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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
21 July 2011 (21.07.2011)

PCT

(10) International Publication Number
WO 2011/086143 A2

(51) International Patent Classification:
A61K 39/395 (2006.01) *C12N 15/63* (2006.01)
C07K 16/28 (2006.01) *C12N 15/13* (2006.01)
A61P 35/00 (2006.01) *C07K 19/00* (2006.01)
A61P 31/14 (2006.01) *A61K 47/48* (2006.01)
C12N 5/10 (2006.01) *A61P 1/16* (2006.01)

(21) International Application Number:
PCT/EP2011/050420

(22) International Filing Date:
13 January 2011 (13.01.2011)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/294,942 14 January 2010 (14.01.2010) US

(71) Applicant *(for all designated States except US)*: **GLAXO GROUP LIMITED** [GB/GB]; Glaxo Wellcome House, Berkeley Avenue, Greenford Middlesex UB6 0NN (GB).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **DUNLEVY, Grainne** [GB/GB]; Domantis Limited, 315 Cambridge Business Park, Cambridge Cambridgeshire CB4 0WG (GB). **HOLMES, Steven** [GB/GB]; c/o Domantis Limited, 315 Cambridge Science Park, Cambridge Cambridgeshire CB4 0WG (GB). **HONG, Zhi** [US/US]; GlaxoSmithKline, Five Moore Drive, Research Triangle Park, North Carolina 27709 (US). **SEPP, Armin** [EE/GB]; Domantis Limited, 315 Cambridge Science Park, Cambridge Cambridgeshire CB4 0WG (GB). **WALKER, Adam** [GB/GB]; Domantis Limited, 315 Cambridge Science Park, Cambridge Cambridgeshire CB4 0WG (GB).

(74) Agents: **KUCERNAK (NEE WILSON), Lynn** et al.; GlaxoSmithKline, Global Patents CN925.1, 980 Great West Road, Brentford Middlesex TW8 9GS (GB).

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

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

— *of inventorship (Rule 4.17(iv))*

Published:

— *without international search report and to be republished upon receipt of that report (Rule 48.2(g))*

(54) Title: LIVER TARGETING MOLECULES

(57) Abstract: The present invention relates to molecules that can be targeted to the liver. These liver targeting molecules (e.g.fusions and conjugates) comprise proteins, antibodies or antibody fragments such as immunoglobulin (antibody) single variable domains (dAbs) and also one or more additional molecules which it is desired to deliver to the liver such as interferons. The invention further relates to uses, formulations, compositions and devices comprising such liver targeting molecules. The invention also relates to immunoglobulin (antibody) single variable domains which bind to hepatocytes.

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Liver Targeting Molecules

The present invention relates to molecules that can be targeted to the liver. These liver targeting molecules (e.g.fusions and conjugates) comprise proteins, antibodies or antibody fragments such as immunoglobulin (antibody) single variable domains (dAbs) and also one or more additional molecules which it is desired to deliver to the liver such as interferons. The invention further relates to uses, formulations, compositions and devices comprising such liver targeting molecules. The invention also relates to immunoglobulin (antibody) single variable domains which bind to hepatocytes.

BACKGROUND OF THE INVENTION

Liver disease is a term describing a number of disease states including (but not limited to) the following:

1.) Hepatitis, an inflammation of the liver caused in many cases by viral infection;
2.) Cirrhosis, which involves fibroid deposition following tissue remodelling in the liver typically after viral infection or exposure to liver-toxic agents such as alcohol; and
3.) Liver cancer, including primary hepatocellular carcinoma (HCC) and secondary tumour formation following metastasis of tumours at extra-hepatic sites.

Chronic infection with hepatitis C virus (HCV) is one of the major causes of cirrhosis and HCC. Global burden of HCV related disease is high with endemic infection in many countries. According to WHO figures an estimated 170 million people (3% of the global population) are infected with an estimated 3-4 million new cases annually (reviewed, for example, by Soriano, Peters and Zeuzem. Clinical Infectious Diseases. 2009; 48:313-20). Approximately 70% of infected individuals develop chronic infection with 20% of this group progressing to cirrhosis within a 20 year period. Liver cirrhosis following HCV infection is also associated with increased risk of developing liver cancer and it is estimated that annually 3-4% of patients with HCV

induced cirrhosis go on to develop HCC (reviewed, for example, by Webster et al. Lancet Infect Dis 2009; 9:108-17).

Current standard in HCV therapy consists of combination regimens of pegylated interferon-α (PEG-IFN-α) and the nucleoside analogue Ribavirin (RBV). The main aim of anti HCV therapy is to produce sustained virologic response (SVR) currently defined as failure to detect HCV RNA in peripheral blood, using highly sensitive PCR detection methods, 24 weeks after treatment ends. SVR is currently achievable in a large proportion of patients infected with HCV genotypes 2 and 3 using current standard therapy, however the proportion of patients infected with genotypes 1 and 4 achieving SVR is typically much lower (reviewed, for example, in Deutsch and Hadziyannis. Journal of Viral Hepatitis 2008; 15:2-11) due in part to compliance issues as a result of side effects associated with PEG-IFN-α treatment. Alternatives to IFN therapy are currently being developed and typically involve inhibition of viral targets (protease, polymerase and helicase proteins) with small molecule compounds.

However issues with viral resistance and side effects have hampered development and widespread use of these compounds in many cases. IFN therapy, on the other hand, is not associated with viral resistance therefore novel IFN-based therapeutics with better efficacy and tolerability profiles could represent an opportunity to significantly improve upon the current standard of HCV therapy.

IFN associated side effects are thought to be due in part to induction of IFN-responsive genes following systemic exposure to IFN-α (reviewed, for example, in Myint et al. Metab Brain Dis 2009; 24:55-(68). Since the primary site of HCV infection is in the liver (specifically hepatocytes) it could therefore be of potential benefit to avoid exposure of peripheral blood cells to IFN, thereby potentially reducing side effects associated with IFN therapy. IFN-α specifically targeted to the liver may also exhibit improved antiviral efficacy as a biproduct of directing the therapeutic molecule to the site of HCV infection, thus increasing concentrations at the hepatocyte,which could in turn allow treatment with lower total doses of IFN enabling dose intensification. In animal models of human hepatitis B virus (HBV) infection IFN-β directed to the liver specific antigen Asialoglycoprotein receptor

(ASGPR) displayed significantly improved antiviral efficacy *in vivo* (Eto & Takahashi Nature Medicine 1999; 5:577-581).

The asialglycoprotein receptor binds asialoglycoproteins i.e. glycoproteins from which a sialic acid residue has been removed to expose one or more (typically) galactose residues. The ASGPR is expressed on liver cells which remove target glycoproteins from the circulation. The ASGPR molecule is hetero-oligomeric comprising two different subunits: H1 and H2.

There is thus a need to provide new therapeutic compositions which target molecules, including IFN, to the liver to treat and/or prevent liver diseases.

An antibody based approach to target molecules, including IFN for HCV treatment, may therefore provide a method of developing novel therapeutics with improved efficacy and tolerability profiles for use in treatment of a range of liver diseases.

SUMMARY OF THE INVENTION

The present invention provides compositions and methods for targeting molecules to hepatocytes in the liver.

In one embodiment the invention a provides liver targeting composition which comprise a single molecule (e.g., as a single fusion or conjugate) which comprises (a) a ligand such as an antibody or an antibody fragment (e.g., a domain antibody (dAb)) which binds to liver cells, for example liver hepatocytes (e.g. to the ASGPR receptor on hepatocytes) and also (b) one or more therapeutic molecules for delivery to the liver. In particular the invention provides a liver targeting composition comprising a single molecule (such as a fusion or conjugate) comprising a ligand, such as an antibody or an antibody fragment (e.g. a domain antibody) which binds to the H1 subunit of ASGPR.

These liver targeting compositions can also comprise further proteins or polypeptides e.g. half life extending proteins or polypeptides e.g., a further dAb e.g., a dAb which binds to serum albumin or e.g., polyethyleneglygol PEG. These may be fused or conjugated to the single molecule, and may be fused or conjugated to the ligand, or to the therapeutic molecule, or to both the ligand and the therapeutic molecule. Methods of extending and/or measuring the *in vivo* half-life of molecules are known to those skilled in the art and are described in detail in, for example, WO2006/059110 and WO2008/096158.

In one embodiment the liver targeting composition comprises an antibody fragment (a) which is a single immunoglobulin variable domain (domain antibody (dAb)) which binds specifically to a hepatocyte e.g., to the ASGPR receptor on the hepatocytes, especially to the H1 subunit thereof. The dAb can be a human Vh or a human V Kappa. The dAb can also bind to a human and/or mouse ASGPR receptor.

Compositions of the invention also include ligands, for example a single immunoglobulin variable domain (dAb) which binds specifically to a hepatocyte e.g. to the ASGPR receptor on hepatocytes. For example the dAb provided by the invention can be a human Vh or a human V Kappa. The dAb can also bind to a human and/or mouse ASGPR receptor and/or ASGPR receptors from other animals.

In one embodiment, the dAb which binds to the ASGPR receptor on hepatocytes binds to human and/or mouse ASGPR, with high affinity as measured by Biacore [using the HBS-P buffer system (0.01M Hepes, pH7.4, 0.15M NaCl, 0.05% surfactant P20)] in the region of 1pM to about 100nM, for example about 1pM to about 10nM.or example about 1pM to about 1nM. In one embodiment the dAb will bind to both the human and to the mouse ASGPR with high affinity, as aforementioned.

For example, the dAb provided by the invention which specifically binds to the ASGPR receptor on hepatocytes can be one which comprises an amino acid sequence that is at least 80% identical (e.g., 85%, 90%, 95% or 100% identical) to the amino acid sequence encoded by the nucleotide sequences identified as: (anti human ASGPR VH dAbs) DOM26h-1 (Seq ID No: 155); DOM26h-10 (Seq ID No: 157); DOM26h-

100 (Seq ID No: 159); DOM26h-101 (Seq ID No: 161); DOM26h-102 (Seq ID No: 163); DOM26h-103 (Seq ID No: 165); DOM26h-104 (Seq ID No: 167); DOM26h-105 (Seq ID No: 169); DOM26h-106 (Seq ID No: 171); DOM26h-107 (Seq ID No: 173); DOM26h-108 (Seq ID No: 175); DOM26h-109 (Seq ID No: 177); DOM26h-11 (Seq ID No: 179); DOM26h-110 (Seq ID No: 181); DOM26h-111 (Seq ID No: 183); DOM26h-112 (Seq ID No: 185); DOM26h-113 (Seq ID No: 187); DOM26h-114 (Seq ID No: 189); DOM26h-115 (Seq ID No: 191); DOM26h-116 (Seq ID No: 193); DOM26h-117 (Seq ID No: 195); DOM26h-118 (Seq ID No: 197); DOM26h-119 (Seq ID No: 199); DOM26h-12; (Seq ID No: 201) DOM26h-120 (Seq ID No: 203); DOM26h-121 (Seq ID No: 205); DOM26h-122 (Seq ID No: 207); DOM26h-123 (Seq ID No: 209); DOM26h-124; (Seq ID No: 211); DOM26h-125 (Seq ID No: 213); DOM26h-126 (Seq ID No: 215); DOM26h-127 (Seq ID No: 217); DOM26h-128 (Seq ID No: 219); DOM26h-129 (Seq ID No: 221); DOM26h-130 (Seq ID No: 223); DOM26h-131 (Seq ID No: 225); DOM26h-132 (Seq ID No: 227); DOM26h-133 (Seq ID No: 229); DOM26h-134 (Seq ID No: 231); DOM26h-135 (Seq ID No: 233); DOM26h-136 (Seq ID No: 235); DOM26h-137 (Seq ID No: 237); DOM26h-138 (Seq ID No: 239); DOM26h-139 (Seq ID No: 241); DOM26h-140 (Seq ID No: 243); DOM26h-141 (Seq ID No: 245); DOM26h-142 (Seq ID No: 247); DOM26h-143 (Seq ID No: 249); DOM26h-144 (Seq ID No: 251); DOM26h-145 (Seq ID No: 253); DOM26h-146 (Seq ID No: 255); DOM26h-147 (Seq ID No: 257); DOM26h-148 (Seq ID No: 259); DOM26h-149 (Seq ID No: 261); DOM26h-15 (Seq ID No: 263); DOM26h-150 (Seq ID No: 265); DOM26h-151 (Seq ID No: 267); DOM26h-152 (Seq ID No: 269); DOM26h-153 (Seq ID No: 271); DOM26h-154 (Seq ID No: 273); DOM26h-155 (Seq ID No: 275); DOM26h-156 (Seq ID No: 277); DOM26h-157 (Seq ID No: 279); DOM26h-158 (Seq ID No: 281); DOM26h-159 (Seq ID No: 283); DOM26h-159-1 (Seq ID No: 285); DOM26h-159-2 (Seq ID No: 287); DOM26h-159-3 (Seq ID No: 289); DOM26h-159-4 (Seq ID No: 291); DOM26h-159-5 (Seq ID No: 293); DOM26h-160 (Seq ID No: 295); DOM26h-168 (Seq ID No: 297); DOM26h-169 (Seq ID No: 299); DOM26h-17 (Seq ID No: 301); DOM26h-170 (Seq ID No: 303); DOM26h-171 (Seq ID No: 305); DOM26h-172 (Seq ID No: 307); DOM26h-173 (Seq ID No: 309); DOM26h-174 (Seq ID No: 311); DOM26h-175 (Seq ID No: 313); DOM26h-176 (Seq ID No: 315); DOM26h-177 (Seq ID No: 317); DOM26h-178 (Seq ID No: 319); DOM26h-179 (Seq ID No: 321); DOM26h-180 (Seq ID No:

323); DOM26h-181 (Seq ID No: 325); DOM26h-182 (Seq ID No: 327); DOM26h-183 (Seq ID No: 329); DOM26h-184 (Seq ID No: 331); DOM26h-185 (Seq ID No: 333); DOM26h-186 (Seq ID No: 335); DOM26h-187 (Seq ID No: 337); DOM26h-188 (Seq ID No: 339); DOM26h-189 (Seq ID No: 341); DOM26h-19 (Seq ID No: 343); DOM26h-190 (Seq ID No: 345); DOM26h-191 (Seq ID No: 347); DOM26h-192 (Seq ID No: 349); DOM26h-193 (Seq ID No: 351); DOM26h-194 (Seq ID No: 353); DOM26h-195 (Seq ID No: 355); DOM26h-196 (Seq ID No: 357); DOM26h-197 (Seq ID No: 359); DOM26h-198 (Seq ID No: 361); DOM26h-199 (Seq ID No: 363); DOM26h-2 (Seq ID No: 365); DOM26h-20 (Seq ID No: 367); DOM26h-200 (Seq ID No: 369); DOM26h-201 (Seq ID No: 371); DOM26h-202 (Seq ID No: 373); DOM26h-203 (Seq ID No: 375); DOM26h-204 (Seq ID No: 377); DOM26h-205 (Seq ID No: 379); DOM26h-206 (Seq ID No: 381); DOM26h-207 (Seq ID No: 383); DOM26h-208 (Seq ID No: 385); DOM26h-209 (Seq ID No: 387); DOM26h-21 (Seq ID No: 389); DOM26h-210 (Seq ID No: 391); DOM26h-211 (Seq ID No: 393); DOM26h-212 (Seq ID No: 395); DOM26h-213 (Seq ID No: 397); DOM26h-214 (Seq ID No: 399); DOM26h-215 (Seq ID No: 401); DOM26h-216 (Seq ID No: 403); DOM26h-217 (Seq ID No: 405); DOM26h-218 (Seq ID No: 407); DOM26h-219 (Seq ID No: 409); DOM26h-22 (Seq ID No: 411); DOM26h-220 (Seq ID No: 413); DOM26h-221 (Seq ID No: 415); DOM26h-222 (Seq ID No: 417); DOM26h-223 (Seq ID No: 419); DOM26h-23 (Seq ID No: 421); DOM26h-24 (Seq ID No: 423); DOM26h-29-1 (Seq ID No: 425); DOM26h-4 (Seq ID No: 427); DOM26h-41 (Seq ID No: 429); DOM26h-42 (Seq ID No: 431); DOM26h-43 (Seq ID No: 433); DOM26h-44 (Seq ID No: 435); DOM26h-45 (Seq ID No: 437); DOM26h-46 (Seq ID No: 439); DOM26h-47 (Seq ID No: 441); DOM26h-48 (Seq ID No: 443); DOM26h-49 (Seq ID No: 445); DOM26h-50 (Seq ID No: 447); DOM26h-51 (Seq ID No: 449); DOM26h-52 (Seq ID No: 451); DOM26h-53 (Seq ID No: 453); DOM26h-54 (Seq ID No: 455); DOM26h-55 (Seq ID No: 457); DOM26h-56 (Seq ID No: 459); DOM26h-57 (Seq ID No: 461); DOM26h-58 (Seq ID No: 463); DOM26h-59 (Seq ID No: 465); DOM26h-60 (Seq ID No: 467); DOM26h-61 (Seq ID No: 469); DOM26h-62 (Seq ID No: 471); DOM26h-63 (Seq ID No: 473); DOM26h-64 (Seq ID No: 475); DOM26h-65 (Seq ID No: 477); DOM26h-66 (Seq ID No: 479); DOM26h-67 (Seq ID No: 481); DOM26h-68 (Seq ID No: 483); DOM26h-69 (Seq ID No: 485); DOM26h-70 (Seq ID No: 487); DOM26h-71 (Seq ID No: 489); DOM26h-72 (Seq ID No: 491); DOM26h-

73 (Seq ID No: 493); DOM26h-74 (Seq ID No: 495); DOM26h-75 (Seq ID No: 497); DOM26h-76 (Seq ID No: 499); DOM26h-77 (Seq ID No: 501); DOM26h-78 (Seq ID No: 503); DOM26h-79 (Seq ID No: 505); DOM26h-80 (Seq ID No: 507); DOM26h-81 (Seq ID No: 509); DOM26h-82 (Seq ID No: 511); DOM26h-83 (Seq ID No: 513); DOM26h-84 (Seq ID No: 515); DOM26h-85 (Seq ID No: 517); DOM26h-86 (Seq ID No: 519); DOM26h-87 (Seq ID No: 521); DOM26h-88 (Seq ID No: 523); DOM26h-89 (Seq ID No: 525); DOM26h-90 (Seq ID No: 527); DOM26h-91 (Seq ID No: 529); DOM26h-92 (Seq ID No: 531); DOM26h-93 (Seq ID No: 533); DOM26h-94 (Seq ID No: 535); DOM26h-95 (Seq ID No: 537); DOM26h-96 (Seq ID No: 539); DOM26h-97 (Seq ID No: 541); DOM26h-98 (Seq ID No: 543); DOM26h-99 (Seq ID No: 545); DOM26h-99-1 (Seq ID No: 547); DOM26h-99-2 (Seq ID No: 549); (anti human ASGPR Vκ Clones) DOM26h-161 (Seq ID No: 551); DOM26h-162 (Seq ID No: 553); DOM26h-163 (Seq ID No: 555); DOM26h-164 (Seq ID No: 557); DOM26h-165 (Seq ID No: 559); DOM26h-166 (Seq ID No: 561); DOM26h-167 (Seq ID No: 563); DOM26h-224 (Seq ID No: 565); DOM26h-25 (Seq ID No: 567); DOM26h-26 (Seq ID No: 569); DOM26h-27 (Seq ID No: 571); DOM26h-28 (Seq ID No: 573); DOM26h-29 (Seq ID No: 575); DOM26h-30 (Seq ID No: 577); DOM26h-31 (Seq ID No: 579); DOM26h-32 (Seq ID No: 581); DOM26h-33 (Seq ID No: 583); DOM26h-34 (Seq ID No: 585); DOM26h-35 (Seq ID No: 587); DOM26h-36 (Seq ID No: 589); DOM26h-37 (Seq ID No: 591); DOM26h-38 (Seq ID No: 593); DOM26h-39 (Seq ID No: 595); DOM26h-40 (Seq ID No: 597); DOM26h-6 (Seq ID No: 599); DOM26h-8 (Seq ID No: 601); DOM26h-9 (Seq ID No: 603).

In another embodiment, the dAb provided by the invention which specifically binds to the ASGPR receptor on hepatocyes may be one which comprises an amino acid sequence that is at least 80% identical (e.g. 85%, 90%, 95% or 100% identical) to the affinity-matured dAb clone sequences encoded by the nucleotide sequences identified in Figure 32 as DOM26h-161-84 (Seq ID No: 867); DOM26h-161-86 (Seq ID No: 869); DOM26h-161-87 (Seq ID No: 871); DOM26h-196-61 (Seq ID No: 873); DOM26h-210-2 (Seq ID No: 875); DOM26h-220-1 (Seq ID No: 877); or DOM26h-220-43 (Seq ID No: 879).

In another example, the dAb which binds to the ASGPR receptor on hepatocytes is one which comprises an amino acid sequence that is at least 80% identical (e.g. 85%, 90%, 95% or 100% identical) to the amino acid sequence encoded by the nucleotide sequences identified as: (anti mouse ASGPR VH dAbs) DOM26m-10 (Seq ID No: 605); DOM26m-13 (Seq ID No: 607); DOM26m-16 (Seq ID No: 609); DOM26m-165 (Seq ID No: 611); DOM26m-17 (Seq ID No: 613); DOM26m-27 (Seq ID No: 615); DOM26m-28 (Seq ID No: 617); DOM26m-29 (Seq ID No: 619); DOM26m-30 (Seq ID No: 621); DOM26m-31 (Seq ID No: 623); DOM26m-32 (Seq ID No: 625); DOM26m-33 (Seq ID No: 627); DOM26m-33-1 (Seq ID No: 629); DOM26m-33-10 (Seq ID No: 631); DOM26m-33-11 (Seq ID No: 633); DOM26m-33-12 (Seq ID No: 635); DOM26m-33-2 (Seq ID No: 637); DOM26m-33-3 (Seq ID No: 639); DOM26m-33-4 (Seq ID No: 641); DOM26m-33-5 (Seq ID No: 643); DOM26m-33-6 (Seq ID No: 645); DOM26m-33-7 (Seq ID No: 647); DOM26m-33-8 (Seq ID No: 649); DOM26m-33-9 (Seq ID No: 651); DOM26m-34 (Seq ID No: 653); DOM26m-35 (Seq ID No: 655); DOM26m-36 (Seq ID No: 657); DOM26m-37 (Seq ID No: 659); DOM26m-38 (Seq ID No: 661); DOM26m-39 (Seq ID No: 663); DOM26m-4 (Seq ID No: 665); DOM26m-40 (Seq ID No: 667); DOM26m-41 (Seq ID No: 669); DOM26m-42 (Seq ID No: 671); DOM26m-43 (Seq ID No: 673); DOM26m-44 (Seq ID No: 675); DOM26m-45 (Seq ID No: 677); DOM26m-46 (Seq ID No: 679); DOM26m-47 (Seq ID No: 681); DOM26m-48 (Seq ID No: 683); DOM26m-52 (Seq ID No: 685); DOM26m-52-1 (Seq ID No: 687); DOM26m-52-2 (Seq ID No: 689); DOM26m-52-3 (Seq ID No: 691); DOM26m-52-4 (Seq ID No: 693); DOM26m-52-5 (Seq ID No: 695); DOM26m-52-6 (Seq ID No: 697); DOM26m-52-7 (Seq ID No: 699); DOM26m-6 (Seq ID No: 701); DOM26m-60 (Seq ID No: 703); DOM26m-61-1 (Seq ID No: 705); DOM26m-61-2 (Seq ID No: 707); DOM26m-61-3 (Seq ID No: 709); DOM26m-61-4 (Seq ID No: 711); DOM26m-61-5 (Seq ID No: 713); DOM26m-61-6 (Seq ID No: 715); DOM26m-7 (Seq ID No: 717); DOM26m-73 (Seq ID No: 719); DOM26m-74 (Seq ID No: 721); DOM26m-75 (Seq ID No: 723); DOM26m-76 (Seq ID No: 725); DOM26m-77 (Seq ID No: 727); DOM26m-78 (Seq ID No: 729); DOM26m-79 (Seq ID No: 731); DOM26m-8 (Seq ID No: 733); DOM26m-80 (Seq ID No: 735); DOM26m-81 (Seq ID No: 737); DOM26m-82 (Seq ID No: 739); DOM26m-83 (Seq ID No: 741); DOM26m-9 (Seq ID No: 743);

(anti mouse ASGPR Vk dAbs) DOM26m-1 (Seq ID No: 745); DOM26m-100 (Seq ID No: 747); DOM26m-101 (Seq ID No: 749); DOM26m-102 (Seq ID No: 751); DOM26m-103 (Seq ID No: 753); DOM26m-106 (Seq ID No: 755); DOM26m-108 (Seq ID No: 757); DOM26m-109 (Seq ID No: 759); DOM26m-109-1 (Seq ID No: 761); DOM26m-109-2 (Seq ID No: 763); DOM26m-12 (Seq ID No: 765); DOM26m-18 (Seq ID No: 767); DOM26m-19 (Seq ID No: 769); DOM 26m-2 (Seq ID No: 771); DOM26m-20 (Seq ID No: 773); DOM26m-20-1 (Seq ID No: 775); DOM26m-20-2 (Seq ID No: 777); DOM26m-20-3 (Seq ID No: 779); DOM26m-20-4 (Seq ID No: 781); DOM26m-20-5 (Seq ID No: 783); DOM26m-20-6 (Seq ID No: 785); DOM26m-22 (Seq ID No: 787); DOM26m-23 (Seq ID No: 789); DOM26m-24 (Seq ID No: 791); DOM26m-25 (Seq ID No: 793); DOM26m-26 (Seq ID No: 795); DOM26m-3 (Seq ID No: 797); DOM26m-50 (Seq ID No: 799); DOM26m-50-1 (Seq ID No: 801); DOM26m-50-2 (Seq ID No: 803); DOM26m-50-3 (Seq ID No: 805); DOM26m-50-4 (Seq ID No: 807); DOM26m-50-5 (Seq ID No: 809); DOM26m-50-6 (Seq ID No: 811); DOM26m-51 (Seq ID No: 813); DOM26m-53 (Seq ID No: 815); DOM26m-54 (Seq ID No: 817); DOM26m-55 (Seq ID No: 819); DOM26m-56 (Seq ID No: 821); DOM26m-57 (Seq ID No: 823); DOM26m-58 (Seq ID No: 825); DOM26m-59 (Seq ID No: 827); DOM26m-61 (Seq ID No: 829); DOM26m-63 (Seq ID No: 831); DOM26m-64 (Seq ID No: 833); DOM26m-66 (Seq ID No: 835); DOM26m-69 (Seq ID No: 837); DOM26m-85 (Seq ID No: 839); DOM26m-86 (Seq ID No: 841); DOM26m-87 (Seq ID No: 843); DOM26m-89 (Seq ID No: 845); DOM26m-90 (Seq ID No: 847); DOM26m-91 (Seq ID No: 849); DOM26m-92 (Seq ID No: 851); DOM26m-93 (Seq ID No: 853); DOM26m-94 (Seq ID No: 855); DOM26m-95 (Seq ID No: 857); DOM26m-96 (Seq ID No: 859); DOM26m-97 (Seq ID No: 861); DOM26m-98 (Seq ID No: 863); DOM26m-99 (Seq ID No: 865).

In an embodiment the ligand e.g. the dAb, can be one which competes for binding to the ASGPR receptor with any one of the DOM 26 dAbs described herein (with an amino acid sequence shown in Figures 15, 16, 19 and 20).

In yet another aspect there is provided a dAb which binds to ASGPR comprising at least one CDR selected from the group consisting of: CDR1, CDR2, and CDR3, wherein the CDR1, CDR2, or CDR3 is at least 80% identical (e.g. 85%, 90%, 95% or

100% identical) to a CDR1, CDR2, or CDR3 sequence in any one of the amino DOM 26 amino acid sequences as described herein. The CDRs can be identified in the amino acid sequences as follows: V kappa sequences: CDR1 is residues 24-34, CDR2 is residues 50-56, CDR3 is residues 89-97; for V H sequences: CDR1 is residues 31-35, CDR2 is residues 50-65, CDR3 is residues 95-102.

In one embodiment, the dAbs of the present invention show cross-reactivity between human ASGPR and ASGPR from another species such as mouse, dog or cynomolgus macaque. In one embodiment, the dAbs of the present invention show cross-reactivity between human and mouse ASGPR. In this embodiment, the variable domains specifically bind human and mouse ASGPR. In one embodiment the invention provides a variable domain which is cross reactive for human and mouse ASGPR and which is an amino acid sequence selected from: DOM 26m-52, DOM 26h-99, DOM 26h-161, DOM 26h-163, DOM 26h-186, DOM 26h-196, DOM 26h-210, and DOM 26h-220 or an amino acid sequence which is at least 80% identical (e.g. 85%, 90%, 95% or 100%) identical to an amino acid sequence selected from: DOM 26m-52, DOM 26h-99, DOM 26h-161, DOM 26h-163, DOM 26h-186, DOM 26h-196, DOM 26h-210, and DOM 26h-220.

As described above, cross-reactivity is particularly useful, since drug development typically requires testing of lead drug candidates in animal systems, such as mouse models, before the drug is tested in humans. The provision of a drug that can bind to a human protein as well as the species homologue such as the equivalent mouse protein allows one to test results in these systems and make side-by-side comparisons of data using the same drug. This avoids the complication of needing to find a drug that works against, for example, a mouse ASGPR and a separate drug that works against human ASGPR, and also avoids the need to compare results in humans and mice using non-identical or surrogate drugs.

In another embodiment the invention provides a liver targeting composition which comprise a single molecule (e.g. present as a single fusion or conjugate) which comprises (a) a dAb which binds to the ASGPR receptor on hepatocytes, e.g. any one

of the ASGPR dAbs as described herein and also (b) one or more therapeutic molecules for delivery to the liver.

In one embodiment of the above the molecule (b) which it is desired to deliver to the liver can be an interferon, for example it can be interferon alpha 2, interferon alpha 5, interferon alpha 6, or Consensus interferon, or it can be a mutant or derivative of any of these which retains some interferon activity.

In another embodiment the present invention provides a composition which comprises any one of the liver targeting compositions as described herein, and also a further drug for delivery to the liver for example Ribavirin and/or a drug for systemic delivery. Such a composition can be a combined preparation for simultaneous, separate or sequential use in therapy, e.g to treat or prevent a liver disease or condition such as an inflammatory liver disease e.g. fibrosis or a viral liver disease e.g. Hepatitis (e.g. Hepatitis C), or Cirrhosis or liver cancer.

In one embodiment, the drug which it is desired to deliver to the liver may comprise one or more of the following: Nexavar® (also known as Sorafenib) – a small molecule used in the treatment of primary hepatocellular carcinoma; Erbitux® (also known as Cetuximab) – a monoclonal antibody used in the treatment of primary liver cancers, or bowel cancer metastases in the liver; Avastin® (also known as bevacizumab) and Herceptin® (also known as trastuzumab), which are used to treat bowel or breast cancer metastases respectively in the liver.

Nexavar® could, for example, be conveniently chemically conjugated to an antibody or dAb or the like which binds to the ASGPR receptor. Erbitux®, Avastin® or Herceptin® containing-fusions could conveniently be prepared by fusing a nucleotide sequence encoding the Erbitux®, Avastin® or Herceptin® antibody with a nucleotide sequence encoding an antibody, dAb or the like which binds to the ASGPR receptor.

The therapeutic molecule(s) for delivery to the liver (e.g. interferon) when present as a fusion (or conjugate) with a liver targeting dAb can be linked to either

the N-terminal or C-terminal of the dAb or at points within the dAb sequence. In one embodiment one or more interferon molecules e.g. interferon alpha 2 are present as a fusion (or conjugate) at the N terminal of the dAb.

An amino acid or chemical linker may also optionally be present joining the therapeutic molecule(s) for delivery to the liver (e.g. interferon) with the dAb. The linker can be for example a TVAAPR or TVAAPS linker sequence, a helical linker or it can be a gly-ser linker.

Alternatively the linker can be e.g. a PEG linker. The linker can also be a peptide linker, a linker containing a functionality such as a protease cleavage site, or a chelating group e.g. for attachment of a radioisotope or other imaging agent.

In certain embodiments, the dAbs, fusions (or conjugates) of the invention can comprise further molecules e.g. further peptides or polypeptides, such as half-life extending polypeptides (e.g. a dAb or antibody fragment which binds to serum albumin), or one or more PEG molecules.

As used herein, "fusion" refers to a fusion protein that comprises as one moiety a dAb that binds to hepatocytes (e.g. to the ASGPR on hepatocytes) and one or more further molecules which are therapeutic molecules which it is desired to deliver to the liver (e.g. interferon). The dAb that binds to hepatocytes (e.g. to the ASGPR on hepatocytes) and the therapeutic molecules are present as discrete parts (moieties) of a single continuous polypeptide chain. The dAb and the therapeutic molecules can be directly bonded to each other through a peptide bond or linked through a suitable amino acid, or peptide or polypeptide linker. Additional moieties e.g. peptides or polypeptides (e.g. third, fourth) and/or linker sequences, can be present as appropriate. The dAb can be in an N-terminal location, C-terminal location or it can be internal relative to the therapeutic molecules.

As used herein, "conjugate" refers to a composition comprising a dAb that binds to hepatocytes (e.g. to the ASGPR on hepatocytes) to which one or more therapeutic molecules for delivery to the liver are covalently or non-covalently bonded. The therapeutic molecule can be covalently bonded to the dAb directly or

indirectly through a suitable linker moiety. The therapeutic molecule can be bonded to the dAb at any suitable position, such as the amino-terminus, the carboxyl-terminus or through suitable amino acid side chains (e.g., the ε amino group of lysine, or thiol group of cysteine). Alternatively, the therapeutic molecule can be noncovalently bonded to the dAb directly (e.g., electrostatic interaction, hydrophobic interaction) or indirectly (e.g., through noncovalent binding of complementary binding partners (e.g., biotin and avidin), wherein one partner is covalently bonded to insulinotropic / incretin molecule and the complementary binding partner is covalently bonded to the dAb). The dAb can be in an N-terminal location, C-terminal location or it can be internal relative to the therapeutic molecule.

The invention also provides compositions comprising nucleic acids encoding the fusions described herein for example comprising any one of the nucleic acids encoding the DOM 26 dAbs as shown in Figures 13-14 and 17-18.

Also provided are host cells e.g. non-embryonic host cells e.g. prokaryotic or eukaryotic hosts cells such as bacterial host cells (e.g. E. coli) or or yeast host cells or mammalian cells that comprise these nucleic acids.

The invention further provides a method for producing a fusion protein of the present invention which method comprises maintaining a host cell such as those described above that comprises a recombinant nucleic acid and/or construct that encodes a fusion of the invention under conditions suitable for expression of said recombinant nucleic acid, whereby a fusion protein is produced.

The invention also provides pharmaceutical compositions comprising the compositions of the invention.

The invention further provides a composition of the invention for use in medicine, e.g. for use in the treatment or prevention of e.g. a liver disease or condition or disorder such as a viral liver disease (e.g. Hepatitis e.g. Hepatitis C), cirrhosis, or liver cancer, and which comprises administering to said individual a therapeutically effective amount of a composition of the invention.

The invention also provides a method for treating (therapeutically or prophylactically) a patient or subject having a disease or disorder, such as those described herein e.g. a liver disease or condition or disorder such as a viral liver disease (e.g. Hepatitis e.g. Hepatitis C), cirrhosis, or liver cancer, and which comprises administering to said individual a therapeutically effective amount of a composition of the invention.

The compositions e.g. pharmaceutical compositions, of the invention may be administered alone or in combination with other molecules or moieties e.g. polypeptides, therapeutic proteins and/or molecules (e.g., other proteins (including antibodies), peptides, or small molecule drugs.

The invention also provides compositions of the invention for use in the treatment of a liver disease or condition or disorder such as a viral liver disease (e.g. Hepatitis e.g. Hepatitis C), cirrhosis, or liver cancer.

The invention also provides for use of a composition of the invention in the manufacture of a medicament for treatment of a liver disease or condition or disorder such as a viral liver disease (e.g. Hepatitis e.g. Hepatitis C), cirrhosis, or liver cancer.

The invention also relates to use of any of the compositions described herein for use in therapy, diagnosis or prophylaxis of a liver disease or condition such as a viral liver disease (e.g. Hepatitis e.g. Hepatitis C), cirrhosis, or liver cancer disease or disorder. The invention also relates to prophylactic use of any of the compositions described herein after infection with a liver infecting blood borne pathogen.

The compositions of the invention, e.g. the dAb component of the composition, can be further formatted to have a larger hydrodynamic size to further extend the half life, for example, by attachment of a PEG group, serum albumin, transferrin, transferrin receptor or at least the transferrin-binding portion thereof, an antibody Fc region, or by conjugation to an antibody domain. For example, the dAb that binds serum albumin can be formatted as a larger antigen-binding fragment of an antibody (e.g., formatted as a Fab, Fab', $F(ab)_2$, $F(ab')_2$, IgG, scFv).

In other embodiments of the invention described throughout this disclosure, instead of the use of a "dAb" in a fusion of the invention, it is contemplated that the skilled addressee can use a domain that comprises the CDRs of a dAb that binds specifically to hepatocytes e.g. the ASGPR receptor on hepatocytes (e.g., the CDRs can be grafted onto a suitable protein scaffold or skeleton, eg an affibody, an SpA scaffold, an LDL receptor class A domain or an EGF domain). The disclosure as a whole is to be construed accordingly to provide disclosure of such domains in place of a dAb.

In certain embodiments, the invention provides a composition according to the invention that comprises a dual-specific ligand or multi-specific ligand that comprises a first dAb according to the invention that binds hepatocytes (e.g. the ASGPR receptor on hepatocytes) and a second dAb that has the same or a different binding specificity from the first dAb and optionally in the case of multi-specific ligands further dAbs. The second dAb (or further dAbs) may optionally bind a different target.

Thus, in one aspect, the invention provides the compositions of the invention for delivery by parenteral administration e.g. by subcutaneous, intramuscular or intravenous injection, inhalation, nasal delivery, transmucossal delivery, oral delivery, delivery to the GI tract of a patient, rectal delivery or ocular delivery. In one aspect, the invention provides the use of the compositions of the invention in the manufacture of a medicament for delivery by subcutaneous injection, inhalation, intravenous delivery, nasal delivery, transmucossal delivery, oral delivery, delivery to the GI tract of a patient, rectal delivery, transdermal or ocular delivery.

In one aspect, the invention provides a method for delivery to a patient by subcutaneous injection, pulmonary delivery, intravenous delivery, nasal delivery, transmucossal delivery, oral delivery, delivery to the GI tract of a patient, rectal or ocular delivery, wherein the method comprises administering to the patient a pharmaceutically effective amount of a fusion or conjugate of the invention.

In one aspect, the invention provides an oral, injectable, inhalable, or nebulisable formulation comprising a fusion or conjugate of the invention.

The formulation can be in the form of a tablet, pill, capsule, liquid or syrup.

The term "subject" or "individual" is defined herein to include animals such as mammals, including, but not limited to, primates (*e.g.*, humans), cows, sheep, goats, horses, dogs, cats, rabbits, guinea pigs, rats, mice or other bovine, ovine, equine, canine, feline, rodent or murine species.

The invention also provides a kit for use in administering compositions according to the invention to a subject (*e.g.*, human patient), comprising a composition of the invention, a drug delivery device and, optionally, instructions for use. The composition can be provided as a formulation, such as a freeze dried formulation or a slow release formulation. In certain embodiments, the drug delivery device is selected from the group consisting of a syringe, an inhaler, an intranasal or ocular administration device (*e.g.*, a mister, eye or nose dropper), and a needleless injection device.

The compositions (*e.g* dAbs and liver targeting compositions) of this invention can be lyophilized for storage and reconstituted in a suitable carrier prior to use. Any suitable lyophilization method (*e.g.*, spray drying, cake drying) and/or reconstitution techniques can be employed. It will be appreciated by those skilled in the art that lyophilisation and reconstitution can lead to varying degrees of antibody activity loss and that use levels may have to be adjusted to compensate. In a particular embodiment, the invention provides a composition comprising a lyophilized (freeze dried) composition as described herein. Preferably, the lyophilized (freeze dried) composition loses no more than about 20%, or no more than about 25%, or no more than about 30%, or no more than about 35%, or no more than about 40%, or no more than about 45%, or no more than about 50% of its activity (*e.g.*, binding activity for serum albumin) when rehydrated. Activity is the amount of composition required to produce the effect of the composition before it was lyophilized. The activity of the

composition can be determined using any suitable method before lyophilization, and the activity can be determined using the same method after rehydration to determine amount of lost activity.

The invention also provides sustained or slow release formulations comprising the compositions of the invention, such sustained release formulations can comprise the composition of the invention in combination with, e.g. hyaluronic acid, microspheres or liposomes and other pharmaceutically or pharmacalogically acceptable carriers, excipients and/or diluents.

In one aspect, the invention provides a pharmaceutical composition comprising a composition of the invention, and a pharmaceutically or physiologically acceptable carrier, excipient or diluent.

BRIEF DESCRIPTION OF THE DRAWINGS:

Figure 1: shows binding of β-GalNAc-PAA-biotin to human $(His)_6$-ASGPR H1 (– – –), mouse $(His)_6$-ASGPR H1 (.....) and human $(His)_6$-GP6 irrelevant control antigen (———). Antigens were immobilised on a biacore CM5 chip surface and 100nM ligand passed over at a flow rate of 10 μl min^{-1}. Sensorgram illustrates that ligand binds to human and mouse $(His)_6$-ASGPR H1 antigens but not $(His)_6$-GP6 irrlevant control antigen.

Figure 2: shows 4-12% Bis-Tris gel loaded with 2μg of Ni-NTA purified human $(His)_6$-ASGPR H1 (lane 2) or mouse $(His)_6$-ASGPR H1 (lane 3) expressed in HEK293E. 10 μl Mark 12 molecular weight standards (Invitrogen) were loaded in lane 1 and molecular masses (in kilodaltons) of individual marker bands are given to the left of lane 1. Gel was stained with 1x SureBlue. Gel illustrates that human and mouse $(His)_6$-ASGPR H1 migrate close to the expected molecular mass based on amino acid sequence.

Figure 3: Vκ and V_H dAbs selected against recombinant human and mouse ASGPR proteins binding specifically to the target antigen. Antigens were coated on the surface of a CM5 BIAcore chip and protein L purified Vκ dAb DOM26m-20 (top panel) or protein A purified V_H dAb DOM26h-61 (bottom panel) was passed over the chip surface at a concentration of 2.5μM using a flow-rate of 10μl per second. In the top panel binding of dAb to $(His)_6$- mouse ASGPR H1 (——) or human c-kit $(His)_6$ negative control antigen (– – –) is shown. In the bottom panel dAb binding to $(His)_6$- human ASGPR H1 (——) or human c-kit $(His)_6$ negative control antigen (– – –) is shown.

Figure 4: shows dAb clones selected against recombinant $(His)_6$- mouse ASGPR H1 antigen binding specifically to murine liver cell lines in a flow cytometry cell binding assay. Binding of dAbs with c-terminal FLAG epitope tags cross-linked with anti-FLAG M2 monoclonal antibody to murine hepatoma cell line Hepa1c1c7 (top panel) or murine fibroblast negative control cell line L929 (bottom panel) was tested in this assay. Goat polyclonal antibody specific for mouse IgG (GaM-FITC) was used as secondary detection reagent. VκD (human germ-line Vκ sequence with a c-terminal FLAG epitope tag) was used as a non-specific dAb binding control. Results obtained with anti-FLAG M2 in the absence of dAb (FLAG only) and secondary detection reagent in the absence of dAb or anti-FLAG M2 (GaM-FITC) are also shown together with unstained cells. For each dAb a half-log dilution series was tested starting at 10μM final concentration in the assay (right hand bar in each series).

Figure 5: shows binding and localisation of anti-mouse ASGPR dAb DOM26m-33 following incubation with Hepa1c1c7 murine liver cell line. After incubation for 30 minutes in the presence of 5μM DOM26m-33 with a c-terminal FLAG epitope tag cells were fixed with 4% paraformaldehyde/0.2% saponin and stained with monoclonal anti-FLAG M2 Cy3 conjugate to determine dAb localisation or rabbit polyclonal antibody specific for either EEA1 or LAMP1 to determine localisation of early endosome and lysosome respectively. The top panel shows similarity between the pattern of localisation for DOM26m-33 and EEA1, with some overlap in the observed staining pattern. The bottom panel shows that the pattern of localisation for

DOM26m-33 and LAMP1 are distinct, with no overlap in the observed staining pattern.

Figure 6: shows BIAcore sensorgram from epitope mapping experiment to determine whether mouse ASGPR specific dAbs DOM26m-33 and DOM26m-52 bind to distinct epitopes within the antigen. dAbs were passed over BIAcore CM5 chip surface coated with $(His)_6$ mouse ASGPR H1 at a concentration of 1μM dAb using a flow rate of 10μl per second. Injection events are as follows:
1=injection of dAb 1
2=injection of dAb 2
3=co injection of dAb 1 followed by dAb 2
4= co injection of dAb 2 followed by dAb 1
*=regeneration of chip surface with 15 second pulse of 0.1M glycine, pH 2.0
In this experiment co injection of DOM26m-33 and DOM26m-52 inhibits binding (in comparison to dAb injected alone) by >20%, therefore DOM26m-33 and DOM26m-52 bind to partially overlapping epitopes within mouse ASGPR H1 subunit. Antibody binding of mouse ASGPR H1 was unaffected by regeneration with 0.1M glycine, pH 2.0 in these experiments.

Figure 7: shows localisation of ^{111}In labelled dAbs in balb/c mice at 3 hours post injection. Following intravenous dosing of 12 MBq of radiolabelled dAb via tail vein injection mice were imaged using a nanospect camera. Images show that at 3 hours signal is observed in kidney and bladder with all three dAb molecules, whereas liver localisation in only observed with anti murine ASGPR dAb DOM26m-33.

Figure 8: shows biodistribution of ^{111}In labelled dAbs 3 hours after dosing intravenously in balb/c mice via the tail vein. Approximately 0.5MBq radiolabelled dAb was injected in each case. Results show accumulation of radiolabelled dAb in mouse liver is 12.4 times higher in mice injected with DOM26m-33 than in mice injected with Vκ dummy and 4.9 times higher than in mice injected with V_H dummy

Figure 9: shows 4-12% Bis-Tris gel loaded with 2μg per lane of protein L purified mIFNa2-dAb fusions reduced with 10mM DTT. Lane designations as follows:
mIFNa2-Vκ dummy (lane 2),
mIFNa2-Vκ dummy with C-terminal cysteine point mutation (lane 3)
mIFNa2-V_H dummy (lane 4)
mIFNa2-V_H dummy with C-terminal cysteine point mutation (lane 5)
mIFNa2-DOM26m-33 (lane 6)
mIFNa2-DOM26m-33 with C-terminal cysteine point mutation (lane 7)
10 μl Mark 12 molecular weight standards (Invitrogen) were loaded in lane 1 and molecular masses (in kilodaltons) of individual marker bands are given to the left of lane 1. Gel was stained with 1x SureBlue. Gel illustrates that mouse IFNa2-dAb fusions migrate close to the expected molecular mass of approximately 33 KDa.

Figure 10: shows activity of mouse IFN-dAb fusions in CHO ISRE-Luc transient transfection assay. CHO-K1 cells were incubated with the indicated concentrations of mouse IFN-alpha standard or mouse IFN-dAb fusion protein. Top panel shows results obtained with mouse IFNa2-DOM26m-33 fusion proteins, middle panel shows results obtained with mouse IFNa2-V_H dummy 2 fusion proteins and lower panel shows results obtained with mouse IFNa2-Vκ dummy fusion proteins. Symbols denote the following:
▲= mouse IFNa2-dAb fusions
■= mouse IFNa2-dAb fusions with C-terminal cysteine mutation
▼= mouse IFN-alpha standard.

Figure 11a shows binding of mouse mouse IFNa2-DOM26m-33 fusions to (His)6 mouse ASGPR H1 coated on the surface of BIAcore CM5 chip.
Traces represent binding of DOM26m-33 only (·····) shown in all panels for comparison, mouse IFNa2-dAb fusions (– – –) and mouse IFNa2-dAb fusions with C-terminal cysteine mutation (_____).

Figure 11b shows binding of mouse mouse IFNa2-DOM26m-33 fusions to (His)6 mouse ASGPR H1 coated on the surface of BIAcore CM5 chip.

Traces represent binding of DOM26m-33 only (·····) shown in all panels for comparison, mouse IFNa2-dAb fusions (– – –) and mouse IFNa2-dAb fusions with C-terminal cysteine mutation (_____).

Figure 11c shows binding of mouse mouse IFNa2-DOM26m-33 fusions to (His)6 mouse ASGPR H1 coated on the surface of BIAcore CM5 chip.
Traces represent binding of DOM26m-33 only (·····) shown in all panels for comparison, mouse IFNa2-dAb fusions (– – –) and mouse IFNa2-dAb fusions with C-terminal cysteine mutation (_____).

Figure 12: shows murine ASGPR specific dAb clones grouped according to epitopes bound within the antigen.

Figure 13: shows nucleotide sequences of anti-human Vh ASGPR dAbs.
(Seq ID No.s 155-549; odd numbers only)

Figure 14: shows nucleotide sequences of anti-human V kappa ASGPR dAbs.
(Seq ID No.s 551-603; odd numbers only)

Figure 15: shows amino acid sequences of anti-human Vh ASGPR dAbs.
(Seq ID No.s 156-550; even numbers only)

Figure 16: shows amino acid sequences of anti-human V kappa ASGPR dAbs.
(Seq ID No.s 552-604; even numbers only)

Figure 17: shows nucleotide sequences of anti-mouse Vh ASGPR dAbs.
(Seq ID No.s 605-743; odd numbers only)

Figure 18: shows nucleotide sequences of anti-mouse V kappa ASGPR dAbs.
(Seq ID No.s 745-865; odd numbers only)

Figure 19: shows amino acid sequences of anti-mouse Vh ASGPR dAbs.
(Seq ID No.s 606-744; even numbers only)

Figure 20: shows amino acid sequences of anti-mouse V kappa ASGPR dAbs. (Seq ID No.s 746-866; even numbers only)

Figure 21 shows binding of ASGPR specific dAbs DOM26h-196 (━ ━ ━) and DOM26h-196-61 (———) to human $(His)_6$-ASGPR H1. Biotinylated $(His)_6$-ASGPR H1 was immobilised on a Biacore streptavidin chip surface and 62nM dAb passed over at a flow rate of 40 $\mu l.min^{-1}$. Sensorgram illustrates that DOM26h-196-61 binds to human $(His)_6$-ASGPR H1 antigen with higher affinity than that of the DOM26h-196 parental clone.

Figure 22 shows 4-12% Bis-Tris gel loaded with 2μg of Ni-NTA purified human $(His)_6$-ASGPR H1 stalk domain (lane 2), human $(His)_6$-ASGPR H1 stalk domain treated with PNGase F (lane 3), human $(His)_6$-ASGPR H1 lectin domain (lane4), human $(His)_6$-ASGPR H1 lectin domain treated with PNGase F (lane 5). 10 μl Novex Sharp prestained molecular weight standards (Invitrogen) were loaded in lane 1 and molecular masses (in kilodaltons) of individual marker bands are given to the left of lane 1. Gel was stained with 1x SureBlue. Gel shows that stalk domain is extensively glycosylated as the protein only runs at the expected molecular mass following treatment with PNGase F, whereas lectin domain runs at the expected molecular mass in the presence or absence of PNGase F digestion.

Figure 23 shows binding of ASGPR specific dAb DOM26h-196-61 to biotinylated $(His)_6$- human ASGPR H1 lectin domain residues cysteine 154-leucine 291 (———), $(His)_6$-mouse ASGPR H1 full extracellular domain residues serine 60-asparagine 284 (▬ ▬ ▬) and $(His)_6$-human ASGPR H1 stalk domain residues glutamine 62-cysteine 153 (·····). Biotinylated antigens were immobilised on a Biacore streptavidin chip surface and dAb passed over at a concentration of 60nM and flow rate of 40 $\mu l.min^{-1}$. Sensorgram illustrates that DOM26h-196-61 binds to human ASGPR H1 lectin domain and mouse ASGPR H1 extracellular domain but not human ASGPR H1 stalk domain.

Figure 24 shows localisation of ^{111}In labelled dAbs in balb/c mice at 3 hours post injection. Following intravenous dosing of 12 MBq of radiolabelled dAb via tail vein injection mice were imaged using a nanospect camera. Images show that at 3 hours signal is observed in kidney and bladder with all dAb molecules, whereas liver localisation is only observed with anti ASGPR V_H dAb DOM26h-196-61 and anti ASGPR V_κ dAb DOM26h-161-84.

Figure 25 a & b shows biodistribution of ^{111}In labelled dAbs 3 hours after dosing intravenously in balb/c mice via the tail vein. Approximately 0.5MBq radiolabelled dAb was injected in each case. Results show accumulation of radiolabelled ASGPR dAb in mouse liver is considerably higher than that observed with either V_κ/V_H dummy 2 dAbs.

As used herein, "interferon activity" refers to a molecule which, as determined suing the B16-Blue assay (Invirogen) performed as described herein (Example 12), has at least 10, 15, 20, 25, 30, 35, 40, 45 or even 50% of the amount of interferon activity of an equivalent amount of recombinant mouse interferon alpha (e.g. from PBL Biomedical Laboratories).

Figure 26 shows 4-12% Bis-Tris gel loaded with 2μg per lane of protein L purified mIFNa2-dAb fusions reduced with 10mM DTT. Lane designations as follows:
mIFNa2-Vκ dummy (lane 2)
mIFNa2-V_H dummy 2 (lane 3)
mIFNa2-DOM26h-161-84 (lane 4)
mIFNa2-DOM26h-196-61 (lane 5)
10 μl Novex Sharp prestained molecular weight standards (Invitrogen) were loaded in lane 1 and molecular masses (in kilodaltons) of individual marker bands are given to the left of lane 1. Gel was stained with 1x SureBlue. Gel illustrates that mouse IFNa2-dAb fusions migrate close to the expected molecular mass of approximately 33 KDa.

Figure 27 shows activity of mouse IFN-dAb fusions (+/- DOTA conjugation) in B16 mouse IFNα/β reporter cell line. B16 cells were incubated with the indicated concentrations of mouse IFN-alpha standard or mouse IFN-dAb fusion protein and interferon activity assayed by measuring the level of reporter gene expression which is directly proportional to absorbance measured at 640nm. Top panel shows results obtained with mouse IFNa2-V_H dummy 2 fusion protein, bottom panel shows results obtained with mouse IFNa2-DOM26h-196-61 fusion protein. Symbols denote the following:

▲= mouse IFNa2-dAb fusion

■= mouse IFNa2-dAb fusion conjugated to NHS:DOTA

⦸= mouse IFN-alpha standard

Figure 28 shows binding of mouse IFNa2-dAb fusions to biotinylated $(His)_6$-human ASGPR H1 lectin domain and $(His)_6$-mouse ASGPR H1 coated on the surface of a BIAcore streptavidin chip. Fusion proteins were passed over the chip surface at a concentration of 1μM and a flow rate of 40 $\mu l.min^{-1}$.

Top panel shows binding of mouse IFNa2-DOM36h-196-61 fusion protein (——) and mouse IFNa2- V_H dummy 2 fusion protein (_ _ _) to $(His)_6$-human ASGPR H1 lectin domain. Bottom panel shows binding of mouse IFNa2-DOM36h-196-61 fusion protein

(——) and mouse IFNa2- V_H dummy 2 fusion protein (_ _ _) to $(His)_6$-mouse ASGPR H1.

Figure 29 shows localisation of ^{111}In labelled mouse IFNa2-dAb fusions in balb/c mice at 3 hours post injection. Following intravenous dosing of 12 MBq of radiolabelled dAb via tail vein injection mice were imaged using a nanospect camera. Images show that at 3 hours signal is observed in liver, kidney and bladder with mouse IFNa2-V_H dummy 2 and mouse IFNa2-DOM26h-196-61 fusion proteins, however the liver appears brighter in the image in the right hand panel, indicating a greater level of liver uptake of mouse IFNa2-DOM26h-196-61 compared to mouse IFNa2-V_H dummy 2.

Figure 30 shows biodistribution of ^{111}In labelled mouse IFNa2-dAb fusion protein 3 hours after dosing intravenously in balb/c mice via the tail vein. Approximately 0.5MBq radiolabelled dAb was injected in each case. Results show both mouse IFNa2-DOM26h-196-61 (black bars) and mouse IFNa2-V_H dummy 2 (grey bars) accumulate in the liver and kidney, however the liver/kidney ratio of mouse IFNa2-DOM26h-196-61 is approximately 2.2 fold higher than that of mouse IFNa2-V_H dummy 2, indicative of successful liver targeting of mouse IFNa2 by genetic fusion to ASGPR dAb DOM26h-196-61.

Figures 31 and 32 show the amino acid (Seq ID No.s 868-880; even numbers only) and nucleotide (Seq ID No.s 867-879; odd numbers only) sequences respectively of the various affinity-matured DOM26h clones.

DETAILED DESCRIPTION OF THE INVENTION

Within this specification the invention has been described, with reference to embodiments, in a way which enables a clear and concise specification to be written. It is intended and should be appreciated that embodiments may be variously combined or separated without departing from the invention. For the avoidance of doubt, it is expressly stated that features of the invention disclosed herein in relation to one embodiment of the invention may be combined with any one or more other features of the invention disclosed in relation to other embodiments of the invention, unless the context dictates otherwise.

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art (e.g., in cell culture, molecular genetics, nucleic acid chemistry, hybridization techniques and biochemistry). Standard techniques are used for molecular, genetic and biochemical methods (see generally, Sambrook *et al.*, Molecular Cloning: A Laboratory Manual, 2d ed. (1989) Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y. and

Ausubel *et al.*, Short Protocols in Molecular Biology (1999) 4th Ed, John Wiley & Sons, Inc. which are incorporated herein by reference) and chemical methods.

The term "analogue" as used herein referring to a polypeptide means a modified peptide wherein one or more amino acid residues of the peptide have been substituted by other amino acid residues and/or wherein one or more amino acid residues have been deleted from the peptide and/or wherein one or more amino acid residues have been added to the peptide. Such addition or deletion of amino acid residues can take place at the N-terminal of the peptide and/or at the C-terminal of the peptide or they can be within the peptide.

The term ASGPR receptor as used herein refers to the Asialoglycoprotein receptor present on the surface of hepatocytes (see Meier et al., J. Mol. Biol., 2000, 300, pp 857-865), and more specifically to the H1 subunit thereof.

As used herein "fragment," when used in reference to a polypeptide, is a polypeptide having an amino acid sequence that is the same as part but not all of the amino acid sequence of the entire naturally occurring polypeptide. Fragments may be "free-standing" or comprised within a larger polypeptide of which they form a part or region as a single continuous region in a single larger polypeptide.

As used herein, “peptide” refers to about two to about 50 amino acids that are joined together via peptide bonds.

As used herein, “polypeptide” refers to at least about 50 amino acids that are joined together by peptide bonds. Polypeptides generally comprise tertiary structure and fold into functional domains.

As used herein, “display system” refers to a system in which a collection of polypeptides or peptides are accessible for selection based upon a desired characteristic, such as a physical, chemical or functional characteristic. The display system can be a suitable repertoire of polypeptides or peptides (*e.g.*, in a solution,

immobilized on a suitable support). The display system can also be a system that employs a cellular expression system (*e.g.*, expression of a library of nucleic acids in, *e.g.*, transformed, infected, transfected or transduced cells and display of the encoded polypeptides on the surface of the cells) or an acellular expression system (*e.g.*, emulsion compartmentalization and display). Exemplary display systems link the coding function of a nucleic acid and physical, chemical and/or functional characteristics of a polypeptide or peptide encoded by the nucleic acid. When such a display system is employed, polypeptides or peptides that have a desired physical, chemical and/or functional characteristic can be selected and a nucleic acid encoding the selected polypeptide or peptide can be readily isolated or recovered. A number of display systems that link the coding function of a nucleic acid and physical, chemical and/or functional characteristics of a polypeptide or peptide are known in the art, for example, bacteriophage display (phage display, for example phagemid display), ribosome display, emulsion compartmentalization and display, yeast display, puromycin display, bacterial display, display on plasmid, covalent display and the like. (See, *e.g.*, EP 0436597 (Dyax), U.S. Patent No. 6,172,197 (McCafferty *et al.*), U.S. Patent No. 6,489,103 (Griffiths *et al.*).)

As used herein, "functional" describes a polypeptide or peptide that has biological activity, such as specific binding activity. For example, the term "functional polypeptide" includes an antibody or antigen-binding fragment thereof that binds a target antigen through its antigen-binding site.

As used herein, "target ligand" refers to a ligand which is specifically or selectively bound by a polypeptide or peptide. For example, when a polypeptide is an antibody or antigen-binding fragment thereof, the target ligand can be any desired antigen or epitope. Binding to the target antigen is dependent upon the polypeptide or peptide being functional.

As used herein an antibody refers to IgG, IgM, IgA, IgD or IgE or a fragment (such as a Fab , $F(ab')_2$, Fv, disulphide linked Fv, scFv, closed conformation multispecific antibody, disulphide-linked scFv, diabody) whether derived from any

species naturally producing an antibody, or created by recombinant DNA technology; whether isolated from serum, B-cells, hybridomas, transfectomas, yeast or bacteria.

As used herein, "antibody format" refers to any suitable polypeptide structure in which one or more antibody variable domains can be incorporated so as to confer binding specificity for antigen on the structure. A variety of suitable antibody formats are known in the art, such as, chimeric antibodies, humanized antibodies, human antibodies, single chain antibodies, bispecific antibodies, antibody heavy chains, antibody light chains, homodimers and heterodimers of antibody heavy chains and/or light chains, antigen-binding fragments of any of the foregoing (*e.g.*, a Fv fragment (*e.g.*, single chain Fv (scFv), a disulfide bonded Fv), a Fab fragment, a Fab' fragment, a $F(ab')_2$ fragment), a single antibody variable domain (*e.g.*, a dAb, V_H, V_{HH}, $V_{L)}$, and modified versions of any of the foregoing (*e.g.*, modified by the covalent attachment of polyethylene glycol or other suitable polymer or a humanized V_{HH}).

The phrase "immunoglobulin single variable domain" refers to an antibody variable domain (V_H, V_{HH}, V_L) that specifically binds an antigen or epitope independently of other V regions or domains. An immunoglobulin single variable domain can be present in a format (*e.g.,* homo- or hetero-multimer) with other variable regions or variable domains where the other regions or domains are not required for antigen binding by the single immunoglobulin variable domain (*i.e.*, where the immunoglobulin single variable domain binds antigen independently of the additional variable domains). A "domain antibody" or "dAb" is the same as an "immunoglobulin single variable domain" as the term is used herein. A "single immunoglobulin variable domain" is the same as an "immunoglobulin single variable domain" as the term is used herein. A "single antibody variable domain" is the same as an "immunoglobulin single variable domain" as the term is used herein. An immunoglobulin single variable domain is in one embodiment a human antibody variable domain, but also includes single antibody variable domains from other species such as rodent (for example, as disclosed in WO 00/29004, the contents of which are incorporated herein by reference in their entirety), nurse shark and *Camelid* V_{HH} dAbs. Camelid V_{HH} are immunoglobulin single variable domain polypeptides that are derived from species including camel, llama, alpaca, dromedary, and guanaco,

which produce heavy chain antibodies naturally devoid of light chains. The V_{HH} may be humanized.

A "domain" is a folded protein structure which has tertiary structure independent of the rest of the protein. Generally, domains are responsible for discrete functional properties of proteins, and in many cases may be added, removed or transferred to other proteins without loss of function of the remainder of the protein and/or of the domain. A "single antibody variable domain" is a folded polypeptide domain comprising sequences characteristic of antibody variable domains. It therefore includes complete antibody variable domains and modified variable domains, for example, in which one or more loops have been replaced by sequences which are not characteristic of antibody variable domains, or antibody variable domains which have been truncated or comprise N- or C-terminal extensions, as well as folded fragments of variable domains which retain at least the binding activity and specificity of the full-length domain.

The term "library" refers to a mixture of heterogeneous polypeptides or nucleic acids. The library is composed of members, each of which has a single polypeptide or nucleic acid sequence. To this extent, "library" is synonymous with "repertoire." Sequence differences between library members are responsible for the diversity present in the library. The library may take the form of a simple mixture of polypeptides or nucleic acids, or may be in the form of organisms or cells, for example bacteria, viruses, animal or plant cells and the like, transformed with a library of nucleic acids. In one embodiment, each individual organism or cell contains only one or a limited number of library members. In one embodiment, the nucleic acids are incorporated into expression vectors, in order to allow expression of the polypeptides encoded by the nucleic acids. In an aspect, therefore, a library may take the form of a population of host organisms, each organism containing one or more copies of an expression vector containing a single member of the library in nucleic acid form which can be expressed to produce its corresponding polypeptide member. Thus, the population of host organisms has the potential to encode a large repertoire of diverse polypeptides.

As used herein, the term "dose" refers to the quantity of fusion or conjugate administered to a subject all at one time (unit dose), or in two or more administrations over a defined time interval. For example, dose can refer to the quantity of fusion or conjugate administered to a subject over the course of one day (24 hours) (daily dose), two days, one week, two weeks, three weeks or one or more months (*e.g.*, by a single administration, or by two or more administrations). The interval between doses can be any desired amount of time.

As used herein, "interferon activity" refers to a molecule which, as determined using the B16-Blue assay (Invivogen) performed as described herein (Example 12), has at least 10, 15, 20, 25, 30, 35, 40, 45 or even 50% of the amount of activity of an equal amount of recombinant mouse interferon alpha (e.g. from PBL Biomedical Laboratories).

The phrase, "half-life," refers to the time taken for the serum or plasma concentration of the fusion or conjugate to reduce by 50%, *in vivo*, for example due to degradation and/or clearance or sequestration by natural mechanisms. The compositions of the invention are stabilized *in vivo* and their half-life increased by binding to serum albumin molecules e.g. human serum albumin (HSA) which resist degradation and/or clearance or sequestration. These serum albumin molecules are naturally occurring proteins which themselves have a long half-life *in vivo*. The half-life of a molecule is increased if its functional activity persists, *in vivo*, for a longer period than a similar molecule which is not specific for the half-life increasing molecule.

As used herein, "hydrodynamic size" refers to the apparent size of a molecule (e.g., a protein molecule, ligand) based on the diffusion of the molecule through an aqueous solution. The diffusion, or motion of a protein through solution can be processed to derive an apparent size of the protein, where the size is given by the "Stokes radius" or "hydrodynamic radius" of the protein particle. The "hydrodynamic size" of a protein depends on both mass and shape (conformation), such that two

proteins having the same molecular mass may have differing hydrodynamic sizes based on the overall conformation of the protein.

Calculations of "homology" or "identity" or "similarity" between two sequences (the terms are used interchangeably herein) are performed as follows. The sequences are aligned for optimal comparison purposes (e.g., gaps can be introduced in one or both of a first and a second amino acid or nucleic acid sequence for optimal alignment and non-homologous sequences can be disregarded for comparison purposes). In an embodiment, the length of a reference sequence aligned for comparison purposes is at least 30%, or at least 40%, or at least 50%, or at least 60%, or at least 70%, 80%, 90%, 100% of the length of the reference sequence. The amino acid residues or nucleotides at corresponding amino acid positions or nucleotide positions are then compared. When a position in the first sequence is occupied by the same amino acid residue or nucleotide as the corresponding position in the second sequence, then the molecules are identical at that position (as used herein amino acid or nucleic acid "homology" is equivalent to amino acid or nucleic acid "identity"). The percent identity between the two sequences is a function of the number of identical positions shared by the sequences, taking into account the number of gaps, and the length of each gap, which need to be introduced for optimal alignment of the two sequences. Amino acid and nucleotide sequence alignments and homology, similarity or identity, as defined herein may be prepared and determined using the algorithm BLAST 2 Sequences, using default parameters (Tatusova, T. A. *et al.*, *FEMS Microbiol Lett*, *174*:187-188 (1999).

NUCLEIC ACIDS, HOST CELLS :

The invention relates to isolated and/or recombinant nucleic acids encoding the compositions of the invention that are described herein.

Nucleic acids referred to herein as "isolated" are nucleic acids which have been separated away from other material (*e.g.*, other nucleic acids such as genomic DNA, cDNA and/or RNA) in its original environment (*e.g.*, in cells or in a mixture of

nucleic acids such as a library). An isolated nucleic acid can be isolated as part of a vector (*e.g.*, a plasmid).

Nucleic acids referred to herein as "recombinant" are nucleic acids which have been produced by recombinant DNA methodology, including methods which rely upon artificial recombination, such as cloning into a vector or chromosome using, for example, restriction enzymes, homologous recombination, viruses and the like, and nucleic acids prepared using the polymerase chain reaction (PCR).

The invention also relates to a recombinant host cell e.g. mammalian or microbial, which comprises a (one or more) recombinant nucleic acid or expression construct comprising nucleic acid(s) encoding a composition e.g. fusion, of the invention as described herein. There is also provided a method of preparing a composition, e.g. fusion, of the invention as described herein, comprising maintaining a recombinant host cell e.g.mammalian or microbial, of the invention under conditions appropriate for expression of the fusion polypeptide. The method can further comprise the step of isolating or recovering the fusion, if desired.

For example, a nucleic acid molecule (*i.e.*, one or more nucleic acid molecules) encoding a composition of the invention e.g. a liver targeting composition of the invention, or an expression construct (*i.e.*, one or more constructs) comprising such nucleic acid molecule(s), can be introduced into a suitable host cell to create a recombinant host cell using any method appropriate to the host cell selected (*e.g.*, transformation, transfection, electroporation, infection), such that the nucleic acid molecule(s) are operably linked to one or more expression control elements (*e.g.*, in a vector, in a construct created by processes in the cell, integrated into the host cell genome). The resulting recombinant host cell can be maintained under conditions suitable for expression (*e.g.*, in the presence of an inducer, in a suitable non-human animal, in suitable culture media supplemented with appropriate salts, growth factors, antibiotics, nutritional supplements, etc.), whereby the encoded peptide or polypeptide is produced. If desired, the encoded peptide or polypeptide can be isolated or recovered (*e.g.*, from the animal, the host cell, medium, milk). This process

encompasses expression in a host cell of a transgenic animal (see, *e.g.*, WO 92/03918, GenPharm International), especially a transgenic non-human animal.

The compositions, e.g. fusion polypeptides, of the invention described herein can also be produced in a suitable *in vitro* expression system, e.g. by chemical synthesis or by any other suitable method.

As described and exemplified herein, compositions e.g. fusions and conjugates of the invention, generally bind ASGPR with high affinity.

For example, the fusions or conjugates can bind human ASGPR with an affinity (KD; KD=K_{off} (kd)/K_{on} (ka) [as determined by surface plasmon resonance] of about 5 micromolar to about 1 pM , e.g. about 10 nM to about 1 pM e.g. about 1nM to about 1pM.

The compositions e.g. dAbs and/or liver targeting compositions, of the invention can be expressed in *E. coli* or in *Pichia* species (e.g., *P. pastoris*). In one embodiment, the a liver targeting fusion is secreted in *E. coli* or in *Pichia* species (e.g., *P. pastoris*); or in mammalian cell culture (e.g. CHO, or HEK 293 cells). Although, the fusions or conjugates described herein can be secretable when expressed in *E. coli* or in *Pichia* species or mammalian cells they can be produced using any suitable method, such as synthetic chemical methods or biological production methods that do not employ *E. coli* or *Pichia* species.

Generally, the compositions of the invention will be utilised in purified form together with pharmacologically or physiologically appropriate carriers. Typically, these carriers can include aqueous or alcoholic/aqueous solutions, emulsions or suspensions, any including saline and/or buffered media. Parenteral vehicles can include sodium chloride solution, Ringer's dextrose, dextrose and sodium chloride and lactated Ringer's. Suitable physiologically-acceptable adjuvants, if necessary to keep a polypeptide complex in suspension, may be chosen from thickeners such as carboxymethylcellulose, polyvinylpyrrolidone, gelatin and alginates.

Intravenous vehicles include fluid and nutrient replenishers and electrolyte replenishers, such as those based on Ringer's dextrose. Preservatives and other additives, such as antimicrobials, antioxidants, chelating agents and inert gases, may also be present (Mack (1982) *Remington's Pharmaceutical Sciences*, 16th Edition). A variety of suitable formulations can be used, including extended release formulations.

The route of administration of pharmaceutical compositions according to the invention may be any of those commonly known to those of ordinary skill in the art. For therapy, compositions of the invention can be administered to any patient in accordance with standard techniques.

The administration can be by any appropriate mode, including by subcutaneous injection, parenterally, intravenously, intramuscularly, intraperitoneally, orally, transdermally, *via* the pulmonary route, or also, appropriately, by direct infusion with a catheter. The dosage and frequency of administration will depend on the age, sex and condition of the patient, concurrent administration of other drugs, counterindications and other parameters to be taken into account by the clinician. Administration can be local or systemic as indicated.

The compositions of this invention can be lyophilised for storage and reconstituted in a suitable carrier prior to use. This technique has been shown to be effective with conventional immunoglobulins and art-known lyophilisation and reconstitution techniques can be employed. It will be appreciated by those skilled in the art that lyophilisation and reconstitution can lead to varying degrees of antibody activity loss (e.g. with conventional immunoglobulins, IgM antibodies tend to have greater activity loss than IgG antibodies) and that use levels may have to be adjusted upward to compensate.

Treatment or therapy performed using the compositions described herein is considered “effective” if one or more symptoms or signs are reduced or alleviated (e.g., by at least 10% or at least one point on a clinical assessment scale), relative to such symptoms present before treatment, or relative to such symptoms in an

individual (human or model animal) not treated with such composition or other suitable control. Symptoms will obviously vary depending upon the precise nature of the disease or disorder targeted, but can be measured by an ordinarily skilled clinician or technician.

Similarly, prophylaxis performed using a composition as described herein is "effective" if the onset or severity of one or more symptoms or signs is delayed, reduced or abolished relative to such symptoms in a similar individual (human or animal model) not treated with the composition.

The compositions of the present invention may be administered in conjunction with other therapeutic or active agents e.g. other polypeptides or peptides or small molecules. These further agents can include various drugs, such as for example ribavirin.

The compositions of the invention can be administered and/ or formulated together with one or more additional therapeutic or active agents. When a composition of the invention is administered with an additional therapeutic agent, e.g. the liver targeting composition (e.g. a fusion or conjugate) can be administered before, simultaneously, with, or subsequent to administration of the additional agent e.g. ribavirin. Generally, the composition of the invention and the additional agent are administered in a manner that provides an overlap of therapeutic effect.

Compositions of the invention comprising dAbs, provide several further advantages. The Domain antibody component is very stable, is small relative to antibodies and other antigen-binding fragments of antibodies, can be produced in high yields by expression in *E. coli* or yeast (*e.g.*, *Pichia pastoris*). Accordingly, compositions of the invention that comprise the dAb that binds hepatocytes (e.g. the ASGPR receptor on hepatocytes) can be produced more easily than therapeutics that are generally produced in mammalian cells (*e.g.*, human, humanized or chimeric antibodies) and dAbs that are not immunogenic can be used (*e.g.*, a human dAb can be used for treating or diagnosing disease in humans).

Additionally, the compositions described herein can have an enhanced safety profile and fewer side effects than the therapeutic molecule(s) e.g. interferon alone alone as a result of the specific targeting to the liver. Similarly, administration of the compositions of the invention can have reduced toxicity toward particular organs and/or bodily tissues outside of the liver than administration of the therapeutic molecule(s) alone and can also have improved efficacy e.g. as a result of specifically directing the therapeutic molecule to the liver at effective doses for systemic delivery, when administration of such molecules might otherwise be toxic to other organs and tissues

EXAMPLES:

Example 1: Cloning and Expression of Human and Mouse Asialoglycoprotein H1 Receptor Subunits

Full length human and mouse asialoglycoprotein receptor H1 subunit (ASGPR H1) cDNA was custom synthesised by DNA2.0 (Mealo Park CA, USA). DNA encoding the extracellular domain (Q62-L291 for human and S60-N284 for mouse) with an N-terminal $(His)_6$ tag was amplified by PCR using primers DLT007 and DLT008 (human) or DLT009 and DLT010 (mouse). Sequences are shown in Table 1 below.

Table 1:

DLT007	GGATCCACCGGCCATCATCATCATCATCACCAGAACTCCC AACTCCAGGAA (Seq ID No.1)	Human $(His)_6$ ASGPR H1 5' primer
DLT008	AAGCTTTTATTACAGGAGTGGAGGCTCTTGTGA (Seq ID No. 2)	Human $(His)_6$ ASGPR H1 3' primer
DLT009	GGATCCACCGGCCATCATCATCATCATCACAGTCAAAATT CCCAATTGCGC (Seq ID No. 3)	Mouse $(His)_6$ ASGPR H1 5' primer
DLT010	AAGCTTTTATTAATTGGCTTTGTCCAGCTTTGT (Seq ID No. 4)	Mouse $(His)_6$ ASGPR H1 3' primer

PCR fragments were inserted into holding vector pCR-Zero Blunt (Invitrogen) by Topoisomerase cloning and sequenced to obtain error-free clones using M13 forward and M13 reverse primers. $(His)_6$-ASGPR H1 encoding DNA was obtained by gel purification following BamHI/HindIII digestion of pCR-Zero Blunt containing the insert and inserts ligated into the corresponding sites in pDOM50, a mammalian expression vector which is a pTT5 derivative with an N-terminal V-J2-C mouse IgG secretory leader sequence to facilitate expression into the cell media.

Leader sequence (amino acid):

METDTLLLWVLLLWVPGSTG (Seq ID No. 5)

Leader sequence (nucleotide):
ATGGAGACCGACACCCTGCTGCTGTGGGTGCTGCTGCTGTGGGTGCCCGG ATCCACCGGGC (Seq ID No. 6)

Plasmid DNA was prepared using QIAfilter megaprep (Qiagen). 1μg DNA/ml was transfected with 293-Fectin into HEK293E cells and grown in serum free media. The protein is expressed in culture for 5 days and purified from culture supernatant using Ni-NTA resin and eluted with PBS + 0.5M Imidazole. The proteins were buffer exchanged into PBS.
N-termini of the receptor subunits were determined by Edman sequencing. The N-terminus of the Human $(His)_6$-ASGPR H1 subunit was identified as: HHHHHHQNSQLQEEL (Seq ID No. 7) with an additional sequence identified as: LRGLREFTS (Seq ID No. 8) corresponding to a cleavage product. However the sequence corresponding to the intact receptor was present in an approximately 5 fold molar excess compared to that of the cleavage product. The N-terminus of Mouse $(His)_6$-ASGPR H1 subunit was identified as: HHHHHHSQNXQLRED (Seq ID No. 9) with no additional sequences identified.
To assay for potential ligand binding activity receptor subunits were immobilised on a biacore CM5 chip surface and binding to the synthetic ligand β-GalNAc-PAA-biotin (Glycotech) was analysed (Figure 1). Purity of HEK293E receptor eluted from Ni-NTA was also analysed by non-reducing SDS-PAGE (Figure 2). SDS-PAGE analysis

shows that human and mouse $(His)_6$-ASGPR H1 subunits migrate close to the expected molecular mass based on amino acid sequence (27.2 KDa for human and 26.5 KDa for mouse. More than one species migrating close to the expected molecular mass was observed in both human and mouse $(His)_6$-ASGPR H1 samples, typical of glycosylated protein samples.

Sequences:

$(His)_6$- Human ASGPR H1

HHHHHHQNSQLQEELRGLRETFSNFTASTEAQVKGLSTQGGNVGRKMKSLE
SQLEKQQKDLSEDHSSLLLHVKQFVSDLRSLSCQMAALQGNGSERTCCPVN
WVEHERSCYWFSRSGKAWADADNYCRLEDAHLVVVTSWEEQKFVQHHIGP
VNTWMGLHDQNGPWKWVDGTDYETGFKNWRPEQPDDWYGHGLGGGEDC
AHFTDDGRWNDDVCQRPYRWVCETELDKASQEPPLL (Seq ID No. 10)

CATCATCATCATCATCACCAGAACTCCCAACTCCAGGAAGAACTTCGAGG
ACTGAGGGAGACTTTCTCCAATTTCACCGCAAGCACGGAGGCTCAAGTGA
AGGGCCTCAGCACCCAGGGCGGGAATGTGGGCAGGAAAATGAAATCCCT
GGAGAGCCAGCTCGAAAAGCAGCAGAAAGATCTGTCCGAGGACCACTCT
AGCCTGTTGTTGCACGTGAAACAGTTTGTTTCCGACCTTAGGAGTCTTTCT
TGCCAAATGGCCGCCCTCCAGGGAAACGGGTCCGAGAGAACTTGCTGCCC
CGTCAATTGGGTGGAGCACGAGCGGTCTTGTTATTGGTTTAGCCGAAGCG
GAAAAGCCTGGGCCGATGCAGATAACTACTGCCGGCTTGAGGACGCCCAT
CTGGTCGTGGTGACCAGTTGGGAGGAACAGAAATTCGTACAGCATCATAT
CGGGCCTGTTAACACATGGATGGGCCTTCATGACCAGAATGGTCCTTGGA
AGTGGGTTGACGGAACCGATTACGAAACCGGATTCAAGAACTGGCGGCCT
GAACAGCCAGACGACTGGTATGGACACGGCCTCGGAGGCGGGGAGGACT
GCGCGCATTTCACAGACGATGGCCGGTGGAATGATGATGTGTGCCAAAGG
CCTTACAGATGGGTCTGCGAGACAGAGCTGGATAAGGCTTCACAAGAGCC
TCCACTCCTG (Seq ID No. 11)

$(His)_6$- Mouse ASGPR H1

HHHHHHSQNSQLREDLLALRQNFSNLTVSTEDQVKALSTQGSSVGRKMKLV
ESKLEKQQKDLTEDHSSLLLHVKQLVSDVRSLSCQMAAFRGNGSERTCCPIN
WVEYEGSCYWFSSSVRPWTEADKYCQLENAHLVVVTSRDEQNFLQRHMGP
LNTWIGLTDQNGPWKWVDGTDYETGFQNWRPEQPDNWYGHGLGGGEDCA
HFTTDGRWNDDVCRRPYRWVCETKLDKAN (Seq ID No. 12)

CATCATCATCATCATCACAGTCAAAATTCCCAATTGCGCGAGGATCTGCTC
GCACTGCGACAGAACTTTAGCAACCTTACCGTGTCTACGGAAGACCAGGT
GAAGGCATTGTCAACTCAGGGGTCATCTGTGGGAAGAAAAATGAAGCTCG
TGGAGTCAAAGCTGGAGAAGCAGCAAAAGGACCTCACCGAAGACCATTC
CTCTCTCCTGCTGCACGTGAAGCAGCTGGTTTCTGACGTAAGGAGCCTGAG
CTGCCAGATGGCTGCTTTTCGAGGTAACGGCTCTGAGCGCACATGCTGTCC
TATTAATTGGGTGGAGTATGAGGGAAGTTGTTACTGGTTCTCAAGCTCCGT
GAGGCCATGGACCGAAGCTGACAAATATTGCCAGCTCGAAAATGCTCACC
TCGTGGTAGTGACCTCTAGGGATGAGCAAAATTTCCTGCAGCGACACATG
GGGCCGCTTAATACCTGGATCGGGCTGACGGACCAGAACGGACCCTGGAA
GTGGGTTGACGGTACCGATTATGAAACTGGATTCCAAAACTGGCGGCCAG
AGCAGCCGGACAACTGGTATGGCCACGGCCTCGGAGGGGGCGAGGACTG
TGCTCATTTTACAACGGATGGCCGGTGGAACGACGATGTGTGCAGAAGGC
CATATCGGTGGGTCTGCGAGACAAAGCTGGACAAAGCCAAT (Seq ID No.
13)

EXAMPLE 2-Methods for Selecting dAbs

Domantis' 4G and 6G naïve phage libraries, phage libraries displaying antibody single variable domains expressed from the GAS1 leader sequence (see WO2005/093074) for 4G and additionally with heat/cool preselection for 6G (see WO04/101790) were divided into four pools; pool 1 contained libraries 4VH11-13 and 6VH2, pool 2 contained libraries 4VH14-16 and 6VH3, pool 3 contained libraries 4VH17-19 and 6VH4 and pool 4 contained libraries 4K and 6K. Library aliquots were of sufficient size to allow 10-fold over representation of each library. Selections were carried out using passively coated and biotinylated human and mouse $(His)_6$-ASGPR H1 antigens. Selections using passively coated antigen were carried out as follows. After coating antigen on immunotubes (Nunc) in TBS supplemented with 5mM $Ca2^+$

(TBS/Ca^{2+}) tubes were blocked with 2% Marvel in TBS/Ca^{2+} (MTBS/Ca^{2+}). Library aliquots were incubated with antigen-coated immunotubes in MTBS/Ca^{2+} before washing tubes with TBS/Ca^{2+}. Bound phage was then eluted with 1mg/ml Trypsin. The concentration of antigen during coating was decreased from 1mg/ml to 40μg/ml as the rounds progressed and the titres increased as the rounds progressed.
Selections using biotinylated antigen were carried out as follows. Library aliquots were incubated with antigen in MTBS/Ca^{2+} for one hour before capture on streptavidin Dynabeads (Invitrogen) or Tosyl activated beads (Invitrogen) coated with neutravidin (Perbio), washed with 0.1% Tween-TBS/Ca^{2+} and TBS/Ca^{2+} then eluted with 1mg/ml Trypsin. The concentrations of antigen were decreased from 100nM to 1nM as the rounds progressed and the titres increased as the rounds progressed.
Following both types of selection eluted phage was used to infect log phase TG1 cells (Gibson, 1984) then infected cells were plated on tetracycline plates (15μg/ml tetracycline). Cells infected with the phage were then grown up in 2xTY with tetracycline overnight at 37°C before the phage were precipitated from the culture supernatant using PEG-NaCl and used for subsequent rounds of selection.

EXAMPLE 3-Screening Selection Outputs for Liver Cell Specific dAbs

After 3 rounds of selection, the dAb genes from each library pool were subcloned from the pDOM4 phage vector into the pDOM10 soluble expression vector. pDOM4 is a derivative of the fd phage vector in which the gene III signal peptide sequence is replaced with the yeast glycolipid anchored surface protein (GAS) signal peptide. It also contains a c-Myc tag between the leader sequence and gene III. In each case after selection a pool of phage DNA from appropriate round of selection is prepared using a QIAfilter midiprep kit (Qiagen), the DNA is digested using the restriction enzymes Sal1 and Not1 and the enriched dAb genes are ligated into the corresponding sites in pDOM10.
The pDOM10 vector is a pUC119-based vector. Expression of proteins is driven by the LacZ promoter. A GAS1 leader sequence (see WO 2005/093074) ensures secretion of isolated, soluble dAbs into the periplasm and culture supernatant of E. coli. dAbs are cloned SalI/NotI in this vector, which appends a FLAG epitope tag at the C-terminus of the dAb.

The ligated DNA is used to transform E. coli TOP10 cells which are then grown overnight on agar plates containing the antibiotic carbenicillin. The resulting colonies are individually assessed for antigen binding.

The antigen binding of individual dAb clones was assessed either by ELISA or on BIAcore. The ELISA assay took the following format. Human or mouse $(His)_6$-ASGPR H1 was coated at 1μg/ml onto a Maxisorp (NUNC) plate overnight at 4°C. The plate was then blocked with 2% Tween-TBS/Ca^{2+}, followed by incubation with dAb supernatant diluted 1:1 with 0.1% Tween-TBS/Ca^{2+}, followed by detection with 1:5000 anti-flag (M2)-HRP (SIGMA). All steps after blocking were carried out at room temperature. The binding of the dAb supernatant to a control antigen (human c-kit-$(His)_6$) was also analysed at the same time. In some cases dAb supernatants from selections using human antigen were also screened for binding to HepG2 and HeLa cells using the meso scale discovery (MSD) assay. Cells were plated using MULTI-ARRAY 96-well, SECTOR Imager High Bind Plates (Meso-scale) at a density of $1x10^5$ cells per well and left to incubate overnight at 37°C, 5% CO_2. The following day dAb anti-FLAG M2 complexes were prepared at 2x final concentration by dilution of dAb and biotinylated anti FLAG M2 monoclonal antibody (Sigma) in MSD assay buffer (1xPBS with 1mM $MgCl_2$, 1mM $CaCl_2$, 10% Foetal Bovine Serum and1% BSA). dAb-anti FLAG complexes were incubated in a 1:1 molar ratio at room temperature for one hour. Cells were then washed 3x with 200μl PBS before addition of 25μl per well dAb-anti FLAG complex and incubation for one hour at room temperature for one hour with gentle agitation. Cells were then washed as above and 25μl per well streptavidin-Sulfotag (Meso-scale) diluted to 1μg/ml in assay buffer was then added. Cells were then incubated for one hour at room temperature, in the dark with gentle agitiation. Cells were then washed as above before resuspension in 150μl per well of 1x MSD read buffer without surfactant (Meso-scale) and read on a SECTOR Imager 6000 (Meso-scale) at 620nm emission. Clones DOM26h-25, DOM26h-34, DOM26h-161, DOM26h-162, DOM26h-163, DOM26h-164, DOM26h-165, DOM26h-166 and DOM26h-167 and DOM26h-168 through to DOM26h-224 were screened in this assay.

Those dAbs that showed specific binding to $(His)_6$ ASGPR H1 by ELISA or MSD assay were screened by BIAcore. Screening by BIAcore took place using dAb supernatant expressed as above diluted 1:2 with HBS-P BIAcore running buffer. Each dAb was then injected over a blank flow cell and a flow cell coated with human or mouse $(His)_6$-ASGPR H1 on a CM5 chip. Any dAb clone that showed specific binding to $(His)_6$-ASGPR H1 was streaked out and sequenced.
All unique dAb clones were expressed in 50ml cultures (OnEX plus carbenicillin) overnight at 37°C and purified on protein A (V_H dAbs) or protein L (Vκ dAbs). Purified dAbs were passed over a CM5 BIAcore chip coated with either human or mouse $(His)_6$-ASGPR H1 at 20µg/ml (Figure 3). Those dAbs that bound specifically to $(His)_6$-ASGPR H1 were then analysed in the flow cytometry cell binding assay (Figure 4).

Two cell lines were used as human ASGPR positive lines (HepG2 and Hep3b) and one as a negative control human line (HeLa). Two cell lines were used as mouse ASGPR positive cell lines (Hepa1c1c7 and NMuLi) and one as a negative control mouse line (L929). The flow cytometry cell binding assay was carried out as follows. Cells were harvested, and washed in PBS supplemented with 5% FCS and 0.5% BSA (FACS buffer). Cells were divided between the appropriate number of wells at a concentration of 1×10^5 cells per well and incubated for one hour at 4°C. The cells were then incubated for one hour with the appropriate concentration of dAb which had previously been cross-linked by incubation with 5µg/ml anti-FLAG M2 (Sigma) for 30minutes at 4°C. The cells were then washed with FACS buffer and incubated for one hour at 4°C with Goat anti-mouse FITC (Sigma) diluted 1:100 in FACS buffer. The cells were then washed with FACs buffer and resuspended in 200µl FACS buffer before analysis by flow cytometry (FACS Canto II, using FACS Diva software). CDR sequences (determined using the method of Kabat) of clones specific for the human liver cell line HepG2 are described in the Table 2 below:

Table 2:

dAb	CDR1	CDR2	CDR3
DOM26h-25	RASGDIGHALW	RGGSALQS	GQSHVRPFT

DOM26h-34	QASKNIGERLV	GFASLLQS	GQYRWVPAT
DOM26h-61	STYPMH	SISPSGDS	NALRFDY
DOM26h-99	KPYAMH	SISSTGLS	DASRFRQPFDY
DOM26h-104	PKYGMA	RIGATGSE	HRGTAHSSFFDY
DOM26h-110	SANGMH	VISATGDQ	GYDRRHRKFDY
DOM26h-159	ADYSMY	DISPSGSM	GLPGQNMHVGFDY
DOM26h-161	RASQAIGRWLL	YAASRLQS	QQAYSLPPT
DOM26h-162	RASMSIDESLW	RGGSGLQS	GQAARRPYT
DOM26h-163	RASHYIGNELW	RRGSGLQS	GQARHRPYT
DOM26h-164	RASSNIGRSLV	AGGSLLQS	GQYAEEPFT
DOM26h-166	RASSYIGGELW	SGTSGLQS	GQAAKRPFT
DOM26h-165	RASVKIGERLW	RDASLLQS	GQSWMRPYT
DOM26h-167	RASSWINSDLV	AGGSLLQS	GQYLEEPYT
Seq ID No.s	14-27	28-41	42-55

CDR sequences (determined using the method of Kabat) of clones specific for the mouse liver cell line Hepa1c1c7 are described in the Table 3 below:

Table 3:

dAb	**CDR1**	**CDR2**	**CDR3**
DOM26m-7	DDYEMG	LISAQGRV	NSPSYLLNFDY
DOM26m-20	RASKYIGSDLY	GGGSRLQS	GQKWARPLT
DOM26m-29	EDSGMI	GIASEGST	SGLSFDY
DOM26m-33	AKYDMI	GINHSGSR	SGSSFDY
DOM26m-50	RASISIYEHLN	WDSSGLQS	VQHHSHPPT
DOM26m-52	REHPMS	SISKHGSE	SVREFDY
DOM26m-54	RASLNIDTDLV	AGWSGLQS	GQFAREPFT
DOM26m-58	RASQPIRNALT	YRTSHLQS	QQTWTMPLT
Seq ID No.s	56-63	64-71	72-79

Lead dAbs were analysed by size exclusion chromatography with multi-angle LASER light scattering (SEC-MALLS) to determine whether they were monomeric or formed higher order oligomers in solution. SEC-MALLS was carried out as follows. Proteins (at a concentration of 1mg/mL in Dulbecco's PBS or 0.1M Tris-Glycine, pH 8.0) were separated according to their hydrodynamic properties by size exclusion chromatography (column: TSK3000; S200). Following separation, the propensity of the protein to scatter light is measured using a multi-angle LASER light scattering (MALLS) detector. The intensity of the scattered light while protein passes through

the detector is measured as a function of angle. This measurement taken together with the protein concentration determined using the refractive index (RI) detector allows calculation of the molar mass using appropriate equations (integral part of the analysis software Astra v.5.3.4.12). Results are shown in Table 4 below.

Table 4:

Name	**Mean Molar mass over main peak**	**In-solution state**
DOM26m-7	14.5 kDa 28 kDa 49kDa	monomer (65%) dimer (25%) tetramer (10%)
DOM26m-20	13 kDa	monomer (100%)
***DOM26m-29**	? kDa 42 kDa	monomer/dimer (80%) trimer/tetramer (20%
DOM26m-33	15.6 kDa	monomer (90%)
DOM26m-50	12kDa	monomer (100%)
DOM26m-52	29 kDa	dimer (70%)
DOM26m-54	Not determined (protein failed to elute)	Not determined (protein failed to elute)
DOM26m-58	14 kDa	monomer (100%)

DOM26h-25	13.8 kDa	Monomer
DOM26h-34	12.6 kDa	Monomer
DOM26h-61	31 kDa 41 kDa 100kDa HMWS	dimer (45%) tri/tetramer (35%) octamer (10%) soluble aggregate (5%)
DOM26h-99	22.2 kDa 7 kDa	dimer (95%) contaminant(5%)
DOM26h-104	17 kDa	monomer/dimer (80%)
DOM26h-110	20 kDa	monomer/dimer (90%)
DOM26h-159	17.7 kDa	monomer/dimer (90%)
DOM26h-161	12.6 kDa	Monomer
DOM26h-162	12.3 kDa	Monomer
DOM26h-163	18 kDa	monomer/dimmer
DOM26h-164	17 kDa	monomer
DOM26h-165	13.2 kDa	Monomer
DOM26h-166	12.6 kDa	Monomer
DOM26h-167	18 kDa	Monomer

*= main peak elutes at the buffer front, hence no Mw determination was possible

Lead dAbs were also analysed by differential scanning calorimetry (DSC) to determine the apparent melting temperature. DSC was carried out as follows. Protein was heated at a constant rate of 180°C/hrs (at 1mg/mL in PBS) and a detectable heat change associated with thermal denaturation measured. The transition midpoint (appTm) is determined, which is described as the temperature where 50% of the protein is in its native conformation and the other 50% is denatured. Here, DSC determined the apparent transition midpoint (appTm) as most of the proteins examined do not fully refold. The higher the Tm, the more stable the molecule. The software package used was OriginR v7.0383. Results are shown in Table 5 below.

Table 5:

Name	App Tm 1 /°C	App Tm 2 /°C
DOM26m-7	62.0	63.7
DOM26m-20	63.3	63.2
DOM26m-29	61.4	-
DOM26m-33	60.9	60.8
DOM26m-50	72.4	-
DOM26m-52	61.0	64.9
DOM26m-54	62.2	62.2
DOM26m-58	62.9	62.7
DOM26h-25	60.5	61.7
DOM26h-34	57.1	60.2
DOM26h-61	61.7	66.6
DOM26h-99	57.0	60.0
DOM26h-104	60.0	64.0
DOM26h-110	57.8	59.6
DOM26h-159	62.7	65.4
DOM26h-161	64.9	-
DOM26h-162	58.2	67.2
DOM26h-163	58.2	66.6
DOM26h-164	55.1	73.3
DOM26h-165	64.3	-

DOM26h-166	62.7	-
DOM26h-167	63.4	-

In some cases App Tm 2 could not be determined due to insufficient refolding of protein after determination of App Tm 1 (DOM26m-29, DOM26m-50 and DOM26h-161 for example) or because the molecule unfolds via a single transition (as in the case of DOM26h-161, DOM26h-165, DOM26h-166 and DOM26h-167).

EXAMPLE 4- Analysis of ASGPR-Specific dAb Binding to Murine Liver Cell Lines by Immunofluorescence Confocal Microscopy

In order to study cell surface binding, internalisation and intracellular localisation of ASGPR specific dAbs confocal microscopy assays were developed. Briefly, cells were grown on glass chamber slides and incubated with 5μM ASGPR specific dAbs with a c-terminal FLAG epitope tag at 37°C for 45 minutes. Cells were then fixed with 2% formaldehyde at room temperature for 10 minutes. Following washing with 5%FCS/PBS the cells were then co-stained with and either a rabbit polyclonal antibody specific to early endosomal antigen 1 (EEA1) as an early endosomal marker or rabbit polyclonal specific to lysosomal associated membrane protein 1 (LAMP1) as a lysosomal marker. The antibodies were diluted in 5%FCS/PBS including Saponin at a final concentration of 0.2% and incubated at room temperature for 1 hour with the cells. Following washing steps, the dAbs and polyclonal antibodies were detected using an anti-FLAG M2-Cy3 conjugated monoclonal and anti-rabbit Alexa Fluor 488 antibody respectively. The cells were also co-stained with 4',6-diamidino-2-phenylindole (DAPI) as a marker for DNA. The cells were prepared for imaging and visualised using confocal microscopy.

The results showed that the murine ASGPR specific dAb clone DOM26m-33 bound to the murine liver cell line Hepa1c1c7 and was internalised into early endosomes, as shown by partial co localisation of anti-FLAG and anti-EEA1 staining (Figure 5). However, the staining pattern was predominantly cell surface indicating that no significant internalisation is occurring. Under no circumstances was co localisation of anti-FLAG and LAMP1 staining observed, therefore it seems likely that ASGPR specific dAb clone DOM26m-33 is not targeted for degradation in the lysosome.

No staining of L929 murine fibroblast negative control cells with DOM26m-33 was observed, demonstrating that the staining pattern observed with this dAb in experiments with the Hepa1c1c7 line was liver cell specific. Similarly no staining of Hepa1c1c7 with VH germline sequence VHD2 was observed.

EXAMPLE 5- Epitope Mapping by Surface Plasmon Resonance

After coating a BIAcore CM5 chip with $(His)_6$ mouse ASGPR H1, protein A or protein L purified dAb proteins were injected one after the other and in combination over the same antigen surface. The resulting binding RUs were determined in order to see whether the maximal binding capacity of the chip by one dAb molecule can be exceeded by simultaneously injecting a second dAb onto the same antigen surface. If so, the second dAb clearly binds a different epitope compared to the first one. 1μM concentrations of each dAb were injected at a flow rate of 10 μl per second, both in single injection and co-injection experiments. If injection of the second dAb in the presence of the first dAb reduced the observed binding to the chip surface by greater than 20% (in comparison to observed binding of the second dAb to the chip surface in the absence of the first dAb) both dAbs were assumed to bind overlapping epitopes within the antigen (Figure 6). Based on results obtained in these experiments murine ASGPR specific dAb clones could be grouped according to epitopes bound within the antigen as shown in Figure 12.

Epitope mapping by BIAcore shows that several distinct epitopes within the $(His)_6$ mouse ASGPR H1 antigen are bound by these 8 clones. Epitope mapping data also show that Vκ and V_H clones bind to overlapping epitopes in some cases, therefore all 8 clones were used to generate further libraries for affinity maturation.

EXAMPLE 6- Binding of ASPGR Specific dAbs to Murine Liver *In Vivo*

Anti-mouse ASGPR dAb DOM26m-33 and Vκ dummy/V_H dummy 2 germline control dAbs were used to generate point mutations such that the arginine residue at the C-terminus of Vκ clones and the serine residue at the C-terminus of V_H clones was mutated to cysteine. Therefore Vκ dummy carried the point mutation R108C, V_H dummy 2 carried the point mutation S127C and DOM26m-33 carried the point

mutation S116C. dAbs were amplified from pDOM10 by PCR using primers DOM008 and PBS-ECVH2 for V_H dAbs and primers DOM008 and PBS-ECVK2 for Vκ clones. Oligonucleotide sequences are shown in Table 6 below.

Table 6:

DOM008	AGCGGATAAC AATTTCACAC AGGA (Seq ID No. 80)	PUC reverse primer sequence complementary to region of pDOM10 vector upstream of leader and dAb sequence. Adds a SalI site for cloning into pDOM10.
PBS-ECVH2	CTAGCGTTGGCTTTGCGGCCGCGGATCCTTA TTAGCACGAGACGGTGAC (Seq ID No. 81)	3' reverse primer for VH domains. Changes terminal serine to a cysteine. Also adds a NotI site for cloning into pDOM10.
PBS-ECVK2	AGCCGGATCCGCGGCCGCTTATTAGCATTTG ATTTCCACCTTGGTCCC (Seq ID No. 82)	3' reverse primer for V_κ domains. Changes terminal arginine to cysteine. Also adds a NotI site for cloning into pDOM10.

dAb inserts were then digested with SalI and NotI restriction enzymes and cloned into the corresponding sites in pDOM10. dAbs were expressed in 500ml cultures (OnEX plus carbenicillin) for 3 days at 30°C and purified on protein A (V_H dAbs) or protein L (Vκ dAbs). dAbs were then conjugated with DOTA-Maleimide and labeled with ^{111}In. Briefly, dAb solution (and all buffers used in the conjugation method) was passed through Chelex 100 resin to remove cations. Chelex treated dAb solution was then reduced by addition of 0.5M TCEP, 1% (v/v). After 30 minutes reducing agent was removed by size exclusion chromatography using a PD10 column. Conjugation was carried out overnight at room temperature by addition of 30 fold molar excess of DOTA-Maleimide dissoloved in 25 mM HEPES, pH 7. DOTA-Maleimide conjugated dAb was purified from the reaction mixture using protein A streamline resin and eluted in 0.1M Glycine, pH2. Eluate was neutralized by addition of 1/10 volume 1M Tris, pH 8.0. 1/3 volume 2 M ammonium actetate was then added to neutralized eluate to adjust pH to 5.5 and protein concentration calculated by measuring absorbance at 280nm. The degree of conjugation was determined by mass spectrometric analysis. Purified DOTA-Maleimide conjugated dAb solution was then radiolabeled in 35µl reaction volumes by addition of 5-20µl $^{111}InCl_3$ (dissolved in 0.05M HCl) and 1 – 4 µl of 1 M ammonium acetate, pH 5.5 to 25µg DOTA-Maleimide conjugated dAb. Reaction was allowed to proceed at 37°C for 1 – 3 hours before radiolabelling

efficiency was analysed using thin layer chromatography. Following successful radiolabelling reaction mixture was quenched using 0.001% (v/v) 0.1M EDTA. Approximately 12 MBq radiolabeled dAb was injected into isofluorane anaesthetized balb/c mice intravenously via the tail vein before imaging over a 7 day time course using the Nanospect/CT preclinical *in vivo* imaging system. Analysis of images showed that in mice injected with ^{111}In labeled DOM26m-33 signal was observed in the kidney, bladder and liver after 3 hours (Figure 7). However in Mice injected with ^{111}In labeled Vκ dummy or V_H dummy 2 no signal was observed in the liver over 7 days post injection, therefore liver specific binding of DOM26m-33 *in vivo* is a direct consequence of ASGPR binding. Signal was observed in the kidney and bladder in all cases due to excretion via this route. In order to quantitatively determine the *in vivo* distribution of ^{111}In labeled dAbs whole body autoradiography experiments were carried out. Balb/c mice were dosed with approximately 0.5MBq of radiolabelled dAb as above. Mice were then sacrificed 3 hours after injection before removing organs and counting in a gamma counter. Counts detected in various organs were expressed as percent injected dose. Results of these experiments show that counts in the liver of mice injected with DOM26m-33 were 12.4 times higher compared to counts in the liver of mice injected with Vκ dummy and 4.9 times higher compared to counts in the liver of mice injected with V_H dummy 2 (Figure 8).

EXAMPLE 7- Cloning and Expression of Murine Interferon Alpha Fused to ASGPR Specific dAbs

Mouse Interferon-alpha 2 cDNA was custom synthesised by DNA2.0. DNA encoding the full length protein (without the signal peptide sequence) with a partial linker sequence (described below) and an AvrII restriction site appended to the c-terminus, was amplified by PCR using primers DX132 and DX133. Oligonucleotide sequences are shown in Table 7 below.

DX132	GGATCCACCGGCTGCGATCTGCCTCACACTTA (Seq ID No. 83)	Addition of 5' BamHI to Mouse IFNa2 for cloning into pDOM50
DX133	CCTAGGAGCGGCGACGGTCTCCTTCTCTTCACTCAGTCT	Addition of 3' TVAAPS and AvrII site to Mouse IFNa2 for cloning

	(Seq ID No. 84)	into pDOM50

Table 7:

PCR fragments were inserted into holding vector pCR-Zero Blunt (Invitrogen) by Topoisomerase cloning and sequenced to obtain error-free clones using M13 forward amd M13 reverse primers. Mouse IFNa2 encoding DNA was obtained by gel purification following BamHI/AvrII digestion of pCR-Zero Blunt containing the insert and inserts ligated into the corresponding sites in pDOM50 to produce the vector pDOM38mIFN-N1.

Anti-mouse ASGPR dAbs (or germline control dAbs Vκ dummy and V_H dummy 2) were then cloned into pDOM38mIFN-N1 to produce Mouse IFNa2 fused at the C-terminus to dAb sequence with the intervening linker sequence TVAAPS as described below:

Following PCR amplification of dAb nucleotide sequence with primers DX008 and DX018 for Vκ clones or DX009 and DX019 for V_H clones PCR fragments were inserted into holding vector and sequenced to obtain error-free clones as above. DNA encoding dAb sequence was obtained by gel purification following NheI/HindIII digestion of pCR-Zero Blunt containing the insert and inserts ligated into pDOM38mIFN-N1 digested with AvrII/HindIII.

Constructs with c-terminal residue of dAb mutated to cysteine was also produced as above, except antisense primers used in place of DX018 and DX019 were DLT048 for Vκ clones and DLT049 for V_H clones. Oligonucleotide sequences are shown in Table 8 below.

Table 8:

DX008	GCTAGCGACATCCAGATGACCCAG TCTCCAT (Seq ID No. 85)	Addition of 5' NheI to Vκ for cloning into pDOM38mIFN-N1
DX009	GCTAGCGAGGTGCAGCTGTTGGA GTCTGGG (Seq ID No. 86)	Addition of 5' NheI to V_H for cloning into pDOM38mIFN-N1
DX018	AAGCTTTTATTACCGTTTGATTTCC ACCTTGGTCCC (Seq ID No. 87)	Addition of 3' 2x STOP and HindIII to Vκ for cloning into pDOM38mIFN-N1
DX019	AAGCTTTTATTAGCTCGAGACGGT GACCAGGGTTCCC (Seq ID No. 88)	Addition of 3' 2x STOP and HindIII to V_H for cloning into pDOM387h-14-N1

DLT048	AAGCTTTTATTAGCATTTGATTTCC ACCTTGGTCCC (Seq ID No. 89)	Addition of 3' 2x STOP and HindIII to Vκ for cloning into pDOM38mIFN-N1. Also mutates C-terminal serine to cysteine.
DLT049	AAGCTTTTATTAGCACGAGACGGT GACCAGGGTTCC (Seq ID No. 90)	Addition of 3' 2x STOP and HindIII to V_H for cloning into pDOM38mIFN-N1. Also mutates C-terminal serine to cysteine.

Linker Sequence (amino acid):

TVAAPS (Seq ID No. 91)

Linker Sequence (nucleotide):

ACCGTCGCCGCTCCTAGC (Seq ID No. 92)

Plasmid DNA was prepared using QIAfilter megaprep (Qiagen). 1μg DNA/ml was transfected with 293-Fectin into HEK293E cells and grown in serum free media. The protein is expressed in culture for 5 days and purified from culture supernatant using protein L streamline resin, eluted with 0.1M glycine pH 2.0 and neutralised with 1M Tris pH 8.0. The proteins were buffer exchanged into PBS. Purity was assessed by reducing SDS-PAGE as above (Figure 9).

Interferon activity of mouse IFNa2-dAb fusions was assayed using a luciferase reporter assay (CHO-ISRE Luc assay). CHO-K1 cells were transiently transfected with the luciferase reporter construct pISRE-Luc (Clontech; http://www.clontech.com/images/pt/PT3372-5.pdf). Following overnight incubation transfected cells were plated onto 96 well microtitre plates and incubated for 4 hours at 37°C before treatment with mouse IFNa2-dAb fusions for one hour. IFN-stimulated cells were then treated with Bright-Glo Luciferase reagent (http://www.promega.com/tbs/tm052/tm052.pdf) and read on a Wallac microplate reader. Recombinant mouse Interferon-alpha expressed in *E coli* (PBL Biomedical Laboratories) was used as a standard. Results show that mouse IFNa2-dAb fusions are active in this assay (Figure 10).

ASGPR binding activity of mouse IFNa2-dAb fusions was also tested by biacore as above. DOM26m-33 binding activity was retained in the context of an in-line fusion to mouse IFNa2 (Figure 11).

Sequences:

Mouse IFNa2

CDLPHTYNLRNKRALKVLAQMRRLPFLSCLKDRQDFGFPLEKVDNQQIQKA
QAIPVLRDLTQQTLNLFTSKASSAAWNTTLLDSFCNDLHQQLNDLQTCLMQQ
VGVQEPPLTQEDALLAVRKYFHRITVYLREKKHSPCAWEVVRAEVWRALSSS
VNLLPRLSEEKE (Seq ID No. 93)

TGCGATCTGCCTCACACTTATAACCTCAGGAACAAGAGGGCCTTGAAGGT
CCTGGCACAGATGAGGAGGCTCCCCTTTCTCTCCTGCCTGAAGGACAGGC
AGGACTTTGGATTCCCCCTGGAGAAGGTGGATAACCAGCAGATCCAGAAG
GCTCAAGCCATCCCTGTGCTGCGAGATCTTACTCAGCAGACCTTGAACCTC
TTCACATCAAAGGCTTCATCTGCTGCTTGGAATACAACCCTCCTAGACTCA
TTCTGCAATGACCTCCACCAGCAGCTCAATGACCTGCAAACCTGTCTGATG
CAGCAGGTGGGGGTGCAGGAACCTCCTCTGACCCAGGAAGACGCCCTGCT
GGCTGTGAGGAAATATTTCCACAGGATCACTGTGTACCTGAGAGAGAAGA
AACACAGCCCCTGTGCCTGGGAGGTGGTCAGAGCAGAAGTCTGGAGAGCC
CTGTCTTCCTCAGTCAACTTGCTGCCAAGACTGAGTGAAGAGAAGGAG
(Seq ID No. 94)

EXAMPLE 8- Affinity Maturation of DOM26m and DOM26h Leads

Error-prone PCR libraries were assembled for clones DOM26m-20, -50, -29, -33, -52 and DOM26h-61, -99, -104, -110 and -159. The parent clones in pDOM5 vector were subjected to two rounds of error-prone PCR using GeneMorph II kit (Stratagene). In the PCR reaction 0.75 μg of vector was amplified for 30 cycles using primers AS9 and AS339, according to manufacturer's protocol. In the second round of amplification 0.1 μl of the first amplification reaction product was reamplified in 100 μl volume for 35 cycles using primers AS639 and AS65. The reaction product was purified by electrophoresis using 2% E-Gels (Invitrogen) and Qiagen Gel Purification kit (Qiagen). The purified reaction product was cut with 200 units of Sal I (High concentration, NEB) and 100 units Not I (High concentration, NEB) in 100 μl volume

at 37C for 18 hours. The digested DOM26m and DOM26h inserts were gel purified using 2% E-gels and eluted into 20 µl of water.

Each library insert was ligated into 1 µl of 30 nM pIE2a^{2}A vector (see WO2006018650) using T4 DNA Ligase (NEB) in an overnight reaction at 160C in 25 µl volume. An aliquot of 0.1 µl of the ligated library was used to quantify the number of ligated vector molecules. The reaction yield in the form of circularized vectors was measured by qPCR (Mini-Opticon, iQ SYBR Green pre-mix, Bio-Rad cat no. 170-8880) using primers AS79 and AS80 (p174, R17058). Amplification cycles were: 2 min 94°C, followed by 40 cycles of 15 sec 94°C, 30 sec 60°C and 30 sec 72°C . The amount of DNA was quantified on a BioRad MiniOpticon Real-Time PCR Machine (Bio-Rad Laboratories, Hercules CA) and analysed using Opticon Monitor version 3.1.32 (2005) software provided by Bio-Rad Laboratories. Standard curve from a sample of known DNA concentration covered the range from 500 to $5x10^8$ molecules per reaction.Typical reaction yield (of independent ligations that equals to library diversity) varied between $2x10^8$ and $2x10^9$ circularized copies of vector per reaction.

0.5 µl of the ligation mix was also used to transform a 10 µl of XL10-Gold cells (Stratagene). The inserts from the colonies were amplified using primers AS79 and AS80, SuperTaq DNA polymerase. The reaction products were purified using Millipore Multiscreen plates and 8 clones were sequenced for each library using T7 primer. On average, the libraries contained 1.8-2.8 amino acid mutations per gene (p179, R17058).

The rest of the ligation mix was PCR amplified in 15 µl volume using SuperTaq DNA polymerase with primers AS11 and AS17 to generate the PCR fragments required for the selection.

Selections

Nine rounds of selection were carried out in total, whilst keeping all the libraries separate and using a series of nested primer sets AS12+AS18, AS13+AS19, AS14+AS20, AS15+AS21, AS16+AS22, AS29+AS153, AS106+AS154, AS109+AS155 and AS98+AS156, according to the method described in WO2006018650, except that KOD Hot-Start DNA polymerase (Merck) was used

throughout the process. In the first round of selection $5x10^9$ molecules of library were emulsified in 1 ml of emulsion, whereas in the subsequent eight rounds $5x10^8$ molecules per reaction were used. Affinity capture of protein DNA complexes was carried out using mouse ASGPR biotinylated with NHS-LC-biotin (Pierce, according to manufacturer's protocol). M280 Streptavidin Dynabeads at $3x10^7$ beads per reaction (Invitrogen) were used throughout to capture ligand-dAb-DNA complexes. 4-6 fmol of mouse ASGPR was pre-coated onto beads (in round 1) or used in solution 200 µl volume during the capture phase (rounds 2-9).

Following the final round of selection, the amplified DNA was cut with SalI/NotI enzymes and the dAb insert gel purified on 2% E-Gel. The purified insert was cloned into SalI/NotI-cut pDOM10 vector and transformed into Mach1 Chemically competent cells (Invitrogen). 96 colonies were picked for each library. The bacterial colonies were used to run PCR reactions and to inoculate 100 µl stock LB and 600 µl TB/OnEx (Merck) cultures. The TB/OnEx cultures were used for autoinduction expression during 72h incubation at 300C, 750 RPM in 2.2 ml DeepWell plates. The expression products were screened on BIAcore using HBS-P buffer and SA chips (all BIAcore) coated with biotinylated proteins, human ASGPR in channel 2, mouse ASGPR in channel 3 and either protein A or protein L in channel 4. Channel 1 was left uncoated. The colony PCR was performed using SuperTaq with primers AS9 and AS65. The PCR reaction products were purified using Multiscreen plates (Millipore) and sequenced using M13 reverse primer.

Results

A number of clones were identified by sequence enrichment (DOM26m-20 and DOM26h-61 libraries) or BIAcore screening of supernatants (DOM26m-52 library). No improved clones or sequence enrichments were observed for the rest of the libraries.

Further affinitiy maturation of DOM26m and DOM26h leads was carried out using doped libraries. Libraries were assembled by PCR using SuperTaq DNA polymerase and targetd dAb genes in pDOM5 vector. The doped oligonucleotides consisted of fixed positions (indicated by a capital letter and in which case 100% of

oligonucleotides have the indicated nucleotide at that position) and mixed nucleotide composition, indicated by lower case in which case 85% of oligonucleotides will have the dominant nucleotide at this position and 15% will have an equal split between the remaining three nucleotides.

DOM26m-20: In the first reaction CDR1 of DOM26m-20 was randomized using oligonucleotides AS9 and AS1253, while CDR2 was randomized using oligonucleotides AS1257 and AS339. The reaction products were gel purified, mixed and spliced by SOE-PCR (Horton *et al.* Gene, 77, p61 (1989)) using primers AS65 and AS639 as secondary nested primers, providing a library with both CDR1 and CDR2 randomisation. CDR3 was randomized using primersAS9 and AS1259.

DOM26m-50: In the first reaction CDR1 of DOM26m-20 was randomized using oligonucleotides AS9 and AS1254, while CDR2 was randomized using oligonucleotides AS1258 and AS339. The reaction products were gel purified, mixed and spliced by SOE-PCR using primers AS65 and AS639 as secondary nested primers, providing a library with both CDR1 and CDR2 randomisation. CDR3 was randomized using primersAS9 and AS1260.

DOM26m-29: In the first reaction CDR1 of DOM26m-20 was randomized using oligonucleotides AS9 and AS1261, while CDR2 was randomized using oligonucleotides AS1267 and AS339. The reaction products were gel purified, mixed and spliced by SOE-PCR using primers AS65 and AS639 as secondary nested primers, providing a library with both CDR1 and CDR2 randomisztion. CDR3 was randomized using primersAS9 and AS1270.

DOM26m-33: In the first reaction CDR1 of DOM26m-20 was randomized using oligonucleotides AS9 and AS1262, while CDR2 was randomized using oligonucleotides AS1268 and AS339. The reaction products were gel purified, mixed and spliced by SOE-PCR using primers AS65 and AS639 as secondary nested primers, providing a library with both CDR1 and CDR2 randomisation. CDR3 was randomized using primersAS9 and AS1271.

DOM26h-99: Separate libraries for each CDR was assembled by SOE-PCR. CDR1: the first amplifications with primer pairs AS1290+AS339 and AS9+AS1310 for CDR1, AS 1294+AS339 and AS9+AS1278 for CDR2 and AS1298+AS339 and AS9+AS1304 for CDR3. The amplification products for individual CDRs were mixed, spliced by SOE PCR and reamplified using primers AS639 and AS65.

DOM26h-159: Separate libraries for each CDR was assembled by SOE-PCR. CDR1: the first amplifications with primer pairs AS1322+AS339 and AS9+AS1310 for CDR1, AS 1323+AS339 and AS9+AS1278 for CDR2 and AS1324+AS339 and AS9+AS1304 for CDR3. The amplification products for individual CDRs were mixed, spliced by SOE PCR and reamplified using primers AS639 and AS65.
DOM26m-52-3: The first amplifications were carried out with primer pairs AS1287+AS339 and AS9+AS1263 for CDR1, AS1325+AS339 and AS9+AS1327 for CDR2 (first library), AS1326+AS339 and AS9+AS1327 for CDR2 (second library), and AS9+AS1272 for CDR3. The amplification products for individual CDRs1-2 were mixed, spliced by SOE PCR and reamplified using primers AS639 and AS65.

All assembled library fragments were gel purifed, SalI/NotI cut and ligated into pIE2a^{2}A vector as described above, with ligation yields exceeding 10^9 independent ligations per reaction, as measured by qPCR and described above. (23, 27, 28 R17479)

Selections

Nine rounds of selection were carried out in total, whilst keeping all the libraries separate and using a series of nested primer sets AS12+AS18, AS13+AS19, AS14+AS20, AS15+AS21, AS16+AS22, AS29+AS153, AS106+AS154, AS109+AS155 and AS98+AS156, as described above. In the first round of selection $2.5x10^9$ molecules of library were emulsified in 1 ml of emulsion, whereas in the subsequent eight rounds $5x10^8$ molecules per reaction were used. Affinity capture of protein DNA complexes was carried out using mouse or human ASGPR biotinylated with NHS-LC-biotin (Pierce, according to manufacturer's protocol). M280 Streptavidin Dynabeads at $3x10^7$ beads per reaction (Invitrogen) were used throughout to capture ligand-dAb-DNA complexes. 2-6 fmol of mouse ASGPR was pre-coated onto beads (in round 1) or used in solution 200 µl volume during the capture phase (rounds 2-9).
Following the final round of selection, the amplified DNA was cut with SalI/NotI enzymes and the dAb insert gel purified on 2% E-Gel. The purified insert was cloned into SalI/NotI-cut pDOM10 vector and transformed into Mach1 Chemically

competent cells (Invitrogen). 96 colonies were picked for each library and processed as described above for the error-prone PCR library.

Results

A number of clones were identified by sequence enrichment (DOM26m-20 and DOM26h-61 libraries) or BIAcore screening of supernatants (DOM26m-52 library). No improved clones or sequence enrichments were observed for the rest of the libraries.

Oligonucleotide sequences are shown in Table 9 below:

Table 9:

AS9	CAGGAAACAGCTATGACCATG	Seq ID No. 95
AS11	TTCGCTATTACGCCAGCTGG	Seq ID No. 96
AS12	AAAGGGGGATGTGCTGCAAG	Seq ID No. 97
AS13	AAGGCGATTAAGTTGGGTAAC	Seq ID No. 98
AS14	CCAGGGTTTTCCCAGTCAC	Seq ID No. 99
AS15	GAGATGGCGCCCAACAGTC	Seq ID No. 100
AS16	CTGCCACCATACCCACGCC	Seq ID No. 101
AS17	CAGTCAGGCACCGTGTATG	Seq ID No. 102
AS18	AACAATGCGCTCATCGTCATC	Seq ID No. 103
AS19	TCGGCACCGTCACCCTGG	Seq ID No. 104
AS20	TGCTGTAGGCATAGGCTTGG	Seq ID No. 105
AS21	CCTCTTGCGGGATATCGTC	Seq ID No. 106
AS22	TCCATTCCGACAGCATCGC	Seq ID No. 107
AS29	GAAACAAGCGCTCATGAGCC	Seq ID No. 108
AS65	TTGTAAAACGACGGCCAGTG	Seq ID No. 109
AS79	GGCGTAGAGGATCGAGATC	Seq ID No. 110
AS80	TTGTTACCGGATCTCTCGAG	Seq ID No. 111
AS98	CCAGCAACCGCACCTGTG	Seq ID No. 112
AS106	AGTGGCGAGCCCGATCTTC	Seq ID No. 113
AS109	CGATATAGGCGCCAGCAACC	Seq ID No. 114
AS153	CAGTCACTATGGCGTGCTGC	Seq ID No. 115
AS154	TAGCGCTATATGCGTTGATGC	Seq ID No. 116
AS155	TTCTATGCGCACCCGTTCTC	Seq ID No. 117
AS156	AGCACTGTCCGACCGCTTTG	Seq ID No. 118
AS339	TTCAGGCTGCGCAACTGTTG	Seq ID No. 119
AS63	CGCCAAGCTTGCATGCAAATTC	Seq ID No. 120

9	
AS1253	GGCTTTACCTGGTTTCTGCTGGTACCAATAMAAMTCMCTMCCMATATAMTTMCTMGCMCGGCAAGTGATGGTGACACGG Seq ID No. 121
AS1257	TATTGGTACCAGCAGAAACCAGGTAAAGCCCCTAAGCTCCTGATKGGKGGKGGKTCKCGKTTKCAKAGTGGGGTCTCATC Seq ID No. 122
AS1259	TGTGTGTGGCGGCCGCCCGTTTGATTTCCACCTTGGTCCCTTGGCCGAACGTMAGMGGMCTMGCMCAMTTMTGMCCMCAGTAGTACGTAGC Seq ID No. 123
AS1254	GGCTTTCCCTGGTTTCTGCTGGTACCAATTMAAMTGMTCATAMATMCTMATMCTMGCMCGGCAAGTGATGGTGACACGG Seq ID No. 124
AS1258	AATTGGTACCAGCAGAAACCAGGGAAAGCCCCTACGCTCCTGATKTGKGAKTCKTCKGGKTTKCAKAGTGGGGTCCCATC Seq ID No. 125
AS1260	TGTGTGTGGCGGCCGCCCGTTTGATTTCCACCTTGGTCCCTTGGCCGAACGTMGGMGGMTGMCTMTGMTGMTGMACMCAGTAGTACGTAGC Seq ID No. 126
AS1261	TGAGACCCACTCCAGACCCTTCCCTGGAGCCTGGCGGGCCCAMATMATMCCMCTMTCMTCAAAGGTGAATCCGGAG Seq ID No. 127
AS1262	TGAGACCCACTCTAGACCCTTCCCTGGAGCCTGGCGGACCCAMATMATMTCATAMTTMGCAAAGGTGAATCCGGAG Seq ID No. 128
AS1263	TGAGACCCACTCTAGACCCTTCCCTGGAGCCTGGCGGACCCAMCTMATMGGMTGMTCMCTAAAGGTGAATCCGGAG Seq ID No. 129
AS1267	CTCCAGGGAAGGGTCTGGAGTGGGTCTCAGGKATKGCKTCKGAKGGKAGKACKACKTACTACGCKGAKTCKGTKAAKGGKCGGTTCACCATC Seq ID No. 130
AS1268	CTCCAGGGAAGGGTCTAGAGTGGGTCTCAGGKATKAAKCAKTCKGGKTCKCGKACKTACTACGCKGAKTCKGTKAAKGGKCGGTTCACCATC Seq ID No. 131
AS1270	TGTGTGTGGCGGCCGCGCTCGAGACGGTGACCAGGGTTCCCTGACCCCAGTAMTCMAAMGAMAGMCCMGATTTCGCACAGTAATA Seq ID No. 132
AS1271	TGTGTGTGGCGGCCGCGCTCGAGACGGTGACCAGGGTTCCCTGACCCCAGTAMTCMAAMGAMGAMCCMGATTTCGCACAGTAATA Seq ID No. 133
AS1272	TGTGTGTGGCGGCCGCGCTCGAGACGGTGACCAGGGTTCCCTGACCCCAGTAMTCMAAMTCMCGMACMGATTTCACACAGTAATA Seq ID No. 134
AS1278	TGAGACCCACTCTAGACCCTTCCCTGGAGCCTGGCGGACCCA Seq ID No. 135
AS1287	TGGGTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCA Seq ID No. 136
AS1294	GAAGGGTCTAGAGTGGGTCTCATCKATTAGKTCKACKGGKCTKAGKACKTACTACGCKGAKTCKGTGAAKGGKCGGTTCACCATCTCCCG Seq ID No. 137
AS1298	CGGTATATTACTGTGCGAAAGAKGCKTCKCGKTTKAGKCAKCCKTTKGAKTACTGGGGTCAGGGAACCCTGGTC Seq ID No. 138
AS1304	TTTCGCACAGTAATATACCGC Seq ID No. 139
AS1310	AAAGGTGAATCCGGAGGCTGCACAGGAGAGACGCAG Seq ID No. 140
AS1322	GCCTCCGGATTCACCTTTGCKGAKTATTCKATGTATTGGGTCCGCCAGGCTCCAGG Seq ID No. 141
AS1323	GAAGGGTCTAGAGTGGGTCTCAGAKATKAGKCCKTCKGGKAGKATKACKTACTACGCKGAKTCKGTKAAKGGKCGGTTCACCATCTCCCGTGACAATTC Seq ID No. 142
AS1324	CGGTATATTACTGTGCGAAAGGKCTKCCKGGKCAKAAKATKCAKGTKGGKTTKGAKTACTGGGGTCAGGGAACCCTGGTC Seq ID No. 143
AS1325	GGGTCTCATCGATTAGTAAGCATGGTNNKNNKNNKTACTACGCAGACTCCGTG Seq ID No. 144
AS13	GGGTCTCATCGATTAGTAAGNNKNNKNNKGTGACATACTACGCAGAC

26	Seq ID No. 145
AS13 27	CTTACTAATCGATGAGACCC Seq ID No. 146

EXAMPLE 9 - Cloning and Expression of Human Asialoglycoprotein H1 Receptor Lectin and Stalk Domains

Full length human asialoglycoprotein receptor H1 subunit (ASGPR H1) cDNA was synthesised by DNA2.0 (see example 1). DNA encoding the stalk domain (Q62-C153) with an N-terminal $(His)_6$ tag was generated by site directed mutagenesis of Human $(His)_6$ ASGPR H1 Q62-L291 in pDOM50 expression vector (see example1) using the Quikchange site directed mutagenesis kit (Stratagene) according to manufacturer's instructions. Primers LT020 and LT021 were used to introduce a double stop codon in this construct such that translation of Human $(His)_6$ ASGPR H1 Q62-L291 in pDOM50 terminates immediately after residue C153. DNA encoding the lectin domain (C154-L291) with an N-terminal $(His)_6$ tag was amplified by PCR using primers LT013 and LT014.

LT020	CCGAGAGAACTTGCTAATAATGCCCCGTCAATTGGG (Seq ID No. 147)	Human $(His)_6$ ASGPR H1 stalk domain 5' primer
LT021	CCCAATTGACGGGGCATTATTAGCAAGTTCTCTCGG (Seq ID No. 148)	Human $(His)_6$ ASGPR H1 stalk domain 3' primer
LT022	GCCCGGATCCACCGGCCATCATCATCATCATCACGGG TCGTGCCCCGTCAATTGGGTG (Seq ID No. 149)	Human $(His)_6$ ASGPR H1 lectin domain 5' primer
LT013	GGGTGCCCGGATCCACCGGCCATCATCATCATCATCA CGGGTCGCACGAGCGGTCTTGTTATTGGAGC (Seq ID No. 150)	Human $(His)_6$ ASGPR H1 lectin domain 3' primer

PCR fragment was digested with BamHI/HindIII, gel purified and ligated into the corresponding sites in pDOM50 (see example 1).

Leader sequence (amino acid):
METDTLLLWVLLLWVPGSTG (Seq ID No. 5)

Leader sequence (nucleotide):
ATGGAGACCGACACCCTGCTGCTGTGGGTGCTGCTGCTGTGGGTGCCCGG ATCCACCGGGC (Seq ID No. 6)

Plasmid DNA was prepared using QIAfilter megaprep (Qiagen). 1µg DNA/ml was transfected with 293-Fectin into HEK293E cells and grown in serum free media. The protein was expressed in culture for 5 days and purified from culture supernatant using Ni-NTA resin and eluted with PBS + 0.5M Imidazole. The proteins were buffer exchanged into PBS.

Purity of lectin and stalk domains eluted from Ni-NTA was analysed by non-reducing SDS-PAGE (Figure 14). SDS-PAGE analysis shows that human $(His)_6$-ASGPR H1 stalk domain migrates close to the expected molecular mass (10KDa based on amino acid sequence) only when treated with 500 units of PNGase F (New England Biolabs) for 2 hours at 37◦C, consistent with N-linked glycosylation of residues in the stalk domain. Human $(His)_6$-ASGPR H1 lectin domain migrates close to the expected molecular mass of 17.2 KDa irrespective of PNGase F treatment, indicating that the lectin domain of human ASGPR H1is not extensively modified by N-linked glycosylation.

Sequences:

$(His)_6$- Human ASGPR H1 Stalk Domain

HHHHHHQNSQLQEELRGLRETFSNFTASTEAQVKGLSTQGGNVGRKMKSLE SQLEKQQKDLSEDHSSLLLHVKQFVSDLRSLSCQMAALQGNGSERTC (Seq ID No. 151)

CATCATCATCATCATCACCAGAACTCCCAACTCCAGGAAGAACTTCGAGG ACTGAGGGAGACTTTCTCCAATTTCACCGCAAGCACGGAGGCTCAAGTGA AGGGCCTCAGCACCCAGGGCGGGAATGTGGGCAGGAAAATGAAATCCCT GGAGAGCCAGCTCGAAAAGCAGCAGAAAGATCTGTCCGAGGACCACTCT AGCCTGTTGTTGCACGTGAAACAGTTTGTTTCCGACCTTAGGAGTCTTTCT TGCCAAATGGCCGCCCTCCAGGGAAACGGGTCCGAGAGAACTTGC (Seq ID No. 152)

$(His)_6$- Human ASGPR H1 Lectin Domain

HHHHHHGSCPVNWVEHERSCYWFSRSGKAWADADNYCRLEDAHLVVVTS
WEEQKFVQHHIGPVNTWMGLHDQNGPWKWVDGTDYETGFKNWRPEQPDD
WYGHGLGGGEDCAHFTDDGRWNDDVCQRPYRWVCETELDKASQEPPLL
(Seq ID No. 153)

CATCATCATCATCATCACGGGTCGTGCCCCGTCAATTGGGTGGAGCACGA
GCGGTCTTGTTATTGGTTTAGCCGAAGCGGAAAAGCCTGGGCCGATGCAG
ATAACTACTGCCGGCTTGAGGACGCCCATCTGGTCGTGGTGACCAGTTGG
GAGGAACAGAAATTCGTACAGCATCATATCGGGCCTGTTAACACATGGAT
GGGCCTTCATGACCAGAATGGTCCTTGGAAGTGGGTTGACGGAACCGATT
ACGAAACCGGATTCAAGAACTGGCGGCCTGAACAGCCAGACGACTGGTAT
GGACACGGCCTCGGAGGCGGGGAGGACTGCGCGCATTTCACAGACGATG
GCCGGTGGAATGATGATGTGTGCCAAAGGCCTTACAGATGGGTCTGCGAG
ACAGAGCTGGATAAGGCTTCACAAGAGCCTCCACTCCTG (Seq ID No. 154)

EXAMPLE 10 - Surface Plasmon Resonance to Determine Binding of ASGPR dAbs to Human ASGPR Stalk Domain, Human ASGPR Lectin Domain and Mouse ASGPR Extracellular Domain

To assay for potential dAb binding activity human $(His)_6$-ASGPR H1 stalk domain, human $(His)_6$-ASGPR H1 lectin domain and mouse $(His)_6$-ASGPR H1 extracellular domain were biotinylated and immobilised on a biacore Streptavidin chip surface. ASGPR dAbs DOM26h-161-84, DOM26h-210-2, DOM26h-220-1 and DOM26h-196-61with C-terminal FLAG epitope tags (expressed and purified from pDOM10 as in example 6) were passed over the chip surface at a flow rate of $40\mu l.min^{-1}$ and shown to bind human $(His)_6$-ASGPR H1 lectin domain and mouse $(His)_6$-ASGPR H1 extracellular domain. No binding to human $(His)_6$-ASGPR H1 stalk domain was observed with any of these clones (Figure 15 shows an example of DOM26h-196-61 binding to $(His)_6$-ASGPR H1 stalk domain, human $(His)_6$-ASGPR H1 lectin domain and mouse $(His)_6$-ASGPR H1 extracellular domain).

EXAMPLE 11 - Binding of ASPGR Lectin Domain Specific dAbs to Murine Liver *In Vivo*

ASGPR dAbs were expressed in 500ml cultures (OnEX plus carbenicillin) for 3 days at 30°C and purified on protein A (V_H dAbs) or protein L (Vκ dAbs). dAbs were then conjugated with DOTA-NHS and labelled with ^{111}In. Briefly, dAb solution (and all

buffers used in the conjugation method) was passed through Chelex 100 resin to remove cations. Conjugation was carried out overnight at room temperature by addition of 4 fold molar excess of DOTA-NHS dissoloved to 20mM in 1xPBS. DOTA-NHS conjugated dAb was purified from the reaction mixture using protein A (V_H dAbs) or protein L (Vκ dAbs) streamline resin and eluted in 0.1M Glycine, pH2. Eluate was neutralized by addition of 1/10 volume 1M Tris, pH 8.0. 1/3 volume 2 M ammonium actetate was then added to neutralized eluate to adjust pH to 5.5 and protein concentration calculated by measuring absorbance at 280nm. The degree of conjugation was determined by mass spectrometric analysis. Purified DOTA-NHS conjugated dAb solution was then radiolabeled in 35µl reaction volumes by addition of 5-20µl $^{111}InCl_3$ (dissolved in 0.05M HCl) and 1 – 4 µl of 1 M ammonium acetate, pH 5.5 to 25µg DOTA-NHS conjugated dAb. Reaction was allowed to proceed at 37°C for 1 – 3 hours before radiolabelling efficiency was analysed using thin layer chromatography. Following successful radiolabelling reaction mixture was quenched using 0.001% (v/v) 0.1M EDTA.

Approximately 12 MBq radiolabelled dAb was injected into isofluorane anaesthetized balb/c mice intravenously via the tail vein before imaging over a 72 hour time course using the Nanospect/CT preclinical *in vivo* imaging system. Analysis of images showed that in mice injected with ^{111}In labeled DOM26h-161-84 and DOM26h-196-61 signal was observed in the kidney, bladder and liver after 3 hours (Figure 16). In comparison mice injected with ^{111}In labeled Vκ dummy or V_H dummy 2 no signal was observed in the liver over 7 days post injection (Figure 8), therefore liver specific binding of DOM26h-161-84 and DOM26h-196-61 *in vivo* is a direct consequence of ASGPR lectin domain binding. Signal was observed in the kidney and bladder in all cases due to excretion via this route. In order to quantitatively determine the *in vivo* distribution of ^{111}In labelled ASGPR lectin domain specific dAbs whole body autoradiography experiments were carried out. Balb/c mice were injected with approximately 0.5MBq of radiolabelled dAb as above. Mice were then sacrificed 3 hours after injection before removing organs and counting in a gamma counter. Counts detected in various organs were expressed as percentage of injected dose. Results of these experiments show that counts in the liver of mice injected with DOM26h-196-61 were approximately 35 times higher compared to counts in the liver

of mice injected with VH dummy 2. Similarly counts in the liver of mice injected with DOM26h-161-84 were 46 times higher compared to counts in the liver of mice injected with Vκ dummy (Figure 17).

EXAMPLE 12 - Cloning and Expression of Murine Interferon Alpha Fused to ASGPR Lectin Domain Specific dAbs

ASGPR lectin domain specific dAbs DOM26h-161-84 and DOM26h-196-61 were cloned into vector pDOM38mIFNa2-N1 as described in example 7. Plasmid DNA was prepared using QIAfilter megaprep (Qiagen). 1μg DNA/ml was transfected with 293-Fectin into HEK293E cells and grown in serum free media. The protein is expressed in culture for 5 days and purified from culture supernatant using protein A or protein L streamline resin, eluted with 25mM Na Acetate pH 3.0, neutralised with 1M Na Acetate pH 6.0 and NaCl added to a final concentration of 150mM. Purity was assessed by SDS-PAGE (Figure 18).

Interferon activity of mouse IFNa2-dAb fusions was assayed using a reporter cell assay consisting of B16 murine hepatoma cells stably transfected with an alkaline phosphatase reporter gene under the control of an interferon inducible element (hereafter referred to as the B16-Blue™ assay, supplied by Invivogen). Mouse IFNa2-dAb fusions were diluted in growth media (RPMI supplemented with 10% (v/v) fetal bovine serum, 50U/ml penicillin, 50μg/ml streptomycin, 100μg/ml Normocin, 100μg/ml Zeocin and 2mM L-Glutamine) and 20μl volumes added to each well of a 96 well microtitre plate. Cells were suspended in growth medium at a concentration of 420,000 cells/ml and 180μl per well added to the diluted mouse IFNa2-dAb fusions before incubation for 24 hours at 37°C/5% CO_2.Quanti-Blue detection substrate was suspended according to manufacturer's instructions and 180μl per well added to fresh microtitre plates. 20μl per well of supernatant from cells incubated with mouse IFNa2-dAb fusions was then added and plates incubated for 1-5 hours before measuring absorbance at 640nm in an M5e plate reader (Molecular Technologies). Recombinant mouse Interferon-alpha expressed in *E coli* (PBL Biomedical Laboratories) was used as a standard. Results show that mouse IFNa2-dAb fusions are active in this assay (Figure 19).

Binding of mouse IFNa2-dAb fusions to human $(His)_6$ lectin domain and mouse $(His)_6$ extracellular domain was tested by BIAcore (method described in example 10). Binding of DOM26h-161-84, DOM26h-196-61 and DOM26h-210-2 to human $(His)_6$ lectin domain and mouse $(His)_6$ extracellular domain was retained in the context of an in-line fusion to mouse IFNa2 (an example of mouse IFNa2 fused to DOM26h-196-61 binding to human $(His)_6$ lectin domain and mouse $(His)_6$ extracellular domain is shown in Figure 20).

Mouse IFNa2-dAb fusions were analysed by size exclusion chromatography with multi-angle LASER light scattering (SEC-MALLS) to determine whether they were monomeric or formed higher order oligomers in solution. SEC-MALLS was carried out as follows. Proteins (at a concentration of 1mg/mL in 25mM NaAcetate, 150mM NaCl, pH5.5) were separated according to their hydrodynamic properties by size exclusion chromatography (column: TSK3000). Following separation, the propensity of the protein to scatter light is measured using a multi-angle LASER light scattering (MALLS) detector. The intensity of the scattered light while protein passes through the detector is measured as a function of angle. This measurement taken together with the protein concentration determined using the refractive index (RI) detector allows calculation of the molar mass using appropriate equations (integral part of the analysis software Astra v.5.3.4.12).

Name	**Mean Molar mass over main peak**	**In-solution state**
mIFNa2-Vκ dummy	34.1 KDa	Monomer
mIFNa2-V_H dummy 2	35.4 KDa	Monomer
mIFNa2-DOM26h-161-84	64.3 KDa	Dimer
mIFNa2-DOM26h-196-61	35.2 KDa	Monomer
mIFNa2-DOM26h-210-2	35.3 KDa	Monomer

Lead dAbs were also analysed by differential scanning calorimetry (DSC) to determine the apparent melting temperature. DSC was carried out as follows. Protein was heated at a constant rate of 180°C/hrs (at 1mg/mL in Na Acetate, 150mM NaCl, pH5.5) and a detectable heat change associated with thermal denaturation measured. The transition midpoint (appTm) is determined, which is described as the temperature where 50% of the protein is in its native conformation and the other 50% is denatured. Here, DSC determined the apparent transition midpoint (appTm) as most of the

proteins examined do not fully refold. The higher the Tm, the more stable the molecule. The software package used was OriginR v7.0383.

Name	App Tm 1 /°C	App Tm 2 /°C
mIFNa2-Vκ dummy	64.63	75.63
mIFNa2-V_H dummy 2	60.99	76.73
mIFNa2-DOM26h-161-84	69.9	-
mIFNa2-DOM26h-196-61	62.0	71.0
mIFNa2-DOM26h-210-2	61.5	71.0

EXAMPLE 13- Binding of Mouse ASGPR-dAb Fusion Proteins to Murine Liver *In Vivo*

Fusion proteins consisting of mouse IFNa2 fused to either V_H dummy 2 or DOM26h-196-61 (described in example 12) were labelled with ^{111}In as described in example11. NHS:DOTA conjugation protocol was modified slightly by replacing 1xPBS at all steps with 25mM Na Acetate, 150mM NaCl, pH5.5.

Approximately 12 MBq radiolabelled IFN-dAb fusion was injected into isofluorane anaesthetized balb/c mice intravenously via the tail vein before imaging over a 72 hour time course using the Nanospect/CT preclinical *in vivo* imaging system. Analysis of images showed that in mice injected with ^{111}In labelled mouse IFNa2 fused to either V_H dummy 2 or DOM26h-196-61 signal was observed in the kidney, bladder and liver after 3 hours (Figure 21). However the images collected from mice injected with both types of fusion protein show that the extent of uptake in liver and kidney appears to be equal in mice injected with mouse IFNa2 fused to DOM26h-196-61. Whilst some liver uptake is also observed in mice injected with mouse IFNa2 fused to V_H dummy 2 the majority of the signal was observed in the kidney (Figure 21). These images show that a greater level of liver uptake is observed in mice injected with mouse IFNa2 fused to DOM26h-196-61 compared to mice injected with mouse IFNa2 fused to V_H dummy 2, however in order to quantitatively determine the *in vivo* distribution of ^{111}In labelled mouse IFNa2-dAb fusions whole body autoradiography experiments were carried out. Balb/c mice were injected with approximately 0.5MBq

of radiolabelled protein as above. Mice were then sacrificed 3 hours after injection before removing organs and counting in a gamma counter. Counts detected in various organs were expressed as percent injected dose. Results of these experiments show that counts in the liver of mice injected with mouse IFNa2 fused to DOM26h-196-61 were approximately 1.5 times higher compared to counts in the liver of mice injected with mouse IFNa2 fused to VH dummy 2 (Figure 22). Comparison of the ratio of uptake in liver vs kidney also revealed differences in the two dose groups. In mice injected with mouse IFNa2 fused to V_H dummy 2 the ratio was calculated at 1.2, however in the mice injected with mouse IFNa2 fused to DOM26h-196-61 this ratio was increased to 2.6, further evidence of the increased liver uptake of mouse IFNa2 due to fusion to the N-terminus of the ASGPR lectin domain specific dAb DOM26h-196-61.

CLAIMS:

1. A liver targeting composition that comprises (a) a protein ligand that binds to liver hepatocytes and (b) at least one therapeutic molecule for delivery to the liver.

2. The composition according to claim 1, wherein said protein ligand (a) and said at least one therapeutic molecule (b) are present together as a single fusion or conjugate.

3. The composition according to claim 1 or 2, wherein said protein ligand (a) binds to the ASGPR receptor on hepatocytes.

4. The composition according to claim 1 -3 , wherein said protein ligand (a) is an antibody or an antibody fragment.

5. The composition according to claim 4, wherein the antibody fragment is a single immunoglobulin variable domain (dAb).

6. The composition according to claim 5, wherein the dAb is selected from: a human Vh sequence, and a human V kappa sequence.

7. The composition according to any preceding claim, wherein the dAb can bind to at least one ASGPR receptor chosen from: the human and/or mouse ASGPR receptor.

8. The composition according to any preceding claim, wherein (b) said at least one therapeutic molecule for delivery to the liver comprises a protein or peptide molecule.

9. The composition according to claim 8, wherein (b) said at least one therapeutic molecule for delivery to the liver comprises an interferon molecule or a mutant, analogue or derivative thereof, which retains interferon activity.

10. The composition according to claim 9, wherein said interferon molecule is selected from the group consisting of: interferon alpha 2, interferon alpha 5, interferon alpha 6, and consensus interferon.

11. The composition according to any preceding claim wherein said dAb binds to the human and/or mouse ASGPR receptor with an affinity measured by Biacore between 1pM and about 10nM.

12. The composition according to claim 11, wherein the affinity of said dAb is between 1pM and about 1nM.

13. The composition according to any preceding claim, wherein said protein ligand (a) comprises a dAb amino acid sequence that binds to human ASGPR and which dAb amino acid sequence is selected from a sequence that is 100%, 95%, 90%, 85% or 80% identical to any one of the amino acid sequences identified as:

DOM26h-1 (Seq ID No: 155); DOM26h-10 (Seq ID No: 157); DOM26h-100 (Seq ID No: 159); DOM26h-101 (Seq ID No: 161); DOM26h-102 (Seq ID No: 163); DOM26h-103 (Seq ID No: 165); DOM26h-104 (Seq ID No: 167); DOM26h-105 (Seq ID No: 169); DOM26h-106 (Seq ID No: 171); DOM26h-107 (Seq ID No: 173); DOM26h-108 (Seq ID No: 175); DOM26h-109 (Seq ID No: 177); DOM26h-11 (Seq ID No: 179); DOM26h-110 (Seq ID No: 181); DOM26h-111 (Seq ID No: 183); DOM26h-112 (Seq ID No: 185); DOM26h-113 (Seq ID No: 187); DOM26h-114 (Seq ID No: 189); DOM26h-115 (Seq ID No: 191); DOM26h-116 (Seq ID No: 193); DOM26h-117 (Seq ID No: 195); DOM26h-118 (Seq ID No: 197); DOM26h-119 (Seq ID No: 199); DOM26h-12; (Seq ID No: 201) DOM26h-120 (Seq ID No: 203); DOM26h-121 (Seq ID No: 205); DOM26h-122 (Seq ID No: 207); DOM26h-123 (Seq ID No: 209); DOM26h-124; (Seq ID No: 211); DOM26h-125 (Seq ID No: 213); DOM26h-126 (Seq ID No: 215); DOM26h-127 (Seq ID No: 217); DOM26h-128 (Seq ID No: 219); DOM26h-129 (Seq ID No: 221); DOM26h-130 (Seq ID No: 223); DOM26h-131 (Seq ID No: 225); DOM26h-132 (Seq ID No: 227); DOM26h-133 (Seq ID No: 229); DOM26h-134 (Seq ID No: 231); DOM26h-135 (Seq ID No: 233); DOM26h-136 (Seq ID No: 235); DOM26h-137 (Seq ID No: 237); DOM26h-138 (Seq

ID No: 239); DOM26h-139 (Seq ID No: 241); DOM26h-140 (Seq ID No: 243); DOM26h-141 (Seq ID No: 245); DOM26h-142 (Seq ID No: 247); DOM26h-143 (Seq ID No: 249); DOM26h-144 (Seq ID No: 251); DOM26h-145 (Seq ID No: 253); DOM26h-146 (Seq ID No: 255); DOM26h-147 (Seq ID No: 257); DOM26h-148 (Seq ID No: 259); DOM26h-149 (Seq ID No: 261); DOM26h-15 (Seq ID No: 263); DOM26h-150 (Seq ID No: 265); DOM26h-151 (Seq ID No: 267); DOM26h-152 (Seq ID No: 269); DOM26h-153 (Seq ID No: 271); DOM26h-154 (Seq ID No: 273); DOM26h-155 (Seq ID No: 275); DOM26h-156 (Seq ID No: 277); DOM26h-157 (Seq ID No: 279); DOM26h-158 (Seq ID No: 281); DOM26h-159 (Seq ID No: 283); DOM26h-159-1 (Seq ID No: 285); DOM26h-159-2 (Seq ID No: 287); DOM26h-159-3 (Seq ID No: 289); DOM26h-159-4 (Seq ID No: 291); DOM26h-159-5 (Seq ID No: 293); DOM26h-160 (Seq ID No: 295); DOM26h-168 (Seq ID No: 297); DOM26h-169 (Seq ID No: 299); DOM26h-17 (Seq ID No: 301); DOM26h-170 (Seq ID No: 303); DOM26h-171 (Seq ID No: 305); DOM26h-172 (Seq ID No: 307); DOM26h-173 (Seq ID No: 309); DOM26h-174 (Seq ID No: 311); DOM26h-175 (Seq ID No: 313); DOM26h-176 (Seq ID No: 315); DOM26h-177 (Seq ID No: 317); DOM26h-178 (Seq ID No: 319); DOM26h-179 (Seq ID No: 321); DOM26h-180 (Seq ID No: 323); DOM26h-181 (Seq ID No: 325); DOM26h-182 (Seq ID No: 327); DOM26h-183 (Seq ID No: 329); DOM26h-184 (Seq ID No: 331); DOM26h-185 (Seq ID No: 333); DOM26h-186 (Seq ID No: 335); DOM26h-187 (Seq ID No: 337); DOM26h-188 (Seq ID No: 339); DOM26h-189 (Seq ID No: 341); DOM26h-19 (Seq ID No: 343); DOM26h-190 (Seq ID No: 345); DOM26h-191 (Seq ID No: 347); DOM26h-192 (Seq ID No: 349); DOM26h-193 (Seq ID No: 351); DOM26h-194 (Seq ID No: 353); DOM26h-195 (Seq ID No: 355); DOM26h-196 (Seq ID No: 357); DOM26h-197 (Seq ID No: 359); DOM26h-198 (Seq ID No: 361); DOM26h-199 (Seq ID No: 363); DOM26h-2 (Seq ID No: 365); DOM26h-20 (Seq ID No: 367); DOM26h-200 (Seq ID No: 369); DOM26h-201 (Seq ID No: 371); DOM26h-202 (Seq ID No: 373); DOM26h-203 (Seq ID No: 375); DOM26h-204 (Seq ID No: 377); DOM26h-205 (Seq ID No: 379); DOM26h-206 (Seq ID No: 381); DOM26h-207 (Seq ID No: 383); DOM26h-208 (Seq ID No: 385); DOM26h-209 (Seq ID No: 387); DOM26h-21 (Seq ID No: 389); DOM26h-210 (Seq ID No: 391); DOM26h-211 (Seq ID No: 393); DOM26h-212 (Seq ID No: 395); DOM26h-213 (Seq ID No: 397); DOM26h-214 (Seq ID No: 399); DOM26h-215 (Seq ID No: 401); DOM26h-216 (Seq ID No: 403);

DOM26h-217 (Seq ID No: 405); DOM26h-218 (Seq ID No: 407); DOM26h-219 (Seq ID No: 409); DOM26h-22 (Seq ID No: 411); DOM26h-220 (Seq ID No: 413); DOM26h-221 (Seq ID No: 415); DOM26h-222 (Seq ID No: 417); DOM26h-223 (Seq ID No: 419); DOM26h-23 (Seq ID No: 421); DOM26h-24 (Seq ID No: 423); DOM26h-29-1 (Seq ID No: 425); DOM26h-4 (Seq ID No: 427); DOM26h-41 (Seq ID No: 429); DOM26h-42 (Seq ID No: 431); DOM26h-43 (Seq ID No: 433); DOM26h-44 (Seq ID No: 435); DOM26h-45 (Seq ID No: 437); DOM26h-46 (Seq ID No: 439); DOM26h-47 (Seq ID No: 441); DOM26h-48 (Seq ID No: 443); DOM26h-49 (Seq ID No: 445); DOM26h-50 (Seq ID No: 447); DOM26h-51 (Seq ID No: 449); DOM26h-52 (Seq ID No: 451); DOM26h-53 (Seq ID No: 453); DOM26h-54 (Seq ID No: 455); DOM26h-55 (Seq ID No: 457); DOM26h-56 (Seq ID No: 459); DOM26h-57 (Seq ID No: 461); DOM26h-58 (Seq ID No: 463); DOM26h-59 (Seq ID No: 465); DOM26h-60 (Seq ID No: 467); DOM26h-61 (Seq ID No: 469); DOM26h-62 (Seq ID No: 471); DOM26h-63 (Seq ID No: 473); DOM26h-64 (Seq ID No: 475); DOM26h-65 (Seq ID No: 477); DOM26h-66 (Seq ID No: 479); DOM26h-67 (Seq ID No: 481); DOM26h-68 (Seq ID No: 483); DOM26h-69 (Seq ID No: 485); DOM26h-70 (Seq ID No: 487); DOM26h-71 (Seq ID No: 489); DOM26h-72 (Seq ID No: 491); DOM26h-73 (Seq ID No: 493); DOM26h-74 (Seq ID No: 495); DOM26h-75 (Seq ID No: 497); DOM26h-76 (Seq ID No: 499); DOM26h-77 (Seq ID No: 501); DOM26h-78 (Seq ID No: 503); DOM26h-79 (Seq ID No: 505); DOM26h-80 (Seq ID No: 507); DOM26h-81 (Seq ID No: 509); DOM26h-82 (Seq ID No: 511); DOM26h-83 (Seq ID No: 513); DOM26h-84 (Seq ID No: 515); DOM26h-85 (Seq ID No: 517); DOM26h-86 (Seq ID No: 519); DOM26h-87 (Seq ID No: 521); DOM26h-88 (Seq ID No: 523); DOM26h-89 (Seq ID No: 525); DOM26h-90 (Seq ID No: 527); DOM26h-91 (Seq ID No: 529); DOM26h-92 (Seq ID No: 531); DOM26h-93 (Seq ID No: 533); DOM26h-94 (Seq ID No: 535); DOM26h-95 (Seq ID No: 537); DOM26h-96 (Seq ID No: 539); DOM26h-97 (Seq ID No: 541); DOM26h-98 (Seq ID No: 543); DOM26h-99 (Seq ID No: 545); DOM26h-99-1 (Seq ID No: 547); DOM26h-99-2 (Seq ID No: 549); DOM26h-161 (Seq ID No: 551); DOM26h-162 (Seq ID No: 553); DOM26h-163 (Seq ID No: 555); DOM26h-164 (Seq ID No: 557); DOM26h-165 (Seq ID No: 559); DOM26h-166 (Seq ID No: 561); DOM26h-167 (Seq ID No: 563); DOM26h-224 (Seq ID No: 565); DOM26h-25 (Seq ID No: 567); DOM26h-26 (Seq ID No: 569); DOM26h-27 (Seq ID No: 571); DOM26h-28 (Seq ID No: 573); DOM26h-29 (Seq ID No: 575); DOM26h-

30 (Seq ID No: 577); DOM26h-31 (Seq ID No: 579); DOM26h-32 (Seq ID No: 581); DOM26h-33 (Seq ID No: 583); DOM26h-34 (Seq ID No: 585); DOM26h-35 (Seq ID No: 587); DOM26h-36 (Seq ID No: 589); DOM26h-37 (Seq ID No: 591); DOM26h-38 (Seq ID No: 593); DOM26h-39 (Seq ID No: 595); DOM26h-40 (Seq ID No: 597); DOM26h-6 (Seq ID No: 599); DOM26h-8 (Seq ID No: 601); DOM26h-9 (Seq ID No: 603).

14. The composition according to any one of claims 1-12, wherein said protein ligand (a) comprises a dAb amino acid sequence that binds to human ASGPR and wherein said dAb amino acid sequence is selected from a sequence that is 100%, 95%, 90%, 85% or 80% identical to the amino acid encoded by the nucleotide sequence identified as DOM26h-161-84 (Seq ID No: 867); DOM26h-161-86 (Seq ID No: 869); DOM26H-161-87 (Seq ID No: 871); DOM26h-196-61 (Seq ID No: 873); DOM26h-210-2 (Seq ID No: 875); DOM26h-220-1 (Seq ID No: 877); or DOM26h-220-43 (Seq ID No: 879).

15. The composition according to any preceding claim, wherein said protein ligand (a) comprises a dAb amino acid sequence that competes for binding to human ASGPR with any one of the amino acid sequences of claims 13 or 14.

16. The composition according to any preceding claim, wherein said protein ligand (a) comprises a dAb amino acid sequence that binds to mouse ASGPR and which is selected from a sequence that is 100%, 95%, 90%, 85% or 80% identical to the amino acid encoded by the nucleotide sequences identified as:

DOM26m-10 (Seq ID No: 605); DOM26m-13 (Seq ID No: 607); DOM26m-16 (Seq ID No: 609); DOM26m-165 (Seq ID No: 611); DOM26m-17 (Seq ID No: 613); DOM26m-27 (Seq ID No: 615); DOM26m-28 (Seq ID No: 617); DOM26m-29 (Seq ID No: 619); DOM26m-30 (Seq ID No: 621); DOM26m-31 (Seq ID No: 623); DOM26m-32 (Seq ID No: 625); DOM26m-33 (Seq ID No: 627); DOM26m-33-1 (Seq ID No: 629); DOM26m-33-10 (Seq ID No: 631); DOM26m-33-11 (Seq ID No: 633); DOM26m-33-12 (Seq ID No: 635); DOM26m-33-2 (Seq ID No: 637); DOM26m-33-3 (Seq ID No: 639); DOM26m-33-4 (Seq ID No: 641); DOM26m-33-5

(Seq ID No: 643); DOM26m-33-6 (Seq ID No: 645); DOM26m-33-7 (Seq ID No: 647); DOM26m-33-8 (Seq ID No: 649); DOM26m-33-9 (Seq ID No: 651); DOM26m-34 (Seq ID No: 653); DOM26m-35 (Seq ID No: 655); DOM26m-36 (Seq ID No: 657); DOM26m-37 (Seq ID No: 659); DOM26m-38 (Seq ID No: 661); DOM26m-39 (Seq ID No: 663); DOM26m-4 (Seq ID No: 665); DOM26m-40 (Seq ID No: 667); DOM26m-41 (Seq ID No: 669); DOM26m-42 (Seq ID No: 671); DOM26m-43 (Seq ID No: 673); DOM26m-44 (Seq ID No: 675); DOM26m-45 (Seq ID No: 677); DOM26m-46 (Seq ID No: 679); DOM26m-47 (Seq ID No: 681); DOM26m-48 (Seq ID No: 683); DOM26m-52 (Seq ID No: 685); DOM26m-52-1 (Seq ID No: 687); DOM26m-52-2 (Seq ID No: 689); DOM26m-52-3 (Seq ID No: 691); DOM26m-52-4 (Seq ID No: 693); DOM26m-52-5 (Seq ID No: 695); DOM26m-52-6 (Seq ID No: 697); DOM26m-52-7 (Seq ID No: 699); DOM26m-6 (Seq ID No: 701); DOM26m-60 (Seq ID No: 703); DOM26m-61-1 (Seq ID No: 705); DOM26m-61-2 (Seq ID No: 707); DOM26m-61-3 (Seq ID No: 709); DOM26m-61-4 (Seq ID No: 711); DOM26m-61-5 (Seq ID No: 713); DOM26m-61-6 (Seq ID No: 715); DOM26m-7 (Seq ID No: 717); DOM26m-73 (Seq ID No: 719); DOM26m-74 (Seq ID No: 721); DOM26m-75 (Seq ID No: 723); DOM26m-76 (Seq ID No: 725); DOM26m-77 (Seq ID No: 727); DOM26m-78 (Seq ID No: 729); DOM26m-79 (Seq ID No: 731); DOM26m-8 (Seq ID No: 733); DOM26m-80 (Seq ID No: 735); DOM26m-81 (Seq ID No: 737); DOM26m-82 (Seq ID No: 739); DOM26m-83 (Seq ID No: 741); DOM26m-9 (Seq ID No: 743); DOM26m-1 (Seq ID No: 745); DOM26m-100 (Seq ID No: 747); DOM26m-101 (Seq ID No: 749); DOM26m-102 (Seq ID No: 751); DOM26m-103 (Seq ID No: 753); DOM26m-106 (Seq ID No: 755); DOM26m-108 (Seq ID No: 757); DOM26m-109 (Seq ID No: 759); DOM26m-109-1 (Seq ID No: 761); DOM26m-109-2 (Seq ID No: 763); DOM26m-12 (Seq ID No: 765); DOM26m-18 (Seq ID No: 767); DOM26m-19 (Seq ID No: 769); DOM 26m-2 (Seq ID No: 771); DOM26m-20 (Seq ID No: 773); DOM26m-20-1 (Seq ID No: 775); DOM26m-20-2 (Seq ID No: 777); DOM26m-20-3 (Seq ID No: 779); DOM26m-20-4 (Seq ID No: 781); DOM26m-20-5 (Seq ID No: 783); DOM26m-20-6 (Seq ID No: 785); DOM26m-22 (Seq ID No: 787); DOM26m-23 (Seq ID No: 789); DOM26m-24 (Seq ID No: 791); DOM26m-25 (Seq ID No: 793); DOM26m-26 (Seq ID No: 795); DOM26m-3 (Seq ID No: 797); DOM26m-50 (Seq ID No: 799); DOM26m-50-1 (Seq ID No: 801); DOM26m-50-2 (Seq ID No: 803); DOM26m-50-3

(Seq ID No: 805); DOM26m-50-4 (Seq ID No: 807); DOM26m-50-5 (Seq ID No: 809); DOM26m-50-6 (Seq ID No: 811); DOM26m-51 (Seq ID No: 813); DOM26m-53 (Seq ID No: 815); DOM26m-54 (Seq ID No: 817); DOM26m-55 (Seq ID No: 819); DOM26m-56 (Seq ID No: 821); DOM26m-57 (Seq ID No: 823); DOM26m-58 (Seq ID No: 825); DOM26m-59 (Seq ID No: 827); DOM26m-61 (Seq ID No: 829); DOM26m-63 (Seq ID No: 831); DOM26m-64 (Seq ID No: 833); DOM26m-66 (Seq ID No: 835); DOM26m-69 (Seq ID No: 837); DOM26m-85 (Seq ID No: 839); DOM26m-86 (Seq ID No: 841); DOM26m-87 (Seq ID No: 843); DOM26m-89 (Seq ID No: 845); DOM26m-90 (Seq ID No: 847); DOM26m-91 (Seq ID No: 849); DOM26m-92 (Seq ID No: 851); DOM26m-93 (Seq ID No: 853); DOM26m-94 (Seq ID No: 855); DOM26m-95 (Seq ID No: 857); DOM26m-96 (Seq ID No: 859); DOM26m-97 (Seq ID No: 861); DOM26m-98 (Seq ID No: 863); DOM26m-99 (Seq ID No: 865).

17. The composition according to any one of claims 1-12, wherein said protein ligand (a) comprises a dAb amino acid sequence that competes for binding to human ASGPR with any one of the amino acid sequences of claim 16.

18. The composition according to any one of the preceding claims, wherein said protein ligand (a) comprises a dAb amino acid sequence that comprises at least one CDR selected from: CDR1, CDR2, and CDR3, wherein the CDR1, CDR2, or CDR3 is at least 80% identical to a CDR1, CDR2, or CDR3 sequence in any one of the sequences of claims 13, 14 or 16.

19. The composition according to any one of the preceding claims, wherein an amino acid or chemical linker is present.

20. The composition according to claim 19, wherein the linker is selected from: a TVAAPS linker, a TVAAPR linker, a helical linker, a gly-ser linker, and a PEG linker.

21. The composition according to any one of the preceding claims, wherein said at least one therapeutic molecule (b) is present at the N-terminal of said dAb.

22. The pharmaceutical composition comprising a liver targeting composition according to any of the preceding claims in combination with a pharmaceutically or physiologically acceptable carrier, excipient or diluent.

23. The pharmaceutical composition according to claim 22, which comprises further therapeutic or active agents.

24. A composition that comprises (a) a liver targeting composition according to any one of claims 1-22 and (b) further therapeutic or active agents, for separate, sequential or concurrent administration to a subject.

25. A dAb amino acid sequence that binds to human ASGPR and wherein said dAb amino acid sequence is selected from a sequence that is 100%, 95%, 90%, 85% or 80% identical to any one of the amino acid sequences identified as:

DOM26h-1; DOM26h-10, DOM26h-100; DOM26h-101; DOM26h-102; DOM26h-103; DOM26h-104; DOM26h-105; DOM26h-106; DOM26h-107; DOM26h-108; DOM26h-109; DOM26h-11; DOM26h-110; DOM26h-111; DOM26h-112; DOM26h-113; DOM26h-114; DOM26h-115; DOM26h-116; DOM26h-117; DOM26h-118; DOM26h-119; DOM26h-12; DOM26h-120; DOM26h-121; DOM26h-122; DOM26h-123; DOM26h-124; DOM26h-125; DOM26h-126; DOM26h-127 ; DOM26h-128; DOM26h-129; DOM26h-130; DOM26h-131; DOM26h-132; DOM26h-133; DOM26h-134; DOM26h-135; DOM26h-136; DOM26h-137; DOM26h-138; DOM26h-139; DOM26h-140; DOM26h-141; DOM26h-142; DOM26h-143; DOM26h-144; DOM26h-145; DOM26h-146; DOM26h-147; DOM26h-148; DOM26h-149; DOM26h-15; DOM26h-150; DOM26h-151; DOM26h-152; DOM26h-153; DOM26h-154; DOM26h-155; DOM26h-156; DOM26h-157; DOM26h-158; DOM26h-159; DOM26h-159-1; DOM26h-159-2; DOM26h-159-3; DOM26h-159-4; DOM26h-159-5; DOM26h-160; DOM26h-168; DOM26h-169; DOM26h-17; DOM26h-170; DOM26h-171; DOM26h-172; DOM26h-173; DOM26h-174; DOM26h-175; DOM26h-176; DOM26h-177; DOM26h-178; DOM26h-179; DOM26h-180; DOM26h-181; DOM26h-182; DOM26h-183; DOM26h-184; DOM26h-185;

DOM26h-186; DOM26h-187; DOM26h-188; DOM26h-189; DOM26h-19; DOM26h-190; DOM26h-191; DOM26h-192; DOM26h-193; DOM26h-194; DOM26h-195; DOM26h-196; DOM26h-197; DOM26h-198; DOM26h-199; DOM26h-2; DOM26h-20; DOM26h-200; DOM26h-201; DOM26h-202; DOM26h-203; DOM26h-204; DOM26h-205; DOM26h-206; DOM26h-207; DOM26h-208; DOM26h-209; DOM26h-21; DOM26h-210; DOM26h-211; DOM26h-212; DOM26h-213; DOM26h-214; DOM26h-215; DOM26h-216; DOM26h-217; DOM26h-218; DOM26h-219; DOM26h-22; DOM26h-220; DOM26h-221; DOM26h-222; DOM26h-223; DOM26h-23; DOM26h-24; DOM26h-29-1; DOM26h-4; DOM26h-41; DOM26h-42; DOM26h-43; DOM26h-44; DOM26h-45; DOM26h-46; DOM26h-47; DOM26h-48; DOM26h-49; DOM26h-50; DOM26h-51; DOM26h-52; DOM26h-53; DOM26h-54; DOM26h-55; DOM26h-56; DOM26h-57; DOM26h-58; DOM26h-59; DOM26h-60; DOM26h-61; DOM26h-62; DOM26h-63; DOM26h-64; DOM26h-65; DOM26h-66; DOM26h-67; DOM26h-68; DOM26h-69; DOM26h-70; DOM26h-71; DOM26h-72; DOM26h-73; DOM26h-74; DOM26h-75; DOM26h-76; DOM26h-77; DOM26h-78; DOM26h-79; DOM26h-80; DOM26h-81; DOM26h-82; DOM26h-83; DOM26h-84; DOM26h-85; DOM26h-86; DOM26h-87; DOM26h-88; DOM26h-89; DOM26h-90; DOM26h-91; DOM26h-92; DOM26h-93; DOM26h-94; DOM26h-95; DOM26h-96; DOM26h-97; DOM26h-98; DOM26h-99; DOM26h-99-1; DOM26h-99-2; DOM26h-161 ; DOM26h-162; DOM26h-163; DOM26h-164; DOM26h-165; DOM26h-166; DOM26h-167; DOM26h-224 ; DOM26h-25; DOM26h-26; DOM26h-27; DOM26h-28; DOM26h-29 ; DOM26h-30; DOM26h-31; DOM26h-32; DOM26h-33; DOM26h-34; DOM26h-35; DOM26h-36; DOM26h-37; DOM26h-38; DOM26h-39; DOM26h-40; DOM26h-6; DOM26h-8; DOM26h-9.

26. A dAb amino acid sequence that binds to human ASGPR and wherein said dAb amino acid sequence is selected from a sequence that is 100%, 95%, 85%, or 80% identical to the amino acid sequence identified as: DOM26h-161-84; DOM26h-161-86; DOM26h-161-87; DOM26h-196-61; DOM26h-210-2; DOM26h-220-1; or DOM26h-220-43.

27. A dAb amino acid sequence that competes for binding to human ASGPR with any one of the amino acid sequences of claim 25 or 26.

28. A dAb amino acid sequence that binds to mouse ASGPR and wherein said dAb amino acid sequence is selected from a sequence that is 100%, 95%, 90%, 85% or 80% identical to any one of the amino acid sequences identified as:

DOM26m-10; DOM26m-13; DOM26m-16; DOM26m-165; DOM26m-17; DOM26m-27; DOM26m-28; DOM26m-29; DOM26m-30; DOM26m-31; DOM26m-32; DOM26m-33; DOM26m-33-1; DOM26m-33-10; DOM26m-33-11; DOM26m-33-12; DOM26m-33-2; DOM26m-33-3; DOM26m-33-4; DOM26m-33-5; DOM26m-33-6; DOM26m-33-7; DOM26m-33-8; DOM26m-33-9; DOM26m-34; DOM26m-35; DOM26m-36; DOM26m-37; DOM26m-38; DOM26m-39; DOM26m-4; DOM26m-40; DOM26m-41; DOM26m-42; DOM26m-43; DOM26m-44; DOM26m-45; DOM26m-46; DOM26m-47; DOM26m-48; DOM26m-52; DOM26m-52-1; DOM26m-52-2; DOM26m-52-3; DOM26m-52-4; DOM26m-52-5; DOM26m-52-6; DOM26m-52-7; DOM26m-6; DOM26m-60; DOM26m-61-1 ; DOM26m-61-2; DOM26m-61-3; DOM26m-61-4; DOM26m-61-5; DOM26m-61-6; DOM26m-7; DOM26m-73; DOM26m-74; DOM26m-75; DOM26m-76; DOM26m-77; DOM26m-78; DOM26m-79; DOM26m-8; DOM26m-80; DOM26m-81; DOM26m-82; DOM26m-83; DOM26m-9; DOM26m-1; DOM26m-100; DOM26m-101; DOM26m-102; DOM26m-103; DOM26m-106; DOM26m-108; DOM26m-109; DOM26m-109-1; DOM26m-109-2; DOM26m-12; DOM26m-18; DOM26m-19; DOM26m-20; DOM26m-20-1; DOM26m-20-2; DOM26m-20-3; DOM26m-20-4; DOM26m-20-5; DOM26m-20-6; DOM26m-22 ; DOM26m-23; DOM26m-24; DOM26m-25; DOM26m-26; DOM26m-3 ; DOM26m-50; DOM26m-50-1; DOM26m-50-2 ; DOM26m-50-3; DOM26m-50-4; DOM26m-50-5; DOM26m-50-6; DOM26m-51; DOM26m-53; DOM26m-54; DOM26m-55; DOM26m-56; DOM26m-57; DOM26m-58; DOM26m-59; DOM26m-61; DOM26m-63; DOM26m-64; DOM26m-66; DOM26m-69; DOM26m-85; DOM26m-86; DOM26m-87; DOM26m-89; DOM26m-90; DOM26m-91; DOM26m-92; DOM26m-93; DOM26m-94; DOM26m-95; DOM26m-96; DOM26m-97; DOM26m-98; DOM26m-99.

29. A dAb amino acid sequence that competes for binding to mouse ASGPR with any one of the amino acid sequences of claim 28.

30. A dAb amino acid sequence according to any one of claims 25-27 and further in accordance with claim 28 or 29, which cross-reacts with mouse and human ASGPR.

31. A dAb amino acid sequence according to any one of claims 25-30, wherein said dAb amino acid sequence comprises at least one CDR selected from the group consisting of: CDR1, CDR2, and CDR3, wherein the CDR1, CDR2, or CDR3 is 100%, 95%, 90%, 85% or 80% identical to a CDR1, CDR2, or CDR3 sequence in any one of the sequences of claims 25 -30.

32. A composition according to any one the preceding claims for use in medicine.

33. A method of treating or preventing at least one liver disease or disorder or condition by administering to a subject a therapeutically or prophylactically effective amount of a ccomposition according to any one of claims 1-31.

34. The method of claim 33, wherein said at least one liver disease or disorder or condition is selected from: an inflammatory liver disease, a viral liver disease, cirrhosis and liver cancer.

35. The method according to claim 34, wherein said at least one liver disease is selected from: Hepatitis B and Hepatitis C and the inflammatory liver disease is fibrosis.

36. A method of treating or preventing at least one liver disease or disorder or condition by administering to a subject a therapeutically or prophylactically effective amount of a composition according to of a composition according to any one of claims 1-31.

37. The method according to claim 36, wherein said at least one liver disease or disorder or condition is selected from: a viral liver disease, cirrhosis and liver cancer.

38. The method according to claim 37, wherein said at least one viral liver disease is selected from: Hepatitis B and Hepatitis C.

39. The method according to any one of claims 33-38, wherein said composition is delivered to a subject by subcutaneous, intravenous or intramuscular injection.

40. The method as claimed in any one of claims 33-39 wherein said composition is delivered to the subject via parenteral, oral, rectal, transmucosal, ocular, pulmonary or GI tract delivery.

41. An injectable, oral, inhalable or nebulisable formulation which comprises a composition according to any one of claims 1-31.

42. A sustained release formulation which comprises a composition according to any one of claims 1-31.

43. A freeze dried formulation which comprises a composition according to any one of claims 1-31.

44. A delivery device comprising a composition according to any one of claims 1-31.

45. An isolated or recombinant nucleic acid encoding a dAb that binds to the ASGPR receptor on hepatocytes wherein said nucleotide sequence is selected from a sequence that is 100%, 95%, 90%, 85% or 80% identical to any one of the DOM 26 nucleic acid sequences shown in Figures 13, 14 , 17, 18 or 32.

46. A vector comprising a nucleic acid of claim 45.

47. A host cell comprising the nucleic acid of claim 45 or the vector of claim 46.

48. A method of producing a fusion polypeptide comprising (a) a dAb that binds to ASGPR receptor on hepatocytes and also (b) at least one therapeutic

molecule for delivery to the liver, wherein said method comprises maintaining a host cell of claim 47 under conditions suitable for expression of said nucleic acid or vector, whereby a fusion polypeptide is produced.

Figure 1

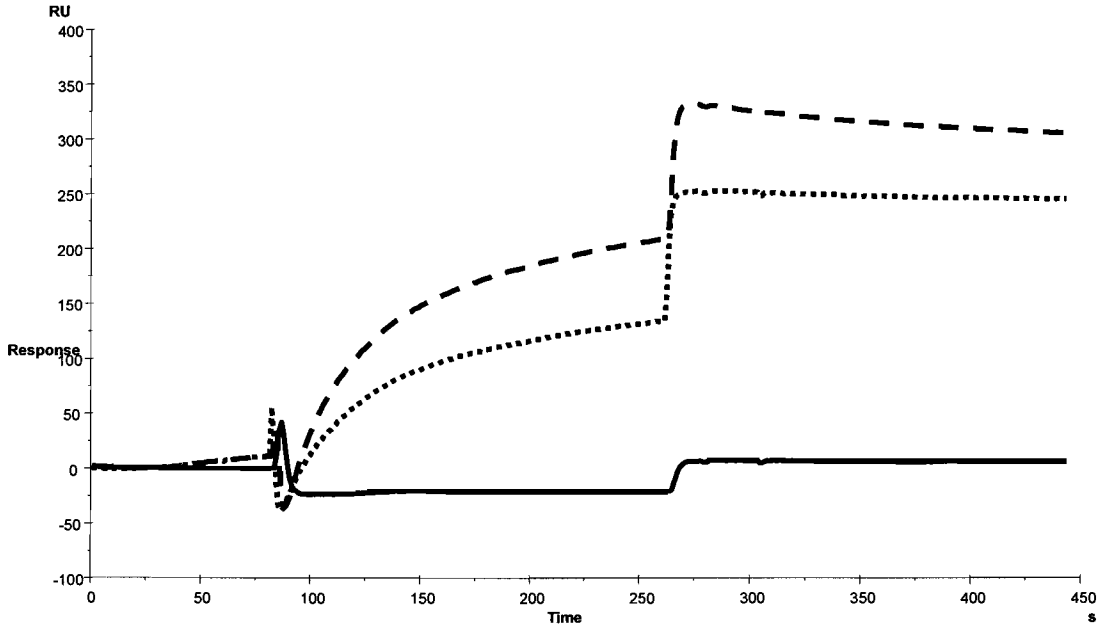


Figure 1 shows binding of β-GalNAc-PAA-biotin to human $(His)_6$-ASGPR H1 (– – –), mouse $(His)_6$-ASGPR H1 (.....) and human $(His)_6$-GP6 irrelevant control antigen (———).

Figure 2

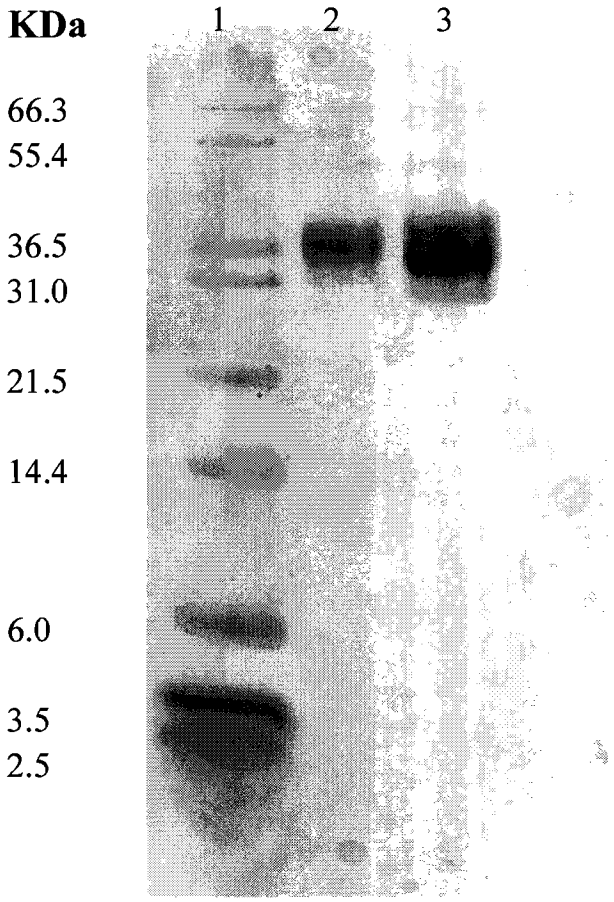


Figure 2 shows 4-12% Bis-Tris gel loaded with 2μg of Ni-NTA purified human $(His)_6$-ASGPR H1 (lane 2) or mouse $(His)_6$-ASGPR H1 (lane 3). Molecular weight standards (Invitrogen) were loaded in lane 1

Figure 3

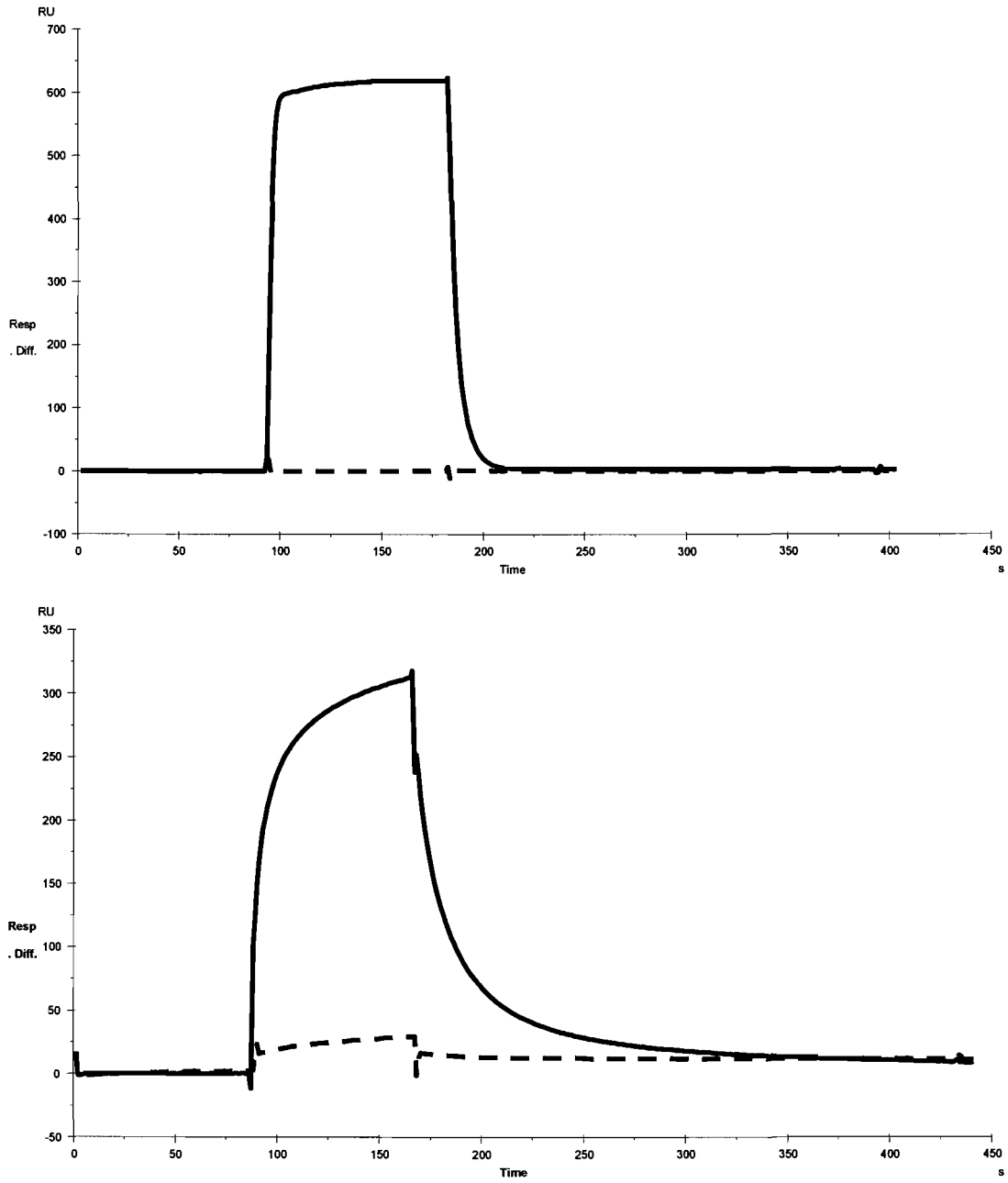


Figure 3: Vκ and V_H dAbs selected against recombinant human and mouse ASGPR proteins binding specifically to the target antigen. Antigens were coated on the surface of a CM5 BIAcore chip and protein L purified Vκ dAb DOM26m-20 (top panel) or protein A purified V_H dAb DOM26h-61 (bottom panel) was passed over the chip surface at a concentration of 2.5μM using a flow-rate of 10μl per second. In the top panel binding of dAb to $(His)_6$- mouse ASGPR H1 (——) or human c-kit $(His)_6$

negative control antigen (– – –) is shown. In the bottom panel dAb binding to $(His)_6$- human ASGPR H1 (———) or human c-kit $(His)_6$ negative control antigen (– – –) is shown.

Figure 4

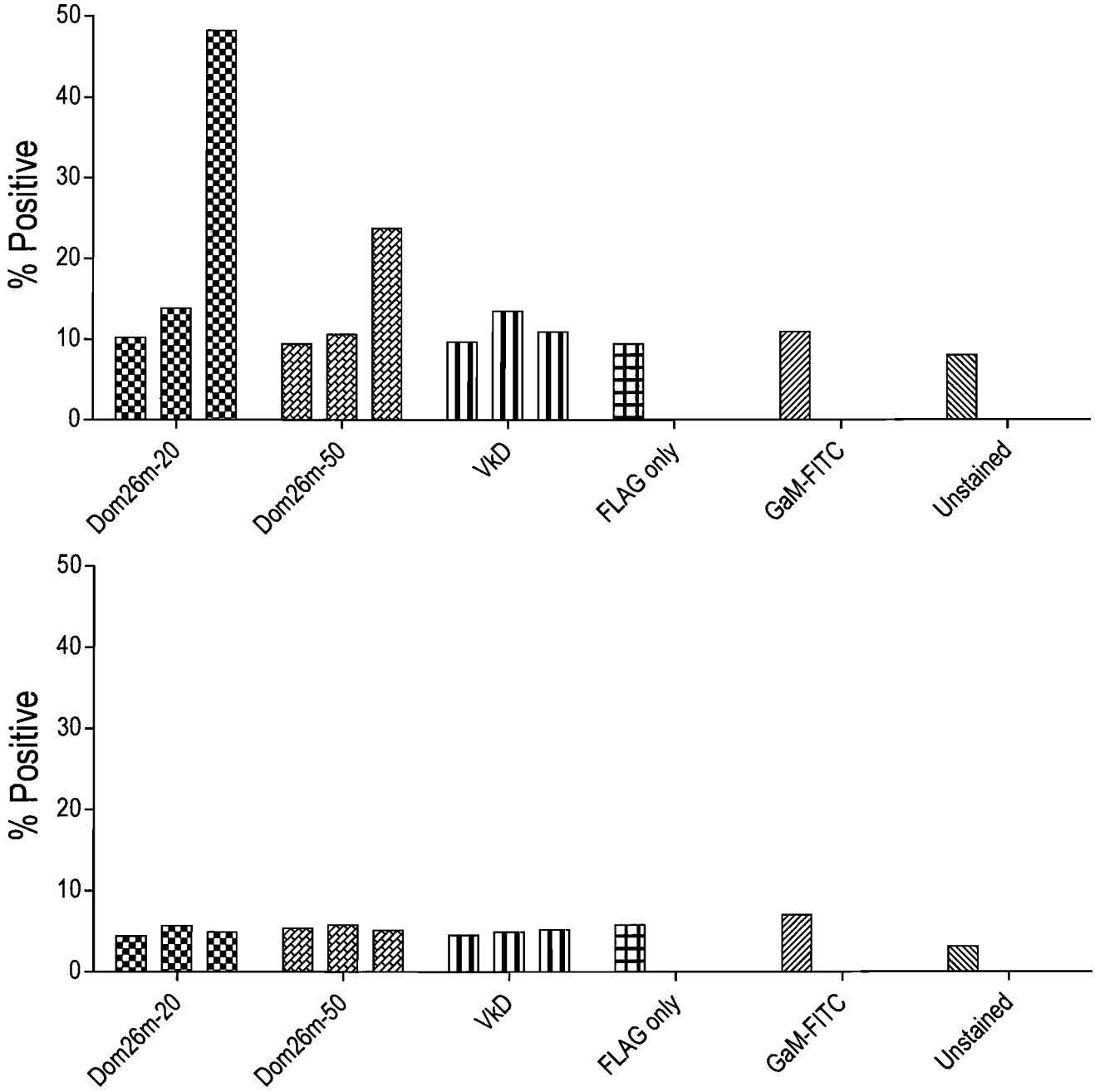
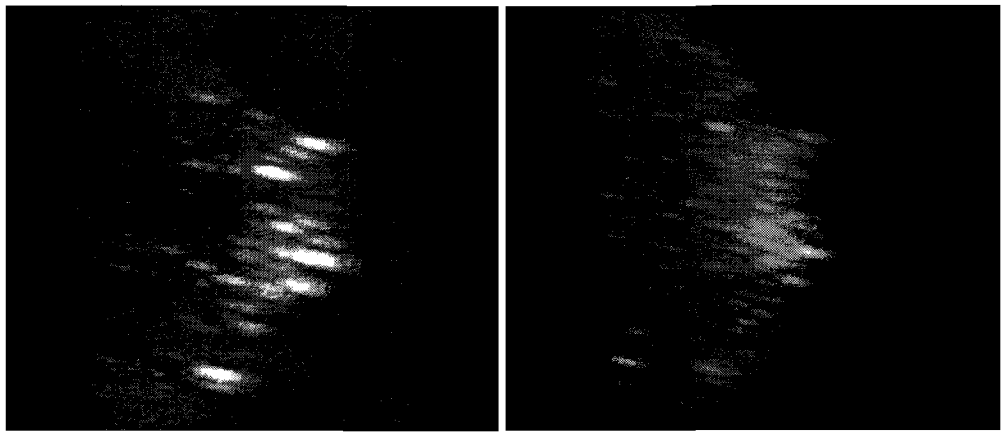
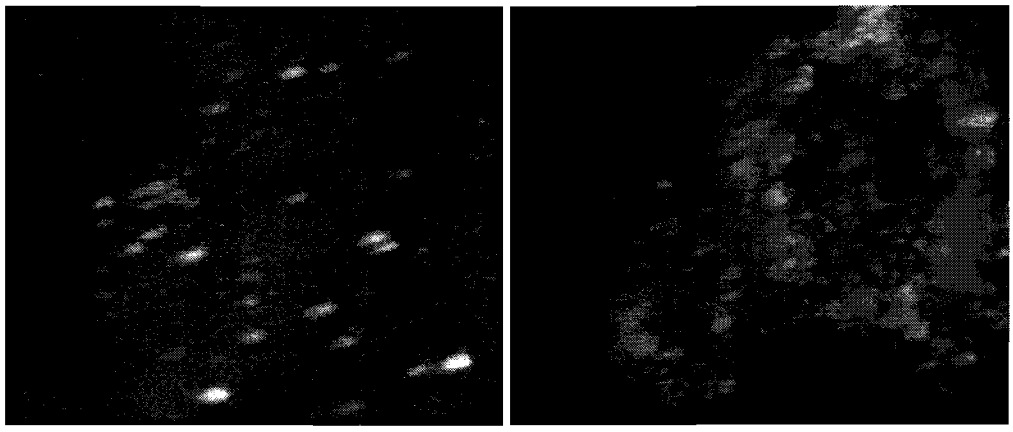


Figure 4 shows dAb clones selected against recombinant $(His)_6$- mouse ASGPR H1 antigen binding specifically to murine liver cell lines in a flow cytometry cell binding assay.

Figure 5



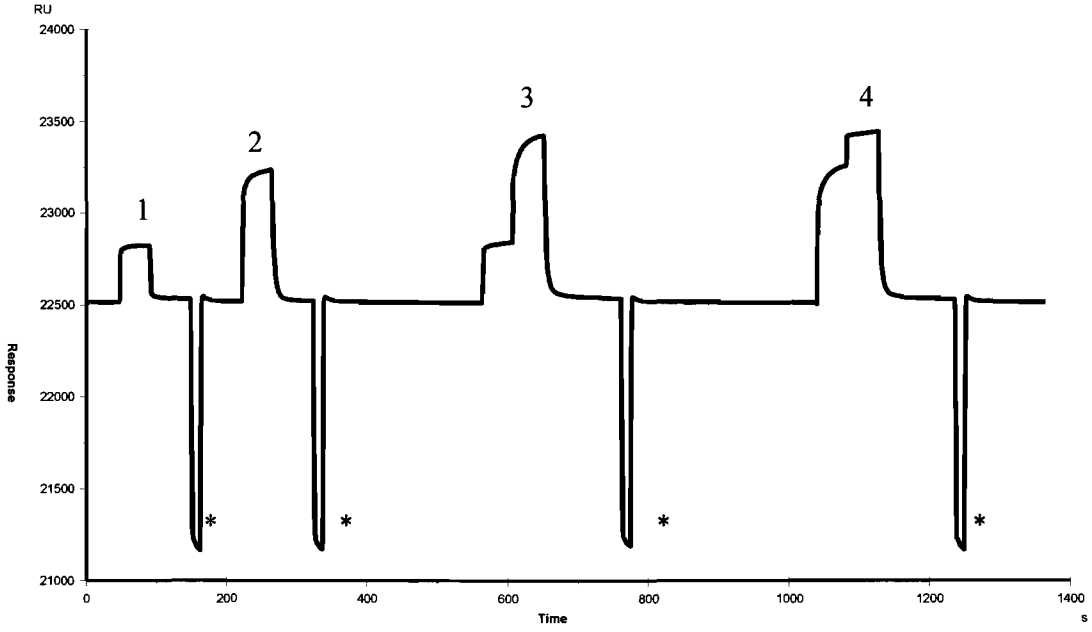
DOM26m-33 EEA1



DOM26m-33 LAMP1

Figure 5 shows binding and localisation of anti-mouse ASGPR dAb DOM26m-33 following incubation with Hepa1c1c7 murine liver cell line.

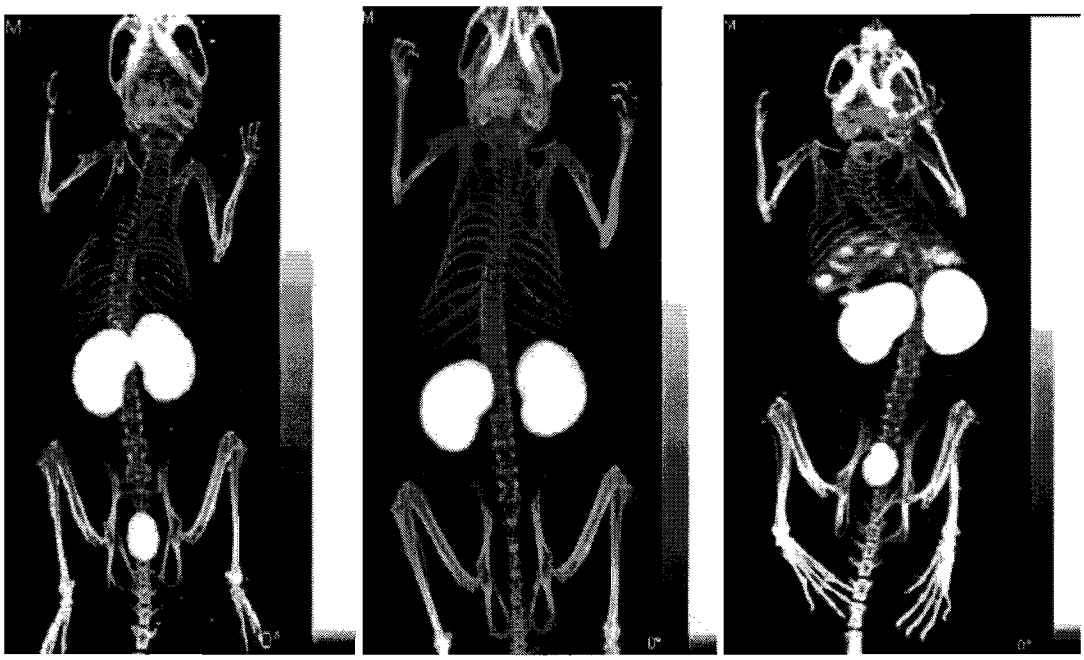
Figure 6



dAb 1	dAb 2	dAb 1 RU	dAb 2 RU	dAb 1+dAb 2 co inject RU	dAb 2+dAb 1 co inject RU	dAb 1 % binding co inject	dAb 2 % binding co inject
DOM26m-33	DOM26m-52	306.2	717.5	149	498.3	48.7	69.4

Figure 6 shows BIAcore sensorgram from epitope mapping experiment to determine whether mouse ASGPR specific dAbs DOM26m-33 and DOM26m-52 bind to distinct epitopes within the antigen.

Figure 7



Vκ dummy V_H dummy 2 DOM26m-33

Figure 7 shows localisation of ^{111}In labelled dAbs in balb/c mice at 3 hours post injection.

Figure 8

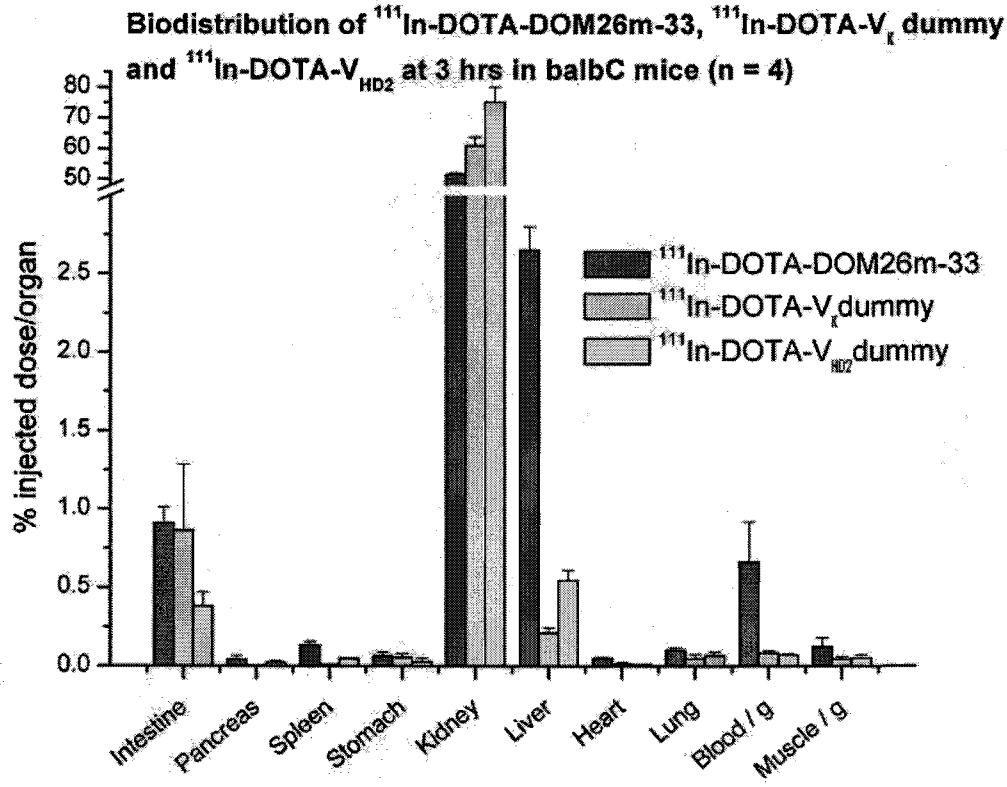


Figure 8 shows biodistribution of ^{111}In labelled dAbs 3 hours after dosing intravenously in balb/c mice via the tail vein.

Figure 9

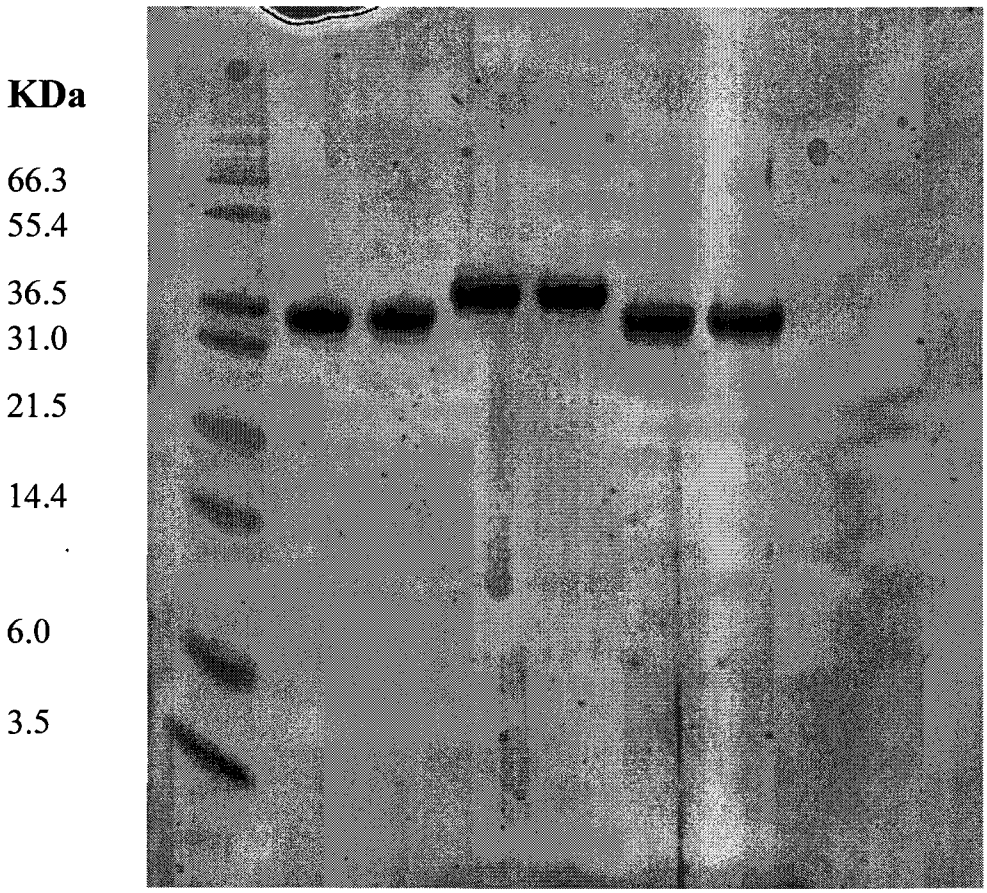


Figure 9 shows 4-12% Bis-Tris gel loaded with 2μg per lane of protein L purified mIFNa2-dAb fusions reduced with 10mM DTT. Lane designations as follows:

mIFNa2-Vκ dummy (lane 2),

mIFNa2-Vκ dummy with C-terminal cysteine point mutation (lane 3)

mIFNa2-V_H dummy (lane 4)

mIFNa2-V_H dummy with C-terminal cysteine point mutation (lane 5)

mIFNa2-DOM26m-33 (lane 6)

mIFNa2-DOM26m-33 with C-terminal cysteine point mutation (lane 7)

10 μl Mark 12 molecular weight standards (Invitrogen) were loaded in lane 1 and molecular masses (in kilodaltons) of individual marker bands are given to the left of lane 1. Gel was stained with 1x SureBlue. Gel illustrates that mouse IFNa2-dAb fusions migrate close to the expected molecular mass of approximately 33 KDa.

Figure 10

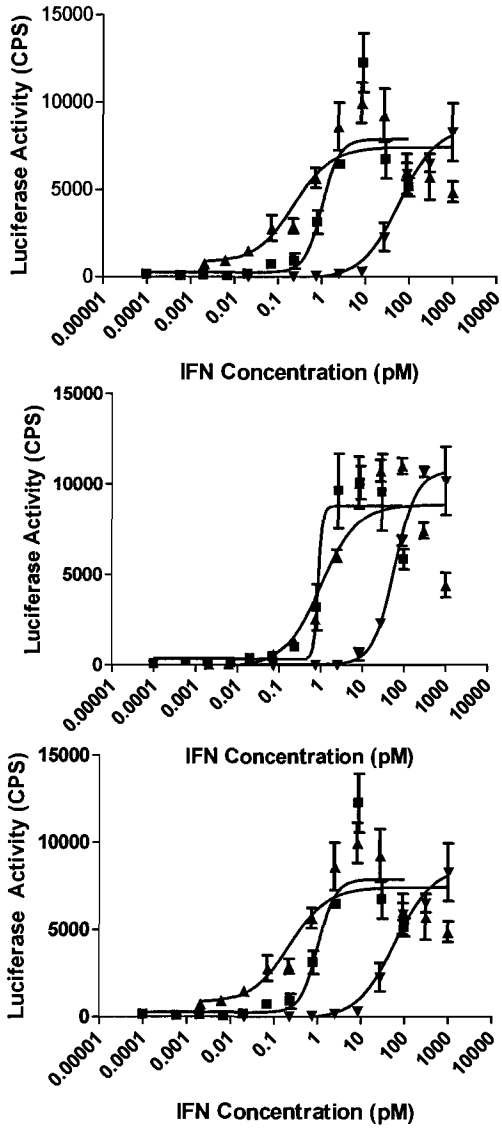


Figure 10 shows activity of mouse IFN-dAb fusions in CHO ISRE-Luc transient transfection assay. Symbols denote the following:

▲= mouse IFNa2-dAb fusions

■= mouse IFNa2-dAb fusions with C-terminal cysteine mutation

▼= mouse IFN-alpha standard

Figure 11:a

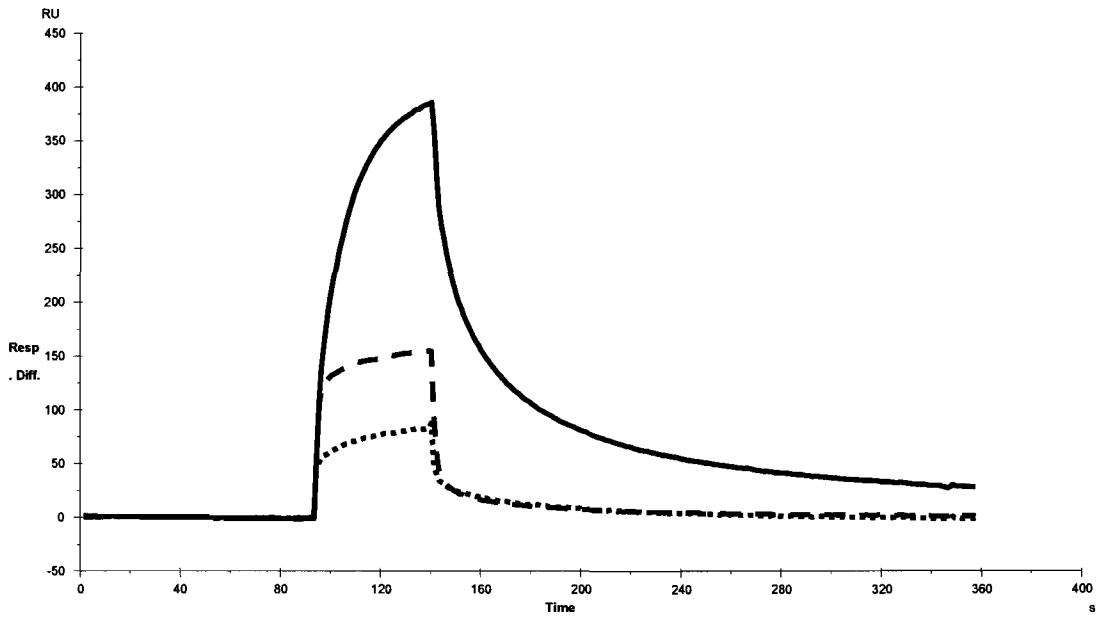


Figure 11a shows binding of mouse mouse IFNa2-DOM26m-33 fusions to (His)6 mouse ASGPR H1 coated on the surface of BIAcore CM5 chip.
Traces represent binding of DOM26m-33 only (·····) shown in all panels for comparison, mouse IFNa2-dAb fusions (– – –) and mouse IFNa2-dAb fusions with C-terminal cysteine mutation (———).

Figure 11:b

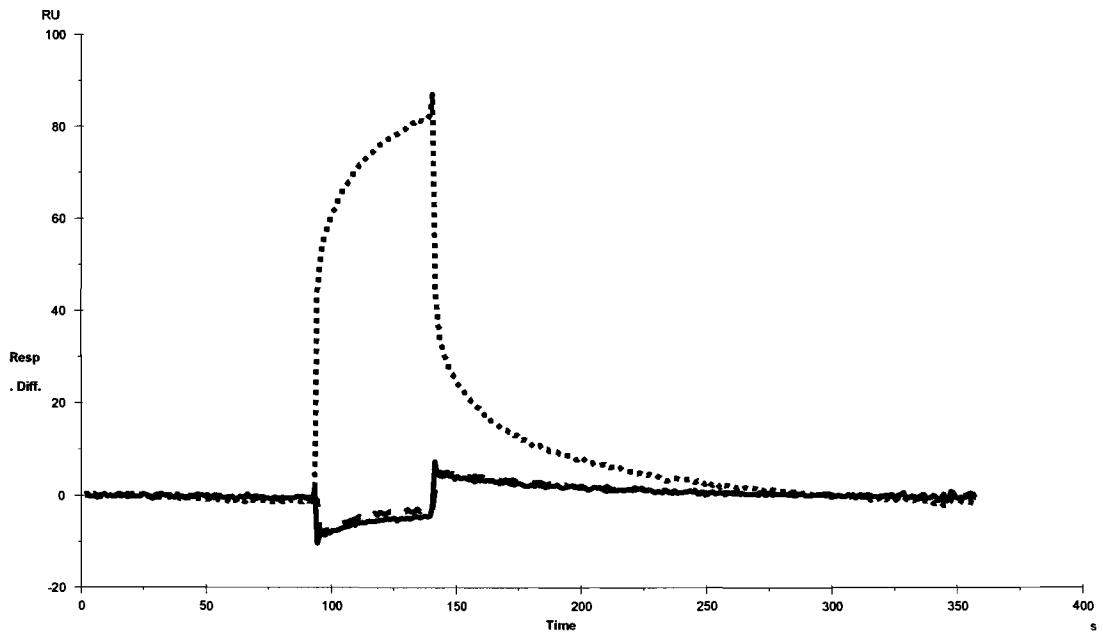


Figure 11b shows binding of mouse mouse IFNa2-DOM26m-33 fusions to (His)6 mouse ASGPR H1 coated on the surface of BIAcore CM5 chip.
Traces represent binding of DOM26m-33 only (·····) shown in all panels for comparison, mouse IFNa2-dAb fusions (– – –) and mouse IFNa2-dAb fusions with C-terminal cysteine mutation (———).

Figure 11:c

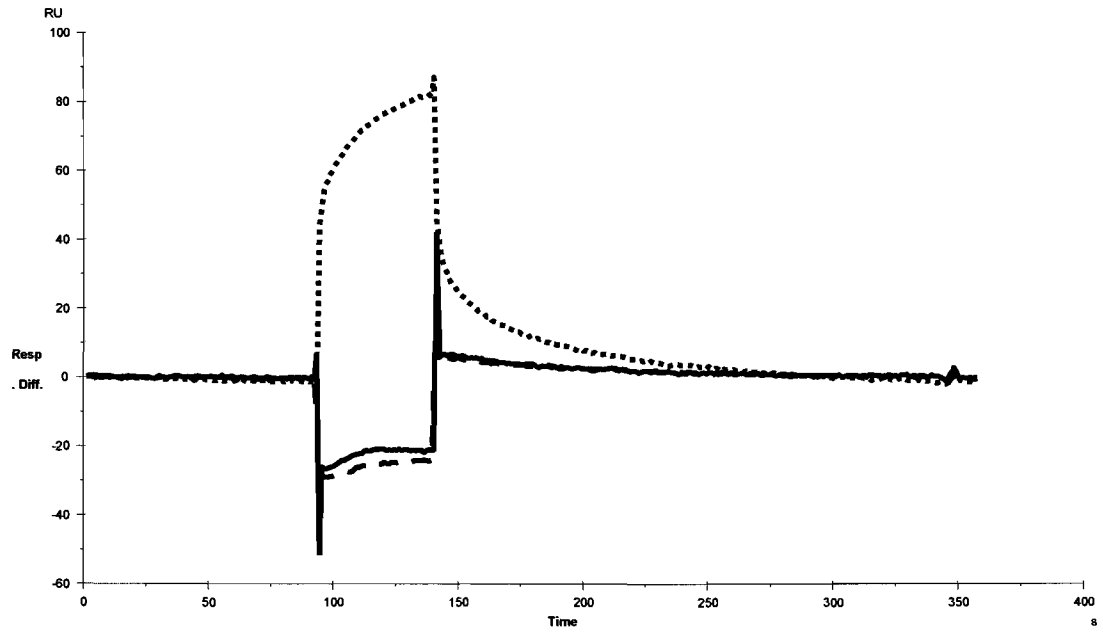


Figure 11c shows binding of mouse mouse IFNa2-DOM26m-33 fusions to (His)6 mouse ASGPR H1 coated on the surface of BIAcore CM5 chip.
Traces represent binding of DOM26m-33 only (·····) shown in all panels for comparison, mouse IFNa2-dAb fusions (– – –) and mouse IFNa2-dAb fusions with C-terminal cysteine mutation (———).

Figure 12: murine ASGPR clones grouped according to epitope bound

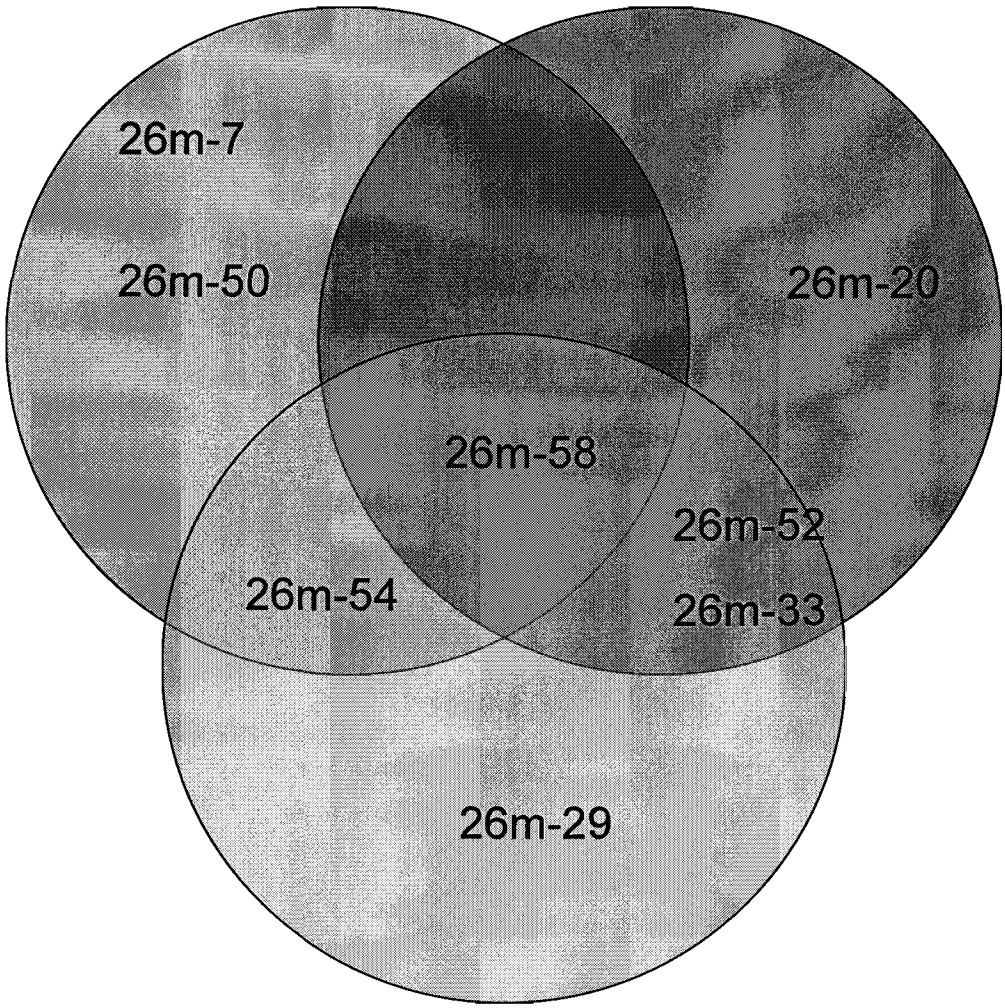


Figure 13: Nucleotide Sequence of V_H ASGPR dAbs

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CCAGGGAAGG GTCTAGAGTG GGTCTCATCT ATTAAGCCTT CGGGTACGAT TACATACTAC
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CTGCAAATGA ACAGCCTGCG TGCCGAGGAC ACCGCGGTAT ATTACTGTGC GAAAGTGAAG
AGTGGTTATC CTAGGGTGTT TACGGATGCG TTTGACTACT GGGGTCAGGG AACCCTGGTC
ACCGTCTCGA GC

>DOM26h-10
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GCAGACTCCG TGAAGGGCCG GTTCACCATC TCCCGCGACA ATTCCAAGAA CACGCTGTAT
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>DOM26h-100
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CTGCAAATGA ATAGCCTGCG TGCCGAGGAC ACCGCGGTAT ATTACTGTGC GAAACATAAT
CAGAGGCTTG GTAGGTTTGA CTACTGGGGT CAGGGAACCC TGGTCACCGT CTCGAGC

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GCAGACTCCG TGAAGGGCCG GTTCACCATC TCCCGCGACA ATTCCAAGAA CACGCTGTAT
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TCCTGTGCAG CCTCCGGATT CACCTTTGAG CATAATGAGA TGGGTTGGGT CCGCCAGGCT
CCAGGGAAGG GTCTGGAGTG GGTCTCAATT ATTGATCCTA GTGGTCATCA TACATACTAC
GCAGACTCCG TGAAGGGCCG GTTCACCATC TCCCGCGACA ATTCCAAGAA CACGCTGTAT

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GATAATTTTG ACTACTGGGG TCAGGGAACC CTGGTCACCG TCTCGAGC

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GCAGACTCCG TGAAGGGCCG GTTCACCATC TCCCGCGACA ATTCCAAGAA CACGCTGTAT
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Figure 14: Nucleotide Sequence of V_H ASGPR dAbs

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CGTTTCAGTG GCAGTGGATC TGGGACAGAT TTCACTCTCA CCATCAGCAG TCTGCAACCT
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CGTTTCAGTG GCAGTGGATC TGGGACAGAT TTCACTCTCA CCATCAGCAG TCTGCAACCT
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CGTTTCAGTG GCAGTGGGTC TGGGACAGAT TTCACTCTCA CCATCAGCAG TCTGCAACCT
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CGTTTCAGTG GCAGTGGATC TGGGACAGAT TTCACTCTCA CCATCAGCAG TCTGCAACCT
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GAAGATTTTG CTACGTACTA CTGTCAACAG TTTTATCGGC ATCCTACTAC GTTCGGCCAA
GGGACCAAGG TGGAAATCAA ACGG

Figure 15: Alignment of Amino Acid Sequences of V_H Clones

Kabat Residue	'	'	'	'	5	'	'	'	'	10	'	'	'	'	15	'	'	'	'	20
VHDUM-1	E	V	Q	L	L	E	S	G	G	G	L	V	Q	P	G	G	S	L	R	L
DOM26h-1	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26h-10	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
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DOM26h-102	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26h-103	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
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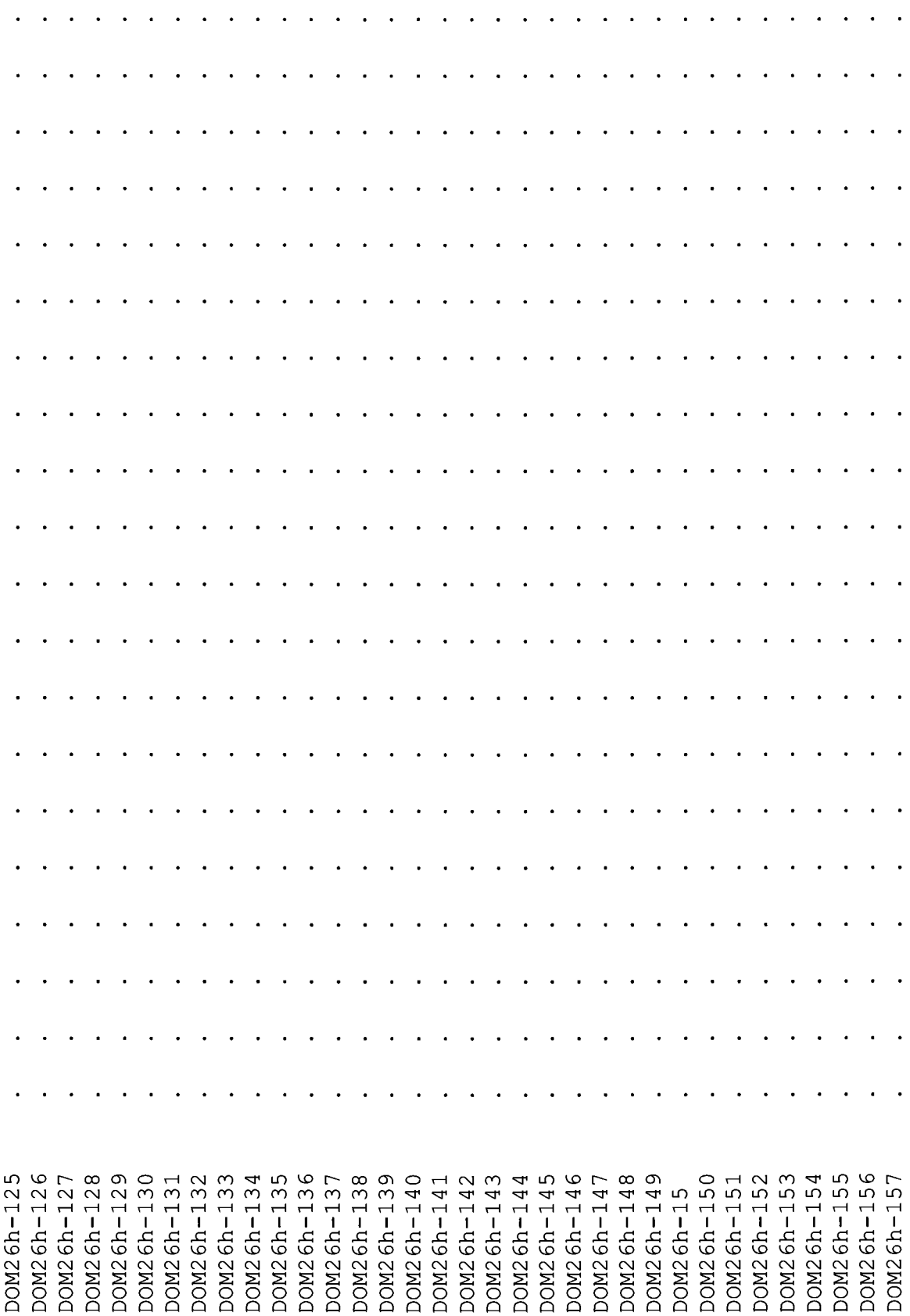
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DOM26h-129	.	.	.	.	.	.	.	.	.	E	.	Q	D	.	G	.	.	.	.	.
DOM26h-130	.	.	.	.	.	.	.	.	.	D	M	A	D	.	T	.	.	.	.	.
DOM26h-131	.	.	.	.	.	.	.	.	.	A	K	.	D	.	M	.	.	.	.	.
DOM26h-132	.	.	.	.	.	.	.	.	.	L	N	K	P	.	A	.	.	.	.	.
DOM26h-133	.	.	.	.	.	.	.	.	.	G	N	I	T	.	G	.	.	.	.	.
DOM26h-134	.	.	.	.	.	.	.	.	.	.	D	S	P	.	.	.	.	.	.	.
DOM26h-135	.	.	.	.	.	.	.	.	.	E	G	S	N	.	H	.	.	.	.	.
DOM26h-136	.	.	.	.	.	.	.	.	.	G	Q	.	M	.	G	.	.	.	.	.
DOM26h-137	.	.	.	.	.	.	.	.	.	N	N	S	P	.	F	.	.	.	.	.
DOM26h-138	.	.	T	.	.	.	.	.	.	D	Q	E	T	.	G	.	.	.	.	.
DOM26h-139	.	.	.	.	.	.	.	.	.	P	.	.	N	.	H	.	.	.	.	.
DOM26h-140	.	.	.	.	.	.	.	.	.	H	D	K	T	.	M	.	.	.	.	.
DOM26h-141	.	.	.	.	.	.	.	.	.	D	H	.	L	.	G	.	.	.	.	.
DOM26h-142	.	.	.	.	.	.	.	.	.	E	R	.	P	.	M	.	.	.	.	.
DOM26h-143	.	.	.	.	.	.	.	.	.	A	A	.	P	.	G	.	.	.	.	.
DOM26h-144	.	.	.	.	.	.	.	.	.	A	G	T	N	.	.	.	.	.	.	.
DOM26h-145	.	.	.	.	.	.	.	.	.	.	A	.	P	.	H	.	.	.	.	.
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DOM26h-147	.	.	.	.	.	.	.	.	.	R	Y	G	N	.	G	.	.	.	.	.
DOM26h-148	.	.	.	.	.	.	.	.	.	D	G	.	.	.	M	.	.	.	.	.
DOM26h-149	.	.	.	.	.	.	.	.	.	M	D	T	G	.	M	.	.	.	.	.
DOM26h-15	.	.	.	.	.	.	.	.	.	P	K	.	S	.	F	.	.	.	.	.
DOM26h-150	.	.	.	.	.	.	.	.	.	.	A	.	D	.	M	.	.	.	.	.
DOM26h-151	.	.	.	.	.	.	.	.	.	E	D	T	L	.	F	.	.	.	.	.
DOM26h-152	.	.	.	.	.	.	.	.	.	V	N	.	S	.	G	.	.	.	.	.
DOM26h-153	.	.	.	.	.	.	.	.	.	N	Q	Q	D	.	.	.	.	.	.	.
DOM26h-154	.	.	.	.	.	.	.	.	.	G	D	G	N	.	G	.	A	.	.	.
DOM26h-155	.	.	.	.	.	.	.	.	.	D	N	.	G	.	M	.	.	.	.	.
DOM26h-156	.	.	.	.	.	.	.	.	.	.	N	.	V	.	G	.	.	.	.	.
DOM26h-157	.	.	.	.	.	.	.	.	.	H	D	K	T	.	M	.	.	.	.	.
DOM26h-158	.	.	.	.	.	.	.	.	.	D	L	.	D	.	G	.	.	.	.	.
DOM26h-159	.	.	.	.	.	.	.	.	.	A	D	.	S	.	Y	.	.	.	.	.

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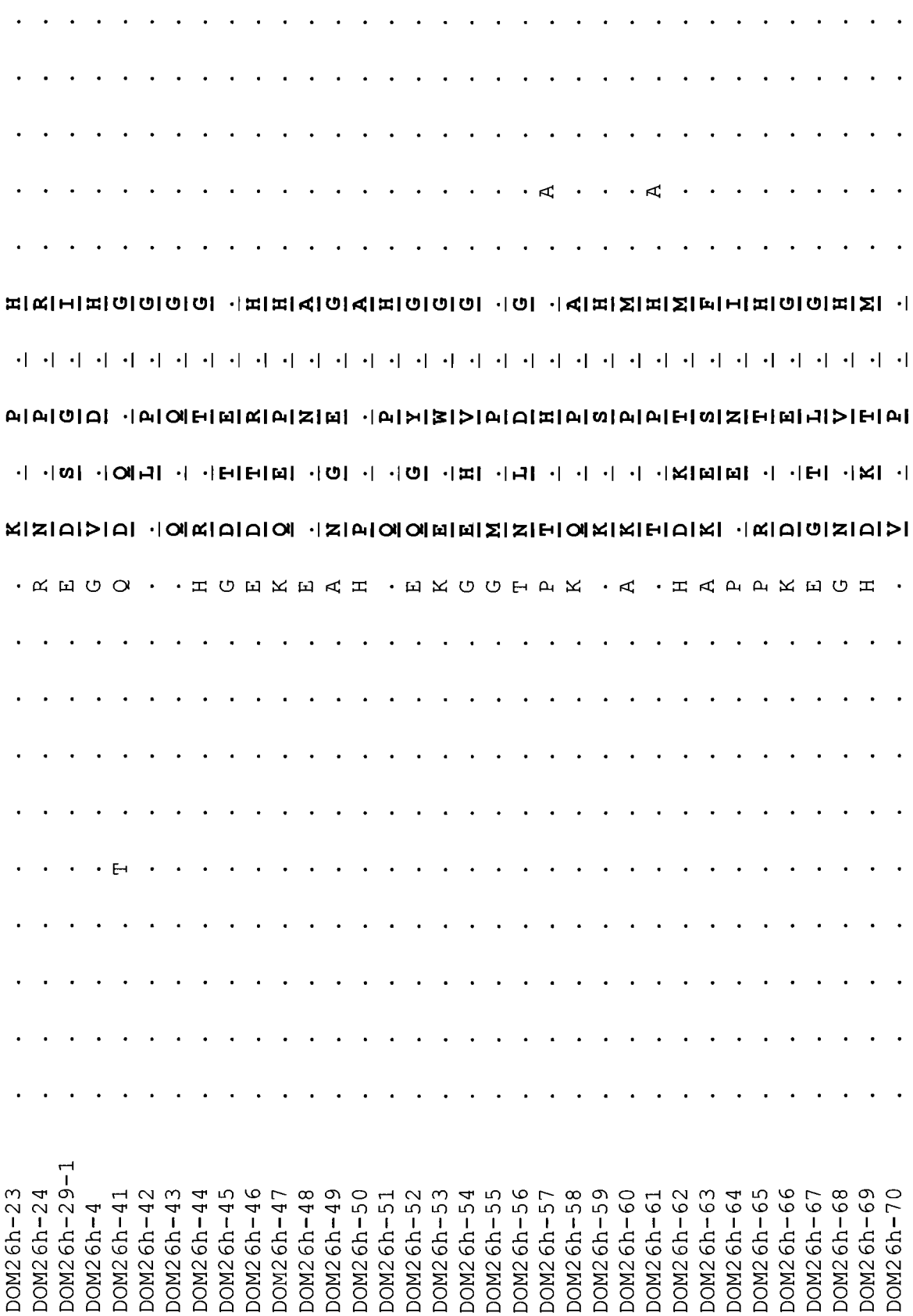
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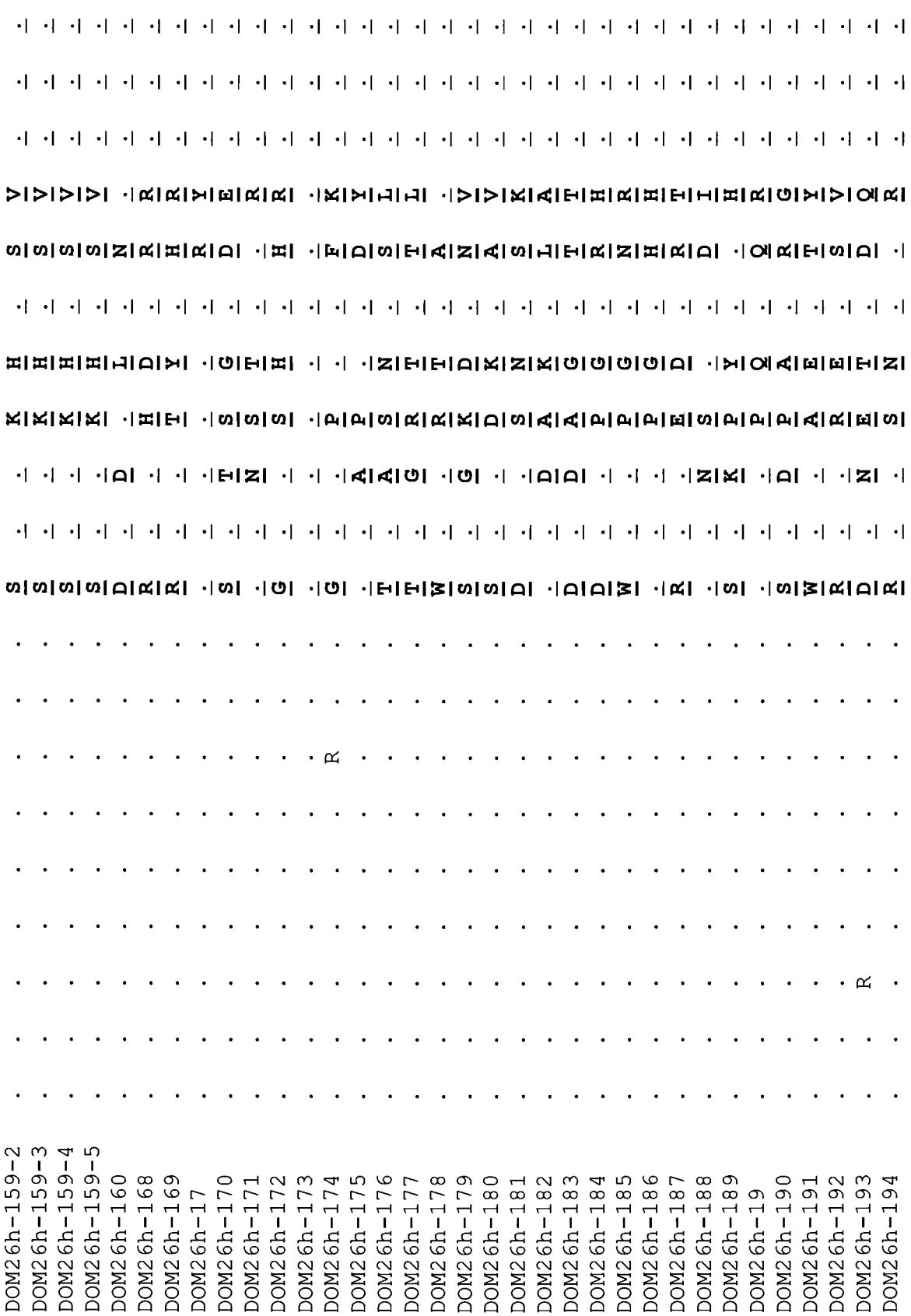
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DOM26h-99-2	.	.	.	.	.	.	.	.	.	S	.	.	S	T	.	L	.	.	.	.

Kabat Residue	'	'	'	'	64	'	'	'	'	69	'	'	'	'	74	'	'	'	'	79
VHDUM-1	**A**	**D**	**S**	**V**	**K**	**G**	R	F	T	I	S	R	D	N	S	K	N	T	L	Y
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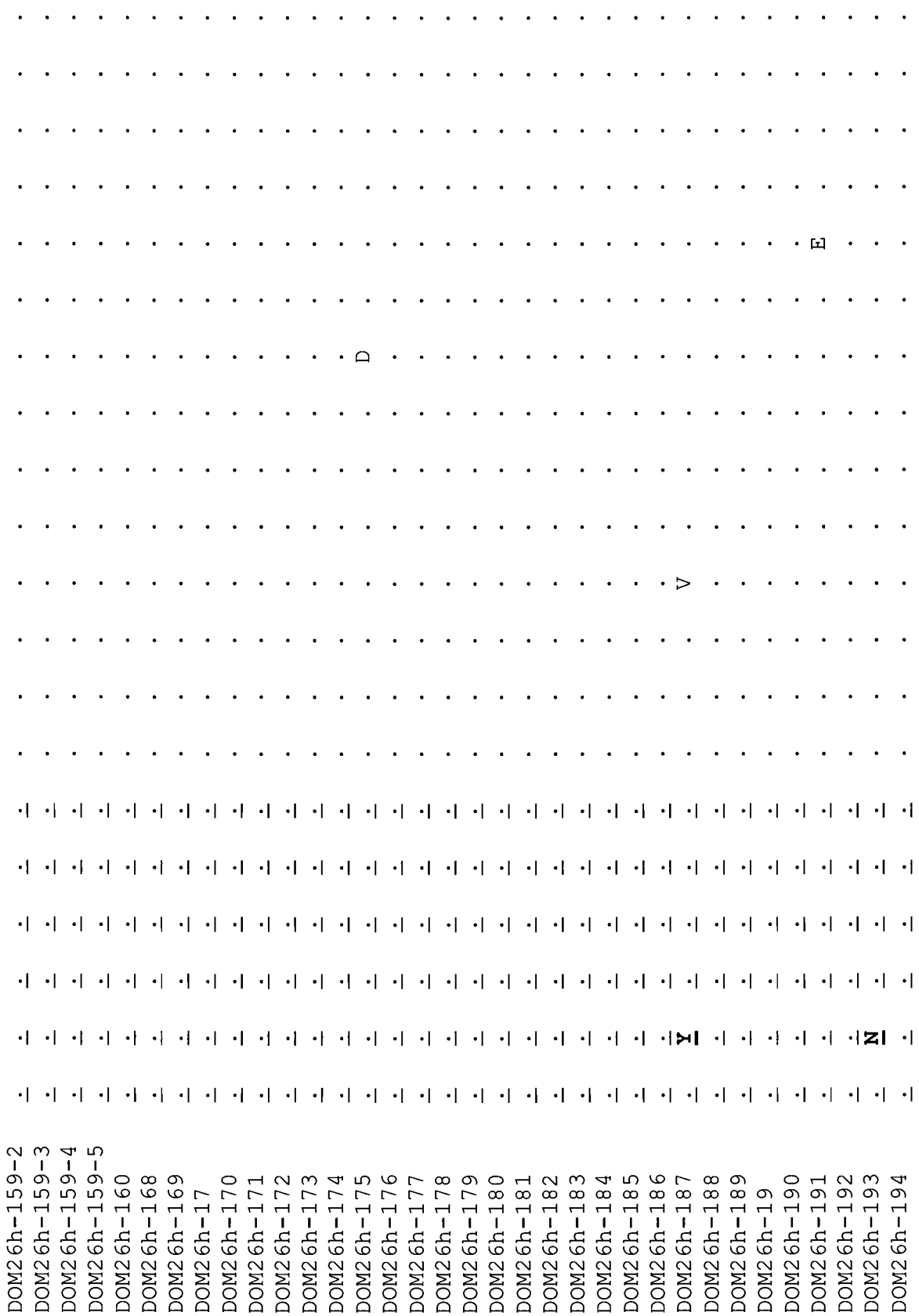
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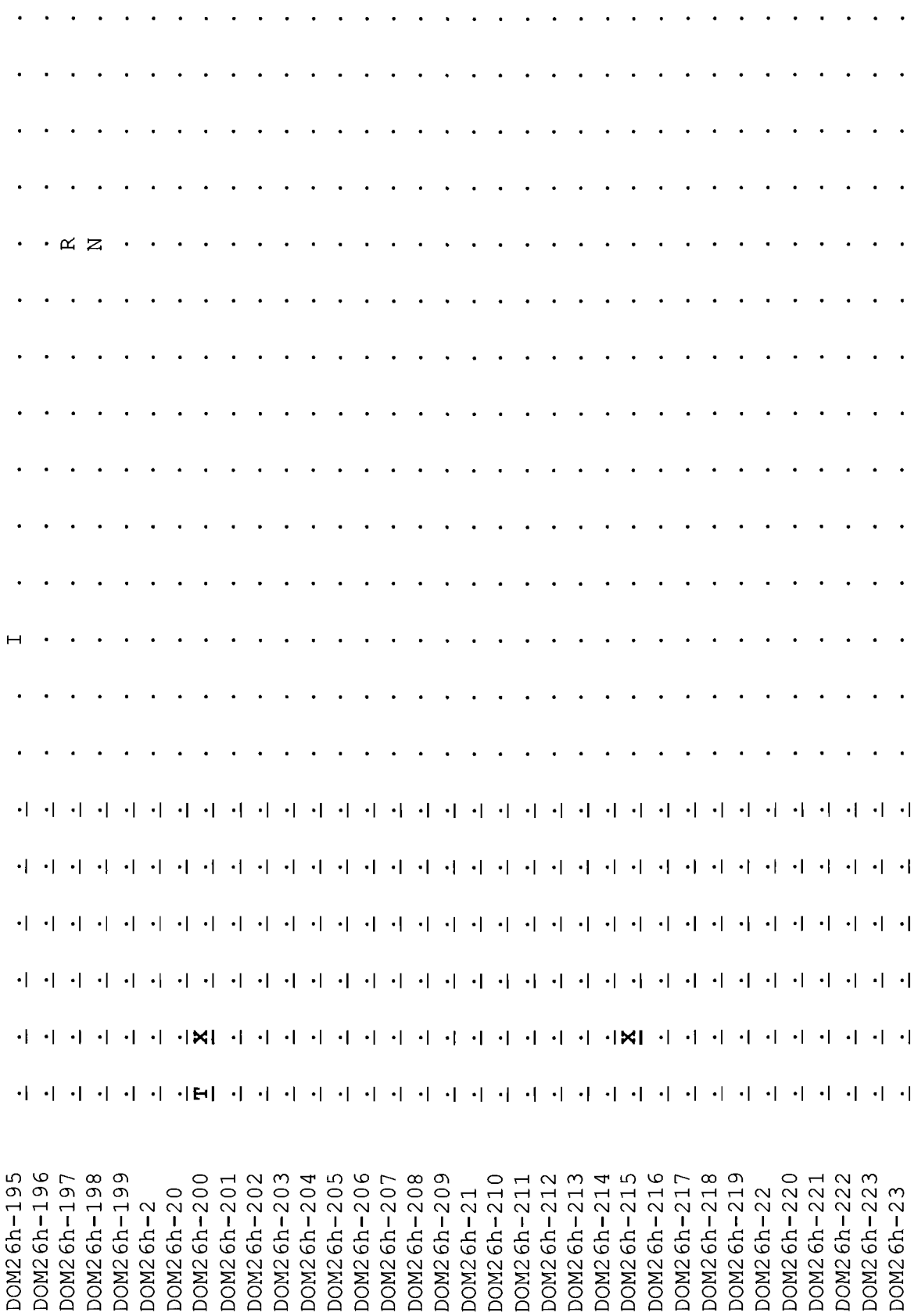
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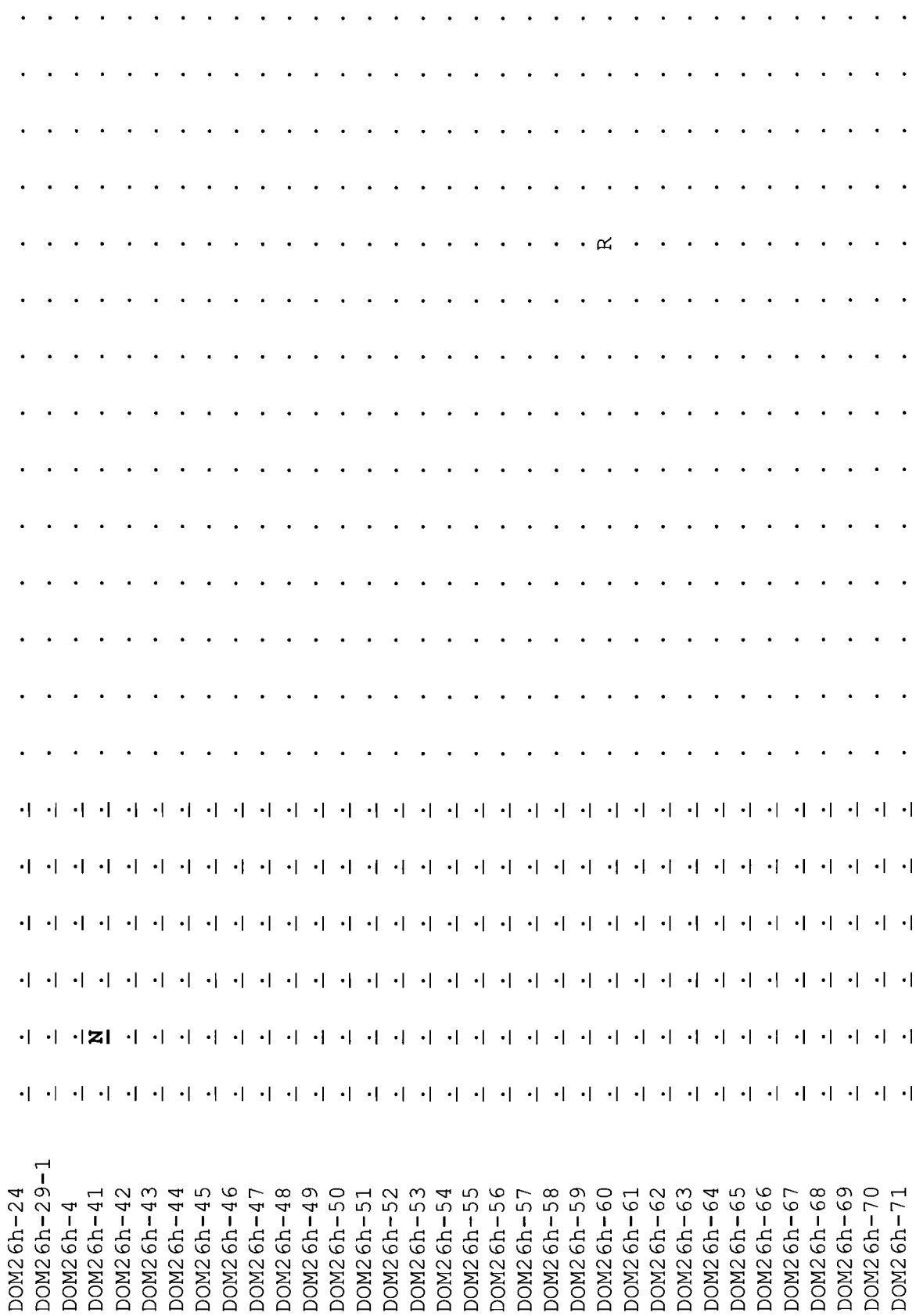
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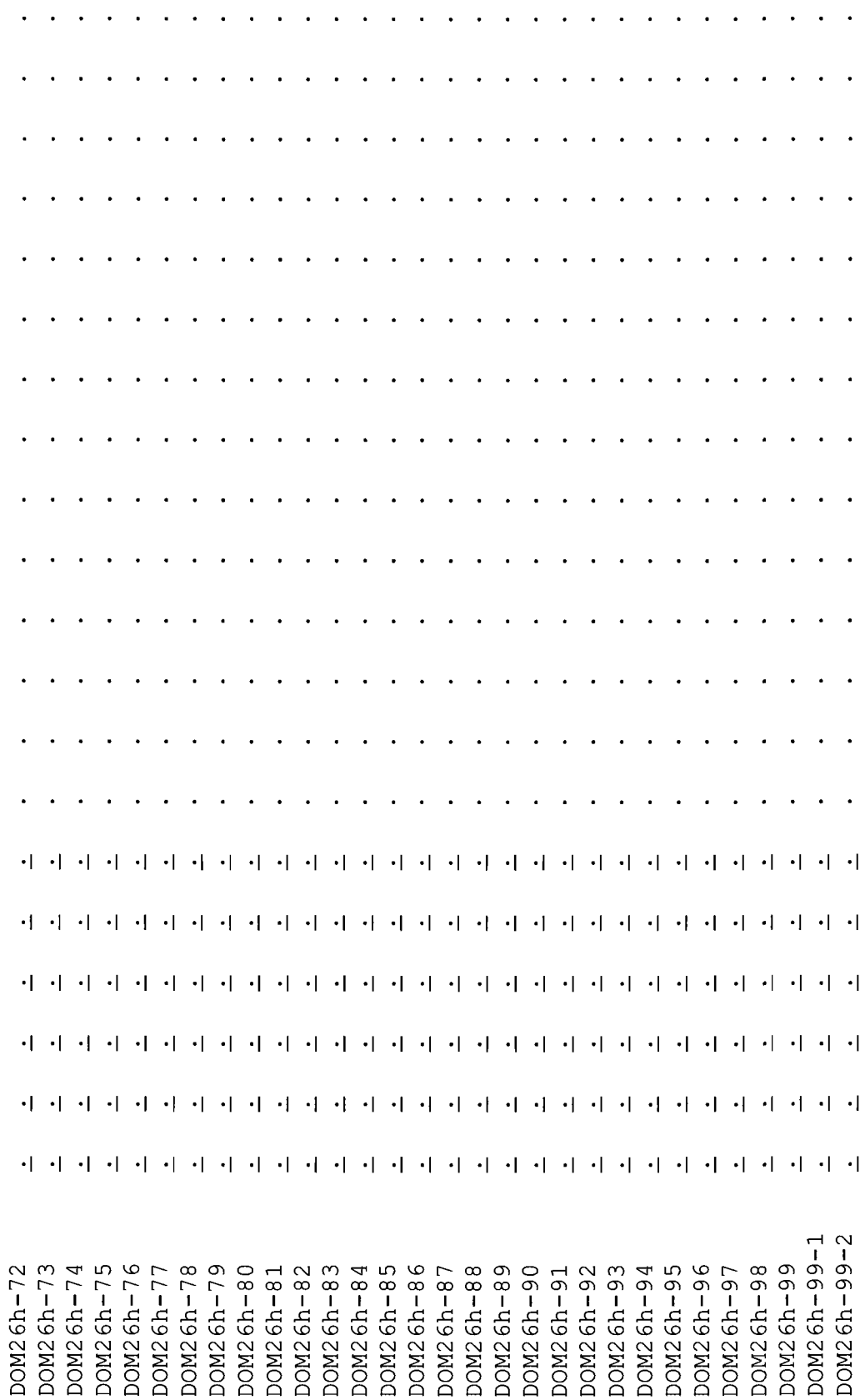
DOM26h-69
DOM26h-70
DOM26h-71
R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DOM26h-82
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DOM26h-89
DOM26h-90
DOM26h-91
DOM26h-92
DOM26h-93
DOM26h-94
DOM26h-95
DOM26h-96
DOM26h-97
DOM26h-98
DOM26h-99
DOM26h-99-1
DOM26h-99-2

Kabat Residue	'	'	'	'	82b	'	'	'	'	86	'	'	'	'	91	'	'	'	'	96
VHDUM-1	L	Q	M	N	S	L	R	A	E	D	T	A	V	Y	Y	C	A	K	**S**	**Y**
DOM26h-1	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	**V**	**K**
DOM26h-10	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	**L**	**F**
DOM26h-100	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	**Y**	**P**
DOM26h-101	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	**Y**	**R**
DOM26h-102	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	**V**	**S**
DOM26h-103	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	**G**	**L**
DOM26h-104	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	**H**	**R**
DOM26h-105	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	**I**	**N**
DOM26h-106	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	**H**	**I**
DOM26h-107	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	**D**	**I**
DOM26h-108	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	**F**	**P**
DOM26h-109	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	**M**	**S**
DOM26h-11	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	E	**H**	**R**
DOM26h-110	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	**G**	.
DOM26h-111	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	**M**	**S**
DOM26h-112	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	**L**	**N**
DOM26h-113	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	E	**G**	**V**
DOM26h-114	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	**G**	**L**
DOM26h-115	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	**L**	**Q**
DOM26h-116	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	**M**	.
DOM26h-117	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	**F**	**S**
DOM26h-118	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	**H**	**N**
DOM26h-119	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	**L**	**G**
DOM26h-12	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	**L**	**P**
DOM26h-120	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	**K**	**G**
DOM26h-121	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	**M**	**M**
DOM26h-122	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	**F**	**N**
DOM26h-123	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	**Q**	**S**
DOM26h-124	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	**D**	**A**
DOM26h-125	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	**M**	**G**
DOM26h-126	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	**W**	**P**
DOM26h-127	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	**N**	**W**

DOM26h-128	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	**G**	**S**
DOM26h-129	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	E	**.**	**G**
DOM26h-130	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	**G**	**.**
DOM26h-131	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	**L**	**D**
DOM26h-132	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	**G**	**D**
DOM26h-133	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	**L**	**E**
DOM26h-134	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	**G**	**F**
DOM26h-135	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	**G**	**I**
DOM26h-136	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	**W**	**P**
DOM26h-137	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	**G**	**P**
DOM26h-138	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	**L**	**N**
DOM26h-139	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	**N**	**V**
DOM26h-140	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	**L**	**G**
DOM26h-141	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	**F**	**R**
DOM26h-142	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	**F**	**K**
DOM26h-143	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	**W**	**P**
DOM26h-144	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	**G**	**L**
DOM26h-145	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	**D**	**V**
DOM26h-146	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	**W**	**T**
DOM26h-147	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	**F**	**H**
DOM26h-148	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	**G**	**M**
DOM26h-149	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	**L**	**D**
DOM26h-15	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	**D**	**L**
DOM26h-150	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	**M**	**T**
DOM26h-151	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	**V**	**R**
DOM26h-152	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	**F**	**P**
DOM26h-153	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	**G**	**L**
DOM26h-154	M	N	S	L	R	A	E	D	T	A	V	Y	Y	C	A	K	M	N	**N**	**H**
DOM26h-155	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	**M**	**P**
DOM26h-156	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	**F**	**P**
DOM26h-157	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	**M**	**S**
DOM26h-158	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	**F**	**P**
DOM26h-159	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	**G**	**L**
DOM26h-159-1	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	V	.	**Q**	**T**

DOM26h-159-2	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	V	.	Q	T	
DOM26h-159-3	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	V	.	Q	T	
DOM26h-159-4	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	V	.	Q	T	
DOM26h-159-5	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	V	.	Q	T	
DOM26h-160		.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	W	T
DOM26h-168	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	R	P	
DOM26h-169	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	M	P	
DOM26h-17	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	R	A	
DOM26h-170	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	L	S	
DOM26h-171	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	X	P	
DOM26h-172	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	V	P	
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DOM26h-174	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	H	V	
DOM26h-175	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	E	L	
DOM26h-176	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	L	I	
DOM26h-177	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	A	G	
DOM26h-178	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	L	G	
DOM26h-179	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	L	R	
DOM26h-180	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	D	V	
DOM26h-181	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	L	R	
DOM26h-182	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	A	
DOM26h-183	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	L	S	
DOM26h-184	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	M	G	
DOM26h-185	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	E	G	S	
DOM26h-186	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	R	S	
DOM26h-187	.	.	.	.	P	.	H	.	.	.	.	.	.	.	.	.	.	.	D	I	
DOM26h-188	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	V	Q	
DOM26h-189	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	G	V	
DOM26h-19	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	R	R	
DOM26h-190	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	E	Q	S	
DOM26h-191	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	P	.	
DOM26h-192	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	Q	S	
DOM26h-193	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	L	I	
DOM26h-194	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	H	G	

DOM26h-195	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	**P**	**S**
DOM26h-196	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	**H**	**K**
DOM26h-197	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	**C**	**G**
DOM26h-198	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	**L**	**D**
DOM26h-199	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	**A**	**S**
DOM26h-2	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	**M**	.
DOM26h-20	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	**G**
DOM26h-200	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	**L**	**S**
DOM26h-201	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	**L**	**S**
DOM26h-202	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	**R**	**N**
DOM26h-203	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	**R**	**G**
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DOM26h-205	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	**N**	.
DOM26h-206	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	**V**	**K**
DOM26h-207	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	Q	**I**	**I**
DOM26h-208	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	**G**	**V**
DOM26h-209	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	T	**L**	**N**
DOM26h-21	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	E	**R**	**A**
DOM26h-210	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	**G**	**G**
DOM26h-211	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	**I**	**D**
DOM26h-212	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	**V**	**N**
DOM26h-213	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	**R**	**N**
DOM26h-214	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	**H**	**T**
DOM26h-215	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	V	.	**H**	**A**
DOM26h-216	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	**L**	**T**
DOM26h-217	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	**L**	**P**
DOM26h-218	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	**Q**	**A**
DOM26h-219	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	Q	**A**	**G**
DOM26h-22	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	**Q**	**S**
DOM26h-220	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	**L**	**R**
DOM26h-221	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	**P**	**R**
DOM26h-222	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	**M**	**N**
DOM26h-223	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	**R**	**P**
DOM26h-23	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	**T**	**V**

DOM26h-24	. . . . .
DOM26h-29-1	. . . . .
DOM26h-4	. . . . .
DOM26h-41	. . . . .
DOM26h-42	. . . . .
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DOM26h-44	. . . . .
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DOM26h-74	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	M	P
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DOM26h-76	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	F	D
DOM26h-77	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	D	T
DOM26h-78	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	D	V
DOM26h-79	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	L	S
DOM26h-80	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	D	V
DOM26h-81	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	E	G	T
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DOM26h-85	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	M	R
DOM26h-86	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	G	S
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DOM26h-89	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	A	S
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DOM26h-92	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	H	T
DOM26h-93	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	D	V
DOM26h-94	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	W	R
DOM26h-95	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	D	I
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DOM26h-98	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	D	A
DOM26h-99	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	D	A
DOM26h-99-1	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	N	A
DOM26h-99-2	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	D	A

Kabat Residue	'	'	'	'	100a	'	'	'	'	100f	'	'	'	'	104	'	'	'	'	109
VHDUM-1	G	A	-	-	-	-	-	-	-	-	F	D	Y	W	G	Q	G	T	L	V
DOM26h-1	S	G	Y	P	R	V	F	T	D	A	.	.	.	.	.	.	.	.	.	.
DOM26h-10	P	R	G	Q	R	K	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26h-100	Y	.	N	R	S	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26h-101	R	M	T	R	K	.	.	.	.	.	.	.	.	R	.	.	.	.	.	.
DOM26h-102	D	M	S	G	S	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26h-103	H	Y	D	S	R	S	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26h-104	.	T	A	H	S	S	F	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26h-105	P	H	T	N	K	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
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DOM26h-107	E	S	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26h-108	L	L	T	P	E	L	V	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26h-109	A	G	F	A	P	S	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26h-11	V	D	G	H	K	S	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26h-110	D	R	R	H	R	K	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26h-111	R	N	P	D	F	P	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26h-112	V	S	S	A	E	S	S	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26h-113	.	S	S	T	S	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26h-114	S	G	S	D	I	V	S	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26h-115	R	L	F	D	K	R	S	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26h-116	K	G	P	S	G	Y	D	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26h-117	P	Y	E	H	L	S	G	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26h-118	Q	R	L	G	R	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26h-119	K	T	S	G	S	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
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DOM26h-121	P	T	S	T	V	S	.	.	.	.	.	.	.	.	.	.	.	.	.	.
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DOM26h-126	T	R	G	N	N	T	V	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26h-127	S	Q	D	I	G	V	.	.	.	.	.	.	.	.	.	.	.	.	.	.

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DOM26h-159-3	R	H	.	.	.	.	.	.	.	.	Y	.	I	.	.	.	.	.	.	.
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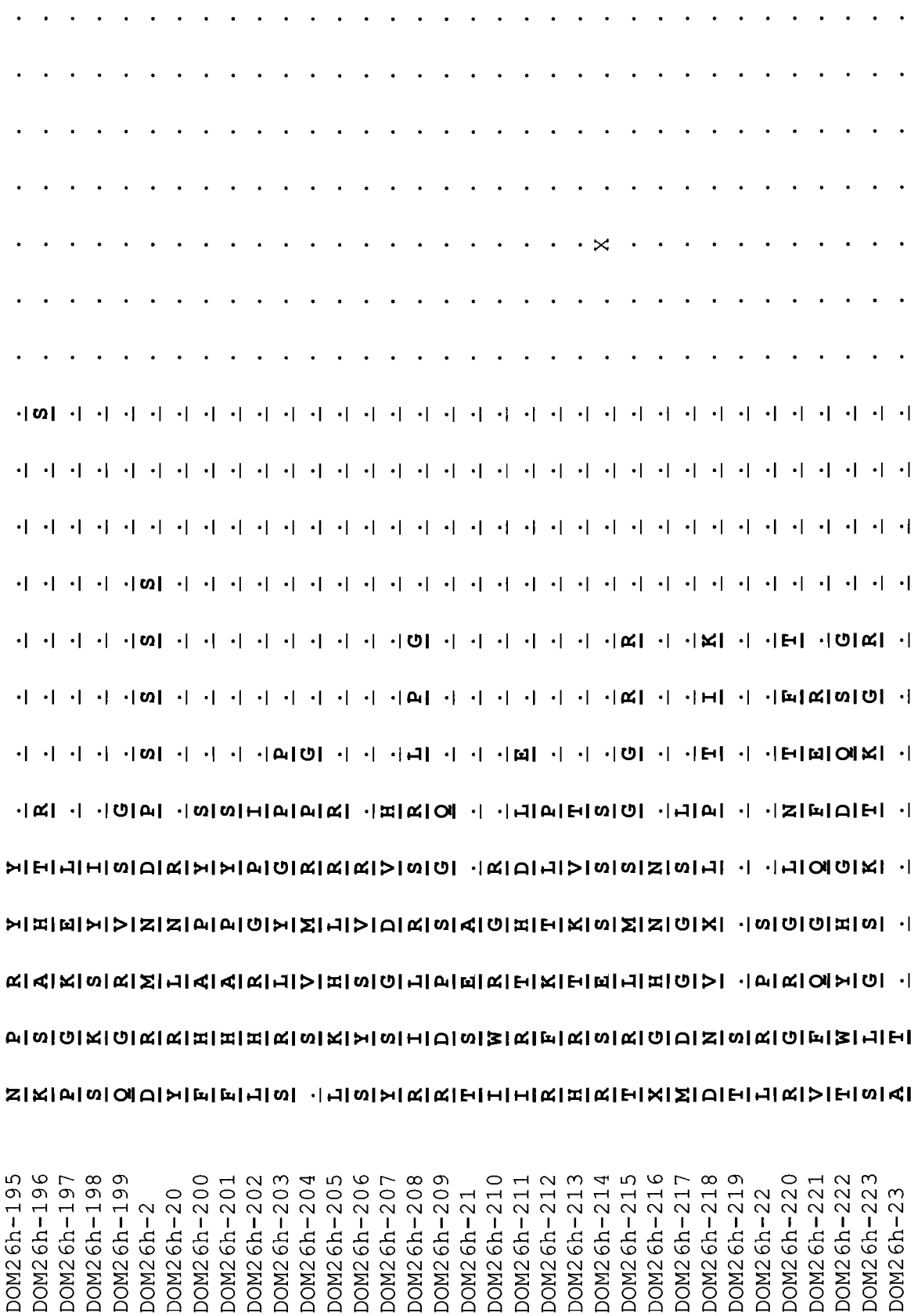
DOM26h-159-5	R	H	.	.	.	.	.	.	.	.	Y	.	I	.	.	.	.	.	.	.
DOM26h-160	S	.	S	M	L	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26h-168	L	R	V	G	W	Y	G	A	A	.	.	.	.	.	.	.	.	.	.	.
DOM26h-169	R	Y	Y	A	T	X	R	X	.	.	.	.	.	.	.	.	.	.	.	.
DOM26h-17	T	S	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26h-170	P	G	K	R	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26h-171	.	X	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26h-172	W	.	V	S	K	T	R	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26h-173	R	S	R	W	Q	G	T	L	.	.	.	.	.	.	.	.	.	.	.	.
DOM26h-174	P	G	R	E	L	G	K	R	Y	.	.	.	.	.	.	.	.	.	.	.
DOM26h-175	D	E	S	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26h-176	K	S	F	A	K	R	Y	E	.	.	.	.	.	.	.	.	.	.	.	.
DOM26h-177	S	S	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26h-178	R	T	K	H	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26h-179	A	G	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26h-180	D	S	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26h-181	D	G	V	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26h-182	T	S	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26h-183	S	G	N	.	.	.	.	.	.	.	.	E	L	R	.	S	.	.	.	.
DOM26h-184	S	T	T	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26h-185	.	S	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26h-186	K	Y	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26h-187	T	T	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26h-188	P	T	G	D	A	V	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26h-189	P	R	P	R	W	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26h-19	Y	Q	G	Y	P	M	S	S	R	.	.	.	.	.	.	.	.	.	.	.
DOM26h-190	.	.	L	D	R	T	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26h-191	S	L	Y	D	Q	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26h-192	R	M	R	R	P	I	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26h-193	R	I	A	S	H	L	D	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26h-194	.	G	T	R	S	R	.	.	.	.	.	.	.	.	.	.	.	.	.	.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DOM26h-46	M	S	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26h-47	A	S	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26h-48	.	N	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26h-49	P	N	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26h-50	.	S	H	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26h-51	Q	D	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26h-52	S	T	E	R	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26h-53	P	.	S	T	E	S	S	T	.	.	.	.	.	.	.	.	.	.	.	.
DOM26h-54	K	.	M	T	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26h-55	.	N	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26h-56	S	G	K	.	.	.	.	.	.	.	.	E	L	L	.	S	.	.	.	.
DOM26h-57	T	S	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26h-58	.	N	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26h-59	T	H	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
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DOM26h-61	L	R	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26h-62	R	T	K	H	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26h-63	L	V	D	D	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26h-64	V	.	E	D	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26h-65	R	Q	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26h-66	H	G	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
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DOM26h-68	Q	S	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26h-69	R	S	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26h-70	P	P	K	D	F	G	D	V	E	.	.	.	.	.	.	.	.	.	.	.
DOM26h-71	.	K	R	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.

Kabat Residue	-	-	-	-
VHDUM-1	T	V	S	S
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DOM26h-200	.	.	.	.
DOM26h-201	.	.	.	.
DOM26h-202	.	.	.	.
DOM26h-203	.	.	.	.
DOM26h-204	.	.	.	.
DOM26h-205	.	.	.	.
DOM26h-206	.	.	.	.
DOM26h-207	.	.	.	.
DOM26h-208	.	.	.	.
DOM26h-209	.	.	.	.
DOM26h-21	.	.	.	.
DOM26h-210	.	.	.	.
DOM26h-211	.	.	.	.
DOM26h-212	.	.	.	.
DOM26h-213	.	.	.	.
DOM26h-214	.	.	.	.
DOM26h-215	.	.	.	.
DOM26h-216	.	.	.	.
DOM26h-217	.	.	.	.
DOM26h-218	.	.	.	.
DOM26h-219	.	.	.	.
DOM26h-22	.	.	.	.
DOM26h-220	.	.	.	.
DOM26h-221	.	.	.	.
DOM26h-222	.	.	.	.
DOM26h-223	.	.	.	.
DOM26h-23	.	.	.	.

DOM26h-24	.	.	.	.
DOM26h-29-1	.	.	.	.
DOM26h-4	.	.	.	.
DOM26h-41	.	.	.	.
DOM26h-42	.	.	.	.
DOM26h-43	.	.	.	.
DOM26h-44	.	.	.	.
DOM26h-45	.	.	.	.
DOM26h-46	.	.	.	.
DOM26h-47	.	.	.	.
DOM26h-48	.	.	.	.
DOM26h-49	.	.	.	.
DOM26h-50	.	.	.	.
DOM26h-51	.	.	.	.
DOM26h-52	.	.	.	.
DOM26h-53	.	.	.	.
DOM26h-54	.	.	.	.
DOM26h-55	.	.	.	.
DOM26h-56	.	.	.	.
DOM26h-57	.	.	.	.
DOM26h-58	.	.	.	.
DOM26h-59	.	.	.	.
DOM26h-60	.	.	.	.
DOM26h-61	.	.	.	.
DOM26h-62	.	.	.	.
DOM26h-63	.	.	.	.
DOM26h-64	.	.	.	.
DOM26h-65	.	.	.	.
DOM26h-66	.	.	.	.
DOM26h-67	.	.	.	.
DOM26h-68	.	.	.	.
DOM26h-69	.	.	.	.
DOM26h-70	.	.	.	.
DOM26h-71	.	.	.	.

DOM26h-72	.	.	.	.
DOM26h-73	.	.	.	.
DOM26h-74	.	.	P	.
DOM26h-75	.	.	.	.
DOM26h-76	.	.	.	.
DOM26h-77	.	.	.	.
DOM26h-78	.	.	.	.
DOM26h-79	.	.	.	.
DOM26h-80	.	.	.	.
DOM26h-81	.	.	.	.
DOM26h-82	.	.	.	.
DOM26h-83	.	.	.	.
DOM26h-84	.	.	.	.
DOM26h-85	.	.	.	.
DOM26h-86	.	.	.	.
DOM26h-87	.	.	.	.
DOM26h-88	.	.	.	.
DOM26h-89	.	.	.	.
DOM26h-90	.	.	.	.
DOM26h-91	.	.	.	.
DOM26h-92	.	.	.	.
DOM26h-93	.	.	.	.
DOM26h-94	.	.	.	.
DOM26h-95	.	.	.	.
DOM26h-96	.	.	.	.
DOM26h-97	.	.	.	.
DOM26h-98	.	.	.	.
DOM26h-99	.	.	.	.
DOM26h-99-1	.	.	.	.
DOM26h-99-2	.	.	.	.

Figure 16: Alignment of Amino Acid Sequences of Vκ Clones

Kabat Residue	'	'	'	'	5	'	'	'	'	10	'	'	'	'	15	'	'	'	'	20
VKDUM-1	D	I	Q	M	T	Q	S	P	S	S	L	S	A	S	V	G	D	R	V	T
DOM26h-161	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26h-162	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26h-163	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26h-164	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26h-165	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26h-166	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26h-167	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26h-25	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26h-26	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26h-27	.	.	.	.	.	.	.	.	.	F	.	.	.	.	.	.	.	.	.	.
DOM26h-28	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26h-29	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26h-30	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26h-31	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26h-32	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26h-33	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26h-34	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26h-35	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26h-36	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26h-37	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.

Kabat Residue	'	'	'	'	25	'	'	'	'	30	'	'	'	'	35	'	'	'	'	40
VKDUM-1	I	T	C	**R**	**A**	**S**	**Q**	**S**	**I**	**S**	**S**	**Y**	**L**	**N**	W	Y	Q	Q	K	P
DOM26h-161	.	.	.	.	.	.	.	**A**	.	**G**	**R**	**W**	.	**L**	.	.	.	.	.	.
DOM26h-162	.	.	.	.	.	.	**M**	.	.	**D**	**E**	**S**	.	**W**	.	.	.	.	.	.
DOM26h-163	.	.	.	.	.	.	**H**	**Y**	.	**G**	**N**	**E**	.	**W**	.	.	.	.	.	.

DOM26h-164	.	.	.	.	.	.	S	N	.	G	R	S	.	V	.	.	.	.	.	.
DOM26h-165	.	.	.	.	.	.	V	K	.	G	E	R	.	W	.	.	.	.	.	.
DOM26h-166	.	.	.	.	.	.	S	Y	.	G	G	E	.	W	.	.	.	.	.	.
DOM26h-167	.	.	.	.	.	.	S	W	.	N	.	D	.	V	.	.	.	.	.	.
DOM26h-25	.	.	.	.	.	.	G	D	.	G	H	A	.	W	.	.	.	.	.	.
DOM26h-26	.	.	.	.	.	.	.	A	.	M	D	N	.	W	.	.	.	.	.	.
DOM26h-27	.	.	.	.	.	.	K	F	.	G	.	E	.	G	.	F	.	.	.	.
DOM26h-28	.	.	.	.	.	.	L	P	.	V	R	S	.	V	.	.	.	.	.	.
DOM26h-29	.	.	.	.	.	.	S	H	.	P	V	D	.	E	.	.	.	.	.	.
DOM26h-30	.	.	.	.	T	.	K	H	.	H	.	A	.	W	.	.	.	.	.	.
DOM26h-31	.	.	.	.	.	.	S	P	.	N	A	S	.	W	.	.	.	.	.	.
DOM26h-32	.	.	.	.	.	.	I	D	.	A	K	G	.	A	.	.	.	.	.	.
DOM26h-33	.	.	.	.	.	.	G	T	.	M	G	S	.	W	.	.	.	.	.	.
DOM26h-34	.	.	.	Q	.	.	K	N	.	G	E	R	.	V	.	.	.	.	.	.
DOM26h-35	.	.	.	.	.	.	K	N	.	G	T	R	.	V	.	.	.	.	.	.
DOM26h-36	.	.	.	.	.	.	K	P	.	G	E	R	.	G	.	.	.	.	.	.
DOM26h-37	.	.	.	.	.	.	S	N	.	G	.	R	.	V	.	.	.	.	.	.

Kabat Residue	'	'	'	'	45	'	'	'	'	50	'	'	'	'	55	'	'	'	'	60
VKDUM-1	G	K	A	P	K	L	L	I	Y	A	A	S	S	L	Q	S	G	V	P	S
DOM26h-161	.	.	.	.	.	.	.	.	.	.	.	.	R	.	.	.	.	.	.	.
DOM26h-162	.	.	.	.	.	.	.	.	R	G	G	.	G	.	.	.	.	.	.	.
DOM26h-163	.	.	.	.	.	.	.	.	R	R	G	.	G	.	.	.	.	.	.	.
DOM26h-164	.	.	.	.	.	.	.	.	A	G	G	.	L	.	.	.	.	.	.	.
DOM26h-165	.	E	.	.	.	.	.	.	R	D	.	.	L	.	.	.	.	.	.	.
DOM26h-166	.	.	.	.	.	.	.	.	S	G	T	.	G	.	.	.	.	.	.	.
DOM26h-167	.	E	.	.	.	.	.	.	A	G	G	.	L	.	.	.	.	.	.	.
DOM26h-25	.	.	.	.	.	.	.	.	R	G	G	.	A	.	.	.	.	.	.	.
DOM26h-26	.	.	.	.	.	.	.	.	R	G	G	.	G	.	.	.	.	.	.	.
DOM26h-27	.	.	.	.	.	.	.	.	G	V	T	.	V	.	.	R	.	.	.	.
DOM26h-28	.	.	.	.	.	.	.	.	G	G	G	.	V	.	.	.	.	.	.	.
DOM26h-29	.	.	.	.	.	.	.	.	G	G	S	.	W	.	.	.	.	.	.	.
DOM26h-30	.	.	.	.	.	.	.	.	A	H	G	.	R	.	.	.	.	.	.	.

DOM26h-31	.	.	.	.	.	.	.	.	T	Q	S	.	A	.	.	.	.	.	.
DOM26h-32	.	.	.	.	M	.	.	.	T	G	W	.	G	.	.	.	.	.	.
DOM26h-33	.	.	.	.	.	.	.	.	R	D	V	.	R	.	.	.	.	.	.
DOM26h-34	.	.	.	.	.	.	.	.	G	F	.	.	L	.	.	.	.	.	.
DOM26h-35	.	.	.	.	.	.	.	.	G	V	V	.	L	.	.	.	.	.	.
DOM26h-36	.	.	.	.	.	.	.	.	W	R	R	.	Y	.	.	.	.	.	.
DOM26h-37	.	.	.	.	.	.	.	.	L	W	G	.	V	.	.	.	.	.	.

Kabat Residue	'	'	'	'	65	'	'	'	'	70	'	'	'	'	75	'	'	'	'	80
VKDUM-1	R	F	S	G	S	G	S	G	T	D	F	T	L	T	I	S	S	L	Q	P
DOM26h-161	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26h-162	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26h-163	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26h-164	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26h-165	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26h-166	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26h-167	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26h-25	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26h-26	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26h-27	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26h-28	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26h-29	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26h-30	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26h-31	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26h-32	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26h-33	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26h-34	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26h-35	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26h-36	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26h-37	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	G	.	.	.	.

Kabat Residue	'	'	'	'	85	'	'	'	'	90	'	'	'	'	95	'	'	'	'	100

	E	D	F	A	T	Y	Y	C	Q	S	Y	S	P	T	P	N	T	F	G	Q
VKDUM-1	.	.	.	.	.	.	.	.	G	A	A	A	L	L	P	P	-	.	.	.
DOM26h-161	.	.	.	.	.	.	.	.	-	-	-	-	-	-	-	-	-	.	.	.
DOM26h-162	.	.	.	.	.	.	.	.	-	-	-	-	-	-	-	-	-	.	.	.
DOM26h-163	.	.	.	.	.	.	.	.	-	-	-	-	-	-	-	-	-	.	.	.
DOM26h-164	.	.	.	.	.	.	.	.	-	-	-	-	-	-	-	-	-	.	.	.
DOM26h-165	.	.	.	.	.	.	.	.	-	-	-	-	-	-	-	-	-	.	.	.
DOM26h-166	.	.	.	.	.	.	.	.	-	-	-	-	-	-	-	-	-	.	.	.
DOM26h-167	.	.	.	.	.	.	.	.	-	-	-	-	-	-	-	-	-	.	.	.
DOM26h-25	.	.	.	.	.	.	.	.	-	-	-	-	-	-	-	-	-	.	.	.
DOM26h-26	.	.	.	.	.	.	.	.	-	-	-	-	-	-	-	-	-	.	.	.
DOM26h-27	.	.	.	.	.	.	.	.	-	-	-	-	-	-	-	-	-	.	.	.
DOM26h-28	.	.	.	.	.	.	.	.	-	-	-	-	-	-	-	-	-	.	.	.
DOM26h-29	.	.	.	.	.	.	.	.	-	-	-	-	-	-	-	-	-	.	.	.
DOM26h-30	.	.	.	.	.	.	.	.	-	-	-	-	-	-	-	-	-	.	.	.
DOM26h-31	.	.	.	.	.	.	.	.	-	-	-	-	-	-	-	-	-	.	.	.
DOM26h-32	.	.	.	.	.	.	.	.	-	-	-	-	-	-	-	-	-	.	.	.
DOM26h-33	.	.	.	.	.	.	.	.	-	-	-	-	-	-	-	-	-	.	.	.
DOM26h-34	.	.	.	.	.	.	.	.	-	-	-	-	-	-	-	-	-	.	.	.
DOM26h-35	.	.	.	.	.	.	.	.	-	-	-	-	-	-	-	-	-	.	.	.
DOM26h-36	.	.	.	.	.	.	.	.	-	-	-	-	-	-	-	-	-	.	.	.
DOM26h-37	.	.	.	.	.	.	.	.	-	-	-	-	-	-	-	-	-	.	.	.

Kabat Residue	G	T	K	V	E	I	K	R
					105			
VKDUM-1	-	-	-	-	-	-	-	-
DOM26h-161	.	.	.	.	.	.	.	.
DOM26h-162	.	.	.	.	.	.	.	.
DOM26h-163	.	.	R	.	.	.	.	.
DOM26h-164	.	.	R	.	.	.	.	.
DOM26h-165	.	.	.	.	.	.	.	.
DOM26h-166	.	.	.	.	.	.	.	.
DOM26h-167	.	.	.	.	.	V	.	.
DOM26h-25	.	.	.	.	.	.	.	.
DOM26h-26	.	.	.	.	.	.	.	.

DOM26h-27	.	.	.	.	.	.	.	.	.	.	.	.
DOM26h-28	.	.	.	.	.	.	.	.	.	.	.	.
DOM26h-29	.	.	.	.	.	.	.	.	.	.	.	.
DOM26h-30	.	.	.	.	.	.	.	.	.	.	.	.
DOM26h-31	.	.	.	.	.	.	.	.	.	.	.	.
DOM26h-32	.	.	.	.	.	.	.	.	.	.	.	.
DOM26h-33	.	.	.	.	.	.	.	.	.	.	.	.
DOM26h-34	.	.	.	.	.	.	.	.	.	.	.	.
DOM26h-35	.	.	.	.	.	.	.	.	.	.	.	.
DOM26h-36	.	.	.	.	.	.	.	.	.	.	.	.
DOM26h-37	.	.	.	.	.	.	.	.	.	.	.	.

Figure 17: Nucleotide sequences of Mouse Vh ASGPR dAbs

Nucleotide Sequence of V_H Clones

>DOM26m-10
GAGGTGCAGC TGTTGGAGTC TGGGGGAGGC TTGGTACAGC CTGGGGGGTC CCTGCGTCTC
TCCTGTGCAG CCTCCGGATT CACCTTTGCT GATTATCCGA TGGAGTGGGC CCGCCAGGCT
CCAGGGAAGG GTCTTGAGTG GGTCTCAGGT ATTTCGCGGG ATGGTAGTCG TACATACTAC
GCAGACTCCG TGAAGGGCCG GTTCACCATC TCCCGCGACA ATTCCAAGAA CACGCTGTAT
CTGCAAATGA ACAGCCTGCG TGCCGAGGAT ACCGCGGTAT ATTACTGTGC GAAAATGGGG
TCGAATTTTG ACTACTGGGG TCAGGGAACC CTGGTCACCG TCTCGAGC

>DOM26m-13
GAGGTGCAGC TGTTGGAGTC TGGGGGAGGC TTGGTACAGC CTGGGGGGTC CCTGCGTCTC
TCCTGTGCAG CCTCCGGATT CACCTTTGAT GCTTATGCTA TGGGTTGGGT CCGCCAGGCT
CCAGGGAAGG GTCTAGAGTG GGTCTCAGAT ATTGGGACTA ATGGTGGGCA TACATACTAC
GCAGACTCCG TGAAGGGCCG GTTCACCATC TCCCGCGACA ATTCCAAGAA CACGCTGTAT
CTGCAAATGA ACAGCCTGCG TGCCGAGGAC ACCGCGGTAT ATTACTGTGC GAAATTTGAT
CCTATTCGTC GGGAGTTTGA CTACTGGGGT CAGGGAACCC TGGTCACCGT CTCGAGC

>DOM26m-16
GAGGTGCAGC TGTTGGAGTC TGGGGGAGGC TTGGTACAGC CTGGGGGGTC CCTGCGTCTC
TCCTGTGCAG CCTCCGGATT CACCTTTGGG TTGTATTCTA TGGAGTGGGT CCGCCAGGCT
CCAGGGAAGG GTCTAGAGTG GGTCTCAGGG ATTACTCGTT CTGGTGATAA GACATACTAC
GCAGACTCCG TGAAGGGCCG GTTCACCATC TCCCGCGACA ATTCCAAGAA CACGCTGTAT
CTGCAAATGA ACAGCCTGCG TGCCGAGGAC ACCGCGGTAT ATTACTGTGC GAAACCTAGG
AATCGTACGT TTAGGATGTT TGACTACTGG GGTCAGGGAA CCCTGGTCAC CGTCTCGAGC

>DOM26m-165
GAGGTGCAGC TGTTGGAGTC TGGGGGGGGC TTGGTACAGC CTGGGGGGTC CCTGCGTCTC
TCCTGTGCAG CCTCCGGATT CACCTTTCCT AAGTATGTTA TGAGTTGGGT CCGCCAGGCT
CCAGGGAAGG GTCTGGAGTG GGTCTCAACG ATTAATCAGG CGGGTTTGAG GACATACTAC
GCAGACTCCG TGAAGGGCCG GTTCACCATC TCCCGCGACA ATTCCAAGAA CACGCTGTAT
CTGCAAATGA ACAGCCTGCG TGCCGAGGAC ACCGCGGTAT ATTACTGTGT GAAACATGCT
ACTCGTTTGA TGTCTGGTGG TCGGCGTTTT GACTACTGGG GTCAGGGAAC CCTGGTCACC
GTCTCGAGC

>DOM26m-17
GAGGTGCAGC TGTTGGAGTC TGGGGGAGGC TTGGTACAGC CTGGGGGGTC CCTGCGTCTC
TCCTGTGCAG CCTCCGGATT CACCTTTAGG CAGTATCCGA TGTCGTGGGT CCGCCAGGCT
CCAGGGAAGG GTCTAGAGTG GGTCTCAACG ATTGATCCGG AGGGTTTTGT GACATACTAC
GCAGACTCCG TGAAGGGCCG GTTCACCATC TCCCGCGACA ATTCCAAGAA CACGCTGTAT
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Figure 18: Nucleotide sequences of mouse Vκ ASGPR dAbs

Nucleotide Sequence of Vκ Clones

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Figure 19: Alignment of Amino Acid Sequences of V_H Clones

Kabat Residue	'	'	'	'	5	'	'	'	'	10	'	'	'	'	15	'	'	'	'	20
VHDUM-1	E	V	Q	L	L	E	S	G	G	G	L	V	Q	P	G	G	S	L	R	L
DOM26m-10	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
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DOM26m-16	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-165	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-17	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-27	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-28	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-29	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-30	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
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DOM26m-33	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-33-1	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-33-10	.	.	.	.	M	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-33-11	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-33-12	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-33-2	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-33-3	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-33-4	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-33-5	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-33-6	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-33-7	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-33-8	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-33-9	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-34	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-35	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-36	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-37	.	.	.	.	S	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-38	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-39	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.

DOM26m-4 . . . .
DOM26m-40 . . . .
DOM26m-41 . . . .
DOM26m-42 . . . .
DOM26m-43 . . . .
DOM26m-44 . . . .
DOM26m-45 . . . .
DOM26m-46 . . . .
DOM26m-47 . . . .
DOM26m-48 . . . .
DOM26m-52 . . . .
DOM26m-52-1 . . . .
DOM26m-52-2 . . . .
DOM26m-52-3 . . . .
DOM26m-52-4 . . . .
DOM26m-52-5 . . . .
DOM26m-52-6 . . . .
DOM26m-52-7 . . . .
DOM26m-6 . . . .
DOM26m-60 . . . .
DOM26m-61-1 . . . .
DOM26m-61-2 . . . . R . . . .
DOM26m-61-3 . . . .
DOM26m-61-4 . . . .
DOM26m-61-5 . . . .
DOM26m-61-6 . . . .
DOM26m-7 . . . .
DOM26m-73 . . . .
DOM26m-74 . . . .
DOM26m-75 . . . .
DOM26m-76 . . . .
DOM26m-77 . . . .
DOM26m-78 . . . .
DOM26m-79 . . . .
DOM26m-8 . . . .

DOM26m-80	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-81	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-82	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-83	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-9	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
Kabat Residue	'	'	'	'	25	'	'	'	'	30	'	'	'	'	35	'	'	'	'	40
VHDUM-1	S	C	A	A	S	G	F	T	F	S	S	Y	A	M	S	W	V	R	Q	A
DOM26m-10	.	.	.	.	.	.	.	.	.	A	D	.	P	.	E	.	A	.	.	.
DOM26m-13	.	.	.	.	.	.	.	.	.	D	A	.	.	.	G	.	.	.	.	.
DOM26m-16	.	.	.	.	.	.	.	.	.	G	L	.	S	.	E	.	.	.	.	.
DOM26m-165	.	.	.	.	.	.	.	.	.	P	K	.	V	.	.	.	.	.	.	.
DOM26m-17	.	.	.	.	.	.	.	.	.	R	Q	.	P	.	.	.	.	.	.	.
DOM26m-27	.	.	.	.	.	.	.	.	.	E	T	Q	P	.	I	.	.	.	.	.
DOM26m-28	.	.	.	.	.	.	.	.	.	E	D	T	D	.	E	.	.	.	.	.
DOM26m-29	.	.	.	.	.	.	.	.	.	E	D	S	G	.	I	.	A	.	.	.
DOM26m-30	.	.	.	.	.	.	.	.	.	A	N	.	E	.	I	.	.	.	.	.
DOM26m-31	.	.	.	.	.	.	.	.	.	A	.	.	G	.	I	.	.	.	.	.
DOM26m-32	.	.	.	.	.	.	.	.	.	G	M	.	D	.	E	.	.	.	.	.
DOM26m-33	.	.	.	.	.	.	.	.	.	A	K	.	D	.	I	.	.	.	.	.
DOM26m-33-1	.	.	.	.	.	.	.	.	.	A	K	.	D	.	I	.	.	.	.	.
DOM26m-33-10	.	.	.	.	.	.	.	.	.	A	K	.	D	.	I	.	.	.	.	.
DOM26m-33-11	.	.	.	.	.	.	.	.	.	A	K	.	D	.	I	.	.	.	.	.
DOM26m-33-12	.	.	.	.	.	.	.	.	.	A	K	.	D	.	I	.	.	.	.	.
DOM26m-33-2	.	.	.	.	.	.	.	.	.	A	K	.	D	.	I	.	.	.	.	.
DOM26m-33-3	.	.	.	.	.	.	.	.	.	A	K	.	D	.	I	.	.	.	.	.
DOM26m-33-4	.	.	.	.	.	.	.	.	.	.	T	.	P	.	L	.	A	.	.	.
DOM26m-33-5	.	.	.	.	.	.	.	.	.	A	G	A	N	.	I	.	.	.	.	.
DOM26m-33-6	.	.	.	.	.	.	.	.	.	A	K	.	.	I	I	.	.	.	.	.
DOM26m-33-7	.	.	.	.	.	.	.	.	.	A	K	.	D	.	I	.	.	.	.	.
DOM26m-33-8	.	.	.	.	.	.	.	.	.	A	K	.	D	.	I	.	.	.	.	.
DOM26m-33-9	.	.	.	.	.	.	.	.	.	A	K	.	D	.	I	.	.	.	.	.
DOM26m-34	.	.	.	.	.	.	.	.	.	A	D	.	G	.	I	.	.	.	.	.
DOM26m-35	.	.	.	.	.	.	.	.	.	H	R	.	T	.	G	.	.	.	.	.

DOM26m-36	.	.	.	.	.	.	.	.	.	.	.	.	P	.	F	.	.	.	.	.
DOM26m-37	.	.	.	.	.	.	.	.	.	P	.	.	T	.	G	.	.	.	.	.
DOM26m-38	.	.	.	.	.	.	.	.	.	H	E	.	N	.	W	.	.	.	.	.
DOM26m-39	.	.	.	.	.	.	.	.	.	G	F	.	E	.	T	.	.	.	.	.
DOM26m-4	.	.	.	.	.	.	.	.	.	A	K	.	D	.	I	.	.	.	.	.
DOM26m-40	.	.	.	.	.	.	.	.	.	R	G	.	T	.	G	.	.	.	.	.
DOM26m-41	.	.	.	.	.	.	.	.	.	G	D	A	N	.	G	.	.	.	.	.
DOM26m-42	.	.	.	.	.	.	.	.	.	A	N	.	G	.	Y	.	A	.	.	.
DOM26m-43	.	.	.	.	.	.	.	.	.	E	A	E	T	.	G	.	.	.	.	.
DOM26m-44	.	.	.	.	.	.	.	.	.	N	D	.	D	.	G	.	.	.	.	.
DOM26m-45	.	.	.	.	.	.	.	.	.	D	G	.	D	.	A	.	.	.	.	.
DOM26m-46	.	.	.	.	.	.	.	.	.	D	H	.	L	.	G	.	.	.	.	.
DOM26m-47	.	.	.	.	.	.	.	.	.	.	A	.	G	.	M	.	.	.	.	.
DOM26m-48	.	.	.	.	.	.	.	.	.	G	E	V	T	.	G	.	.	.	.	.
DOM26m-52	.	.	.	.	.	.	.	.	.	R	E	H	P	.	.	.	.	.	.	.
DOM26m-52-1	.	.	.	.	.	.	.	.	.	R	E	H	P	.	.	.	.	.	.	.
DOM26m-52-2	.	.	.	.	.	.	.	.	.	R	E	H	P	.	.	.	.	.	.	.
DOM26m-52-3	.	.	.	.	.	.	.	.	.	R	E	H	P	.	.	.	.	.	.	.
DOM26m-52-4	.	.	.	.	.	.	.	.	.	R	E	H	P	.	.	.	.	.	.	.
DOM26m-52-5	.	.	.	.	.	.	.	.	.	R	E	H	P	.	.	.	.	.	.	.
DOM26m-52-6	.	.	.	.	.	.	.	.	.	R	E	H	P	.	.	.	.	.	.	.
DOM26m-52-7	.	.	.	.	.	.	.	.	.	R	E	H	P	.	.	.	.	.	.	.
DOM26m-6	.	.	.	.	.	.	.	.	.	.	N	.	P	.	.	.	.	.	.	.
DOM26m-60	.	.	.	.	.	.	.	.	.	H	D	K	T	.	M	.	.	.	.	.
DOM26m-61-1	.	.	.	.	.	.	.	.	.	.	T	.	P	.	H	.	.	.	.	.
DOM26m-61-2	.	.	.	.	.	.	.	.	.	.	T	.	P	.	H	.	.	.	.	.
DOM26m-61-3	.	.	.	.	.	.	.	.	.	.	T	.	P	.	H	.	.	.	.	.
DOM26m-61-4	.	.	.	.	.	.	.	.	.	.	T	.	P	.	L	.	A	.	.	.
DOM26m-61-5	.	.	.	.	.	.	.	.	.	.	T	.	P	.	H	.	.	.	.	.
DOM26m-61-6	.	.	.	.	.	.	.	.	.	.	T	.	P	.	H	.	.	.	.	.
DOM26m-7	.	.	.	.	.	.	.	.	.	D	D	.	E	.	G	.	.	.	.	.
DOM26m-73	.	.	.	.	.	.	.	.	.	K	R	.	P	.	G	.	.	.	.	.
DOM26m-74	.	.	.	.	.	.	.	.	.	A	R	.	E	.	V	.	.	.	.	.
DOM26m-75	.	.	.	.	.	.	.	.	.	A	D	.	P	.	E	.	A	.	.	.
DOM26m-76	.	.	.	.	.	.	.	.	.	K	R	.	P	.	G	.	.	.	.	.

DOM26m-77	.	.	.	.	.	.	.	.	.	W	.	.	P	.	.	.	.	.	.	.
DOM26m-78	.	.	.	.	.	.	.	.	.	T	D	S	D	.	E	.	.	.	.	.
DOM26m-79	.	.	.	.	.	.	.	.	.	A	K	.	D	.	I	.	.	.	.	.
DOM26m-8	.	.	.	.	.	.	.	.	.	.	H	.	P	.	.	.	.	.	.	.
DOM26m-80	.	.	.	.	.	.	.	.	.	W	.	.	P	.	.	.	.	.	.	.
DOM26m-81	.	.	.	.	.	.	.	.	.	.	G	E	T	.	G	.	.	.	.	.
DOM26m-82	.	.	.	.	.	.	.	.	.	P	N	.	I	.	.	.	.	.	.	.
DOM26m-83	.	.	.	.	.	.	.	.	.	T	D	A	D	.	E	.	.	.	.	.
DOM26m-9	.	.	.	.	.	.	.	.	.	P	.	.	I	.	V	.	.	.	.	.

Kabat Residue	'	'	'	'	45	'	'	'	'	50	'	'	'	'	54	'	'	'	'	59
VHDUM-1	P	G	K	G	L	E	W	V	S	A	I	S	G	S	G	G	S	T	Y	Y
DOM26m-10	.	.	.	.	.	.	.	.	.	G	.	.	R	D	.	S	R	.	.	.
DOM26m-13	.	.	.	.	.	.	.	.	.	D	.	G	T	N	.	.	H	.	.	.
DOM26m-16	.	.	.	.	.	.	.	.	.	G	.	T	R	.	.	D	K	.	.	.
DOM26m-165	.	.	.	.	.	.	.	.	.	T	.	N	Q	A	.	L	R	.	.	.
DOM26m-17	.	.	.	.	.	.	.	.	.	T	.	D	P	E	.	F	V	.	.	.
DOM26m-27	.	.	.	.	.	.	.	.	.	G	.	E	.	D	.	.	R	.	.	.
DOM26m-28	.	.	.	.	.	.	.	.	.	W	.	P	A	H	.	.	H	.	.	.
DOM26m-29	.	.	.	.	.	.	.	.	.	G	.	A	S	E	.	S	T	.	.	.
DOM26m-30	.	.	.	.	.	.	.	.	.	G	.	N	R	A	.	Q	R	.	.	.
DOM26m-31	.	.	.	.	.	.	.	.	.	G	.	E	S	.	.	.	V	.	.	.
DOM26m-32	.	.	.	.	.	.	.	.	.	W	.	G	H	.	.	N	D	.	.	.
DOM26m-33	.	.	.	.	.	.	.	.	.	G	.	N	H	.	.	S	R	.	.	.
DOM26m-33-1	.	.	.	.	.	.	.	.	.	G	.	N	H	.	.	S	R	.	.	.
DOM26m-33-10	.	.	.	.	.	.	.	.	.	G	.	N	H	.	.	S	R	.	.	.
DOM26m-33-11	.	.	.	.	.	.	.	.	.	G	.	N	H	.	.	S	R	.	.	.
DOM26m-33-12	.	.	.	.	.	.	.	.	.	G	.	N	H	.	.	S	R	.	.	.
DOM26m-33-2	.	.	.	.	.	.	.	.	.	G	.	N	H	.	.	S	R	.	.	.
DOM26m-33-3	.	.	.	.	.	.	.	.	.	G	.	N	H	.	.	S	R	.	.	.
DOM26m-33-4	.	.	.	.	.	.	.	.	.	S	.	.	P	.	.	D	.	.	.	.
DOM26m-33-5	.	.	.	.	.	.	.	.	.	G	.	N	H	.	.	S	R	.	.	.
DOM26m-33-6	.	.	.	.	.	.	.	.	.	G	.	N	H	.	.	S	R	.	.	.
DOM26m-33-7	.	.	.	.	.	.	.	.	.	G	.	N	H	.	.	S	R	.	.	.

DOM26m-33-8	.	.	.	.	.	.	.	.	.	G	.	N	H	.	.	S	R	.	.	.
DOM26m-33-9	.	.	.	.	.	.	.	.	.	G	.	N	H	.	.	S	R	.	.	.
DOM26m-34	.	.	.	.	.	.	.	.	.	G	.	.	P	P	.	D	R	.	.	.
DOM26m-35	.	.	.	.	.	.	.	.	.	D	.	.	P	.	.	R	E	.	.	.
DOM26m-36	.	.	.	.	.	.	.	.	.	D	.	.	I	D	.	T	L	.	.	.
DOM26m-37	.	.	.	.	.	.	.	.	.	D	.	.	P	D	.	R	.	.	.	.
DOM26m-38	.	.	.	.	.	.	.	.	.	G	.	P	.	G	.	.	R	.	.	.
DOM26m-39	.	.	.	.	.	.	.	.	.	T	.	.	S	H	.	I	R	.	.	.
DOM26m-4	.	.	.	.	.	.	.	.	.	G	.	N	H	.	.	S	R	.	.	.
DOM26m-40	.	.	.	.	.	.	.	.	.	D	.	D	A	T	.	R	R	.	.	.
DOM26m-41	.	.	.	.	.	.	.	.	.	D	.	G	P	H	.	E	N	.	.	.
DOM26m-42	.	.	.	.	.	.	.	.	.	G	.	N	P	L	.	S	R	.	.	.
DOM26m-43	.	.	.	.	.	.	.	.	.	D	.	D	.	R	.	E	R	.	.	.
DOM26m-44	.	.	.	.	.	.	.	.	.	D	.	.	S	T	.	R	A	.	.	.
DOM26m-45	.	.	.	.	.	.	.	.	.	W	.	.	.	D	.	L	N	.	.	.
DOM26m-46	.	.	.	.	.	.	.	.	.	D	.	A	P	.	.	H	L	.	.	.
DOM26m-47	.	.	.	.	.	.	.	.	.	D	.	D	S	T	.	R	G	.	.	.
DOM26m-48	.	.	.	.	.	.	.	.	.	D	.	N	A	T	.	D	T	.	.	.
DOM26m-52	.	.	.	.	.	.	.	.	.	S	.	.	K	H	.	S	E	.	.	.
DOM26m-52-1	.	.	.	.	.	.	.	.	.	S	.	.	K	H	.	S	E	.	.	.
DOM26m-52-2	.	.	.	.	.	.	.	.	.	S	.	.	R	H	.	S	E	.	.	.
DOM26m-52-3	.	.	.	.	.	.	.	.	.	S	.	.	K	H	.	S	V	.	.	.
DOM26m-52-4	.	.	.	.	.	.	.	.	.	S	.	.	K	H	.	S	E	.	.	.
DOM26m-52-5	.	.	.	.	.	.	.	.	.	S	.	.	K	H	.	S	E	.	.	.
DOM26m-52-6	.	.	.	.	.	.	.	.	.	S	.	.	K	H	.	S	E	S	.	.
DOM26m-52-7	.	.	.	.	.	.	.	.	.	S	.	.	P	.	.	D	.	.	.	.
DOM26m-6	.	.	.	.	.	.	.	.	.	G	.	.	A	T	.	T	F	.	.	.
DOM26m-60	.	.	.	.	.	.	.	.	.	D	.	.	P	N	.	A	F	.	.	.
DOM26m-61-1	.	.	.	.	.	.	.	.	.	S	.	.	P	.	.	D	.	.	H	.
DOM26m-61-2	.	W	.	.	.	.	.	.	.	S	.	.	P	.	.	D	.	.	H	.
DOM26m-61-3	.	.	.	.	.	.	.	.	.	S	.	.	P	.	.	D	.	.	.	.
DOM26m-61-4	.	.	.	.	.	.	.	.	.	S	.	.	P	.	.	D	.	.	.	.
DOM26m-61-5	.	.	.	.	.	.	.	.	.	S	.	.	P	.	.	D	.	.	.	.
DOM26m-61-6	.	.	.	.	.	.	.	.	.	S	.	.	P	.	.	D	.	.	H	.
DOM26m-7	.	.	.	.	.	.	.	.	.	L	.	.	A	Q	.	R	V	.	.	.

DOM26m-73	.	.	.	.	.	.	.	.	.	.	.	.	D	G	.	L	R	.	.	.
DOM26m-74	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-75	.	.	.	.	.	.	.	.	.	G	.	.	R	D	.	S	R	.	.	.
DOM26m-76	.	.	.	.	.	.	.	.	.	.	.	.	D	G	.	L	R	.	.	.
DOM26m-77	.	.	.	.	.	.	.	.	.	S	.	.	P	Q	.	F	H	.	.	.
DOM26m-78	.	.	.	.	.	.	.	.	.	V	.	T	.	H	.	.	V	.	.	.
DOM26m-79	.	.	.	.	.	.	.	.	.	G	.	N	H	.	.	S	R	.	.	.
DOM26m-8	.	.	.	.	.	.	.	.	.	S	.	.	P	.	.	F	F	.	.	.
DOM26m-80	.	.	.	.	.	.	.	.	.	S	.	.	P	Q	.	F	H	.	.	.
DOM26m-81	.	.	.	.	.	.	.	.	.	D	.	.	R	D	.	W	N	.	.	.
DOM26m-82	.	.	.	.	.	.	.	.	.	C	.	.	R	M	.	A	F	.	.	.
DOM26m-83	.	.	.	.	.	.	.	.	.	V	.	T	A	Q	.	.	D	.	.	.
DOM26m-9	.	.	.	.	.	.	.	.	.	S	.	.	A	.	.	Q	Y	.	.	.

Kabat Residue	'	'	'	'	64	'	'	'	'	69	'	'	'	'	74	'	'	'	'	79
VHDUM-1	A	D	S	V	K	G	R	F	T	I	S	R	D	N	S	K	N	T	L	Y
DOM26m-10	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-13	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-16	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-165	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-17	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-27	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-28	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-29	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-30	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-31	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-32	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-33	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	M	.	.
DOM26m-33-1	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	M	.	.
DOM26m-33-10	.	.	.	.	E	.	.	.	.	.	.	.	.	.	.	.	.	M	.	.
DOM26m-33-11	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	M	.	.
DOM26m-33-12	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	M	.	.
DOM26m-33-2	.	.	F	.	.	.	.	.	.	.	.	.	.	.	.	.	.	M	.	.
DOM26m-33-3	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	M	.	.

DOM26m-33-4	.	**G**	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-33-5	.	**G**	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-33-6	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	M	.	.
DOM26m-33-7	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	M	.	.
DOM26m-33-8	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	M	.	.
DOM26m-33-9	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	M	.	.
DOM26m-34	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-35	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-36	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-37	.	**H**	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-38	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-39	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-4	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	M	.	.
DOM26m-40	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-41	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-42	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-43	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-44	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-45	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-46	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-47	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-48	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-52	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-52-1	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-52-2	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-52-3	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-52-4	.	.	.	.	.	.	.	.	.	N	.	.	.	.	.	.	.	.	.	.
DOM26m-52-5	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-52-6	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-52-7	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-6	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-60	.	.	.	.	.	.	.	.	.	.	.	.	.	.	P	.	.	.	.	.
DOM26m-61-1	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-61-2	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-61-3	.	**N**	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.

DOM26m-61-4	.	**G**	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-61-5	.	**G**	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-61-6	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-7	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-73	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-74	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-75	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-76	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-77	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-78	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-79	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	M	.	.
DOM26m-8	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-80	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-81	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-82	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-83	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-9	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.

Kabat Residue	'	'	'	'	82b	'	'	'	'	86	'	'	'	'	91	'	'	'	'	96
VHDUM-1	L	Q	M	N	S	L	R	A	E	D	T	A	V	Y	Y	C	A	K	**S**	**Y**
DOM26m-10	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	**M**	**G**
DOM26m-13	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	**F**	**D**
DOM26m-16	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	**P**	**R**
DOM26m-165	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	V	.	**H**	**A**
DOM26m-17	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-27	.	.	.	.	.	.	.	.	.	.	A	.	.	.	.	.	.	.	.	**G**
DOM26m-28	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	**G**
DOM26m-29	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	**G**
DOM26m-30	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	**A**	**G**
DOM26m-31	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	**G**
DOM26m-32	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	**G**
DOM26m-33	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	**G**
DOM26m-33-1	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	**L**	**V**
DOM26m-33-10	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	**G**

DOM26m-33-11	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	G
DOM26m-33-12	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	G
DOM26m-33-2	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	L	D
DOM26m-33-3	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	L	E
DOM26m-33-4	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	V	.	.	V
DOM26m-33-5	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	V	.	.	V
DOM26m-33-6	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	A	G
DOM26m-33-7	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	R	G
DOM26m-33-8	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	T	G
DOM26m-33-9	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	G
DOM26m-34	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	A	G
DOM26m-35	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	F	G
DOM26m-36	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	G	R
DOM26m-37	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	F	G
DOM26m-38	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	T	K
DOM26m-39	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	R	R
DOM26m-4	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	G
DOM26m-40	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	W	V
DOM26m-41	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	F	P
DOM26m-42	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	T	E
DOM26m-43	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	F	D
DOM26m-44	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	M	N
DOM26m-45	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	Q	.
DOM26m-46	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	F	R
DOM26m-47	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	M	V
DOM26m-48	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	W	G
DOM26m-52	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	V	.	.	V
DOM26m-52-1	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	V	.	Q	T
DOM26m-52-2	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	V	.	Q	T
DOM26m-52-3	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	V	.	.	V
DOM26m-52-4	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	V	.	.	V
DOM26m-52-5	.	.	.	Y	.	.	.	.	.	.	.	.	.	.	.	.	V	.	.	V
DOM26m-52-6	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	V	.	.	V
DOM26m-52-7	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	V	.	.	V
DOM26m-6	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	E	.	I

DOM26m-60	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	L	D
DOM26m-61-1	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	V	.	N	A
DOM26m-61-2	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	V	.	N	A
DOM26m-61-3	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	V	.	N	A
DOM26m-61-4	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	N	T
DOM26m-61-5	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	N	A
DOM26m-61-6	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	N	A
DOM26m-7	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	N	S
DOM26m-73	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	R	S
DOM26m-74	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	R	T
DOM26m-75	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	M	G
DOM26m-76	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	R	S
DOM26m-77	.	.	.	.	N	.	.	.	.	.	.	.	.	.	.	.	.	E	K	I
DOM26m-78	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	A	G
DOM26m-79	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	G
DOM26m-8	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	D	S
DOM26m-80	.	.	.	.	N	.	.	.	.	.	.	.	.	.	.	.	.	E	K	I
DOM26m-81	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	L	V
DOM26m-82	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	W	N
DOM26m-83	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	A	G
DOM26m-9	.	.	.	.	.	.	H	.	.	.	.	.	.	.	.	.	.	.	W	V

Kabat Residue	'	'	'	'	100a	'	'	'	'	100f	'	'	'	'	104	'	'	'	'	109
VHDUM-1	G	A	-	-	-	-	-	-	-	-	F	D	Y	W	G	Q	G	T	L	V
DOM26m-10	S	N	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-13	P	I	R	R	E	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-16	N	R	T	F	R	M	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-165	T	R	L	M	S	G	G	R	R	.	.	.	.	.	.	.	.	.	.	.
DOM26m-17	R	L	K	G	V	L	R	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-27	S	S	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-28	D	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-29	L	S	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-30	S	S	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
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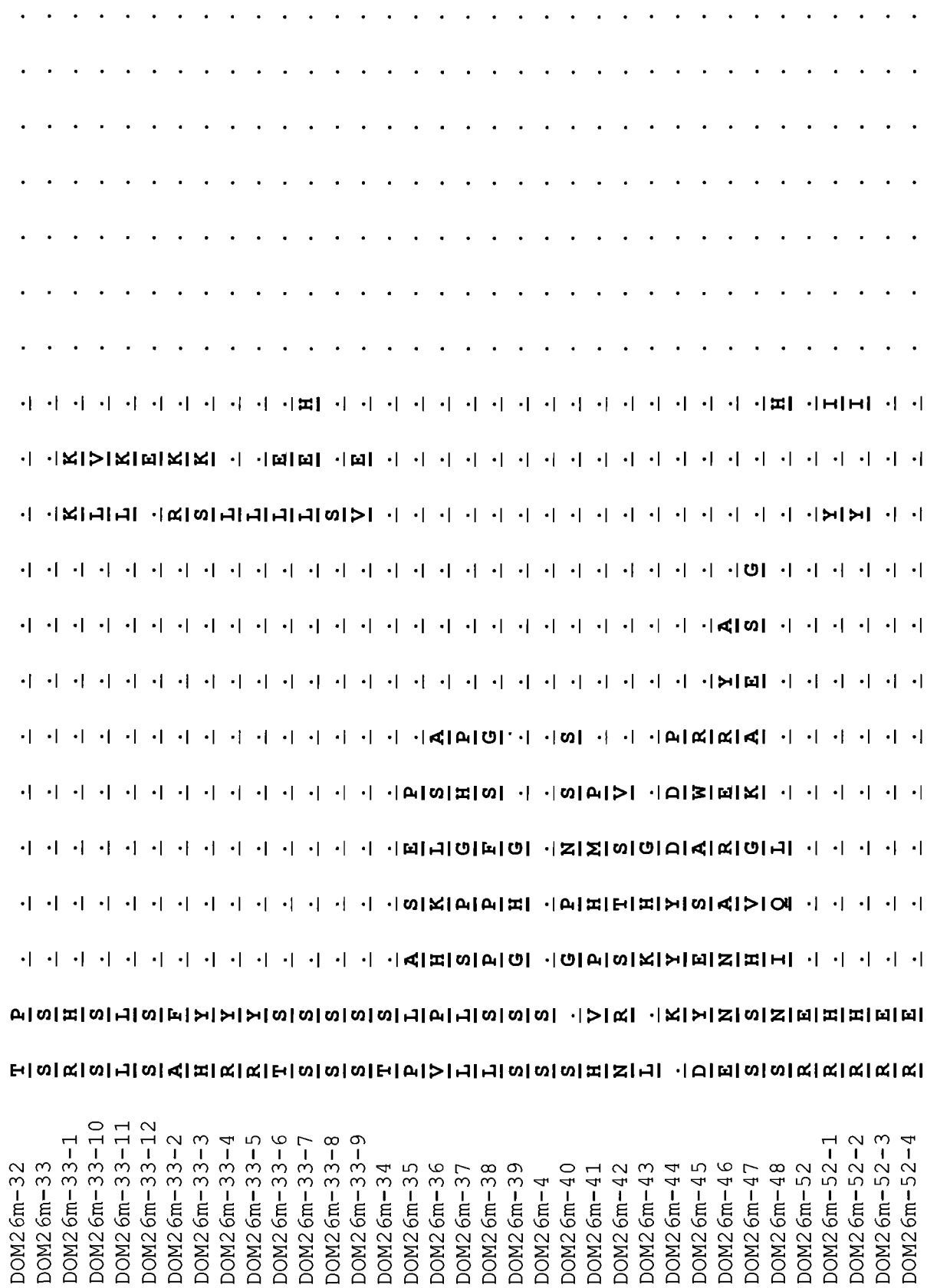
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DOM26m-52-3
DOM26m-52-4

DOM26m-52-5	R	E	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-52-6	R	E	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-52-7	R	E	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-6	K	R	L	N	N	R	V	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-60	N	G	G	A	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-61-1	L	R	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-61-2	L	R	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-61-3	L	R	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-61-4	L	R	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-61-5	L	R	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-61-6	L	R	.	.	.	.	.	.	.	.	S	.	.	.	.	.	.	.	.	.
DOM26m-7	P	S	Y	L	L	N	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-73	K	N	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-74	R	D	K	G	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-75	S	N	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-76	K	N	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-77	R	R	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-78	T	S	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-79	S	S	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-8	R	L	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-80	R	R	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-81	N	S	D	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-82	E	S	S	D	.	.	.	.	.	.	.	G	.	.	.	H	V	.	.	.
DOM26m-83	T	S	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-9	S	G	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.

Kabat Residue	'	'	'	'
VHDUM-1	T	V	S	S
DOM26m-10	.	.	.	.
DOM26m-13	.	.	.	.
DOM26m-16	.	.	.	.
DOM26m-165	.	.	.	.
DOM26m-17	.	.	.	.
DOM26m-27	.	.	.	.

DOM26m-28	.	.	.	.
DOM26m-29	.	.	.	.
DOM26m-30	.	.	.	.
DOM26m-31	.	.	.	.
DOM26m-32	.	.	.	.
DOM26m-33	.	.	.	.
DOM26m-33-1	.	.	.	.
DOM26m-33-10	.	.	.	.
DOM26m-33-11	I	.	.	.
DOM26m-33-12	.	.	.	.
DOM26m-33-2	.	.	.	.
DOM26m-33-3	.	.	.	.
DOM26m-33-4	.	.	.	.
DOM26m-33-5	.	.	.	.
DOM26m-33-6	.	.	.	.
DOM26m-33-7	.	.	.	.
DOM26m-33-8	.	.	.	.
DOM26m-33-9	I	.	.	.
DOM26m-34	.	.	.	.
DOM26m-35	.	.	.	.
DOM26m-36	.	.	.	.
DOM26m-37	.	.	.	.
DOM26m-38	.	.	.	.
DOM26m-39	.	.	.	.
DOM26m-4	.	.	.	.
DOM26m-40	.	.	.	.
DOM26m-41	.	.	.	.
DOM26m-42	.	.	.	.
DOM26m-43	.	.	.	.
DOM26m-44	.	.	.	.
DOM26m-45	.	.	.	.
DOM26m-46	.	.	.	.
DOM26m-47	.	.	.	.
DOM26m-48	.	.	.	.
DOM26m-52	.	.	.	.

DOM26m-52-1	.	.	.	.
DOM26m-52-2	.	.	.	.
DOM26m-52-3	.	.	.	.
DOM26m-52-4	.	.	.	.
DOM26m-52-5	.	.	.	.
DOM26m-52-6	.	.	.	.
DOM26m-52-7	.	.	.	.
DOM26m-6	.	.	.	.
DOM26m-60	.	.	.	.
DOM26m-61-1	.	.	.	.
DOM26m-61-2	A	.	.	.
DOM26m-61-3	.	.	.	.
DOM26m-61-4	.	.	.	.
DOM26m-61-5	.	.	.	.
DOM26m-61-6	A	.	.	.
DOM26m-7	.	.	.	.
DOM26m-73	.	.	.	.
DOM26m-74	.	.	.	.
DOM26m-75	.	.	.	.
DOM26m-76	.	.	.	.
DOM26m-77	.	.	.	.
DOM26m-78	.	.	.	.
DOM26m-79	.	.	.	.
DOM26m-8	.	.	.	.
DOM26m-80	.	.	.	.
DOM26m-81	.	.	.	.
DOM26m-82	.	.	G	.
DOM26m-83	.	.	.	.
DOM26m-9	.	.	.	.

Figure 20: Alignment of Amino Acid Sequences of Vκ Clones

Kabat Residue	'	'	'	'	5	'	'	'	'	10	'	'	'	'	15	'	'	'	'	20
VKDUM-1	D	I	Q	M	T	Q	S	P	S	S	L	S	A	S	V	G	D	R	V	T
DOM26m-20-6	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-22	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-23	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-24	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-25	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-26	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-3	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-50	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-50-1	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-50-2	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-50-3	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-50-4	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-50-5	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-50-6	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-51	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-53	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-54	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-55	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-56	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-57	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-58	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-59	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-61	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-63	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-64	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-66	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-69	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-85	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.

DOM26m-86	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-87	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-89	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-90	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-91	.	.	.	.	.	.	.	.	.	.	.	P	.	.	.	.	.	.	.	.
DOM26m-92	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-93	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-94	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-95	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-96	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-97	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-98	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-99	.	.	.	.	.	.	.	.	.	Y	.	.	.	.	.	.	.	.	.	.

Kabat Residue	'	'	'	'	25	'	'	'	'	30	'	'	'	'	35	'	'	'	'	40
VKDUM-1	I	T	C	R	A	S	Q	S	I	S	S	Y	L	N	W	Y	Q	Q	K	P
DOM26m-20-6	.	.	.	.	.	.	K	Y	.	G	.	D	.	Y	.	.	.	.	.	.
DOM26m-22	.	.	.	.	.	.	.	P	.	G	M	T	.	S	.	.	.	.	.	.
DOM26m-23	.	.	.	.	.	.	R	H	.	G	.	D	.	Y	.	.	.	.	.	.
DOM26m-24	.	.	.	.	.	.	.	W	.	.	D	N	.	S	.	.	.	.	.	.
DOM26m-25	.	.	.	.	.	.	.	H	.	R	Q	.	.	D	.	.	.	.	.	.
DOM26m-26	.	.	.	.	.	.	.	G	.	N	G	R	.	.	.	.	.	.	.	.
DOM26m-3	.	.	.	.	.	.	.	Q	.	R	D	A	.	S	.	.	.	.	.	.
DOM26m-50	.	.	.	.	.	.	I	.	.	Y	E	H	.	.	.	.	.	.	.	.
DOM26m-50-1	.	.	.	.	G	R	I	.	.	Y	E	H	.	.	.	.	.	.	.	.
DOM26m-50-2	.	.	.	.	.	.	I	.	.	Y	E	H	.	.	.	.	.	.	.	.
DOM26m-50-3	.	.	.	.	.	.	I	.	.	Y	E	H	.	.	.	.	.	.	.	.
DOM26m-50-4	.	.	.	.	.	.	I	.	.	Y	E	H	.	.	.	.	.	.	.	.
DOM26m-50-5	.	.	.	.	.	.	I	.	.	Y	E	H	.	.	.	.	.	.	.	.
DOM26m-50-6	.	.	.	.	.	.	I	.	.	Y	E	H	.	.	.	.	.	.	.	.
DOM26m-51	.	.	.	.	.	.	.	G	.	A	K	S	.	M	.	.	.	.	.	.
DOM26m-53	.	.	.	.	.	.	.	Y	.	.	T	N	.	L	.	.	.	.	.	.
DOM26m-54	.	.	.	.	.	.	L	N	.	D	T	D	.	V	.	.	.	.	.	.
DOM26m-55	.	.	.	Q	.	.	.	N	.	N	G	N	.	H	.	.	.	.	.	.

DOM26m-56	.	.	.	.	.	.	R	H	.	G	.	D	.	Y	.	.	.	.	.	.
DOM26m-57	.	.	.	.	.	.	R	M	.	N	E	M	.	A	.	.	.	.	.	.
DOM26m-58	.	.	.	.	.	.	.	P	.	R	N	A	.	T	.	.	.	.	.	.
DOM26m-59	.	.	.	.	.	.	.	G	.	G	N	H	.	S	.	.	.	.	.	.
DOM26m-61	.	.	.	.	.	.	.	P	.	.	H	.	.	L	.	.	.	.	.	.
DOM26m-63	.	.	.	.	.	.	.	Q	.	R	D	E	.	L	.	.	.	.	.	.
DOM26m-64	.	.	.	.	.	.	.	R	.	K	G	G	.	D	.	.	.	.	.	.
DOM26m-66	.	.	.	.	.	.	.	Y	.	F	V	Q	.	A	.	.	.	.	.	.
DOM26m-69	.	.	.	.	.	.	.	Y	.	Y	.	M	.	S	.	.	.	.	.	.
DOM26m-85	.	.	.	.	.	.	.	A	.	G	.	F	.	E	.	.	.	.	.	.
DOM26m-86	.	.	.	.	.	.	.	A	.	G	.	W	.	E	.	.	.	.	.	.
DOM26m-87	.	.	.	.	.	.	.	K	.	G	P	.	.	M	.	.	.	.	.	.
DOM26m-89	.	.	.	.	.	.	.	N	.	G	P	.	.	L	.	.	.	.	.	.
DOM26m-90	.	.	.	.	.	.	.	A	.	G	.	W	.	E	.	.	.	.	.	.
DOM26m-91	.	.	.	.	.	.	.	D	.	G	R	F	.	L	.	.	.	.	.	.
DOM26m-92	.	.	.	.	.	.	.	K	.	G	P	.	.	M	.	.	.	.	.	.
DOM26m-93	.	.	.	.	.	.	.	E	.	G	P	.	.	M	.	.	.	.	.	.
DOM26m-94	.	.	.	.	.	.	.	A	.	G	.	W	.	E	.	.	.	.	.	.
DOM26m-95	.	.	.	.	.	.	.	P	.	G	Q	W	.	D	.	.	.	.	.	.
DOM26m-96	.	.	.	.	.	.	R	D	.	H	G	K	.	G	.	.	.	.	.	.
DOM26m-97	.	.	.	.	.	.	.	K	.	G	P	.	.	M	.	.	.	.	.	.
DOM26m-98	.	.	.	.	.	.	.	T	.	Y	P	A	.	L	.	.	.	.	.	.
DOM26m-99	.	.	.	.	.	.	.	M	.	W	K	N	.	S	.	.	.	.	.	.

Kabat Residue	'	'	'	'	45	'	'	'	'	50	'	'	'	'	55	'	'	'	'	60
VKDUM-1	G	K	A	P	K	L	L	I	Y	A	A	S	S	L	Q	S	G	V	P	S
DOM26m-20-6	.	.	.	.	.	.	.	.	G	V	G	.	R	.	.	.	.	.	S	.
DOM26m-22	.	.	.	.	.	.	.	.	.	E	V	.	K	.	.	.	.	.	.	.
DOM26m-23	.	.	.	.	.	.	.	.	R	E	G	.	W	.	.	.	.	.	.	.
DOM26m-24	.	.	.	.	.	.	.	.	H	R	V	.	R	.	.	.	.	.	.	.
DOM26m-25	.	.	.	.	.	.	.	.	.	H	S	.	R	.	.	.	.	.	.	.
DOM26m-26	.	.	.	.	T	.	.	.	.	E	.	.	K	.	.	.	.	.	.	.
DOM26m-3	.	.	.	.	.	.	.	.	.	Y	T	.	I	.	.	N	.	.	.	.
DOM26m-50	.	.	.	.	T	.	.	.	W	D	S	.	G	.	.	.	.	.	.	.

DOM26m-50-1	.	.	.	.	T	.	.	.	W	D	S	.	G	.	.	.	.	.	.	.
DOM26m-50-2	.	.	.	.	T	.	.	.	W	D	S	.	G	.	.	.	.	.	.	.
DOM26m-50-3	.	.	.	.	T	.	.	.	W	D	S	.	G	.	.	.	.	.	.	.
DOM26m-50-4	.	.	.	.	T	.	.	.	W	D	S	.	G	.	.	.	.	.	.	.
DOM26m-50-5	.	.	.	.	T	.	.	.	W	D	S	.	G	.	.	.	.	.	.	.
DOM26m-50-6	.	.	.	.	T	.	.	.	W	D	S	.	G	.	.	.	.	.	.	.
DOM26m-51	.	.	.	.	.	.	.	.	.	K	S	.	M	.	.	.	.	.	.	.
DOM26m-53	.	.	.	.	.	.	.	.	R	S	G	.	G	.	.	.	.	.	.	.
DOM26m-54	.	.	.	.	.	.	.	.	A	G	W	.	G	.	.	.	.	.	.	.
DOM26m-55	.	.	.	.	.	.	.	.	.	E	V	.	K	.	.	.	.	.	.	.
DOM26m-56	.	.	.	.	.	.	.	.	R	E	G	.	W	.	.	.	.	.	.	.
DOM26m-57	.	.	.	.	.	.	.	.	L	G	P	.	.	.	.	.	.	.	.	.
DOM26m-58	.	.	.	.	.	.	.	.	.	R	T	.	H	.	.	.	.	.	.	.
DOM26m-59	.	.	.	.	.	.	.	.	.	R	T	.	F	.	.	G	.	.	.	.
DOM26m-61	.	.	.	.	.	.	.	.	.	N	R	.	Q	.	.	.	.	.	.	.
DOM26m-63	.	.	.	.	.	.	.	.	.	Y	T	.	I	.	.	N	.	.	.	.
DOM26m-64	.	.	.	.	.	.	.	.	.	N	G	.	L	.	.	.	.	.	.	.
DOM26m-66	.	.	.	.	.	.	.	.	.	D	.	.	V	.	.	.	.	.	.	.
DOM26m-69	.	.	.	.	.	.	.	.	.	Y	G	.	W	.	.	.	.	.	.	.
DOM26m-85	.	.	.	.	.	.	.	.	.	H	T	.	T	.	.	.	.	.	.	.
DOM26m-86	.	.	.	.	.	.	.	.	.	H	T	.	M	.	.	.	.	.	.	.
DOM26m-87	.	.	.	.	.	.	.	.	.	H	N	.	T	.	.	.	.	.	.	.
DOM26m-89	.	.	.	.	.	.	.	.	.	G	G	.	W	.	.	.	.	.	.	.
DOM26m-90	.	.	.	.	.	.	.	.	.	H	T	.	T	.	.	.	.	.	.	.
DOM26m-91	.	.	.	.	.	.	.	.	.	R	D	.	M	.	.	.	R	.	.	.
DOM26m-92	.	.	.	.	.	.	.	.	.	H	Y	.	T	.	.	.	.	.	.	.
DOM26m-93	.	.	.	.	.	.	.	.	.	H	Y	.	T	.	.	.	.	.	.	.
DOM26m-94	.	.	.	.	.	.	.	.	.	H	T	.	T	.	.	.	.	.	.	.
DOM26m-95	.	.	.	.	.	.	.	.	.	.	I	.	M	.	.	.	.	.	.	.
DOM26m-96	.	.	.	.	E	.	.	.	W	G	.	.	R	.	.	.	.	.	.	.
DOM26m-97	.	.	.	.	.	.	.	.	.	H	Y	.	T	.	.	.	.	.	.	.
DOM26m-98	.	.	.	.	.	.	.	.	.	G	G	.	W	.	.	.	.	.	.	.
DOM26m-99	.	.	.	.	.	.	.	.	.	R	V	.	T	.	.	.	.	.	.	.

Kabat Residue	'	'	'	'	65	'	'	'	'	70	'	'	'	'	75	'	'	'	'	80
VKDUM-1	R	F	S	G	S	G	S	G	T	D	F	T	L	T	I	S	S	L	Q	P
DOM26m-20-6	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-22	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-23	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-24	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-25	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-26	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-3	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-50	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-50-1	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-50-2	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-50-3	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-50-4	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-50-5	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-50-6	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-51	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-53	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-54	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-55	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-56	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-57	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-58	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-59	.	.	.	.	.	.	F	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-61	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-63	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-64	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-66	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-69	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-85	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-86	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-87	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-89	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-90	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-91	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.

DOM26m-92	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-93	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-94	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-95	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-96	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-97	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-98	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26m-99	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.

Kabat Residue	'	'	'	'	85	'	'	'	'	90	'	'	'	'	95	'	'	'	'	100
VKDUM-1	E	D	F	A	T	Y	Y	C	Q	Q	S	Y	S	T	P	N	T	F	G	Q
DOM26m-20-6	.	.	.	.	.	.	.	.	G	.	K	W	A	R	.	L	.	.	.	.
DOM26m-22	.	.	.	.	.	.	.	.	.	.	I	R	F	R	.	F	.	Y	.	.
DOM26m-23	.	.	.	.	.	.	.	.	G	.	H	R	.	H	.	A	.	.	.	.
DOM26m-24	.	.	.	.	.	.	.	.	.	.	Y	W	Y	W	.	P	.	.	.	.
DOM26m-25	.	.	.	.	.	.	.	.	.	.	Y	S	D	W	.	P	.	.	.	.
DOM26m-26	.	.	C	.	.	.	.	.	.	.	.	M	G	R	.	A	.	.	.	.
DOM26m-3	.	.	.	.	.	.	.	.	.	.	N	.	L	F	.	A	.	.	.	.
DOM26m-50	.	.	.	.	.	.	.	.	V	.	H	H	.	H	.	P	.	.	.	.
DOM26m-50-1	.	.	.	.	.	.	.	.	V	.	H	H	.	H	.	P	.	.	.	.
DOM26m-50-2	.	.	.	.	.	.	.	.	V	.	H	Q	.	Q	.	.	.	.	.	.
DOM26m-50-3	.	.	.	.	.	.	.	.	V	.	H	Q	.	H	.	.	.	.	.	.
DOM26m-50-4	.	.	.	.	.	.	.	.	V	.	Q	H	.	H	.	.	.	.	.	.
DOM26m-50-5	.	.	.	.	.	.	.	.	V	H	Q	H	R	H	Q	.	.	.	.	.
DOM26m-50-6	.	.	.	.	.	.	.	.	I	H	R	H	N	Q	.	.	.	.	.	.
DOM26m-51	.	.	.	.	.	.	.	.	.	.	V	.	T	M	.	L	.	.	.	.
DOM26m-53	.	.	.	.	.	.	.	.	R	.	V	E	Y	M	.	Y	.	.	.	.
DOM26m-54	.	.	.	.	.	.	.	.	G	.	F	A	R	E	.	F	.	.	.	.
DOM26m-55	.	.	.	.	.	.	.	.	.	.	T	.	V	R	.	T	.	.	.	.
DOM26m-56	.	.	.	.	.	.	.	.	G	.	H	R	.	H	.	A	.	.	.	.
DOM26m-57	.	.	.	.	.	.	.	.	G	.	F	.	G	L	.	V	.	.	.	.
DOM26m-58	.	.	.	.	.	.	.	.	.	.	T	W	T	M	.	L	.	.	.	.
DOM26m-59	.	.	.	.	.	.	.	.	.	.	F	W	T	W	.	.	.	.	.	.
DOM26m-61	.	.	.	.	.	.	.	.	.	.	V	.	T	W	.	F	.	.	.	.

DOM26m-63	.	.	.	.	.	.	.	.	.	.	N	.	L	F	.	A	.	.	.	.
DOM26m-64	.	.	.	.	.	.	.	.	.	.	A	T	E	L	.	F	.	.	.	.
DOM26m-66	.	.	.	.	.	.	.	.	.	.	T	.	M	P	.	L	.	.	.	.
DOM26m-69	.	.	.	.	.	.	.	.	.	.	T	.	F	W	.	F	.	.	.	.
DOM26m-85	.	.	.	.	.	.	.	.	.	.	Y	A	I	W	.	P	.	.	.	.
DOM26m-86	.	.	.	.	.	.	.	.	.	.	Y	A	I	W	.	P	.	.	.	.
DOM26m-87	.	.	.	.	.	.	.	.	.	.	L	F	D	M	.	F	.	.	.	.
DOM26m-89	.	.	.	.	.	.	.	.	.	.	T	V	K	W	.	H	.	.	.	.
DOM26m-90	.	.	.	.	.	.	.	.	.	.	Y	A	I	W	.	P	.	.	.	.
DOM26m-91	.	.	.	.	.	.	.	.	.	.	V	.	G	L	.	F	.	.	.	.
DOM26m-92	.	.	.	.	.	.	.	.	.	.	T	V	K	W	.	H	.	.	.	.
DOM26m-93	.	.	.	.	.	.	.	.	.	.	L	F	D	M	.	F	.	.	.	.
DOM26m-94	.	.	.	.	.	.	.	.	.	.	Y	A	I	W	.	P	.	.	.	.
DOM26m-95	.	.	.	.	.	.	.	.	.	.	.	R	K	.	.	F	.	.	.	.
DOM26m-96	.	.	.	.	.	.	.	.	G	.	V	A	.	R	.	G	.	.	.	.
DOM26m-97	.	.	.	.	.	.	.	.	.	.	L	F	D	M	.	F	.	.	.	.
DOM26m-98	.	.	.	.	.	.	.	.	.	.	T	V	K	W	.	H	.	.	.	.
DOM26m-99	.	.	.	.	.	.	.	.	.	.	Y	Q	L	S	.	F	.	.	.	.

Kabat Residue	'	'	'	'	105	'	'	'
VKDUM-1	G	T	K	V	E	I	K	R
DOM26m-20-6	.	I	.	.	.	.	.	.
DOM26m-22	.	.	.	.	.	.	.	.
DOM26m-23	.	.	.	.	.	.	.	.
DOM26m-24	.	.	.	.	.	.	.	.
DOM26m-25	.	.	.	.	.	.	.	.
DOM26m-26	.	.	.	.	.	.	.	.
DOM26m-3	.	.	.	.	.	.	.	.
DOM26m-50	.	.	.	.	.	.	.	.
DOM26m-50-1	.	.	.	.	.	.	.	.
DOM26m-50-2	.	.	.	.	.	.	.	.
DOM26m-50-3	.	.	.	.	.	.	.	.
DOM26m-50-4	.	.	.	.	.	.	.	.
DOM26m-50-5	.	.	.	.	.	.	.	.

DOM26m-50-6	.	.	.	.	.	.	.	.
DOM26m-51	.	.	.	.	.	.	.	.
DOM26m-53	.	.	.	.	.	.	.	.
DOM26m-54	.	.	.	.	.	.	.	.
DOM26m-55	.	.	.	.	.	.	.	.
DOM26m-56	.	.	.	.	.	.	.	.
DOM26m-57	.	.	.	.	.	.	.	.
DOM26m-58	.	.	.	.	.	.	.	.
DOM26m-59	.	.	.	.	.	.	.	.
DOM26m-61	.	.	.	.	.	.	.	.
DOM26m-63	.	.	.	.	.	.	.	.
DOM26m-64	.	.	.	.	.	.	.	.
DOM26m-66	.	.	.	.	.	.	.	.
DOM26m-69	.	.	.	.	.	.	.	.
DOM26m-85	.	.	.	.	.	.	.	.
DOM26m-86	.	.	.	.	.	.	.	.
DOM26m-87	.	.	.	.	.	.	.	.
DOM26m-89	.	.	.	.	.	.	.	.
DOM26m-90	.	.	.	.	.	.	.	.
DOM26m-91	.	.	.	.	.	.	.	.
DOM26m-92	.	.	.	.	.	.	.	.
DOM26m-93	.	.	.	.	.	.	.	.
DOM26m-94	.	.	.	.	.	.	.	.
DOM26m-95	.	.	.	.	.	.	.	.
DOM26m-96	.	.	.	.	.	.	.	.
DOM26m-97	.	.	.	.	.	.	.	.
DOM26m-98	.	.	.	.	.	.	.	.
DOM26m-99	.	.	.	.	.	.	.	.

Figure 21

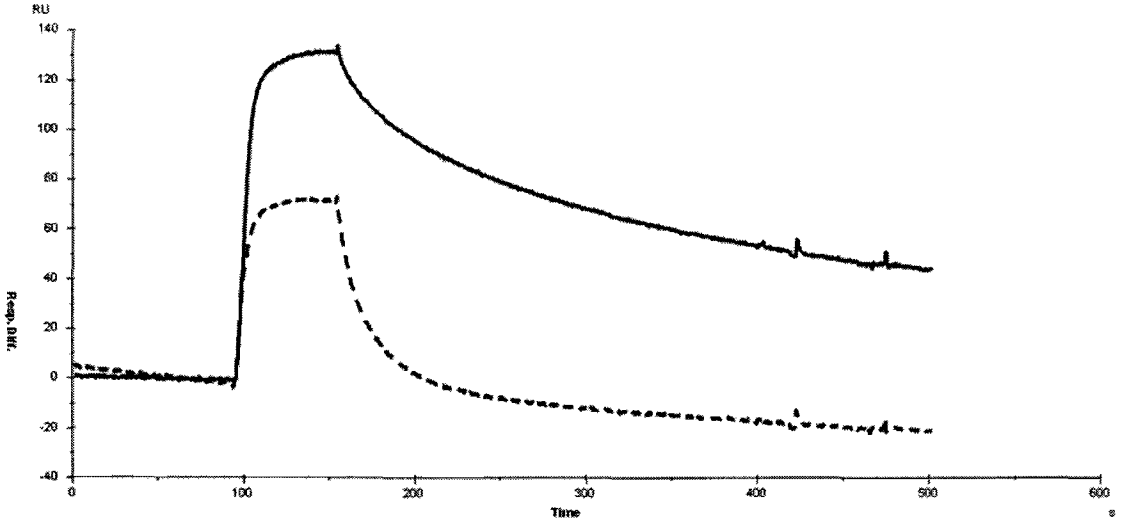


Figure 21 shows binding of ASGPR specific dAbs DOM26h-196 (– – –) and DOM26h-196-61 (———) to human $(His)_6$-ASGPR H1. Biotinylated $(His)_6$-ASGPR H1 was immobilised on a Biacore streptavidin chip surface and 62nM dAb passed over at a flow rate of 40 $\mu l.min^{-1}$. Sensorgram illustrates that DOM26h-196-61 binds to human $(His)_6$-ASGPR H1 antigen with higher affinity than that of the DOM26h-196 parental clone.

Figure 22

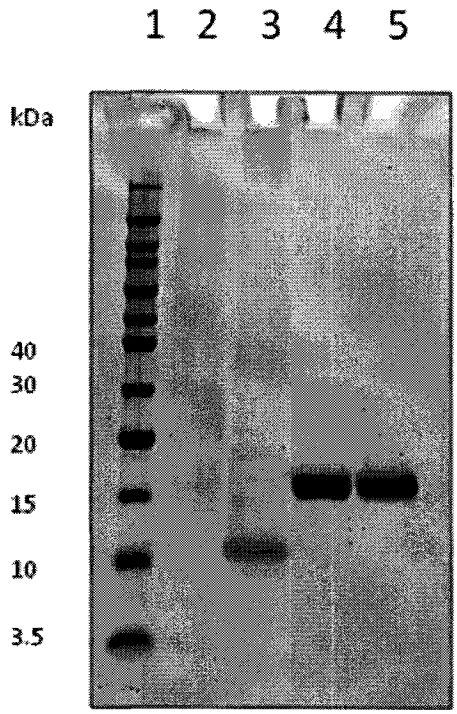


Figure 22 shows 4-12% Bis-Tris gel loaded with 2μg of Ni-NTA purified human $(His)_6$-ASGPR H1 stalk domain (lane 2), human $(His)_6$-ASGPR H1 stalk domain treated with PNGase F (lane 3), human $(His)_6$-ASGPR H1 lectin domain (lane4), human $(His)_6$-ASGPR H1 lectin domain treated with PNGase F (lane 5). 10 μl Novex Sharp prestained molecular weight standards (Invitrogen) were loaded in lane 1 and molecular masses (in kilodaltons) of individual marker bands are given to the left of lane 1. Gel was stained with 1x SureBlue. Gel shows that stalk domain is extensively glycosylated as the protein only runs at the expected molecular mass following treatment with PNGase F, whereas lectin domain runs at the expected molecular mass in the presence or absence of PNGase F digestion.

Figure 23

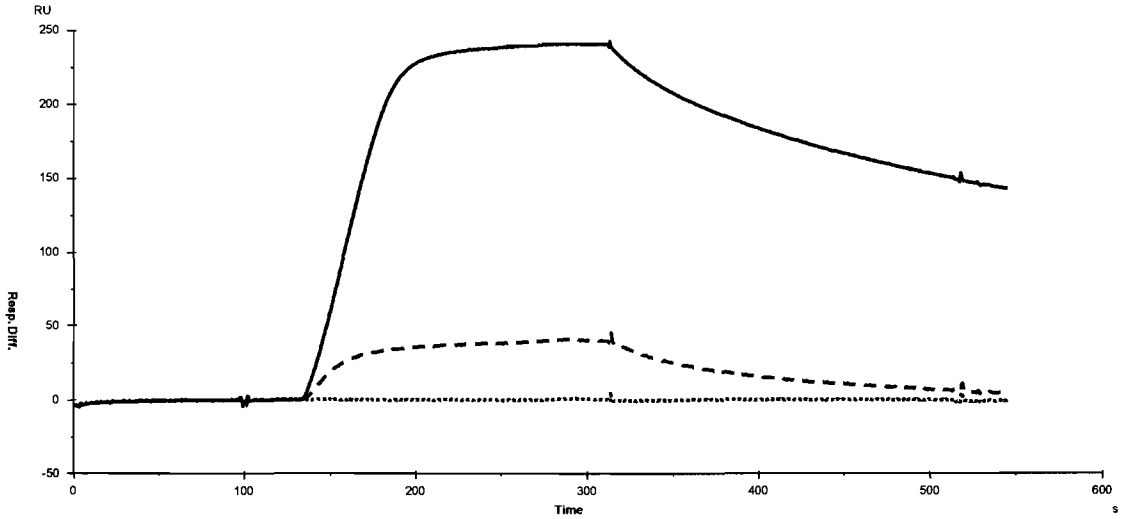
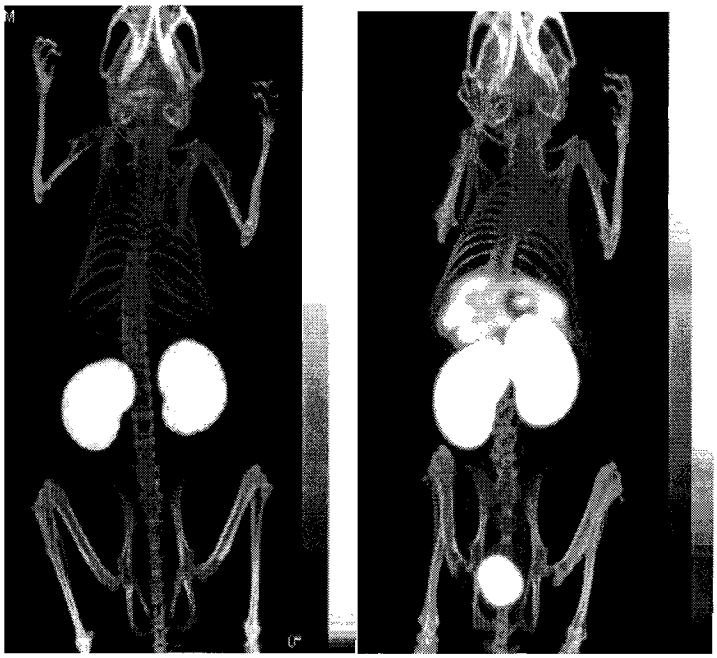
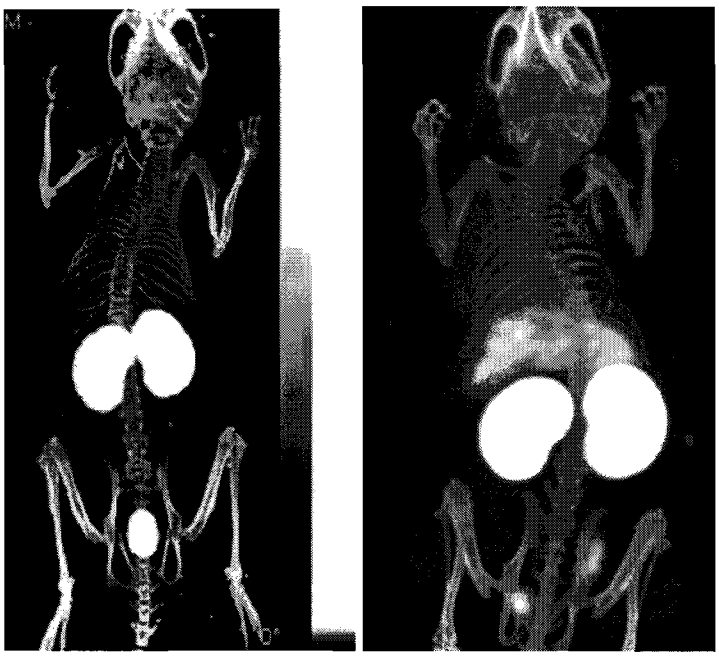


Figure 23 shows binding of ASGPR specific dAb DOM26h-196-61 to biotinylated $(His)_6$- human ASGPR H1 lectin domain residues cysteine 154-leucine 291 (———), $(His)_6$-mouse ASGPR H1 full extracellular domain residues serine 60-asparagine 284 (_ _ _) and $(His)_6$-human ASGPR H1 stalk domain residues glutamine 62-cysteine 153 (.....). Biotinylated antigens were immobilised on a Biacore streptavidin chip surface and dAb passed over at a concentration of 60nM and flow rate of 40 $\mu l.min^{-1}$. Sensorgram illustrates that DOM26h-196-61 binds to human ASGPR H1 lectin domain and mouse ASGPR H1 extracellular domain but not human ASGPR H1 stalk domain.

Figure 24



V_H dummy 2 DOM26h-196-61



Vκ dummy DOM26h-161-84

Figure 24 shows localisation of ^{111}In labelled dAbs in balb/c mice at 3 hours post injection. Following intravenous dosing of 12 MBq of radiolabelled dAb via tail vein injection mice were imaged using a nanospect camera. Images show that at 3 hours signal is observed in kidney and bladder with all dAb molecules, whereas liver localisation is only observed with anti ASGPR V_H dAb DOM26h-196-61 and anti ASGPR V_κ dAb DOM26h-161-84.

Figure 25(a)

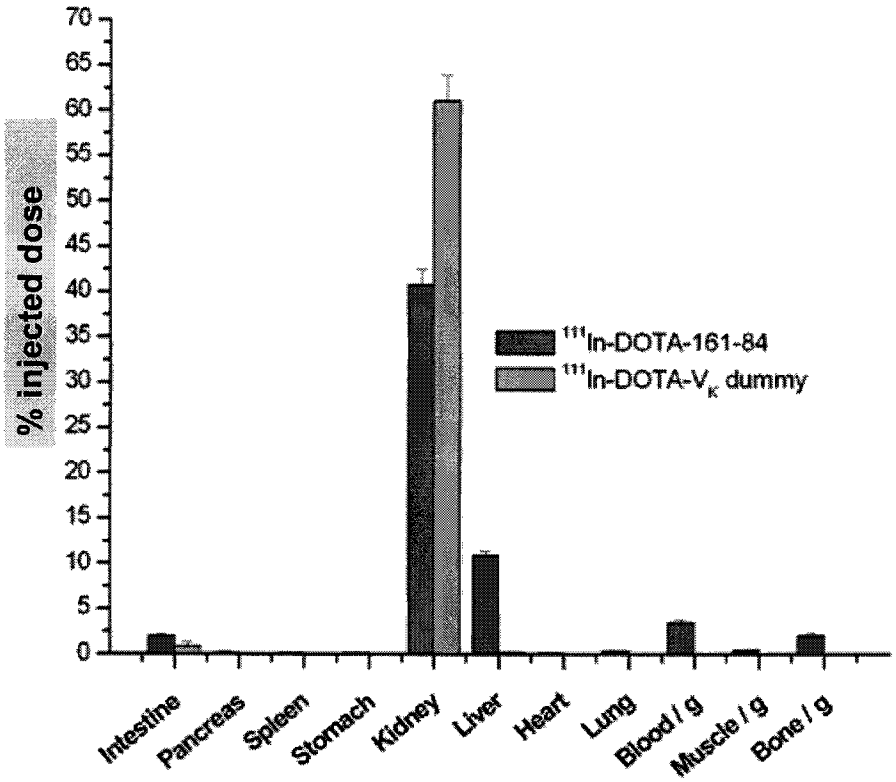

% injected dose
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0
111In-DOTA-161-84
111In-DOTA-VK dummy
Intestine
Pancreas
Spleen
Stomach
Kidney
Liver
Heart
Lung
Blood / g
Muscle / g
Bone / g

Figure 25(b)

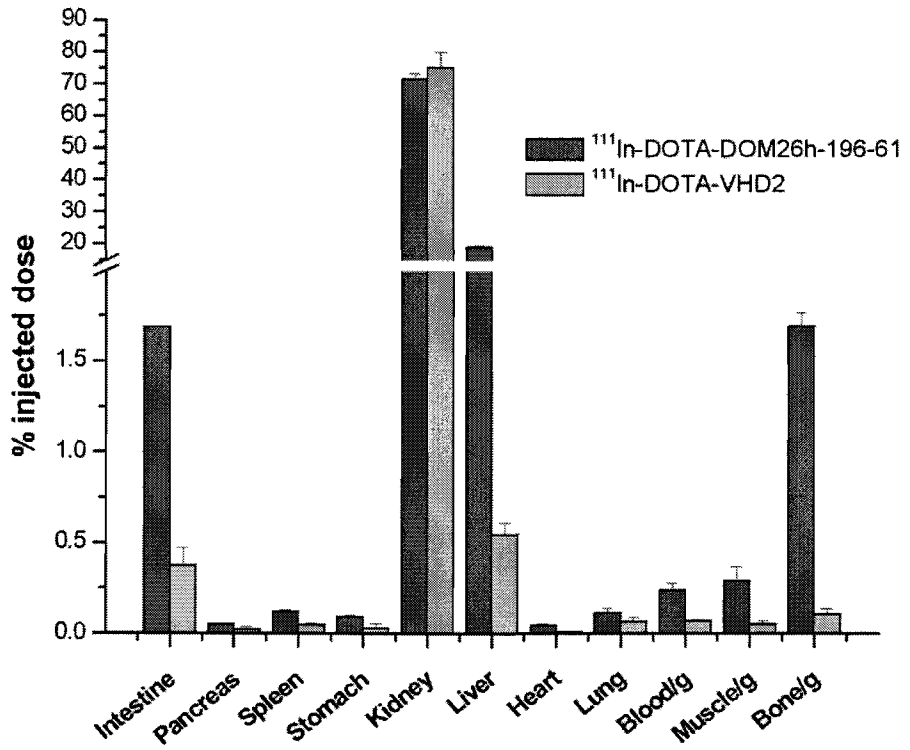


Figure 25 a & b shows biodistribution of ^{111}In labelled dAbs 3 hours after dosing intravenously in balb/c mice via the tail vein. Approximately 0.5MBq radiolabelled dAb was injected in each case. Results show accumulation of radiolabelled ASGPR dAb in mouse liver is considerably higher than that observed with either V_κ/V_H dummy 2 dAbs.

Figure 26

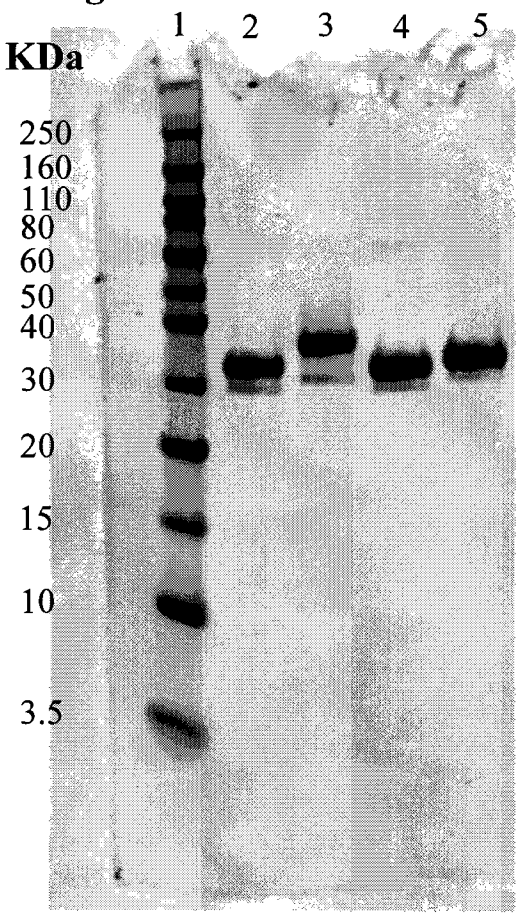


Figure 26 shows 4-12% Bis-Tris gel loaded with 2μg per lane of protein L purified mIFNa2-dAb fusions reduced with 10mM DTT. Lane designations as follows:

mIFNa2-Vκ dummy (lane 2)

mIFNa2-V_H dummy 2 (lane 3)

mIFNa2-DOM26h-161-84 (lane 4)

mIFNa2-DOM26h-196-61 (lane 5)

10 μl Novex Sharp prestained molecular weight standards (Invitrogen) were loaded in lane 1 and molecular masses (in kilodaltons) of individual marker bands are given to the left of lane 1. Gel was stained with 1x SureBlue. Gel illustrates that mouse IFNa2-dAb fusions migrate close to the expected molecular mass of approximately 33 KDa.

Figure 27

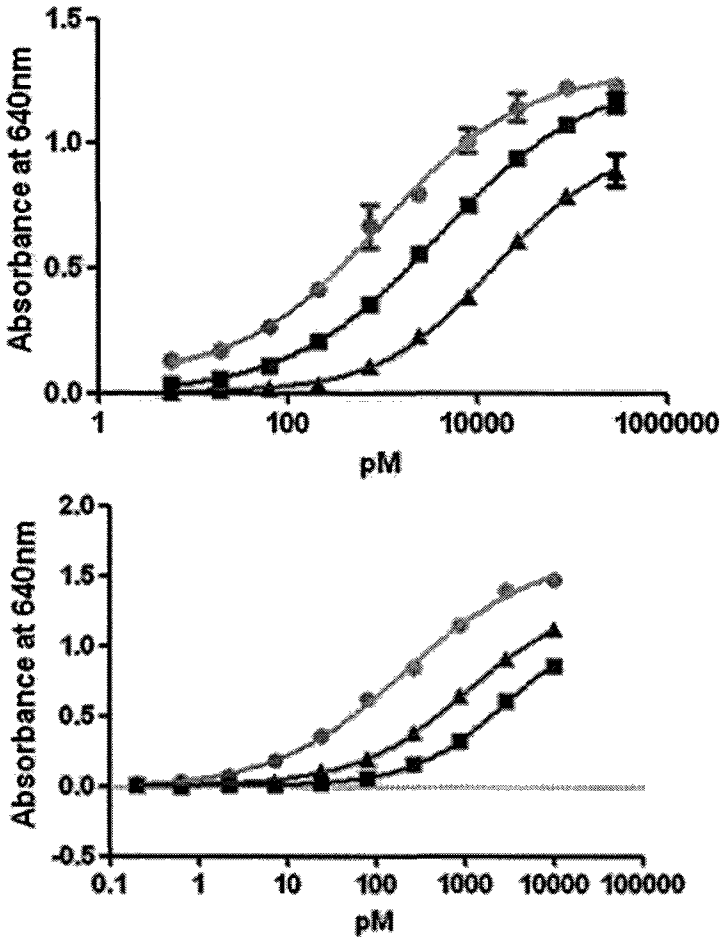


Figure 27 shows activity of mouse IFN-dAb fusions (+/- DOTA conjugation) in B16 mouse IFNα/β reporter cell line. B16 cells were incubated with the indicated concentrations of mouse IFN-alpha standard or mouse IFN-dAb fusion protein and interferon activity assayed by measuring the level of reporter gene expression which is directly proportional to absorbance measured at 640nm. Top panel shows results obtained with mouse IFNa2-V_H dummy 2 fusion protein, bottom panel shows results obtained with mouse IFNa2-DOM26h-196-61 fusion protein. Symbols denote the following:

▲= mouse IFNa2-dAb fusion

■= mouse IFNa2-dAb fusion conjugated to NHS:DOTA

●= mouse IFN-alpha standard

Figure 28

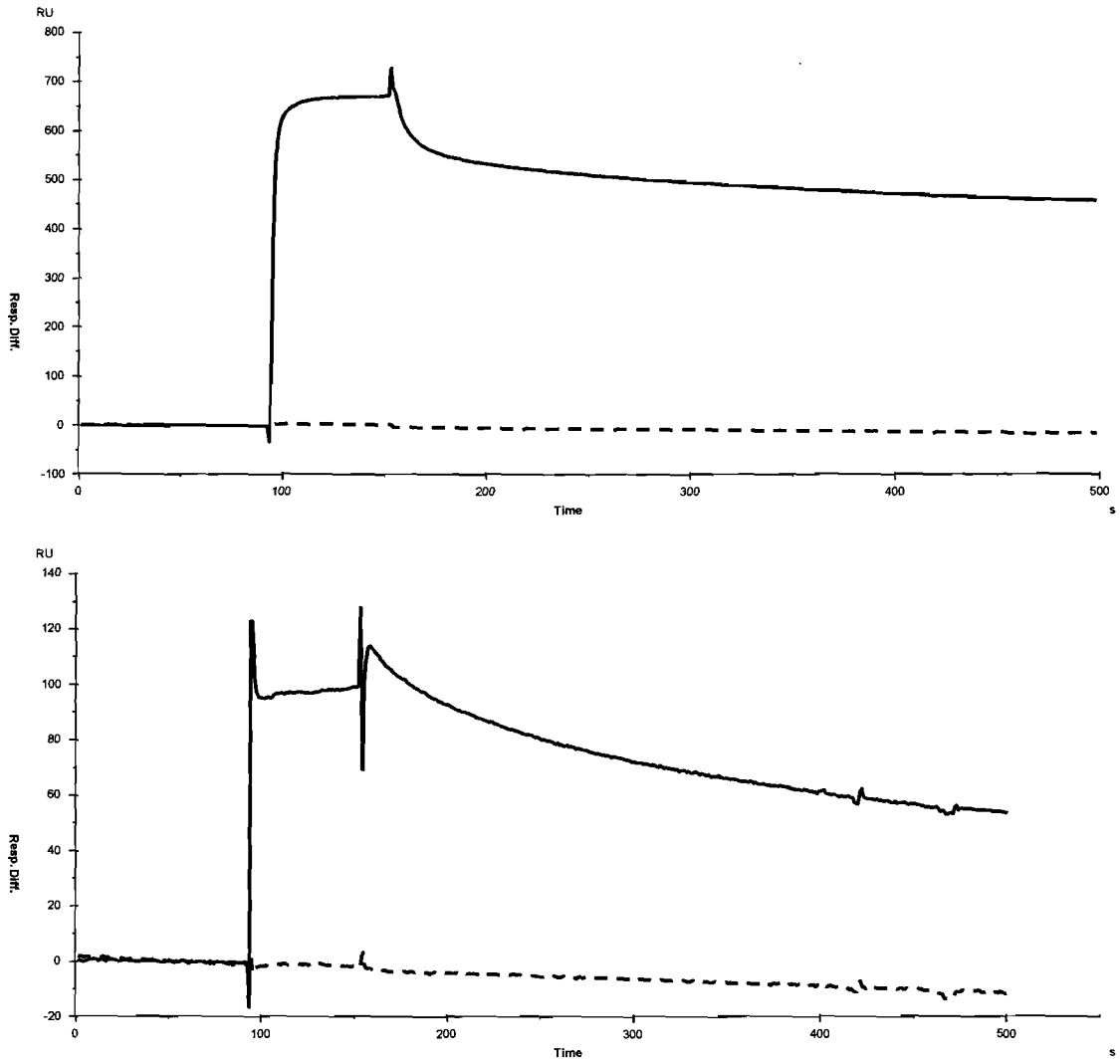
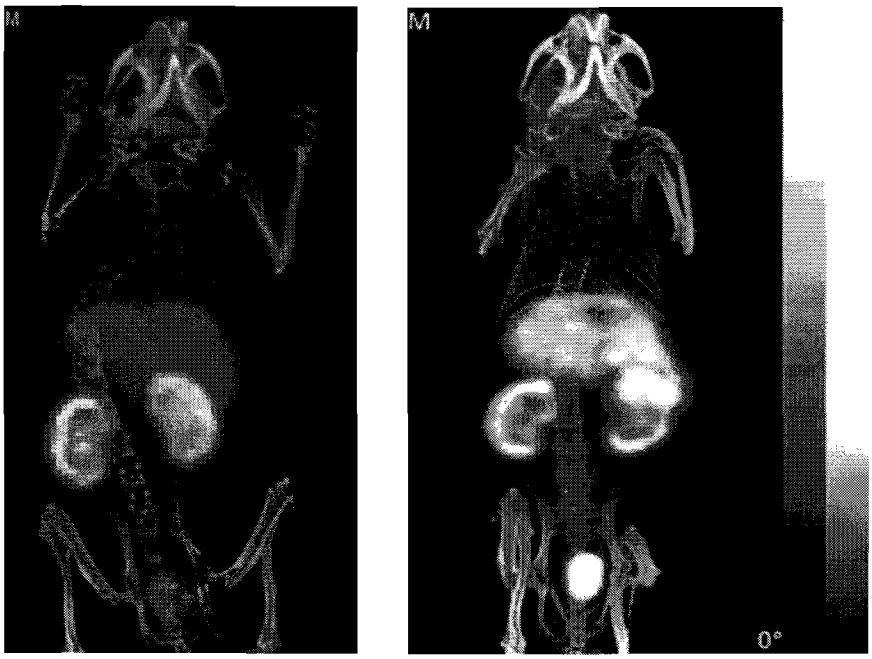


Figure 28 shows binding of mouse IFNa2-dAb fusions to biotinylated $(His)_6$-human ASGPR H1 lectin domain and $(His)_6$-mouse ASGPR H1 coated on the surface of a BIAcore streptavidin chip. Fusion proteins were passed over the chip surface at a concentration of 1μM and a flow rate of 40 $\mu l.min^{-1}$.

Top panel shows binding of mouse IFNa2-DOM36h-196-61 fusion protein (———) and mouse IFNa2- V_H dummy 2 fusion protein (– – –) to $(His)_6$-human ASGPR H1 lectin domain. Bottom panel shows binding of mouse IFNa2-DOM36h-196-61 fusion protein (———) and mouse IFNa2- V_H dummy 2 fusion protein (– – –) to $(His)_6$-mouse ASGPR H1.

Figure 29



Mouse IFNa2-V_H dummy 2 **Mouse IFNa2-DOM26h-196-61**

Figure 29 shows localisation of ^{111}In labelled mouse IFNa2-dAb fusions in balb/c mice at 3 hours post injection. Following intravenous dosing of 12 MBq of radiolabelled dAb via tail vein injection mice were imaged using a nanospect camera. Images show that at 3 hours signal is observed in liver, kidney and bladder with mouse IFNa2-V_H dummy 2 and mouse IFNa2-DOM26h-196-61 fusion proteins, however the liver appears brighter in the image in the right hand panel, indicating a greater level of liver uptake of mouse IFNa2-DOM26h-196-61 compared to mouse IFNa2-V_H dummy 2.

Figure 30

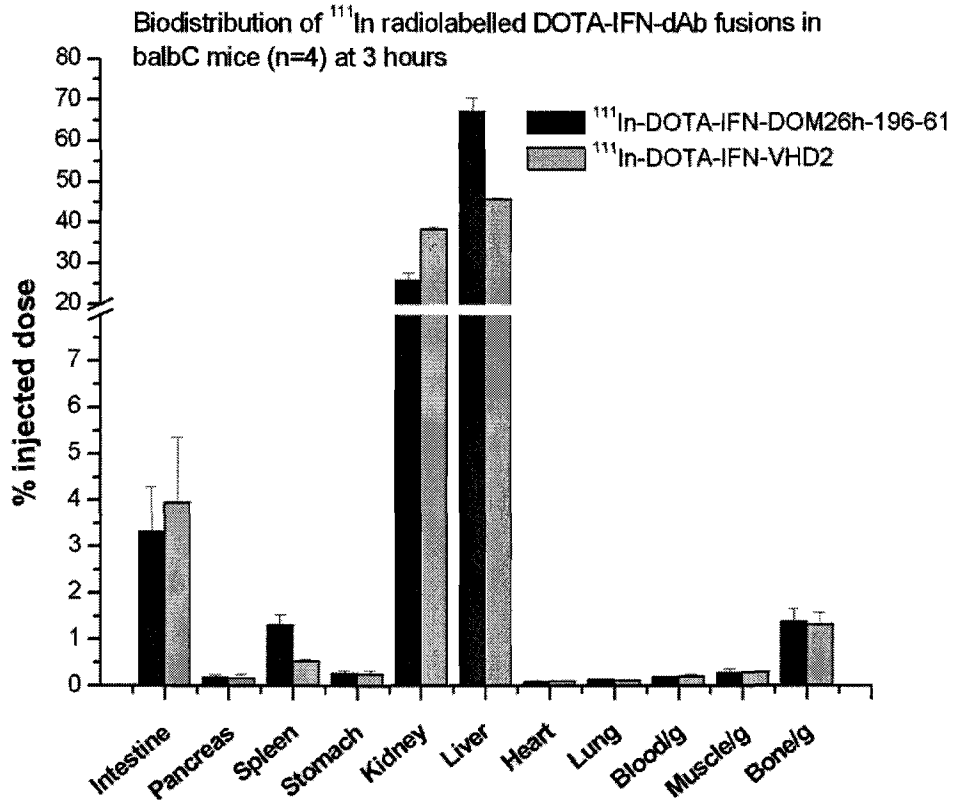


Figure 30 shows biodistribution of ^{111}In labelled mouse IFNa2-dAb fusion protein 3 hours after dosing intravenously in balb/c mice via the tail vein. Approximately 0.5MBq radiolabelled dAb was injected in each case. Results show both mouse IFNa2-DOM26h-196-61 (black bars) and mouse IFNa2-V_H dummy 2 (grey bars) accumulate in the liver and kidney, however the liver/kidney ratio of mouse IFNa2-DOM26h-196-61 is approximately 2.2 fold higher than that of mouse IFNa2-V_H dummy 2, indicative of successful liver targeting of mouse IFNa2 by genetic fusion to ASGPR dAb DOM26h-196-61.

Figure 31 DOM26h affinity matured clones Amino Acid Sequences

DOM26h-161 affinity matured clones Amino Acid Sequence

Kabat Residue	'	'	'	'	5	'	'	'	'	10	'	'	'	'	15	'	'	'	'	20
VKDUM-1	D	I	Q	M	T	Q	S	P	S	S	L	S	A	S	V	G	D	R	V	T
DOM26h-161-84	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26h-161-86	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26h-161-87	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.

Kabat Residue	'	'	'	'	25	'	'	'	'	30	'	'	'	'	35	'	'	'	'	40
VKDUM-1	I	T	C	**R**	**A**	**S**	**Q**	**S**	**I**	**S**	**S**	**Y**	**L**	**N**	W	Y	Q	Q	K	P
DOM26h-161-84	.	.	.	.	.	.	.	**A**	.	**G**	**R**	**W**	.	**L**	.	.	.	.	.	.
DOM26h-161-86	.	.	.	.	.	.	.	**A**	.	**G**	**R**	**W**	.	**L**	.	.	.	.	.	.
DOM26h-161-87	.	.	.	.	.	.	.	**A**	.	**G**	**R**	**W**	.	**L**	.	.	.	.	.	.

Kabat Residue	'	'	'	'	45	'	'	'	'	50	'	'	'	'	55	'	'	'	'	60
VKDUM-1	G	K	A	P	K	L	L	I	Y	**A**	**A**	**S**	**S**	**L**	**Q**	**S**	G	V	P	S
DOM26h-161-84	.	.	.	.	.	.	.	.	G	**P**	**G**	.	**R**	.	**R**	.	.	.	.	.
DOM26h-161-86	.	.	.	.	.	H	.	.	G	**P**	**G**	.	**R**	.	.	.	.	.	.	.
DOM26h-161-87	.	.	.	.	.	.	.	.	G	**P**	**G**	.	**R**	.	.	.	.	.	.	.

Kabat Residue	'	'	'	'	65	'	'	'	'	70	'	'	'	'	75	'	'	'	'	80
VKDUM-1	R	F	S	G	S	G	S	G	T	D	F	T	L	T	I	S	S	L	Q	P
DOM26h-161-84	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26h-161-86	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26h-161-87	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	G	.	.	.	.

Kabat Residue	'	'	'	'	85	'	'	'	'	90	'	'	'	'	95	'	'	'	'	100
VKDUM-1	E	D	F	A	T	Y	Y	C	**Q**	**Q**	**S**	**Y**	**S**	**T**	**P**	**N**	**T**	F	G	Q
DOM26h-161-84	.	.	.	V	.	.	.	.	.	.	**A**	.	**A**	**W**	.	**P**	.	.	.	.
DOM26h-161-86	.	.	.	.	.	.	.	.	.	.	**A**	.	**Q**	**L**	.	**V**	.	.	.	.
DOM26h-161-87	.	.	.	.	.	.	.	.	.	.	**A**	.	.	**L**	.	**P**	.	.	.	.

Kabat Residue	'	'	'	'	105	'	'	'
VKDUM-1	G	T	K	V	E	I	K	R
DOM26h-161-84	.	.	.	.	.	.	.	.
DOM26h-161-86	.	.	.	.	.	.	.	.
DOM26h-161-87	.	.	.	.	.	.	.	.

Kabat Residue
VKDUM-1
DOM26h-161-84
DOM26h-161-86
DOM26h-161-87

DOM26h-196 affinity matured clones Amino Acid Sequence

Kabat Residue	'	'	'	'	5	'	'	'	'	10	'	'	'	'	15	'	'	'	'	20
VHDUM-1	E	V	Q	L	L	E	S	G	G	G	L	V	Q	P	G	G	S	L	R	L
DOM26h-196-61	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.

Kabat Residue	'	'	'	'	25	'	'	'	'	30	'	'	'	'	35	'	'	'	'	40
VHDUM-1	S	C	A	A	S	G	F	T	F	S	**S**	**Y**	**A**	**M**	**S**	W	V	R	Q	A
DOM26h-196-61	.	.	.	.	.	.	.	.	.	E	**K**	.	.	.	**A**	.	.	.	.	.

Kabat Residue	'	'	'	'	45	'	'	'	'	50	'	'	'	'	54	'	'	'	'	59
VHDUM-1	P	G	K	G	L	E	W	V	S	**A**	**I**	**S**	**G**	**S**	**G**	**G**	**S**	**T**	**Y**	**Y**
DOM26h-196-61	.	.	.	.	.	.	.	.	.	**R**	.	.	**A**	**R**	.	**V**	**T**	.	.	.

Kabat Residue	'	'	'	'	64	'	'	'	'	69	'	'	'	'	74	'	'	'	'	79
VHDUM-1	**A**	**D**	**S**	**V**	**K**	**G**	R	F	T	I	S	R	D	N	S	K	N	T	L	Y
DOM26h-196-61	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.

Kabat Residue	'	'	'	'	82b	'	'	'	'	86	'	'	'	'	91	'	'	'	'	96
VHDUM-1	L	Q	M	N	S	L	R	A	E	D	T	A	V	Y	Y	C	A	K	**S**	**Y**
DOM26h-196-61	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	**H**	**K**

Kabat Residue	'	'	'	'	100a	'	'	'	'	103	'	'	'	'	108	'	'	'	'	113
VHDUM-1	**G**	**A**	**-**	**-**	**-**	**-**	**F**	**D**	**Y**	W	G	Q	G	T	L	V	T	V	S	S
DOM26h-196-61	**R**	**H**	**E**	**H**	**T**	**R**	.	.	**S**	.	.	.	.	.	.	.	.	.	.	.

Kabat Residue
VHDUM-1
DOM26h-196-61

DOM26h-210 affinity matured clones Amino Acid Sequence

Kabat Residue	'	'	'	'	5	'	'	'	'	10	'	'	'	'	15	'	'	'	'	20
VHDUM-1	E	V	Q	L	L	E	S	G	G	G	L	V	Q	P	G	G	S	L	R	L
DOM26h-210-2	.	L	.	.	.	.	F	.	.	.	.	.	.	.	.	.	.	.	.	.

Kabat Residue	'	'	'	'	25	'	'	'	'	30	'	'	'	'	35	'	'	'	'	40
VHDUM-1	S	C	A	A	S	G	F	T	F	S	**S**	**Y**	**A**	**M**	**S**	W	V	R	Q	A
DOM26h-210-2	.	.	T	T	.	.	.	.	.	.	**R**	.	**T**	.	**G**	.	.	.	.	.

Kabat Residue	'	'	'	'	45	'	'	'	'	50	'	'	'	'	54	'	'	'	'	59
VHDUM-1	P	G	K	G	L	E	W	V	S	**A**	**I**	**S**	**G**	**S**	**G**	**G**	**S**	**T**	**Y**	**Y**
DOM26h-210-2	.	.	.	.	.	.	.	.	.	.	.	**G**	**P**	**P**	.	**S**	**N**	.	.	.

Kabat Residue	'	'	'	'	64	'	'	'	'	69	'	'	'	'	74	'	'	'	'	79
VHDUM-1	**A**	**D**	**S**	**V**	**K**	**G**	R	F	T	I	S	R	D	N	S	K	N	T	L	Y
DOM26h-210-2	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.

Kabat Residue	'	'	'	'	82b	'	'	'	'	86	'	'	'	'	91	'	'	'	'	96
VHDUM-1	L	Q	M	N	S	L	R	A	E	D	T	A	V	Y	Y	C	A	K	**S**	**Y**
DOM26h-210-2	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	**W**	**V**

Kabat Residue	'	'	'	'	100a	'	'	'	'	104	'	'	'	'	109	'	'	'	'	
VHDUM-1	**G**	**A**	**-**	**-**	**-**	**F**	**D**	**Y**	W	G	Q	G	T	L	V	T	V	S	S	
DOM26h-210-2	**M**	**L**	**R**	**G**	**R**	.	.	.	.	.	.	.	.	.	.	.	.	.	.	

Kabat Residue
VHDUM-1
DOM26h-210-2

DOM26h-210 affinity matured clones Amino Acid Sequence

Kabat Residue	'	'	'	'	5	'	'	'	'	10	'	'	'	'	15	'	'	'	'	20
VHDUM-1	E	V	Q	L	L	E	S	G	G	G	L	V	Q	P	G	G	S	L	R	L
DOM26h-220-1	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26h-220-43	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.

Kabat Residue	'	'	'	'	25	'	'	'	'	30	'	'	'	'	35	'	'	'	'	40
VHDUM-1	S	C	A	A	S	G	F	T	F	S	**S**	**Y**	**A**	**M**	**S**	W	V	R	Q	A
DOM26h-220-1	.	.	.	.	.	.	.	.	.	E	**D**	**.**	**G**	**.**	**G**	.	.	.	.	.
DOM26h-220-43	.	.	.	.	.	.	.	.	.	G	**A**	**A**	**G**	**.**	**G**	.	.	.	.	.

Kabat Residue	'	'	'	'	45	'	'	'	'	50	'	'	'	'	54	'	'	'	'	59
VHDUM-1	P	G	K	G	L	E	W	V	S	**A**	**I**	**S**	**G**	**S**	**G**	**G**	**S**	**T**	**Y**	**Y**
DOM26h-220-1	.	.	.	.	.	.	.	.	.	**.**	**.**	**G**	**R**	**N**	**.**	**S**	**Q**	**.**	**.**	**.**
DOM26h-220-43	.	.	.	.	.	.	.	.	.	**.**	**.**	**G**	**R**	**N**	**.**	**S**	**Q**	**.**	**.**	**.**

Kabat Residue	'	'	'	'	64	'	'	'	'	69	'	'	'	'	74	'	'	'	'	79
VHDUM-1	**A**	**D**	**S**	**V**	**K**	**G**	R	F	T	I	S	R	D	N	S	K	N	T	L	Y
DOM26h-220-1	**.**	**.**	**.**	**.**	**.**	**.**	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM26h-220-43	**.**	**.**	**.**	**.**	**.**	**.**	.	.	.	.	.	.	.	.	.	.	.	.	.	.

Kabat Residue	'	'	'	'	82b	'	'	'	'	86	'	'	'	'	91	'	'	'	'	96
VHDUM-1	L	Q	M	N	S	L	R	A	E	D	T	A	V	Y	Y	C	A	K	**S**	**Y**
DOM26h-220-1	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	**L**	**R**
DOM26h-220-43	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	**L**	**R**

Kabat Residue	'	'	'	'	100a	'	'	'	'	100o	'	'	'	'	105	'	'	'	'	110
VHDUM-1	**G**	**A**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**F**	**D**	**Y**	W	G	Q	G	T	L	V	T
DOM26h-220-1	**R**	**G**	**R**	**G**	**L**	**N**	**F**	**F**	**T**	**L**	**.**	**.**	.	.	.	.	.	.	.	.
DOM26h-220-43	**R**	**G**	**R**	**G**	**L**	**N**	**T**	**F**	**T**	**L**	**.**	**.**	.	.	.	.	.	.	.	.

Kabat Residue	'	'	'
VHDUM-1	V	S	S
DOM26h-220-1	.	.	.
DOM26h-220-43	.	.	.

Figure 32

DOM26h-161 affinity matured clones nucleotide sequences

>DOM26h-161-84
GACATCCAGA TGACCCAGTC TCCATCCTCC CTGTCTGCAT CTGTAGGAGA CCGTGTCACC
ATTACTTGCC GGGCAAGTCA GGCGATTGGG CGGTGGTTAT TGTGGTATCA GCAGAAACCA
GGGAAAGCCC CTAAGCTCCT GATCGGTCCG GGTTCCCGGT TGCGAAGTGG GGTCCCATCA
CGTTTCAGTG GCAGTGGATC TGGGACAGAT TTCACTCTCA CCATCAGCAG TCTACAACCT
GAAGATTTTG TTACGTACTA CTGTCAACAG GCGTATGCCT GGCCTCCGAC GTTCGGCCAA
GGGACCAAGG TGGAAATCAA ACGG

>DOM26h-161-86
GACATCCAGA TGACCCAGTC CCCATCCTCC CTGTCTGCAT CTGTAGGAGA CCGTGTCACC
ATTACTTGCC GGGCAAGTCA GGCGATTGGG CGGTGGTTAT TGTGGTATCA GCAGAAACCA
GGGAAAGCCC CTAAGCACCT GATCGGTCCG GGTTCCCGGT TGCAAAGTGG GGTCCCATCA
CGTTTCAGTG GCAGTGGATC TGGGACAGAT TTCACTCTCA CCATCAGCAG TCTGCAACCT
GAAGATTTTG CTACGTACTA CTGTCAACAG GCGTATCAGC TGCCTGTCAC GTTCGGCCAA
GGGACCAAGG TGGAAATCAA ACGG

>DOM26h-161-87
GACATCCAGA TGACCCAGTC CCCATCCTCC CTGTCTGCAT CTGTAGGAGA CCGTGTCACC
ATTACTTGCC GGGCAAGTCA GGCGATTGGG CGGTGGTTAT TGTGGTATCA GCAGAAACCA
GGGAAAGCCC CTAAGCTCCT GATCGGTCCG GGTTCCCGGT TGCAAAGTGG GGTCCCATCA
CGTTTCAGTG GCAGTGGATC TGGGACAGAT TTCACTCTCA CCATCGGCAG TCTGCAACCT
GAAGATTTTG CTACGTACTA CTGTCAACAG GCGTATAGTC TGCCTCCGAC GTTCGGCCAA
GGGACCAAGG TGGAAATCAA ACGG

Figure 32

DOM26h-196 affinity matured clones nucleotide sequences

>DOM26h-196-61
GAGGTGCAGC TGTTGGAGTC TGGGGGAGGC TTGGTACAGC CTGGGGGGTC CCTGCGTCTC

TCCTGTGCAG CCTCCGGATT CACCTTTGAG AAGTATGCGA TGGCGTGGGT CCGCCAGGCC
CCAGGGAAGG GTCTGGAGTG GGTCTCACGG ATTTCGGCGA GGGGTGTGAC GACATACTAC
GCAGACTCCG TGAAGGGCCG GTTCACCATC TCCCGCGACA ATTCCAAGAA CACGCTGTAT
CTGCAAATGA ACAGCCTGCG TGCTGAGGAC ACCGCGGTAT ATTACTGTGC GAAACATAAG
CGGCACGAGC ATACTCGTTT TGACTCCTGG GGTCAGGGAA CCCTGGTCAC CGTCTCGAGC

>DOM26h-210-2
GAGTTGCAGC TGTTGGAGTT TGGGGGAGGC TTGGTACAGC CTGGGGGGTC CCTGCGTCTC
TCCTGTACAA CCTCCGGATT CACCTTTTCG AGGTATACTA TGGGTTGGGT CCGCCAGGCT
CCAGGGAAGG GTCTAGAGTG GGTCTCAGCC ATTGGCCCGC CCGGGTCGAA CACATACTAC
GCAGACTCCG TGAAGGGTCG GTTCACCATC TCCCGCGACA ATTCCAAGAA CACGCTGTAT
CTGCAAATGA ACAGCCTGCG TGCCGAGGAC ACCGCGGTAT ATTACTGTGC GAAATGGGTG
ATGTTGCGGG GGCGCTTTGA CTACTGGGGT CAGGGAACCC TGGTCACCGT CTCGAGC

DOM26h-220 affinity matured clones nucleotide sequences

>DOM26h-220-1
GAGGTGCAGC TGTTGGAGTC TGGGGGAGGC TTGGTACAGC CTGGGGGGTC CCTGCGTCTC
TCCTGTGCAG CCTCCGGATT CACCTTTGAG GATTATGGTA TGGGGTGGGT CCGCCAGGCT
CCAGGAAAGG GTCTAGAGTG GGTCTCAGCG ATTGGCCGCA ACGGGTCGCA GACATACTAC
GCAGACTCCG TGAAGGGCCG GTTCACCATC TCCCGCGACA ATTCCAAGAA CACGCTGTAT
CTGCAAATGA ACAGCCTGCG TGCCGAGGAT ACCGCGGTAT ATTACTGTGC GAAACTTCGG
AGGGGGCGGG GTCTGAATAC GTTTACGTTA GACTACTGGG GTCAAGGAAC CCTGGTCACC
GTCTCAAGC

>DOM26h-220-43
GAGGTGCAGC TGTTGGAGTC TGGGGGAGGC TTGGTACAGC CTGGGGGGTC CCTGCGTCTC
TCCTGTGCAG CCTCCGGATT CACCTTTGGG GCGGCCGGTA TGGGGTGGGT CCGCCAGGCT
CCAGGAAAGG GTCTAGAGTG GGTCTCAGCG ATTGGCCGCA ACGGGTCGCA GACATACTAC
GCAGACTCCG TGAAGGGCCG GTTCACCATC TCCCGCGACA ATTCCAAGAA CACGCTGTAT
CTGCAAATGA ACAGCCTGCG TGCCGAGGAT ACCGCGGTAT ATTACTGTGC GAAACTTCGG
AGGGGGCGGG GTCTGAATAC GTTTACGTTA GACTACTGGG GTCAAGGAAC CCTGGTCACC
GTCTCAAGC