

VIRAL PARTICLES RETARGETED TO NERVOUS SYSTEM TISSUES**CROSS-REFERENCE TO RELATED APPLICATIONS**

[0001] This application claims priority to U.S. Provisional Application No. 63/619,765, filed on January 11, 2024, the disclosure of which is hereby incorporated by reference in its entirety.

SEQUENCE LISTING

[0002] The official copy of the sequence listing is submitted electronically via EFS-Web with a file named, "11566WO01 Sequence Listing XML.xml," created on January 10, 2025, and having a size of 665 kilobytes, and is filed concurrently with the specification. The sequence listing contained in the XML formatted document is part of the specification and is herein incorporated by reference in its entirety.

TECHNICAL FIELDS

[0003] The disclosure herein relates to methods of making and using recombinant viral particles, e.g., recombinant AAV particles, comprising capsid proteins retargeted to p75 neurotrophin receptor (p75^{NTR}), useful for modification of p75^{NTR}-expressing cells, e.g., nervous system cells, such as dorsal root ganglion and trigeminal ganglion cells, *in vitro* or *in vivo*.

BACKGROUND OF THE INVENTION

[0004] The delivery of genes into particular target cells has become one of the most important technologies in modern medicine for the potential treatment of a variety of chronic and genetic diseases. Ideally, a gene delivery vehicle is able to stably introduce genetic material into desired cells and avoid introducing genetic material into non-target cells.

[0005] Viral particles, particularly those based on adeno-associated viruses (AAV), as gene delivery vehicles have been the focus of much research since AAVs are capable of transducing a wide range of primate species and tissues *in vivo* with no evidence of toxicity or pathogenicity. (Muzyczka, et al. (1992) *Current Topics in Microbiology and Immunology*, 158:97-129). Moreover, AAV safely transduces postmitotic tissues. Although the virus can

occasionally integrate into host chromosomes, it does so very infrequently into a safe-harbor locus in human chromosome 19, and only when the replication (Rep) proteins are supplied in trans. AAV genomes rapidly circularize and concatemerize in infected cells, and exist in a stable, episomal state in infected cells to provide long-term stable expression of their payloads.

[0006] Additionally, manipulating and redirecting AAV infection to specific cells has been achieved in recent years. Many of the advances in targeted gene therapy using viral particles may be summarized as non-recombinatorial (non-genetic) or recombinatorial (genetic) modification of the viral particle, which result in the pseudotyping, expanding, and/or retargeting of the natural tropism of the viral particle. (Reviewed in Nicklin and Baker (2002) *Curr. Gene Ther.* 2:273-93; Verheij and Rottier (2012) *Advances Virol* 2012:1-15).

[0007] In a direct recombinatorial targeting approach, a targeting ligand is directly inserted into, or coupled to, a viral capsid, i.e., protein viral capsid genes are modified to express capsid proteins comprising a heterologous targeting ligand. The targeting ligand then redirects, e.g., binds, a receptor or marker preferentially or exclusively expressed on a target cell. (Stachler et al. (2006) *Gene Ther.* 13:926–931; White et al. (2004) *Circulation* 109:513–519; see also Park et al., (2007) *Frontiers in Bioscience* 13:2653–59; Girod et al. (1999) *Nature Medicine* 5:1052–56; Grifman et al. (2001) *Molecular Therapy* 3:964–75; Shi et al. (2001) *Human Gene Therapy* 12:1697–1711; Shi and Bartlett (2003) *Molecular Therapy* 7:515–525).

[0008] In indirect recombinatorial approaches, a viral capsid is modified with a heterologous “scaffold”, which then links to an adaptor that includes a targeting ligand. The adaptor binds to the scaffold and the target cell. (Arnold et al. (2006) *Mol. Ther.* 5:125-132; Ponnazhagen et al. (2002) *J. Virol.* 76:12900–907; see also WO 97/05266) Scaffolds such as (1) Fc binding molecules (e.g., Fc receptors, Protein A, etc.), which bind to the Fc of antibody adaptors, (2) (strept)avidin, which binds to biotinylated adaptors, (3) biotin, which binds to adaptors fused with (strept)avidin, (4) a detectable label, which is useful for detection and/or isolation of viral particles, bound by a bispecific adaptor able to non-covalently bind the detectable label and target molecule, and recently (5) protein:protein binding pairs that form isopeptide bonds have been described for a variety of viral particles. (See, e.g., Gigout et al. (2005) *Molecular Therapy* 11:856–865; Stachler et al. (2008)

Molecular Therapy 16:1467–1473; Quetglas et al. (2010) *Virus Research* 153:179–196; Ohno et al. (1997) *Nature Biotechnology* 15:763–767; Klimstra et al. (2005) *Virology* 338:9–21).

[0009] With the advances providing the ability to direct AAV infection, there remains a need to discover targets for the specific transfer of nucleic acids of interest to a cell of interest, e.g., a p75^{NTR}-expressing cell, e.g., a mammalian nervous system cell.

SUMMARY OF THE INVENTION

[0010] It is shown herein that an AAV capsid protein may be modified to allow for the targeted introduction of a nucleotide of interest into p75^{NTR}-expressing cells, e.g., mammalian nervous system cells.

[0011] Viral particles as described herein are particularly suited for the targeted introduction of a nucleotide of interest specifically to a p75^{NTR}-expressing cell since the viral capsid or viral capsid protein(s) described herein comprise a targeting ligand that binds p75^{NTR}. In some embodiments, a viral capsid or viral capsid protein comprises a first member of a binding pair, associated with its cognate second member of the binding pair, wherein the second member is linked (e.g., fused to) a targeting ligand that binds a nervous system cell-specific surface protein. In some embodiments, the targeting ligand is operably linked to the second member, e.g., fused to the second member, optionally via a linker. In some embodiments, a targeting ligand may be a binding moiety, e.g., a natural ligand, antibody, a multispecific binding molecule, etc. In some embodiments, the targeting ligand is an antibody or portion thereof. In some embodiments, the targeting ligand is an antibody comprising a variable domain that binds p75^{NTR}, e.g., on a nervous system cell, and a heavy chain constant domain. In some embodiments, the targeting ligand is an antibody comprising a variable domain that binds p75^{NTR} on a target cell and an IgG heavy chain constant domain. In some embodiments, the targeting ligand is an antibody comprising a variable domain that binds a nervous system cell-specific surface protein on a target cell and an IgG heavy chain constant domain, wherein the IgG heavy chain constant domain is operably linked, e.g., via a linker, to a protein (e.g., second member of a protein:protein binding pair) that forms an isopeptide covalent bond with the first member. In some embodiments, a capsid protein described herein comprises a first member comprising SpyTag operably linked to the viral

capsid protein, and covalently linked to the SpyTag, a second member comprising SpyCatcher linked to a targeting ligand comprising an antibody variable domain and an IgG heavy chain domain, wherein SpyCatcher and the IgG heavy chain domain are linked via an amino acid linker, e.g., GSGESG. (SEQ ID NO: 638). In some embodiments, the targeting ligand binds mammalian p75^{NTR}, e.g., human p75^{NTR}. In some embodiments, the targeting ligand comprises a heavy chain variable domain, light chain variable domain, heavy chain variable domain/light chain variable domain pair, HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, LCDR3, and/or set of HCDR1-HCDR2-HCDR3-LCDR1-LCDR2-LCDR3 comprising an amino acid sequence of a heavy chain variable domain, light chain variable domain, heavy chain variable domain/light chain variable domain pair, HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, LCDR3, and/or set of HCDR1-HCDR2-HCDR3-LCDR1-LCDR2-LCDR3 as set forth in or encoded by a sequence or sequences as set forth in Table 1 and/or any one of SEQ ID NOs: 1-617.

[0012] Also described herein are pharmaceutical compositions comprising the recombinant AAV particle as disclosed herein, methods of delivering a nucleotide of interest to a mammalian p75^{NTR}-expressing cell using the recombinant AAV particle as disclosed herein, and methods of using the recombinant AAV particle as disclosed herein for, e.g., the manufacture of a medicament for, treating or preventing pain, itch, or a neurological disease or disorder in a subject in need thereof.

[0013] Further described herein are compositions comprising an AAV particle and a multispecific binding protein that binds to p75^{NTR}. In some embodiments, the composition comprises (a) an AAV particle encapsulating a nucleotide of interest; and (b) a multispecific binding protein comprising: (i) a first antigen-binding domain that binds a mammalian p75 neurotrophin receptor (p75^{NTR}), and (ii) a second antigen-binding domain that binds to one or more epitopes of an AAV capsid protein of the AAV particle. In some embodiments, the composition further comprises a pharmaceutically acceptable carrier or excipient.

[0014] Also described herein are methods of using the composition comprising an AAV particle and a multispecific binding protein that binds to p75^{NTR} as described herein. In some embodiments, a method of delivering a nucleotide of interest to a mammalian p75^{NTR}-expressing cell comprises contacting the mammalian p75^{NTR}-expressing cell with the composition as described herein. In some embodiments, a method of treating or preventing

pain, itch, or a neurological disease or disorder in a subject in need thereof comprises administering to the patient the composition disclosed herein, wherein the nucleotide of interest encodes a therapeutic protein, a suicide gene, an antibody or a fragment thereof, a CRISPR/Cas system or a portion(s) thereof, an antisense oligonucleotide, a ribozyme, an RNAi molecule, or a shRNA molecule. In some embodiments, provided herein is the use of the composition disclosed herein for, e.g., the manufacture of a medicament for, treating or preventing pain, itch, or a neurological disease or disorder, wherein the nucleotide of interest encodes a therapeutic protein, a suicide gene, an antibody or a fragment thereof, a CRISPR/Cas system or a portion(s) thereof, an antisense oligonucleotide, a ribozyme, an RNAi molecule, or a shRNA molecule.

BRIEF DESCRIPTION OF THE DRAWINGS

[0015] **Figures 1A-1B** show WT AAV9 and AAV9-based retargeted virus infections delivering green fluorescent protein (GFP) to NIH 3T3 cell lines that are genetically modified to express mouse, cynomolgus or human P75^{NTR}. Parental NIH 3T3 cells (3T3) or NIH 3T3 cells expressing human TrkA (3T3-hTrkA) alone were used as controls. **(A)** The scatter plots are obtained from use of flow cytometry to quantify green fluorescent protein (GFP) expression by parental NIH 3T3 cells or NIH 3T3 cells positive (+) for control target human TrkA expression after infection with WT AAV9 particles, detargeted AAV9 W503A particles, detargeted AAV9 W503A SpyTag particles conjugated to an antibody targeting Betv1, or detargeted AAV9 W503A SpyTag particles conjugated to different antibodies targeting P75^{NTR} (blockers: REGN14152, REGN14155, REGN14177, and REGN14187; non-blockers: REGN19516, REGN19517, REGN19515, REGN19514, and REGN19513). Also shown are scatter plots obtained from flow cytometry evaluation of GFP expression by cells positive (+) for mouse p75^{NTR} (3T3-m P75), cynomolgus p75^{NTR} (3T3-mf P75) or human p75^{NTR} (3T3-h P75) after infection with WT AAV9 particles, detargeted AAV9 W503A particles, detargeted AAV9 W503A SpyTag conjugated to an antibody targeting BetV1, or detargeted AAV9 W503A AAV9 SpyTag conjugated to antibodies targeting anti-P75^{NTR}. Viruses express GFP as a marker of transduction. **(B)** The graphs quantify the percentage (left) and mean fluorescence intensity (right) of GFP+ cells from the flow cytometry plots in **Figure 1A**.

[0016] **Figure 2** displays GFP gene expression assessed by confocal imaging in whole dorsal root ganglia (DRG; cervical, thoracic and lumbar segments of wild type C57BL/6J mice) three weeks after tail vein injection of $4E+11$ vg/mouse of WT AAV9 (top), detargeted AAV9 W503A (middle), and detargeted AAV9 W503A conjugated to an example antibody targeting p75^{NTR} (bottom). Scale bar, 500 μ m.

[0017] **Figure 3** displays quantification of GFP fluorescence in DRG of wild type C57BL/6J mice three weeks after tail vein injection of $4E+11$ vg/mouse of WT AAV9, detargeted AAV9 W503A, and detargeted AAV9 W503A conjugated to antibodies targeting p75^{NTR} (blockers: REGN14152, REGN14155, REGN14177, and REGN14187; non-blockers: REGN19516, REGN19517, REGN19515, REGN19514, and REGN19513). **(A)** The percentage of pixels in the DRG that are GFP positive are shown. **(B)** Mean GFP intensity measured as the average pixel value of all pixels in the DRG above an intensity threshold specific to GFP injected tissue.

[0018] **Figure 4** shows confocal imaging of the whole liver to evaluate AAV-driven GFP expression following tail vein, intravenous delivery of **(A)** WT AAV9, **(B)** detargeted AAV9 W503A, and **(C)** detargeted AAV9 W503A conjugated to an example antibody targeting p75^{NTR}. **(D)** The graph shows quantification of mean GFP fluorescence pixel intensity of whole images of the liver for WT AAV9, detargeted AAV9 W503A, and detargeted AAV9 W503A conjugated to antibodies targeting p75^{NTR} (blockers: REGN14152, REGN14155, REGN14177, and REGN14187; non-blockers: REGN19516, REGN19517, REGN19515, REGN19514, and REGN19513). Scale bar, 500 μ m.

[0019] **Figure 5** shows GFP expression in DRG three weeks after tail vein intravenous administration of AAVs at varying doses in wildtype C57BL/6J mice. Lumbar DRG at L1 and L4 are shown as representative examples of all DRG for: **(A)-(C)** WT AAV9 injected intravenously at **(A)** $2.5E+10$ vg, **(B)** $1E+11$ vg, and **(C)** $4E+11$ vg; **(D)-(F)** detargeted AAV9 W503A injected at **(D)** $2.5E+10$ vg, **(E)** $1E+11$ vg, and **(F)** $4E+11$ vg; and **(G)-(I)** detargeted AAV9 W503A conjugated to antibodies targeting p75^{NTR} injected intravenously at **(G)** $2.5E+10$ vg, **(H)** $1E+11$ vg, and **(I)** $4E+11$ vg. Scale bar, 500 μ m.

[0020] **Figure 6** shows the GFP intensity in individual DRG neurons in tissue collected from C57BL/6J mice three weeks following intravenous injection of AAV. DRGs were cryosectioned and labeled with anti-TUBB3 to identify individual neurons. Using a

mask to outline the area of individual neurons in DRG, the GFP fluorescence intensity was measured per cell for three doses of AAV (2.5E+10 vg, 1E+11 vg, and 4E+11 vg) and three formats of AAV injected (WT AAV9, detargeted AAV9 W503A, or detargeted AAV9 W503A conjugated to an example antibody targeting p75^{NTR}).

[0021] **Figures 7A-7C** show immunohistochemistry (IHC) staining for eGFP expression in the **(A)-(B)** spinal cord and DRG, and **(C)** liver, heart, and kidney of WT C57BL/6J mice following injection of 4E+11 vg/mouse of wildtype AAV9, detargeted AAV9 W503A or detargeted AAV9 W503A conjugated to an example antibody targeting p75^{NTR}. **Figure 7A** depicts representative images of eGFP IHC at lower magnification for sections of spinal cord and DRG, while **Figure 7B** depicts representative eGFP IHC at higher magnification of coronal sections of planes featuring DRG. Naïve indicates DRG harvest from mice that were no injected with AAV as a control for background signal. **Figure 7C** shows immunohistochemistry staining for eGFP expression in the liver, heart, and kidney of WT C57BL/6J mice following intravenous injection of 4E+11 vg/mouse of AAV9, detargeted AAV9 W503A or detargeted AAV9 W503A conjugated to an example antibody targeting p75^{NTR}.

[0022] **Figure 8** shows fluorescent images of AAV-driven GFP expression in **(A)** trigeminal ganglion, **(B)** DRG, **(C)** kidney, **(D)** liver, and **(E)** colon following unilateral, subcutaneous injection of 2.5E+10 vg of WT AAV9, detargeted AAV9 W503A, or detargeted AAV9 W503A conjugated to an example antibody targeting p75^{NTR} in the mouse whisker pad. Scale bars, 500 µm.

[0023] **Figure 9** shows fluorescent images of AAV-driven GFP expression in in trigeminal ganglion and DRG following unilateral, intra-synovial injection of 5E+10 vg of WT AAV9 (top), detargeted AAV9 W503A (middle), or detargeted AAV9 W503A particles conjugated to any example antibody targeting p75^{NTR} (bottom) into C57BL/6J mouse knee. Scale bar, 500 µm.

[0024] **Figure 10** displays quantification of GFP fluorescent area in DRG of wild type C57BL/6J mice three weeks after injection of **(A)** 5E+10 vg into the synovial space in the knee or **(B)** varying doses via tail intravenous vein injection of WT AAV9, detargeted AAV9 W503A, and detargeted AAV9 W503A conjugated to an example antibody targeting p75^{NTR}. The percentage of pixels that are labeled as GFP positive due to being above a

fluorescence threshold are measured in maximum projection images of confocal Z stacks of whole DRG.

[0025] **Figure 11** demonstrates that delivery of detargeted AAV9 W503A particles conjugated to an exemplified antibody targeting p75^{NTR} and encapsulating a nucleic acid molecule expressing guide RNAs targeting mouse Nav1.7 to the masseter muscle significantly reduces mechanical pain induced by Complete Freud's Adjuvant (CFA). Mice genetically modified to express Cas9 were injected with detargeted AAV9 W503A conjugated to a representative antibody targeting p75^{NTR} and encapsulating a nucleic acid molecule expressing guide RNAs targeting either mouse Nav1.7 (7.48×10^9 vg, n=8) or mouse transthyretin (TTR) (1.44×10^{12} vg, n=7) into the masseter muscle. Three weeks after AAV injections, CFA was injected into the masseter muscle to induce inflammation and hypersensitivity to mechanical stimulus.

[0026] **Figure 12** shows that anti-p75^{NTR} antibody is internalized in *ex vivo* dorsal root ganglion (DRG) tissue. Live, time-lapse confocal imaging of DRGs grown *ex vivo*. Alexa 647 conjugated antibodies were applied at t=0, maximum projections of 3 confocal optical slices 10 μ m apart are shown. Axons are labeled within 5 minutes of addition of fluorescently conjugated anti-p75^{NTR} antibody to the culture media. Internalization into neuronal cell bodies is seen 1-4 hours post antibody addition.

[0027] **Figures 13A-13B** show that anti-p75^{NTR} antibody is internalized in *ex vivo* DRG tissue. Live, time-lapse confocal imaging of DRGs grown *ex vivo*. Alexa 647 conjugated antibodies were applied at t=0, maximum projections of 3 confocal optical slices 10 μ m apart are shown. Axons are labeled within 5 minutes of addition of fluorescently conjugated anti-p75^{NTR} antibody to the culture media. Internalization into neuronal cell bodies is seen 1-4 hours post antibody addition.

[0028] **Figures 14A-14F** show that anti-p75^{NTR} antibody internalizes in DRGs following intraplantar injection. Maximum projection of confocal Z stack images of whole DRGs harvested 5 days post injection of fluorescently conjugated antibody into the hind foot pad. **Figures 14A-14C** depict representative images showing lumbar DRG ipsilateral to intraplantar injection of anti-Fel D1 (**Figure 14A**), or anti-p75^{NTR} antibody, REGN14155 (**Figure 14B**), or anti-p75^{NTR} antibody, REGN14187 (**Figure 14C**). **Figures 14D-14F** depict representative images showing Lumbar DRG contralateral to intraplantar injection of anti-Fel

D1 (**Figure 14D**), or anti-p75^{NTR} antibody, REGN14155 (**Figure 14E**), or anti-p75^{NTR} antibody, REGN14187 (**Figure 14F**). CT-B labels DRG neurons on the ipsilateral side of injection (**Figures 14A-14C**), but not the contralateral side (**Figures 14D-14F**). Anti-p75^{NTR} antibody shows uptake in DRGs on both sides. CT-B, Cholera Toxin subunit B - Alexa 488.

[0029] **Figures 15A-15C** show that anti-p75^{NTR} antibody internalizes in trigeminal ganglion (TG) following intraplantar injection. Maximum projection of confocal Z stack images of whole trigeminal ganglia harvested 5 days post injection of fluorescently conjugated antibody into the hind foot pad. Transmitted light and fluorescent image of trigeminal ganglion from: intraplantar injection of anti-Fel D1 (**Figure 15A**); intraplantar injection of anti-p75^{NTR} antibody, REGN14155 (**Figure 15B**); intraplantar injection of anti-p75^{NTR} antibody, REGN14187 (**Figure 15C**).

[0030] **Figures 16A-16F** show that anti-p75^{NTR} antibody internalizes in DRGs and TG following intramuscular injection. Maximum projection of confocal Z stack images of whole DRGs harvested 5 days post injection of fluorescently conjugated antibody into the gastrocnemius muscle. **Figure 16A** depicts lumbar DRG ipsilateral to intramuscular injection of anti-Fel D antibody. **Figure 16B** depicts lumbar DRG ipsilateral to intramuscular injection of anti-p75^{NTR} antibody, REGN14187. **Figure 16C** depicts lumbar DRG contralateral to intramuscular injection of anti-Fel D1 antibody. **Figure 16D** depicts lumbar DRG contralateral to intramuscular injection of anti-p75^{NTR} REGN14187. **Figure 16E** depicts trigeminal ganglia from mouse injected with anti-Fel D1 antibody in gastrocnemius muscle. **Figure 16F** depicts trigeminal ganglia from mouse injected with anti-p75^{NTR} antibody, REGN14187, in gastrocnemius muscle. CT-B labels DRG neurons on the ipsilateral side of injection (**Figures 16A-16B**), but not the contralateral side (**Figures 16C-16D**) or TG (**Figures 16E-16F**). Anti-p75^{NTR} antibody shows uptake in DRGs on both sides and uptake in trigeminal ganglion. CT-B, Cholera Toxin subunit B - Alexa 488.

[0031] **Figure 17** shows that anti-p75^{NTR} antibody internalizes in all lumbar DRGs 3 days following subcutaneous injection. Fluorescent anti-p75^{NTR} antibody is detected in all lumbar DRGs 3 days post subcutaneous injection of 0.5 mg/kg fluorescently tagged antibody. Alexa Fluor 647 (A647) fluorescent image of lumbar DRGs overlaid onto transmitted light image of DRG is shown.

[0032] **Figures 18A-18B** show that anti-p75^{NTR} antibody internalizes in DRG neurons 3 days following subcutaneous injection. 20X confocal single slice images with 1.5x zoom allow visualization of intracellular distribution of fluorescently tagged anti-p75^{NTR} antibody, REGN14187, in DRG neurons. Punctate, intracellular anti-p75^{NTR} antibody is detected in neurons.

[0033] **Figures 19A-19C** show that anti-p75^{NTR} antibody internalizes in DRG neurons that express the marker of peripheral neurons, peripherin. Widefield, fluorescent images of DRG sections from mice that were injected with subcutaneously anti-p75^{NTR} antibody, REGN14187, then stained with anti-peripherin to identify neurons.

[0034] **Figures 20A-20N** show that anti-p75^{NTR} antibody internalizes in DRGs, TG, colon, eye and sympathetic ganglia 5 days following subcutaneous injection. Fluorescent anti-p75^{NTR} antibody is detected in TG (**Figure 20B**), cervical DRG (**Figure 20D**), thoracic DRG (**Figure 20E**) and lumbar DRGs (**Figure 20F**) 5 days post subcutaneous injection of 0.7 mg/kg fluorescently tagged antibody. A647 fluorescent image of TG and DRGs overlaid onto transmitted light image of DRG is shown in **Figures 20A-20F**. Fluorescent anti-p75^{NTR} antibody is detected in colon (**Figure 20H**). Higher magnification image of colon tissue shows that fluorescent anti-p75^{NTR} antibody internalizes in cells in the myenteric plexus (**Figure 20I**). Fluorescent anti-p75^{NTR} antibody is detected in the eye (**Figure 20K**). A647 fluorescent confocal image of colon or eye tissue is shown in **Figures 20G-20K**. Fluorescent anti-p75^{NTR} antibody is detected in sympathetic ganglia (**Figure 20M**). A647 fluorescent widefield image of ventral side of the thoracic spinal cord and is shown in **Figures 20L-20M**. In all tissue, subcutaneous injection of fluorescent anti-Fel D1 does not show fluorescent signal (**Figures 20A, 20C, 20G, 20J, and 20L**). Co-labeling with neuron and glial markers in DRG confirmed that anti-p75^{NTR} antibodies internalized in DRG neurons and not surrounding satellite glia (**Figure 20N**).

[0035] **Figures 21A-21F** show that anti-p75^{NTR} antibody has undetectable presence in cerebellum (**Figure 21A**), hippocampus (**Figure 21B**), liver (**Figure 21C**) and spinal cord (**Figure 21F**) following subcutaneous injection. Low detection of anti-p75^{NTR} antibody is detected in choroid plexus (**Figure 21B**), kidney (**Figure 21C**) and heart (**Figure 21E**) following subcutaneous injection. Confocal images of DAPI and A647 channels are shown.

[0036] **Figures 22A-22D** show that anti-p75^{NTR} antibody is detected in choroid plexus following subcutaneous injection. 10X confocal images of sagittal brain sections show anti-p75^{NTR} antibody observed in choroid plexus (arrows) 5 days following subcutaneous injection, with little or no detection in other regions of the brain.

[0037] **Figures 23A-23D** show that low levels of anti-p75^{NTR} antibodies are detected in the brain following ICV injection. Fluorescent, 5x confocal images of sagittal brain sections demonstrate low accumulation of anti-p75^{NTR} specific labeling in ventral and cortical regions (**Figure 23D**). Both anti-Fel D1 (**Figure 23B**) and anti-p75^{NTR} antibodies (**Figure 23D**) show accumulation in the ventricle, the site of injection.

[0038] **Figures 24A-24H** shows that internalization of fluorescent anti-p75^{NTR} antibody of the disclosure into neurons was observed following intravenous injection of REGN19516 in the trigeminal ganglia (**Figure 15D**) and DRG (**Figure 24H**). Intravenous injection of fluorescent isotype control antibody, REGN1945, did not demonstrate labeling in TG or DRGs (**Figures 24B, 24F**).

DETAILED DESCRIPTION

[0039] Dorsal Root Ganglions (DRG) and Trigeminal Ganglions (TG) in the peripheral nervous system play a crucial role in pain transmission since they contain the cell bodies of first order pain neurons that underlie nociception. As key drivers of chronic pain states, DRG and TG neurons are target cells for pain therapeutics. In addition, due to their high level of vascularization, DRG and TG are particularly amenable to systemic delivery of therapeutics, which include naked nucleic acids, lipid nanoparticles, sh/siRNAs, or viral vectors. Among those possible therapeutic vehicles, retargeted AAV constitute a particularly promising approach to deliver pain therapeutics specifically to DRG and TG sensory neurons, while reducing off-target effects and toxicity in other tissues such as the central nervous system, liver, pulmonary and cardiac systems.

[0040] To enhance delivery of therapeutic payloads to specific, e.g., nervous system, tissues and mitigate off-target effects, described herein are viral particles, e.g., AAV viral particles, that target p75^{NTR}.

[0041] Neurotrophins regulate development, maintenance, and function of vertebrate nervous systems. Neurotrophins activate two different classes of receptors, the Trk family of

receptor tyrosine kinases and p75^{NTR}, a member of the tumor necrosis factor (TNF) receptor superfamily. p75^{NTR} (also known as nerve growth factor receptor) binds with approximately equal affinity to each of the four identified mammalian neurotrophins: nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3), and neurotrophin-4 (NT-4).

[0042] The multifunctional neurotrophin receptor p75^{NTR} is expressed by DRG and TG. Indeed, the strong potential of p75^{NTR} as surface antigen of choice for antibody-mediated retargeting of AAV to DRG and TG sensory neurons has been demonstrated by internal biodistribution studies using fluo-labeled anti-p75^{NTR} monoclonal antibodies that showed robust binding in those tissues *in vivo*, while displaying minimal binding in the CNS or peripheral organs, after intraplantar, intramuscular, or subcutaneous injection.

[0043] Described herein are p75^{NTR}-retargeted AAV, generated by conjugating a diverse panel of anti-p75^{NTR} monoclonal antibodies to liver-detargeted AAV9 capsid variants through a SpyTag-SpyCatcher conjugation system. All of the anti-p75^{NTR} antibodies were first shown to have robust binding *in vitro* to cell lines overexpressing mouse, non-human primate, or human p75^{NTR} proteins. In addition, all the liver-detargeted AAV9 conjugated to the anti-p75^{NTR} antibodies show strong and specific transduction of the p75^{NTR}-expressing cell lines, validating the capacity of the p75^{NTR}-retargeted AAV to target efficiently p75^{NTR} *in vitro*. *In vivo*, using the measurement of a reporter viral transgene expression level as readout, some p75^{NTR}-retargeted AAV showed enhanced transduction of DRG neurons after intravenous delivery at a fixed dose of 4E+11 vg/mouse in comparison to wild type AAV9.

[0044] The gene encoding human p75^{NTR} (*NGFR*) is located on the long arm of chromosome 17, comprises 6 coding exons and is approximately 19,716 nucleotides in length. An exemplary human *NGFR* CDS DNA sequence is assigned NCBI Version Number NM_002507.3 (SEQ ID NO: 618) and an exemplary human p75^{NTR} (*NGFR*) amino acid sequence is assigned NCBI Version Number NP_002498.1 (SEQ ID NO: 619). The gene encoding mouse p75^{NTR} (*Ngfr*) is located on chromosome 11, comprises 6 coding exons, and is 18,918 nucleotides in length. An exemplary mouse *Ngfr* CDS DNA sequence is assigned NCBI Version Number NM_033217.3 (SEQ ID NO: 620) and an exemplary mouse p75^{NTR} (*Ngfr*) amino acid sequence is assigned NCBI Version Number NP_150086.2 (SEQ ID NO: 621).

[0045] 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 to which this invention belongs.

[0046] Singular forms “a”, “an”, and “the” include plural references unless the context clearly dictates otherwise. Thus, for example, a reference to “a method” includes one or more methods, and/or steps of the type described herein and/or which will become apparent to those persons skilled in the art upon reading this disclosure.

[0047] The “percent (%) identity” or the like may be readily determined for amino acid or nucleotide sequences, over the full-length of a protein, or a portion thereof. A portion may be at least about 5 amino acids or 24 nucleotides, respectively, in length, and may be up to about 700 amino acids or 2100 nucleotides, respectively. Generally, when referring to “identity”, “homology”, or “similarity” between two different adeno-associated viruses, “identity”, “homology” or “similarity” is determined in reference to “aligned” sequences. “Aligned” sequences or “alignments” refer to multiple nucleic acid sequences or protein (amino acids) sequences, often containing corrections for missing or additional bases or amino acids as compared to a reference sequence.

[0048] Alignments may be performed using any of a variety of publicly or commercially available Multiple Sequence Alignment Programs. Sequence alignment programs are available for amino acid sequences, e.g., the “Clustal X”, “MAP”, “PIMA”, “MSA”, “BLOCKMAKER”, “MEME”, and “Match-Box” programs. Generally, any of these programs are used at default settings, although one of skill in the art can alter these settings as needed. Alternatively, one of skill in the art can utilize another algorithm or computer program which provides at least the level of identity or alignment as that provided by the referenced algorithms and programs. See, e.g., J. D. Thomson et al, Nucl. Acids. Res., “A comprehensive comparison of multiple sequence alignments”, 27(13):2682-2690 (1999).

[0049] Multiple sequence alignment programs are also available for nucleic acid sequences. Examples of such programs include, “Clustal W”, “CAP Sequence Assembly”, “MAP”, and “MEME”, which are accessible through Web Servers on the internet. Other sources for such programs are known to those of skill in the art. Alternatively, Vector NTI utilities are also used. There are also a number of algorithms known in the art that can be used to measure nucleotide sequence identity, including those contained in the programs

described above. As another example, polynucleotide sequences can be compared using FASTATM, a program in GCG Version 6.1. FastaTM provides alignments and percent sequence identity of the regions of the best overlap between the query and search sequences. For instance, percent sequence identity between nucleic acid sequences can be determined using FASTATM with its default parameters (a word size of 6 and the NOPAM factor for the scoring matrix) as provided in GCG Version 6.1, herein incorporated by reference.

[0050] “Significant identity” encompasses amino acid or nucleic acid sequences alignments that are at least 90%, e.g., at least 93%, e.g., at least 95%, e.g., at least 96%, e.g., at least 97%, e.g., at least 98%, e.g., at least 99%, or e.g., at least 100% identical.

[0051] The term “chimeric” encompasses a functional gene or polypeptide comprising nucleic acid sequences or amino acid sequences, respectively, from at least two different AAV serotype, e.g., portions of a gene or polypeptide of at least a first and second AAV, wherein the at least first and second portions are operably linked to form a functional chimeric AAV nucleic acid that encodes a functional amino acid. Unless specified as chimeric, nucleotide sequences, genes, polypeptides, and amino acids are considered non-chimeric in that the nucleotide sequences, genes, polypeptides, and amino acids comprise a nucleic acid sequence or amino acid sequence having significant identity to a nucleic acid sequence or amino acid sequence, respectively, of a single AAV serotype.

[0052] The term “antibody” includes immunoglobulin molecules comprising four polypeptide chains, two heavy (H) chains and two light (L) chains inter-connected by disulfide bonds. Each heavy chain comprises a heavy chain variable domain (V_H) and a heavy chain constant region (C_H). The heavy chain constant region comprises at least three domains, C_{H1}, C_{H2}, C_{H3} and optionally C_{H4}. Each light chain comprises a light chain variable domain (C_H) and a light chain constant region (C_L). The heavy chain and light chain variable domains can be further subdivided into regions of hypervariability, termed complementarity determining regions (CDR), interspersed with regions that are more conserved, termed framework regions (FR). Each heavy and light chain variable domain comprises three CDRs and four FRs, arranged from amino-terminus to carboxy-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3, FR4 (heavy chain CDRs may be abbreviated as HCDR1, HCDR2 and HCDR3; light chain CDRs may be abbreviated as LCDR1, LCDR2 and LCDR3. Typical tetrameric antibody structures comprise two identical

antigen-binding domains, each of which formed by association of the V_H and V_L domains, and each of which together with respective C_H and C_L domains form the antibody Fv region. Single domain antibodies comprise a single antigen-binding domain, e.g., a V_H or a V_L . The antigen-binding domain of an antibody, e.g., the part of an antibody that recognizes and binds to the first member of a specific binding pair of an antigen, is also referred to as a “paratope.” It is a small region (of 5 to 10 amino acids) of an antibody's Fv region, part of the fragment antigen-binding (Fab region), and may contain parts of the antibody's heavy and/or light chains. A paratope specifically binds a first member of a specific binding pair when the paratope binds the first member of a specific binding pair with a high affinity. The term “high affinity” antibody refers to an antibody that has a K_D with respect to its target first member of a specific binding pair about of 10^{-9} M or lower (e.g., about 1×10^{-9} M, 1×10^{-10} M, 1×10^{-11} M, or about 1×10^{-12} M). In one embodiment, K_D is measured by surface plasmon resonance, e.g., BIACORE™; in another embodiment, K_D is measured by ELISA.

[0053] The phrase “complementarity determining region,” or the term “CDR,” includes an amino acid sequence encoded by a nucleic acid sequence of an organism's immunoglobulin genes that normally (i.e., in a wild-type animal) appears between two framework regions in a variable region of a light or a heavy chain of an immunoglobulin molecule (e.g., an antibody or a T cell receptor). A CDR can be encoded by, for example, a germ line sequence or a rearranged or unrearranged sequence, and, for example, by a naive or a mature B cell or a T cell. A CDR can be somatically mutated (e.g., vary from a sequence encoded in an animal's germ line), humanized, and/or modified with amino acid substitutions, additions, or deletions. In some circumstances (e.g., for a CDR3), CDRs can be encoded by two or more sequences (e.g., germ line sequences) that are not contiguous (e.g., in an unrearranged nucleic acid sequence) but are contiguous in a B cell nucleic acid sequence, e.g., as the result of splicing or connecting the sequences (e.g., V-D-J recombination to form a heavy chain CDR3).

[0054] The phrase “light chain” includes an immunoglobulin light chain sequence from any organism, and unless otherwise specified includes human κ and λ light chains and a VpreB, as well as surrogate light chains. Light chain variable domains typically include three light chain CDRs and four framework (FR) regions, unless otherwise specified. Generally, a full-length light chain includes, from amino terminus to carboxyl terminus, a variable domain

that includes FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4, and a light chain constant region. A light chain variable domain is encoded by a light chain variable region gene sequence, which generally comprises V_L and J_L segments, derived from a repertoire of V and J segments present in the germ line. Sequences, locations and nomenclature for V and J light chain segments for various organisms can be found in IMGT database, www.imgt.org. Light chains include those, e.g., that do not selectively bind either a first or a second first member of a specific binding pair selectively bound by the first member of a specific binding pair-binding protein in which they appear. Light chains also include those that bind and recognize, or assist the heavy chain or another light chain with binding and recognizing, one or more first member of a specific binding pairs selectively bound by the first member of a specific binding pair-binding protein in which they appear. Common or universal light chains include those derived from a human V κ 1-39J κ gene or a human V κ 3-20J κ gene, and include somatically mutated (e.g., affinity matured) versions of the same. Exemplary human V_L segments include a human V κ 1-39 gene segment, a human V κ 3-20 gene segment, a human V λ 1-40 gene segment, a human V λ 1-44 gene segment, a human V λ 2-8 gene segment, a human V λ 2-14 gene segment, and human V λ 3-21 gene segment, and include somatically mutated (e.g., affinity matured) versions of the same. Light chains can be made that comprise a variable domain from one organism (e.g., human or rodent, e.g., rat or mouse; or bird, e.g., chicken) and a constant region from the same or a different organism (e.g., human or rodent, e.g., rat or mouse; or bird, e.g., chicken).

[0055] The term “about” or “approximately” includes being within a statistically meaningful range of a value. Such a range can be within an order of magnitude, preferably within 50%, more preferably within 20%, still more preferably within 10%, and even more preferably within 5% of a given value or range. The allowable variation encompassed by the term “about” or “approximately” depends on the particular system under study, and can be readily appreciated by one of ordinary skill in the art.

[0056] The phrase “heavy chain,” or “immunoglobulin heavy chain” includes an immunoglobulin heavy chain sequence, including immunoglobulin heavy chain constant region sequence, from any organism. Heavy chain variable domains include three heavy chain CDRs and four FR regions, unless otherwise specified. Fragments of heavy chains include CDRs, CDRs and FRs, and combinations thereof. A typical heavy chain has,

following the variable domain (from N-terminal to C-terminal), a C_H1 domain, a hinge, a C_H2 domain, and a C_H3 domain. A functional fragment of a heavy chain includes a fragment that is capable of specifically recognizing an first member of a specific binding pair (*e.g.*, recognizing the first member of a specific binding pair with a K_D in the micromolar, nanomolar, or picomolar range), that is capable of expressing and secreting from a cell, and that comprises at least one CDR. Heavy chain variable domains are encoded by variable region nucleotide sequence, which generally comprises V_H, D_H, and J_H segments derived from a repertoire of V_H, D_H, and J_H segments present in the germline. Sequences, locations and nomenclature for V, D, and J heavy chain segments for various organisms can be found in IMGT database, which is accessible via the internet on the world wide web (www) at the URL "imgt.org."

[0057] The term "heavy chain only antibody," "heavy chain only antigen binding protein," "single domain antigen binding protein," "single domain binding protein" or the like refers to a monomeric or homodimeric immunoglobulin molecule comprising an immunoglobulin-like chain comprising a variable domain operably linked to a heavy chain constant region, that is unable to associate with a light chain because the heavy chain constant region typically lacks a functional C_H1 domain. Accordingly, the term "heavy chain only antibody," "heavy chain only antigen binding protein," "single domain antigen binding protein," "single domain binding protein" or the like encompasses a both (i) a monomeric single domain antigen binding protein comprising one of the immunoglobulin-like chain comprising a variable domain operably linked to a heavy chain constant region lacking a functional C_H1 domain, or (ii) a homodimeric single domain antigen binding protein comprising two immunoglobulin-like chains, each of which comprising a variable domain operably linked to a heavy chain constant region lacking a functional C_H1 domain. In various aspects, a homodimeric single domain antigen binding protein comprises two identical immunoglobulin-like chains, each of which comprising an identical variable domain operably linked to an identical heavy chain constant region lacking a functional C_H1 domain. Additionally, each immunoglobulin-like chain of a single domain antigen binding protein comprises a variable domain, which may be derived from heavy chain variable region gene segments (*e.g.*, V_H, D_H, J_H), light chain gene segments (*e.g.*, V_L, J_L), or a combination thereof, linked to a heavy chain constant region (C_H) gene sequence comprising a deletion or

inactivating mutation in a C_H1 encoding sequence (and, optionally, a hinge region) of a heavy chain constant region gene, e.g., IgG, IgA, IgE, IgD, or a combination thereof. A single domain antigen binding protein comprising a variable domain derived from heavy chain gene segments may be referred to as a "V_H-single domain antibody" or "V_H-single domain antigen binding protein", *see, e.g.*, U.S. Patent No. 8,754,287; U.S. Patent Publication Nos. 20140289876; 20150197553; 20150197554; 20150197555; 20150196015; 20150197556 and 20150197557, each of which is incorporated in its entirety by reference. A single domain antigen binding protein comprising a variable domain derived from light chain gene segments may be referred to as a or "V_L-single domain antigen binding protein," *see, e.g.*, U.S. Publication No. 20150289489, incorporated in its entirety by reference.

[0058] The phrase "light chain" includes an immunoglobulin light chain sequence from any organism, and unless otherwise specified includes human kappa (κ) and lambda (λ) light chains and a VpreB, as well as surrogate light chains. Light chain variable domains typically include three light chain CDRs and four framework (FR) regions, unless otherwise specified. Generally, a full-length light chain includes, from amino terminus to carboxyl terminus, a variable domain that includes FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4, and a light chain constant region amino acid sequence. Light chain variable domains are encoded by the light chain variable region nucleotide sequence, which generally comprises light chain V_L and light chain J_L gene segments, derived from a repertoire of light chain V and J gene segments present in the germline. Sequences, locations and nomenclature for light chain V and J gene segments for various organisms can be found in IMGT database, which is accessible via the internet on the world wide web (www) at the URL "imgt.org." Light chains include those, *e.g.*, that do not selectively bind either a first or a second first member of a specific binding pair selectively bound by the first member of a specific binding pair-binding protein in which they appear. Light chains also include those that bind and recognize, or assist the heavy chain with binding and recognizing, one or more first member of a specific binding pairs selectively bound by the first member of a specific binding pair-binding protein in which they appear. Light chains also include those that bind and recognize, or assist the heavy chain with binding and recognizing, one or more first member of a specific binding pairs selectively bound by the first member of a specific binding pair-binding protein in which they appear. Common or universal light chains include those derived from a human

Vκ1-39Jκ5 gene or a human Vκ3-20Jκ1 gene, and include somatically mutated (*e.g.*, affinity matured) versions of the same.

[0059] The phrase "operably linked", as used herein, includes a physical juxtaposition (*e.g.*, in three-dimensional space) of components or elements that interact, directly or indirectly with one another, or otherwise coordinate with each other to participate in a biological event, which juxtaposition achieves or permits such interaction and/or coordination. To give but one example, a regulatory element (*e.g.*, an expression control sequence) in a nucleic acid is said to be "operably linked" to a coding sequence when it is located relative to the coding sequence such that its presence or absence impacts expression and/or activity of the coding sequence. In many embodiments, "operable linkage" involves covalent linkage of relevant components or elements with one another. Those skilled in the art will readily appreciate that, in some embodiments, covalent linkage is not required to achieve effective operable linkage. For example, proteins operably linked together may be associated with each other, *e.g.*, via a covalent bond or a non-covalent bond. As a non-limiting example, a capsid protein as described herein may be operably linked to a targeting ligand, where the capsid protein is non-covalently bound to the targeting ligand, or covalently bound to the targeting ligand, optionally with or without a scaffold and/or adaptor between the capsid protein and the targeting ligand. As another example, in some embodiments, nucleic acid regulatory elements that are operably linked with coding sequences that they control are contiguous with the nucleotide of interest. Alternatively or additionally, in some embodiments, one or more such regulatory elements acts in trans or at a distance to control a coding sequence of interest. In some embodiments, the term "regulatory element" as used herein refers to polynucleotide sequences which are necessary and/or sufficient to affect the expression and processing of coding sequences to which they are ligated. In some embodiments, a regulatory element may be or comprise appropriate transcription initiation, termination, promoter and/or enhancer sequences; efficient RNA processing signals such as splicing and polyadenylation signals; sequences that stabilize cytoplasmic mRNA; sequences that enhance translation efficiency (*e.g.*, Kozak consensus sequence); sequences that enhance protein stability; and/or, in some embodiments, sequences that enhance protein secretion. In some embodiments, one or more regulatory elements are preferentially or exclusively active in a particular host cell or organism, or type thereof. To give but one example, in

prokaryotes, regulatory elements may typically include promoter, ribosomal binding site, and transcription termination sequence; in eukaryotes, in many embodiments, regulatory elements may typically include promoters, enhancers, and/or transcription termination sequences. Those of ordinary skill in the art will appreciate from context that, in many embodiments, the term "regulatory elements" refers to components whose presence is essential for expression and processing, and in some embodiments includes components whose presence is advantageous for expression (including, for example, leader sequences, targeting sequences, and/or fusion partner sequences).

[0060] "Retargeting" or "redirecting" may include a scenario in which the wildtype particle targets several cells within a tissue and/or several organs within an organism, and general targeting of the tissue or organs is reduced or abolished by insertion of the heterologous amino acid, and retargeting to more a specific cell in the tissue or a specific organ in the organism is achieved with the targeting ligand (e.g., via a targeting ligand) that binds a marker expressed by the specific cell. Such retargeting or redirecting may also include a scenario in which the wildtype particle targets a tissue, and targeting of the tissue is reduced to or abolished by insertion of the heterologous amino acid, and retargeting to a completely different tissue is achieved with the targeting ligand.

[0061] "Specific binding pair," "binding pair," "protein:protein binding pair" and the like includes two members (e.g., a first member (e.g., a first polypeptide) and a second cognate member (e.g., a second polypeptide)) that interact to form a bond (e.g., a non-covalent bond between a first member epitope and a second member antigen-binding portion of an antibody that recognizes the epitope; a covalent bond between e.g., proteins capable of forming isopeptide bonds; split inteins that recognize each other and, through the process of protein trans-splicing, mediate ligation of the flanking proteins and their own removal). In some embodiments, the term "cognate" refers to components that function together. Epitopes and cognate antibodies thereto, particularly epitopes that may also act as a detectable label (e.g., c-myc) are well-known in the art. Specific protein:protein binding pairs capable of interacting to form a covalent isopeptide bond are reviewed in Veggiani et al. (2014) *Trends Biotechnol.* 32:506, and include peptide:peptide binding pairs such as SpyTag:SpyCatcher, SpyTag002:SpyCatcher002; SpyTag:KTag; isopeptag:pilin C, SnoopTag:SnoopCatcher, etc., and variants thereof, e.g., SpyTag003:SpyCatcher003. Generally, a first member of a

protein:protein binding pair refers to member of a protein:protein binding pair, which is generally less than 30 amino acids in length, and which forms a spontaneous covalent isopeptide bond with the second cognate protein, wherein the second cognate protein is generally larger, but may also be less than 30 amino acids in length such as in the SpyTag:KTag system.

[0062] The term "isopeptide bond" refers to an amide bond between a carboxyl or carboxamide group and an amino group at least one of which is not derived from a protein main chain or alternatively viewed is not part of the protein backbone. An isopeptide bond may form within a single protein or may occur between two peptides or a peptide and a protein. Thus, an isopeptide bond may form intramolecularly within a single protein or intermolecularly i.e., between two peptide/protein molecules, e.g. between two peptide linkers. Typically, an isopeptide bond may occur between a lysine residue and an asparagine, aspartic acid, glutamine, or glutamic acid residue or the terminal carboxyl group of the protein or peptide chain or may occur between the alpha-amino terminus of the protein or peptide chain and an asparagine, aspartic acid, glutamine or glutamic acid. Each residue of the pair involved in the isopeptide bond is referred to herein as a reactive residue. In preferred embodiments of the invention, an isopeptide bond may form between a lysine residue and an asparagine residue or between a lysine residue and an aspartic acid residue. Particularly, isopeptide bonds can occur between the side chain amine of lysine and carboxamide group of asparagine or carboxyl group of an aspartate.

[0063] The SpyTag:SpyCatcher system is described in U.S. Patent No. 9,547,003 and Zaveri et al. (2012) *PNAS* 109:E690-E697, each of which is incorporated herein in its entirety by reference, and is derived from the CnaB2 domain of the *Streptococcus pyogenes* fibronectin-binding protein FbaB. By splitting the domain, Zakeri et al. obtained a peptide "SpyTag" having the sequence AHIVMVDAYKPTK (SEQ ID NO: 622) which forms an amide bond to its cognate protein "SpyCatcher," an 112 amino acid polypeptide having the amino acid sequence set forth in SEQ ID NO: 623. (Zakeri (2012), *supra*). An additional specific binding pair derived from CnaB2 domain is SpyTag:KTag, which forms an isopeptide bond in the presence of SpyLigase (SEQ ID NO: 632). (Fierer (2014) *PNAS* 111:E1176-1181) SpyLigase was engineered by excising the β strand from SpyCatcher that contains a reactive lysine, resulting in KTag, 10-residue first member of a protein:protein

binding pair having the amino acid sequence ATHIKFSKRD (SEQ ID NO: 624). The SpyTag002:SpyCatcher002 system is described in Keeble et al (2017) *Angew Chem Int Ed Engl* 56:16521-25, incorporated herein in its entirety by reference. SpyTag002 has the amino acid sequence VPTIVMVDAYKRYK, set forth as SEQ ID NO: 626, and binds SpyCatcher002 (SEQ ID NO: 627). SpyTag003 has the amino acid sequence RGVPHIVMVDAYKRYK, set forth as SEQ ID NO: 628, and binds SpyCatcher003 (SEQ ID NO: 629).

[0064] The SnoopTag:SnoopCatcher system is described in Veggiani (2016) *PNAS* 113:1202-07. The D4 Ig-like domain of RrgA, an adhesion from *Streptococcus pneumoniae*, was split to form SnoopTag (residues 734-745; SEQ ID NO: 630) and SnoopCatcher (residues 749-860; SEQ ID NO: 631). Incubation of SnoopTag and SnoopCatcher results in a spontaneous isopeptide bond that is specific between the complementary proteins. Veggiani (2016)), *supra*.

[0065] The isopeptag:pilin-C specific binding pair was derived from the major pilin protein Spy0128 from *Streptococcus pyogenes*. (Zakeir and Howarth (2010) *J. Am. Chem. Soc.* 132:4526-27). Isopeptag has the amino acid sequence TDKDMTITFTNKKDAE, set forth as SEQ ID NO: 625, and binds pilin-C (residues 18-299 of Spy0128). Incubation of Isopeptag and pilin-C results in a spontaneous isopeptide bond that is specific between the complementary proteins. Zakeir and Howarth (2010), *supra*.

[0066] The term “detectable label” includes a polypeptide sequence that is a member of a specific binding pair, e.g., that specifically binds via a non-covalent bond with another polypeptide sequence, e.g., an antibody paratope, with high affinity. Exemplary and non-limiting detectable labels include hexahistidine tag, FLAG tag, Strep II tag, streptavidin-binding peptide (SBP) tag, calmodulin-binding peptide (CBP), glutathione S-transferase (GST), maltose-binding protein (MBP), S-tag, HA tag, and the myc tag from c-myc (SEQ ID NO: 639). (Reviewed in Zhao et al. (2013) *J. Analytical Meth. Chem.* 1-8; incorporated herein by reference). A common detectable label for primate AAV is the B1 epitope (SEQ ID NO: 640). Some AAV capsid proteins described herein, which do not naturally comprise the B1 epitope, may be modified herein to comprise a B1 epitope. Generally, AAV capsid proteins described herein may comprise a sequence with substantial homology to the B1 epitope within the last 10 amino acids of the capsid protein. Accordingly, in some

embodiments, a non-primate AAV capsid protein of the invention may be modified with one but less than five point mutations within the last 10 amino acids of the capsid protein such that the AAV capsid protein comprises a B1 epitope.

[0067] The term "target cells" includes any cells in which expression of a nucleotide of interest is desired. Preferably, target cells exhibit a receptor on their surface that allows the cell to be targeted with a targeting ligand, as described below.

[0068] The term "transduction" or "infection" or the like refers to the introduction of a nucleic acid into a target cell nucleus by a viral particle. The term efficiency in relation to transduction or the like, e.g., "transduction efficiency" refers to the fraction (e.g., percentage) of cells expressing a nucleotide of interest after incubation with a set number of viral particles comprising the nucleotide of interest. Well-known methods of determining transduction efficiency include flow cytometry of cells transduced with a fluorescent reporter gene, RT-PCR for expression of the nucleotide of interest, etc.

[0069] Generally, "reference" viral capsid protein/capsid/particle are identical to test viral capsid protein/capsid/particle but for the change for which the effect is to be tested. For example, to determine the effect, e.g., on transduction efficiency, of inserting a first member of a specific binding pair into a test viral particle, the transduction efficiencies of the test viral particle (in the absence or presence of an appropriate targeting ligand) can be compared to the transduction efficiencies of a reference viral particle (in the absence or presence of an appropriate targeting ligand if necessary) which is identical to the test viral particle in every instance (e.g., additional point mutations, nucleotide of interest, numbers of viral particles and target cells, etc.) except for the presence of a first member of a specific binding pair. In some embodiments, a reference viral capsid protein is one that is able to form a capsid with a second viral capsid protein modified to comprise at least a first member of a protein:protein binding pair, where the reference viral capsid protein does not comprise the first member of a protein:protein binding pair, preferably wherein the capsid formed by the reference viral capsid protein and the modified viral capsid protein is a mosaic capsid.

Adeno-associated viruses (AAV)

[0070] "AAV" is an abbreviation for adeno-associated virus and may be used to refer to the virus itself or derivatives thereof. AAVs are small, non-enveloped, single-stranded

DNA viruses. Generally, a wildtype AAV genome is 4.7 kb and is characterized by two inverted terminal repeats (ITR) and two open reading frames (ORFs), *rep* and *cap*. The wildtype *rep* reading frame encodes four proteins of molecular weight 78 kD (“Rep78”), 68 kD (“Rep68”), 52 kD (“Rep52”) and 40 kD (“Rep 40”). Rep78 and Rep68 are transcribed from the p5 promoter, and Rep52 and Rep40 are transcribed from the p19 promoter. These proteins function mainly in regulating the transcription and replication of the AAV genome. The wildtype *cap* reading frame encodes three structural (capsid) viral proteins (VPs) having molecular weights of 83-85 kD (VP1), 72-73 kD (VP2) and 61-62 kD (VP3). More than 80% of total proteins in an AAV virion (capsid) comprise VP3; in mature virions VP1, VP2 and VP3 are found at relative abundance of approximately 1:1:10, although ratios of 1:1:8 have been reported. Padron et al. (2005) J. Virology 79:5047-58.

[0071] The genomic sequences of various serotypes of AAV, as well as the sequences of the native inverted terminal repeats (ITRs), Rep proteins, and capsid subunits are known in the art. Such sequences may be found in the literature or in public databases such as GenBank. See, e.g., GenBank Accession Numbers NC_002077 (AAV1), AF063497 (AAV1), NC001401 (AAV-2), AF043303 (AAV2), NC_001729 (AAV3), NC_001829 (AAV4), U89790 (AAV4), NC_006152 (AAV5), AF513851 (AAV7), AF513852 (AAV8), and NC_006261 (AAV8); the disclosures of which are incorporated by reference herein for teaching AAV nucleic acid and amino acid sequences. See also, e.g., Srivistava et al. (1983) J. Virology 45:555; Chiorini et al. (1998) J. Virology 71:6823; Chiorini et al. (1999) J. Virology 73: 1309; Bantel-Schaal et al. (1999) J. Virology 73:939; Xiao et al. (1999) J. Virology 73:3994; Muramatsu et al. (1996) Virology 221:208; Shade et al., (1986) J. Virol. 58:921; Gao et al. (2002) Proc. Nat. Acad. Sci. USA 99: 11854; Moris et al. (2004) Virology 33:375-383; US Patent Publication 20170130245; international patent publications WO 00/28061, WO 99/61601, WO 98/11244; and U.S. Pat. No. 6,156,303, each of which is incorporated by reference in its entirety by reference. Table 2 herein provides sequences of various non-primate AAV.

[0072] “AAV” encompasses all subtypes and both naturally occurring and modified forms that are well-known in the art. AAV includes primate AAV (e.g., AAV type 1 (AAV1), primate AAV type 2 (AAV2), primate AAV type 3 (AAV3B), primate AAV type 4 (AAV4), primate AAV type 5 (AAV5), primate AAV type 6 (AAV6), primate AAV type 7

(AAV7), primate AAV type 8 (AAV8), primate AAV type 9 (AAV9), AAV10, AAV11, AAV12, AAV13, AAVDJ, Anc80L65, AAV2G9, AAV-LK03, primate AAV type rh10 (AAV rh10), AAV type h10 (AAV h10), AAV type hu11 (AAV hu11), AAV type rh32.33 (AAV rh32.33), AAV retro (AAV retro), AAV PHP.B, AAV PHP.eB, AAV PHP.S, AAV2/8, etc., non-primate animal AAV (e.g., avian AAV (AAAV)) and other non-primate animal AAV such as mammalian AAV (e.g., bat AAV, sea lion AAV, bovine AAV, canine AAV, equine AAV, caprine AAV, and ovine AAV etc.), squamate AAV (e.g., snake AAV, bearded dragon AAV), etc. "Primate AAV" refers to AAV generally isolated from primates. Similarly, "non-primate animal AAV" refers to AAV isolated from non-primate animals.

[0073] As used herein, "of a [specified] AAV" in relation to a gene (e.g., *rep*, *cap*, etc.), capsid protein (e.g., a VP1 capsid protein, a VP2 capsid protein, a VP3 capsid protein, etc.), region of a capsid protein of a specified AAV (e.g., PLA₂ region, VP1-u region, VP1/VP2 common region, VP3 region), nucleotide sequence (e.g., ITR sequence), e.g., a *cap* gene or capsid protein of AAV etc., encompasses, in addition to the gene or the polypeptide respectively comprising a nucleic acid sequence or amino acid sequence set forth herein for the specified AAV, also variants of the gene or polypeptide, including variants comprising the least number of nucleotides or amino acids required to retain one or more biological functions. As used herein, a variant gene or a variant polypeptide comprises a nucleic acid sequence or amino acid sequence that differs from the nucleic acid sequence or amino acid sequence set forth herein for the gene or polypeptide of a specified AAV, wherein the difference(s) does not generally alter at least one biological function of the gene or polypeptide, and/or the phylogenetic characterization of the gene or polypeptide, e.g., where the difference(s) may be due to degeneracy of the genetic code, isolate variations, length of the sequence, etc. For example, *rep* gene and the *cap* gene as used here may encompass *rep* and *cap* genes that differ from the wildtype gene in that the genes may encode one or more Rep proteins and Cap proteins, respectively. In some embodiments, a Rep gene encodes at least Rep78 and/or Rep68. In some embodiments, *cap* gene includes those may differ from the wildtype in that one or more alternative start codons or sequences between one or more alternative start codons are removed such that the *cap* gene encodes only a single Cap protein, e.g., wherein the VP2 and/or VP3 start codons are removed or substituted such that the *cap* gene encodes a functional VP1 capsid protein but not a VP2 capsid protein or a VP3

capsid protein. Accordingly, as used herein, a *rep* gene encompasses any sequence that encodes a functional Rep protein. A *cap* gene encompasses any sequence that encodes at least one functional *cap* gene.

[0074] It is well-known that the wildtype *cap* gene expresses all three VP1, VP2, and VP3 capsid proteins from a single open reading frame of the *cap* gene under control of the p40 promoter found in the *rep* ORF. The term "capsid protein," "Cap protein" and the like includes a protein that is part of the capsid of the virus. For adeno-associated viruses, the capsid proteins are generally referred to as VP1, VP2 and/or VP3, and may be encoded by the single *cap* gene. For AAV, the three AAV capsid proteins are produced in nature an overlapping fashion from the *cap* ORF alternative translational start codon usage, although all three proteins use a common stop codon. The ORF of a wildtype *cap* gene encodes from 5' to 3' three alternative start codons: "the VP1 start codon," "the VP2 start codon," and "the VP3 start codon"; and one "common stop codon". The largest viral protein, VP1, is generally encoded from the VP1 start codon to the "common stop codon." VP2 is generally encoded from the VP2 start codon to the common stop codon. VP3 is generally encoded from the VP3 start codon to the common stop codon. Accordingly, VP1 comprises at its N-terminus sequence that it does not share with the VP2 or VP3, referred to as the VP1-unique region (VP1-u). The VP1-u region is generally encoded by the sequence of a wildtype *cap* gene starting from the VP1 start codon to the "VP2 start codon." VP1-u comprises a phospholipase A2 domain (PLA₂), which may be important for infection, as well as nuclear localization signals which may aid the virus in targeting to the nucleus for uncoating and genome release. The VP1, VP2, and VP3 capsid proteins share the same C-terminal sequence that makes up the entirety of VP3, which may also be referred to herein as the VP3 region. The VP3 region is encoded from the VP3 start codon to the common stop codon. VP2 has an additional ~ 60 amino acids that it shares with the VP1. This region is called the VP1/VP2 common region.

[0075] In some embodiments, one or more of the Cap proteins of the invention may be encoded by one or more *cap* genes having one or more ORFs. In some embodiments, the VP proteins of the invention may be expressed from more than one ORF comprising nucleotide sequence encoding any combination of VP1, VP2, and/or VP3 by use of separate nucleotide sequences operably linked to at least one expression control sequence for

expression in packaging cell, each producing one or more of VP1, VP2, and/or VP3 capsid proteins of the invention. In some embodiments, a VP capsid protein of the invention may be expressed individually from an ORF comprising nucleotide sequence encoding any one of VP1, VP2, or VP3 by use of separate nucleotide sequences operably linked to one expression control sequence for expression in a viral replication cell, each producing only one of VP1, VP2, or VP3 capsid protein. In another embodiment, VP proteins may be expressed from one ORF comprising nucleotide sequences encoding VP1, VP2, and VP3 capsid proteins operably linked to at least one expression control sequence for expression in a viral replication cell, each producing VP1, VP2, and VP3 capsid protein. Accordingly, although amino acid positions provided herein may be provided in relation to the VP1 capsid protein of the referenced AAV, a skilled artisan would be able to respectively and readily determine the position of that same amino acid within the VP2 and/or VP3 capsid protein of the AAV, and the corresponding position of amino acids among different AAV.

[0076] The phrase “Inverted terminal repeat” or “ITR” includes symmetrical nucleic acid sequences in the genome of adeno-associated viruses required for efficient replication. ITR sequences are located at each end of the AAV DNA genome. The ITRs serve as the origins of replication for viral DNA synthesis and are essential cis components for generating AAV particles, e.g., packaging into AAV particles.

[0077] AAV ITR comprise recognition sites for replication proteins Rep78 or Rep68. A “D” region of the ITR comprises the DNA nick site where DNA replication initiates and provides directionality to the nucleic acid replication step. An AAV replicating in a mammalian cell typically comprises two ITR sequences.

[0078] A single ITR may be engineered with Rep binding sites on both strands of the “A” regions and two symmetrical D regions on each side of the ITR palindrome. Such an engineered construct on a double-stranded circular DNA template allows Rep78 or Rep68 initiated nucleic acid replication that proceeds in both directions. A single ITR is sufficient for AAV replication of a circular particle. In methods of producing an AAV viral particle of the invention, the *rep* encoding sequence encodes a Rep protein or Rep protein equivalent that is capable of binding an ITR comprised on the transfer plasmid.

[0079] The Cap proteins of the invention, when expressed with appropriate Rep proteins by a packaging cell, may encapsidate a transfer plasmid comprising a nucleotide of

interest and an even number of two or more ITR sequences. In some embodiments, a transfer plasmid comprises one ITR sequence. In some embodiments, a transfer plasmid comprises two ITR sequences.

[0080] Either Rep78 and/or Rep68 bind to unique and known sites on the sequence of the ITR hairpin, and act to break and unwind the hairpin structures on the end of an AAV genome, thereby providing access to replication machinery of the viral replication cell. As is well-known, Rep proteins may be expressed from more than one ORF comprising nucleotide sequence encoding any combination of Rep78, Rep68, Rep 52 and/or Rep40 by use of separate nucleotide sequences operably linked to at least one expression control sequence for expression in a viral replication cell, each producing one or more of Rep78, Rep68, Rep 52 and/or Rep40 Rep proteins. Alternatively, Rep proteins may be expressed individually from an ORF comprising a nucleotide sequence encoding any one of Rep78, Rep68, Rep 52, or Rep40 by use of separate nucleotide sequences operably linked to one expression control sequence for expression in a packaging cell, each producing only one Rep78, Rep68, Rep 52, or Rep40 Rep protein. In another embodiment, Rep proteins may be expressed from one ORF comprising nucleotide sequences encoding Rep78 and Rep52 Rep proteins operably linked to at least one expression control sequence for expression in a viral replication cell each producing Rep78 and Rep52 Rep protein.

[0081] In a method of producing an AAV virion, e.g., viral particle, of the invention, a *rep* encoding sequence and a *cap* gene of the invention may be provided a single packaging plasmid. However, a skilled artisan will recognize that such proviso is not necessary. Such viral particles may or may not include a genome.

[0082] A “chimeric AAV capsid protein” includes an AAV capsid protein that comprises amino acid sequences, e.g., portions, from two or more different AAV and that is capable of forming and/or forms an AAV viral capsid/viral particle. A chimeric AAV capsid protein is encoded by a chimeric AAV capsid gene, e.g., a chimeric nucleotide comprising a plurality, e.g., at least two, nucleic acid sequences, each of which plurality is identical to a portion of a capsid gene encoding a capsid protein of distinct AAV, and which plurality together encodes a functional chimeric AAV capsid protein. Association of a chimeric capsid protein to a specific AAV indicates that the capsid protein comprises one or more portions from a capsid protein of that AAV and one or more portions from a capsid protein of a

different AAV. For example, a chimeric AAV2 capsid protein includes a capsid protein comprising one or more portions of a VP1, VP2, and/or VP3 capsid protein of AAV2 and one or more portions of a VP1, VP2, and/or VP3 capsid protein of a different AAV.

[0083] The term “portion” refers to at least 5 amino acids or at least 15 nucleotides, but less than the full-length polypeptide or nucleic acid molecule, with 100% identity to a sequence from which the portion is derived, *see* Penzes (2015) *J. General Virol.* 2769. A “portion” encompasses any contiguous segment of amino acids or nucleotides sufficient to determine that the polypeptide or nucleic acid molecule from which the portion is derived is “of a [specified] AAV” or has “significant identity” to a particular AAV, e.g., a non-primate animal AAV or remote AAV. In some embodiments, a portion comprises at least 5 amino acids or 15 nucleotides with 100% identity to a sequence associated with the specified AAV. In some embodiments, a portion comprises at least 10 amino acids or 30 nucleotides with 100% identity to a sequence associated with the specified AAV. In some embodiments, a portion comprises at least 15 amino acids or 45 nucleotides with 100% identity to a sequence associated with the specified AAV. In some embodiments, a portion comprises at least 20 amino acids or 60 nucleotides with 100% identity to a sequence associated with the specified AAV. In some embodiments, a portion comprises at least 25 amino acids or 75 nucleotides with 100% identity to a sequence associated with the specified AAV. In some embodiments, a portion comprises at least 30 amino acids or 90 nucleotides with 100% identity to a sequence associated with the specified AAV. In some embodiments, a portion comprises at least 35 amino acids or 105 nucleotides with 100% identity to a sequence associated with the specified AAV. In some embodiments, a portion comprises at least 40 amino acids or 120 nucleotides with 100% identity to a sequence associated with the specified AAV. In some embodiments, a portion comprises at least 45 amino acids or 135 nucleotides with 100% identity to a sequence associated with the specified AAV. In some embodiments, a portion comprises at least 50 amino acids or 150 nucleotides with 100% identity to a sequence associated with the specified AAV. In some embodiments, a portion comprises at least 60 amino acids or 180 nucleotides with 100% identity to a sequence associated with the specified AAV. In some embodiments, a portion comprises at least 70 amino acids or 210 nucleotides with 100% identity to a sequence associated with the specified AAV. In some embodiments, a portion comprises at least 80 amino acids or 240 nucleotides with 100%

identity to a sequence associated with the specified AAV. In some embodiments, a portion comprises at least 90 amino acids or 270 nucleotides with 100% identity to a sequence associated with the specified AAV. In some embodiments, a portion comprises at least 100 amino acids or 300 nucleotides with 100% identity to a sequence associated with the specified AAV.

Virus capsid proteins, viral particles, viral nucleic acids

[0084] In some embodiments, a Cap protein, e.g., a VP1 capsid protein as described herein, a VP2 capsid protein as described herein, and/or a VP3 capsid protein as described herein, is modified to comprise any one or combination of e.g., insertion of a targeting ligand, a chemical modification, a first member of a binding pair, a detectable label, point mutation, etc.

[0085] Generally, modification of gene or a polypeptide of a specified AAV, or variants thereof, results in nucleic acid sequence or an amino acid sequence that differs from the nucleic acid sequence or amino acid sequence set forth herein for the specified AAV, wherein the modification alters, confers, or removes one or more biological functions, but does not change the phylogenetic characterization of, the gene or polypeptide as an AAV gene or AAV polypeptide. Modifications may include any one or a combination of: substitution of sequences of a first AAV serotype with sequences of a second AAV serotype to create chimerism; chemical modification; an insertion of: a first member of a binding pair, and/or a point mutation; etc., such that the natural tropism of the capsid protein is reduced to abolished, the tropism of the capsid protein may be more easily redirected, and/or such that the capsid protein comprises a detectable label. Modifications as described herein generally do not alter and preferably decrease the low to no recognition of the modified capsid by pre-existing antibodies found in the general population that were produced during the course of infection with another AAV, e.g., infection with serotypes such as AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAV9, AAV10, AAV11, AAV12, AAV13, AAVDJ, Anc80L65, AAV2G9, AAV-LK03, virions based on such serotypes, virions from currently used AAV gene therapy modalities, or a combination thereof.

[0086] In some embodiments, a Cap protein, e.g., a VP1 capsid protein as described herein, a VP2 capsid protein as described herein, and/or a VP3 capsid protein as described herein, is unmodified, *i.e.*, comprises a wildtype AAV sequence.

Targeting ligand

[0087] Modifications described herein may pertain to the association (e.g., display, operable linkage, binding, etc.) of a targeting ligand to a modified capsid protein and/or capsid comprising a modified capsid protein. Generally, a targeting ligand as described herein binds a surface protein expressed by a mammalian nervous system cell, e.g., a protein that is expressed on the surface of a mammalian nervous system cell, e.g., a mammalian nervous system cell-specific surface protein. In some embodiments, a modified capsid protein and/or modified capsid comprises a targeting ligand that binds mammalian p75^{NTR}, e.g., a human p75^{NTR}.

[0088] Table 1 provides a summary of the SEQ ID NO for each binding portion (e.g., heavy chain variable domain (HCVR), light chain variable domain (LCVR), and CDR1, CDR2, and CDR3) and the full heavy chain (HC) and light chain (LC) sequences of non-limiting and exemplary anti-human-p75^{NTR} monoclonal antibodies (mAb ID) that may be used to redirect an AAV capsid as described herein. In some embodiments, an AAV capsid as described herein comprises a targeting ligand that binds human p75^{NTR}, wherein the targeting ligand comprises heavy chain variable domain, light chain variable domain, heavy chain variable domain/light chain variable domain pair, HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, LCDR3, and/or set of HCDR1-HCDR2-HCDR3-LCDR1-LCDR2-LCDR3 amino acid sequence(s) at least 90% identical to, respectively, an amino acid sequence of a heavy chain variable domain, light chain variable domain, heavy chain variable domain/light chain variable domain pair, HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, LCDR3, and/or set of HCDR1-HCDR2-HCDR3-LCDR1-LCDR2-LCDR3 set forth in or encoded by a sequence or sequences as set forth in Table 1 and/or any one of SEQ ID NOs: 1-617. In some embodiments, an AAV capsid as described herein comprises a targeting ligand that binds human p75^{NTR}, wherein the targeting ligand comprises a heavy chain variable domain, light chain variable domain, heavy chain variable domain/light chain variable domain pair, HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, LCDR3, and/or set of HCDR1-HCDR2-

HCDR3-LCDR1-LCDR2-LCDR3 amino acid sequence at least 95% identical to, respectively, amino acid sequence(s) of a heavy chain variable domain, light chain variable domain, heavy chain variable domain/light chain variable domain pair, HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, LCDR3, and/or set of HCDR1-HCDR2-HCDR3-LCDR1-LCDR2-LCDR3 set forth in or encoded by a sequence or sequences as set forth in Table 1 and/or any one of SEQ ID NOs: 1-617. In some embodiments, an AAV capsid as described herein comprises a targeting ligand that binds human p75^{NTR}, wherein the targeting ligand comprises a heavy chain variable domain, light chain variable domain, heavy chain variable domain/light chain variable domain pair, HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, LCDR3, and/or set of HCDR1-HCDR2-HCDR3-LCDR1-LCDR2-LCDR3 amino acid sequence at least 97% identical to amino acid sequence(s) of a heavy chain variable domain, light chain variable domain, heavy chain variable domain/light chain variable domain pair, HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, LCDR3, and/or set of HCDR1-HCDR2-HCDR3-LCDR1-LCDR2-LCDR3 set forth in or encoded by a sequence or sequences as set forth in Table 1 and/or any one of SEQ ID NOs: 1-617. In some embodiments, an AAV capsid as described herein comprises a targeting ligand that binds human p75^{NTR}, wherein the targeting ligand comprises a heavy chain variable domain, light chain variable domain, heavy chain variable domain/light chain variable domain pair, HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, LCDR3, and/or set of HCDR1-HCDR2-HCDR3-LCDR1-LCDR2-LCDR3 amino acid sequence(s) at least 98% identical to amino acid sequence(s) of a heavy chain variable domain, light chain variable domain, heavy chain variable domain/light chain variable domain pair, HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, LCDR3, and/or set of HCDR1-HCDR2-HCDR3-LCDR1-LCDR2-LCDR3 set forth in or encoded by a sequence or sequences as set forth in Table 1 and/or any one of SEQ ID NOs: 1-617. In some embodiments, an AAV capsid as described herein comprises a targeting ligand that binds human p75^{NTR}, wherein the targeting ligand comprises a heavy chain variable domain, light chain variable domain, heavy chain variable domain/light chain variable domain pair, HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, LCDR3, and/or set of HCDR1-HCDR2-HCDR3-LCDR1-LCDR2-LCDR3 amino acid sequences 99% identical to amino acid sequences of a heavy chain variable domain, light chain variable domain, heavy chain variable domain/light chain variable domain pair, HCDR1, HCDR2, HCDR3, LCDR1,

LCDR2, LCDR3, and/or set of HCDR1-HCDR2-HCDR3-LCDR1-LCDR2-LCDR3 set forth in or encoded by a sequence or sequences as set forth in Table 1 and/or any one of SEQ ID NOs: 1-617. Also described herein are antibodies, or antigen-binding fragments thereof, comprising a set of six CDRs (*i.e.*, HCDR1-HCDR2-HCDR3-LCDR1-LCDR2-LCDR3) contained within an HCVR/LCVR amino acid sequence pair as defined by any of the exemplary anti-p75^{NTR} antibodies listed in Table 1. In some embodiments, a targeting ligand as described herein comprises the HCDR1-HCDR2-HCDR3-LCDR1-LCDR2-LCDR3 amino acid sequences set contained within an HCVR/LCVR amino acid sequence pair selected from the group consisting of SEQ ID NOs: 2/10, 22/30, 42/50, 58/66, 78/86, 98/106, 116/124, 136/144, 155/162, 173/179, 189/197, 207/215, 227/235, 245/251, 261/269, 279/287, 297/304, 315/323, 331/339, 349/357, 369/377, 387/391, 401/409, 417/409, 427/409, 437/409, 445/409, 455/409, 465/409, 475/409, 484/409, 493/409, 503/409, 513/409, 519/409, 529/537, 549/557, 569/577, 589/597, and 609/597. In some embodiments, a targeting ligand as described herein comprises an HCVR/LCVR amino acid sequence pair selected from the group consisting of SEQ ID NOs: 2/10, 22/30, 42/50, 58/66, 78/86, 98/106, 116/124, 136/144, 155/162, 173/179, 189/197, 207/215, 227/235, 245/251, 261/269, 279/287, 297/304, 315/323, 331/339, 349/357, 369/377, 387/391, 401/409, 417/409, 427/409, 437/409, 445/409, 455/409, 465/409, 475/409, 484/409, 493/409, 503/409, 513/409, 519/409, 529/537, 549/557, 569/577, 589/597, and 609/597.

Table 1. SEQ ID NOs of Amino Acid Sequences of Domains in Antibodies or Antigen-binding Fragments (e.g., Fabs or scFv Molecules) that may be used to retarget AAV to human p75^{NTR}. SEQ ID NOs for corresponding DNA sequences are presented in parentheses below each amino acid sequence.

mAb ID	HCVR	HCDR1	HCDR2	HCDR3	LCVR	LCDR1	LCDR2	LCDR3	HC	LC
REGN14148	2 (1)	4 (3)	6 (5)	8 (7)	10 (9)	12 (11)	14 (13)	16 (15)	18 (17)	20 (19)
REGN14149	22 (21)	24 (23)	26 (25)	28 (27)	30 (29)	32 (31)	34 (33)	36 (35)	38 (37)	40 (39)
REGN14150	42 (41)	44 (43)	46 (45)	48 (47)	50 (49)	12 (11)	14 (13)	52 (51)	54 (53)	56 (55)
REGN14151	58 (57)	60 (59)	62 (61)	64 (63)	66 (65)	68 (67)	70 (69)	72 (71)	74 (73)	76 (75)

REGN14152	78 (77)	80 (79)	82 (81)	84 (83)	86 (85)	88 (87)	90 (89)	92 (91)	94 (93)	96 (95)
REGN14153	98 (97)	100 (99)	102 (101)	104 (103)	106 (105)	108 (107)	34 (33)	110 (109)	112 (111)	114 (113)
REGN14154	116 (115)	118 (117)	120 (119)	122 (121)	124 (123)	126 (125)	128 (127)	130 (129)	132 (131)	134 (133)
REGN14155	136 (135)	138 (137)	140 (139)	142 (141)	144 (143)	146 (145)	90 (147)	149 (148)	151 (150)	153 (152)
REGN14156	155 (154)	100 (156)	158 (157)	160 (159)	162 (161)	164 (163)	90 (165)	167 (166)	169 (168)	171 (170)
REGN14157	173 (172)	100 (156)	175 (174)	177 (176)	179 (178)	181 (180)	70 (69)	183 (182)	185 (184)	187 (186)
REGN14158	189 (188)	191 (190)	193 (192)	195 (194)	197 (196)	199 (198)	14 (13)	201 (200)	203 (202)	205 (204)
REGN14159	207 (206)	209 (208)	211 (210)	213 (212)	215 (214)	217 (216)	219 (218)	221 (220)	223 (222)	225 (224)
REGN14160	227 (226)	229 (228)	231 (230)	233 (232)	235 (234)	237 (236)	14 (13)	239 (238)	241 (240)	243 (242)
REGN14161	245 (244)	100 (156)	247 (246)	249 (248)	251 (250)	253 (252)	70 (69)	255 (254)	257 (256)	259 (258)
REGN14162	261 (260)	263 (262)	265 (264)	267 (266)	269 (268)	271 (270)	90 (165)	273 (272)	275 (274)	277 (276)
REGN14163	279 (278)	281 (280)	283 (282)	285 (284)	287 (286)	289 (288)	14 (13)	291 (290)	293 (292)	295 (294)
REGN14164	297 (296)	299 (298)	193 (300)	302 (301)	304 (303)	237 (305)	307 (306)	309 (308)	311 (310)	313 (312)
REGN14165	315 (314)	317 (316)	319 (318)	321 (320)	323 (322)	12 (11)	14 (13)	325 (324)	327 (326)	329 (328)
REGN14175	331 (330)	333 (332)	335 (334)	337 (336)	339 (338)	237 (236)	341 (340)	343 (342)	345 (344)	347 (346)
REGN14176	349 (348)	351 (350)	353 (352)	355 (354)	357 (356)	359 (358)	361 (360)	363 (362)	365 (364)	367 (366)
REGN14177	369 (368)	371 (370)	373 (372)	375 (374)	377 (376)	379 (378)	90 (165)	381 (380)	383 (382)	385 (384)
REGN14178	387 (386)	138 (137)	319 (318)	389 (388)	391 (390)	393 (392)	361 (360)	395 (394)	397 (396)	399 (398)
REGN14179	401 (400)	403 (402)	405 (404)	407 (406)	409 (408)	237 (236)	14 (13)	411 (410)	413 (412)	415 (414)
REGN14180	417 (416)	419 (418)	421 (420)	423 (422)	409 (408)	237 (236)	14 (13)	411 (410)	425 (424)	415 (414)

REGN14181	427 (426)	429 (428)	431 (430)	433 (432)	409 (408)	237 (236)	14 (13)	411 (410)	435 (434)	415 (414)
REGN14182	437 (436)	191 (438)	335 (439)	441 (440)	409 (408)	237 (236)	14 (13)	411 (410)	443 (442)	415 (414)
REGN14183	445 (444)	447 (446)	449 (448)	451 (450)	409 (408)	237 (236)	14 (13)	411 (410)	453 (452)	415 (414)
REGN14184	455 (454)	457 (456)	459 (458)	461 (460)	409 (408)	237 (236)	14 (13)	411 (410)	463 (462)	415 (414)
REGN14185	465 (464)	467 (466)	469 (468)	471 (470)	409 (408)	237 (236)	14 (13)	411 (410)	473 (472)	415 (414)
REGN14186	475 (474)	477 (476)	158 (478)	480 (479)	409 (408)	237 (236)	14 (13)	411 (410)	482 (481)	415 (414)
REGN14187	484 (483)	486 (485)	283 (487)	489 (488)	409 (408)	237 (236)	14 (13)	411 (410)	491 (490)	415 (414)
REGN14188	493 (492)	495 (494)	497 (496)	499 (498)	409 (408)	237 (236)	14 (13)	411 (410)	501 (500)	415 (414)
REGN14189	503 (502)	505 (504)	507 (506)	509 (508)	409 (408)	237 (236)	14 (13)	411 (410)	511 (510)	415 (414)
REGN14190	513 (512)	138 (137)	319 (318)	515 (514)	409 (408)	237 (236)	14 (13)	411 (410)	517 (516)	415 (414)
REGN14191	519 (518)	521 (520)	523 (522)	525 (524)	409 (408)	237 (236)	14 (13)	411 (410)	527 (526)	415 (414)
REGN19513	529 (528)	531 (530)	533 (532)	535 (534)	537 (536)	539 (538)	541 (540)	543 (542)	545 (544)	547 (546)
REGN19514	549 (548)	551 (550)	553 (552)	555 (554)	557 (556)	559 (558)	561 (560)	563 (562)	565 (564)	567 (566)
REGN19515	569 (568)	571 (570)	573 (572)	575 (574)	577 (576)	579 (578)	581 (580)	583 (582)	585 (584)	587 (586)
REGN19516	589 (588)	591 (590)	593 (592)	595 (594)	597 (596)	599 (598)	601 (600)	603 (602)	605 (604)	607 (606)
REGN19517	609 (608)	611 (610)	613 (612)	615 (614)	597 (596)	599 (598)	601 (600)	603 (602)	617 (616)	607 (606)

REGN14148

HCVR DNA Sequence

GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTG
 AGACTCTCCTGTGCGGCCTCTGGATTACCTTTAATAACTATTGGATGAGCTGGA
 TCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCAACATAAAGCCAGATG

GAAGTGAGAAATCATATGTGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAG
ACAACGCCAAGAAATCACTGTTTCTGCAAATGACCAGCCTGAGAGCCGAGGACA
CGGCTGTTTATTACTGTGCGACGAACTGGGGGTTTGACTGGGGCCAGGGAACCTT
GGTCACCGTCTCCTCA

(SEQ ID NO: 1)

HCVR Amino Acid Sequence

EVQLVESGGGLVQPGGSLRLSCAASGFTFNWMSWIRQAPGKGLEWVANIKPDGS
EKSYVDSVKGRFTISRDNAKKSLFLQMTSLRAEDTAVYYCATNWGFDWGQGLVT
VSS

(SEQ ID NO: 2)

CDR1 DNA Sequence

GGA TTC ACC TTT AAT AAC TAT TGG

(SEQ ID NO: 3)

CDR1 Amino Acid Sequence

G F T F N N Y W

(SEQ ID NO: 4)

CDR2 DNA Sequence

ATA AAG CCA GAT GGA AGT GAG AAA

(SEQ ID NO: 5)

CDR2 Amino Acid Sequence

I K P D G S E K

(SEQ ID NO: 6)

CDR3 DNA Sequence

GCG ACG AAC TGG GGG TTT GAC

(SEQ ID NO: 7)

CDR3 Amino Acid Sequence

A T N W G F D

(SEQ ID NO: 8)

LCVR DNA Sequence

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTGGGAGACAGAG
TCACCGTCACTTGCCGGGCAAGTCAGGACATTAGAAATGATTTAGGCTGGTTTCA
GCAGAAACCAGGGAAAGCCCCTAAGCGCCTGATCTATGCTGCATCCAGTTTGCA
AAGTGGGGTCCCATCAAGGTTCAGCGGCAGTGGATCTGGGACAGACTTCACTCT
CACAATCAGCAGCCTGCAGCCTGAAGATTTTGCAACTTATTACTGTCTACAGTAT
AATAGTTACCCGTGGACGTTTCGGCCAAGGGACCAAGGTGGAAATCAAA

(SEQ ID NO: 9)

LCVR Amino Acid Sequence

DIQMTQSPSSLSASVGDRVTVTCRASQDIRNDLGWFQKPGKAPKRLIYAASSLQSG
VPSRFSGSGSGTDFLTITSSLQPEDFATYYCLQYNSYPWTFGQGTKVEIK

(SEQ ID NO: 10)

CDR1 DNA Sequence

CAG GAC ATT AGA AAT GAT

(SEQ ID NO: 11)

CDR1 Amino Acid Sequence

Q D I R N D

(SEQ ID NO: 12)

CDR2 DNA Sequence

GCT GCA TCC

(SEQ ID NO: 13)

CDR2 Amino Acid Sequence

A A S

(SEQ ID NO: 14)

CDR3 DNA Sequence

CTA CAG TAT AAT AGT TAC CCG TGG ACG

(SEQ ID NO: 15)

CDR3 Amino Acid Sequence

L Q Y N S Y P W T

(SEQ ID NO: 16)

HC DNA Sequence

GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTG
AGACTCTCCTGTGCGGCCTCTGGATTACCTTTAATAACTATTGGATGAGCTGGA

TCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCAACATAAAGCCAGATG
GAAGTGAGAAATCATATGTGGACTCTGTGAAGGGCCGATTACCATCTCCAGAG
ACAACGCCAAGAAATCACTGTTTCTGCAAATGACCAGCCTGAGAGCCGAGGACA
CGGCTGTTTATTACTGTGCGACGAACTGGGGGTTTGACTGGGGCCAGGGAACCCCT
GGTCACCGTCTCCTCAGCCTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCGCCC
TGCTCCAGGAGCACCTCCGAGAGCACAGCCGCCCTGGGCTGCCTGGTCAAGGAC
TACTTCCCCGAACCGGTGACGGTGTCTGTGGAACCTCAGGCGCCCTGACCAGCGGC
GTGCACACCTTCCCGGCTGTCTACAGTCTCAGGACTCTACTCCCTCAGCAGCG
TGGTGACCGTGCCCTCCAGCAGCTTGGGCACGAAGACCTACACCTGCAACGTAG
ATCACAAGCCCAGCAACACCAAGGTGGACAAGAGAGTTGAGTCCAAATATGGTC
CCCCATGCCCACCGTGCCCAGCACCACTGTGGCAGGACCATCAGTCTTCCTGTT
CCCCCAAAACCCAAGGACACTCTCATGATCTCCCGGACCCCTGAGGTACGTGC
GTGGTGGTGGACGTGAGCCAGGAAGACCCCGAGGTCCAGTTCAACTGGTACGTG
GATGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTTCAA
CAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAAC
GGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGGCCTCCCGTCTCCATCGAG
AAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAGCCACAGGTGTACACCCTG
CCCCCATCCCAGGAGGAGATGACCAAGAACCAGGTACAGCTGACCTGCCTGGTC
AAAGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCG
GAGAACAACCTACAAGACCACGCCTCCCGTGTCTGGACTCCGACGGCTCCTTCTTCC
TCTACAGCAGGCTCACCGTGGACAAGAGCAGGTGGCAGGAGGGGAATGTCTTCT
CATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACACAGAAGTCCCTCTC
CCTGTCTCTGGGTAAATGA

(SEQ ID NO: 17)

HC Amino Acid Sequence

EVQLVESGGGLVQPGGSLRLSCAASGFTFNNYWMSWIRQAPGKGLEWVANIKPDGS
EKSYVDSVKGRFTISRDNKKSLFLQMTSLRAEDTAVYYCATNWGFDWGQGLVT
VSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPA
VLQSSGLYSLSSVTVPSSSLGKTYTCNVDHKPSNTKVDKRVESKYGPCCPPCPAPP

VAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTK
PREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQ
VYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSGDSF
FLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLGLGK*

(SEQ ID NO: 18)

LC DNA Sequence

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTGGGAGACAGAG
TCACCGTCACTTGCCGGGCAAGTCAGGACATTAGAAATGATTTAGGCTGGTTTCA
GCAGAAACCAGGGAAAGCCCCTAAGCGCCTGATCTATGCTGCATCCAGTTTGA
AAGTGGGGTCCCATCAAGGTTTCAGCGGCAGTGGATCTGGGACAGACTTCACTCT
CACAATCAGCAGCCTGCAGCCTGAAGATTTTGCAACTTATTACTGTCTACAGTAT
AATAGTTACCCGTGGACGTTTCGGCCAAGGGACCAAGGTGGAAATCAAACGAACT
GTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTG
GAACTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGT
ACAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTAC
AGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCCTGACGCTGAG
CAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGG
CCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTTAG

(SEQ ID NO: 19)

LC Amino Acid Sequence

DIQMTQSPSSLSASVGDRVTVTCRASQDIRNDLGWFQQKPGKAPKRLIYAASSLQSG
VPSRFSGSGSGTDFTLTISSLQPEDFATYYCLQYNSTPWTFGQGTKVEIKRTVAAPSV
FIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDST
YLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC*

(SEQ ID NO: 20)

REGN14149

HCVR DNA Sequence

GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
 AGACTCTCCTGTGCAGCCTCTGGATTACCTTTACCACCTATGCCATGAGCTGGG
 TCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTCTCAGCTATTAGTGCTACTG
 GTAGTGGCACATACTATGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCAGAG
 AGAATTCCAAGAACACGCTGTATCTGCAAATGAAAAGCCTGAGAGCCGAGGACA
 CGGCCGTATATTACTGTGTGAAAGGTCCGTATAGTAACAGCCGGAACGTGGGCTT
 CCAGCACTGGGGCCAGGGCACCCCTGGTCACCGTCTCCTCA

(SEQ ID NO: 21)

HCVR Amino Acid Sequence

EVQLVESGGGLVQPGGSLRLSCAASGFTFTTYAMSWVRQAPGKGLEWVSAISATGS
 GTYYADSVKGRFTISRENSKNTLYLQMKSLRAEDTAVYYCVKGPYSNSRNVGFQH
 WGQGTLLTVSS

(SEQ ID NO: 22)

CDR1 DNA Sequence

GGA TTC ACC TTT ACC ACC TAT GCC

(SEQ ID NO: 23)

CDR1 Amino Acid Sequence

G F T F T T Y A

(SEQ ID NO: 24)

CDR2 DNA Sequence

ATT AGT GCT ACT GGT AGT GGC ACA

(SEQ ID NO: 25)

CDR2 Amino Acid Sequence

I S A T G S G T

(SEQ ID NO: 26)

CDR3 DNA Sequence

GTG AAA GGT CCG TAT AGT AAC AGC CGG AAC GTG GGC TTC CAG CAC

(SEQ ID NO: 27)

CDR3 Amino Acid Sequence

V K G P Y S N S R N V G F Q H

(SEQ ID NO: 28)

LCVR DNA Sequence

GATATTGTGATGACTCAGTCTCCACTCTCCCTGCCCCGTCACCCCTGGAGAGCCGG
CCTCCATCTCCTGCAGGTCTAGTCAGAGCCTCCTACATAGTAATGGATACAAC
TTTGGATTGGTACCTGCAGAAGCCAGGGCAGTCTCCACAACCTCTGATCTATTTG
GGTTCTAATCGGGCCTCCGGGGTCCCTGACAGGTTTCAGTGGCAGTGGATCAGGC
ACAGATTTTACACTGAAAATCAGCAGAGTGGAGGCTGAGGATGTTGGGGTTTATT
TCTGCATGCAACATCTACAACTCCCATGTACACTTTTGGCCAGGGGACCAAGCT
GGAGATCAAA

(SEQ ID NO: 29)

LCVR Amino Acid Sequence

DIVMTQSPLSLPVTGPGEPAISCRSSQSLLHSNGYNYLDWYLQKPGQSPQLLIYLGSN
RASGVDPDRFSGSGSGTDFTLKISRVEAEDVGVYFCMQHLQTPMYTFGQGGTKLEIK

(SEQ ID NO: 30)

CDR1 DNA Sequence

CAG AGC CTC CTA CAT AGT AAT GGA TAC AAC TAT

(SEQ ID NO: 31)

CDR1 Amino Acid Sequence

Q S L L H S N G Y N Y

(SEQ ID NO: 32)

CDR2 DNA Sequence

TTG GGT TCT

(SEQ ID NO: 33)

CDR2 Amino Acid Sequence

L G S

(SEQ ID NO: 34)

CDR3 DNA Sequence

ATG CAA CAT CTA CAA ACT CCC ATG TAC ACT

(SEQ ID NO: 35)

CDR3 Amino Acid Sequence

M Q H L Q T P M Y T

(SEQ ID NO: 36)

HC DNA Sequence

GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
AGACTCTCCTGTGCAGCCTCTGGATTACCTTTACCACCTATGCCATGAGCTGGG
TCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTCTCAGCTATTAGTGCTACTG
GTAGTGGCACATACTATGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCAGAG
AGAATTCCAAGAACACGCTGTATCTGCAAATGAAAAGCCTGAGAGCCGAGGACA
CGGCCGTATATTACTGTGTGAAAGGTCCGTATAGTAACAGCCGGAACGTGGGCTT
CCAGCACTGGGGCCAGGGCACCTGGTCACCGTCTCCTCAGCCTCCACCAAGGG
CCCATCGGTCTTCCCCCTGGCGCCCTGCTCCAGGAGCACCTCCGAGAGCACAGCC
GCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCTGTGGA
ACTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGCTGTCTACAGTCCTC
AGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGACG
AAGACCTACACCTGCAACGTAGATCACAAGCCCAGCAACACCAAGGTGGACAAG
AGAGTTGAGTCCAAATATGGTCCCCCATGCCCACCGTGCCCAGCACCACTGTGG
CAGGACCATCAGTCTTCTGTTCCCCCAAAACCCAAGGACACTCTCATGATCTC
CCGGACCCCTGAGGTCACGTGCGTGGTGGTGGACGTGAGCCAGGAAGACCCCGA
GGTCCAGTTCAACTGGTACGTGGATGGCGTGGAGGTGCATAATGCCAAGACAAA
GCCGCGGGAGGAGCAGTTCAACAGCACGTACCGTGTGGTCAGCGTCTCACCCT
CCTGCACCAGGACTGGCTGAACGGCAAGGAGTACAAGTGCAAGGTCTCCAACAA
AGGCCTCCCGTCTCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCG
AGAGCCACAGGTGTACACCCTGCCCCCATCCCAGGAGGAGATGACCAAGAACCA
GGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTACCCCAGCGACATCGCCGTGGAG
TGGGAGAGCAATGGGCAGCCGGAGAACAACACTACAAGACCACGCCTCCCGTGCTG
GACTCCGACGGCTCCTTCTTCTCTACAGCAGGCTCACCGTGGACAAGAGCAGGT
GGCAGGAGGGGAATGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACC
ACTACACACAGAAGTCCCTCTCCCTGTCTCTGGGTAAATGA

(SEQ ID NO: 37)

HC Amino Acid Sequence

EVQLVESGGGLVQPGGSLRLSCAASGFTFTTYAMSWVRQAPGKGLEWVSAISATGS
GTYTADSVKGRFTISRENSKNTLYLQMKSRLAEDTAVYYCVKGPYSNSRNVGFQH
WGQGLTVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGAL
TSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYG
PPCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVDVVSQEDPEVQFNWYVDG
VEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISK
AKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTP
PVLDSDDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK*

(SEQ ID NO: 38)

LC DNA Sequence

GATATTGTGATGACTCAGTCTCCACTCTCCCTGCCCCGTCACCCCTGGAGAGCCGG
CCTCCATCTCCTGCAGGTCTAGTCAGAGCCTCCTACATAGTAATGGATACAACATA
TTTGGATTGGTACCTGCAGAAGCCAGGGCAGTCTCCACAACCTCTGATCTATTTG
GGTTCTAATCGGGCCTCCGGGGTCCCTGACAGGTTTCAGTGGCAGTGGATCAGGC
ACAGATTTTACACTGAAAATCAGCAGAGTGGAGGCTGAGGATGTTGGGGTTTATT
TCTGCATGCAACATCTACAACTCCCATGTACACTTTTGGCCAGGGGACCAAGCT
GGAGATCAAACGAACTGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGAT
GAGCAGTTGAAATCTGGAAGTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATC
CCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAAC
CCCAGGAGAGTGTACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGC
AGCACCTGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGC
GAAGTCACCCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGA
GAGTGTTAG

(SEQ ID NO: 39)

LC Amino Acid Sequence

DIVMTQSPLSLPVTGPASISCRSSQSLHSNGYNYLDWYLQKPGQSPQLLIYLGSN
RASGVDPDRFSGSGSGTDFTLKISRVEAEDVGVYFCMQHLQTPMYTFGQGTKLEIKRT
VAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQ
DSKDSTYLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC*

(SEQ ID NO: 40)

REGN14150

HCVR DNA Sequence

CAGGTTACAGTGGTGCAGTCTGGAGCTGAGGTGAAGAAGCCTGGGGCCTCAGTG
AAAGTCTCCTGTAAGGCTTCTGGTTACACCTTTAGTAGCCATGGTATCACCTGGG
TGCGACAGGCCCTGGACAAGGGCTTGAGTGGATGGGATGGATCAGCGCTTATA
ATGGTGACACAACTATGCACAGAAAGTCCAGGGCAGAGTCACCATGACCACAG
ACACATCCACGAGTACAGCCTACATGGAAGTGGAGAGCCTGAGATCTGACGACA
CGGCCGTGTTTTACTGTGCGGATATAGGGGAATAGTAGGTCGTAATTACAATA
CTATGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCA

(SEQ ID NO: 41)

HCVR Amino Acid Sequence

QVQLVQSGAEVKKPGASVKVSCKASGYTFSSHGITWVRQAPGQGLEWMGWISAYN
GDTNYAQKVQGRVTMTTDTSTSTAYMELRSLRSDDTAVFYCARYRGIVGRNYNY
GMDVWGQGTTVTVSS

(SEQ ID NO: 42)

CDR1 DNA Sequence

GGT TAC ACC TTT AGT AGC CAT GGT

(SEQ ID NO: 43)

CDR1 Amino Acid Sequence

G Y T F S S H G

(SEQ ID NO: 44)

CDR2 DNA Sequence

ATC AGC GCT TAT AAT GGT GAC ACA

(SEQ ID NO: 45)

CDR2 Amino Acid Sequence

I S A Y N G D T

(SEQ ID NO: 46)

CDR3 DNA Sequence

GCG CGA TAT AGG GGA ATA GTA GGT CGT AAT TAC AAC TAC TAT GGT ATG
GAC GTC

(SEQ ID NO: 47)

CDR3 Amino Acid Sequence

A R Y R G I V G R N Y N Y Y G M D V

(SEQ ID NO: 48)

LCVR DNA Sequence

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGAGAGAG
TCACCATCACTTGCCGGGCAAGTCAGGACATTAGAAATGATTTAGGCTGGTATCA

GCAGAAACCAGGGAAAGCCCCTAAGCGCCTGATGTATGCTGCATCCAGTTTGCA
AAGTGGGGTCCCATCAAGGTTCAAGCGCAGTGGATCTGGGACAGAATTCCTCT
CACAATCAGCACCTGCAGCCTGAAGATTTTGCAACTTATTACTGTCTACAGCAT
AATAGTTACCCCCTCACTTTCGGCGGAGGGACCAAGGTGGAGATCAAA

(SEQ ID NO: 49)

LCVR Amino Acid Sequence

DIQMTQSPSSLSASVGERVTITCRASQDIRNDLGWYQQKPGKAPKRLMYAASSLQSG
VPSRFSGSGSGTEFTLTISTLQPEDFATYYCLQHNSYPLTFGGGTKVEIK

(SEQ ID NO: 50)

CDR1 DNA Sequence

CAG GAC ATT AGA AAT GAT

(SEQ ID NO: 11)

CDR1 Amino Acid Sequence

Q D I R N D

(SEQ ID NO: 12)

CDR2 DNA Sequence

GCT GCA TCC

(SEQ ID NO: 13)

CDR2 Amino Acid Sequence

A A S

(SEQ ID NO: 14)

CDR3 DNA Sequence

CTA CAG CAT AAT AGT TAC CCC CTC ACT

(SEQ ID NO: 51)

CDR3 Amino Acid Sequence

L Q H N S Y P L T

(SEQ ID NO: 52)

HC DNA Sequence

CAGGTT CAGCTGGTGCAGTCTGGAGCTGAGGTGAAGAAGCCTGGGGCCTCAGTG
AAAGTCTCCTGTAAGGCTTCTGGTTACACCTTTAGTAGCCATGGTATCACCTGGG
TGCGACAGGCCCCTGGACAAGGGCTTGAGTGGATGGGATGGATCAGCGCTTATA
ATGGTGACACAACTATGCACAGAAAGTCCAGGGCAGAGTCACCATGACCACAG
ACACATCCACGAGTACAGCCTACATGGAACTGAGGAGCCTGAGATCTGACGACA
CGGCCGTGTTTTACTGTGCGGATATAGGGGAATAGTAGGTCTGTAATTACAATA
CTATGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCAGCCTCC
ACCAAGGGCCCATCGGTCTTCCCCCTGGCGCCCTGCTCCAGGAGCACCTCCGAGA
GCACAGCCGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGG
TGTCGTGGAACCTCAGGCGCCCTGACCAGCGGCGTGACACCTTCCCGGCTGTCCT
ACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGC
TTGGGCACGAAGACCTACACCTGCAACGTAGATCACAAGCCCAGCAACACCAAG
GTGGACAAGAGAGTTGAGTCCAAATATGGTCCCCCATGCCCACCGTGCCCAGCA
CCACCTGTGGCAGGACCATCAGTCTTCCTGTTCCCCC AAAACCCAAGGACACTC
TCATGATCTCCCGGACCCCTGAGGTACGTGCGTGGTGGTGGACGTGAGCCAGG
AAGACCCCGAGGTCCAGTTCAACTGGTACGTGGATGGCGTGGAGGTGCATAATG
CCAAGACAAAGCCGCGGGAGGAGCAGTTCAACAGCACGTACCGTGTGGTCAGCG
TCCTCACCGTCTGCACCAGGACTGGCTGAACGGCAAGGAGTACAAGTGCAAGG

TCTCCAACAAAGGCCTCCCGTCCTCCATCGAGAAAACCATCTCCAAAGCCAAAG
GGCAGCCCCGAGAGCCACAGGTGTACACCCTGCCCCCATCCCAGGAGGAGATGA
CCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTACCCCAGCGACA
TCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACCTACAAGACCACG
CCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCTCTACAGCAGGCTCACCGTGG
ACAAGAGCAGGTGGCAGGAGGGGAATGTCTTCTCATGCTCCGTGATGCATGAGG
CTCTGCACAACCACTACACACAGAAGTCCCTCTCCCTGTCTCTGGGTAAATGA

(SEQ ID NO: 53)

HC Amino Acid Sequence

QVQLVQSGAEVKKPGASVKVSCKASGYTFSSHGITWVRQAPGQGLEWMGWISAYN
GDTNYAQKVQGRVTMTTDTSTSTAYMELRSLRSDDTAVFYCARYRGIVGRNYY
GMDVWVGQGTTVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSW
NSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGKTYTCNVDPKPSNTKVDKRV
ESKYGPPCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNW
YVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIE
KTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENN
YKTTTPVLDSGDSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLG
K*

(SEQ ID NO: 54)

LC DNA Sequence

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGAGAGAG
TCACCATCACTTGCCGGGCAAGTCAGGACATTAGAAATGATTTAGGCTGGTATCA
GCAGAAACCAGGGAAAGCCCCTAAGCGCCTGATGTATGCTGCATCCAGTTTGCA
AAGTGGGGTCCCATCAAGGTTCAAGCGCAGTGGATCTGGGACAGAATTCCTCT
CACAATCAGCACCCCTGCAGCCTGAAGATTTTGCAACTTATTACTGTCTACAGCAT
AATAGTTACCCCCTCACTTTCGGCGGAGGGACCAAGGTGGAGATCAAACGAACT
GTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTG

GAAC TGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGT
ACAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTAC
AGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCTGACGCTGAG
CAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGG
CCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTTAG

(SEQ ID NO: 55)

LC Amino Acid Sequence

DIQMTQSPSSLSASVGERVTITCRASQDIRNDLGWYQQKPGKAPKRLMYAASSLQSG
VPSRFSGSGSGTEFTLTISTLQPEDFATYYCLQHNSYPLTFGGGTKVEIKRTVAAPSVF
IFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDY
SLSSLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC*

(SEQ ID NO: 56)

REGN14151

HCVR DNA Sequence

CAGGTACAGCTGCAGCAGTCAGGTCCAGGACTGGTGAAGCCCTCGCAGACCCTC
TCACTCACCTGTGCCTTCTCCGGGGACAGTGTCTCTAGGAACAGTGCTGCTTGGA
ACTGGATCAGGCAGTCCCCATCGAGAGGCCTTGAGTGGCTGGGAAGGACATACT
ACAGGTCCAAGTGGTATAATGATTATGCAGTATCTGTGAAAAGTCGAATAACCAT
CAACCCAGACACAGCCAAGAACCAGTTCTCCCTGCAGCTGAAATCTGTGACTCCC
GAGGACACGGCTGTGTATTACTGTGCAAGAGAGGGGCCCTATTTGACTACTGG
GGCCAGGGAACCCTGGTCACCGTCTCCTCA

(SEQ ID NO: 57)

HCVR Amino Acid Sequence

QVQLQQSGPGLVKPSQTLSTCAFSGDSVSRNSAAWNWIRQSPSRGLEWLGRYYR
SKWYNDYAVSVKSRITINPD TAKNQFSLQLKSVTPEDTAVYYCAREGPYFDYWGQG
TLVTVSS

(SEQ ID NO: 58)

CDR1 DNA Sequence

GGG GAC AGT GTC TCT AGG AAC AGT GCT GCT

(SEQ ID NO: 59)

CDR1 Amino Acid Sequence

G D S V S R N S A A

(SEQ ID NO: 60)

CDR2 DNA Sequence

ACA TAC TAC AGG TCC AAG TGG TAT AAT

(SEQ ID NO: 61)

CDR2 Amino Acid Sequence

T Y Y R S K W Y N

(SEQ ID NO: 62)

CDR3 DNA Sequence

GCA AGA GAG GGG CCC TAT TTT GAC TAC

(SEQ ID NO: 63)

CDR3 Amino Acid Sequence

A R E G P Y F D Y

(SEQ ID NO: 64)

LCVR DNA Sequence

GACATCGTGATGACCCAGTCTCCAGACTCCCTGGCTGTGTCTCTGGGCGAGAGGG
CCACCATCAACTGCAAGTCCAGCCAGAGTGTTTTACACAGCTCCAACAATATGAA
CTACTTAGCTTGGTACCAGCAGAAACCAGGACAGCCTCCTAAGTTGCTCATTAC
TGGGCATCTACCCGGAAATCCGGGGTCCCTGACCGATTCAAGTGGCAGCGGGTCT
GGGACAGATTTCACTCTCACCATCAGCAGCCTTCAGGCTGCTGATGTGGCAGTTT
ATTACTGTCTGCAATATTATAATACTCCTCGAACGTTTCGGCCAAGGGACCAAGGT
GGAAATCAAA

(SEQ ID NO: 65)

LCVR Amino Acid Sequence

DIVMTQSPDSLAVSLGERATINCKSSQSVLHSSNNMNYLAWYQQKPGQPPKLLIYW
ASTRKSGVPDRFSGSGSGTDFTLTISSLQAADVAVYYCLQYYNTPRTFGQGTKVEIK

(SEQ ID NO: 66)

CDR1 DNA Sequence

CAG AGT GTT TTA CAC AGC TCC AAC AAT ATG AAC TAC

(SEQ ID NO: 67)

CDR1 Amino Acid Sequence

Q S V L H S S N N M N Y

(SEQ ID NO: 68)

CDR2 DNA Sequence

TGG GCA TCT

(SEQ ID NO: 69)

CDR2 Amino Acid Sequence

W A S

(SEQ ID NO: 70)

CDR3 DNA Sequence

CTG CAA TAT TAT AAT ACT CCT CGA ACG

(SEQ ID NO: 71)

CDR3 Amino Acid Sequence

L Q Y Y N T P R T

(SEQ ID NO: 72)

HC DNA Sequence

CAGGTACAGCTGCAGCAGTCAGGTCCAGGACTGGTGAAGCCCTCGCAGACCCTC
TCACTCACCTGTGCCTTCTCCGGGGACAGTGTCTCTAGGAACAGTGCTGCTTGGA
ACTGGATCAGGCAGTCCCCATCGAGAGGCCTTGAGTGGCTGGGAAGGACATACT
ACAGGTCCAAGTGGTATAATGATTATGCAGTATCTGTGAAAAGTCGAATAACCAT
CAACCCAGACACAGCCAAGAACCAGTTCTCCCTGCAGCTGAAATCTGTGACTCCC
GAGGACACGGCTGTGTATTACTGTGCAAGAGAGGGGCCCTATTTGACTACTGG
GGCCAGGGAACCCTGGTCACCGTCTCCTCAGCCTCCACCAAGGGCCCATCGGTCT
TCCCCCTGGCGCCCTGCTCCAGGAGCACCTCCGAGAGCACAGCCGCCCTGGGCTG
CCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCGTGGAATCAGGCGC

CCTGACCAGCGGCGTGACACACCTTCCC GGCTGTCCTACAGTCCTCAGGACTCTAC
TCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACGAAGACCTAC
ACCTGCAACGTAGATCACAAAGCCCAGCAACACCAAGGTGGACAAGAGAGTTGAG
TCCAAATATGGTCCCCCATGCCCACCGTGCCCAGCACCACTGTGGCAGGACCAT
CAGTCTTCCTGTTCCCCCAAAACCCAAGGACACTCTCATGATCTCCCGGACCCC
TGAGGTCACGTGCGTGGTGGTGGACGTGAGCCAGGAAGACCCCGAGGTCCAGTT
CAACTGGTACGTGGATGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGA
GGAGCAGTTCAACAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAG
GACTGGCTGAACGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGGCCTCCCG
TCCTCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAGCCACAG
GTGTACACCTGCCCCCATCCCAGGAGGAGATGACCAAGAACCAGGTCAGCCTG
ACCTGCCTGGTCAAAGGCTTCTACCCAGCGACATCGCCGTGGAGTGGGAGAGC
AATGGGCAGCCGGAGAACAACACTACAAGACCACGCCTCCCGTGCTGGACTCCGAC
GGCTCCTTCTTCTCTACAGCAGGCTCACCGTGGACAAGAGCAGGTGGCAGGAG
GGGAATGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACAC
AGAAGTCCCTCTCCCTGTCTCTGGGTAAATGA

(SEQ ID NO: 73)

HC Amino Acid Sequence

QVQLQQSGPGLVKPSQTLSTLCAFSGDSVSRNSAAWNWIRQSPSRGLEWLGRYYR
SKWYNDYAVSVKSRITINPDTAKNQFSLQLKSVTPEDTAVYYCAREGPYFDYWGQG
TLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVH
TFPAVLQSSGLYSLSSVTVPSSSLGKTYTCNVDPKPSNTKVDKRVERSKYGPPCPPC
PAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNA
KTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPR
EPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSD
GSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK*

(SEQ ID NO: 74)

LC DNA Sequence

GACATCGTGATGACCCAGTCTCCAGACTCCCTGGCTGTGTCTCTGGGCGAGAGGG
CCACCATCAACTGCAAGTCCAGCCAGAGTGTTTTACACAGCTCCAACAATATGAA
CTACTTAGCTTGGTACCAGCAGAAACCAGGACAGCCTCCTAAGTTGCTCATTAC
TGGGCATCTACCCGGAAATCCGGGGTCCCTGACCGATTCAAGTGGCAGCGGGTCT
GGGACAGATTTCACTCTCACCATCAGCAGCCTTCAGGCTGCTGATGTGGCAGTTT
ATTACTGTCTGCAATATTATAATACTCCTCGAACGTTTCGGCCAAGGGACCAAGGT
GGAAATCAAACGAACTGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGAT
GAGCAGTTGAAATCTGGAAGTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATC
CCAGAGAGGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAACT
CCCAGGAGAGTGTACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGC
AGCACCTTGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGC
GAAGTCACCCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGA
GAGTGTTAG

(SEQ ID NO: 75)

LC Amino Acid Sequence

DIVMTQSPDSLAVSLGERATINCKSSQSVLHSSNMNYLAWYQQKPGQPPKLLIYW
ASTRKSQVDFRFSGSGSGTDFTLTISLQAADVAVYYCLQYYNTPRTFGQGTKVEIK
RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVT
EQDSKDSTYLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC*

(SEQ ID NO: 76)

REGN14152

HCVR DNA Sequence

GAGGTGCAGCTGGTGGAGTCTGAGGGAGGCTGGGTACAGCCTGGGGGGTCCCTG
AGACTCTCCTGTGCAGCCTCTGGAATCACCTTTAGCATCTATGCCATGGCCTGGG
TCCGCCAGGCTCCAGGGAAGGGACTTGAGTGGGTCTCAACTATTAGTGGTAGTG
GTGATTCCACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCAGAGA

CAATTCCAAGAACACGCTGTTTCTGCAAATGAACAGCCTGAGAGCCGTGGACAC
GGCCATATATTACTGTGCGAAAAGAGGATTTGCAGCTTTTGA CTACTGGGGCCAG
GGAACCCTGGTCACCGTCTCCTCA

(SEQ ID NO: 77)

HCVR Amino Acid Sequence

EVQLVESEGGWVQPGGSLRLSCAASGITFSIYAMAWVRQAPGKGLEWVSTISGSGDS
TYYADSVKGRFTISRDN SKNTLFLQMNSLR AVDTAIYYCAKRGFAAFDYWGQGT LV
TVSS

(SEQ ID NO: 78)

CDR1 DNA Sequence

GGA ATC ACC TTT AGC ATC TAT GCC

(SEQ ID NO: 79)

CDR1 Amino Acid Sequence

G I T F S I Y A

(SEQ ID NO: 80)

CDR2 DNA Sequence

ATT AGT GGT AGT GGT GAT TCC ACA

(SEQ ID NO: 81)

CDR2 Amino Acid Sequence

I S G S G D S T

(SEQ ID NO: 82)

CDR3 DNA Sequence

GCG AAA AGA GGA TTT GCA GCT TTT GAC TAC

(SEQ ID NO: 83)

CDR3 Amino Acid Sequence

A K R G F A A F D Y

(SEQ ID NO: 84)

LCVR DNA Sequence

GAAATTGTGTTGACGCAGTCTCCAGGCACCCTGTCTTTGTCTCCAGGGGAAAGAG
CCACCCTCTCCTGTAGGGCCAGTCAGAGTGTTAGCAGCACCTACTTAGCCTGGTA
CCAGCAGAAACCTGGCCAGTCTCCAGGCTCCTCATCTATGGTGCATCAAACAGG
GCCACTGGCATCCCAGACAGGTTCAGTGGCAGTGGGTCTGGGACAGACTTCACT
CTCACCATCAGCAGACTGGAGCCTGAAGATTTTGCAGTGTATTACTGTCAGCAGT
ATGGTAGCTCACGTCTGCTCAGTTTCGGCGGAGGGACCAAGGTGGAGATCAAA

(SEQ ID NO: 85)

LCVR Amino Acid Sequence

EIVLTQSPGTLSSLSPGERATLSCRASQSVSSTYLAWYQQKPGQSPRLLIYGASNRATGI
PDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYGSSRLLSFGGGTKVEIK

(SEQ ID NO: 86)

CDR1 DNA Sequence

CAG AGT GTT AGC AGC ACC TAC

(SEQ ID NO: 87)

CDR1 Amino Acid Sequence

Q S V S S T Y

(SEQ ID NO: 88)

CDR2 DNA Sequence

GGT GCA TCA

(SEQ ID NO: 89)

CDR2 Amino Acid Sequence

G A S

(SEQ ID NO: 90)

CDR3 DNA Sequence

CAG CAG TAT GGT AGC TCA CGT CTG CTC AGT

(SEQ ID NO: 91)

CDR3 Amino Acid Sequence

Q Q Y G S S R L L S

(SEQ ID NO: 92)

HC DNA Sequence

GAGGTGCAGCTGGTGGAGTCTGAGGGAGGCTGGGTACAGCCTGGGGGGTCCCTG
AGACTCTCCTGTGCAGCCTCTGGAATCACCTTTAGCATCTATGCCATGGCCTGGG
TCCGCCAGGCTCCAGGGAAGGGACTTGAGTGGGTCTCAACTATTAGTGGTAGTG

GTGATTCCACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCAGAGA
CAATTCCAAGAACACGCTGTTTCTGCAAATGAACAGCCTGAGAGCCGTGGACAC
GGCCATATATTACTGTGCGAAAAGAGGATTTGCAGCTTTTGACTACTGGGGCCAG
GGAACCCTGGTCACCGTCTCCTCAGCCTCCACCAAGGGCCCATCGGTCTTCCCCC
TGGCGCCCTGCTCCAGGAGCACCTCCGAGAGCACAGCCGCCCTGGGCTGCCTGG
TCAAGGACTACTTCCCCGAACCGGTGACGGTGTCTGTGGAATCAGGCGCCCTGA
CCAGCGGCGTGCACACCTTCCCCGGCTGTCTACAGTCTCAGGACTCTACTCCCT
CAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACGAAGACCTACACCTG
CAACGTAGATCACAAGCCCAGCAACACCAAGGTGGACAAGAGAGTTGAGTCCAA
ATATGGTCCCCCATGCCACCGTGCCAGCACCACCTGTGGCAGGACCATCAGTC
TTCCTGTTCCCCCAAACCCAAAGGACACTCTCATGATCTCCCGGACCCCTGAGG
TCACGTGCGTGGTGGTGGACGTGAGCCAGGAAGACCCCGAGGTCCAGTTCAACT
GGTACGTGGATGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAG
CAGTTCAACAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACT
GGCTGAACGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGGCCTCCCGTCCT
CCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAGCCACAGGTGT
ACACCCTGCCCCCATCCCAGGAGGAGATGACCAAGAACCAGGTGAGCCTGACCT
GCCTGGTCAAAGGCTTCTACCCAGCGACATCGCCGTGGAGTGGGAGAGCAATG
GGCAGCCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGCT
CCTTCTTCTCTACAGCAGGCTCACCGTGGACAAGAGCAGGTGGCAGGAGGGGA
ATGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACACAGAA
GTCCCTCTCCCTGTCTCTGGGTAAATGA

(SEQ ID NO: 93)

HC Amino Acid Sequence

EVQLVESEGGWVQPGGSLRLSCAASGITFSIYAMAWVRQAPGKGLEWVSTISGSGDS
TYYADSVKGRFTISRDN SKNTLFLQMNSLRAVDTAIYYCAKRGFAAFDYWGQGLTV
TVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFP
AVLQSSGLYSLSSVVTVPSSSLGTKYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAP
PVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKT

KPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREP
QVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGS
FFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLGLK*

(SEQ ID NO: 94)

LC DNA Sequence

GAAATTGTGTTGACGCAGTCTCCAGGCACCCTGTCTTTGTCTCCAGGGGAAAGAG
CCACCCTCTCCTGTAGGGCCAGTCAGAGTGTTAGCAGCACCTACTTAGCCTGGTA
CCAGCAGAAACCTGGCCAGTCTCCCAGGCTCCTCATCTATGGTGCATCAAACAGG
GCCACTGGCATCCCAGACAGGTTTCAGTGGCAGTGGGTCTGGGACAGACTTCACT
CTCACCATCAGCAGACTGGAGCCTGAAGATTTTGCAGTGTATTACTGTCAGCAGT
ATGGTAGCTCACGTCTGCTCAGTTTCGGCGGAGGGACCAAGGTGGAGATCAAAC
GAACTGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAA
ATCTGGAAGTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCC
AAAGTACAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAGT
GTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCTGACG
CTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCAT
CAGGGCCTGAGCTCGCCCGTCAAAAGAGCTTCAACAGGGGAGAGTGTTAG

(SEQ ID NO: 95)

LC Amino Acid Sequence

EIVLTQSPGTLSSLSPGERATLSCRASQSVSSTYLAWYQQKPGQSPRLLIYGASNRATGI
PDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYGSSRLLSFGGGTKVEIKRTVAAPSVF
IFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTY
SLSSLTLSKADYEKHKVYACEVTHQGLSPVTKSFNRGEC*

(SEQ ID NO: 96)

REGN14153

HCVR DNA Sequence

GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
 AGACTCTCCTGTGCAGCCTCTGGATTACCTTTAGTAGTTATGCCATGAACTGGG
 TCCGCCAGGCTCCAGGGGAGGGCCTGGAGTGGGTCTCAACTTTGACTGGTAGTG
 GTGGTAGTACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCAGAG
 ACAATTCCAAGAACACGCTGTTTCTGCACATGAGCAGCCTGAGAGCCGAGGACA
 CGGCCGTATATTACTGTGCGAAAGGTGGAGTGGGATCTACTAAGGTTGTCTACTA
 CGGTTTGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCA

(SEQ ID NO: 97)

HCVR Amino Acid Sequence

EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYAMNWVRQAPGEGLEWVSTLTGSGG
 STYYADSVKGRFTISRDN SKNTLFLHMS SLRAEDTAVYYCAKGGVGSTKV VYYGLD
 VWGQGTTVTVSS

(SEQ ID NO: 98)

CDR1 DNA Sequence

GGA TTC ACC TTT AGT AGT TAT GCC

(SEQ ID NO: 99)

CDR1 Amino Acid Sequence

G F T F S S Y A

(SEQ ID NO: 100)

CDR2 DNA Sequence

TTG ACT GGT AGT GGT GGT AGT ACA

(SEQ ID NO: 101)

CDR2 Amino Acid Sequence

L T G S G G S T

(SEQ ID NO: 102)

CDR3 DNA Sequence

GCG AAA GGT GGA GTG GGA TCT ACT AAG GTT GTC TAC TAC GGT TTG GAC
GTC

(SEQ ID NO: 103)

CDR3 Amino Acid Sequence

A K G G V G S T K V V Y Y G L D V

(SEQ ID NO: 104)

LCVR DNA Sequence

GATATTGTGATGACTCAGTCTCCACTTTCCTGCCCCGTCATCCCTGGAGAGCCGG
CCTCCATCTCCTGCAGGTCTAGTCAGAGCCTCCTGCATCGTAATGGATACAACCTT
TTTGGATTGGTACCTGCGGAAGCCAGGGCAGTCTCCACAGCTCCTGATCTATTTG
GGTTCTAATCGGGCCTCCGGGGTCCCTGACAGGTTTCAGTGGCAGTGGATCAGGC
ACAGATTTTACACTGAAAATCAGCAGAGTGGAGGCTGAGGATGTTGGGGTTTATT
ACTGCATGCAAGCTCTACAACTCCGCTCACTTTCGGCGGAGGGACCAAGGTGG
AGATCAAA

(SEQ ID NO: 105)

LCVR Amino Acid Sequence

DIVMTQSPLSLPVIPGEPASISCRSSQSLHRNGYNFLDWYLRKPGQSPQLLIYLGSNR
ASGVDPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQALQTPLTFGGGTKVEIK

(SEQ ID NO: 106)

CDR1 DNA Sequence

CAG AGC CTC CTG CAT CGT AAT GGA TAC AAC TTT

(SEQ ID NO: 107)

CDR1 Amino Acid Sequence

Q S L L H R N G Y N F

(SEQ ID NO: 108)

CDR2 DNA Sequence

TTG GGT TCT

(SEQ ID NO: 33)

CDR2 Amino Acid Sequence

L G S

(SEQ ID NO: 34)

CDR3 DNA Sequence

ATG CAA GCT CTA CAA ACT CCG CTC ACT

(SEQ ID NO: 109)

CDR3 Amino Acid Sequence

M Q A L Q T P L T

(SEQ ID NO: 110)

HC DNA Sequence

GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
AGACTCTCCTGTGCAGCCTCTGGATTACCTTTAGTAGTTATGCCATGAACTGGG
TCCGCCAGGCTCCAGGGGAGGGCTGGAGTGGGTCTCAACTTTGACTGGTAGTG
GTGGTAGTACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCAGAG
ACAATTCCAAGAACACGCTGTTTCTGCACATGAGCAGCCTGAGAGCCGAGGACA
CGGCCGTATATTACTGTGCGAAAGGTGGAGTGGGATCTACTAAGGTTGTCTACTA
CGGTTTGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCAGCCTCCACC
AAGGGCCCATCGGTCTTCCCCCTGGCGCCCTGCTCCAGGAGCACCTCCGAGAGCA
CAGCCGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTC
GTGGAAGTCAGGCGCCCTGACCAGCGGCGTGACACCTTCCCGGCTGTCCTACAG
TCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGG
GCACGAAGACCTACACCTGCAACGTAGATCACAAGCCCAGCAACACCAAGGTGG
ACAAGAGAGTTGAGTCCAAATATGGTCCCCCATGCCCACCGTGCCCAGCACCAC
CTGTGGCAGGACCATCAGTCTTCCTGTTCCCCCAAACCCAAGGACACTCTCAT
GATCTCCCGGACCCCTGAGGTCACGTGCGTGGTGGTGGACGTGAGCCAGGAAGA
CCCCGAGGTCCAGTTCAACTGGTACGTGGATGGCGTGGAGGTGCATAATGCCAA
GACAAAGCCGCGGGAGGAGCAGTTCAACAGCACGTACCGTGTGGTCAGCGTCCT
CACCGTCCTGCACCAGGACTGGCTGAACGGCAAGGAGTACAAGTGCAAGGTCTC
CAACAAAGGCCTCCCGTCCTCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCA
GCCCCGAGAGCCACAGGTGTACACCCTGCCCCCATCCCAGGAGGAGATGACCAA
GAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTACCCCAGCGACATCGCC
GTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACACTACAAGACCACGCCTCC
CGTGCTGGACTCCGACGGCTCCTTCTTCTCTACAGCAGGCTCACCGTGGACAAG
AGCAGGTGGCAGGAGGGGAATGTCTTCTCATGCTCCGTGATGCATGAGGCTCTG
CACAACCACTACACACAGAAGTCCCTCTCCCTGTCTCTGGGTAAATGA

(SEQ ID NO: 111)

HC Amino Acid Sequence

EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYAMNWVRQAPGEGLEWVSTLTGSGG
STYYADSVKGRFTISRDN SKNTLFLHMSSLRAEDTAVYYCAKGGVGSTKVVYYGLD
VWGQGTTVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGA
LTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKYTCNV DHKPSNTKVDKRVESKY
GPPCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVD
GVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTIS
KAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
TPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSV MHEALHNHYTQKSLSLGLGK*

(SEQ ID NO: 112)

LC DNA Sequence

GATATTGTGATGACTCAGTCTCCACTTTCCCTGCCCCGTCATCCCTGGAGAGCCGG
CCTCCATCTCCTGCAGGTCTAGTCAGAGCCTCCTGCATCGTAATGGATACAACTT
TTTGGATTGGTACCTGCGGAAGCCAGGGCAGTCTCCACAGCTCCTGATCTATTTG
GGTTCTAATCGGGCCTCCGGGGTCCCTGACAGGTTCA GTGGCAGTGGATCAGGC
ACAGATTTTACACTGAAAATCAGCAGAGTGGAGGCTGAGGATGTTGGGGTTTATT
ACTGCATGCAAGCTCTACAACTCCGCTCACTTTTCGGCGGAGGGACCAAGGTGG
AGATCAAACGAAGTGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGA
GCAGTTGAAATCTGGAAGTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCC
AGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCC
CAGGAGAGTGTACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAG
CACCTGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGA
AGTCACCCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGA
GTGTTAG

(SEQ ID NO: 113)

LC Amino Acid Sequence

DIVMTQSPLSLPVIPGEPASISCRSSQSLLHRNGYNFLDWYLRKPGQSPQLLIYLGSNR
ASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQALQTPLTFGGGTKVEIKRTVA
APSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDS
KDSTYLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC*

(SEQ ID NO: 114)

REGN14154

HCVR DNA Sequence

CAGCTGCAGCTGCAGGAGTCGGGCCCAGGACTGGTGAAGCCTTCGGAGACCCTG
TCCCTCACTTGCACTGTCTCGGGTGGCTCCAGCAGCAGAAGTAGTTACTACTGGG
GCTGGATCCGCCAGCCCCAGGGAAGGGACTGGAGTGGATTGGGAGTATCTATT
ATAGTGGGAACACCTACTACAACCCGTCCCTCCAGAGTCGAGTCACCATATCCGT
AGACACGTCCAAGAACCAGTTCTCCCTGAACTGAACTCTGTGACCGCCGCAGA
CACGGCTGTATTTTATTGTGCGAGACACAAACCTACTACGTGGGCTTTTGATATC
TGGGGCCAAGGGACAATGGTCACCGTCTCTTCA

(SEQ ID NO: 115)

HCVR Amino Acid Sequence

QLQLQESGPGLVKPSETLSLTCTVSGGSSSRSSYYWGWIRQPPGKLEWIGSIYYSGN
TYYNPSLQSRVTISVDTSKNQFSLKLNSVTAADTAVFYCARHKPTTWAFDIWGQGT
MVTVSS

(SEQ ID NO: 116)

CDR1 DNA Sequence

GGT GGC TCC AGC AGC AGA AGT AGT TAC TAC

(SEQ ID NO: 117)

CDR1 Amino Acid Sequence

G G S S S R S S Y Y

(SEQ ID NO: 118)

CDR2 DNA Sequence

ATC TAT TAT AGT GGG AAC ACC

(SEQ ID NO: 119)

CDR2 Amino Acid Sequence

I Y Y S G N T

(SEQ ID NO: 120)

CDR3 DNA Sequence

GCG AGA CAC AAA CCT ACT ACG TGG GCT TTT GAT ATC

(SEQ ID NO: 121)

CDR3 Amino Acid Sequence

A R H K P T T W A F D I

(SEQ ID NO: 122)

LCVR DNA Sequence

GACATCCAGATGACCCAGTCTCCTTCCACCCTGTCTGCATCTGTAGGAGACAGAG
TCACCATCACTTGCCGGGCCAGTCAGAGTATCAGTAGTTGGTTGGCCTGGTATCA
GCAGAAACCAGGGAAAGTCCCAAAGTTGCTGATCTATAAGGCGTCTAATTTAGA
AAGTGGGGTCCCCTCAAGGTTTCAGCGGCAGTGGATCTGGGACAGAATTCCTCT

CACCATCAGCGACCTGCAGCCTGATGATTTTGCAAGTTATTACTGCCAACAGTAT
AGTACTTATTCTCGGACGTTTCGGCCGAGGGACCAAGGTGGAGATCAA

(SEQ ID NO: 123)

LCVR Amino Acid Sequence

DIQMTQSPSTLSASVGDRVTITCRASQSISSWLAWYQQKPGKVPKLLIYKASNLESGV
PSRFSGSGSGTEFTLTISDLQPDDFASYCQQYSTYSRTFGRGTKVEIK

(SEQ ID NO: 124)

CDR1 DNA Sequence

CAG AGT ATC AGT AGT TGG

(SEQ ID NO: 125)

CDR1 Amino Acid Sequence

Q S I S S W

(SEQ ID NO: 126)

CDR2 DNA Sequence

AAG GCG TCT

(SEQ ID NO: 127)

CDR2 Amino Acid Sequence

K A S

(SEQ ID NO: 128)

CDR3 DNA Sequence

CAA CAG TAT AGT ACT TAT TCT CGG ACG

(SEQ ID NO: 129)

CDR3 Amino Acid Sequence

Q Q Y S T Y S R T

(SEQ ID NO: 130)

HC DNA Sequence

CAGCTGCAGCTGCAGGAGTCGGGCCCAGGACTGGTGAAGCCTTCGGAGACCCTG
TCCCTCACTTGCACTGTCTCGGGTGGCTCCAGCAGCAGAAGTAGTTACTACTGGG
GCTGGATCCGCCAGCCCCAGGGAAGGGACTGGAGTGGATTGGGAGTATCTATT
ATAGTGGGAACACCTACTACAACCCGTCCCTCCAGAGTCGAGTCACCATATCCGT
AGACACGTCCAAGAACCAGTTCTCCCTGAAACTGAACTCTGTGACCGCCGCAGA
CACGGCTGTATTTTATTGTGCGAGACACAAACCTACTACGTGGGCTTTTGATATC
TGGGGCCAAGGGACAATGGTCACCGTCTCTTCAGCCTCCACCAAGGGCCCATCG
GTCTTCCCCCTGGCGCCCTGCTCCAGGAGCACCTCCGAGAGCACAGCCGCCCTGG
GCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCTGTGGAACCTCAG
GCGCCCTGACCAGCGCGTGCACACCTTCCCGGCTGTCTACAGTCCTCAGGACT
CTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACGAAGACC
TACACCTGCAACGTAGATCACAAGCCCAGCAACACCAAGGTGGACAAGAGAGTT
GAGTCCAAATATGGTCCCCCATGCCCACCGTGCCCAGCACCACTGTGGCAGGA
CCATCAGTCTTCCTGTTCCCCCAAACCCAAGGACACTCTCATGATCTCCCGGA
CCCCTGAGGTCACGTGCGTGGTGGTGGACGTGAGCCAGGAAGACCCCGAGGTCC
AGTTCAACTGGTACGTGGATGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGC
GGGAGGAGCAGTTCAACAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGC
ACCAGGACTGGCTGAACGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGGCC
TCCCGTCCTCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAGC
CACAGGTGTACACCCTGCCCCCATCCCAGGAGGAGATGACCAAGAACCAGGTCA

GCCTGACCTGCCTGGTCAAAGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGG
AGAGCAATGGGCAGCCGGAGAACAACACTACAAGACCACGCCTCCCGTGCTGGACT
CCGACGGCTCCTTCTTCCTCTACAGCAGGCTCACCGTGGACAAGAGCAGGTGGCA
GGAGGGGAATGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTAC
ACACAGAAGTCCCTCTCCCTGTCTCTGGGTAAATGA

(SEQ ID NO: 131)

HC Amino Acid Sequence

QLQLQESGPGLVKPSETLSLTCTVSGGSSSRSSYYWGWIRQPPGKLEWIGSIYYSGN
TYYNPSLQSRVTISVDTSKNQFSLKLN SVTAADTAVFYCARHKPTTWAFDIWQQGT
MVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVH
TFPAVLQSSGLYSLSSVTVPSSSLGKTYTCNV DHKPSNTKVDKRVESKYGPPCPPC
PAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNA
KTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPR
EPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSD
GSFFLYSRLTVDKSRWQEGNVFSCSV MHEALHNHYTQKSLSLSLGK*

(SEQ ID NO: 132)

LC DNA Sequence

GACATCCAGATGACCCAGTCTCCTTCCACCCTGTCTGCATCTGTAGGAGACAGAG
TCACCATCACTTGCCGGGCCAGTCAGAGTATCAGTAGTTGGTTGGCCTGGTATCA
GCAGAAACCAGGGAAAGTCCCAAAGTTGCTGATCTATAAGGCGTCTAATTTAGA
AAGTGGGGTCCCCTCAAGGTTCAAGCGGCAGTGGATCTGGGACAGAATTCCTCT
CACCATCAGCGACCTGCAGCCTGATGATTTTGCAAGTTATTACTGCCAACAGTAT
AGTACTTATTCTCGGACGTTTCGGCCGAGGGACCAAGGTGGAGATCAAACGAACT
GTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTG
GAACTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGT
ACAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTAC
AGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCTGACGCTGAG

CAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGG
CCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTTAG

(SEQ ID NO: 133)

LC Amino Acid Sequence

DIQMTQSPSTLSASVGDRVITICRASQSISSWLAWYQQKPGKVPKLLIYKASNLESGV
PSRFSGSGSGTEFTLTISDLQPDDFASYCQQYSTYSRTFGRGTKVEIKRTVAAPSVFI
FPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTY
SLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC*

(SEQ ID NO: 134)

REGN14155

HCVR DNA Sequence

CAGGTTACAGTGGTGCAGTCTGGAGGTGAGGTGAAGAAGCCTGGGGACTCAGTG
AAGGTCTCCTGCAAGGCTTCTGGTTACACCTTTACCAGCTATGGTATCAGCTGGG
TGCGACAGGCCCCTGGACAAGGGCTTGAGTGGATGGGATGGATCAGCGTCTACA
GTGGTAAAAAAACTACGCACGGAAGGTCCAGGACAGAGTCACCATGACCACA
GACACATCCACGAGCACAGCCTACATGGAGGTGAGGAGCCTGCGATCTGACGAC
ACGGCCATATATTATTGTACAAGAAGGGGAGTGTCTTCGATGGTCGGTGCTTTTG
AAATCTGGGGCCAAGGGACAATGGTCAACCGTCTCTTCA

(SEQ ID NO: 135)

HCVR Amino Acid Sequence

QVQLVQSGGEVKKPGDSVKVSKASGYTFTSYGISWVRQAPGQGLEWMGWISVYS
GKKNYARKVQDRVMTTDTSTSTAYMEVRSLRSDDTAIYYCTRRGVSSMVGAFEI
WGQGTMTVTVSS

(SEQ ID NO: 136)

CDR1 DNA Sequence

GGT TAC ACC TTT ACC AGC TAT GGT

(SEQ ID NO: 137)

CDR1 Amino Acid Sequence

G Y T F T S Y G

(SEQ ID NO: 138)

CDR2 DNA Sequence

ATC AGC GTC TAC AGT GGT AAA AAA

(SEQ ID NO: 139)

CDR2 Amino Acid Sequence

I S V Y S G K K

(SEQ ID NO: 140)

CDR3 DNA Sequence

ACA AGA AGG GGA GTG TCT TCG ATG GTC GGT GCT TTT GAA ATC

(SEQ ID NO: 141)

CDR3 Amino Acid Sequence

T R R G V S S M V G A F E I

(SEQ ID NO: 142)

LCVR DNA Sequence

GAAATTGTGTTGACGCAGTCTCCAGGCATTCTGTCTTTGTCTCCAGGGGAAAGAG
CCACCCTCTCCTGCAAGGCCAGTCAGAGTGTTAGCAACAGCTACTTAGCCTGGTA
CCAGCAGAAACCTGGCCAGGCTCCCAGGCTCCTCATCTATGGAGCATCTAGTAG
GGCCACTGGCATCCCAGACAGGTTCAGTGGCAGTGGGTCTGGGACAGACTTCAC
TGTCACCATCAGCAGACTGGAGCCTGAAGATTTTGCAGTCTATTACTGTCAGCAG
TATGGTAGCTCACCGCTCACTTTCGGCGGAGGGACCAAGGTGGAGATCAAA

(SEQ ID NO: 143)

LCVR Amino Acid Sequence

EIVLTQSPGILSLSPGERATLSCKASQSVSNSYLAWYQQKPGQAPRLLIYGASSRATGI
PDRFSGSGSGTDFTVTISRLEPEDFAVYYCQQYGSSPLTFGGGTKVEIK

(SEQ ID NO: 144)

CDR1 DNA Sequence

CAG AGT GTT AGC AAC AGC TAC

(SEQ ID NO: 145)

CDR1 Amino Acid Sequence

Q S V S N S Y

(SEQ ID NO: 146)

CDR2 DNA Sequence

GGA GCA TCT

(SEQ ID NO: 147)

CDR2 Amino Acid Sequence

G A S

(SEQ ID NO: 90)

CDR3 DNA Sequence

CAG CAG TAT GGT AGC TCA CCG CTC ACT

(SEQ ID NO: 148)

CDR3 Amino Acid Sequence

Q Q Y G S S P L T

(SEQ ID NO: 149)

HC DNA Sequence

CAGGTTACAGCTGGTGCAGTCTGGAGGTGAGGTGAAGAAGCCTGGGGACTCAGTG
AAGGTCTCCTGCAAGGCTTCTGGTTACACCTTTACCAGCTATGGTATCAGCTGGG
TGCGACAGGCCCCTGGACAAGGGCTTGAGTGGATGGGATGGATCAGCGTCTACA
GTGGTAAAAAACTACGCACGGAAGGTCCAGGACAGAGTCACCATGACCACA
GACACATCCACGAGCACAGCCTACATGGAGGTGAGGAGCCTGCGATCTGACGAC
ACGGCCATATATTATTGTACAAGAAGGGGAGTGTCTTCGATGGTCGGTGCTTTTG
AAATCTGGGGCCAAGGGACAATGGTCAACGTCTCTTCAGCCTCCACCAAGGGCC
CATCGGTCTTCCCCCTGGCGCCCTGCTCCAGGAGCACCTCCGAGAGCACAGCCGC
CCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCGTGGAAC
TCAGGCGCCCTGACCAGCGGCGTGACACCTTCCCGGCTGTCCTACAGTCCTCAG
GACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACGAA
GACCTACACCTGCAACGTAGATCACAAGCCCAGCAACACCAAGGTGGACAAGAG
AGTTGAGTCCAAATATGGTCCCCCATGCCCACCGTGCCCAGCACCACTGTGGCA
GGACCATCAGTCTTCTGTTCCCCCAAAACCAAGGACACTCTCATGATCTCCC
GGACCCCTGAGGTACGTGCGTGGTGGTGGACGTGAGCCAGGAAGACCCCGAGG

TCCAGTTCAACTGGTACGTGGATGGCGTGGAGGTGCATAATGCCAAGACAAAGC
CGCGGGAGGAGCAGTTCAACAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCC
TGCACCAGGACTGGCTGAACGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAG
GCCTCCCGTCCTCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAG
AGCCACAGGTGTACACCCTGCCCCCATCCCAGGAGGAGATGACCAAGAACCAGG
TCAGCCTGACCTGCCTGGTCAAAGGCTTCTACCCCAGCGACATCGCCGTGGAGTG
GGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGA
CTCCGACGGCTCCTTCTTCTCTACAGCAGGCTCACCGTGGACAAGAGCAGGTGG
CAGGAGGGGAATGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACT
ACACACAGAAGTCCCTCTCCCTGTCTCTGGGTAAATGA

(SEQ ID NO: 150)

HC Amino Acid Sequence

QVQLVQSGGEVKKPGDSVKVSKASGYTFTSYGISWVRQAPGQGLEWMGWISVYS
GKKNYARKVQDRVTMTTDTSTSTAYMEVRSLSDDTAIYYCTRRGVSSMVGAFEI
WGQGTMTVTSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGAL
TSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKYTCNVDHKPSNTKVDKRVESKYG
PPCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVDVDSQEDPEVQFNWYVDG
VEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISK
AKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTP
PVLDSGDGSFFLYSRLTVDKSRWQEGNVFSCSVMEALHNHYTQKSLSLSLGK*

(SEQ ID NO: 151)

LC DNA Sequence

GAAATTGTGTTGACGCAGTCTCCAGGCATTCTGTCTTTGTCTCCAGGGGAAAGAG
CCACCCTCTCCTGCAAGGCCAGTCAGAGTGTTAGCAACAGCTACTTAGCCTGGTA
CCAGCAGAAACCTGGCCAGGCTCCCAGGCTCCTCATCTATGGAGCATCTAGTAG
GGCCACTGGCATCCCAGACAGGTTCAGTGGCAGTGGGTCTGGGACAGACTTCAC
TGTCACCATCAGCAGACTGGAGCCTGAAGATTTTGCAGTCTATTACTGTCAGCAG

TATGGTAGCTCACCGCTCACTTTCGGCGGAGGGACCAAGGTGGAGATCAAACGA
ACTGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAAT
CTGGAACCTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAA
AGTACAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGT
CACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCTGACGCT
GAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCA
GGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTTAG

(SEQ ID NO: 152)

LC Amino Acid Sequence

EIVLTQSPGILSLSPGERATLSCKASQSVSNSYLAWYQQKPGQAPRLLIYGASSRATGI
PDRFSGSGSGTDFTVTISRLEPEDFAVYYCQQYGSSPLTFGGGTKVEIKRTVAAPSVFI
FPSPDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTY
SLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC*

(SEQ ID NO: 153)

REGN14156

HCVR DNA Sequence

GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGAGTCCCTG
AGACTCTCCTGTGCAGCCTCTGGATTACCTTTAGCAGCTATGCCATGACCTGGG
TCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTCTCAACTATTAGTGGTAGTG
GTGGTAACACATACTACGCAGTCTCCGTGAAGGGCCGGTTCACCATCTCCAGAG
ACACTTCCAAGAACACGCTGTATCTGCAAATGAACGGCCTGAGAGCCGAGGACA
CGGCCGTATATTACTGTGCGACCCTCACCAGTGGCTGGTACCTTTTTGAGTACTG
GGGCCAGGGAACCCTGGTCACCGTCTCCTCA

(SEQ ID NO: 154)

HCVR Amino Acid Sequence

EVQLVESGGGLVQPGESLRLSCAASGFTFSSYAMTWVRQAPGKGLEWVSTISGSGG
NTYYAVSVKGRFTISRDTSKNTLYLQMNGLRAEDTAVYYCATLTSGWYLFYWGQ
GTLVTVSS

(SEQ ID NO: 155)

CDR1 DNA Sequence

GGA TTC ACC TTT AGC AGC TAT GCC

(SEQ ID NO: 156)

CDR1 Amino Acid Sequence

G F T F S S Y A

(SEQ ID NO: 100)

CDR2 DNA Sequence

ATT AGT GGT AGT GGT GGT AAC ACA

(SEQ ID NO: 157)

CDR2 Amino Acid Sequence

I S G S G G N T

(SEQ ID NO: 158)

CDR3 DNA Sequence

GCG ACC CTC ACC AGT GGC TGG TAC CTT TTT GAG TAC

(SEQ ID NO: 159)

CDR3 Amino Acid Sequence

A T L T S G W Y L F E Y

(SEQ ID NO: 160)

LCVR DNA Sequence

GAAATTGTGTTGACGCAGTCTCCAGGCACCCTGTCTTTGGCTCCAGGGGAAAGAG
CCACCCTCTCCTGCAGGGCCAGTCAGAGTGTTAGCAGCAGCTTCTTTGCCTGGTA
CCAGCAGAAACCTGGCCAGGCTCCAGGCTCCTCATCTATGGTGCATCCAGCAG
GGCCACTGGCATCCCAGACAGGTTCAGTGGCAGTGGGTCTGGGACAGACTTCAC
TCTCACCATCAGCAGACTGGAGCCTGAAGATTTTGCAGTGTATTACTGTCAGCAG
TATGGAAGCTCACCTCCGTGGACGTTTCGGCCAAGGGACCAAGGTGGAAATCAAA

(SEQ ID NO: 161)

LCVR Amino Acid Sequence

EIVLTQSPGTLAPGERATLSCRASQSVSSSFFAWYQQKPGQAPRLLIYGASSRATGI
PDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYGSSPPWTFGQGTKVEIK

(SEQ ID NO: 162)

CDR1 DNA Sequence

CAG AGT GTT AGC AGC AGC TTC

(SEQ ID NO: 163)

CDR1 Amino Acid Sequence

Q S V S S S F

(SEQ ID NO: 164)

CDR2 DNA Sequence

GGT GCA TCC

(SEQ ID NO: 165)

CDR2 Amino Acid Sequence

G A S

(SEQ ID NO: 90)

CDR3 DNA Sequence

CAG CAG TAT GGA AGC TCA CCT CCG TGG ACG

(SEQ ID NO: 166)

CDR3 Amino Acid Sequence

Q Q Y G S S P P W T

(SEQ ID NO: 167)

HC DNA Sequence

GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGAGTCCCTG
AGACTCTCCTGTGCAGCCTCTGGATTACCTTTAGCAGCTATGCCATGACCTGGG
TCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTCTCAACTATTAGTGGTAGTG
GTGGTAACACATACTACGCAGTCTCCGTGAAGGGCCGGTTCACCATCTCCAGAG
ACACTTCCAAGAACACGCTGTATCTGCAAATGAACGGCCTGAGAGCCGAGGACA
CGGCCGTATATTACTGTGCGACCCTCACCAGTGGCTGGTACCTTTTTGAGTACTG
GGGCCAGGGAACCCTGGTCACCGTCTCCTCAGCCTCCACCAAGGGCCCATCGGTC
TCCCCCTGGCGCCCTGCTCCAGGAGCACCTCCGAGAGCACAGCCGCCCTGGGCT
GCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCTGTGGAATCAGGCG
CCCTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCAGGACTCTA

CTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACGAAGACCTAC
ACCTGCAACGTAGATCACAAAGCCCAGCAACACCAAGGTGGACAAGAGAGTTGAG
TCCAAATATGGTCCCCCATGCCCACCGTGCCCAGCACACCTGTGGCAGGACCAT
CAGTCTTCTGTTCCTCCCCAAAACCCAAGGACACTCTCATGATCTCCCGGACCCC
TGAGGTCACGTGCGTGGTGGTGGACGTGAGCCAGGAAGACCCCGAGGTCCAGTT
CAACTGGTACGTGGATGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGA
GGAGCAGTTCAACAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAG
GACTGGCTGAACGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGGCCTCCCG
TCCTCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAGCCACAG
GTGTACACCCTGCCCCCATCCCAGGAGGAGATGACCAAGAACCAGGTCAGCCTG
ACCTGCCTGGTCAAAGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGGAGAGC
AATGGGCAGCCGGAGAACAACACTACAAGACCACGCCTCCCGTGCTGGACTCCGAC
GGCTCCTTCTTCTCTACAGCAGGCTCACCGTGGACAAGAGCAGGTGGCAGGAG
GGGAATGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACAC
AGAAGTCCCTCTCCCTGTCTCTGGGTAAATGA

(SEQ ID NO: 168)

HC Amino Acid Sequence

EVQLVESGGGLVQPGESLRLSAASGFTFSSYAMTWVRQAPGKGLEWVSTISGSGG
NTYYAVSVKGRFTISRDTSKNTLYLQMNGLR AEDTAVYYCATLTSGWYLF EYW GQ
GTLTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGV
HTFPAVLQSSGLYSLSSVVTVPSSSLGTKYTCNVDHKPSNTKVDKRVESKYGPPCPP
CPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVDVVSQEDPEVQFNWYVDGVEVHN
AKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQP
REPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDS
DGSFFLYSRLTVDKSRWQEGNVFSCSV MHEALHNHYTQKSLSLSLGK*

(SEQ ID NO: 169)

LC DNA Sequence

GAAATTGTGTTGACGCAGTCTCCAGGCACCCTGTCTTTGGCTCCAGGGGAAAGAG
CCACCCTCTCCTGCAGGGCCAGTCAGAGTGTTAGCAGCAGCTTCTTTGCCTGGTA
CCAGCAGAAACCTGGCCAGGCTCCCAGGCTCCTCATCTATGGTGCATCCAGCAG
GGCCACTGGCATCCCAGACAGGTTCAGTGGCAGTGGGTCTGGGACAGACTTCAC
TCTCACCATCAGCAGACTGGAGCCTGAAGATTTTGCAGTGTATTACTGTCAGCAG
TATGGAAGCTCACCTCCGTGGACGTTCCGGCCAAGGGACCAAGGTGGAAATCAAA
CGAACTGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGA
AATCTGGAAGTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGC
CAAAGTACAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAG
TGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCTGAC
GCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCA
TCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTTAG

(SEQ ID NO: 170)

LC Amino Acid Sequence

EIVLTQSPGTLAPGERATLSCRASQSVSSFFAWYQQKPGQAPRLLIYGASSRATGI
PDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYGSSPPWTFGQGTKVEIKRTVAAPSV
FIFPPSDEQLKSGTASVVCLLNFPYPREAKVQWKVDNALQSGNSQESVTEQDSKDST
YLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC*

(SEQ ID NO: 171)

REGN14157

HCVR DNA Sequence

GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
AGACTCTCCTGTGCAGCCTCTGGATTACCTTTAGCAGCTATGCCATGAGCTGGG
TCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTCTCAGCTATTAGTGGTAGTG
GTGATAACACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCAGAG
ACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGAGAGTCGAGGATA

CGGCCGTATATTATTGTGCGAAAGAGAAGAGCAGTGGCTGGTACGAATACTGGG
GCCAGGGAACCCTGGTCACCGTCTCCTCA

(SEQ ID NO: 172)

HCVR Amino Acid Sequence

EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSAISGSGD
NTYYADSVKGRFTISRDN SKNTLYLQMNSLRVEDTAVYYCAKEKSSGWYEYWGQG
TLVTVSS

(SEQ ID NO: 173)

CDR1 DNA Sequence

GGA TTC ACC TTT AGC AGC TAT GCC

(SEQ ID NO: 156)

CDR1 Amino Acid Sequence

G F T F S S Y A

(SEQ ID NO: 100)

CDR2 DNA Sequence

ATT AGT GGT AGT GGT GAT AAC ACA

(SEQ ID NO: 174)

CDR2 Amino Acid Sequence

I S G S G D N T

(SEQ ID NO: 175)

CDR3 DNA Sequence

GCG AAA GAG AAG AGC AGT GGC TGG TAC GAA TAC

(SEQ ID NO: 176)

CDR3 Amino Acid Sequence

A K E K S S G W Y E Y

(SEQ ID NO: 177)

LCVR DNA Sequence

GACATCGTGATGACCCAGTCTCCAGACTCCCTGGCTGTGTCTCTGGGCGAGAGGG
CCACCATCAACTGCAAGTCCAGCCAGAGTGTTTTATACAGTTCCAACAATAAGAA
TTACTTAGCTTGGTACCAGCAGAAACCAGGACAGACTCCTAAACTGCTCATTAC
TGGGCATCTACCCGGGAATCCGGGGTCCCTGACCGATTTCAGTGGCAGCGGGTCT
GGGACAGATTTCACTCTCACCATCAGCAGCCTGCAGGCTGAAGATGTGGCAGTTT
ATTACTGTCAGCAATATTATTTTATTCGCTACACTTTTGGCCAGGGGACCAAGCT
GGAGATCAAA

(SEQ ID NO: 178)

LCVR Amino Acid Sequence

DIVMTQSPDSLAVSLGERATINCKSSQSVLYSSNNKNYLAWYQQKPGQTPKLLIYWA
STRESGVPDRFSGSGSGTDFLTITISLQAEDVAVYYCQYYFIPYTFGQGTKLEIK

(SEQ ID NO: 179)

CDR1 DNA Sequence

CAG AGT GTT TTA TAC AGT TCC AAC AAT AAG AAT TAC

(SEQ ID NO: 180)

CDR1 Amino Acid Sequence

Q S V L Y S S N N K N Y

(SEQ ID NO: 181)

CDR3 DNA Sequence

CAG CAA TAT TAT TTT ATT CCG TAC ACT

(SEQ ID NO: 182)

CDR3 Amino Acid Sequence

Q Q Y Y F I P Y T

(SEQ ID NO: 183)

HC DNA Sequence

GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
AGACTCTCCTGTGCAGCCTCTGGATTACCTTTAGCAGCTATGCCATGAGCTGGG
TCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTCTCAGCTATTAGTGGTAGTG
GTGATAACACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCAGAG
ACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGAGAGTCGAGGATA
CGGCCGTATATTATTGTGCGAAAGAGAAGAGCAGTGGCTGGTACGAATACTGGG
GCCAGGGAACCCTGGTCACCGTCTCCTCAGCCTCCACCAAGGGCCCATCGGTCTT
CCCCCTGGCGCCCTGCTCCAGGAGCACCTCCGAGAGCACAGCCGCCCTGGGCTG
CCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCGTGGAATCAGGCGC
CCTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCAGGACTCTAC
TCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACGAAGACCTAC
ACCTGCAACGTAGATCACAAAGCCCAGCAACACCAAGGTGGACAAGAGAGTTGAG
TCCAAATATGGTCCCCCATGCCCACCGTGCCCAGCACACCTGTGGCAGGACCAT

CAGTCTTCCTGTTCCCCCAAAACCCAAGGACACTCTCATGATCTCCCGGACCCC
TGAGGTCACGTGCGTGGTGGTGGACGTGAGCCAGGAAGACCCCGAGGTCCAGTT
CAACTGGTACGTGGATGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGA
GGAGCAGTTCAACAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAG
GACTGGCTGAACGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGGCCTCCCG
TCCTCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAGCCACAG
GTGTACACCCCTGCCCCCATCCCAGGAGGAGATGACCAAGAACCAGGTCAGCCTG
ACCTGCCTGGTCAAAGGCTTCTACCCAGCGACATCGCCGTGGAGTGGGAGAGC
AATGGGCAGCCGGAGAACAACACTACAAGACCACGCCTCCCGTGTGACTCCGAC
GGCTCCTTCTTCTCTACAGCAGGCTCACCGTGGACAAGAGCAGGTGGCAGGAG
GGGAATGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACAC
AGAAGTCCCTCTCCCTGTCTCTGGGTAAATGA

(SEQ ID NO: 184)

HC Amino Acid Sequence

EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSAISGSGD
NTYYADSVKGRFTISRDN SKNTLYLQMNSLRVEDTAVYYCAKEKSSGWY EYWGQG
TLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVH
TFPAVLQSSGLYSLSSVVTVPSSSLGTKYTCNVDHKPSNTKVDKRVESKYGPPCPPC
PAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVDVVSQEDPEVQFNWYVDGVEVHNA
KTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPR
EPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSD
GSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK*

(SEQ ID NO: 185)

LC DNA Sequence

GACATCGTGATGACCCAGTCTCCAGACTCCCTGGCTGTGTCTCTGGGCGAGAGGG
CCACCATCAACTGCAAGTCCAGCCAGAGTGTTTTATACAGTTCCAACAATAAGAA
T TACTTAGCTTGGTACCAGCAGAAACCAGGACAGACTCCTAAACTGCTCATTTAC

TGGGCATCTACCCGGAATCCGGGGTCCCTGACCGATTCACTGGCAGCGGGTCT
GGGACAGATTTCACTCTCACCATCAGCAGCCTGCAGGCTGAAGATGTGGCAGTTT
ATTACTGTCAGCAATATTATTTTATTCCTGACACTTTTGGCCAGGGGACCAAGCT
GGAGATCAAACGAACTGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGAT
GAGCAGTTGAAATCTGGAAGTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATC
CCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAACT
CCCAGGAGAGTGTACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGC
AGCACCTGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGC
GAAGTACCCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGA
GAGTGTTAG

(SEQ ID NO: 186)

LC Amino Acid Sequence

DIVMTQSPDSLAVSLGERATINCKSSQSVLYSSNNKNYLAWYQQKPGQTPKLLIYWA
STRESGVDPDRFSGSGSGTDFTLTISSLQAEDVAVYYCQQYYFIPYTFGGGTKLEIKRT
VAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQ
DSKDSTYLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC*

(SEQ ID NO: 187)

REGN14158

HCVR DNA Sequence

CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTG
AGACTCTCCTGTGCAGCCTCTGGATTACCTTCAGTCACTATGGCATGCACTGGG
TCCGCCAGGCTCCAGGCAAGGGGCTGGAGTGGATGGCAGTTATATCATATGATG
GAAGTAACAAATATTATGCAGACTCCGTGAAGGGCCGATTCACCATCTCCAGAG
ACAATTCCAGGAACACGCTGTATCTGCAAATGAACAGCCTGAGAACTGAGGACA
CGGCTGTGTTTTATTGTGCGAAAGAGTCGAGTATAACAGCCCGTCCGAGAGACTA
CAACTACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCA

(SEQ ID NO: 188)

HCVR Amino Acid Sequence

QVQLVESGGGVVQPGRSLRLSCAASGFTFSHYGMHWVRQAPGKGLEWMAVISYDG
SNKYYADSVKGRFTISRDNRSNTLYLQMNSLRTEDTAVFYCAKESITARPRDYNYG
MDVWGQGTTVTVSS

(SEQ ID NO: 189)

CDR1 DNA Sequence

GGA TTC ACC TTC AGT CAC TAT GGC

(SEQ ID NO: 190)

CDR1 Amino Acid Sequence

G F T F S H Y G

(SEQ ID NO: 191)

CDR2 DNA Sequence

ATA TCA TAT GAT GGA AGT AAC AAA

(SEQ ID NO: 192)

CDR2 Amino Acid Sequence

I S Y D G S N K

(SEQ ID NO: 193)

CDR3 DNA Sequence

GCG AAA GAG TCG AGT ATA ACA GCC CGT CCG AGA GAC TAC AAC TAC GGT
ATG GAC GTC

(SEQ ID NO: 194)

CDR3 Amino Acid Sequence

A K E S S I T A R P R D Y N Y G M D V

(SEQ ID NO: 195)

LCVR DNA Sequence

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAG
TCACCATCACTTGCCGGGCAAGTCAGAGCATTAGCGGCTATTTAAATTGGTTTCA
GCAGAAACCAGGGAAAGCCCCTAAACTCCTAATCTATGCTGCATCCACTTTGCAA
ACTGGGGTCCCATCAAGGTTTCAGCGGCAGTGGATCTGGGACAGATTTCACTCTCA
TCATCAGCAGTCTGCAGCCTGACGATTTTGCAACTTACCACTGTCAACAGAGTTA
CACTTCCCCTTTCACTTTTCGGCCCTGGGACCAAAGTGGATATCAAA

(SEQ ID NO: 196)

LCVR Amino Acid Sequence

DIQMTQSPSSLSASVGDRVTITCRASQSIGYLNWFQQKPGKAPKLLIYAASTLQTGV
PSRFSGSGSGTDFTLISSLQPDDFATYHCQQSYTSPFTFGPGTKVDIK

(SEQ ID NO: 197)

CDR1 DNA Sequence

CAG AGC ATT AGC GGC TAT

(SEQ ID NO: 198)

CDR1 Amino Acid Sequence

Q S I S G Y

(SEQ ID NO: 199)

CDR2 DNA Sequence

GCT GCA TCC

(SEQ ID NO: 13)

CDR2 Amino Acid Sequence

A A S

(SEQ ID NO: 14)

CDR3 DNA Sequence

CAA CAG AGT TAC ACT TCC CCT TTC ACT

(SEQ ID NO: 200)

CDR3 Amino Acid Sequence

Q Q S Y T S P F T

(SEQ ID NO: 201)

HC DNA Sequence

CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTG
AGACTCTCCTGTGCAGCCTCTGGATTACCTTCAGTCACTATGGCATGCACTGGG
TCCGCCAGGCTCCAGGCAAGGGGCTGGAGTGGATGGCAGTTATATCATATGATG
GAAGTAACAAATATTATGCAGACTCCGTGAAGGGCCGATTACCATCTCCAGAG
ACAATTCCAGGAACACGCTGTATCTGCAAATGAACAGCCTGAGAACTGAGGACA

CGGCTGTGTTTTATTGTGCGAAAGAGTCGAGTATAACAGCCCGTCCGAGAGACTA
CAACTACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCAGC
CTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCGCCCTGCTCCAGGAGCACCTCC
GAGAGCACAGCCGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTG
ACGGTGTCGTGGAACCTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGCT
GTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCA
GCAGCTTGGGCACGAAGACCTACACCTGCAACGTAGATCACAAGCCCAGCAACA
CCAAGGTGGACAAGAGAGTTGAGTCCAAATATGGTCCCCCATGCCCACCGTGCC
CAGCACCACTGTGGCAGGACCATCAGTCTTCTGTTCCCCCAAACCCAAGGA
CACTCTCATGATCTCCCGGACCCCTGAGGTCACGTGCGTGGTGGTGGACGTGAGC
CAGGAAGACCCCGAGGTCCAGTTCAACTGGTACGTGGATGGCGTGGAGGTGCAT
AATGCCAAGACAAAGCCGCGGGAGGAGCAGTTCAACAGCACGTACCGTGTGGTC
AGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAACGGCAAGGAGTACAAGTGC
AAGGTCTCCAACAAAGGCCTCCCGTCCTCCATCGAGAAAACCATCTCCAAAGCC
AAAGGGCAGCCCCGAGAGCCACAGGTGTACACCCTGCCCCCATCCCAGGAGGAG
ATGACCAAGAACCAGGTACGCTGACCTGCCTGGTCAAAGGCTTCTACCCCAGC
GACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACCTACAAGAC
CACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCTCTACAGCAGGCTCACC
GTGGACAAGAGCAGGTGGCAGGAGGGGAATGTCTTCTCATGCTCCGTGATGCAT
GAGGCTCTGCACAACCACTACACACAGAAGTCCCTCTCCCTGTCTCTGGGTAAAT
GA

(SEQ ID NO: 202)

HC Amino Acid Sequence

QVQLVESGGGVVQPGRSLRLSCAASGFTFSHYGMHWVRQAPGKGLEWMAVISYDG
SNKYYADSVKGRFTISRDNRSNTLYLQMNSLRTEDTAVFYCAKESSITARPRDYNYG
MDVWGQGTTVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNS
GALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGKTYTCNVDHKPSNTKVDKRVES
KYGPPCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWY
VDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEK

TISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNY
KTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLGLGK*

(SEQ ID NO: 203)

LC DNA Sequence

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAG
TCACCATCACTTGCCGGGCAAGTCAGAGCATTAGCGGCTATTTAAATTGGTTTCA
GCAGAAACCAGGGAAAGCCCCTAAACTCCTAATCTATGCTGCATCCACTTTGCAA
ACTGGGGTCCCATCAAGGTTTCAGCGGCAGTGGATCTGGGACAGATTTCACTCTCA
TCATCAGCAGTCTGCAGCCTGACGATTTTGCAACTTACCACTGTCAACAGAGTTA
CACTTCCCCTTTCACTTTCGGCCCTGGGACCAAAGTGGATATCAAACGAACTGTG
GCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAA
CTGCCTCTGTTGTGTGCCTGCTGAATAAATTCTATCCCAGAGAGGCCAAAGTACA
GTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTACAGA
GCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCCTGACGCTGAGCAA
AGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCT
GAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTTAG

(SEQ ID NO: 204)

LC Amino Acid Sequence

DIQMTQSPSSLSASVGDRVTITCRASQSIGYLNWFQQKPGKAPKLLIYAASLTQTGV
PSRFSGSGSGTDFTLISSLQPDDFATYHCQQSYTSPFTFGPGTKVDIKRTVAAPSVFIF
PPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYS
LSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC*

(SEQ ID NO: 205)

REGN14159

HCVR DNA Sequence

GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGCACAGCGGGGGGGGTCCCTG
AGACTCTCCTGTGCAGCCTCTGGATTACCTTTAGCGACTATGCCGTGAGCTGGG
TCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTCTCAGGTATTAGCCGTGGTG
GTGATTACACGTACTACGCAGACTCCGTGAAGGGCCGGTTCATCATCTCCAGAGA
CAATTCCAAGAATATGTTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACAC
GGCCGTATATTATTGTGCGAAAACTGGGGATCACTTGACTACTGGGGCCAGGG
AACCCTGGTCACCGTCTCCTCA

(SEQ ID NO: 206)

HCVR Amino Acid Sequence

EVQLVESGGGLAQRGGSLRLSCAASGFTFS DYAVSWVRQAPGKGLEWVSGISRGGD
YTTYADSVKGRFIISRDN SKNMLYLQMNSLRAEDTAVYYCAKNWGS LDYWGQGT
LTVSS

(SEQ ID NO: 207)

CDR1 DNA Sequence

GGA TTC ACC TTT AGC GAC TAT GCC

(SEQ ID NO: 208)

CDR1 Amino Acid Sequence

G F T F S D Y A

(SEQ ID NO: 209)

CDR2 DNA Sequence

ATT AGC CGT GGT GGT GAT TAC ACG

(SEQ ID NO: 210)

CDR2 Amino Acid Sequence

I S R G G D Y T

(SEQ ID NO: 211)

CDR3 DNA Sequence

GCG AAA AAC TGG GGA TCA CTT GAC TAC

(SEQ ID NO: 212)

CDR3 Amino Acid Sequence

A K N W G S L D Y

(SEQ ID NO: 213)

LCVR DNA Sequence

GAAATTGTGTTGACACAGTCTCCAGCCACCCTGTCTTTGTCTCCAGGGGAAAGAG
CCACCCTCTCCTGCAGGGCCAGTCAGAGTGTTAGCAGCTACTTAGCCTGGTACCA
ACAGAAACCTGGCCAGGCTCCCAGACTCCTCATCTATGATGCATCCAACAGGGTC
ACTGGCATCCCAGCCAGGTTTCAGTGGCAGTGGGTCTGGGACAGACTTCACTCTCA
CCATCAGCAGCCTAGAGCCTGAAGATTTTGCAGTTTATTACTGTCAGCAGCGTAG
CAACTGGCCTCGAACTTTTGGCCAGGGGACCAAGCTGGAGATCAAA

(SEQ ID NO: 214)

LCVR Amino Acid Sequence

EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIYDASNRVTGI
PARFSGSGSGTDFTLTSSLEPEDFAVYYCQQRSNWPRTFGQGTKLEIK

(SEQ ID NO: 215)

CDR1 DNA Sequence

CAG AGT GTT AGC AGC TAC

(SEQ ID NO: 216)

CDR1 Amino Acid Sequence

Q S V S S Y

(SEQ ID NO: 217)

CDR2 DNA Sequence

GAT GCA TCC

(SEQ ID NO: 218)

CDR2 Amino Acid Sequence

D A S

(SEQ ID NO: 219)

CDR3 DNA Sequence

CAG CAG CGT AGC AAC TGG CCT CGA ACT

(SEQ ID NO: 220)

CDR3 Amino Acid Sequence

Q Q R S N W P R T

(SEQ ID NO: 221)

HC DNA Sequence

GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGCACAGCGGGGGGGGTCCCTG
AGACTCTCCTGTGCAGCCTCTGGATTACCTTTAGCGACTATGCCGTGAGCTGGG
TCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTCTCAGGTATTAGCCGTGGTG
GTGATTACACGTACTACGCAGACTCCGTGAAGGGCCGGTTCATCATCTCCAGAGA
CAATTCCAAGAATATGTTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACAC
GGCCGTATATTATTGTGCGAAAACTGGGGATCACTTGACTACTGGGGCCAGGG
AACCTTGGTCACCGTCTCCTCAGCCTCCACCAAGGGCCCATCGGTCTTCCCCCTG
GCGCCCTGCTCCAGGAGCACCTCCGAGAGCACAGCCGCCCTGGGCTGCCTGGTC
AAGGACTACTTCCCCGAACCGGTGACGGTGTCGTGGAAGTCAAGCGCCCTGACC
AGCGGCGTGCACACCTTCCCGGGCTGTCTACAGTCCTCAGGACTCTACTCCCTCA
GCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACGAAGACCTACACCTGCA
ACGTAGATCACAAGCCCAGCAACACCAAGGTGGACAAGAGAGTTGAGTCCAAAT
ATGGTCCCCCATGCCCACCGTGCCAGCACCACCTGTGGCAGGACCATCAGTCTT
CCTGTTCCCCCAAACCAAGGACACTCTCATGATCTCCCGGACCCCTGAGGTC
ACGTGCGTGGTGGTGGACGTGAGCCAGGAAGACCCCGAGGTCCAGTTCAACTGG
TACGTGGATGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCA
GTTCAACAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGG
CTGAACGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGGCCTCCCGTCTCTCC
ATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAGCCACAGGTGTAC
ACCCTGCCCCCATCCCAGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGC
CTGGTCAAAGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGG
CAGCCGGAGAACAACACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCC
TTCTTCTCTACAGCAGGCTCACCGTGGACAAGAGCAGGTGGCAGGAGGGGAAT
GTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACACAGAAGT
CCCTCTCCCTGTCTCTGGGTAAATGA

(SEQ ID NO: 222)

HC Amino Acid Sequence

EVQLVESGGGLAQRGGSLRLSCAASGFTFSDYAVSWVRQAPGKGLEWVSGISRGGD
YTTYADSVKGRFIISRDNSKNMLYLQMNSLRAEDTAVYYCAKNWGSLDYWGQGT
LTVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTF
PAVLQSSGLYSLSSVTVPSSSLGKTYTCNVDPKPSNTKVDKRVERESKYGPPCPPCPA
PPVAGPSVFLFPPKPKDTLMISRTPEVTCVVDVDSQEDPEVQFNWYVDGVEVHNAK
TKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPRE
PQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDG
SFFFLYSRLTVDKSRWQEGNVFSCSVMEALHNHYTQKSLSLGLGK*

(SEQ ID NO: 223)

LC DNA Sequence

GAAATTGTGTTGACACAGTCTCCAGCCACCCTGTCTTTGTCTCCAGGGGAAAGAG
CCACCCTCTCCTGCAGGGCCAGTCAGAGTGTTAGCAGCTACTTAGCCTGGTACCA
ACAGAAACCTGGCCAGGCTCCCAGACTCCTCATCTATGATGCATCCAACAGGGTC
ACTGGCATCCCAGCCAGGTTTCAGTGGCAGTGGGTCTGGGACAGACTTCACTCTCA
CCATCAGCAGCCTAGAGCCTGAAGATTTTGCAGTTTATTACTGTCAGCAGCGTAG
CAACTGGCCTCGAACTTTTGGCCAGGGGACCAAGCTGGAGATCAAACGAACTGT
GGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGA
ACTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGGCCAAAGTAC
AGTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCACAG
AGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCTGACGCTGAGCA
AAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCC
TGAGCTCGCCCGTCAAAAGAGCTTCAACAGGGGAGAGTGTTAG

(SEQ ID NO: 224)

LC Amino Acid Sequence

EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIYDASNRVTGI
PARFSGSGSGTDFTLTISILEPEDFAVYYCQQRSNWPRTFGQGTKLEIKRTVAAPSVFI

FPPSDEQLKSGTASVVCLLNNFYBPREAKVQWKVDNALQSGNSQESVTEQDSKDSTY
SLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC*

(SEQ ID NO: 225)

REGN14160

HCVR DNA Sequence

CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTG
AGACTCTCCTGTGCAGCCTCTGGATTACCTTCAGTTACTATGTCATGCACTGGGT
CCGCCAGGCTCCAGGCAAGGGGCTGGAATGGGTGACAGTTATATCATATGATGG
AACTAAGAAACACTATGCAGACTCCGTGAAGGGCCGATTACCATCTCCAGAGA
CAATTCCAAGAACACCTTGTATCTGCAAATGAACAGCCTGAGAGCTGACGACAC
GGCTGTGTATTACTGTGCGAAAACGCATAGTACGTCATCCAGGGCCGACTACTTC
TACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCA

(SEQ ID NO: 226)

HCVR Amino Acid Sequence

QVQLVESGGGVVQPGRSLRLSCAASGFTFSYYVMHWVRQAPGKGLEWVTVISYDG
TKKHYADSVKGRFTISRDN SKNTLYLQMNSLRADDTAVYYCAKTHSTSSRADYFYG
MDVWGQGTTVTVSS

(SEQ ID NO: 227)

CDR1 DNA Sequence

GGA TTC ACC TTC AGT TAC TAT GTC

(SEQ ID NO: 228)

CDR1 Amino Acid Sequence

G F T F S Y Y V

(SEQ ID NO: 229)

CDR2 DNA Sequence

ATA TCA TAT GAT GGA ACT AAG AAA

(SEQ ID NO: 230)

CDR2 Amino Acid Sequence

I S Y D G T K K

(SEQ ID NO: 231)

CDR3 DNA Sequence

GCG AAA ACG CAT AGT ACG TCA TCC AGG GCC GAC TAC TTC TAC GGT ATG
GAC GTC

(SEQ ID NO: 232)

CDR3 Amino Acid Sequence

A K T H S T S S R A D Y F Y G M D V

(SEQ ID NO: 233)

LCVR DNA Sequence

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAG
TCACCATCACTTGCCGGGCAAGTCAGAGCATTAGCAGCTATTTAAATTGGTATCA
GCAGAAACCAGGGAAAGCCCCCTCAGTTCCTGATCTATGCTGCATCCAGTTTGCAA
AGTGGGGTCCCATCAAGGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCA
CCATCAGCAGTCTGCAACCTGAAGATTTTGCAACTTACTACTGTCAACAGAGTTA
CAGTACCCCTCACTTTTCGGCGGAGGGACCAAGGTGGAGATCAAA

(SEQ ID NO: 234)

LCVR Amino Acid Sequence

DIQMTQSPSSLSASVGDRVITTCRASQSISSYLNWYQQKPGKAPQFLIYAASSLQSGV
PSRFSGSGSGTDFTLTISLQPEDFATYYCQQSYSTLLTFGGGTKVEIK

(SEQ ID NO: 235)

CDR1 DNA Sequence

CAG AGC ATT AGC AGC TAT

(SEQ ID NO: 236)

CDR1 Amino Acid Sequence

Q S I S S Y

(SEQ ID NO: 237)

CDR2 DNA Sequence

GCT GCA TCC

(SEQ ID NO: 13)

CDR2 Amino Acid Sequence

A A S

(SEQ ID NO: 14)

CDR3 DNA Sequence

CAA CAG AGT TAC AGT ACC CTC CTC ACT

(SEQ ID NO: 238)

CDR3 Amino Acid Sequence

Q Q S Y S T L L T

(SEQ ID NO: 239)

HC DNA Sequence

CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTG
AGACTCTCCTGTGCAGCCTCTGGATTACCTTCAGTTACTATGTCATGCACTGGGT
CCGCCAGGCTCCAGGCAAGGGGCTGGAATGGGTGACAGTTATATCATATGATGG
AACTAAGAAACACTATGCAGACTCCGTGAAGGGCCGATTACCATCTCCAGAGA
CAATTCCAAGAACACCTTGTATCTGCAAATGAACAGCCTGAGAGCTGACGACAC
GGCTGTGTATTACTGTGCGAAAACGCATAGTACGTCATCCAGGGCCGACTACTTC
TACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCAGCCTCCA
CCAAGGGCCCATCGGTCTTCCCCCTGGCGCCCTGCTCCAGGAGCACCTCCGAGAG
CACAGCCGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGT
GTCGTGGAACCTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGCTGTCTTA
CAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCT
TGGGCACGAAGACCTACACCTGCAACGTAGATCACAAAGCCAGCAACACCAAGG
TGGACAAGAGAGTTGAGTCCAAATATGGTCCCCCATGCCCACCGTGCCCAGCAC
CACCTGTGGCAGGACCATCAGTCTTCCTGTTCCCCCAAAACCCAAGGACACTCT
CATGATCTCCCGGACCCCTGAGGTCACGTGCGTGGTGGTGGACGTGAGCCAGGA
AGACCCCGAGGTCCAGTTCAACTGGTACGTGGATGGCGTGGAGGTGCATAATGC
CAAGACAAAGCCGCGGGAGGAGCAGTTCAACAGCACGTACCGTGTGGTCAGCGT
CCTCACCGTCCTGCACCAGGACTGGCTGAACGGCAAGGAGTACAAGTGCAAGGT
CTCCAACAAAGGCCTCCCGTCCTCCATCGAGAAAACCATCTCCAAGCCAAAGG
GCAGCCCCGAGAGCCACAGGTGTACACCCTGCCCCCATCCCAGGAGGAGATGAC
CAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTACCCAGCGACAT
CGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACACTACAAGACCACGC

CTCCCGTGCTGGACTCCGACGGCTCCTTCTTCTCTACAGCAGGCTCACCGTGGA
CAAGAGCAGGTGGCAGGAGGGGAATGTCTTCTCATGCTCCGTGATGCATGAGGC
TCTGCACAACCACTACACACAGAAGTCCCTCTCCCTGTCTCTGGGTAAATGA

(SEQ ID NO: 240)

HC Amino Acid Sequence

QVQLVESGGGVVQPGRSLRLSCAASGFTFSYVMHWVRQAPGKGLEWVTVISYDG
TKKHYADSVKGRFTISRDN SKNTLYLQMNSLRADDTAVYYCAKTHSTSSRADYFYG
MDVWGQGTITVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNS
GALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGKTYTCNV DHKPSNTKVDKRVES
KYGPPCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWY
VDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEK
TISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNY
KTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLGLGK*

(SEQ ID NO: 241)

LC DNA Sequence

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAG
TCACCATCACTTGCCGGGCAAGTCAGAGCATTAGCAGCTATTTAAATTGGTATCA
GCAGAAACCAGGGAAAGCCCCTCAGTTCCTGATCTATGCTGCATCCAGTTTGCAA
AGTGGGGTCCCATCAAGGTTCAAGTGGCAGTGGATCTGGGACAGATTTCACTCTCA
CCATCAGCAGTCTGCAACCTGAAGATTTTGCAACTTACTACTGTCAACAGAGTTA
CAGTACCCCTCCTCACTTTTCGGCGGAGGGACCAAGGTGGAGATCAAACGAACTGT
GGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGA
ACTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTAC
AGTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTACACAG
AGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCTGACGCTGAGCA
AAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCC
TGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTTAG

(SEQ ID NO: 242)

LC Amino Acid Sequence

DIQMTQSPSSLSASVGDRVITTCRASQSISSYLNWYQQKPGKAPQFLIYAASSLQSGV
PSRFSGSGSGTDFTLTISLQPEDFATYYCQSYSTLLTFGGGTKVEIKRTVAAPSVFIF
PPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSTYS
LSSTLTLSKADYEEKHKVYACEVTHQGLSSPVTKSFNRGEC*

(SEQ ID NO: 243)

REGN14161

HCVR DNA Sequence

GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
AGACTCTCCTGTGCAGCCTCTGGATTCACCTTTAGCAGCTATGCCATGACCTGGG
TCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTCTCAACTATTAATACTAATG
GTGGTAGCACATTCTTCGCAGACTCCGTGAAGGGCCGTTTCACCATCTCCAGAGA
CAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACAC
GGCCATATATTACTGTGCGAAAGAAAAACGGGGCGGTATGGACGTCTGGGGCCA
AGGGACCACGGTCACCGTCTCCTCA

(SEQ ID NO: 244)

HCVR Amino Acid Sequence

EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYAMTWVRQAPGKGLEWVSTINTNGG
STFFADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAIYYCAKEKRGGM DVWGQGT
TVSS

(SEQ ID NO: 245)

CDR1 DNA Sequence

GGA TTC ACC TTT AGC AGC TAT GCC

(SEQ ID NO: 156)

CDR1 Amino Acid Sequence

G F T F S S Y A

(SEQ ID NO: 100)

CDR2 DNA Sequence

ATT AAT ACT AAT GGT GGT AGC ACA

(SEQ ID NO: 246)

CDR2 Amino Acid Sequence

I N T N G G S T

(SEQ ID NO: 247)

CDR3 DNA Sequence

GCG AAA GAA AAA CGG GGC GGT ATG GAC GTC

(SEQ ID NO: 248)

CDR3 Amino Acid Sequence

A K E K R G G M D V

(SEQ ID NO: 249)

LCVR DNA Sequence

GACATCGTGATGACCCAGTCTCCAGACTCCCTGGCTGTGTCTCTGGGCGAGAGGG
CCACCATCAACTGCAAGTCCAGCCAGAGTGTTTTATATGGCTCCAACAAAAAGA
ACTACTTAGCTTGGTACCAACAGAAACCAGGACAGCCTCCTAAGCTGCTCATTTA
CTGGGCATCTACCCGGGAATCCGGGGTCCCTGACCGATTCAAGTGGCAGCGGGTCT
GGGACAGATTTCACTCTCACCATCAGTAGCCTGCAGGCTGAAGATGTGGCAGTTT
ATTACTGTCAGCAATATTATAGTACTCTCACGTGGACGTTTCGGCCAAGGGACCAA
GGTGGAAATCAAA

(SEQ ID NO: 250)

LCVR Amino Acid Sequence

DIVMTQSPDSLAVSLGERATINCKSSQSVLYGSNKKNYLAWYQQKPGPPKLLIYW
ASTRESGVPDRFSGSGSGTDFTLTISLQAEDVAVYYCQQYYSTLTWTFGQGTKVEI
K

(SEQ ID NO: 251)

CDR1 DNA Sequence

CAG AGT GTT TTA TAT GGC TCC AAC AAA AAG AAC TAC

(SEQ ID NO: 252)

CDR1 Amino Acid Sequence

Q S V L Y G S N K K N Y

(SEQ ID NO: 253)

CDR2 DNA Sequence

TGG GCA TCT

(SEQ ID NO: 69)

CDR2 Amino Acid Sequence

W A S

(SEQ ID NO: 70)

CDR3 DNA Sequence

CAG CAA TAT TAT AGT ACT CTC ACG TGG ACG

(SEQ ID NO: 254)

CDR3 Amino Acid Sequence

Q Q Y Y S T L T W T

(SEQ ID NO: 255)

HC DNA Sequence

GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
AGACTCTCCTGTGCAGCCTCTGGATTACCTTTAGCAGCTATGCCATGACCTGGG
TCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTCTCAACTATTAATACTAATG
GTGGTAGCACATTCTTCGCAGACTCCGTGAAGGGCCGTTTCACCATCTCCAGAGA
CAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACAC
GGCCATATATTACTGTGCGAAAGAAAAACGGGGCGGTATGGACGTCTGGGGCCA
AGGGACCACGGTCACCGTCTCCTCAGCCTCCACCAAGGGCCCATCGGTCTTCCCC
CTGGCGCCCTGCTCCAGGAGCACCTCCGAGAGCACAGCCGCCCTGGGCTGCCTG
GTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCGTGGAACCTCAGGCGCCCTG
ACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCAGGACTCTACTCCC
TCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACGAAGACCTACACCT
GCAACGTAGATCACAAGCCCAGCAACACCAAGGTGGACAAGAGAGTTGAGTCCA
AATATGGTCCCCCATGCCACCGTGCCAGCACCACCTGTGGCAGGACCATCAGT
CTTCCTGTTCCCCCAAAACCCAAGGACACTCTCATGATCTCCCGGACCCCTGAG

GTCACGTGCGTGGTGGTGGACGTGAGCCAGGAAGACCCCGAGGTCCAGTTCAAC
TGGTACGTGGATGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGA
GCAGTTCAACAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGAC
TGGCTGAACGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGGCCTCCCGTCC
TCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAGCCACAGGTG
TACACCCTGCCCCATCCCAGGAGGAGATGACCAAGAACCAGGTACGCCTGACC
TGCCTGGTCAAAGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGGAGAGCAAT
GGGCAGCCGGAGAACAACACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGC
TCCTTCTTCTCTACAGCAGGCTCACCGTGGACAAGAGCAGGTGGCAGGAGGGG
AATGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACACAGA
AGTCCCTCTCCCTGTCTCTGGGTAAATGA

(SEQ ID NO: 256)

HC Amino Acid Sequence

EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYAMTWVRQAPGKGLEWVSTINTNGG
STFFADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAIYYCAKEKRGGMDVWGQTT
VTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTF
PAVLQSSGLYSLSSVVTVPSSSLGTKYTCNVDHKPSNTKVDKRVESKYGPPCPPCPA
PPVAGPSVFLFPPKPKDTLMISRTPEVTCVVDVDSQEDPEVQFNWYVDGVEVHNAK
TKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPRE
PQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSG
SFFLYSRLTVDKSRWQEGNVFSCSVMH EALHNHYTQKSLSLSLGK*

(SEQ ID NO: 257)

LC DNA Sequence

GACATCGTGATGACCCAGTCTCCAGACTCCCTGGCTGTGTCTCTGGGCGAGAGGG
CCACCATCAACTGCAAGTCCAGCCAGAGTGTTTTATATGGCTCCAACAAAAAGA
ACTACTTAGCTTGGTACCAACAGAAACCAGGACAGCCTCCTAAGCTGCTCATTTA
CTGGGCATCTACCCGGGAATCCGGGGTCCCTGACCGATTCAGTGGCAGCGGGTCT

GGGACAGATTTCACTCTCACCATCAGTAGCCTGCAGGCTGAAGATGTGGCAGTTT
ATTACTGTCAGCAATATTATAGTACTCTCACGTGGACGTTTCGGCCAAGGGACCAA
GGTGGAAATCAAACGAACTGTGGCTGCACCATCTGTCCTCATCTTCCC GCCATCT
GATGAGCAGTTGAAATCTGGAAGTGCCTCTGTTGTGTGCCTGCTGAATAACTTCT
ATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCCAATCGGGTA
ACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCA
GCAGCACCCCTGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCT
GCCAAGTCACCCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGG
GAGAGTGTTAG

(SEQ ID NO: 258)

LC Amino Acid Sequence

DIVMTQSPDSLAVSLGERATINCKSSQSVLYGSNKKNYLAWYQQKPGQPPLLIYW
ASTRESGVPDRFSGSGSGTDFTLTISSLQAEDVAVYYCQQYYSTLTWTFGQGTKVEI
KRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESV
TEQDSKDSSTLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC*

(SEQ ID NO: 259)

REGN14162

HCVR DNA Sequence

CAGGTGCAGCTGCAGGAGTCGGGCCCAGGACTGGTGAAGCCTTCGGAGACCCTG
TCCCTCACCTGCACTGTTTCTGGTGACTCCATCAGTACTTACTACTGGAGCTGGAT
CCGGCAGCCCCCAGGAAAGGGACTGGAGTGGATTGGGTTTTTCCATTACAGTGG
GAGCAGCAAATACAAGCCCTCCCTCAAGAGTCGAGTCACCATATCACTAGACAC
GTCCAAGAATCAGTTCTCCCTGAACCTGCGGTCTGTGACCGCTGCGGACACGGCC
GTGTATTATTGTGCGAGATTAGGCTGGGGATTGACTACTGGGGCCAGGGAACCC
TGGTCACCGTCTCCTCA

(SEQ ID NO: 260)

HCVR Amino Acid Sequence

QVQLQESGPGLVKPSSETLSLTCTVSGDSISTYYWSWIRQPPGKGLEWIGFFHYSGSSK
YKPSLKS RVTISLDTSKNQFSLNLRSVTAADTAVYYCARLGWGF₁FDYWGGQGLVTVS
S

(SEQ ID NO: 261)

CDR1 DNA Sequence

GGT GAC TCC ATC AGT ACT TAC TAC

(SEQ ID NO: 262)

CDR1 Amino Acid Sequence

G D S I S T Y Y

(SEQ ID NO: 263)

CDR2 DNA Sequence

TTC CAT TAC AGT GGG AGC AGC

(SEQ ID NO: 264)

CDR2 Amino Acid Sequence

F H Y S G S S

(SEQ ID NO: 265)

CDR3 DNA Sequence

GCG AGA TTA GGC TGG GGA TTT GAC TAC

(SEQ ID NO: 266)

CDR3 Amino Acid Sequence

A R L G W G F D Y

(SEQ ID NO: 267)

LCVR DNA Sequence

GAAATTGTGTTGACGCAGTCTCCAGGCACCCTGTCTTTGTCTCCAGGGGAAAGAG
CCACCCTCTCCTGCAGGGCCAGTCAGAGTGTTAGCAGCAACTACTTAGCCTGGTA
CCAGCAGAAACCTGGCCAGGCTCCCAGGCTCCTCATCTATGGTGCATCCAGCAG
GGCCACTGGCATCCCAGACAGGTTCAGTGGCAGTGGGTCTGGGACAGACTTCAC
TCTCACCATCAGCAGACTGGAGCCTGAAGATTTTGCAGTGTATTACTGTCAGCAG
TATGGTAGCTCAGCATTCACTTTCGGCCCTGGGACCAAAGTGGATATCAAA

(SEQ ID NO: 268)

LCVR Amino Acid Sequence

EIVLTQSPGTLSSLSPGERATLSCRASQSVSSNYLAWYQQKPGQAPRLLIYGASSRATG
IPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYGSSAFTFGPGTKVDIK

(SEQ ID NO: 269)

CDR1 DNA Sequence

CAG AGT GTT AGC AGC AAC TAC

(SEQ ID NO: 270)

CDR1 Amino Acid Sequence

Q S V S S N Y

(SEQ ID NO: 271)

CDR2 DNA Sequence

GGT GCA TCC

(SEQ ID NO: 165)

CDR2 Amino Acid Sequence

G A S

(SEQ ID NO: 90)

CDR3 DNA Sequence

CAG CAG TAT GGT AGC TCA GCA TTC ACT

(SEQ ID NO: 272)

CDR3 Amino Acid Sequence

Q Q Y G S S A F T

(SEQ ID NO: 273)

HC DNA Sequence

CAGGTGCAGCTGCAGGAGTCGGGCCCAGGACTGGTGAAGCCTTCGGAGACCCTG
TCCCTCACCTGCACTGTTTCTGGTGACTCCATCAGTACTTACTACTGGAGCTGGAT
CCGGCAGCCCCCAGGAAAGGGACTGGAGTGGATTGGGTTTTTCCATTACAGTGG
GAGCAGCAAATACAAGCCCTCCCTCAAGAGTCGAGTCACCATATCACTAGACAC
GTCCAAGAATCAGTTCTCCCTGAACCTGCGGTCTGTGACCGCTGCGGACACGGCC
GTGTATTATTGTGCGAGATTAGGCTGGGGATTTGACTACTGGGGCCAGGGAACCC
TGGTCACCGTCTCCTCAGCCTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCGCC
CTGCTCCAGGAGCACCTCCGAGAGCACAGCCGCCCTGGGCTGCCTGGTCAAGGA

CTACTTCCCCGAACCGGTGACGGTGTCTGTGGAATCAGGCGCCCTGACCAGCGG
CGTGACACCTTCCCCGGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGC
GTGGTGACCGTGCCCTCCAGCAGCTTGGGCACGAAGACCTACACCTGCAACGTA
GATCACAAGCCCAGCAACACCAAGGTGGACAAGAGAGTTGAGTCCAAATATGGT
CCCCCATGCCCACCGTGCCCAGCACACCTGTGGCAGGACCATCAGTCTTCCTGT
TCCCCCAAACCCAAGGACACTCTCATGATCTCCCGGACCCCTGAGGTCACGTG
CGTGGTGGTGGACGTGAGCCAGGAAGACCCCGAGGTCCAGTTCAACTGGTACGT
GGATGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTTCA
ACAGCACGTACCGTGTGGTCAGCGTCCTACCGTCCTGCACCAGGACTGGCTGAA
CGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGGCCTCCCGTCCTCCATCGA
GAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAGCCACAGGTGTACACCCT
GCCCCATCCCAGGAGGAGATGACCAAGAACCAGGTACGCTGACCTGCCTGGT
CAAAGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCC
GGAGAACAACACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTC
CTCTACAGCAGGCTCACCGTGGACAAGAGCAGGTGGCAGGAGGGGAATGTCTTC
TCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACACAGAAGTCCCTCT
CCCTGTCTCTGGGTAAATGA

(SEQ ID NO: 274)

HC Amino Acid Sequence

QVQLQESGPGLVKPSSETLSLTCTVSGDSISTYYWSWIRQPPGKGLEWIGFFHYSGSSK
YKPSLKSRTISLDTSKNQFSLNLRSVTAADTAVYYCARLGWGFQDYWGQGLVTVS
SASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL
QSSGLYSLSSVTVPSSSLGKTYTCNVDPKPSNTKVDKRVESKYGPPCPPCPAPPVA
GPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPR
EEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVY
TLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFL
YSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK*

(SEQ ID NO: 275)

LC DNA Sequence

GAAATTGTGTTGACGCAGTCTCCAGGCACCCTGTCTTTGTCTCCAGGGGAAAGAG
CCACCCTCTCCTGCAGGGCCAGTCAGAGTGTTAGCAGCAACTACTTAGCCTGGTA
CCAGCAGAAACCTGGCCAGGCTCCCAGGCTCCTCATCTATGGTGCATCCAGCAG
GGCCACTGGCATCCCAGACAGGTTCAGTGGCAGTGGGTCTGGGACAGACTTCAC
TCTACCATCAGCAGACTGGAGCCTGAAGATTTTGCAGTGTATTACTGTCAGCAG
TATGGTAGCTCAGCATTCACTTTCGGCCCTGGGACCAAAGTGGATATCAAACGAA
CTGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCT
GGAAGTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAG
TACAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCA
CAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCTGACGCTGA
GCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGG
GCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTTAG

(SEQ ID NO: 276)

LC Amino Acid Sequence

EIVLTQSPGTLSPGERATLSCRASQSVSSNYLAWYQQKPGQAPRLLIYGASSRATG
IPDRFSGSGSTDFLTISRLEPEDFAVYYCQQYGSSAFTFGPGTKVDIKRTVAAPSVF
IFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDY
SLSSLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC*

(SEQ ID NO: 277)

REGN14163

HCVR DNA Sequence

GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTG
AGACTCTCCTGTGCAGCCTCTGGATTACCTTTAGTAACTATTGGATGAACTGGG
TCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCAACATAAAGCAAGATG
GAAGTGAGAAGTACTATGTGGACTCTGTGAAGGGCCGATTACCATCTCCAGAG

ACAACGCCAAGAACTCACTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACA
CGGCTGTGTATTACTGTGCGAGACGTGGATACACCTATGGCAGCTTTGACTACTG
GGGCCAGGGAACCCTGGTCACCGTCTCCTCA

(SEQ ID NO: 278)

HCVR Amino Acid Sequence

EVQLVESGGGLVQPGGSLRLSCAASGFTFSNYWMNWVRQAPGKGLEWVANIKQDG
SEKYYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARRGYTYGSFDYWG
QGTLVTVSS

(SEQ ID NO: 279)

CDR1 DNA Sequence

GGA TTC ACC TTT AGT AAC TAT TGG

(SEQ ID NO: 280)

CDR1 Amino Acid Sequence

G F T F S N Y W

(SEQ ID NO: 281)

CDR2 DNA Sequence

ATA AAG CAA GAT GGA AGT GAG AAG

(SEQ ID NO: 282)

CDR2 Amino Acid Sequence

I K Q D G S E K

(SEQ ID NO: 283)

CDR3 DNA Sequence

GCG AGA CGT GGA TAC ACC TAT GGC AGC TTT GAC TAC

(SEQ ID NO: 284)

CDR3 Amino Acid Sequence

A R R G Y T Y G S F D Y

(SEQ ID NO: 285)

LCVR DNA Sequence

GACATCCAGATGACCCAGTCTCCATCTTCCGTGTCTGCATCTGTAGGAGACAGAG
TCACCATCACTTGTCTGGGCGCGTCAGGGTTTTAGCATCTGGTTAGCCTGGTATCA
GCAGAAACCAGGGAAAGCCCCCTAAGGTCCTGATCTATGCTGCATCCACTTTGCA
GAGTGGGGTCCCATCAAGGTTTCAGCGGCAGTGGATCTGGGACAGATTTCACTCTC
ACCATCAGCAGCCTGCAGCCTGAAGATTTTGCAACTTACTTTTGTC AACAGGCTA
ACAGTTTCCCTCCC ACTTTTCGGCGGAGGGACCAAGGTGGAGATCAAA

(SEQ ID NO: 286)

LCVR Amino Acid Sequence

DIQMTQSPSSVSASVGDRVITTCRARQGFSIWLAWYQQKPGKAPKVLIIYAASLTQSG
VPSRFSGSGSGTDFTLTISSLQPEDFATYFCQQANSFPPTFGGGTKVEIK

(SEQ ID NO: 287)

CDR1 DNA Sequence

CAG GGT TTT AGC ATC TGG

(SEQ ID NO: 288)

CDR1 Amino Acid Sequence

Q G F S I W

(SEQ ID NO: 289)

CDR2 DNA Sequence

GCT GCA TCC

(SEQ ID NO: 13)

CDR2 Amino Acid Sequence

A A S

(SEQ ID NO: 14)

CDR3 DNA Sequence

CAA CAG GCT AAC AGT TTC CCT CCC ACT

(SEQ ID NO: 290)

CDR3 Amino Acid Sequence

Q Q A N S F P P T

(SEQ ID NO: 291)

HC DNA Sequence

GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTG
AGACTCTCCTGTGCAGCCTCTGGATTACCTTTAGTAACTATTGGATGAACTGGG
TCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCAACATAAAGCAAGATG

GAAGTGAGAAGTACTATGTGGACTCTGTGAAGGGCCGATTACCATCTCCAGAG
ACAACGCCAAGAAGTCACTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACA
CGGCTGTGTATTACTGTGCGAGACGTGGATACACCTATGGCAGCTTTGACTACTG
GGGCCAGGGAACCCTGGTCACCGTCTCCTCAGCCTCCACCAAGGGCCCCATCGGTC
TTCCCCCTGGCGCCCTGCTCCAGGAGCACCTCCGAGAGCACAGCCGCCCTGGGCT
GCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCTGTGGAAGTCAAGGCG
CCCTGACCAGCGGCGTGCACACCTTCCCGGTGTCTACAGTCCTCAGGACTCTA
CTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACGAAGACCTAC
ACCTGCAACGTAGATCACAAAGCCCAGCAACACCAAGGTGGACAAGAGAGTTGAG
TCCAAATATGGTCCCCCATGCCCACCGTGCCCAGCACACCTGTGGCAGGACCAT
CAGTCTTCCTGTTCCCCCCTAAACCAAGGACACTCTCATGATCTCCCGGACCCC
TGAGGTCACGTGCGTGGTGGTGGACGTGAGCCAGGAAGACCCCGAGGTCCAGTT
CAACTGGTACGTGGATGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGA
GGAGCAGTTCAACAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAG
GACTGGCTGAACGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGGCCTCCCG
TCCTCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAGCCACAG
GTGTACACCTGCCCCCATCCCAGGAGGAGATGACCAAGAACCAGGTCAGCCTG
ACCTGCCTGGTCAAAGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGGAGAGC
AATGGGCAGCCGGAGAACAACACTACAAGACCACGCCTCCCGTGCTGGACTCCGAC
GGCTCCTTCTTCTCTACAGCAGGCTCACCGTGGACAAGAGCAGGTGGCAGGAG
GGGAATGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACAC
AGAAGTCCCTCTCCCTGTCTCTGGGTAAATGA

(SEQ ID NO: 292)

HC Amino Acid Sequence

EVQLVESGGGLVQPGGSLRLSCAASGFTFSNYWMNWVRQAPGKGLEWVANIKQDG
SEKYYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARRGYTYGSFDYWG
QGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSG
VHTFPAVLQSSGLYSLSSVVTVPSSSLGTKYTCNVDHKPSNTKVDKRVESKYGPC
PPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVDVVSQEDPEVQFNWYVDGVEV

HNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAK
GQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPV
LDSGDSFFLYSRLTVDKSRWQEGNVFSCSVMEALHNHYTQKSLSLGLGK*

(SEQ ID NO: 293)

LC DNA Sequence

GACATCCAGATGACCCAGTCTCCATCTTCCGTGTCTGCATCTGTAGGAGACAGAG
TCACCATCACTTGTCTGGGCGCGTCAGGGTTTTAGCATCTGGTTAGCCTGGTATCA
GCAGAAACCAGGGAAAGCCCCTAAGGTCCTGATCTATGCTGCATCCACTTTGCA
GAGTGGGGTCCCATCAAGGTTACAGCGGCAGTGGATCTGGGACAGATTTCACTCTC
ACCATCAGCAGCCTGCAGCCTGAAGATTTTGCAACTTACTTTTGCAACAGGCTA
ACAGTTTCCCTCCCCTTTTCGGCGGAGGGACCAAGGTGGAGATCAAACGAACTG
TGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGG
AACTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTA
CAGTGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTACACA
GAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCTGACGCTGAGC
AAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGC
CTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTTAG

(SEQ ID NO: 294)

LC Amino Acid Sequence

DIQMTQSPSSVSASVGDRVITTCRARQGFSIWLAWYQQKPGKAPKVLIIYAASLTQSG
VPSRFSGSGSGTDFTLTISLQPEDFATYFCQQANSFPPTFGGGTKVEIKRTVAAPSVFI
FPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTY
SLSSTLTLSKADYEEKHKVYACEVTHQGLSPVTKSFNRGEC*

(SEQ ID NO: 295)

REGN14164

HCVR DNA Sequence

CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTG
AGACTCTCCTGTGCAGCCTCTGGATTACCTTCAGTAACTATGGCATGTACTGGG
TCCGCCAGGCTCCAGGCAAGGGTCTGGAGTGGGTGTCAATTATATCATATGATGG
AAGTAATAAATACTATGCAGACTCCGTGAAGGGCCGATTACACAGCTCCAGAGA
CAATTCCAAGAACACGCTGTATCTTCAAATGAACAGCCTGAGAGGTGAGGACAC
GGCTGTGTATTACTGTGCGAAAGATAGAGGAGCTGGAACCTACAGCCTTCCACTA
CGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCA

(SEQ ID NO: 296)

HCVR Amino Acid Sequence

QVQLVESGGGVVQPGRSLRLSCAASGFTFSNYGMYWVRQAPGKGLEWVSIISYDGS
NKYYADSVKGRFTSSRDNSKNTLYLQMNSLRGEDTAVYYCAKDRGAGTTAFHYG
MDVWGQGTTVTVSS

(SEQ ID NO: 297)

CDR1 DNA Sequence

GGA TTC ACC TTC AGT AAC TAT GGC

(SEQ ID NO: 298)

CDR1 Amino Acid Sequence

G F T F S N Y G

(SEQ ID NO: 299)

CDR2 DNA Sequence

ATA TCA TAT GAT GGA AGT AAT AAA

(SEQ ID NO: 300)

CDR2 Amino Acid Sequence

I S Y D G S N K

(SEQ ID NO: 193)

CDR3 DNA Sequence

GCG AAA GAT AGA GGA GCT GGA ACT ACA GCC TTC CAC TAC GGT ATG GAC
GTC

(SEQ ID NO: 301)

CDR3 Amino Acid Sequence

A K D R G A G T T A F H Y G M D V

(SEQ ID NO: 302)

LCVR DNA Sequence

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAG
TCACCATCACTTGCCGGGCAAGTCAGAGCATTAGCAGTTATTTAAATTGGTATCA
GCAGAAACCAGGGAAAGCCCCTAAGGTCCTGATCTATGCTGCATTCAGTTTGCA
AAGTGGGGTCCCTTCAAGGTTCAAGTGGCAGTGGATCTGGGACAGATTTCACTCTA
ACTATCAGTAGCCTGCAACCTGAGGATTTCGCAACTTACTATTGTCACCAGACTT
ATAGTGTTCCCTCCGATCACCTTCGGCCAAGGGACCAAGCTGGAGATCAAA

(SEQ ID NO: 303)

LCVR Amino Acid Sequence

DIQMTQSPSSLSASVGDRVITICRASQSISSYLNWYQQKPGKAPKVLIIYAAFSLQSGV
PSRFSGSGSGTDFLTISLQPEDFATYYCHQTYSVPPITFGQGTKLEIK

(SEQ ID NO: 304)

CDR1 DNA Sequence

CAG AGC ATT AGC AGT TAT

(SEQ ID NO: 305)

CDR1 Amino Acid Sequence

Q S I S S Y

(SEQ ID NO: 237)

CDR2 DNA Sequence

GCT GCA TTC

(SEQ ID NO: 306)

CDR2 Amino Acid Sequence

A A F

(SEQ ID NO: 307)

CDR3 DNA Sequence

CAC CAG ACT TAT AGT GTT CCT CCG ATC ACC

(SEQ ID NO: 308)

CDR3 Amino Acid Sequence

H Q T Y S V P P I T

(SEQ ID NO: 309)

HC DNA Sequence

CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTG
AGACTCTCCTGTGCAGCCTCTGGATTACCTTCAGTAACTATGGCATGTACTGGG
TCCGCCAGGCTCCAGGCAAGGGTCTGGAGTGGGTGTCAATTATATCATATGATGG
AAGTAATAAATACTATGCAGACTCCGTGAAGGGCCGATTACACAGCTCCAGAGA
CAATTCCAAGAACACGCTGTATCTTCAAATGAACAGCCTGAGAGGTGAGGACAC
GGCTGTGTATTACTGTGCGAAAGATAGAGGAGCTGGAACACAGCCTTCCACTA
CGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCAGCCTCCACC
AAGGGCCCATCGGTCTTCCCCCTGGCGCCCTGCTCCAGGAGCACCTCCGAGAGCA
CAGCCGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTC
GTGGAACCTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAG
TCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGG
GCACGAAGACCTACACCTGCAACGTAGATCACAAGCCCAGCAACACCAAGGTGG
ACAAGAGAGTTGAGTCCAAATATGGTCCCCCATGCCCACCGTGCCCAGCACCA
CTGTGGCAGGACCATCAGTCTTCTGTTCCTTCCCCCAAACCCAAGGACACTCTCAT
GATCTCCCGGACCCCTGAGGTACGTCGCTGGTGGTGGACGTGAGCCAGGAAGA
CCCCGAGGTCCAGTTCAACTGGTACGTGGATGGCGTGGAGGTGCATAATGCCAA
GACAAAGCCGCGGGAGGAGCAGTTCAACAGCACGTACCGTGTGGTCAGCGTCCT
CACCGTCCTGCACCAGGACTGGCTGAACGGCAAGGAGTACAAGTGCAAGGTCTC
CAACAAAGGCCTCCCGTCCTCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCA
GCCCCGAGAGCCACAGGTGTACACCCTGCCCCCATCCCAGGAGGAGATGACCAA
GAACCAGGTACGCCTGACCTGCCTGGTCAAAGGCTTCTACCCCAGCGACATCGCC
GTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACACTACAAGACCACGCCTCC
CGTGCTGGACTCCGACGGCTCCTTCTTCTCTACAGCAGGCTCACCGTGGACAAG
AGCAGGTGGCAGGAGGGGAATGTCTTCTCATGCTCCGTGATGCATGAGGCTCTG
CACAACCACTACACACAGAAGTCCCTCTCCCTGTCTCTGGGTAAATGA

(SEQ ID NO: 310)

HC Amino Acid Sequence

QVQLVESGGGVVQPGRSLRLSCAASGFTFSNYGMYWVRQAPGKGLEWVSIISYDGS
NKYYADSVKGRFTSSRDNSKNTLYLQMNSLRGEDTAVYYCAKDRGAGTTAFHYG
MDVWGQGTTVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNS
GALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGKTYTCNVDPKPSNTKVDKRVES
KYGPPCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWY
VDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEK
TISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNY
KTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMEALHNHYTQKSLSLGLGK*

(SEQ ID NO: 311)

LC DNA Sequence

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAG
TCACCATCACTTGCCGGGCAAGTCAGAGCATTAGCAGTTATTTAAATTGGTATCA
GCAGAAACCAGGGAAAGCCCCCTAAGGTCCTGATCTATGCTGCATTCAAGTTTGCA
AAGTGGGGTCCCTTCAAGGTTCAAGTGGCAGTGGATCTGGGACAGATTTCACTCTA
ACTATCAGTAGCCTGCAACCTGAGGATTCGCAACTTACTATTGTCACCAGACTT
ATAGTGTTCCCTCCGATCACCTTCGGCCAAGGGACCAAGCTGGAGATCAAACGAA
CTGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCT
GGAAGTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAG
TACAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCA
CAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCCTGACGCTGA
GCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGG
GCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTTAG

(SEQ ID NO: 312)

LC Amino Acid Sequence

DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKVLIIYAAFSLQSGV
PSRFSGSGSGTDFTLTISLQPEDFATYYCHQTYSVPPITFGQGTKLEIKRTVAAPSVFI

FPSPDEQLKSGTASVVCLLNNFYPPREAKVQWKVDNALQSGNSQESVTEQDSKDSTY
SLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC*

(SEQ ID NO: 313)

REGN14165

HCVR DNA Sequence

CAGGTTCAGCTGGTGCAGTCTGGAGGTGAGGTGAAGAAGCCTGGGGCCTCAGTG
AAGGTCTCCTGCAAGGCTTCTGGTTACACCTTTACCAACTATGGAATCAGCTGGA
TACGACAGGCCCCTGGACAAGGGCTTGAGTGGATGGGATGGATCAGCGCTTACA
ATGGTAACACAACTATGCACAGAAGGTCCAGGGCAGAGTCACCATGACCACAG
ACACATCCACGACCACAGCCTACATGGAGCTGAGGAGCCTGAGATCTGACGACA
CGGCCGTATATTTCTGTGCGAGAGATCGGGGACAACTGGATCGAGGAGGAACT
ACTACTTCTACATTATGAGCGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTC
A

(SEQ ID NO: 314)

HCVR Amino Acid Sequence

QVQLVQSGGEVKKPGASVKVSKASGYTFTNYGISWIRQAPGQGLEWMGWISAYN
GNTNYAQKVQGRVTMTTDTSTTTAYMELRSLRSDDTAVYFCARDRGQLDRGGNYY
FYIMSVWGQGTTTVTVSS

(SEQ ID NO: 315)

CDR1 DNA Sequence

GGT TAC ACC TTT ACC AAC TAT GGA

(SEQ ID NO: 316)

CDR1 Amino Acid Sequence

G Y T F T N Y G

(SEQ ID NO: 317)

CDR2 DNA Sequence

ATC AGC GCT TAC AAT GGT AAC ACA

(SEQ ID NO: 318)

CDR2 Amino Acid Sequence

I S A Y N G N T

(SEQ ID NO: 319)

CDR3 DNA Sequence

GCG AGA GAT CGG GGA CAA CTG GAT CGA GGA GGA AAC TAC TAC TTC TAC
ATT ATG AGC GTC

(SEQ ID NO: 320)

CDR3 Amino Acid Sequence

A R D R G Q L D R G G N Y Y F Y I M S V

(SEQ ID NO: 321)

LCVR DNA Sequence

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAG
TCACCATCACTTGCCGGGCAAGTCAGGACATTAGAAATGATTTAGGCTGGTATCA
GCAGAAACCAGGGAAAGCCCCTAAGCGCCTAATCTATGCTGCATCCAATTTGCA
AAGTGGGGTCCCATCAAGGTTTCAGCGGCAGTGGATCTGGGACAGAATTCCTCT

CACAATCAGCAGCCTGCAGCCTGAAGATTTTGCAACTTATTACTGTCTACAGCAT
AGTAGTTACCCGTGGACGTTTCGGCCAAGGGACCAAGGTGGAAATCAAA

(SEQ ID NO: 322)

LCVR Amino Acid Sequence

DIQMTQSPSSLSASVGDRVITTCRASQDIRNDLGWYQQKPGKAPKRLIYAASNLQSG
VPSRFSGSGSGTEFTLTISLQPEDFATYYCLQHSSYPWTFGQGTKVEIK

(SEQ ID NO: 323)

CDR1 DNA Sequence

CAG GAC ATT AGA AAT GAT

(SEQ ID NO: 11)

CDR1 Amino Acid Sequence

Q D I R N D

(SEQ ID NO: 12)

CDR2 DNA Sequence

GCT GCA TCC

(SEQ ID NO: 13)

CDR2 Amino Acid Sequence

A A S

(SEQ ID NO: 14)

CDR3 DNA Sequence

CTA CAG CAT AGT AGT TAC CCG TGG ACG

(SEQ ID NO: 324)

CDR3 Amino Acid Sequence

L Q H S S Y P W T

(SEQ ID NO: 325)

HC DNA Sequence

CAGGTTACAGCTGGTGCAGTCTGGAGGTGAGGTGAAGAAGCCTGGGGCCTCAGTG
AAGGTCTCCTGCAAGGCTTCTGGTTACACCTTTACCAACTATGGAATCAGCTGGA
TACGACAGGCCCCCTGGACAAGGGCTTGAGTGGATGGGATGGATCAGCGCTTACA
ATGGTAACACAACTATGCACAGAAGGTCCAGGGCAGAGTCACCATGACCACAG
ACACATCCACGACCACAGCCTACATGGAGCTGAGGAGCCTGAGATCTGACGACA
CGGCCGTATATTTCTGTGCGAGAGATCGGGGACAACTGGATCGAGGAGGAACT
ACTACTTCTACATTATGAGCGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTC
AGCCTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCGCCCTGCTCCAGGAGCACC
TCCGAGAGCACAGCCGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCG
GTGACGGTGTCTGTGGAACCTCAGGCGCCCTGACCAGCGGCGTGACACCTTCCCCG
GCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCT
CCAGCAGCTTGGGCACGAAGACCTACACCTGCAACGTAGATCACAAGCCCAGCA
ACACCAAGGTGGACAAGAGAGTTGAGTCCAAATATGGTCCCCCATGCCCACCGT
GCCCAGCACCACTGTGGCAGGACCATCAGTCTTCCTGTTCCCCCAAAACCCAA
GGACACTCTCATGATCTCCCGGACCCCTGAGGTCACGTGCGTGGTGGTGGACGTG
AGCCAGGAAGACCCCGAGGTCCAGTTCAACTGGTACGTGGATGGCGTGGAGGTG
CATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTTCAACAGCACGTACCGTGTG
GTCAGCGTCCCTACCGTCTGCAACAGGACTGGCTGAACGGCAAGGAGTACAAG
TGCAAGGTCTCCAACAAAGGCCTCCCGTCTCCATCGAGAAAACCATCTCCAAA
GCCAAAGGGCAGCCCCGAGAGCCACAGGTGTACACCCTGCCCCCATCCCAGGAG

GAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTACCCC
AGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACACTACAA
GACCACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCTCTACAGCAGGCTC
ACCGTGGACAAGAGCAGGTGGCAGGAGGGGAATGTCTTCTCATGCTCCGTGATG
CATGAGGCTCTGCACAACCACTACACACAGAAGTCCCTCTCCCTGTCTCTGGGTA
AATGA

(SEQ ID NO: 326)

HC Amino Acid Sequence

QVQLVQSGGEVKKPGASVKVSKASGYTFTNYGISWIRQAPGQGLEWMGWISAYN
GNTNYAQKVQGRVTMTTDTSTTTAYMELRSLRSDDTAVYFCARDRGQLDRGGNY
FYIMSVWGQGTITVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPTVS
WNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGKTYTCNVDPKPSNTKVDKR
VESKYGPPCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFN
WYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSS
IEKTSKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPN
NYKTTTPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSL
GK*

(SEQ ID NO: 327)

LC DNA Sequence

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAG
TCACCATCACTTGCCGGGCAAGTCAGGACATTAGAAATGATTTAGGCTGGTATCA
GCAGAAACCAGGGAAAGCCCCTAAGCGCCTAATCTATGCTGCATCCAATTTGCA
AAGTGGGGTCCCATCAAGGTTTCAGCGGCAGTGGATCTGGGACAGAATTCATCT
CACAATCAGCAGCCTGCAGCCTGAAGATTTTGCAACTTATTACTGTCTACAGCAT
AGTAGTTACCCGTGGACGTTTCGGCCAAGGGACCAAGGTGGAAATCAAACGAACT
GTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTG
GAACTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGT

ACAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTAC
AGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCTGACGCTGAG
CAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGG
CCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTTAG

(SEQ ID NO: 328)

LC Amino Acid Sequence

DIQMTQSPSSLSASVGDRVITITCRASQDIRNDLGWYQQKPGKAPKRLIYAASNLSG
VPSRFSGSGSGTEFTLTISLQPEDFATYYCLQHSSYPWTFGQGTKVEIKRTVAAPSVF
IFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTY
SLSSLTLSKADYEEKHKVYACEVTHQGLSSPVTKSFNRGEC*

(SEQ ID NO: 329)

REGN14175

HCVR DNA Sequence

CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTG
AGACTCTCCTGTGCAGCCTCTGGATTCAGATTCAGTAGTTATGGCATGCACTGGG
TCCGCCAGGCTCCAGGCAAGGGGCTGGAGTGGGTGGCAGTCATTTCATATGATG
GAAGTGATAAATATTATGCAGACTCCGTGAAGGGCCGATTCACCATCTCCAGAG
ACAATTCCAAGAACACGCTTTATATGCAAATGAACAGACTGAAAAGTGAGGACA
CGGCTGTTTATTATTGTGCGAAAGAGAGAAGTACAGCAGCTCGTCGGGGGGACT
ACTACGACTACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCT
CA

(SEQ ID NO: 330)

HCVR Amino Acid Sequence

QVQLVESGGGVVQPGRSLRLSCAASGFRFSSYGMHWVRQAPGKGLEWVAVISYDG
SDKYYADSVKGRFTISRDN SKNTLYMQMNR LKSEDTAVYYCAKERSTAARRGDYY
DYGMDVWGQGTTVTVSS

(SEQ ID NO: 331)

CDR1 DNA Sequence

GGA TTC AGA TTC AGT AGT TAT GGC

(SEQ ID NO: 332)

CDR1 Amino Acid Sequence

G F R F S S Y G

(SEQ ID NO: 333)

CDR2 DNA Sequence

ATT TCA TAT GAT GGA AGT GAT AAA

(SEQ ID NO: 334)

CDR2 Amino Acid Sequence

I S Y D G S D K

(SEQ ID NO: 335)

CDR3 DNA Sequence

GCG AAA GAG AGA AGT ACA GCA GCT CGT CGG GGG GAC TAC TAC GAC TAC
GGT ATG GAC GTC

(SEQ ID NO: 336)

CDR3 Amino Acid Sequence

A K E R S T A A R R G D Y Y D Y G M D V

(SEQ ID NO: 337)

LCVR DNA Sequence

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTTTGCATCTGTGGGAGACAGAG
TCACCATCACTTGCCGGGCAAGTCAGAGCATTAGCAGCTATTTAAATTGGTATCA
CCAGAAACCAGGGAGAGCCCCCTAAACTCCTGATCTTTGCTTCATTCAGTTTGCAA
AGTGGGGTCCCGTCAAGGTTCAAGTGGCAGTGGATCTGGAACAGATTTCACTCTCA
CCATCAGCAGTGTGGAACCTGAAGATTTTGCATCTTACTACTGTCAACAGAGTTA
CAGTACCCCATTCATTTTCGGCCCTGGGACCAAAGTGGATATCAAA

(SEQ ID NO: 338)

LCVR Amino Acid Sequence

DIQMTQSPSSLFASVGDRVITICRASQSISSYLNWYHQKPGRAPKLLIFASFLQSGVP
SRFSGSGSGTDFLTISSVEPEDFASYCQSYSTPFTFGPGTKVDIK

(SEQ ID NO: 339)

CDR1 DNA Sequence

CAG AGC ATT AGC AGC TAT

(SEQ ID NO: 236)

CDR1 Amino Acid Sequence

Q S I S S Y

(SEQ ID NO: 237)

CDR2 DNA Sequence

GCT TCA TTC

(SEQ ID NO: 340)

CDR2 Amino Acid Sequence

A S F

(SEQ ID NO: 341)

CDR3 DNA Sequence

CAA CAG AGT TAC AGT ACC CCA TTC ACT

(SEQ ID NO: 342)

CDR3 Amino Acid Sequence

Q Q S Y S T P F T

(SEQ ID NO: 343)

HC DNA Sequence

CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTG
AGACTCTCCTGTGCAGCCTCTGGATTCAGATTCAGTAGTTATGGCATGCACTGGG
TCCGCCAGGCTCCAGGCAAGGGGCTGGAGTGGGTGGCAGTCATTTTCATATGATG
GAAGTGATAAATATTATGCAGACTCCGTGAAGGGCCGATTCACCATCTCCAGAG
ACAATTCCAAGAACACGCTTTATATGCAAATGAACAGACTGAAAAGTGAGGACA
CGGCTGTTTATTATTGTGCGAAAGAGAGAAGTACAGCAGCTCGTCGGGGGGACT
ACTACGACTACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCT
CAGCCTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCGCCCTGCTCCAGGAGCAC
CTCCGAGAGCACAGCCGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACC

GGTGACGGTGTCGTGGAACCTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCCC
GGCTGTCTTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCC
TCCAGCAGCTTGGGCACGAAGACCTACACCTGCAACGTAGATCACAAAGCCCAGC
AACACCAAGGTGGACAAGAGAGTTGAGTCCAAATATGGTCCCCCATGCCACCG
TGCCCAGCACCTGTGGCAGGACCATCAGTCTTCCTGTTCCCCCAAAACCCA
AGGACACTCTCATGATCTCCCGGACCCCTGAGGTACAGTGCGTGGTGGTGGACGT
GAGCCAGGAAGACCCCGAGGTCCAGTTCAACTGGTACGTGGATGGCGTGGAGGT
GCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTTCAACAGCACGTACCGTGT
GGTCAGCGTCCTACCGTCCTGCACCAGGACTGGCTGAACGGCAAGGAGTACAA
GTGCAAGGTCTCCAACAAAGGCCTCCCGTCCTCCATCGAGAAAACCATCTCCAA
AGCCAAAGGGCAGCCCCGAGAGCCACAGGTGTACACCTGCCCCCATCCCAGGA
GGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTACCC
CAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACACTACA
AGACCACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCTCTACAGCAGGCT
CACCGTGGACAAGAGCAGGTGGCAGGAGGGGAATGTCTTCTCATGCTCCGTGAT
GCATGAGGCTCTGCACAACCACTACACACAGAAGTCCCTCTCCCTGTCTCTGGGT
AAATGA

(SEQ ID NO: 344)

HC Amino Acid Sequence

QVQLVESGGGVVQPGRSLRLSCAASGFRFSSYGMHWVRQAPGKGLEWVAVISYDG
SDKYYADSVKGRFTISRDN SKNTLYMQMNR LKSEDTAVYYCAKERSTAARRGDYY
DYGMDVWGQGTTVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVS
WNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGKTYTCNV DHKPSNTKVDKR
VESKYGPPCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFN
WYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSS
IEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPEN
NYKTTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSL
GK*

(SEQ ID NO: 345)

LC DNA Sequence

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTTTGCATCTGTGGGAGACAGAG
TCACCATCACTTGCCGGGCAAGTCAGAGCATTAGCAGCTATTTAAATTGGTATCA
CCAGAAACCAGGGAGAGCCCCCTAAACTCCTGATCTTTGCTTCATTCAGTTTGCAA
AGTGGGGTCCCGTCAAGGTTCAGTGGCAGTGGATCTGGAACAGATTTCACTCTCA
CCATCAGCAGTGTGGAACCTGAAGATTTTGCATCTTACTACTGTCAACAGAGTTA
CAGTACCCCATTCACTTTCGGCCCTGGGACCAAAGTGGATATCAAACGAACTGTG
GCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAA
CTGCCTCTGTTGTGTGCCTGCTGAATAAATTCTATCCCAGAGAGGCCAAAGTACA
GTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTACAGA
GCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCTGACGCTGAGCAA
AGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCT
GAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTTAG

(SEQ ID NO: 346)

LC Amino Acid Sequence

DIQMTQSPSSLFASVGDRVITICRASQSISSYLNWYHQKPGRAPKLLIFASFSLQSGVP
SRFSGSGSGTDFLTIISSVEPEDFASYCQQSYSTPFTFGPGTKVDIKRTVAAPSVFIFP
PSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSL
SSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC*

(SEQ ID NO: 347)

REGN14176

HCVR DNA Sequence

CAGGTTCACTGGTGCAGTCTGGAAGTGAAGAAGCCTGGGGCCTCAGTG
ACGGTCTCCTGCAAGGCTTCTGGTTACACTTTTACCAGCTATAGTGTCACTGGG
TGCGACAGGCCCCTGGACAAGGGCTTGAGTGGATGGGATGGATCAACGCTTACA

ATGGTGACACAACTATGCACAGAGGTTCCACGGCAGAGTCACCATGACCACAG
ACACATCCACGAGCACAGCCTATATGGACTTGAGGAGCCTGAGATCTGACGACA
CGGCCGTGTATTACTGTGCGAGAGATCGGATAAGTGGAACCTTAGACTACTGGG
GCCAGGGAACCCTGGTCACCGTCTCCTCA

(SEQ ID NO: 348)

HCVR Amino Acid Sequence

QVQLVQSGTEVKKPGASVTVSCKASGYTFTSYSVSWVRQAPGQGLEWMGWINAYN
GDTNYAQRFHGRVTMTTDTSTSTAYMDLRSLRSDDTAVYYCARDRISGTLDYWGQ
GTLVTVSS

(SEQ ID NO: 349)

CDR1 DNA Sequence

GGT TAC ACT TTT ACC AGC TAT AGT

(SEQ ID NO: 350)

CDR1 Amino Acid Sequence

G Y T F T S Y S

(SEQ ID NO: 351)

CDR2 DNA Sequence

ATC AAC GCT TAC AAT GGT GAC ACA

(SEQ ID NO: 352)

CDR2 Amino Acid Sequence

I N A Y N G D T

(SEQ ID NO: 353)

CDR3 DNA Sequence

GCG AGA GAT CGG ATA AGT GGA ACC TTA GAC TAC

(SEQ ID NO: 354)

CDR3 Amino Acid Sequence

A R D R I S G T L D Y

(SEQ ID NO: 355)

LCVR DNA Sequence

GATGTTGTGATGACTCAGTCTCCACTCTCCCTGCCCCGTCACCCTTGGACAGTCGG
CCTCCATCTCCTGCAGGTCTAGTCAAAGCCTCGTATACAGTAATGGAAACACCTA
CTTGAATTGGTTTCAGCAGAGGCCAGGCCAATCTCCACGGCGCCTATTTTATAAG
GTTTCTAACCGGGACTCTGGGGTCCCAGACAGATTCAGCGGCATTGGGTCAGGC
ACTGATTTACACTGAAAATCAGCAGGGTGGAGGCTGAGGATGTTGGATTTTATT
ACTGCATGCAAGGTACACACTGGCCTCGGACTTTTGGCCAGGGGACCAAGCTGG
AGATCAAA

(SEQ ID NO: 356)

LCVR Amino Acid Sequence

DVVMTQSPLSLPVTLGQASISCRSSQSLVYSNGNTYLNWFQQRPGQSPRRIFYKVS
NRDSGVPDRFSGIGSGTDFTLKISRVEAEDVGFYYCMQGTHWPRTFGQGTKLEIK

(SEQ ID NO: 357)

CDR1 DNA Sequence

CAA AGC CTC GTA TAC AGT AAT GGA AAC ACC TAC

(SEQ ID NO: 358)

CDR1 Amino Acid Sequence

Q S L V Y S N G N T Y

(SEQ ID NO: 359)

CDR2 DNA Sequence

AAG GTT TCT

(SEQ ID NO: 360)

CDR2 Amino Acid Sequence

K V S

(SEQ ID NO: 361)

CDR3 DNA Sequence

ATG CAA GGT ACA CAC TGG CCT CGG ACT

(SEQ ID NO: 362)

CDR3 Amino Acid Sequence

M Q G T H W P R T

(SEQ ID NO: 363)

HC DNA Sequence

CAGGTT CAGCTGGTGCAGTCTGGAAGTGAAGAAGCCTGGGGCCTCAGTG
ACGGTCTCCTGCAAGGCTTCTGGTTACACTTTTACCAGCTATAGTGT CAGCTGGG
TGCGACAGGCCCCTGGACAAGGGCTTGAGTGGATGGGATGGATCAACGCTTACA
ATGGTGACACAACTATGCACAGAGGTTCCACGGCAGAGTCAACATGACCACAG
ACACATCCACGAGCACAGCCTATATGGACTTGAGGAGCCTGAGATCTGACGACA
CGGCCGTGTATTACTGTGCGAGAGATCGGATAAGTGGAACCTTAGACTACTGGG
GCCAGGGAACCCTGGTCACCGTCTCCTCAGCCTCCACCAAGGGCCCATCGGTCTT
CCCCCTGGCGCCCTGCTCCAGGAGCACCTCCGAGAGCACAGCCGCCCTGGGCTG
CCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCTGGAAGTCAAGGCGC
CCTGACCAGCGGCGTGCACACCTTCCCGGCTGTCTACAGTCCTCAGGACTCTAC
TCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACGAAGACCTAC
ACCTGCAACGTAGATCACAAAGCCCAGCAACACCAAGGTGGACAAGAGAGTTGAG
TCCAAATATGGTCCCCCATGCCCACCGTGCCCAGCACCACTGTGGCAGGACCAT
CAGTCTTCTGTTCCTCCCCAAAACCAAGGACACTCTCATGATCTCCCGGACCCC
TGAGGTCACGTGCGTGGTGGTGGACGTGAGCCAGGAAGACCCCGAGGTCCAGTT
CAACTGGTACGTGGATGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGA
GGAGCAGTTCAACAGCACGTACCGTGTGGTCAAGCGTCCTCACCGTCCTGCACCAG
GACTGGCTGAACGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGGCCTCCCG
TCCTCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAGCCACAG
GTGTACACCCTGCCCCCATCCCAGGAGGAGATGACCAAGAACCAGGTCAGCCTG
ACCTGCCTGGTCAAAGGCTTCTACCCAGCGACATCGCCGTGGAGTGGGAGAGC
AATGGGCAGCCGGAGAACAACACTACAAGACCACGCCTCCCGTGCTGGACTCCGAC
GGCTCCTTCTTCTCTACAGCAGGCTCACCGTGGACAAGAGCAGGTGGCAGGAG
GGGAATGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACAC
AGAAGTCCCTCTCCCTGTCTCTGGGTAAATGA

(SEQ ID NO: 364)

HC Amino Acid Sequence

QVQLVQSGTEVKKPGASVTVSCKASGYTFTSYSVSWVRQAPGQGLEWMGWINAYN
GDTNYAQRFHGRVTMTDTSTSTAYMDLRSLSRSDDTAVYYCARDRISGTLDYWGQ

GTLTVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGV
HTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYTCNVDPKPSNTKVDKRVESKYGPPCPP
CPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHN
AKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQP
REPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDS
DGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLGLK*

(SEQ ID NO: 365)

LC DNA Sequence

GATGTTGTGATGACTCAGTCTCCACTCTCCCTGCCCCGTCACCCCTGGACAGTCGG
CCTCCATCTCCTGCAGGTCTAGTCAAAGCCTCGTATACAGTAATGGAAACACCTA
CTTGAATTGGTTTCAGCAGAGGCCAGGCCAATCTCCACGGCGCCTATTTTATAAG
GTTTCTAACCGGGACTCTGGGGTCCCAGACAGATTCAGCGGCATTGGGTCAGGC
ACTGATTTCACTGAAAATCAGCAGGGTGGAGGCTGAGGATGTTGGATTTTATT
ACTGCATGCAAGGTACACACTGGCCTCGGACTTTTGGCCAGGGGACCAAGCTGG
AGATCAAACGAAGTGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGA
GCAGTTGAAATCTGGAAGTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCC
AGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCC
CAGGAGAGTGTACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAG
CACCTGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGA
AGTCACCCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGA
GTGTTAG

(SEQ ID NO: 366)

LC Amino Acid Sequence

DVVMTQSPLSLPVTLGQASISCRSSQSLVYSNGNTYLNWFQQRPGQSPRRLFYKVS
NRDSGVPDRFSGIGSGTDFTLKISRVEAEDVGFYYCMQGTHWPRTFGQGTKLEIKRT
VAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQ
DSKDSTYLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC*

(SEQ ID NO: 367)

REGN14177

HCVR DNA Sequence

CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCAAGCCTGGAGGGTCCCTG
AGACTCTCCTGTGCAGCCTCTGGATTACCTTCAGCGACTATTACATGAGCTGGA
TCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTTTCATACATCAGTAAAAGTG
GTACTACCAAATACTACGCAGACTCTGTGAAGGGCCGATTCACCATCTCCAGGG
ACAACGCCAAGAAGTCAAGTGTATCTGCAAATGAACAGTTTGAGAGCCGAGGACA
CGGCCGTCTATTACTGTGAGAAAAGGGGCAGCTTGGGCCAGGGAACCCTGGTCA
CCGTCTCCTCA

(SEQ ID NO: 368)

HCVR Amino Acid Sequence

QVQLVESGGGLVKPGGSLRLSCAASGFTFSYYMSWIRQAPGKGLEWVSYISKSGTT
KYYADSVKGRFTISRDNKNSVYLMNSLRAEDTAVYYCEKRGSLGQGLVTVSS

(SEQ ID NO: 369)

CDR1 DNA Sequence

GGA TTC ACC TTC AGC GAC TAT TAC

(SEQ ID NO: 370)

CDR1 Amino Acid Sequence

G F T F S D Y Y

(SEQ ID NO: 371)

CDR2 DNA Sequence

ATC AGT AAA AGT GGT ACT ACC AAA

(SEQ ID NO: 372)

CDR2 Amino Acid Sequence

I S K S G T T K

(SEQ ID NO: 373)

CDR3 DNA Sequence

GAG AAA AGG GGC AGC

(SEQ ID NO: 374)

CDR3 Amino Acid Sequence

E K R G S

(SEQ ID NO: 375)

LCVR DNA Sequence

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAG
TCACCATCACTTGCCAGGCGAGTCAGGACATTAGCAAGTATTTAAATTGGTATCA
GCAGAAGCCAGGGAAAGCCCCTAAGCTCCTGATCTACGGTGCATCCTATTTGGA
AACAGGGGTCCCATCAAGGTTTCAGTGGAAGTGGATCTGGGACAGATTTTACTTTT
ACCATCAGCAGCCTGCAGCCTGAAGATATTGCAACATATTTCTGTCAACAATATG
ATATTGTCCGGTTCACTTTTGGCCAGGGGACCAAGCTGGAGATCAAA

(SEQ ID NO: 376)

LCVR Amino Acid Sequence

DIQMTQSPSSLSASVGDRVITTCQASQDISKYLNWYQQKPGKAPKLLIYGASYLETG
VPSRFSGSGSGTDFTFITISLQPEDIATYFCQQYDIVRFTFGQGTKLEIK

(SEQ ID NO: 377)

CDR1 DNA Sequence

CAG GAC ATT AGC AAG TAT

(SEQ ID NO: 378)

CDR1 Amino Acid Sequence

Q D I S K Y

(SEQ ID NO: 379)

CDR2 DNA Sequence

GGT GCA TCC

(SEQ ID NO: 165)

CDR2 Amino Acid Sequence

G A S

(SEQ ID NO: 90)

CDR3 DNA Sequence

CAA CAA TAT GAT ATT GTC CGG TTC ACT

(SEQ ID NO: 380)

CDR3 Amino Acid Sequence

Q Q Y D I V R F T

(SEQ ID NO: 381)

HC DNA Sequence

CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCAAGCCTGGAGGGTCCCTG
AGACTCTCCTGTGCAGCCTCTGGATTACCTTCAGCGACTATTACATGAGCTGGA
TCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTTTCATACATCAGTAAAAGTG
GTACTACCAAATACTACGCAGACTCTGTGAAGGGCCGATTACCATCTCCAGGG
ACAACGCCAAGAAGTCAAGTGTATCTGCAAATGAACAGTTTGAGAGCCGAGGACA
CGGCCGTCTATTACTGTGAGAAAAGGGGCAGCTTGGGCCAGGGAACCCCTGGTCA
CCGTCTCCTCAGCCTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCGCCCTGCTC
CAGGAGCACCTCCGAGAGCACAGCCGCCCTGGGCTGCCTGGTCAAGGACTACTT
CCCCGAACCGGTGACGGTGTCTGTGGAAGTCAAGCGCCCTGACCAGCGGCGTGCA
CACCTTCCCGGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTG
ACCGTGCCCTCCAGCAGCTTGGGCACGAAGACCTACACCTGCAACGTAGATCAC
AAGCCCAGCAACACCAAGGTGGACAAGAGAGTTGAGTCCAAATATGGTCCCCCA
TGCCCACCGTGCCAGCACCACCTGTGGCAGGACCATCAGTCTTCTGTTCCTCC
CAAAACCCAAGGACACTCTCATGATCTCCCGGACCCCTGAGGTACAGTGCGTGGT
GGTGGACGTGAGCCAGGAAGACCCCGAGGTCCAGTTCAACTGGTACGTGGATGG
CGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTTCAACAGCA
CGTACCGTGTGGTCAGCGTCCTCACCCTCCTGCACCAGGACTGGCTGAACGGCAA
GGAGTACAAGTGCAAGGTCTCCAACAAAGGCCTCCCGTCTCCATCGAGAAAAC
CATCTCCAAAGCCAAAGGGCAGCCCCGAGAGCCACAGGTGTACACCTGCCCCC
ATCCCAGGAGGAGATGACCAAGAACCAGGTACAGCCTGACCTGCCTGGTCAAAGG
CTTCTACCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAA
CAACTACAAGACCACGCCTCCCGTGTCTGGACTCCGACGGCTCCTTCTTCTCTAC
AGCAGGCTCACCGTGGACAAGAGCAGGTGGCAGGAGGGGAATGTCTTCTCATGC
TCCGTGATGCATGAGGCTCTGCACAACCACTACACACAGAAGTCCCTCTCCCTGT
CTCTGGGTAAATGA

(SEQ ID NO: 382)

HC Amino Acid Sequence

QVQLVESGGGLVKPGGSLRLSCAASGFTFSDYMSWIRQAPGKGLEWVSYISKSGTT
KYYADSVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCEKRGSLGQGTLLTVSSA
STKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQS
SGLYSLSSVVTVPSSSLGTKYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPPVAGP
SVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREE
QFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTL
PPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYS
RLTVDKSRWQEGNVFSCSVMEALHNHYTQKSLSLSLGK*

(SEQ ID NO: 383)

LC DNA Sequence

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAG
TCACCATCACTTGCCAGGCGAGTCAGGACATTAGCAAGTATTTAAATTGGTATCA
GCAGAAGCCAGGGAAAGCCCCTAAGCTCCTGATCTACGGTGCATCCTATTTGGA
AACAGGGGTCCCATCAAGGTTTCAGTGGAAGTGGATCTGGGACAGATTTTACTTTT
ACCATCAGCAGCCTGCAGCCTGAAGATATTGCAACATATTTCTGTCAACAATATG
ATATTGTCCGGTTCATTTTGGCCAGGGGACCAAGCTGGAGATCAAACGAACTGT
GGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGA
ACTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTAC
AGTGGAAGGTGGATAACGCCCTCCAATCGGGTAACCTCCAGGAGAGTGTACACAG
AGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCTGACGCTGAGCA
AAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCC
TGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTTAG

(SEQ ID NO: 384)

LC Amino Acid Sequence

DIQMTQSPSSLSASVGDRVITTCQASQDISKYLNWYQQKPGKAPKLLIYGASYLETG
VPSRFSGSGSGTDFTFITISLQPEDIATYFCQQYDIVRFTFGQGTKLEIKRTVAAPSVFI
FPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTY
SLSSLTLSKADYEEKHKVYACEVTHQGLSSPVTKSFNRGEC*

(SEQ ID NO: 385)

REGN14178

HCVR DNA Sequence

CAGGTT CAGCTGGTGCAGTCTGGACCTGAGGTGAAGAAGCCTGGGGCCTCAGTG
AAGGTCTCCTGCAAGGCTTCTGGTTACACCTTTACCAGCTATGGTTTCAGTTGGG
TGCGACAGGCCCTGGACAAGGGCTTGAGTGGATGGGATGGATCAGCGCTTACA
ATGGTAACACAACTATGCACAGAAGTTCCAGGACAGAGTCACCATGACCACAG
ACTCATCCACGAGCACAGCCTACATGGAGCTGAGGAGCCTGAGATCTGACGACA
CGGCCGTTTATTCCTGTGCGAGAGATCGTGGATTTTGGAGAGCCTATTATGTCTTT
GACTACTGGGGCCAGGGAACCCTGGTCAACCGTCTCCTCA

(SEQ ID NO: 386)

HCVR Amino Acid Sequence

QVQLVQSGPEVKKPGASVKVSKASGYTFTSYGFSWVRQAPGQGLEWMGWISAYN
GNTNYAQKFQDRVMTTDSSTSTAYMELRSLRSDDTAVYSCARDRGFWRAYVYFD
YWGQGTLLTVSS

(SEQ ID NO: 387)

CDR1 DNA Sequence

GGT TAC ACC TTT ACC AGC TAT GGT

(SEQ ID NO: 137)

CDR1 Amino Acid Sequence

G Y T F T S Y G

(SEQ ID NO: 138)

CDR2 DNA Sequence

ATC AGC GCT TAC AAT GGT AAC ACA

(SEQ ID NO: 318)

CDR2 Amino Acid Sequence

I S A Y N G N T

(SEQ ID NO: 319)

CDR3 DNA Sequence

GCG AGA GAT CGT GGA TTT TGG AGA GCC TAT TAT GTC TTT GAC TAC

(SEQ ID NO: 388)

CDR3 Amino Acid Sequence

A R D R G F W R A Y Y V F D Y

(SEQ ID NO: 389)

LCVR DNA Sequence

GATGTTGTGATGACTCAGTCTCCACTCTCCCTGCCCGTCACCCCTGGACAGCCGG
CCTCCATCTCCTGCAGGTCTAGTCAAAGCCTCGTGTACAGTGATGGAAACAATA
CTTGAATTGGTTTCAGCGGAGGCCAGGCCAATCTCCAAGGCGCCTAATTTATAAG
GTTTCTGATCGGGACTCTGGGGTCCCAGACAGATTCAGCGGCAGTGGGTCAGGC
ACTGATTTCACTGAAAATCAGCAGGGTGGAGGCTGAGGATGTTGGGGTTTATT

ACTGCATGCAATATACACACTGGCCGTACACTTTTGGCCAGGGGACCAAGCTGG
AGATCAAA

(SEQ ID NO: 390)

LCVR Amino Acid Sequence

DVVMTQSPLSLPVTLGQPASISCRSSQSLVYSDGNNYLNWFQRRPGQSPRRLIYKVS
DRDSGVPDRFSGSGGTDFTLKISRVEAEDVGVYYCMQYTHWPYTFGQGTKLEIK

(SEQ ID NO: 391)

CDR1 DNA Sequence

CAA AGC CTC GTG TAC AGT GAT GGA AAC AAC TAC

(SEQ ID NO: 392)

CDR1 Amino Acid Sequence

Q S L V Y S D G N N Y

(SEQ ID NO: 393)

CDR2 DNA Sequence

AAG GTT TCT

(SEQ ID NO: 360)

CDR2 Amino Acid Sequence

K V S

(SEQ ID NO: 361)

CDR3 DNA Sequence

ATG CAA TAT ACA CAC TGG CCG TAC ACT

(SEQ ID NO: 394)

CDR3 Amino Acid Sequence

M Q Y T H W P Y T

(SEQ ID NO: 395)

HC DNA Sequence

CAGGTTACAGTGGTGCAGTCTGGACCTGAGGTGAAGAAGCCTGGGGCCTCAGTG
AAGGTCTCCTGCAAGGCTTCTGGTTACACCTTTACCAGCTATGGTTTCAGTTGGG
TGCGACAGGCCCCTGGACAAGGGCTTGAGTGGATGGGATGGATCAGCGCTTACA
ATGGTAACACAACTATGCACAGAAGTTCCAGGACAGAGTCACCATGACCACAG
ACTCATCCACGAGCACAGCCTACATGGAGCTGAGGAGCCTGAGATCTGACGACA
CGGCCGTTTATTCTGTGCGAGAGATCGTGGATTTTGGAGAGCCTATTATGTCTTT
GACTACTGGGGCCAGGGAACCCCTGGTCACCGTCTCCTCAGCCTCCACCAAGGGC
CCATCGGTCTTCCCCCTGGCGCCCTGCTCCAGGAGCACCTCCGAGAGCACAGCCG
CCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCTGTGGAA
CTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCA
GGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACGA
AGACCTACACCTGCAACGTAGATCACAAGCCCAGCAACACCAAGGTGGACAAGA
GAGTTGAGTCCAAATATGGTCCCCCATGCCCACCGTGCCCAGCACCACTGTGGC
AGGACCATCAGTCTTCTGTTCCCCCAAAACCCAAGGACACTCTCATGATCTCC
CGGACCCCTGAGGTACAGTGCGTGGTGGTGGACGTGAGCCAGGAAGACCCCGAG
GTCCAGTTCAACTGGTACGTGGATGGCGTGGAGGTGCATAATGCCAAGACAAAG
CCGCGGGAGGAGCAGTTCAACAGCACGTACCGTGTGGTCAGCGTCCTCACCGTC
CTGCACCAGGACTGGCTGAACGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAA
GGCCTCCCGTCTCTCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGA
GAGCCACAGGTGTACACCCTGCCCCCATCCCAGGAGGAGATGACCAAGAACCAG

GTCAGCCTGACCTGCCTGGTCAAAGGCTTCTACCCCAGCGACATCGCCGTGGAGT
GGGAGAGCAATGGGCAGCCGGAGAACAACACTACAAGACCACGCCTCCCGTGCTGG
ACTCCGACGGCTCCTTCTTCTCTACAGCAGGCTCACCGTGGACAAGAGCAGGTG
GCAGGAGGGGAATGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCAC
TACACACAGAAGTCCCTCTCCCTGTCTCTGGGTAAATGA

(SEQ ID NO: 396)

HC Amino Acid Sequence

QVQLVQSGPEVKKPGASVKVSKASGYTFTSYGFSWVRQAPGQGLEWMGWISAYN
GNTNYAQKFQDRVMTTDSSTSTAYMELRSLRSDDTAVYSCARDRGFWRAYVYFD
YWQGQTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGA
LTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGKTYTCNVDHKPSNTKVDKRVESKY
GPPCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVD
GVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTIS
KAKGQPREPQVYITLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
TPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMEALHNHYTQKSLSLGLK*

(SEQ ID NO: 397)

LC DNA Sequence

GATGTTGTGATGACTCAGTCTCCACTCTCCCTGCCCCGTACCCCTTGGACAGCCGG
CCTCCATCTCCTGCAGGTCTAGTCAAAGCCTCGTGTACAGTGATGGAAACAACATA
CTTGAATTGGTTTCAGCGGAGGCCAGGCCAATCTCCAAGGCGCCTAATTTATAAG
GTTTCTGATCGGGACTCTGGGGTCCCAGACAGATTCAGCGGCAGTGGGTCAGGC
ACTGATTTCACTGAAAATCAGCAGGGTGGAGGCTGAGGATGTTGGGGTTTATT
ACTGCATGCAATATACACACTGGCCGTACACTTTTGGCCAGGGGACCAAGCTGG
AGATCAAACGAACGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGA
GCAGTTGAAATCTGGAACCTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCC
AGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCC
CAGGAGAGTGTACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAG

CACCCTGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGA
AGTCACCCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGA
GTGTTAG

(SEQ ID NO: 398)

LC Amino Acid Sequence

DVVMTQSPLSLPVTLGQPASISCRSSQSLVYSDGNNYLNWFQRRPGQSPRRLIYKVS
DRDSGVPDRFSGSGSGTDFTLKISRVEADVGVYYCMQYTHWPYTFGQGTKLEIKR
TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTE
QDSKDSTYLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC*

(SEQ ID NO: 399)

REGN14179

HCVR DNA Sequence

GAAGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGCAGGTCCCTG
AGACTCTCCTGTGCAGCCTCTGGATTACCTTTGATGCTTATGCCATGCACTGGGT
CCGTCAAGTTCCAGGAAAGGGCCTGCAGTGGGTCTCAGGTATTAGTTGGAATAG
TGATAATATAGACTATACGGACTCTGTGAAGGGCCGATTACCATCTCCAGAGAC
AACGCCAAGAACTCCCTGTATCTGCAAAATGGACAGTCTGAGAGATGAGGACACG
GCCTTGATTTCTGTGCAAAAGATAGGGTTCGGGGAGTTCGTTACTACTACCACT
ACGGCATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCA

(SEQ ID NO: 400)

HCVR Amino Acid Sequence

EVQLVESGGGLVQPGRSLRLSCAASGFTFDAYAMHWVRQVPKGKLQWVSGISWNS
DNIDYTDSVKGRFTISRDNANKNSLYLQMDSLREDTALYFCAKDRVRGVRYYYHYG
MDVWGQGTTVTVSS

(SEQ ID NO: 401)

CDR1 DNA Sequence

GGA TTC ACC TTT GAT GCT TAT GCC

(SEQ ID NO: 402)

CDR1 Amino Acid Sequence

G F T F D A Y A

(SEQ ID NO: 403)

CDR2 DNA Sequence

ATT AGT TGG AAT AGT GAT AAT ATA

(SEQ ID NO: 404)

CDR2 Amino Acid Sequence

I S W N S D N I

(SEQ ID NO: 405)

CDR3 DNA Sequence

GCA AAA GAT AGG GTT CGG GGA GTT CGT TAC TAC TAC CAC TAC GGC ATG
GAC GTC

(SEQ ID NO: 406)

CDR3 Amino Acid Sequence

A K D R V R G V R Y Y Y H Y G M D V

(SEQ ID NO: 407)

LCVR DNA Sequence

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAG
TCACCATCACTTGCCGGGCAAGTCAGAGCATTAGCAGCTATTTAAATTGGTATCA
GCAGAAACCAGGGAAAGCCCCCTAAGCTCCTGATCTATGCTGCATCCAGTTTGCA
AAGTGGGGTCCCGTCAAGGTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTC
ACCATCAGCAGTCTGCAACCTGAAGATTTTGCAACTTACTACTGTCAACAGAGTT
ACAGTACCCCTCCGATCACCTTCGGCCAAGGGACACGACTGGAGATTAAA

(SEQ ID NO: 408)

LCVR Amino Acid Sequence

DIQMTQSPSSLSASVGDRVITTCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGV
PSRFSGSGSGTDFLTITSLQPEDFATYYCQQSYSTPPITFGQGTRLEIK

(SEQ ID NO: 409)

CDR1 DNA Sequence

CAG AGC ATT AGC AGC TAT

(SEQ ID NO: 236)

CDR1 Amino Acid Sequence

Q S I S S Y

(SEQ ID NO: 237)

CDR2 DNA Sequence

GCT GCA TCC

(SEQ ID NO: 13)

CDR2 Amino Acid Sequence

A A S

(SEQ ID NO: 14)

CDR3 DNA Sequence

CAA CAG AGT TAC AGT ACC CCT CCG ATC ACC

(SEQ ID NO: 410)

CDR3 Amino Acid Sequence

Q Q S Y S T P P I T

(SEQ ID NO: 411)

HC DNA Sequence

GAAGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGCAGGTCCCTG
AGACTCTCCTGTGCAGCCTCTGGATTACCTTTGATGCTTATGCCATGCACTGGGT
CCGTCAAGTTCCAGGAAAGGGCCTGCAGTGGGTCTCAGGTATTAGTTGGAATAG
TGATAATATAGACTATACGGACTCTGTGAAGGGCCGATTACCATCTCCAGAGAC
AACGCCAAGAAGTCCCTGTATCTGCAAATGGACAGTCTGAGAGATGAGGACACG
GCCTTGTATTTCTGTGCAAAAGATAGGGTTCGGGGAGTTCGTTACTACTACCACT
ACGGCATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCAGCCTCCA
CCAAGGGCCCATCGGTCTTCCCCCTGGCGCCCTGCTCCAGGAGCACCTCCGAGAG
CACAGCCGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGT
GTCGTGGAAGTCAAGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCTA
CAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCT
TGGGCACGAAGACCTACACCTGCAACGTAGATCACAAAGCCCAGCAACACCAAGG
TGGACAAGAGAGTTGAGTCCAAATATGGTCCCCCATGCCCACCGTGCCCAGCAC

CACCTGTGGCAGGACCATCAGTCTTCCTGTTCCCCCAAACCCAAGGACACTCT
CATGATCTCCCGGACCCCTGAGGTCACGTGCGTGGTGGTGGACGTGAGCCAGGA
AGACCCCGAGGTCCAGTTCAACTGGTACGTGGATGGCGTGGAGGTGCATAATGC
CAAGACAAAGCCGCGGGAGGAGCAGTTCAACAGCACGTACCGTGTGGTCAGCGT
CCTCACCGTCCTGCACCAGGACTGGCTGAACGGCAAGGAGTACAAGTGCAAGGT
CTCCAACAAAGGCCTCCCGTCCTCCATCGAGAAAACCATCTCCAAAGCCAAAGG
GCAGCCCCGAGAGCCACAGGTGTACACCCTGCCCCCATCCCAGGAGGAGATGAC
CAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTACCCCAGCGACAT
CGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACACTACAAGACCACGC
CTCCCGTGCTGGACTCCGACGGCTCCTTCTTCTCTACAGCAGGCTCACCGTGGA
CAAGAGCAGGTGGCAGGAGGGGAATGTCTTCTCATGCTCCGTGATGCATGAGGC
TCTGCACAACCACTACACACAGAAGTCCCTCTCCCTGTCTCTGGGTAAATGA

(SEQ ID NO: 412)

HC Amino Acid Sequence

EVQLVESGGGLVQPGRSLRLSCAASGFTFDAYAMHWVRQVPGKGLQWVSGISWNS
DNIDYTDVSKGRFTISRDNAKNSLYLQMDSLRDEDTALYFCAKDRVRGVRYYYHYG
MDVWGQGTITVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTWSNS
GALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYTCNVDPKPSNTKVDKRVES
KYGPPCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWY
VDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEK
TISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNY
KTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMEALHNHYTQKSLSLSLGK*

(SEQ ID NO: 413)

LC DNA Sequence

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAG
TCACCATCACTTGCCGGGCAAGTCAGAGCATTAGCAGCTATTTAAATTGGTATCA
GCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCTATGCTGCATCCAGTTTGCA

AAGTGGGGTCCCGTCAAGGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTC
ACCATCAGCAGTCTGCAACCTGAAGATTTTGCAACTTACTACTGTCAACAGAGTT
ACAGTACCCCTCCGATCACCTTCGGCCAAGGGACACGACTGGAGATTAACGAA
CTGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCT
GGAAGTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAG
TACAGTGGAAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCA
CAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCTGACGCTGA
GCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGG
GCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTTAG

(SEQ ID NO: 414)

LC Amino Acid Sequence

DIQMTQSPSSLSASVGDRVITITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGV
PSRFSGSGSGTDFLTITSLQPEDFATYYCQQSYSTPPITFGQGTRLEIKRTVAAPSVFIF
PPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYS
LSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC*

(SEQ ID NO: 415)

REGN14180

HCVR DNA Sequence

GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
AGACTCTCCTGTACAGCCTCTGGATTACCTTTAGCAGCTTTGTCATGAGCTGGG
TCCGCCAGGCTCCAGGGAAGGGACTGGAGTGGGTCTCAGCTATTCGGGATACTG
GTGATAACACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCAGAG
ACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGAGAACCGAGGACA
CGGCCGTAATTTACTGTGCGAGAGGGGGGAGAACTAGAATTCCGTTTGACTACT
GGGGCCAGGGAACCCTGGTCACCGTCTCCTCA

(SEQ ID NO: 416)

HCVR Amino Acid Sequence

EVQLVESGGGLVQPGGSLRLSCTASGFTFSSFVMSWVRQAPGKGLEWVSAIRDTGD
NTYYADSVKGRFTISRDN SKNTLYLQMNSLRTEDTAVIYCARGGRTRIPFDYWGQG
TLVTVSS

(SEQ ID NO: 417)

CDR1 DNA Sequence

GGA TTC ACC TTT AGC AGC TTT GTC

(SEQ ID NO: 418)

CDR1 Amino Acid Sequence

G F T F S S F V

(SEQ ID NO: 419)

CDR2 DNA Sequence

ATT CCG GAT ACT GGT GAT AAC ACA

(SEQ ID NO: 420)

CDR2 Amino Acid Sequence

I R D T G D N T

(SEQ ID NO: 421)

CDR3 DNA Sequence

GCG AGA GGG GGG AGA ACT AGA ATT CCG TTT GAC TAC

(SEQ ID NO: 422)

CDR3 Amino Acid Sequence

A R G G R T R I P F D Y

(SEQ ID NO: 423)

LCVR DNA Sequence

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAG
TCACCATCACTTGCCGGGCAAGTCAGAGCATTAGCAGCTATTTAAATTGGTATCA
GCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCTATGCTGCATCCAGTTTGCA
AAGTGGGGTCCCGTCAAGGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTC
ACCATCAGCAGTCTGCAACCTGAAGATTTTGCAACTTACTACTGTCAACAGAGTT
ACAGTACCCCTCCGATCACCTTCGGCCAAGGGACACGACTGGAGATTAAA

(SEQ ID NO: 408)

LCVR Amino Acid Sequence

DIQMTQSPSSLSASVGDRVITTCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGV
PSRFSGSGSGTDFTLTISLQPEDFATYYCQSYSTPPITFGQGTRLEIK

(SEQ ID NO: 409)

CDR1 DNA Sequence

CAG AGC ATT AGC AGC TAT

(SEQ ID NO: 236)

CDR1 Amino Acid Sequence

Q S I S S Y

(SEQ ID NO: 237)

CDR2 DNA Sequence

GCT GCA TCC

(SEQ ID NO: 13)

CDR2 Amino Acid Sequence

A A S

(SEQ ID NO: 14)

CDR3 DNA Sequence

CAA CAG AGT TAC AGT ACC CCT CCG ATC ACC

(SEQ ID NO: 410)

CDR3 Amino Acid Sequence

Q Q S Y S T P P I T

(SEQ ID NO: 411)

HC DNA Sequence

GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
 AGACTCTCCTGTACAGCCTCTGGATTACCTTTAGCAGCTTTGTCATGAGCTGGG
 TCCGCCAGGCTCCAGGGAAGGGACTGGAGTGGGTCTCAGCTATTCGGGATACTG
 GTGATAACACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCAGAG
 ACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGAGAACCGAGGACA
 CGGCCGTAATTTACTGTGCGAGAGGGGGGAGAACTAGAATTCCGTTTGACTACT
 GGGGCCAGGGAACCCTGGTCACCGTCTCCTCAGCCTCCACCAAGGGCCCATCGG
 TCTTCCCCCTGGCGCCCTGCTCCAGGAGCACCTCCGAGAGCACAGCCGCCCTGGG

CTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCGTGGAATCAGGC
GCCCTGACCAGCGGCGTGCACACCTTCCCGGCTGTCTACAGTCCTCAGGACTCT
ACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACGAAGACCT
ACACCTGCAACGTAGATCACAAGCCCAGCAACACCAAGGTGGACAAGAGAGTTG
AGTCCAAATATGGTCCCCCATGCCCACCGTGCCCAGCACCACCTGTGGCAGGACC
ATCAGTCTTCCTGTTCCCCCAAAACCAAGGACACTCTCATGATCTCCCGGACC
CCTGAGGTCACGTGCGTGGTGGTGGACGTGAGCCAGGAAGACCCCGAGGTCCAG
TTCAACTGGTACGTGGATGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGG
GAGGAGCAGTTCAACAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACC
AGGACTGGCTGAACGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGGCCTCC
CGTCCTCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAGCCAC
AGGTGTACACCCTGCCCCATCCCAGGAGGAGATGACCAAGAACCAGGTCAGCC
TGACCTGCCTGGTCAAAGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGGAGA
GCAATGGGCAGCCGAGACAACAATAAGACCACGCCTCCCGTGCTGGACTCCG
ACGGCTCCTTCTTCCTCTACAGCAGGCTCACCGTGGACAAGAGCAGGTGGCAGG
AGGGGAATGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCAACAACCTACAC
ACAGAAAGTCCCTCTCCCTGTCTCTGGGTAAATGA

(SEQ ID NO: 424)

HC Amino Acid Sequence

EVQLVESGGGLVQPGGSLRLSCTASGFTFSSFVMSWVRQAPGKGLEWVSAIRDTGD
NTYYADSVKGRFTISRDN SKNTLYLQMNSLRTEDTAVIYCARGGRTRIPFDYWQQG
TLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVH
TFPAVLQSSGLYSLSSVTVPSSSLGKTYTCNV DHKPSNTKVDKRVESKYGPPCPPC
PAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNA
KTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPR
EPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSD
GSFFLYSRLTVDKSRWQEGNVFSCSV MHEALHNHYTQKSLSLSLGK*

(SEQ ID NO: 425)

LC DNA Sequence

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAG
TCACCATCACTTGCCGGGCAAGTCAGAGCATTAGCAGCTATTTAAATTGGTATCA
GCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCTATGCTGCATCCAGTTTGCA
AAGTGGGGTCCCGTCAAGGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTC
ACCATCAGCAGTCTGCAACCTGAAGATTTTGCAACTTACTACTGTCAACAGAGTT
ACAGTACCCCTCCGATCACCTTCGGCCAAGGGACACGACTGGAGATTAAACGAA
CTGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCT
GGAAGTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAG
TACAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCA
CAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCTGACGCTGA
GCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGG
GCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTTAG

(SEQ ID NO: 414)

LC Amino Acid Sequence

DIQMTQSPSSLSASVGDRVITITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGV
PSRFSGSGSGTDFLTISLQPEDFATYYCQSYSTPPITFGQGTRLEIKRTVAAPSVFIF
PPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDESTYS
LSSLTTLISKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC*

(SEQ ID NO: 415)

REGN14181

HCVR DNA Sequence

CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTG
AGACTCTCCTGTGCAGCCTCTGGATTCATCTTCAGTAACTATGGCATGCACTGGG
TCCGCCAGGCTCCAGGCAAGGGGCTGGAGTGGGTGGCAATTATATCTTTTGATGG
AAATAATAAATACTATGCAGACTCCGTGAAGCGCCGATTCACCATCTCCAGAGA

CAATTTCAAGAGCACGCTGTATCTGCAATTGAACAGCCTGACAATTGAGGACAC
GGCTGTATATTTCTGTGCGAAAGAGTTTAGCAGGCGGAATTTCTTTGACCACTGG
GGCCAGGGAACCCTGGTCACCGTCTCCTCA

(SEQ ID NO: 426)

HCVR Amino Acid Sequence

QVQLVESGGGVVQPGRSLRLSCAASGFIFSNYGMHWVRQAPGKGLEWVAIISFDGN
NKYYADSVKRRFTISRDNFKSTLYLQLNSLTIEDTAVYFCAKEFSRRNFFDHWGQGT
LTVVSS

(SEQ ID NO: 427)

CDR1 DNA Sequence

GGA TTC ATC TTC AGT AAC TAT GGC

(SEQ ID NO: 428)

CDR1 Amino Acid Sequence

G F I F S N Y G

(SEQ ID NO: 429)

CDR2 DNA Sequence

ATA TCT TTT GAT GGA AAT AAT AAA

(SEQ ID NO: 430)

CDR2 Amino Acid Sequence

I S F D G N N K

(SEQ ID NO: 431)

CDR3 DNA Sequence

GCG AAA GAG TTT AGC AGG CGG AAT TTC TTT GAC CAC

(SEQ ID NO: 432)

CDR3 Amino Acid Sequence

A K E F S R R N F F D H

(SEQ ID NO: 433)

LCVR DNA Sequence

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAG
TCACCATCACTTGCCGGGCAAGTCAGAGCATTAGCAGCTATTTAAATTGGTATCA
GCAGAAACCAGGGAAAGCCCCCTAAGCTCCTGATCTATGCTGCATCCAGTTTGCA
AAGTGGGGTCCCGTCAAGGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTC
ACCATCAGCAGTCTGCAACCTGAAGATTTTGCAACTTACTACTGTCAACAGAGTT
ACAGTACCCCTCCGATCACCTTCGGCCAAGGGACACGACTGGAGATTAAA

(SEQ ID NO: 408)

LCVR Amino Acid Sequence

DIQMTQSPSSLSASVGDRVITTCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGV
PSRFSGSGSGTDFTLTISLQPEDFATYYCQSYSTPPITFGQGTRLEIK

(SEQ ID NO: 409)

CDR1 DNA Sequence

CAG AGC ATT AGC AGC TAT

(SEQ ID NO: 236)

CDR1 Amino Acid Sequence

Q S I S S Y

(SEQ ID NO: 237)

CDR2 DNA Sequence

GCT GCA TCC

(SEQ ID NO: 13)

CDR2 Amino Acid Sequence

A A S

(SEQ ID NO: 14)

CDR3 DNA Sequence

CAA CAG AGT TAC AGT ACC CCT CCG ATC ACC

(SEQ ID NO: 410)

CDR3 Amino Acid Sequence

Q Q S Y S T P P I T

(SEQ ID NO: 411)

HC DNA Sequence

CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTG
AGACTCTCCTGTGCAGCCTCTGGATTCATCTTCAGTAACTATGGCATGCACTGGG
TCCGCCAGGCTCCAGGCAAGGGGCTGGAGTGGGTGGCAATTATATCTTTTGATGG

AAATAATAAATACTATGCAGACTCCGTGAAGCGCCGATTACCATCTCCAGAGA
CAATTTCAAGAGCACGCTGTATCTGCAATTGAACAGCCTGACAATTGAGGACAC
GGCTGTATATTTCTGTGCGAAAGAGTTTAGCAGGCGGAATTTCTTTGACCACTGG
GGCCAGGGAACCTTGGTCACCGTCTCCTCAGCCTCCACCAAGGGCCCATCGGTCT
TCCCCCTGGCGCCCTGCTCCAGGAGCACCTCCGAGAGCACAGCCGCCCTGGGCTG
CCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCGTGGAATCAGGCGC
CCTGACCAGCGGCGTGCACACCTTCCCGGCTGTCTACAGTCCTCAGGACTCTAC
TCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACGAAGACCTAC
ACCTGCAACGTAGATCACAAAGCCCAGCAACACCAAGGTGGACAAGAGAGTTGAG
TCCAAATATGGTCCCCCATGCCCACCGTGCCCAGCACCACTGTGGCAGGACCAT
CAGTCTTCCTGTTCCCCCAAAACCCAAGGACACTCTCATGATCTCCCGGACCCC
TGAGGTCACGTGCGTGGTGGTGGACGTGAGCCAGGAAGACCCCGAGGTCCAGTT
CAACTGGTACGTGGATGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGA
GGAGCAGTTCAACAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAG
GACTGGCTGAACGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGGCCTCCCG
TCCTCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAGCCACAG
GTGTACACCTTGCCCCCATCCCAGGAGGAGATGACCAAGAACCAGGTCAGCCTG
ACCTGCCTGGTCAAAGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGGAGAGC
AATGGGCAGCCGGAGAACAACACTACAAGACCACGCCTCCCGTGCTGGACTCCGAC
GGCTCCTTCTTCTCTACAGCAGGCTCACCGTGGACAAGAGCAGGTGGCAGGAG
GGGAATGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACAC
AGAAGTCCCTCTCCCTGTCTCTGGGTAAATGA

(SEQ ID NO: 434)

HC Amino Acid Sequence

QVQLVESGGGVVQPGRSLRLSCAASGFIFSNYGMHWVRQAPGKGLEWVAIISFDGN
NKYYADSVKRRFTISRDNFKSTLYLQLNSLTIEDTAVYFCAKEFSRRNFFDHWGQGT
LVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHT
FPAVLQSSGLYSLSSVVTVPSSSLGTKYTCNVDHKPSNTKVDKRVESKYGPPCPPCP
APPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNA

KTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPR
EPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSD
GSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLGLK*

(SEQ ID NO: 435)

LC DNA Sequence

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAG
TCACCATCACTTGCCGGGCAAGTCAGAGCATTAGCAGCTATTTAAATTGGTATCA
GCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCTATGCTGCATCCAGTTTGCA
AAGTGGGGTCCCGTCAAGGTTCAAGTGGCAGTGGATCTGGGACAGATTTCACTCTC
ACCATCAGCAGTCTGCAACCTGAAGATTTTGCAACTTACTACTGTCAACAGAGTT
ACAGTACCCCTCCGATCACCTTCGGCCAAGGGACACGACTGGAGATTAAACGAA
CTGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCT
GGAAGTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCAGAGAGGCCAAAG
TACAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCA
CAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCTGACGCTGA
GCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGG
GCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTTAG

(SEQ ID NO: 414)

LC Amino Acid Sequence

DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGV
PSRFGSGSGTDFLTISLQPEDFATYYCQSYSTPPITFGQGRLEIKRTVAAPSVFIF
PPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYS
LSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC*

(SEQ ID NO: 415)

REGN14182

HCVR DNA Sequence

CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTG
 AGACTCTCCTGTGCAGCCTCTGGATTACCTTCAGTCATTATGGCATGCACTGGG
 TCCGCCAGGCTCCAGGCAAGGGGCTGGAGTGGATGGCTATCATCTCATATGACG
 GAAGTGATAAATACTATGCAGACTCCGTGAAGGGCCGATTACCATCTCCAGAG
 ACAATTCCGAGAACACACTATATCTGCAAATGAGCAGCCTGAGAACTGAAGACA
 CGGCTGTGTATTACTGTGCGAAAGCCAGTATAACTGGAACCTACTACTTCTTCTA
 CGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCA

(SEQ ID NO: 436)

HCVR Amino Acid Sequence

QVQLVESGGGVVQPGRSLRLSCAASGFTFSHYGMHWVRQAPGKGLEWMAIISYDG
 SDKYYADSVKGRFTISRDNSENTLYLQMSSLRTEDTAVYYCAKASITGTYFFYGM
 DVWGQGTTTVTVSS

(SEQ ID NO: 437)

CDR1 DNA Sequence

GGA TTC ACC TTC AGT CAT TAT GGC

(SEQ ID NO: 438)

CDR1 Amino Acid Sequence

G F T F S H Y G

(SEQ ID NO: 191)

CDR2 DNA Sequence

ATC TCA TAT GAC GGA AGT GAT AAA

(SEQ ID NO: 439)

CDR2 Amino Acid Sequence

I S Y D G S D K

(SEQ ID NO: 335)

CDR3 DNA Sequence

GCG AAA GCC AGT ATA ACT GGA ACT TAC TAC TTC TTC TAC GGT ATG GAC
GTC

(SEQ ID NO: 440)

CDR3 Amino Acid Sequence

A K A S I T G T Y Y F F Y G M D V

(SEQ ID NO: 441)

LCVR DNA Sequence

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAG
TCACCATCACTTGCCGGGCAAGTCAGAGCATTAGCAGCTATTTAAATTGGTATCA
GCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCTATGCTGCATCCAGTTTGCA
AAGTGGGGTCCCGTCAAGGTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTC
ACCATCAGCAGTCTGCAACCTGAAGATTTGCAACTTACTACTGTCAACAGAGTT
ACAGTACCCCTCCGATCACCTTCGGCCAAGGGACACGACTGGAGATTAAA

(SEQ ID NO: 408)

LCVR Amino Acid Sequence

DIQMTQSPSSLSASVGDRVITICRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGV
PSRFSGSGSGTDFTLTISSLQPEDFATYYCQSYSTPPITFGQGTRLEIK

(SEQ ID NO: 409)

CDR1 DNA Sequence

CAG AGC ATT AGC AGC TAT

(SEQ ID NO: 236)

CDR1 Amino Acid Sequence

Q S I S S Y

(SEQ ID NO: 237)

CDR2 DNA Sequence

GCT GCA TCC

(SEQ ID NO: 13)

CDR2 Amino Acid Sequence

A A S

(SEQ ID NO: 14)

CDR3 DNA Sequence

CAA CAG AGT TAC AGT ACC CCT CCG ATC ACC

(SEQ ID NO: 410)

CDR3 Amino Acid Sequence

Q Q S Y S T P P I T

(SEQ ID NO: 411)

HC DNA Sequence

CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTG
AGACTCTCCTGTGCAGCCTCTGGATTACCTTCAGTCATTATGGCATGCACTGGG
TCCGCCAGGCTCCAGGCAAGGGGCTGGAGTGGATGGCTATCATCTCATATGACG
GAAGTGATAAATACTATGCAGACTCCGTGAAGGGCCGATTACCATCTCCAGAG
ACAATTCCGAGAACACACTATATCTGCAAATGAGCAGCCTGAGAACTGAAGACA
CGGCTGTGTATTACTGTGCGAAAGCCAGTATAACTGGAACTTACTACTTCTTCTA
CGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCAGCCTCCACC
AAGGGCCCATCGGTCTTCCCCCTGGCGCCCTGCTCCAGGAGCACCTCCGAGAGCA
CAGCCGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTC
GTGGAACCTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAG
TCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGG
GCACGAAGACCTACACCTGCAACGTAGATCACAAGCCCAGCAACACCAAGGTGG
ACAAGAGAGTTGAGTCCAAATATGGTCCCCCATGCCCACCGTGCCCAGCACCA
CTGTGGCAGGACCATCAGTCTTCTGTTCCTTCCCCCAAACCCAAGGACACTCTCAT
GATCTCCCGGACCCCTGAGGTCACGTGCGTGGTGGTGGACGTGAGCCAGGAAGA
CCCCGAGGTCCAGTTCAACTGGTACGTGGATGGCGTGGAGGTGCATAATGCCAA
GACAAAGCCGCGGGAGGAGCAGTTCAACAGCACGTACCGTGTGGTCAGCGTCCT
CACCGTCCTGCACCAGGACTGGCTGAACGGCAAGGAGTACAAGTGCAAGGTCTC
CAACAAAGGCCTCCCGTCCTCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCA
GCCCCGAGAGCCACAGGTGTACACCCTGCCCCCATCCCAGGAGGAGATGACCAA
GAACCAGGTACGCCTGACCTGCCTGGTCAAAGGCTTCTACCCCAGCGACATCGCC
GTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACACTACAAGACCACGCCTCC
CGTGCTGGACTCCGACGGCTCCTTCTTCTCTACAGCAGGCTCACCGTGGACAAG
AGCAGGTGGCAGGAGGGGAATGTCTTCTCATGCTCCGTGATGCATGAGGCTCTG
CACAACCACTACACACAGAAGTCCCTCTCCCTGTCTCTGGGTAAATGA

(SEQ ID NO: 442)

HC Amino Acid Sequence

QVQLVESGGGVVQPGRSLRLSCAASGFTFSHYGMHWVRQAPGKGLEWMAIISYDG
SDKYYADSVKGRFTISRDNSENTLYLQMSSLRTEDTAVYYCAKASITGTYFFYGM
DVWGQGTTTVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSG
ALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGKTYTCNVDHKPSNTKVDKRVESK
YGPPCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYV
DGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKT
ISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYK
TTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLGLGK*

(SEQ ID NO: 443)

LC DNA Sequence

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAG
TCACCATCACTTGCCGGGCAAGTCAGAGCATTAGCAGCTATTTAAATTGGTATCA
GCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCTATGCTGCATCCAGTTTGCA
AAGTGGGGTCCCGTCAAGGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTC
ACCATCAGCAGTCTGCAACCTGAAGATTTTGCAACTTACTACTGTCAACAGAGTT
ACAGTACCCCTCCGATCACCTTCGGCCAAGGGACACGACTGGAGATTAAACGAA
CTGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCT
GGAAGTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAG
TACAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCA
CAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCCTGACGCTGA
GCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGG
GCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTTAG

(SEQ ID NO: 414)

LC Amino Acid Sequence

DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGV
PSRFSGSGSGTDFTLTISLQPEDFATYYCQSYSTPPITFGQGRLEIKRTVAAPSVFIF

PPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYS
LSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC*

(SEQ ID NO: 415)

REGN14183

HCVR DNA Sequence

GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
AGACTCTCCTGTGCAGTCTCTGGATTACCTTTAGCAGCTATGTCATGAGCTGGG
TCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTCTCAGCTATTAGTGATAGTG
GTGGTAACACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCAGAG
ACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCAGAGAGCCGAGGACA
CGGCCGTGTATTATTGTGCGAAGGGGGGGCGCAGCAGGTTCCCTTTTGACTIONTG
GGGCCAGGGAACCCTGGTCACCGTCTCCTCA

(SEQ ID NO: 444)

HCVR Amino Acid Sequence

EVQLVESGGGLVQPGGSLRLSCAVSGFTFSSYVMSWVRQAPGKGLEWVSAISDSGG
NTYYADSVKGRFTISRDNKNTLYLQMNSQRAEDTAVYYCAKGGRSRFPFDYWGQ
GTLVTVSS

(SEQ ID NO: 445)

CDR1 DNA Sequence

GGA TTC ACC TTT AGC AGC TAT GTC

(SEQ ID NO: 446)

CDR1 Amino Acid Sequence

G F T F S S Y V

(SEQ ID NO: 447)

CDR2 DNA Sequence

ATT AGT GAT AGT GGT GGT AAC ACA

(SEQ ID NO: 448)

CDR2 Amino Acid Sequence

I S D S G G N T

(SEQ ID NO: 449)

CDR3 DNA Sequence

GCG AAG GGG GGG CGC AGC AGG TTC CCT TTT GAC TAC

(SEQ ID NO: 450)

CDR3 Amino Acid Sequence

A K G G R S R F P F D Y

(SEQ ID NO: 451)

LCVR DNA Sequence

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAG
TCACCATCACTTGCCGGGCAAGTCAGAGCATTAGCAGCTATTTAAATTGGTATCA
GCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCTATGCTGCATCCAGTTTGCA
AAGTGGGGTCCCGTCAAGGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTC
ACCATCAGCAGTCTGCAACCTGAAGATTTTGCAACTTACTACTGTCAACAGAGTT
ACAGTACCCCTCCGATCACCTTCGGCCAAGGGACACGACTGGAGATTAAA

(SEQ ID NO: 408)

LCVR Amino Acid Sequence

DIQMTQSPSSLSASVGDRVITICRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGV
PSRFSGSGSGTDFLTISLQPEDFATYYCQSYSTPPITFGQGTRLEIK

(SEQ ID NO: 409)

CDR1 DNA Sequence

CAG AGC ATT AGC AGC TAT

(SEQ ID NO: 236)

CDR1 Amino Acid Sequence

Q S I S S Y

(SEQ ID NO: 237)

CDR2 DNA Sequence

GCT GCA TCC

(SEQ ID NO: 13)

CDR2 Amino Acid Sequence

A A S

(SEQ ID NO: 14)

CDR3 DNA Sequence

CAA CAG AGT TAC AGT ACC CCT CCG ATC ACC

(SEQ ID NO: 410)

CDR3 Amino Acid Sequence

Q Q S Y S T P P I T

(SEQ ID NO: 411)

HC DNA Sequence

GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
AGACTCTCCTGTGCAGTCTCTGGATTACCTTTAGCAGCTATGTCATGAGCTGGG
TCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTCTCAGCTATTAGTGATAGTG
GTGGTAACACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCAGAG
ACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCAGAGAGCCGAGGACA
CGGCCGTGTATTATTGTGCGAAGGGGGGGCGCAGCAGGTTCCCTTTTACTACTG
GGGCCAGGGAACCCTGGTCACCGTCTCCTCAGCCTCCACCAAGGGCCCATCGGTC
TCCCCCTGGCGCCCTGCTCCAGGAGCACCTCCGAGAGCACAGCCGCCCTGGGCT
GCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCTGTGGAAGTCAAGGCG
CCCTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCAGGACTCTA
CTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACGAAGACCTAC
ACCTGCAACGTAGATCACAAAGCCCAGCAACACCAAGGTGGACAAGAGAGTTGAG
TCCAAATATGGTCCCCCATGCCCACCGTGCCCAGCACCACTGTGGCAGGACCAT
CAGTCTTCCTGTTCCCCC AAAACCAAGGACACTCTCATGATCTCCCGGACCCC
TGAGGTCACGTGCGTGGTGGTGGACGTGAGCCAGGAAGACCCCGAGGTCCAGTT
CAACTGGTACGTGGATGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGA
GGAGCAGTTCAACAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAG
GACTGGCTGAACGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGGCCTCCCG
TCCTCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAGCCACAG
GTGTACACCCTGCCCCCATCCCAGGAGGAGATGACCAAGAACCAGGTCAGCCTG
ACCTGCCTGGTCAAAGGCTTCTACCCAGCGACATCGCCGTGGAGTGGGAGAGC
AATGGGCAGCCGGAGAACAATAAGACCACGCCTCCCGTGCTGGACTCCGAC
GGCTCCTTCTTCTCTACAGCAGGCTCACCGTGGACAAGAGCAGGTGGCAGGAG

GGGAATGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACAC
AGAAGTCCCTCTCCCTGTCTCTGGGTAAATGA

(SEQ ID NO: 452)

HC Amino Acid Sequence

EVQLVESGGGLVQPGGSLRLSCAVSGFTFSSYVMSWVRQAPGKGLEWVSAISDSGG
NTYYADSVKGRFTISRDN SKNTLYLQMNSQRAEDTAVYYCAKGGRSRFPFDYWGQ
GTLTVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGV
HTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNV DHKPSNTKVDKRVESKYGPPCPP
CPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHN
AKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQP
REPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDS
DGSFFLYSRLTVDKSRWQEGNVFSCSV MHEALHNHYTQKSLSLSLGK*

(SEQ ID NO: 453)

LC DNA Sequence

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAG
TCACCATCACTTGCCGGGCAAGTCAGAGCATTAGCAGCTATTTAAATTGGTATCA
GCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCTATGCTGCATCCAGTTTGCA
AAGTGGGGTCCCGTCAAGGTTCAAGTGGCAGTGGATCTGGGACAGATTTCACTCTC
ACCATCAGCAGTCTGCAACCTGAAGATTTTGCAACTTACTACTGTCAACAGAGTT
ACAGTACCCCTCCGATCACCTTCGGCCAAGGGACACGACTGGAGATTAAACGAA
CTGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCT
GGAAGTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAG
TACAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCA
CAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCCTGACGCTGA
GCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGG
GCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTTAG

(SEQ ID NO: 414)

LC Amino Acid Sequence

DIQMTQSPSSLSASVGDRVITICRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGV
PSRFSGSGSGTDFTLTISLQPEDFATYYCQQSYSTPPITFGQGTRLEIKRTVAAPSVFIF
PPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYS
LSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC*

(SEQ ID NO: 415)

REGN14184

HCVR DNA Sequence

GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
AGACTCTCCTGTGCAGCCTCTAAATTCATCTTTAGCAACTATGCCATGACCTGGG
TCCGCCAGGCTCCAGGGAAGGGGCTGGAATGGGTCTCAATTATTAGTGGTAGTG
GTGGAATTCATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCAGAG
ACAATTCCAAGAACACGCTATATCTGCAAATGAACAGCCTGAGAGCCGAGGACA
CGGCCGTTTATTACTGTGCGAAAGGGGGAACAGCTCGAAGCTGGTTCGACCCCT
GGGGCCAGGGAACCCTGGTCACCGTCTCCTCA

(SEQ ID NO: 454)

HCVR Amino Acid Sequence

EVQLVESGGGLVQPGGSLRLSCAASKFIFSNYAMTWVRQAPGKGLEWVSIISGSGGN
SYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCAKGGTARSWFDPWGQG
TLVTVSS

(SEQ ID NO: 455)

CDR1 DNA Sequence

AAA TTC ATC TTT AGC AAC TAT GCC

(SEQ ID NO: 456)

CDR1 Amino Acid Sequence

K F I F S N Y A

(SEQ ID NO: 457)

CDR2 DNA Sequence

ATT AGT GGT AGT GGT GGA AAT TCA

(SEQ ID NO: 458)

CDR2 Amino Acid Sequence

I S G S G G N S

(SEQ ID NO: 459)

CDR3 DNA Sequence

GCG AAA GGG GGA ACA GCT CGA AGC TGG TTC GAC CCC

(SEQ ID NO: 460)

CDR3 Amino Acid Sequence

A K G G T A R S W F D P

(SEQ ID NO: 461)

LCVR DNA Sequence

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAG
TCACCATCACTTGCCGGGCAAGTCAGAGCATTAGCAGCTATTTAAATTGGTATCA

GCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCTATGCTGCATCCAGTTTGCA
AAGTGGGGTCCCGTCAAGGTTCAAGTGGCAGTGGATCTGGGACAGATTTCACTCTC
ACCATCAGCAGTCTGCAACCTGAAGATTTTGCAACTTACTACTGTCAACAGAGTT
ACAGTACCCCTCCGATCACCTTCGGCCAAGGGACACGACTGGAGATTAAA

(SEQ ID NO: 408)

LCVR Amino Acid Sequence

DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGV
PSRFSGSGSGTDFLTITSLQPEDFATYYCQSYSTPPITFGQGTRLEIK

(SEQ ID NO: 409)

CDR1 DNA Sequence

CAG AGC ATT AGC AGC TAT

(SEQ ID NO: 236)

CDR1 Amino Acid Sequence

Q S I S S Y

(SEQ ID NO: 237)

CDR2 DNA Sequence

GCT GCA TCC

(SEQ ID NO: 13)

CDR2 Amino Acid Sequence

A A S

(SEQ ID NO: 14)

CDR3 DNA Sequence

CAA CAG AGT TAC AGT ACC CCT CCG ATC ACC

(SEQ ID NO: 410)

CDR3 Amino Acid Sequence

Q Q S Y S T P P I T

(SEQ ID NO: 411)

HC DNA Sequence

GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
AGACTCTCCTGTGCAGCCTCTAAATTCATCTTTAGCAACTATGCCATGACCTGGG
TCCGCCAGGCTCCAGGGAAGGGGCTGGAATGGGTCTCAATTATTAGTGGTAGTG
GTGGAAATTCATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCAGAG
ACAATTCCAAGAACACGCTATATCTGCAAATGAACAGCCTGAGAGCCGAGGACA
CGGCCGTTTATTACTGTGCGAAAGGGGGAACAGCTCGAAGCTGGTTCGACCCCT
GGGGCCAGGGAACCCTGGTCACCGTCTCCTCAGCCTCCACCAAGGGCCCATCGG
TCTTCCCCCTGGCGCCCTGCTCCAGGAGCACCTCCGAGAGCACAGCCGCCCTGGG
CTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCTGTGGAATCAGGC
GCCCTGACCAGCGGCGTGCACACCTTCCCGGCTGTCTTACAGTCCTCAGGACTCT
ACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACGAAGACCT
ACACCTGCAACGTAGATCACAAAGCCCAGCAACACCAAGGTGGACAAGAGAGTTG
AGTCCAAATATGGTCCCCCATGCCCACCGTGCCCAGCACCACTGTGGCAGGACC
ATCAGTCTTCCTGTTCCCCCAAAACCAAGGACACTCTCATGATCTCCCGGACC
CCTGAGGTCACGTGCGTGGTGGTGGACGTGAGCCAGGAAGACCCCGAGGTCCAG
TTCAACTGGTACGTGGATGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGG
GAGGAGCAGTTCAACAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACC
AGGACTGGCTGAACGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGGCCTCC

CGTCCTCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAGCCAC
AGGTGTACACCCTGCCCCATCCCAGGAGGAGATGACCAAGAACCAGGTCAGCC
TGACCTGCCTGGTCAAAGGCTTCTACCCAGCGACATCGCCGTGGAGTGGGAGA
GCAATGGGCAGCCGGAGAACAACCTACAAGACCACGCCTCCCGTGCTGGACTCCG
ACGGCTCCTTCTTCCTCTACAGCAGGCTCACCGTGGACAAGAGCAGGTGGCAGG
AGGGGAATGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACAC
ACAGAAGTCCCTCTCCCTGTCTCTGGGTAAATGA

(SEQ ID NO: 462)

HC Amino Acid Sequence

EVQLVESGGGLVQPGGSLRLSCAASKFIFSNYAMTWVRQAPKGLEWVSIISGSGGN
SYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCAKGGTARSWFDPWGQG
TLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVH
TFPAVLQSSGLYSLSSVTVPSSSLGKTYTCNV DHKPSNTKVDKRVESKYGPPCPPC
PAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNA
KTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPR
EPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSD
GSFFLYSRLTVDKSRWQEGNVFSCSV MHEALHNHYTQKSLSLGLK*

(SEQ ID NO: 463)

LC DNA Sequence

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAG
TCACCATCACTTGCCGGGCAAGTCAGAGCATTAGCAGCTATTTAAATTGGTATCA
GCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCTATGCTGCATCCAGTTTGCA
AAGTGGGGTCCCGTCAAGGTTCAAGTGGCAGTGGATCTGGGACAGATTTCACTCTC
ACCATCAGCAGTCTGCAACCTGAAGATTTTGCAACTTACTACTGTCAACAGAGTT
ACAGTACCCCTCCGATCACCTTCGGCCAAGGGACACGACTGGAGATTAAACGAA
CTGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCT
GGAAGTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCAGAGAGGCCAAAG

TACAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCA
CAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCCTGACGCTGA
GCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGG
GCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTTAG

(SEQ ID NO: 414)

LC Amino Acid Sequence

DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGV
PSRFSGSGSGTDFLTISLQPEDFATYYCQSYSTPPITFGQGTRLEIKRTVAAPSVFIF
PPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYS
LSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC*

(SEQ ID NO: 415)

REGN14185

HCVR DNA Sequence

GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
AGACTCTCCTGTGCAGCCTCTGGATTCACTCTTAGCAGCTATGCCATGAGCTGGG
TCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTCTCAGCAATTAGTGATAGTG
GTGATAACAAATACACGCAGACTCCGTGAAGGGCCGGTTCTCCATCTCCAGAG
ACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACG
CGGCCGTATATTACTGTGCGAAAGGGGGGAGAACTAGAACTCCTTTTGACTATTG
GGGCCAGGGAACCCTGGTCACCGTCTCCTCA

(SEQ ID NO: 464)

HCVR Amino Acid Sequence

EVQLVESGGGLVQPGGSLRLSCAASGFTLSSYAMSWVRQAPGKGLEWVSAISDSGD
NKYHADSVKGRFSISRDN SKNTLYLQMNSLRAEDAAVYYCAKGGRTTRTPFDYWGQ
GTLVTVSS

(SEQ ID NO: 465)

CDR1 DNA Sequence

GGA TTC ACT CTT AGC AGC TAT GCC

(SEQ ID NO: 466)

CDR1 Amino Acid Sequence

G F T L S S Y A

(SEQ ID NO: 467)

CDR2 DNA Sequence

ATT AGT GAT AGT GGT GAT AAC AAA

(SEQ ID NO: 468)

CDR2 Amino Acid Sequence

I S D S G D N K

(SEQ ID NO: 469)

CDR3 DNA Sequence

GCG AAA GGG GGG AGA ACT AGA ACT CCT TTT GAC TAT

(SEQ ID NO: 470)

CDR3 Amino Acid Sequence

A K G G R T R T P F D Y

(SEQ ID NO: 471)

LCVR DNA Sequence

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAG
TCACCATCACTTGCCGGGCAAGTCAGAGCATTAGCAGCTATTTAAATTGGTATCA
GCAGAAACCAGGGAAAGCCCCCTAAGCTCCTGATCTATGCTGCATCCAGTTTGCA
AAGTGGGGTCCCGTCAAGGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTC
ACCATCAGCAGTCTGCAACCTGAAGATTTTGCAACTTACTACTGTCAACAGAGTT
ACAGTACCCCTCCGATCACCTTCGGCCAAGGGACACGACTGGAGATTAAA

(SEQ ID NO: 408)

LCVR Amino Acid Sequence

DIQMTQSPSSLSASVGDRVITTCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGV
PSRFSGSGSGTDFLTITSLQPEDFATYYCQQSYSTPPITFGQGTRLEIK

(SEQ ID NO: 409)

CDR1 DNA Sequence

CAG AGC ATT AGC AGC TAT

(SEQ ID NO: 236)

CDR1 Amino Acid Sequence

Q S I S S Y

(SEQ ID NO: 237)

CDR2 DNA Sequence

GCT GCA TCC

(SEQ ID NO: 13)

CDR2 Amino Acid Sequence

A A S

(SEQ ID NO: 14)

CDR3 DNA Sequence

CAA CAG AGT TAC AGT ACC CCT CCG ATC ACC

(SEQ ID NO: 410)

CDR3 Amino Acid Sequence

Q Q S Y S T P P I T

(SEQ ID NO: 411)

HC DNA Sequence

GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
AGACTCTCCTGTGCAGCCTCTGGATTCACTCTTAGCAGCTATGCCATGAGCTGGG
TCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTCTCAGCAATTAGTGATAGTG
GTGATAACAAATACACGCAGACTCCGTGAAGGGCCGGTTCTCCATCTCCAGAG
ACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACG
CGGCCGTATATTACTGTGCGAAAGGGGGGAGAACTAGAACTCCTTTTGACTATTG
GGGCCAGGGAACCCTGGTCACCGTCTCCTCAGCCTCCACCAAGGGCCCATCGGTC
TTCCCCCTGGCGCCCTGCTCCAGGAGCACCTCCGAGAGCACAGCCGCCCTGGGCT
GCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCTGTGGAACCTCAGGCG
CCCTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCAGGACTCTA
CTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACGAAGACCTAC
ACCTGCAACGTAGATCACAAAGCCCAGCAACACCAAGGTGGACAAGAGAGTTGAG
TCCAAATATGGTCCCCCATGCCCACCGTGCCCAGCACCACTGTGGCAGGACCAT

CAGTCTTCCTGTTCCCCCAAACCCAAGGACACTCTCATGATCTCCCGGACCCC
TGAGGTCACGTGCGTGGTGGTGGACGTGAGCCAGGAAGACCCCGAGGTCCAGTT
CAACTGGTACGTGGATGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGA
GGAGCAGTTCAACAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAG
GACTGGCTGAACGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGGCCTCCCG
TCCTCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAGCCACAG
GTGTACACCCCTGCCCCCATCCCAGGAGGAGATGACCAAGAACCAGGTCAGCCTG
ACCTGCCTGGTCAAAGGCTTCTACCCAGCGACATCGCCGTGGAGTGGGAGAGC
AATGGGCAGCCGGAGAACAACACTACAAGACCACGCCTCCCGTGCTGGACTCCGAC
GGCTCCTTCTTCTCTACAGCAGGCTCACCGTGGACAAGAGCAGGTGGCAGGAG
GGGAATGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACAC
AGAAGTCCCTCTCCCTGTCTCTGGGTAAATGA

(SEQ ID NO: 472)

HC Amino Acid Sequence

EVQLVESGGGLVQPGGSLRLSCAASGFTLSSYAMSWVRQAPGKGLEWVSAISDSGD
NKYHADSVKGRFSISRDN SKNTLYLQMNSLRAEDAAVYYCAKGGRTTRTPFDYWGQ
GTLTVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGV
HTFPAVLQSSGLYSLSSVTVPSSSLGKTYTCNV DHKPSNTKVDKRVESKYGPPCPP
CPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVDVSQEDPEVQFNWYVDGVEVHN
AKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQP
REPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDS
DGSFFLYSRLTVDKSRWQEGNVFSCSV MHEALHNHYTQKSLSLSLGK*

(SEQ ID NO: 473)

LC DNA Sequence

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAG
TCACCATCACTTGCCGGGCAAGTCAGAGCATTAGCAGCTATTTAAATTGGTATCA
GCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCTATGCTGCATCCAGTTTGCA

AAGTGGGGTCCCGTCAAGGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTC
ACCATCAGCAGTCTGCAACCTGAAGATTTTGCAACTTACTACTGTCAACAGAGTT
ACAGTACCCCTCCGATCACCTTCGGCCAAGGGACACGACTGGAGATTAACGAA
CTGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCT
GGAAGTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAG
TACAGTGGAAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCA
CAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCTGACGCTGA
GCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGG
GCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTTAG

(SEQ ID NO: 414)

LC Amino Acid Sequence

DIQMTQSPSSLSASVGDRVITITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGV
PSRFSGSGSGTDFLTITSLQPEDFATYYCQQSYSTPPITFGQGTRLEIKRTVAAPSVFIF
PPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYS
LSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC*

(SEQ ID NO: 415)

REGN14186

HCVR DNA Sequence

GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
AGACTCTCCTGTGCAGCCTCTGGATTCACCTTTAGCGCCTATGCCATGACCTGGG
TCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTCTCACTTATTAGTGGAAGTG
GTGGTAACACATACTATGCAGACACCGTGAAGGGCCGGTCCACCATCTCCAGAG
ACAAC TCCAAGACCACGCTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACA
CGGCCGTATATTACTGTGCGAAATGGGGCCTAATGGTGTATGCTATGAGGGCCTT
TGACTATTGGGGCCAGGGAACCTGGTCACCGTCTCCTCA

(SEQ ID NO: 474)

HCVR Amino Acid Sequence

EVQLVESGGGLVQPGGSLRLSCAASGFTFSAYAMTWVRQAPGKGLEWVSLISGSGG
NTYYADTVKGRSTISRDNSTTLYLQMNSLRAEDTAVYYCAKWGLMVYAMRAFD
YWGQGTLVTVSS

(SEQ ID NO: 475)

CDR1 DNA Sequence

GGA TTC ACC TTT AGC GCC TAT GCC

(SEQ ID NO: 476)

CDR1 Amino Acid Sequence

G F T F S A Y A

(SEQ ID NO: 477)

CDR2 DNA Sequence

ATT AGT GGA AGT GGT GGT AAC ACA

(SEQ ID NO: 478)

CDR2 Amino Acid Sequence

I S G S G G N T

(SEQ ID NO: 158)

CDR3 DNA Sequence

GCG AAA TGG GGC CTA ATG GTG TAT GCT ATG AGG GCC TTT GAC TAT

(SEQ ID NO: 479)

CDR3 Amino Acid Sequence

A K W G L M V Y A M R A F D Y

(SEQ ID NO: 480)

LCVR DNA Sequence

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAG
TCACCATCACTTGCCGGGCAAGTCAGAGCATTAGCAGCTATTTAAATTGGTATCA
GCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCTATGCTGCATCCAGTTTGCA
AAGTGGGGTCCCGTCAAGGTTCAAGTGGCAGTGGATCTGGGACAGATTTCACTCTC
ACCATCAGCAGTCTGCAACCTGAAGATTTTGCAACTTACTACTGTCAACAGAGTT
ACAGTACCCCTCCGATCACCTTCGGCCAAGGGACACGACTGGAGATTTAA

(SEQ ID NO: 408)

LCVR Amino Acid Sequence

DIQMTQSPSSLSASVGDRVITTCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGV
PSRFSGSGSGTDFTLTISLQPEDFATYYCQSYSTPPITFGQGTRLEIK

(SEQ ID NO: 409)

CDR1 DNA Sequence

CAG AGC ATT AGC AGC TAT

(SEQ ID NO: 236)

CDR1 Amino Acid Sequence

Q S I S S Y

(SEQ ID NO: 237)

CDR2 DNA Sequence

GCT GCA TCC

(SEQ ID NO: 13)

CDR2 Amino Acid Sequence

A A S

(SEQ ID NO: 14)

CDR3 DNA Sequence

CAA CAG AGT TAC AGT ACC CCT CCG ATC ACC

(SEQ ID NO: 410)

CDR3 Amino Acid Sequence

Q Q S Y S T P P I T

(SEQ ID NO: 411)

HC DNA Sequence

GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
 AGACTCTCCTGTGCAGCCTCTGGATTACCTTTAGCGCCTATGCCATGACCTGGG
 TCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTCTCACTTATTAGTGGAAGTG
 GTGGTAACACATACTATGCAGACACCGTGAAGGGCCGGTCCACCATCTCCAGAG
 ACAACTCCAAGACCACGCTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACA
 CGGCCGTATATTACTGTGCGAAATGGGGCCTAATGGTGTATGCTATGAGGGCCTT
 TGACTATTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCAGCCTCCACCAAGGGC
 CCATCGGTCTTCCCCCTGGCGCCCTGCTCCAGGAGCACCTCCGAGAGCACAGCCG

CCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCGTGGAA
CTCAGGCGCCCTGACCAGCGGCGTGACACCTTCCCGGCTGTCCTACAGTCCTCA
GGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGTTGGGCACGA
AGACCTACACCTGCAACGTAGATCACAAAGCCCAGCAACACCAAGGTGGACAAGA
GAGTTGAGTCCAAATATGGTCCCCCATGCCCACCGTGCCCAGCACCACTGTGGC
AGGACCATCAGTCTTCTGTTCCTGTTCCCCCAAAACCCAAGGACACTCTCATGATCTCC
CGGACCCCTGAGGTACGTGCGTGGTGGTGGACGTGAGCCAGGAAGACCCCGAG
GTCCAGTTCAACTGGTACGTGGATGGCGTGGAGGTGCATAATGCCAAGACAAAG
CCGCGGGAGGAGCAGTTCAACAGCACGTACCGTGTGGTCAGCGTCCTACCGTC
CTGCACCAGGACTGGCTGAACGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAA
GGCCTCCCGTCCTCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGA
GAGCCACAGGTGTACACCCTGCCCCATCCCAGGAGGAGATGACCAAGAACCAG
GTCAGCCTGACCTGCCTGGTCAAAGGCTTCTACCCCAGCGACATCGCCGTGGAGT
GGGAGAGCAATGGGCAGCCGGAGAACAACACTACAAGACCACGCCTCCCGTGCTGG
ACTCCGACGGCTCCTTCTTCTCTACAGCAGGCTCACCGTGGACAAGAGCAGGTG
GCAGGAGGGGAATGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCAC
TACACACAGAAGTCCCTCTCCCTGTCTCTGGGTAAATGA

(SEQ ID NO: 481)

HC Amino Acid Sequence

EVQLVESGGGLVQPGGSLRLSCAASGFTFSAYAMTWVRQAPGKGLEWVSLISGGG
NTYYADTVKGRSTISRDNSTTLYLQMNSLRAEDTAVYYCAKWGLMVYAMRAFD
YWQGQTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGA
LTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGKTYTCNVDPHKPSNTKVDKRVESKY
GPPCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVD
GVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTIS
KAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
TPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMEALHNHYTQKSLSLGLK*

(SEQ ID NO: 482)

LC DNA Sequence

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAG
TCACCATCACTTGCCGGGCAAGTCAGAGCATTAGCAGCTATTTAAATTGGTATCA
GCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCTATGCTGCATCCAGTTTGCA
AAGTGGGGTCCCGTCAAGGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTC
ACCATCAGCAGTCTGCAACCTGAAGATTTTGCAACTTACTACTGTCAACAGAGTT
ACAGTACCCCTCCGATCACCTTCGGCCAAGGGACACGACTGGAGATTAAACGAA
CTGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCT
GGAAGTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAG
TACAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCA
CAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCTGACGCTGA
GCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGG
GCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTTAG

(SEQ ID NO: 414)

LC Amino Acid Sequence

DIQMTQSPSSLSASVGDRVITITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGV
PSRFSGSGSGTDFLTITSLQPEDFATYYCQSYSTPPITFGQGTRLEIKRTVAAPSVFIF
PPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSTYS
LSSLTTLTKADYEEKHKVYACEVTHQGLSSPVTKSFNRGEC*

(SEQ ID NO: 415)

REGN14187

HCVR DNA Sequence

GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCGGGGGGGTCCCTG
AGACTCTCCTGTGCAGCCTCTGGATTACCTTTAGTTACTATTGGATGAACTGGG
TCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCAACATAAAGCAAGATG
GAAGTGAGAAATACTATGTGGACTCTGTGAAGGGCCGAGTCACCATCTCCAGAG

ACAACGCCAAGAACTCACTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACA
CGGGTGTGTATTACTGTGCGACAGATAAGGTTTCGCGGGCGATACCACGACCACT
ACGGTTTGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCA

(SEQ ID NO: 483)

HCVR Amino Acid Sequence

EVQLVESGGGLVQPGGSLRLSCAASGFTFSYYWMNWVRQAPGKGLEWVANIKQDG
SEKYYVDSVKGRVTISRDNAKNSLYLQMNSLRAEDTGVYYCATDKVRGRYHDHYG
LDVWGQGTTVTVSS

(SEQ ID NO: 484)

CDR1 DNA Sequence

GGA TTC ACC TTT AGT TAC TAT TGG

(SEQ ID NO: 485)

CDR1 Amino Acid Sequence

G F T F S Y Y W

(SEQ ID NO: 486)

CDR2 DNA Sequence

ATA AAG CAA GAT GGA AGT GAG AAA

(SEQ ID NO: 487)

CDR2 Amino Acid Sequence

I K Q D G S E K

(SEQ ID NO: 283)

CDR3 DNA Sequence

GCG ACA GAT AAG GTT CGC GGG CGA TAC CAC GAC CAC TAC GGT TTG GAC
GTC

(SEQ ID NO: 488)

CDR3 Amino Acid Sequence

A T D K V R G R Y H D H Y G L D V

(SEQ ID NO: 489)

LCVR DNA Sequence

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAG
TCACCATCACTTGCCGGGCAAGTCAGAGCATTAGCAGCTATTTAAATTGGTATCA
GCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCTATGCTGCATCCAGTTTGCA
AAGTGGGGTCCCGTCAAGGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTC
ACCATCAGCAGTCTGCAACCTGAAGATTTTGCAACTTACTACTGTCAACAGAGTT
ACAGTACCCCTCCGATCACCTTCGGCCAAGGGACACGACTGGAGATTAAA

(SEQ ID NO: 408)

LCVR Amino Acid Sequence

DIQMTQSPSSLSASVGDRVITICRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGV
PSRFSGSGSGTDFLTISLQPEDFATYYCQQSYSTPPITFGQGTRLEIK

(SEQ ID NO: 409)

CDR1 DNA Sequence

CAG AGC ATT AGC AGC TAT

(SEQ ID NO: 236)

CDR1 Amino Acid Sequence

Q S I S S Y

(SEQ ID NO: 237)

CDR2 DNA Sequence

GCT GCA TCC

(SEQ ID NO: 13)

CDR2 Amino Acid Sequence

A A S

(SEQ ID NO: 14)

CDR3 DNA Sequence

CAA CAG AGT TAC AGT ACC CCT CCG ATC ACC

(SEQ ID NO: 410)

CDR3 Amino Acid Sequence

Q Q S Y S T P P I T

(SEQ ID NO: 411)

HC DNA Sequence

GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCGGGGGGGTCCCTG
AGACTCTCCTGTGCAGCCTCTGGATTACCTTTAGTTACTATTGGATGAACTGGG

TCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCAACATAAAGCAAGATG
GAAGTGAGAAATACTATGTGGACTCTGTGAAGGGCCGAGTCACCATCTCCAGAG
ACAACGCCAAGAACTCACTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACA
CGGGTGTGTATTACTGTGCGACAGATAAGGTTTCGCGGGCGATACCACGACCACT
ACGGTTTGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCAGCCTCCAC
CAAGGGCCCATCGGTCTTCCCCCTGGCGCCCTGCTCCAGGAGCACCTCCGAGAGC
ACAGCCGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGT
CGTGGAATCAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGTGTCTCTACA
GTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTG
GGCACGAAGACCTACACCTGCAACGTAGATCACAAGCCCAGCAACACCAAGGTG
GACAAGAGAGTTGAGTCCAAATATGGTCCCCCATGCCCACCGTGCCCAGCACCA
CCTGTGGCAGGACCATCAGTCTTCTGTTCCTGTTCCCCC AAAACCAAGGACACTCTCA
TGATCTCCCGGACCCCTGAGGTCACGTGCGTGGTGGTGGACGTGAGCCAGGAAG
ACCCCGAGGTCCAGTTCAACTGGTACGTGGATGGCGTGGAGGTGCATAATGCCA
AGACAAAGCCGCGGGAGGAGCAGTTCAACAGCACGTACCGTGTGGTCAGCGTCC
TCACCGTCTGCACCAGGACTGGCTGAACGGCAAGGAGTACAAGTGCAAGGTCT
CCAACAAAGGCCTCCCGTCTCCATCGAGAAAACCATCTCCAAAGCCAAAGGGC
AGCCCCGAGAGCCACAGGTGTACACCCTGCCCCCATCCCAGGAGGAGATGACCA
AGAACCAGGTACGCTGACCTGCCTGGTCAAAGGCTTCTACCCCAGCGACATCG
CCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACA ACTACAAGACCACGCCT
CCCGTGCTGGACTCCGACGGCTCCTTCTTCTCTACAGCAGGCTCACCGTGGACA
AGAGCAGGTGGCAGGAGGGGAATGTCTTCTCATGCTCCGTGATGCATGAGGCTC
TGCACAACCACTACACACAGAAGTCCCTCTCCCTGTCTCTGGGTAAATGA

(SEQ ID NO: 490)

HC Amino Acid Sequence

EVQLVESGGGLVQPGGSLRLSCAASGFTFSYYWMNWVRQAPGKGLEWVANIKQDG
SEKYYVDSVKGRVTISRDNKNSLYLQMNSLRAEDTGVIYCATDKVRGRYHDHYG
LDVWGQGTITVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNS
GALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGKTYTCNVDPKPSNTKVDKRVES

KYGPPCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWY
VDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEK
TISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNY
KTTTPVLDSGDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNYHTQKSLSLSLGK*

(SEQ ID NO: 491)

LC DNA Sequence

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAG
TCACCATCACTTGCCGGGCAAGTCAGAGCATTAGCAGCTATTTAAATTGGTATCA
GCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCTATGCTGCATCCAGTTTGCA
AAGTGGGGTCCCGTCAAGGTTCAAGTGGCAGTGGATCTGGGACAGATTTCACTCTC
ACCATCAGCAGTCTGCAACCTGAAGATTTTGCAACTTACTACTGTCAACAGAGTT
ACAGTACCCCTCCGATCACCTTCGGCCAAGGGACACGACTGGAGATTAAACGAA
CTGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCT
GGAAGTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAG
TACAGTGGAAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCA
CAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCCTGACGCTGA
GCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGG
GCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTTAG

(SEQ ID NO: 414)

LC Amino Acid Sequence

DIQMTQSPSSLSASVGDRVITITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGV
PSRFSGSGSGTDFLTITSLQPEDFATYYCQQSYSTPPITFGQGRLEIKRTVAAPSVFIF
PPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKSTYS
LSSTLTLSKADYEEKHKVYACEVTHQGLSSPVTKSFNRGEC*

(SEQ ID NO: 415)

REGN14188

HCVR DNA Sequence

GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
AGACTCTCCTGTGCAGCCTCTGGATTACCTTTACCAACTATGCCATGAGCTGGG
TCCGCCAGGCTCCAGGGAAGGGTCTGGAGTGGGTCTCAACTATTAGTGATAGTG
GTGGTGGCACATACTACGCAGACTCCGTGAGGGGCCGGTTCACCATCTCCAGAG
ACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACA
CGGCCATATATTTCTGTGCGAAAGGGACAAGATCTCGTTTCCCCTTGGACTIONT
GGGCCAGGGAACCCTGGTCACCGTCTCCTCA

(SEQ ID NO: 492)

HCVR Amino Acid Sequence

EVQLVESGGGLVQPGGSLRLSCAASGFTFTNYAMSWVRQAPGKGLEWVSTISDSGG
GTYTADSVRGRFTISRDNKNTLYLQMNSLRAEDTAIFYCAKGRSRFPLDYWGQG
TLVTVSS

(SEQ ID NO: 493)

CDR1 DNA Sequence

GGA TTC ACC TTT ACC AAC TAT GCC

(SEQ ID NO: 494)

CDR1 Amino Acid Sequence

G F T F T N Y A

(SEQ ID NO: 495)

CDR2 DNA Sequence

ATT AGT GAT AGT GGT GGT GGC ACA

(SEQ ID NO: 496)

CDR2 Amino Acid Sequence

I S D S G G G T

(SEQ ID NO: 497)

CDR3 DNA Sequence

GCG AAA GGG ACA AGA TCT CGT TTC CCC TTG GAC TAC

(SEQ ID NO: 498)

CDR3 Amino Acid Sequence

A K G T R S R F P L D Y

(SEQ ID NO: 499)

LCVR DNA Sequence

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAG
TCACCATCACTTGCCGGGCAAGTCAGAGCATTAGCAGCTATTTAAATTGGTATCA
GCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCTATGCTGCATCCAGTTTGCA
AAGTGGGGTCCCGTCAAGGTTCAAGTGGCAGTGGATCTGGGACAGATTTCACTCTC
ACCATCAGCAGTCTGCAACCTGAAGATTTGCAACTTACTACTGTCAACAGAGTT
ACAGTACCCCTCCGATCACCTTCGGCCAAGGGACACGACTGGAGATTAAA

(SEQ ID NO: 408)

LCVR Amino Acid Sequence

DIQMTQSPSSLSASVGDRVITICRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGV
PSRFSGSGSGTDFLTISLQPEDFATYYCQSYSTPPITFGQGTRLEIK

(SEQ ID NO: 409)

CDR1 DNA Sequence

CAG AGC ATT AGC AGC TAT

(SEQ ID NO: 236)

CDR1 Amino Acid Sequence

Q S I S S Y

(SEQ ID NO: 237)

CDR2 DNA Sequence

GCT GCA TCC

(SEQ ID NO: 13)

CDR2 Amino Acid Sequence

A A S

(SEQ ID NO: 14)

CDR3 DNA Sequence

CAA CAG AGT TAC AGT ACC CCT CCG ATC ACC

(SEQ ID NO: 410)

CDR3 Amino Acid Sequence

Q Q S Y S T P P I T

(SEQ ID NO: 411)

HC DNA Sequence

GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
AGACTCTCCTGTGCAGCCTCTGGATTACCTTTACCAACTATGCCATGAGCTGGG
TCCGCCAGGCTCCAGGGAAGGGTCTGGAGTGGGTCTCAACTATTAGTGATAGTG
GTGGTGGCACATACTACGCAGACTCCGTGAGGGGCGGTTACCATCTCCAGAG
ACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACA
CGGCCATATATTTCTGTGCGAAAGGGACAAGATCTCGTTTCCCCTTGGACTACTG
GGGCCAGGGAACCCTGGTCACCGTCTCCTCAGCCTCCACCAAGGGCCCATCGGTC
TCCCCCTGGCGCCCTGCTCCAGGAGCACCTCCGAGAGCACAGCCGCCCTGGGCT
GCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCTGGAACCTCAGGCG
CCCTGACCAGCGGCGTGCACACCTTCCCGGTGTCCTACAGTCCTCAGGACTCTA
CTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACGAAGACCTAC
ACCTGCAACGTAGATCACAAAGCCCAGCAACACCAAGGTGGACAAGAGAGTTGAG
TCCAAATATGGTCCCCCATGCCCACCGTGCCCAGCACCACTGTGGCAGGACCAT
CAGTCTTCCTGTTCCCCCAAACCCAAGGACACTCTCATGATCTCCCGGACCCC
TGAGGTACAGTGCCTGGTGGTGGACGTGAGCCAGGAAGACCCCGAGGTCCAGTT
CAACTGGTACGTGGATGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGA
GGAGCAGTTCAACAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAG
GACTGGCTGAACGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGGCCTCCCG
TCCTCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAGCCACAG
GTGTACACCCTGCCCCCATCCCAGGAGGAGATGACCAAGAACCAGGTCAGCCTG
ACCTGCCTGGTCAAAGGCTTCTACCCAGCGACATCGCCGTGGAGTGGGAGAGC
AATGGGCAGCCGGAGAACAACCTACAAGACCACGCCTCCCGTGCTGGACTCCGAC
GGCTCCTTCTTCCTCTACAGCAGGCTCACCGTGGACAAGAGCAGGTGGCAGGAG
GGGAATGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACAC
AGAAGTCCCTCTCCCTGTCTCTGGGTAAATGA

(SEQ ID NO: 500)

HC Amino Acid Sequence

EVQLVESGGGLVQPGGSLRLSCAASGFTFTNYAMSWVRQAPGKGLEWVSTISDSGG
GTYTADSVRGRFTISRDN SKNTLYLQMNSLRAEDTAIFYCAKGTRSRFPLDYWGQG
TLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVH
TFPAVLQSSGLYSLSSVTVPSSSLGKTYTCNV DHKPSNTKVDKRVESKYGPPCPPC
PAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNA
KTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPR
EPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSD
GSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK*

(SEQ ID NO: 501)

LC DNA Sequence

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAG
TCACCATCACTTGCCGGGCAAGTCAGAGCATTAGCAGCTATTTAAATTGGTATCA
GCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCTATGCTGCATCCAGTTTGCA
AAGTGGGGTCCCGTCAAGGTTCAAGTGGCAGTGGATCTGGGACAGATTTCACTCTC
ACCATCAGCAGTCTGCAACCTGAAGATTTTGCAACTTACTACTGTCAACAGAGTT
ACAGTACCCCTCCGATCACCTTCGGCCAAGGGACACGACTGGAGATTAAACGAA
CTGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCT
GGAAGTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAG
TACAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCA
CAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCCTGACGCTGA
GCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGG
GCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTTAG

(SEQ ID NO: 414)

LC Amino Acid Sequence

DIQMTQSPSSLSASVGDRVITICRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGV
PSRFSGSGSGTDFTLTISLQPEDFATYYCQSYSTPPITFGQGRLEIKRTVAAPSVFIF

PPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSTYS
LSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC*

(SEQ ID NO: 415)

REGN14189

HCVR DNA Sequence

GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
AGCCTCTCCTGTGCAGCCTCTGGATTACCTTTATCAACTATGCCATGACCTGGGT
CCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTCTCAATTATAAGTGGTAGTGG
TGGTAGAAAGTACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCAGAGA
CAATTCCAAGAACACGCTGTCTCTGCAAATGAACAGCCTGAGAGCCGAGGACAC
GGCCGTATATTACTGTGCGAGATTTCCGGGTTTAGCAGCAGCCGTCTTAGACTAC
TGGGGCCAGGGAACCCTGGTCACCGTCTCCTCA

(SEQ ID NO: 502)

HCVR Amino Acid Sequence

EVQLVESGGGLVQPGGSLSLSCAASGFTFINYAMTWVRQAPGKGLEWVSIISGSGGR
KYYADSVKGRFTISRDNKNTLSLQMNSLRAEDTAVYYCARFPGLAAAVLDYWGQ
GTLVTVSS

(SEQ ID NO: 503)

CDR1 DNA Sequence

GGA TTC ACC TTT ATC AAC TAT GCC

(SEQ ID NO: 504)

CDR1 Amino Acid Sequence

G F T F I N Y A

(SEQ ID NO: 505)

CDR2 DNA Sequence

ATA AGT GGT AGT GGT GGT AGA AAG

(SEQ ID NO: 506)

CDR2 Amino Acid Sequence

I S G S G G R K

(SEQ ID NO: 507)

CDR3 DNA Sequence

GCG AGA TTT CCG GGT TTA GCA GCA GCC GTC TTA GAC TAC

(SEQ ID NO: 508)

CDR3 Amino Acid Sequence

A R F P G L A A A V L D Y

(SEQ ID NO: 509)

LCVR DNA Sequence

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAG
TCACCATCACTTGCCGGGCAAGTCAGAGCATTAGCAGCTATTTAAATTGGTATCA
GCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCTATGCTGCATCCAGTTTGCA
AAGTGGGGTCCCGTCAAGGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTC
ACCATCAGCAGTCTGCAACCTGAAGATTTTGCAACTTACTACTGTCAACAGAGTT
ACAGTACCCCTCCGATCACCTTCGGCCAAGGGACACGACTGGAGATTAAA

(SEQ ID NO: 408)

LCVR Amino Acid Sequence

DIQMTQSPSSLSASVGDRVITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGV
PSRFSGSGSGTDFLTISLQPEDFATYYCQSYSTPPITFGQGTRLEIK

(SEQ ID NO: 409)

CDR1 DNA Sequence

CAG AGC ATT AGC AGC TAT

(SEQ ID NO: 236)

CDR1 Amino Acid Sequence

Q S I S S Y

(SEQ ID NO: 237)

CDR2 DNA Sequence

GCT GCA TCC

(SEQ ID NO: 13)

CDR2 Amino Acid Sequence

A A S

(SEQ ID NO: 14)

CDR3 DNA Sequence

CAA CAG AGT TAC AGT ACC CCT CCG ATC ACC

(SEQ ID NO: 410)

CDR3 Amino Acid Sequence

Q Q S Y S T P P I T

(SEQ ID NO: 411)

HC DNA Sequence

GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
AGCCTCTCCTGTGCAGCCTCTGGATTACCTTTATCAACTATGCCATGACCTGGGT
CCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTCTCAATTATAAGTGGTAGTGG
TGGTAGAAAGTACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCAGAGA
CAATTCCAAGAACACGCTGTCTCTGCAAATGAACAGCCTGAGAGCCGAGGACAC
GGCCGTATATTACTGTGCGAGATTTCCGGGTTTAGCAGCAGCCGTCTTAGACTAC
TGGGGCCAGGGAACCCTGGTCACCGTCTCCTCAGCCTCCACCAAGGGCCCATCG
GTCTTCCCCCTGGCGCCCTGCTCCAGGAGCACCTCCGAGAGCACAGCCGCCCTGG
GCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCTGTGGAACCTCAG
GCGCCCTGACCAGCGGCGTGCACACCTTCCCGGCTGTCTACAGTCCTCAGGACT
CTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACGAAGACC
TACACCTGCAACGTAGATCACAAGCCCAGCAACACCAAGGTGGACAAGAGAGTT
GAGTCCAAATATGGTCCCCCATGCCACCGTGCCCAGCACCACTGTGGCAGGA
CCATCAGTCTTCCTGTTCCCCCAAAACCAAGGACACTCTCATGATCTCCCGGA
CCCCTGAGGTCACGTGCGTGGTGGTGGACGTGAGCCAGGAAGACCCCGAGGTCC
AGTTCAACTGGTACGTGGATGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGC
GGGAGGAGCAGTTCAACAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCTGC
ACCAGGACTGGCTGAACGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGGCC
TCCCGTCTCTCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAGC
CACAGGTGTACACCCTGCCCCCATCCCAGGAGGAGATGACCAAGAACCAGGTCA
GCCTGACCTGCCTGGTCAAAGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGG
AGAGCAATGGGCAGCCGAGAGAACAATAAGACCACGCCTCCCGTGTGGACT
CCGACGGCTCCTTCTTCCTCTACAGCAGGCTCACCGTGGACAAGAGCAGGTGGCA

GGAGGGGAATGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTAC
ACACAGAAGTCCCTCTCCCTGTCTCTGGGTAAATGA

(SEQ ID NO: 510)

HC Amino Acid Sequence

EVQLVESGGGLVQPGGSLSLSCAASGFTFINYAMTWVRQAPGKGLEWVSIISGSGGR
KYYADSVKGRFTISRDN SKNTLSLQMNSLRAEDTAVYYCARFPGLAAAVLDYWGQ
GTLTVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGV
HTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNV DHKPSNTKVDKRVESKYGPPCPP
CPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHN
AKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQP
REPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDS
DGSFFLYSRLTVDKSRWQEGNVFSCSV MHEALHNHYTQKSLSLSLGK*

(SEQ ID NO: 511)

LC DNA Sequence

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAG
TCACCATCACTTGCCGGGCAAGTCAGAGCATTAGCAGCTATTTAAATTGGTATCA
GCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCTATGCTGCATCCAGTTTGCA
AAGTGGGGTCCCGTCAAGGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTC
ACCATCAGCAGTCTGCAACCTGAAGATTTTGCAACTTACTACTGTCAACAGAGTT
ACAGTACCCCTCCGATCACCTTCGGCCAAGGGACACGACTGGAGATTAAACGAA
CTGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCT
GGAAGTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCAGAGAGGCCAAAG
TACAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCA
CAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCCTGACGCTGA
GCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGG
GCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTTAG

(SEQ ID NO: 414)

LC Amino Acid Sequence

DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGV
PSRFSGSGSGTDFTLTISLQPEDFATYYCQQSYSTPPITFGQGTRLEIKRTVAAPSVFIF
PPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSTYS
LSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC*

(SEQ ID NO: 415)

REGN14190

HCVR DNA Sequence

CAGGTTTCAGCTGGTGCAGTCTGGAGCTGAGGTGAAGAAGCCTGGGGCCTCAGTG
AAGGTCTCCTGCAAGGCTTCTGGTTACACCTTTACCAGCTATGGTATCAGCTGGG
TGCGACAGGCCCTGGACAAGGACTTGAGTGGATGGGATGGATCAGCGCTTACA
ATGGTAACACAAAGTATGCACAGAAGTTCCAGGGCAGAGTCACCATGACCAGAG
ACACATCCACGAGCACAGCCTACATGGAGCTGAGGAGCCTGAGATCTGACGACA
CGGCCGTTTATTACTGTGCGAGATGGGTCTCTATGTTTCGGGGAGTCCCGGGGA
CTCCTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCA

(SEQ ID NO: 512)

HCVR Amino Acid Sequence

QVQLVQSGAEVKKPGASVKVSKASGYTFTSYGISWVRQAPGQGLEWMGWISAYN
GNTKYAQKFQGRVTMTRDTSTAYMELRSLRSDDTAVYYCARWVSMFRGVPGDS
WGQGTLLTVSS

(SEQ ID NO: 513)

CDR1 DNA Sequence

GGT TAC ACC TTT ACC AGC TAT GGT

(SEQ ID NO: 137)

CDR1 Amino Acid Sequence

G Y T F T S Y G

(SEQ ID NO: 138)

CDR2 DNA Sequence

ATC AGC GCT TAC AAT GGT AAC ACA

(SEQ ID NO: 318)

CDR2 Amino Acid Sequence

I S A Y N G N T

(SEQ ID NO: 319)

CDR3 DNA Sequence

GCG AGA TGG GTC TCT ATG TTT CGG GGA GTC CCG GGG GAC TCC

(SEQ ID NO: 514)

CDR3 Amino Acid Sequence

A R W V S M F R G V P G D S

(SEQ ID NO: 515)

LCVR DNA Sequence

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAG
TCACCATCACTTGCCGGGCAAGTCAGAGCATTAGCAGCTATTAAATTGGTATCA

GCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCTATGCTGCATCCAGTTTGCA
AAGTGGGGTCCCGTCAAGGTTCAAGTGGCAGTGGATCTGGGACAGATTTCACTCTC
ACCATCAGCAGTCTGCAACCTGAAGATTTTGCAACTTACTACTGTCAACAGAGTT
ACAGTACCCCTCCGATCACCTTCGGCCAAGGGACACGACTGGAGATTAAA

(SEQ ID NO: 408)

LCVR Amino Acid Sequence

DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGV
PSRFSGSGSGTDFLTITSLQPEDFATYYCQSYSTPPITFGQGTRLEIK

(SEQ ID NO: 409)

CDR1 DNA Sequence

CAG AGC ATT AGC AGC TAT

(SEQ ID NO: 236)

CDR1 Amino Acid Sequence

Q S I S S Y

(SEQ ID NO: 237)

CDR2 DNA Sequence

GCT GCA TCC

(SEQ ID NO: 13)

CDR2 Amino Acid Sequence

A A S

(SEQ ID NO: 14)

CDR3 DNA Sequence

CAA CAG AGT TAC AGT ACC CCT CCG ATC ACC

(SEQ ID NO: 410)

CDR3 Amino Acid Sequence

Q Q S Y S T P P I T

(SEQ ID NO: 411)

HC DNA Sequence

CAGGTT CAGCTGGTGCAGTCTGGAGCTGAGGTGAAGAAGCCTGGGGCCTCAGTG
AAGGTCTCCTGCAAGGCTTCTGGTTACACCTTTACCAGCTATGGTATCAGCTGGG
TGCGACAGGCCCCTGGACAAGGACTTGAGTGGATGGGATGGATCAGCGCTTACA
ATGGTAACACAAAGTATGCACAGAAGTTCCAGGGCAGAGTCACCATGACCAGAG
ACACATCCACGAGCACAGCCTACATGGAGCTGAGGAGCCTGAGATCTGACGACA
CGGCCGTTTATTACTGTGCGAGATGGGTCTCTATGTTTCGGGGAGTCCCGGGGGA
CTCCTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCAGCCTCCACCAAGGGCCCA
TCGGTCTTCCCCCTGGCGCCCTGCTCCAGGAGCACCTCCGAGAGCACAGCCGCCC
TGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCTGTGGAATC
AGGCGCCCTGACCAGCGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCAGGA
CTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACGAAGA
CCTACACCTGCAACGTAGATCACAAGCCCAGCAACACCAAGGTGGACAAGAGAG
TTGAGTCCAAATATGGTCCCCCATGCCCACCGTGCCCAGCACCACTGTGGCAGG
ACCATCAGTCTTCCTGTTCCCCCAAAACCCAAGGACACTCTCATGATCTCCCGG
ACCCCTGAGGTCACGTGCGTGGTGGTGGACGTGAGCCAGGAAGACCCCGAGGTC
CAGTTCAACTGGTACGTGGATGGCGTGGAGGTGCATAATGCCAAGACAAAGCCG
CGGGAGGAGCAGTTCAACAGCACGTACCGTGTGGTCAGCGTCCTACCGTCCTG
CACCAGGACTGGCTGAACGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGGC

CTCCCGTCCTCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAG
CCACAGGTGTACACCCTGCCCCCATCCCAGGAGGAGATGACCAAGAACCAGGTC
AGCCTGACCTGCCTGGTCAAAGGCTTCTACCCCAGCGACATCGCCGTGGAGTGG
GAGAGCAATGGGCAGCCGGAGAACAACCTACAAGACCACGCCTCCCGTGTCTGGAC
TCCGACGGCTCCTTCTTCTCTACAGCAGGCTCACCGTGGACAAGAGCAGGTGGC
AGGAGGGGAATGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTA
CACACAGAAGTCCCTCTCCCTGTCTCTGGGTAAATGA

(SEQ ID NO: 516)

HC Amino Acid Sequence

QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYGISWVRQAPGQGLEWMGWISAYN
GNTKYAQKFQGRVTMTRDTSTSTAYMELRSLRSDDTAVYYCARWVSMFRGVPGDS
WGQGLTVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGAL
TSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKYTCNVDHKPSNTKVDKRVESKYG
PPCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVDVVSQEDPEVQFNWYVDG
VEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISK
AKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTP
PVLDSGDGSFFLYSRLTVDKSRWQEGNVFSCSVMEALHNHYTQKSLSLGLGK*

(SEQ ID NO: 517)

LC DNA Sequence

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAG
TCACCATCACTTGCCGGGCAAGTCAGAGCATTAGCAGCTATTTAAATTGGTATCA
GCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCTATGCTGCATCCAGTTTGCA
AAGTGGGGTCCCGTCAAGGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTC
ACCATCAGCAGTCTGCAACCTGAAGATTTTGCAACTTACTACTGTCAACAGAGTT
ACAGTACCCCTCCGATCACCTTCGGCCAAGGGACACGACTGGAGATTAAACGAA
CTGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCT
GGAAGTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCAGAGAGGCCAAAG

TACAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCA
CAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCCTGACGCTGA
GCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGG
GCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTTAG

(SEQ ID NO: 414)

LC Amino Acid Sequence

DIQMTQSPSSLSASVGDRVITICRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGV
PSRFSGSGSGTDFLTISLQPEDFATYYCQSYSTPPITFGQGTRLEIKRTVAAPSVFIF
PPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYS
LSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC*

(SEQ ID NO: 415)

REGN14191

HCVR DNA Sequence

CAGGTGCAGCTGGTGCAGTCTGGGGCTGAAGTGAAGAAGCCTGGGGCCTCAGTG
AAGGTCTCCTGCAAGGCTTCTGGATACACCTTACCGGCTACTATTTACACTGGC
TGCGACAGGCCCTGGACAAGGACTTGAGTGGATGGGATGGATCAACCCTAACA
GTGGTCGCCCCAACTATGCACAGAAAGTTTCAGGGCAGGGTCACCATGACCAGGG
ACACGTCCATCAGCACGGCCTACATGGAAGTGCACAGTCTGAGATCTGACGACA
CGGCCGTGTATTATTGTGCGAAAGAAACGGGAAGTACGAGGGGCTGGTTCGACC
CCTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCA

(SEQ ID NO: 518)

HCVR Amino Acid Sequence

QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYLHWLRQAPGQGLEWMGWINPN
SGRPNYAQKFQGRVTMTRDTSISTAYMELHSLRSDDTAVYYCAKETGTTRGWFD
WGQGLVTVSS

(SEQ ID NO: 519)

CDR1 DNA Sequence

GGA TAC ACC TTC ACC GGC TAC TAT

(SEQ ID NO: 520)

CDR1 Amino Acid Sequence

G Y T F T G Y Y

(SEQ ID NO: 521)

CDR2 DNA Sequence

ATC AAC CCT AAC AGT GGT CGC CCA

(SEQ ID NO: 522)

CDR2 Amino Acid Sequence

I N P N S G R P

(SEQ ID NO: 523)

CDR3 DNA Sequence

GCG AAA GAA ACG GGA ACT ACG AGG GGC TGG TTC GAC CCC

(SEQ ID NO: 524)

CDR3 Amino Acid Sequence

A K E T G T T R G W F D P

(SEQ ID NO: 525)

LCVR DNA Sequence

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAG
TCACCATCACTTGCCGGGCAAGTCAGAGCATTAGCAGCTATTTAAATTGGTATCA
GCAGAAACCAGGGAAAGCCCCCTAAGCTCCTGATCTATGCTGCATCCAGTTTGCA
AAGTGGGGTCCCGTCAAGGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTC
ACCATCAGCAGTCTGCAACCTGAAGATTTTGCAACTTACTACTGTCAACAGAGTT
ACAGTACCCCTCCGATCACCTTCGGCCAAGGGACACGACTGGAGATTAAA

(SEQ ID NO: 408)

LCVR Amino Acid Sequence

DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGV
PSRFSGSGSGTDFLTITISLQPEDFATYYCQQSYSTPPITFGQGTRLEIK

(SEQ ID NO: 409)

CDR1 DNA Sequence

CAG AGC ATT AGC AGC TAT

(SEQ ID NO: 236)

CDR1 Amino Acid Sequence

Q S I S S Y

(SEQ ID NO: 237)

CDR2 DNA Sequence

GCT GCA TCC

(SEQ ID NO: 13)

CDR2 Amino Acid Sequence

A A S

(SEQ ID NO: 14)

CDR3 DNA Sequence

CAA CAG AGT TAC AGT ACC CCT CCG ATC ACC

(SEQ ID NO: 410)

CDR3 Amino Acid Sequence

Q Q S Y S T P P I T

(SEQ ID NO: 411)

HC DNA Sequence

CAGGTGCAGCTGGTGCAGTCTGGGGCTGAAGTGAAGAAGCCTGGGGCCTCAGTG
AAGGTCTCCTGCAAGGCTTCTGGATACACCTTCACCGGCTACTATTTACACTGGC
TGCGACAGGCCCCTGGACAAGGACTTGAGTGGATGGGATGGATCAACCCTAACA
GTGGTCGCCCCAACTATGCACAGAAGTTTCAGGGCAGGGTCACCATGACCAGGG
ACACGTCCATCAGCACGGCCTACATGGAACTGCACAGTCTGAGATCTGACGACA
CGGCCGTGTATTATTGTGCGAAAGAAACGGGAACTACGAGGGGCTGGTTCGACC
CCTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCAGCCTCCACCAAGGGCCCATC
GGTCTTCCCCCTGGCGCCCTGCTCCAGGAGCACCTCCGAGAGCACAGCCGCCCTG
GGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCTGTGGAAGTCA
GGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCAGGAC
TCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACGAAGAC
CTACACCTGCAACGTAGATCACAAGCCCAGCAACACCAAGGTGGACAAGAGAGT
TGAGTCCAAATATGGTCCCCCATGCCCACCGTGCCCAGCACCACTGTGGCAGGA

CCATCAGTCTTCCTGTTCCCCCAAAACCCAAGGACACTCTCATGATCTCCCGGA
CCCCTGAGGTCACGTGCGTGGTGGTGGACGTGAGCCAGGAAGACCCCGAGGTCC
AGTTCAACTGGTACGTGGATGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGC
GGGAGGAGCAGTTCAACAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGC
ACCAGGACTGGCTGAACGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGGCC
TCCCGTCCTCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAGC
CACAGGTGTACACCCTGCCCCCATCCAGGAGGAGATGACCAAGAACCAGGTCA
GCCTGACCTGCCTGGTCAAAGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGG
AGAGCAATGGGCAGCCGGAGAACAACACTACAAGACCACGCCTCCCGTGCTGGACT
CCGACGGCTCCTTCTTCTCTACAGCAGGCTCACCGTGGACAAGAGCAGGTGGCA
GGAGGGGAATGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTAC
ACACAGAAGTCCCTCTCCCTGTCTCTGGGTAAATGA

(SEQ ID NO: 526)

HC Amino Acid Sequence

QVQLVQSGAEVKKPGASVKVSKASGYTFTGYLHWLRQAPGQGLEWMGWINPN
SGRPNYAQKFQGRVTMTRDTSISTAYMELHSLRSDDTAVYYCAKETGTRGWFDP
WGQGLTVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGAL
TSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGKTYTCNVDPHKPSNTKVDKRVESKYG
PPCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDG
VEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISK
AKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTP
PVLDSGDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLGLK*

(SEQ ID NO: 527)

LC DNA Sequence

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAG
TCACCATCACTTGCCGGGCAAGTCAGAGCATTAGCAGCTATTTAAATTGGTATCA
GCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCTATGCTGCATCCAGTTTGCA

AAGTGGGGTCCCGTCAAGGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTC
ACCATCAGCAGTCTGCAACCTGAAGATTTTGCAACTTACTACTGTCAACAGAGTT
ACAGTACCCCTCCGATCACCTTCGGCCAAGGGACACGACTGGAGATTAAACGAA
CTGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCT
GGAAGTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAG
TACAGTGGAAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCA
CAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCTGACGCTGA
GCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGG
GCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTTAG

(SEQ ID NO: 414)

LC Amino Acid Sequence

DIQMTQSPSSLSASVGDRVITITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGV
PSRFSGSGSGTDFLTITSLQPEDFATYYCQQSYSTPPITFGQGTRLEIKRTVAAPSVFIF
PPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYS
LSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC*

(SEQ ID NO: 415)

REGN19513

HCVR DNA Sequence

GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTGCAGCCTGGGGGGTCCCTG
AGGCTCTCCTGTGCAGCCTCTGGATTCACCTTTAACAACATATGCCATGACCTGGG
TCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTCTCAGCTGTTACTGGTAGTG
GTCGTGACACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCGTCTCCAGAG
ACAATTCCAAGAACACGCTGTATCTGCAAATGAGCAGCCTGAGAGCCGAGGACA
CGGCCGTATATTTCTGTGCGAAGAAAGCTGCGGACTACTATTACGGTATGGACGT
CTGGGGCCAAGGGACCACGGTCACCGTCTCCTCA

(SEQ ID NO: 528)

HCVR Amino Acid Sequence

EVQLVESGGGLVQPGGSLRLSCAASGFTFNYYAMTWVRQAPGKGLEWVSAVTGSG
RDTYYADSVKGRFTVSRDNSKNTLYLQMSSLRAEDTAVYFCAKKAADYYYGMDV
WGQGTTVTVSS

(SEQ ID NO: 529)

CDR1 DNA Sequence

GGA TTC ACC TTT AAC AAC TAT GCC

(SEQ ID NO: 530)

CDR1 Amino Acid Sequence

G F T F N N Y A

(SEQ ID NO: 531)

CDR2 DNA Sequence

GTT ACT GGT AGT GGT CGT GAC ACA

(SEQ ID NO: 532)

CDR2 Amino Acid Sequence

V T G S G R D T

(SEQ ID NO: 533)

CDR3 DNA Sequence

GCG AAG AAA GCT GCG GAC TAC TAT TAC GGT ATG GAC GTC

(SEQ ID NO: 534)

CDR3 Amino Acid Sequence

A K K A A D Y Y Y G M D V

(SEQ ID NO: 535)

LCVR DNA Sequence

GACATCCAGATGACCCAGTCTCCATCTTCCGTGTCTGCATCTGTGGGAGACAGAG
TCACCATCACTTGTCTGGGCGAGTCAGGGTATTAGCAGCTGGTCAGCCTGGTATCA
GCAGAAACCAGGAAAAGCCCCTAAACTCCTGATCTATACTACATCCAGTTTCCAA
AGTGGGGTCCCATCAAGGTTCAAGCGGCAGTGGATCTGGGACAGATTTCACTCTCA
CCATCAGCAGCCTGCAGCCTGAAGATTTTGCAAGTTACTATTGTCAACAGGCTCA
CGACTTCTCGCTCACTTTCGGCGGAGGGACCAAGGTGGAGATCAAA

(SEQ ID NO: 536)

LCVR Amino Acid Sequence

DIQMTQSPSSVSASVGDRVITTCRASQGISSWSAWYQQKPGKAPKLLIYTTSSFQSGV
PSRFSGSGSGTDFTLTISLQPEDFASYCQQAHDFTLFGGGTKVEIK

(SEQ ID NO: 537)

CDR1 DNA Sequence

CAG GGT ATT AGC AGC TGG

(SEQ ID NO: 538)

CDR1 Amino Acid Sequence

Q G I S S W

(SEQ ID NO: 539)

CDR2 DNA Sequence

ACT ACA TCC

(SEQ ID NO: 540)

CDR2 Amino Acid Sequence

T T S

(SEQ ID NO: 541)

CDR3 DNA Sequence

CAA CAG GCT CAC GAC TTC TCG CTC ACT

(SEQ ID NO: 542)

CDR3 Amino Acid Sequence

Q Q A H D F S L T

(SEQ ID NO: 543)

HC DNA Sequence

GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTGCAGCCTGGGGGGTCCCTG
AGGCTCTCCTGTGCAGCCTCTGGATTACCTTTAACAACCTATGCCATGACCTGGG
TCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTCTCAGCTGTTACTGGTAGTG
GTCGTGACACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCGTCTCCAGAG
ACAATTCCAAGAACACGCTGTATCTGCAAATGAGCAGCCTGAGAGCCGAGGACA
CGGCCGTATATTTCTGTGCGAAGAAAGCTGCGGACTACTATTACGGTATGGACGT
CTGGGGCCAAGGGACCACGGTCACCGTCTCCTCAGCCTCCACCAAGGGCCCATC
GGTCTTCCCCCTGGCGCCCTGCTCCAGGAGCACCTCCGAGAGCACAGCCGCCCTG

GGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCGTGGA ACTCA
GGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCAGGAC
TCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACGAAGAC
CTACACCTGCAACGTAGATCACAAGCCCAGCAACACCAAGGTGGACAAGAGAGT
TGAGTCCAAATATGGTCCCCCATGCCCACCCTGCCCAGCACCTGAGTTCCTGGGG
GGACCATCAGTCTTCTGTTCCTTCCCCCAAAACCCAAGGACACTCTCATGATCTCCC
GGACCCCTGAGGTACGTGCGTGGTGGTGGACGTGAGCCAGGAAGACCCCGAGG
TCCAGTTCAACTGGTACGTGGATGGCGTGGAGGTGCATAATGCCAAGACAAAGC
CGCGGGAGGAGCAGTTCAACAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCC
TGCACCAGGACTGGCTGAACGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAG
GCCTCCCGTCCTCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAG
AGCCACAGGTGTACACCCTGCCCCATCCCAGGAGGAGATGACCAAGAACCAGG
TCAGCCTGACCTGCCTGGTCAAAGGCTTCTACCCCAGCGACATCGCCGTGGAGTG
GGAGAGCAATGGGCAGCCGGAGAACA ACTACAAGACCACGCCTCCCGTGCTGGA
CTCCGACGGCTCCTTCTTCTCTACAGCAGGCTCACCGTGGACAAGAGCAGGTGG
CAGGAGGGGAATGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACT
ACACACAGAAGTCCCTCTCCCTGTCTCTGGGTAAATGA

(SEQ ID NO: 544)

HC Amino Acid Sequence

EVQLVESGGGLVQPGGSLRLSCAASGFTFNNYAMTWVRQAPGKGLEWVSAVTGSG
RDTYYADSVKGRFTVSRDNSKNTLYLQMSSLRAEDTAVYFCAKKAADYYYGMDV
WGQGTITVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGAL
TSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKYTCNVDPKPSNTKVDKRVESKYG
PPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSDPEVQFNWYVDG
VEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISK
AKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTP
PVLDSGDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLGLK*

(SEQ ID NO: 545)

LC DNA Sequence

GACATCCAGATGACCCAGTCTCCATCTTCCGTGTCTGCATCTGTGGGAGACAGAG
TCACCATCACTTGTCTGGGCGAGTCAGGGTATTAGCAGCTGGTCAGCCTGGTATCA
GCAGAAACCAGGAAAAGCCCCTAAACTCCTGATCTATACTACATCCAGTTTCCAA
AGTGGGGTCCCATCAAGGTTTCAGCGGCAGTGGATCTGGGACAGATTTCCTCTCA
CCATCAGCAGCCTGCAGCCTGAAGATTTTGCAAGTTACTATTGTCAACAGGCTCA
CGACTTCTCGCTCACTTTCGGCGGAGGGACCAAGGTGGAGATCAAACGAACTGT
GGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGA
ACTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGGCCAAAGTAC
AGTGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTACACAG
AGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCTGACGCTGAGCA
AAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCC
TGAGCTCGCCCGTCAAAAGAGCTTCAACAGGGGAGAGTGTTAG

(SEQ ID NO: 546)

LC Amino Acid Sequence

DIQMTQSPSSVSASVGDRVITTCRASQGISSWSAWYQQKPGKAPKLLIYTTSSFQSGV
PSRFSGSGSGTDFLTISLQPEDFASYCQQAHDFTLFGGGTKVEIKRTVAAPSVFI
FPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTY
SLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC*

(SEQ ID NO: 547)

REGN19514

HCVR DNA Sequence

GAGGTGCAGCTGGTGGAGTCTGGGGGAGACTTGGTCCAGCCGGGGGGGTCCCTG
AGACTCTCCTGTGTAGCCTCTGGATTACCTTTAGTAGCTTTTGGATGAGCTGGGT
CCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCAACATAAAACAAGATG
GAAGTGAGAACTACTATGTGGACTCTGTGAAGGGCCGATTACCATCTCCAGAG

ACAACGCCAAGAACTCACTGTATCTGCAAATGAACAGCCTGAGAGCAGAGGACA
CGGCTATGTATTACTGTGCGGTAAACTGGGGAACTACTGGGGCCAGGGAACCC
TGGTCACCGTCTCCTCA

(SEQ ID NO: 548)

HCVR Amino Acid Sequence

EVQLVESGGDLVQPGGSLRLSCVASGFTFSSFWMSWVRQAPGKGLEWVANIKQDGS
ENYYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAMYYCAVNWGNWYWGQGLV
TVSS

(SEQ ID NO: 549)

CDR1 DNA Sequence

GGA TTC ACC TTT AGT AGC TTT TGG

(SEQ ID NO: 550)

CDR1 Amino Acid Sequence

G F T F S S F W

(SEQ ID NO: 551)

CDR2 DNA Sequence

ATA AAA CAA GAT GGA AGT GAG AAC

(SEQ ID NO: 552)

CDR2 Amino Acid Sequence

I K Q D G S E N

(SEQ ID NO: 553)

CDR3 DNA Sequence

GCG GTA AAC TGG GGA AAC TAC

(SEQ ID NO: 554)

CDR3 Amino Acid Sequence

A V N W G N Y

(SEQ ID NO: 555)

LCVR DNA Sequence

GACATCGTGATGACCCAGTCTCCAGACTCCCTGGCTGTGTCTCTGGGCGTGCGGG
CCACCATCAACTGCAGGTCCAGCCAGAGTGTTTTATACAGCTCCAACAATAAAA
ACTACTTAGCTTGGTTCATGCAGAAGCCAGGACAGCCTCCCAAGTTGCTCATTTA
CTGGGCATCTACCCGGGACTCCGGGGTCCCTGACCGATTTCAGTGGCAGCGGGTCT
GGGACAGATTTCACTCTCACCATCACCAGTCTACAGGCTGAAGATGTGGCAGTTT
ATTACTGTCAGCAAAATTATGGTATTCCTTGACGTTTCGGCCAAGGGACCAAGGT
GGAAATCAAA

(SEQ ID NO: 556)

LCVR Amino Acid Sequence

DIVMTQSPDSLAVSLGVRATINCRSSQSVLYSSNNKNYLAWFMQKPGQPPKLLIYWA
STRDSGVPDRFSGSGSGTDFTLTITSLQAEDVAVYYCQQNYGIPWTFGQGTKVEIK

(SEQ ID NO: 557)

CDR1 DNA Sequence

CAG AGT GTT TTA TAC AGC TCC AAC AAT AAA AAC TAC

(SEQ ID NO: 558)

CDR1 Amino Acid Sequence

Q S V L Y S S N N K N Y

(SEQ ID NO: 559)

CDR2 DNA Sequence

TGG GCA TCT

(SEQ ID NO: 560)

CDR2 Amino Acid Sequence

W A S

(SEQ ID NO: 561)

CDR3 DNA Sequence

CAG CAA AAT TAT GGT ATT CCT TGG ACG

(SEQ ID NO: 562)

CDR3 Amino Acid Sequence

Q Q N Y G I P W T

(SEQ ID NO: 563)

HC DNA Sequence

GAGGTGCAGCTGGTGGAGTCTGGGGGAGACTTGGTCCAGCCGGGGGGGTCCCTG
AGACTCTCCTGTGTAGCCTCTGGATTACCTTTAGTAGCTTTTGGATGAGCTGGGT

CCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCAACATAAAACAAGATG
GAAGTGAGAACTACTATGTGGACTCTGTGAAGGGCCGATTACCATCTCCAGAG
ACAACGCCAAGAACTCACTGTATCTGCAAATGAACAGCCTGAGAGCAGAGGACA
CGGCTATGTATTACTGTGCGGTAAACTGGGGAACTACTGGGGCCAGGGAACCC
TGGTCACCGTCTCCTCAGCCTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCGCC
CTGCTCCAGGAGCACCTCCGAGAGCACAGCCGCCCTGGGCTGCCTGGTCAAGGA
CTACTTCCCCGAACCGGTGACGGTGTCTGTGGAACCTCAGGCGCCCTGACCAGCGG
CGTGACACCTTCCCCGGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGC
GTGGTGACCGTGCCCTCCAGCAGCTTGGGCACGAAGACCTACACCTGCAACGTA
GATCACAAGCCCAGCAACACCAAGGTGGACAAGAGAGTTGAGTCCAAATATGGT
CCCCCATGCCACCCTGCCAGCACCTGAGTTCCTGGGGGGACCATCAGTCTTCC
TGTTCCCCCAAAACCAAGGACACTCTCATGATCTCCCGGACCCCTGAGGTAC
GTGCGTGGTGGTGGACGTGAGCCAGGAAGACCCCGAGGTCCAGTTCAACTGGTA
CGTGGATGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTT
CAACAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTG
AACGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGGCCTCCCGTCCTCCATC
GAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAGCCACAGGTGTACACC
CTGCCCCCATCCAGGAGGAGATGACCAAGAACCAGGTGAGCCTGACCTGCCTG
GTCAAAGGCTTCTACCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAG
CCGGAGAACAACACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCT
TCCTCTACAGCAGGCTCACCGTGGACAAGAGCAGGTGGCAGGAGGGGAATGTCT
TCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACACAGAAGTCCCT
CTCCCTGTCTCTGGGTAAATGA

(SEQ ID NO: 564)

HC Amino Acid Sequence

EVQLVESGGDLVQPGGSLRLSCVASGFTFSSFWMSWVRQAPGKGLEWVANIKQDGS
ENYYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAMYYCAVNWGNWYWGQGLV
TVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFP
AVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAP

EFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKT
KPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREP
QVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGS
FFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLGLK*

(SEQ ID NO: 565)

LC DNA Sequence

GACATCGTGATGACCCAGTCTCCAGACTCCCTGGCTGTGTCTCTGGGCGTGC GGG
CCACCATCAACTGCAGGTCCAGCCAGAGTGTTTTATACAGCTCCAACAATAAAA
ACTACTTAGCTTG GTTCATGCAGAAGCCAGGACAGCCTCCCAAGTTGCTCATTTA
CTGGGCATCTACCCGGGACTCCGGGGTCCCTGACCGATTCA GTGGCAGCGGGTCT
GGGACAGATTTCACTCTCACCATCACCAGTCTACAGGCTGAAGATGTGGCAGTTT
ATTACTGTCAGCAAAATTATGGTATTCCTTGACGTTTCGGCCAAGGGACCAAGGT
GGAAATCAAACGAAGTGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGAT
GAGCAGTTGAAATCTGGAAGTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATC
CCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAACT
CCCAGGAGAGTGTACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGC
AGCACCTTGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGC
GAAGTCACCCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGA
GAGTGTTAG

(SEQ ID NO: 566)

LC Amino Acid Sequence

DIVMTQSPDSLAVSLGVRATINCRSSQSVLYSSNNKNYLAWFMQKPGQP PKLLIYWA
STRDSGVPDRFSGSGSGTDFLTITSLQAEDVAVYYCQQNYGIPWTFGQG TKVEIKRT
VAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQ
DSKDSTYLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC*

(SEQ ID NO: 567)

REGN19515

HCVR DNA Sequence

CAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGTCCTCGGTG
AAGGTCTCCTGCAAGTCTTCTGGAGGCACCTTCAGTAGTTATGGTATCAGCTGGG
TGCGACAGGCCCCTGGACAAGGGCTTGAGTGGATGGGAGGGATCATCCCTCTCT
TTGGTACAACAAATTACGCACAGAAGTTCCAGGCCAGAGTCACGATTACCTCGG
TCGAATCAACGACCACAGCCTACATGGAAGTGAACAGCCTGAGATCTGAGGACA
CGGCCGTATATTACTGTGCGAAAGATCGACGTGGATACAGCTCTGTTTCCCTACC
TCAGTTCCACTCCTTCGGTTTGGACGTCTGGGGCCAAGGGACCACGGTCACCGTC
TCCTCA

(SEQ ID NO: 568)

HCVR Amino Acid Sequence

QVQLVQSGAEVKKPGSSVKVSCKSSGGTFSSYGISWVRQAPGQGLEWMGGIPLFGT
TNYAQKFQARVTITSVESITTTAYMELNSLRSEDTAVYYCAKDRRGYSSVSLPQFHSF
GLDVWGQGTTVTVSS

(SEQ ID NO: 569)

CDR1 DNA Sequence

GGA GGC ACC TTC AGT AGT TAT GGT

(SEQ ID NO: 570)

CDR1 Amino Acid Sequence

G G T F S S Y G

(SEQ ID NO: 571)

CDR2 DNA Sequence

ATC ATC CCT CTC TTT GGT ACA ACA

(SEQ ID NO: 572)

CDR2 Amino Acid Sequence

I I P L F G T T

(SEQ ID NO: 573)

CDR3 DNA Sequence

GCGAAAGATCGACGTGGATACAGCTCTGTTTCCCTACCTCAGTTCCACTCCTTCG
GTTTGGACGTC

(SEQ ID NO: 574)

CDR3 Amino Acid Sequence

AKDRRGYSSVSLPQFHSFGLDV

(SEQ ID NO: 575)

LCVR DNA Sequence

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAG
TCACCATCACTTGCCGGGCAAGTCAGAGCATTAGCAGCTATTTAAATTGGTATCA
GCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCTATGCTGCATCCAGTTTGCA
AAGTGGGGTCCCGTCAAGGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTC
ACCATCAGCAGTCTGCAACCTGAAGATTTTGCAACTTACTACTGTCAACAGAGTT
ACAGTACCCCTCCGATCACCTTCGGCCAAGGGACACGACTGGAGATTAAA

(SEQ ID NO: 576)

LCVR Amino Acid Sequence

DIQMTQSPSSLSASVGDRVITTCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGV
PSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPPITFGQGTRLEIK

(SEQ ID NO: 577)

CDR1 DNA Sequence

CAG AGC ATT AGC AGC TAT

(SEQ ID NO: 578)

CDR1 Amino Acid Sequence

Q S I S S Y

(SEQ ID NO: 579)

CDR2 DNA Sequence

GCT GCA TCC

(SEQ ID NO: 580)

CDR2 Amino Acid Sequence

A A S

(SEQ ID NO: 581)

CDR3 DNA Sequence

CAA CAG AGT TAC AGT ACC CCT CCG ATC ACC

(SEQ ID NO: 582)

CDR3 Amino Acid Sequence

Q Q S Y S T P P I T

(SEQ ID NO: 583)

HC DNA Sequence

CAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGTCTCGGTG
AAGGTCTCCTGCAAGTCTTCTGGAGGCACCTTCAGTAGTTATGGTATCAGCTGGG
TGCGACAGGCCCCTGGACAAGGGCTTGAGTGGATGGGAGGGATCATCCCTCTCT
TTGGTACAACAAATTACGCACAGAAGTTCCAGGCCAGAGTCACGATTACCTCGG
TCGAATCAACGACCACAGCCTACATGGAAGTGAACAGCCTGAGATCTGAGGACA
CGGCCGTATATTACTGTGCGAAAGATCGACGTGGATACAGCTCTGTTTCCCTACC
TCAGTTCCACTCCTTCGGTTTGGACGTCTGGGGCCAAGGGACCACGGTCACCGTC
TCCTCAGCCTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCGCCCTGCTCCAGGA
GCACCTCCGAGAGCACAGCCGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCG
AACCGGTGACGGTGTCTGTGGAAGTCAAGGCGCCCTGACCAGCGGCGTGCACACCT
TCCCGGCTGTCTTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGT
GCCCTCCAGCAGCTTGGGCACGAAGACCTACACCTGCAACGTAGATCACAAAGCC
CAGCAACACCAAGGTGGACAAGAGAGTTGAGTCCAAATATGGTCCCCCATGCC
ACCCTGCCCAGCACCTGAGTTCCTGGGGGGACCATCAGTCTTCCTGTTCCCCCA
AAACCAAGGACACTCTCATGATCTCCCGGACCCCTGAGGTACAGTGCGTGGTG
GTGGACGTGAGCCAGGAAGACCCCGAGGTCCAGTTCAACTGGTACGTGGATGGC
GTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTTCAACAGCAC
GTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAACGGCAA
GGAGTACAAGTGCAAGGTCTCCAACAAAGGCCTCCCGTCCTCCATCGAGAAAAC
CATCTCCAAAGCCAAAGGGCAGCCCCGAGAGCCACAGGTGTACACCTGCCCCC
ATCCCAGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGG
CTTCTACCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAA
CAACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCTCTAC
AGCAGGCTCACCGTGGACAAGAGCAGGTGGCAGGAGGGGAATGTCTTCTCATGC

TCCGTGATGCATGAGGCTCTGCACAACCACTACACACAGAAGTCCCTCTCCCTGT
CTCTGGGTAAATGA

(SEQ ID NO: 584)

HC Amino Acid Sequence

QVQLVQSGAEVKKPGSSVKVSCKSSGGTFSSYGISWVRQAPGQGLEWMGGIIPFGT
TNYAQKFQARVTITSVESSTTTAYMELNSLRSEDTAVYYCAKDRRGYSSVSLPQFHSF
GLDVWGQGTTTVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWN
SGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGKTYTCNVDPHKPSNTKVDKRVE
SKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVDSQEDPEVQFNW
YVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIE
KTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENN
YKTTTPVLDSGDSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLG
K*

(SEQ ID NO: 585)

LC DNA Sequence

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAG
TCACCATCACTTGCCGGGCAAGTCAGAGCATTAGCAGCTATTTAAATTGGTATCA
GCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCTATGCTGCATCCAGTTTGCA
AAGTGGGGTCCCGTCAAGGTTCAAGTGGCAGTGGATCTGGGACAGATTTCACTCTC
ACCATCAGCAGTCTGCAACCTGAAGATTTGCAACTTACTACTGTCAACAGAGTT
ACAGTACCCCTCCGATCACCTTCGGCCAAGGGACACGACTGGAGATTAAACGAA
CTGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCT
GGAAGTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAG
TACAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCA
CAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCTGACGCTGA
GCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGG
GCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTTAG

(SEQ ID NO: 586)

LC Amino Acid Sequence

DIQMTQSPSSLSASVGDRVITTCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGV
PSRFSGSGSGTDFTLTISLQPEDFATYYCQQSYSTPPITFGQGTRLEIKRTVAAPSVFIF
PPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYS
LSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC*

(SEQ ID NO: 587)

REGN19516

HCVR DNA Sequence

CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTG
AGACTCTCCTGTGCAGCGTCTGGATTCACCTTCAGCGCCTATGTCATGCACTGGG
TCCGCCAGGCTCCAGGCAAGGGGCTGGAGTGGATTACAGTTATTGATTATGATGC
AAAGAATAAATACTATGCAGACTCCGTGAGGGGCCGATTACCGTCTCCAGAGA
CAATTCCAAGAACACGCTGTTTCTGCAAATGAACAGCCTGAGAGCCGAGGACAC
GGCTGTGTATTACTGTGCGAGAAATAGAGGTGGCTACAATTACTTTGACTACTGG
GGCCAGGGAACCCTGGTCACCGTCTCCTCA

(SEQ ID NO: 588)

HCVR Amino Acid Sequence

QVQLVESGGGVVQPGRSLRLSCAASGFTFSAYVMHWVRQAPGKGLEWITVIDYDA
KNKYYADSVRGRFTVSRDNSKNTLFLQMNSLRAEDTAVYYCARNRGGYNYFDYW
GQGTLLTVSS

(SEQ ID NO: 589)

CDR1 DNA Sequence

GGA TTC ACC TTC AGC GCC TAT GTC

(SEQ ID NO: 590)

CDR1 Amino Acid Sequence

G F T F S A Y V

(SEQ ID NO: 591)

CDR2 DNA Sequence

ATT GAT TAT GAT GCA AAG AAT AAA

(SEQ ID NO: 592)

CDR2 Amino Acid Sequence

I D Y D A K N K

(SEQ ID NO: 593)

CDR3 DNA Sequence

GCG AGA AAT AGA GGT GGC TAC AAT TAC TTT GAC TAC

(SEQ ID NO: 594)

CDR3 Amino Acid Sequence

A R N R G G Y N Y F D Y

(SEQ ID NO: 595)

LCVR DNA Sequence

GAAATAGTTTTGACACAGAGTCCCGGCACACTGTCACTCTCTCCCGGGGAAAGA
 GCCACCTTGTCATGTAGAGCAAGTCAGTCAGTCTCTAGCTCTTATCTCGCCTGGT
 ACCAGCAGAAGCCGGGACAGGCCCTAGACTGCTGATCTACGGGGCAAGTTCCA
 GGGCCACCGGAATCCCGACCGGTTTCAGTGGAAGCGGAAGCGGAACCGATTTTA
 CTTTGACGATTTCTAGACTGGAGCCAGAGGATTTGCCGTTTACTATTGTCAACA
 GTACGGAAGCAGCCCGTGGACGTTTGGCCAGGGCACGAAGGTAGAAATCAAG

(SEQ ID NO: 596)

LCVR Amino Acid Sequence

EIVLTQSPGTLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLLIYGASSRATGI
 PDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYGSSPWTFGQGTKVEIK

(SEQ ID NO: 597)

CDR1 DNA Sequence

CAG TCA GTC TCT AGC TCT TAT

(SEQ ID NO: 598)

CDR1 Amino Acid Sequence

Q S V S S S Y

(SEQ ID NO: 599)

CDR2 DNA Sequence

GGG GCA AGT

(SEQ ID NO: 600)

CDR2 Amino Acid Sequence

G A S

(SEQ ID NO: 601)

CDR3 DNA Sequence

CAA CAG TAC GGA AGC AGC CCG TGG ACG

(SEQ ID NO: 602)

CDR3 Amino Acid Sequence

Q Q Y G S S P W T

(SEQ ID NO: 603)

HC DNA Sequence

CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTG
AGACTCTCCTGTGCAGCGTCTGGATTACCTTCAGCGCCTATGTCATGCACTGGG
TCCGCCAGGCTCCAGGCAAGGGGCTGGAGTGGATTACAGTTATTGATTATGATGC
AAAGAATAAATACTATGCAGACTCCGTGAGGGGGCCGATTACCGTCTCCAGAGA
CAATTCCAAGAACACGCTGTTTCTGCAAATGAACAGCCTGAGAGCCGAGGACAC
GGCTGTGTATTACTGTGCGAGAAATAGAGGTGGCTACAATTACTTTGACTACTGG
GGCCAGGGAACCTGGTCACCGTCTCCTCAGCCTCCACCAAGGGCCCATCGGTCT
TCCCCCTGGCGCCCTGCTCCAGGAGCACCTCCGAGAGCACAGCCGCCCTGGGCTG
CCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCTGTGGAACCTCAGGCGC
CCTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCAGGACTCTAC
TCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACGAAGACCTAC
ACCTGCAACGTAGATCACAAAGCCCAGCAACACCAAGGTGGACAAGAGAGTTGAG
TCCAAATATGGTCCCCCATGCCCACCCTGCCCAGCACCTGAGTTCCTGGGGGGAC
CATCAGTCTTCTGTTCCTTCCCCCAAAACCCAAGGACACTCTCATGATCTCCCGGAC
CCCTGAGGTACAGTGCGTGGTGGTGGACGTGAGCCAGGAAGACCCCGAGGTCCA
GTTCAACTGGTACGTGGATGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCG

GGAGGAGCAGTTCAACAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCA
CCAGGACTGGCTGAACGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGGCCT
CCCGTCCTCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAGCC
ACAGGTGTACACCCTGCCCCCATCCCAGGAGGAGATGACCAAGAACCAGGTCAG
CCTGACCTGCCTGGTCAAAGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGGA
GAGCAATGGGCAGCCGGAGAACAACACTACAAGACCACGCCTCCCGTGCTGGACTC
CGACGGCTCCTTCTTCTCTACAGCAGGCTCACCGTGGACAAGAGCAGGTGGCA
GGAGGGGAATGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTAC
ACACAGAAGTCCCTCTCCCTGTCTCTGGGTAAATGA

(SEQ ID NO: 604)

HC Amino Acid Sequence

QVQLVESGGGVVQPGRSLRLSCAASGFTFSAYVMHWVRQAPGKLEWITVIDYDA
KNKYYADSVRGRFTVSRDNSKNTLFLQMNSLRAEDTAVYYCARNRGGYNYFDYW
GQGLTVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTS
GVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKYTCNVDPHKPSNTKVDKRVESKYGPP
CPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGV
EVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKA
KGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPP
VLDSGDGSFFLYSRLTVDKSRWQEGNVFSCSVMHREALHNHYTQKSLSLSLGK*

(SEQ ID NO: 605)

LC DNA Sequence

GAAATAGTTTTGACACAGAGTCCCGGCACACTGTCACTCTCTCCCGGGGAAAGA
GCCACCTTGTCATGTAGAGCAAGTCAGTCAGTCTCTAGCTCTTATCTCGCCTGGT
ACCAGCAGAAGCCGGGACAGGCCCCTAGACTGCTGATCTACGGGGCAAGTTCCA
GGGCCACCGGAATCCCCGACCGGTTTCAGTGGAAGCGGAAGCGGAACCGATTTTA
CTTTGACGATTTCTAGACTGGAGCCAGAGGATTTGCGCGTTTACTATTGTCAACA
GTACGGAAGCAGCCCGTGGACGTTTGGCCAGGGCACGAAGGTAGAAATCAAGCG

AACTGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAA
TCTGGAAGTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCA
AAGTACAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAGTG
TCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCTTGACGC
TGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATC
AGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTTAG

(SEQ ID NO: 606)

LC Amino Acid Sequence

EIVLTQSPGTLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLLIYGASSRATGI
PDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYGSSPWTFGQGTKVEIKRTVAAPSVFI
FPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTY
SLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC*

(SEQ ID NO: 607)

REGN19517

HCVR DNA Sequence

GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
AGACTCTCCTGTGCAGCCTCTGGATTACCTTTAGCAGTTATGTCATGAGCTGGG
TCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTCTCAGATATTAGTGGTCGTG
GTGGTAGCACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATTTCCAGAG
ACAATTCCAAGAGCACGCTGCATCTGCAAATGAACAGCCTGAGAGCCGAGGACA
CGGCCGTATATTACTGTGCGAAAGTGGGGCACCTCGTCCGGGATCACTACTACTA
CTACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCA

(SEQ ID NO: 608)

HCVR Amino Acid Sequence

EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYVMSWVRQAPGKGLEWVSDISGRGG
STYYADSVKGRFTISRDNKSTLHLQMNSLRAEDTAVYYCAKVGHLLVRDHYYYYG
MDVWGQGTTVTVSS

(SEQ ID NO: 609)

CDR1 DNA Sequence

GGA TTC ACC TTT AGC AGT TAT GTC

(SEQ ID NO: 610)

CDR1 Amino Acid Sequence

G F T F S S Y V

(SEQ ID NO: 611)

CDR2 DNA Sequence

ATT AGT GGT CGT GGT GGT AGC ACA

(SEQ ID NO: 612)

CDR2 Amino Acid Sequence

I S G R G G S T

(SEQ ID NO: 613)

CDR3 DNA Sequence

GCG AAA GTG GGG CAC CTC GTC CGG GAT CAC TAC TAC TAC TAC GGT ATG
GAC GTC

(SEQ ID NO: 614)

CDR3 Amino Acid Sequence

A K V G H L V R D H Y Y Y Y G M D V

(SEQ ID NO: 615)

LCVR DNA Sequence

GAAATAGTTTTGACACAGAGTCCCGGCACACTGTCACTCTCTCCCGGGGAAAGA
GCCACCTTGTCATGTAGAGCAAGTCAGTCAGTCTCTAGCTCTTATCTCGCCTGGT
ACCAGCAGAAGCCGGGACAGGCCCCTAGACTGCTGATCTACGGGGCAAGTTCCA
GGGCCACCGGAATCCCCGACCGGTTTCAGTGGAAGCGGAAGCGGAACCGATTTTA
CTTTGACGATTTCTAGACTGGAGCCAGAGGATTTTCGCCGTTTACTATTGTCAACA
GTACGGAAGCAGCCCGTGGACGTTTGGCCAGGGCACGAAGGTAGAAATCAAG

(SEQ ID NO: 596)

LCVR Amino Acid Sequence

EIVLTQSPGTLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLLIYGASSRATGI
PDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYGSSPWTFGQGTKVEIK

(SEQ ID NO: 597)

CDR1 DNA Sequence

CAG TCA GTC TCT AGC TCT TAT

(SEQ ID NO: 598)

CDR1 Amino Acid Sequence

Q S V S S S Y

(SEQ ID NO: 599)

CDR2 DNA Sequence

GGG GCA AGT

(SEQ ID NO: 600)

CDR2 Amino Acid Sequence

G A S

(SEQ ID NO: 601)

CDR3 DNA Sequence

CAA CAG TAC GGA AGC AGC CCG TGG ACG

(SEQ ID NO: 602)

CDR3 Amino Acid Sequence

Q Q Y G S S P W T

(SEQ ID NO: 603)

HC DNA Sequence

GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
AGACTCTCCTGTGCAGCCTCTGGATTACCTTTAGCAGTTATGTCATGAGCTGGG
TCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTCTCAGATATTAGTGGTCGTG
GTGGTAGCACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATTTCCAGAG
ACAATTCCAAGAGCACGCTGCATCTGCAAATGAACAGCCTGAGAGCCGAGGACA
CGGCCGTATATTACTGTGCGAAAGTGGGGCACCTCGTCCGGGATCACTACTACTA
CTACGGTATGGACGTCTGGGGCCAAGGGACACGGTCACCGTCTCCTCAGCCTCC
ACCAAGGGCCCATCGGTCTTCCCCCTGGCGCCCTGCTCCAGGAGCACCTCCGAGA
GCACAGCCGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGG

TGTCGTGGAACCTCAGGCGCCCTGACCAGCGGCGTGACACACCTTCCCGGCTGTCCT
ACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGC
TTGGGCACGAAGACCTACACCTGCAACGTAGATCACAAAGCCCAGCAACACCAAG
GTGGACAAGAGAGTTGAGTCCAAATATGGTCCCCCATGCCACCCTGCCAGCA
CCTGAGTTCCTGGGGGGACCATCAGTCTTCCTGTTCCCCCAAAACCAAGGACA
CTCTCATGATCTCCCGGACCCCTGAGGTCACGTGCGTGGTGGTGGACGTGAGCCA
GGAAGACCCCGAGGTCCAGTTCAACTGGTACGTGGATGGCGTGGAGGTGCATAA
TGCCAAGACAAAGCCGCGGGAGGAGCAGTTCAACAGCACGTACCGTGTGGTCAG
CGTCCTCACCGTCCTGCACCAGGACTGGCTGAACGGCAAGGAGTACAAGTGCAA
GGTCTCCAACAAAGGCCTCCCGTCCTCCATCGAGAAAACCATCTCCAAAGCCAA
AGGGCAGCCCCGAGAGCCACAGGTGTACACCCTGCCCCCATCCCAGGAGGAGAT
GACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTACCCCAGCGA
CATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACACTACAAGACCA
CGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCCTCTACAGCAGGCTCACCGT
GGACAAGAGCAGGTGGCAGGAGGGGAATGTCTTCTCATGCTCCGTGATGCATGA
GGCTCTGCACAACCACTACACACAGAAGTCCCTCTCCCTGTCTCTGGGTAAATGA

(SEQ ID NO: 616)

HC Amino Acid Sequence

EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYVMSWVRQAPGKGLEWVSDISGRGG
STYYADSVKGRFTISRDNKSTLHLQMNSLRAEDTAVYYCAKVGHLVRDHYYYYYG
MDVWGQGTTVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTWSNS
GALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGKTYTCNVDPKPSNTKVDKRVES
KYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWY
VDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEK
TISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNY
KTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMEALHNHYTQKSLSLGLGK*

(SEQ ID NO: 617)

LC DNA Sequence

GAAATAGTTTTGACACAGAGTCCCGGCACACTGTCACTCTCTCCCGGGGAAAGA
 GCCACCTTGTCATGTAGAGCAAGTCAGTCAGTCTCTAGCTCTTATCTCGCCTGGT
 ACCAGCAGAAGCCGGGACAGGCCCTAGACTGCTGATCTACGGGGCAAGTTCCA
 GGGCCACCGGAATCCCCGACCGGTTCAAGTGAAGCGGAAGCGGAACCGATTTTA
 CTTTGACGATTTCTAGACTGGAGCCAGAGGATTTCCCGGTTTACTATTGTCAACA
 GTACGGAAGCAGCCCGTGGACGTTTGGCCAGGGCACGAAGGTAGAAATCAAGCG
 AACTGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAA
 TCTGGAAGTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCA
 AAGTACAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAGTG
 TCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCCTGACGC
 TGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATC
 AGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTTAG

(SEQ ID NO: 606)

LC Amino Acid Sequence

EIVLTQSPGTLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLLIYGASSRATGI
 PDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYGSSPWTFGQGTKVEIKRTVAAPSVFI
 FPPSDEQLKSGTASVVCLLNNFYFPREAKVQWKVDNALQSGNSQESVTEQDSKDSTY
 SLSSLTLTSLKADYEKHKVYACEVTHQGLSPVTKSFNRGEC*

(SEQ ID NO: 607)

[0089] Non-limiting examples of targeting ligands that bind p75^{NTR} include: (i) Fab fragments; (ii) F(ab')₂ fragments; (iii) Fd fragments; (iv) Fv fragments; (v) single-chain Fv (scFv) molecules; (vi) dAb fragments; and (vii) minimal recognition units consisting of the amino acid residues that mimic the hypervariable region of an antibody (e.g., an isolated complementarity determining region (CDR) such as a CDR3 peptide), or a constrained FR3-CDR3-FR4 peptide. Other engineered molecules, such as domain-specific antibodies, single domain antibodies, domain-deleted antibodies, chimeric antibodies, CDR-grafted

antibodies, diabodies, triabodies, tetrabodies, minibodies, nanobodies (e.g. monovalent nanobodies, bivalent nanobodies, etc.), small modular immunopharmaceuticals (SMIPs), and shark variable IgNAR domains, are also encompassed within the expression "targeting ligand," as used herein. In non-limiting embodiments, an anti-p75^{NTR} targeting ligand that binds p75^{NTR} useful for retargeting viral capsids as described herein comprise comprises an scFv. As a non-limiting example, an scFv sequences in V_L-(Gly₄Ser)₃-V_H format useful for retargeting viral capsids as described herein may comprise a heavy chain variable domain, light chain variable domain, heavy chain variable domain/light chain variable domain pair, HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, LCDR3, and/or set of HCDR1-HCDR2-HCDR3-LCDR1-LCDR2-LCDR3 that is 90%, 95%, 97%, 98%, 99% or 100% identical, respectively, to any one of the amino acid sequences of a heavy chain variable domain, light chain variable domain, heavy chain variable domain/light chain variable domain pair, HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, LCDR3, and/or set of HCDR1-HCDR2-HCDR3-LCDR1-LCDR2-LCDR3 as set forth in or encoded by a sequence or sequences set forth in Table 1 and/or any one of SEQ ID NOs: 1-617.

[0090] In some embodiments, the targeting ligand comprises an amino acid sequence or is encoded by a polynucleotide sequence selected from any of the HCDR1 amino acid or nucleic acid sequences listed in Table 1, or a substantially similar sequence thereof having at least about 70-99.9% (*e.g.*, at least 70, 72, 74, 75, 76, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 99.5 or 99.9%) sequence identity thereto.

[0091] In some embodiments, the targeting ligand comprises an amino acid sequence or is encoded by a polynucleotide sequence selected from any of the HCDR2 amino acid or nucleic acid sequences listed in Table 1, or a substantially similar sequence thereof having at least about 70-99.9% (*e.g.*, at least 70, 72, 74, 75, 76, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 99.5 or 99.9%) sequence identity thereto.

[0092] In some embodiments, the targeting ligand comprises an amino acid sequence or is encoded by a polynucleotide sequence selected from any of the HCDR3 amino acid or nucleic acid sequences listed in Table 1, or a substantially similar sequence thereof having at least about 70-99.9% (*e.g.*, at least 70, 72, 74, 75, 76, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 99.5 or 99.9%) sequence identity thereto.

[0093] In some embodiments, the targeting ligand comprises a set of HCDR1-HCDR2-HCDR3 amino acid sequences comprising or encoded by a set of HCDR1-HCDR2-HCDR3 amino acid or nucleic acid sequences listed in Table 1, or substantially similar sequences thereof having at least about 70-99.9% (*e.g.*, at least 70, 72, 74, 75, 76, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 99.5 or 99.9%) sequence identity thereto.

[0094] In some embodiments, the targeting ligand comprises an amino acid sequence or is encoded by a polynucleotide sequence selected from any of the LCDR1 amino acid or nucleic acid sequences listed in Table 1, or a substantially similar sequence thereof having at least about 70-99.9% (*e.g.*, at least 70, 72, 74, 75, 76, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 99.5 or 99.9%) sequence identity thereto.

[0095] In some embodiments, the targeting ligand comprises an amino acid sequence or is encoded by a polynucleotide sequence selected from any of the LCDR2 amino acid or nucleic acid sequences listed in Table 1, or a substantially similar sequence thereof having at least about 70-99.9% (*e.g.*, at least 70, 72, 74, 75, 76, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 99.5 or 99.9%) sequence identity thereto.

[0096] In some embodiments, the targeting ligand comprises an amino acid sequence or is encoded by a polynucleotide sequence selected from any of the LCDR3 amino acid or nucleic acid sequences listed in Table 1, or a substantially similar sequence thereof having at least about 70-99.9% (*e.g.*, at least 70, 72, 74, 75, 76, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 99.5 or 99.9%) sequence identity thereto.

[0097] In some embodiments, the targeting ligand comprises a set of LCDR1-LCDR2-LCDR3 amino acid sequences comprising or encoded by a set of LCDR1-LCDR2-LCDR3 amino acid or nucleic acid sequences listed in Table 1, or substantially similar sequences thereof having at least about 70-99.9% (*e.g.*, at least 70, 72, 74, 75, 76, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 99.5 or 99.9%) sequence identity thereto.

[0098] In some embodiments, the targeting ligand comprises a set of HCDR1-HCDR2-HCDR3-LCDR1-LCDR2-LCDR3 amino acid sequences comprising or encoded by a set of HCDR1-HCDR2-HCDR3-LCDR1-LCDR2-LCDR3 amino acid or nucleic acid sequences listed in Table 1, or substantially similar sequences thereof having at least about

70-99.9% (*e.g.*, at least 70, 72, 74, 75, 76, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 99.5 or 99.9%) sequence identity thereto.

[0099] In some embodiments, the targeting ligand comprises an amino acid sequence or is encoded by a polynucleotide sequence selected from any of the HCVR amino acid or nucleic acid sequences listed in Table 1, or a substantially similar sequence thereof having at least about 70-99.9% (*e.g.*, at least 70, 72, 74, 75, 76, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 99.5 or 99.9%) sequence identity thereto.

[00100] In some embodiments, the targeting ligand comprises an amino acid sequence or is encoded by a polynucleotide sequence selected from any of the LCVR amino acid or nucleic acid sequences listed in Table 1, or a substantially similar sequence thereof having at least about 70-99.9% (*e.g.*, at least 70, 72, 74, 75, 76, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 99.5 or 99.9%) sequence identity thereto.

[00101] In some embodiments, the targeting ligand comprises an amino acid sequence or is encoded by a polynucleotide sequence selected from any of the heavy chain (HC) amino acid or nucleic acid sequences listed in Table 1, or a substantially similar sequence thereof having at least about 70-99.9% (*e.g.*, at least 70, 72, 74, 75, 76, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 99.5 or 99.9%) sequence identity thereto.

[00102] In some embodiments, the targeting ligand comprises an amino acid sequence or is encoded by a polynucleotide sequence selected from any of the light chain (LC) amino acid or nucleic acid sequences listed in Table 1, or a substantially similar sequence thereof having at least about 70-99.9% (*e.g.*, at least 70, 72, 74, 75, 76, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 99.5 or 99.9%) sequence identity thereto.

[00103] A targeting ligand that binds p75^{NTR} may be associated with (*e.g.*, displayed by, operably linked to, bound to) a modified AAV capsid protein and resulting AAV capsids according to well-known methods, *e.g.*, a direct approach in which the targeting ligand is directly inserted into (*e.g.*, using recombinatorial methods) according to well-known methods. *See, e.g.*, Stachler et al. (2006), *supra*; White et al. (2004), *supra*; Girod et al. (1999), *supra*; Grifman et al. (2001), *supra*; Shi et al. (2001), *supra*; Shi and Bartlett (2003), *supra*. A targeting ligand that binds p75^{NTR} may be coupled to a modified AAV capsid protein and resulting AAV capsids using well-known chemical linkers, *e.g.*, wherein the AAV capsid protein may be chemically modified to comprise a dibenzocycotyne group or

an azide group, and optionally wherein a targeting ligand as described herein is attached to the dibenzocycotyne group or the azide group, *see, e.g.*, U.S. 2022/028234, incorporated herein by reference in its entirety; wherein targeting ligand is covalently linked to a primary amino acid group of an AAV capsid protein, *e.g.*, via a -CSNH- bond, etc. In some embodiments, a modified capsid as described herein comprises a targeting ligand, *e.g.*, an anti-p75^{NTR} antibody or binding portion thereof, directly inserted into or coupled to it according to well-known direct recombinatorial methods.

[00104] In various embodiments, an anti-p75^{NTR} antigen-binding protein described herein demonstrates less than 10% to 70% inhibition of nerve growth factor (NGF)-dependent activation of tropomyosin receptor kinase A (TrkA) signaling by the extracellular domain of p75^{NTR} as measured in a cell-based assay.

[00105] In various embodiments, an anti-p75^{NTR} antigen-binding protein described herein demonstrates less than 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, or 68% inhibition of NGF-dependent activation of TrkA signaling by the extracellular domain of p75^{NTR} as measured in a cell-based assay.

[00106] In various embodiments, an anti-p75^{NTR} antigen-binding protein described herein demonstrates less than 50% inhibition of NGF-dependent activation of TrkA signaling by the extracellular domain of p75^{NTR} as measured in a cell-based assay.

[00107] In various embodiments, the cell-based assay is performed as described in Example 8 presented herein.

Multispecific Targeting Ligands

[00108] In some embodiments, the targeting ligand comprises a multispecific binding molecule, *e.g.*, a bispecific antigen-binding molecule, *e.g.*, a bispecific antibody. In some embodiments, the multispecific antigen-binding molecule comprises a first antigen-binding domain and a second antigen-binding domain.

[00109] In some embodiments, the first antigen-binding domain binds to a mammalian p75 neurotrophin receptor (p75^{NTR}). Accordingly, in some embodiments, the first antigen-binding domain comprises an anti-p75^{NTR} antigen-binding protein as disclosed herein, or an antigen-binding portion thereof as described herein.

[00110] In some embodiments, the second antigen-binding domain binds to a first member of a protein:protein binding pair, e.g., a detectable label, comprised within, displayed by, etc., an AAV capsid protein, e.g., at a variable loop of an AAV capsid.

[00111] In some embodiments, the second antigen-binding domain of a multispecific targeting ligand described herein binds to a first member of a protein:protein binding pair, wherein the first member of the protein:protein binding pair is heterologous to the AAV capsid protein. “Heterologous” in this context means heterologous as compared to the AAV serotype from which the capsid protein is derived. In some embodiments, the second antigen-binding domain specifically binds to a c-myc epitope, e.g., comprising an amino acid sequence set forth as SEQ ID NO: 639. In some embodiments, the second antigen-binding domain comprises an antibody paratope that specifically binds to a c-myc epitope, e.g., comprising an amino acid sequence set forth as SEQ ID NO: 639. Thus, the present disclosure includes bispecific antigen-binding molecules, e.g., antibodies, wherein one domain of antigen-binding domain binds to a heterologous detectable label displayed by an AAV capsid (e.g., c-myc, B1, etc.), and the other antigen-binding domain binds to a mammalian p75^{NTR}. Accordingly, in some embodiments, the multispecific antigen-binding domain comprising the first and second antigen-binding domains retargets an AAV particle comprising an AAV capsid protein comprising the heterologous epitope to mammalian cell expressing p75^{NTR}.

[00112] In some embodiments, the second antigen-binding domain of a multispecific targeting ligand described herein binds to a first member of a protein:protein binding pair, wherein the first member of a protein:protein binding pair comprises one or more epitopes of a capsid of an AAV particle. Thus, the present disclosure includes bispecific antigen-binding molecules, e.g., antibodies, wherein one domain of antigen-binding domain binds to a capsid of an AAV particle (e.g., a capsid comprising a wild-type and/or non-wild-type AAV capsid protein(s)), and the other antigen-binding domain binds to a mammalian p75^{NTR}. Accordingly, in some embodiments, the multispecific antigen-binding domain comprising the first and second antigen-binding domains as described herein retargets an AAV particle (i.e., comprising an AAV capsid protein comprising one or more epitopes, e.g., epitopes comprised within a wildtype AAV capsid protein, recognized by at least one of the antigen-binding domains) to a cell expressing a mammalian p75^{NTR}.

[00113] In some embodiments, the epitope of the capsid of the AAV particle may comprise any of various serotype-specific or serotype-non-specific (i.e., “universal”) epitopes understood by one of ordinary skill in the art.

[00114] In some embodiments, the one or more epitope(s) of the capsid of the AAV particle are comprised of any amino acid residues of a capsid protein VP1, VP2 or VP3, or a combination thereof. The AAV particle can be derived from any AAV serotype described herein. In some embodiments, the one or more epitope(s) comprise any variable region of a capsid, or any combination thereof, e.g., a variable region comprised of a capsid protein VP1, VP2 or VP3, or a combination thereof (e.g., variable region I, II, III, IV, V, VI, VII, VIII, IX, or a combination thereof, as described in Emmanuel, et al., *Journal of Virology*, 2022, 96, 3).

[00115] As a non-limiting example, one or more epitope(s) of an AAV1 capsid may comprise any amino acid residue or combination thereof of a variable region I, II, III, IV, V, VI, VII, VIII, IX, or combination thereof. In some embodiments, the one or more AAV1 epitope(s) comprise any of residues 456–459, 492–499, 582, 583, 588–591, 593–595, 597, or any combination thereof, as described in Tseng, et al., *Front Immunol.* 2014, 5: 9.

[00116] As a non-limiting example, one or more epitope(s) of an AAV2 capsid may comprise any amino acid residue or combination thereof of a variable region I, II, III, IV, V, VI, VII, VIII, IX, or combination thereof. In some embodiments, the one or more AAV2 epitope(s) comprise any of residues 253, 254, 258, 261–264, 272–281, 369–378, 381, 384, 385, 474–483, 492–502, 534, 548, 556, 560–573, 585–589, 601–610, 658–660, 708, 717, or any combination thereof, as described in Tseng, et al., *Front Immunol.* 2014, 5: 9.

[00117] As a non-limiting example, one or more epitope(s) of an AAV5 capsid may comprise any amino acid residue or combination thereof of a variable region I, II, III, IV, V, VI, VII, VIII, IX, or combination thereof. In some embodiments, the one or more AAV5 epitope(s) comprise any of residues 246, 254–261, 374, 375, 483, 485–492, 494, 496, 499–501, 530, 532–538, 653, 654, 656, 657, 704–708, or any combination thereof as described in Tseng, et al., *Front Immunol.* 2014, 5: 9.

[00118] As a non-limiting example, one or more epitope(s) of an AAV8 capsid may comprise any amino acid residue or combination thereof of a variable region I, II, III, IV, V, VI, VII, VIII, IX, or combination thereof. In some embodiments, the one or more AAV8

epitope(s) comprise any of residues 586–591 or any combination thereof as described in Tseng, et al., *Front Immunol.* 2014, 5: 9.

[00119] As a non-limiting example, one or more epitope(s) of an AAV9 capsid may comprise any amino acid residue or combination thereof of a variable region I, II, III, IV, V, VI, VII, VIII, IX, or combination thereof. In some embodiments, the one or more AAV8 epitope(s) comprise any of residues 221, 228, 246–248, 250–256, 258–260, any of residues 262–273 of variable region I, any of residues 274, 275, 278, 291, 293, 324, 325, any of residues 327–333 of variable region II, any of residues 334, 335, 338, 341, 363–365, 369–373, 375, 376, any of residues 382–387, 389, 391 of variable region III, any of residues 438–441, 443, any of residues 446, 448, 449, 451–460, 462, 464–473 of variable region IV, any of residues 488, 491–501, 503–506, 510–515 of variable region V, any of residues 528–534, 545 of variable region VI, any of residues 547–560 of variable region VII, residue 572, any of residues 579, 584, 587–590 of variable region VIII, any of residues 651–653, 655–676, 678, any of residues 701–720, 722, 724–728 of variable region IX, or any of residues 730, 731, or any combination thereof, as described in Emmanuel, et al., *Journal of Virology*, 2022, 96, 3.

Binding pairs

[00120] In some embodiments, a targeting ligand that binds p75^{NTR} may be associated with (e.g., displayed by, operably linked to, bound to) a modified AAV capsid protein and resulting AAV capsids according to indirect recombinatorial approaches, wherein the AAV capsid protein is modified to comprise a first member of a binding pair (e.g., a heterologous scaffold), and optionally wherein the first member of the binding pair is linked to (e.g., covalently or non-covalently bound to) a second cognate member of the binding pair (e.g., an adaptor), further optionally wherein the second cognate member of the binding pair is fused to the targeting ligand. Non-limiting and exemplary binding pairs are listed in Buning and Srivastava (2019) *Mol. Ther. Methods Clin Dev* 12:248-265.

[00121] Accordingly, in some embodiments, modifications of a capsid protein as described herein include those that generally result from modifications at the genetic level, e.g., via modification of a *cap* gene, such as modifications that insert first member of a binding pair (e.g., a protein:protein binding pair, a protein:nucleic acid binding pair), a detectable label, etc., for display by the Cap protein.

[00122] In some embodiments, the first member forms a binding pair with an immunoglobulin constant domain. In some embodiments, the first member forms a binding pair with a metal ion, e.g., Ni^{2+} , Co^{2+} , Cu^{2+} , Zn^{2+} , Fe^{3+} , etc. In some embodiments, the first member is selected from the group consisting of Streptavidin, Strep II, HA, L14, 4C-RGD, LH, and Protein A.

[00123] In some embodiments, the binding pair comprises an enzyme:nucleic acid binding pair. In some embodiments, the first member comprises a HUH-endonuclease or HUH-tag and the second member comprises a nucleic acid binding domain. In some embodiments, the first member comprises a HUH tag. *See, e.g.*, U.S. 2021/0180082, incorporated herein in its entirety by reference.

[00124] In some embodiments, a capsid protein of the invention comprises at least a first member of a peptide:peptide binding pair.

[00125] In some embodiments, each of a first member and a second member of a peptide:peptide binding pair comprises an intein. *See, e.g.*, Wagner et al., (2021) *Adv. Sci.* 8: 2004018 (1 of 22); Muik et al. (2017) *Biomaterials* 144: 84, each of which is incorporated herein in its entirety by reference.

[00126] In some embodiments, a first member is a B cell epitope, e.g., is between about 1 amino acid and about 35 amino acids in length, and forms a binding pair with an antibody paratope, e.g., an immunoglobulin variable domain. In some embodiments, a capsid protein of the invention may be modified to comprise a detectable label as a first member of a binding pair. Many detectable labels are known in the art. (See, e.g.: Nilsson et al. (1997) “Affinity fusion strategies for detection, purification, and immobilization of modified proteins”; Protein Expression and Purification 11: 1-16, Terpe et al. (2003); “Overview of tag protein fusions: From molecular and biochemical fundamentals to commercial systems” Applied Microbiology and Biotechnology 60:523-533; and references therein). Detectable labels include, but are not limited to, a polyhistidine detectable labels (e.g., a His-6, His-8, or His-10) that binds immobilized divalent cations (e.g., Ni^{2+}), a biotin moiety (e.g., on an *in vivo* biotinylated polypeptide sequence) that binds immobilized avidin, a GST (glutathione S-transferase) sequence that binds immobilized glutathione, an S tag that binds immobilized S protein, an antigen that binds an immobilized antibody or domain or fragment thereof (including, e.g., T7, myc, FLAG, and B tags that bind corresponding antibodies), a FLASH

Tag (a high detectable label that couples to specific arsenic based moieties), a receptor or receptor domain that binds an immobilized ligand (or vice versa), protein A or a derivative thereof (e.g., Z) that binds immobilized IgG, maltose-binding protein (MBP) that binds immobilized amylose, an albumin-binding protein that binds immobilized albumin, a chitin binding domain that binds immobilized chitin, a calmodulin binding peptide that binds immobilized calmodulin, and a cellulose binding domain that binds immobilized cellulose. Another exemplary detectable label is a SNAP-tag. In some embodiments, a detectable label disclosed herein comprises a detectable label recognized by an antibody paratope, wherein the detectable label and the antibody paratope form a protein:protein binding pair.

[00127] In some embodiments, a capsid protein of the invention comprises a first member of a protein:protein binding pair comprising a detectable label, which may also be used for the detection and/or isolation of the Cap protein and/or as a first member of a protein:protein binding pair. In some embodiments, a detectable label acts as a first member of a protein:protein binding pair for the binding of a targeting ligand comprising a multispecific binding protein that may bind both the detectable label and a target expressed by a cell of interest. In some embodiments, a Cap protein of the invention comprises a first member of a protein:protein binding pair comprising c-myc (EQKLISEEDL; SEQ ID NO: 639). Use of a detectable label as a first member of a protein:protein binding pair is described in, e.g., WO2019006043, incorporated herein in its entirety by reference.

[00128] In some embodiments, the first member comprises a B1 epitope (SEQ ID NO: 640). In some embodiments, a capsid protein is modified to comprise a B1 epitope in the VP3 region. In some embodiments, the first member is selected from the group consisting of FLAG, HA and c-myc (EQKLISEEDL; SEQ ID NO: 639).

[00129] In some embodiments, a capsid protein comprises a first member of a protein:protein binding pair, wherein the protein:protein binding pair forms a covalent isopeptide bond. In some embodiments, the first member of a peptide:peptide binding pair is covalently bound via an isopeptide bond to a cognate second member of the peptide:peptide binding pair, and optionally wherein the cognate second member of the peptide:peptide binding pair is fused with a targeting ligand, which targeting ligand binds a target expressed by a cell of interest. In some embodiments, the protein:protein binding pair may be selected from the group consisting of SpyTag:SpyCatcher, SpyTag002:SpyCatcher002,

SpyTag003:SpyCatcher003, SpyTag:KTag, Isopeptag:pilin-C, and SnoopTag:SnoopCatcher. In some embodiments, wherein the first member is SpyTag (or a biologically active portion or variant thereof) and the protein (second cognate member) is SpyCatcher (or a biologically active portion or variant thereof). In some embodiments, wherein the first member is SpyTag (or a biologically active portion or variant thereof) and the protein (second cognate member) is KTag (or a biologically active portion or variant thereof). In some embodiments, wherein the first member is KTag (or a biologically active portion or variant thereof) and the protein (second cognate member) is SpyTag (or a biologically active portion or variant thereof). In some embodiments, wherein the first member is SnoopTag (or a biologically active portion or variant thereof) and the protein (second cognate member) is SnoopCatcher (or a biologically active portion or variant thereof). In some embodiments, wherein the first member is Isopeptag (or a biologically active portion or variant thereof) and the protein (second cognate member) is Pilin-C (or a biologically active portion or variant thereof). In some embodiments, wherein the first member is SpyTag002 (or a biologically active portion or variant thereof) and the protein (second cognate member) is SpyCatcher002 (or a biologically active portion or variant thereof). In some embodiments, wherein the first member is SpyTag003 (or a biologically active portion or variant thereof) and the protein (second cognate member) is SpyCatcher003 (or a biologically active portion or variant thereof). In some embodiments, a Cap protein of the invention comprises a SpyTag, or a biologically active portion or variant thereof. Use of a first member of a protein:protein binding pair is described in WO2019006046, incorporated herein in its entirety.

[00130] In some embodiments, a first member of a protein:protein binding pair and/or detectable label is operably linked to (translated in frame with, chemically attached to, and/or displayed by) a Cap protein of the invention via a first or second linker, e.g., an amino acid spacer that is at least one amino acid in length. In some embodiments, the first member of a protein:protein binding pair is flanked by a first and/or second linker, e.g., a first and/or second amino acid spacer, each of which spacer is at least one amino acid in length.

[00131] In some embodiments, the first and/or second linkers are not identical. In some embodiments, the first and/or second linker is each independently one or two amino acids in length. In some embodiments, the first and/or second linker is each independently one, two or three amino acids in length. In some embodiments, the first and/or second linker

is each independently one, two, three, or four amino acids in length. In some embodiments, the first and/or second linker is each independently one, two, three, four, or five amino acids in length. In some embodiments, the first and/or second linker are each independently one, two, three, four, or five amino acids in length. In some embodiments, the first and/or second linker is each independently one, two, three, four, five, or six amino acids in length. In some embodiments, the first and/or second linker is each independently one, two, three, four, five, six, or seven amino acids in length. In some embodiments, the first and/or second linker is each independently one, two, three, four, five, six, seven, or eight amino acids in length. In some embodiments, the first and/or second linker is each independently one, two, three, four, five, six, seven, eight or nine amino acids in length. In some embodiments, the first and or second linker is each independently one, two, three, four, five, six, seven, eight, nine, or ten amino acids in length. In some embodiments, the first and or second linker is each independently one, two, three, four, five, six, seven, eight, nine, ten, or more amino acids in length.

[00132] In some embodiments, the first and second linkers are identical in sequence and/or in length and are each one amino acid in length. In some embodiments, the first and second linkers are identical in length, and are each one amino acid in length. In some embodiments, the first and second linkers are identical in length, and are each two amino acids in length. In some embodiments, the first and second linkers are identical in length, and are each three amino acids in length. In some embodiments, the first and second linkers are identical in length, and are each four amino acids in length, e.g., the linker is GLSG (SEQ ID NO: 633). In some embodiments, the first and second linkers are identical in length, and are each five amino acids in length. In some embodiments, the first and second linkers are identical in length, and are each six amino acids in length, e.g., the first and second linkers each comprise a sequence of GLSGSG (SEQ ID NO: 634). In some embodiments, the first and second linkers are identical in length, and are each seven amino acids in length. In some embodiments, the first and second linkers are identical in length, and are each eight amino acids in length, e.g., the first and second linkers each comprise a sequence of GLSGLSGS (SEQ ID NO: 635). In some embodiments, the first and second linkers are identical in length, and are each nine amino acids in length. In some embodiments, the first and second linkers are identical in length, and are each ten amino acids in length, e.g., the first and second

linkers each comprise a sequence of GLSGLSGLSG (SEQ ID NO: 636) or GLSGGSGLSG (SEQ ID NO: 637). In some embodiments, the first and second linkers are identical in length, and are each more than ten amino acids in length.

[00133] Generally, a first member of a protein:protein binding pair amino acid sequence as described herein, e.g., comprising a first member of a specific binding pair by itself or in combination with one or more linkers, is between about 5 amino acids to about 50 amino acids in length. In some embodiments, the first member of a protein:protein binding pair amino acid sequence is at least 5 amino acids in length. In some embodiments, the first member of a protein:protein binding pair amino acid sequence is 6 amino acids in length. In some embodiments, the first member of a protein:protein binding pair amino acid sequence is 7 amino acids in length. In some embodiments, the first member of a protein:protein binding pair amino acid sequence is 8 amino acids in length. In some embodiments, the first member of a protein:protein binding pair amino acid sequence is 9 amino acids in length. In some embodiments, the first member of a protein:protein binding pair amino acid sequence is 10 amino acids in length. In some embodiments, the first member of a protein:protein binding pair amino acid sequence is 11 amino acids in length. In some embodiments, the first member of a protein:protein binding pair amino acid sequence is 12 amino acids in length. In some embodiments, the first member of a protein:protein binding pair amino acid sequence is 13 amino acids in length. In some embodiments, the first member of a protein:protein binding pair amino acid sequence is 14 amino acids in length. In some embodiments, the first member of a protein:protein binding pair amino acid sequence is 15 amino acids in length. In some embodiments, the first member of a protein:protein binding pair amino acid sequence is 16 amino acids in length. In some embodiments, the first member of a protein:protein binding pair amino acid sequence is 17 amino acids in length. In some embodiments, the first member of a protein:protein binding pair amino acid sequence is 18 amino acids in length. In some embodiments, the first member of a protein:protein binding pair amino acid sequence is 19 amino acids in length. In some embodiments, the first member of a protein:protein binding pair amino acid sequence is 20 amino acids in length. In some embodiments, the first member of a protein:protein binding pair amino acid sequence is 21 amino acids in length. In some embodiments, the first member of a protein:protein binding pair amino acid sequence is 22 amino acids in length. In some embodiments, the first member of a

[illegible]

first member of a protein:protein binding pair amino acid sequence is 46 amino acids in length. In some embodiments, the first member of a protein:protein binding pair amino acid sequence is 47 amino acids in length. In some embodiments, the first member of a protein:protein binding pair amino acid sequence is 48 amino acids in length. In some embodiments, the first member of a protein:protein binding pair amino acid sequence is 49 amino acids in length. In some embodiments, the first member of a protein:protein binding pair amino acid sequence is 50 amino acids in length.

Modified Capsids Comprising Modified Capsid Proteins

[00134] In some embodiments a viral capsid comprising a modified viral capsid protein as described herein is a mosaic capsid, e.g., comprises at least two sets of VP1, VP2, and/or VP3 proteins, each set of which is encoded by a different *cap* gene. A mosaic capsid herein generally refers to a mosaic of a first viral capsid protein modified to comprise a first member of a binding pair and a second corresponding viral capsid protein lacking the first member of a binding pair. In relation to a mosaic capsid, the second viral capsid protein lacking the first member of a binding pair may be referred to as a reference capsid protein encoded by a reference *cap* gene. In some mosaic capsid embodiments, preferably when the VP1, VP2, and/or VP3 capsid proteins modified with a first member of protein:protein pair is not a chimeric capsid protein, a VP1, VP2, and/or VP3 reference capsid protein may comprise an amino acid sequence identical to that of the viral VP1, VP2, and/or VP3 capsid protein modified with a first member of a binding pair, except that the reference capsid protein lacks the first member of a binding pair. In some mosaic capsid embodiments, a VP1, VP2, and/or VP3 reference capsid protein corresponds to the viral VP1, VP2, and/or VP3 capsid protein modified with a first member of a binding pair, except that the reference capsid protein lacks the first member of a binding pair. In some embodiments, a VP1 reference capsid protein corresponds to the viral VP1 capsid protein modified with a first member of a binding pair, except that the reference capsid protein lacks the first member of a binding pair. In some embodiments, a VP2 reference capsid protein corresponds to the viral VP2 capsid protein modified with a first member of a binding pair, except that the reference capsid protein lacks the first member of a binding pair. In some embodiments, a VP3 reference capsid protein corresponds to the viral VP3 capsid protein modified with a first member of a binding pair, except that the reference capsid protein lacks the first member of a binding pair.

In some mosaic capsid embodiments comprising a chimeric VP1, VP2, and/or VP3 capsid protein further modified to comprise a first member of a binding pair, a reference protein may be a corresponding capsid protein from which portions thereof form part of the chimeric capsid protein. As a non-limiting example in some embodiments, mosaic capsid comprising a chimeric AAV2/AAAV VP1 capsid protein modified to comprise a first member of a binding pair may further comprise as a reference capsid protein: an AAV2 VP1 capsid protein lacking the first member, an AAAV VP1 capsid protein lacking the first member, a chimeric AAV2/AAAV VP1 capsid protein lacking the first member. Similarly, in some embodiments, a mosaic capsid comprising a chimeric AAV2/AAAV VP2 capsid protein modified to comprise a first member of a binding pair may further comprise as a reference capsid protein: an AAV2 VP2 capsid protein lacking the first member, an AAAV VP1 capsid protein lacking the first member, a chimeric AAV2/AAAV VP2 capsid protein lacking the first member. In some embodiments, a mosaic capsid comprising a chimeric AAV2/AAAV VP3 capsid protein modified to comprise a first member of a binding pair may further comprise as a reference capsid protein: an AAV2 VP2 capsid protein lacking the first member, an AAAV VP1 capsid protein lacking the first member, a chimeric AAV2/AAAV VP3 capsid protein lacking the first member. In some mosaic capsid embodiments, a reference capsid protein may be any capsid protein so long as it that lacks the first member of the binding pair and is able to form a capsid with the first capsid protein modified with the first member of a binding pair.

[00135] Generally, mosaic particles may be generated by transfecting mixtures of the modified and reference *Cap* genes into production cells at the indicated ratios. The protein subunit ratios, e.g., modified VP protein:unmodified VP protein ratios, in the particle may, but do not necessarily, stoichiometrically reflect the ratios of the at least two species of the *cap* gene encoding the first capsid protein modified with a first member of a binding pair and the one or more reference *cap* genes, e.g., modified *cap* gene:reference *cap* gene(s) transfected into packaging cells. In some embodiments, the protein subunit ratios in the particle do not stoichiometrically reflect the modified *cap* gene:reference *cap* gene(s) ratio transfected into packaging cells.

[00136] In some mosaic viral particle embodiments, the protein subunit ratio ranges from about 1:59 to about 59:1. In some mosaic viral particle embodiments, the protein

subunit is at least about 1:1 (e.g., the mosaic viral particle comprises about 30 modified capsid proteins and about 30 reference capsid protein). In some mosaic viral particle embodiments, the protein subunit ratio is at least about 1:2 (e.g., the mosaic viral particle comprises about 20 modified capsid proteins and about 40 reference capsid proteins). In some mosaic viral particle embodiments, the protein subunit ratio is at least about 3:5. In some mosaic viral particle embodiments, the protein subunit ratio is at least about 1:3 (e.g., the mosaic viral particle comprises about 15 modified capsid proteins and about 45 reference capsid proteins). In some mosaic viral particle embodiments, the protein subunit ratio is at least about 1:4 (e.g., the mosaic viral particle comprises about 12 modified capsid proteins and 48 reference capsid proteins). In some mosaic viral particle embodiments, the protein subunit ratio is at least about 1:5 (e.g., the mosaic viral particle comprises 10 modified capsid proteins and 50 reference capsid proteins). In some mosaic viral particle embodiments, the protein subunit ratio is at least about 1:6. In some mosaic viral particle embodiments, the protein subunit ratio is at least about 1:7. In some mosaic viral particle embodiments, the protein subunit ratio is at least about 1:8. In some mosaic viral particle embodiments, the protein subunit ratio is at least about 1:9 (e.g., the mosaic viral particle comprises about 6 modified capsid proteins and about 54 reference capsid proteins). In some mosaic viral particle embodiments, the protein subunit ratio is at least about 1:10. In some mosaic viral particle embodiments, the protein subunit ratio is at least about 1:11 (e.g., the mosaic viral particle comprises about 5 modified capsid proteins and about 55 reference capsid proteins). In some mosaic viral particle embodiments, the protein subunit ratio is at least about 1:12. In some mosaic viral particle embodiments, the protein subunit ratio is at least about 1:13. In some mosaic viral particle embodiments, the protein subunit ratio is at least about 1:14 (e.g., the mosaic viral particle comprises about 4 modified capsid proteins and about 56 reference capsid proteins). In some mosaic viral particle embodiments, the protein subunit ratio is at least about 1:15. In some mosaic viral particle embodiments, the protein subunit ratio is at least about 1:19 (e.g., the mosaic viral particle comprises about 3 modified capsid proteins and about 57 reference capsid proteins). In some mosaic viral particle embodiments, the protein subunit ratio is at least about 1:29 (e.g., the mosaic viral particle comprises about 2 modified capsid proteins and about 58 reference capsid proteins). In some mosaic viral particle embodiments, the protein subunit ratio is at least about 1:59. In some mosaic viral

particle embodiments, the protein subunit ratio is at least about 2:1 (e.g., the mosaic viral particle comprises about 40 modified capsid proteins and about 20 reference capsid proteins). In some mosaic viral particle embodiments, the protein subunit ratio is at least about 5:3. In some mosaic viral particle embodiments, the protein subunit ratio is at least about 3:1 (e.g., the mosaic viral particle comprises about 45 modified capsid proteins and about 15 reference capsid proteins). In some mosaic viral particle embodiments, the protein subunit ratio is at least about 4:1 (e.g., the mosaic viral particle comprises about 48 modified capsid proteins and 12 reference capsid proteins). In some mosaic viral particle embodiments, the protein subunit ratio is at least about 5:1 (e.g., the mosaic viral particle comprises 50 modified capsid proteins and 10 reference capsid proteins). In some mosaic viral particle embodiments, the protein subunit ratio is at least about 6:1. In some mosaic viral particle embodiments, the protein subunit ratio is at least about 7:1. In some mosaic viral particle embodiments, the protein subunit ratio is at least about 8:1. In some mosaic viral particle embodiments, the protein subunit ratio is at least about 9:1 (e.g., the mosaic viral particle comprises about 54 modified capsid proteins and about 6 reference capsid proteins). In some mosaic viral particle embodiments, the protein subunit ratio is at least about 10:1. In some mosaic viral particle embodiments, the protein subunit ratio is at least about 11:1 (e.g., the mosaic viral particle comprises about 55 modified capsid proteins and about 5 reference capsid proteins). In some mosaic viral particle embodiments, the protein subunit ratio is at least about 12:1. In some mosaic viral particle embodiments, the protein subunit ratio is at least about 13:1. In some mosaic viral particle embodiments, the protein subunit ratio is at least about 14:1 (e.g., the mosaic viral particle comprises about 56 modified capsid proteins and about 4 reference capsid proteins). In some mosaic viral particle embodiments, the protein subunit ratio is at least about 15:1. In some mosaic viral particle embodiments, the protein subunit ratio is at least about 19:1 (e.g., the mosaic viral particle comprises about 57 modified capsid proteins and about 3 reference capsid proteins). In some mosaic viral particle embodiments, the protein subunit ratio is at least about 29:1 (e.g., the mosaic viral particle comprises about 58 modified capsid proteins and about 2 reference capsid proteins). In some mosaic viral particle embodiments, the protein subunit ratio is at least about 59:1.

[00137] In some non-mosaic viral particle embodiments, the protein subunit ratio may be 1:0 wherein each capsid protein of the non-mosaic viral particle is modified with a first

member of a binding pair. In some non-mosaic viral particle embodiments, the protein subunit ratio may be 0:1 wherein each capsid protein of the non-mosaic viral particle is not modified with a first member of a binding pair.

Insertion sites

[00138] Due to the high conservation of at least large stretches and the large member of closely related family members, the corresponding insertion sites for AAV other than the enumerated AAV can be identified by performing an amino acid alignment or by comparison of the capsid structures. See, e.g., Rutledge et al. (1998) *J. Virol.* 72:309-19; Mietzsch et al. (2019) *Viruses* 11, 362, 1-34, and U.S. Patent No. 9,624,274 for exemplary alignments of different AAV capsid proteins, each of which is incorporated herein by reference in its entirety. For example, Mietzsch et al. (2019) provide an overlay of ribbons from different dependoparvovirus, depicting the variable regions VR I to VR IX. Using such structural analysis as described therein, and sequence analysis, a skilled artisan may determine which amino acids within the variable region correspond to amino acid sequence of AAV that can accommodate the insertion of, e.g., a targeting ligand as described herein, a first member of a binding pair and/or detectable label.

[00139] Generally, the targeting ligand, first member of a binding pair, and/or detectable label may be inserted into a variable region or variable loop of an AAV capsid protein, a GH loop of an AAV capsid protein, etc.

[00140] In some embodiments, the first member of a binding pair and/or detectable label is inserted in a VP1 capsid protein of a non-primate animal AAV after an amino acid position corresponding with an amino acid position selected from the group consisting of G453 of AAV2 capsid protein VP1, N587 of AAV2 capsid protein VP1, G453 of AAV9 capsid protein VP1, and A589 of AAV9 capsid protein VP1. In some embodiments, the first member of a binding pair and/or detectable label is inserted in a VP1 capsid protein of a non-primate animal AAV between amino acids that correspond with N587 and R588 of an AAV2 VP1 capsid. Additional suitable insertion sites of a non-primate animal VP1 capsid protein include those corresponding to I-1, I-34, I-138, I-139, I-161, I-261, I-266, I-381, I-447, I-448, I-459, I-471, I-520, I-534, I-570, I-573, I-584, I-587, I-588, I-591, I-657, I-664, I-713 and I-716 of the VP1 capsid protein of AAV2 (Wu et al. (2000) *J. Virol.* 74:8635-8647). A modified virus capsid protein as described herein may be a non-primate animal capsid protein

comprising a first member of a binding pair and/or detectable label inserted into a position corresponding with a position of an AAV2 capsid protein selected from the group consisting of I-1, I-34, I-138, I-139, I-161, I-261, I-266, I-381, I-447, I-448, I-459, I-471, I-520, I-534, I-570, I-573, I-584, I-587, I-588, I-591, I-657, I-664, I-713, I-716, and a combination thereof. Additional suitable insertion sites of a non-primate animal AAV that include those corresponding to I-587 or I-590 of AAV1, I-589 of AAV1, I-585 of AAV3, I-584 or I-585 of AAV4, and I-575 or I-585 of AAV5. In some embodiments, a modified virus capsid protein as described herein may be a non-primate animal capsid protein comprising a targeting ligand, first member of a binding pair and/or detectable label inserted into a position corresponding with a position selected from the group consisting of I-587 (AAV1), I-589 (AAV1), I-585 (AAV3), I-585 (AAV4), I-585 (AAV5), and a combination thereof.

[00141] In some embodiments, the first member of a binding pair and/or detectable label is inserted in a VP1 capsid protein of a non-primate animal AAV after an amino acid position corresponding with an amino acid position selected from the group consisting of I444 of an avian AAV capsid protein VP1, I580 of an avian AAV capsid protein VP1, I573 of a bearded dragon AAV capsid protein VP1, I436 of a bearded dragon AAV capsid protein VP1, I429 of a sea lion AAV capsid protein VP1, I430 of a sea lion AAV capsid protein VP1, I431 of a sea lion AAV capsid protein VP1, I432 of a sea lion AAV capsid protein VP1, I433 of a sea lion AAV capsid protein VP1, I434 of a sea lion AAV capsid protein VP1, I436 of a sea lion AAV capsid protein VP1, I437 of a sea lion AAV capsid protein VP1, and I565 of a sea lion AAV capsid protein VP1.

[00142] The nomenclature I-###, I# or the like herein refers to the insertion site (I) with ### naming the amino acid number relative to the VP1 protein of an AAV capsid protein, however such the insertion may be located directly N- or C-terminal, preferably C-terminal of one amino acid in the sequence of 5 amino acids N- or C-terminal of the given amino acid, preferably 3, more preferably 2, especially 1 amino acid(s) N- or C-terminal of the given amino acid. Additionally, the positions referred to herein are relative to the VP1 protein encoded by an AAV capsid gene, and corresponding positions (and point mutations thereof) may be easily identified for the VP2 and VP3 capsid proteins encoding by the capsid gene by performing a sequence alignment of the VP1, VP2 and VP3 proteins encoded by the appropriate AAV capsid gene.

[00143] Accordingly, an insertion into the corresponding position of the coding nucleic acid of one of these sites of the cap gene leads to an insertion into VP1, VP2 and/or VP3, as the capsid proteins are encoded by overlapping reading frames of the same gene with staggered start codons. Therefore, for AAV2, for example, according to this nomenclature insertions between amino acids 1 and 138 are only inserted into VP1, insertions between 138 and 203 are inserted into VP1 and VP2, and insertions between 203 and the C-terminus are inserted into VP1, VP2 and VP3, which is of course also the case for the insertion site I-587. Therefore, the present invention encompasses structural genes of AAV with corresponding insertions in the VP1, VP2 and/or VP3 proteins.

[00144] Also provided herein are nucleic acids that encode a VP3 capsid protein of the invention. AAV capsid proteins may be, but are not necessarily, encoded by overlapping reading frames of the same gene with staggered start codons. In some embodiments, a nucleic acid that encodes a VP3 capsid protein of the invention does not also encode a VP2 capsid protein or VP1 capsid protein of the invention. In some embodiments, a nucleic acid that encodes a VP3 capsid protein of the invention may also encode a VP2 capsid protein of the invention but does not also encode a VP1 capsid of the invention. In some embodiments, a nucleic acid that encodes a VP3 capsid protein of the invention may also encode a VP2 capsid protein of the invention and a VP1 capsid of the invention.

[00145] In some embodiments, a viral capsid comprising the modified viral capsid protein comprising the first and second members of a binding pair (e.g., wherein the second member is operably linked to a targeting ligand, comprises a multispecific binding protein, etc.) is able to infect a specific cell, e.g., has an enhanced capacity to target and bind a specific cell compared to that of a control viral capsid that is identical to the modified viral capsid protein except that it lacks either or both the first and second members of a binding pair, e.g., comprises a control capsid protein. In some embodiments, a viral capsid comprising a modified viral capsid protein as described herein bound to the first and second members of a binding pair linked to a targeting ligand exhibits a detectable transduction efficiency compared to the undetectable transduction efficiency of a control viral capsid. In some embodiments, a viral capsid comprising a modified viral capsid protein as described herein bound to the first and second members of a binding pair linked to a targeting ligand exhibits a transduction efficiency that is 10% greater than the transduction efficiency of a

control viral capsid. In some embodiments, a viral capsid comprising a modified viral capsid protein as described herein bound to the first and second members of a binding pair linked to a targeting ligand exhibits a transduction efficiency that is 20% greater than the transduction efficiency of a control viral capsid. In some embodiments, a viral capsid comprising a modified viral capsid protein as described herein bound to an appropriate the first and second members of a binding pair linked to a targeting ligand exhibits a transduction efficiency that is 30% greater than the transduction efficiency of a control viral capsid. In some embodiments, a viral capsid comprising a modified viral capsid protein as described herein bound to an appropriate the first and second members of a binding pair linked to a targeting ligand exhibits a transduction efficiency that is 40% greater than the transduction efficiency of a control viral capsid. In some embodiments, a viral capsid comprising a modified viral capsid protein as described herein bound to an appropriate the first and second members of a binding pair linked to a targeting ligand exhibits a transduction efficiency that is 50% greater than the transduction efficiency of a control viral capsid. In some embodiments, a viral capsid comprising a modified viral capsid protein as described herein bound to an appropriate the first and second members of a binding pair linked to a targeting ligand exhibits a transduction efficiency that is 60% greater than the transduction efficiency of a control viral capsid. In some embodiments, a viral capsid comprising a modified viral capsid protein as described herein bound to an appropriate the first and second members of a binding pair linked to a targeting ligand exhibits a transduction efficiency that is 70% greater than the transduction efficiency of a control viral capsid. In some embodiments, a viral capsid comprising a modified viral capsid protein as described herein bound to an appropriate the first and second members of a binding pair linked to a targeting ligand exhibits a transduction efficiency that is 75% greater than the transduction efficiency of a control viral capsid. In some embodiments, a viral capsid comprising a modified viral capsid protein as described herein bound to an appropriate the first and second members of a binding pair linked to a targeting ligand exhibits a transduction efficiency that is 80% greater than the transduction efficiency of a control viral capsid. In some embodiments, a viral capsid comprising a modified viral capsid protein as described herein bound to an appropriate the first and second members of a binding pair linked to a targeting ligand exhibits a transduction efficiency that is 85% greater than the transduction efficiency of a control viral capsid. In some

embodiments, a viral capsid comprising a modified viral capsid protein as described herein bound to an appropriate the first and second members of a binding pair linked to a targeting ligand exhibits a transduction efficiency that is 90% greater than the transduction efficiency of a control capsid. In some embodiments, a viral capsid comprising a modified viral capsid protein as described herein bound to an appropriate the first and second members of a binding pair linked to a targeting ligand exhibits a transduction efficiency that is 95% greater than the transduction efficiency of a control viral capsid. In some embodiments, a viral capsid comprising a modified viral capsid protein as described herein bound to the first and second members of a binding pair linked to a targeting ligand exhibits a transduction efficiency that is 99% greater than the transduction efficiency of a control viral capsid.

[00146] In some embodiments, a viral capsid comprising the modified viral capsid protein comprising the first and second members of a binding pair (e.g., wherein the second member is operably linked to a targeting ligand, comprises a multispecific binding protein, etc.) is able to infect a specific cell, e.g., has an enhanced capacity to target and bind a specific cell compared to that of a control viral capsid that is identical to the modified viral capsid protein except that it lacks either or both the first and second members of a binding pair, e.g., comprises a control capsid protein. In some embodiments, a viral capsid comprising a modified viral capsid protein as described herein bound to the first and second members of a binding pair linked to a targeting ligand exhibits a detectable transduction efficiency compared to the undetectable transduction efficiency of a control viral capsid. In some embodiments, a viral capsid comprising a modified viral capsid protein as described herein bound to the first and second members of a binding pair linked to a targeting ligand exhibits a transduction efficiency that is 10% greater than the transduction efficiency of a control viral capsid. In some embodiments, a viral capsid comprising a modified viral capsid protein as described herein bound to the first and second members of a binding pair linked to a targeting ligand exhibits a transduction efficiency that is 20% greater than the transduction efficiency of a control viral capsid. In some embodiments, a viral capsid comprising a modified viral capsid protein as described herein bound to an appropriate the first and second members of a binding pair linked to a targeting ligand exhibits a transduction efficiency that is 30% greater than the transduction efficiency of a control viral capsid. In some embodiments, a viral capsid comprising a modified viral capsid protein as described herein

bound to an appropriate the first and second members of a binding pair linked to a targeting ligand exhibits a transduction efficiency that is 40% greater than the transduction efficiency of a control viral capsid. In some embodiments, a viral capsid comprising a modified viral capsid protein as described herein bound to an appropriate the first and second members of a binding pair linked to a targeting ligand exhibits a transduction efficiency that is 50% greater than the transduction efficiency of a control viral capsid. In some embodiments, a viral capsid comprising a modified viral capsid protein as described herein bound to an appropriate the first and second members of a binding pair linked to a targeting ligand exhibits a transduction efficiency that is 60% greater than the transduction efficiency of a control viral capsid. In some embodiments, a viral capsid comprising a modified viral capsid protein as described herein bound to an appropriate the first and second members of a binding pair linked to a targeting ligand exhibits a transduction efficiency that is 70% greater than the transduction efficiency of a control viral capsid. In some embodiments, a viral capsid comprising a modified viral capsid protein as described herein bound to an appropriate the first and second members of a binding pair linked to a targeting ligand exhibits a transduction efficiency that is 75% greater than the transduction efficiency of a control viral capsid. In some embodiments, a viral capsid comprising a modified viral capsid protein as described herein bound to an appropriate the first and second members of a binding pair linked to a targeting ligand exhibits a transduction efficiency that is 80% greater than the transduction efficiency of a control viral capsid. In some embodiments, a viral capsid comprising a modified viral capsid protein as described herein bound to an appropriate the first and second members of a binding pair linked to a targeting ligand exhibits a transduction efficiency that is 85% greater than the transduction efficiency of a control viral capsid. In some embodiments, a viral capsid comprising a modified viral capsid protein as described herein bound to an appropriate the first and second members of a binding pair linked to a targeting ligand exhibits a transduction efficiency that is 90% greater than the transduction efficiency of a control capsid. In some embodiments, a viral capsid comprising a modified viral capsid protein as described herein bound to an appropriate the first and second members of a binding pair linked to a targeting ligand exhibits a transduction efficiency that is 95% greater than the transduction efficiency of a control viral capsid. In some embodiments, a viral capsid comprising a modified viral capsid protein as described herein bound to the first and second

members of a binding pair linked to a targeting ligand exhibits a transduction efficiency that is 99% greater than the transduction efficiency of a control viral capsid. In some embodiments, a viral capsid comprising a modified viral capsid protein as described herein bound to the first and second members of a binding pair linked to a targeting ligand exhibits a transduction efficiency that is at least 1.5-fold greater than the transduction efficiency of a control viral capsid. In some embodiments, a viral capsid comprising a modified viral capsid protein as described herein bound to the first and second members of a binding pair linked to a targeting ligand exhibits a transduction efficiency that is at least 2-fold greater than the transduction efficiency of a control viral capsid. In some embodiments, a viral capsid comprising a modified viral capsid protein as described herein bound to an appropriate the first and second members of a binding pair linked to a targeting ligand exhibits a transduction efficiency that is at least 3-fold greater than the transduction efficiency of a control viral capsid. In some embodiments, a viral capsid comprising a modified viral capsid protein as described herein bound to an appropriate the first and second members of a binding pair linked to a targeting ligand exhibits a transduction efficiency that is at least 4-fold greater than the transduction efficiency of a control viral capsid. In some embodiments, a viral capsid comprising a modified viral capsid protein as described herein bound to an appropriate the first and second members of a binding pair linked to a targeting ligand exhibits a transduction efficiency that is at least 5-fold greater than the transduction efficiency of a control viral capsid. In some embodiments, a viral capsid comprising a modified viral capsid protein as described herein bound to an appropriate the first and second members of a binding pair linked to a targeting ligand exhibits a transduction efficiency that is at least 6-fold greater than the transduction efficiency of a control viral capsid. In some embodiments, a viral capsid comprising a modified viral capsid protein as described herein bound to an appropriate the first and second members of a binding pair linked to a targeting ligand exhibits a transduction efficiency that is at least 7-fold greater than the transduction efficiency of a control viral capsid. In some embodiments, a viral capsid comprising a modified viral capsid protein as described herein bound to an appropriate the first and second members of a binding pair linked to a targeting ligand exhibits a transduction efficiency that is at least 8-fold greater than the transduction efficiency of a control viral capsid. In some embodiments, a viral capsid comprising a modified viral capsid protein as described herein bound to an appropriate

the first and second members of a binding pair linked to a targeting ligand exhibits a transduction efficiency that is at least 9-fold greater than the transduction efficiency of a control viral capsid. In some embodiments, a viral capsid comprising a modified viral capsid protein as described herein bound to an appropriate the first and second members of a binding pair linked to a targeting ligand exhibits a transduction efficiency that is at least 10-fold greater than the transduction efficiency of a control viral capsid. In some embodiments, a viral capsid comprising a modified viral capsid protein as described herein bound to an appropriate the first and second members of a binding pair linked to a targeting ligand exhibits a transduction efficiency that is at least 20-fold greater than the transduction efficiency of a control capsid. In some embodiments, a viral capsid comprising a modified viral capsid protein as described herein bound to an appropriate the first and second members of a binding pair linked to a targeting ligand exhibits a transduction efficiency that is at least 30-fold greater than the transduction efficiency of a control viral capsid. In some embodiments, a viral capsid comprising a modified viral capsid protein as described herein bound to the first and second members of a binding pair linked to a targeting ligand exhibits a transduction efficiency that is at least 40-fold greater than the transduction efficiency of a control viral capsid. In some embodiments, a viral capsid comprising a modified viral capsid protein as described herein bound to the first and second members of a binding pair linked to a targeting ligand exhibits a transduction efficiency that is at least 50-fold greater than the transduction efficiency of a control viral capsid. In some embodiments, a viral capsid comprising a modified viral capsid protein as described herein bound to the first and second members of a binding pair linked to a targeting ligand exhibits a transduction efficiency that is at least 60-fold greater than the transduction efficiency of a control viral capsid. In some embodiments, a viral capsid comprising a modified viral capsid protein as described herein bound to the first and second members of a binding pair linked to a targeting ligand exhibits a transduction efficiency that is at least 70-fold greater than the transduction efficiency of a control viral capsid. In some embodiments, a viral capsid comprising a modified viral capsid protein as described herein bound to the first and second members of a binding pair linked to a targeting ligand exhibits a transduction efficiency that is at least 80-fold greater than the transduction efficiency of a control viral capsid. In some embodiments, a viral capsid comprising a modified viral capsid protein as described herein bound to the first and second

members of a binding pair linked to a targeting ligand exhibits a transduction efficiency that is at least 90-fold greater than the transduction efficiency of a control viral capsid. In some embodiments, a viral capsid comprising a modified viral capsid protein as described herein bound to the first and second members of a binding pair linked to a targeting ligand exhibits a transduction efficiency that is at least 100-fold greater than the transduction efficiency of a control viral capsid. In some embodiments, a viral particle of the invention comprising a viral capsid protein comprising an amino acid sequence of a capsid protein of a non-primate animal AAV, a remote AAV, or a combination thereof, and optionally comprising a first and second members of a binding pair (e.g., wherein the second member is operably linked to a targeting ligand, comprises a multispecific binding protein, etc.) is better able to evade neutralization by pre-existing antibodies in serum isolated from a human patient compared to an appropriate control viral particle (e.g., comprising a viral capsid of an AAV serotype from which a portion is included in the viral capsid of the invention, e.g., as part of the viral capsid protein comprising an amino acid sequence of a capsid protein of a non-primate animal AAV, a remote AAV, or a combination thereof), which also optionally comprises a first and second members of a binding pair (e.g., wherein the second member is operably linked to a targeting ligand, comprises a multispecific binding protein, etc.). In some embodiments, a viral particle of the invention comprising a viral capsid protein comprising an amino acid sequence of a capsid protein of a non-primate animal AAV, a remote AAV, or a combination thereof requires at least 2-fold more total IVIG or IgG for neutralization (e.g., 50% or more infection inhibition) compared to an appropriate control viral particle, e.g., (e.g., a viral particle of the invention has an IC₅₀ value that is at least 2-fold that of a control virus particle).

[00147] In some embodiments of the invention comprising a detectable label, a targeting ligand comprises a multispecific binding molecule comprising (i) an antibody paratope that specifically binds the detectable label and (ii) a second binding domain that specifically binds a receptor, which may be conjugated to the surface of a bead (e.g., for purification) or expressed by a target cell. Accordingly, a multispecific binding molecule comprising (i) an antibody paratope that specifically binds the detectable label and (ii) a second binding domain that specifically binds a receptor targets the viral particle. Such “targeting” or “directing” may include a scenario in which the wildtype viral particle targets several cells within a tissue and/or several organs within an organism, which broad targeting

of the tissue or organs is reduced to abolished by insertion of the detectable label, and which retargeting to more specific cells in the tissue or more specific organ in the organism is achieved with the multispecific binding molecule. Such retargeting or redirecting may also include a scenario in which the wildtype viral particle targets a tissue, which targeting of the tissue is reduced to abolished by insertion of the detectable label, and which retargeting to a completely different tissue is achieved with the multispecific binding molecule. An antibody paratope as described herein generally comprises at a minimum a complementarity determining region (CDR) that specifically recognizes the detectable label, e.g., a CDR3 region of a heavy and/or light chain variable domain. In some embodiments, a multispecific binding molecule comprises an antibody (or portion thereof) that comprises the antibody paratope that specifically binds the detectable label. For example, a multispecific binding molecule may comprise a single domain heavy chain variable region or a single domain light chain variable region, wherein the single domain heavy chain variable region or single domain light chain variable region comprises an antibody paratope that specifically binds the detectable label. In some embodiments, a multispecific binding molecule may comprise an Fv region, e.g., a multispecific binding molecule may comprise an scFv, that comprises an antibody paratope that specifically binds the detectable label. In some embodiments, a multispecific binding molecule as described herein comprises an antibody paratope that specifically binds c-myc (SEQ ID NO: 639).

[00148] In some embodiments, the modified capsid may further comprise a mutation, e.g., a substitution, insertion, or deletion of an amino acid, that reduces or abolishes the natural tropism of the capsid protein. In some embodiments, the modified capsid protein is derived from an AAV9 serotype, and the further mutation comprises a W503A mutation. In some embodiments, the modified capsid protein is derived from an AAV6 serotype, and the further mutation comprises a K531A or K531E mutation. In some embodiments, the modified capsid protein is derived from an AAV2 serotype, and the further mutation comprises a R484A, R487A, R487G, K532A, K532D, R585A, R585S, R585Q, R585A, R588A, or R588T mutation.

[00149] In one embodiment, herein is provided a recombinant AAV9 particle comprising: (i) a modified AAV9 capsid protein comprising a first member and a second member of a protein:protein binding pair, and (ii) a targeting ligand that binds a human p75

neurotrophin receptor (p75^{NTR}), wherein the modified AAV9 capsid protein is operably linked with the targeting ligand, wherein the second member of the protein:protein binding pair comprises the targeting ligand that binds human p75^{NTR}, wherein the first member of the protein:protein binding pair and the second member of the protein:protein binding pair are associated to direct the tropism of the recombinant AAV9 particle to the human p75^{NTR}-expressing cell, wherein the targeting ligand is an antibody or a portion thereof, e.g., an antigen-binding portion thereof, wherein the modified AAV9 capsid protein further comprises a W503A mutation, and wherein the first member of the protein:protein binding pair is inserted, optionally via a linker as disclosed herein, at position G453.

[00150] In one embodiment, herein is provided a recombinant AAV9 particle comprising: (i) a modified AAV9 capsid protein comprising a first member and a second member of a protein:protein binding pair, and (ii) a targeting ligand that binds a human p75 neurotrophin receptor (p75^{NTR}), wherein the modified AAV9 capsid protein is operably linked with the targeting ligand, wherein the second member of the protein:protein binding pair comprises the targeting ligand that binds human p75^{NTR}, wherein the first member of the protein:protein binding pair and the second member of the protein:protein binding pair are associated to direct the tropism of the AAV9 particle to the human p75^{NTR}-expressing cell, wherein the targeting ligand is an antibody or a portion thereof, e.g., an antigen-binding portion thereof, that comprises an HCVR amino acid sequence as set forth in SEQ ID NO: 589 and an LCVR amino acid sequence as set forth in SEQ ID NO: 597, wherein the modified AAV9 capsid protein further comprises a W503A mutation, and wherein the first member of the protein:protein binding pair is inserted, optionally via a linker as disclosed herein, at position G453.

[00151] In one embodiment, herein is provided a recombinant AAV9 particle comprising: (i) a modified AAV9 capsid protein comprising a first member and a second member of a protein:protein binding pair, and (ii) a targeting ligand that binds a human p75 neurotrophin receptor (p75^{NTR}), wherein the modified AAV9 capsid protein is operably linked with the targeting ligand, wherein the second member of the protein:protein binding pair comprises the targeting ligand that binds human p75^{NTR}, wherein the first member of the protein:protein binding pair and the second member of the protein:protein binding pair are associated to direct the tropism of the AAV9 particle to the human p75^{NTR}-expressing

cell, wherein the targeting ligand is an antibody or a portion thereof, e.g., an antigen-binding portion thereof, that comprises an HCVR amino acid sequence as set forth in SEQ ID NO: 589 and an LCVR amino acid sequence as set forth in SEQ ID NO: 597, wherein the modified AAV9 capsid protein further comprises a W503A mutation, and wherein the first member of the protein:protein binding pair is inserted, optionally via a linker as disclosed herein, at position G453.

[00152] In one embodiment, herein is provided a recombinant AAV9 particle comprising: (i) a modified AAV9 capsid protein comprising a first member and a second member of a protein:protein binding pair, and (ii) a targeting ligand that binds a human p75 neurotrophin receptor (p75^{NTR}), wherein the modified AAV9 capsid protein is operably linked with the targeting ligand, wherein the second member of the protein:protein binding pair comprises the targeting ligand that binds human p75^{NTR}, wherein the first member of the protein:protein binding pair and the second member of the protein:protein binding pair are associated to direct the tropism of the AAV9 particle to the human p75^{NTR}-expressing cell, wherein the targeting ligand is an antibody or a portion thereof, e.g., an antigen-binding portion thereof, that comprises an HCVR amino acid sequence as set forth in SEQ ID NO: 529 and an LCVR amino acid sequence as set forth in SEQ ID NO: 537, wherein the modified AAV9 capsid protein further comprises a W503A mutation, and wherein the first member of the protein:protein binding pair is inserted, optionally via a linker as disclosed herein, at position G453.

[00153] In one embodiment, herein is provided a recombinant AAV9 particle comprising: (i) a modified AAV9 capsid protein comprising a first member and a second member of a protein:protein binding pair, and (ii) a targeting ligand that binds a human p75 neurotrophin receptor (p75^{NTR}), wherein the modified AAV9 capsid protein is operably linked with the targeting ligand, wherein the second member of the protein:protein binding pair comprises the targeting ligand that binds human p75^{NTR}, wherein the first member of the protein:protein binding pair and the second member of the protein:protein binding pair are associated to direct the tropism of the AAV9 particle to the human p75^{NTR}-expressing cell, wherein the targeting ligand is an antibody or a portion thereof, e.g., an antigen-binding portion thereof, that comprises an HCVR amino acid sequence as set forth in SEQ ID NO: 549 and an LCVR amino acid sequence as set forth in SEQ ID NO: 557, wherein the

modified AAV9 capsid protein further comprises a W503A mutation, and wherein the first member of the protein:protein binding pair is inserted, optionally via a linker as disclosed herein, at position G453.

[00154] In one embodiment, herein is provided a recombinant AAV9 particle comprising: (i) a modified AAV9 capsid protein comprising a first member and a second member of a protein:protein binding pair, and (ii) a targeting ligand that binds a human p75 neurotrophin receptor (p75^{NTR}), wherein the modified AAV9 capsid protein is operably linked with the targeting ligand, wherein the second member of the protein:protein binding pair comprises the targeting ligand that binds human p75^{NTR}, wherein the first member of the protein:protein binding pair and the second member of the protein:protein binding pair are associated to direct the tropism of the AAV9 particle to the human p75^{NTR}-expressing cell, wherein the targeting ligand is an antibody or a portion thereof, e.g., an antigen-binding portion thereof, that comprises an HCVR amino acid sequence as set forth in SEQ ID NO: 569 and an LCVR amino acid sequence as set forth in SEQ ID NO: 577, wherein the modified AAV9 capsid protein further comprises a W503A mutation, and wherein the first member of the protein:protein binding pair is inserted, optionally via a linker as disclosed herein, at position G453.

[00155] In one embodiment, herein is provided a recombinant AAV9 particle comprising: (i) a modified AAV9 capsid protein comprising a first member and a second member of a protein:protein binding pair, and (ii) a targeting ligand that binds a human p75 neurotrophin receptor (p75^{NTR}), wherein the modified AAV9 capsid protein is operably linked with the targeting ligand, wherein the second member of the protein:protein binding pair comprises the targeting ligand that binds human p75^{NTR}, wherein the first member of the protein:protein binding pair and the second member of the protein:protein binding pair are associated to direct the tropism of the AAV9 particle to the human p75^{NTR}-expressing cell, wherein the targeting ligand is an antibody or a portion thereof, e.g., an antigen-binding portion thereof, that comprises an HCVR amino acid sequence as set forth in SEQ ID NO: 609 and an LCVR amino acid sequence as set forth in SEQ ID NO: 597, wherein the modified AAV9 capsid protein further comprises a W503A mutation, and wherein the first member of the protein:protein binding pair is inserted, optionally via a linker as disclosed herein, at position G453.

[00156] One embodiment of the present invention is a multimeric structure comprising a modified viral capsid protein of the present invention. A multimeric structure comprises at least 5, preferably at least 10, more preferably at least 30, most preferably at least 60 modified viral capsid proteins comprising a first member of a specific binding pair as described herein. They can form regular viral capsids (empty viral particles) or viral particles (capsids encapsidating a nucleotide of interest). The formation of viral particles comprising a viral genome is a highly preferred feature for use of the modified viral capsids described herein.

[00157] A further embodiment of the present invention is the use of at least one modified viral capsid protein and/or a nucleic acid encoding same, preferably at least one multimeric structure (e.g., viral particle) for the manufacture of and use in transfer of a nucleotide of interest to a target cell.

Methods of Use and Making

[00158] A further embodiment of the modified viral capsids described herein is their use for delivering a nucleotide of interest, e.g., a reporter gene or a therapeutic gene, to a target cell. Generally, packaging of a nucleotide of interest comprises replacing an AAV genome between AAV ITR sequences with a gene of interest to create a transfer plasmid, which is then encapsulated in an AAV capsid according to well-known methods. Thus, a modified viral capsid as described herein may encapsulate a transfer plasmid and/or a nucleotide of interest, which may generally comprise 5' and 3' inverted terminal repeat (ITR) sequences flanking a gene of interest, e.g., reporter gene(s) or therapeutic gene(s), or a portion of the gene of interest (which may be under the control of a viral or non-viral promoter). According to well-known methods of packaging AAV viral particles, the modified viral capsids, the 5' ITR, and the 3' ITR need not be of the same AAV serotype. In one embodiment, a transfer plasmid and/or nucleotide of interest comprises from 5' to 3': a 5' ITR, a promoter, a gene (e.g., a reporter and/or therapeutic gene) and a 3' ITR.

[00159] A consideration for AAV transfer plasmid design is that a wildtype AAV genome is ~4.7kb. Thus, included herein are the well-known strategies that provide for packaging nucleotides of interest that exceed the packaging capacity of an individual AAV. Such strategies include, but are not limited to dual-vector strategies that exploit ITR-mediated

recombination to express genes of interest that are larger than a wildtype AAV genome by way of transcript splicing across intermolecularly recombined ITRs from two complementary vector genomes, vector recombination by homology, RNA trans-splicing, and/or protein “trans-splicing” via split intein designs. *See, e.g., Nakai, H. et al. (2000) Nat. Biotechnol. 18:527–532; Sun, L. (2000) Nat. Med. 6: 599–602 (2000); Ghosh, A., et al. (2008) Mol. Ther. 16:124–130 (2008); Lai, Y (2005) Nat. Biotechnol. 23:1435–1439; Chew, W. L. et al. (2016) Nat. Methods 13:868–874; Li, J. (2008) Hum. Gene Ther. 19:958–964, each of which reference is incorporated herein in its entirety by reference.*

[00160] Dual AAV vector strategies to transfer of a large gene into target cells have been described, which rely on different mechanisms including, but not limited to, trans-splicing, including overlapping regions in the dual vectors, and a hybrid of the two. Tomabene and Trapani (2020) *Human Gene Ther.* 31:47-56; *see also* U.S. Patent No. 8,236,557, each of which is incorporated herein by reference in its entirety.

[00161] A trans-splicing approach takes advantage of the ability of AAV ITR sequences to concatemerize to reconstitute full-length genomes, wherein each of two or more viral capsids respectively encapsulate one of two or more transfer plasmids, each of which transfer plasmid comprises a portion of the gene of interest. For example, in a dual vector approach, the two transfer plasmids may be designed as follows: the 5'-transfer plasmid comprises the promoter, the 5' portion of the coding sequence of the gene of interest, and a splicing donor (SD) signal; the 3'-transfer plasmid comprises a splicing acceptor (SA) signal, the 3' portion of the gene of interest, and the polyA signal. Upon tail-to-head ITR-mediated concatemerization of the two AAV genomes, the SD and SA signals will allow splicing of the recombined genome.

[00162] A large gene of interest is also split when taking an overlapping region approach. In the overlapping region approach, the 5' and 3' portions (and thus the 5' transfer plasmid and 3' transfer plasmid) share a recombinogenic sequence, e.g., region of homology, e.g., each portion comprises an overlapping sequence. The gene of interest is made whole in a targeted cell via homologous recombination mediated by the recombinogenic sequence, e.g., homology/overlapping region.

[00163] In a hybrid approach, the 5'-transfer plasmid and 3'-transfer plasmid each comprise a highly recombinogenic sequence, wherein the recombinogenic sequence is placed

downstream of an SD signal of a 5' portion of the coding sequence of the gene of interest and upstream of an SA signal of a 3' portion of the coding sequence of the gene of interest. In this hybrid system, the gene of interest may be made whole either via ITR-mediated concatemerization and splicing and/or by homologous recombination.

[00164] Trans-splicing at the RNA or protein levels may also be utilized. In an RNA trans-splicing approach, two transfer plasmids may respectively encode for 5' and 3' fragments of the pre-mRNA of a large gene and share an intronic hybridization domain that can favor trans-splicing, leading to joining of the two half-transcripts into an intact full-length mRNA.

[00165] Protein trans-splicing occurs post-translationally and is catalyzed by intervening proteins called split-inteins. Split-inteins are expressed as two independent polypeptides (N-intein and C-intein) at the extremities of two host proteins. The N-intein and C-intein polypeptides remain catalytically inactive until they encounter each other. Upon encountering each other, each intein precisely excises itself from the host protein while mediating ligation of the N- and C- host polypeptides via a peptide bond. Split-intein use has been used in AAV-based delivery of therapeutic genes of interest in muscle, liver, and retinal diseases. For example, on co-delivery of two halves of the mini-dystrophin cDNA fused to N- and C-intein coding sequences, efficient production of the two polypeptides was shown. Li et al. (2008) *Hum Gene Ther* 19:958-64. Similarly, AAV-split-inteins have been widely used for the expression and ligation of the clustered regularly interspaced short palindromic repeats (CRISPR)-Cas9 nuclease.

[00166] The above dual vector approaches are well-known in the art. *See, e.g.,* Tomabene and Trapani (2020), *supra*; U.S. Patent No. 8,236,557. Thus, in some embodiments, a modified viral capsid described herein encapsulates a nucleotide of interest, wherein the nucleotide of interest comprises a portion of a gene of interest. In some embodiments, a nucleotide of interest comprising a portion of a gene of interest further comprises a splicing donor signal or a splicing acceptor signal and/or a recombinogenic sequence. In some embodiments, a nucleotide of interest comprising a portion of a gene of interest comprises an intronic hybridization domain encoding sequence. In some embodiments, a nucleotide of interest comprising a portion of a gene of interest comprises a N-intein or C-intein encoding sequence.

[00167] Design of the transfer plasmid/nucleotide of interest includes including one or more regulatory elements, e.g., promoter and/or enhancer elements, that will control expression of the gene of interest. Non-limiting examples of useful promoters include, e.g., cytomegalovirus (CMV)-promoter, the spleen focus forming virus (SFFV)-promoter, the elongation factor 1 alpha (EF1a)-promoter (the 1.2 kb EF1a-promoter or the 0.2 kb EF1a-promoter), the chimeric EF 1 a/IF4-promoter, and the phospho-glycerate kinase (PGK)-promoter. An internal enhancer may also be present in the viral construct to increase expression of the gene of interest. For example, the CMV enhancer (Karasuyama et al. 1989, J. Exp. Med. 169:13, which is incorporated herein by reference in its entirety) may be used. In some embodiments, the CMV enhancer can be used in combination with the chicken β -actin promoter, e.g., CBA. In some embodiments, the regulatory element further comprises a chimeric chicken β -actin promoter/minute virus of mice (MVM) intron and a bovine growth hormone (BGH) polyadenylation sequence. In some embodiments, the regulatory element comprises a CBh regulatory element (See, Gray, et al., Hum Gene Ther. 2011 Sep; 22(9): 1143–1153, incorporated herein by reference in its entirety). In some embodiments, tissue specific regulatory elements, e.g., a nervous system specific promoter and/or regulatory element, may be used to drive the expression of the gene of interest.

[00168] In some embodiments, bidirectional promoter vectors have also been employed for delivery of dual therapeutic gene cassettes. An example of this is the bidirectional chicken β -actin ubiquitous promoter that drives the simultaneous expression of the hexosaminidase α - and β -subunits of the HexA enzyme, the two respective genes involved in Tay-Sachs and Sandhoff diseases. Lahey, et al. (2020) *Mol. Ther.* 28: 2150–2160, incorporated herein in its entirety by reference. In some embodiments, a transfer plasmid and/or nucleotide of interest herein comprises a bidirectional promoter, wherein the bidirectional promoter drives the expression of two different genes of interest.

[00169] A variety of reporter genes (or detectable moieties) can be encapsidated in a multimeric structure comprising the modified viral capsid proteins described herein. Exemplary reporter genes include, for example, β -galactosidase (encoded *lacZ* gene), Green Fluorescent Protein (GFP), enhanced Green Fluorescent Protein (eGFP), MmGFP, blue fluorescent protein (BFP), enhanced blue fluorescent protein (eBFP), mPlum, mCherry, tdTomato, mStrawberry, J-Red, DsRed, mOrange, mKO, mCitrine, Venus, YPet, yellow

fluorescent protein (YFP), enhanced yellow fluorescent protein (eYFP), Emerald, CyPet, cyan fluorescent protein (CFP), Cerulean, T-Sapphire, luciferase, alkaline phosphatase, or a combination thereof. The methods described herein demonstrate the construction of targeting particles that employ the use of a reporter gene that encodes green fluorescent protein, however, persons of skill upon reading this disclosure will understand that the viral capsids described herein can be generated in the absence of a reporter gene or with any reporter gene known in the art.

[00170] A variety of therapeutic genes can also be encapsidated in a multimeric structure comprising the modified viral capsid proteins described herein, e.g., as part of a transfer particle. Non-limiting examples of a therapeutic gene include those that encode a toxin (e.g., a suicide gene), a therapeutic antibody or fragment thereof, a CRISPR/Cas system or portion(s) thereof, antisense RNA, siRNA, shRNA, etc.

[00171] In some embodiments, the nucleotide of interest targets, e.g., reduces or ablates the expression and/or activity of, a gene or gene product associated with pain, itch (also known as pruritis), and/or a neurological disease or disorder. Non-limiting examples of gene or gene products associated with pain, itch, and/or a neurological disease or disorder include voltage-gated sodium channel Nav1.7, voltage-gated sodium channel Nav1.8, voltage-gated sodium channel Nav1.9, voltage-gated sodium channel Nav1.6, tropomyosin receptor kinase A (TrkA), tropomyosin receptor kinase C (TrkC), acid-sensing ion channel subunit 1 (ASIC1), acid-sensing ion channel subunit 3 (ASIC3), transient receptor potential vanilloid 1 (TRPV1), transient receptor potential vanilloid 4 (TRPV4), transient receptor potential cation channel, subfamily A, member 1 (TRPA1), transient receptor potential cation channel subfamily C, member 6 (TRPC6), transient receptor potential cation channel subfamily M, member 8 (TRPM8), *fatty acid amide hydrolase* (FAAH), piezo type mechanosensitive ion channel component 1 (PIEZO1), piezo type mechanosensitive ion channel component 2 (PIEZO2), sodium voltage-gated channel alpha subunit 9 (SCN9A), Enkephalin, RET proto-oncogene (RET), interleukin 4 receptor (IL4R), interleukin 13 receptor (IL13R), interleukin 31 receptor (IL31R), interleukin 6 receptor (e.g., IL6 receptor alpha (IL6Ra) and glycoprotein 130 (gp130)), FXYD domain containing ion transport regulator 2 (FXYD2), calcitonin related polypeptide alpha (CALCA), hyperpolarization-activated, cyclic nucleotide-gated channel (HCN), and P2X purinoceptor 3 (P2X3).

[00172] In some embodiments, the therapeutic gene, i.e., the nucleotide of interest, encodes guide RNAs targeting a gene associated with pain. In some embodiments, the therapeutic gene further encodes a Cas protein, e.g., Cas9. In some embodiments, the gene associated with pain is Nav1.7. Accordingly, in such embodiments, the guide RNAs targeting Nav1.7 and/or Cas protein can be specifically delivered to p75^{NTR}-expressing cells, e.g., nervous system cells, to direct the CRISPR-mediated inhibition of the Nav1.7, thus resulting in a reduction in pain.

[00173] In some embodiments, the gene or gene product associated with a neurological disease or disorder is Sodium Voltage-Gated Channel Alpha Subunit 9 (SCN9A). In some embodiments, the nucleotide of interest targets a gene or gene product associated with pain, e.g., pain targets which may be expressed in DRG and/or TG, such as, but not limited to Nav1.7, Nav1.8, Nav1.9, TRPV1, TRPV4, TRPA1, TRPC6, TRPM8, PIEZO1, PIEZO2, CALCA, HCN, TrkA, TrkC, ASIC1, ASIC3, and P2X3.

[00174] A further embodiment of the present invention is a process for the preparation of a modified capsid protein, the method comprising the steps of:

(a) expressing a nucleic acid encoding the modified capsid protein under suitable conditions, and

(b) isolating the expressed capsid protein of step (a).

[00175] In some embodiments, a viral particle as described herein comprises a mosaic capsid, e.g., a capsid comprising capsid proteins genetically modified as described herein (in the absence or presence of a covalent bond with a targeting ligand) in a certain ratio with reference capsid proteins. A method for making such a mosaic viral particle comprises

(a) expressing a nucleic acid encoding the modified capsid protein and a nucleotide encoding a reference capsid protein at a ratio (wt/wt) of at least about 60:1 to about 1:60, e.g., 2:1, 1:1, 3:5, 1:2, 1:3, etc. under suitable conditions, and

(b) isolating the expressed capsid protein of step (a).

[00176] In some embodiments, a composition described herein comprises, or a method described herein combines, a modified *cap* gene: reference *cap* gene (or combination of reference *cap* genes) at a ratio that ranges from at least about 1:60 to about 60:1, e.g., 2:1, 1:1, 3:5, 1:2, 1:3, etc. In some embodiments, the ratio is at least about 1:2. In some embodiments, the ratio is at least about 1:3. In some embodiments, the ratio is at least about

[illegible]

[00177] In some embodiments, VP protein subunit ratios in the mosaic viral particle may, but do not necessarily, stoichiometrically reflect the ratios of modified *cap* gene:reference *cap* gene. As a non-limiting exemplary embodiment, a mosaic capsid formed according to the method may be considered to, but does not necessarily, have a modified capsid protein:reference capsid protein ratio similar to the ratio (wt:wt) of nucleic acids encoding same used to produce the mosaic capsid. In some embodiments, a mosaic capsid comprises a protein subunit ratio of about 1:59 to about 59:1.

[00178] Further embodiments of the present invention is a method for altering the tropism of a virus, the method comprising the steps of: (a) inserting a nucleic acid encoding an amino acid sequence into a nucleic acid sequence encoding an viral capsid protein to form a nucleotide sequence encoding a genetically modified capsid protein comprising the amino acid sequence and/or (b) culturing a packaging cell in conditions sufficient for the production of viral particles, wherein the packaging cell comprises the nucleic acid. A further embodiment of the present invention is a method for displaying a targeting ligand on the surface of a capsid protein, the method comprising the steps of: (a) expressing a nucleic acid encoding a modified viral capsid protein as described herein (and optionally with a nucleotide encoding a reference capsid protein) under suitable conditions, wherein the nucleic acid encodes a capsid protein comprising a first member of a specific binding pair, (b) isolating the expressed capsid protein comprising a first member of a specific binding pair of step (a) or capsid comprising same, and (c) incubating the capsid protein or capsid with a second cognate member of the specific binding pair under conditions suitable for allowing the formation of an isopeptide bond between the first and second member, wherein the second cognate member of the specific binding pair is fused with a targeting ligand.

[00179] In some embodiments, the packaging cell further comprises a helper plasmid and/or a transfer plasmid comprising a nucleotide of interest. In some embodiments, the methods further comprise isolating self-complementary adeno-associated viral particles from culture supernatant. In some embodiments, the methods further comprise lysing the packaging cell and isolating single-stranded adeno-associated viral particles from the cell lysate. In some embodiments, the methods further comprise (a) clearing cell debris, (b) treating the supernatant containing viral particles with nucleases, e.g., DNase I and MgCl₂,

(c) concentrating viral particles, (d) purifying the viral particles, and (e) any combination of (a)-(d).

[00180] Packaging cells useful for production of the viral particles described herein include, e.g., animal cells permissive for the virus, or cells modified to be permissive for the virus; or the packaging cell construct, for example, with the use of a transformation agent such as calcium phosphate. Non-limiting examples of packaging cell lines useful for producing viral particles described herein include, e.g., human embryonic kidney 293 (HEK-293) cells (e.g., American Type Culture Collection [ATCC] No. CRL-1573), HEK-293 cells that contain the SV40 Large T-antigen (HEK-293T or 293T), HEK293T/17 cells, human sarcoma cell line HT-1080 (CCL-121), lymphoblast-like cell line Raji (CCL-86), glioblastoma-astrocytoma epithelial-like cell line U87-MG (HTB-14), T-lymphoma cell line HuT78 (TIB-161), NIH/3T3 cells, Chinese Hamster Ovary cells (CHO) (e.g., ATCC Nos. CRL9618, CCL61, CRL9096), HeLa cells (e.g., ATCC No. CCL-2), Vero cells, NIH 3T3 cells (e.g., ATCC No. CRL-1658), Huh-7 cells, BHK cells (e.g., ATCC No. CCL10), PC12 cells (ATCC No. CRL1721), COS cells, COS-7 cells (ATCC No. CRL1651), RAT1 cells, mouse L cells (ATCC No. CCL1.3), HLHepG2 cells, CAP cells, CAP-T cells, and the like.

[00181] L929 cells, the FLY viral packaging cell system outlined in Cosset et al (1995) J Virol 69,7430-7436, NS0 (murine myeloma) cells, human amniocytic cells (e.g., CAP, CAP-T), yeast cells (including, but not limited to, *S. cerevisiae*, *Pichia pastoris*), plant cells (including, but not limited to, Tobacco NTL, BY-2), insect cells (including but not limited to SF9, S2, SF21, Tni (e.g. High 5)) or bacterial cells (including, but not limited to, *E. coli*).

[00182] For additional packaging cells and systems, packaging techniques and particles for packaging the nucleic acid genome into the pseudotyped viral particle see, for example, Polo, et al, Proc Natl Acad Sci USA, (1999) 96:4598-4603. Methods of packaging include using packaging cells that permanently express the viral components, or by transiently transfecting cells with plasmids.

[00183] Further embodiments include methods comprising contacting a modified Cap protein as described herein with the targeting vector in conditions sufficient to operably link the modified Cap protein with the targeting vector, e.g., in conditions sufficient to promote association of the targeting vector to the modified Cap protein, e.g., via chemical linkage and/or association of first and second members of a specific binding pair, wherein the first

member is inserted into the modified Cap protein the first member and the targeting vector is fused to the second member of the specific binding pair.

[00184] Further embodiments include methods of redirecting a virus and/or delivering a reporter or therapeutic gene to a target cell, the method comprising a method for transducing cells *in vitro* (e.g., *ex vivo*) or *in vivo*, the method comprising the steps of: contacting the target cell with a viral particle comprising a capsid described herein, wherein the capsid comprises a targeting ligand that specifically binds a receptor expressed by the target cell. In some embodiments, the target cell is *in vitro* (e.g., *ex vivo*). In other embodiments, the target cell is *in vivo* in a subject, e.g., a human.

Target Cells

[00185] Once a particular population of target cells is identified in which expression of a nucleotide of interest is desired, a target cell surface protein, e.g., a receptor, is selected that is specifically expressed on that population of target cells. The target cell surface protein may be expressed exclusively on that population of cells or to a greater extent on that population of cells than on other populations of cells. The more specific the expression, the more specifically delivery can be directed to the target cells. Depending on the context, the desired amount of specificity of the marker (and thus of the gene delivery) may vary. For example, for introduction of a toxic gene, a high specificity is most preferred to avoid killing non-targeted cells. For expression of a protein for harvest, or expression of a secreted product where a global impact is desired, less marker specificity may be needed.

[00186] As discussed above, the target cell surface protein may be any receptor for which a targeting ligand can be identified or created. Preferably the target receptor is a peptide or polypeptide, such as a receptor. However, in other embodiments the target receptor may be a carbohydrate or other molecule that can be recognized by a binding partner. If a binding partner, e.g., ligand, for the target receptor is already known, it may be used as the affinity molecule. However, if a binding molecule is not known, antibodies to the target receptor may be generated using standard procedures. The antibodies can then be used as a targeting ligand.

[00187] Thus, target cells may be chosen based on a variety of factors, including, for example, (1) the application (e.g., therapy, expression of a protein to be collected, and

conferring disease resistance) and (2) expression of a marker with the desired amount of specificity.

[00188] Target cells are not limited in any way and include both germline cells and cell lines and somatic cells and cell lines. When the target cells are germline cells, the target cells are preferably selected from the group consisting of single-cell embryos and embryonic stem cells (ES).

[00189] In some embodiments, the target cell surface protein is p75^{NTR}. In some embodiments, the target cell is a cell expressing p75^{NTR}. Non-limiting examples of tissues comprising cells that express p75^{NTR} include dorsal root ganglia (DRG), trigeminal ganglia, sympathetic ganglia, dermal fibers, retina, myenteric plexus, celiac ganglion, and the like. Non-limiting examples of cell types that express p75^{NTR} include neurons, Mueller glia, Leydig cells, ionocytes, dendritic cells, Schwann cells, salivary gland cells, retinal bipolar neurons, basal respiratory cells, basal squamous epithelial cells, oligodendrocytes and the like. In some embodiments, the target cell is a dorsal root ganglion (DRG) neuron. In some embodiments, the target cell is a trigeminal ganglion (TG) neuron.

Pharmaceutical compositions, dosage forms and administration

[00190] A further embodiment provides a medicament comprising at least one modified viral capsid protein and appropriate targeting ligand, e.g., that binds p75^{NTR}, according to this invention and/or a nucleic acid according to this invention. Preferably such medicament is useful as a gene transfer particle.

[00191] Also disclosed herein are pharmaceutical compositions comprising the viral particles described herein and a pharmaceutically acceptable carrier and/or excipient. In addition, disclosed herein are pharmaceutical dosage forms comprising the viral particle described herein.

[00192] As discussed herein, the viral particles described herein can be used for various therapeutic applications (*in vivo* and *ex vivo*) and as research tools.

[00193] Pharmaceutical compositions based on the viral particles disclosed herein can be formulated in any conventional manner using one or more physiologically acceptable carriers and/or excipients. The viral particles may be formulated for administration by, for

example, injection, inhalation or insulation (either through the mouth or the nose) or by oral, buccal, parenteral or rectal administration, or by administration directly to a tumor.

[00194] The pharmaceutical compositions can be formulated for a variety of modes of administration, including systemic, topical or localized administration. Techniques and formulations can be found in, for example, Remington's Pharmaceutical Sciences, Meade Publishing Co., Easton, Pa. For systemic administration, injection is preferred, including intramuscular, intravenous, intraperitoneal, and subcutaneous. For the purposes of injection, the pharmaceutical compositions can be formulated in liquid solutions, preferably in physiologically compatible buffers, such as Hank's solution or Ringer's solution. In addition, the pharmaceutical compositions may be formulated in solid form and redissolved or suspended immediately prior to use. Lyophilized forms of the pharmaceutical composition are also suitable.

[00195] For oral administration, the pharmaceutical compositions may take the form of, for example, tablets or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g. pregelatinized maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g. lactose, microcrystalline cellulose or calcium hydrogen phosphate); lubricants (e.g. magnesium stearate, talc or silica); disintegrants (e.g. potato starch or sodium starch glycolate); or wetting agents (e.g. sodium lauryl sulfate). The tablets can also be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (e.g. sorbitol syrup, cellulose derivatives or hydrogenated edible fats); emulsifying agents (e.g. lecithin or acacia); non-aqueous vehicles (e.g. oil, oily esters, ethyl alcohol or fractionated vegetable oils); and preservatives (e.g. methyl or propyl-p-hydroxybenzoates or sorbic acid). The preparations can also contain buffer salts, flavoring, coloring and sweetening agents as appropriate.

[00196] The pharmaceutical compositions can be formulated for parenteral administration by injection, e.g. by bolus injection or continuous infusion. Formulations for injection can be presented in a unit dosage form, e.g. in ampoules or in multi-dose containers, with an optionally added preservative. The pharmaceutical compositions can further be

formulated as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain other agents including suspending, stabilizing and/or dispersing agents.

[00197] Additionally, the pharmaceutical compositions can also be formulated as a depot preparation. These long-acting formulations can be administered by implantation (e.g., subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds may be formulated with suitable polymeric or hydrophobic materials (e.g., as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt. Other suitable delivery systems include microspheres, which offer the possibility of local noninvasive delivery of drugs over an extended period of time. This technology can include microspheres having a precapillary size, which can be injected via a coronary catheter into any selected part of an organ without causing inflammation or ischemia. The administered therapeutic is then slowly released from the microspheres and absorbed by the surrounding cells present in the selected tissue.

[00198] Systemic administration can also be by transmucosal or transdermal means. For transmucosal or transdermal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art, and include, for example, for transmucosal administration, bile salts, and fusidic acid derivatives. In addition, detergents may be used to facilitate permeation. Transmucosal administration can occur using nasal sprays or suppositories. For topical administration, the viral particles described herein can be formulated into ointments, salves, gels, or creams as generally known in the art. A wash solution can also be used locally to treat an injury or inflammation in order to accelerate healing.

[00199] Pharmaceutical forms suitable for injectable use can include sterile aqueous solutions or dispersions; formulations including sesame oil, peanut oil or aqueous propylene glycol; and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases, the form must be sterile and must be fluid. It must be stable under the conditions of manufacture and certain storage parameters (e.g., refrigeration and freezing) and must be preserved against the contaminating action of microorganisms, such as bacteria and fungi.

[00200] If formulations disclosed herein are used as a therapeutic to boost an immune response in a subject, a therapeutic agent can be formulated into a composition in a neutral or

salt form. Pharmaceutically acceptable salts include the acid addition salts (formed with the free amino groups of the protein) and which are formed with inorganic acids such as, for example, hydrochloric or phosphoric acids, or such organic acids as acetic, oxalic, tartaric, mandelic, and the like. Salts formed with the free carboxyl groups can also be derived from inorganic bases such as, for example, sodium, potassium, ammonium, calcium, or ferric hydroxides, and such organic bases as isopropylamine, trimethylamine, histidine, procaine and the like.

[00201] A carrier can also be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), suitable mixtures thereof, and vegetable oils. The proper fluidity can be maintained, for example, by the use of a coating, such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. The prevention of the action of microorganisms can be brought about by various antibacterial and antifungal agents known in the art. In many cases, it will be preferable to include isotonic agents, for example, sugars or sodium chloride. Prolonged absorption of the injectable compositions can be brought about by the use in the compositions of agents delaying absorption, for example, aluminum monostearate and gelatin.

[00202] Sterile injectable solutions can be prepared by incorporating the active compounds or constructs in the required amount in the appropriate solvent with various of the other ingredients enumerated above, as required, followed by filtered sterilization.

[00203] Upon formulation, solutions can be administered in a manner compatible with the dosage formulation and in such amount as is therapeutically effective. The formulations are easily administered in a variety of dosage forms, such as the type of injectable solutions described above, but slow release capsules or microparticles and microspheres and the like can also be employed.

[00204] For parenteral administration in an aqueous solution, for example, the solution should be suitably buffered if necessary and the liquid diluent first rendered isotonic with sufficient saline or glucose. These particular aqueous solutions are especially suitable for intravenous, intratumorally, intramuscular, subcutaneous and intraperitoneal administration. In this context, sterile aqueous media that can be employed will be known to those of skill in the art in light of the present disclosure. For example, one dosage could be dissolved in 1 ml

of isotonic NaCl solution and either added to 1000 ml of hypodermoclysis fluid or injected at the proposed site of infusion.

[00205] The person responsible for administration will, in any event, determine the appropriate dose for the individual subject. For example, a subject may be administered viral particles described herein on a daily or weekly basis for a time period or on a monthly, bi-yearly or yearly basis depending on need or exposure to a pathogenic organism or to a condition in the subject (e.g., cancer).

[00206] In addition to the compounds formulated for parenteral administration, such as intravenous, intratumorally, intradermal or intramuscular injection, other pharmaceutically acceptable forms include, e.g., tablets or other solids for oral administration; liposomal formulations; time release capsules; biodegradable and any other form currently used.

[00207] One may also use intranasal or inhalable solutions or sprays, aerosols or inhalants. Nasal solutions can be aqueous solutions designed to be administered to the nasal passages in drops or sprays. Nasal solutions can be prepared so that they are similar in many respects to nasal secretions. Thus, the aqueous nasal solutions usually are isotonic and slightly buffered to maintain a pH of 5.5 to 7.5. In addition, antimicrobial preservatives, similar to those used in ophthalmic preparations, and appropriate drug stabilizers, if required, may be included in the formulation. Various commercial nasal preparations are known and can include, for example, antibiotics and antihistamines and are used for asthma prophylaxis.

[00208] Oral formulations can include excipients as, for example, pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, magnesium carbonate and the like. These compositions take the form of solutions, suspensions, tablets, pills, capsules, sustained release formulations or powders. In certain defined embodiments, oral pharmaceutical compositions will include an inert diluent or assimilable edible carrier, or they may be enclosed in hard or soft shell gelatin capsule, or they may be compressed into tablets, or they may be incorporated directly with the food of the diet. For oral therapeutic administration, the active compounds may be incorporated with excipients and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, and the like.

[00209] The tablets, troches, pills, capsules and the like may also contain the following: a binder, as gum tragacanth, acacia, cornstarch, or gelatin; excipients, such as

dicalcium phosphate; a disintegrating agent, such as corn starch, potato starch, alginic acid and the like; a lubricant, such as magnesium stearate; and a sweetening agent, such as sucrose, lactose or saccharin may be added or a flavoring agent, such as peppermint, oil of wintergreen, or cherry flavoring. When the dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier. Various other materials may be present as coatings or to otherwise modify the physical form of the dosage unit. For instance, tablets, pills, or capsules may be coated with shellac, sugar or both. A syrup or elixir may contain the active compounds sucrose as a sweetening agent methyl and propylparabens as preservatives, a dye and flavoring, such as cherry or orange flavor.

[00210] Further embodiments disclosed herein can concern kits for use with methods and compositions. Kits can also include a suitable container, for example, vials, tubes, mini- or microfuge tubes, test tube, flask, bottle, syringe or other container. Where an additional component or agent is provided, the kit can contain one or more additional containers into which this agent or component may be placed. Kits herein will also typically include a means for containing the viral particles and any other reagent containers in close confinement for commercial sale. Such containers may include injection or blow-molded plastic containers into which the desired vials are retained. Optionally, one or more additional active agents such as, e.g., anti-inflammatory agents, anti-viral agents, anti-fungal or anti-bacterial agents or anti-tumor agents may be needed for compositions described.

[00211] Compositions disclosed herein may be administered by any means known in the art. For example, compositions may include administration to a subject intravenously, intrasynovially, intratumorally, intradermally, intraarterially, intraperitoneally, intralesionally, intracranially, intraarticularly, intraprostatically, intrapleurally, intratracheally, intranasally, intravitreally, intravaginally, intrarectally, topically, intratumorally, intramuscularly, intrathecally, subcutaneously, subconjunctival, intravesicularly, mucosally, intrapericardially, intraumbilically, intraocularly, orally, locally, by inhalation, by injection, by infusion, by continuous infusion, by localized perfusion, via a catheter, via a lavage, in a cream, or in a lipid composition.

[00212] Compositions may be administered to a subject intravenously, intratumorally, intradermally, intraarterially, intraperitoneally, intralesionally, intracranially, intraarticularly, intraprostatically, intrapleurally, intratracheally, intranasally, intravitreally, intravaginally,

intrarectally, topically, intratumorally, intramuscularly, intrathecally, intracisternally, intracerebroventricularly, intraparenchymal, subcutaneously, subconjunctival, intravesicularly, mucosally, intrapericardially, intraumbilically, intraocularly, orally, locally, by inhalation, by injection, by infusion, by continuous infusion, by localized perfusion, via a catheter, via a lavage, in a cream, or in a lipid composition.

[00213] Any method known to one skilled in the art may be used for large scale production of viral particles, packaging cells and particle constructs described herein. For example, master and working seed stocks may be prepared under GMP conditions in qualified primary CEFs or by other methods. Packaging cells may be plated on large surface area flasks, grown to near confluence and viral particles purified. Cells may be harvested and viral particles released into the culture media isolated and purified, or intracellular viral particles released by mechanical disruption (cell debris can be removed by large-pore depth filtration and host cell DNA digested with endonuclease). Virus particles may be subsequently purified and concentrated by tangential-flow filtration, followed by diafiltration. The resulting concentrated bulk may be formulated by dilution with a buffer containing stabilizers, filled into vials, and lyophilized. Compositions and formulations may be stored for later use. For use, lyophilized viral particles may be reconstituted by addition of diluent.

[00214] Certain additional agents used in the combination therapies can be formulated and administered by any means known in the art.

[00215] Compositions as disclosed herein can also include adjuvants such as aluminum salts and other mineral adjuvants, tensioactive agents, bacterial derivatives, vehicles and cytokines. Adjuvants can also have antagonizing immunomodulating properties. For example, adjuvants can stimulate Th1 or Th2 immunity. Compositions and methods as disclosed herein can also include adjuvant therapy.

Methods of and Compositions for use in Treatment/Prevention

[00216] Further provided herein are methods of treatment and/or prevention of a disease or disorder associated with a cell expressing p75^{NTR}, the method comprising administering a composition as described herein, e.g., an AAV particle comprising a p75^{NTR}-targeting ligand, to a subject in need thereof. Also provided are compositions, e.g., AAV particles comprising a p75^{NTR}-targeting ligand and pharmaceutical compositions thereof, for

use in, e.g., the manufacture of a medicament for, treating and/or preventing a disease or disorder associated with a cell expressing p75^{NTR}.

[00217] As used herein “a disease or disorder associated with a cell expressing p75^{NTR}” refers to a disease or disorder resulting from abnormal, e.g., increased or decreased, expression and/or activity of a gene or gene product in a cell that also expresses p75^{NTR}.

[00218] In some embodiments, the disease or disorder is associated with dysregulated expression of a gene or gene product, e.g., protein, in a cell/tissue, e.g., a nervous system cell/tissue, as compared to a control cell/tissue. In some embodiments, the cell/tissue (a) is derived from an animal having the disease or disorder, or (b) expresses the gene or gene product, e.g., protein, at levels that are comparable to levels that are associated with the disease or disorder in the animal. In some embodiments, the control cell/tissue (a) is derived from a control animal that does not have a disease or disorder, or (b) expresses the dysregulated gene or gene product, e.g., protein, at normal level, *i.e.*, levels that are not associated with the disease or disorder in the animal. In some embodiments, the gene or gene product, e.g., protein, is expressed at higher levels in the cell/tissue than a control cell/tissue. In some embodiments, the gene or gene product, e.g., protein, is Nav1.7.

[00219] Generally, methods of treating a disease or disorder comprise administering to a subject having or at risk of developing such disease or disorder a viral particle, e.g., AAV particle, or pharmaceutical composition as described herein, wherein the viral particle comprises:

- (i) a viral capsid, e.g., AAV capsid, modified to comprise a first member of a protein:protein binding pair,

- (ii) a second member of the protein:protein binding pair, wherein the second member of the protein:protein binding pair comprises a targeting ligand that binds p75^{NTR},

wherein the first member of the protein:protein binding pair and the second member of the protein:protein binding pair are associated to direct the tropism of the viral capsid to a p75^{NTR}-expressing cell in the subject in need thereof, and

- (iii) a nucleotide of interest encapsidated within the viral capsid.

[00220] In some embodiments, the nucleotide of interest encodes a therapeutic protein, a suicide gene, an antibody or a fragment thereof, a CRISPR/Cas system or a portion(s) thereof, an antisense oligonucleotide, a ribozyme, an RNAi molecule, or a shRNA molecule.

For example, in some embodiments, the nucleotide of interest may encode gRNA targeting a gene expressing a pain-related protein, e.g., Nav1.7, for CRISPR/Cas9-mediated silencing, e.g., via genome editing with nuclease-active Cas9, via genome interference with nuclease-dead Cas9, etc. In some embodiments, the nucleotide of interest may encode an RNAi molecule, e.g., shRNA, targeting mRNA that translates a pain-related protein, e.g., Nav1.7.

[00221] In some embodiments, AAV particles comprising a p75NTR-targeting ligand as described herein are used for treating or preventing a disease or disorder, such as but not limited to, a central nervous system (CNS) disease or disorder (e.g., a brain disease or disorder or a spinal cord disease or disorder), a peripheral nervous system disease or disorder, an autonomic nervous system disease or disorder, an enteric nervous system disease or disorder or an eye disease or disorder.

[00222] Also provided herein are methods of treating a pain-related disease or disorder, i.e., a disease or disorder associated with one or more cell or tissue of the nervous system that regulates pain. Non-limiting examples of pain-related disorders include peripheral chronic pain, small fiber peripheral neuropathies, chemotherapy-induced neuropathies, painful diabetic-induced neuropathies, trigeminal neuralgia, trigeminal chronic pain, migraine, post-herpetic neuralgia, temporomandibular joint pain, osteoarthritis, myofascial pain syndrome, herpes zoster, pelvic and back pain.

[00223] In some embodiments, AAV particles comprising a p75NTR-targeting ligand as described herein are used for treating or preventing pain. Non-limiting examples of pain include, but are not limited to, peripheral chronic pain (e.g., by delivering Nav1.7 siRNA or another siRNA targeting any other various gene or gene products associated with pain, e.g., chronic pain such as peripheral chronic pain, contemplated herein), somatic pain, small fiber peripheral neuropathy, chemotherapy-induced neuropathy, painful diabetic-induced neuropathy, chronic itch, trigeminal neuralgia, post-herpetic neuralgia, temporo-mandibular pain, migraine, dysautonomia, Sickle cell disease, joint pain, back pain, or myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS).

[00224] In some embodiments, methods of treating or preventing pain as described herein comprise the targeted delivery of guide RNAs (gRNAs) targeting a gene associated with pain and/or Cas, e.g., Cas9, to tissues expressing p75NTR, resulting in the CRISPR-mediated inhibition of the gene associated with pain and thus a reduction in pain.

Accordingly, in such embodiments, the method comprises administering to a subject in need thereof an AAV particle conjugated to an anti-p75NTR targeting ligand, e.g., an antibody, and encapsulating a nucleic acid molecule encoding gRNAs targeting a gene associated with pain. In some embodiments, the targeted gene associated with pain is Nav1.7. In some embodiments, the nucleic acid molecule further encodes a Cas protein, e.g., Cas9. In some embodiments, a Cas protein, e.g., Cas9, is delivered separately from the gRNAs. In some embodiments, the treatment or prevention of pain is indicated by a significant increase in mechanical pain thresholds, i.e., a significant decrease in mechanical pain sensitivity (see, e.g., Example 7 below). In some embodiments, the mechanical pain threshold of the treated subject is increased relative to a control subject that has not been treated by the methods described herein. In some embodiments, the mechanical pain threshold of the treated subject is increased relative to the same subject prior to treatment by the methods described herein.

[00225] In some embodiments, AAV particles comprising a p75NTR-targeting ligand as described herein are used for treating or preventing itch (e.g., chronic itch).

[00226] In some embodiments, AAV particles comprising a p75NTR-targeting ligand as described herein are used for treating or preventing a neurological disease or disorder. Non-limiting examples of neurological diseases or disorders include, but are not limited to, lysosomal storage diseases, amyloidosis, neuropathy, neurodegenerative diseases, leukodystrophy, neuropsychiatric diseases, traumatic brain injury, neurodevelopmental diseases, and neuromuscular diseases, seizure, behavioral disorders, ocular diseases or disorders, viral or microbial infections, inflammation, ischemia, and cancer. Specific examples of neurological disorders include, but are not limited to, neurodegenerative diseases (e.g., Parkinson's disease, striatonigral degeneration, Shy-Draeger syndrome, tauopathies (e.g., Alzheimer disease), motor neuron disease, and nervous system heterodegenerative disorders (e.g., Alexander's disease, Cockayne syndrome, Canavan disease, hepatolenticular degeneration, hereditary sensory ataxia, dementia (e.g., spinocerebellar ataxia), cancer (e.g., central nervous system (CNS) cancers, including brain metastases resulting from cancer elsewhere in the body).

[00227] In some embodiments, AAV particles comprising a p75NTR-targeting ligand as described herein are used for treating or preventing, for example, without limitation, chronic pain (e.g., peripheral chronic pain), somatic pain, chronic itch, migraine, trigeminal

neuralgia, post-herpetic neuralgia, joint pain, back pain, Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis.

[00228] In some embodiments, AAV particles comprising a p75NTR-targeting ligand as described herein are used for treating or preventing glioblastoma multiforme (GBM). Glioblastoma multiforme (GBM) is a rapidly-growing type of tumor typically of the brain or spinal cord. It is the most common type of primary malignant brain tumor in adults. Only 25% of glioblastoma patients survive more than one year and 5% of patients survive more than five years. Symptoms of can depend on the brain region where the glioblastoma is located. For instance, the tumor can grow in areas of the brain that lead to difficulties in forming words or in moving limbs. Expanding tumors can increase pressure within the skull, leading to headaches. Other symptoms include impaired vision, nausea and vomiting, loss of appetite, mood swings, loss of balance, problems with memory or concentration, problems speaking and/or seizures.

Table 2. Non-primate adeno-associated viruses (AAV).

Description	Accession Number/ GI Number	IFR	Region encoding the non-structural/rep protein (Accession Number/ GI Number of protein)	Region encoding the capsid protein (Accession Number/ GI Number of protein)
<i>Avian adeno-associated virus</i>				
Avian adeno-associated virus isolate YZ-1, complete genome	GQ368252.1/ GI: 255710032		243-2237 (ACU30841.1/ GI:255710033)	2255-4471 (ACU30842.1/ GI:255710034)
Avian adeno-associated virus isolate ZN1, complete genome	KF937794.1/ GI: 588284633	1-142 4540-4682	244-2235 (AHK22792.1/ GI: 588284634)	2253-4469 (AHK22793.1/ GI: 588284635)
<i>Avian adeno-associated virus ATCC VR-865</i>				
Avian adeno-associated virus ATCC VR-865, complete genome	AY186198.1/ GI:31414777	1-142 4552-4694	244-2232 (AAO32086.1/ GI:31414778)	2250-4481 (AAO32087.1/ GI:31414779)
Avian adeno-associated virus ATCC VR-865, complete genome	NC_004828.1 /GI:31543992	1-142 4552-4694	244-2232 (NP_852780.1/ GI:31543993)	2250-4481 (NP_852781.1/ GI:31543994)
Avian adeno-associated virus ATCC VR-865, complete genome	AY629582.1/ GI:48996102	1-142 4552-4694	244-2232 (AAT48612.1/ GI:48996103)	2250-4481 (AAT48613.1/ GI:48996104)
<i>Avian adeno-associated virus strain DA-1</i>				
Avian adeno-associated virus strain DA-1, complete genome	AY629583.1/ GI: 48996105	1-142 4540-4682	244-2235 (AAT48614.1/ GI:48996106)	2253-4469 (AAT48615.1/ GI:48996107)
Avian adeno-associated virus strain DA-1, complete genome	NC_006263.1 /GI: 51949968	1-142 4540-4682	244-2235 (YP_077182.1/ GI:51949969)	2253-4469 (YP_077183.1/ GI:51949970)
<i>Bat adeno-associated virus YNM</i>				
Bat adeno-associated virus YNM, complete sequence	GU226971.1/ GI:289719008		200-2041 (ADD17085.1/ GI:289719009)	2059-4233 (ADD17086.1/ GI:289719010)
Bat adeno-associated virus YNM, complete genome	NC_014468.1 /GI:304422916		200-2041 (YP_00385857.1/ GI:304422917)	2059-4233 (YP_00385857.2/ GI:304422918)
<i>Bovine adeno-associated virus</i>				
Bovine adeno-associated virus, complete genome	AY388617.1/ GI:38679253		368-2200 (AAR26464.1/ GI:38679254)	2216-4426 (AAR26465.1/ GI:38679255)
Bovine adeno-associated virus, complete genome	NC_005889.1 /GI:48696557		368-2200 (YP_024970.1/ GI:48696558)	2216-4426 (YP_024971.1/ GI:48696559)
<i>Bovine parvovirus – 2</i>				
Bovine parvovirus 2 putative non-structural protein and putative capsid protein genes, complete cds.	AF406966.1/ GI: 15825370		306-1919 (AAL09671.1/ GI:15825371)	2268-5384 (AAL09672.1/ GI:15825372)

Table 2 - continued

Bovine parvovirus 2, complete genome	NC_006259.1 /GI:51949957		306-1919 (YP_077175.1/ GI:51949958)	2268-5384 (YP_077176.1/ GI:51949959)
<i>California sea lion adeno-associated virus 1</i>				
California sea lion adeno-associated virus 1 isolate 1136 Rep78 and VP1 genes, complete cds.	JN420371.1/ GI:343458966		284-2086 (AEM37641.1/ GI:343458967)	2117-4273 (AEM37642.1/ GI:343458968)
California sea lion adeno-associated virus 1 isolate 1187 Rep78 and VP1 genes, complete cds.	JN420372.1/ GI:343458969		291-2093 (AEM37643.1/ GI:343458970)	2124-4280 (AEM37644.1/ GI:343458971)
<i>Goose parvovirus</i>				
Goose parvovirus virulent B strain, complete genome	(U25749.1/GI:1113795)	1-444 4663-5106	537-2420 (AAA83229.1/ GI:1113796)	2439-4637 (AAA83230.1/ GI:1113797)
				2874-4637 (AAA83231.1/ GI:1113798) 3033-4637 (AAA83232.1/ GI:1113799)
Goose parvovirus, complete genome	(NC_001701.1/GI:9628649)	1-444 4663-5106	537-2420 (NP_043514.1/ GI:9628650)	2439-4637 (NP_043515.1/ GI:9628651) 2874-4637 (NP_043516.1/ GI:9628652) 3033-4637 (NP_043517.1/ GI:9628653)
Goose parvovirus strain 82-0321V, complete genome	(EU583389.1 /GI:190888188)	1-381 4600-4980	474-2357 (ACE95848.1/ GI:190888189)	2376-4574 (ACE95849.1/ GI:190888190)
Goose parvovirus strain 82-0321, complete genome	(EU583390.1 /GI:190888191)	1-416 4635-5050	509-2392 (ACE95850.1/ GI:190888192)	2411-4609 (ACE95851.1/ GI:190888193)
Goose parvovirus strain 06-0329, complete genome	(EU583391.1 /GI:190888194)	1-418 4637-5054	511-2394 (ACE95852.1/ GI:190888195)	2413-4611 (ACE95853.1/ GI:190888196)
Goose parvovirus strain VG32/1, complete genome	(EU583392.1 /GI:190888197)	1-443 4662-5104	536-2419 (ACE95854.1/ GI:190888198)	2438-4636 (ACE95855.1/ GI:190888199)

Table 2 - continued

Goose parvovirus strain SH, complete genome	(JF333590.1/ GI:343113618)	1-444 4663-5106	537-2420 (AEL87777.1/ GI:343113619)	2439-4637 (AEL87778.1/ GI:343113620) 2874-4637 (AEL87779.1/ GI:343113621) 3033-4637 (AEL87780.1/ GI:343113622)
Goose parvovirus strain GDaGPV, complete genome	(HQ891825.1/ GI:359843307)	1-444 4663-5106	537-2420 (AEV89789.1/ GI:359843308)	2439-4637 (AEV89790.1/ GI:359843309) 2874-4637 (AEV89791.1/ GI:359843310) 3033-4637 (AEV89792.1/ GI:359843311)
Goose parvovirus strain SHFX1201, complete genome	(KC478066.1/ GI:459360514)	1-416	509-2392 (AGG56527.1/ GI:459360515)	2411-4609 (AGG56528.1/ GI:459360516)
Goose parvovirus strain Y, complete genome	(KC178571.1/ GI:513129761)	1-444	537-2420 (AGO17637.1/ GI:513129762)	2439-4637 (AGO17638.1/ GI:513129763)
Goose parvovirus strain E, complete genome	(KC184133.1/ GI:513129764)	1-443	536-2419 (AGO17639.1/ GI:513129765)	2438-4636 (AGO17640.1/ GI:513129766)
Goose parvovirus strain SYG61v, complete genome	(KC996729.1/ GI:531997217)	1-442	535-2418 (AGT62580.1/ GI:531997218)	2437-4635 (AGT62581.1/ GI:531997219)
Goose parvovirus strain YZ99-6, complete genome	(KC996730.1/ GI:531997220)	1-414	507-2390 (AGT62582.1/ GI:531997221)	2409-4607 (AGT62583.1/ GI:531997222)
Goose parvovirus nonstructural protein NS (ns) and capsid protein VP (vp) genes, complete cds.	(AF416726.1/ GI:17226299)		1-1884 (AAL37721.1/ GI:17226300) 529-1884 (ABP93843.1/ GI:145694447)	1903-4101 (AAL37722.1/ GI:17226301)
Goose parvovirus strain DY NS1 (NS1), NS2 (NS2), VP1 (VP1), VP2 (VP2), and VP3 (VP3) genes, complete cds.	(EF515837.1/ GI:145694445)		1-1884 (ABP93842.1/ GI:145694446)	1903-4101 (ABP82770.1/ GI:145573169) 2338-4101 (ABP93844.1/ GI:145694448) 2497-4101 (ABP93845.1/ GI:145694449)

Table 2 - continued

Goose parvovirus strain PT NS1 protein and VP1 protein genes, complete cds.	(JF926695.1/ GI:354463162)		9-1892 (AER25356.1/ GI:354463163)	1911-4109 (AER25357.1/ GI:354463164)
Goose parvovirus strain D NS1 protein and VP1 protein genes, complete cds.	(JF926696.1/ GI:354463165)		6-1889 (AER25358.1/ GI:354463166)	1908-4106 (AER25359.1/ GI:354463167)
<i>Mouse adeno-associated virus 1</i>				
Mouse adeno-associated virus 1 rep gene, partial cds; and VP1 capsid, VP2 capsid, and VP3 capsid genes, complete cds.	DQ100362.1/ GI:73665994		1-327 (AAZ79671.1/ GI:73665995)	344-2485 (AAZ79672.1/ GI:73665996) 731-2485 (AAZ79673.1/ GI:73665997) 911-2485 (AAZ79674.1/ GI:73665998)
<i>Muscovy duck parvovirus</i>				
Barbaric duck parvovirus REP protein (rep) and three capsid protein VP (vp) genes, complete cds	U22967.1/GI:1113784	1-457 4678-5132	548-2431 (AAA83224.1/ GI:1113785)	2450-4648 (AAA83225.1/ GI:1113786) 2885-4648 (AAA83226.1/ GI:1113787) 3044-4648 (AAA83227.1/ GI:1113788)
Muscovy duck parvovirus, complete genome	NC_006147.2 /GI:51593841	1-457 4678-5132	548-2431 (YP_068410.1/ GI:51593842)	2450-4648 (YP_068411.1/ GI:51593843) 2885-4648 (YP_068412.1/ GI:51593844) 3044-4648 (YP_068413.1/ GI:51593845)
Muscovy duck parvovirus strain P REP protein and VP1 protein genes, complete cds.	JF926697.1/ GI:354463168		61-1944 (AER25360.1/ GI:354463169)	1963-4161 (AER25361.1/ GI:354463170)
Muscovy duck parvovirus strain P1 REP protein and VP1 protein genes, complete cds.	JF926698.1/ GI:354463171		61-1944 (AER25362.1/ GI:354463172)	1963-4161 (AER25363.1/ GI:354463173)

Table 2 - continued

Muscovy duck parvovirus isolate SAAS-SHNH, complete genome	KC171936.1/ GI:459256867	1-381 4681-5061	512-2395 (AGG53766.1/ GI:459256868)	2414-4612 (AGG53768.1/ GI:459256870) 2849-4612 (AGG53769.1/ GI:459256871) 3008-4612 (AGG53767.1/ GI:459256869)
<i>Serpentine adeno-associated virus 2</i>				
Serpentine adeno-associated virus 2 non-structural protein 1 and capsid protein genes, partial cds	EU872429.1/ GI:215401981		1-642 (ACJ66590.1/ GI:215401982)	661-1297 (ACJ66591.1/ GI:215401983)
<i>Snake parvovirus 1</i>				
Snake parvovirus 1 non-structural protein 1 (NS1) and capsid protein (VP1) genes, complete cds	AY349010.1/ GI:38017148		324-2012 (AAR07954.1/ GI:38017149)	2030-4210 (AAR07955.1/ GI:38017150)
Snake parvovirus 1, complete genome	NC_006148.1 /GI:51555744		324-2012 (YP_068093.1/ GI:51555745)	2030-4210 (YP_068094.1/ GI:51555746)

Table 3. Brief Description of the Sequences in the Sequence Listing

SEQ ID NO	BRIEF DESCRIPTION
1-617	Anti-p75 ^{NTR} antibody amino acid and DNA sequences
618	Human <i>NGFR</i> CDS
619	Human NGFR (p75 ^{NTR}) Protein
620	Mouse <i>Ngfr</i> CDS
621	Mouse Ngfr (p75 ^{NTR}) Protein
622	SpyTag Protein
623	SpyCatcher Protein
624	KTag Protein
625	Isopeptag protein
626	SpyTag002 protein
627	SpyCatcher002 protein
628	SpyTag003 protein
629	SpyCatcher003 protein
630	SnoopTag
631	SnoopCatcher
632	SpyLigase
633	GLSG protein linker
634	GLSGSG protein linker
635	GLSGLSGS protein linker
636	GLSGLSGLSG protein linker
637	GLSGGSLSG protein linker
638	GSGESG protein linker
639	c-myc protein
640	B1 epitope protein
641	hp75-mFc protein (REGN6869)
642	hp75 ^{NTR} EC domain (AAs K29-N250 of REGN6869)
643	Fc portion of mIgG2a at C-term of hp75 (REGN6869)
644	hNTF-3 (UniProt: P20783-1)
645	Macaque <i>Ngfr</i> CDS (encodes NCBI: XP_005583674.1)
646	Macaque Ngfr (p75 ^{NTR}) Protein (NCBI: XP_005583674.1)

EXAMPLES

[00229] The following examples are provided for illustrative purposes only and are not intended to limit the scope of the invention.

Example 1. Determination of the ability of anti-p75^{NTR} (p75) monoclonal antibody supernatants to block binding of human p75 dimer to plate-coated human NT-3.

Table 4-1. mAb clone IDs

Corresponding REGN#	Lot #s	Clone Name
REGN14148	REGN14148-L1	927-61-H10
REGN14149	REGN14149-L1	927-62-F02
REGN14150	REGN14150-L1	927-62-E06
REGN14151	REGN14151-L1	927-62-E08
REGN14152	REGN14152-L1	927-62-B09
REGN14153	REGN14153-L1	927-62-H09
REGN14154	REGN14154-L1	927-62-B10
REGN14155	REGN14155-L1	927-62-E11
REGN14156	REGN14156-L1	927-63-B06
REGN14157	REGN14157-L1	927-61-D03
REGN14158	REGN14158-L1	927-61-F03
REGN14159	REGN14159-L1	927-61-B04
REGN14160	REGN14160-L1	927-61-C04
REGN14161	REGN14161-L1	927-61-F04
REGN14162	REGN14162-L1	927-61-D07
REGN14163	REGN14163-L1	927-61-D08
REGN14164	REGN14164-L1	927-61-F08
REGN14165	REGN14165-L1	927-61-H09
REGN14175	REGN14175-L1	927-64-D04
REGN14176	REGN14176-L1	927-64-G11
REGN14177	REGN14177-L1	927-65-H06
REGN14178	REGN14178-L1	927-65-F08
REGN14179	REGN14179-L1	927-68-D02
REGN14180	REGN14180-L1	927-68-A05
REGN14181	REGN14181-L1	927-68-C06
REGN14182	REGN14182-L1	927-68-C11
REGN14183	REGN14183-L1	927-69-A02
REGN14184	REGN14184-L1	927-69-H02
REGN14185	REGN14185-L1	927-69-H03

REGN14186	REGN14186-L1	927-69-G06
REGN14187	REGN14187-L1	927-70-C12
REGN14188	REGN14188-L1	927-71-H02
REGN14189	REGN14189-L1	927-71-E03
REGN14190	REGN14190-L1	927-71-C04
REGN14191	REGN14191-L1	927-71-E12
REGN19516	REGN19516-L1	927-9-72A4
REGN19517	REGN19517-L1	927-9-72C7
REGN19515	REGN19515-L1	927-7-71F5
REGN19514	REGN19514-L1	927-1-61H4
REGN19513	REGN19513-L1	927-4-65A5

Table 4-2. Reagents used and lot numbers

Reagent	Source	Identifier	Lot#
Proteins			
Human p75-ecto domain.mFc	Regeneron	REGN6869	REGN6869-L1
Human NT-3	R&D Systems	267-N3-025/CF	L1
Control Antibodies			
Human/Canine NGFR monoclonal mouse IgG1 clone # 74902	R&D Systems	MAB367	GUC31921
2° Antibody Reagent			
Peroxidase AffiniPure Goat Anti-Mouse IgG (subclasses 1+2a+2b+3), Fcγ Fragment Specific	Jackson ImmunoResearch Laboratories Inc	115-035-164	1298A4
Coat Dilution Buffer			
1xPBS with Ca ²⁺ /Mg ²⁺	Irvine Scientific	Cat#9236	2120708
Sample Dilution Buffer and Blocking Solution			
1xPBS with Ca ²⁺ /Mg ²⁺	Irvine Scientific	Cat#9236	2120708
BSA	Sigma	Cat#A8577-1L	SLBS07831
Plate Washing Solution			
PBS-Tween dry packets	Sigma-Aldrich	P3563	
ELISA Development Solution			
3-3', 5-5'-tetramethylbenzidine (TMB) Substrate A	BD Biosciences	51-2606KC	9263288
3-3', 5-5'-tetramethylbenzidine (TMB) Substrate B	BD Biosciences	51-2607KC	8352533
Stop Solution			
1 M Sulfuric Acid	BDH	BDH7500-1	18H2956683
Reagent Dilution Plate			
Deep Well Dilution Plate	VWR	10755	10755-250
ELISA Microtiter Plate			
Microplate, 96 well, ps, half area, clear	Greiner	675061	F181236P
Equipment			

VICTOR™ X4 Multilabel Plate Reader	Perkin Elmer	2030-0040	N/A
AquaMax® Microplate Washer	MDS Analytical Technologies	Model #2000	N/A

[00230] An ELISA-based blocking assay was developed to determine the ability of anti-p75 monoclonal antibody supernatants to block the binding of the human p75 neurotrophin receptor mouse Fc dimer (human p75-mFc), to plate-coated human neurotrophin-3 (hNT-3).

[00231] The recombinant human hp75-mFc protein (REGN6869) (SEQ ID NO: 641) used in the experiments comprises a portion of the human p75NTR extracellular domain (amino acids K29-N250) (REGN6869) (SEQ ID NO: 642), fused to the Fc portion of the mouse IgG2a at the C-terminus of human p75NTR (REGN6869) (SEQ ID NO: 643). The human NTF-3 (UniProt accession number P20783.1) expressed with amino acids W139-T257 (K196R) (SEQ ID NO: 644) was commercially obtained from R&D Systems.

[00232] In this assay, hNT-3 was passively absorbed at a concentration of 2 µg/mL in PBS on a 96-well microtiter plate overnight at 4°C. Nonspecific binding sites were subsequently blocked using a 0.5% (w/v) solution of BSA in PBS for 1 hour at room temperature. In a separate microtiter plate, a fixed amount of 1 nM human p75NTR-mFc was bound for one hour with anti-hp75 monoclonal antibody supernatants or sample media at a dilution of 1:5 or 0.5 mg/ml of the control anti-human/canine NGFR-mIgG1 monoclonal antibody in assay buffer. The fixed concentration of human p75^{NTR}-mFc was selected to be near the concentration that generated 50% of the maximal binding (EC50 value) to plate-adhered hNT-3 protein. After the incubation, the antibody-protein complexes were transferred to the microtiter plate coated with hNT-3. After one hour incubation at room temperature, the wells were washed, and hNT-3 bound human p75-mFc was detected with a horseradish peroxidase-conjugated goat anti-mouse IgG Fcγ fragment specific polyclonal antibody. The plates were then developed using TMB substrate solution (BD Biosciences) according to manufacturer's recommendation and absorbance at 450 nm was measured on a Victor[®] Multilabel Plate Reader (PerkinElmer[®]).

[00233] Percent blocking for the tested anti-p75^{NTR} monoclonal antibody supernatants was calculated using the formula below:

$$\% \text{ Blocking} = 100 - \left(\frac{[\text{Experimental Signal}_{(\text{anti-p75}^{\text{NTR}})} - \text{Background Signal}_{(\text{buffer})}]}{[\text{Maximum Signal}_{(1 \text{ nM hp75}^{\text{NTR}}\text{-mFc)} - \text{Background Signal}_{(\text{buffer})}]} \right) \times 100$$

[00234] Antibodies that blocked binding of human p75^{NTR}-mFc to human NT-3 with a value greater than or equal to 50% were classified as blockers.

[00235] The ability of thirty-five anti-p75^{NTR} monoclonal antibody supernatants to block human p75-mFc binding to plate-coated human NT-3 was assessed using a sandwich ELISA-based blocking assay. The results are shown in Table 4-3.

Table 4-3. Summary of anti-p75^{NTR} antibody supernatants blocking human p75-mFc dimer binding to human NT-3

REGN#	Lot #	Clone Name	% Blocking
REGN14148	REGN14148-L1	927-61-H10	121
REGN14149	REGN14149-L1	927-62-F02	76
REGN14150	REGN14150-L1	927-62-E06	121
REGN14151	REGN14151-L1	927-62-E08	114
REGN14152	REGN14152-L1	927-62-B09	110
REGN14153	REGN14153-L1	927-62-H09	128
REGN14154	REGN14154-L1	927-62-B10	130
REGN14155	REGN14155-L1	927-62-E11	96
REGN14156	REGN14156-L1	927-63-B06	127
REGN14157	REGN14157-L1	927-61-D03	103
REGN14158	REGN14158-L1	927-61-F03	2
REGN14159	REGN14159-L1	927-61-B04	97
REGN14160	REGN14160-L1	927-61-C04	34
REGN14161	REGN14161-L1	927-61-F04	128
REGN14162	REGN14162-L1	927-61-D07	31
REGN14163	REGN14163-L1	927-61-D08	118
REGN14164	REGN14164-L1	927-61-F08	85
REGN14165	REGN14165-L1	927-61-H09	131
REGN14175	REGN14175-L1	927-64-D04	-19
REGN14176	REGN14176-L1	927-64-G11	124
REGN14177	REGN14177-L1	927-65-H06	-155
REGN14178	REGN14178-L1	927-65-F08	152
REGN14179	REGN14179-L1	927-68-D02	-68

REGN14180	REGN14180-L1	927-68-A05	121
REGN14181	REGN14181-L1	927-68-C06	56
REGN14182	REGN14182-L1	927-68-C11	100
REGN14183	REGN14183-L1	927-69-A02	103
REGN14184	REGN14184-L1	927-69-H02	65
REGN14185	REGN14185-L1	927-69-H03	98
REGN14186	REGN14186-L1	927-69-G06	132
REGN14187	REGN14187-L1	927-70-C12	-28
REGN14188	REGN14188-L1	927-71-H02	132
REGN14189	REGN14189-L1	927-71-E03	117
REGN14190	REGN14190-L1	927-71-C04	64
REGN14191	REGN14191-L1	927-71-E12	91
REGN19516	REGN19516-L1	927-9-72A4	NT
REGN19517	REGN19517-L1	927-9-72C7	NT
REGN19515	REGN19515-L1	927-7-71F5	NT
REGN19514	REGN19514-L1	927-1-61H4	NT
REGN19513	REGN19513-L1	927-4-65A5	NT
Human/Canine NGFR-mIgG1 clone # 74902	N/A	N/A	105

N/A: Not Applicable; NT: Not Tested

[00236] Twenty-eight anti-p75^{NTR} monoclonal antibody supernatants blocked human p75-mFc from binding to plate-coated human NT-3 with a percent blockade of greater than or equal to 50% and were classified as blockers. Seven anti-p75^{NTR} monoclonal antibody supernatants were classified as non-blockers since their blockade was below 50%. In this assay the control anti-human/canine NGFR-mIgG1 antibody blocked the human p75 binding to human NT-3.

Example 2. Anti-p75^{NTR} (p75) monoclonal antibody supernatants binding to engineered cells expressing human p75^{NTR} (hp75), monkey p75^{NTR} (mfp75) or mouse p75^{NTR} (mp75) using electrochemiluminescence.

Table 5-1. Reagents used and lot numbers

Cell Lines	Source	Identifier	
NIH3T3/hp75 ^{NTR}	Regeneron	ACL16057	
NIH3T3/mfp75	Regeneron	ACL16597	
NIH3T3/mp75	Regeneron	ACL16515	
NIH3T3/SRELuc	Regeneron	ACL12741	

Reagent	Source	Identifier	Lot #
ME20.4 Purified anti-human CD271 (NGFR), mouse IgG1	Biolegend	345102	N/A
SULFO-TAG [Ruthenium (II) tris-bipyridine-(4-methylsulfone)] NHS Ester	Meso Scale Discovery	R91AN-2	S0090069
AffiniPure Goat Anti-Human IgG, Fcγ Fragment Specific -SULFOTAG labeled lot from REGN	Jackson ImmunoResearch	109-005-098	N/A
AffiniPure Goat Anti-Mouse IgG, Fcγ(subclasses 1+2a+2b+3) Fragment Specific -SULFOTAG labeled lot from REGN	Jackson ImmunoResearch	115-005-164	N/A
1xPBS with Ca ²⁺ /Mg ²⁺	GIBCO	14040-117	2120708
BSA	Sigma	A8577-1L	SLCB3639
PBS dry packets	Sigma	P3813-10PAK	SLCB3110
MULTI-ARRAY 96-well High Bind Plate	Meso Scale Discovery	L15XB-3/LX11XB-3	22JOJA
Deep Well Dilution Plate	VWR	10755-250	80841-931C-931
Milli-Q pure water	N/A	N/A	N/A
MSD Read Buffer T (4x), Surfactant Free	Meso Scale Discovery	R92TD-1	Y0060032
Equipment	Source	Model	
AquaMax® Microplate Washer	Molecular Devices	Model #2000	N/A
SECTOR Imager	Meso Scale Discovery	Model # 600	N/A

N/A: Not Applicable

[00237] The same mAb clone IDs as used in Example 1 were used in the present Example. The ability of anti-human p75 monoclonal antibody supernatants to bind human p75 neurotrophin receptor (hp75) (NCBI accession number NP_002498.1) (SEQ ID NO: 619), or *Macaca fascicularis* p75 neurotrophin receptor (mfp75) (NCBI accession number XP_005583674.1) (SEQ ID NO: 646), or mouse neurotrophin receptor (mp75) (GenBank accession number AAH38365) (SEQ ID NO: 621) expressing cells was determined using an electrochemiluminescence based assay.

[00238] Briefly, NIH3T3 cells were engineered to express hp75, or mfp75, or mp75 by transfecting the cells with hygromycin resistant pLVxEF1a.hNGFR expression plasmid encoding hp75 (amino acids M1-V399, NCBI accession number NP_002498.1) (SEQ ID NO: 619), or pLVx.mfNGFR expression plasmid encoding mfp75 (M1-V427, NCBI accession number XP_005583674.1) (SEQ ID NO: 646), or pLVxEF1a.mNGFR expression plasmid

encoding mp75 (amino acids M1-V427, GenBank accession number AAH38365 (SEQ ID NO: 621). The p75 negative NIH3T3/SRELuc (NIH3T3/SRELuc) cells showed no detectable expression of p75 by fluorescence activated cell sorting (FACS) with a commercial p75 antibody and were included in the experiments as a background binding control.

[00239] Experiments were carried out according to the following procedure. NIH3T3/hp75, NIH3T3/mfp75, NIH3T3/mp75 and NIH3T3/SRELuc cells cultured in flasks were rinsed once with 1xPBS buffer without $\text{Ca}^{2+}/\text{Mg}^{2+}$ and incubated for 10 minutes at 37°C with Enzyme Free Cell Dissociation Solution to detach cells. The cell pellets were washed once with 1xPBS with $\text{Ca}^{2+}/\text{Mg}^{2+}$ and counted with a Cellometer™ Auto T4 cell counter (Nexcelom Bioscience, Lawrence, MA). Approximately 2.0×10^4 NIH3T3/hp75, NIH3T3/mfp75, NIH3T3/mp75 or NIH3T3/SRELuc cells per well were seeded separately onto 96-well carbon electrode plates (Meso Scale Discovery, Rockville, MD) and incubated for 1 hour at 37°C to allow the cells to adhere. Nonspecific binding sites were blocked by incubating with 2% BSA (w/v) in 1xPBS with $\text{Ca}^{2+}/\text{Mg}^{2+}$ for 1 hour at room temperature. To the plate-bound cells, anti-p75 monoclonal antibody supernatants at a dilution of 1:10, 0.5 µg/ml of the control antibody in assay buffer and buffer with no antibody were added followed by 1 hour incubation at room temperature. Plates were then washed to remove unbound antibodies using an AquaMax2000 plate washer with a cell washing head (MDS Analytical Technologies, Sunnyvale, CA). The plate-bound anti-p75-hIgG samples were detected with SULFO-TAG™-conjugated goat polyclonal anti-human IgG antibody specific for heavy and light chains (Jackson ImmunoResearch Labs, West Grove, PA) and the plate-bound anti-p75-mIgG (ME20.4 purified anti-hp75) was detected with SULFO-TAG™-conjugated goat polyclonal anti-mouse IgG antibody specific for Fcγ fragment (Jackson ImmunoResearch Labs, West Grove, PA) for 1 hour at room temperature. After washes, plates were developed with Read Buffer (Meso Scale Discovery, Rockville, MD) according to the manufacturer's recommended procedure and luminescent signals were recorded with a SECTOR Imager 600 (Meso Scale Discovery, Rockville, MD). The ratio of binding signals on the NIH3T3/hp75, NIH3T3/mfp75, or NIH3T3/mp75 to NIH3T3/SRELuc was calculated and reported as an indication of the binding specificity of anti-p75 antibodies. Antibodies with binding signal on NIH3T3/hp75, NIH3T3/mfp75, or NIH3T3/mp75 cells greater than or equal to 200 RLU, with a binding ratio of greater than or equal to 3, were classified as specific binders. Antibodies with a binding

signal less than 200 RLU or with a binding ratio less than 3 were classified as non-specific binders or non-binders.

[00240] The ability of the anti-p75^{NTR} monoclonal antibody supernatants to bind specifically to NIH3T3 cells expressing human, monkey or mouse p75 was evaluated using an electrochemiluminescence based binding assay. The experimental results are summarized in Table 5-2 and Table 5-3.

Table 5-2. Summary of anti-p75^{NTR} antibody supernatants binding to cells engineered to express human or monkey p75

REGN#	Lot #	Clone Name	Antibody Binding Signal (RLU)			Ratio to NIH3T3/SRELuc	
			NIH3T3/hp75	NIH3T3/mfp75	NIH3T3/SRELuc, p75 negative	hp75	mfp75
REGN14148	REGN14148-L1	927-61-H10	27252	20082	971	28	21
REGN14149	REGN14149-L1	927-62-F02	31541	25225	1902	17	13
REGN14150	REGN14150-L1	927-62-E06	14766	18677	312	47	60
REGN14151	REGN14151-L1	927-62-E08	28223	26117	1814	16	14
REGN14152	REGN14152-L1	927-62-B09	26754	25739	282	95	91
REGN14153	REGN14153-L1	927-62-H09	24540	22368	628	39	36
REGN14154	REGN14154-L1	927-62-B10	29803	24819	891	33	28
REGN14155	REGN14155-L1	927-62-E11	9089	11137	151	60	74
REGN14156	REGN14156-L1	927-63-B06	8373	13491	172	49	78
REGN14157	REGN14157-L1	927-61-D03	30313	19727	435	70	45
REGN14158	REGN14158-L1	927-61-F03	20215	18688	761	27	25
REGN14159	REGN14159-L1	927-61-B04	22082	19332	771	29	25
REGN14160	REGN14160-L1	927-61-C04	23734	15804	314	76	50
REGN14161	REGN14161-L1	927-61-F04	32101	20504	245	131	84
REGN14162	REGN14162-L1	927-61-D07	25958	18828	502	52	38
REGN14163	REGN14163-L1	927-61-D08	10843	14406	724	15	20
REGN14164	REGN14164-L1	927-61-F08	25543	19642	577	44	34
REGN14165	REGN14165-L1	927-61-H09	25439	18636	784	32	24
REGN14175	REGN14175-L1	927-64-D04	20559	17940	1056	20	17
REGN14176	REGN14176-L1	927-64-G11	8377	9617	257	33	37
REGN14177	REGN14177-L1	927-65-H06	31385	20878	691	45	30
REGN14178	REGN14178-L1	927-65-F08	13908	14071	177	79	80
REGN14179	REGN14179-L1	927-68-D02	22848	19748	840	27	24
REGN14180	REGN14180-L1	927-68-A05	29857	21588	414	72	52

REGN14181	REGN14181-L1	927-68-C06	20974	15678	647	32	24
REGN14182	REGN14182-L1	927-68-C11	25414	23984	1671	15	14
REGN14183	REGN14183-L1	927-69-A02	26378	22919	648	41	35
REGN14184	REGN14184-L1	927-69-H02	23055	19429	703	33	28
REGN14185	REGN14185-L1	927-69-H03	23885	20768	500	48	42
REGN14186	REGN14186-L1	927-69-G06	24961	19838	434	58	46
REGN14187	REGN14187-L1	927-70-C12	31482	21476	1327	24	16
REGN14188	REGN14188-L1	927-71-H02	25485	18338	1164	22	16
REGN14189	REGN14189-L1	927-71-E03	26747	19575	1398	19	14
REGN14190	REGN14190-L1	927-71-C04	27661	19243	1663	17	12
REGN14191	REGN14191-L1	927-71-E12	26353	19343	270	98	72
REGN19516	REGN19516-L1	927-9-72A4	3919	4643	118	33	39
REGN19517	REGN19517-L1	927-9-72C7	18966	16234	306	62	53
REGN19515	REGN19515-L1	927-7-71F5	10051	9246	178	56	52
REGN19514	REGN19514-L1	927-1-61H4	16064	14521	329	49	44
REGN19513	REGN19513-L1	927-4-65A5	16489	10787	466	35	23
Anti-p75-mIgG1 clone ME20.4	Biolegend	345102	15897	12505	69	230	181
Buffer (Secondary Antibody only: anti-Human IgG, Fcγ Fragment Specific - SULFOTAG	N/A	N/A	88	122	65	1	2
Buffer (Secondary Antibody only: anti-Mouse IgG, Fcγ Fragment Specific - SULFOTAG	N/A	N/A	19	24	22	2	1

N/A: Not Applicable

Table 5-3. Summary of anti-p75NTR antibody supernatants binding to cells engineered to express mouse p75

REGN#	Lot #	Clone Name	Antibody Binding Signal (RLU)		Ratio to NIH3T3/SRELuc
			NIH3T3/mp75	NIH3T3/SRELuc, p75 negative	mp75
REGN14148	REGN14148-L1	927-61-H10	18814	529	36
REGN14149	REGN14149-L1	927-62-F02	21598	1706	13
REGN14150	REGN14150-L1	927-62-E06	12783	257	50

REGN14151	REGN14151-L1	927-62-E08	15793	1183	13
REGN14152	REGN14152-L1	927-62-B09	21783	371	59
REGN14153	REGN14153-L1	927-62-H09	20019	242	83
REGN14154	REGN14154-L1	927-62-B10	21952	725	30
REGN14155	REGN14155-L1	927-62-E11	14074	192	73
REGN14156	REGN14156-L1	927-63-B06	14990	123	122
REGN14157	REGN14157-L1	927-61-D03	1596	198	8
REGN14158	REGN14158-L1	927-61-F03	13454	462	29
REGN14159	REGN14159-L1	927-61-B04	17701	513	35
REGN14160	REGN14160-L1	927-61-C04	15041	159	95
REGN14161	REGN14161-L1	927-61-F04	16458	126	131
REGN14162	REGN14162-L1	927-61-D07	18272	341	54
REGN14163	REGN14163-L1	927-61-D08	19172	792	24
REGN14164	REGN14164-L1	927-61-F08	14725	353	42
REGN14165	REGN14165-L1	927-61-H09	16586	346	48
REGN14175	REGN14175-L1	927-64-D04	16081	599	27
REGN14176	REGN14176-L1	927-64-G11	12763	158	81
REGN14177	REGN14177-L1	927-65-H06	22346	416	54
REGN14178	REGN14178-L1	927-65-F08	15845	120	132
REGN14179	REGN14179-L1	927-68-D02	20374	636	32
REGN14180	REGN14180-L1	927-68-A05	18286	403	45
REGN14181	REGN14181-L1	927-68-C06	16142	371	44
REGN14182	REGN14182-L1	927-68-C11	20613	1037	20
REGN14183	REGN14183-L1	927-69-A02	22225	203	110
REGN14184	REGN14184-L1	927-69-H02	19167	356	54
REGN14185	REGN14185-L1	927-69-H03	22846	262	87
REGN14186	REGN14186-L1	927-69-G06	18164	210	87
REGN14187	REGN14187-L1	927-70-C12	18600	697	27
REGN14188	REGN14188-L1	927-71-H02	45193	323	140
REGN14189	REGN14189-L1	927-71-E03	40545	512	79
REGN14190	REGN14190-L1	927-71-C04	34513	422	82
REGN14191	REGN14191-L1	927-71-E12	42533	354	120
REGN19516	REGN19516-L1	927-9-72A4	26133	263	99
REGN19517	REGN19517-L1	927-9-72C7	35924	298	121
REGN19515	REGN19515-L1	927-7-71F5	18407	58	317
REGN19514	REGN19514-L1	927-1-61H4	7677	225	34
REGN19513	REGN19513-L1	927-4-65A5	13173	90	146
Anti-p75-mIgG1 clone ME20.4	Biologend	345102	30	29	1

Buffer (Secondary Antibody only: anti-Human IgG, Fcγ Fragment Specific - SULFOTAG	Jackson Immuno Research	N/A	17	31	1
Buffer (Secondary Antibody only: anti-Mouse IgG, Fcγ Fragment Specific - SULFOTAG	Jackson Immuno Research	N/A	24	41	1

[00241] A total of 40 anti-p75^{NTR} monoclonal antibodies in crude supernatants were tested for binding to NIH3T3/hp75, NIH3T3/mfp75, NIH3T3/mp75 and NIH3T3/SREluc cells. All tested anti-p75 monoclonal antibodies displayed binding signals greater than 3000 RLU on NIH3T3/hp75 cells with ratios of binding on NIH3T3/hp75 to NIH3T3/SREluc cells greater than 14 suggesting these antibodies are capable of specific binding to human p75. When tested for specific binding to NIH3T3/mfp75, all anti-p75 antibodies displayed binding signals greater than 4000 RLU and ratio of binding on NIH3T3/mfp75 to NIH3T3/SREluc cells greater than 11 and were characterized as mfp75 binders.

[00242] These forty anti-p75 antibodies displayed binding signals greater than 1500 RLU on NIH3T3/mp75 cells with ratios of binding on NIH3T3/mp75 to NIH3T3/SREluc cells greater than 7 and were characterized as mouse p75 binders.

[00243] The commercial positive control anti-p75-mIgG1 clone ME20.4 tested at 0.5 mg/ml bound to NIH3T3/hp75 and NIH3T3/mfp75 cells with signals of 15897 RLU and 12505 RLU and with ratios of binding to negative NIH3T3/SREluc cells of 230 and 181, respectively, and was classified as a hp75 and mfp75 specific binder. When tested for binding to NIH3T3/mp75, anti-p75-mIgG1 clone ME20.4 bound to NIH3T3/mp75 and NIH3T3/SREluc cells with similar signals of 30 RLU and 29 RLU, respectively, suggesting that this antibody does not bind to mouse p75.

[00244] Minimal binding signal was observed for the SULFO-TAGTM-conjugated goat polyclonal anti-human IgG and SULFO-TAGTM-conjugated goat polyclonal anti-mouse IgG detection antibodies.

Example 3. Biacore binding kinetics of anti-p75^{NTR} monoclonal antibodies binding to p75^{NTR} reagents measured at 25°C.

Table 6-1. mAb clone IDs

REGN#	Lot #	Description
REGN14149	REGN14149-L1	Bivalent hIgG4P
REGN14152	REGN14152-L1	Bivalent hIgG4P
REGN14155	REGN14155-L1	Bivalent hIgG4P
REGN14162	REGN14162-L1	Bivalent hIgG4P
REGN14177	REGN14177-L1	Bivalent hIgG4P
REGN14187	REGN14187-L1	Bivalent hIgG4P
REGN1945	REGN1945-L49	Bivalent hIgG4P (iso-type control)

Table 6-2. Reagents used and lot numbers

Common Name (Source)	REGN#	Lot#
hNGFR.mmH	REGN6870	REGN6870-L1
hNGFR.mFc	REGN6869	REGN6869-L1
mNGFR.mmH	REGN6871	REGN6871-L1
mNGFR.mFc	REGN6872	REGN6872-L1
mfNGFR.mmh	REGN6942	REGN6942-L1

[00245] Equilibrium dissociation constants (KD) for p75^{NTR} binding to purified anti-p75^{NTR} monoclonal antibodies were determined using a real-time surface plasmon resonance (SPR) based Biacore T200 biosensor. All binding studies were performed in 10 mM HEPES, 150 mM NaCl, 3 mM EDTA, 0.05% and 0.05% v/v surfactant Tween-20, pH 7.4 (HBS-EP) running buffer at 25°C. The Biacore CM5 sensor surface was first derivatized by amine coupling with a monoclonal mouse anti-human Fc antibody (REGN2567) to capture anti-p75^{NTR} monoclonal antibodies. Different concentrations of p75^{NTR} reagents, human p75^{NTR} extracellular domain expressed with a C-terminal myc-myc-hexahistidine tag (hp75^{NTR}-MMH; REGN6870), monkey p75^{NTR} extracellular domain expressed with a C-terminal myc-myc-hexahistidine tag (mfP75^{NTR}-MMH; REGN6942), mouse p75^{NTR} extracellular domain expressed with a C-terminal myc-myc-hexahistidine tag (mp75^{NTR}-MMH; REGN6871), mouse P75^{NTR} extracellular domain expressed with a C-terminal mouse IgG2a Fc tag (mp75^{NTR}-mFc; REGN6872), and human p75^{NTR} extracellular domain expressed with a C-terminal mouse IgG2a Fc tag (hp75^{NTR}-mFc; REGN6869), at concentrations ranging from

1.56 nM to 100 nM in a series of 4-fold dilutions prepared in HBS-EP running buffer were injected at a flow rate of 50 μ L/min for 2 minutes. The dissociation of different p75^{NTR} reagents bound to anti-p75^{NTR} monoclonal antibodies was monitored for 10 minutes in HBS-EP running buffer. At the end of each cycle, the anti-p75^{NTR} monoclonal antibodies capture surface was regenerated using a 12 second injection of 20 mM H3PO4. The association rate (k_a) and dissociation rate (k_d) were determined by fitting the real-time binding sensorgrams to a 1:1 binding model with mass transport limitation using Scrubber 2.0c curve-fitting software. Binding dissociation equilibrium constant (K_D) and dissociative half-life ($t_{1/2}$) were calculated from the kinetic rates as:

$$K_D (M) = \frac{k_d}{k_a}, \quad \text{and} \quad t_{1/2} (\text{min}) = \frac{\ln(2)}{60 * k_d}$$

[00246] The equilibrium and kinetic binding parameters for anti-p75^{NTR} monoclonal antibodies binding to hp75^{NTR}-MMH, mfp75^{NTR}-MMH, hp75^{NTR}-mFc, mp75^{NTR}-MMH, and mp75^{NTR}-mFc at 25°C are shown in Table 6-3 through Table 6-7, respectively.

[00247] At 25°C, anti-p75^{NTR} monoclonal antibodies bound to hp75^{NTR}-MMH with K_D values ranging from 151 pM to 2.84 nM, as shown in Table 6-3.

[00248] At 25°C, anti-p75^{NTR} monoclonal antibodies bound to mfp75^{NTR}-MMH with K_D values ranging from 219 pM to 1.56 nM, as shown in Table 6-4.

[00249] At 25°C, anti-p75^{NTR} monoclonal antibodies bound to hp75^{NTR}-mFc with K_D values ranging from 27.2 pM to 378 pM, as shown in Table 6-5.

[00250] At 25°C, anti-p75^{NTR} monoclonal antibodies bound to mp75^{NTR}-MMH with K_D values ranging from 195 pM to 2.59 nM, as shown in Table 6-6.

[00251] At 25°C, anti-p75^{NTR} monoclonal antibodies bound to mp75^{NTR}-mFc with K_D values ranging from 6.99 pM to 94.0 pM, as shown in Table 6-7.

Table 6-3. Kinetic binding parameters for the interaction of hp75^{NTR}-MMH with anti-p75^{NTR} monoclonal antibodies at 25°C.

REGN#	mAb Capture Level (RU)	100 nM Ag Bound (RU)	k_a (1/Ms)	k_d (1/s)	K_D (M)	$t_{1/2}$ (min)
REGN14149-L1	278 $\pm$ 0.2	37	1.33E+05	3.79E-04	2.84E-09	30
REGN14152-L1	280 $\pm$ 0.7	81	1.27E+06	2.96E-04	2.34E-10	39

REGN14155-L1	270 ± 0.7	66	1.26E+06	1.90E-04	1.51E-10	61
REGN14162-L1	280 ± 0.2	82	8.36E+05	3.14E-04	3.76E-10	37
REGN14177-L1	278 ± 0.3	54	5.00E+05	1.06E-04	2.11E-10	110
REGN14187-L1	272 ± 0.5	72	8.08E+05	2.48E-04	3.06E-10	47
REGN1945-L49	275 ± 0.4	3	NB	NB	NB	NB

Table 6-4. Kinetic binding parameters for the interaction of mfp75^{NTR}-MMH with anti-p75^{NTR} monoclonal antibodies at 25°C.

REGN#	mAb Capture Level (RU)	25 nM Ag Bound (RU)	k_a (1/Ms)	k_d (1/s)	K_D (M)	$t_{1/2}$ (min)
REGN14149-L1	277 ± 0.5	11	2.51E+05	3.93E-04	1.56E-09	29
REGN14152-L1	278 ± 0.2	63	9.20E+05	3.14E-04	3.41E-10	37
REGN14155-L1	268 ± 0.2	45	9.17E+05	2.00E-04	2.19E-10	58
REGN14162-L1	278 ± 0.2	55	7.58E+05	3.21E-04	4.23E-10	36
REGN14177-L1	277 ± 0.1	28	3.93E+05	1.07E-04	2.73E-10	108
REGN14187-L1	270 ± 0.3	45	7.86E+05	2.58E-04	3.29E-10	45
REGN1945-L49	274 ± 0.4	-2	NB	NB	NB	NB

Table 6-5. Kinetic binding parameters for the interaction of hp75^{NTR}-mFc with anti-p75^{NTR} monoclonal antibodies at 25°C.

REGN#	mAb Capture Level (RU)	100 nM Ag Bound (RU)	k_a (1/Ms)	k_d (1/s)	K_D (M)	$t_{1/2}$ (min)
REGN14149-L1	277 ± 0.4	83	1.76E+05	6.67E-05	3.78E-10	173
REGN14152-L1	279 ± 0.4	163	1.88E+06	8.10E-05	4.30E-11	143
REGN14155-L1	269 ± 0.3	137	1.84E+06	5.01E-05	2.72E-11	231
REGN14162-L1	279 ± 0.3	158	9.47E+05	6.68E-05	7.06E-11	173
REGN14177-L1	278 ± 0.2	102	5.32E+05	2.34E-05	4.40E-11	493
REGN14187-L1	272 ± 0.4	153	8.83E+05	1.06E-04	1.20E-10	109
REGN1945-L49	275 ± 0.1	6	NB	NB	NB	NB

Table 6-6. Kinetic binding parameters for the interaction of mp75^{NTR}-MMH with anti-p75^{NTR} monoclonal antibodies at 25°C.

REGN#	mAb Capture Level (RU)	100 nM Ag Bound (RU)	k_a (1/Ms)	k_d (1/s)	K_D (M)	$t_{1/2}$ (min)
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REGN14149-L1	277 ± 0.3	40	1.42E+05	3.66E-04	2.59E-09	32
REGN14152-L1	279 ± 0.3	82	1.05E+06	5.71E-04	5.45E-10	20
REGN14155-L1	269 ± 0.2	68	9.58E+05	1.87E-04	1.95E-10	62
REGN14162-L1	279 ± 0.2	84	7.83E+05	3.42E-04	4.37E-10	34
REGN14177-L1	277 ± 0.1	45	3.80E+05	6.26E-04	1.65E-09	18
REGN14187-L1	271 ± 0.2	74	1.82E+06	5.90E-04	3.24E-10	20
REGN1945-L49	275 ± 0.1	2	NB	NB	NB	NB

Table 6-7. Kinetic binding parameters for the interaction of mp75^{NTR}-mFc with anti-p75^{NTR} monoclonal antibodies at 25°C.

REGN#	mAb Capture Level (RU)	100 nM Ag Bound (RU)	k_a (1/Ms)	k_d (1/s)	K_D (M)	$t_{1/2}$ (min)
REGN14149-L1	277 ± 0.3	117	6.29E+05	4.87E-05	7.74E-11	237
REGN14152-L1	279 ± 0.3	174	6.65E+06	9.45E-05	1.42E-11	122
REGN14155-L1	268 ± 0.3	155	6.30E+06	4.40E-05	6.99E-12	262
REGN14162-L1	278 ± 0.4	176	3.84E+06	5.60E-05	1.46E-11	206
REGN14177-L1	277 ± 0.2	115	8.25E+05	7.76E-05	9.40E-11	149
REGN14187-L1	270 ± 0.6	181	3.60E+06	2.30E-04	6.37E-11	50
REGN1945-L49	274 ± 0.1	8	NB	NB	NB	NB

Example 4. Octet cross-competition between different anti-p75^{NTR} monoclonal antibodies.

Table 7-1. mAb Clone IDs

REGN#	Lot #	Description
REGN14149	REGN14149-L1	Bivalent hIgG4P
REGN14152	REGN14152-L1	Bivalent hIgG4P
REGN14155	REGN14155-L1	Bivalent hIgG4P
REGN14162	REGN14162-L1	Bivalent hIgG4P
REGN14177	REGN14177-L1	Bivalent hIgG4P
REGN14187	REGN14187-L1	Bivalent hIgG4P
REGN1945	REGN1945-L49	Bivalent hIgG4P (iso-type control)

Table 7-2. Reagents used and lot numbers

Common Name (Source)	REGN#	Lot#
hNGFR.mmH	REGN6870	REGN6870-L1

[00252] Binding competition between different anti-p75^{NTR} monoclonal antibodies (mAbs) was determined using a real time, label-free bio-layer interferometry (BLI) assay on the Octet HTX biosensor platform (Pall ForteBio Corp.). The entire experiment was performed at 25°C in 10 mM HEPES buffer containing 150 mM NaCl, 3 mM EDTA, 1 mg/mL BSA, 0.02% NaN₃, and 0.05% v/v Surfactant Tween-20 at pH7.4 (HBS-EP) with the plate shaking at a speed of 1000 rpm. To assess the ability of one antibody to compete with another antibody for binding to p75^{NTR}, around 0.2 nm of recombinant human p75^{NTR} extracellular domain expressed with a C-terminal myc-myc-hexahistidine (hp75^{NTR}-MMH) (REGN6870) was first captured onto anti-Penta-His antibody coated Octet biosensor tips (ForteBio Inc, # 18-5122) by submerging the biosensor tips in wells containing 45 µg/mL solution of the hp75^{NTR}-MMH for 120 seconds. The antigen captured biosensor tips were then saturated with a first anti-p75^{NTR} monoclonal antibody (subsequently referred to as mAb-1) by dipping into wells containing 50 µg/mL solution of mAb-1 for 4 minutes. The biosensor tips were then subsequently dipped into wells containing 50 µg/mL solution of a second anti-p75^{NTR} monoclonal antibody (subsequently referred to as mAb-2) for 3 minutes. The biosensor tips were washed in HBS-EBT buffer in between every step of the experiment. The real-time binding response was monitored and the binding response at the end of every step was recorded. The response of mAb-2 binding to hp75^{NTR}-MMH pre-complexed with mAb-1 was compared to the binding response hp75^{NTR}-MMH alone (sample of isotype control), and if pre-bound mAb-1 reduced binding of mAb-2 by more than 50%, mAb-1 is considered as competitor to mAb-2. Competitors of each antibody tested are summarized in Table 7-3.

Table 7-3. Cross-competition between different anti-p75^{NTR} monoclonal antibodies for binding to hp75^{NTR}-MMH

Pre-bound mAb-1	mAb-2 blocked by mAb-1 (> 50%)
REGN14149	REGN14149
	REGN14177
REGN14177	REGN14149
	REGN14177
	REGN14152
	REGN14162
REGN14152	REGN14177
	REGN14152

	REGN14162
	REGN14155
REGN14162	REGN14177
	REGN14152
	REGN14162
	REGN14155
REGN14155	REGN14152
	REGN14162
	REGN14155
REGN14187	REGN14187

Example 5. Biacore binding kinetics for the interaction of 35 anti-human p75^{NTR} monoclonal antibodies from CHOt supernatants with p75^{NTR} reagents at 25°C.

Table 8-1. Reagent/mAb clone IDs

mAb#	CloneID#	Ab PID	REGN#	Lot #
1	927-1-61H10	PN62924	REGN14148	primary sup
2	927-2-62F2	PN62928	REGN14149	primary sup
3	927-2-62F6	PN62934	REGN14150	primary sup
4	927-2-62E8	PN62937	REGN14151	primary sup
5	927-2-62B9	PN62939	REGN14152	primary sup
6	927-2-62H9	PN62940	REGN14153	primary sup
7	927-2-62B10	PN62941	REGN14154	primary sup
8	927-2-62F11	PN62945	REGN14155	primary sup
9	927-3-63B6	PN62949	REGN14156	primary sup
10	927-1-61D3	PN62902	REGN14157	primary sup
11	927-1-61F3	PN62903	REGN14158	primary sup
12	927-1-61B4	PN62905	REGN14159	primary sup
13	927-1-61C4	PN62906	REGN14160	primary sup
14	927-1-61F4	PN62907	REGN14161	primary sup
15	927-1-61D7	PN62916	REGN14162	primary sup
16	927-1-61D8	PN62918	REGN14163	primary sup
17	927-1-61F8	PN62919	REGN14164	primary sup
18	927-1-61H9	PN62921	REGN14165	primary sup
19	927-4-64D4	PN62957	REGN14175	primary sup
20	927-4-64G11	PN62961	REGN14176	primary sup
21	927-4-65H6	PN62969	REGN14177	primary sup

22	927-4-65F8	PN62971	REGN14178	primary sup
23	927-5-68D2	PN62987	REGN14179	primary sup
24	927-5-68A5	PN63002	REGN14180	primary sup
25	927-5-68C6	PN63009	REGN14181	primary sup
26	927-8-68C11	PN63028	REGN14182	primary sup
27	927-8-69A2	PN63034	REGN14183	primary sup
28	927-8-69H2	PN63037	REGN14184	primary sup
29	927-8-69H3	PN63041	REGN14185	primary sup
30	927-8-69G6	PN63047	REGN14186	primary sup
31	927-8-70C12	PN63065	REGN14187	primary sup
32	927-8-71H2	PN63067	REGN14188	primary sup
33	927-8-71E3	PN63069	REGN14189	primary sup
34	927-7-71C4	PN63072	REGN14190	primary sup
35	927-7-71E12	PN63090	REGN14191	primary sup

Table 8-2. Reagents used and lot numbers

AbPID	Lot #	Common Name	Monomer MW (g/mol)
REGN6870	REGN6870-L1	p75 ^{NTR} .mmh	27000

[00253] Equilibrium dissociation constants (KD) for the interaction of anti-p75^{NTR} monoclonal antibodies with human p75^{NTR} ecto domain recombinant proteins were determined using a real-time surface plasmon resonance (SPR) based Biacore 8K biosensor. All binding studies were performed in 10 mM HEPES, 150 mM NaCl, 3 mM EDTA, and 0.05% v/v surfactant Tween-20, pH 7.4 (HBS-EP) running buffer at 25°C. The Biacore CM5 sensor surface was first derivatized by amine coupling with a monoclonal mouse anti-human Fc antibody (REGN2567) followed by a step to capture anti-p75^{NTR} monoclonal antibodies in CHO conditioned media. Human p75^{NTR} extracellular domain expressed with a C-terminal myc-myc-hexahistidine tag (hp75^{NTR}-mmh; REGN6870) at concentrations of 100 nM in HBS-EP running buffer were injected at a flow rate of 50 µL/min for 1.5 minutes. The dissociation of p75^{NTR} bound to anti-p75^{NTR} monoclonal antibodies was monitored for 2 minutes in HBS-EP running buffer. At the end of each cycle, the anti-p75^{NTR} monoclonal antibodies capture surface was regenerated using a 12-second injection of 20mM H3PO4. The association rate (ka) and dissociation rate (kd) were determined by fitting the real-time binding sensorgrams to

a 1:1 binding model with mass transport limitation using Scrubber 2.0c software. The dissociation equilibrium constant (K_D) and dissociative half-life ($t_{1/2}$) were calculated from the kinetic rate constants as:

$$K_D (M) = \frac{k_d}{k_a}, \quad \text{and} \quad t_{1/2} (\text{min}) = \frac{\ln(2)}{60 \cdot k_d}$$

[00254] The equilibrium binding constant and the kinetic binding constants are summarized in Table 8-3 for human p75^{NTR}. At 25°C, anti-p75^{NTR} monoclonal antibodies bound to p75^{NTR}-mmh with K_D values ranging from 373 pM to 82 nM, as shown in Table 8-3.

Table 8-3. Equilibrium and kinetic binding parameters for the interaction of p75^{NTR}-mmh with anti-p75^{NTR} monoclonal antibodies at 25°C.

REGN#	AbID#	CloneID#	mAb Capture Level (RU)	100nM Ag Bound (RU)	k_a (1/Ms)	k_d (1/s)	K_D (M)	$t_{1/2}$ (min)
REGN14148	PN62924	927-1-61H10	2256	136	3.26E+05	2.54E-03	7.79E-09	4.5
REGN14149	PN62928	927-2-62F2	3854	146	1.22E+05	3.88E-04	3.17E-09	30
REGN14150	PN62934	927-2-62E6	190	45	5.68E+05	4.28E-04	7.53E-10	27
REGN14151	PN62937	927-2-62E8	996	76	1.11E+05	2.52E-04	2.26E-09	46
REGN14152	PN62939	927-2-62B9	1406	309	3.14E+05	4.63E-04	1.47E-09	25
REGN14153	PN62940	927-2-62H9	1695	231	2.02E+05	1.08E-03	5.33E-09	11
REGN14154	PN62941	927-2-62B10	1195	213	2.83E+05	1.10E-03	3.91E-09	10
REGN14155	PN62945	927-2-62E11	228	52	4.45E+05	2.19E-04	4.93E-10	53
REGN14156	PN62949	927-3-63B6	666	89	3.90E+05	4.29E-03	1.10E-08	2.7
REGN14157	PN62902	927-1-61D3	1172	90	1.05E+05	1.81E-03	1.72E-08	6
REGN14158	PN62903	927-1-61F3	652	89	1.61E+05	1.22E-03	7.53E-09	9
REGN14159	PN62905	927-1-61B4	1848	190	2.15E+05	2.55E-03	1.19E-08	4.5
REGN14160	PN62906	927-1-61C4	538	73	1.60E+05	9.27E-04	5.80E-09	12
REGN14161	PN62907	927-1-61F4	759	156	4.65E+05	4.13E-03	8.89E-09	2.8
REGN14162	PN62916	927-1-61D7	39	9	4.06E+05	7.89E-04	1.95E-09	15
REGN14163	PN62918	927-1-61D8	280	51	3.72E+05	1.66E-03	4.46E-09	7
*REGN14164	PN62919	927-1-61F8	540	107	2.68E+05	≤ 1.00E-04	3.73E-10	≥ 116
REGN14165	PN62921	927-1-61H9	1078	210	3.31E+05	2.26E-03	6.84E-09	5.1
REGN14175	PN62957	927-4-64D4	38	7	3.38E+05	4.59E-03	1.36E-08	2.5
REGN14176	PN62961	927-4-64G11	245	61	4.53E+05	9.21E-04	2.03E-09	13
REGN14177	PN62969	927-4-65H6	1440	197	2.16E+05	1.10E-04	5.08E-10	105

REGN14178	PN62971	927-4-65F8	238	63	5.43E+05	1.77E-03	3.26E-09	7
REGN14179	PN62987	927-5-68D2	3229	286	1.82E+05	5.87E-04	3.23E-09	20
*REGN14180	PN63002	927-5-68A5	2172	277	2.22E+05	$\leq 1.00E-04$	4.50E-10	≥ 116
REGN14181	PN63009	927-5-68C6	1247	118	7.80E+05	4.31E-02	5.52E-08	0.27
REGN14182	PN63028	927-8-68C11	2877	223	2.64E+05	1.83E-03	6.95E-09	6
REGN14183	PN63034	927-8-69A2	3625	325	2.26E+05	3.39E-04	1.50E-09	34
REGN14184	PN63037	927-8-69H2	3891	162	4.50E+05	3.69E-02	8.20E-08	0.31
REGN14185	PN63041	927-8-69H3	3741	218	1.76E+05	1.33E-03	7.58E-09	9
REGN14186	PN63047	927-8-69G6	1297	183	3.44E+05	9.65E-03	2.81E-08	1.2
REGN14187	PN63065	927-8-70C12	488	106	3.36E+05	2.47E-04	7.36E-10	47
REGN14188	PN63067	927-8-71H2	1475	132	2.08E+05	6.78E-03	3.26E-08	1.7
REGN14189	PN63069	927-8-71E3	861	116	4.72E+05	1.55E-02	3.29E-08	0.7

* No dissociation was observed under the current experimental conditions and the k_d value was manually fixed at $1.00E-04 \text{ s}^{-1}$ while fitting the real time binding sensorgrams to determine the k_a value.

Example 6. AAV retargeting using anti-p75NTR (p75) monoclonal antibodies

Materials and Methods

Table 9. Reagents/equipment used, source, identifier (where applicable) and lot/serial number (where applicable).

Reagent / Equipment	Source	Identifier	Lot #
Microscopy			
LSM 880 Confocal	Zeiss		SN# 2802000260
LSM 900 Confocal	Zeiss		SN# 2901000127
Axio Zoom	Zeiss		
Axio observer 7FL	Zeiss		
96 well glass bottom plate	Cellvis	P96-1.5H-N	
μ -Slide 18 well glass bottom	Ibidi	81817	211201/4
μ -Slide 8 well glass bottom	Ibidi	80827	211112/5
Coverslips	VWR	16004-348	
DAPI (4',6-Diamidino-2-Phenylindole, Dilactate)	Invitrogen	D3571	2445405
PBS	Gibco	20012-043	2323501 (one example)
Paraformaldehyde 16%	Electron Microscopy Sciences	15710	220218-50
Immunohistochemistry			

Sucrose	Sigma	S9378	SLCC8491
Tissue-Tek OCT Compound	Sakura	4583	1170-00
Normal Goat Serum	Invitrogen	01-6201	VA293799
Triton X-100	Sigma	T9284	SLBZ2181
Alexa Fluor™ 647 conjugated primary mouse anti-Tubulin β 3	Biologend	801210	B367545
Aquamount	Lerner Laboratories	13800	529075

[00255] *AAV capsid protein constructs*

[00256] GeneBlocks encoding the desired SpyTag insertions, flanking linker amino acids, and additional mutations were purchased from IDT and cloned into BsiWI and XcmI-digested pAAV R2C9 wt using Gibson Assembly according to the manufacturer's protocol (NEB).

[00257] *Cloning SpyCatcher to antibodies*

[00258] GeneBlocks encoding antibody heavy were purchased from IDT and cloned into a CMV hIgG4US SapI SpyCatcher backbone using Gibson assembly. This vector contains a pair of SapI sites pointing in opposite directions that cleave at the end of the mROR1 signal sequence and at the beginning of hIgG4. Gene blocks were ordered encoding anti-p75^{NTR} Vh sequences of interest that contain overlaps with the 3' end of mROR1 signal sequence and the 5' end of hIgG4US so that the sequences could be inserted via Gibson Assembly.

[00259] *Preparation of AAV viral vectors*

[00260] Virus was generated by transfecting HEK293T packaging cells using PEI Pro with the following plasmids: pAd Helper, an AAV9 ITR-containing genome plasmid encoding eGFP under the control of a Cbh promoter, and a pAAV-CAP plasmid encoding AAV *Rep* and *Cap* genes, either with or without additional plasmids encoding either the heavy and light chains of an antibody. The antibody heavy chain constructs are all fused to SpyCatcher at their C terminus as described in WO2019006046, incorporated herein in its

entirety by reference. Transfection complexes were prepared in incomplete DMEM (no additional supplements) and incubated at room temperature for 10 minutes.

[00261] Each virus was generated by transfecting 15cm plates of HEK293T packaging cells with the following plasmids and quantities:

WT AAV9/Detargeted AAV9 W503A, delivering eGFP as packaged genome

pAd Helper	16 ug
pscAAV-CBh-eGFP	8 ug
pAAV9-CAP wt or pAAV9 N272A or pAAV9 W503A	8 ug

Retargeted AAV9 W503A-Spytag with SpyCatcher-Anti-p75^{NTR} mAb, delivering eGFP as packaged genome

pAd Helper	16 ug
pscAAV-CBh-eGFP	8 ug
pAAV9 CAP G453 Linker 10 SpyTag W503A	1 ug
pAAV9-CAP W503A	7 ug
Heavy chain plasmid with C-terminal SpyCatcher	1.5 ug
Light chain plasmid	3 ug

Retargeted AAV9 W503A-Spytag with SpyCatcher Anti- Betv1 17067P2 mAb, delivering eGFP as packaged genome

pAd Helper	16 ug
pscAAV-CBh-eGFP	8 ug
pAAV9 CAP G453 Linker 10 SpyTag W503A	1 ug
pAAV9-CAP W503A	7 ug
Heavy chain plasmid with C terminal SpyCatcher	1.5 ug
Light chain plasmid	3 ug

[00262] Post incubation, complexes are added to DMEM supplemented with 10% FBS, 1X NEAA, 1% Pen/Strep, and 1% L-Glutamine.

[00263] Transfected packaging cells were incubated for 3 days at 37°C, then virus was collected from cell lysates using a standard freeze-thaw protocol. In brief, packaging cells were lifted by scraping and pelleted. Supernatant was removed, and cells were resuspended in a solution of 50mM Tris-HCl; 150mM NaCl; and 2 mM MgCl₂ [pH 8.0]. Intracellular virus particles were released by inducing cell lysis via three consecutive freeze-thaw cycles, consisting of shuttling cell suspension between dry ice/ethanol bath and 37°C water bath with vigorous vortexing. Viscosity was reduced by treating lysate with EMD Millipore Benzonase (50 U/ml of cell lysate) for 60 min at 37°C, with occasional mixing. Debris was then pelleted by centrifugation, and the resulting supernatant was filtered through a 0.22 µm PVDF Millex-GV Filter. For crude virus to be tested *in vitro*, the filtered lysate is added directly to an Amicon Ultra-15 Centrifugal Filter Unit with Ultracel-100 membrane (100 KDa MWCO) filter cartridge. The filter unit was centrifuged at 5–10-minute intervals until desired volume was reached in the upper chamber, then concentrated crude virus was pipetted into a low-protein-binding tube and stored at 4 °C. For virus to be tested *in vivo*, the clarified lysate is further purified using a four step iodixanol density gradient. Gradients are loaded into a Beckman 70Ti rotor and spun at 66,100 rpm for 1.5 h at 10C using max acceleration and deceleration. After ultracentrifugation, iodixanol purified virions are extracted from the 40-60% interface. AAVs in iodixanol solution are diluted in DPBS+/+ .001% pluronic F68 so that the iodixanol concentration is less than 1%. Purified virus is then concentrated to desired volume using a 100kDa MWCO Amicon ultrafiltration unit.

[00264] Titer (viral genomes per milliliter; vg/mL) was determined by qPCR using a standard curve of a virus of known concentration.

[00265] *Cells*

[00266] NIH3T3 cell lines were maintained in DMEM supplemented with 10% BCS, 1% Pen/Strep, and 1% L-glutamine. NIH3T3, 3T3/SRE-luc/hTrkA cl.C2, 3T3/mP75, 3T3/SRE-luc/mf P75, and 3T3/SRE-luc/hTrkA cl.C2/hP75 cell lines were generated by lentiviral transduction of the parental NIH 3T3 cell line with a vector expressing the corresponding cDNA. All cell lines were obtained from the Regeneron TC core facility.

[00267] *Cell Infection/Transduction and Flow Cytometric Analysis*

[00268] To infect cells, viral particles were added directly to the media of cells in culture, and the mixture was incubated at 37°C. Three days post-infection, cells were trypsinized, resuspended in PBS with 2% FBS, and the percentage of GFP+ cells was collected on a Biorad ZE5 flow cytometer and analyzed using FlowJo software.

[00269] *Mouse Model*

[00270] Wildtype C57Bl/6J mice were purchased from the Jackson Laboratory.

[00271] *In vivo analysis of AAV9 GFP vectors*

[00272] For intravenous AAV delivery, adult (3-7 months old) wildtype male and female C57BL/6 mice were tail vein injected with 2.5E+10, 1E+11, or 4E+11 vg/mouse of either WT AAV9, detargeted AAV9 W503A, or detargeted AAV9 W503A conjugated to antibodies targeting p75^{NTR} (REGN14152, REGN14155, REGN14177, REGN14187, REGN19516, REGN19517, REGN19515, REGN19514, and REGN19513). Mice were sacrificed 3 weeks post injection, and the following organs were harvested for confocal imaging and immunohistochemistry: liver, brain, heart, kidney, eye, colon, sciatic nerve, spinal column, dorsal root ganglia (DRG), and trigeminal ganglion. DRG and trigeminal ganglion were fixed in 4% Paraformaldehyde for 2 hours, while larger organs were fixed overnight. After fixation, tissues were washed and stored in PBS at 4°C. Prior to imaging, tissues were transferred into PBS + 1 µg/ml DAPI or, for whole mount confocal imaging, in PBS. DRG and TG were imaged on a Zeiss LSM880 at 10x with optical slices 10 µm apart. Brain and visceral organs were imaged on a Zeiss LSM900 at 5x and 10x.

[00273] For focal, subcutaneous injections, mice were briefly anesthetized with 2-3% isoflurane and injected with 2.5E+10, 5E+10, or 1E+11 in 5-20 µl unilaterally either in the whisker pad or synovial fluid in the knee. After 3 weeks, DRG and trigeminal ganglion were collected and fixed in 4% Paraformaldehyde for 2 hours, while larger organs were fixed overnight. After fixation, tissues were washed and stored in PBS at 4°C. Prior to imaging, tissue were transferred into PBS + 1 µg/ml DAPI or, for whole mount confocal imaging, in PBS. DRG and TG were imaged on a Zeiss LSM900 at 10x with optical slices 10 µm apart. Brain and visceral organs were imaged on a Zeiss LSM900 at 5x and 10x.

[00274] For quantitative analysis of whole DRG, maximum projection images of Z stacks were taken of the whole DRG, with images being taken every 10 μm . A region of interest was drawn around the whole DRG and a threshold was set to identify GFP positive pixels. The area that the GFP positive pixels occupied in the DRG was measured, as well as their mean fluorescent signal intensity.

[00275] To measure GFP fluorescence intensity in the liver, confocal images were acquired on a LSM900 with a 5x objective. The mean fluorescent intensity of the whole image in the GFP channel was measured.

[00276] To identify DRG neurons and measure GFP intensity in individual neurons, DRG were cryoprotected in 30% sucrose and cryosectioned. Immunohistochemistry was performed on slices with an anti-beta tubulin 3 (TUBB3) to identify neurons. Sections were blocked and permeabilized with 0.1% Triton X-100 and 10% Normal Goat Serum, then labeled with 1:500 anti-TUBB3 in 5% Normal Goat Serum. Images were taken on a Zeiss Axio Observed 7F with a 20X objective. A threshold was applied to the TUBB3 channel of acquired images and a particle analysis algorithm was used in ImageJ to outline individual neurons. The GFP fluorescence intensity was measured per cell in the green channel using the single cell masks.

[00277] For immunohistochemistry staining of GFP on Paraffin embedded sections, whole spinal cords were fixed in 10% neutral buffered formalin solution, and then transferred to 70% ethanol 40 hours later. Spinal cord sections were decalcified in EDTA for 2-3 days and then paraffin embedded. Organs were stored in 70% ethanol at room temperature for ~2 weeks prior to paraffin embedding. Tissues were sectioned using standardized plane sectioning at 4 μm thickness.

[00278] Slices underwent standardized CC1 antigen retrieval (56 minutes) and were then treated with an antibody to eGFP (Abcam, AB13970) at a concentration of 4 $\mu\text{g}/\text{mL}$ for 5 hours. Following secondary antibody incubation, eGFP was detected with the Discovery Dab Map detection kit. Immunohistochemistry was performed on the Ventana Discovery Ultra platform. After staining, slides were imaged on an Aperio slide scanner at 40x magnification.

[00279] Liver sections underwent standardized ER2 antigen retrieval (30 minutes) and were then treated with an antibody to eGFP (Abcam, AB183734) at a concentration of 2.34 $\mu\text{g}/\text{mL}$ for 1 hour. Following secondary antibody incubation, eGFP was detected with the

Refine Dab Detection kit. Immunohistochemistry was performed on the Leica Bond RX platform. After staining, slides were imaged on an Aperio slide scanner at 40x magnification.

Results

Anti-p75^{NTR} SpyTag-SpyCatcher conjugation to AAV9 enhances GFP expression in p75^{NTR}-expressing cell lines.

[00280] To determine whether AAV9 particles could be retargeted to p75^{NTR}-expressing cells, WT AAV9 particles, detargeted AAV9 W503A particles, detargeted AAV9 W503A SpyTag particles conjugated to an antibody targeting Betv1 (as an isotype control), or detargeted AAV9 W503A SpyTag particles conjugated to different antibodies targeting p75^{NTR}, were administered to wild type NIH 3T3 cells or NIH 3T3 cells expressing an alternative neurotrophin receptor, TrkA, as controls, or NIH 3T3 cells expressing mouse, cynomolgus, or human p75^{NTR} and expression of eGFP delivered by the AAV was measured. As shown in **Figures 1A and 1B**, anti-p75^{NTR} SpyTag-SpyCatcher conjugation to AAV9 enhances GFP expression in p75^{NTR}-expressing cell lines.

[00281] *Anti-p75^{NTR} SpyTag-SpyCatcher conjugation to AAV9 enhances GFP expression in DRG neurons.*

[00282] To determine whether AAV9 particles could be retargeted to p75^{NTR}-expressing dorsal root ganglia, 4E+11 vg/mouse of WT AAV9, detargeted AAV9 W503A, and detargeted AAV9 W503A conjugated to antibodies targeting p75^{NTR} were administered to wild type C57BL/6J mice and GFP expression was measured in cervical, thoracic and lumbar segments. As shown in **Figure 2**, GFP expression in DRG driven by detargeted AAV9 W503A conjugated to an example antibody targeting p75^{NTR} (bottom) is brighter than wildtype AAV9 (top) or de-targeted AAV9 W503A (middle). Moreover, as shown in **Figure 3**, detargeted AAV9 W503A is expressed in a smaller area of the DRG compared to WT AAV9, but the percent area of the DRG expressing GFP is increased when detargeted AAV9 W503A is conjugated to antibodies targeting p75^{NTR}. Finally, as shown in **Figure 3**, mean pixel value of GFP fluorescence is higher in DRG harvested from detargeted AAV9 W503A conjugated to antibodies targeting p75^{NTR} when compared to detargeted AAV9 W503A alone or WT AAV9. Accordingly, **Figures 2 and 3** demonstrate that anti-p75^{NTR}

SpyTag-SpyCatcher conjugation to AAV9 enhances mean GFP fluorescence in DRG neurons.

[00283] *Liver-detargeted mutations reduce AAV-driven GFP expression in liver.*

[00284] To determine whether retargeting AAV9 particles could reduce infection of liver cells, for which AAV9 exhibits natural tropism, $4\text{E}+11$ vg/mouse of WT AAV9, detargeted AAV9 W503A, and detargeted AAV9 W503A conjugated to an example antibody targeting p75^{NTR} were administered to wild type C57BL/6J mice and GFP expression was measured in whole liver by confocal imaging. As demonstrated in **Figure 4**, GFP expression in the liver following injection of $4\text{E}+11$ vg detargeted AAV9 W503A (regardless of whether or not the AAV is conjugated to an anti-p75^{NTR} antibody) is significantly lower than expression following injection with WT AAV9. Accordingly, **Figure 4** shows that liver-detargeted mutations reduce AAV-driven GFP expression in liver.

[00285] *AAV-driven GFP expression in DRG is dose dependent for intravenous administration of AAV9 W503A conjugated to anti-p75^{NTR}.*

[00286] To evaluate the effects of AAV9 p75^{NTR} retargeting at various doses of AAV, $2.5\text{E}+10$ vg, $1\text{E}+11$ vg, or $4\text{E}+11$ vg of WT AAV9, detargeted AAV9 W503A, or detargeted AAV9 W503A conjugated to an example antibody targeting p75^{NTR} was administered to wild type C57BL/6J mice and GFP expression in lumbar DRG at L1 and L4 was assessed. At the lowest AAV dose tested, $2.5\text{E}+10$ vg injected intravenously, WT AAV9 (**Figure 5, panel A**) and detargeted AAV9 W503A (**Figure 5, panel D**) exhibit low transduction in DRG, while detargeted AAV9 W503A conjugated to an example antibody targeting p75^{NTR} (**Figure 5, panel G**) shows higher transduction in DRG. Similar observations are made at higher doses of AAV injected: 3 weeks following a $1\text{E}+11$ vg injection, many neurons are seen to express GFP in DRG when WT AAV9 (**Figure 5, panel B**) is injected. $1\text{E}+11$ vg injection of detargeted AAV9 W503A (**Figure 5, panel E**) shows lower GFP expression in DRG relative to WT AAV9 (**Figure 5, panel B**), while injections of detargeted AAV9 W503A conjugated to an example antibody targeting p75^{NTR} (**Figure 5, panel H**) shows higher transduction than the 2 other conditions. $4\text{E}+11$ vg injection of detargeted AAV9 W503A (**Figure 5, panel F**) shows lower GFP expression in DRG relative to WT AAV9 (**Figure 5, panel C**), while

injections of detargeted AAV9 W503A conjugated to antibodies targeting p75^{NTR} (**Figure 5, panel I**) shows higher transduction than the 2 other conditions. Accordingly, **Figure 5** shows that increased transduction of DRG neurons with detargeted AAV W503A conjugated to antibodies targeting p75^{NTR} allows for lower doses of AAV administered.

[00287] As further quantified in **Figure 6**, increasing doses of AAV injected intravenously enhanced the mean GFP expression per DRG cell. At all three doses of AAV tested, DRG neurons from mice injected with detargeted AAV9 W503A conjugated to an example antibody targeting p75^{NTR} had higher levels of GFP expression than WT AAV9 or detargeted AAV9 W503A.

[00288] *Detargeting and retargeting of AAV9 W503A conjugated to anti-p75^{NTR}.*

[00289] To further confirm that AAV9 W503A conjugated to anti-p75^{NTR} is retargeted to nervous system tissues and detargeted from tissues for which AAV9 exhibits natural tropism, immunohistochemistry (IHC) staining for eGFP expression was performed on spinal cord, DRG, liver, heart, and kidney sections of WT C57BL/6J mice following injection of 4E+11 vg/mouse of wildtype AAV9, detargeted AAV9 W503A or detargeted AAV9 W503A conjugated to an example antibody targeting p75^{NTR}. As shown in **Figure 7A**, compared to mice injected with WT AAV9 or detargeted AAV9 W503A, spinal cord and DRG sections from mice injected with detargeted AAV9 W503A particles conjugated to an example antibody that targets p75^{NTR} show enhanced GFP expression in the DRG, dorsal root axons traveling into the spinal cord, and axon terminal in the dorsal horn of the spinal cord. Spinal cords from mice injected with WT AAV9 show transduction within the gray matter of the spinal cord, while detargeted AAV9 W503A and detargeted AAV9 W503A conjugated to an example antibody targeting p75^{NTR} show reduced transduction of cells in the spinal cord. As shown in **Figure 7B**, compared to mice injected with WT AAV9 or detargeted AAV9 W503A, DRG sections from mice injected with detargeted AAV9 W503A particles conjugated to an example antibody targeting p75^{NTR} show enhanced GFP expression in the DRG neurons. As shown in **Figure 7C**, WT AAV9 can transduce liver effectively and the amount of GFP expression, as detected by IHC, is higher with WT AAV9 injection compared to detargeted AAV9 W503A alone or detargeted AAV9 W503A conjugated to an example antibody that binds to p75^{NTR}. Similar to liver, detargeting mutations on AAV9 reduce GFP

expression in heart and kidney when the AAV is injected intravenously, regardless of the presence or absence of an anti-p75^{NTR} antibody on the viral particle.

[00290] *Delivery of AAV9 W503A conjugated to anti-p75^{NTR} via focal injection.*

[00291] To assess the delivery of detargeted AAV9 W503A conjugated to an example antibody targeting p75^{NTR} following subcutaneous administration, 2.5E+10 vg of WT AAV9, detargeted AAV9 W503A, or detargeted AAV9 W503A conjugated to an example antibody targeting p75^{NTR} was injected subcutaneously into the whisker pad of WT C57BL/6J mice. As shown in **Figure 8, panel A**, when WT AAV9 or detargeted AAV9 W503A are injected into the whisker pad on one side of the animal, there is low transduction observed in trigeminal ganglion both ipsilateral and contralateral to the injection site, indicating low systemic delivery of AAV following subcutaneous injection. In contrast, three weeks following subcutaneous injection of 2.5E+10 vg of detargeted AAV9 W503A conjugated to an example antibody targeting p75^{NTR} into one whisker pad, GFP transduction is observed in the trigeminal ganglion ipsilateral to the injection site, suggesting that the AAV is delivered via retrograde transport from the injection site along trigeminal axons. As shown in **Figure 8, panel B**, DRG harvested from mice three weeks following subcutaneous injection in one whisker pad have little to no GFP expression. A few cells are seen to have GFP expression in mice injected with detargeted AAV9 W503A conjugated to an antibody that binds to p75^{NTR}. As shown in **Figure 8, panel C**, no GFP fluorescence is observed in kidney following injection of 2.5E+10 VG into whisker pad. Finally, as shown in **Figure 8, panels D and E**, GFP expression is observed in the liver (**Figure 8, panel D**) and colon (**Figure 8, panel E**) following subcutaneous injection of WT AAV9 but not detargeted AAV9 W503A, with or without an example antibody targeting p75^{NTR} conjugated to the AAV. Accordingly, **Figure 8** demonstrates that detargeted AAV9 W503A conjugated to an example antibody targeting p75^{NTR} is able to specifically target trigeminal ganglia on the same side of the body as the whisker pad into which the AAV is injected, with no observable off-target infection other cells.

[00292] To assess the delivery of detargeted AAV9 W503A conjugated to an example antibody targeting p75^{NTR} following intra-synovial administration, 5E+10 vg of WT AAV9, detargeted AAV9 W503A, or detargeted AAV9 W503A particles conjugated to any example

antibody targeting p75^{NTR} was injected intra-synovially into C57BL/6J mouse knee. As shown in **Figure 9**, compared to mice injected with WT AAV9 or detargeted AAV9 W503A, whole DRG from mice injected with detargeted AAV9 W503A particles conjugated to any example antibody targeting p75^{NTR} show enhanced GFP expression in the DRG and trigeminal ganglion. GFP expression in L3 and L5 DRGs ipsilateral to the injection site, which contain DRG neurons that innervate the injected knee, exhibit higher GFP expression than distal cervical DRGs or L3 and L5 DRG on the contralateral side to the injection site which do not innervate the injection site, suggesting that AAV is delivered to DRG neurons via retrograde transport from the injection site along DRG axons. Accordingly, **Figure 9** demonstrates that detargeted AAV9 W503A conjugated to an example antibody targeting p75^{NTR} is able to specifically target DRG and trigeminal ganglion on the same side of the body as the knee into which the AAV is injected, while WT AAV9 or detargeted AAV9 W503A without a conjugated anti-p75^{NTR} antibody exhibit no observable infection in the same cells.

[00293] To compare focal versus systemic administration, 5E+10 vg of WT AAV9, detargeted AAV9 W503A, and detargeted AAV9 W503A conjugated to an example antibody targeting p75^{NTR} was injected into the synovial space in the knee, and varying doses of the same were administered systemically via tail vein intravenous injection. As shown in **Figure 10, panel A**, following injection of WT AAV9 or detargeted AAV9 W503A in the knee, there is a minimal amount of GFP expression in DRG, whether ipsilateral or contralateral to the injection site or in distal DRG (cervical, thoracic or L1 DRG). Injection of detargeted AAV9 W503A conjugated to an example antibody targeting p75^{NTR} in the knee increases the GFP expression in DRG innervating the knee (L2-L5) in the ipsilateral side to injection, with lower GFP transduction observed in distal cervical, thoracic and L1 DRG and L2-L5 on the side contralateral to the injected knee. Higher transduction in DRGs that innervate the injected knee suggests that AAV is delivered to DRG neurons via retrograde transport from the injection site along DRG axons. As shown in **Figure 10, panel B**, the percent area of the DRG that expresses GFP is dose dependent when AAV is administered intravenously. Anti-p75^{NTR} conjugated to detargeted AAV W503A enhances GFP expression in DRG at every dose tested as compared to WT AAV9 and detargeted AAV9 W503A levels. Comparison of transduced GFP area in the DRG following local knee injection of 5E+10 viral genomes of

AAV to transduced GFP area in the DRG following intravenous delivery of AAV shows that GFP expression in the DRGs innervating the injected knee is similar to GFP expression in DRGs of the same level and location following intravenous injection of 4E+11 viral genomes of detargeted AAV9 W503A conjugated to an example antibody targeting p75^{NTR}. Thus, **Figure 10** demonstrates that similar transduction levels in DRG can be achieved with lower AAV doses following focal injections (as compared to systemic injections) in a manner dependent on anti-p75^{NTR} conjugated to detargeted AAV W503A.

[00294] *Silencing Nav1.7 for chronic pain reduction.*

[00295] Expression of Nav1.7 in DRG and trigeminal ganglia is associated with chronic pain. Accordingly, there is need in the art for the compositions and methods of use thereof to specifically reduce Nav1.7 expression in DRG and trigeminal ganglia.

[00296] To demonstrate the reduction of expression of Nav1.7 *in vitro*, an AAV9 particle comprising (a) anti-p75^{NTR} conjugated to detargeted AAV W503A encapsulating (b) a nucleotide encoding one or more Nav1.7 silencing molecule (*e.g.*, an RNAi molecule, such as shRNA targeting Nav1.7 mRNA for degradation, and/or gRNA, targeting Nav1.7 for silencing via CRISPR/Cas9) is administered to a cell expressing Nav1.7 and p75^{NTR} (*e.g.*, endogenously, exogenously via a transgene, *etc.*). Genomic modifications of a Nav1.7 locus, mRNA levels of Nav1.7 and/or protein levels of Nav1.7 in the cells is assessed using any methods known in the art.

[00297] To reduce the expression Nav1.7 *in vivo*, an AAV9 particle comprising (a) anti-p75^{NTR} conjugated to detargeted AAV9 W503A encapsulating (b) a nucleotide encoding one or more Nav1.7 silencing molecule (*e.g.*, an RNAi molecule, such as shRNA targeting Nav1.7 mRNA for degradation, and/or gRNA, targeting Nav1.7 for silencing via CRISPR/Cas9) is injected focally, *e.g.*, subcutaneously, intra-synovially, *etc.*, or systemically, *e.g.*, intravenously, into an animal expressing Nav1.7 and p75^{NTR}. Genomic modifications of a Nav1.7 locus, mRNA levels of Nav1.7 and/or protein levels of Nav1.7 in cells of the animal, *e.g.*, DRG, trigeminal ganglia, *etc.*, is assessed using any methods known in the art. The animals may be transgenic animals expressing human Nav1.7 and/or p75^{NTR}. The animals may be further modified in a manner that models chronic pain associated with

Nav1.7 in humans. Any methods known in the art to assess pain in animals may be used to evaluate the model.

Example 7. Delivery of p75^{NTR}-retargeted AAV9 encapsulating a nucleic acid molecule encoding Nav1.7 gRNA reduces mechanical pain in mice expressing Cas9

Materials and Methods

[00298] Eight- to ten-week-old mice genetically modified to express Cas9 were injected into the masseter muscle, on the left side of the face, with detargeted AAV9 W503A conjugated to an example antibody targeting p75^{NTR} and encapsulating a nucleic acid molecule expressing guide RNAs targeting either mouse Nav1.7 (7.48×10^9 vg, n=8; experimental group) or mouse TTR (1.44×10^{12} vg, n=7; control group). Three weeks following AAV injections, the mice received a 20 μ l injection of Complete Freud's Adjuvant (CFA) in the masseter muscle, in the same location, to induce inflammatory pain. Mechanical pain hypersensitivity was measured using the well documented Von Frey test. In brief, mice are put into small individual boxes and a series of Von Frey hairs are applied to the facial area corresponding to the inflamed masseter muscle to determine mechanosensitivity thresholds. Measurements of mechanical thresholds were taken three weeks post-AAV injection, 2 days post-CFA injection (when the mechanical pain is at its peak) and 15 days post-CFA (when the mechanical pain has resolved).

Results

[00299] Two days post-CFA administration, the mice that had been administered the p75^{NTR}-retargeted AAV encapsulating the nucleic acid molecule expressing Nav1.7 gRNAs had significantly higher mechanical thresholds than mice treated with the p75^{NTR}-retargeted AAV encapsulating a nucleic acid molecule expressing TTR gRNAs (**Figure 11**). Fifteen days post-CFA administration, mechanical thresholds were back to pre-CFA treatment levels with no significant difference between the two groups (**Figure 11**). Lower mechanical sensitivity following CFA injection in mice treated with Nav1.7 gRNAs than in mice treated with TTR gRNAs (**Figure 11**) confirms the therapeutic delivery to the sensory neurons underlying the CFA-induced mechanical pain. Accordingly, it is demonstrated that delivery

to the masseter muscle of detargeted AAV9 W503A conjugated to a representative antibody targeting p75^{NTR} and encapsulating a nucleic acid molecule expressing guide RNAs targeting mouse Nav1.7 significantly reduces CFA-induced mechanical allodynia.

Example 8. Cell based assay testing regulation of TrkA signaling with NGF.

Table 10-1. mAb Clone IDs

REGN #	Clone ID	Ab PID
REGN14160	927-1-61C4	PN62906
REGN14149	927-2-62F2	PN62928
REGN14152	927-2-62B9	PN62939
REGN14158	927-1-61F3	PN62903
REGN14155	927-2-62E11	PN62945
REGN14157	927-1-61D3	PN62902
REGN14159	927-1-61B4	PN62905
REGN14161	927-1-61F4	PN62907
REGN14163	927-1-61D8	PN62918
REGN14164	927-1-61F8	PN62919
REGN14165	927-1-61H9	PN62921
REGN14148	927-1-61H10	PN62924
REGN14162	927-1-61D7	PN62916
REGN14150	927-2-62E6	PN62934
REGN14151	927-2-62E8	PN62937
REGN14177	927-4-65H6	PN62969
REGN14153	927-2-62H9	PN62940
REGN14154	927-2-62B10	PN62941
REGN14187	927-8-70C12	PN63065
REGN14156	927-3-63B6	PN62949
REGN14175	927-4-64D4	PN62957
REGN14176	927-4-64G11	PN62961
REGN14178	927-4-65F8	PN62971

REGN14179	927-5-68D2	PN62987
REGN14180	927-5-68A5	PN63002
REGN14181	927-5-68C6	PN63009
REGN14182	927-8-68C11	PN63028
REGN14183	927-8-69A2	PN63034
REGN14184	927-8-69H2	PN63037
REGN14185	927-8-69H3	PN63041
REGN14186	927-8-69G6	PN63047
REGN14188	927-8-71H2	PN63067
REGN14189	927-8-71E3	PN63069
REGN14190	927-7-71C4	PN63072
REGN14191	927-7-71E12	PN63090
REGN19514	927-1-61H4	PN62909
REGN19513	927-4-65A5	PN62965
REGN19515	927-7-71F5	PN63075
REGN19516	927-9-72A4	PN63091
REGN19517	927-9-72C7	PN63092

Table 10-2. Reagents used

Reagent	Source	Identification
3T3/SRE-luc/hTrkA cl.C2	Regeneron	Benchling ACL17401
3T3/SRE-luc/hTrkA/cl.C2/hp75 ^{NTR}	Regeneron	Benchling ACL17435
3T3/hp75 ^{NTR} /SRE-luc cl.4B5	Regeneron	Benchling ACL17229
Opti-MEM Reduced Serum Media	ThermoFisher Scientific	31985070
RPMI 1640	Gibco	11875119
Fetal Bovine Serum	Seradigm	1500-500

Penicillin-Streptomycin-Glutamine (100X)	ThermoFisher Scientific	10378016
ONE-Glo Luciferase Assay System	Promega	E6130
Nunc 96-Well Polypropylene Storage Microplates (for dilutions)	ThermoFisher Scientific	249946
Nunc F96 MicroWell Polystyrene Plate, cell culture, white	ThermoFisher Scientific	136102
Universal Lids	VWR	29444-106
Envision Plate Reader	Perkin Elmer	Model 2104, serial #1040546
NGF	Regeneron	REGN205, lot #951130
p75 ^{NTR} -mFc	Regeneron	REGN6869, lot # REGN6869-L1
IgG Control antibody	Regeneron	REGN2390, Lot # REGN2390-L4

[00300] p75^{NTR} (also known as p75, NGFR, or CD271) is a single pass, transmembrane receptor and a member of the tumor necrosis factor receptor (TNFR) superfamily that can bind neurotrophins. One of its functional roles may be to enhance signaling of neurotrophins via the tropomyosin receptor kinase (Trk) family of receptors (Conroy and Coulson, 2022, PMID: 35051416). Upon ligand binding, Trk receptors initiate signaling pathways, including the mitogen-activated protein kinase (MAPK) cascade.

[00301] In order to assess the effects of anti-human p75^{NTR} antibodies, bioassays were established in NIH/3T3 cells (mouse fibroblast cells, ATCC) that stably expressed the serum response element fused to firefly luciferase reporter (SRE-luc, which measures MAPK signaling pathway activation, SA Biosciences CLS-010L), along with full-length human TrkA (amino acids 1-790 of UniProt accession number P04629-2) (SEQ ID NO: 647). The cell line was single cell cloned and named 3T3/SRE-luc/hTrkA cl. C2. 3T3/SRE-luc/hTrkA cl.C2 cells were further engineered to stably express full-length human p75^{NTR} NCBI

accession number NP_002498.1 (amino acids 1-427 of UniProt accession number P08138) (SEQ ID NO: 619) and the resulting cell line was named 3T3/SRE-luc/hTrkA cl.C2/hp75^{NTR}.

[00302] Cell based assay testing regulation of NGF-dependent TrkA signaling by the extracellular domain of p75^{NTR} in the presence of various anti-p75^{NTR} antibodies.

[00303] 3T3/SRE-luc/hTrkA cl.C2 cells were plated at 20,000 cells per well in assay media (Opti-MEM media containing 0.1% fetal bovine serum and 1X Penicillin-Streptomycin-Glutamine) and incubated overnight at 37°C in 5% CO₂. The following day, supernatants containing the antibodies of the invention (subclass hIgG1) or 100 nM of irrelevant IgG control antibody, REGN2390, were preincubated at room temperature for 30 minutes with 5 nM of the extracellular region of human p75^{NTR} (amino acids 1-250 of NCBI accession number NP_002498.1) (SEQ ID NO: 642) fused to the Fc domain of mouse IgG2a (amino acids 98-330 of UniProt accession number P01863) (SEQ ID NO: 643), referred to hereafter as hp75^{NTR}-mFc or REGN6869 (SEQ ID NO: 641). This was followed by an additional 30 minute incubation with 200 pM mature human neuronal growth factor (NGF) β (hNGFβ) (amino acids 122-241 of UniProt accession number P01138) (SEQ ID NO: 648), referred to hereinafter as NGF or REGN205, before adding to cells. To measure the extent of TrkA activation in the absence of soluble p75^{NTR}-mFc, 200 pM of NGF with 100 nM of irrelevant Fc fusion protein, REGN1666 (SEQ ID NO: 649), was added to the cells. After a 5 hour incubation at 37°C in 5% CO₂, luciferase activity was evaluated by the addition of OneGlo™ luciferase assay system reagent (Promega, cat. #E6130) and Relative Luminescence Units (RLU) were measured using an Envision Plate reader (Perkin Elmer). Results were analyzed using the following equation:

$$\% \text{ Inhibition} = 100 \times \frac{\text{RLU}_{\text{mAb}} - \text{RLU}_{\text{soluble p75}}}{\text{RLU}_{\text{NGF}} - \text{RLU}_{\text{soluble p75}}}$$

[00304] In this equation, “RLU_{mAb}” refers to RLU value from cells treated with supernatants containing antibodies of the invention, 5 nM p75^{NTR}-mFc and 200 pM NGF. “RLU_{soluble p75}” refers to the RLU value from cells treated with 100nM irrelevant antibody, 5 nM p75^{NTR}-mFc and 200pM NGF and is defined as 0% inhibition. “RLU_{NGF}” refers to the

RLU value from cells treated with 100 nM REGN1666 and 200 pM NGF and is defined as 100% inhibition.

[00305] Cell based assay testing the effects of anti-p75^{NTR} antibodies on NGF-dependent TrkA signaling when co-expressed with p75^{NTR}.

[00306] For the assay, 3T3/SRE-luc/hTrkA cl.C2 and 3T3/SRE-luc/hTrkA cl.C2/hp75^{NTR} cells were plated at 20,000 cells per well in assay media and incubated overnight at 37°C in 5% CO₂. The following day, supernatants containing representative anti-p75^{NTR} antibodies (subclass hIgG1) or control antibody, 40 nM REGN2390, were preincubated with 3T3/SRE-luc/hTrkA cl.C2 or 3T3/SRE-luc cl.C2/hp75^{NTR} cells for 30 minutes at 37°C in 5% CO₂ before the addition of 200 pM NGF (REGN205). To measure the extent of TrkA activation in the presence or absence of co-expressed p75^{NTR}, the following conditions were included: no NGF, 200 pM and 50 nM NGF. After a 5 hour incubation at 37°C in 5% CO₂, luciferase activity was evaluated by the addition of OneGlo™ luciferase assay system reagent (Promega, cat. #E6130) and RLUs were measured using an Envision Plate reader (Perkin Elmer). Results were analyzed using the following equations to calculate inhibition by anti-p75^{NTR} antibodies:

$$\% \text{ Activation } [\eta] = 100 \times \frac{\text{RLU}_{\eta} - \text{RLU}_{\text{NGF min}}}{\text{RLU}_{\text{NGF max}} - \text{RLU}_{\text{NGF min}}}$$

$$\% \text{ Inhibition} = 100 \times \frac{\% \text{ Activation } [200\text{pM NGF}]_{\text{p75\&TrkA}} - \% \text{ Activation } [\text{mAb}]_{\text{p75\&TrkA}}}{\% \text{ Activation } [200\text{pM NGF}]_{\text{p75\&TrkA}} - \% \text{ Activation } [\text{mAb}]_{\text{TrkA}}}$$

[00307] “RLU_η” refers to RLU values for conditions containing 200 pM NGF alone, or antibody with 200 pM NGF (mAb). “RLU_{NGF min}” and “RLU_{NGF max}” refer to the minimum and maximum RLU values from cells alone without NGF and with 50 nM NGF, respectively. “p75&TrkA” and “TrkA” refer to cells co-expressing two receptors or TrkA alone.

[00308] As shown in Table 10-3, 40 representative anti-p75^{NTR} antibodies as disclosed herein were each incubated with the soluble, extracellular domain of p75^{NTR}, p75^{NTR}-mFc, to examine effects on NGF dependent activation of TrkA signaling in 3T3/SRE-luc/hTrkA cl.C2 cells; blocking of p75^{NTR} inhibition of TrkA signaling ranged from 2.76% to 112.50%.

[00309] As shown in Table 10-4, 40 representative anti-p75^{NTR} antibodies as disclosed herein were tested for their effects on inhibiting the enhancement of NGF-dependent TrkA signaling when TrkA was co-expressed with p75^{NTR} in 3T3/SRE-luc/hTrkA cl.C2/hp75NTR cells. Antibodies showed inhibition of TrkA signaling ranging from -61.42% to 189.33%. Irrelevant control antibody, REGN2390, showed -13.53% inhibition.

Table 10-3. Effects of anti-p75NTR antibodies on the inhibition of NGF-dependent TrkA signaling by the extracellular domain of p75NTR in 3T3/SRE-luc/hTrkA cl.C2 cells

Antibody	clone ID	PID	% Inhibition
REGN14160	927-1-61C4	PN62906	85.49
REGN14149	927-2-62F2	PN62928	95.42
REGN14152	927-2-62B9	PN62939	100.51
REGN14158	927-1-61F3	PN62903	85.95
REGN14155	927-2-62E11	PN62945	68.11
REGN14157	927-1-61D3	PN62902	88.32
REGN14159	927-1-61B4	PN62905	101.31
REGN14161	927-1-61F4	PN62907	89.49
REGN14163	927-1-61D8	PN62918	83.47
REGN14164	927-1-61F8	PN62919	87.26
REGN14165	927-1-61H9	PN62921	102.30
REGN14148	927-1-61H10	PN62924	74.17
REGN14162	927-1-61D7	PN62916	91.35
REGN14150	927-2-62E6	PN62934	92.44
REGN14151	927-2-62E8	PN62937	87.01
REGN14177	927-4-65H6	PN62969	103.00
REGN14153	927-2-62H9	PN62940	81.86
REGN14154	927-2-62B10	PN62941	84.09
REGN14187	927-8-70C12	PN63065	103.63
REGN14156	927-3-63B6	PN62949	108.65
REGN14175	927-4-64D4	PN62957	80.97

REGN14176	927-4-64G11	PN62961	111.66
REGN14178	927-4-65F8	PN62971	103.57
REGN14179	927-5-68D2	PN62987	106.77
REGN14180	927-5-68A5	PN63002	109.00
REGN14181	927-5-68C6	PN63009	112.50
REGN14182	927-8-68C11	PN63028	100.92
REGN14183	927-8-69A2	PN63034	84.39
REGN14184	927-8-69H2	PN63037	104.42
REGN14185	927-8-69H3	PN63041	100.92
REGN14186	927-8-69G6	PN63047	90.32
REGN14188	927-8-71H2	PN63067	81.40
REGN14189	927-8-71E3	PN63069	98.82
REGN14190	927-7-71C4	PN63072	87.52
REGN14191	927-7-71E12	PN63090	94.02
REGN19514	927-1-61H4	PN62909	2.76
REGN19513	927-4-65A5	PN62965	18.88
REGN19515	927-7-71F5	PN63075	9.35
REGN19516	927-9-72A4	PN63091	34.47
REGN19517	927-9-72C7	PN63092	46.75

Table 10-4. Inhibition of p75NTR-dependent enhancement of NGF-dependent TrkA signaling in 3T3/SRE-luc/hTrkA cl.C2/hp75NTR cells co-expressing TrkA and p75NTR by various anti-p75NTR antibodies

REGN#	clone ID	PID	% Inhibition
REGN14160	927-1-61C4	PN62906	127.59
REGN14149	927-2-62F2	PN62928	26.69
REGN14152	927-2-62B9	PN62939	130.03
REGN14158	927-1-61F3	PN62903	109.19
REGN14155	927-2-62E11	PN62945	175.06
REGN14157	927-1-61D3	PN62902	140.02
REGN14159	927-1-61B4	PN62905	162.20
REGN14161	927-1-61F4	PN62907	184.69
REGN14163	927-1-61D8	PN62918	130.05

REGN14164	927-1-61F8	PN62919	90.16
REGN14165	927-1-61H9	PN62921	128.58
REGN14148	927-1-61H10	PN62924	152.63
REGN14162	927-1-61D7	PN62916	121.08
REGN14150	927-2-62E6	PN62934	96.95
REGN14151	927-2-62E8	PN62937	106.66
REGN14177	927-4-65H6	PN62969	-35.05
REGN14153	927-2-62H9	PN62940	106.96
REGN14154	927-2-62B10	PN62941	109.42
REGN14187	927-8-70C12	PN63065	44.52
REGN14156	927-3-63B6	PN62949	146.98
REGN14175	927-4-64D4	PN62957	146.25
REGN14176	927-4-64G11	PN62961	131.25
REGN14178	927-4-65F8	PN62971	121.69
REGN14179	927-5-68D2	PN62987	88.04
REGN14180	927-5-68A5	PN63002	127.94
REGN14181	927-5-68C6	PN63009	143.03
REGN14182	927-8-68C11	PN63028	170.56
REGN14183	927-8-69A2	PN63034	189.33
REGN14184	927-8-69H2	PN63037	148.91
REGN14185	927-8-69H3	PN63041	167.62
REGN14186	927-8-69G6	PN63047	129.25
REGN14188	927-8-71H2	PN63067	118.70
REGN14189	927-8-71E3	PN63069	113.41
REGN14190	927-7-71C4	PN63072	110.60
REGN14191	927-7-71E12	PN63090	121.94
REGN19514	927-1-61H4	PN62909	-35.43
REGN19513	927-4-65A5	PN62965	-61.42
REGN19515	927-7-71F5	PN63075	-25.33
REGN19516	927-9-72A4	PN63091	36.50
REGN19517	927-9-72C7	PN63092	31.71
N.A.	REGN2390	N.A.	-13.53

Example 9. Fluorescent antibody biodistribution in vivo.

Table 11-1. mAb clone IDs:

REGN#	AbPID	Lot #	Description
REGN14149	PN62928	L2	Anti p75 – A647
REGN14152	PN62939	L2	Anti p75 – A647
REGN14155	PN62945	L2	Anti p75 – A647
REGN14162	PN62916	L2	Anti p75 – A647
REGN14177	PN62969	L2	Anti p75 – A647
REGN14187	PN63065	L2	Anti p75 – A647
REGN19516	PN63091	L2	Anti p75 – A647
REGN1945	PN1238	L140	Anti Fel d 1 – A647
REGN7540	H1H10154B	L17	Anti EGFRvIII – A647

Table 11-2. Reagents used and lot numbers

Reagent / Equipment	Source	Identifier	Lot #
<u>Explant culture</u>			
Neurobasal-A, phenol red free	Gibco	12349-015	2423531
L-Glutamine	Gibco	25030-081	2152911
B27 plus	Gibco	A35828-01	2365741
NGF factor 7s	Invitrogen	13290-010	2423040
Heat inactivated FBS	Gibco	A38400-01	2293181RP
Matrigel (ECM from Engelbreth-Holm-Swarm murine Sarcoma)	Sigma	E1270	0000147401
Penn/Strep	Gibco	15140-122	2211099
Poly-DL-Ornithine hydrobromide	Sigma	P8638	SLBS5349
Laminin	Invitrogen	23017-015	2258501
<u>Microscopy</u>			
LSM 880 Confocal, 20X objective	Zeiss		SN# 2802000260
LSM 900 Confocal	Zeiss		SN# 2901000127
Axio zoom V16	Zeiss		

μ-Slide 18 well glass bottom	Ibidi	81817	211201/4
μ-Slide 8 well glass bottom	Ibidi	80827	211112/5
Coverslips	VWR	16004-348	
DAPI (4',6-Diamidino-2-Phenylindole, Dilactate)	Invitrogen	D3571	2445405
PBS	Gibco	20012-043	2323501 (one example)
<u>In vivo</u>			
Cholera toxin subunit B, Alexa fluor 488	Molecular Probes	C22841	1696218
Paraformaldehyde 16%	Electron Microscopy Sciences	15710	220218-50
Digital Stereotax	Zeiss	940	
Hamilton Syringe	Hamilton	65460-02	1041045
Hamilton needles 26s/2"	Hamilton	7758-02	1063366
Sutures – Monocryl 6-0 P-1	Ethicon	Y489	SHMKJM
Bupivacaine HCl 0.25%	Hospira	NDC 0409-1159-18	PAA127872
Lidocaine 2%	Covetrus	NDC 11695-4149-1 (#002468)	210570
Paralube Vet ointment	Dechra	NDC 17033-211-38	2079
<u>Immunohistochemistry</u>			
Sucrose	Sigma	S9378	SLCC8491
Tissue-Tek OCT Compound	Sakura	4583	1170-00
Normal Goat Serum	Invitrogen	01-6201	VA293799
Triton X-100	Sigma	T9284	SLBZ2181
Anti-peripherin rabbit	Millipore	AB1540	3563191

Alexa fluor 488 Donkey anti Rabbit IgG (H+L)	Invitrogen	A21206	2376850
Aquamount	Lerner Laboratories	13800	529075

[00310] Time lapse imaging of free uptake of anti-p75^{NTR} antibodies in DRG explants.

[00311] To evaluate free antibody uptake in DRG neurons for the purpose of identifying potential receptors to cargo delivery, *ex vivo* DRG explants were used in conjunction with fluorescently tagged antibodies.

[00312] Dorsal root ganglia (DRG) explants were plated in Ibidi μ -slide 8 well glass bottom dishes. Glass was coated with Poly-dl-Ornithine (0.5 mg/ml) and Laminin (10 μ g/ml). Following CO₂ euthanasia, DRGs were harvested from mice into ice cold L15+10% FBS. A thin layer of ice cold Matrigel was pipetted onto the bottom of each coated Ibidi well and 3 DRGs were placed onto the Matrigel immediately. Plates with DRGs were placed in the incubator at 37°C 5% CO₂ for 15 minutes to allow polymerization. Then, just enough serum-containing media to cover the explant (Phenol red-free Neurobasal-A, 10% FBS, 2% B-27, 2 mM L-Glut, 1% P/S, 50 ng/ml NGF) was added to each well and explants were placed in incubator to allow tissue to adhere. After 2 hours, low serum media (Phenol red-free Neurobasal-A, 2% FBS, 2% B-27, 2 mM L-Glut, 1% P/S, 50 ng/ml NGF) was supplemented to fill the culture well. Media was exchanged 3 times a week. After 48-72 hours, time-lapse imaging of live explants was performed on a Zeiss LSM880 confocal with a full incubation chamber on the stage set to 37°C and 5% CO₂. Once the system stabilized and multi-region positions were programmed for each explant location, 100 nM anti-p75^{NTR}-A647 or anti-Fel D1-A647 were added directly to the explants in their native media on the stage and time-lapse acquisition was initiated. Imaging was performed with a 20X Plan-Apochromat 0.8 NA objective. Three optical slices 10 μ m apart were acquired per explant with a 1 Airy diameter pinhole opening. After 18 hours of imaging, explants were fixed in 4% PFA in PBS for 20 minutes for post-fix imaging.

[00313] *In vivo* detection of anti-p75^{NTR} antibody distribution.

[00314] To evaluate the ability of p75^{NTR} antibodies to internalize in DRGs *in vivo* a comparison of various injection routes was tested.

[00315] For all *in vivo* antibody injections, animals were euthanized with CO₂ in accordance with the guidelines approved by Regeneron Institutional Animal Care and Use Committee. Following euthanasia, DRGs, Trigeminal Ganglion (TG) and other tissue were collected into 4% PFA in PBS. DRG and TG were fixed for one hour at room temperature and other visceral and central nervous tissue were fixed overnight at 4°C. After fixation, tissues were washed and stored in PBS at 4°C. Prior to imaging, tissue were transferred into PBS + 1 µg/ml DAPI and for whole mount confocal imaging in PBS. DRG and TG were imaged on a Zeiss LSM880 at 10x with optical slices 10 µm apart. Brain and visceral organs were imaged on a Zeiss LSM900 at 5x and 10x. For all images, unless stated, the maximum projection of a Z stack collected with 1 Airy pinhole opening is presented.

[00316] To evaluate anti-p75^{NTR} delivery in comparison to the retrogradely travelling ligand Cholera Toxin Subunit B (CT-B), a mix of Alexa 647 fluorescent antibody and Alexa 488 fluorescent CT-B was injected in the foot pad or the gastrocnemius muscle. Tissue was collected five days later, and fluorescence was evaluated in whole DRGs with confocal microscopy.

[00317] For intraplantar injections, 3.5-month-old male C57Bl/6J mice were injected in the right foot pad with 5 µg Cholera Toxin Subunit B conjugated to Alexa 488 (Molecular Probes) resuspended in PBS, mixed with 0.7 mg/kg Alexa 647-conjugated anti-p75^{NTR} antibodies of the present disclosure. Five days post injection, mice were asphyxiated with CO₂ and tissue was collected.

[00318] For intramuscular injections, 4-month-old male C57Bl/6J were placed under 2% Isoflurane anesthesia and received an injection into the right gastrocnemius muscle of 10 µg of Alexa 647-conjugated anti-p75^{NTR} antibody mixed with 5 µg Cholera Toxin Subunit B conjugated to Alexa 488. Tissue was collected after 5 days and processed as stated above.

[00319] For subcutaneous injections, a pilot study was conducted with 2 mice injected with 0.7 mg/kg antibody and tissue was collected after 5 days. To compare, 6 anti-p75^{NTR} antibodies of the disclosure were injected subcutaneously. 3-month-old female C57Bl/6J mice were injected into the ventral inguinal area with Alexa 647-conjugated anti-p75^{NTR} antibodies at a concentration of 0.5 mg/kg and tissue was collected after 3 days and processed as stated above.

[00320] For intravenous injections, mice were restrained and 100 μ l of Alexa 647-conjugated anti-p75^{NTR} antibodies were injected into the lateral caudal tail vein at a final concentration of 0.5 mg/kg. Tissue was collected after 3 days and processed as stated above.

[00321] For intracerebroventricular (ICV) injections, mice were placed under 2% isoflurane anesthesia, lubricant was placed on their eyes and the injection area was sterilized and injected with 2 mg/kg Lidocaine, 1 mg/kg Bupivacaine at the site of incision. Animals were placed in a stereotax instrument, and a vertical 2-3 mm incision was made in the scalp over Bregma. After identifying the coordinates for Bregma, 2 μ g Alexa 647-conjugated anti-p75^{NTR} antibodies were injected unilaterally into the lateral ventricle. Five minutes following the injection, the needle was removed slowly, and the scalp was sutured shut.

[00322] To confirm that anti-p75^{NTR} antibodies internalized into DRG neurons, IHC was performed on sections of DRG that were harvested 5 days post 0.7 mg/kg subcutaneous injection of representative anti-p75^{NTR} antibody, REGN14187. Tissue was cryoprotected by transferring to 30% sucrose overnight and then frozen in OCT on dry ice. 16 μ m DRG sections were prepared on a cryostat and placed on slides. Sections were permeabilized in 0.1% Triton-X-100 for 10 minutes, then blocked with 10% Normal Goat Serum (NGS) with 0.1% Triton X-100 for 30 minutes. Sections were labeled with primary antibody against peripherin diluted 1:500 in 5% NGS overnight at 4°C. After washing in PBS for 10 minutes, sections were incubated with secondary antibody diluted 1:1000 for 3 hours at room temperature, then washed with PBS for 10 minutes and mounted with aquamount.

[00323] Results.

[00324] REGN14155 and REGN14187 anti-p75^{NTR} antibodies were internalized in DRG neurons *ex vivo*.

[00325] Anti-p75^{NTR}-A647 was observed to bind to axons emanating from DRG explants within 5 minutes following addition of the fluorescently-conjugated antibody to the culture dish (**Figure 12**, REGN14152 and REGN14162 at 3 min. and **Figure 13**, REGN14152 and REGN14187 at 5 min). Time lapse acquisition revealed that anti-p75^{NTR}-A647 fluorescence was detected intracellularly at the soma in neurons in explants around 1-4 hours after antibody addition (**Figure 14B**, close up of an ROI shown in the right box in **Figure 14A**, REGN14152). Bright internalization was observed in more than half the neurons by 17 hours

after antibody addition. Isotype controls displayed no axonal labeling or internalization in neurons (**Figure 12** Anti-EGFRVIII and **Figure 13** REGN1945).

[00326] Anti-p75^{NTR} antibodies bind to DRGs *in vivo* following intraplantar and subcutaneous injections.

[00327] Five days after intraplantar and intramuscular injections, whole mount imaging of harvested DRGs revealed Cholera Toxin B-A488 uptake in a small population of neurons in the Lumbar DRGs on the ipsilateral (**Figures 14A-14C**), but not the contralateral side (**Figures 14D-14F**). 5 days post intramuscular injection (**Figures 16A-16B**: ipsilateral; **Figures 16C-16D**: contralateral). Conversely, anti-p75^{NTR} was detected in a large percent of neurons in Lumbar DRGs on both sides (**Figures 14B, 14C, 14E, 14F**) in addition to being detected in neurons in the Trigeminal Ganglion (TG) (**Figures 15B-15C, Figure 16F**). Intraplantar injection of fluorescent isotype control antibody, REGN1945, did not demonstrate labeling in DRGs or TG (**Figures 14A-14D, Figure 15A, and Figures 16A, 16C, and 16E**).

[00328] A comparison of 6 anti-p75^{NTR} antibodies of the disclosure injected subcutaneously demonstrated that all of the antibodies tested exhibited similar uptake into lumbar DRGs (**Figure 17**).

[00329] Higher resolution imaging of L4 DRGs revealed punctate, intracellular distribution of anti-p75^{NTR} in DRG neurons (**Figure 18**)

[00330] Anti-p75^{NTR} antibodies of the disclosure internalized into neurons in the DRG that were labeled by anti-peripherin (**Figure 19**).

[00331] Anti-p75^{NTR} antibodies of the disclosure internalized into neurons all along the anterior-posterior axis and were observed in cervical, thoracic and lumbar DRG (**Figures 20B, 20D, and 20F**). Fluorescent signal was also detected in the TG (**Figure 20B**), myenteric plexus (parasympathetic neurons) (**Figures 20H and 20I**), eye (**Figure 20K**), sympathetic ganglia, for example, thoracic sympathetic ganglia (**Figure 20M**) and superior cervical ganglia. Neuronal structures were labeled in the retina. A representative anti-Fel D1 antibody, REGN1945, did not show labeling following subcutaneous injection (**Figures 20A, 20C, 20G, 20J, and 20L**).

[00332] Imaging in other tissues from the same animals injected subcutaneously with anti-p75^{NTR} antibodies did not reveal significant biodistribution of REGN14155 or REGN14187 to the brain, with the exception of antibody detected in the choroid plexus (**Figure**

21B). No signal was detected in the liver (**Figure 21D**) or spinal cord (**Figure 21F**). Sparse signal was detected in the kidney (**Figure 21C**) and heart (**Figure 21E**).

[00333] A closer look at the choroid plexus following subcutaneous injection of anti-p75^{NTR} antibodies shows internalization in the choroid cells (**Figure 22**).

[00334] ICV injection of REGN14187 labeled the choroid plexus, cortical regions and cells in ventral areas in the brain (**Figure 23**). A representative anti-Fel D1 antibody did not show labeling aside from the site of injection at the ventricle (**Figure 23B**).

[00335] Internalization of fluorescent anti-p75^{NTR} antibodies of the disclosure into neurons was observed following intravenous injection of REGN19516 in the Trigeminal ganglia (**Figure 24D**) and DRG (**Figure 24H**). Intravenous injection of fluorescent isotype control antibody, REGN1945, did not demonstrate labeling in TG or DRGs (**Figures 24B, Figure 24F**).

[00336] Anti-p75^{NTR} antibodies were internalized in DRG and TG neurons *in vivo* following a broad variety of injection routes.

[00337] When injected unilaterally in foot pad or gastrocnemius muscle, anti-p75^{NTR} antibodies were internalized in DRG neurons on both ipsilateral and contralateral sides, suggesting that uptake is driven by systemic delivery to the DRG and not solely by retrograde transport from the injection site.

[00338] The anti-p75^{NTR} antibodies of the disclosure tested exhibited interference with downstream p75^{NTR} signaling by weak or strong blocking of receptor activity. Antibody dependent prevention of NGF binding to p75^{NTR} receptors and a reduction of downstream signaling may reduce the prosurvival effects of NGF in the homeostatic environment.

[00339] While the invention has been particularly shown and described with reference to a number of embodiments, it would be understood by those skilled in the art that changes in the form and details may be made to the various embodiments disclosed herein without departing from the spirit and scope of the invention and that the various embodiments disclosed herein are not intended to act as limitations on the scope of the claims. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, some preferred methods and materials are now described. All publications cited herein are incorporated herein by reference to describe in their entirety.

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 to which this invention belongs.

CLAIMS

What is claimed is:

1. A recombinant adeno-associated virus (AAV) particle comprising:
 - (i) a modified AAV capsid protein, and
 - (ii) a targeting ligand that binds a mammalian p75 neurotrophin receptor (p75^{NTR}),
wherein the modified AAV capsid protein is operably linked with the targeting ligand.
2. The recombinant AAV particle of claim 1, wherein:
 - (a) the modified AAV capsid protein comprises a first member and a second member of a protein:protein binding pair, and
 - (b) the second member of the protein:protein binding pair comprises the targeting ligand that binds the mammalian p75^{NTR},
wherein the first member of the protein:protein binding pair and the second member of the protein:protein binding pair are associated to direct the tropism of the AAV particle to a mammalian p75^{NTR}-expressing cell.
3. The recombinant AAV particle of claim 1 or claim 2, wherein the mammalian p75^{NTR} is a human p75^{NTR}.
4. The recombinant AAV particle of claim 2 or claim 3, wherein the mammalian p75^{NTR}-expressing cell is selected from the group consisting of: a neuron, a Mueller glial cell, a Leydig cell, an ionocyte, a dorsal root ganglion (DRG) cell, a trigeminal ganglion cell, a sympathetic ganglion cell, a dermal fiber cell, a retina cell, a myenteric plexus cell, a celiac ganglion cell, a dendritic cell, a Schwann cell, a salivary gland cell, a retinal bipolar neuron, a basal respiratory cell, a basal squamous epithelial cell, and an oligodendrocyte.
5. The recombinant AAV particle of any one of claims 2-4, comprising the modified AAV capsid protein bound to the mammalian p75^{NTR} expressed on the surface of the mammalian p75^{NTR}-expressing cell.

6. The recombinant AAV particle of any one of claims 2-5, comprising the modified AAV capsid protein bound to the mammalian p75^{NTR} expressed on the surface of the mammalian p75^{NTR}-expressing cell,
wherein the mammalian p75^{NTR} is a human p75^{NTR}, and
wherein the mammalian p75^{NTR}-expressing cell is a non-human animal cell genetically modified to express the human p75^{NTR}.
7. The recombinant AAV particle of any one of claims 2-6, comprising the modified AAV capsid protein bound to the mammalian p75^{NTR} expressed on the surface of the mammalian p75^{NTR}-expressing cell,
wherein the mammalian p75^{NTR} is a human p75^{NTR}, and
wherein the mammalian p75^{NTR}-expressing cell is a rodent cell genetically modified to express the human p75^{NTR}.
8. The recombinant AAV particle of claim 7, wherein the rodent p75^{NTR}-expressing cell is a rat p75^{NTR}-expressing cell or a mouse p75^{NTR}-expressing cell.
9. The recombinant AAV particle of any one of claims 2-5, comprising the modified AAV capsid protein bound to the mammalian p75^{NTR} expressed on the surface of the mammalian p75^{NTR}-expressing cell,
wherein the mammalian p75^{NTR} is a human p75^{NTR}, and
wherein the mammalian p75^{NTR}-expressing cell is a human p75^{NTR}-expressing cell.
10. The recombinant AAV particle of any one of claims 1-9, wherein the recombinant AAV particle is *in vitro*.
11. The recombinant AAV particle of any one of claims 1-9, wherein the recombinant AAV particle is *in vivo*.
12. The recombinant AAV particle of any one of claims 1-11, wherein the targeting ligand is an antibody or a portion thereof.

13. The recombinant AAV particle of any one of claims 1-12, wherein the targeting ligand comprises a heavy chain variable domain, light chain variable domain, heavy chain variable domain/light chain variable domain pair, HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, LCDR3, and/or set of HCDR1-HCDR2-HCDR3-LCDR1-LCDR2-LCDR3 amino acid sequence(s) at least 90% identical to, respectively, an amino acid sequence of a heavy chain variable domain, light chain variable domain, heavy chain variable domain/light chain variable domain pair, HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, LCDR3, and/or set of HCDR1-HCDR2-HCDR3-LCDR1-LCDR2-LCDR3 as set forth in or encoded by any one of SEQ ID NOs: 1-617.

14. The recombinant AAV particle of any one of claims 1-13, wherein the targeting ligand comprises the HCDR1-HCDR2-HCDR3-LCDR1-LCDR2-LCDR3 amino acid sequence set contained within an HCVR/LCVR amino acid sequence pair selected from the group consisting of SEQ ID NOs: 2/10, 22/30, 42/50, 58/66, 78/86, 98/106, 116/124, 136/144, 155/162, 173/179, 189/197, 207/215, 227/235, 245/251, 261/269, 279/287, 297/304, 315/323, 331/339, 349/357, 369/377, 387/391, 401/409, 417/409, 427/409, 437/409, 445/409, 455/409, 465/409, 475/409, 484/409, 493/409, 503/409, 513/409, 519/409, 529/537, 549/557, 569/577, 589/597, and 609/597, optionally wherein the targeting ligand comprises the HCDR1-HCDR2-HCDR3-LCDR1-LCDR2-LCDR3 amino acid sequence set contained within an HCVR/LCVR amino acid sequence pair selected from the group consisting of 529/537, 549/557, 569/577, 589/597, and 609/597.

15. The recombinant AAV particle of any one of claims 1-14, wherein the targeting ligand comprises an HCVR/LCVR amino acid sequence pair selected from the group consisting of SEQ ID NOs: 2/10, 22/30, 42/50, 58/66, 78/86, 98/106, 116/124, 136/144, 155/162, 173/179, 189/197, 207/215, 227/235, 245/251, 261/269, 279/287, 297/304, 315/323, 331/339, 349/357, 369/377, 387/391, 401/409, 417/409, 427/409, 437/409, 445/409, 455/409, 465/409, 475/409, 484/409, 493/409, 503/409, 513/409, 519/409, 529/537, 549/557, 569/577, 589/597, and 609/597, optionally wherein the targeting ligand comprises an HCVR/LCVR amino acid sequence pair selected from the group consisting of 529/537, 549/557, 569/577, 589/597, and 609/597.

16. The recombinant AAV particle of any one of claims 2-15, wherein:
- (a) the first member of the protein:protein binding pair comprises SpyTag, Isopeptag, SnoopTag, SpyTag002, SpyTag003, or any biologically active portions or variants thereof,
 - (b) the second member of the protein:protein binding pair comprises
 - (i) SpyCatcher, KTag, pilin-C, SnoopCatcher, SpyCatcher002, SpyCatcher003, or any biologically active portions or variants thereof, and
 - (ii) the targeting ligand that binds the mammalian p75^{NTR}, and
 - (c) the first member of the protein:protein binding pair and the second member of the protein:protein binding pair are linked by an isopeptide bond.
17. The recombinant AAV particle of claim 16, wherein:
- (a) the first member of the protein:protein binding pair comprises SpyTag, or any biologically active portion or variant thereof, and
 - (b) the second member of the protein:protein binding pair comprises SpyCatcher, or any biologically active portion or variant thereof, fused to the targeting ligand that binds the mammalian p75^{NTR}.
18. The recombinant AAV particle of any one of claims 2-17, comprising a first and/or second linker operably linking the first member of the protein:protein binding pair to the modified AAV capsid protein.
19. The recombinant AAV particle of claim 18, wherein the first and second linker are not identical, or the first and second linker are identical.
20. The recombinant AAV particle of claim 18 or claim 19, wherein the first linker is 10 amino acids in length and/or the second linker is 10 amino acids in length.
21. The recombinant AAV particle of any one of claims 1-20, wherein the modified AAV capsid protein comprises a modified VP1 capsid protein, a modified VP2 capsid protein, and/or a modified VP3 capsid protein, and

wherein the modified VP1 capsid protein, the modified VP2 capsid protein, and/or the modified VP3 capsid protein comprises an insertion of a first member of a protein:protein binding pair and/or the targeting ligand, and

and wherein a portion of the modified VP1 capsid protein, the modified VP2 capsid protein, and/or the modified VP3 capsid protein, that comprises the insertion of the first member of the protein:protein binding pair and/or the targeting ligand, further comprises an amino acid sequence at least 90% identical to a corresponding capsid protein of a wild-type AAV.

22. The recombinant AAV particle of claim 21, wherein the modified VP1 capsid protein, the modified VP2 capsid protein, and/or the modified VP3 capsid protein further comprises, in addition to the insertion of the first member of the protein:protein binding pair and/or the targeting ligand:

- (i) a substitution, insertion, or deletion of an amino acid,
- (ii) a chimeric amino acid sequence, or
- (iii) any combination of (i) and (ii).

23. The recombinant AAV particle of claim 22, wherein the substitution, insertion, or deletion of an amino acid reduces the natural tropism of the AAV particle and/or creates a detectable label.

24. The recombinant AAV particle of any one of claims 1-23, wherein the AAV is selected from the group consisting of AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAV9, a non-primate animal AAV listed in Table 2, and any chimera thereof.

25. The recombinant AAV particle of any one of claims 1-24, wherein the AAV is AAV2.

26. The recombinant AAV particle of any one of claims 1-25, wherein the recombinant AAV particle comprises a modified AAV2 VP1 capsid protein that comprises a first member

of a protein:protein binding pair inserted at an amino acid position I-453 and/or I-587, and optionally linked to the AAV sequence via a linker on one or both sides.

27. The recombinant AAV particle of claim 26, wherein the recombinant AAV particle comprises the modified AAV2 VP1 capsid protein that comprises the first member of the protein:protein binding pair inserted, optionally via a linker, at position G453,

optionally wherein the modified AAV2 VP1 capsid protein further comprises a mutation selected from R585A, R588A, R484A, R487A, K532A, and any combination thereof.

28. The recombinant AAV particle or composition of claim 26 or claim 27, wherein the recombinant AAV particle comprises a mosaic AAV capsid comprising a second set of AAV2 VP1 capsid proteins lacking the first member of the protein:protein binding pair,

optionally wherein the second set of AAV2 VP1 capsid proteins comprises a mutation selected from R585A, R588A, R484A, R487A, K532A and any combination thereof.

29. The recombinant AAV particle of any one of claims 1-24, wherein the AAV is AAV9.

30. The recombinant AAV particle of claim 29, wherein the modified AAV capsid protein comprises a modified AAV9 VP1 capsid protein that comprises a first member of a protein:protein binding pair inserted, optionally via a linker, at position I-453 or I-589.

31. The recombinant AAV particle of claim 30, wherein the recombinant AAV particle comprises the modified AAV9 VP1 capsid protein that comprises the first member of the protein:protein binding pair inserted, optionally via a linker, at position G453,

optionally wherein the modified AAV9 VP1 capsid protein further comprises a mutation selected from N272A, W503A, and a combination thereof.

32. The recombinant AAV particle of claim 30 or claim 31, wherein the recombinant AAV particle comprises a mosaic AAV capsid comprising a second set of AAV9 VP1 capsid proteins lacking the first member of the protein:protein binding pair,
optionally wherein the second set of AAV9 VP1 capsid proteins comprises a mutation selected from N272A, W503A, and a combination thereof.
33. The recombinant AAV particle any one of claims 1-24, wherein the AAV is a non-primate animal AAV.
34. The recombinant AAV particle of claim 33, wherein the non-primate animal AAV is an avian AAV (AAAV).
35. The recombinant AAV particle of claim 34, wherein the modified AAV capsid protein comprises a modified AAAV VP1 capsid protein that comprises a first member of a protein:protein binding pair inserted, optionally via a linker, at position I-444 or I-580.
36. The recombinant AAV particle of claim 33, wherein the non-primate animal AAV is a squamate AAV.
37. The recombinant AAV particle of claim 36, wherein the squamate AAV is a bearded dragon AAV.
38. The recombinant AAV particle of claim 37, wherein the modified AAV capsid protein comprises a modified bearded dragon AAV VP1 capsid protein that comprises a first member of a protein:protein binding pair inserted, optionally via a linker, at position I-573 or I-436.
39. The recombinant AAV particle of claim 33, wherein the non-primate animal AAV is a non-primate mammalian AAV.

40. The recombinant AAV particle of claim 39, wherein the non-primate mammalian AAV is a sea lion AAV.

41. The recombinant AAV particle of claim 40, wherein the modified AAV capsid protein comprises a modified sea lion AAV VP1 capsid protein that comprises a first member of a protein:protein binding pair inserted, optionally via a linker, at a position selected from the group consisting of I-429, I-430, I-431, I-432, I-433, I-434, I-436, I-437, and I-565.

42. The recombinant AAV particle of any one of claims 1-41, wherein the recombinant AAV particle comprises a mosaic AAV capsid, optionally wherein the mosaic AAV capsid comprises (i) a first plurality of reference AAV capsid proteins, each of which is not associated with the targeting ligand, and (ii) a second plurality of AAV capsid proteins, each of which is associated with the targeting ligand, optionally wherein the mosaic AAV capsid comprises the first plurality of reference AAV capsid proteins and the second plurality of AAV capsid proteins at a ratio of 1:7.

43. The recombinant AAV particle of any one of claims 1-42, further comprising a nucleotide of interest encapsidated within the recombinant AAV particle.

44. The recombinant AAV particle of claim 43, wherein the nucleotide of interest is a reporter gene.

45. The recombinant AAV particle of claim 43 or claim 44, wherein the nucleotide of interest encodes β -galactosidase, green fluorescent protein (GFP), enhanced Green Fluorescent Protein (eGFP), MmGFP, blue fluorescent protein (BFP), enhanced blue fluorescent protein (eBFP), mPlum, mCherry, tdTomato, mStrawberry, J-Red, DsRed, mOrange, mKO, mCitrine, Venus, YPet, yellow fluorescent protein (YFP), enhanced yellow fluorescent protein (eYFP), Emerald, CyPet, cyan fluorescent protein (CFP), Cerulean, T-Sapphire, luciferase, alkaline phosphatase, or a combination thereof.

46. The recombinant AAV particle of claim 43, wherein the nucleotide of interest encodes a therapeutic protein, a suicide gene, an antibody or a fragment thereof, a CRISPR/Cas system or a portion(s) thereof, an antisense oligonucleotide, a ribozyme, an RNAi molecule, or a shRNA molecule.

47. The recombinant AAV particle of claim 46, wherein the nucleotide of interest targets a gene or gene product associated with pain, itch, or a neurological disease or disorder.

48. The recombinant AAV particle of claim 47, wherein the gene or gene product associated with pain, itch, or a neurological disease or disorder is voltage-gated sodium channel Nav1.7, voltage-gated sodium channel Nav1.8, voltage-gated sodium channel Nav1.9, voltage-gated sodium channel Nav1.6, tropomyosin receptor kinase A (TrkA), tropomyosin receptor kinase C (TRKC), acid-sensing ion channel subunit 1 (ASIC1), acid-sensing ion channel subunit 3 (ASIC3), transient receptor potential vanilloid 1 (TRPV1), transient receptor potential vanilloid 4 (TRPV4), transient receptor potential cation channel, subfamily A, member 1 (TRPA1), transient receptor potential cation channel subfamily M, member 8 (TRPM8), fatty acid amide hydrolase (FAAH), piezo type mechanosensitive ion channel component 1 (PIEZO1), piezo type mechanosensitive ion channel component 2 (PIEZO2), enkephalin, RET proto-oncogene (RET), interleukin 4 receptor (IL4R), interleukin 13 receptor (IL13R), interleukin 31 receptor (IL31R), interleukin 6 receptor alpha (IL6Ra), glycoprotein 130(gp130), FXYD domain containing ion transport regulator 2 (FXYD2), P2X purinoceptor 3 (P2X3).

49. The recombinant AAV particle of any one of claims 46-48, wherein the nucleotide of interest encodes a molecule that reduces or ablates the expression of voltage-gated sodium channel Nav1.7.

50. The recombinant AAV particle of any one of claims 46-49, wherein the nucleotide of interest encodes gRNA that targets a gene encoding voltage-gated sodium channel Nav1.7 for silencing via CRISPR-Cas9.

51. The recombinant AAV particle of any one of claims 46-49, wherein the nucleotide of interest encodes shRNA that targets mRNA encoding voltage-gated sodium channel Nav1.7 for silencing via RNAi.
52. A pharmaceutical composition comprising (a) the recombinant AAV particle according to any one of claims 43-50, and (b) a pharmaceutically acceptable carrier or excipient.
53. A method of delivering a nucleotide of interest to a mammalian p75^{NTR}-expressing cell comprising contacting the mammalian p75^{NTR}-expressing cell with (a) the recombinant AAV particle according to any one of claims 43-51, or (b) the pharmaceutical composition of claim 52.
54. The method of claim 53, wherein the contacting is performed *ex vivo*.
55. The method of claim 54, wherein the contacting is performed in a subject.
56. The method of claim 55, wherein the subject is a primate animal, preferably a human.
57. The method of any one of claims 53-56, wherein the p75^{NTR}-expressing cell is selected from the group consisting of: a neuron, a Mueller glial cell, a Leydig cell, an ionocyte, a dorsal root ganglion (DRG) cell, a trigeminal ganglion cell, a sympathetic ganglion cell, a dermal fiber cell, a retina cell, a myenteric plexus cell, a celiac ganglion cell, a dendritic cell, a Schwann cell, a salivary gland cell, a retinal bipolar neuron, a basal respiratory cell, a basal squamous epithelial cell, and an oligodendrocyte.
58. The method of any one of claims 53-57, wherein the mammalian p75^{NTR} is human p75^{NTR}.
59. The method of any one of claims 53-58, wherein the nucleotide of interest encodes a therapeutic protein, a suicide gene, an antibody or a fragment thereof, a CRISPR/Cas system

or a portion(s) thereof, an antisense oligonucleotide, a ribozyme, an RNAi molecule, or a shRNA molecule.

60. The method of claim 59, wherein the nucleotide of interest targets a gene or gene product associated with pain, itch, or a neurological disease or disorder.

61. The method of claim 60, wherein the gene or gene product associated with pain, itch, or a neurological disease or disorder is voltage-gated sodium channel Nav1.7, voltage-gated sodium channel Nav1.8, voltage-gated sodium channel Nav1.9, voltage-gated sodium channel Nav1.6, tropomyosin receptor kinase A (TrkA), tropomyosin receptor kinase C (TRKC), acid-sensing ion channel subunit 1 (ASIC1), acid-sensing ion channel subunit 3 (ASIC3), transient receptor potential vanilloid 1 (TRPV1), transient receptor potential vanilloid 4 (TRPV4), transient receptor potential cation channel, subfamily A, member 1 (TRPA1), transient receptor potential cation channel subfamily M, member 8 (TRPM8), fatty acid amide hydrolase (FAAH), piezo type mechanosensitive ion channel component 1 (PIEZO1), piezo type mechanosensitive ion channel component 2 (PIEZO2), enkephalin, RET proto-oncogene (RET), interleukin 4 receptor (IL4R), interleukin 13 receptor (IL13R), interleukin 31 receptor (IL31R), interleukin 6 receptor alpha (IL6Ra), glycoprotein 130(gp130), FXYD domain containing ion transport regulator 2 (FXYD2), P2X purinoceptor 3 (P2X3).

62. The method of claim any one of claims 59-61, wherein the nucleotide of interest encodes a molecule that reduces or ablates the expression of voltage-gated sodium channel Nav1.7.

63. The method of any one of claims 59-62, wherein the nucleotide of interest encodes gRNA that targets a gene encoding voltage-gated sodium channel Nav1.7 for silencing via CRISPR-Cas9.

64. The method of any one of claims 59-62, wherein the nucleotide of interest encodes shRNA that targets mRNA encoding voltage-gated sodium channel Nav1.7 for silencing via RNAi.
65. A method of treating or preventing pain, itch, or a neurological disease or disorder in a subject in need thereof comprising:
administering to the patient (a) a recombinant AAV particle according to any one of claims 1-51, or (b) the pharmaceutical composition of claim 52,
wherein the recombinant AAV particle comprises a nucleotide of interest encapsidated within the recombinant AAV particle, and
wherein the nucleotide of interest encodes a therapeutic protein, a suicide gene, an antibody or a fragment thereof, a CRISPR/Cas system or a portion(s) thereof, an antisense oligonucleotide, a ribozyme, an RNAi molecule, or a shRNA molecule.
66. The method of claim 65, wherein the administering comprises intramuscular, subcutaneous, or intravenous administration.
67. The method of claim 65, wherein the administering comprises intrathecal, intracisternal, intracerebroventricular, or intraparenchymal administration.
68. The method of claim 65, wherein the administering comprises intravitreal administration into the eye.
69. The method of any one of claims 65-68, wherein the pain is peripheral chronic pain, a chronic neuropathic pain, somatic pain, chronic post-operative pain, small fiber peripheral neuropathy, chemotherapy-induced neuropathy, painful diabetic-induced neuropathy, post-herpetic neuralgia, osteoarthritis, back pain, joint pain, trigeminal neuralgia, trigeminal pain, temporo-mandibular pain, migraine, dysautonomia, myofascial pain syndrome or myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS).

70. The method of claim 69, wherein the chronic neuropathic pain is trigeminal pain or trigeminal neuralgia.
71. The method of any one of claims 65-68, wherein the itch is chronic itch.
72. The method of any one of claims 65-68, wherein the neurological disease or disorder is a neurodegenerative disease, a neurodevelopmental disease, a chronic neuropathic pain, a physical injury, a neuropsychiatric disease, or a neurological cancer.
73. The method of claim 72, wherein the neurodegenerative disease or disorder is Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), or multiple sclerosis (MS).
74. The method of claim 72, wherein the physical injury is traumatic brain injury, spinal cord injury, stroke, or brain edema.
75. The method of claim 72, wherein the neurological cancer is a brain cancer or a peripheral nerve cancer.
76. The method of any one of claims 65-75, wherein the pain, itch, or a neurological disease or disorder is associated with a sensory neuron, a dorsal root ganglion cell, a trigeminal ganglion cell, or a population thereof.
77. The method of claim 65, wherein the nucleotide of interest encodes a molecule that reduces or ablates the expression of voltage-gated sodium channel Nav1.7.
78. The method of claim 77, wherein the nucleotide of interest encodes gRNA that targets a gene encoding voltage-gated sodium channel Nav1.7 for silencing via CRISPR-Cas9.
79. The method of claim 77, wherein the nucleotide of interest encodes shRNA that targets mRNA encoding voltage-gated sodium channel Nav1.7 for silencing via RNAi.

80. Use of the recombinant AAV particle according to any one of claims 1-51 or the pharmaceutical composition of claim 52 for the manufacture of a medicament for treating or preventing pain, itch, or a neurological disease or disorder,

wherein the recombinant AAV particle comprises a nucleotide of interest encapsidated within the AAV particle, and

wherein the nucleotide of interest encodes a therapeutic protein, a suicide gene, an antibody or a fragment thereof, a CRISPR/Cas system or a portion(s) thereof, an antisense oligonucleotide, a ribozyme, an RNAi molecule, or a shRNA molecule.

81. The recombinant AAV particle or pharmaceutical composition thereof for use according to claim 80, wherein the pain is peripheral chronic pain, a chronic neuropathic pain, somatic pain, chronic post-operative pain, small fiber peripheral neuropathy, chemotherapy-induced neuropathy, painful diabetic-induced neuropathy, post-herpetic neuralgia, osteoarthritis, back pain, joint pain, trigeminal neuralgia, trigeminal pain, temporo-mandibular pain, migraine, dysautonomia, myofascial pain syndrome or myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS).

82. The recombinant AAV particle or pharmaceutical composition thereof for use according to claim 81, wherein the chronic neuropathic pain is trigeminal pain or trigeminal neuralgia.

83. The recombinant AAV particle or pharmaceutical composition thereof for use according to claim 80, wherein the itch is chronic itch.

84. The recombinant AAV particle or pharmaceutical composition thereof for use according to claim 80, wherein the neurological disease or disorder is a neurodegenerative disease, a neurodevelopmental disease, a chronic neuropathic pain, a physical injury, a neuropsychiatric disease, or a neurological cancer.

85. The recombinant AAV particle or pharmaceutical composition thereof for use according to claim 84, wherein the neurodegenerative disease or disorder is Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), or multiple sclerosis (MS).

86. The recombinant AAV particle or pharmaceutical composition thereof for use according to claim 84, wherein the physical injury is traumatic brain injury, spinal cord injury, stroke, or brain edema.

87. The recombinant AAV particle or pharmaceutical composition thereof for use according to claim 84, wherein the neurological cancer is a brain cancer or a peripheral nerve cancer.

88. The recombinant AAV particle or pharmaceutical composition thereof for use according to any one of claims 80-87, wherein the pain, itch, or a neurological disease or disorder is associated with a sensory neuron, a dorsal root ganglion cell, a trigeminal ganglion cell, or a population thereof.

89. The recombinant AAV particle or pharmaceutical composition thereof for use according to claim 80, wherein the nucleotide of interest encodes a molecule that reduces or ablates the expression of voltage-gated sodium channel Nav1.7.

90. The recombinant AAV particle or pharmaceutical composition thereof for use according to claim 89, wherein the nucleotide of interest encodes gRNA that targets a gene encoding voltage-gated sodium channel Nav1.7 for silencing via CRISPR-Cas9.

91. The recombinant AAV particle or pharmaceutical composition thereof for use according to claim 89, wherein the nucleotide of interest encodes shRNA that targets mRNA encoding voltage-gated sodium channel Nav1.7 for silencing via RNAi.

92. A composition comprising:

- (a) an AAV particle encapsulating a nucleotide of interest; and
 - (b) a multispecific binding protein comprising:
 - (i) a first antigen-binding domain that binds a mammalian p75 neurotrophin receptor (p75^{NTR}), and
 - (ii) a second antigen-binding domain that binds to one or more epitopes of an AAV capsid protein of the AAV particle;
- optionally wherein the composition further comprises:
- (c) a pharmaceutically acceptable carrier or excipient.

93. A method of delivering a nucleotide of interest to a mammalian p75^{NTR}-expressing cell, comprising contacting the mammalian p75^{NTR}-expressing cell with the composition of claim 92.

94. A method of treating or preventing pain, itch, or a neurological disease or disorder in a subject in need thereof comprising:

- administering to the patient the composition of claim 92,
- wherein the nucleotide of interest encodes a therapeutic protein, a suicide gene, an antibody or a fragment thereof, a CRISPR/Cas system or a portion(s) thereof, an antisense oligonucleotide, a ribozyme, an RNAi molecule, or a shRNA molecule.

95. Use of the composition of claim 92 for the manufacture of a medicament for treating or preventing pain, itch, or a neurological disease or disorder,

- wherein the nucleotide of interest encodes a therapeutic protein, a suicide gene, an antibody or a fragment thereof, a CRISPR/Cas system or a portion(s) thereof, an antisense oligonucleotide, a ribozyme, an RNAi molecule, or a shRNA molecule.