ANISOU 1051  N   LEU A 368     4830   4891   4859     14      7     46
N
ATOM   1052  CA  LEU A 368      19.456  -7.190 -17.282  1.00 37.80
C
ANISOU 1052  CA  LEU A 368     4781   4779   4800    -21     24      8
C
ATOM   1053  CB  LEU A 368      19.625  -8.079 -18.516  1.00 37.58
C
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ANISOU 1053  CB  LEU A 368     4733   4775   4770    -33      5      0
C
ATOM   1054  CG  LEU A 368      18.982  -7.599 -19.827  1.00 37.13
C
ANISOU 1054  CG  LEU A 368     4703   4665   4738    -43     63    -35
C
ATOM   1055  CD1 LEU A 368      19.398  -6.178 -20.237  1.00 34.47
C
ANISOU 1055  CD1 LEU A 368     4419   4312   4366    -26    110   -219
C
ATOM   1056  CD2 LEU A 368      19.275  -8.606 -20.956  1.00 37.22
C
ANISOU 1056  CD2 LEU A 368     4639   4690   4810    -62     -1    -69
C
ATOM   1057  C   LEU A 368      17.999  -6.740 -17.158  1.00 37.59
C
ANISOU 1057  C   LEU A 368     4799   4734   4747    -15     12     21
C
ATOM   1058  O   LEU A 368      17.086  -7.556 -17.070  1.00 38.09
O
ANISOU 1058  O   LEU A 368     4826   4762   4883      0      0     19
O
ATOM   1059  N   VAL A 369      17.785  -5.433 -17.182  1.00 36.66
N
ANISOU 1059  N   VAL A 369     4710   4628   4590    -14      8    -31
N
ATOM   1060  CA  VAL A 369      16.437  -4.899 -17.150  1.00 35.51
C
ANISOU 1060  CA  VAL A 369     4618   4432   4441    -32     24    -25
C
ATOM   1061  CB  VAL A 369      16.240  -3.901 -15.978  1.00 35.04
C
ANISOU 1061  CB  VAL A 369     4579   4397   4336    -16      9    -42
C
ATOM   1062  CG1 VAL A 369      14.774  -3.571 -15.809  1.00 32.99
C
ANISOU 1062  CG1 VAL A 369     4372   4088   4074   -154     64    -67
C
ATOM   1063  CG2 VAL A 369      16.828  -4.445 -14.690  1.00 33.45
C
ANISOU 1063  CG2 VAL A 369     4399   4030   4280    -68     82    -84
C
ATOM   1064  C   VAL A 369      16.149  -4.214 -18.495  1.00 35.59
C
ANISOU 1064  C   VAL A 369     4633   4477   4411     -5     55    -52
C
ATOM   1065  O   VAL A 369      16.819  -3.261 -18.862  1.00 33.94
O
ANISOU 1065  O   VAL A 369     4433   4347   4113    -86     75     14
O
ATOM   1066  N   LYS A 370      15.142  -4.699 -19.212  1.00 35.68
N
ANISOU 1066  N   LYS A 370     4629   4439   4486      5     61    -52
N
ATOM   1067  CA  LYS A 370      14.862  -4.155 -20.524  1.00 36.56
C
ANISOU 1067  CA  LYS A 370     4733   4538   4619     -4     54    -72
C
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ATOM   1068  CB  LYS A 370      15.582  -4.963 -21.616  1.00 37.40
C
ANISOU 1068  CB  LYS A 370     4812   4631   4766     21     15    -67
C
ATOM   1069  CG  LYS A 370      14.926  -6.255 -22.047  1.00 38.42
C
ANISOU 1069  CG  LYS A 370     4880   4762   4953    -43    -18    -43
C
ATOM   1070  CD  LYS A 370      15.576  -6.722 -23.346  1.00 38.00
C
ANISOU 1070  CD  LYS A 370     4710   5016   4710   -111    -78   -144
C
ATOM   1071  CE  LYS A 370      14.530  -7.210 -24.325  1.00 42.54
C
ANISOU 1071  CE  LYS A 370     5280   5298   5583     88    107   -138
C
ATOM   1072  NZ  LYS A 370      14.737  -6.578 -25.665  1.00 40.11
N
ANISOU 1072  NZ  LYS A 370     5090   5259   4890      7     15    108
N
ATOM   1073  C   LYS A 370      13.393  -3.913 -20.847  1.00 36.36
C
ANISOU 1073  C   LYS A 370     4750   4479   4586     26     55    -79
C
ATOM   1074  O   LYS A 370      12.496  -4.426 -20.174  1.00 35.86
O
ANISOU 1074  O   LYS A 370     4750   4336   4537     38     36    -46
O
ATOM   1075  N   GLY A 371      13.164  -3.101 -21.873  1.00 36.40
N
ANISOU 1075  N   GLY A 371     4754   4514   4560     14    101    -70
N
ATOM   1076  CA  GLY A 371      11.821  -2.792 -22.348  1.00 36.43
C
ANISOU 1076  CA  GLY A 371     4719   4559   4561     16     44    -51
C
ATOM   1077  C   GLY A 371      10.981  -1.871 -21.467  1.00 36.58
C
ANISOU 1077  C   GLY A 371     4751   4566   4581     22      1    -59
C
ATOM   1078  O   GLY A 371       9.739  -1.850 -21.601  1.00 36.50
O
ANISOU 1078  O   GLY A 371     4704   4546   4617     42     12    -66
O
ATOM   1079  N   PHE A 372      11.624  -1.118 -20.566  1.00 35.97
N
ANISOU 1079  N   PHE A 372     4631   4483   4552    -15    -16    -47
N
ATOM   1080  CA  PHE A 372      10.853  -0.250 -19.635  1.00 34.98
C
ANISOU 1080  CA  PHE A 372     4543   4431   4315    -24    -65    -38
C
ATOM   1081  CB  PHE A 372      11.347  -0.338 -18.188  1.00 34.15
C
ANISOU 1081  CB  PHE A 372     4462   4305   4208    -30    -25      7
C
ATOM   1082  CG  PHE A 372      12.732   0.220 -17.952  1.00 31.81
C
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ANISOU 1082  CG  PHE A 372     4269   4040   3776      7     34     78
C
ATOM   1083  CD1 PHE A 372      12.902   1.534 -17.521  1.00 29.99
C
ANISOU 1083  CD1 PHE A 372     4046   4049   3299    -75     66     87
C
ATOM   1084  CE1 PHE A 372      14.158   2.046 -17.270  1.00 29.52
C
ANISOU 1084  CE1 PHE A 372     4091   3871   3254    -37     73     41
C
ATOM   1085  CZ  PHE A 372      15.278   1.245 -17.432  1.00 30.63
C
ANISOU 1085  CZ  PHE A 372     4204   3924   3509     -6     99     84
C
ATOM   1086  CE2 PHE A 372      15.126  -0.073 -17.842  1.00 30.13
C
ANISOU 1086  CE2 PHE A 372     4163   4003   3281    -10    108    120
C
ATOM   1087  CD2 PHE A 372      13.849  -0.580 -18.094  1.00 29.81
C
ANISOU 1087  CD2 PHE A 372     4076   3919   3330    -84    142    106
C
ATOM   1088  C   PHE A 372      10.664   1.198 -20.081  1.00 34.59
C
ANISOU 1088  C   PHE A 372     4487   4398   4257    -43   -112    -70
C
ATOM   1089  O   PHE A 372      11.487   1.745 -20.787  1.00 33.11
O
ANISOU 1089  O   PHE A 372     4403   4216   3961    -15   -136    -82
O
ATOM   1090  N   TYR A 373       9.549   1.783 -19.647  1.00 34.91
N
ANISOU 1090  N   TYR A 373     4521   4486   4255    -49   -176    -43
N
ATOM   1091  CA  TYR A 373       9.193   3.175 -19.910  1.00 35.31
C
ANISOU 1091  CA  TYR A 373     4589   4543   4284    -16   -143    -35
C
ATOM   1092  CB  TYR A 373       8.567   3.358 -21.307  1.00 35.68
C
ANISOU 1092  CB  TYR A 373     4580   4691   4283    -10   -157    -87
C
ATOM   1093  CG  TYR A 373       8.621   4.789 -21.762  1.00 34.18
C
ANISOU 1093  CG  TYR A 373     4411   4534   4041    -21   -162    -10
C
ATOM   1094  CD1 TYR A 373       9.690   5.243 -22.509  1.00 34.45
C
ANISOU 1094  CD1 TYR A 373     4413   4527   4147     23   -212    -54
C
ATOM   1095  CE1 TYR A 373       9.774   6.554 -22.912  1.00 34.42
C
ANISOU 1095  CE1 TYR A 373     4358   4572   4148   -101   -173    -16
C
ATOM   1096  CZ  TYR A 373       8.780   7.423 -22.558  1.00 34.48
C
ANISOU 1096  CZ  TYR A 373     4422   4435   4243    -45    -91      0
C
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ATOM   1097  OH  TYR A 373       8.873   8.715 -22.969  1.00 36.84
O
ANISOU 1097  OH  TYR A 373     4769   4819   4407    -28   -199     64
O
ATOM   1098  CE2 TYR A 373       7.702   7.007 -21.797  1.00 35.52
C
ANISOU 1098  CE2 TYR A 373     4524   4712   4258     83   -192    -76
C
ATOM   1099  CD2 TYR A 373       7.622   5.698 -21.414  1.00 33.27
C
ANISOU 1099  CD2 TYR A 373     4467   4373   3798    -92   -214     63
C
ATOM   1100  C   TYR A 373       8.202   3.675 -18.866  1.00 35.10
C
ANISOU 1100  C   TYR A 373     4544   4556   4234     -5   -101     20
C
ATOM   1101  O   TYR A 373       7.290   2.959 -18.526  1.00 35.49
O
ANISOU 1101  O   TYR A 373     4648   4556   4281     -4   -149   -115
O
ATOM   1102  N   PRO A 374       8.373   4.908 -18.352  1.00 34.96
N
ANISOU 1102  N   PRO A 374     4537   4551   4194     45    -66     59
N
ATOM   1103  CA  PRO A 374       9.466   5.844 -18.520  1.00 35.26
C
ANISOU 1103  CA  PRO A 374     4581   4561   4251     42    -69     28
C
ATOM   1104  CB  PRO A 374       8.950   7.099 -17.813  1.00 35.21
C
ANISOU 1104  CB  PRO A 374     4553   4560   4265     58    -42     60
C
ATOM   1105  CG  PRO A 374       7.997   6.614 -16.837  1.00 35.05
C
ANISOU 1105  CG  PRO A 374     4419   4469   4428     84    -49     79
C
ATOM   1106  CD  PRO A 374       7.309   5.495 -17.527  1.00 35.26
C
ANISOU 1106  CD  PRO A 374     4566   4516   4316     65   -103     72
C
ATOM   1107  C   PRO A 374      10.783   5.361 -17.913  1.00 35.32
C
ANISOU 1107  C   PRO A 374     4595   4588   4236     62    -26      0
C
ATOM   1108  O   PRO A 374      10.835   4.264 -17.344  1.00 35.13
O
ANISOU 1108  O   PRO A 374     4500   4669   4178     31    -57    -52
O
ATOM   1109  N   SER A 375      11.825   6.180 -18.055  1.00 35.27
N
ANISOU 1109  N   SER A 375     4649   4543   4206     33    -50    -18
N
ATOM   1110  CA  SER A 375      13.189   5.833 -17.672  1.00 35.64
C
ANISOU 1110  CA  SER A 375     4661   4565   4316     56     -9     -5
C
ATOM   1111  CB  SER A 375      14.180   6.826 -18.293  1.00 35.47
C
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ANISOU 1111  CB  SER A 375     4643   4554   4277     90    -42     37
C
ATOM   1112  OG  SER A 375      14.059   8.122 -17.713  1.00 35.13
O
ANISOU 1112  OG  SER A 375     4615   4635   4097    -15   -115     99
O
ATOM   1113  C   SER A 375      13.422   5.744 -16.151  1.00 36.11
C
ANISOU 1113  C   SER A 375     4725   4626   4366     77     20      5
C
ATOM   1114  O   SER A 375      14.398   5.153 -15.722  1.00 35.49
O
ANISOU 1114  O   SER A 375     4766   4553   4165    116     99    -42
O
ATOM   1115  N   ASP A 376      12.533   6.347  15.358  1.00 36.79
N
ANISOU 1115  N   ASP A 376     4838   4675   4462     79     35      8
N
ATOM   1116  CA  ASP A 376      12.622   6.326 -13.893  1.00 37.26
C
ANISOU 1116  CA  ASP A 376     4809   4708   4637     54     59    -73
C
ATOM   1117  CB  ASP A 376      11.505   7.175 -13.281  1.00 37.66
C
ANISOU 1117  CB  ASP A 376     4923   4705   4679     39     24    -73
C
ATOM   1118  CG  ASP A 376      11.316   8.474 -14.010  1.00 37.98
C
ANISOU 1118  CG  ASP A 376     5073   4681   4676    103     74    -82
C
ATOM   1119  OD1 ASP A 376      10.191   8.720 -14.495  1.00 38.29
O
ANISOU 1119  OD1 ASP A 376     5022   4872   4652    110     58   -124
O
ATOM   1120  OD2 ASP A 376      12.302   9.227 -14.118  1.00 35.66
O
ANISOU 1120  OD2 ASP A 376     4760   4253   4535    135     89    -76
O
ATOM   1121  C   ASP A 376      12.549   4.905 -13.354  1.00 37.15
C
ANISOU 1121  C   ASP A 376     4817   4718   4579     80     84    -76
C
ATOM   1122  O   ASP A 376      11.569   4.191 -13.564  1.00 36.68
O
ANISOU 1122  O   ASP A 376     4770   4615   4551     97    140   -112
O
ATOM   1123  N   ILE A 377      13.600   4.508 -12.637  1.00 37.17
N
ANISOU 1123  N   ILE A 377     4813   4723   4588     72     69   -107
N
ATOM   1124  CA  ILE A 377      13.763   3.128 -12.208  1.00 37.39
C
ANISOU 1124  CA  ILE A 377     4797   4801   4607     45     40    -64
C
ATOM   1125  CB  ILE A 377      14.301   2.230 -13.385  1.00 37.15
C
ANISOU 1125  CB  ILE A 377     4748   4758   4609     63     21    -92
C
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ATOM   1126  CG1 ILE A 377      14.247   0.732 -13.024  1.00 36.97
C
ANISOU 1126  CG1 ILE A 377     4634   4816   4597     20    -23    -72
C
ATOM   1127  CD1 ILE A 377      14.240  -0.238 -14.232  1.00 36.57
C
ANISOU 1127  CD1 ILE A 377     4633   4701   4559     59     46    -11
C
ATOM   1128  CG2 ILE A 377      15.680   2.712 -13.815  1.00 35.92
C
ANISOU 1128  CG2 ILE A 377     4679   4583   4385     86     48    -83
C
ATOM   1129  C   ILE A 377      14.714   3.107 -11.004  1.00 37.34
C
ANISOU 1129  C   ILE A 377     4800   4829   4556     19     37    -66
C
ATOM   1130  O   ILE A 377      15.420   4.080 -10.762  1.00 37.26
O
ANISOU 1130  O   ILE A 377     4794   4872   4491     24     40    -63
O
ATOM   1131  N   ALA A 378      14.715   2.004 -10.259  1.00 37.20
N
ANISOU 1131  N   ALA A 378     4763   4859   4511     46     40    -67
N
ATOM   1132  CA  ALA A 378      15.600   1.828  -9.108  1.00 37.25
C
ANISOU 1132  CA  ALA A 378     4784   4835   4533      7     69    -43
C
ATOM   1133  CB  ALA A 378      14.914   2.277  -7.836  1.00 36.48
C
ANISOU 1133  CB  ALA A 378     4699   4751   4411      9     47    -91
C
ATOM   1134  C   ALA A 378      16.010   0.362  -9.005  1.00 36.92
C
ANISOU 1134  C   ALA A 378     4754   4825   4447     10     95    -25
C
ATOM   1135  O   ALA A 378      15.193  -0.530  -9.200  1.00 36.27
O
ANISOU 1135  O   ALA A 378     4740   4750   4291     -5    121    -49
O
ATOM   1136  N   VAL A 379      17.279   0.120  -8.715  1.00 36.82
N
ANISOU 1136  N   VAL A 379     4725   4842   4420      2     94      1
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ATOM   1137  CA  VAL A 379      17.784  -1.248  -8.628  1.00 37.12
C
ANISOU 1137  CA  VAL A 379     4726   4809   4568    -25     45     13
C
ATOM   1138  CB  VAL A 379      18.544  -1.709  -9.905  1.00 36.60
C
ANISOU 1138  CB  VAL A 379     4604   4751   4550     -2     47    -13
C
ATOM   1139  CG1 VAL A 379      18.767  -3.219  -9.875  1.00 35.07
C
ANISOU 1139  CG1 VAL A 379     4394   4622   4307    -46     -4     35
C
ATOM   1140  CG2 VAL A 379      17.795  -1.317 -11.182  1.00 35.08
C
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ANISOU 1140  CG2 VAL A 379     4482   4481   4363     10    124     -1
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ATOM   1141  C   VAL A 379      18.671  -1.420  -7.396  1.00 38.16
C
ANISOU 1141  C   VAL A 379     4798   4927   4773    -24      7      3
C
ATOM   1142  O   VAL A 379      19.429  -0.532  -7.037  1.00 38.18
O
ANISOU 1142  O   VAL A 379     4785   4914   4805    -16    -25     12
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ATOM   1143  N   GLU A 380      18.537  -2.590  -6.782  1.00 39.23
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ANISOU 1143  N   GLU A 380     4938   5049   4919    -34    -11     35
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ATOM   1144  CA  GLU A 380      19.132  -2.979  -5.521  1.00 39.91
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ANISOU 1144  CA  GLU A 380     5001   5151   5009    -14    -15     58
C
ATOM   1145  CB  GLU A 380      18.105  -2.836  -4.402  1.00 40.43
C
ANISOU 1145  CB  GLU A 380     5124   5190   5045     -5    -16     64
C
ATOM   1146  CG  GLU A 380      18.362  -1.738  -3.389  1.00 42.17
C
ANISOU 1146  CG  GLU A 380     5360   5320   5342     32   -171     80
C
ATOM   1147  CD  GLU A 380      17.614  -2.017  -2.100  1.00 42.78
C
ANISOU 1147  CD  GLU A 380     5158   5727   5370    116      5    121
C
ATOM   1148  OE1 GLU A 380      18.231  -2.566  -1.163  1.00 47.83
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ANISOU 1148  OE1 GLU A 380     6101   6126   5945   -126     75     20
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ATOM   1149  OE2 GLU A 380      16.400  -1.757  -2.035  1.00 44.96
O
ANISOU 1149  OE2 GLU A 380     5954   5476   5650    139    -62     98
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ATOM   1150  C   GLU A 380      19.455  -4.455  -5.653  1.00 39.85
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ANISOU 1150  C   GLU A 380     5002   5135   5004    -37      4     77
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ATOM   1151  O   GLU A 380      18.764  -5.188  -6.373  1.00 40.25
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ANISOU 1151  O   GLU A 380     5041   5193   5055    -78     -3    155
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ATOM   1152  N   TRP A 381      20.525  -4.883  -4.991  1.00 39.62
N
ANISOU 1152  N   TRP A 381     4988   5103   4960    -22     19     92
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ATOM   1153  CA  TRP A 381      20.811  -6.302  -4.832  1.00 39.46
C
ANISOU 1153  CA  TRP A 381     4896   5090   5004     38     -4     35
C
ATOM   1154  CB  TRP A 381      22.186  -6.672  -5.399  1.00 36.87
C
ANISOU 1154  CB  TRP A 381     4655   4832   4520     30     23    -91
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ATOM   1155  CG  TRP A 381      22.339  -6.667  -6.907  1.00 35.55
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ANISOU 1155  CG  TRP A 381     4204   4698   4603     56   -104     34
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ATOM   1156  CD1 TRP A 381      22.580  -5.579  -7.708  1.00 34.03
C
ANISOU 1156  CD1 TRP A 381     4124   4434   4368     59    -71    -36
C
ATOM   1157  NE1 TRP A 381      22.702  -5.972  -9.020  1.00 32.72
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ANISOU 1157  NE1 TRP A 381     4017   4085   4329     60    -50    143
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ATOM   1158  CE2 TRP A 381      22.554  -7.332  -9.093  1.00 33.85
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ANISOU 1158  CE2 TRP A 381     3981   4555   4323    111    -94    101
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ATOM   1159  CD2 TRP A 381      22.337  -7.806  -7.779  1.00 33.47
C
ANISOU 1159  CD2 TRP A 381     3886   4432   4397     76    -69    127
C
ATOM   1160  CE3 TRP A 381      22.170  -9.179  -7.580  1.00 32.88
C
ANISOU 1160  CE3 TRP A 381     3976   4447   4068    -65   -127     39
C
ATOM   1161  CZ3 TRP A 381      22.231 -10.030  -8.681  1.00 35.44
C
ANISOU 1161  CZ3 TRP A 381     4009   4794   4660    101    -42    213
C
ATOM   1162  CH2 TRP A 381      22.435  -9.520  -9.972  1.00 34.99
C
ANISOU 1162  CH2 TRP A 381     4060   4680   4552     47      1    121
C
ATOM   1163  CZ2 TRP A 381      22.611  -8.179 -10.191  1.00 33.99
C
ANISOU 1163  CZ2 TRP A 381     4025   4431   4455     65    -84    182
C
ATOM   1164  C   TRP A 381      20.740  -6.654  -3.337  1.00 40.26
C
ANISOU 1164  C   TRP A 381     5035   5192   5067     47    -30     55
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ATOM   1165  O   TRP A 381      20.945  -5.799  -2.475  1.00 39.66
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ANISOU 1165  O   TRP A 381     4949   5140   4979    133    -91     17
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ATOM   1166  N   GLU A 382      20.443  -7.914  -3.051  1.00 41.50
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ANISOU 1166  N   GLU A 382     5218   5300   5247     27    -21     45
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ATOM   1167  CA  GLU A 382      20.251  -8.407  -1.685  1.00 42.87
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ANISOU 1167  CA  GLU A 382     5409   5466   5411     39    -22     74
C
ATOM   1168  CB  GLU A 382      18.793  -8.269  -1.244  1.00 43.55
C
ANISOU 1168  CB  GLU A 382     5498   5513   5534     40      6     64
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ATOM   1169  CG  GLU A 382      18.342  -6.887  -0.771  1.00 46.25
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ANISOU 1169  CG  GLU A 382     5998   5768   5807    -22     21     16
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ATOM   1170  CD  GLU A 382      16.931  -6.573  -1.248  1.00 44.15
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ANISOU 1170  CD  GLU A 382     5607   6334   4832    111     89    195
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ATOM   1171  OE1 GLU A 382      16.003  -6.614  -0.420  1.00 48.91
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ANISOU 1171  OE1 GLU A 382     6266   6173   6143     76    184     79
O
ATOM   1172  OE2 GLU A 382      16.748  -6.330  -2.470  1.00 51.39
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ANISOU 1172  OE2 GLU A 382     6325   6387   6814    -32    -58     41
O
ATOM   1173  C   GLU A 382      20.600  -9.891  -1.653  1.00 43.58
C
ANISOU 1173  C   GLU A 382     5532   5524   5502     23    -11     78
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ATOM   1174  O   GLU A 382      20.553 -10.579  -2.697  1.00 42.96
O
ANISOU 1174  O   GLU A 382     5527   5460   5335     -5    -20     53
O
ATOM   1175  N   SER A 383      20.946 -10.360  -0.445  1.00 44.09
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ANISOU 1175  N   SER A 383     5623   5628   5499     25     18    122
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ATOM   1176  CA  SER A 383      21.216 -11.777  -0.161  1.00 44.79
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ANISOU 1176  CA  SER A 383     5700   5676   5639      6     37    118
C
ATOM   1177  CB  SER A 383      22.699 -12.113  -0.341  1.00 44.80
C
ANISOU 1177  CB  SER A 383     5702   5678   5642     31     37    101
C
ATOM   1178  OG  SER A 383      22.882 -13.478  -0.685  1.00 45.36
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ANISOU 1178  OG  SER A 383     5763   5641   5831     -6     83    127
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ATOM   1179  C   SER A 383      20.796 -12.028   1.283  1.00 45.26
C
ANISOU 1179  C   SER A 383     5775   5768   5653     -9     11    120
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ATOM   1180  O   SER A 383      20.992 -11.161   2.160  1.00 45.04
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ANISOU 1180  O   SER A 383     5758   5784   5569     19     43    149
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ATOM   1181  N   ASN A 384      20.208 -13.202   1.518  1.00 46.24
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ANISOU 1181  N   ASN A 384     5912   5856   5798      7     -6    130
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ATOM   1182  CA  ASN A 384      19.541 -13.516   2.797  1.00 47.30
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ANISOU 1182  CA  ASN A 384     5994   6002   5973      9     40     89
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ATOM   1183  CB  ASN A 384      20.223 -14.686   3.546  1.00 47.81
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ANISOU 1183  CB  ASN A 384     6076   6055   6032     50     28     85
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ATOM   1184  CG  ASN A 384      21.711 -14.835   3.202  1.00 49.23
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ANISOU 1184  CG  ASN A 384     6239   6244   6220     11    -19     15
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ATOM   1185  OD1 ASN A 384      22.561 -14.139   3.771  1.00 51.62
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ANISOU 1185  OD1 ASN A 384     6694   6509   6407    -81   -122    -51
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ATOM   1186  ND2 ASN A 384      22.030 -15.768   2.276  1.00 50.24
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ANISOU 1186  ND2 ASN A 384     6461   6386   6242    154     -7     90
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ATOM   1187  C   ASN A 384      19.305 -12.315   3.720  1.00 47.46
C
ANISOU 1187  C   ASN A 384     6002   5998   6034      3     30     68
C
ATOM   1188  O   ASN A 384      19.988 -12.138   4.745  1.00 47.50
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ANISOU 1188  O   ASN A 384     5997   6046   6002    -31     14    128
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ATOM   1189  N   GLY A 385      18.354 -11.468   3.321  1.00 48.01
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ANISOU 1189  N   GLY A 385     6027   6061   6150     -4     39     51
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ATOM   1190  CA  GLY A 385      17.871 -10.396   4.198  1.00 48.23
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ANISOU 1190  CA  GLY A 385     6064   6061   6200     13     51     19
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ATOM   1191  C   GLY A 385      18.621  -9.098   4.087  1.00 48.46
C
ANISOU 1191  C   GLY A 385     6080   6127   6205     -3     47     15
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ATOM   1192  O   GLY A 385      18.014  -8.041   3.849  1.00 49.13
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ANISOU 1192  O   GLY A 385     6172   6193   6300      0     74     -4
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ATOM   1193  N   GLN A 386      19.938  -9.186   4.258  1.00 48.32
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ANISOU 1193  N   GLN A 386     6069   6151   6136     -3    -15     14
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ATOM   1194  CA  GLN A 386      20.841  -8.054   4.091  1.00 48.32
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ANISOU 1194  CA  GLN A 386     6053   6229   6077    -28    -15     30
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ATOM   1195  CB  GLN A 386      22.184  -8.360   4.790  1.00 48.91
C
ANISOU 1195  CB  GLN A 386     6138   6313   6130    -23    -19     49
C
ATOM   1196  CG  GLN A 386      22.173  -8.184   6.332  1.00 49.93
C
ANISOU 1196  CG  GLN A 386     6349   6323   6297     12     17    -18
C
ATOM   1197  CD  GLN A 386      21.542  -6.872   6.784  1.00 53.93
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ANISOU 1197  CD  GLN A 386     7210   6843   6437     62     21     77
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ATOM   1198  OE1 GLN A 386      22.249  -5.898   7.064  1.00 52.63
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ANISOU 1198  OE1 GLN A 386     6586   6564   6846   -191    -29     -6
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ANISOU 1199  NE2 GLN A 386     6207   6607   6405    -46     59     43
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ATOM   1200  C   GLN A 386      21.064  -7.587   2.620  1.00 47.59
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ANISOU 1200  C   GLN A 386     5946   6111   6025    -11    -32     25
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ATOM   1201  O   GLN A 386      20.871  -8.355   1.660  1.00 47.43
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ANISOU 1201  O   GLN A 386     5872   6171   5978    -14      5     -8
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ATOM   1202  N   PRO A 387      21.469  -6.317   2.452  1.00 46.79
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ANISOU 1202  N   PRO A 387     5884   5981   5912      8    -30     38
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ATOM   1203  CA  PRO A 387      21.779  -5.739   1.158  1.00 46.49
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ANISOU 1203  CA  PRO A 387     5862   5936   5864      6    -19     30
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ATOM   1204  CB  PRO A 387      21.498  -4.243   1.368  1.00 46.62
C
ANISOU 1204  CB  PRO A 387     5909   5918   5886    -16    -15     26
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ATOM   1205  CG  PRO A 387      21.249  -4.046   2.854  1.00 46.58
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ANISOU 1205  CG  PRO A 387     5910   5950   5836    -20    -43     57
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ATOM   1206  CD  PRO A 387      21.622  -5.325   3.529  1.00 47.03
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ANISOU 1206  CD  PRO A 387     5913   5996   5958     15    -45     16
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ATOM   1207  C   PRO A 387      23.235  -5.928   0.705  1.00 46.20
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ANISOU 1207  C   PRO A 387     5849   5892   5812    -33    -23     39
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ATOM   1208  O   PRO A 387      24.173  -5.617   1.452  1.00 46.11
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ANISOU 1208  O   PRO A 387     5879   5882   5758    -50    -52     64
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ATOM   1209  N   GLU A 388      23.408  -6.433  -0.517  1.00 45.47
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ANISOU 1209  N   GLU A 388     5756   5801   5720    -47    -20     52
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ATOM   1210  CA  GLU A 388      24.694  -6.403  -1.195  1.00 44.97
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ANISOU 1210  CA  GLU A 388     5683   5738   5662    -18    -10     44
C
ATOM   1211  CB  GLU A 388      24.706  -7.402  -2.338  1.00 44.97
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ANISOU 1211  CB  GLU A 388     5665   5761   5658    -20    -28     47
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ATOM   1212  CG  GLU A 388      24.340  -8.830  -1.945  1.00 46.39
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ANISOU 1212  CG  GLU A 388     5861   5872   5891    -63    -42     82
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ATOM   1213  CD  GLU A 388      25.323  -9.460  -0.970  1.00 48.03
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ANISOU 1213  CD  GLU A 388     6158   6071   6019    -44    -74     23
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ATOM   1214  OE1 GLU A 388      26.552  -9.400  -1.201  1.00 47.49
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ANISOU 1214  OE1 GLU A 388     6152   6000   5891      0     39      1
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ATOM   1215  OE2 GLU A 388      24.856 -10.029   0.035  1.00 49.67
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ANISOU 1215  OE2 GLU A 388     6394   6329   6149    -70     29     56
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ATOM   1216  C   GLU A 388      24.879  -4.998  -1.738  1.00 44.67
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ANISOU 1216  C   GLU A 388     5627   5760   5582    -57     10     43
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ATOM   1217  O   GLU A 388      24.084  -4.530  -2.545  1.00 45.07
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ANISOU 1217  O   GLU A 388     5666   5799   5660    -63     32     78
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ATOM   1218  N   ASN A 389      25.901  -4.298  -1.279  1.00 44.47
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ANISOU 1218  N   ASN A 389     5659   5699   5537    -59     24     35
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ANISOU 1219  CA  ASN A 389     5629   5641   5462    -27     10     35
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ATOM   1220  CB  ASN A 389      26.024  -1.961  -0.492  1.00 44.59
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ANISOU 1220  CB  ASN A 389     5722   5687   5532     -8     38     20
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ATOM   1221  CG  ASN A 389      24.585  -1.678  -0.037  1.00 46.42
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ANISOU 1221  CG  ASN A 389     5840   6045   5752    -29     -7     33
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ATOM   1222  OD1 ASN A 389      23.682  -1.555  -0.863  1.00 47.34
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ANISOU 1222  OD1 ASN A 389     6045   6314   5625    -18   -114     -3
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ATOM   1223  ND2 ASN A 389      24.374  -1.565   1.288  1.00 48.67
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ANISOU 1223  ND2 ASN A 389     6260   6364   5865    -48    -31    -51
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ATOM   1224  C   ASN A 389      27.307  -2.672  -2.610  1.00 43.16
C
ANISOU 1224  C   ASN A 389     5533   5513   5352    -26     18     33
C
ATOM   1225  O   ASN A 389      27.627  -1.534  -2.972  1.00 43.60
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ANISOU 1225  O   ASN A 389     5592   5599   5374    -86     14     23
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ATOM   1226  N   ASN A 390      27.945  -3.773  -2.997  1.00 41.86
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ANISOU 1226  N   ASN A 390     5352   5379   5173     23     45     56
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ATOM   1227  CA  ASN A 390      29.083  -3.793  -3.919  1.00 41.00
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ATOM   1228  CB  ASN A 390      29.966  -4.979  -3.549  1.00 41.19
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ANISOU 1228  CB  ASN A 390     5221   5310   5120     45     27     70
C
ATOM   1229  CG  ASN A 390      31.368  -4.870  -4.090  1.00 41.56
C
ANISOU 1229  CG  ASN A 390     5312   5363   5115     -2     43     34
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ATOM   1230  OD1 ASN A 390      31.868  -3.776  -4.364  1.00 41.19
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ANISOU 1230  OD1 ASN A 390     5395   5253   5003    -42    153     41
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ATOM   1231  ND2 ASN A 390      32.025  -6.025  -4.233  1.00 41.17
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ANISOU 1231  ND2 ASN A 390     5229   5437   4976    143     37     31
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ATOM   1232  C   ASN A 390      28.594  -3.918  -5.382  1.00 40.10
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ANISOU 1232  C   ASN A 390     5080   5147   5009     44     50     76
C
ATOM   1233  O   ASN A 390      28.961  -4.838  -6.130  1.00 39.50
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ANISOU 1233  O   ASN A 390     5007   5028   4970      3     76    100
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ATOM   1234  N   TYR A 391      27.732  -2.989  -5.776  1.00 38.85
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ANISOU 1234  N   TYR A 391     4892   5023   4845     30     31     97
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ATOM   1235  CA  TYR A 391      27.123  -3.060  -7.093  1.00 37.67
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ANISOU 1235  CA  TYR A 391     4723   4859   4729     39     55     30
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ATOM   1236  CB  TYR A 391      25.674  -3.607  -7.023  1.00 37.59
C
ANISOU 1236  CB  TYR A 391     4770   4816   4693     80     13     10
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ATOM   1237  CG  TYR A 391      24.671  -2.674  -6.375  1.00 38.73
C
ANISOU 1237  CG  TYR A 391     4872   5036   4808    -63    -19     82
C
ATOM   1238  CD1 TYR A 391      24.362  -2.780  -5.014  1.00 37.63
C
ANISOU 1238  CD1 TYR A 391     4713   4862   4722    177    116     46
C
ATOM   1239  CE1 TYR A 391      23.443  -1.907  -4.407  1.00 38.01
C
ANISOU 1239  CE1 TYR A 391     4865   4872   4702    -18     48    130
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ATOM   1240  CZ  TYR A 391      22.846  -0.928  -5.185  1.00 38.97
C
ANISOU 1240  CZ  TYR A 391     4955   4954   4896     -4    -26     90
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ATOM   1241  OH  TYR A 391      21.946  -0.056  -4.628  1.00 37.74
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ANISOU 1241  OH  TYR A 391     4898   4791   4649    209    262    -75
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ATOM   1242  CE2 TYR A 391      23.138  -0.815  -6.539  1.00 35.97
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ATOM   1243  CD2 TYR A 391      24.039  -1.671  -7.119  1.00 36.37
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ANISOU 1243  CD2 TYR A 391     4651   4617   4551    -25     77     44
C
ATOM   1244  C   TYR A 391      27.200  -1.701  -7.765  1.00 36.92
C
ANISOU 1244  C   TYR A 391     4614   4817   4594     42     51     55
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ATOM   1245  O   TYR A 391      27.351  -0.657  -7.114  1.00 36.53
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ANISOU 1245  O   TYR A 391     4501   4815   4562    -50    -10     88
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ATOM   1246  N   LYS A 392      27.118  -1.716  -9.081  1.00 36.62
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ANISOU 1246  N   LYS A 392     4561   4727   4624     54     58      1
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ATOM   1247  CA  LYS A 392      27.049  -0.484  -9.842  1.00 35.22
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ANISOU 1247  CA  LYS A 392     4471   4551   4359     25     92     57
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ATOM   1248  CB  LYS A 392      28.381  -0.165 -10.507  1.00 34.96
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ANISOU 1248  CB  LYS A 392     4479   4541   4263     56     38     59
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ATOM   1249  CG  LYS A 392      29.467   0.393  -9.610  1.00 33.97
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ANISOU 1249  CG  LYS A 392     4364   4380   4162      9    118    142
C
ATOM   1250  CD  LYS A 392      29.178   1.783  -9.077  1.00 30.65
C
ANISOU 1250  CD  LYS A 392     3873   4093   3676    -50    -59     22
C
ATOM   1251  CE  LYS A 392      30.097   2.063  -7.905  1.00 34.02
C
ANISOU 1251  CE  LYS A 392     4211   4391   4322     54    232    178
C
ATOM   1252  NZ  LYS A 392      29.956   3.443  -7.308  1.00 33.12
N
ANISOU 1252  NZ  LYS A 392     4344   4095   4143     80      8     56
N
ATOM   1253  C   LYS A 392      25.990  -0.715 -10.856  1.00 34.87
C
ANISOU 1253  C   LYS A 392     4403   4536   4310     11    107     58
C
ATOM   1254  O   LYS A 392      25.872  -1.819 -11.377  1.00 35.62
O
ANISOU 1254  O   LYS A 392     4423   4675   4433     32    181    150
O
ATOM   1255  N   THR A 393      25.182   0.301 -11.113  1.00 34.71
N
ANISOU 1255  N   THR A 393     4367   4517   4301     -7     76     10
N
ATOM   1256  CA  THR A 393      24.148   0.202 -12.152  1.00 34.16
C
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ANISOU 1256  CA  THR A 393     4265   4432   4281      0     19      3
C
ATOM   1257  CB  THR A 393      22.709   0.335 -11.564  1.00 34.10
C
ANISOU 1257  CB  THR A 393     4267   4421   4266     -9     30    -26
C
ATOM   1258  OG1 THR A 393      22.539  -0.610 -10.500  1.00 33.81
O
ANISOU 1258  OG1 THR A 393     4259   4412   4172     -1    -82     -7
O
ATOM   1259  CG2 THR A 393      21.632   0.074 -12.619  1.00 32.60
C
ANISOU 1259  CG2 THR A 393     4085   4261   4038     42     66     47
C
ATOM   1260  C   THR A 393      24.399   1.248 -13.221  1.00 33.43
C
ANISOU 1260  C   THR A 393     4164   4382   4153     14      6     11
C
ATOM   1261  O   THR A 393      24.712   2.402 -12.916  1.00 32.42
O
ANISOU 1261  O   THR A 393     3933   4348   4036     27    -28     52
O
ATOM   1262  N   THR A 394      24.280   0.831 -14.475  1.00 33.41
N
ANISOU 1262  N   THR A 394     4194   4326   4173    -21      1     -3
N
ATOM   1263  CA  THR A 394      24.354   1.770 -15.604  1.00 32.96
C
ANISOU 1263  CA  THR A 394     4273   4227   4022     -7      8    -20
C
ATOM   1264  CB  THR A 394      24.438   1.072 -17.010  1.00 32.13
C
ANISOU 1264  CB  THR A 394     4197   4083   3928     -5     10     -4
C
ATOM   1265  OG1 THR A 394      23.164   0.562 -17.403  1.00 30.15
O
ANISOU 1265  OG1 THR A 394     4301   3693   3462    100    189    -92
O
ATOM   1266  CG2 THR A 394      25.420  -0.023 -17.015  1.00 32.17
C
ANISOU 1266  CG2 THR A 394     4155   4105   3960     10     -1    -49
C
ATOM   1267  C   THR A 394      23.180   2.745 -15.578  1.00 33.10
C
ANISOU 1267  C   THR A 394     4317   4262   3996     22    -31    -57
C
ATOM   1268  O   THR A 394      22.111   2.399 -15.084  1.00 31.47
O
ANISOU 1268  O   THR A 394     4242   4074   3640     41    -14    -63
O
ATOM   1269  N   PRO A 395      23.384   3.974  16.096  1.00 33.99
N
ANISOU 1269  N   PRO A 395     4452   4367   4095     17      0    -46
N
ATOM   1270  CA  PRO A 395      22.219   4.810 -16.436  1.00 34.48
C
ANISOU 1270  CA  PRO A 395     4508   4400   4191      5      0     -2
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ATOM   1271  CB  PRO A 395      22.838   6.025 -17.138  1.00 34.62
C
ANISOU 1271  CB  PRO A 395     4510   4435   4207     39     10     16
C
ATOM   1272  CG  PRO A 395      24.252   6.053 -16.758  1.00 34.22
C
ANISOU 1272  CG  PRO A 395     4486   4452   4064      2    -63    -21
C
ATOM   1273  CD  PRO A 395      24.661   4.648 -16.377  1.00 33.86
C
ANISOU 1273  CD  PRO A 395     4399   4344   4121     12    -25   -108
C
ATOM   1274  C   PRO A 395      21.270   4.066 -17.399  1.00 34.85
C
ANISOU 1274  C   PRO A 395     4538   4450   4251    -27     24     75
C
ATOM   1275  O   PRO A 395      21.690   3.069 -18.027  1.00 33.16
O
ANISOU 1275  O   PRO A 395     4370   4274   3952    -56     11     94
O
ATOM   1276  N   PRO A 396      19.994   4.510 -17.489  1.00 35.07
N
ANISOU 1276  N   PRO A 396     4573   4414   4338    -15     31     90
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ATOM   1277  CA  PRO A 396      19.125   3.923 -18.487  1.00 35.48
C
ANISOU 1277  CA  PRO A 396     4599   4477   4402     -4     21     48
C
ATOM   1278  CB  PRO A 396      17.743   4.529 -18.186  1.00 35.53
C
ANISOU 1278  CB  PRO A 396     4659   4433   4407    -25     75     67
C
ATOM   1279  CG  PRO A 396      17.867   5.217 -16.873  1.00 35.18
C
ANISOU 1279  CG  PRO A 396     4624   4408   4334    -59      3     93
C
ATOM   1280  CD  PRO A 396      19.303   5.531 -16.681  1.00 35.32
C
ANISOU 1280  CD  PRO A 396     4594   4469   4356    -36     28     82
C
ATOM   1281  C   PRO A 396      19.586   4.324 -19.886  1.00 35.60
C
ANISOU 1281  C   PRO A 396     4558   4488   4477     -4     25     45
C
ATOM   1282  O   PRO A 396      19.954   5.475 -20.105  1.00 34.99
O
ANISOU 1282  O   PRO A 396     4438   4447   4409    -29     -6     -1
O
ATOM   1283  N   VAL A 397      19.574   3.361 -20.811  1.00 35.51
N
ANISOU 1283  N   VAL A 397     4544   4506   4441     17     17     29
N
ATOM   1284  CA  VAL A 397      19.934   3.603 -22.199  1.00 35.28
C
ANISOU 1284  CA  VAL A 397     4527   4479   4397     49     41    -32
C
ATOM   1285  CB  VAL A 397      21.078   2.664 -22.649  1.00 35.15
C
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ANISOU 1285  CB  VAL A 397     4516   4432   4406     15     -5     15
C
ATOM   1286  CG1 VAL A 397      21.631   3.022 -24.077  1.00 32.51
C
ANISOU 1286  CG1 VAL A 397     4128   4063   4159    162   -111     -9
C
ATOM   1287  CG2 VAL A 397      22.212   2.715 -21.598  1.00 34.48
C
ANISOU 1287  CG2 VAL A 397     4490   4344   4264     57    -19    107
C
ATOM   1288  C   VAL A 397      18.679   3.500 -23.052  1.00 35.75
C
ANISOU 1288  C   VAL A 397     4638   4562   4383     61     96   -101
C
ATOM   1289  O   VAL A 397      17.902   2.554 -22.928  1.00 35.03
O
ANISOU 1289  O   VAL A 397     4596   4513   4200    112    126   -186
O
ATOM   1290  N   LEU A 398      18.454   4.511 -23.882  1.00 36.47
N
ANISOU 1290  N   LEU A 398     4739   4629   4488     94     73   -100
N
ATOM   1291  CA  LEU A 398      17.325   4.490 -24.793  1.00 37.45
C
ANISOU 1291  CA  LEU A 398     4793   4772   4664     41     20    -48
C
ATOM   1292  CB  LEU A 398      17.122   5.874 -25.398  1.00 37.18
C
ANISOU 1292  CB  LEU A 398     4747   4739   4639     16     -9    -44
C
ATOM   1293  CG  LEU A 398      16.080   5.972 -26.506  1.00 37.09
C
ANISOU 1293  CG  LEU A 398     4734   4681   4674     50    -12     25
C
ATOM   1294  CD1 LEU A 398      14.703   6.031 -25.905  1.00 33.79
C
ANISOU 1294  CD1 LEU A 398     4353   4255   4230     41     -3     61
C
ATOM   1295  CD2 LEU A 398      16.370   7.193 -27.347  1.00 35.57
C
ANISOU 1295  CD2 LEU A 398     4571   4494   4446    -15     49     72
C
ATOM   1296  C   LEU A 398      17.556   3.429 -25.888  1.00 38.23
C
ANISOU 1296  C   LEU A 398     4890   4908   4728     11     15    -44
C
ATOM   1297  O   LEU A 398      18.563   3.460 -26.582  1.00 38.51
O
ANISOU 1297  O   LEU A 398     4999   4941   4690      0     55    -39
O
ATOM   1298  N   ASP A 399      16.635   2.480 -25.991  1.00 38.60
N
ANISOU 1298  N   ASP A 399     4899   4972   4792    -36    -27    -45
N
ATOM   1299  CA  ASP A 399      16.765   1.320  26.873  1.00 39.01
C
ANISOU 1299  CA  ASP A 399     4912   5053   4854    -29     24    -35
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ATOM   1300  CB  ASP A 399      16.199   0.086 -26.161  1.00 38.88
C
ANISOU 1300  CB  ASP A 399     4905   4978   4887     15    -41    -51
C
ATOM   1301  CG  ASP A 399      16.844  -1.192 -26.597  1.00 38.32
C
ANISOU 1301  CG  ASP A 399     4804   4963   4792    -65   -106   -121
C
ATOM   1302  OD1 ASP A 399      17.484  -1.181 -27.654  1.00 37.78
O
ANISOU 1302  OD1 ASP A 399     4733   4944   4677   -131    237     20
O
ATOM   1303  OD2 ASP A 399      16.695  -2.218 -25.888  1.00 34.88
O
ANISOU 1303  OD2 ASP A 399     4527   4630   4095   -144   -197   -160
O
ATOM   1304  C   ASP A 399      16.021   1.580 -28.189  1.00 39.56
C
ANISOU 1304  C   ASP A 399     4970   5121   4940    -44    -39    -55
C
ATOM   1305  O   ASP A 399      15.173   2.463 -28.256  1.00 39.73
O
ANISOU 1305  O   ASP A 399     4986   5183   4925   -115    -74    -71
O
ATOM   1306  N   SER A 400      16.337   0.812 -29.230  1.00 40.64
N
ANISOU 1306  N   SER A 400     5096   5273   5071    -57    -46    -54
N
ATOM   1307  CA  SER A 400      15.840   1.082 -30.596  1.00 41.15
C
ANISOU 1307  CA  SER A 400     5251   5323   5061    -17    -32     -8
C
ATOM   1308  CB  SER A 400      16.537   0.177 -31.634  1.00 41.51
C
ANISOU 1308  CB  SER A 400     5316   5343   5111    -10    -34     -7
C
ATOM   1309  OG  SER A 400      16.267  -1.193 -31.421  1.00 41.13
O
ANISOU 1309  OG  SER A 400     5528   5227   4871    -68    -46    -78
O
ATOM   1310  C   SER A 400      14.306   1.094 -30.795  1.00 41.37
C
ANISOU 1310  C   SER A 400     5252   5362   5103    -45    -34     -4
C
ATOM   1311  O   SER A 400      13.809   1.646 -31.793  1.00 41.91
O
ANISOU 1311  O   SER A 400     5272   5451   5198    -42    -44     15
O
ATOM   1312  N   ASP A 401      13.567   0.507 -29.850  1.00 40.91
N
ANISOU 1312  N   ASP A 401     5201   5318   5025    -65    -57    -11
N
ATOM   1313  CA  ASP A 401      12.096   0.529 -29.865  1.00 40.44
C
ANISOU 1313  CA  ASP A 401     5132   5251   4983    -27    -42     18
C
ATOM   1314  CB  ASP A 401      11.534  -0.798 -29.335  1.00 40.38
C
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ANISOU 1314  CB  ASP A 401     5139   5233   4968    -25    -21     -7
C
ATOM   1315  CG  ASP A 401      11.904  -1.060 -27.886  1.00 38.85
C
ANISOU 1315  CG  ASP A 401     4987   4862   4910    -73    -13     26
C
ATOM   1316  OD1 ASP A 401      12.436  -0.155 -27.202  1.00 37.74
O
ANISOU 1316  OD1 ASP A 401     4636   5156   4545     38     31    174
O
ATOM   1317  OD2 ASP A 401      11.649  -2.183 -27.431  1.00 39.72
O
ANISOU 1317  OD2 ASP A 401     5010   5104   4977     -4     75      7
O
ATOM   1318  C   ASP A 401      11.449   1.680 -29.094  1.00 39.90
C
ANISOU 1318  C   ASP A 401     5041   5177   4940    -43    -37     66
C
ATOM   1319  O   ASP A 401      10.225   1.774 -29.043  1.00 40.25
O
ANISOU 1319  O   ASP A 401     5049   5289   4953    -69    -45    118
O
ATOM   1320  N   GLY A 402      12.250   2.543 -28.477  1.00 39.08
N
ANISOU 1320  N   GLY A 402     4955   5065   4828    -36    -20     89
N
ATOM   1321  CA  GLY A 402      11.704   3.649 -27.704  1.00 37.86
C
ANISOU 1321  CA  GLY A 402     4786   4893   4704    -52    -13     78
C
ATOM   1322  C   GLY A 402      11.595   3.341 -26.218  1.00 37.33
C
ANISOU 1322  C   GLY A 402     4692   4826   4663    -63    -17     32
C
ATOM   1323  O   GLY A 402      11.207   4.196 -25.442  1.00 36.37
O
ANISOU 1323  O   GLY A 402     4563   4782   4474    -59     -1     82
O
ATOM   1324  N   SER A 403      11.926   2.109 -25.833  1.00 37.09
N
ANISOU 1324  N   SER A 403     4673   4844   4574     62     36     47
N
ATOM   1325  CA  SER A 403      11.950   1.716 -24.434  1.00 36.37
C
ANISOU 1325  CA  SER A 403     4631   4747   4437    -49    -21    -12
C
ATOM   1326  CB  SER A 403      11.448   0.278 -24.256  1.00 36.02
C
ANISOU 1326  CB  SER A 403     4574   4762   4349     -7    -46      2
C
ATOM   1327  OG  SER A 403      12.414  -0.692 -24.631  1.00 33.78
O
ANISOU 1327  OG  SER A 403     4447   4556   3833   -138    -49      0
O
ATOM   1328  C   SER A 403      13.386   1.883 -23.941  1.00 36.54
C
ANISOU 1328  C   SER A 403     4660   4740   4482    -12     25     -5
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ATOM   1329  O   SER A 403      14.295   2.067 -24.761  1.00 36.38
O
ANISOU 1329  O   SER A 403     4672   4720   4430    -40     37     14
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ATOM   1330  N   PHE A 404      13.581   1.845 -22.620  1.00 35.39
N
ANISOU 1330  N   PHE A 404     4542   4621   4282    -38     41    -73
N
ATOM   1331  CA  PHE A 404      14.907   1.883 -22.036  1.00 34.51
C
ANISOU 1331  CA  PHE A 404     4526   4498   4089      6     74    104
C
ATOM   1332  CB  PHE A 404      14.966   2.842 -20.820  1.00 33.40
C
ANISOU 1332  CB  PHE A 404     4419   4290   3980     33     38    -95
C
ATOM   1333  CG  PHE A 404      14.744   4.276 -21.166  1.00 30.44
C
ANISOU 1333  CG  PHE A 404     4161   4147   3255    -31     -6   -191
C
ATOM   1334  CD1 PHE A 404      15.823   5.101 -21.466  1.00 26.60
C
ANISOU 1334  CD1 PHE A 404     3621   3887   2596     99    -79   -402
C
ATOM   1335  CE1 PHE A 404      15.644   6.447 -21.816  1.00 26.39
C
ANISOU 1335  CE1 PHE A 404     3482   3882   2662    -15      8   -185
C
ATOM   1336  CZ  PHE A 404      14.347   6.978 -21.858  1.00 32.27
C
ANISOU 1336  CZ  PHE A 404     4351   4333   3573     50    -33   -132
C
ATOM   1337  CE2 PHE A 404      13.225   6.145 -21.550  1.00 29.16
C
ANISOU 1337  CE2 PHE A 404     3933   3731   3415    -11     40    -51
C
ATOM   1338  CD2 PHE A 404      13.445   4.805 -21.208  1.00 30.50
C
ANISOU 1338  CD2 PHE A 404     4166   4173   3248   -128    106   -201
C
ATOM   1339  C   PHE A 404      15.373   0.499 -21.608  1.00 34.61
C
ANISOU 1339  C   PHE A 404     4525   4477   4146     26     99   -204
C
ATOM   1340  O   PHE A 404      14.573  -0.420 -21.433  1.00 33.02
O
ANISOU 1340  O   PHE A 404     4344   4311   3889     47    220   -276
O
ATOM   1341  N   PHE A 405      16.690   0.368 -21.449  1.00 34.74
N
ANISOU 1341  N   PHE A 405     4575   4438   4184     43     52   -212
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ATOM   1342  CA  PHE A 405      17.272  -0.759 -20.737  1.00 34.42
C
ANISOU 1342  CA  PHE A 405     4502   4382   4192     -2     44   -125
C
ATOM   1343  CB  PHE A 405      17.776  -1.837 -21.701  1.00 32.43
C
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ANISOU 1343  CB  PHE A 405     4151   4159   4010    -72    155    -97
C
ATOM   1344  CG  PHE A 405      19.014  -1.437 -22.476  1.00 33.02
C
ANISOU 1344  CG  PHE A 405     4397   3928   4220      8    -32   -287
C
ATOM   1345  CD1 PHE A 405      20.277  -1.889 -22.081  1.00 29.57
C
ANISOU 1345  CD1 PHE A 405     4067   3437   3730    -38   -280   -316
C
ATOM   1346  CE1 PHE A 405      21.400  -1.541 -22.787  1.00 25.41
C
ANISOU 1346  CE1 PHE A 405     3611   3087   2955   -141    -47    125
C
ATOM   1347  CZ  PHE A 405      21.292  -0.716 -23.897  1.00 32.01
C
ANISOU 1347  CZ  PHE A 405     4279   3768   4114   -148    -68   -437
C
ATOM   1348  CE2 PHE A 405      20.048  -0.245 -24.310  1.00 27.60
C
ANISOU 1348  CE2 PHE A 405     3778   3209   3499    -32   -193   -158
C
ATOM   1349  CD2 PHE A 405      18.915  -0.607 -23.606  1.00 29.13
C
ANISOU 1349  CD2 PHE A 405     4022   3536   3508    -50     -6   -170
C
ATOM   1350  C   PHE A 405      18.415  -0.275 -19.858  1.00 34.59
C
ANISOU 1350  C   PHE A 405     4492   4419   4230    -18     50   -131
C
ATOM   1351  O   PHE A 405      18.909   0.844 -20.028  1.00 33.97
O
ANISOU 1351  O   PHE A 405     4478   4384   4045    -56     30    -88
O
ATOM   1352  N   LEU A 406      18.811  -1.132 -18.922  1.00 34.15
N
ANISOU 1352  N   LEU A 406     4406   4368   4199    -66     89    -89
N
ATOM   1353  CA  LEU A 406      20.063  -0.990 -18.217  1.00 34.71
C
ANISOU 1353  CA  LEU A 406     4441   4465   4282    -10     69    -40
C
ATOM   1354  CB  LEU A 406      19.973   0.066 -17.112  1.00 34.26
C
ANISOU 1354  CB  LEU A 406     4416   4403   4198      0      3     -2
C
ATOM   1355  CG  LEU A 406      19.362  -0.080 -15.723  1.00 32.70
C
ANISOU 1355  CG  LEU A 406     4113   4273   4036    -57    -11      1
C
ATOM   1356  CD1 LEU A 406      18.140   0.758 -15.580  1.00 31.62
C
ANISOU 1356  CD1 LEU A 406     3956   4197   3860    -42    -51    147
C
ATOM   1357  CD2 LEU A 406      19.149  -1.480 -15.240  1.00 30.79
C
ANISOU 1357  CD2 LEU A 406     3828   4056   3815   -202    -43   -257
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ATOM   1358  C   LEU A 406      20.593  -2.310 -17.687  1.00 35.03
C
ANISOU 1358  C   LEU A 406     4496   4493   4320    -22     88    -40
C
ATOM   1359  O   LEU A 406      19.908  -3.316 -17.763  1.00 35.15
O
ANISOU 1359  O   LEU A 406     4419   4618   4318     -7    134    -19
O
ATOM   1360  N   TYR A 407      21.835  -2.297 -17.198  1.00 35.31
N
ANISOU 1360  N   TYR A 407     4535   4528   4351     -7     40    -34
N
ATOM   1361  CA  TYR A 407      22.410  -3.423 -16.471  1.00 35.65
C
ANISOU 1361  CA  TYR A 407     4544   4568   4430     -6     40    -15
C
ATOM   1362  CB  TYR A 407      23.581  -4.065 -17.216  1.00 34.84
C
ANISOU 1362  CB  TYR A 407     4429   4478   4327    -14     12    -49
C
ATOM   1363  CG  TYR A 407      23.321  -4.723 -18.548  1.00 34.08
C
ANISOU 1363  CG  TYR A 407     4249   4291   4407     40     57      9
C
ATOM   1364  CD1 TYR A 407      23.139  -3.959 -19.694  1.00 32.26
C
ANISOU 1364  CD1 TYR A 407     3966   3991   4300     71     69    -29
C
ATOM   1365  CE1 TYR A 407      22.945  -4.551 -20.936  1.00 31.35
C
ANISOU 1365  CE1 TYR A 407     3804   3854   4251      1     -7     29
C
ATOM   1366  CZ  TYR A 407      22.964  -5.923 -21.046  1.00 32.84
C
ANISOU 1366  CZ  TYR A 407     3810   4228   4440      0     45      0
C
ATOM   1367  OH  TYR A 407      22.771  -6.460 -22.284  1.00 34.03
O
ANISOU 1367  OH  TYR A 407     4198   4350   4380     16     61      8
O
ATOM   1368  CE2 TYR A 407      23.163  -6.726 -19.925  1.00 31.27
C
ANISOU 1368  CE2 TYR A 407     3774   3877   4229     25     90    -36
C
ATOM   1369  CD2 TYR A 407      23.354  -6.119 -18.681  1.00 32.21
C
ANISOU 1369  CD2 TYR A 407     3878   4149   4210    -57     57     56
C
ATOM   1370  C   TYR A 407      22.935  -2.988 -15.099  1.00 35.88
C
ANISOU 1370  C   TYR A 407     4601   4620   4411    -27     26     -8
C
ATOM   1371  O   TYR A 407      23.460  -1.890 -14.934  1.00 35.29
O
ANISOU 1371  O   TYR A 407     4616   4570   4220     18    -14     -3
O
ATOM   1372  N   SER A 408      22.794  -3.888 -14.134  1.00 36.43
N
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ANISOU 1372  N   SER A 408     4686   4700   4454    -17     21      8
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ATOM   1373  CA  SER A 408      23.367  -3.750 -12.801  1.00 36.52
C
ANISOU 1373  CA  SER A 408     4655   4722   4499    -22     28     33
C
ATOM   1374  CB  SER A 408      22.296  -3.911 -11.702  1.00 36.58
C
ANISOU 1374  CB  SER A 408     4665   4728   4507    -32     27     15
C
ATOM   1375  OG  SER A 408      22.782  -3.508 -10.426  1.00 34.60
O
ANISOU 1375  OG  SER A 408     4359   4564   4222     70    111    165
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ATOM   1376  C   SER A 408      24.397  -4.849 -12.686  1.00 36.40
C
ANISOU 1376  C   SER A 408     4657   4704   4467    -12     38     50
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ATOM   1377  O   SER A 408      24.159  -5.985 -13.121  1.00 36.21
O
ANISOU 1377  O   SER A 408     4674   4649   4435    -17     72     98
O
ATOM   1378  N   LYS A 409      25.553  -4.484 -12.145  1.00 36.10
N
ANISOU 1378  N   LYS A 409     4657   4695   4362      4    -34     66
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ATOM   1379  CA  LYS A 409      26.659  -5.409 -11.944  1.00 35.94
C
ANISOU 1379  CA  LYS A 409     4630   4629   4395      7    -40     60
C
ATOM   1380  CB  LYS A 409      27.906  -4.935 -12.709  1.00 35.47
C
ANISOU 1380  CB  LYS A 409     4588   4563   4326    -11    -12     65
C
ATOM   1381  CG  LYS A 409      29.104  -5.896 -12.600  1.00 36.03
C
ANISOU 1381  CG  LYS A 409     4596   4593   4500    -14     25    105
C
ATOM   1382  CD  LYS A 409      30.197  -5.695 -13.673  1.00 36.06
C
ANISOU 1382  CD  LYS A 409     4630   4581   4491     54    -44    108
C
ATOM   1383  CE  LYS A 409      31.116  -4.491 -13.396  1.00 33.48
C
ANISOU 1383  CE  LYS A 409     4373   4343   4003     26   -214      0
C
ATOM   1384  NZ  LYS A 409      31.618  -4.426 -11.979  1.00 34.29
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ANISOU 1384  NZ  LYS A 409     4556   4113   4356     53     22    193
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ATOM   1385  C   LYS A 409      26.941  -5.580 -10.425  1.00 35.82
C
ANISOU 1385  C   LYS A 409     4612   4607   4388     -8    -73    104
C
ATOM   1386  O   LYS A 409      27.346  -4.637  -9.738  1.00 35.11
O
ANISOU 1386  O   LYS A 409     4621   4589   4130    -13   -162     98
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ATOM   1387  N   LEU A 410      26.673  -6.777  -9.920  1.00 35.61
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ANISOU 1387  N   LEU A 410     4529   4579   4420     14    -95    141
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ATOM   1388  CA  LEU A 410      26.958  -7.114  -8.531  1.00 35.76
C
ANISOU 1388  CA  LEU A 410     4598   4561   4426      4      1    114
C
ATOM   1389  CB  LEU A 410      25.857  -7.992  -7.911  1.00 35.47
C
ANISOU 1389  CB  LEU A 410     4524   4542   4409     -3    -25     72
C
ATOM   1390  CG  LEU A 410      26.145  -8.413  -6.445  1.00 35.65
C
ANISOU 1390  CG  LEU A 410     4571   4520   4452     10     25    122
C
ATOM   1391  CD1 LEU A 410      26.011  -7.260  -5.456  1.00 33.68
C
ANISOU 1391  CD1 LEU A 410     4444   4388   3963     51     76    155
C
ATOM   1392  CD2 LEU A 410      25.311  -9.570  -6.007  1.00 35.81
C
ANISOU 1392  CD2 LEU A 410     4430   4679   4494    -71     30    184
C
ATOM   1393  C   LEU A 410      28.292  -7.843  -8.495  1.00 35.82
C
ANISOU 1393  C   LEU A 410     4590   4560   4458     39    -21    187
C
ATOM   1394  O   LEU A 410      28.479  -8.850  -9.213  1.00 35.64
O
ANISOU 1394  O   LEU A 410     4599   4489   4455     42    -33    257
O
ATOM   1395  N   THR A 411      29.225  -7.315  -7.707  1.00 36.06
N
ANISOU 1395  N   THR A 411     4693   4596   4410     41    -16    193
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ATOM   1396  CA  THR A 411      30.513  -7.989  -7.514  1.00 37.46
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ANISOU 1396  CA  THR A 411     4777   4828   4625     24      0    147
C
ATOM   1397  CB  THR A 411      31.705  -7.010  -7.613  1.00 37.32
C
ANISOU 1397  CB  THR A 411     4746   4809   4625     10    -29    154
C
ATOM   1398  OG1 THR A 411      31.761  -6.416  -8.930  1.00 37.50
O
ANISOU 1398  OG1 THR A 411     4710   4871   4664     84    -11    125
O
ATOM   1399  CG2 THR A 411      33.018  -7.757  -7.351  1.00 36.73
C
ANISOU 1399  CG2 THR A 411     4767   4595   4593      3     22    161
C
ATOM   1400  C   THR A 411      30.540  -8.758  -6.171  1.00 38.50
C
ANISOU 1400  C   THR A 411     4928   4919   4780     58    -33    132
C
ATOM   1401  O   THR A 411      30.377  -8.166  -5.098  1.00 38.70
O
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ANISOU 1401  O   THR A 411     4944   5052   4708     98     23    156
O
ATOM   1402  N   VAL A 412      30.733 -10.070  -6.231  1.00 40.03
N
ANISOU 1402  N   VAL A 412     5107   5068   5034     48    -15    105
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ATOM   1403  CA  VAL A 412      30.898 -10.879  -4.999  1.00 41.18
C
ANISOU 1403  CA  VAL A 412     5270   5215   5159     42    -14    107
C
ATOM   1404  CB  VAL A 412      29.671 -11.783  -4.715  1.00 40.91
C
ANISOU 1404  CB  VAL A 412     5223   5145   5175     45    -26    100
C
ATOM   1405  CG1 VAL A 412      28.459 -10.957  -4.333  1.00 41.72
C
ANISOU 1405  CG1 VAL A 412     5340   5253   5258      8      5     95
C
ATOM   1406  CG2 VAL A 412      29.378 -12.688  -5.898  1.00 41.30
C
ANISOU 1406  CG2 VAL A 412     5288   5262   5143     56    -93     79
C
ATOM   1407  C   VAL A 412      32.130 -11.777  -5.058  1.00 41.92
C
ANISOU 1407  C   VAL A 412     5342   5298   5284     55      2     92
C
ATOM   1408  O   VAL A 412      32.501 -12.230  -6.148  1.00 42.01
O
ANISOU 1408  O   VAL A 412     5411   5272   5277     51    -15     74
O
ATOM   1409  N   ASP A 413      32.741 -12.050  -3.895  1.00 43.17
N
ANISOU 1409  N   ASP A 413     5497   5486   5417     25    -27     44
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ATOM   1410  CA  ASP A 413      33.828 -13.058  -3.794  1.00 44.45
C
ANISOU 1410  CA  ASP A 413     5685   5613   5589     20    -20     37
C
ATOM   1411  CB  ASP A 413      34.281 -13.268  -2.345  1.00 45.14
C
ANISOU 1411  CB  ASP A 413     5771   5740   5638     27    -24     76
C
ATOM   1412  CG  ASP A 413      34.976 -12.041  -1.745  1.00 46.83
C
ANISOU 1412  CG  ASP A 413     6015   5966   5809    -56    -80     52
C
ATOM   1413  OD1 ASP A 413      35.210 -11.035  -2.457  1.00 48.90
O
ANISOU 1413  OD1 ASP A 413     6156   6319   6102    -40     23    125
O
ATOM   1414  OD2 ASP A 413      35.288 -12.084  -0.535  1.00 49.87
O
ANISOU 1414  OD2 ASP A 413     6489   6388   6071     31     24     57
O
ATOM   1415  C   ASP A 413      33.345 -14.385  -4.372  1.00 44.46
C
ANISOU 1415  C   ASP A 413     5701   5572   5620     -1      2     46
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ATOM   1416  O   ASP A 413      32.224 -14.799  -4.093  1.00 44.32
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ANISOU 1416  O   ASP A 413     5691   5550   5596      4     41     42
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ATOM   1417  N   LYS A 414      34.185 -15.020  -5.195  1.00 44.94
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ANISOU 1417  N   LYS A 414     5770   5623   5682      8     -7     53
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ATOM   1418  CA  LYS A 414      33.820 -16.224  -5.971  1.00 45.58
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ANISOU 1418  CA  LYS A 414     5844   5751   5721    -21    -31     35
C
ATOM   1419  CB  LYS A 414      34.997 -16.633  -6.850  1.00 45.72
C
ANISOU 1419  CB  LYS A 414     5836   5796   5740    -19    -14     37
C
ATOM   1420  CG  LYS A 414      34.725 -17.758  -7.819  1.00 45.82
C
ANISOU 1420  CG  LYS A 414     5880   5705   5824     30    -23     30
C
ATOM   1421  CD  LYS A 414      35.966 -18.024  -8.634  1.00 47.84
C
ANISOU 1421  CD  LYS A 414     6077   6009   6089     18     52     -1
C
ATOM   1422  CE  LYS A 414      35.693 -18.974  -9.784  1.00 48.47
C
ANISOU 1422  CE  LYS A 414     6126   6229   6062     23     11   -100
C
ATOM   1423  NZ  LYS A 414      36.972 -19.359 -10.462  1.00 49.66
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ANISOU 1423  NZ  LYS A 414     6253   6358   6256     15     38    -89
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ATOM   1424  C   LYS A 414      33.401 -17.438  -5.138  1.00 46.06
C
ANISOU 1424  C   LYS A 414     5882   5808   5809    -53    -60     44
C
ATOM   1425  O   LYS A 414      32.556 -18.234  -5.566  1.00 47.07
O
ANISOU 1425  O   LYS A 414     5999   5982   5903    -24   -123     54
O
ATOM   1426  N   SER A 415      34.012 -17.606  -3.971  1.00 46.26
N
ANISOU 1426  N   SER A 415     5896   5861   5817    -68    -56     60
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ATOM   1427  CA  SER A 415      33.679 -18.728  -3.088  1.00 46.61
C
ANISOU 1427  CA  SER A 415     5930   5891   5888    -68    -54     52
C
ATOM   1428  CB  SER A 415      34.552 -18.712  -1.810  1.00 46.81
C
ANISOU 1428  CB  SER A 415     5974   5905   5906    -59    -48     70
C
ATOM   1429  OG  SER A 415      34.803 -17.392  -1.321  1.00 46.84
O
ANISOU 1429  OG  SER A 415     6000   5875   5923     99    111     22
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ATOM   1430  C   SER A 415      32.167 -18.732  -2.781  1.00 46.70
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ANISOU 1430  C   SER A 415     5922   5886   5935    -46    -18     49
C
ATOM   1431  O   SER A 415      31.521 -19.780  -2.836  1.00 47.24
O
ANISOU 1431  O   SER A 415     5992   5952   6003    -61    -44     28
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ATOM   1432  N   ARG A 416      31.617 -17.544  -2.512  1.00 46.83
N
ANISOU 1432  N   ARG A 416     5915   5904   5972    -34     -6     62
N
ATOM   1433  CA  ARG A 416      30.171 -17.325  -2.328  1.00 46.36
C
ANISOU 1433  CA  ARG A 416     5861   5859   5894    -34      0     66
C
ATOM   1434  CB  ARG A 416      29.887 -15.849  -2.088  1.00 46.60
C
ANISOU 1434  CB  ARG A 416     5918   5875   5912      0     41     69
C
ATOM   1435  CG  ARG A 416      29.867 -15.452  -0.644  1.00 47.76
C
ANISOU 1435  CG  ARG A 416     6143   6052   5950    -60     -4     53
C
ATOM   1436  CD  ARG A 416      29.723 -13.956  -0.492  1.00 47.81
C
ANISOU 1436  CD  ARG A 416     5941   6058   6165   -177    -24      4
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ATOM   1437  NE  ARG A 416      30.998 -13.332  -0.127  1.00 51.98
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ANISOU 1437  NE  ARG A 416     6596   6580   6574     64     83    221
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ATOM   1438  CZ  ARG A 416      31.182 -12.562   0.945  1.00 48.85
C
ANISOU 1438  CZ  ARG A 416     5973   6438   6150   -125     66   -142
C
ATOM   1439  NH1 ARG A 416      30.168 -12.312   1.763  1.00 53.54
N
ANISOU 1439  NH1 ARG A 416     6843   6710   6787      7      1     33
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ATOM   1440  NH2 ARG A 416      32.379 -12.028   1.196  1.00 52.19
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ANISOU 1440  NH2 ARG A 416     6821   6562   6445    124     29     86
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ATOM   1441  C   ARG A 416      29.326 -17.787  -3.503  1.00 46.10
C
ANISOU 1441  C   ARG A 416     5811   5841   5864    -26    -12     80
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ATOM   1442  O   ARG A 416      28.229 -18.318  -3.299  1.00 46.58
O
ANISOU 1442  O   ARG A 416     5912   5852   5931      3    -22    129
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ATOM   1443  N   TRP A 417      29.814 -17.566  -4.727  1.00 45.76
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ANISOU 1443  N   TRP A 417     5753   5790   5841     39      6     47
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ATOM   1444  CA  TRP A 417      29.109 -18.028  -5.933  1.00 45.44
C
ANISOU 1444  CA  TRP A 417     5708   5726   5828     -4    -12     32
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ATOM   1445  CB  TRP A 417      29.750 -17.485  -7.222  1.00 43.60
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ANISOU 1445  CB  TRP A 417     5388   5589   5589     11   -113     20
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ATOM   1446  CG  TRP A 417      29.056 -17.925  -8.508  1.00 43.73
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ANISOU 1446  CG  TRP A 417     5357   5558   5700     39    -41     38
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ATOM   1447  CD1 TRP A 417      29.598 -18.674  -9.537  1.00 41.28
C
ANISOU 1447  CD1 TRP A 417     4777   5490   5416    116    -99     22
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ATOM   1448  NE1 TRP A 417      28.662 -18.887 -10.523  1.00 44.32
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ANISOU 1448  NE1 TRP A 417     5725   5455   5657   -184     23    161
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ATOM   1449  CE2 TRP A 417      27.488 -18.279 -10.152  1.00 41.66
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ANISOU 1449  CE2 TRP A 417     5146   5311   5372     46     -8    -11
C
ATOM   1450  CD2 TRP A 417      27.698 -17.665  -8.888  1.00 43.53
C
ANISOU 1450  CD2 TRP A 417     5499   5455   5584     22     36     94
C
ATOM   1451  CE3 TRP A 417      26.634 -16.972  -8.286  1.00 42.96
C
ANISOU 1451  CE3 TRP A 417     5359   5442   5518     17     14     67
C
ATOM   1452  CZ3 TRP A 417      25.417 -16.905  -8.962  1.00 42.84
C
ANISOU 1452  CZ3 TRP A 417     5360   5442   5473    -41     61     -2
C
ATOM   1453  CH2 TRP A 417      25.246 -17.517 -10.217  1.00 43.50
C
ANISOU 1453  CH2 TRP A 417     5561   5399   5567    -97    121     76
C
ATOM   1454  CZ2 TRP A 417      26.263 -18.206 -10.824  1.00 42.87
C
ANISOU 1454  CZ2 TRP A 417     5358   5337   5590     -6     99     73
C
ATOM   1455  C   TRP A 417      29.072 -19.558  -5.927  1.00 46.18
C
ANISOU 1455  C   TRP A 417     5795   5803   5946      7    -35     30
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ATOM   1456  O   TRP A 417      28.009 -20.167  -6.166  1.00 46.90
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ANISOU 1456  O   TRP A 417     5817   5939   6064     -1    -68     67
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ATOM   1457  N   GLN A 418      30.217 -20.167  -5.598  1.00 46.23
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ANISOU 1457  N   GLN A 418     5783   5839   5941     48    -14     42
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ATOM   1458  CA  GLN A 418      30.356 -21.636  -5.575  1.00 46.42
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ANISOU 1458  CA  GLN A 418     5870   5841   5926     17     -2     41
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ATOM   1459  CB  GLN A 418      31.842 -22.049  -5.700  1.00 46.09
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ANISOU 1459  CB  GLN A 418     5815   5825   5872     36     19     53
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ATOM   1460  CG  GLN A 418      32.458 -21.757  -7.083  1.00 46.48
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ANISOU 1460  CG  GLN A 418     5847   5833   5976     34     73    -10
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ATOM   1461  CD  GLN A 418      34.002 -21.715  -7.095  1.00 46.67
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ANISOU 1461  CD  GLN A 418     5898   5914   5920     16     24     20
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ATOM   1462  OE1 GLN A 418      34.665 -21.686  -6.048  1.00 47.82
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ANISOU 1462  OE1 GLN A 418     6033   6136   6000     53    -33     66
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ATOM   1463  NE2 GLN A 418      34.571 -21.701  -8.297  1.00 47.35
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ANISOU 1463  NE2 GLN A 418     5961   6023   6004     33     66     26
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ATOM   1464  C   GLN A 418      29.653 -22.299  -4.363  1.00 46.78
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ANISOU 1464  C   GLN A 418     5905   5866   6002     -9     -3     20
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ATOM   1465  O   GLN A 418      29.001 -23.337  -4.506  1.00 47.00
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ANISOU 1465  O   GLN A 418     5932   5847   6078    -40    -29     35
O
ATOM   1466  N   GLN A 419      29.777 -21.696  -3.180  1.00 47.14
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ANISOU 1466  N   GLN A 419     6009   5940   5961    -18     -9     36
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ATOM   1467  CA  GLN A 419      29.014 -22.148  -2.017  1.00 48.11
C
ANISOU 1467  CA  GLN A 419     6130   6033   6117    -16    -35     52
C
ATOM   1468  CB  GLN A 419      29.192 -21.182  -0.827  1.00 47.74
C
ANISOU 1468  CB  GLN A 419     6122   5956   6058    -21    -65      7
C
ATOM   1469  CG  GLN A 419      30.584 -21.313  -0.189  1.00 48.88
C
ANISOU 1469  CG  GLN A 419     6202   6136   6231    -31    -83     18
C
ATOM   1470  CD  GLN A 419      30.835 -20.383   1.010  1.00 48.22
C
ANISOU 1470  CD  GLN A 419     6253   6005   6062     61   -160    -28
C
ATOM   1471  OE1 GLN A 419      30.374 -19.232   1.050  1.00 51.84
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ANISOU 1471  OE1 GLN A 419     6788   6288   6621     72     49     14
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ATOM   1472  NE2 GLN A 419      31.595 -20.883   1.981  1.00 48.48
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ANISOU 1472  NE2 GLN A 419     6320   6025   6074     22    -59    -61
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ATOM   1473  C   GLN A 419      27.538 -22.358  -2.393  1.00 47.88
C
ANISOU 1473  C   GLN A 419     6103   5976   6111    -20    -69     81
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ATOM   1474  O   GLN A 419      26.977 -23.449  -2.213  1.00 48.69
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ANISOU 1474  O   GLN A 419     6259   5993   6247    -19    -60    110
O
ATOM   1475  N   GLY A 420      26.911 -21.333  -2.954  1.00 47.48
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ANISOU 1475  N   GLY A 420     6057   5915   6069    -12    -64     79
N
ATOM   1476  CA  GLY A 420      25.605 -21.536  -3.553  1.00 46.95
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ANISOU 1476  CA  GLY A 420     5936   5893   6010     15    -32     74
C
ATOM   1477  C   GLY A 420      24.588 -20.527  -3.120  1.00 46.55
C
ANISOU 1477  C   GLY A 420     5880   5886   5920     12    -26     49
C
ATOM   1478  O   GLY A 420      23.394 -20.701  -3.397  1.00 46.93
O
ANISOU 1478  O   GLY A 420     5889   5969   5972     -9     -8     74
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ATOM   1479  N   ASN A 421      25.070 -19.488  -2.433  1.00 46.34
N
ANISOU 1479  N   ASN A 421     5839   5872   5896     40    -50     46
N
ATOM   1480  CA  ASN A 421      24.289 -18.301  -2.077  1.00 45.85
C
ANISOU 1480  CA  ASN A 421     5786   5865   5770     64    -39      9
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ATOM   1481  CB  ASN A 421      25.211 -17.091  -1.903  1.00 45.59
C
ANISOU 1481  CB  ASN A 421     5783   5824   5712     51    -56     13
C
ATOM   1482  CG  ASN A 421      25.560 -16.808  -0.438  1.00 46.44
C
ANISOU 1482  CG  ASN A 421     5950   5950   5741     86     -2    -15
C
ATOM   1483  OD1 ASN A 421      26.110 -17.659   0.284  1.00 43.48
O
ANISOU 1483  OD1 ASN A 421     5884   5482   5152    142     48     64
O
ATOM   1484  ND2 ASN A 421      25.277 -15.577  -0.009  1.00 47.25
N
ANISOU 1484  ND2 ASN A 421     6145   5952   5855    165    -93   -103
N
ATOM   1485  C   ASN A 421      23.213 -17.924  -3.095  1.00 45.79
C
ANISOU 1485  C   ASN A 421     5772   5862   5764     76    -20     43
C
ATOM   1486  O   ASN A 421      23.401 -18.062  -4.327  1.00 45.60
O
ANISOU 1486  O   ASN A 421     5768   5864   5693     63    -16     71
O
ATOM   1487  N   VAL A 422      22.089 -17.454  -2.553  1.00 45.55
N
ANISOU 1487  N   VAL A 422     5739   5837   5731     49    -11     67
N
ATOM   1488  CA  VAL A 422      21.035 -16.834  -3.337  1.00 45.24
C
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ANISOU 1488  CA  VAL A 422     5704   5739   5744     26     10     70
C
ATOM   1489  CB  VAL A 422      19.661 -17.027  -2.690  1.00 45.54
C
ANISOU 1489  CB  VAL A 422     5700   5790   5810     24      9     65
C
ATOM   1490  CG1 VAL A 422      18.638 -16.039  -3.274  1.00 46.04
C
ANISOU 1490  CG1 VAL A 422     5848   5757   5887     73     42     96
C
ATOM   1491  CG2 VAL A 422      19.197 -18.476  -2.879  1.00 45.88
C
ANISOU 1491  CG2 VAL A 422     5756   5710   5965     34    -24      7
C
ATOM   1492  C   VAL A 422      21.346 -15.357  -3.459  1.00 44.78
C
ANISOU 1492  C   VAL A 422     5682   5693   5638     10     15     94
C
ATOM   1493  O   VAL A 422      21.613 -14.670  -2.457  1.00 44.88
O
ANISOU 1493  O   VAL A 422     5745   5738   5570      0     98    124
O
ATOM   1494  N   PHE A 423      21.369 -14.880  -4.698  1.00 44.38
N
ANISOU 1494  N   PHE A 423     5592   5648   5622      7    -27    107
N
ATOM   1495  CA  PHE A 423      21.495 -13.452  -4.933  1.00 43.56
C
ANISOU 1495  CA  PHE A 423     5497   5571   5482      0    -24    111
C
ATOM   1496  CB  PHE A 423      22.798 -13.133  -5.646  1.00 43.29
C
ANISOU 1496  CB  PHE A 423     5394   5556   5497     -7    -79    107
C
ATOM   1497  CG  PHE A 423      24.008 -13.224  -4.759  1.00 44.33
C
ANISOU 1497  CG  PHE A 423     5633   5632   5577    -92     29    161
C
ATOM   1498  CD1 PHE A 423      24.936  14.249   4.937  1.00 42.42
C
ANISOU 1498  CD1 PHE A 423     5139   5468   5509     38    -37    193
C
ATOM   1499  CE1 PHE A 423      26.047 -14.339  -4.131  1.00 42.33
C
ANISOU 1499  CE1 PHE A 423     5468   5273   5342   -127    119    -44
C
ATOM   1500  CZ  PHE A 423      26.245 -13.401  -3.133  1.00 45.72
C
ANISOU 1500  CZ  PHE A 423     5685   6031   5653   -193    105    211
C
ATOM   1501  CE2 PHE A 423      25.328 -12.362  -2.944  1.00 41.37
C
ANISOU 1501  CE2 PHE A 423     4978   5384   5355    209    -92    166
C
ATOM   1502  CD2 PHE A 423      24.217 -12.288  -3.751  1.00 43.86
C
ANISOU 1502  CD2 PHE A 423     5670   5522   5470    -44    136     92
C
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ATOM   1503  C   PHE A 423      20.288 -12.976  -5.723  1.00 43.24
C
ANISOU 1503  C   PHE A 423     5452   5530   5446     -1    -11    102
C
ATOM   1504  O   PHE A 423      19.889 -13.612  -6.714  1.00 42.35
O
ANISOU 1504  O   PHE A 423     5366   5482   5242    -37    -48    112
O
ATOM   1505  N   SER A 424      19.699 -11.880  -5.251  1.00 42.62
N
ANISOU 1505  N   SER A 424     5361   5473   5357      9     17     73
N
ATOM   1506  CA  SER A 424      18.502 -11.336  -5.875  1.00 42.62
C
ANISOU 1506  CA  SER A 424     5334   5509   5350     15     32     50
C
ATOM   1507  CB  SER A 424      17.269 -11.580  -4.983  1.00 42.80
C
ANISOU 1507  CB  SER A 424     5346   5561   5353     30     34     25
C
ATOM   1508  OG  SER A 424      17.321 -10.787  -3.812  1.00 42.53
O
ANISOU 1508  OG  SER A 424     5276   5654   5226     85     74     39
O
ATOM   1509  C   SER A 424      18.626  -9.859  -6.300  1.00 42.35
C
ANISOU 1509  C   SER A 424     5296   5467   5328     20     18     77
C
ATOM   1510  O   SER A 424      19.033  -8.992  -5.518  1.00 41.38
O
ANISOU 1510  O   SER A 424     5174   5364   5184    -26     -2     71
O
ATOM   1511  N   CYS A 425      18.282  -9.603  -7.563  1.00 42.32
N
ANISOU 1511  N   CYS A 425     5228   5490   5359     38      3    113
N
ATOM   1512  CA  CYS A 425      18.182  -8.238  -8.086  1.00 42.32
C
ANISOU 1512  CA  CYS A 425     5236   5477   5364     15      4    122
C
ATOM   1513  CB  CYS A 425      18.691  -8.193  -9.527  1.00 42.07
C
ANISOU 1513  CB  CYS A 425     5168   5425   5391      5    -28    131
C
ATOM   1514  SG  CYS A 425      18.168  -6.769 -10.529  1.00 41.39
S
ANISOU 1514  SG  CYS A 425     4930   5467   5327     77    -26    166
S
ATOM   1515  C   CYS A 425      16.729  -7.761  -7.995  1.00 42.83
C
ANISOU 1515  C   CYS A 425     5386   5497   5390     14      2    110
C
ATOM   1516  O   CYS A 425      15.813  -8.361  -8.585  1.00 42.19
O
ANISOU 1516  O   CYS A 425     5252   5457   5320     -2     48    124
O
ATOM   1517  N   SER A 426      16.521  -6.693  -7.231  1.00 43.33
N
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ANISOU 1517  N   SER A 426     5489   5511   5460      6    -17    101
N
ATOM   1518  CA  SER A 426      15.185  -6.185  -7.025  1.00 43.91
C
ANISOU 1518  CA  SER A 426     5550   5598   5534    -21    -15     67
C
ATOM   1519  CB  SER A 426      14.815  -6.219  -5.538  1.00 44.36
C
ANISOU 1519  CB  SER A 426     5616   5660   5575    -47    -55     69
C
ATOM   1520  OG  SER A 426      15.437  -5.186  -4.808  1.00 45.92
O
ANISOU 1520  OG  SER A 426     5898   5798   5752    -91    -95     43
O
ATOM   1521  C   SER A 426      14.983  -4.801  -7.660  1.00 43.57
C
ANISOU 1521  C   SER A 426     5506   5553   5493    -13    -31     57
C
ATOM   1522  O   SER A 426      15.711  -3.850  -7.371  1.00 43.22
O
ANISOU 1522  O   SER A 426     5456   5506   5457     -9    -46     60
O
ATOM   1523  N   VAL A 427      13.976  -4.725  -8.528  1.00 42.97
N
ANISOU 1523  N   VAL A 427     5449   5498   5380    -15    -21     49
N
ATOM   1524  CA  VAL A 427      13.734  -3.579  -9.400  1.00 42.05
C
ANISOU 1524  CA  VAL A 427     5340   5430   5205      0    -15     33
C
ATOM   1525  CB  VAL A 427      13.627  -4.051 -10.884  1.00 41.86
C
ANISOU 1525  CB  VAL A 427     5301   5420   5181     17     -2    -11
C
ATOM   1526  CG1 VAL A 427      13.382  -2.874 -11.821  1.00 40.21
C
ANISOU 1526  CG1 VAL A 427     5056   5232   4987     44     57     23
C
ATOM   1527  CG2 VAL A 427      14.872  -4.811 -11.296  1.00 41.53
C
ANISOU 1527  CG2 VAL A 427     5292   5317   5170      0   -112     30
C
ATOM   1528  C   VAL A 427      12.453  -2.820  -9.041  1.00 41.50
C
ANISOU 1528  C   VAL A 427     5362   5341   5064    -13      8     28
C
ATOM   1529  O   VAL A 427      11.390  -3.408  -8.880  1.00 40.96
O
ANISOU 1529  O   VAL A 427     5279   5330   4951     -6     48     98
O
ATOM   1530  N   MET A 428      12.559  -1.500  -8.969  1.00 41.12
N
ANISOU 1530  N   MET A 428     5318   5327   4978    -22      7      9
N
ATOM   1531  CA  MET A 428      11.395  -0.647  -8.805  1.00 40.47
C
ANISOU 1531  CA  MET A 428     5291   5197   4889    -14     60    -23
C
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ATOM   1532  CB  MET A 428      11.585   0.281  -7.620  1.00 40.36
C
ANISOU 1532  CB  MET A 428     5204   5222   4908    -56     23     -2
C
ATOM   1533  CG  MET A 428      12.037  -0.413  -6.373  1.00 41.31
C
ANISOU 1533  CG  MET A 428     5409   5218   5068    -29     52     -5
C
ATOM   1534  SD  MET A 428      11.727   0.663  -4.974  1.00 42.39
S
ANISOU 1534  SD  MET A 428     5767   5498   4839    -41    119    -25
S
ATOM   1535  CE  MET A 428       9.947   0.788  -5.114  1.00 40.75
C
ANISOU 1535  CE  MET A 428     5472   5091   4920     29     70    102
C
ATOM   1536  C   MET A 428      11.096   0.175 -10.057  1.00 39.15
C
ANISOU 1536  C   MET A 428     5085   5011   4777     14     40   -108
C
ATOM   1537  O   MET A 428      11.944   0.908 -10.555  1.00 38.37
O
ANISOU 1537  O   MET A 428     5039   4855   4683     13     60    -72
O
ATOM   1538  N   HIS A 429       9.876   0.038 -10.556  1.00 37.88
N
ANISOU 1538  N   HIS A 429     4935   4841   4613     56     57   -125
N
ATOM   1539  CA  HIS A 429       9.427   0.779 -11.730  1.00 36.90
C
ANISOU 1539  CA  HIS A 429     4763   4738   4517     31     43   -119
C
ATOM   1540  CB  HIS A 429       9.829   0.086 -13.033  1.00 35.73
C
ANISOU 1540  CB  HIS A 429     4590   4600   4386     -2     24    -67
C
ATOM   1541  CG  HIS A 429       9.560   0.914 -14.246  1.00 33.46
C
ANISOU 1541  CG  HIS A 429     4228   4253   4232     12    111   -213
C
ATOM   1542  ND1 HIS A 429       8.334   0.950 -14.870  1.00 31.22
N
ANISOU 1542  ND1 HIS A 429     4260   3907   3694     25     43   -229
N
ATOM   1543  CE1 HIS A 429       8.385   1.778 -15.894  1.00 30.83
C
ANISOU 1543  CE1 HIS A 429     4069   3810   3833    -36     51   -163
C
ATOM   1544  NE2 HIS A 429       9.602   2.278 -15.960  1.00 31.02
N
ANISOU 1544  NE2 HIS A 429     4048   3977   3758     10   -105   -163
N
ATOM   1545  CD2 HIS A 429      10.353   1.763 -14.935  1.00 32.35
C
ANISOU 1545  CD2 HIS A 429     4277   3969   4045     86     47   -124
C
ATOM   1546  C   HIS A 429       7.929   0.843 -11.664  1.00 36.82
C
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ANISOU 1546  C   HIS A 429     4799   4771   4418     26      9   -122
C
ATOM   1547  O   HIS A 429       7.297  -0.115 -11.229  1.00 36.28
O
ANISOU 1547  O   HIS A 429     4722   4796   4265     10    -12   -179
O
ATOM   1548  N   GLU A 430       7.374   1.964 -12.119  1.00 36.71
N
ANISOU 1548  N   GLU A 430     4815   4761   4371     55     19   -106
N
ATOM   1549  CA  GLU A 430       5.934   2.203 -12.098  1.00 36.80
C
ANISOU 1549  CA  GLU A 430     4811   4731   4437     41      6    -42
C
ATOM   1550  CB  GLU A 430       5.594   3.547 -12.773  1.00 36.76
C
ANISOU 1550  CB  GLU A 430     4791   4744   4430     -9    -30    -31
C
ATOM   1551  CG  GLU A 430       5.694   3.553 -14.307  1.00 35.19
C
ANISOU 1551  CG  GLU A 430     4490   4486   4392     25     72    100
C
ATOM   1552  CD  GLU A 430       5.001   4.742 -14.895  1.00 34.83
C
ANISOU 1552  CD  GLU A 430     4558   4546   4128    -71    229     48
C
ATOM   1553  OE1 GLU A 430       5.453   5.862 -14.630  1.00 30.64
O
ANISOU 1553  OE1 GLU A 430     4122   4033   3484   -100    187     82
O
ATOM   1554  OE2 GLU A 430       3.991   4.560 -15.606  1.00 34.10
O
ANISOU 1554  OE2 GLU A 430     4321   4585   4048    -96    202    -27
O
ATOM   1555  C   GLU A 430       5.110   1.099 -12.716  1.00 36.55
C
ANISOU 1555  C   GLU A 430     4793   4631   4463     48    -12    -17
C
ATOM   1556  O   GLU A 430       4.035   0.794 -12.223  1.00 36.45
O
ANISOU 1556  O   GLU A 430     4876   4636   4334     94     23   -111
O
ATOM   1557  N   ALA A 431       5.613   0.513 -13.803  1.00 36.85
N
ANISOU 1557  N   ALA A 431     4769   4635   4595     51    -26     26
N
ATOM   1558  CA  ALA A 431       4.836  -0.427 -14.622  1.00 36.97
C
ANISOU 1558  CA  ALA A 431     4763   4665   4617     35      0    -11
C
ATOM   1559  CB  ALA A 431       5.256  -0.312 -16.072  1.00 36.63
C
ANISOU 1559  CB  ALA A 431     4680   4637   4600     53    -51     -6
C
ATOM   1560  C   ALA A 431       4.901  -1.891 -14.129  1.00 37.11
C
ANISOU 1560  C   ALA A 431     4752   4712   4633    -16     12    -11
C
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ATOM   1561  O   ALA A 431       4.366  -2.798 -14.764  1.00 37.32
O
ANISOU 1561  O   ALA A 431     4770   4750   4656    -49     59    -15
O
ATOM   1562  N   LEU A 432       5.562  -2.117 -13.003  1.00 36.79
N
ANISOU 1562  N   LEU A 432     4741   4648   4588     -2      5      7
N
ATOM   1563  CA  LEU A 432       5.501  -3.419 -12.333  1.00 37.15
C
ANISOU 1563  CA  LEU A 432     4763   4747   4605     -3     -9      8
C
ATOM   1564  CB  LEU A 432       6.813  -3.728 -11.587  1.00 36.16
C
ANISOU 1564  CB  LEU A 432     4697   4593   4448     14    -19     45
C
ATOM   1565  CG  LEU A 432       8.039  -3.920 -12.494  1.00 35.48
C
ANISOU 1565  CG  LEU A 432     4565   4483   4433     11    -70     72
C
ATOM   1566  CD1 LEU A 432       9.375  -3.695 -11.782  1.00 33.76
C
ANISOU 1566  CD1 LEU A 432     4494   4326   4005     44    -80    116
C
ATOM   1567  CD2 LEU A 432       8.019  -5.273 -13.221  1.00 34.94
C
ANISOU 1567  CD2 LEU A 432     4448   4511   4315     30    -64    152
C
ATOM   1568  C   LEU A 432       4.287  -3.470 -11.401  1.00 37.38
C
ANISOU 1568  C   LEU A 432     4819   4804   4578    -12     -9     34
C
ATOM   1569  O   LEU A 432       3.802  -2.445 -10.931  1.00 37.28
O
ANISOU 1569  O   LEU A 432     4766   4889   4509     32      1     67
O
ATOM   1570  N   HIS A 433       3.768  -4.663 -11.178  1.00 38.17
N
ANISOU 1570  N   HIS A 433     4911   4926   4663    -24    -11     39
N
ATOM   1571  CA  HIS A 433       2.747  -4.869 -10.161  1.00 38.86
C
ANISOU 1571  CA  HIS A 433     4958   5015   4789    -27     -2     49
C
ATOM   1572  CB  HIS A 433       2.447  -6.358 -10.078  1.00 39.24
C
ANISOU 1572  CB  HIS A 433     4992   5068   4847    -27      6     41
C
ATOM   1573  CG  HIS A 433       1.480  -6.722  -9.003  1.00 41.29
C
ANISOU 1573  CG  HIS A 433     5182   5325   5179    -26     27     73
C
ATOM   1574  ND1 HIS A 433       0.117  -6.574  -9.150  1.00 42.44
N
ANISOU 1574  ND1 HIS A 433     5238   5453   5433    -68     34     41
N
ATOM   1575  CE1 HIS A 433      -0.482  -6.986  -8.046  1.00 42.23
C
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ANISOU 1575  CE1 HIS A 433     5381   5485   5176     10    -17    -10
C
ATOM   1576  NE2 HIS A 433       0.443  -7.399  -7.197  1.00 41.94
N
ANISOU 1576  NE2 HIS A 433     5411   5442   5079    -19     12     -1
N
ATOM   1577  CD2 HIS A 433       1.678  -7.241  -7.769  1.00 40.89
C
ANISOU 1577  CD2 HIS A 433     5136   5376   5025     -8    -29     20
C
ATOM   1578  C   HIS A 433       3.279  -4.308  -8.824  1.00 38.60
C
ANISOU 1578  C   HIS A 433     4959   4969   4737    -33      8     95
C
ATOM   1579  O   HIS A 433       4.392  -4.632  -8.416  1.00 38.55
O
ANISOU 1579  O   HIS A 433     4974   5004   4668    -49    -28    116
O
ATOM   1580  N   ASN A 434       2.522  -3.420  -8.187  1.00 38.26
N
ANISOU 1580  N   ASN A 434     4920   4949   4665    -74     17    108
N
ATOM   1581  CA  ASN A 434       2.994  -2.709  -6.994  1.00 38.50
C
ANISOU 1581  CA  ASN A 434     4948   4950   4727    -75     13     90
C
ATOM   1582  CB  ASN A 434       2.999  -3.639  -5.763  1.00 38.77
C
ANISOU 1582  CB  ASN A 434     4941   5054   4733   -120     20     41
C
ATOM   1583  CG  ASN A 434       1.631  -4.134  -5.413  1.00 38.47
C
ANISOU 1583  CG  ASN A 434     4913   5088   4614   -105     23      7
C
ATOM   1584  OD1 ASN A 434       1.466  -5.285  -5.048  1.00 38.40
O
ANISOU 1584  OD1 ASN A 434     5064   4785   4740   -130    -43     51
O
ATOM   1585  ND2 ASN A 434       0.635  -3.275  -5.548  1.00 35.57
N
ANISOU 1585  ND2 ASN A 434     4416   4664   4435   -105    161    -54
N
ATOM   1586  C   ASN A 434       4.372  -2.064  -7.143  1.00 38.65
C
ANISOU 1586  C   ASN A 434     4962   4997   4727    -89     12     73
C
ATOM   1587  O   ASN A 434       5.092  -1.904  -6.156  1.00 38.37
O
ANISOU 1587  O   ASN A 434     4948   4953   4677   -158     44     68
O
ATOM   1588  N   HIS A 435       4.729  -1.721  -8.384  1.00 38.28
N
ANISOU 1588  N   HIS A 435     4930   4968   4646    -59    -13     18
N
ATOM   1589  CA  HIS A 435       5.963  -1.016  -8.726  1.00 37.58
C
ANISOU 1589  CA  HIS A 435     4881   4891   4504    -25      5     35
C
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ATOM   1590  CB  HIS A 435       5.952   0.417  -8.155  1.00 37.74
C
ANISOU 1590  CB  HIS A 435     4898   4903   4537    -23    -29     -1
C
ATOM   1591  CG  HIS A 435       4.584   1.032  -8.082  1.00 37.92
C
ANISOU 1591  CG  HIS A 435     4873   4934   4598    -13     14    -80
C
ATOM   1592  ND1 HIS A 435       3.749   1.135  -9.174  1.00 37.42
N
ANISOU 1592  ND1 HIS A 435     4902   4856   4459    161     35   -122
N
ATOM   1593  CE1 HIS A 435       2.607   1.686  -8.810  1.00 38.63
C
ANISOU 1593  CE1 HIS A 435     4913   4743   5020     62     15     82
C
ATOM   1594  NE2 HIS A 435       2.681   1.979  -7.524  1.00 36.99
N
ANISOU 1594  NE2 HIS A 435     4821   4801   4432     32    -57      3
N
ATOM   1595  CD2 HIS A 435       3.903   1.573  -7.044  1.00 38.62
C
ANISOU 1595  CD2 HIS A 435     4975   4958   4739    -34      6    -67
C
ATOM   1596  C   HIS A 435       7.236  -1.770  -8.330  1.00 37.17
C
ANISOU 1596  C   HIS A 435     4870   4880   4372    -25     31     22
C
ATOM   1597  O   HIS A 435       8.273  -1.176  -8.127  1.00 35.86
O
ANISOU 1597  O   HIS A 435     4733   4829   4063     47     22     64
O
ATOM   1598  N   TYR A 436       7.153  -3.088  -8.248  1.00 37.91
N
ANISOU 1598  N   TYR A 436     4963   4964   4476      1     14     15
N
ATOM   1599  CA  TYR A 436       8.235  -3.873  -7.684  1.00 38.88
C
ANISOU 1599  CA  TYR A 436     5029   4992   4751      2     12     -9
C
ATOM   1600  CB  TYR A 436       8.058  -3.997  -6.158  1.00 38.93
C
ANISOU 1600  CB  TYR A 436     5047   4980   4765      8    -25     -6
C
ATOM   1601  CG  TYR A 436       9.235  -4.641  -5.455  1.00 39.72
C
ANISOU 1601  CG  TYR A 436     5116   5014   4959     60      6    -69
C
ATOM   1602  CD1 TYR A 436       9.202  -5.986  -5.059  1.00 40.15
C
ANISOU 1602  CD1 TYR A 436     5192   5178   4884     57     49     35
C
ATOM   1603  CE1 TYR A 436      10.302  -6.573  -4.438  1.00 39.78
C
ANISOU 1603  CE1 TYR A 436     5150   5156   4806     17    -21     78
C
ATOM   1604  CZ  TYR A 436      11.426  -5.797  -4.193  1.00 40.05
C
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ANISOU 1604  CZ  TYR A 436     5151   5177   4887     17     10     47
C
ATOM   1605  OH  TYR A 436      12.530  -6.318  -3.580  1.00 39.84
O
ANISOU 1605  OH  TYR A 436     5240   5038   4856     63    -12      9
O
ATOM   1606  CE2 TYR A 436      11.465  -4.467  -4.566  1.00 40.35
C
ANISOU 1606  CE2 TYR A 436     5160   5135   5036     62    -59     13
C
ATOM   1607  CD2 TYR A 436      10.389  -3.905  -5.195  1.00 40.97
C
ANISOU 1607  CD2 TYR A 436     5145   5122   5300     80      3    -58
C
ATOM   1608  C   TYR A 436       8.303  -5.264  -8.287  1.00 39.02
C
ANISOU 1608  C   TYR A 436     5083   5005   4736    -49    -25     -2
C
ATOM   1609  O   TYR A 436       7.289  -5.871  -8.531  1.00 38.66
O
ANISOU 1609  O   TYR A 436     5121   4885   4682    -64    -60      4
O
ATOM   1610  N   THR A 437       9.514  -5.755  -8.503  1.00 39.50
N
ANISOU 1610  N   THR A 437     5159   5021   4828    -10      2    -25
N
ATOM   1611  CA  THR A 437       9.734  -7.163  -8.753  1.00 40.83
C
ANISOU 1611  CA  THR A 437     5264   5167   5080    -30     15     33
C
ATOM   1612  CB  THR A 437       9.495  -7.556 -10.250  1.00 40.93
C
ANISOU 1612  CB  THR A 437     5246   5166   5137    -33      3    -17
C
ATOM   1613  OG1 THR A 437       9.270  -8.968 -10.336  1.00 41.06
O
ANISOU 1613  OG1 THR A 437     5236   5079   5286     15    103    -13
O
ATOM   1614  CG2 THR A 437      10.665  -7.153 -11.145  1.00 39.50
C
ANISOU 1614  CG2 THR A 437     5153   4957   4898     -9      5     -1
C
ATOM   1615  C   THR A 437      11.121  -7.579  -8.248  1.00 41.64
C
ANISOU 1615  C   THR A 437     5343   5262   5214    -19    -19     68
C
ATOM   1616  O   THR A 437      11.926  -6.731  -7.857  1.00 41.69
O
ANISOU 1616  O   THR A 437     5358   5239   5240    -28    -17    144
O
ATOM   1617  N   GLN A 438      11.371  -8.886  -8.250  1.00 42.72
N
ANISOU 1617  N   GLN A 438     5471   5368   5392    -15     17     61
N
ATOM   1618  CA  GLN A 438      12.573  -9.499  -7.668  1.00 43.76
C
ANISOU 1618  CA  GLN A 438     5564   5521   5541      0     12     72
C
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ATOM   1619  CB  GLN A 438      12.260 -10.041  -6.266  1.00 43.80
C
ANISOU 1619  CB  GLN A 438     5570   5515   5557     21    -19     59
C
ATOM   1620  CG  GLN A 438      13.471 -10.272  -5.363  1.00 45.09
C
ANISOU 1620  CG  GLN A 438     5780   5691   5659     13     21     68
C
ATOM   1621  CD  GLN A 438      13.088 -10.493  -3.894  1.00 44.91
C
ANISOU 1621  CD  GLN A 438     5851   5578   5634      4     82     72
C
ATOM   1622  OE1 GLN A 438      12.943 -11.640  -3.453  1.00 46.59
O
ANISOU 1622  OE1 GLN A 438     5980   5851   5871    -13    157     97
O
ATOM   1623  NE2 GLN A 438      12.927  -9.394  -3.132  1.00 45.98
N
ANISOU 1623  NE2 GLN A 438     5903   5784   5783    -47    135     46
N
ATOM   1624  C   GLN A 438      12.951 -10.641  -8.584  1.00 43.72
C
ANISOU 1624  C   GLN A 438     5579   5440   5593      3     -9     94
C
ATOM   1625  O   GLN A 438      12.083 -11.348  -9.079  1.00 43.70
O
ANISOU 1625  O   GLN A 438     5600   5396   5605     -1    -19    100
O
ATOM   1626  N   LYS A 439      14.239 -10.788  -8.859  1.00 44.68
N
ANISOU 1626  N   LYS A 439     5693   5568   5715     -2    -26     96
N
ATOM   1627  CA  LYS A 439      14.741 -11.933  -9.615  1.00 45.43
C
ANISOU 1627  CA  LYS A 439     5800   5662   5798    -16     -9     70
C
ATOM   1628  CB  LYS A 439      15.058 -11.555 -11.064  1.00 45.89
C
ANISOU 1628  CB  LYS A 439     5825   5736   5873     -5     -9     40
C
ATOM   1629  CG  LYS A 439      13.856 -11.073 -11.880  1.00 46.21
C
ANISOU 1629  CG  LYS A 439     5900   5781   5874     51    -46     49
C
ATOM   1630  CD  LYS A 439      12.907 -12.194 -12.253  1.00 46.24
C
ANISOU 1630  CD  LYS A 439     5775   5776   6016    -18    -95     97
C
ATOM   1631  CE  LYS A 439      11.616 -11.657 -12.829  1.00 47.33
C
ANISOU 1631  CE  LYS A 439     6039   5979   5962    -62     19     23
C
ATOM   1632  NZ  LYS A 439      10.782 -12.775 -13.332  1.00 47.50
N
ANISOU 1632  NZ  LYS A 439     6069   6016   5962    -55    -46     41
N
ATOM   1633  C   LYS A 439      15.969 -12.490  -8.917  1.00 46.09
C
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ANISOU 1633  C   LYS A 439     5848   5746   5916     -7     -7     78
C
ATOM   1634  O   LYS A 439      16.907 -11.749  -8.596  1.00 46.55
O
ANISOU 1634  O   LYS A 439     5959   5751   5975      6     -6    117
O
ATOM   1635  N   SER A 440      15.946 -13.796  -8.655  1.00 46.72
N
ANISOU 1635  N   SER A 440     5934   5839   5979    -31    -11     81
N
ATOM   1636  CA  SER A 440      17.032 -14.454  -7.942  1.00 46.85
C
ANISOU 1636  CA  SER A 440     5928   5897   5975     -7    -17     88
C
ATOM   1637  CB  SER A 440      16.496 -15.469  -6.913  1.00 47.28
C
ANISOU 1637  CB  SER A 440     5941   6005   6016     -9    -20     46
C
ATOM   1638  OG  SER A 440      16.183 -14.836  -5.671  1.00 48.78
O
ANISOU 1638  OG  SER A 440     6002   6424   6105    -24     17     60
O
ATOM   1639  C   SER A 440      17.973 -15.124  -8.918  1.00 46.89
C
ANISOU 1639  C   SER A 440     5980   5868   5969    -17    -17     95
C
ATOM   1640  O   SER A 440      17.545 -15.633  -9.959  1.00 47.05
O
ANISOU 1640  O   SER A 440     6023   5846   6007    -34    -57    109
O
ATOM   1641  N   LEU A 441      19.258 -15.097  -8.571  1.00 47.27
N
ANISOU 1641  N   LEU A 441     6010   5908   6042     16    -21     93
N
ATOM   1642  CA  LEU A 441      20.323 -15.741  -9.329  1.00 47.61
C
ANISOU 1642  CA  LEU A 441     6027   5975   6087     14      1     78
C
ATOM   1643  CB  LEU A 441      21.264 -14.677  -9.907  1.00 47.64
C
ANISOU 1643  CB  LEU A 441     6073   5959   6066     37      7    102
C
ATOM   1644  CG  LEU A 441      22.391 -15.101 -10.862  1.00 47.04
C
ANISOU 1644  CG  LEU A 441     5967   5906   5997     40      6     66
C
ATOM   1645  CD1 LEU A 441      21.849 -15.691 -12.147  1.00 47.09
C
ANISOU 1645  CD1 LEU A 441     6088   5875   5927     76     24     60
C
ATOM   1646  CD2 LEU A 441      23.266 -13.921 -11.162  1.00 47.11
C
ANISOU 1646  CD2 LEU A 441     5985   5891   6020     25     -6     88
C
ATOM   1647  C   LEU A 441      21.101 -16.740  -8.437  1.00 48.31
C
ANISOU 1647  C   LEU A 441     6136   6022   6196     33     -7     89
C
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ATOM   1648  O   LEU A 441      21.434 -16.440  -7.269  1.00 47.92
O
ANISOU 1648  O   LEU A 441     6026   5982   6196      0    -72     71
O
ATOM   1649  N   SER A 442      21.366 -17.924  -8.998  1.00 49.31
N
ANISOU 1649  N   SER A 442     6259   6162   6314     38     26     67
N
ATOM   1650  CA  SER A 442      22.025 -19.032  -8.263  1.00 50.46
C
ANISOU 1650  CA  SER A 442     6432   6297   6442     43     18     55
C
ATOM   1651  CB  SER A 442      20.983 -19.965  -7.635  1.00 50.19
C
ANISOU 1651  CB  SER A 442     6428   6217   6421     34     26     71
C
ATOM   1652  OG  SER A 442      20.685 -19.603  -6.297  1.00 50.93
O
ANISOU 1652  OG  SER A 442     6648   6207   6496     55    -43     19
O
ATOM   1653  C   SER A 442      22.947 -19.865  -9.145  1.00 51.22
C
ANISOU 1653  C   SER A 442     6514   6433   6515     40     21     51
C
ATOM   1654  O   SER A 442      22.689 -20.034 -10.346  1.00 51.69
O
ANISOU 1654  O   SER A 442     6550   6551   6539     26     -4     45
O
ATOM   1655  N   LEU A 443      24.012 -20.392  -8.537  1.00 52.28
N
ANISOU 1655  N   LEU A 443     6616   6628   6619     21      5     55
N
ATOM   1656  CA  LEU A 443      24.886 -21.388  -9.174  1.00 53.25
C
ANISOU 1656  CA  LEU A 443     6742   6744   6746     33      0     26
C
ATOM   1657  CB  LEU A 443      25.940 -21.890  -8.178  1.00 53.57
C
ANISOU 1657  CB  LEU A 443     6795   6808   6748     31     -4     40
C
ATOM   1658  CG  LEU A 443      27.061 -22.777  -8.734  1.00 53.94
C
ANISOU 1658  CG  LEU A 443     6821   6927   6747     71     10     64
C
ATOM   1659  CD1 LEU A 443      27.662 -22.226 -10.044  1.00 55.71
C
ANISOU 1659  CD1 LEU A 443     7063   7076   7027     -4     40     67
C
ATOM   1660  CD2 LEU A 443      28.135 -22.952  -7.702  1.00 55.22
C
ANISOU 1660  CD2 LEU A 443     6963   7124   6892     17      6     -2
C
ATOM   1661  C   LEU A 443      24.112 -22.576  -9.771  1.00 53.71
C
ANISOU 1661  C   LEU A 443     6819   6793   6792      4      2     27
C
ATOM   1662  O   LEU A 443      23.550 -23.410  -9.032  1.00 53.76
O
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ANISOU 1662  O   LEU A 443     6815   6847   6764     25      9     84
O
ATOM   1663  N   SER A 444      24.103 -22.645 -11.106  1.00 54.22
N
ANISOU 1663  N   SER A 444     6928   6846   6826    -17     15     25
N
ATOM   1664  CA  SER A 444      23.320 -23.649 -11.835  1.00 54.89
C
ANISOU 1664  CA  SER A 444     6984   6928   6940    -35     12     13
C
ATOM   1665  CB  SER A 444      23.149 -23.261 -13.303  1.00 54.86
C
ANISOU 1665  CB  SER A 444     6962   6941   6939    -49     23     16
C
ATOM   1666  OG  SER A 444      22.201 -24.103 -13.928  1.00 54.82
O
ANISOU 1666  OG  SER A 444     7079   6949   6799    -69     14    -88
O
ATOM   1667  C   SER A 444      23.919 -25.055 -11.752  1.00 55.51
C
ANISOU 1667  C   SER A 444     7024   6992   7072    -18     33      3
C
ATOM   1668  O   SER A 444      25.131 -25.226 -11.969  1.00 55.87
O
ANISOU 1668  O   SER A 444     7048   7066   7112    -44     54    -23
O
ATOM   1669  N   PRO A 445      23.069 -26.066 -11.448  1.00 55.87
N
ANISOU 1669  N   PRO A 445     7077   7024   7123    -21     55     28
N
ATOM   1670  CA  PRO A 445      23.527 -27.447 -11.334  1.00 56.18
C
ANISOU 1670  CA  PRO A 445     7138   7066   7139    -14     43     20
C
ATOM   1671  CB  PRO A 445      22.634 -28.013 -10.213  1.00 56.09
C
ANISOU 1671  CB  PRO A 445     7127   7062   7121    -19     38     43
C
ATOM   1672  CG  PRO A 445      21.374 -27.115 -10.201  1.00 55.99
C
ANISOU 1672  CG  PRO A 445     7107   7028   7136    -18     60     17
C
ATOM   1673  CD  PRO A 445      21.619 -25.973 -11.182  1.00 55.94
C
ANISOU 1673  CD  PRO A 445     7068   7042   7143    -13     32     27
C
ATOM   1674  C   PRO A 445      23.313 -28.224 -12.636  1.00 56.28
C
ANISOU 1674  C   PRO A 445     7162   7119   7100    -20      5      9
C
ATOM   1675  O   PRO A 445      22.773 -27.671 -13.598  1.00 56.74
O
ANISOU 1675  O   PRO A 445     7250   7159   7148    -40     -2     46
O
ATOM   1676  C1  NAG C   1      23.582  33.784  -6.381  1.00 62.40
C
ANISOU 1676  C1  NAG C   1     7883   7954   7870    -44     -8    -30
C
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ATOM   1677  C2  NAG C   1      23.462  33.722  -7.905  1.00 65.49
C
ANISOU 1677  C2  NAG C   1     8282   8330   8269    -28      6     -4
C
ATOM   1678  N2  NAG C   1      23.093  35.025  -8.441  1.00 66.24
N
ANISOU 1678  N2  NAG C   1     8456   8344   8368     18     29     25
N
ATOM   1679  C7  NAG C   1      23.585  35.522  -9.579  1.00 67.45
C
ANISOU 1679  C7  NAG C   1     8530   8535   8561     -1     -2     14
C
ATOM   1680  O7  NAG C   1      23.964  34.827 -10.522  1.00 67.51
O
ANISOU 1680  O7  NAG C   1     8538   8539   8571     59     54     -2
O
ATOM   1681  C8  NAG C   1      23.648  37.017  -9.676  1.00 66.89
C
ANISOU 1681  C8  NAG C   1     8466   8432   8517     -1     16     31
C
ATOM   1682  C3  NAG C   1      22.443  32.665  -8.344  1.00 65.88
C
ANISOU 1682  C3  NAG C   1     8333   8317   8379    -25      6    -44
C
ATOM   1683  O3  NAG C   1      22.590  32.483  -9.734  1.00 66.07
O
ANISOU 1683  O3  NAG C   1     8394   8322   8385    -34     33    -29
O
ATOM   1684  C4  NAG C   1      22.599  31.331  -7.598  1.00 65.99
C
ANISOU 1684  C4  NAG C   1     8321   8333   8418      5      7    -11
C
ATOM   1685  O4  NAG C   1      21.474  30.499  -7.821  1.00 66.44
O
ANISOU 1685  O4  NAG C   1     8287   8408   8547     13     31      9
O
ATOM   1686  C5  NAG C   1      22.752  31.577  -6.097  1.00 66.41
C
ANISOU 1686  C5  NAG C   1     8343   8413   8474    -27     15    -25
C
ATOM   1687  C6  NAG C   1      22.991  30.280  -5.319  1.00 70.02
C
ANISOU 1687  C6  NAG C   1     8892   8745   8966     21     22     38
C
ATOM   1688  O6  NAG C   1      23.519  30.524  -4.020  1.00 73.85
O
ANISOU 1688  O6  NAG C   1     9391   9317   9349     -6    -44    -16
O
ATOM   1689  O5  NAG C   1      23.817  32.482  -5.871  1.00 63.94
O
ANISOU 1689  O5  NAG C   1     8161   8050   8084     80     50     57
O
ATOM   1690  C1  NAG C   2      21.730  29.460  -8.798  1.00 65.34
C
ANISOU 1690  C1  NAG C   2     8142   8275   8407     44     10      1
C
ATOM   1691  C2  NAG C   2      21.096  28.144  -8.338  1.00 65.73
C
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ANISOU 1691  C2  NAG C   2     8184   8346   8442     35    -16     -3
C
ATOM   1692  N2  NAG C   2      21.683  27.718  -7.084  1.00 64.89
N
ANISOU 1692  N2  NAG C   2     8185   8149   8320     -5     14     -2
N
ATOM   1693  C7  NAG C   2      20.978  27.261  -6.059  1.00 63.76
C
ANISOU 1693  C7  NAG C   2     8044   7955   8225     -2     10    -19
C
ATOM   1694  O7  NAG C   2      19.755  27.237  -6.045  1.00 64.27
O
ANISOU 1694  O7  NAG C   2     8126   7933   8360     58    -45    -18
O
ATOM   1695  C8  NAG C   2      21.759  26.753  -4.886  1.00 63.17
C
ANISOU 1695  C8  NAG C   2     8009   7902   8089    -43      0    -70
C
ATOM   1696  C3  NAG C   2      21.272  27.045  -9.384  1.00 66.30
C
ANISOU 1696  C3  NAG C   2     8307   8391   8490     -9     39    -16
C
ATOM   1697  O3  NAG C   2      20.552  25.897  -9.004  1.00 66.84
O
ANISOU 1697  O3  NAG C   2     8376   8464   8554     36     21    -17
O
ATOM   1698  C4  NAG C   2      20.804  27.518 -10.758  1.00 67.01
C
ANISOU 1698  C4  NAG C   2     8356   8544   8559     11      6     16
C
ATOM   1699  O4  NAG C   2      21.178  26.580 -11.745  1.00 68.38
O
ANISOU 1699  O4  NAG C   2     8536   8661   8781     48      1    -50
O
ATOM   1700  C5  NAG C   2      21.470  28.857 -11.105  1.00 66.52
C
ANISOU 1700  C5  NAG C   2     8316   8433   8524     47     10    -29
C
ATOM   1701  C6  NAG C   2      20.959  29.383 -12.447  1.00 65.54
C
ANISOU 1701  C6  NAG C   2     8421   8024   8454     24     13     40
C
ATOM   1702  O6  NAG C   2      20.896  30.794 -12.448  1.00 66.76
O
ANISOU 1702  O6  NAG C   2     8300   8669   8396    -35     74    -46
O
ATOM   1703  O5  NAG C   2      21.262  29.813 -10.083  1.00 65.04
O
ANISOU 1703  O5  NAG C   2     8097   8260   8355     41     32     14
O
ATOM   1704  C1  BMA C   3      20.170  25.602 -12.036  1.00 69.16
C
ANISOU 1704  C1  BMA C   3     8600   8769   8908      4     18      7
C
ATOM   1705  C2  BMA C   3      20.218  25.313 -13.529  1.00 70.30
C
ANISOU 1705  C2  BMA C   3     8850   8920   8938     19     27     -8
C
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ATOM   1706  O2  BMA C   3      21.569  24.990 -13.866  1.00 70.44
O
ANISOU 1706  O2  BMA C   3     8922   8873   8967    -10      1     -5
O
ATOM   1707  C3  BMA C   3      19.301  24.146 -13.887  1.00 71.64
C
ANISOU 1707  C3  BMA C   3     8983   9046   9190      8     23     33
C
ATOM   1708  O3  BMA C   3      19.431  23.763 -15.259  1.00 75.50
O
ANISOU 1708  O3  BMA C   3     9547   9570   9568    -21     91    -86
O
ATOM   1709  C4  BMA C   3      19.635  22.931 -13.035  1.00 69.90
C
ANISOU 1709  C4  BMA C   3     8765   8895   8898     29     63    -28
C
ATOM   1710  O4  BMA C   3      18.694  21.909 -13.353  1.00 69.61
O
ANISOU 1710  O4  BMA C   3     8791   8790   8869     -4     63     40
O
ATOM   1711  C5  BMA C   3      19.565  23.304 -11.562  1.00 68.25
C
ANISOU 1711  C5  BMA C   3     8529   8638   8763     43     25     26
C
ATOM   1712  C6  BMA C   3      19.992  22.163 -10.656  1.00 66.92
C
ANISOU 1712  C6  BMA C   3     8364   8482   8579      9     30    -59
C
ATOM   1713  O6  BMA C   3      20.187  22.675  -9.336  1.00 64.81
O
ANISOU 1713  O6  BMA C   3     8159   8199   8264     28    -14    -16
O
ATOM   1714  O5  BMA C   3      20.426  24.412 -11.292  1.00 68.53
O
ANISOU 1714  O5  BMA C   3     8472   8748   8818      3     -2     14
O
ATOM   1715  C1  MAN C   4      18.485  24.451 -16.100  1.00 80.48
C
ANISOU 1715  C1  MAN C   4    10175  10231  10170     54    -11     39
C
ATOM   1716  C2  MAN C   4      17.857  23.471 -17.095  1.00 83.30
C
ANISOU 1716  C2  MAN C   4    10595  10536  10515    -34      3    -45
C
ATOM   1717  O2  MAN C   4      16.758  24.059 -17.785  1.00 86.66
O
ANISOU 1717  O2  MAN C   4    10987  10961  10976     56    -72     11
O
ATOM   1718  C3  MAN C   4      18.909  22.950 -18.097  1.00 83.53
C
ANISOU 1718  C3  MAN C   4    10571  10594  10570     -3     -6    -16
C
ATOM   1719  O3  MAN C   4      18.291  22.361 -19.225  1.00 83.93
O
ANISOU 1719  O3  MAN C   4    10617  10659  10610     21      0    -35
O
ATOM   1720  C4  MAN C   4      19.916  24.011 -18.569  1.00 83.25
C
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ANISOU 1720  C4  MAN C   4    10531  10556  10544      0     21    -13
C
ATOM   1721  O4  MAN C   4      21.086  23.342 -18.983  1.00 82.77
O
ANISOU 1721  O4  MAN C   4    10525  10482  10441     -7     36    -14
O
ATOM   1722  C5  MAN C   4      20.281  25.007 -17.461  1.00 82.93
C
ANISOU 1722  C5  MAN C   4    10477  10508  10524     23     16     -3
C
ATOM   1723  C6  MAN C   4      21.110  26.187 -17.945  1.00 82.33
C
ANISOU 1723  C6  MAN C   4    10560  10453  10268    -61    -54   -113
C
ATOM   1724  O6  MAN C   4      21.526  26.916 -16.808  1.00 84.80
O
ANISOU 1724  O6  MAN C   4    10612  10772  10835     71     57    111
O
ATOM   1725  O5  MAN C   4      19.111  25.485 -16.823  1.00 81.69
O
ANISOU 1725  O5  MAN C   4    10367  10342  10328    -38     18      6
O
ATOM   1726  C1  NAG C   5      15.457  23.728 -17.226  1.00 89.09
C
ANISOU 1726  C1  NAG C   5    11237  11320  11293    -16     29    -14
C
ATOM   1727  C2  NAG C   5      14.333  24.200 -18.167  1.00 90.32
C
ANISOU 1727  C2  NAG C   5    11439  11436  11441      8    -17     15
C
ATOM   1728  N2  NAG C   5      13.146  24.596 -17.413  1.00 90.36
N
ANISOU 1728  N2  NAG C   5    11463  11426  11444      5      8    -13
N
ATOM   1729  C7  NAG C   5      12.233  25.470 -17.860  1.00 91.03
C
ANISOU 1729  C7  NAG C   5    11565  11585  11434     -4     21    -26
C
ATOM   1730  O7  NAG C   5      12.477  26.652 -18.106  1.00 90.45
O
ANISOU 1730  O7  NAG C   5    11527  11441  11396    -12     27     -5
O
ATOM   1731  C8  NAG C   5      10.835  24.956 -18.055  1.00 90.77
C
ANISOU 1731  C8  NAG C   5    11519  11492  11476    -12     -1    -20
C
ATOM   1732  C3  NAG C   5      13.944  23.170 -19.237  1.00 91.25
C
ANISOU 1732  C3  NAG C   5    11585  11552  11533      1     -6     -9
C
ATOM   1733  O3  NAG C   5      14.135  23.730 -20.517  1.00 91.88
O
ANISOU 1733  O3  NAG C   5    11692  11628  11590     -8      8     -1
O
ATOM   1734  C4  NAG C   5      14.713  21.851 -19.167  1.00 91.47
C
ANISOU 1734  C4  NAG C   5    11616  11584  11554     13    -11     -4
C
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ATOM   1735  O4  NAG C   5      13.982  20.876 -19.882  1.00 91.95
C
ANISOU 1735  O4  NAG C   5    11633  11671  11632    -13    -47    -33
C
ATOM   1736  C5  NAG C   5      14.961  21.352 -17.736  1.00 91.25
C
ANISOU 1736  C5  NAG C   5    11588  11546  11537      9    -15    -10
C
ATOM   1737  C6  NAG C   5      16.052  20.276 -17.726  1.00 92.24
C
ANISOU 1737  C6  NAG C   5    11575  11579  11891      0    -46   -137
C
ATOM   1738  O6  NAG C   5      16.007  19.560 -16.510  1.00 90.72
C
ANISOU 1738  O6  NAG C   5    11735  11388  11344    -24    -54     91
C
ATOM   1739  O5  NAG C   5      15.297  22.377 -16.797  1.00 90.15
C
ANISOU 1739  O5  NAG C   5    11430  11414  11406      5    -15     26
C
ATOM   1740  C1  MAN C   7      20.272  21.548  -8.453  1.00 64.56
C
ANISOU 1740  C1  MAN C   7     8141   8188   8199     -9     -4    -47
C
ATOM   1741  C2  MAN C   7      19.819  21.886  -7.041  1.00 64.34
C
ANISOU 1741  C2  MAN C   7     8131   8140   8175      3      1    -13
C
ATOM   1742  O2  MAN C   7      19.851  20.689  -6.290  1.00 64.37
C
ANISOU 1742  O2  MAN C   7     8170   8136   8152     13     14    -72
C
ATOM   1743  C3  MAN C   7      20.773  22.900  -6.390  1.00 64.46
C
ANISOU 1743  C3  MAN C   7     8127   8187   8177    -25     13    -19
C
ATOM   1744  O3  MAN C   7      20.410  23.129  -5.037  1.00 63.53
C
ANISOU 1744  O3  MAN C   7     7975   8057   8105    -67    -15   -101
C
ATOM   1745  C4  MAN C   7      22.239  22.434  -6.476  1.00 64.50
C
ANISOU 1745  C4  MAN C   7     8179   8148   8180      7     13    -40
C
ATOM   1746  O4  MAN C   7      23.132  23.509  -6.221  1.00 64.35
C
ANISOU 1746  O4  MAN C   7     8206   8105   8139     46     -5    -78
C
ATOM   1747  C5  MAN C   7      22.602  21.790  -7.827  1.00 64.16
C
ANISOU 1747  C5  MAN C   7     8159   8123   8096     -6      0    -11
C
ATOM   1748  C6  MAN C   7      23.842  20.915  -7.667  1.00 63.34
C
ANISOU 1748  C6  MAN C   7     7929   7985   8151    -24    -13     57
C
ATOM   1749  O6  MAN C   7      24.053  20.180  -8.846  1.00 61.06
C
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ANISOU 1749  O6  MAN C   7     7751   7711   7737     40    -16    -78
O
ATOM   1750  O5  MAN C   7      21.565  20.982  -8.380  1.00 64.42
O
ANISOU 1750  O5  MAN C   7     8221   8144   8112    -36     17    -13
O
ATOM   1751  C1  NAG C   8      18.593  20.003  -6.270  1.00 63.46
C
ANISOU 1751  C1  NAC C   8     8070   8012   8030     -5     -1    -34
C
ATOM   1752  C2  NAG C   8      18.856  18.592  -5.766  1.00 64.09
C
ANISOU 1752  C2  NAG C   8     8169   8111   8072     -6    -10     14
C
ATOM   1753  N2  NAG C   8      19.889  17.946  -6.563  1.00 63.96
N
ANISOU 1753  N2  NAG C   8     8038   8176   8088     48    -11     12
N
ATOM   1754  C7  NAG C   8      21.157  17.831  -6.142  1.00 67.85
C
ANISOU 1754  C7  NAG C   8     8475   8217   9086    -90     51    262
C
ATOM   1755  O7  NAG C   8      21.540  18.162  -5.017  1.00 63.54
O
ANISOU 1755  O7  NAG C   8     8084   8252   7806    -67   -148   -118
O
ATOM   1756  C8  NAG C   8      22.133  17.253  -7.129  1.00 63.31
C
ANISOU 1756  C8  NAG C   8     8014   8140   7899    131    171    -31
C
ATOM   1757  C3  NAG C   8      17.561  17.785  -5.725  1.00 63.80
C
ANISOU 1757  C3  NAG C   8     8109   8055   8075      0     -8    -41
C
ATOM   1758  O3  NAG C   8      17.802  16.564  -5.040  1.00 64.18
O
ANISOU 1758  O3  NAG C   8     8158   8167   8059     20    -18    -53
O
ATOM   1759  C4  NAG C   8      16.450  18.562  -4.999  1.00 62.99
C
ANISOU 1759  C4  NAG C   8     8022   7934   7977     24    -38    -22
C
ATOM   1760  O4  NAG C   8      15.194  17.950  -5.229  1.00 63.13
O
ANISOU 1760  O4  NAG C   8     8044   7901   8038     54    -37    -48
O
ATOM   1761  C5  NAG C   8      16.391  20.062  -5.340  1.00 62.31
C
ANISOU 1761  C5  NAG C   8     7922   7895   7856      3      2    -21
C
ATOM   1762  C6  NAG C   8      15.637  20.861  -4.271  1.00 61.45
C
ANISOU 1762  C6  NAG C   8     7823   7770   7755    -29    -23    -11
C
ATOM   1763  O6  NAG C   8      16.235  20.685  -2.999  1.00 59.23
O
ANISOU 1763  O6  NAG C   8     7510   7497   7498     24     71   -106
O
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ATOM   1764  O5  NAG C   8      17.675  20.637  -5.415  1.00 62.28
O
ANISOU 1764  O5  NAG C   8     7944   7849   7870    -26    -26      4
O
ATOM   1765  C1  GAL C   9      14.603  17.561  -3.972  1.00 62.63
C
ANISOU 1765  C1  GAL C   9     7968   7907   7920     -3     -4    -28
C
ATOM   1766  C2  GAL C   9      13.290  16.787  -4.178  1.00 62.38
C
ANISOU 1766  C2  GAL C   9     7981   7842   7878     19     -5    -33
C
ATOM   1767  O2  GAL C   9      12.274  17.622  -4.709  1.00 60.03
O
ANISOU 1767  O2  GAL C   9     7846   7411   7550    -14      6   -131
O
ATOM   1768  C3  GAL C   9      12.818  16.148  -2.860  1.00 62.73
C
ANISOU 1768  C3  GAL C   9     8016   7945   7872     38      8    -36
C
ATOM   1769  O3  GAL C   9      11.849  15.158  -3.102  1.00 62.97
O
ANISOU 1769  O3  GAL C   9     7994   7990   7941    -25     39      8
O
ATOM   1770  C4  GAL C   9      13.958  15.500  -2.082  1.00 63.15
C
ANISOU 1770  C4  GAL C   9     8053   7994   7944      4      6     44
C
ATOM   1771  O4  GAL C   9      14.499  14.420  -2.818  1.00 61.84
O
ANISOU 1771  O4  GAL C   9     7873   7903   7720     12      9     65
O
ATOM   1772  C5  GAL C   9      15.022  16.559  -1.867  1.00 63.69
C
ANISOU 1772  C5  GAL C   9     8052   8039   8108     -2    -14     28
C
ATOM   1773  C6  GAL C   9      16.117  16.112  -0.903  1.00 64.97
C
ANISOU 1773  C6  GAL C   9     8268   8195   8220     44    -44     59
C
ATOM   1774  O6  GAL C   9      17.286  16.891  -1.077  1.00 65.24
O
ANISOU 1774  O6  GAL C   9     8290   8153   8345    -73    -89     82
O
ATOM   1775  O5  GAL C   9      15.525  16.843  -3.157  1.00 64.20
O
ANISOU 1775  O5  GAL C   9     8132   8127   8132     15    -28    -36
O
ATOM   1776  C1  FUC C  11      24.736  29.847  -3.954  1.00 77.44
C
ANISOU 1776  C1  FUC C  11     9759   9799   9837     29     -9      1
C
ATOM   1777  C2  FUC C  11      26.080  30.499  -4.293  1.00 78.54
C
ANISOU 1777  C2  FUC C  11     9883   9910  10014     -7      4      2
C
ATOM   1778  O2  FUC C  11      26.808  30.755  -3.112  1.00 79.77
O
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ANISOU 1778  O2  FUC C  11     9917  10007  10050     72    -20    -34
O
ATOM   1779  C3  FUC C  11      26.977  29.696  -5.231  1.00 78.25
C
ANISOU 1779  C3  FUC C  11     9972   9993  10072     -6     44    -18
C
ATOM   1780  O3  FUC C  11      26.852  30.264  -6.510  1.00 79.46
O
ANISOU 1780  O3  FUC C  11    10023  10064  10081    -17     58     20
O
ATOM   1781  C4  FUC C  11      26.769  28.174  -5.286  1.00 77.45
C
ANISOU 1781  C4  FUC C  11    10020  10011  10048    -23     33    -20
C
ATOM   1782  O4  FUC C  11      26.880  27.703  -6.627  1.00 78.56
O
ANISOU 1782  O4  FUC C  11    10076   9967   9991    -28     42    -26
O
ATOM   1783  C5  FUC C  11      25.463  27.641  -4.693  1.00 77.17
C
ANISOU 1783  C5  FUC C  11    10016  10033  10124     13     23     -2
C
ATOM   1784  C6  FUC C  11      24.460  27.240  -5.783  1.00 78.48
C
ANISOU 1784  C6  FUC C  11    10059   9937  10067      0     46    -62
C
ATOM   1785  O5  FUC C  11      24.873  28.467  -3.681  1.00 79.38
O
ANISOU 1785  O5  FUC C  11     9928   9876  10085     -4     13    -44
O
ATOM   1786 ZN   ZN  I   1       1.011   2.625  -6.522  1.00 37.90
ZN
ANISOU 1786 ZN   ZN  I   1     5916   5645   2837   -109   -134   -300
ZN
ATOM   1787 ZN   ZN  I   2      -2.850  29.288   0.411  1.00 66.11
ZN
ANISOU 1787 ZN   ZN  I   2     8310   7792   9014    476     23   -269
ZN
ATOM   1788 ZN   ZN  I   3       0.081  21.125 -18.851  0.50 60.89
ZN
ANISOU 1788 ZN   ZN  I   3     7926   7551   7656     24    -73     15
ZN
ATOM   1789 ZN   ZN  I   4       4.094  -7.924 -14.198  0.50 63.49
ZN
ANISOU 1789 ZN   ZN  I   4     7915   7950   8259    -54    190    -25
ZN
ATOM   1790  OW  HOH W   1      -2.686  -4.705  -7.680  1.00 51.42
O
ANISOU 1790  OW  HOH W   1     6584   6695   6258    189   -102     48
O
ATOM   1791  OW  HOH W   2      15.326   7.920 -11.915  1.00 41.62
O
ANISOU 1791  OW  HOH W   2     5180   5671   4961    -35   -220   -272
O
ATOM   1792  OW  HOH W   3      11.705  21.084 -15.919  1.00 53.41
O
ANISOU 1792  OW  HOH W   3     6696   6842   6755     76    -83     53
O
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ATOM   1793  OW  HOH W   4       4.028   8.613  -6.717  1.00 24.34
O
ANISOU 1793  OW  HOH W   4     3616   2379   3251      0   -336    632
O
ATOM   1794  OW  HOH W   5       4.904   7.310  -3.564  1.00 23.00
O
ANISOU 1794  OW  HOH W   5     3808   3315   1615    -69    307   -476
O
ATOM   1795  OW  HOH W   6       2.707   2.220 -14.972  1.00 23.50
O
ANISOU 1795  OW  HOH W   6     3794   2827   2306     91   -630    374
O
ATOM   1796  OW  HOH W   7       0.086   8.821 -15.891  1.00 13.87
O
ANISOU 1796  OW  HOH W   7     2598   1403   1268    195     51   -373
O
ATOM   1797  OW  HOH W   8      23.163   6.265 -13.153  1.00 41.03
O
ANISOU 1797  OW  HOH W   8     5402   4550   5636    147    229     45
O
ATOM   1798  OW  HOH W   9      20.619   3.699 -13.114  1.00 23.85
O
ANISOU 1798  OW  HOH W   9     3742   2526   2794   -240    -69   -539
O
ATOM   1799  OW  HOH W  10      -2.466  -6.638  -5.878  1.00 44.21
O
ANISOU 1799  OW  HOH W  10     5803   5719   5275   -213    103    100
O
ATOM   1800  OW  HOH W  11      12.642  -1.804  -2.353  1.00 63.47
O
ANISOU 1800  OW  HOH W  11     8214   7905   7995    -35    -45     -9
O
ATOM   1801  OW  HOH W  12      22.639   6.534 -20.972  1.00 33.47
O
ANISOU 1801  OW  HOH W  12     3867   4337   4510   -144    129   -236
O
ATOM   1802  OW  HOH W  13      21.422   1.104  -8.987  1.00 24.16
O
ANISOU 1802  OW  HOH W  13     3539   3414   2226   -145    221     76
O
ATOM   1803  OW  HOH W  14       8.879   4.061 -13.080  1.00 24.97
O
ANISOU 1803  OW  HOH W  14     3170   3239   3075    162    -18   -220
O
ATOM   1804  OW  HOH W  15      11.288   6.795 -26.054  1.00 45.90
O
ANISOU 1804  OW  HOH W  15     5829   5389   6220    -13     40     27
O
ATOM   1805  OW  HOH W  16      14.749  -1.980 -24.051  1.00 16.53
O
ANISOU 1805  OW  HOH W  16     3271   2274    735     26    224   -273
O
ATOM   1806  OW  HOH W  17      -0.444   6.851 -20.367  1.00 17.75
O
ANISOU 1806  OW  HOH W  17     2576   1988   2179    732    234     28
O
ATOM   1807  OW  HOH W  18       2.245  11.930  -0.120  1.00 32.42
O
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ANISOU 1807  OW  HOH W  18     4359   4213   3746   -160     29   -125
O
ATOM   1808  OW  HOH W  19       5.162   7.718 -18.328  1.00 25.83
O
ANISOU 1808  OW  HOH W  19     3497   3439   2878     96   -375   -584
O
ATOM   1809  OW  HOH W  20       0.796   0.967  -5.140  1.00 21.38
O
ANISOU 1809  OW  HOH W  20     3124   2654   2344    142    186   -165
O
ATOM   1810  OW  HOH W  21      -2.715  28.725   2.415  1.00 36.34
O
ANISOU 1810  OW  HOH W  21     4766   4654   4387   -175     10    163
O
ATOM   1811  OW  HOH W  22      30.225  -4.400  -9.331  1.00 25.40
O
ANISOU 1811  OW  HOH W  22     3794   3473   2383   -207    171    921
O
ATOM   1812  OW  HOH W  23       7.961   6.779 -13.116  1.00 20.66
O
ANISOU 1812  OW  HOH W  23     2905   2729   2214     -3    224   -281
O
ATOM   1813  OW  HOH W  24       7.734   8.056  10.907  1.00 11.86
O
ANISOU 1813  OW  HOH W  24     2940   1037    527    120    -14   -462
O
ATOM   1814  OW  HOH W  25      -9.824  -8.657  -5.241  1.00 50.76
O
ANISOU 1814  OW  HOH W  25     6516   6602   6166   -193    254     42
O
ATOM   1815  OW  HOH W  26      -5.085  12.307 -13.493  1.00 33.94
O
ANISOU 1815  OW  HOH W  26     4426   4303   4165      0    -23   -112
O
ATOM   1816  OW  HOH W  27      21.117  -3.680  -2.105  1.00 36.56
O
ANISOU 1816  OW  HOH W  27     4582   4997   4310   -135      5    141
O
ATOM   1817  OW  HOH W  28      26.199   1.780  -6.259  1.00 42.44
O
ANISOU 1817  OW  HOH W  28     5350   5564   5209   -205     54    -69
O
ATOM   1818  OW  HOH W  29      25.352   2.736  -9.492  1.00 26.64
O
ANISOU 1818  OW  HOH W  29     2921   3682   3517   -164   -195     80
O
ATOM   1819  OW  HOH W  30       2.621  13.373 -12.530  1.00 27.62
O
ANISOU 1819  OW  HOH W  30     3212   3716   3565    -15     69    381
O
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[0389] Conclusion: The three-dimensional structure of Fc/TM was found to be very similar to that of other unliganded, unmutated human Fc regions. The dramatic, broad-ranging functional effects of the TM set of substitutions were not caused by major structural rearrangements in the Fc structure, but rather by the localized loss of a few interactions at the mutation sites.

6.34 Example 34: Internalization of anti-IFNAR1 antibodies

[0390] **Purpose:** To investigate the ability of anti-IPNAR1 antibodies to internalize in cells.

[0391] **Methods:** THP-1 cells were cultured in RPMI-1640 media containing 0.05 mM 2-mercaptoethanol and 10% fetal bovine serum at 37°C in 5% CO_2 incubator. THP-1 cells were seeded at 2 x 10^5 cells/ml in fresh growth media one day prior to experiments. At the day of the experiment, cells were washed, counted and resuspended in PBS at 3 x 10^6 cells/ml. The cells were stained with 1 µM CFSE in 37°C CO_2 incubator for 10 min. Following additional two washes with PBS, the cells were placed on ice and incubated with FcR block using 20 µl per 10^6 cells on ice for 5 min and then stained with 1 µg/ml of Alexa647-9D4-TM or Alexa 647-R347 (non-specific control antibody) on ice for 1 h. After removal of unbound mAb by 3 washes with PBS, cells were resuspended in PBS containing 2% BSA and sodium azide. The internalization was initiated by transferring the cells to an environmenttaly controlled chamber under 37°C, 5% CO_2 and 70% humidity and the internalization kinetics of Alexa647-9D4-TM was recorded over time by imaging the fluorescence of cells.

[0392] The fluorescence images of cells were analyzed using an algorithm. The algorithm used CFSE cytosolic dye to identify the boundary of a cell and a membrane region. The algorithm quantified the 9D4-TM associated fluorescence inside cells as well as on membrane. Rate of fluorescence accumulated inside the cells was calculated by model fitting of the data using SAAMII software.

[0393] **Results:** Alexa647-9D4-TM bound to THP-1 cells. No binding of Alexa647-R347, the isotype control of 9D4-TM, was observed on the same cells. This result demonstrated specific binding to THP-1 cells by 9D4-TM (Figure 33). At 4°C, 9D4-TM binding was predominately located at cell surface (0 min - Figure 33). Once the cells were incubated at 37°C, the fluorescence signal for 9D4-TM staining was significantly decreased from cell surface and accumulated in cytosolic compartment as punctuated spots. Kinetic images recorded over 60 min indicated gradual migration of fluorescence from cell surface to punctuated spots located at cytosolic compartment (15, 30 and 50 min time points, Figure 33). The result clearly demonstrated internalization of 9D4-TM on THP-1 cells.

6.35 Example 35: Absence of 9D4-TM mediated CDC activity

[0394] **Purpose:** To determine if 9D4-TM is unable to induce CDC activity a series of experiments were conducted.

[0395] **Methods:** Freshly isolated human blood from healthy, human donors was collected (approximately 100 ml) and spun down for 10 minutes at 3000G to separate serum from cells. The serum fraction was separated into two tubes. The first tube was diluted with phenol-free RPMI 1640 to a final concentration of 10% serum (non-heat inactivated or NHI). The second tube was placed in a 56°C water bath for 30 minutes to heat inactivate the complement components. Subsequently, the second tube was diluted with phenol-free RPMI-1640 media to a final concentration of 10% heat-inactivated (HI) human serum.

[0396] Daudi B cells were used as target cells as they express CD20 (target for positive control antibody) and IFNAR1. Target cells were washed and resuspended in either phenol-free RPMI media with 10% non-heat inactivated serum or in phenol-free RPMI media with 10% heat inactivated serum at a final concentration of 0.4 $x10^6$ cells/mL. Antibody solutions were prepared as a 3x dilution series with the concentrations ranging from 50ug/mL-$1.3x10^{-6}$ µg/mL. Replicate preparations of antibody dilutions were made in either media with heat-inactivated or non-heat-inactivated human serum. The CDC assay was prepared by adding 50µL of NHI or HI media to appropriate wells of a 96 well, round bottom plate. 50µL of antibody dilution series were added to the appropriate wells. Subsequently, 50µL of the target cell preparation was added to the wells, including extra wells with target cells alone for controls. The plates were incubated for 37°C for 4 hours in 5% CO_2. After 3.5 hour incubation, 20uL lysis buffer was added to appropriate control wells designated for determination of maximum lysis signal. The Quantitate™ LDH release assay was performed using protocols defined in Promega non-radioactive cytotoxicity assay, #G1780. Absorbance was measured at 490nM and Kd values were generated using GraphPad Prism 4 analysis software.

[0397] **Results:** Presented in Figure 34 are the results from the CDC performed as described above. The modified anti-IFNAR1 antibody, 9D4-TM exhibited no detectable CDC activity on target Daudi B cells over that observed with the R347 antibody. In contrast, the positive control antibody, which binds CD20 expressed on Daudi B cells, caused a dose-dependent increase in cytotoxicity over background levels. These results confirm that 9D4-TM cannot mediate CDC on IFNAR1 expressing target cells.

6.36 Example 36: The modified anti-IFNAR1 antibody, 9D4-TM does not display any adverse toxicity

[0398] Purpose: To establish that 9D4-TM does not elicit any adverse toxicity, a single-dose toxicity study was performed in cynomolgus monkeys.

[0399] **Methods:** In this study, 4 groups of 10 animals each (5/sex/group) received a single dose of 0, 5, 30, or 100 mg/kg of 9D4-TM on Day 1. After dosing, 2 animals/sex/group were assigned to necropsy on Day 3 with all remaining animals monitored until Day 70 and then removed from study without necropsy. Toxicity was assessed based on mortality, clinical signs (including menses), immunophenotyping, body weights, physical examinations (including heart rate, respiration rate, and body temperature), clinical pathology, organ weights, and microscopic data.

[0400] **Results:** Under the conditions outlined above, there were no 9D4-TM-related adverse changes in mortality, clinical signs (including menses), body weight, physical examinations (heart rate, respiration rate and body temperature), clinical pathology, organ weights and microscopic data. These results suggest that the modified anti-IFNAR1 antibody, 9D4-TM does not elicity any

adverse toxicity.

SEQUENCE LISTING

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<120> Anti-IFNAR1 antibodies with reduced Fc ligand affinity

<130> IA161PCT

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<151> 2008-02-08

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cccggtaaag gcctggagtc gatggggatc atctatcctg gtgactctga tatcagatac 180

agcccgtcct tccaaggcca ggtcaccatc tcagccgaca agtccatcac caccgcctac 240

ctgcagtgga gcagtctgaa ggcctcagac accgccatgt attactgtgc gagacatgac 300

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35 40 45

Gly Ile Ile Tyr Pro Gly Asp Ser Asp Ile Arg Tyr Ser Pro Ser Phe
50 55 60

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

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
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Ala Arg His Asp Ile Glu Gly Phe Asp Tyr Trp Gly Arg Gly Thr Leu
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Val Thr Val Ser Ser
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cctggccagg ctcccaggct cctcatctat ggtgcatcca gcagggccac tggcatccca 180

gacaggttaa gtggcagtgg gtctgggaca gacttcactc tcaccatcac cagactggag 240

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Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Ser
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Phe Phe Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
        35                  40                  45

Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Leu Ser
    50                  55                  60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Thr Arg Leu Glu
65                  70                  75                  80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Asp Ser Ser Ala
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Ile Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys
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cccggtaaag gcctggagtc gatggggatc atctatcctg gtgactctga tatcagatac 180

agcccgtcct tccaaggcca ggtcaccatc tcagccgaca agtccatcac caccgcctac 240

ctgcagtgga gcagtctgaa ggcctcagac accgccatgt attactgtgc gagacatgac 300

atagaggggt ttgactactg gggccgggga accctggtca ccgtctcctc a 351

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Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ile Phe Thr Asn Tyr
            20                  25                  30

Trp Ile Ala Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Ser Met
        35                  40                  45

Gly Ile Ile Tyr Pro Gly Asp Ser Asp Ile Arg Tyr Ser Pro Ser Phe
    50                  55                  60

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

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
                85                  90                  95

Ala Arg His Asp Ile Glu Gly Phe Asp Tyr Trp Gly Arg Gly Thr Leu
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Val Thr Val Ser Ser
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gacaggttaa gtggcagtgg gtctgggaca gacttcactc tcaccatcac cagactggag      240

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<400> 40

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Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Ser
            20                  25                  30

Phe Phe Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
        35                  40                  45

Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Leu Ser
    50                  55                  60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Thr Arg Leu Glu
65                  70                  75                  80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Asp Ser Ser Ala
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Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
            20                  25                  30

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
        35                  40                  45

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
    50                  55                  60

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
65                  70                  75                  80

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
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Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
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Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
        35                  40                  45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
    50                  55                  60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65                  70                  75                  80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95

Arg Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
            100                 105                 110

Pro Ala Pro Glu Phe Glu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
        115                 120                 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
    130                 135                 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145                 150                 155                 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
                165                 170                 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
            180                 185                 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
        195                 200                 205

Lys Ala Leu Pro Ala Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
    210                 215                 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225                 230                 235                 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
                245                 250                 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
            260                 265                 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
        275                 280                 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
    290                 295                 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305                 310                 315                 320

Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
                325                 330
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<210> 44

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<400> 44
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<400> 46
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Patentkrav

1. Modificeret monoklonalt antistof fra IgG-klassen, hvilket antistof er specifikt for IFNAR1, hvor antistoffet i Fc-regionen omfatter en aminosyresubstitution L234F, som nummereret ifølge EU-indekset i henhold til Kabat, og hvor antistoffet udviser reduceret affinitet for mindst én Fc-ligand i sammenligning med et umodificeret antistof.

2. Antistof ifølge krav 1, hvor antistoffet er et antistof fra IgG1- eller IgG4-underklassen.

3. Antistof ifølge krav 1 eller krav 2, hvor antistoffet endvidere omfatter en aminosyresubstitution L235E og/eller P331S.

4. Antistof ifølge et hvilket som helst af kravene 1-3, hvor antistoffet omfatter:
a. en CDR1 fra en variabel region fra en human tung kæde, hvilken CDR1 omfatter SEQ ID NO: 1;
b. en CDR2 fra en variabel region fra en human tung kæde, hvilken CDR2 omfatter SEQ ID NO: 2;
c. en CDR3 fra en variabel region fra en human tung kæde, hvilken CDR3 omfatter SEQ ID NO: 3;
d. en CDR1 fra en variabel region fra en human let kæde, hvilken CDR1 omfatter SEQ ID NO: 4;
e. en CDR2 fra en variabel region fra en human let kæde, hvilken CDR2 omfatter SEQ ID NO: 5; og
f. en CDR3 fra en variabel region fra en human let kæde, hvilken CDR3 omfatter SEQ ID NO: 6.

5. Antistof ifølge et hvilket som helst af kravene 1-3, hvor antistoffet omfatter:
a. en CDR1 fra en variabel region fra en human tung kæde, hvilken CDR1 omfatter SEQ ID NO: 21;
b. en CDR2 fra en variabel region fra en human tung kæde, hvilken CDR2 omfatter SEQ ID NO: 22;
c. en CDR3 fra en variabel region fra en human tung kæde,

hvilken CDR3 omfatter SEQ ID NO: 23;
d. en CDR1 fra en variabel region fra en human let kæde, hvilken CDR1 omfatter SEQ ID NO: 24;
e. en CDR2 fra en variabel region fra en human let kæde, hvilken CDR2 omfatter SEQ ID NO: 25; og
f. en CDR3 fra en variabel region fra en human let kæde, hvilken CDR3 omfatter SEQ ID NO: 26.

6. Antistof ifølge et hvilket som helst af kravene 1-3, hvor antistoffet omfatter:
a. en variabel region fra en human tung kæde, hvilken region omfatter aminosyresekvensen ifølge SEQ ID NO: 38; og
b. en variabel region fra en human let kæde, hvilken region omfatter aminosyresekvensen ifølge SEQ ID NO: 40.

7. Antistof ifølge et hvilket som helst af kravene 1-3, hvor antistoffet omfatter:
a. en variabel region fra en human tung kæde, hvilken region omfatter aminosyresekvensen ifølge SEQ ID NO: 18; og
b. en variabel region fra en human let kæde, hvilken region omfatter aminosyresekvensen ifølge SEQ ID NO: 20.

8. Antistof ifølge et hvilket som helst af kravene 1-3, hvor antistoffet omfatter:
a. en variabel region fra en human tung kæde, hvilken region omfatter aminosyresekvensen ifølge SEQ ID NO: 28; og
b. en variabel region fra en human let kæde, hvilken region omfatter aminosyresekvensen ifølge SEQ ID NO: 30.

9. Antistof ifølge et hvilket som helst af kravene 1-8, hvor antistoffet omfatter sekvensen ifølge SEQ ID NO: 41 fra en konstant region fra en let kæde .

10. Antistof ifølge et hvilket som helst af kravene 1-8, hvor antistoffet omfatter den konstante region, ifølge SEQ ID NO: 42, fra en tung kæde .

11. Antistof ifølge et hvilket som helst af kravene 1-10,

hvor antistoffet omfatter den konstante region fra en let kæde, hvilken region har aminosyresekvensen ifølge SEQ ID NO: 41, og den konstante region fra en tung kæde, hvilken region har aminosyresekvensen ifølge SEQ ID NO: 42.

12. Antistof ifølge et hvilket som helst af kravene 1-11, hvor antistoffet omfatter en tungkæde-aminosyresekvens, som omfatter allelvariation, hvor allelvariationen er mindst en eller flere positioner valgt fra gruppen bestående af 214, 221, 356 og 358 som defineret af EU-indeks-nummereringssystemet.

13. Isoleret nukleinsyre, som omfatter en polynukleotidsekvens, der koder for antistoffet ifølge et hvilket som helst af de foregående krav.

14. Farmaceutisk sammensætning, som omfatter antistoffet ifølge et hvilket som helst af kravene 1-12 og en farmaceutisk acceptabel excipiens.

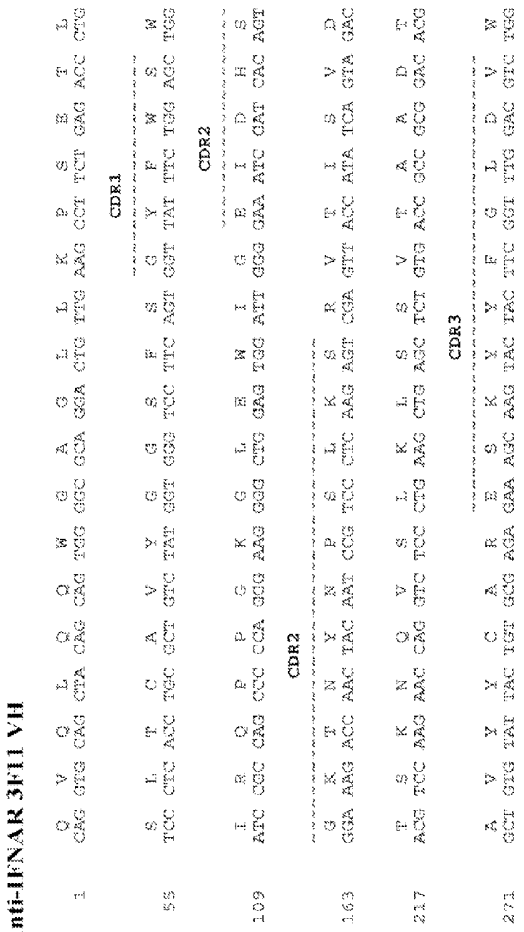
15. Farmaceutisk sammensætning ifølge krav 14 til anvendelse til behandling af en sygdom eller lidelse valgt blandt Graves' sygdom, Hashimotos thyroiditis, Crohns sygdom, psoriasis, psoriasisarthritis, sympatisk oftalmi, autoimmun oophoritis, autoimmun orchitis, autoimmunt lymfoproliferativt syndrom, antiphospholipid-syndrom, Sjögrens syndrom, sklerodermi, Addisons sygdom, polyendokrint mangelsyndrom, Guillain-Barrés syndrom, immun trombocytopenisk purpura, perniciøs anæmi, myasthenia gravis, primær biliær cirrose, blandet bindevævssygdom, vitiligo, autoimmun uveitis, autoimmun hæmolytisk anæmi, autoimmun trombocytopeni, cøliaki, dermatitis herpetiformis, autoimmun hepatitis, pemphigus, pemphigus vulgaris, pemphigus foliaceus, bulløs pemfigoid, autoimmun myocarditis, autoimmun vasculitis, alopecia areata, autoimmun aterosklerose, Behcets sygdom, autoimmun myelopati, autoimmun hæmofili, autoimmun interstitiel cystitis, autoimmun diabetes insipidus, autoimmun endometriose, recidiverende polychondritis, ankyloserende spondylitis, autoimmun

urticaria, dermatomyositis, Miller-Fishers syndrom, IgA-nefropati, Goodpastures syndrom og herpes gestationis.

DRAWINGS

Figure 1A

Anti-IFNAR 3F11 VH



Replacement Sheet 1/54

Figure 1B

Anti-IFNAR 3F11 VK

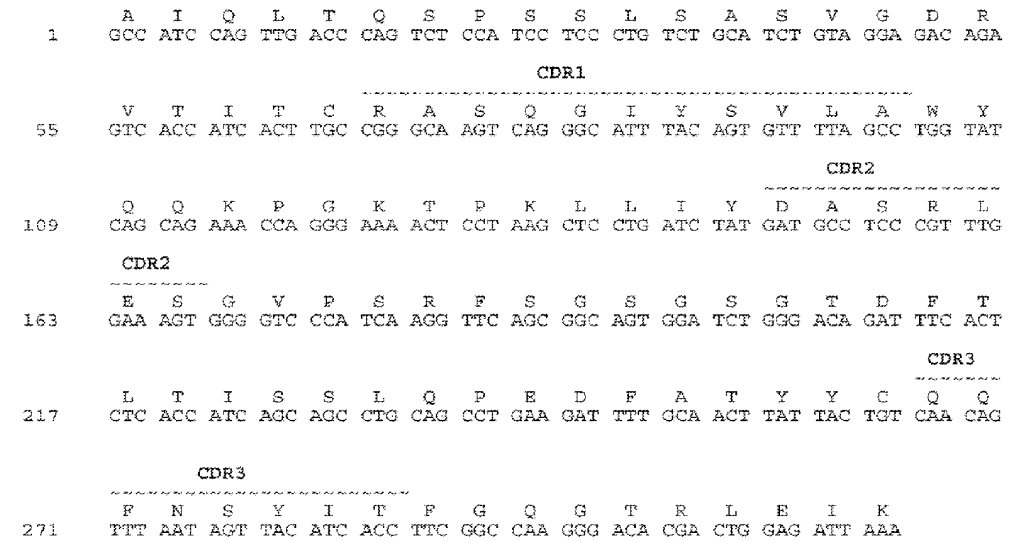


Figure 2A

Anti-IFNAR 4G5 VH

```
      Q   V   Q   L   Q   Q   W   G   A   G   L   L   K   P   S   E   T   L
1     CAG GTG CAG CTA CAG CAG TGG GGC GCA GGA CTG TTG AAG CCT TCG GAG ACC CTG

                                                                  CDR1
      S   L   T   C   A   V   Y   G   G   S   F   S   N   Y   Y   W   S   W
55    TCC CTC ACC TGC GCT GTC TAT GGT GGG TCC TTC AGT AAT TAC TAC TGG AGC TGG

                                                                      CDR2
      I   R   Q   P   P   G   K   G   L   E   W   I   G   E   I   I   L   S
109   ATC CGC CAG CCC CCA GGG AAG GGG CTG GAG TGG ATT GGG GAA ATC ATT CTT AGT

                      CDR2
      G   S   T   N   Y   N   P   S   L   K   S   R   V   T   I   S   V   D
163   GGA AGC ACC AAC TAC AAC CCG TCC CTC AAG AGT CGA GTC ACC ATA TCA GTA GAC

      T   S   K   N   Q   F   S   L   N   L   T   S   V   T   A   A   D   T
217   ACG TCC AAG AAC CAG TTC TCC CTG AAC CTG ACC TCT GTG ACC GCC GCG GAC ACG

                                                         CDR3
      A   V   Y   Y   C   A   R   E   S   K   W   G   Y   Y   F   D   S   W
271   GCT GTG TAT TAC TGT GCG AGA GAG TCT AAA TGG GGT TAC TAC TTT GAC TCC TGG

      G   Q   G   T   L   V   T   V   S   S
325   GGC CAG GGA ACC CTG GTC ACC GTC TCC TCA
```

Replacement Sheet 3/54

Anti-IFNAR 4G5 VK

Figure 2B

```
          A   I   Q   L   T   Q   S   P   S   S   L   S   A   S   V   G   D   R
  1      GCC ATC CAG TTG ACC CAG TCT CCA TCC TCC CTG TCT GCA TCT GTA GGA GAC AGA

                                            CDR1
                              ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
          V   T   I   T   C   R   A   T   Q   D   I   S   I   A   L   V   W   Y
 55      GTC ACC ATC ACT TGC CGG GCA ACT CAG GAC ATT AGC ATT GCT TTA GTC TGG TAT

                                                                  CDR2
                                                          ~~~~~~~~~~~~~~~~~~~
          Q   Q   K   P   G   K   A   P   E   L   L   I   Y   D   A   S   G   L
109      CAG CAG AAA CCA GGG AAA GCT CCT GAG CTC CTG ATC TAT GAT GCC TCC GGT TTG

           CDR2
         ~~~~~~~
          G   S   G   V   P   S   R   F   S   G   S   G   S   G   T   D   F   T
163      GGA AGT GGG GTC CCA TCA AGG TTC AGC GGC AGT GGA TCT GGC ACA GAT TTC ACT

                                                                       CDR3
                                                                      ~~~~~~~
          L   T   I   S   S   L   Q   P   E   D   F   A   T   Y   Y   C   Q   Q
217      CTC ACC ATC AGC AGC CTG CAG CCT GAA GAT TTT GCA ACT TAT TAC TGT CAA CAG

                    CDR3
         ~~~~~~~~~~~~~~~~~~~~~~~~~~~
          F   N   S   Y   P   Y   T   F   G   Q   G   T   K   L   E   I   K
271      TTT AAT AGT TAC CCG TAC ACT TTT GGC CAG GGG ACC AAG CTG GAG ATC AAA
```

Replacement Sheet 4/54

Figure 3A

Anti-IFNAR 11E2 VH

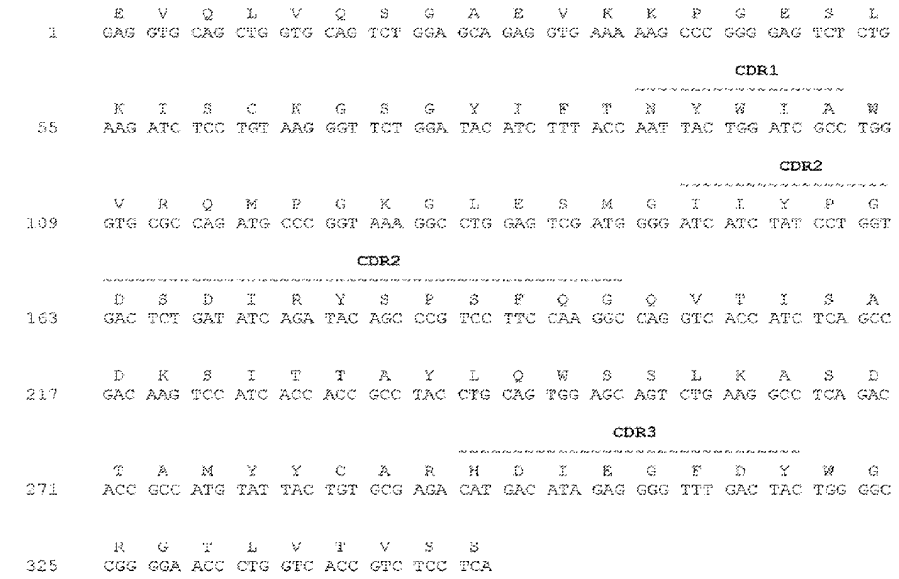


Figure 3B

Anti-IFNAR 11E2 VK

```
         E   I   V   L   T   Q   S   P   G   T   L   S   L   S   P   G   E   R
1       GAA ATT GTG TTG ACG CAG TCT CCA GGC ACC CTG TCT TTG TCT CCA GGG GAA AGA

                                                   CDR1
                                 ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
         A   T   L   S   C   R   A   S   Q   S   V   S   S   S   F   F   A   W
55      GCC ACC CTC TCC TGC AGG GCC AGT CAG AGT GTT AGC AGC AGC TTC TTC GCC TGG

                                                                      CDR2
                                                                 ~~~~~~~~~~~~~~~
         Y   Q   Q   K   P   G   Q   A   P   R   L   L   I   Y   G   A   S   S
109     TAC CAG CAG AAA CCT GGC CAG GCT CCC AGG CTC CTC ATC TAT GGT GCA TCC AGC

          CDR2
        ~~~~~~~~~~~
         R   A   T   G   I   P   D   R   L   S   G   S   G   S   G   T   D   F
163     AGG GCC ACT GGC ATC CCA GAC AGG TTA AGT GGC AGT GGG TCT GGG ACA GAC TTC

                                                                          CDR3
                                                                           ~~~
         T   L   T   I   T   R   L   E   P   E   D   F   A   V   Y   Y   C   Q
217     ACT CTC ACC ATC ACC AGA CTG GAG CCT GAA GAT TTT GCA GTG TAT TAC TGT CAG

                    CDR3
        ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
         Q   Y   D   S   S   A   I   T   F   G   Q   G   T   R   L   E   I   K
271     CAG TAT GAT AGC TCA GCG ATC ACC TTC GGC CAA GGG ACA CGA CTG GAG ATT AAA
```

Replacement Sheet 6/54

Figure 4A

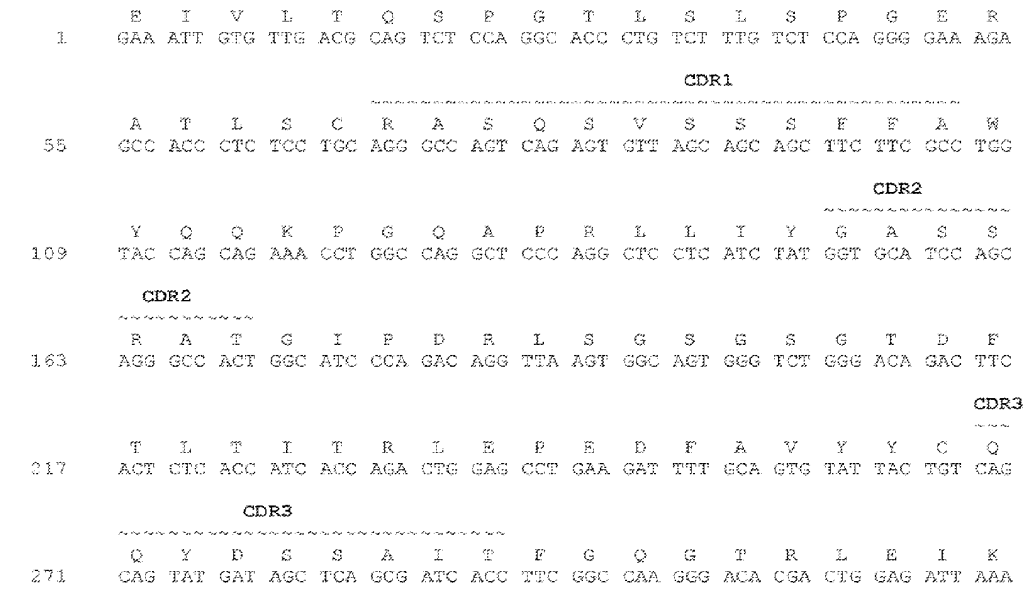
Anti-IFNAR 9D4 VH

```
                E  V  Q  L  V  Q  S  G  A  E  V  K  K  P  G  E  S  L
    1   GAG GTG CAG CTG GTG CAG TCT GGA GCA GAG GTG AAA AAG CCC GGG GAG TCT CTG

                                    CDR1
                ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
                K  I  S  C  K  G  S  G  Y  I  F  T  N  Y  W  I  A  W
   55   AAG ATC TCC TGT AAG GGT TCT GGA TAC ATC TTT ACC AAC TAC TGG ATC GCC TGG

                                                CDR2
                ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
                V  R  Q  M  P  G  K  G  L  E  S  M  G  I  I  Y  P  G
  109   GTG CGC CAG ATG CCC GGT AAA GGC CTG GAG TCG ATG GGG ATC ATC TAT CCT GGT

                                    CDR2
                ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
                D  S  D  I  R  Y  S  P  S  F  Q  G  Q  V  T  I  S  A
  163   GAC TCT GAT ATC AGA TAC AGC CCG TCC TTC CAA GGC CAG GTC ACC ATC TCA GCC

                ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
                D  K  S  I  T  T  A  Y  L  Q  W  S  S  L  K  A  S  D
  217   GAC AAG TCC ATC ACC ACC GCC TAC CTG CAG TGG AGC AGT CTG AAG GCC TCA GAC

                                    CDR3
                ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
                T  A  M  Y  Y  C  A  R  H  D  I  E  G  F  D  Y  W  G
  271   ACC GCC ATG TAT TAC TGT GCG AGA CAT GAC ATA GAG GGG TTT GAC TAC TGG GGC

                R  G  T  L  V  T  V  S  S
  325   CGG GGA ACC CTG GTC ACC GTC TCC TCA
```

Replacement Sheet 7/54

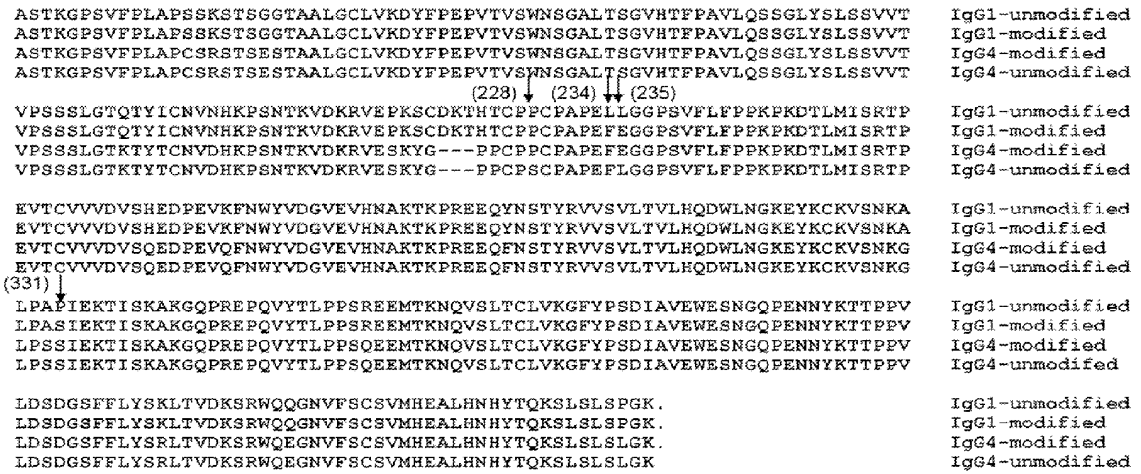
Figure 4B

Anti-IFNAR 9D4 VK



Replacement Sheet 8/54

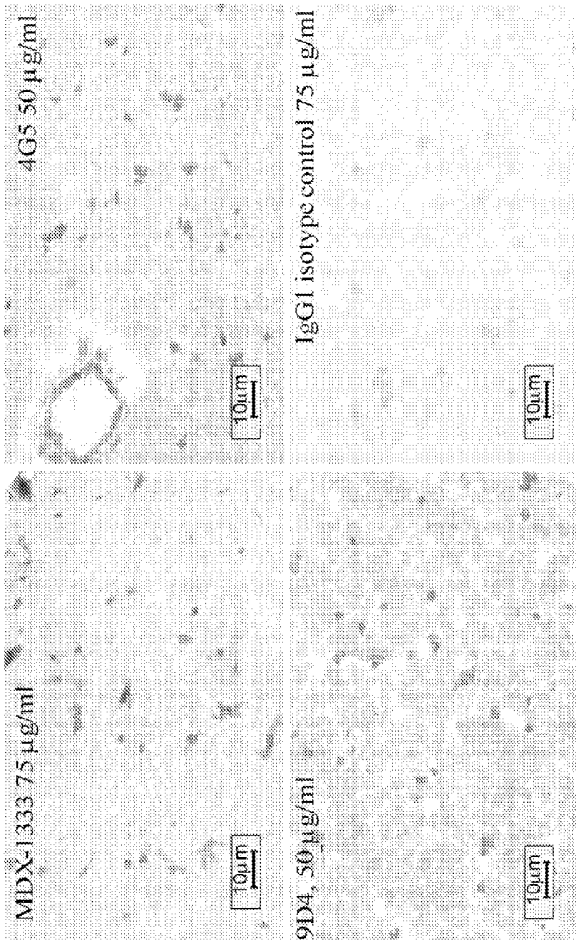
Figure 5



DK/EP 2250279 T3

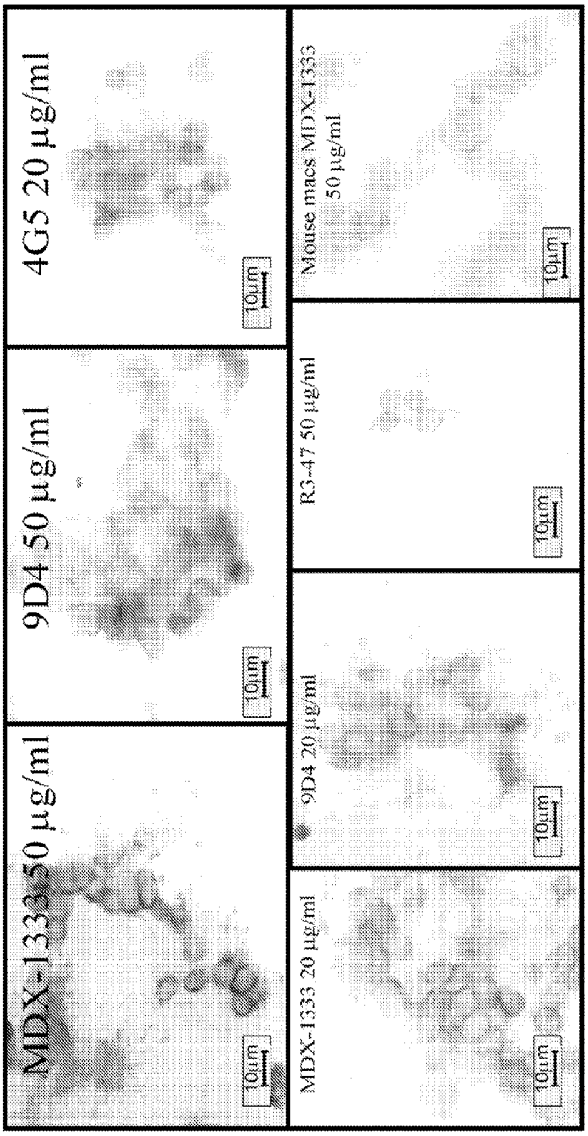
Figure 6A

Human cerebrum



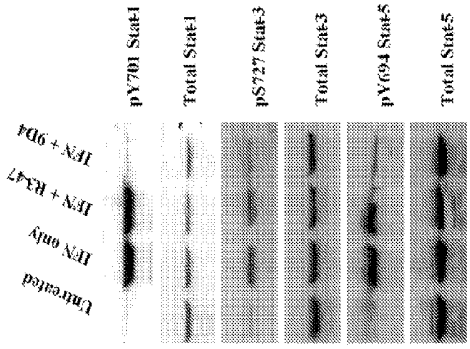
Replacement Sheet 10/54

Figure 6B



Replacement Sheet 11/54

Figure 7



Replacement Sheet 12/54

Figure 8

9D4

Donor #190

Type-I IFN concentration (IU/mL)	IC_{50}(nM)	Percent Inhibition*
50	0.005	97
100	0.008	98
500	0.04	98
1000	0.06	99
2000	0.16	99
5000	0.5	98

9D4

Donor #141

Type-I IFN concentratio (IU/mL)	IC_{50}(nM)	Percent Inhibition*
50	0.02	99.1
100	0.04	99
500**	0.2	98.6
1000	0.2	98
2000**	0.9	100
5000**	2.4	100

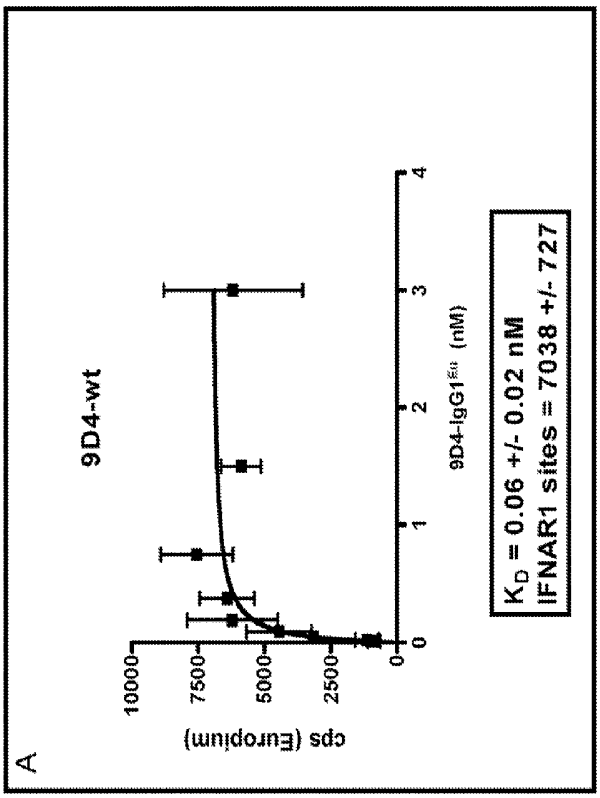
9D4

Donor #237

Type-I IFN concentration (IU/mL)	IC_{50}(nM)	Percent Inhibition*
50	0.008	99
100	0.01	99
500	0.04	99
1000	0.09	98
2000	0.12	99
5000	0.65	98

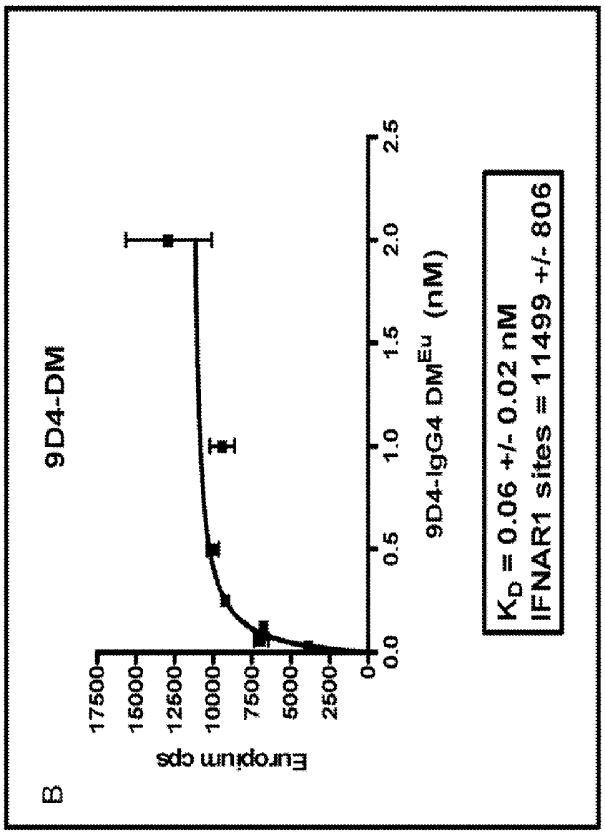
Replacement Sheet 13/54

Figure 9



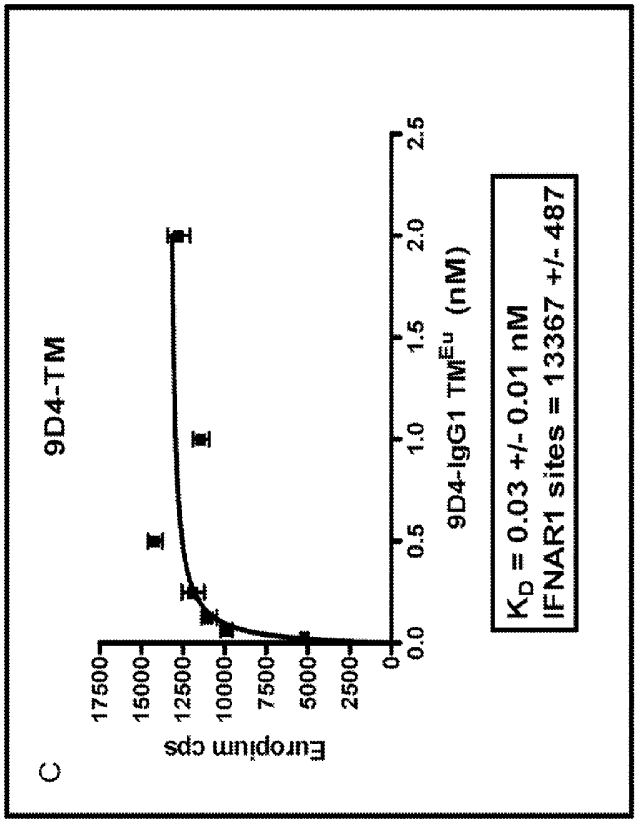
Replacement Sheet 14/54

Figure 9 continued



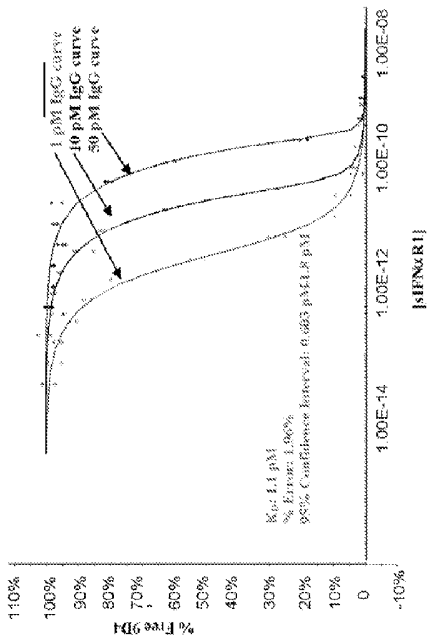
Replacement Sheet 15/54

Figure 9



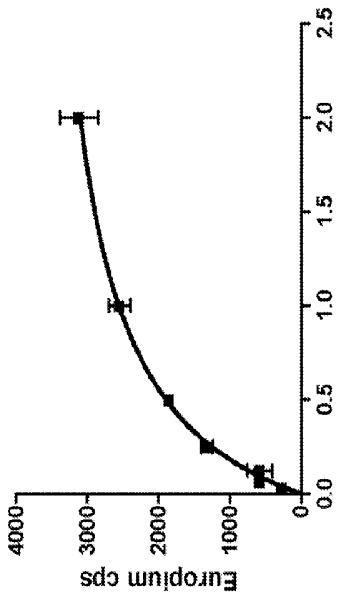
Replacement Sheet 16/54

Figure 10A



Replacement Sheet 17/54

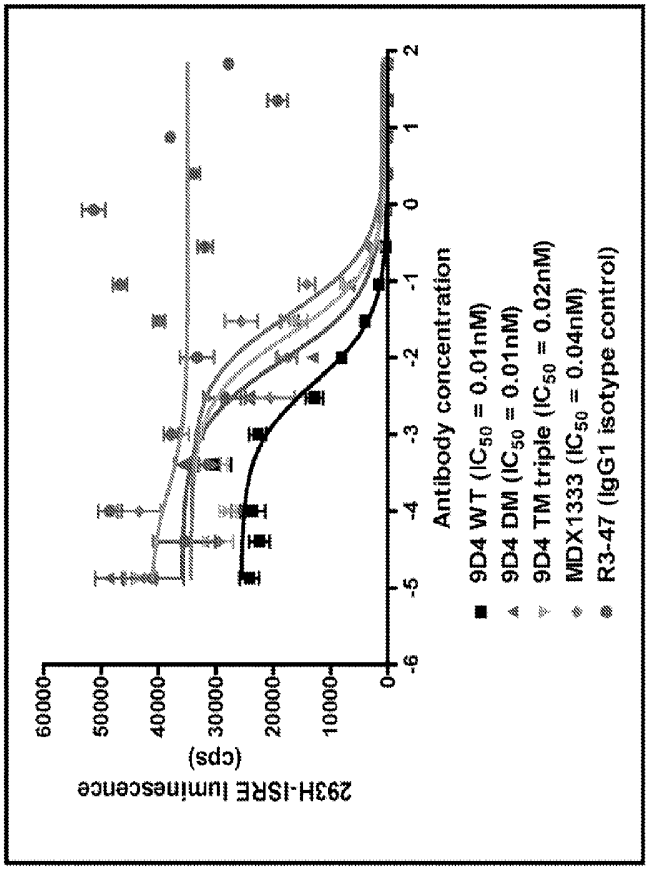
Figure 10B



Kd (nM)	Bmax (cps)
0.29+/-0.11	1448+/-447

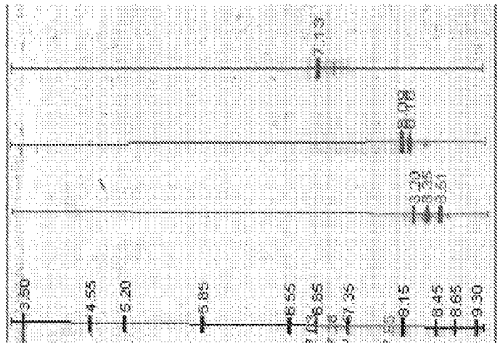
Replacement Sheet 18/54

Figure 11



Replacement Sheet 19/54

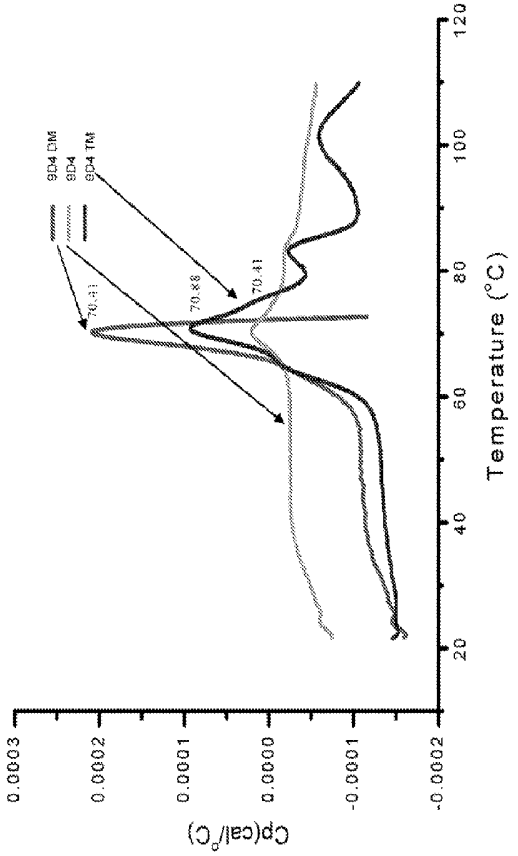
Figure 12A



A.9D4
B.9D4-TM
C.9D4-DM

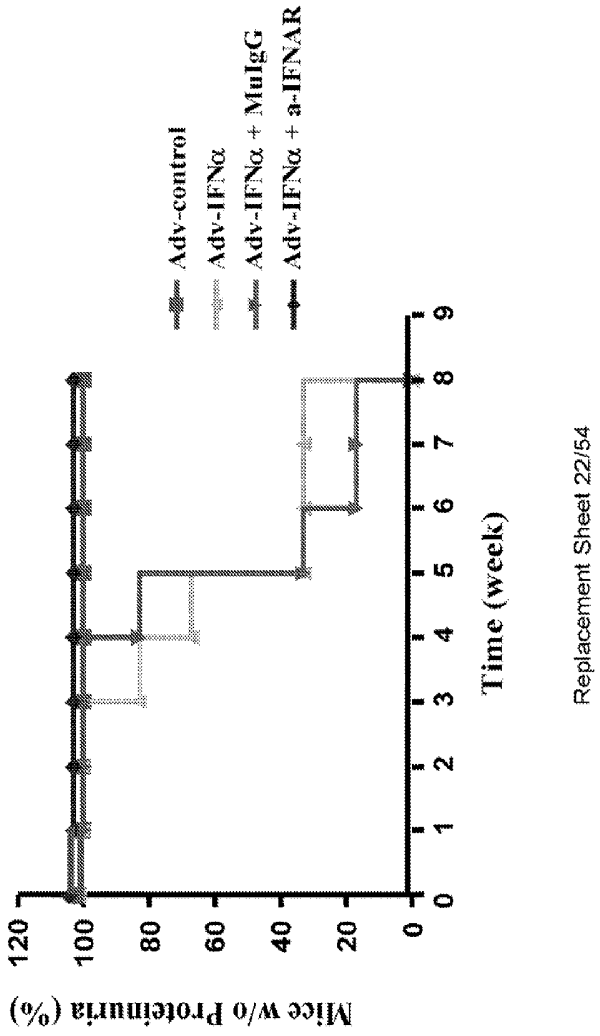
Replacement Sheet 20/54

Figure 12B



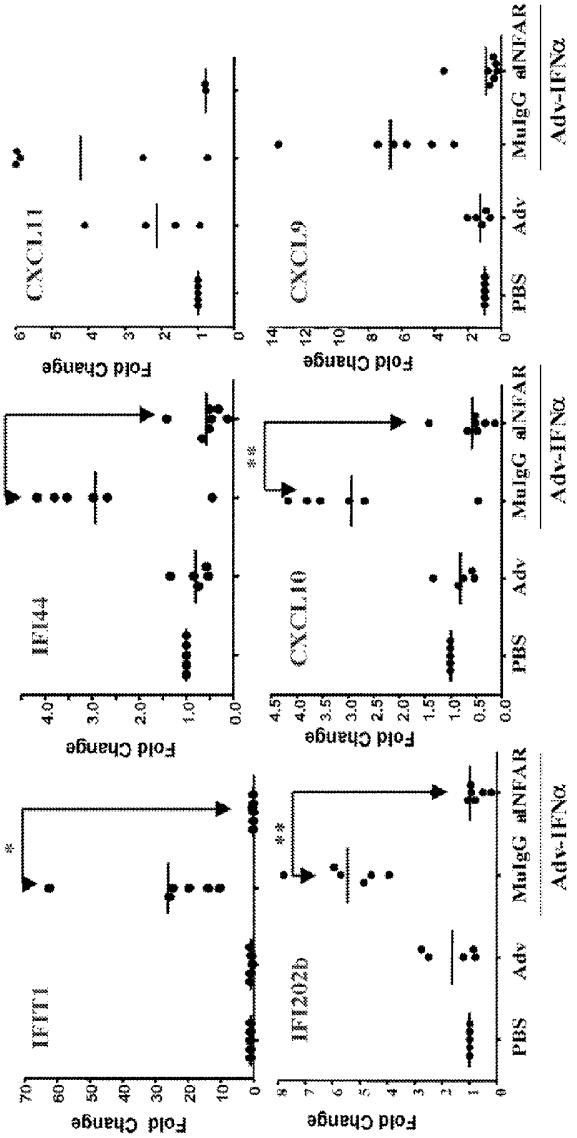
Replacement Sheet 21/54

Figure 13



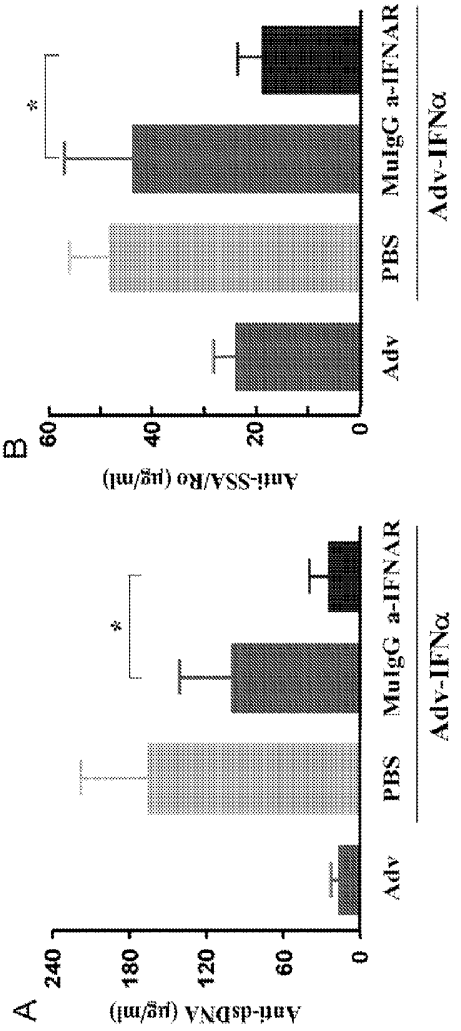
Replacement Sheet 22/54

Figure 14



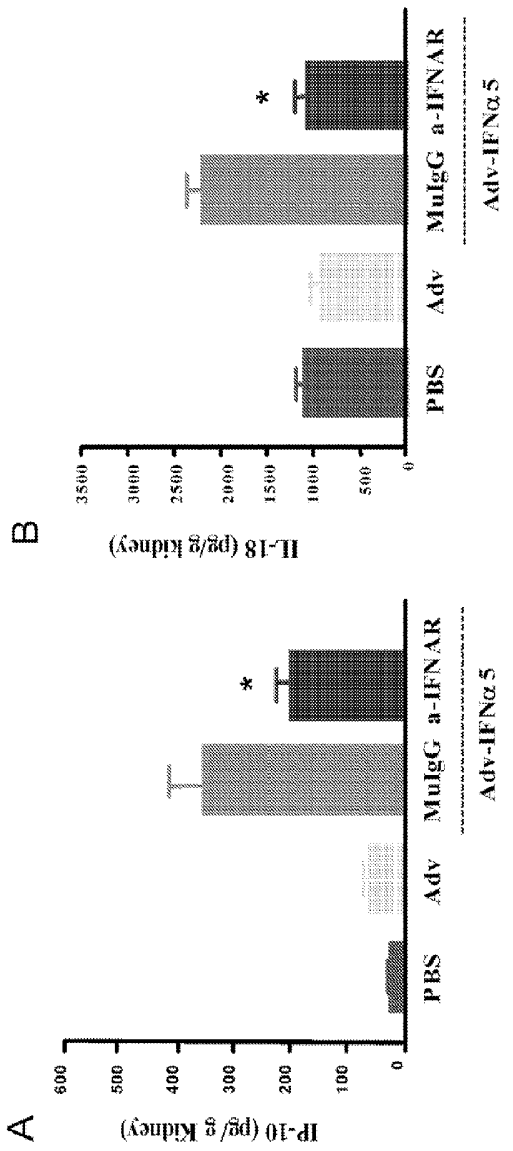
Replacement Sheet 23/54

Figure 15



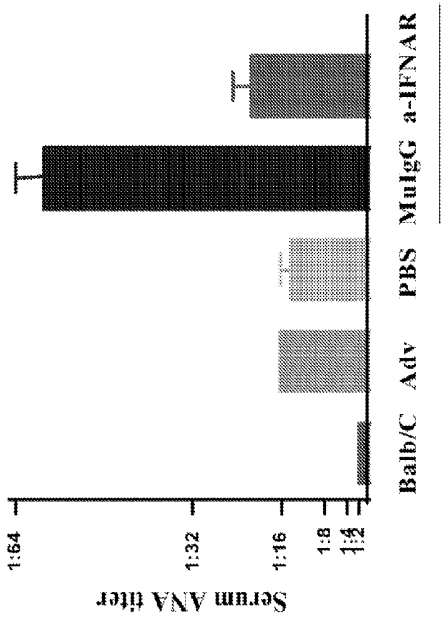
Replacement Sheet 24/54

Figure 16



Replacement Sheet 25/54

Figure 17



Replacement Sheet 26/54

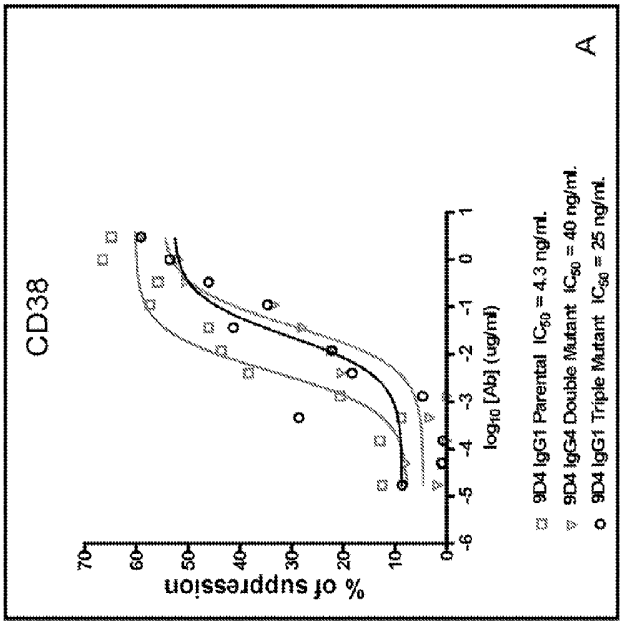
Figure 18

Exp. #	CD38, % max suppression	IC50 nM	CD123, % max. suppression	IC50 nM
1	88%	0.05	NC	NC
2	100%	0.05	70%	0.06
3	81%	0.02	64%	0.04
4	91%	0.04	76%	0.06
5	NC	NC	72%	0.06

NC: not calculated (no induction).

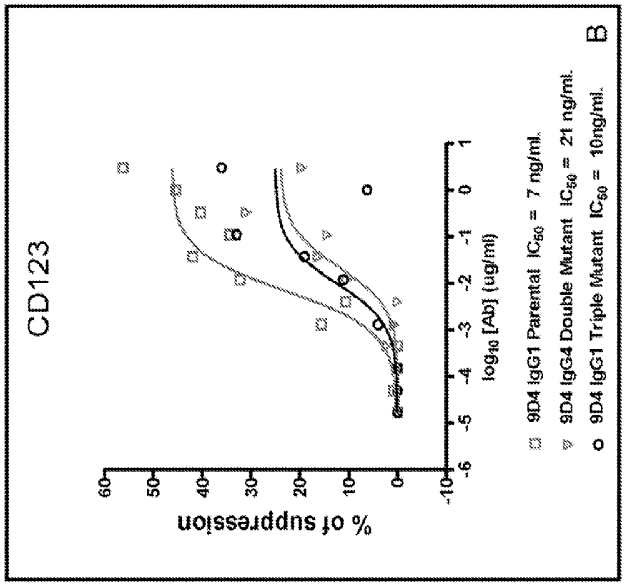
Replacement Sheet 27/54

Figure 19



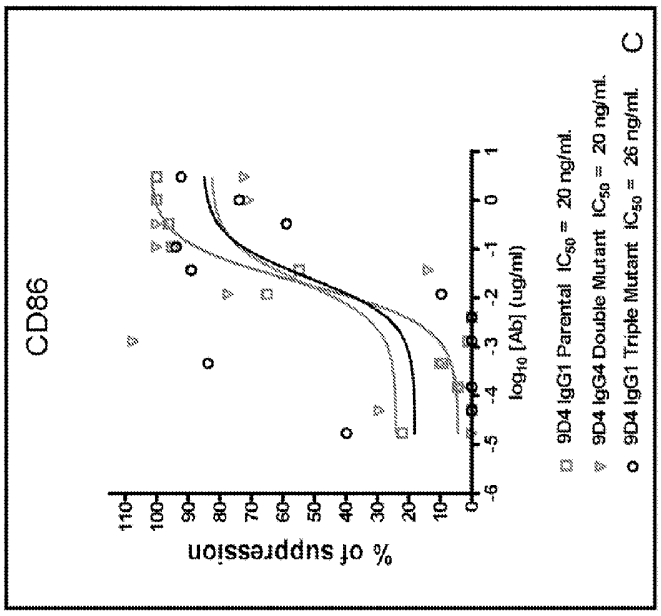
Replacement Sheet 28/54

Figure 19 continued



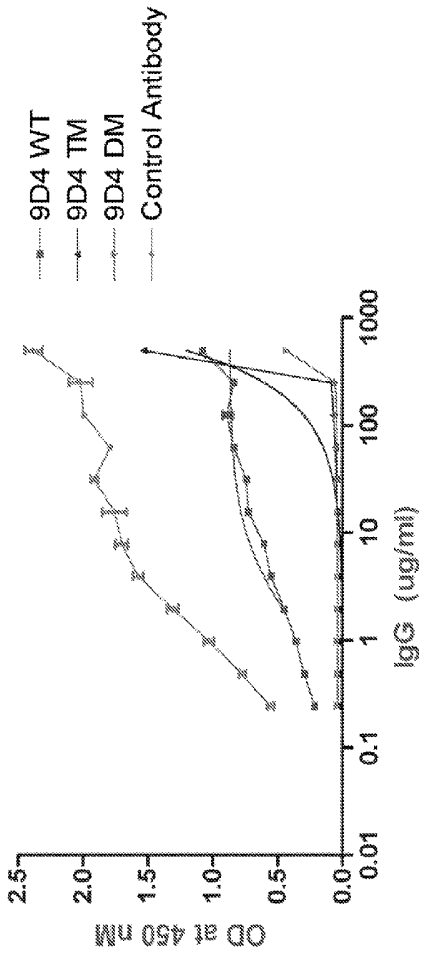
Replacement Sheet 29/54

Figure 19 continued



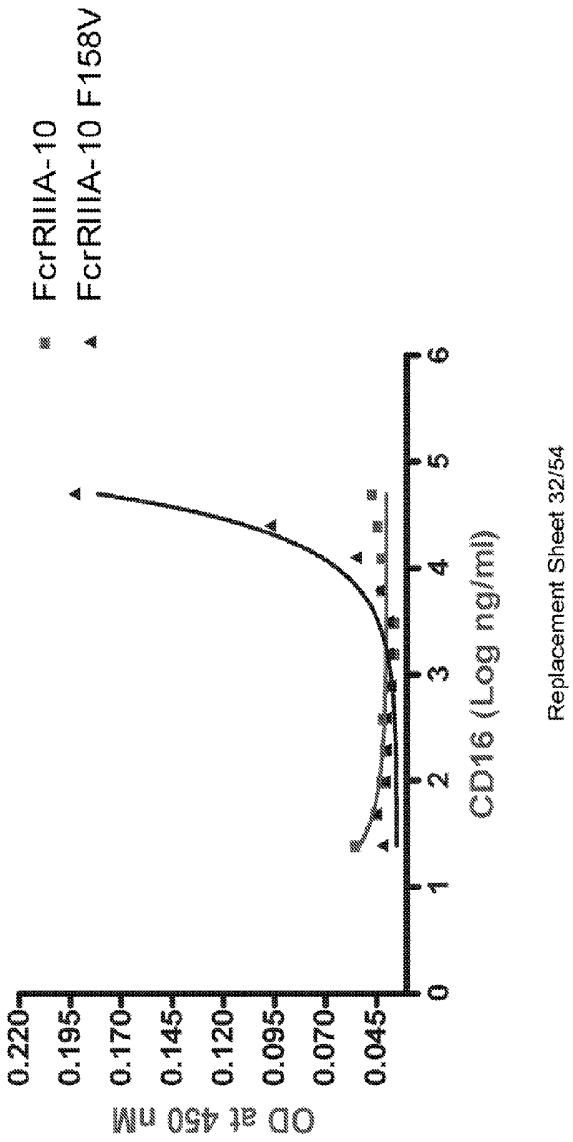
Replacement Sheet 30/54

Figure 20



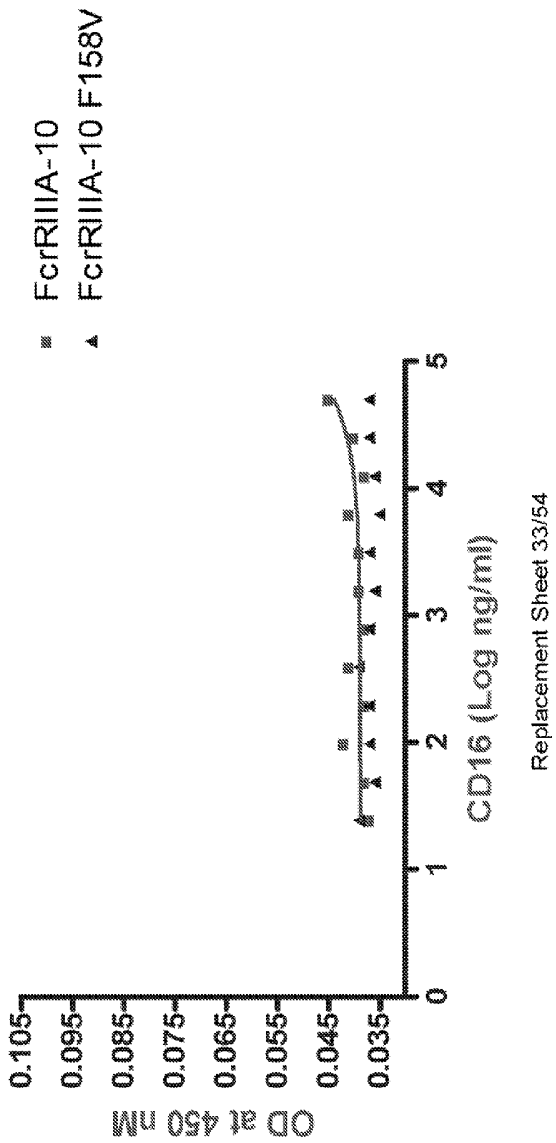
Replacement Sheet 31/54

Figure 21A



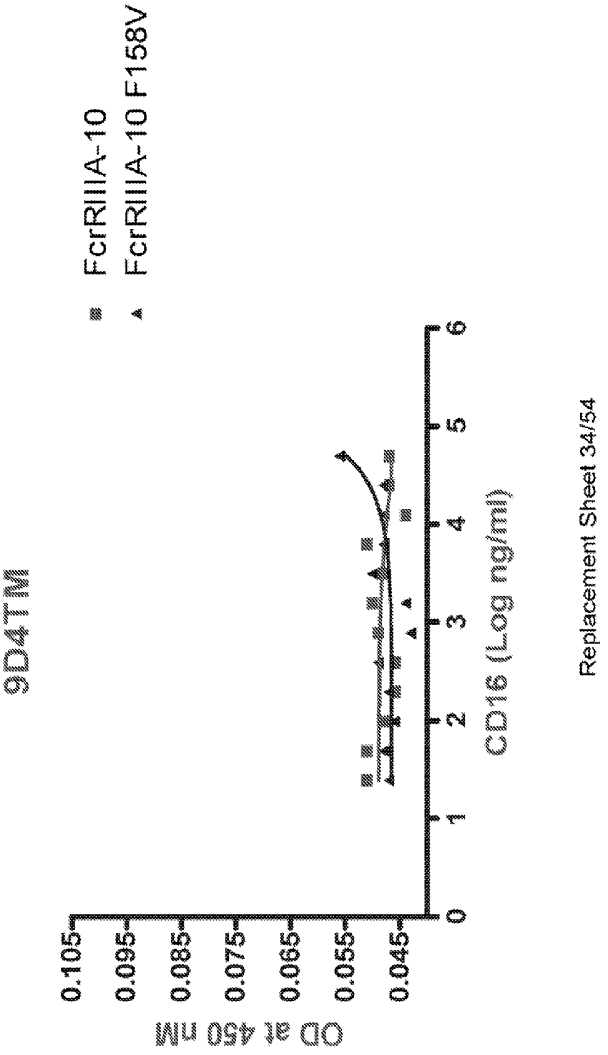
Replacement Sheet 32/54

Figure 21B



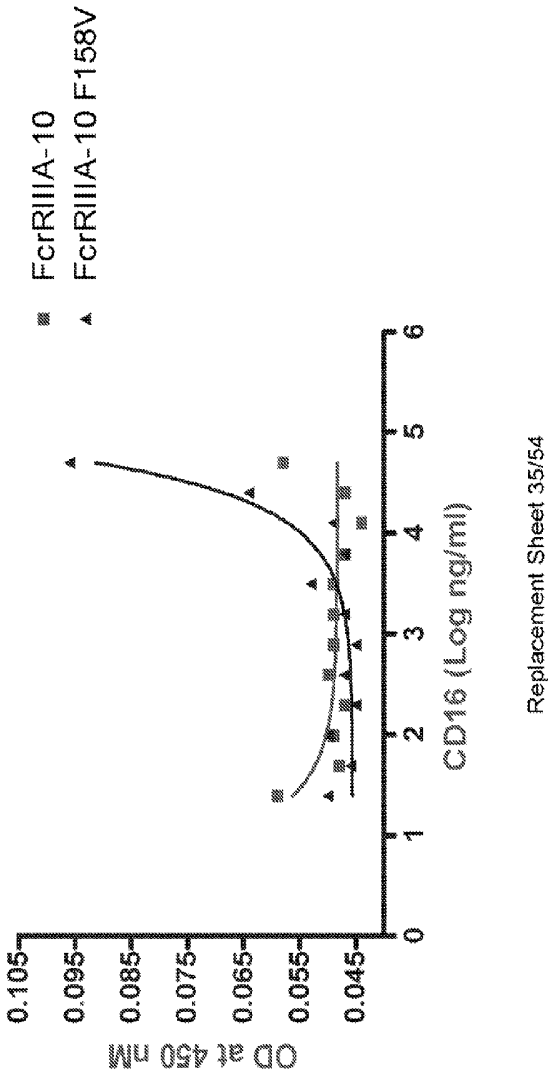
Replacement Sheet 33/54

Figure 21C



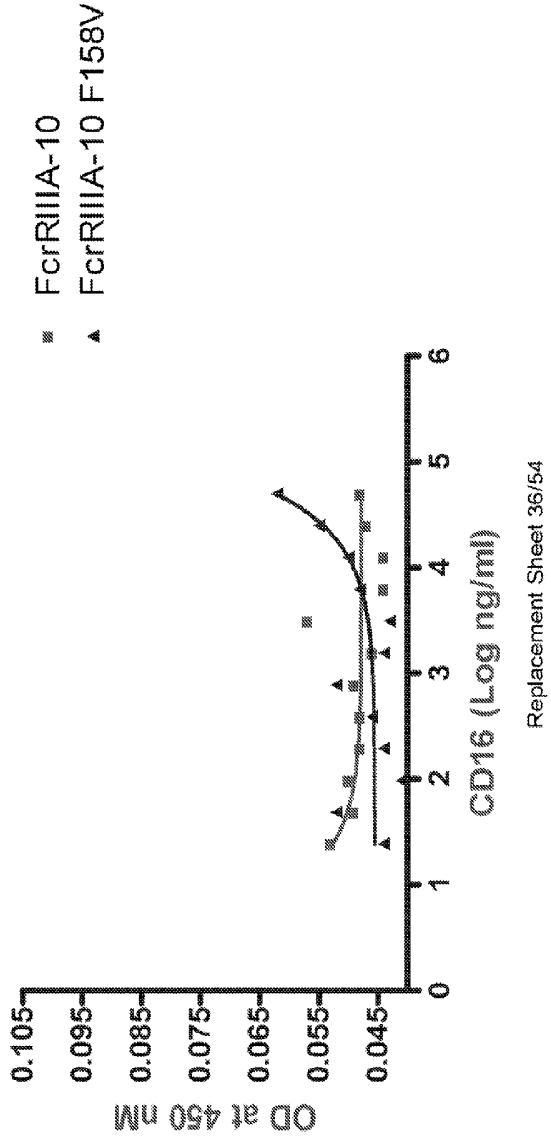
Replacement Sheet 34/54

Figure 22A



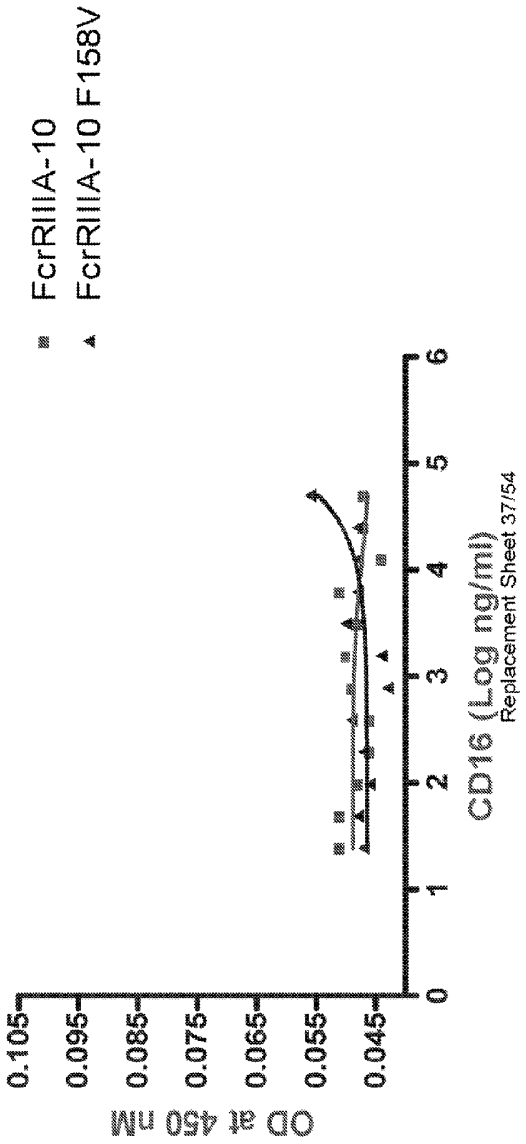
Replacement Sheet 35/54

Figure 22B



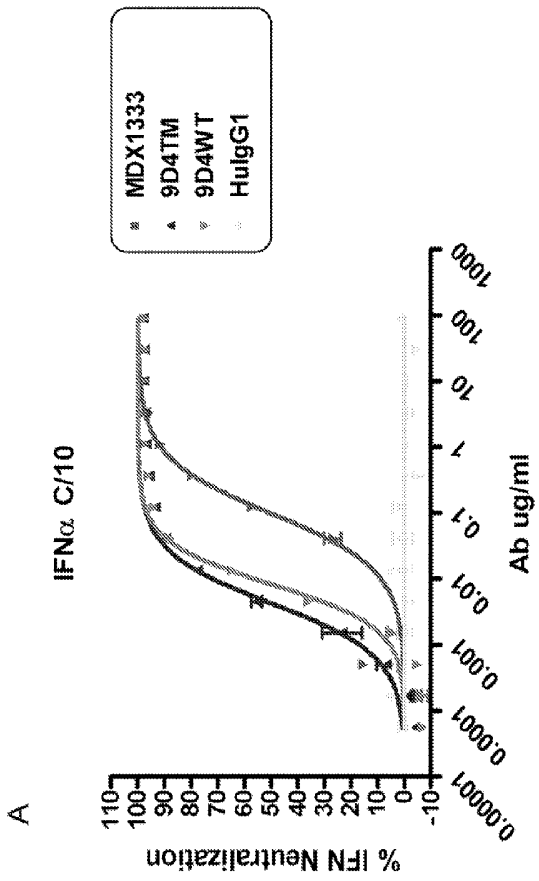
Replacement Sheet 36/54

Figure 22C



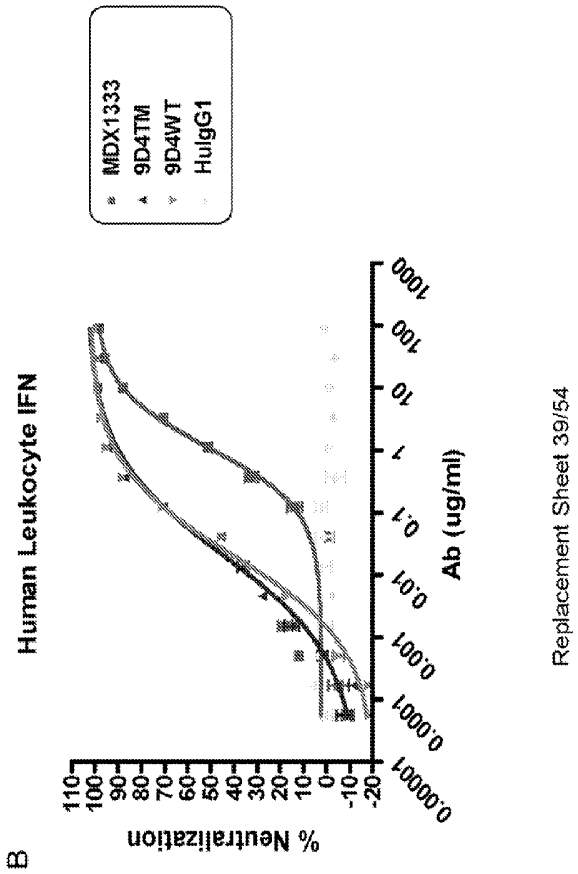
Replacement Sheet 37/54

Figure 23



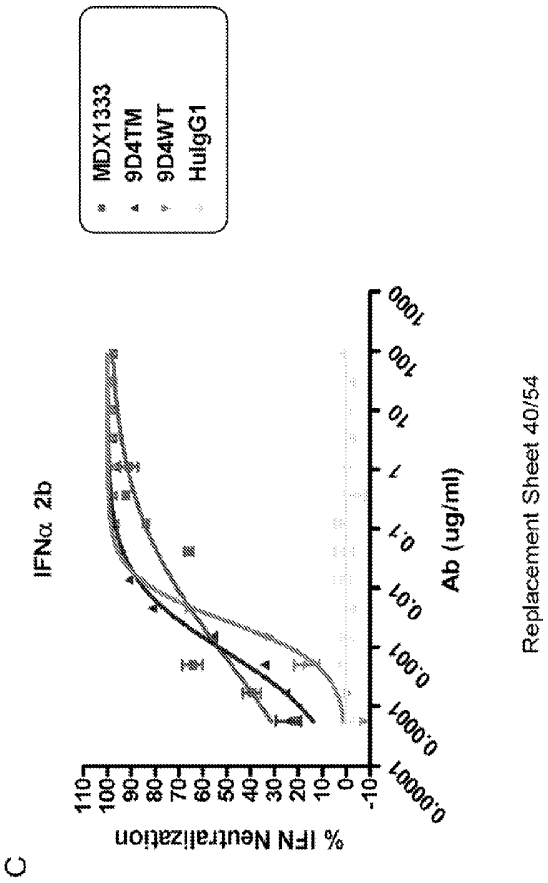
Replacement Sheet 38/54

Figure 23 continued



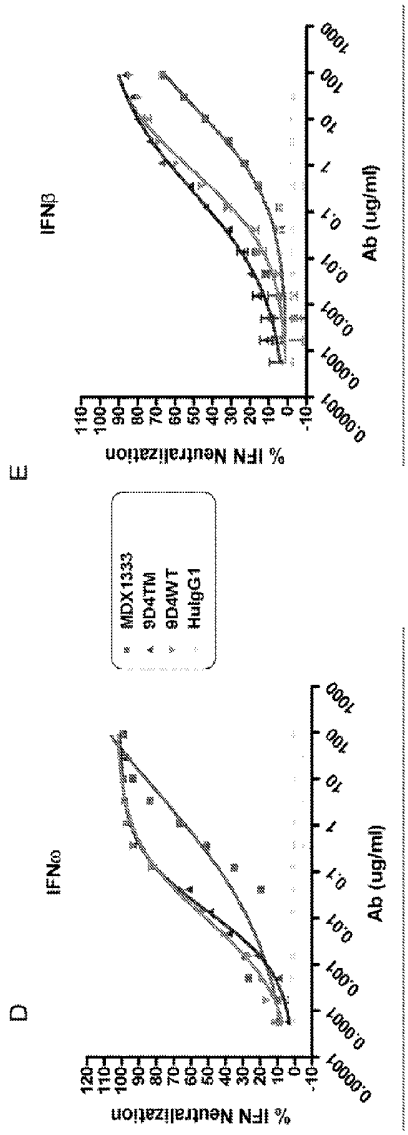
Replacement Sheet 39/54

Figure 23 continued



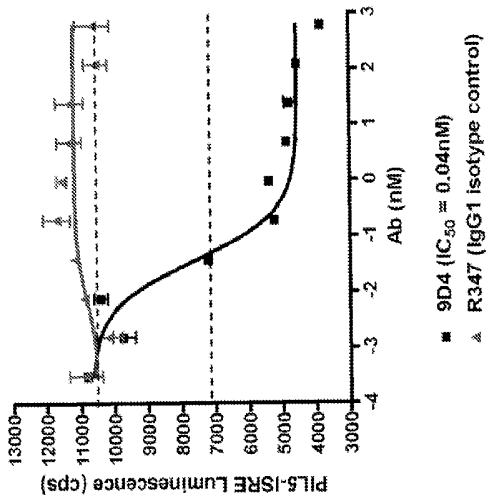
Replacement Sheet 40/54

Figure 23 continued



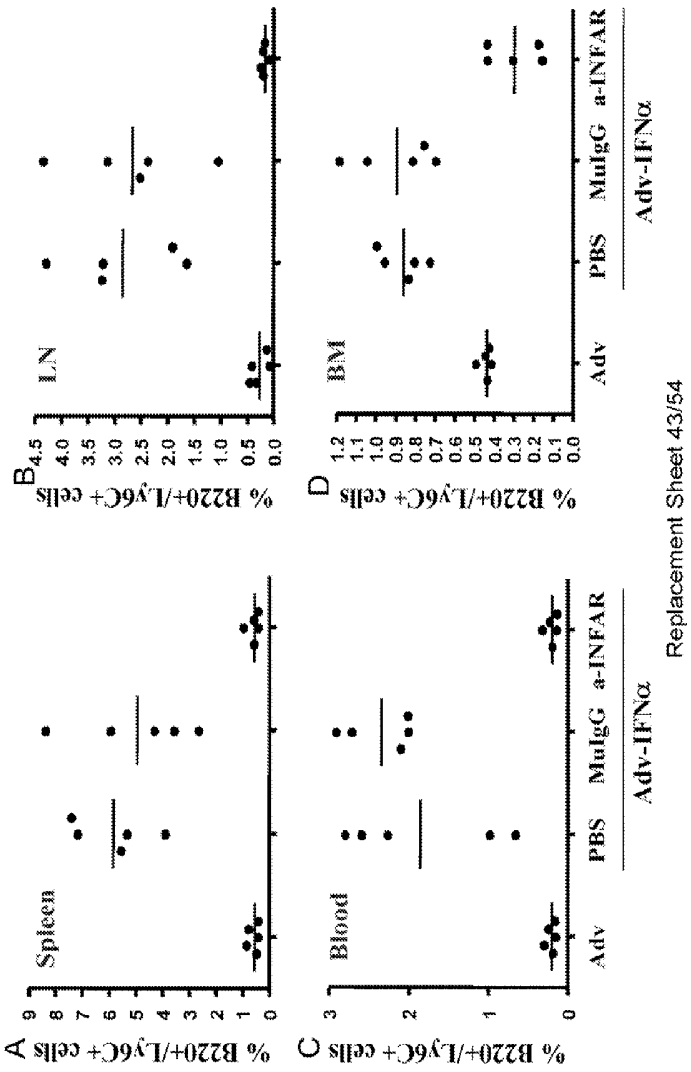
Replacement Sheet 41/54

Figure 24



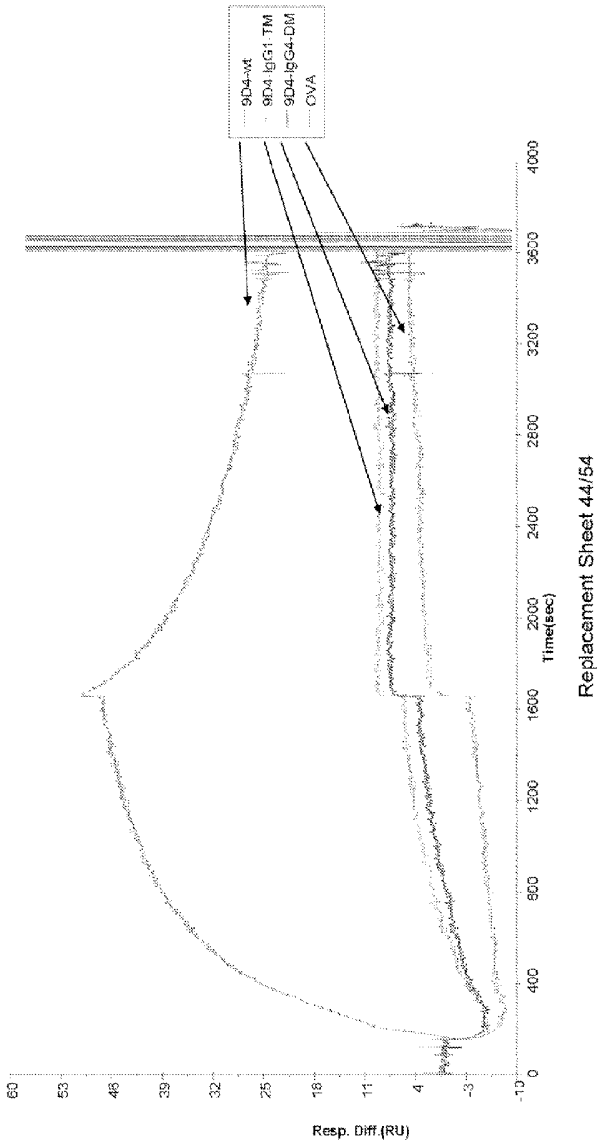
Replacement Sheet 42/54

Figure 25



Replacement Sheet 43/54

Figure 26



Replacement Sheet 44/54

Figure 27A

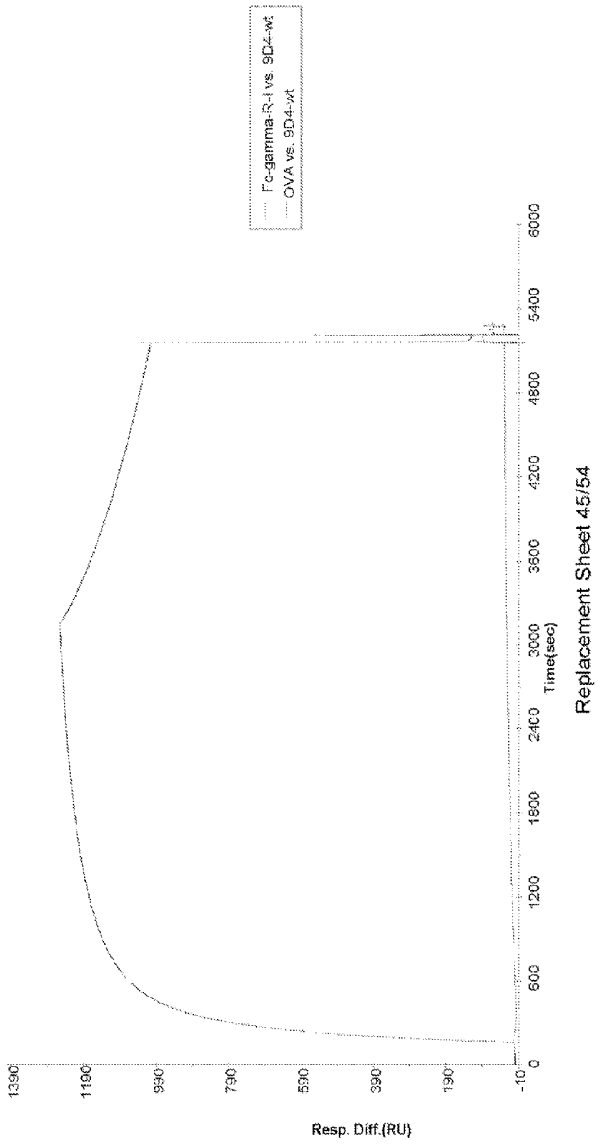

Fc-gamma-R-I vs. 9D4-wt
OVA vs. 9D4-wt
1390
1190
990
790
590
390
190
-10
0
600
1200
1800
2400
3000
3600
4200
4800
5400
6000
Time(sec)
Resp. Diff.(RU)

Figure 27B

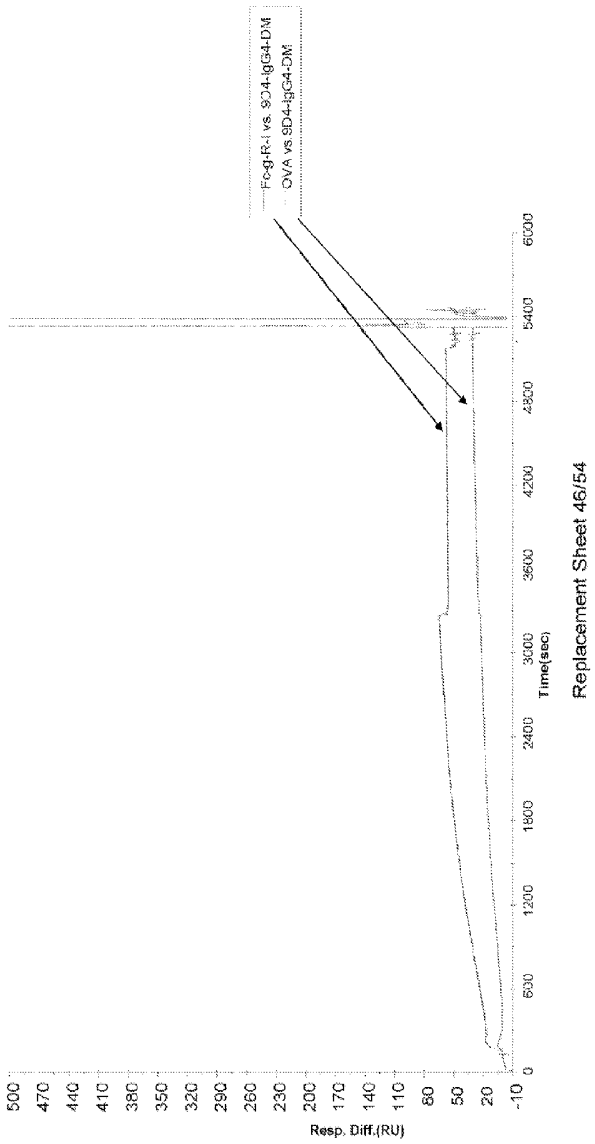

Fc-g-R-I vs. 9D4-IgG4-DM
OVA vs 9D4-IgG4-DM
Resp. Diff.(RU)
500
470
440
410
380
350
320
290
260
230
200
170
140
110
80
50
20
-10
0
600
1200
1800
2400
3000
3600
4200
4800
5400
6000
Time(sec)

Fig 27C

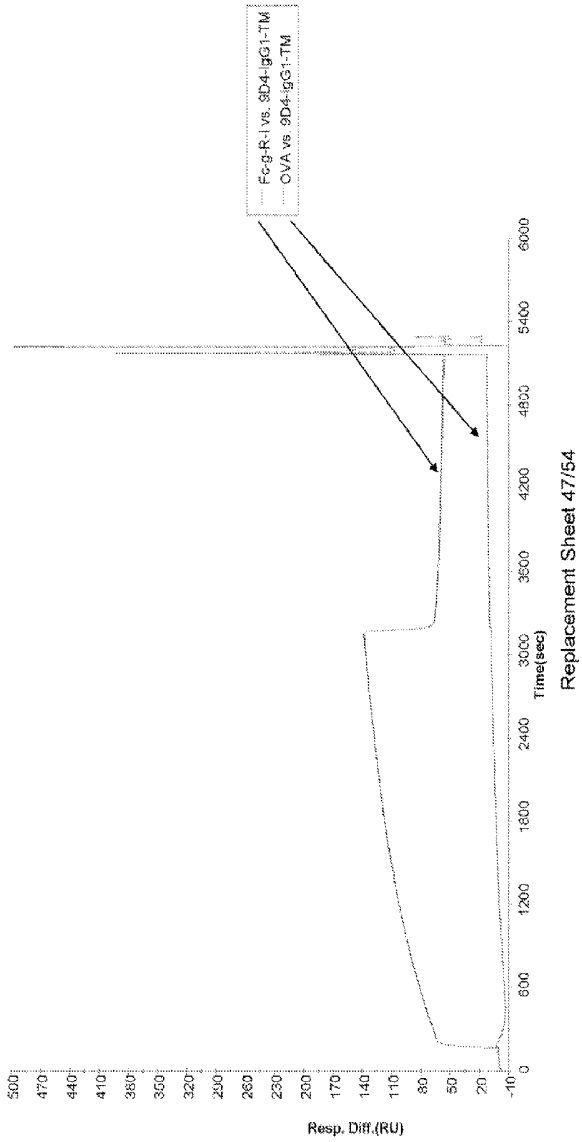
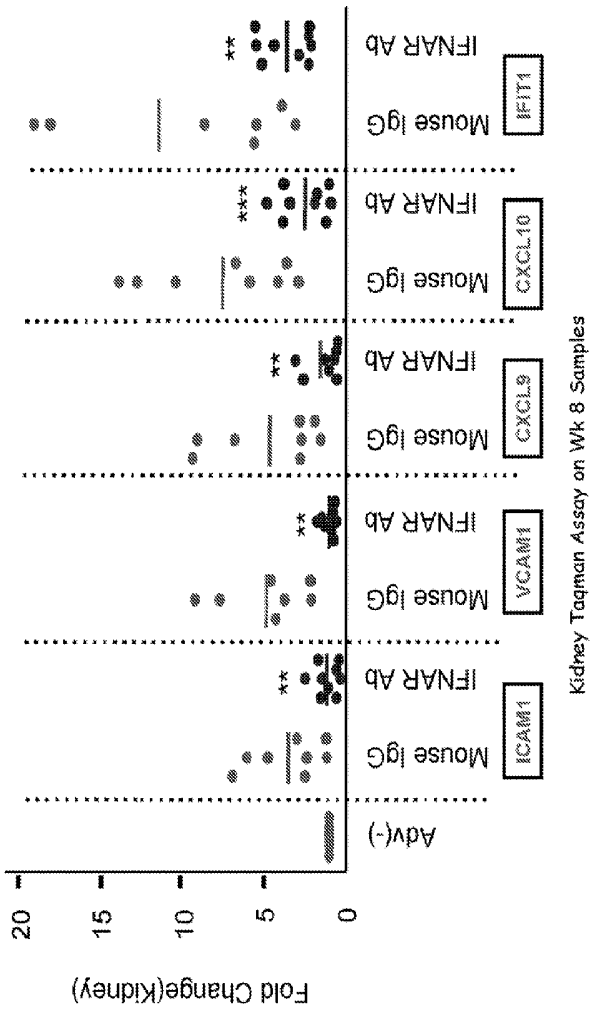
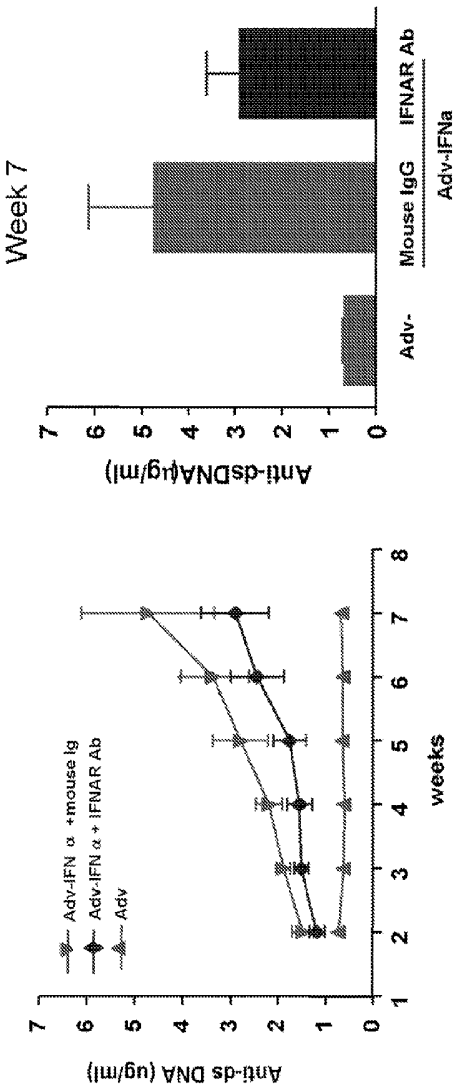


Figure 28



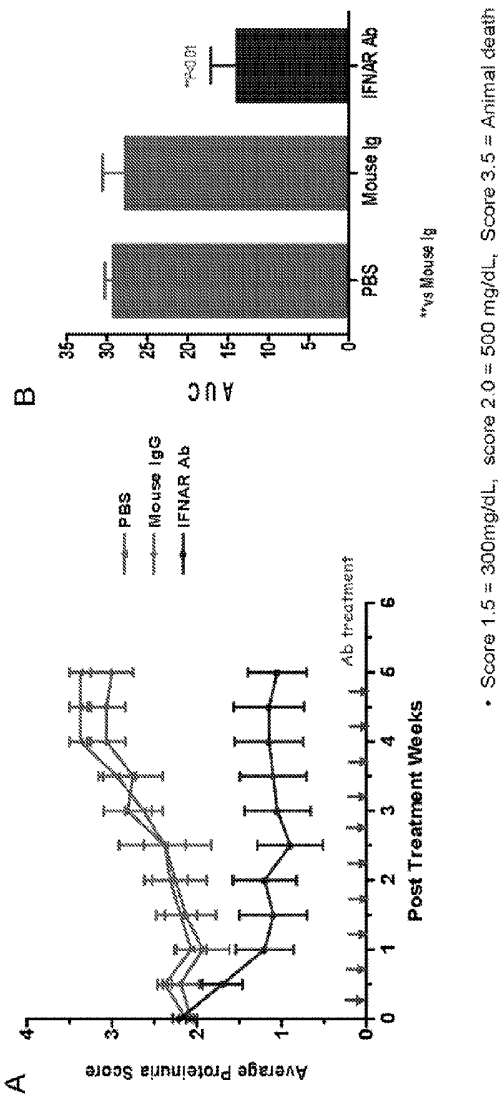
Replacement Sheet 48/54

Figure 29



Replacement Sheet 49/54

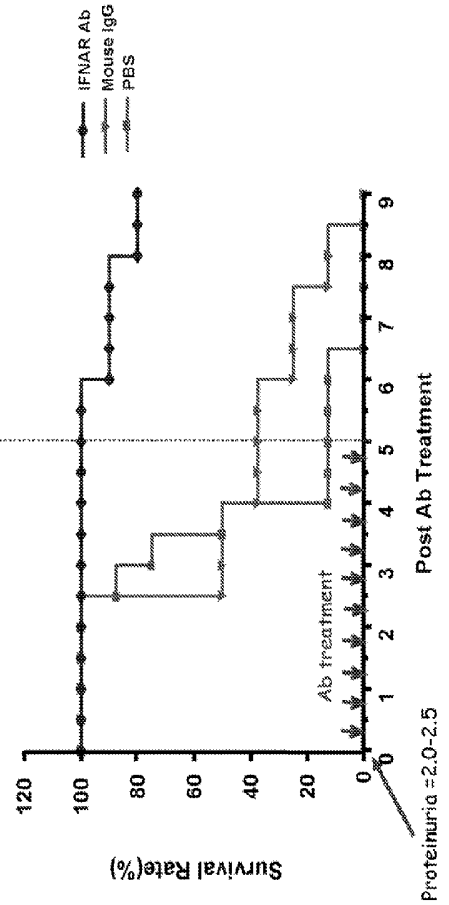
Figure 30



• Score 1.5 = 300mg/dL, score 2.0 = 500 mg/dL, Score 3.5 = Animal death

Replacement Sheet 50/54

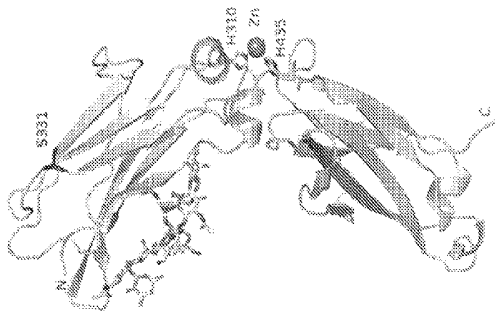
Figure 31



Tx	% Death at wk 5	% No Proteinuria at wk 5
Adv-IFNa + PBS	7/8 (87.5 %)	0/8 (0%)
Adv-IFNa + Mouse IgG	5/8 (62.5%)	0/8 (0%)
Adv-IFNa + IFNAR Ab	0/8 (0%)	5/10 (50%)

Replacement Sheet 51/54

Figure 32



Replacement Sheet 52/54

Fig 33.

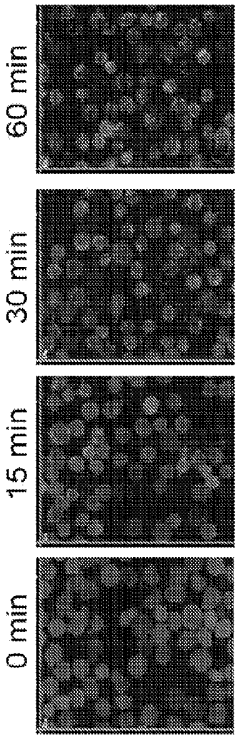
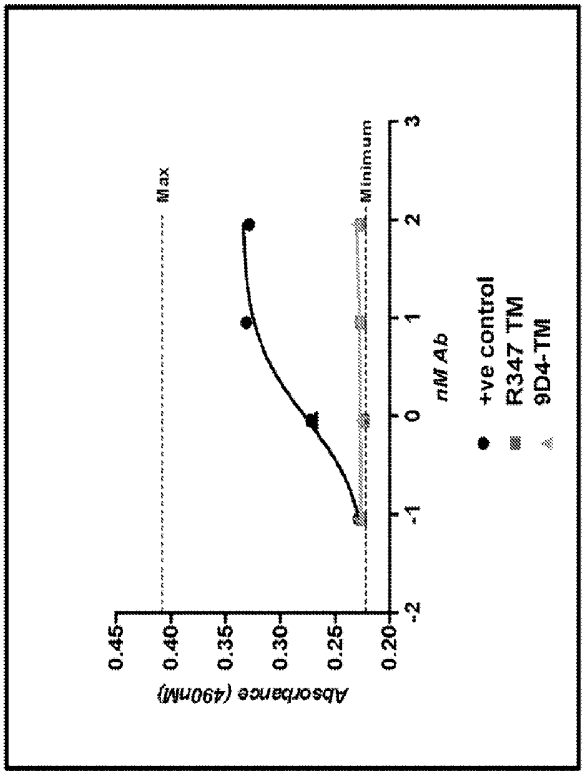


Fig. 34



Replacement Sheet 54/54