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(54) **Title:** VIRAL VECTORS EXHIBITING IMPROVED GENE DELIVERY PROPERTIES

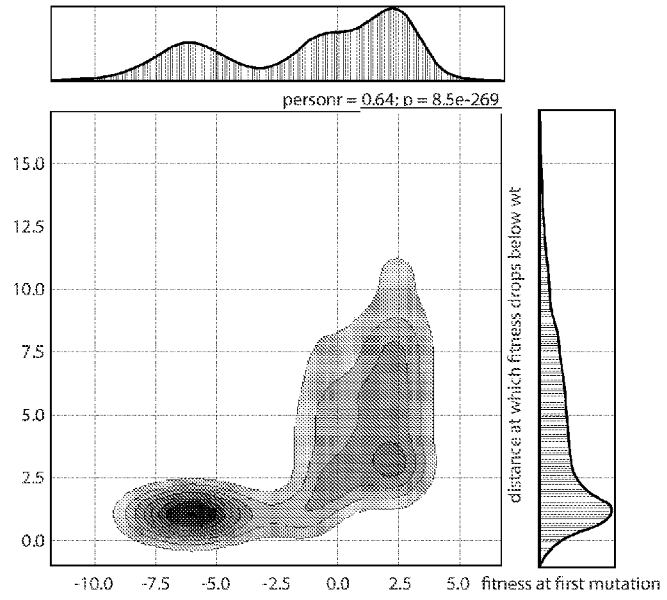

FIG. 3

(57) Abstract: The technology described herein provides viral capsid polypeptides bearing mutations that alters tissue tropism of a virus comprising the viral capsid polypeptide. In various embodiments, tissue tropisimto the heart, kidney, liver, lung, spleen, or blood is altered.

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VIRAL VECTORS EXHIBITING IMPROVED GENE DELIVERY PROPERTIES

CROSS-REFERENCE TO RELATED APPLICATION

[0001] This Application claims benefit under 35 U.S.C. § 119(e) of the U.S. Provisional Application No 62/671,949 filed May 15, 2018, the contents of which is incorporated herein by reference in its entirety.

GOVERNMENT SUPPORT

[0002] This invention was made with government support under RM1 HG008525 and NHGRI CEGS CCV awarded by National Institutes of Health. The government has certain rights in the invention.

TECHNICAL FIELD OF THE INVENTION

[0003] This invention is related to viral vectors with modified tropism.

BACKGROUND OF THE INVENTION

[0004] Adeno-associated virus (AAV) is an attractive agent for use as gene delivery vector. Its simple structure also makes it an attractive target for genetic improvement programs. Nonetheless, there is a continuing need in the art to improve delivery of DNA using AAV and other viral vectors. In particular, there is a need in the art for viral vectors with modified tissue or cell tropism.

SUMMARY OF THE INVENTION

[0005] Described herein are viral vectors with modified tropism. Such vectors provide an improvement in the degree of tissue targeting attainable with such vectors. In particular, viral vectors with capsid polypeptide mutations that modify tropism of the viral particles relative to particles with wild-type capsid polypeptide are described. Through systematic mutation of viral capsid polypeptides, specific amino acid residues and amino acid regions have been identified that when mutated increase or decrease tropism of the virus for certain tissue or cell types. This provides the ability to increase the targeting of a given tissue or cell type by a viral vector, or, conversely, to decrease the targeting of a given tissue or cell type by a viral vector depending upon the site-specific mutation(s) introduced to the capsid polypeptide. Indeed, it has been found herein that not only can one improve the tropism of a viral vector by incorporating amino acid changes that increase tropism for a desired tissue, but nucleic acid delivery can also be improved to a given tissue or cell type by reducing the efficiency with which a viral vector infects tissues or cells other than the desired tissue or cell. Mutations that achieve both of these effects, and their use to improve delivery to desired or targeted tissues or cell types are described herein. Further, it has surprisingly been found that one can combine, within a single viral capsid polypeptide, mutations that improve tropism for a desired or targeted tissue or cell type with mutations that reduce tropism for a non-desired tissue or cell type, and thereby further improve targeting efficiency of the vector.

[0006] One aspect of the technology described herein provides a viral capsid polypeptide bearing a mutation relative to SEQ ID NO: 1 (WT AAV2) that alters tissue tropism of a virus comprising the viral capsid polypeptide, wherein the mutation is selected from the mutations in any one of Tables 1-7.

[0007] In one embodiment of any aspect, the tissue is heart, kidney, liver, lung, spleen, or blood.

[0008] In one embodiment of any aspect, the tropism to the tissue is increased. In one embodiment of any aspect, the tropism to the tissue is decreased.

[0009] Another aspect of the technology described herein provides a viral capsid polypeptide bearing a mutation that corresponds to a mutation of the polypeptide of SEQ ID NO: 1, the mutation selected for the group consisting of the mutations in Tables 1-9 relative to SEQ ID NO: 1.

[0010] Yet another aspect of the technology described herein provides a viral capsid polypeptide comprising a region corresponding to the amino acid sequence of SEQ ID NO: 2, wherein the region corresponding to the amino acid sequence of SEQ ID NO: 2 comprises a mutation relative to SEQ ID NO: 2 that alters tissue tropism of a virus comprising the viral capsid polypeptide, wherein the mutation is selected from the mutations in any one of Tables 10-15.

[0011] Another aspect of the technology described herein provides a nucleic acid encoding any of the the viral capsid polypeptides described herein.

[0012] Another aspect of the technology described herein provides a viral particle comprising any of the the viral capsid polypeptides described herein.

[0013] Another aspect of the technology described herein provides a method of delivering a nucleic acid to a cell, the method comprising; contacting the cell with a viral particle comprising any of the the viral capsid polypeptides described herein

[0014] Another aspect of the technology described herein provides a method of delivering a nucleic acid to a blood cell, the method comprising; contacting a blood cell with a viral particle comprising a viral capsid polypetide comprising a mutation of Table 1.

[0015] Another aspect of the technology described herein provides a method of delivering a nucleic acid to a heart cell, the method comprising; contacting a heart cell with a viral particle comprising a viral capsid polypetide comprising a mutation of Table 2

[0016] Another aspect of the technology described herein provides a method of delivering a nucleic acid to a kidney cell, the method comprising; contacting a kidney cell with a viral particle comprising a viral capsid polypetide comprising a mutation of Table 3.

[0017] Another aspect of the technology described herein provides a method of delivering a nucleic acid to a liver cell, the method comprising; contacting a liver cell with a viral particle comprising a viral capsid polypetide comprising a mutation of Table 4.

[0018] Another aspect of the technology described herein provides a method of delivering a nucleic acid to a lung cell, the method comprising; contacting a lung cell with a viral particle comprising a viral capsid polypetide comprising a mutation of Table 5

[0019] Another aspect of the technology described herein provides a method of delivering a nucleic acid to a spleen cell, the method comprising; contacting a spleen cell with a viral particle comprising a viral capsid polypetide comprising a mutation of Table 6.

[0020] In one embodiment of any aspect, the delivering is at least 1.1-fold more efficient as compared to a wild-type viral capsid polypeptide.

[0021] Another aspect of the technology described herein provides a method of reducing tissue tropism of a virus comprising a viral capsid polypeptide corresponding to the viral capsid polypeptide of SEQ ID NO: 1, the method comprising introducing a mutation set out in any of Tables 7-9 (deenrichment Tables).

[0022] Another aspect of the technology described herein provides a method of increasing delivery of a nucleic acid to a cell of a kidney, heart, or lung, the method comprising; contacting a cell of a kidney, heart, or lung with a viral particle comprising a viral capsid polypeptide comprising a mutation that reduces delivery of a nucleic acid to a cell of a liver, blood, or spleen.

[0023] In one embodiment of any aspect, the mutation that reduces delivery of a nucleic acid to a cell of a liver, blood, or spleen is selected from any of Tables 7-9.

[0024] Another aspect of the technology described herein provides a method of delivering a nucleic acid to a lung cell, the method comprising; contacting a lung cell with a viral particle comprising a viral capsid polypetide comprising a mutation of Table 5 and a mutation selected from any of Tables 7-9.

[0025] Another aspect of the technology described herein provides a method of delivering a nucleic acid to a heart cell, the method comprising; contacting a heart cell with a viral particle comprising a viral capsid polypetide comprising a mutation of Table 2 and a mutation selected from any of Tables 7-9.

[0026] Another aspect of the technology described herein provides a method of delivering a nucleic acid to a kidney cell, the method comprising; contacting a kidney cell with a viral particle comprising a viral capsid polypetide comprising a mutation of Table 3 and a mutation selected from any of Tables 7-9.

[0027] Another aspect of the technology described herein provides an AAV2 capsid polypeptide comprising a mutation in the region of amino acids selected the group consisting of: 440-460 of SEQ ID NO: 1, 475-505 of SEQ ID NO: 1, 518-532 of SEQ ID NO: 1, and 560-590 of SEQ ID NO: 1 that alters tissue tropism of a virus comprising the viral capsid polypeptide.

[0028] Another aspect of the technology described herein provides an AAV2 capsid polypeptide comprising a mutation in the region of amino acids 561-588 of SEQ ID NO: 1 that increases tissue tropism of a virus to the kidney, wherein the mutated region of amino acid 561-588 of SEQ ID NO: 1 has a sequence selected from the group consisting of: DEEEIATTNPVATEQYGDVSENLMHFQN (SEQ ID NO: 3); DEEEIRQTNPVATEGYGEVSTNLMHGNK (SEQ ID NO: 4); DEEEIRTTNPVATEQYGIVnStTNLNEGNR (SEQ ID NO: 5); DEEEIRTTNPVATECYGSVSTDLQSGNL (SEQ ID NO: 6); DENEIRTTNPVATEIYGSVSTeNLQNnGdNR (SEQ ID NO: 7); DEEEIRTTNPVATEQYGSVSeTNpLvQNGdDR (SEQ ID NO: 8); DEEEIRTTNPVATEQYGDVSENLMHFQN (SEQ ID NO: 9).

[0029] Another aspect of the technology described herein provides an AAV2 capsid polypeptide comprising a mutation in the region of amino acids 561-588 of SEQ ID NO: 1 that increases tissue tropism of a virus to the liver, wherein the mutated region of amino acid 561-588 of SEQ ID NO: 1 has a sequence selected from the group consisting of: DEEEIRTTNPVATEQYGVVSDNLQRGNR (SEQ ID NO: 10); DECEIRTTNPVATEQYGSVGENLQRGNR (SEQ ID NO: 11); DEEEIRTTNPVATEQYGVVSENLQRGNR (SEQ ID NO: 12); DESEITTTNPVATEQYGWVSTNQQRGNR (SEQ ID NO: 13); HELEIATTNPVATEQYGSASTNIQRGNR (SEQ ID NO: 14); DEEEIATTNPVATEQYGGVSTNLQRGNR (SEQ ID NO: 15).

[0030] Another aspect of the technology described herein provides an AAV2 capsid polypeptide comprising a mutation in the region of amino acids 561-588 of SEQ ID NO: 1 that increases tissue tropism of a virus to the lung, wherein the mutated region of amino acid 561-588 of SEQ ID NO: 1 has a sequence selected from the group consisting of: DEEEIVTTNPVATEQYGNVSTNLQRGNR (SEQ ID NO: 16); DEDEISTTNPVATEQYGSCSTNLQRGNR (SEQ ID NO: 17); QEEEIRTTNPVATEQYGSVSTNLQRGDR (SEQ ID NO: 18); NEEEIRTTNPCATEVYGSVSTNLQRGNR (SEQ ID NO: 19); DEQEIVTTNPVATEVYGTVSTNLQRGNR (SEQ ID NO: 20).

[0031] Another aspect of the technology described herein provides a method of altering tropism of a virus comprising a capsid polypeptide corresponding to the polypeptide of SEQ ID NO: 1, the method comprising introducing a mutation in at least 2 regions selected from the group consisting of: amino acids 440-460 of SEQ ID NO: 1, amino acids 475-505 of SEQ ID NO: 1, amino acids 518-532 of SEQ ID NO: 1, and amino acids 560-590 of SEQ ID NO: 1.

[0032] Another aspect provides a viral capsid polypeptide bearing a mutation relative to SEQ ID NO: 1 (WT AAV2) that alters packaging efficiency of a virus comprising the viral capsid polypeptide, wherein the mutation is selected from the mutations in Table 16.

[0033] *Definitions*

[0034] As used herein the term "alters tropism" refers to a mutation or set of mutations that changes the efficiency with which a viral vector delivers a nucleic acid to a given tissue or cell type. The tropism of a vims or viral vector is generally defined by the structure of its outer surface that interacts with receptors or other cell surface determinants on target cells. For AAV vectors, among others, viral vector tropism is determined primarily by viral capsid polypeptides, and as described herein, the tropism of such vectors can be changed by changing the amino acid sequence of the viral capsid polypeptide. An amino acid change that changes the efficiency of viral vector delivery of a nucleic acid to a target cell or tissue type by at least 10% relative to a reference vector, often, but not necessarily relative to a wild-type vector, is an altered tropism. To be clear, an altered tropism can be an increase/enrichment by at least 10% (l.lx) or a decrease/de-enrichment by at least 10% (0.9x).

[0035] As used herein, the term “increases tropism: or “increased tropism” refers to an increase in efficiency of viral vector delivery of a nucleic acid to a target cell or tissue type by at least 0.1-fold or 10% relative to a reference vector. In various embodiments, the increase in efficiency of viral vector delivery of a nucleic acid to a target cell or tissue is at least 1.1x (i.e., 10% greater), l.2x (i.e., 20% greater), at least l.5x (i.e., 50% greater), at least 2.0x (i.e., doubled), at least 5.0x or at least 10.0x greater relative to the reference vector.

[0036] As used herein, the term “decreases tropism” or “decreased tropism” refers to a decrease in efficiency of viral vector delivery of a nucleic acid to a target cell or tissue type by at least 10% relative to a reference vector. In various embodiments, the efficiency of viral vector delivery of a nucleic acid to a target cell or tissue is at most 0.9x (10% lower, or 90% of reference), at most 0.8x (20% lower, or 80% of reference), at most 0.7x (30% lower, or 70% of reference), at most 0.5x (50% lower, or 50% of reference), at most 0.3x (70% lower, or 30% of reference), at most 0.2x (80% lower, or 20% of reference), at most 0.1x (90% lower, or 10% of reference) or lower relative to the reference vector.

[0037] As used herein, the term “corresponding to,” when used in reference to an amino acid or polynucleotide sequence means that a given amino acid or polynucleotide sequence in one polypeptide or polynucleotide molecule has structural properties, functional properties, or both that are similar relative to an amino acid or polynucleotide sequence in a similar location in another polypeptide or polynucleotide molecule. Homologues of a given polypeptide in different species “correspond to” each other, as do regions or domains of homologous polypeptides from different species. Similarly, capsid polypeptides of different serotypes of viral vectors, including but not limited to adeno-associated virus (AAV) vectors, “correspond to” each other, as do regions of such polypeptides, defined, for example by alignment of their amino acid sequences. While other alignment parameters can be used to define such regions, for the avoidance of doubt, alignment can be performed using BLAST® (Basic Local Alignment Search Tool) using default parameters of version BLAST+ 2.8.0 released March 28, 2018.

BRIEF DESCRIPTION OF THE DRAWINGS

[0038] **FIG. 1** shows a heat map of all path numbers searched versus that distance from wild-type (e.g., the number of mutations relative to wild-type). Beneficial mutations, neutral mutations, and deleterious mutations are shown. Most mutations are deleterious.

[0039] FIG. 2 shows a heat map of a subset of path numbers searched versus that distance from wild-type (e.g., the number of mutations relative to wild-type. Beneficial mutations, neutral mutations, and deleterious mutations are shown. Heat map highlights that longer paths quickly die off.

[0040] FIG. 3 shows a chart plotting the fitness at first mutation versus the distance at which fitness drops below wild-type (e.g., when the virus is no longer viable). On the x-axis, 0.0 indicates to a neutral mutation (e.g., a mutation that does not alter fitness of the virus), a positive value indicates to a beneficial mutation (e.g., a mutation that increases the fitness of the virus), and a negative value indicates a deleterious mutation (e.g., a mutation that decreases the fitness of the virus). Values on the y-axis indicate the number of mutations relative to wild-type.

[0041] FIG. 4 is a line graph of path proportions showing at what mutation rate the mutation library fails. Random mutations result in a sharp decline at 1 mutation relative to wild-type, whereas fast (e.g., deep search mutations) mutations can tolerate up to 6 mutations. Deep search mutations are more than 40x more efficient that random search at distances greater than or equal to 6 mutations relative to wild-type.

[0042] FIG. 5 shows a heat map of amino acid insertions introduced into the AAV2 viral capsid polypeptide that are beneficial, neutral, or deleterious to viral packaging.

[0043] FIG. 6 shows a heat map of amino acid substitutions introduced into the AAV2 viral capsid polypeptide that are beneficial, neutral, or deleterious to viral packaging.

DETAILED DESCRIPTION OF THE INVENTION

[0044] Described herein are viral vectors with modified tropism. Such vectors provide an improvement in the degree of tissue targeting attainable with such vectors. In particular, viral vectors with capsid polypeptide mutations that modify tropism of the viral particles relative to particles with wild-type capsid polypeptide are described. Through systematic mutation of viral capsid polypeptides, specific amino acid residues and amino acid regions have been identified that when mutated increase or decrease tropism of the virus for certain tissue or cell types. This provides the ability to increase the targeting of a given tissue or cell type by a viral vector, or, conversely, to decrease the targeting of a given tissue or cell type by a viral vector depending upon the site-specific mutation(s) introduced to the capsid polypeptide. Indeed, it has been found herein that not only can one improve the tropism of a viral vector by incorporating amino acid changes that increase tropism for a desired tissue, but nucleic acid delivery can also be improved to a given tissue or cell type by reducing the efficiency with which a viral vector infects tissues or cells other than the desired tissue or cell. Mutations that achieve both of these effects, and their use to improve delivery to desired or targeted tissues or cell types are described herein. Further, it has surprisingly been found that one can combine, within a single viral capsid polypeptide, mutations that improve tropism for a desired or targeted tissue or cell type with mutations that reduce tropism for a non-desired tissue or cell type, and thereby further improve targeting efficiency of the vector.

[0045] Viruses are typically tropic for certain types of cells and or tissues in the natural host. Changes in this tropism, either increased or decreased, may be determined by selection on a natural host cell or tissue or selection on a non-natural host cell or tissue. Indeed, experiments were performed to select for increased infectivity for the following tissues: blood, brain, heart, kidney, liver, lung, and spleen. Substitution, deletion or insertion mutations that increased the infectivity in these tissues were found. These determinations were also combined with the ability of the mutant plasmids to be packaged into virions.

[0046] As detailed below herein, particular mutations have been identified and assessed for effects on viral DNA packaging and viral infectivity of particular tissues. These particular mutations are in the capsid protein. Isolated and purified compositions comprising mutant capsid proteins and nucleic acids encoding them may be used for further viral improvement, for virus preparation and manufacture, and for safety and efficacy studies. Once a mutant protein sequence is identified as beneficial, any nucleic acid codon or codons that specify such protein sequence can be used. Mutations can be combined together in a single viral nucleic acid or a single viral protein sequence for improved properties. The following describes mutations to viral capsid polypeptides that permit viral genome packaging, yet modify viral vector tropism, either positively, negatively, or both when mutations are combined, relative to given tissues or cell types. Also described are methods of using mutated viral capsid polypeptides and viral vectors comprising them to introduce nucleic acids to desired tissue or cell types with improved selectivity for those tissue or cell types. The following provides a description of the various mutations and considerations for their use to generate viral vectors with improved properties.

Generating variants and viral particles

[0047] A DNA library of AAV capsid variants was created. Initially each mutant capsid was generated with a single mutation. All possible single amino acid substitutions, insertions and deletions for AAV2 were generated. In a subsequent step, several mutations were combined within the capsid gene. Libraries of AAV2 capsid gene sequence variants were cloned into a plasmid containing the AAV Inverted Terminal Repeat regions (ITRs). The final ITR plasmids contained a cytomegalovirus (CMV) promoter upstream of the Cap gene.

[0048] AAV virus libraries were produced from the DNA libraries. The capsid library plasmids, AAV pHelper plasmids, and plasmids containing the AAV2 Rep gene were co-transfected into HEK-293 cells using PEI. Capsids were purified using standard techniques for cell lysis (freeze-thaw or addition of 5 M NaCl), treatment with benzonase to remove unpackaged genomes, and purification and concentration by iodixanol ultra-centrifugation

[0049] *In vivo* packaging ability of viral capsid variants was measured. The number of viruses that were packaged (“virus”) compared to the number of input viral genomes (“plasmid”) were determined. Measuring the frequency of capsid (or other library component) mutants before and after selection reveals which mutations are beneficial and which are deleterious based on the particular selection method.

Evaluating viral tropism

[0050] To investigate viral tropism, virus libraries were injected into mice intravenously. Blood was collected 1 hour after injection and tissue samples were collected 1-2 weeks after injection. Viral DNA was extracted from bulk biological samples using standard techniques.

[0051] The frequencies of capsid variants in biological samples, the virus libraries and the DNA libraries were measured using high-throughput DNA sequencing. Mutant frequencies were normalized by dividing the number of reads matching each mutant by the number of reads matching the AAV2 WT sequence within each sample.

[0052] Selection values, indicating enrichment or de-enrichment within a particular sample, are calculated relative to an initial library. Selection values greater than 1 indicate enrichment relative to WT. Selection values less than 1 indicate de-enrichment relative to WT.

[0053] For packaging selection, the frequencies in the viral library were compared to those in the DNA library as a reference. Enrichment means that a mutant packaged more efficiently than the WT.

[0054] For tissue selection, the frequencies in tissue samples were compared to those in the viral library as a reference. Enrichment means that a mutant was delivered more efficiently than the WT to the specified tissue. De-enrichment means that a mutant was delivered less efficiently that WT to the specified tissue.

Viral capsid polypeptide

[0055] Viral tropism refers to the cell or tissue type(s) in a host that recruit and support the growth of a virus. Various factors impact the viral tropism, including the expression of cell surface receptors and/or ligands, transcription factor expression, and expression of tropogens (e.g., cell surface glycoproteins). One aspect of the invention provides a viral capsid polypeptide bearing a mutation relative to wild-type adeno-associated virus 2 (AAV2, e.g., SEQ ID NO: 1) that alters tissue tropism of a virus comprising the viral capsid polypeptide, wherein the mutation is selected from the mutations in any one of Tables 1-9. In one embodiment, the tissue is blood, heart, kidney, liver, lung, or spleen.

[0056] In one embodiment, the tropism is increased, e.g, the virus comprising the mutated viral capsid polypeptide more efficiently delivers nucleic acid to the target cell type as compared a virus comprising the wildtype viral capsid polypeptide. In one embodiment, tropism is at least 1.1-fold (e.g., 10% greater than reference level, or 110% of the level reference level) more efficient as compared to a wild-type viral capsid polypeptide. In one embodiment, the the delivery of a nucleic acid is at least 1.5-fold, at least 2-fold, at least 4-fold, at least 5-fold, at least 10-fold, or more, more efficient as compared a virus comprising the wildtype viral capsid polypeptide. One of ordinary skill in the art can meaure the delivery efficiency of a viral particle comprising any of the viral capsid polypeptides described herein, e.g., using PCR-based asays on an isolated targeted cell or tissue type (e.g., blood, heart, kidney, liver, lung, or spleen) to assess if the nucleic acid is expressed in that targeted cell type. The expression of the nucleic acid delivered by a viral particle comprising either a viral capsid polypeptide as described herein or a wild-type viral capsid polyprotein can be compared to determine the change in expression as a measure of the efficiency of delivery.

[0057] In one embodiment, the tropism is decreased, e.g, the virus comprising the mutated viral capsid polypeptide less efficiently delivers nucleic acid to the target cell type as compared a virus comprising the wildtype viral capsid polypeptide. In one embodiment, the tropism is decreased by at least 10%. In other embodiments, the tropism is decreased by at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 99%, or more as compared to a virus comprising the wildtype viral capsid polypeptide. Methods for measuring tropism are described herein above.

[0058] The following describes single amino acid capsid alterations that increase the tropism of a virus (e.g., AAV2) for a given tissue or cell type, e.g., blood, heart, kidney, liver, lung, or spleen. In one embodiment, a single mutation described herein is introduced to the amino acid sequence of wild-type AAV2 capsid protein (e.g., SEQ ID NO: 1) to increase or decrease tissue or cell type tropism or a virus.

[0059] SEQ ID NO: 1 is an amino acid sequence encoding wild-type AAV2 capsid protein.

MAADGYLPDWLEDTLSEGIRQWWKLKPGPPPPKPAERHKDDSRGLVLPGYKYLGPFNGLDKGEPVNE
ADAAALEHDKAYDRQLDSGDNPYLKYNHADAE FQERLKEDTSFGGNLGRAVFQAKKRVLEPLGLVEE
PVKTAPGKKRPVEHSPVEPDSSSGTGKAGQQPARKRLNFGQTGDADSVPDPQPLGQPPAAPSGLGTN
TMATGSGAPMADNNEGADGVGNSSGNWHCDSTWMGDRVITTSTRTWALPTYNNHLYKQISSQSGASN
DNHYFGYSTPWGYFDFNRFHCHFSPRDWQRLINNNWGFRPKRLNFKLFNIQVKEVTQNDGTTTIANN
LTSTVQVFTDSEYQLPYVLGSAHQGCLPPFPADVFMVPQYGYLTLNNGSQAVGRSSFYCLEYFPSQM
LRTGNNFTFSYTFEDVPFHSSYAHSQSLDRLMNPLIDQYLYYLSRTNTPSGTTTQSRLQFSQAGASD
IRDQSRNWLPGPCYRQQRVSKTSADNNNSEYSWTGATKYHLNGRDSLVNPGPAMASHKDDEEKFFPQ
SGVLIFGKQGSEKTNVDIEKVMITDEEEIRTTNPVATEQYGSVSTNLQRGNRQAATADVNTQGVLPG
MVWQDRDVYLQGPIWAKIPHTDGHFHPSPLMGGFGLKHPPPQILIKNTPVPANPSTTFSAAKFASFI
TQYSTGQVSVEIEWELQKENSKRWNPEIQYTSNYNKSVNVDFTVDTNGVY SEPRPIGTRYLTRNL
(SEQ ID NO: 1)

[0060] As used herein, "mutation" refers to any change in the amino acid sequence, e.g., a substitution, insertion, or deletion of at least one amino acid. For the mutations described herein, a substitution at a particular position is denoted by the wildtype amino acid followed by the position of the substituted amino acid followed by the identity of the substituted amino acid(s) in a parenthetical, e.g., Q101(A) means glutamine is substituted with alanine at position 101. If multiple amino acids can be substituted at a particular position, the parenthetical lists all possible single substitutions, e.g., P3l(IKRT) means that proline at position 31 is substituted with any one of isoleucine, lysine, arginine, or threonine. To denote an insertion, the amino acid position contains a decimal followed by an amino acid(s); the amino acid(s) following the decimal are inserted following the position indicated, e.g, 28.5(AGVY) means any one of alanine, glycine, valine, or tyrosine is inserted immediately after amino acid 28 and immediately before amino acid 29. To denote a deletion of an amino acid, "(-)' follows the amino acid position, e.g., A35(-) means amino acid 35 (alanine) is deleted from the sequence.

[0061] The following provides mutations to the AAV2 capsid polypeptide of SEQ ID NO: 1 that provide tropism altered by the indicated degree for cells of the indicated tissues.

Table 1: Amino acid alterations conferring more efficient delivery to blood.

Amino acid alteration	Fold increase of efficiency
D4(F), D13(HQ), Q21(FS), W22(F), W23(EGLTVY), 23.5(Y), L25(C), K26(N), 28.5(AGVY), P29(DEGSTVY), P31(IKRT), 32.5(F), K33(AFLPST), 33.5(IP), 34.5(EY), A35(-), E36(CDGV), 36.5(CW), R37(GV), 37.5(DHNW), H38(K), 38.5(DHQ), G49(W), V65(KT), K77(EG), D80(KW), R81(TY), Q82(AIL), L83(Q), D84(N), S85(FQR), G86(Q), N88(FH), K92(Q), H95(W), A98(Q), E99(T), Q101(A), E102(HIKT), K105(Y), E106(T), 107.5(F), T108(W), F110(QTW), G112(A), N113(Y), R116(AK), A117(C), Q120(DH), R124(AQ), V125(HITW), P128(G), L129(E), 129.5(P), L131(C), V132(D), 132.5(D), E134(N), 134.5(K), P135(-I), V136(AI), K137(E), 138.5(HKP), A139(FHWY), 139.5(IK), 141.5(FG), 144.5(P), P145(FG), E147(T), 147.5(Y), H148(-Q), S149(DFT), 151.5(I), E152(Y), 152.5(AV), S157(H), T159(H), A162(K), Q164(HRSW), Q165(I), P166(HNQ), 177.5(C), A179(P), 179.5(W), V182(L), D184(W), 188.5(CF), G189(CHQSY), 189.5(AEF), Q190(FNVY), 190.5(CE), P191(FH), 191.5(N), P192(NR), 192.5(F), A193(KQ), A194(-NQ), 194.5(EQW), P195(-), T202(WY), T205(CDF), A209(C), N214(D), G217(D), 237.5(N), A248(C), Q263(T), S264(G), Y272(F), R310(K), N312(E), T324(S), 324.5(R), D327(E), T344(EGHY), S346(Q), L380(V), S384(A), Q401(N), S412(A), 417.5(S), V418(C), L433(V), 445.5(D), S446(-), 446.5(DE), R447(-PWY), 447.5(DEHQ), T448(-DEH), 448.5(D), N449(H), T450(FS), 452.5(P), G453(V), T454(APQ), T455(GMS), T456(A), 456.5(A), 457.5(MT), Q464(R), 464.5(Y), S468(M), C482(MSW), Y483(W), R484(ILQV), 485.5(M), Q486(DE), R487(ACDEFGILMNPQSTVWY), 488.5(DE), S489(DE), 490.5(DE), T491(FN), 491.5(DE), A493(FS), 493.5(ENST), 494.5(E), N495(DEW), 495.5(DE), N496(DE), 496.5(DE), N497(AMP), 498.5(ST), 500.5(D), S501(D), 501.5(DE), 502.5(DE), 503.5(DE), G504(DE), 504.5(E), 505.5(E), K507(-EF), P521(I), M523(C), S525(T), 525.5(DE), K527(PQW), D528(Q), E531(DGMN), K532(ADEFGILMNPQSTVY), 532.5(DEMN), F533(DEY), 533.5(CDEGSV), 536.5(V), V539(C), V571(DE), Q575(A), Y576(M), 577.5(E), V579(VV), 579.5(CDEN), S580(ADE), 580.5(DEILMPY), T581(DSWY), 581.5(DEFILMPQV), N582(-ACDEPQ), 582.5(GP), L583(-DEGPT), 583.5(DEIPV), Q584(-DEFLNTY), 584.5(ADEIMVY), R585(-ADEFGHILMNPQSTVWY), 585.5(DE), G586(-DEP), 586.5(DEFHINVY), N587(-DE), 587.5(DEGPY), R588(-ACDEFGHILMNPQSTVWY), 588.5(DEFQTY), Q589(DEFMNY), 589.5(DEGINS), A590(DEW), 590.5(DEFY), A591(EFPQSY), 591.5(CDEQWY), T592(FY), 592.5(DEQ), A593(GLMTVW), 593.5(CDEILY), 594.5(CDEP), 595.5(C), N596(S), T597(AS), V600(AILST), L601(L), G603(G), V605(C), D608(N), R609(R), V611(C), P616(M), H623(INY), T624(C), L639(C), H641(S), I646(C), N656(AH), 657.5(Q), T660(H), S662(HWY), 662.5(I), A664(W), F666(M), A667(FR), K688(P), V708(WY), and N734(S)	1.1-fold

445.5(D), S446(-), 446.5(DE), R447(-P), 447.5(DEHQ), T448(-DE), N449(H), T454(P), 464.5(Y), C482(M), R484(ILQV), 485.5(M), Q486(DE), R487(ACDEFGILMNPQSTVWY), 488.5(E), S489(DE), 490.5(DE), T491(N), N495(DEW), 495.5(DE), N496(DE), 496.5(DE), S501(D), 501.5(D), 502.5(DE), 503.5(DE), G504(DE), K507(-E), 525.5(D), E531(GMN), K532(ADEFGILMNPSTVY), 532.5(DEM), F533(DE), 533.5(CDEGSV), V571(DE), 577.5(E), V579(V), 579.5(CDE), S580(DE), 580.5(DEILMY), T581(W), 581.5(DEFILMPQV), N582(-ACDEP), 582.5(GP), L583(-DEPT), 583.5(DEIPV), Q584(-DEFLTY), 584.5(DEIV), R585(-ADEFGHILMNPQSTVWY), 585.5(DE), G586(-DE), 586.5(DEFHY), N587(-DE), 587.5(DEP), R588(-ACDEFGHILMNPQSTVWY), 588.5(DEFY), Q589(DEFY), 589.5(DEIN), A590(DEW), 590.5(DE), A591(PY), 591.5(CDEY), T592(FY), 592.5(DE), 593.5(CDE), 594.5(CDE), 595.5(C), N596(S), and A667(FR)	1.5-fold
445.5(D), S446(-), 446.5(DE), R447(-P), 447.5(EHQ), T448(D), T454(P), 464.5(Y), R484(ILQV), 485.5(M), Q486(DE), R487(ACDEFGILMNPQSTVWY), 488.5(E), S489(DE), 490.5(D), N495(DEW), 495.5(DE), N496(DE), 496.5(DE), S501(D), 501.5(D), 502.5(E), 503.5(DE), G504(DE), K507(-), K532(ADEGILMNPSTV), 532.5(DE), F533(DE), 533.5(CDEGSV), V571(DE), 577.5(E), 579.5(DE), S580(DE), 580.5(DEILMY), T581(W), 581.5(DEFILMPQV), N582(-DEP), 582.5(GP), L583(-DEP), 583.5(DEIPV), Q584(-DEFY), 584.5(DEIV), R585(-ADEFGHILMNPQSTVWY), 585.5(DE), G586(-DE), 586.5(DEY), N587(-DE), 587.5(DEP), R588(-ACDEFGHILMNPQSTVWY), 588.5(DE), Q589(DE), 589.5(DEIN), A590(DEW), 590.5(DE), A591(PY), 591.5(DE), T592(FY), 592.5(DE), 593.5(DE), and 594.5(CDE)	2-fold
N496(DE), S501(D), G504(D), K532(DE), 581.5(DEIPV), N582(DE), 582.5(G), L583(-DE), 583.5(DEP), Q584(-DE), 584.5(DE), R585(-ADEFGHILMNPQSTVWY), 585.5(DE), G586(-D), 586.5(DE), N587(-DE), 587.5(DEP), R588(-ACDEFGHILMNPQSTVY), 588.5(DE), 589.5(DE), A590(DE), 590.5(D), 593.5(E), and 594.5(E)	5-fold
R585(D)	10-fold

Table 2: Amino acid alterations conferring more efficient delivery to heart.

Amino acid alteration	Fold increase of efficiency
E17(D), W23(GKRY), 23.5(Y), L25(C), P29(D), P31(INRT), K33(LP), 33.5(P), A35(E), 35.5(EKPQ), E36(DG), 36.5(PS), R37(K), 37.5(HSW), H38(K), 38.5(D), K39(Q), G49(W), A70(KW), K77(EKQ), R81(Y), Q82(I), S85(FQ), K92(Q), A98(Q), Q101(AN), R103(T), E106(W), T108(W), L114(F), R116(FIKQ), V118(AFV), A121(T), G130(EW), L131(C), E134(DNP), 134.5(KLS), P135(-), 135.5(V), V136(R), 136.5(A), 138.5(H), 140.5(PV), 141.5(GP), V146(G), H148(-Q), 148.5(V), P150(FN), 150.5(Y), V151(IN), 151.5(EI), E152(F), 152.5(VW), T159(K), K161(F), A162(KN), Q164(AEFW), N172(Y), 179.5(W), D180(NW), V182(I), D184(W), Q186(F), 188.5(T), G189(DEQY), 189.5(DEFIKV), Q190(-F), 190.5(EIQT), P191(H), 191.5(N), P192(G), 192.5(FK), A193(-), A194(-ENT), 194.5(EW), P195(-), T205(F), S243(C), I260(L), Q263(A), S264(G), S267(S), R310(K), D327(E), T344(EP), S346(Q), S356(N), Q359(D), S384(S), V387(M), R389(S), T414(V), V418(C), S422(G), L433(A), I438(N), Y444(F), 448.5(S), N449(A), T450(M), S452(M), T454(LQ), 455.5(A), T456(AV), Q457(DLV),	1.1-fold

S458(AP), 458.5(Q), R459(FH), Q464(AI), A467(CGNPQ), S468(ADG), D469(AENQST), I470(LMV), R471(CKM), C482(M), Q486(N), R487(ACGIMQSTV), S489(AD), 490.5(N), T491(FLW), 492.5(M), A493(M), N496(DHSY), N497(PV), S498(FM), Y500(M), T506(S), V517(I), S525(AG), H526(CNST), E531(D), K532(ADEFGILMNQRST), I541(C), K544(CGTVY), Q545(E), K549(Q), N551(Y), V552(Q), K556(DNY), D561(Q), R566(ASV), T567(S), S578(TV), V579(V), S580(A), T581(WY), 581.5(IV), N582(DE), L583(DE), 584.5(EIV), R585(-ADFGHILMNQSTVWY), G586(DE), N587(DE), 587.5(D), R588(ACDEFHILMNQSTVY), 588.5(DE), Q589(M), A590(P), A591(ETY), 591.5(CDE), T592(F), 594.5(D), T597(ANSW), Q598(L), V600(AS), W606(F), V611(C), T624(C), H641(QS), L647(F), N656(A), P657(P), S658(P), T659(A), S662(FQ), A664(L), A667(N), Q687(K), V708(WY), N709(A), and N734(P)	
37.5(H), S264(G), D327(E), R389(S), D469(AQS), I470(LM), R471(K), R487(A), S489(D), 490.5(N), T491(W), N496(D), S498(M), K532(ADEL), D561(Q), N582(DE), L583(E), 584.5(V), R585(-AGHIMNQSTVWY), N587(DE), R588(ADEFILMNQSTVY), 588.5(DE), Q589(M), 591.5(D), T597(W), and V600(A)	1.5-fold
R471(K), K532(D), N582(D), L583(E), R585(Q), N587(DE), R588(MQTV), and 588.5(E)	2-fold

Table 3: Amino acid alterations conferring more efficient delivery to kidney.

Amino acid alteration	Fold increase of efficiency
D13(Q), E17(D), Q21(F), W23(G), L25(C), 28.5(Y), P29(D), P31(KRST), K33(ART), 34.5(AY), 35.5(E), E36(DGV), 36.5(S), R37(GK), 37.5(DHSW), H38(KN), 38.5(Q), E63(S), V65(K), A70(K), K77(KQ), A78(E), D80(W), R81(HTY), Q82(I), S85(FGQ), N88(V), K92(Q), E99(A), Q101(N), E102(T), R103(T), E106(W), F110(K), G112(AS), R116(IKQ), V118(AF), Q120(FH), R124(E), L126(DH), E127(L), L129(A), 129.5(P), G130(E), L131(Q), E134(P), 134.5(KPRSWY), P135(-), 135.5(V), V136(AR), 137.5(K), 138.5(PW), 140.5(PV), 141.5(A), 145.5(FY), V146(P), 146.5(E), 147.5(Y), H148(-EQ), S149(D), P150(F), 150.5(Y), V151(IN), 152.5(V), P153(P), A162(T), Q164(EL), Q165(I), D180(NW), S181(E), Q186(WY), L188(F), 188.5(Q), G189(DEQ), 189.5(AKN), Q190(FY), 190.5(EQT), P191(KPP), 191.5(F), P192(V), 192.5(EIK), A193(-), 194.5(DE), T200(Y), N201(HY), T205(D), G217(D), Q263(A), S264(G), R310(K), D327(E), T344(AHP), V387(M), R389(S), T410(Q), A425(S), 446.5(D), 447.5(HQ), N449(ACGS), T456(AG), 456.5(G), R459(HK), Q464(A), A467(GNP), S468(AG), D469(AEQST), I470(LMV), R471(K), C482(M), Q486(D), R487(P), S489(E), 490.5(N), T491(F), A493(FI), N495(E), 495.5(DE), N496(EHS), 496.5(D), N497(P), S498(M), Y500(M), S501(D), 501.5(D), G504(D), N518(S), H526(CS), K532(DER), 532.5(D), F533(Y), K544(ILTV), T550(G), K556(N), D561(Q), R566(AV), S578(TV), V579(V), S580(A), 580.5(IMY), 581.5(EFILMPQV), N582(-ACDEP), 582.5(GP), L583(-DEIP), 583.5(DEIPV), Q584(-EFY), 584.5(DEILV), R585(-DEINPQVW), 585.5(D), G586(-), 586.5(DEIY), N587(-D), 587.5(DEP), R588(-ACDEGHLNPQTV), 588.5(DE), Q589(MP), 589.5(DE), A590(DEPV), 590.5(DE), A591(PST), 591.5(C), A593(M), 593.5(CE), T597(ASW), Q598(L), V600(A), V611(C), H623(IY), H627(F), P630(M), L639(C), H641(NQS), S658(AP), T659(V), F666(M), and V708(WY)	1.1-fold

R389(S), D469(AQ), I470(L), R471(K), 490.5(N), 495.5(DE), N496(EHS), S498(M), S501(D), K532(D), 580.5(I), 581.5(EILMPV), N582(-D), 582.5(GP), L583(DE), 583.5(DEIPV), Q584(-EFY), 584.5(IL), R585(-IP), G586(-), N587(-), 587.5(P), R588(-CDGV), 588.5(D), 589.5(DE), A591(P), 591.5(C), 593.5(C), T597(W), and V600(A)	1.5-fold
R389(S), R471(K), K532(D), 581.5(IM), L583(DE), 583.5(D), 584.5(L), G586(-), N587(-), 587.5(P), R588(-), 591.5(C), and 593.5(C)	2-fold

Table 4: Amino acid alterations conferring more efficient delivery to liver.

Amino acid alteration	Fold increase of efficiency
E17(D), P31(Q), K33(HV), 35.5(KW), E36(D), 36.5(EY), R37(QT), 37.5(H), H38(K), A70(EG), K77(Q), A78(DE), D80(KW), R81(HY), Q82(A), L83(I), D84(N), S85(FGQ), N88(F), L91(Y), A98(Q), E99(AL), Q101(NT), E102(KT), R103(QW), K105(D), E106(A), 107.5(F), F110(QT), V118(CFV), Q120(DN), R124(Q), V125(IT), L126(T), E127(S), L129(HP), 129.5(P), 133.5(T), E134(HRV), 134.5(S), P135(L), 139.5(IQ), P140(I), G141(P), K142(V), 145.5(A), H148(FP), 148.5(D), 149.5(D), 150.5(H), 151.5(K), E152(S), 152.5(A), P153(P), S157(Y), T159(KN), 163.5(Q), Q164(AF), 177.5(F), D178(C), A179(Q), G189(DFQS), 189.5(HISTVY), Q190(F), 190.5(EKLN), P191(GT), 191.5(DN), 192.5(A), A193(-), A194(N), 194.5(W), S196(A), T205(N), A212(E), A248(C), I260(M), Q263(A), S264(G), Y275(W), Q325(T), D327(E), T329(H), T331(Q), T344(AHPY), S356(GN), M371(H), V387(M), R389(S), T414(Y), S423(S), L433(AC), I438(CS), Y444(F), N449(S), T450(IV), S452(A), 455.5(A), T456(V), Q457(T), S458(AP), R459(HKT), L460(CN), A467(CGPQ), S468(G), D469(AENQST), I470(LMV), R471(CKM), C482(IM), Y483(M), Q486(N), 490.5(N), T491(DE), A493(MP), N496(HS), S498(AFLM), Y500(M), T503(V), T506(ACV), K507(S), V517(I), S525(G), H526(ACNST), K532(HINQWY), F533(Y), K544(C), 545.5(D), T550(E), I554(L), K556(ENY), M558(F), D561(Q), E563(D), R566(ACGNSTV), T567(S), S578(DEIT), V579(V), S580(A), T581(DM), L583(I), A590(IP), A591(DEQS), T592(S), A593(DET), N596(C), T597(ACDHLNQW), Q598(ILMV), V600(AST), W606(F), Q607(M), V611(C), H623(NQ), T624(A), L639(C), H641(STVW), N656(H), 657.5(A), S658(W), 658.5(T), S662(F), A663(D), A664(PS), F666(HM), Q687(K), V708(FW), N709(A), and N734(P)	1.1-fold
L91(Y), V118(V), G189(F), S264(G), Y275(W), V387(M), R389(S), R459(H), L460(N), A467(CGPQ), D469(AEQST), I470(LM), R471(K), C482(I), Q486(N), N496(H), S498(M), H526(CNS), K532(N), K544(C), T550(E), K556(Y), R566(AGTV), A590(P), A591(E), A593(DE), T597(HNQ), V611(C), V708(W), and N709(A)	1.5-fold
R389(S), A467(G), D469(AEQS), I470(L), R471(K), Q486(N), N496(H), S498(M), H526(S), T550(E), A593(DE), and T597(N)	2-fold

Table 5: Amino acid alterations conferring more efficient delivery to lung.

Amino acid alteration	Fold increase of efficiency
E17(D), W23(T), L25(C), K33(T), 35.5(DE), E36(DV), 36.5(AP), 37.5(DSW), H38(N), 38.5(DQ), K39(P), 42.5(Y), E63(DR), A70(K), K77(EQR), R81(L), L83(I), D84(N), S85(FQ), K92(Q), A98(FQ), E99(V),	1.1-fold

Q101(N), E102(T), K105(F), F110(K), R116(FIQ), V118(V), E127(GL), L129(A), 129.5(P), 134.5(HKS), 135.5(PV), V136(P), 137.5(K), 140.5(APT), 141.5(AP), 145.5(FY), V146(HI), H148(-EQW), S149(W), 149.5(D), P150(I), V151(N), 151.5(NS), E152(S), 152.5(V), P153(P), S157(W), T159(EIQ), K161(F), A162(W), Q164(DEHLW), S181(E), D184(W), Q186(Y), L188(F), G189(DEQ), 189.5(DEK), 190.5(EINY), P191(GP), 192.5(P), A193(Q), A194(N), 194.5(D), T205(D), N214(D), Q263(AN), S264(G), S267(S), R310(K), T324(S), D327(E), T329(H), T344(AP), S356(N), V387(M), R389(S), T410(DQ), T414(R), V418(C), Y444(F), N449(Q), T450(I), S452(M), T454(IQ), T455(G), S458(AP), 458.5(Q), R459(F), Q461(G), A467(CGNPQ), S468(G), D469(AENQST), I470(LMV), R471(K), 490.5(N), T491(QW), N497(P), N518(M), P521(V), F533(Y), V539(C), K544(C), Q545(N), T550(A), K556(N), D561(Q), S578(T), S580(A), Q589(M), A590(P), A593(T), T597(AS), V600(A), W606(F), V611(C), H623(NY), L639(C), H641(NQS), I646(C), N656(A), P657(P), S658(AP), 658.5(Q), T659(AHV), S662(FQ), A667(N), S679(C), V708(W), and N709(A)	
S264(G), A467(G), D469(AQT), I470(M), R471(K), 490.5(N), and V600(A)	1.5-fold

Table 6: Amino acid alterations conferring more efficient delivery to spleen.	
Amino acid alteration	Fold increase of efficiency
E12(C), E17(D), Q21(DF), W23(G), 23.5(Y), P29(Y), P31(IT), 33.5(P), E36(D), 36.5(C), 37.5(HW), H38(K), 38.5(Q), E63(PS), V65(K), K77(E), D80(GKW), R81(GLTY), Q82(I), L83(I), D84(EN), S85(FQR), N88(F), H95(W), A98(Q), E99(AT), E102(IT), K105(F), E106(W), 107.5(F), T108(W), F110(KQW), G112(A), N113(Y), R116(F), Q120(HK), R124(A), V125(T), L129(E), 129.5(P), G130(ALW), L131(C), 132.5(D), 133.5(I), E134(N), 134.5(KRS), P135(-), 135.5(PVY), V136(-), 136.5(I), 138.5(GHP), A139(FHNVW), 139.5(F), P140(E), 140.5(W), G141(E), 141.5(FG), K142(N), 142.5(I), 144.5(P), P145(F), V146(P), 147.5(LQVY), H148(QY), 148.5(W), S149(D), 149.5(P), P150(Y), 150.5(Q), 151.5(IP), E152(WY), 152.5(A), P153(P), A162(K), Q164(EPRS), P166(Q), A179(P), D184(W), 188.5(D), G189(DEQVY), 189.5(AHY), Q190(F), 190.5(ELQY), 191.5(D), P192(NRY), 192.5(F), A193(K), A194(N), 194.5(EW), P195(-), N201(Y), T205(CDHN), A209(C), N214(D), E216(D), Q263(N), S264(A), Y272(F), N312(K), D327(E), 327.5(G), T344(AEHPY), F370(F), M371(H), V372(I), Q401(N), L445(I), S458(A), R459(K), S468(G), D469(Q), T491(LQ), Y500(W), F533(Y), I541(C), M558(F), V579(V), S580(A), Q589(MN), A590(P), A591(S), A593(MT), T597(AMY), V600(AIT), V605(C), W606(F), D608(N), V611(C), H623(Y), T624(C), L639(C), H641(NQS), 658.5(T), T659(N), S662(H), 662.5(I), A664(Q), A667(F), T716(A), and N734(A)	1.1-fold
Q589(M), and V600(A)	1.5-fold

Table 7: Amino acid alterations that reduce delivery to liver.	
Amino acid alteration	Fold increase of efficiency
4.5(HNV), 21.5(F), 23.5(E), 42.5(T), 45.5(M), K51(Y), Y52(D), P55(Y), G58(C), 82.5(D), 98.5(C), 144.5(N), P166(K), G174(H), D180(M), 180.5(M), 183.5(M), 184.5(M), G217(F), Q259(P), Q263(-), S264(-),	0.1-fold

265.5(D), S267(E), 267.5(E), N268(E), 268.5(E), 269.5(D), N270(HY), R307(Y), 324.5(K), 379.5(DE), L380(E), N381(DMQ), 382.5(D), 383.5(E), 386.5(D), V387(E), G406(E), 412.5(Q), 431.5(Y), R432(-), D439(K), 444.5(CM), 445.5(ACDEGHILMNQS), S446(-), 446.5(ACEFGHIMNPQSTVWY), R447(-IPWY), 447.5(DEFGHIMNPQVW), T448(-DEGHILMNPQVWY), 448.5(DENP), N449(P), 449.5(E), G453(K), 453.5(Y), T454(F), 454.5(Y), T456(H), L460(WY), 460.5(W), S463(QV), 463.5(F), 469.5(E), R471(EG), D472(MT), S474(I), 475.5(SW), 476.5(L), 478.5(L), P479(T), 479.5(D), G480(Y), C482(W), 483.5(QV), R484(EFGHILMSVY), 484.5(N), 485.5(IKM), Q486(AFIMVWY), 486.5(FV), R487(DEFPY), 487.5(FW), V488(EH), 488.5(DEILMPQSWY), S489(-EFHKLMPQTY), 489.5(DGMPQRT), K490(-P), 490.5(HPQ), T491(P), 491.5(PW), 492.5(H), A493(H), 493.5(H), D494(FR), 494.5(AFGHILMNPVY), N495(-ADEFGHILPQSTVWY), 495.5(ACDFGILMNPSTV), N496(-EGL), 496.5(ADEFGHILNPSVY), N497(-), 497.5(ADEFGIPQSY), S498(-CEIPR), 498.5(DEGNPSVY), E499(CI), 499.5(ACDEGILMNPQSTVWY), Y500(-ACEGIKNP), 500.5(ADEFGHILMNPQSTVWY), S501(-IL), 501.5(ACDEFGHILMNQRSTVWY), W502(I), 502.5(ADEFGMNY), T503(E), 503.5(DEFGILMNQSW), G504(-DEHILMNPQSVWY), 504.5(ACDFHILMNPSTVWY), A505(DEILMNPY), 505.5(ACDEFGILMQTV), T506(M), 506.5(ACISVW), K507(-EF), 510.5(K), N511(EY), 523.5(A), 524.5(CGHST), 525.5(ACDFGILNPQSTVWY), H526(DKLP), 526.5(ACDEFGHMPQSVWY), K527(-DW), 527.5(ADEGHILMPQSVWY), D528(FPSW), 528.5(DPT), D529(ES), 529.5(DGLMNV), E530(NPW), 530.5(AEFIMNQTVWY), 531.5(ADFIKLNPQRSTVY), K532(-), 532.5(ACDFGHIKLMPQSTVWY), F533(D), 533.5(ACDFGHILNPQSTVWY), 534.5(F), P535(-F), Q536(-PW), 536.5(CITV), V571(DH), T573(IW), 573.5(T), 575.5(WY), Y576(V), 576.5(W), G577(D), 577.5(DEHIQS), 578.5(CDEILTVY), V579(DW), 579.5(DEINQTVY), S580(-DEQY), 580.5(DMNV), T581(-), 581.5(CDGILMPQY), N582(-FHP), 582.5(DFGHPTVW), 583.5(DEGMNSTVY), Q584(-DEFGHLNPVWY), 584.5(CEILP), R585(D), 585.5(DGI), G586(-), 586.5(ADFILMNQSV), N587(-H), 587.5(ADHMPQTW), R588(-GP), Q589(-D), 589.5(CDEHKNTV), A590(DEFKLMN), 590.5(DEKMQTWY), A591(-), 591.5(GHI), 592.5(ACEGILMTWY), A593(-P), 593.5(AFLMNPQSTVWY), 594.5(ACFGILMPTVWY), 595.5(ACFGILMS), 596.5(EY), 597.5(F), 600.5(F), 606.5(P), D608(W), D610(Y), Q614(T), 617.5(I), S679(F), 705.5(Q), K706(ES), V710(M)	
4.5(FHNV), G5(C), L11(C), E17(F), G18(D), I19(N), 21.5(F), 23.5(DEN), 24.5(H), L25(GH), 25.5(CKY), 28.5(T), P30(DY), 30.5(DKLRY), P32(E), 37.5(M), 42.5(T), 45.5(M), K51(Y), Y52(D), P55(Y), 55.5(K), G58(CE), G62(Q), 79.5(C), 82.5(D), G86(C), 87.5(Q), 90.5(E), Y93(N), 98.5(CE), 103.5(V), K105(M), 116.5(E), 123.5(FQ), 125.5(ES), 132.5(W), K143(Y), 144.5(N), P145(-E), 148.5(M), S156(T), 157.5(N), G163(K), Q164(M), P166(CIK), N172(W), 173.5(NQ), G174(H), D180(M), 180.5(M), 183.5(M), 184.5(M), 189.5(M), G217(F), T251(V), Q259(P), S261(ANT), Q263(-W), S264(-EVW), 265.5(D), 266.5(E), S267(EN), 267.5(E), N268(EQ), 268.5(E), 269.5(D), N270(HQY), H271(EIV), F273(HW), R307(Y), 324.5(K), Q349(AS), F365(W), L378(V), 379.5(DE), L380(E), 380.5(E), N381(ACDGMQS), N382(S), 382.5(D), 383.5(E), 386.5(D), V387(EW), 387.5(P), G406(DEQ), 406.5(Q), N408(G), 412.5(Q), 417.5(M), H426(N), Q428(EH), 431.5(Y), R432(-), D439(K), 444.5(CLM),	0.2-fold

445.5(ACDEGHILMNQST), S446(-ELNV), 446.5(ACDEFGHILMNPQSTVWY), R447(-DEFIPWY), 447.5(ACDEFGHILMNPQVWY), T448(-DEFGHILMNPQVWY), 448.5(DEFHNPY), N449(-P), 449.5(E), T450(-), 450.5(E), 451.5(N), G453(FK), 453.5(INY), T454(F), 454.5(DY), T456(H), 456.5(E), R459(P), 459.5(P), L460(WY), 460.5(W), S463(KQV), 463.5(F), 464.5(SY), 466.5(E), 469.5(E), R471(EGQ), D472(MT), S474(I), R475(H), 475.5(SW), 476.5(L), W477(F), 477.5(L), 478.5(L), P479(T), 479.5(D), G480(Y), 481.5(G), C482(W), 483.5(QV), R484(EFGHILMQSTVY), 484.5(N), 485.5(EIKM), Q486(ACEFILMPVWY), 486.5(FV), R487(DEFKLMPSTY), 487.5(FW), V488(EGHMNY), 488.5(ACDEGILMPQSWY), S489(-EFHIKLMNPQTVY), 489.5(ADGLMPQRST), K490(-DP), 490.5(DHPQ), T491(P), 491.5(AEFHLPTVWY), S492(-), 492.5(EGHQ), A493(H), 493.5(EHMNQ), D494(FR), 494.5(AFGHILMNPVY), N495(-ADEFGHILMPQSTVWY), 495.5(ACDEFGILMNPSTVWY), N496(-EGLMQ), 496.5(ADEFGHILNPSTVWY), N497(-CHW), 497.5(ADEFGIMNPQSTY), S498(-CDEINPRW), 498.5(ADEFGILMNPQSVWY), E499(CIPS), 499.5(ACDEGILMNPQRSTVWY), Y500(-ACEGHIKLNPTV), 500.5(ADEFGHILMNPQSTVWY), S501(-DILP), 501.5(ACDEFGHILMNPQRSTVWY), W502(-CEFILSV), 502.5(ADEFGILMNPSTVWY), T503(AEFGMQ), 503.5(ADEFGILMNPQSTVW), G504(-CDEFHILMNPQSTVWY), 504.5(ACDEFGHILMNPQSTVWY), A505(DEFHILMNPQTVWY), 505.5(ACDEFGILMPQTVWY), T506(MP), 506.5(ACIPSTVW), K507(-EFY), H509(F), 509.5(K), 510.5(K), N511(ACDELWY), 512.5(S), R513(H), D514(LV), S515(I), 523.5(A), 524.5(CGHST), S525(M), 525.5(ACDFGILMNPQSTVWY), H526(DKLP), 526.5(ACDEFGHILMNPQSTVWY), K527(-DEFHPWY), 527.5(ACDEFGHILMPQSVWY), D528(EFMPSVW), 528.5(DEPT), D529(ES), 529.5(DEGLMNPV), E530(NPVW), 530.5(AEFGHIKLMNQRSTVWY), E531(CFIV), 531.5(ADFGIKLMNPQRSTVY), K532(-), 532.5(ACDEFGHIKLMPQSTVWY), F533(ADEGQSV), 533.5(ACDEFGHILNPQSTVWY), F534(I), 534.5(F), P535(-F), Q536(-DFPW), 536.5(ACITV), S537(-), 537.5(T), G538(-), V539(H), 542.5(Q), 544.5(F), S547(-), 548.5(H), 550.5(EKM), 551.5(IMQ), E555(HN), V571(DEFHLMQY), T573(CHIW), 573.5(T), E574(LM), 575.5(WY), Y576(CGHV), 576.5(EFWY), G577(DW), 577.5(ACDEHIMQSV), 578.5(ACDEFILSTVY), V579(DW), 579.5(CDEFGILMNQTVY), S580(-DEFILMNQY), 580.5(ADEFGLMNTV), T581(-), 581.5(ACDEGILMNPQTVY), N582(-AFGHMPWY), 582.5(DFGHPTVW), L583(-DGP), 583.5(DEGMNPSTVY), Q584(-ADEFGHILMNPTVWY), 584.5(CEILP), R585(-DPV), 585.5(DEGILMVW), G586(-), 586.5(ADEFGILMNQSTVY), N587(-H), 587.5(ADEHILMNPQSTVW), R588(-GPWY), 588.5(GHLMP), Q589(-DENTVY), 589.5(ACDEFHKNTVW), A590(DEFHKLMNQY), 590.5(CDEFGIKMQSTWY), A591(-), 591.5(CFGHILMPST), T592(-), 592.5(ACDEFGILMNQSTVWY), A593(-P), 593.5(ACFGILMNPQSTVWY), D594(L), 594.5(ACEFGHILMPQSTVWY), 595.5(ACFGILMNQSVW), 596.5(EY), 597.5(F), G599(W), 600.5(F), 606.5(P), D608(W), D610(Y), 610.5(F), Q614(T), 617.5(I), M634(C), 662.5(W), S679(FIY), E681(D), 704.5(AI), 705.5(Q), K706(EST), 709.5(Q), V710(M), 710.5(D)	
4.5(FHNV), G5(-C), 5.5(K), W10(CEKQRS), 10.5(HI), L11(C), 11.5(K),	0.3-fold

E12(I), D13(IY), E17(F), G18(D), I19(NQ), 21.5(FY), W22(V), 22.5(IM), W23(D), 23.5(ADEFHLNQT), 24.5(DEHIN), L25(GHN), 25.5(CIKLQVY), K26(Y), 26.5(N), 28.5(EILNST), P29(W), P30(DY), 30.5(DKLRY), P32(EGS), 37.5(M), S42(-), 42.5(T), 43.5(V), 45.5(M), K51(CY), Y52(D), P55(Y), 55.5(KY), G58(CE), D60(C), K61(-), G62(Q), L73(K), 78.5(D), 79.5(C), 81.5(W), 82.5(D), 83.5(Y), 84.5(Q), G86(C), 87.5(EQ), P89(H), 90.5(E), Y93(N), 93.5(Y), A96(QV), 98.5(CE), 103.5(V), K105(M), 105.5(C), 111.5(A), 112.5(CQ), N113(DW), 113.5(N), G115(-FP), 116.5(EQ), 117.5(FQ), V118(DR), 118.5(AC), F119(Q), 120.5(GR), 122.5(Q), 123.5(AFQT), R124(-), 124.5(CHK), 125.5(AEFS), L126(-), P128(F), 129.5(F), 130.5(K), 132.5(W), A139(D), P140(D), K142(D), 142.5(E), K143(VY), 143.5(EPTY), R144(P), 144.5(AN), P145(-E), 145.5(EMT), 148.5(M), 150.5(M), S156(T), 157.5(N), G163(K), Q164(M), 164.5(KP), P166(-CIK), 166.5(T), N172(DW), 173.5(INQ), G174(HTY), 174.5(K), D180(M), 180.5(M), 183.5(M), 184.5(M), G189(M), 189.5(M), Q190(M), P192(M), G217(F), S225(R), H229(D), 237.5(Q), T251(V), Q259(PS), S261(ANT), Q263(-DFW), S264(-DEVW), 265.5(ADS), A266(S), 266.5(AE), S267(ENP), 267.5(E), N268(EQ), 268.5(E), 269.5(D), N270(HQY), H271(EINV), F273(HW), R307(Y), P308(-), 324.5(K), Q325(K), A333(N), Q349(AS), F365(W), A367(P), L378(V), T379(G), 379.5(DE), L380(EMQ), 380.5(E), N381(ACDGMQS), N382(CEST), 382.5(D), 383.5(E), 384.5(D), A386(PT), 386.5(D), V387(EW), 387.5(P), S390(DT), 395.5(W), P399(Q), G406(DEQ), 406.5(Q), N408(DGM), F409(H), 412.5(Q), 416.5(E), 417.5(KM), H426(N), Q428(EH), S429(GP), L430(V), 431.5(Y), R432(-I), D439(KNY), 444.5(CLM), L445(FY), 445.5(ACDEGHILMNQST), S446(-ELNV), 446.5(ACDEFGHILMNPQSTVWY), R447(-DEFILMPVWY), 447.5(ACDEFGHILMNPQSVWY), T448(-ACDEFGHILMNPQVWY), 448.5(DEFGHINPY), N449(-DEHP), 449.5(ELP), T450(-), 450.5(E), 451.5(N), G453(AFKLQ), 453.5(INY), T454(FIN), 454.5(DFY), 455.5(H), T456(DEHN), 456.5(EH), S458(DEW), 458.5(HLMN), R459(-P), 459.5(P), L460(WY), 460.5(W), F462(Y), S463(GKQV), 463.5(F), 464.5(SY), 466.5(E), S468(CD), 469.5(E), R471(DEGQV), D472(LMTWY), S474(I), R475(H), 475.5(SW), 476.5(L), W477(F), 477.5(L), 478.5(L), P479(GT), 479.5(D), G480(Y), 481.5(GHY), C482(W), 483.5(QV), R484(EFGHILMQSTVY), 484.5(N), Q485(AG), 485.5(EIKM), Q486(ACEFILMPVWY), 486.5(FV), R487(ACDEFGKLMNPQSTVY), 487.5(FW), V488(EFGHMNQY), 488.5(ACDEFGILMPQSWY), S489(-EFHIKLMNPQTVWY), 489.5(ADEGLMPQRSTV), K490(-DGP), 490.5(CDHMPQTY), T491(-P), 491.5(AEFGHILPQTVWY), S492(-), 492.5(EGHLQ), A493(-H), 493.5(DEHIKMNPQ), D494(FR), 494.5(AFGHILMNPQTVY), N495(-ADEFGHILMPQSTVWY), 495.5(ACDEFGILMNPSTVWY), N496(-EGLMPQW), 496.5(ADEFGHILMNPSTVWY), N497(-CGHLWY), 497.5(ADEFGILMNPQSTY), S498(-CDEINPRW), 498.5(ADEFGHILMNPQSVWY), E499(CIPS), 499.5(ACDEGILMNPQRSTVWY), Y500(-ACEGHIKLNPSTV), 500.5(ADEFGHILMNPQSTVWY), S501(-DILPVW), 501.5(ACDEFGHILMNPQRSTVWY), W502(-ACDEFGILMPQSV), 502.5(ADEFGILMNPQSTVWY), T503(-ADEFGHLMNQW), 503.5(ADEFGILMNPQSTVW), G504(-CDEFHILMNPQSTVWY), 504.5(ACDEFGHILMNPQSTVWY), A505(-CDEFHILMNPQTVWY), 505.5(ACDEFGILMPQSTVWY), T506(FLMP), 506.5(ACIPSTVW), K507(-EFY), H509(FK), 509.5(K), 510.5(K), N511(ACDEGLMSWY), 512.5(S), R513(H), D514(CFILMV), S515(I), N518(V), P521(M), 523.5(A), A524(G), 524.5(ACGHST), S525(M), 525.5(ACDEFGILMNPQSTVWY),	

H526(DIKLMPV), 526.5(ACDEFGHILMNPQSTVWY), K527(-DEFHPSWY), 527.5(ACDEFGHILMPQSTVWY), D528(EFMPSVW), 528.5(DEPT), D529(ES), 529.5(DEGLMNPV), E530(NPVW), 530.5(ACDEFGHIKLMNQRSTVWY), E531(CFILV), 531.5(ADFGIKLMNPQRSTVY), K532(-CP), 532.5(ACDEFGHIKLMNPQSTVWY), F533(ADEGIQSV), 533.5(ACDEFGHILNPQSTVWY), F534(ILVY), 534.5(F), P535(-F), Q536(-ADFGHPWY), 536.5(ACILTV), S537(-), 537.5(T), G538(-), V539(H), 542.5(Q), 543.5(P), K544(-), 544.5(FY), 545.5(W), 546.5(Q), S547(-), 547.5(NSY), E548(F), 548.5(CH), 549.5(D), 550.5(EKMQ), N551(P), 551.5(AEIMQ), 552.5(V), E555(HN), D561(I), 565.5(Y), R566(D), 567.5(E), P570(Q), 570.5(M), V571(ADEFHLMQY), T573(ACGHIWY), 573.5(T), E574(CFLM), 575.5(WY), Y576(ACGHIMV), 576.5(EFWY), G577(DW), 577.5(ACDEHIMQSTV), S578(F), 578.5(ACDEFILNSTVY), V579(DW), 579.5(ACDEFGILMNQTVWY), S580(-DEFILMNQY), 580.5(ACDEFGLMNTV), T581(-P), 581.5(ACDEGILMNPQTVY), N582(-ADFGHKMPSWY), 582.5(DFGHNPSTVW), L583(-DGPW), 583.5(DEGMNPSTVY), Q584(-ADEFGHILMNPTVWY), 584.5(CEFGHILPV), R585(-CDILNPVY), 585.5(DEFGILMNPQSTVW), G586(-), 586.5(ADEFGHILMNQSTVY), N587(-EFHY), 587.5(ADEHILMNPQSTVW), R588(-ADGPSWY), 588.5(DFGHLMP), Q589(-DEINRTVY), 589.5(ACDEFHIKMNPTVWY), A590(DEFHKLMNQY), 590.5(ACDEFGIKLMQSTVWY), A591(-P), 591.5(ACFGHILMNPQSTV), T592(-M), 592.5(ACDEFGILMNQSTVWY), A593(-P), 593.5(ACEFGILMNPQSTVWY), D594(LT), 594.5(ACDEFGHILMNPQSTVWY), V595(WY), 595.5(ACDFGHILMNQSTVW), N596(EPQ), 596.5(DEY), T597(P), 597.5(F), Q598(G), G599(W), 600.5(F), L601(W), P602(C), 606.5(P), D608(W), D610(Y), 610.5(F), Q614(T), I617(K), 617.5(I), H629(W), M634(C), 640.5(N), 657.5(C), 658.5(C), 659.5(C), T660(H), F661(I), 661.5(C), 662.5(W), 663.5(CW), 665.5(RW), F666(C), 667.5(Y), S679(FIY), E681(D), 699.5(E), 703.5(AEL), 704.5(AILN), 705.5(QY), K706(EST), S707(L), 707.5(Y), V708(N), 708.5(I), N709(P), 709.5(PQ), V710(M), 710.5(D), D711(G), T716(R), S721(H), P723(D), R724(F)	
1.5(M), A3(CD), 3.5(I), 4.5(AFHNVY), G5(-C), 5.5(FKM), 6.5(N), W10(ACEGKPQRSTY), 10.5(HI), L11(AC), 11.5(K), E12(FI), D13(EIKWY), T14(CDQ), L15(HT), E17(CFVY), G18(D), I19(EGHNQT), R20(Q), 21.5(FWY), W22(IV), 22.5(IMWY), W23(DK), 23.5(ADEFGHLNQSTWY), 24.5(CDEHILN), L25(EFGHNQR), 25.5(CEIKLNQRSTVWY), K26(Y), 26.5(NQ), P27(T), 28.5(AEFILNPQSTW), P29(DEQRSTW), P30(DFHQRSY), 30.5(DEKLNQRTY), P31(H), 31.5(AFV), P32(EGIRS), 32.5(DEKNP), K33(Q), 33.5(CKNVWY), 34.5(FQ), A35(HNQY), E36(H), 36.5(IN), R37(DN), 37.5(M), H38(W), 38.5(G), K39(F), 39.5(DY), D40(-ACNY), 40.5(Y), D41(H), 41.5(NW), S42(-LVW), 42.5(DT), R43(AT), 43.5(PV), 45.5(M), Y50(HW), K51(ACLMVY), Y52(D), P55(Y), 55.5(EKY), 56.5(K), G58(CE), 58.5(F), L59(CGK), 59.5(H), D60(CY), K61(-IS), 61.5(G), G62(Q), A68(T), L73(HK), E74(TW), 77.5(K), A78(FY), 78.5(ADIQ), Y79(C), 79.5(CK), 80.5(F), 81.5(HW), 82.5(DK), 83.5(HKY), 84.5(NQ), 85.5(KS), G86(-C), 86.5(Q), 87.5(DEFQ), P89(CH), 89.5(GL), 90.5(EMY), L91(Q), 92.5(RY), Y93(GN), 93.5(Y), 94.5(Y), A96(QV), A98(C), 98.5(CE), F100(K), 101.5(E), E102(FQ), 103.5(SV), L104(N), 104.5(EKN), K105(M), 105.5(CRY), E106(CF), 106.5(HNY), D107(CKY), 107.5(N), T108(-), 108.5(QY), S109(N), 109.5(Y), 111.5(AW), 112.5(CQ), N113(DIKLRW), 113.5(FN), G115(-DFMPV), 115.5(DHLVW), R116(EP),	0.5-fold

116.5(EHIKLPQTWY), A117(EKR), 117.5(EFKLPQW), V118(-DKPR), 118.5(ACEGP), F119(CQS), 119.5(AHKLNQRSVY), 120.5(GKLPR), A121(E), 121.5(FG), K122(FNW), 122.5(HIQW), K123(CDHT), 123.5(AFKNQT), R124(-IP), 124.5(CHKPRS), V125(-DPQ), 125.5(ACEFGQRSW), L126(-R), 126.5(CER), E127(-), 127.5(LNSY), P128(CFI), 128.5(AHKTW), L129(DKR), 129.5(F), 130.5(CKSY), 131.5(DEHP), V132(C), 132.5(IW), 135.5(W), 136.5(EM), K137(CDY), 137.5(DLNQSY), 138.5(DNQ), A139(DF), 139.5(D), P140(DE), 140.5(CDEKN), G141(EFKLMQWY), 141.5(DEY), K142(DEGPY), 142.5(DEKPSY), K143(EGVY), 143.5(ELPQSTY), R144(HPSTVW), 144.5(ACFHNSTY), P145(-DENSVY), 145.5(EGMPQT), V146(DE), 146.5(R), E147(FGHKLQY), 147.5(K), 148.5(MR), S149(MPQ), 149.5(CMW), P150(M), 150.5(EM), V151(-), 152.5(HK), S156(AT), 157.5(N), G160(Y), 160.5(N), K161(Y), 161.5(F), G163(CFK), 163.5(DNR), Q164(M), 164.5(KPY), Q165(CHN), 165.5(FIPTV), P166(-ACFIKLNQRSTY), 166.5(FINTY), R168(K), R170(K), N172(-DSVW), 172.5(F), 173.5(DFHINQ), G174(ACDHQSTWY), 174.5(IK), Q175(ANRT), 175.5(I), T176(CG), 176.5(N), G177(-Q), D178(-IW), A179(K), 179.5(CY), D180(MNY), 180.5(M), 181.5(TY), 182.5(CLS), 183.5(M), 184.5(MY), P185(TW), 185.5(FQ), Q186(N), 186.5(CKY), P187(F), 187.5(QY), L188(MT), G189(IM), 189.5(MQ), Q190(MW), P192(CKM), 192.5(HM), 193.5(W), 194.5(M), S196(-), L198(VW), G199(D), 199.5(W), T200(N), M203(DEHW), T205(Y), G206(EKY), S207(D), G208(E), P210(CH), D213(HW), N214(F), N215(I), G217(DEFHITVY), A218(Q), G220(CMN), N223(DH), S225(CR), H229(ADV), T233(DHV), 237.5(HNQ), R238(H), 238.5(T), I240(H), T242(HY), T246(I), T251(V), N254(C), L256(AGKMS), K258(Q), Q259(AGKPRS), 260.5(Q), S261(ACGNT), 262.5(D), Q263(-DFGHLTWY), S264(-DEILQVWY), 265.5(ADENS), A266(S), 266.5(AE), S267(AENP), 267.5(E), N268(AEQ), 268.5(E), 269.5(D), N270(ACDGHQSY), H271(EINV), F273(HW), G280(A), F282(WY), D295(E), R307(-CDMY), P308(-N), L311(Y), K314(CFLQTVWY), I318(F), T324(L), 324.5(K), Q325(HKR), 325.5(R), D327(Q), T329(C), T330(K), T331(H), I332(CS), 332.5(K), A333(DHNY), L336(I), T339(C), V342(M), T344(FI), S346(F), Q349(AMS), F365(W), A367(P), L378(AV), T379(CG), 379.5(DE), L380(CEMNQTV), 380.5(E), N381(ACDGMQS), N382(CDEST), 382.5(D), 383.5(E), S384(G), 384.5(D), Q385(EKLTV), 385.5(K), A386(EHPTVW), 386.5(CDE), V387(CDETWY), 387.5(EKP), G388(M), R389(I), S390(ADGT), 395.5(W), Y397(AN), P399(Q), Q401(FIY), L403(C), R404(K), T405(SY), G406(DENQ), 406.5(Q), N408(DFGMQ), 408.5(N), F409(CH), T410(FM), S412(VW), 412.5(Q), Y413(M), T414(F), E416(G), 416.5(CE), D417(MN), 417.5(KM), V418(Q), P419(W), F420(LM), A425(FQ), H426(N), S427(AN), Q428(EHN), S429(GP), L430(MV), 431.5(Y), R432(-I), 433.5(F), L437(N), D439(KNSY), 444.5(CLM), L445(FMY), 445.5(ACDEGHILMNQSTV), S446(-EGHILMNTV), 446.5(ACDEFGHILMNPQSTVWY), R447(-DEFGILMNPTVWY), 447.5(ACDEFGHILMNPQSVWY), T448(-ACDEFGHILMNPQSVWY), 448.5(ACDEFGHILMNPQY), N449(-DEHMPW), 449.5(AEHLNPS), T450(-CNP), 450.5(DEFGLT), P451(-I), 451.5(NP), S452(NP), 452.5(AL), G453(-AEFIKLNQST), 453.5(FINY), T454(DFHIN), 454.5(DFY), T455(-DEMNY), 455.5(HP), T456(DEFGHIN), 456.5(DEH), Q457(GP), 457.5(ADWY), S458(DEFW), 458.5(DEHILMNT), R459(-P), 459.5(DP), L460(HWY), 460.5(W), Q461(DFI), F462(Y), 462.5(N), S463(CGKNQV), 463.5(F), Q464(K), 464.5(SY), A465(G), 466.5(E), S468(CDEY), 469.5(E), R471(DEGQTV), D472(LMSTWY), Q473(F), S474(CI), R475(H), 475.5(SW), N476(ST), 476.5(L), W477(F), 477.5(L), 478.5(L), P479(GT), 479.5(D), G480(Y), P481(AV), 481.5(GHY),	

C482(GQWY), Y483(AT), 483.5(QV), R484(EFGHIKLMNQSTVY), 484.5(N), Q485(AGSY), 485.5(EIKM), Q486(ACDEFGILMPVWY), 486.5(FV), R487(-ACDEFGKLMNPQSTVWY), 487.5(FW), V488(AEFGHLMNQY), 488.5(ACDEFGILMPQSVWY), S489(-EFGHIKLMNPQTVWY), 489.5(ACDEGLMPQRSTVY), K490(-ACDFGPQWY), 490.5(CDFGHILMPQTVWY), T491(-GP), 491.5(AEFGHILMPQSTVWY), S492(-CGM), 492.5(AEGHILMQSTVY), A493(-HQ), 493.5(ADEHIKMNPQSTV), D494(FR), 494.5(ADFGHILMNPQSTVY), N495(-ADEFGHILMPQSTVWY), 495.5(ACDEFGILMNPQSTVWY), N496(-CDEFGILMPQTVW), 496.5(ADEFGHILMNPQSTVWY), N497(-CEFGHLMWY), 497.5(ADEFGILMNPQSTVY), S498(-CDEINPRTVW), 498.5(ADEFGHILMNPQSTVWY), E499(CIPS), 499.5(ACDEGILMNPQRSTVWY), Y500(-ACDEGHIKLNPQSTVW), 500.5(ADEFGHILMNPQSTVWY), S501(-CDFILPRVW), 501.5(ACDEFGHILMNPQRSTVWY), W502(-ACDEFGILMPQSVY), 502.5(ADEFGHILMNPQSTVWY), T503(-ADEFGHLMNQSWY), 503.5(ADEFGILMNPQSTVW), G504(-CDEFHILMNPQSTVWY), 504.5(ACDEFGHILMNPQSTVWY), A505(-CDEFGHILMNPQSTVWY), 505.5(ACDEFGILMPQSTVWY), T506(FGILMPQ), 506.5(ACIPSTVW), K507(-EFNWY), Y508(IMV), H509(EFKNQR), 509.5(K), 510.5(K), N511(ACDEGLMQSWY), 512.5(S), R513(H), D514(ACFGILMV), S515(CINV), L516(ACS), V517(L), N518(V), P521(MS), M523(CV), 523.5(A), A524(G), 524.5(ACGHSTW), S525(CMNPT), 525.5(ACDEFGHILMNPQSTVWY), H526(DEFGIKLMPRVWY), 526.5(ACDEFGHILMNPQSTVWY), K527(-DEFGHILPSTVWY), 527.5(ACDEFGHILMPQSTVWY), D528(AEFMPQSVW), 528.5(DEPT), D529(ES), 529.5(ADEGLMNPQV), E530(DNPVW), 530.5(ACDEFGHIKLMNQRSTVWY), E531(ACFGILMNPQSTVY), 531.5(ADEFGIKLMNPQRSTVY), K532(-CEP), 532.5(ACDEFGHIKLMNPQSTVWY), F533(ACDEGHIQSTVW), 533.5(ACDEFGHILNPQSTVWY), F534(ILVWY), 534.5(F), P535(-F), Q536(-ADFGHNPSTVWY), 536.5(ACILTV), S537(-DFGQY), 537.5(T), G538(-), V539(HL), L540(M), 541.5(D), 542.5(Q), 543.5(DIKPRT), K544(-F), 544.5(FKMRVWY), Q545(-), 545.5(CFIMNSTW), G546(CFHQ), 546.5(ACEGHMNQSW), S547(-DWY), 547.5(GHLNPSTWY), E548(AFGLP), 548.5(ACGHILNPT), K549(DQ), 549.5(ADLNQSTV), T550(-CY), 550.5(EKMPQRSTV), N551(-CPV), 551.5(ACEILMPQ), 552.5(V), D553(AGST), I554(H), E555(GHNS), 556.5(Q), M558(IV), T560(V), D561(I), 565.5(Y), R566(DFHLQ), 567.5(E), P570(Q), 570.5(M), V571(ADEFHILMQSTY), 572.5(WY), T573(ACDGHIVWY), 573.5(T), E574(ACDFLMSW), Q575(CT), 575.5(WY), Y576(ACGHIMSV), 576.5(EFWY), G577(DW), 577.5(ACDEHIMNQSTV), S578(FHLY), 578.5(ACDEFGHILNSTVY), V579(DFQWY), 579.5(ACDEFGILMNPQTVWY), S580(-DEFHILMNQVY), 580.5(ACDEFGKLMNPSTVY), T581(-GHPQW), 581.5(ACDEGILMNPQTVY), N582(-ACDEFGHIKLMPQRSTWY), 582.5(DFGHNPSTVW), L583(-DEGPWY), 583.5(DEGIMNPQSTVY), Q584(-ADEFGHILMNPSTVWY), 584.5(ACDEFGHILMPQTVWY), R585(-ACDILMNPSTVWY), 585.5(DEFGHILMNPQSTVWY), G586(-HVY), 586.5(ADEFGHILMNPQSTVY), N587(-EFHILVY), 587.5(ADEFGHILMNPQSTVWY), R588(-ACDEFGHILMNPQSTVWY), 588.5(DEFGHLMNPSY), Q589(-DEFGINPRSTVY), 589.5(ACDEFGHIKLMNPSTVWY), A590(DEFHKLMNQTWY), 590.5(ACDEFGIKLMPQSTVWY), A591(-FPWY), 591.5(ACEFGHILMNPQSTVY), T592(-CEGHLMP),	

592.5(ACDEFGILMNPQSTVWY), A593(-FPY), 593.5(ACDEFGHILMNPQSTVWY), D594(LT), 594.5(ACDEFGHILMNPQSTVWY), V595(DEFHNPQWY), 595.5(ACDEFGHILMNQSTVW), N596(EFIPQW), 596.5(DEY), T597(P), 597.5(F), Q598(EGN), G599(W), 600.5(F), L601(W), P602(CQ), M604(C), 606.5(P), D608(W), D610(Y), 610.5(F), 613.5(Y), Q614(T), I617(K), 617.5(I), K620(CMN), H627(M), H629(WY), P630(G), L633(M), M634(C), F637(I), K640(VW), 640.5(N), Q645(M), I646(M), L647(I), N650(C), V653(C), N656(Q), 657.5(C), 658.5(ACHN), 659.5(CDI), T660(HM), 660.5(E), F661(AEILQST), 661.5(CGKPRY), 662.5(CKMQW), 663.5(CGPW), A664(KW), 664.5(CMPR), K665(H), 665.5(HINRTWY), F666(C), 666.5(I), A667(CM), 667.5(QY), T671(R), S674(G), S679(FGHIKRY), V680(C), E681(D), Q687(I), K688(P), E697(D), 697.5(G), I698(D), 699.5(E), 702.5(Q), N703(G), 703.5(AEHLTY), 704.5(AILNS), 705.5(QY), K706(DEST), S707(CEHILMNY), 707.5(MY), V708(ACGHN), 708.5(I), N709(P), 709.5(GPQ), V710(AMNPQ), 710.5(D), D711(GN), T713(C), T716(CKRW), N717(R), V719(KY), S721(CHKLMNR), E722(Q), P723(CDEN), R724(FSY), P725(I), I726(L)	
1.5(MV), A2(CS), 2.5(GIMP), A3(CDEFI), 3.5(ILTVY), D4(CS), 4.5(AFHNVY), G5(-CN), 5.5(CFKM), 6.5(N), W10(ACEGIKPQRSTY), 10.5(HI), L11(ACV), 11.5(K), E12(FHIW), D13(CEGIKVWY), T14(CDFHIPQR), L15(HTW), E17(CFINQRTVY), G18(ADS), I19(AEGHNQST), R20(FILQV), Q21(GHKTV), 21.5(FWY), W22(FIV), 22.5(FILMWY), W23(CDEHKMNQ), 23.5(ACDEFGHLNQSTWY), 24.5(CDEHILNY), L25(AEFGHNQRS), 25.5(CEIKLNQRSTVWY), K26(DHNY), 26.5(HNQ), P27(T), 27.5(G), 28.5(AEFGILNPQSTVWY), P29(DEFGLQRSTW), P30(ADFHQRSY), 30.5(ADEFGIKLNPQRSTY), P31(DHK), 31.5(AFILPV), P32(AEGHILNQRSTY), 32.5(ADEKLNPRSTW), K33(-DGNPQRSY), 33.5(CEFKNPQTVWY), P34(-GLQRTVY), 34.5(CEFGHKQRVY), A35(EGHKNQVY), 35.5(CGHT), E36(FHK), 36.5(FINW), R37(-DN), 37.5(MPQ), H38(CENW), 38.5(CDEGIKNP), K39(AFLVY), 39.5(CDGIY), D40(-ACNY), 40.5(CDGY), D41(EHQRS), 41.5(DFNRTVW), S42(-DKLQRTVW), 42.5(CDGT), R43(ASTV), 43.5(DPRV), 45.5(M), V46(I), L47(F), P48(Y), G49(CFLMQY), Y50(HW), 50.5(N), K51(ACFLMNVY), Y52(D), 53.5(R), P55(Y), 55.5(EKY), 56.5(K), G58(CES), 58.5(F), L59(ACFGKQRW), 59.5(H), D60(CHNTY), K61(-CILQS), 61.5(GK), G62(Q), E67(DLQ), A68(LT), L73(EHKV), E74(QTW), K77(D), 77.5(K), A78(FY), 78.5(ADFHIQR), Y79(-C), 79.5(CK), 80.5(F), R81(CDQ), 81.5(FHW), Q82(EHMN), 82.5(DIK), L83(CGN), 83.5(FGHIKLQWY), 84.5(ENQ), S85(-E), 85.5(GHKS), G86(-ACDEVW), 86.5(FQSVW), D87(ACHK), 87.5(ADEFGQ), N88(A), P89(CDH), 89.5(GL), 90.5(EMY), L91(Q), K92(G), 92.5(RY), Y93(GHNW), 93.5(Y), 94.5(AY), H95(AEGRY), A96(QVW), D97(-G), A98(CDW), 98.5(CE), E99(CG), 99.5(N), F100(K), Q101(DVY), 101.5(E), E102(FQ), R103(IN), 103.5(SV), L104(NT), 104.5(ADEGKNV), K105(FMQW), 105.5(CQRWY), E106(CFIK), 106.5(EFHNRY), D107(-CFKVY), 107.5(NP), T108(-CI), 108.5(IQY), S109(CILN), 109.5(AHY), F110(CEHNY), G111(CE), 111.5(AW), G112(P), 112.5(CQ), N113(CDHIKLQRVW), 113.5(FHN), L114(FN), G115(-DEFMPV), 115.5(ADEHLNVW), R116(EGMP), 116.5(ADEGHIKLPQTWY), A117(CEHKQRWY), 117.5(DEFKLPQW), V118(-DKPRW), 118.5(ACEGMP), F119(ACHQS), 119.5(AHIKLNQRSTVY), Q120(-FKW), 120.5(GKLPR), A121(EFKNQ), 121.5(FGHQ), K122(-DFGNRW), 122.5(DFHIKPQSW), K123(CDFHT), 123.5(AFKNPQT), R124(-CHIP), 124.5(CEFHKPRS), V125(-	0.7-fold

CDEHPQSW), 125.5(ACEFGQRSW), L126(-KQR), 126.5(CER), E127(-P), 127.5(AGILNSTY), P128(CDFILQRSTV), 128.5(AGHKLRSTW), L129(DKR), 129.5(CFQ), G130(EFQ), 130.5(CEHKLSTY), L131(DI), 131.5(ADEFHLP), V132(CR), 132.5(HIKLNVWY), E133(GLS), 133.5(PW), 134.5(HW), P135(H), 135.5(LW), V136(-HY), 136.5(AEHMNQ), K137(-CDPTY), 137.5(CDGHIKLNPQRSVWY), T138(AEGPQ), 138.5(CDEGKNQSW), A139(-CDEFKQTW), 139.5(CDGHRY), P140(DEGHTW), 140.5(CDEKNQ), G141(DEFHIKLMNQRTWY), 141.5(DEHKQRTVY), K142(-CDEGNPY), 142.5(CDEFGIKNPQSWY), K143(EGRVY), 143.5(AEFKLPQSTY), R144(HNPSTVW), 144.5(ACEFHILNPQRSTVWY), P145(-ADEFGILNSVWY), 145.5(DEGKMPQTV), V146(DEKQRTW), 146.5(CEFKLNPRY), E147(FGHKLNQVY), 147.5(EFHK), H148(CGW), 148.5(HKMNR), S149(-ACEHIMNPQR), 149.5(CHIKMNRTW), P150(DFHMR), 150.5(DEMPRW), V151(-CDGY), 151.5(DY), E152(CFP), 152.5(DGHKNY), D154(S), 155.5(D), S156(AT), S157(EFKRTV), 157.5(DNQTW), G158(D), 158.5(P), T159(EFGHPQ), 159.5(Y), G160(Y), 160.5(DNWY), K161(GHNTVY), 161.5(FGILQRSV), A162(IQ), 162.5(EPRT), G163(CFKN), 163.5(DEKNRSTWY), Q164(CMR), 164.5(DEFGIKNPRY), Q165(CHILNVW), 165.5(FIPTV), P166(-ACFHIKLNQRSTY), 166.5(FGHINPSTY), A167(QSV), R168(K), R170(K), N172(-ACDFHLQSVW), 172.5(F), 173.5(ADFHINQWY), G174(ACDEFHQSTWY), 174.5(IKNS), Q175(-ADNRST), 175.5(AFGIKNY), T176(ACGY), 176.5(ENP), G177(-Q), 177.5(EGI), D178(-EIWY), 178.5(INPS), A179(-IKW), 179.5(CDHNPQRSTVWY), D180(-ACFIMNY), 180.5(CFHIMQ), S181(FKL), 181.5(CGHNTVY), 182.5(CHLPS), P183(CS), 183.5(EGKMNY), D184(FGHINPQR), 184.5(MPRY), P185(DEFILNTVWY), 185.5(CFIPQTVW), Q186(FNPTY), 186.5(CDEKSY), P187(FGIL), 187.5(CGKPQWY), L188(EFIMSTW), 188.5(DN), G189(CIMN), 189.5(MQW), Q190(MW), 190.5(CFGH), P191(N), 191.5(CIQW), P192(CKMWY), 192.5(EHMY), A193(DNY), 193.5(DHMRVW), A194(CFGIQV), 194.5(CFMP), P195(DKQRSTY), 195.5(DHMQST), S196(-FK), L198(DVWY), G199(D), 199.5(FHW), T200(AFINQR), N201(CH), T202(KPSV), M203(ACDEFGHIPRTVWY), T205(FKRVY), G206(ACDEHKRY), S207(ADRY), G208(EFHKLQWY), A209(DEMY), P210(CHR), D213(ACFHIKLNTW), N214(ACEFLVY), N215(CHILY), E216(AH), G217(ACDEFHILMNSTVY), A218(Q), G220(ACMNT), N223(ACDHIY), S225(CQR), H229(ADSTV), T233(DHIQVY), M235(L), D237(C), 237.5(EHKNQ), R238(HS), 238.5(TY), I240(H), T242(CHRY), T246(I), P250(S), T251(SV), N254(CQS), L256(ACGKMQRSV), K258(Q), Q259(AGHKPRS), 260.5(MQ), S261(ACGNT), 262.5(D), Q263(-DEFGHLTWY), S264(-DEILQVWY), 265.5(ADEMNQS), A266(S), 266.5(AE), S267(AENP), 267.5(E), N268(ADEQ), 268.5(E), 269.5(D), N270(ACDGHQSY), H271(EFINV), F273(HWY), S276(K), G280(A), F282(LWY), F284(CY), F287(Y), H288(N), S292(C), D295(AE), R307(-CDKMSY), 307.5(FK), P308(-NV), K309(AQ), R310(GILV), L311(CFY), N312(HMT), K314(CFGLQSTVWY), L315(V), I318(F), T324(LM), 324.5(KR), Q325(HKRV), 325.5(FHIKR), N326(DMRWY), D327(QT), G328(AN), T329(CIY), T330(KQ), T331(FHY), I332(ACS), 332.5(K), A333(DFHNTY), N334(S), L336(I), T339(C), V342(ACIM), T344(DFILN), S346(CFHLMPQW), Y348(FRS), Q349(AGMS), V353(CI), S356(A), H358(ACGN), Q359(M), F365(W), A367(CP), V369(PT), M371(CIKQS), G376(CS), L378(ACV), T379(ACGSV), 379.5(DE), L380(CEMNQTVY), 380.5(E), N381(ACDGMQS), N382(CDEST), 382.5(D), 383.5(E), S384(AG), 384.5(D), Q385(EKLMSTV), 385.5(DEK), A386(-	

EHLNPRTVW), 386.5(CDEY), V387(CDEQTWY), 387.5(EGKP), G388(EIM), R389(IL), S390(ADGNT), C394(V), 394.5(N), 395.5(W), Y397(AGN), P399(EIMQR), Q401(CDFIKLNRVWY), L403(C), R404(K), 404.5(N), T405(SY), G406(DENQ), 406.5(Q), 407.5(H), N408(ADFGHLMQTY), 408.5(N), F409(CH), T410(CFHLMY), F411(CTW), S412(IKVWY), 412.5(Q), Y413(FM), T414(FK), 414.5(D), 415.5(APQ), E416(DG), 416.5(CEMR), D417(AIKMNTV), 417.5(DKLMRS), V418(GQ), P419(EINTVW), F420(LM), S422(A), S423(LT), Y424(FH), A425(-CFQV), H426(N), S427(AN), Q428(EHN), S429(CGHPY), L430(MV), D431(M), 431.5(Y), R432(-I), L433(V), 433.5(F), L437(NS), I438(M), D439(KNPSY), 441.5(M), 444.5(CLM), L445(FMY), 445.5(ACDEGHILMNQSTVY), S446(-DEGHILMNQTV), 446.5(ACDEFGHILMNPQSTVWY), R447(-ADEFGILMNPQTVWY), 447.5(ACDEFGHILMNPQSVWY), T448(-ACDEFGHILMNPQSVWY), 448.5(ACDEFGHILMNPQSY), N449(-CDEHILMPVWY), 449.5(AEGHLMNPST), T450(-CFGNPY), 450.5(ADEFGHLTV), P451(-I), 451.5(NP), S452(-DEFGNPQTY), 452.5(ALV), G453(-AEFIKLMNPQST), 453.5(FILNY), T454(-DEFGHILMNP), 454.5(DEFPY), T455(-ADEILMNPQVY), 455.5(HNP), T456(DEFGHIKMNS), 456.5(DEGHIL), Q457(EGHILMPS), 457.5(ADEGHNTWY), S458(DEFHMNW), 458.5(CDEGHILMNT), R459(-EGINPY), 459.5(DEP), L460(AHIMTWY), 460.5(W), Q461(DFHIKV), F462(Y), 462.5(N), S463(ACDGKMNQRV), 463.5(F), Q464(IKLMV), 464.5(SY), A465(G), G466(A), 466.5(E), A467(EM), S468(CDELPQVY), D469(V), 469.5(E), R471(DEGQSTV), D472(GHLMSTVWY), Q473(FHY), S474(CIY), R475(H), 475.5(SW), N476(ST), 476.5(L), W477(F), 477.5(L), L478(FI), 478.5(L), P479(GIT), 479.5(D), G480(Y), P481(ACV), 481.5(GHY), C482(AFGQSWY), Y483(AITW), 483.5(FHQV), R484(EFGHIKLMNQSTVY), 484.5(N), Q485(ACGNSTY), 485.5(EIKMY), Q486(ACDEFGILMPSVWY), 486.5(FV), R487(-ACDEFGIKLMNPQSTVWY), 487.5(FW), V488(AEFGHILMNQTWY), 488.5(ACDEFGILMPQSVWY), S489(-EFGHIKLMNPQTVWY), 489.5(ACDEGLMPQRSTVWY), K490(-ACDEFGMNPQRSTVWY), 490.5(CDEFGHILMPQRSTVWY), T491(-AGPY), 491.5(ADEFGHILMNPQSTVWY), S492(-CFGLMPQT), 492.5(AEGHILMPQSTVY), A493(-HQ), 493.5(ADEGHIKLMNPQSTVY), D494(EFR), 494.5(ADFGHILMNPQSTVWY), N495(-ADEFGHILMPQSTVWY), 495.5(ACDEFGILMNPQSTVWY), N496(-ACDEFGILMPQTVWY), 496.5(ADEFGHILMNPQSTVWY), N497(-CEFGHLMVWY), 497.5(ADEFGILMNPQSTVY), S498(-CDEINPRTVW), 498.5(ADEFGHILMNPQSTVWY), E499(CIPS), 499.5(ACDEGILMNPQRSTVWY), Y500(-ACDEGHIKLNPQSTVW), 500.5(ADEFGHILMNPQSTVWY), S501(-CDEFILMPRTVW), 501.5(ACDEFGHILMNPQRSTVWY), W502(-ACDEFGILMPQSTVY), 502.5(ADEFGHILMNPQSTVWY), T503(-ADEFGHLMNQSWY), 503.5(ADEFGILMNPQSTVW), G504(-ACDEFHILMNPQSTVWY), 504.5(ACDEFGHILMNPQSTVWY), A505(-CDEFGHILMNPQSTVWY), 505.5(ACDEFGILMPQSTVWY), T506(-FGILMPQS), 506.5(ACIPSTVW), K507(-ACEFHLNVWY), Y508(-DIMSTV), H509(EFKNQR), 509.5(K), L510(I), 510.5(K), N511(ACDEGLMQSWY), 512.5(S), R513(HI), D514(ACFGILMSV), S515(ACINTV), L516(ACMRS), V517(L), N518(TVY), P521(FMS), 521.5(M), A522(CV), M523(CLV), 523.5(A), A524(GP), 524.5(ACGHSTW), S525(CMNPT), 525.5(ACDEFGHILMNPQSTVWY), H526(DEFGIKLMPRVWY), 526.5(ACDEFGHILMNPQSTVWY), K527(-DEFGHILPSTVWY), 527.5(ACDEFGHILMPQSTVWY), D528(AEFMPQSVW), 528.5(DEPT), D529(ES), 529.5(ADEGLMNPQTV), E530(DNPVW),	

530.5(ACDEFGHIKLMNQRSTVWY), E531(ACFGHILMNPQSTVY), 531.5(ADEFGIKLMNPQRSTVY), K532(-CDEP), 532.5(ACDEFGHIKLMNPQSTVWY), F533(ACDEGHILNQSTVW), 533.5(ACDEFGHILNPQSTVWY), F534(ILVWY), 534.5(F), P535(-AF), Q536(-ACDEFGHMNPSTVWY), 536.5(ACILTV), S537(-DFGNQTY), 537.5(T), G538(-), V539(HLMQST), L540(M), 540.5(N), I541(DERT), 541.5(ACDQV), 542.5(Q), G543(APS), 543.5(DHIKLMPRTV), K544(-FS), 544.5(AFGHIKLMNRVWY), Q545(-AKLRW), 545.5(ACFHILMNPQSTVWY), G546(ACEFHLPQSVWY), 546.5(ACDEGHILMNQSTVWY), S547(-DGLNQWY), 547.5(ADGHILMNPSTVWY), E548(AFGLMNPS), 548.5(ACDGHILNPSTWY), K549(-DEFGHLPQSY), 549.5(ADFGLMNQSTVY), T550(-CQY), 550.5(AEGIKMPQRSTV), N551(-CEGIPQRSV), 551.5(ACDEFILMPQST), V552(CQS), 552.5(VW), D553(AGST), I554(AHTW), E555(AGHNSTVY), K556(CDM), 556.5(Q), V557(IL), M558(IV), I559(FQV), T560(V), D561(INRVY), I565(T), 565.5(Y), R566(DFHLQY), 567.5(E), T568(P), 569.5(M), P570(QS), 570.5(M), V571(ADEFHILMQSTY), A572(CY), 572.5(WY), T573(ACDGHINSVWY), 573.5(T), E574(ACDFLMSW), 574.5(V), Q575(-CFHILTV), 575.5(AWY), Y576(ACFGHIMSV), 576.5(EFWY), G577(DW), 577.5(ACDEHIMNQSTV), S578(ACFHLY), 578.5(ACDEFGHILNSTVY), V579(DFGLMNQSWY), 579.5(ACDEFGILMNPQSTVWY), S580(-DEFHILMNPQTVY), 580.5(ACDEFGKLMNPQSTVWY), T581(-FGHLNPQWY), 581.5(ACDEFGILMNPQTVY), N582(-ACDEFGHIKLMPQRSTVWY), 582.5(DFGHNPSTVW), L583(-ADEFGMPSWY), 583.5(DEGIMNPQSTVY), Q584(-ADEFGHILMNPSTVWY), 584.5(ACDEFGHILMPQSTVWY), R585(-ACDFGILMNPSTVWY), 585.5(ADEFGHILMNPQSTVWY), G586(-DEHMVY), 586.5(ADEFGHILMNPQSTVY), N587(-EFHILMPTVY), 587.5(ADEFGHILMNPQSTVWY), R588(-ACDEFGHIKLMNPQSTVWY), 588.5(ADEFGHLMNPSTVY), Q589(-ADEFGINPRSTVWY), 589.5(ACDEFGHIKLMNPQSTVWY), A590(DEFHKLMNQTWY), 590.5(ACDEFGIKLMPQSTVWY), A591(-FILNPVWY), 591.5(ACDEFGHILMNPQSTVY), T592(-CDEGHLMNPQVY), 592.5(ACDEFGILMNPQSTVWY), A593(-FLMNPWY), 593.5(ACDEFGHILMNPQSTVWY), D594(ELT), 594.5(ACDEFGHILMNPQSTVWY), V595(ACDEFGHMNPQSTWY), 595.5(ACDEFGHILMNQSTVW), N596(ADEFGHIMPQTWY), 596.5(DENY), T597(FKP), 597.5(F), Q598(AEGHN), G599(SW), V600(M), 600.5(F), L601(VW), P602(CMQ), M604(CS), V605(AFN), 605.5(N), 606.5(P), D608(W), R609(D), D610(Y), 610.5(F), 613.5(Y), Q614(T), G615(S), P616(AC), I617(KM), 617.5(I), K620(ACGHMN), I621(K), H623(CDFLW), H627(MNQ), F628(L), H629(WY), P630(AGQ), 630.5(C), L633(HM), M634(C), F637(I), L639(FV), K640(ANTVW), 640.5(N), H641(CIK), Q645(LMT), I646(MT), L647(IY), N650(CILV), V653(CT), 655.5(M), N656(QW), 657.5(CHSVW), 658.5(ACEHIKNQR), T659(-CQ), 659.5(CDFGIMY), T660(-DHKMQ), 660.5(EFHIKPQWY), F661(AEILMQSTV), 661.5(ACEFGIKLMPRSVY), S662(CPW), 662.5(ACDFKMPQRVW), A663(KLNY), 663.5(CGIMNPRSVWY), A664(KWY), 664.5(ACMPRTWY), K665(CFGHM), 665.5(HILNPQRSTWY), F666(CGWY), 666.5(IV), A667(CIMY), 667.5(QY), I670(V), T671(NRS), Q672(CEGLS), S674(G), V678(C), S679(CFGHIKLRY), V680(CL), E681(DLN), E683(H), E685(L), Q687(IV), K688(HP), N690(R), E697(DI), 697.5(GHNPW), I698(DL), 699.5(E), T701(S), 701.5(A), S702(QV), 702.5(Q), N703(DG), 703.5(AEHLTY), Y704(H), 704.5(ADEILNST), N705(CDPV), 705.5(ENQY),	

K706(DEGRST), S707(CDEGHILMNQTVY), 707.5(MY), V708(ACEGHNRS), 708.5(I), N709(KP), 709.5(GPQ), V710(AELMNPQ), 710.5(D), D711(GN), 711.5(Q), T713(CS), T716(CIKNQRWY), N717(ERS), V719(KNQY), 720.5(N), S721(CFHIKLMNRVW), E722(DQ), P723(ACDENQSV), R724(FHKSWY), P725(ACIQ), I726(LV)	
1.5(MV), A2(CS), 2.5(AGIMP), A3(CDEFILQ), 3.5(ADFILTVY), D4(ACSTV), 4.5(AFGHNVY), G5(-CN), 5.5(CFKM), 6.5(N), D9(A), W10(ACEGIKLPQRSTY), 10.5(HI), L11(ACV), 11.5(K), E12(DFGHILSW), D13(CEGIKLRVWY), T14(CDFGHINPQR), L15(AHTW), E17(CFINQRSTVY), G18(ADS), I19(AEGHNQSTV), R20(FILQSV), Q21(FGHIKNRTVY), 21.5(FWY), W22(FIVY), 22.5(FILMWY), W23(CDEHKLMNQRSTV), 23.5(ACDEFGHLNQSTWY), K24(ALNPQ), 24.5(CDEHILNY), L25(AEFGHNQRST), 25.5(CEGHIKLNQRSTVWY), K26(DHNY), 26.5(HNQ), P27(T), 27.5(G), 28.5(AEFGILNPQSTVWY), P29(DEFGHILQRSTW), P30(ADFHQRSY), 30.5(ADEFGIKLNPQRSTY), P31(DHKLNY), 31.5(AFILPV), P32(AEGHIKLNQRSTY), 32.5(ADEIKLNPRSTWY), K33(-DFGNPQRSTWY), 33.5(CDEFHIKNPQTVWY), P34(-AGKLNQRTVY), 34.5(CEFGHKQRSVY), A35(EGHKLNQVY), 35.5(CEFGHINPTV), E36(CFGHKW), 36.5(DFHIKNW), R37(-DNSW), 37.5(DFMPQW), H38(-CDENVWY), 38.5(ACDEGIKNPR), K39(AFILRVWY), 39.5(CDGIY), D40(-ACGNY), 40.5(CDGSTY), D41(ACEHQRS), 41.5(CDFNRTVW), S42(-DKLQRTVWY), 42.5(ACDGKTY), R43(ASTV), 43.5(DPRV), 45.5(M), V46(I), L47(F), P48(LY), G49(CFLMQY), Y50(HW), 50.5(N), K51(ACFLMNVY), Y52(D), 53.5(R), P55(Y), 55.5(EKY), 56.5(K), G58(CES), 58.5(F), L59(ACFGKQRW), 59.5(H), D60(ACEHNQTY), K61(-ACILQRS), 61.5(GK), G62(Q), E63(HMN), V65(H), E67(CDLQW), A68(LT), A70(Y), A71(GKWY), L73(CEHKVY), E74(LQTVW), K77(CDTY), 77.5(K), A78(FNRY), 78.5(ADFHIQR), Y79(-C), 79.5(CK), D80(AMY), 80.5(F), R81(CDGQ), 81.5(FHW), Q82(-CEGHIMN), 82.5(DIK), L83(ACFGKN), 83.5(EFGHIKLQTVWY), D84(LQS), 84.5(ENQ), S85(-EPW), 85.5(AGHKSY), G86(-ACDESVW), 86.5(FGQSVW), D87(ACFGHKRY), 87.5(ADEFGQY), N88(AHLR), P89(CDH), 89.5(GL), 90.5(EMY), L91(QR), K92(GIRSV), 92.5(RY), Y93(FGHNW), 93.5(Y), N94(W), 94.5(AY), H95(ACDEGLRSY), A96(QVW), D97(-G), A98(CDWY), 98.5(CE), E99(CG), 99.5(KN), F100(KY), Q101(ADPVY), 101.5(E), E102(FLQY), R103(DINY), 103.5(SV), L104(INT), 104.5(ADEGKNV), K105(FMQRW), 105.5(CGLQRVWY), E106(CFIKY), 106.5(EFHNRVY), D107(-CFKNQTVWY), 107.5(NP), T108(-CINPY), 108.5(IQTY), S109(ACFIKLN), 109.5(AHY), F110(ACEHINY), G111(CE), 111.5(AW), G112(AP), 112.5(CQ), N113(CDGHIKLQRTVW), 113.5(FHN), L114(CFGN), G115(-DEFMPSV), 115.5(ADEHLNVW), R116(EGMP), 116.5(ADEGHIKLPQRSTVWY), A117(CEHKQRWY), 117.5(DEFKLPQW), V118(-DKLPRWY), 118.5(ACEGMP), F119(ACHLQSVWY), 119.5(AHIKLNQRSTVY), Q120(-CFIKRW), 120.5(GKLPR), A121(-EFGHKNQW), 121.5(FGHQR), K122(-DFGNRW), 122.5(ADFHIKPQSW), K123(CDEFHQSTY), 123.5(AFKNPQT), R124(-CGHIPY), 124.5(CEFHKPRS), V125(-ACDEHNPQSW), 125.5(ACEFGQRSW), L126(-CEKQRWY), 126.5(CERS), E127(-HIMPWY), 127.5(ADGILNSTY), P128(ACDFILQRSTV), 128.5(AGHKLRSTW), L129(CDGKRWY), 129.5(CDFGQRY), G130(CEFQ), 130.5(CDEHKLQRSTY), L131(DIQVY), 131.5(ACDEFHLPW), V132(-CDRS), 132.5(EHIKLNPRVWY), E133(-GHLS), 133.5(GIPW), E134(-W), 134.5(EHIQW), P135(CDHY),	0.8-fold

135.5(DELNPRWY), V136(-DHQY), 136.5(ACEHILMNPQRTVY), K137(-CDHLPRSTWY), 137.5(ACDEGHIKLNPQRSTVWY), T138(AEGHKNPQR), 138.5(CDEFGKNQSTW), A139(-CDEFIKLPQSTWY), 139.5(ACDGHNRVY), P140(ADEFGHKTW), 140.5(CDEKNQRV), G141(-CDEFHIKLMNQRSTVWY), 141.5(DEFHIKLQRTVY), K142(-ACDEFGINPSY), 142.5(ACDEFGHIKNPQSTVWY), K143(EGIRSVY), 143.5(AEFKLPQRSTWY), R144(AHNPSTVW), 144.5(ACEFGHIKLNPQRSTVWY), P145(-ADEFGIKLNRSTVWY), 145.5(DEGKMNPQRSTVW), V146(-ACDEKLNQRTWY), 146.5(ACEFHIKLNPQRVY), E147(AFGHKLNQTVY), 147.5(EFHIKRS), H148(CGRTW), 148.5(AHKMNPQR), S149(-ACEGHIMNPQRW), 149.5(ACGHIKLMNRSTW), P150(DFHMQR), 150.5(CDEKLMNPQRTVWY), V151(-CDGKWY), 151.5(DWY), E152(CFNPV), 152.5(DGHKNRY), D154(S), 155.5(D), S156(AT), S157(EFKRTV), 157.5(DNQTW), G158(D), 158.5(P), T159(DEFGHPQR), 159.5(Y), G160(CY), 160.5(DFHNWY), K161(-GHLNQSTVY), 161.5(ADFGILQRSTVW), A162(DIKQ), 162.5(ACENPQRST), G163(-CFHKNRV), 163.5(DEKLNPRSTVWY), Q164(CHIMRVW), 164.5(DEFGIKNPQRSY), Q165(CHILNPVW), 165.5(FIPQTV), P166(-ACFGHIKLNQRSTY), 166.5(FGHINPSTY), A167(QSV), R168(K), R170(K), L171(I), N172(-ACDFHLQSVW), 172.5(F), 173.5(ADEFGHINQWY), G174(ACDEFHQSTWY), 174.5(AEFHIKNRSY), Q175(-ACDGNRST), 175.5(AFGIKLNQY), T176(ACDFGY), 176.5(ADENP), G177(-EQ), 177.5(EGIT), D178(-EISWY), 178.5(FINPRS), A179(-IKPSW), 179.5(CDHKNPQRSTVWY), D180(-ACFIMNQVY), 180.5(ACFHILMQR), S181(FKLTY), 181.5(ACGHNSTVY), V182(ACIS), 182.5(CHLPRS), P183(CHRS), 183.5(EGKMNQY), D184(CFGHINPQRTY), 184.5(CLMPRY), P185(CDEFGILNTVWY), 185.5(CFILPQTVW), Q186(FIKNPTY), 186.5(CDEIKNSY), P187(-FGILNQS), 187.5(CEGKNPQWY), L188(CEFIMQSTW), 188.5(ADNQ), G189(-CIMN), 189.5(FLMQW), Q190(CMNRW), 190.5(ACFGHQR), P191(KN), 191.5(CIQVW), P192(-CDFKMSWY), 192.5(EGHLMVY), A193(CDGHILNY), 193.5(DHIMRTVW), A194(CFGIQVW), 194.5(CFKMPT), P195(DEGHKQRSTVY), 195.5(CDHMQST), S196(-FKNPRT), G197(A), L198(ACDFVWY), G199(D), 199.5(FHRW), T200(ACFGINQR), N201(CDH), T202(KPQRSV), M203(ACDEFGHILPQRTVWY), A204(DV), T205(FKMRVWY), G206(ACDEFHKQRY), S207(ACDRY), G208(AEFHKLNQRWY), A209(DEKMRSY), P210(CGHR), D213(ACFGHIKLNTW), N214(ACDEFKLPSVY), N215(CHILY), E216(ADH), G217(ACDEFHILMNSTVY), A218(QST), G220(ACMNT), V221(I), N223(ACDHIMQSTY), S225(CQR), H229(ADSTV), D231(C), T233(DHIMQSVY), M235(LV), 236.5(D), D237(C), 237.5(DEHKNQ), R238(CHS), 238.5(CFTY), I240(H), T242(CFHRY), S243(A), T246(I), L249(C), P250(AQS), T251(CLSV), N253(D), N254(CQS), H255(A), L256(ACGKMQRSV), K258(LQ), Q259(AGHKPRS), 260.5(MQ), S261(ACGNT), 262.5(D), Q263(-DEFGHLTWY), S264(-ADEILQTVWY), 264.5(D), 265.5(ADEMNQST), A266(S), 266.5(AE), S267(AENP), 267.5(E), N268(ADEQ), 268.5(E), 269.5(D), N270(ACDGHQSY), H271(EFINV), F273(HWY), S276(K), G280(A), Y281(H), F282(LWY), F284(CY), F287(Y), H288(N), S292(C), D295(AE), N303(TV), F306(W), R307(-CDKMSTY), 307.5(FKN), P308(-NV), K309(AQS), R310(AGILVW), L311(CFY), N312(DHLMQTWY), K314(CFGHLMQSTVWY), L315(V), I318(F), T324(LMN), 324.5(CKR), Q325(CHKRV), 325.5(FGHIKRST), N326(CDMRWY), 326.5(N),	

D327(QT), 327.5(GHT), G328(AN), 328.5(G), T329(ACIY), T330(KQS), T331(FHY), I332(ACS), 332.5(K), A333(DFHNTY), N334(S), L336(I), T339(C), V342(ACIM), T344(DFIKLMNV), S346(CFHLMPQW), Y348(FNRS), Q349(AGMS), V353(CI), L354(QT), G355(S), S356(A), H358(ACGNST), Q359(DEHM), C361(A), F365(W), A367(CP), V369(PT), M371(CIKLNQS), V372(CI), Y375(W), G376(CS), Y377(F), L378(ACV), T379(ACGSV), 379.5(DE), L380(CEMNQTVY), 380.5(E), N381(ACDGMQS), N382(CDEST), 382.5(D), 383.5(E), S384(AG), 384.5(D), Q385(ACEIKLMRSTVY), 385.5(DEKLPT), A386(-EHLNPRSTVW), 386.5(CDEY), V387(CDEQTWY), 387.5(EGKP), G388(EIM), R389(GIL), S390(ADGNT), 390.5(C), S391(A), C394(V), 394.5(N), 395.5(W), Y397(AGN), P399(EIMQRS), Q401(ACDEFIKLNRVWY), L403(C), R404(K), 404.5(N), T405(SY), G406(DENQ), 406.5(Q), 407.5(H), N408(ADFGHLMQSTWY), 408.5(CN), F409(CHW), T410(CEFHLMQVY), F411(CLTVW), S412(FGIKMVWY), 412.5(Q), Y413(FM), T414(EFIKLNQ), 414.5(D), 415.5(AGNPQS), E416(ADG), 416.5(CEKMNR), D417(AIKMNTV), 417.5(DEKLMQRS), V418(GMQS), P419(EIKNSTVW), F420(LM), S422(A), S423(CLT), Y424(FHT), A425(-CFQV), H426(N), S427(AN), Q428(EHN), S429(CGHPY), L430(MV), D431(M), 431.5(Y), R432(-I), L433(IV), 433.5(F), M434(A), L437(ANSV), I438(GHM), D439(KNPSTY), 441.5(M), L442(ITV), 444.5(CLM), L445(CFIMY), 445.5(ACDEGHILMNQSTVY), S446(-DEGHILMNQTV), 446.5(ACDEFGHILMNPQSTVWY), R447(-ACDEFGHILMNPQSTVWY), 447.5(ACDEFGHILMNPQSVWY), T448(-ACDEFGHILMNPQSVWY), 448.5(ACDEFGHILMNPQSY), N449(-CDEFHILMPTVWY), 449.5(AEGHLMNPST), T450(-CFGNPSY), 450.5(ADEFGHLQTV), P451(-IL), 451.5(NP), S452(-DEFGLNPQTY), 452.5(ALV), G453(-AEFHIKLMNPQST), 453.5(FILNY), T454(-DEFGHILMNPSV), 454.5(ADEFGMPY), T455(-ADEILMNPQSVY), 455.5(FHNPQ), T456(DEFGHIKLMNQSY), 456.5(DEGHILPS), Q457(EGHILMPS), 457.5(ADEFGHLMNPTWY), S458(-DEFHMNVW), 458.5(CDEGHILMNTVW), R459(-DEGINPY), 459.5(DEP), L460(AHIMPTWY), 460.5(W), Q461(DFHIKMV), F462(Y), 462.5(N), S463(ACDGKMNQRTV), 463.5(F), Q464(IKLMRTV), 464.5(SY), A465(G), G466(AD), 466.5(E), A467(EMS), S468(ACDEHLNPQVWY), D469(V), 469.5(E), R471(DEGQSTV), D472(GHLMQSTVWY), Q473(FHSY), S474(ACIY), R475(HK), 475.5(SW), N476(CSTW), 476.5(L), W477(F), 477.5(L), L478(FI), 478.5(L), P479(GIT), 479.5(D), G480(Y), P481(ACV), 481.5(GHY), C482(AFGQSWY), 482.5(F), Y483(AHITVW), 483.5(FHQV), R484(EFGHIKLMNQSTVY), 484.5(N), Q485(ACFGILNSTY), 485.5(EIKMY), Q486(ACDEFGILMPSVWY), 486.5(FV), R487(-ACDEFGHIKLMNPQSTVWY), 487.5(FW), V488(ACEFGHILMNQTWY), 488.5(ACDEFGILMPQSVWY), S489(-ACEFGHIKLMNPQTVWY), 489.5(ACDEGLMPQRSTVWY), K490(-ACDEFGHILMNPQRSTVWY), 490.5(ACDEFGHILMPQRSTVWY), T491(-AGPSY), 491.5(ADEFGHILMNPQSTVWY), S492(-CFGHLMPQTV), 492.5(ADEGHILMPQSTVY), A493(-HQTV), 493.5(ADEFGHIKLMNPQSTVY), D494(EFR), 494.5(ADEFGHILMNPQSTVWY), N495(-ADEFGHILMPQSTVWY), 495.5(ACDEFGILMNPQSTVWY), N496(-ACDEFGILMPQTVWY), 496.5(ADEFGHILMNPQSTVWY), N497(-CEFGHLMVWY), 497.5(ADEFGILMNPQSTVY), S498(-CDEINPQRTVW), 498.5(ADEFGHILMNPQSTVWY), E499(CIPS), 499.5(ACDEGILMNPQRSTVWY), Y500(-ACDEGHIKLNPQSTVW), 500.5(ADEFGHILMNPQSTVWY), S501(-CDEFGILMNPRTVWY), 501.5(ACDEFGHILMNPQRSTVWY), W502(-ACDEFGILMPQSTVY),	

502.5(ADEFGHILMNPQSTVWY), T503(-ADEFGHLMNPQSWY), 503.5(ADEFGILMNPQSTVW), G504(-ACDEFHILMNPQSTVWY), 504.5(ACDEFGHILMNPQSTVWY), A505(-CDEFGHILMNPQSTVWY), 505.5(ACDEFGILMPQSTVWY), T506(-FGILMNPQS), 506.5(ACIPSTVW), K507(-ACEFHLMNVWY), Y508(-DIMSTV), H509(EFKNQR), 509.5(K), L510(I), 510.5(K), N511(ACDEGLMQSWY), 512.5(S), R513(HI), D514(ACFGILMQSTV), S515(ACINTV), L516(ACIMRS), V517(CL), 517.5(C), N518(AILQTVY), P521(CFMS), 521.5(M), A522(CSV), M523(CLV), 523.5(A), A524(GP), 524.5(ACGHSTW), S525(CMNPT), 525.5(ACDEFGHILMNPQSTVWY), H526(-DEFGIKLMPRVWY), 526.5(ACDEFGHILMNPQSTVWY), K527(-DEFGHILPSTVWY), 527.5(ACDEFGHILMPQSTVWY), D528(AEFMPQSVW), 528.5(DEPT), D529(ES), 529.5(ADEGLMNPQTV), E530(DNPVW), 530.5(ACDEFGHIKLMNQRSTVWY), E531(ACFGHILMNPQSTVY), 531.5(ADEFGIKLMNPQRSTVY), K532(-ACDEPR), 532.5(ACDEFGHIKLMNPQSTVWY), F533(ACDEGHILNQSTVW), 533.5(ACDEFGHILNPQSTVWY), F534(ILMVWY), 534.5(F), P535(-AF), Q536(-ACDEFGHIMNPSTVWY), 536.5(ACILTV), S537(-ADFGNQTY), 537.5(T), G538(-), V539(AHLMNQST), L540(IM), 540.5(KN), I541(-DEPQRT), 541.5(ACDEMQRV), F542(P), 542.5(QY), G543(APS), 543.5(DHIKLMPQRSTV), K544(-AFST), 544.5(AEFGHIKLMNRVWY), Q545(-ADGHKLNRWY), 545.5(ACEFHILMNPQSTVWY), G546(ACEFHLNPQSTVWY), 546.5(ACDEFGHILMNQSTVWY), S547(-CDFGHLNQVWY), 547.5(ACDGHILMNPQSTVWY), E548(ADFGLMNPS), 548.5(ACDFGHILNPSTWY), K549(-DEFGHLPQSY), 549.5(ADFGLMNQSTVY), T550(-CQWY), 550.5(AEGIKMNPQRSTV), N551(-ACEFGIKPQRSTV), 551.5(ACDEFILMPQST), V552(CQST), 552.5(VW), D553(AEGST), I554(ACHQSTW), E555(AGHNSTVY), K556(CDMQ), 556.5(Q), V557(IL), M558(HIV), I559(FQV), T560(V), D561(INRVY), E562(D), E563(R), I565(T), 565.5(Y), R566(DFHLQY), T567(P), 567.5(E), T568(P), 569.5(M), P570(QS), 570.5(M), V571(ADEFHILMQSTY), A572(CGY), 572.5(WY), T573(ACDGHINSVWY), 573.5(T), E574(ACDFLMSW), 574.5(V), Q575(-CFHILMSTV), 575.5(AWY), Y576(ACFGHIMSV), 576.5(EFWY), G577(DW), 577.5(ACDEHIMNQSTV), S578(ACFHLNVY), 578.5(ACDEFGHILNSTVY), V579(DFGILMNQSWY), 579.5(ACDEFGILMNPQSTVWY), S580(-CDEFGHILMNPQTVY), 580.5(ACDEFGIKLMNPQSTVWY), T581(-AFGHLNPQWY), 581.5(ACDEFGILMNPQTVWY), N582(-ACDEFGHIKLMPQRSTVWY), 582.5(DFGHNPSTVW), L583(-ADEFGMPSTWY), 583.5(DEGIMNPQSTVY), Q584(-ADEFGHILMNPSTVWY), 584.5(ACDEFGHILMPQSTVWY), R585(-ACDFGHIKLMNPSTVWY), 585.5(ADEFGHILMNPQSTVWY), G586(-DEHMVY), 586.5(ADEFGHILMNPQSTVY), N587(-DEFHILMPQTVY), 587.5(ADEFGHILMNPQSTVWY), R588(-ACDEFGHIKLMNPQSTVWY), 588.5(ADEFGHILMNPQSTVY), Q589(-ADEFGINPRSTVWY), 589.5(ACDEFGHIKLMNPQSTVWY), A590(DEFHKLMNQTWY), 590.5(ACDEFGIKLMPQSTVWY), A591(-FGILNPVWY), 591.5(ACDEFGHILMNPQSTVY), T592(-CDEGHLMNPQVY), 592.5(ACDEFGILMNPQSTVWY), A593(-CFLMNPWY), 593.5(ACDEFGHILMNPQSTVWY), D594(ELT), 594.5(ACDEFGHILMNPQSTVWY), V595(ACDEFGHIMNPQSTWY), 595.5(ACDEFGHILMNQSTVW), N596(ADEFGHIMPQSTWY), 596.5(DENY), T597(EFKPR), 597.5(F), Q598(AEGHNSY), G599(SW), V600(LM), 600.5(F), L601(VWY), P602(CMQ), G603(A), M604(CS),	

V605(ACFMNT), 605.5(N), 606.5(P), D608(ENW), R609(D), D610(Y), 610.5(F), Y612(R), 613.5(Y), Q614(NT), G615(S), P616(AC), I617(KM), 617.5(I), K620(ACGHMN), I621(K), H623(CDFKLSVW), G626(A), H627(AFILMNQW), F628(L), H629(WY), P630(ACGQT), 630.5(C), S631(N), L633(HMY), M634(C), F637(I), L639(FVY), K640(ANRTVWY), 640.5(N), H641(CIK), Q645(LMT), I646(CMT), L647(IY), I648(C), N650(CILTV), P652(A), V653(CT), A655(S), 655.5(MV), N656(QW), 657.5(CDHLSVW), S658(FIMN), 658.5(ACEHIKLNQRWY), T659(-CEQR), 659.5(ACDEFGIMNSVY), T660(-CDEHKMPQR), 660.5(ADEFHIKLPQWY), F661(AEILMQSTV), 661.5(ACDEFGIKLMPRSVY), S662(CPRW), 662.5(ACDFHIKLMPQRSTVW), A663(IKLMNPY), 663.5(CDGILMNPRSTVWY), A664(DHKNRWY), 664.5(ACHLMPRTVWY), K665(ACFGHIMNQRW), 665.5(AHILNPQRSTWY), F666(CGSWY), 666.5(IPV), A667(CILMRY), 667.5(QY), S668(A), F669(Y), I670(V), T671(NRS), Q672(CEGLS), S674(G), T675(S), V678(C), S679(CEFGHIKLRY), V680(CL), E681(DLNST), I682(M), E683(H), E685(ALQT), L686(T), Q687(IMVW), K688(HP), N690(R), E697(-DHIM), 697.5(GHNPQW), I698(-DL), 699.5(E), T701(S), 701.5(A), S702(IQV), 702.5(Q), N703(DG), 703.5(AEHLTY), Y704(H), 704.5(ADEILNST), N705(CDEHILPTV), 705.5(ENQY), K706(DEGRST), S707(CDEGHILMNQTVY), 707.5(MY), V708(ACEGHNRS), 708.5(I), N709(CDKLPQR), 709.5(CGPQ), V710(AELMNPQ), 710.5(D), D711(GNP), 711.5(QY), T713(CS), T716(CFIKNQRVWY), N717(AEFHRSY), V719(KNQRY), 720.5(N), S721(CFHIKLMNQRTVWY), E722(DQ), P723(ACDEHNQSTV), R724(FHKSWY), P725(ACIQV), I726(LV), R733(K), N734(V), L735(C)	
1.5(AGMV), A2(CS), 2.5(AGIMP), A3(-CDEFILQSY), 3.5(ACDFILMTVY), D4(ACHNSTVWY), 4.5(AFGHNVY), G5(-ACN), 5.5(CFKM), Y6(FI), 6.5(N), L7(F), D9(AV), W10(ACEGIKLPQRSTY), 10.5(HI), L11(ACFIV), 11.5(K), E12(DFGHILNQSWY), D13(CEGIKLNRVWY), T14(CDFGHINPQRSV), L15(AFHTW), S16(G), E17(ACFINQRSTVY), G18(ADS), I19(AEFGHNQSTV), R20(EFHILQSV), Q21(FGHIKNRSTVY), 21.5(FWY), W22(FIVY), 22.5(FILMWY), W23(CDEFGHKLMNQRSTVY), 23.5(ACDEFGHLNQSTWY), K24(ALNPQV), 24.5(CDEHILNY), L25(AEFGHNQRSTV), 25.5(CEGHIKLNQRSTVWY), K26(DHNY), 26.5(HKNQ), P27(T), 27.5(G), 28.5(AEFGILNPQSTVWY), P29(ACDEFGHILQRSTVW), P30(ADFHQRSTY), 30.5(ADEFGIKLNPQRSTY), P31(DFGHIKLNRSY), 31.5(AFILPVY), P32(AEGHIKLNQRSTY), 32.5(ADEFHIKLNPRSTVWY), K33(-ADFGNPQRSTWY), 33.5(CDEFHIKNPQTVWY), P34(-AEFGHKLNQRTVWY), 34.5(CEFGHKPQRSTVWY), A35(EGHKLNQVY), 35.5(CEFGHINPQTVY), E36(-CFGHKNTVW), 36.5(DFHIKLNRSW), R37(-DEGNSVW), 37.5(CDEFIMPQRSW), H38(-ACDELNRVWY), 38.5(ACDEGIKNPRSV), K39(AEFILMRTVWY), 39.5(CDGHINSWY), D40(-ACGLNY), 40.5(CDGQSTY), D41(ACEHQRS), 41.5(CDFNRSTVW), S42(-DKLQRTVWY), 42.5(ACDGKTWY), R43(ASTVY), 43.5(DPRSV), 45.5(M), V46(I), L47(F), P48(LY), G49(CFLMQWY), Y50(HW), 50.5(N), K51(ACFLMNQVY), Y52(D), 53.5(R), P55(Y), 55.5(EKY), 56.5(K), G58(CES), 58.5(F), L59(ACFGKQRW), 59.5(H), D60(ACEHNQSTY), K61(-ACILQRSV), 61.5(GK), G62(QS), E63(ADFHMNV), V65(CFH), N66(AG), E67(ACDLPQRVW), A68(CILPST), A70(CFLY), A71(FGKLNTVWY), L73(CEHKNVY), E74(ACLQTVW), K77(CDSTWY), 77.5(K),	0.9-fold

A78(FKNRSY), 78.5(ADFHIQR), Y79(-C), 79.5(CK), D80(AHMQTY), 80.5(F), R81(ACDGLQW), 81.5(FHILW), Q82(-CEFGHIMNRTW), 82.5(DFIKLW), L83(ACFGKNQW), 83.5(EFGHIKLQRSTVWY), D84(HILQSV), 84.5(AENQ), S85(-CEKLPWY), 85.5(AFGHKSY), G86(-ACDEHLSVWY), 86.5(FGQSVW), D87(ACFGHKNRSY), 87.5(ADEFGQSWY), N88(ADHLR), P89(ACDH), 89.5(GL), 90.5(EMY), L91(GQRS), K92(AFGINQRSTV), 92.5(RY), Y93(FGHNW), 93.5(Y), N94(-STW), 94.5(AY), H95(ACDEGLRSY), 95.5(W), A96(GQVW), D97(-G), A98(CDIKNWY), 98.5(CE), E99(CFGNSTY), 99.5(FKN), F100(KY), Q101(ADEPVY), 101.5(E), E102(FILQSY), R103(CDGINY), 103.5(ASV), L104(CINT), 104.5(ADEFGIKNSTVW), K105(EFMQRW), 105.5(CFGLQRSVWY), E106(CFGIKNQSTWY), 106.5(EFHINRTVY), D107(-CFKNQTVWY), 107.5(KNPQSW), T108(-CFINPQY), 108.5(AEFGHIQSTY), S109(ACDEFIKLNY), 109.5(AGHNY), F110(ACEHINPY), G111(CE), 111.5(AW), G112(APT), 112.5(CQ), N113(CDFGHIKLQRTVW), 113.5(FHN), L114(ACEFGHN), G115(-ACDEFMPRSV), 115.5(ADEHLMNVW), R116(EGHLMP), 116.5(ADEGHIKLPQRSTVWY), A117(-CEHKQRWY), 117.5(CDEFKLPQW), V118(-DHIKLPRWY), 118.5(ACEGMP), F119(ACHLQSVWY), 119.5(AHIKLNQRSTVY), Q120(-CFIKLRSTW), 120.5(GIKLPR), A121(-EFGHIKNQTVW), 121.5(FGHQR), K122(-ADEFGNRW), 122.5(ADFHIKLPQSTW), K123(CDEFHQSTVWY), 123.5(AFKNPQT), R124(-CFGHIPTWY), 124.5(CEFHKPRSV), V125(-ACDEFHNPQSWY), 125.5(ACEFGQRSW), L126(-CDEFKQRWY), 126.5(CEGRS), E127(-CDHIMPWY), 127.5(ADGILNSTVY), P128(ACDFILQRSTV), 128.5(AGHKLMRSTW), L129(-CDFGKNRSWY), 129.5(ACDFGQRY), G130(CEFQ), 130.5(CDEHKLQRSTY), L131(DEGHIPQTVY), 131.5(ACDEFHLPRW), V132(-CDRSWY), 132.5(EFHIKLNPRVWY), E133(-ADGHLNST), 133.5(EGIPSW), E134(-ADILPW), 134.5(EHINQRW), P135(CDFHKSTWY), 135.5(CDELNPRSTWY), V136(-DEFGHIKQSTWY), 136.5(ACEGHIKLMNPQRSTVWY), K137(-ACDEHLPRSTWY), 137.5(ACDEFGHIKLNPQRSTVWY), T138(-ADEFGHKNPQRW), 138.5(CDEFGHIKNPQRSTVWY), A139(-CDEFGIKLPQRSTWY), 139.5(ACDEGHLNRVY), P140(-ACDEFGHKRSTVWY), 140.5(ACDEHIKNQRVWY), G141(-CDEFHIKLMNQRSTVWY), 141.5(DEFHIKLQRTVY), K142(-ACDEFGILNPQSY), 142.5(ACDEFGHIKLNPQRSTVWY), K143(-EGIRSVY), 143.5(AEFKLPQRSTWY), R144(AHNPSTVW), 144.5(ACEFGHIKLNPQRSTVWY), P145(-ACDEFGHIKLNQRSTVWY), 145.5(DEGIKMNPQRSTVWY), V146(-ACDEFGKLNQRTWY), 146.5(ACEFHIKLNPQRSVY), E147(-ADFGHKLNQTVY), 147.5(ACDEFGHIKRSVW), H148(-ACEGKRTVW), 148.5(AGHKMNPQRTVW), S149(-ACEGHIMNPQRVW), 149.5(ACGHIKLMNPRSTW), P150(CDFHMNQRSVY), 150.5(CDEKLMNPQRSTVWY), V151(-CDGKRSWY), 151.5(DIRWY), E152(ACFHIKLNPQVW), 152.5(DGHKMNQRY), P153(ISV), 153.5(AP), D154(S), 155.5(D), S156(AGT), S157(AEFGKQRTVW), 157.5(DNQTW), G158(D), 158.5(GP), T159(DEFGHIPQR), 159.5(PY), G160(CY), 160.5(CDFHNSWY), K161(-GHLNQSTVWY), 161.5(ADFGILQRSTVW), A162(DIKLPQW), 162.5(ACELNPQRST), G163(-CDFHKNPRTV), 163.5(DEGHIKLNPRSTVWY), Q164(CDHIMRTVW), 164.5(ADEFGIKNPQRSY), Q165(ACHILNPSVW), 165.5(FIPQTV), P166(-ACFGHIKLNQRSTVY), 166.5(FGHINPSTY), A167(QSV), R168(K), R170(K), L171(I), N172(-ACDFHKLQSVWY), 172.5(F), 173.5(ADEFGHINQWY), G174(ACDEFHQSTWY),	

174.5(ACEFHIKNQRSY), Q175(-ACDGHKNRST), 175.5(ACDFGIKLNQRSY), T176(ACDFGRY), 176.5(ADENP), G177(-EQ), 177.5(CEGILPTY), D178(-AEIRSWY), 178.5(DFINPRSW), A179(-CEFIKPSW), 179.5(ACDEFGHKNPQRSTVWY), D180(-ACFHIMNQVY), 180.5(ACDFGHILMQRSV), S181(FKLNRTY), 181.5(ACGHNSTVY), V182(ACINPRS), 182.5(CHLPRS), P183(CHLRS), 183.5(CDEGKLMNQY), D184(ACFGHILNPQRTWY), 184.5(CLMPRVY), P185(CDEFGILNSTVWY), 185.5(CEFILPQTVW), Q186(-FGIKNPSTY), 186.5(CDEIKNQSY), P187(-ADFGILNQRST), 187.5(CEGKNPQRWY), L188(CDEFIMPQSTW), 188.5(ADIKLNQSV), G189(-CEIKMNRV), 189.5(EFGLMQRW), Q190(-ACGLMNRSVW), 190.5(ACDFGHPQRSY), P191(AHIKLMNVWY), 191.5(CFIPQRTVW), P192(-ACDFKLMQRSTWY), 192.5(EGHKLMNSVY), A193(CDGHIKLMNPQY), 193.5(DHIMPRSTVW), A194(CFGHIKMQVW), 194.5(CFKMNPT), P195(DEGHKQRSTVY), 195.5(CDHMPQRST), S196(-DFGKNPQRTW), G197(AS), L198(ACDFGNRVWY), G199(D), 199.5(CFHRW), T200(ACFGINQRS), N201(CDH), T202(KPQRSVWY), M203(ACDEFGHIKLPQRSTVWY), A204(DV), T205(EFIKMRVWY), G206(ACDEFHKQRSY), S207(ACDGHRY), G208(ADEFHKLNQRVWY), A209(DEGHKMNQRSVY), P210(CGHQR), M211(LV), A212(G), D213(ACEFGHIKLNPSTW), N214(ACDEFIKLPSVY), N215(CDHILY), E216(ADH), G217(ACDEFHILMNQSTVY), A218(QST), G220(ACMNST), V221(I), N223(ACDHIMQSTY), S225(CQR), H229(ACDSTV), D231(C), T233(DHIMQSVY), M235(LV), 236.5(D), D237(CGH), 237.5(DEGHKNQ), R238(CHS), 238.5(CFTY), I240(FHV), T242(CFHRSY), S243(A), T244(C), T246(IV), A248(S), L249(CV), P250(AQS), T251(CLPSV), Y252(F), N253(D), N254(CGQS), H255(A), L256(ACGHKMNQRSV), K258(LQ), Q259(AGHKPRS), 260.5(MNQ), S261(ACGNT), S262(T), 262.5(D), Q263(-DEFGHLTWY), S264(-ADEHILMQTVWY), 264.5(D), 265.5(ADEMNQST), A266(S), 266.5(AE), S267(AENPT), 267.5(E), N268(ADEQ), 268.5(E), 269.5(D), N270(ACDGHQSY), H271(EFINV), F273(HWY), S276(AK), G280(A), Y281(FH), F282(LMVWY), F284(CY), F287(Y), H288(N), C289(S), S292(C), D295(AE), N303(TV), F306(W), R307(-CDIKMSTY), 307.5(FKN), P308(-NV), K309(ACQS), R310(ACFGIKLNSTVW), L311(CFIY), N312(CDHLMQTWY), F313(V), K314(CFGHLMNQRSTVWY), L315(V), I318(FL), 323.5(CT), T324(AHLMN), 324.5(CFKMRT), Q325(CHKRV), 325.5(ACFGHIKRST), N326(CDGLMRTWY), 326.5(N), D327(AGQT), 327.5(AGHT), G328(AN), 328.5(G), T329(ACFIY), T330(KNQS), T331(FHNY), I332(ACSV), 332.5(K), A333(CDFHNSTY), N334(QS), L336(I), T339(C), V342(ACIM), F343(M), T344(CDEFIKLMNRSV), S346(ACEFHIKLMPQVWY), Y348(AEFGHNRSW), Q349(AGMS), V353(CIT), L354(AIMQTVY), G355(S), S356(A), H358(ACGLNQST), Q359(DEHKMTV), C361(A), L362(I), F365(W), A367(CP), V369(CIPT), F370(Y), M371(ACIKLNQSTV), V372(CI), Y375(FW), G376(CS), Y377(F), L378(ACV), T379(ACGSV), 379.5(DE), L380(CEMNQTVY), 380.5(E), N381(ACDGMQS), N382(CDEST), 382.5(D), 383.5(E), S384(AG), 384.5(D), Q385(ACDEIKLMRSTVY), 385.5(ADEHKLPT), A386(-EGHLNPRSTVWY), 386.5(CDEPY), V387(CDEIQTWY), 387.5(EGKP), G388(EIM), R389(GIL), S390(ADGNT), 390.5(C), S391(AG), Y393(F), C394(V), 394.5(N), 395.5(W), Y397(AGN), P399(EIMQRS), Q401(ACDEFIKLMNRSVWY), L403(C), R404(K), 404.5(N), T405(SY), G406(DENQ), 406.5(Q), 407.5(H), N408(ADFGHLMQSTWY), 408.5(CMN), F409(CHW), T410(CEFGHLMQVY), F411(ACLTVW), S412(EFGIKMNQTVWY), 412.5(Q), Y413(FM), T414(EFGIKLMNQ),	

414.5(D), 415.5(ADGNPQS), E416(ADG), 416.5(CEGKMNRS), D417(AEGIKMNSTV), 417.5(DEKLMQRS), V418(CGHLMQS), P419(DEGIKLNRSTVW), F420(LM), S422(A), S423(CLT), Y424(FHT), A425(-CFQSV), H426(N), S427(ANT), Q428(EHNS), S429(CGHPY), L430(MV), D431(M), 431.5(Y), R432(-I), L433(IMSV), 433.5(F), M434(A), L437(ANSV), I438(GHMT), D439(KNPSTY), 441.5(M), L442(ITV), 444.5(CLM), L445(CFIMVY), 445.5(ACDEGHILMNQSTVY), S446(-CDEGHILMNQTV), 446.5(ACDEFGHILMNPQSTVWY), R447(-ACDEFGHILMNPQSTVWY), 447.5(ACDEFGHILMNPQSVWY), T448(-ACDEFGHILMNPQSVWY), 448.5(ACDEFGHILMNPQSY), N449(-ACDEFGHILMPTVWY), 449.5(AEGHLMNPST), T450(-ACDFGLMNPSY), 450.5(ADEFGHLPQSTV), P451(-IL), 451.5(GNP), S452(-DEFGILNPQTY), 452.5(ALV), G453(-AEFHIKLMNPQST), 453.5(FILMNY), T454(-ADEFGHILMNPQSV), 454.5(ADEFGLMPY), T455(-ADEILMNPQSVY), 455.5(FHNPQ), T456(ADEFGHIKLMNPQSY), 456.5(DEGHILPS), Q457(EFGHILMPS), 457.5(ADEFGHILMNPTWY), S458(-DEFHMNVW), 458.5(CDEGHILMNQSTVW), R459(-DEGINPY), 459.5(DEP), L460(AHIMPTWY), 460.5(W), Q461(DEFHIKMSTV), F462(Y), 462.5(N), S463(ACDGKMNQRTV), 463.5(F), Q464(CIKLMRTV), 464.5(SY), A465(G), G466(AD), 466.5(E), A467(EKMS), S468(ACDEFHLNPQVWY), D469(V), 469.5(E), R471(DEGQSTV), D472(GHLMQSTVWY), Q473(FHSY), S474(ACIY), R475(HK), 475.5(SW), N476(CSTW), 476.5(L), W477(FY), 477.5(L), L478(FI), 478.5(L), P479(GIT), 479.5(D), G480(Y), P481(ACV), 481.5(GHY), C482(AFGHNQSWY), 482.5(F), Y483(ACHITVW), 483.5(FHQV), R484(EFGHIKLMNQSTVY), 484.5(N), Q485(ACFGILMNSTY), 485.5(EIKMQY), Q486(ACDEFGILMPSVWY), 486.5(FV), R487(-ACDEFGHIKLMNPQSTVWY), 487.5(FW), V488(ACEFGHILMNQTWY), 488.5(ACDEFGILMPQSVWY), S489(-ACEFGHIKLMNPQTVWY), 489.5(ACDEGLMPQRSTVWY), K490(-ACDEFGHILMNPQRSTVWY), 490.5(ACDEFGHILMPQRSTVWY), T491(-AGMPQSY), 491.5(ADEFGHIKLMNPQSTVWY), S492(-CDFGHLMPQTV), 492.5(ADEGHILMPQSTVY), A493(-HLQRSTV), 493.5(ADEFGHIKLMNPQSTVWY), D494(EFR), 494.5(ADEFGHILMNPQSTVWY), N495(-ADEFGHILMPQSTVWY), 495.5(ACDEFGILMNPQSTVWY), N496(-ACDEFGILMPQTVWY), 496.5(ADEFGHILMNPQSTVWY), N497(-CEFGHLMSTVWY), 497.5(ADEFGILMNPQSTVY), S498(-CDEGINPQRTVW), 498.5(ADEFGHILMNPQSTVWY), E499(CIPS), 499.5(ACDEGHILMNPQRSTVWY), Y500(-ACDEGHIKLMNPQSTVW), 500.5(ADEFGHILMNPQSTVWY), S501(-ACDEFGHILMNPRTVWY), 501.5(ACDEFGHILMNPQRSTVWY), W502(-ACDEFGILMPQSTVY), 502.5(ADEFGHILMNPQSTVWY), T503(-ADEFGHILMNPQSWY), 503.5(ADEFGILMNPQSTVW), G504(-ACDEFHILMNPQSTVWY), 504.5(ACDEFGHILMNPQSTVWY), A505(-CDEFGHILMNPQSTVWY), 505.5(ACDEFGILMPQSTVWY), T506(-FGILMNPQS), 506.5(ACIPSTVW), K507(-ACEFHILMNVWY), Y508(-DFIMSTV), H509(EFKNQR), 509.5(K), L510(I), 510.5(K), N511(ACDEGLMQSWY), 512.5(S), R513(HIV), D514(ACEFGILMQSTV), S515(ACINTV), L516(ACIMRS), V517(CL), 517.5(C), N518(AILQRTVY), P521(CFMNS), 521.5(M), A522(CSV), M523(CLV), 523.5(A), A524(GPS), 524.5(ACGHSTW), S525(CMNPT), 525.5(ACDEFGHILMNPQSTVWY), H526(-DEFGIKLMPRVWY), 526.5(ACDEFGHILMNPQSTVWY), K527(-DEFGHILPRSTVWY), 527.5(ACDEFGHILMPQSTVWY), D528(AEFMPQSVW), 528.5(DEPT), D529(ES), 529.5(ADEGLMNPQTV), E530(DNPVW), 530.5(ACDEFGHIKLMNQRSTVWY).	

E531(ACFGHILMNPQSTVY), 531.5(ADEFGIKLMNPQRSTVY), K532(-ACDEGPR), 532.5(ACDEFGHIKLMNPQSTVWY), F533(ACDEGHILNQSTVW), 533.5(ACDEFGHILNPQSTVWY), F534(ILMVWY), 534.5(F), P535(-AF), Q536(-ACDEFGHILMNPSTVWY), 536.5(ACILTV), S537(-ACDFGHNQTY), 537.5(T), G538(-), V539(ACHILMNQST), L540(IM), 540.5(KN), I541(-ADEFGKPQRTV), 541.5(ACDEGMQRSTV), F542(GP), 542.5(QY), G543(APS), 543.5(ADHIKLMPQRSTV), K544(-AFGINQSTVY), 544.5(ADEFGHIKLMNRSTVWY), Q545(-ADFGHKLNPRSTWY), 545.5(ACEFGHILMNPQSTVWY), G546(ACEFHLNPQSTVWY), 546.5(ACDEFGHILMNQSTVWY), S547(-CDFGHILNQVWY), 547.5(ACDGHILMNPQSTVWY), E548(ADFGILMNPSWY), 548.5(ACDFGHILNPSTWY), K549(-DEFGHILNPQSTY), 549.5(ADEFGLMNQSTVY), T550(-CQSWY), 550.5(ADEGIKMNPQRSTV), N551(-ACDEFGHIKMPQRSTVY), 551.5(ACDEFILMPQST), V552(CEILQST), 552.5(VW), D553(AEGST), I554(ACEHQSTVW), E555(AGHNSTVY), 555.5(N), K556(CDMQW), 556.5(Q), V557(IL), M558(AHILNSTV), I559(FQV), T560(AV), D561(EHILNRSVY), E562(AD), E563(CR), I565(LT), 565.5(Y), R566(DFHLMQY), T567(P), 567.5(E), T568(P), 569.5(M), P570(QS), 570.5(M), V571(ACDEFHILMQSTY), A572(CGY), 572.5(WY), T573(ACDGHINSVWY), 573.5(T), E574(ACDFLMQSW), 574.5(V), Q575(-CFGHIKLMNSTVW), 575.5(AWY), Y576(ACFGHIMSV), 576.5(EFWY), G577(DW), 577.5(ACDEHIMNQSTV), S578(ACFHLNQVY), 578.5(ACDEFGHILNSTVY), V579(CDEFGHILMNQSTWY), 579.5(ACDEFGILMNPQSTVWY), S580(-CDEFGHILMNPQTVWY), 580.5(ACDEFGIKLMNPQRSTVWY), T581(-AFGHLNPQSWY), 581.5(ACDEFGILMNPQTVWY), N582(-ACDEFGHIKLMPQRSTVWY), 582.5(DFGHNPSTVW), L583(-ADEFGMPSTVWY), 583.5(DEGIMNPQSTVY), Q584(-ADEFGHILMNPSTVWY), 584.5(ACDEFGHILMNPQSTVWY), R585(-ACDFGHIKLMNPSTVWY), 585.5(ADEFGHILMNPQSTVWY), G586(-DEFHLMTVY), 586.5(ACDEFGHILMNPQSTVY), N587(-DEFHILMPQSTVY), 587.5(ADEFGHILMNPQSTVWY), R588(-ACDEFGHIKLMNPQSTVWY), 588.5(ADEFGHILMNPQSTVY), Q589(-ADEFGIMNPRSTVWY), 589.5(ACDEFGHIKLMNPQSTVWY), A590(DEFHKLMNQTWY), 590.5(ACDEFGIKLMNPQSTVWY), A591(-FGILNPVWY), 591.5(ACDEFGHILMNPQSTVY), T592(-CDEFGHLMNPQVY), 592.5(ACDEFGILMNPQSTVWY), A593(-CFLMNPWY), 593.5(ACDEFGHILMNPQSTVWY), D594(ELT), 594.5(ACDEFGHILMNPQSTVWY), V595(ACDEFGHILMNPQSTWY), 595.5(ACDEFGHILMNQSTVW), N596(ADEFGHIMPQSTWY), 596.5(DENY), T597(EFGKPRV), 597.5(F), Q598(AEFGHNSY), G599(SW), V600(LM), 600.5(F), L601(MVWY), P602(CMQ), G603(A), M604(ACQS), V605(ACFMNT), 605.5(N), 606.5(P), D608(ENQW), R609(D), D610(Y), 610.5(F), Y612(R), 613.5(Y), Q614(NT), G615(S), P616(ACH), I617(KM), 617.5(I), K620(ACGHMNQS), I621(HKLQRTV), H623(CDFKLSVW), G626(A), H627(AFGILMNQVW), F628(ILM), H629(WY), P630(ACGQTV), 630.5(CV), S631(AHNT), L633(FHMY), M634(CI), F637(IW), L639(FVY), K640(AFNRTVWY), 640.5(N), H641(CIKL), P644(W), Q645(LMT), I646(CLMTV), L647(FIY), I648(CV), N650(CILTV), P652(A), V653(CT), A655(S), 655.5(LMV), N656(FQTW), 657.5(CDFGHLMNQSTVW), S658(AFGIMNQT), 658.5(ACEFGHIKLNQRWY), T659(-CEGIQRY), 659.5(ACDEFGIMNPSVY), T660(-CDEGHKMPQRV), 660.5(ADEFGHIKLPQRWY), F661(AEILMQSTVY),	

661.5(ACDEFGIKLMNPRSVY), S662(CPQRW), 662.5(ACDEFGHIKLMNPQRSTVW), A663(FHIKLMNPRY), 663.5(CDGHILMNPRSTVWY), A664(CDHKNRWY), 664.5(ACDEHLMNPRTVWY), K665(ACFGHIMNPQRSTW), 665.5(AHILNPQRSTVWY), F666(CGLNSWY), 666.5(IPV), A667(CEGILMNPRY), 667.5(HNQY), S668(AG), F669(Y), I670(V), T671(NRS), Q672(CEGLS), S674(G), T675(S), V678(ACT), S679(CEFGHIKLRY), V680(CL), E681(DLMNSTV), I682(M), E683(HIQ), E685(ADLQT), L686(T), Q687(IMVW), K688(HP), N690(R), E697(-DHIMPR), 697.5(GHNPQW), I698(-DL), 699.5(E), T701(S), 701.5(A), S702(IQV), 702.5(Q), N703(DG), 703.5(AEHLTY), Y704(FH), 704.5(ADEILNST), N705(CDEFHIKLMPQTV), 705.5(ENQY), K706(DEGRST), S707(CDEFGHILMNQTVY), 707.5(MY), V708(ACEGHNRST), 708.5(I), N709(CDKLPQRV), 709.5(CGPQ), V710(AELMNPQ), 710.5(D), D711(GNP), 711.5(QY), T713(ACS), T716(ACFIKLNQRVWY), N717(ADEFHRSY), V719(FKLNQRY), 720.5(N), S721(CFHIKLMNQRTVWY), E722(DQ), P723(ACDEHNQSTV), R724(FHKNSWY), P725(ACILQV), I726(LV), R733(K), N734(AEISV), L735(C)	

Table 8: Amino acid alterations that reduce delivery to spleen.

Amino acid alteration	Fold increase of efficiency
D439(K), 444.5(CLM), 445.5(ACELMNST), 446.5(CN), 447.5(INP), 460.5(W), G466(Q), 476.5(L), 478.5(L), R484(EFGLMNSTVY), 485.5(IKM), Q486(IVW), R487(CDFGILNSTVW), 487.5(F), 488.5(WY), K490(EP), 493.5(K), 497.5(D), S498(D), 498.5(DE), E499(C), 499.5(CDE), 503.5(IMQW), 504.5(FLNSTY), A505(E), 505.5(ACLQTVW), 506.5(ACISV), 523.5(A), 524.5(GHS), 525.5(ACDFGHILNQSTVWY), H526(EL), 526.5(CDEFHILMNPQSTWY), K527(-W), 527.5(ACDEHILMPSVWY), 528.5(D), 529.5(D), 530.5(IW), 531.5(IV), K532(P), 532.5(CGHIPQSTVWY), 533.5(CFNPQW), 534.5(F), P535(-F), Q536(-), 536.5(CITV), V571(H), 575.5(W), 576.5(W), G577(D), 577.5(DI), 578.5(CEITY), 579.5(Q), S580(-), T581(DE), 581.5(CY), N582(F), Q584(W), 586.5(F), R588(N), 590.5(K), A591(E), 591.5(DEP), T592(DE), 592.5(CMP), A593(-P), 593.5(FGPW), 595.5(CD), 596.5(DEY), 605.5(N)	0.1-fold
D180(M), 266.5(E), 268.5(E), 379.5(E), 380.5(E), 382.5(D), 433.5(F), D439(K), 444.5(CLM), L445(F), 445.5(ACEGHILMNQSTV), S446(-), 446.5(ACEFHILMNPQSTVWY), R447(EFIWY), 447.5(DEGHILMNPQVW), T448(-DEHINPQV), 448.5(DEP), N449(P), G453(K), 453.5(Y), 454.5(F), S458(E), R459(D), L460(Y), 460.5(W), 462.5(N), 463.5(F), G466(Q), 469.5(E), R471(EG), S474(I), 476.5(L), 478.5(L), P479(T), 479.5(D), C482(W), 483.5(V), R484(EFGHILMNQSTVY), 485.5(EIKM), Q486(EFIMVWY), 486.5(FV), R487(ACDEFGHILMNPQSTVWY), 487.5(FW), V488(H), 488.5(DEILPWY), S489(DLMPQWY), 489.5(DPTW), K490(-CDEPW), 490.5(DE), T491(DP), 491.5(DEFKW), 492.5(DE), A493(D), 493.5(DEK), D494(F), 494.5(DE), N495(FLP), 495.5(CI), N496(D), N497(-), 497.5(DE), S498(DE), 498.5(DE), E499(C), 499.5(ACDEGPQ), Y500(ACDEIPV), 500.5(DELQ), 501.5(CEGNW), W502(-EP), 502.5(ADEFGMNPTWY), T503(DE), 503.5(DEFGILMNQSTVW), G504(-DILNPTVY), 504.5(ACDEFGILMNPQSTVWY), A505(DEHILMNQY), 505.5(ACDEGILMPQSTVW), T506(-F), 506.5(ACIPSTV), K507(-ACEINSWY), Y508(-), H509(FN), 509.5(K), 510.5(K), 517.5(C), 523.5(A),	0.2-fold

524.5(ACGHST), 525.5(ACDEFGHILMNPQSTVWY), H526(DEILPV), 526.5(ACDEFGHILMNPQSTVWY), K527(-FHLPWY), 527.5(ACDEFGHILMPQSTVWY), 528.5(DET), 529.5(ADELMPV), E530(PW), 530.5(CDEFILMNQTVWY), 531.5(ADEFGILNPQTV), K532(-ACFGHILMNPQSTVW), 532.5(ACGHILMPQSTVWY), F533(ADEGSTV), 533.5(ACEFGHILNPQSTVWY), 534.5(F), P535(-F), Q536(-DP), 536.5(ACILTV), S537(-), 537.5(T), 559.5(A), V571(EHS), 571.5(G), 573.5(T), Q575(K), 575.5(WY), Y576(V), 576.5(W), G577(D), 577.5(ACDEHIMQS), S578(DE), 578.5(ACEFILSTY), V579(DEW), 579.5(DEFILNQTY), S580(-DEQ), T581(DEP), 581.5(CDIQY), N582(-CFILY), 582.5(FGT), 583.5(PTVY), Q584(GVW), 584.5(DEIMPV), R585(AEFGHILMNQSTVWY), 585.5(AFILMPSTVY), G586(-DE), 586.5(ACFGILMNPQSTV), N587(-DE), 587.5(ADILMNTV), R588(ACFHILMNQSVWY), 588.5(GIV), 589.5(CFHKPV), A590(M), 590.5(CGKPQST), A591(DEW), 591.5(CDEFGILMPTV), T592(-DE), 592.5(ACEFGILMNPQSTVWY), A593(-DEP), 593.5(ACDFGILMNPSTVWY), D594(LT), 594.5(ACFGHILMPQTVWY), 595.5(CDEFGIQTVW), N596(DE), 596.5(DEY), 605.5(N), 606.5(P), R609(D), D610(Y), 617.5(I)	
D180(M), 180.5(M), S261(D), 264.5(D), 266.5(E), S267(E), 267.5(E), N268(E), 268.5(E), H271(E), 379.5(DE), L380(E), 380.5(E), 382.5(D), 383.5(E), 386.5(D), 431.5(Y), 433.5(F), D439(K), 444.5(CLM), L445(FY), 445.5(ACDEGHILMNQSTV), S446(-EL), 446.5(ACDEFGHILMNPQSTVWY), R447(-DEFIPVWY), 447.5(CDEGHILMNPQVW), T448(-DEGHILNPQVW), 448.5(DEP), N449(DEP), 449.5(E), G453(IK), 453.5(Y), 454.5(EF), T455(E), 457.5(D), S458(DE), 458.5(DE), R459(DE), L460(WY), 460.5(W), Q461(D), 462.5(N), 463.5(F), 464.5(Y), G466(Q), 469.5(E), R471(EGSTV), S474(I), 475.5(W), 476.5(L), 478.5(L), P479(GT), 479.5(D), G480(Y), C482(W), 482.5(F), 483.5(QV), R484(EFGHILMNQSTVY), 485.5(EIKMQY), Q486(DEFIMPVWY), 486.5(FV), R487(-ACDEFGHIKLMNPQSTVWY), 487.5(FW), V488(EFGHY), 488.5(DEILPSWY), S489(-DEFGKLMPQTVWY), 489.5(ADEGPQRSTW), K490(-CDEFGLNPWY), 490.5(CDEFIPVY), T491(DEP), 491.5(DEFHIKLMWY), 492.5(DEY), A493(DE), 493.5(DEHKP), D494(FR), 494.5(DEGP), N495(-AEFGILMPQSTVWY), 495.5(CDEGILPTV), N496(-CDEGILM), 496.5(DE), N497(-CEH), 497.5(DE), S498(-CDEFPR), 498.5(DE), E499(CIP), 499.5(ACDEGLMNPQSTVW), Y500(ACDEGIKLPV), 500.5(ADEFGILNPQST), S501(D), 501.5(ACDEFGHILMNQSTVWY), W502(-ACDEMP), 502.5(ADEFGILMNPSTVWY), T503(-DE), 503.5(ADEFGILMNPQSTVW), G504(-CDEFILNPSTVWY), 504.5(ACDEFGHILMNPQSTVWY), A505(-DEFHILMNPQWY), 505.5(ACDEFGILMPQSTVWY), T506(-FLM), 506.5(ACIPSTVW), K507(-ACEFHILMNQSTVWY), Y508(-), H509(CEFN), 509.5(K), 510.5(K), R513(C), D514(FILV), 517.5(C), 521.5(MS), 523.5(A), 524.5(ACGHST), S525(HM), 525.5(ACDEFGHILMNPQSTVWY), H526(DEILMPV), 526.5(ACDEFGHILMNPQSTVWY), K527(-DEFHILPQVWY), 527.5(ACDEFGHILMPQSTVWY), 528.5(DET), 529.5(ADEGLMNPQV), E530(PW), 530.5(ACDEFGILMNQSTVWY), 531.5(ADEFGILMNPQRSTVY), K532(-ACFGHILMNPQSTVWY), 532.5(ACDEFGHIKLMNPQSTVWY), F533(ACDEGIQSTV), 533.5(ACDEFGHILNPQSTVWY), 534.5(F), P535(-F), Q536(-DPW), 536.5(ACILTV), S537(-), 537.5(T), G538(-), 559.5(A), R566(D), T568(P), P570(Q), 570.5(M), V571(ADEFHS), 571.5(G), 572.5(Y), T573(D), 573.5(MT), Q575(DK), 575.5(FWY), Y576(HMV), 576.5(EFWY), G577(D),	0.3-fold

577.5(ACDEHIMQSTV), S578(DE), 578.5(ACDEFILSTVY), V579(DEW), 579.5(DEFGILMNQTVY), S580(-DEILMQY), 580.5(DEN), T581(-DEP), 581.5(ACDEILMPQY), N582(-ACEFHILMPTVWY), 582.5(DFGHPTVW), L583(-P), 583.5(GNPQSTVY), Q584(DFGILNPTVWY), 584.5(ACDEFGHILMNPQSTV), R585(-ACEFGHILMNQSTVWY), 585.5(ADFGILMNPQSTVWY), G586(-DE), 586.5(ACDFGHILMNPQSTV), N587(-DEILQVY), 587.5(ADEFGILMNPQSTV), R588(-ACEFHILMNPQSTVWY), 588.5(DEGILMPV), Q589(-DR), 589.5(ACDEFHKNPTVW), A590(DELMNQ), 590.5(ACEGIKMPQSTW), A591(-DEWY), 591.5(ACDEFGHILMNPQSTV), T592(-DEP), 592.5(ACDEFGILMNPQSTVWY), A593(-DEP), 593.5(ACDEFGILMNPQSTVWY), D594(LT), 594.5(ACDFGHILMPQSTVWY), V595(DEGHW), 595.5(ACDEFGILQTVW), N596(DEI), 596.5(DEY), T597(E), Q598(FY), 605.5(N), 606.5(P), 607.5(P), D608(W), R609(D), D610(Y), 617.5(I), 640.5(N), 667.5(Y)	
4.5(H), 45.5(M), 50.5(N), G58(C), S156(T), D180(M), 180.5(M), 183.5(M), L256(A), S261(D), S262(T), 262.5(E), Q263(G), S264(W), 264.5(D), 265.5(D), 266.5(E), S267(E), 267.5(E), N268(DE), 268.5(E), 269.5(D), H271(E), Q325(K), 379.5(DE), L380(E), 380.5(E), N381(D), N382(DE), 382.5(D), 383.5(E), 384.5(D), 386.5(D), V387(E), G406(E), A425(-), Q428(E), 431.5(Y), R432(I), 433.5(F), D439(K), 441.5(M), 444.5(CLM), L445(FY), 445.5(ACDEGHILMNQSTVY), S446(-DEILQV), 446.5(ACDEFGHILMNPQSTVWY), R447(-DEFILMPTVWY), 447.5(ACDEFGHILMNPQVWY), T448(-ACDEFGHILMNPQVWY), 448.5(CDEFNPWY), N449(DEFMPW), 449.5(E), T450(E), 450.5(F), 451.5(N), 452.5(AL), G453(DEFIKLNS), 453.5(FILMNVY), T454(-FI), 454.5(DEFLM), T455(-DEMY), 455.5(P), T456(-DEK), 456.5(DE), Q457(DEP), 457.5(DEPW), S458(DEFMWY), 458.5(DEFILMNTWY), R459(-ACDEGIPTV), 459.5(DE), L460(FHWY), 460.5(W), Q461(DE), 462.5(N), S463(G), 463.5(F), 464.5(SY), G466(Q), 469.5(DE), R471(ACDEGMQSTV), D472(Y), S474(I), R475(H), 475.5(SW), N476(TW), 476.5(L), 477.5(L), 478.5(L), P479(GT), 479.5(D), G480(Y), 481.5(H), C482(W), 482.5(FM), Y483(TVW), 483.5(FQV), R484(EFGHIKLMNQSTVY), 484.5(N), Q485(ACGLST), 485.5(EIKMQY), Q486(ADEFGILMNPVWY), 486.5(FV), R487(-ACDEFGHIKLMNPQSTVWY), 487.5(FW), V488(EFGHWY), 488.5(ACDEGILMPQSWY), S489(-CDEFGHIKLMNPQTVWY), 489.5(ACDEGLMPQRSTVWY), K490(-ACDEFGHILMNPQSTVWY), 490.5(ACDEFHIMPQRTVWY), T491(-DEP), 491.5(ACDEFHIKLMNPQSTVWY), S492(-E), 492.5(ADEGHILSVY), A493(-DEHR), 493.5(ADEFHIKLMPQSVWY), D494(FR), 494.5(DEGILMPTVY), N495(-ADEFGHILMPQSTVWY), 495.5(ACDEFGILMPQSTVW), N496(-ACDEGILMPQVW), 496.5(DEFQW), N497(-CEHW), 497.5(DE), S498(-CDEFILPRVW), 498.5(DEFLPQY), E499(CIPQS), 499.5(ACDEGHILMNPQRSTVWY), Y500(-ACDEGIKLNPQV), 500.5(ADEFGHILMNPQSTVY), S501(-DILNVW), 501.5(ACDEFGHILMNQRSTVWY), W502(-ACDEGILMPQSTVY), 502.5(ADEFGHILMNPQSTVWY), T503(-DEGLMPW), 503.5(ADEFGILMNPQSTVW), G504(-CDEFHILMNPQSTVWY), 504.5(ACDEFGHILMNPQSTVWY), A505(-DEFHILMNPQTVWY), 505.5(ACDEFGILMPQSTVWY), T506(-FGILMV), 506.5(ACIPSTVW), K507(-ACEFHILMNQSTVWY), Y508(-), H509(CEFNQ), 509.5(K), 510.5(K), N511(EWY), 512.5(S), R513(CIV),	0.5-fold

D514(ACEFILMQV), 517.5(C), 521.5(MS), M523(V), 523.5(A), 524.5(ACGHSTW), S525(HM), 525.5(ACDEFGHILMNPQSTVWY), H526(-ADEGILMPQTVW), 526.5(ACDEFGHILMNPQSTVWY), K527(-DEFHILMPQSTVWY), 527.5(ACDEFGHILMPQSTVWY), D528(AFQ), 528.5(DEPT), D529(S), 529.5(ADEGLMNPQTV), E530(NPVW), 530.5(ACDEFGHIKLMNQRSTVWY), E531(ACGHILMNV), 531.5(ADEFGIKLMNPQRSTVY), K532(-ACDEFGHILMNPQSTVWY), 532.5(ACDEFGHIKLMNPQSTVWY), F533(ACDEGILMNQSTV), 533.5(ACDEFGHILNPQSTVWY), F534(LVY), 534.5(F), P535(-AF), Q536(-ADEGPWY), 536.5(ACILTV), S537(-DY), 537.5(T), G538(-), V539(H), 542.5(Y), D553(T), I554(E), 559.5(A), E562(A), R566(DEFY), 567.5(E), T568(P), P570(Q), 570.5(M), V571(ADEFHMQSY), 571.5(G), A572(Y), 572.5(WY), T573(DGV), 573.5(MT), E574(D), 574.5(V), Q575(DGKL), 575.5(AFWY), Y576(ACGHIMSV), 576.5(EFWY), G577(DW), 577.5(ACDEHIMNQSTV), S578(DEFILNWY), 578.5(ACDEFGHILNSTVY), V579(ADEFGSWY), 579.5(ACDEFGILMNPQTVWY), S580(-DEFHILMNPQY), 580.5(ACDEFGKLMNPRVW), T581(-DEKP), 581.5(ACDEGILMNPQVWY), N582(-ACDEFHILMPQRSTVWY), 582.5(DFGHPSTVW), L583(-DGP), 583.5(DEGIMNPQSTVY), Q584(-ADEFGHILNPSTVWY), 584.5(ACDEFGHILMNPQSTVWY), R585(-ACDEFGHIKLMNPQSTVWY), 585.5(ADEFGHILMNPQSTVWY), G586(-DEFMW), 586.5(ACDEFGHILMNPQSTV), N587(-DEGHILMPQVY), 587.5(ADEFGILMNPQSTVWY), R588(-ACDEFGHIKLMNPQSTVWY), 588.5(DEFGHILMPTVY), Q589(-DEPR), 589.5(ACDEFGHIKNPSTVWY), A590(DEHKLMNQY), 590.5(ACDEFGIKLMNPQSTVWY), A591(-DEFPWY), 591.5(ACDEFGHILMNPQSTVWY), T592(-DEGPV), 592.5(ACDEFGILMNPQSTVWY), A593(-DEP), 593.5(ACDEFGHILMNPQSTVWY), D594(ELT), 594.5(ACDEFGHILMNPQSTVWY), V595(DEGHLMNPQWY), 595.5(ACDEFGHILMNQSTVW), N596(DEIP), 596.5(DENY), T597(DE), 597.5(F), Q598(FHY), G599(W), 600.5(F), L601(Y), 605.5(N), 606.5(P), 607.5(P), D608(W), R609(D), D610(Y), 610.5(F), 613.5(Y), I617(K), 617.5(I), 640.5(N), T660(H), 662.5(F), 667.5(Y), K706(DEG)	
4.5(H), 38.5(G), K39(E), 45.5(M), G49(H), Y50(H), 50.5(N), G58(C), E74(I), S156(T), 157.5(P), D180(M), 180.5(M), 183.5(M), 184.5(M), 189.5(M), P192(M), A194(C), R238(H), H255(N), L256(ACGHS), 260.5(DST), S261(D), 261.5(S), S262(T), 262.5(EGINS), Q263(AGW), S264(DEW), 264.5(D), 265.5(DE), 266.5(E), S267(E), 267.5(E), N268(DEQ), 268.5(E), 269.5(D), N270(CDGY), H271(E), D295(E), L311(I), 324.5(K), Q325(KR), N326(L), T330(K), Y348(D), T379(A), 379.5(DE), L380(EY), 380.5(E), N381(DGQ), N382(DE), 382.5(D), 383.5(E), 384.5(D), Q385(T), A386(E), 386.5(DE), V387(DE), 387.5(EGP), R389(I), S390(DN), P399(M), 404.5(N), G406(DE), 408.5(N), F409(CH), S412(W), 416.5(N), 417.5(M), A425(-Q), H426(N), Q428(EH), S429(Y), D431(M), 431.5(Y), R432(-I), L433(D), 433.5(F), I438(K), D439(HKT), 441.5(M), L442(FI), 444.5(CLM), L445(CFMY), 445.5(ACDEGHILMNQSTVY), S446(-DEHILMNQTV), 446.5(ACDEFGHILMNPQSTVWY), R447(-ACDEFGHILMNPQSTVWY), 447.5(ACDEFGHILMNPQSVWY), T448(-ACDEFGHILMNPQVWY), 448.5(ACDEFGILMNPWY), N449(-DEFILMPVW), 449.5(AEGHLNPS), T450(-CDEPW), 450.5(DEFHV), 451.5(N), S452(-DEFPVW), 452.5(AILPV), G453(-ADEFHIKLMNPQSTV), 453.5(FILMNTVY), T454(-DEFILMP), 454.5(DEFLMP), T455(-DEILMQY), 455.5(FLPQY), T456(-DEGHIKP),	0.7-fold

456.5(ADEGHILNP), Q457(DEGLP), 457.5(ADEGHILPWY), S458(DEFHMNVWY), 458.5(DEFGHILMNTWY), R459(-ACDEGILMNPQSTVWY), 459.5(DEP), L460(AFHMPWY), 460.5(W), Q461(DEIKV), F462(Y), 462.5(N), S463(CDGKNQ), 463.5(F), Q464(V), 464.5(SY), G466(Q), A467(HMY), S468(CDF), 469.5(DE), R471(ACDEGMQSTV), D472(Y), Q473(FHY), S474(I), R475(H), 475.5(SW), N476(TW), 476.5(L), W477(Y), 477.5(L), L478(FI), 478.5(L), P479(GT), 479.5(D), G480(Y), 481.5(HY), C482(FGWY), 482.5(FM), Y483(ACFHITVW), 483.5(FQV), R484(EFGHIKLMNQSTVY), 484.5(N), Q485(ACFGILNSTVY), 485.5(EIKMQY), Q486(ACDEFGILMNPSVWY), 486.5(FV), R487(-ACDEFGHIKLMNPQSTVWY), 487.5(FW), V488(AEFGHNQTWY), 488.5(ACDEFGILMPQSVWY), S489(-ACDEFGHIKLMNPQTVWY), 489.5(ACDEGLMPQRSTVWY), K490(-ACDEFGHILMNPQRSTVWY), 490.5(ACDEFGHILMNPQRSTVWY), T491(-DEP), 491.5(ACDEFGHIKLMNPQSTVWY), S492(-CEF), 492.5(ADEGHILMPQSTVY), A493(-DEFHILRWY), 493.5(ADEFGHIKLMNPQSTVWY), D494(FR), 494.5(ADEGHILMPSTVWY), N495(-ADEFGHILMPQSTVWY), 495.5(ACDEFGILMPQSTVWY), N496(-ACDEFGILMPQTVW), 496.5(ADEFGHILPQWY), N497(-CEFHIMSVWY), 497.5(ADEGMPY), S498(-CDEFILMPRVWY), 498.5(DEFGILMPQSY), E499(CIPQS), 499.5(ACDEGHILMNPQRSTVWY), Y500(-ACDEGIKLMNPQSTV), 500.5(ADEFGHILMNPQSTVWY), S501(-CDEFILNTVW), 501.5(ACDEFGHILMNQRSTVWY), W502(-ACDEFGILMPQSTVY), 502.5(ADEFGHILMNPQSTVWY), T503(-ADEFGILMPQVWY), 503.5(ADEFGILMNPQSTVW), G504(-ACDEFHILMNPQSTVWY), 504.5(ACDEFGHILMNPQSTVWY), A505(-CDEFHILMNPQSTVWY), 505.5(ACDEFGILMPQSTVWY), T506(-FGILMNPQV), 506.5(ACIPSTVW), K507(-ACEFHILMNQSTVWY), Y508(-DS), H509(CEFNQ), 509.5(K), L510(I), 510.5(K), N511(DELMQWY), 512.5(S), R513(CHIV), D514(ACEFGILMQTV), L516(ACST), V517(L), 517.5(C), N518(R), P521(MS), 521.5(MS), M523(CV), 523.5(A), A524(GP), 524.5(ACGHSTW), S525(AGHMNP), 525.5(ACDEFGHILMNPQSTVWY), H526(-ACDEFGIKLMNPQSTVWY), 526.5(ACDEFGHILMNPQSTVWY), K527(-DEFGHILMPQSTVWY), 527.5(ACDEFGHILMPQSTVWY), D528(AFMPQSVW), 528.5(DEPT), D529(S), 529.5(ADEGLMNPQTV), E530(NPVW), 530.5(ACDEFGHIKLMNQRSTVWY), E531(ACFGHILMNPQSTVY), 531.5(ADEFGIKLMNPQRSTVY), K532(-ACDEFGHILMNPQRSTVWY), 532.5(ACDEFGHIKLMNPQSTVWY), F533(ACDEGHILMNQSTVW), 533.5(ACDEFGHILNPQSTVWY), F534(ILMVWY), 534.5(F), P535(-AF), Q536(-ACDEFGNPTWY), 536.5(ACILTV), S537(-ADFGQY), 537.5(T), G538(-), V539(HLM), 540.5(K), 541.5(Q), F542(P), 542.5(Y), 543.5(CQRY), K544(Q), 544.5(AIKRVY), 545.5(CFNPQVWY), G546(Y), 546.5(EGSTWY), S547(-Q), 547.5(ADNVY), E548(FN), 548.5(CDHMPY), K549(-DILW), 549.5(DH), T550(C), 550.5(KR), N551(CDEIRTV), 551.5(CDEM), D553(AT), I554(EHQ), E555(GHTV), K556(EMW), M558(A), 558.5(E), 559.5(A), T560(A), 560.5(A), E562(A), I565(T), R566(ACDEFGHILMNTVWY), 567.5(E), T568(P), 569.5(M), P570(QS), 570.5(M), V571(ADEFHLMQSTY), 571.5(G), A572(CY), 572.5(VWY), T573(ACDGINSVW), 573.5(MT), E574(DQ), 574.5(V), Q575(-CDGIKLMSTVY), 575.5(AFWY), Y576(ACGHIMSV), 576.5(EFWY), G577(DW), 577.5(ACDEHIMNQSTV), S578(DEFGILNWY), 578.5(ACDEFGHILNSTVY), V579(ACDEFGHLMNQSTWY), 579.5(ACDEFGILMNPQSTVWY), S580(-DEFHILMNPQVY), 580.5(ACDEFGKLMNPQRSTVWY), T581(-CDEFGKPWY),	

581.5(ACDEFGILMNPQTVWY), N582(-ACDEFGHIKLMPQRSTVWY), 582.5(DFGHNPSTVW), L583(-ADEGPST), 583.5(DEGIMNPQSTVY), Q584(-ADEFGHILMNPSTVWY), 584.5(ACDEFGHILMNPQSTVWY), R585(-ACDEFGHIKLMNPQSTVWY), 585.5(ADEFGHILMNPQSTVWY), G586(-DEFHMNWY), 586.5(ACDEFGHILMNPQSTVY), N587(-DEFGHILMPQSTVY), 587.5(ADEFGILMNPQSTVWY), R588(-ACDEFGHIKLMNPQSTVWY), 588.5(ADEFGHILMPQSTVY), Q589(-DEIPRW), 589.5(ACDEFGHIKLNPQSTVWY), A590(DEFHKLMNQWY), 590.5(ACDEFGIKLMNPQSTVWY), A591(-CDEFIMNPTVWY), 591.5(ACDEFGHILMNPQSTVWY), T592(-ADEFGHMNPQVY), 592.5(ACDEFGILMNPQSTVWY), A593(-DEP), 593.5(ACDEFGHILMNPQSTVWY), D594(ELT), 594.5(ACDEFGHILMNPQSTVWY), V595(ADEFGHLMNPQSTWY), 595.5(ACDEFGHILMNQSTVW), N596(DEIPQT), 596.5(DENY), T597(DEHINQ), 597.5(F), Q598(ACEFHIMNVY), G599(CW), 600.5(F), L601(WY), P602(Q), 605.5(N), 606.5(P), 607.5(P), D608(W), R609(D), D610(Y), 610.5(F), 613.5(Y), Q614(T), I617(K), 617.5(I), P630(H), L633(FHY), 640.5(N), I646(M), L647(I), 657.5(C), S658(E), 658.5(C), T659(K), 659.5(CN), T660(H), F661(EQ), 661.5(C), S662(W), 662.5(FHLMW), 663.5(M), 664.5(C), 665.5(N), 667.5(Y), S674(G), 703.5(E), Y704(H), 704.5(DI), N705(EK), K706(DEGRST), S707(D), 707.5(MY), V708(CR), 708.5(I), V710(EN), 710.5(D), D711(N), 711.5(Y)	
4.5(H), 10.5(I), E12(H), R20(Q), W23(M), 23.5(F), 24.5(N), P32(C), A35(Y), 35.5(HY), 36.5(K), 38.5(ADGKV), K39(-AEV), 39.5(D), 40.5(DE), R43(GW), 45.5(M), G49(HM), Y50(H), 50.5(N), G58(C), 58.5(F), G62(Q), E63(CM), E74(I), A78(C), 78.5(Q), 83.5(DH), G86(D), D87(K), A98(N), E106(H), D107(Q), S109(F), 109.5(D), 117.5(K), F119(Q), 119.5(H), 122.5(E), 125.5(C), P128(F), 135.5(M), 143.5(K), R144(N), P150(M), 150.5(M), S156(T), 156.5(T), 157.5(P), T159(C), K161(DN), A162(-), G163(CN), Q164(M), 166.5(N), G174(C), G177(Q), 177.5(I), 179.5(CD), D180(CM), 180.5(CM), 181.5(NW), P183(C), 183.5(M), D184(Y), 184.5(MY), P185(EV), Q186(P), 186.5(C), P187(CK), 189.5(M), Q190(M), 191.5(W), P192(CMW), A193(C), 193.5(W), A194(C), P195(A), 195.5(Y), G197(A), L198(C), 199.5(CF), N201(D), M203(C), G206(F), P210(K), N215(DFM), G217(CEV), A218(Q), N223(CM), S225(C), H229(D), T233(D), 237.5(HQ), R238(H), 238.5(F), I240(CW), T244(C), P250(Q), N254(C), H255(N), L256(ACGHS), Q259(G), 260.5(ACDEMQST), S261(D), 261.5(S), S262(T), 262.5(EGINST), Q263(AGW), 263.5(DG), S264(-DEFLW), 264.5(D), 265.5(DE), 266.5(E), S267(ET), 267.5(E), N268(DEQ), 268.5(E), 269.5(D), N270(ACDGHSY), H271(EFI), F273(HMW), G280(A), F282(WY), H288(N), D295(E), R307(C), 307.5(K), P308(-), K309(CQ), L311(I), F313(C), K314(MV), T324(C), 324.5(CK), Q325(CHKR), N326(CLM), T330(KQ), 332.5(K), A333(C), V342(AI), T344(FI), S346(PW), Y348(DS), Q349(AGS), V353(T), G355(S), F365(W), A367(P), M371(F), T379(AG), 379.5(DE), L380(ENQTY), 380.5(E), N381(ACDGMQ), N382(DE), 382.5(D), 383.5(E), 384.5(D), Q385(PRT), 385.5(AP), A386(ELNRV), 386.5(CDEP), V387(CDE), 387.5(EGKP), R389(GIQY), S390(DGNT), P399(M), Q401(VW), L403(M), R404(K), 404.5(N), G406(DEN), N408(DGM), 408.5(CN), F409(CH), F411(Q), S412(EW), Y413(M), T414(G), 415.5(GMQ), E416(G), 416.5(EGNR), D417(I), 417.5(AKMQR), V418(GIM), P419(HILWY), Y424(C), 424.5(F), A425(-GQ), H426(N), S427(AC), Q428(EH), S429(CY), L430(M), D431(M), 431.5(Y), R432(-I), L433(DQ), 433.5(F), L437(AY), I438(GKT), D439(HKNPSTY), 441.5(M), L442(FI), 444.5(CLM), L445(CFMVY), 445.5(ACDEGHILMNQSTVY), S446(-CDEGHIKLMNQTV),	0.8-fold

446.5(ACDEFGHILMNPQSTVWY), R447(-ACDEFGHILMNPQSTVWY), 447.5(ACDEFGHILMNPQSVWY), T448(-ACDEFGHILMNPQSVWY), 448.5(ACDEFGHILMNPQSWY), N449(-ACDEFGILMPVW), 449.5(AEGHLMNPSTVY), T450(-CDEGPW), 450.5(ADEFGHLMPQSV), 451.5(GNP), S452(-DEFHNPVW), 452.5(AILPV), G453(-ADEFHIKLMNPQSTV), 453.5(FILMNTVY), T454(-DEFHILMNPV), 454.5(ADEFLMPSTY), T455(-DEILMQY), 455.5(AFHLPQTY), T456(-DEGHIKLMP), 456.5(ADEGHILMNPV), Q457(-DEFGLP), 457.5(ADEFGHILMNPVWY), S458(DEFHMNVWY), 458.5(DEFGHILMNPSTWY), R459(-ACDEFGHILMNPQSTVWY), 459.5(DEP), L460(AFHIMNPSTVWY), 460.5(W), Q461(DEIKV), F462(Y), 462.5(N), S463(ACDGKNQR), 463.5(F), Q464(ILV), 464.5(SY), A465(C), G466(CQ), 466.5(E), A467(HIMY), S468(CDFM), D469(V), 469.5(DE), I470(FL), R471(ACDEGKMQSTV), D472(MY), Q473(FHMSY), S474(I), R475(H), 475.5(SW), N476(TW), 476.5(L), W477(Y), 477.5(L), L478(FI), 478.5(L), P479(GIT), 479.5(D), G480(Y), P481(ACV), 481.5(GHY), C482(FGWY), 482.5(FM), Y483(ACFHIMTVW), 483.5(FQV), R484(EFGHIKLMNQSTVY), 484.5(N), Q485(ACFGHILMNSTVY), 485.5(EIKMQY), Q486(ACDEFGILMNPSTVWY), 486.5(CFV), R487(-ACDEFGHIKLMNPQSTVWY), 487.5(FW), V488(AEFGHLMNQTWY), 488.5(ACDEFGILMPQSVWY), S489(-ACDEFGHIKLMNPQTVWY), 489.5(ACDEGLMPQRSTVWY), K490(-ACDEFGHILMNPQRSTVWY), 490.5(ACDEFGHILMNPQRSTVWY), T491(-DEPY), 491.5(ACDEFGHIKLMNPQSTVWY), S492(-CDEFLM), 492.5(ADEGHILMPQSTVY), A493(-DEFHILNPQRVWY), 493.5(ADEFGHIKLMNPQSTVWY), D494(EFR), 494.5(ADEGHILMNPSTVWY), N495(-ADEFGHILMPQSTVWY), 495.5(ACDEFGILMPQSTVWY), N496(-ACDEFGHILMPQTVWY), 496.5(ADEFGHILMPQSTVWY), N497(-ACEFGHILMSVWY), 497.5(ADEFGILMPQVY), S498(-CDEFGILMNPQRTVWY), 498.5(ADEFGILMPQSVWY), E499(CDIPQS), 499.5(ACDEGHILMNPQRSTVWY), Y500(-ACDEGHIKLMNPQSTV), 500.5(ADEFGHILMNPQSTVWY), S501(-CDEFGILMNPTVWY), 501.5(ACDEFGHILMNQRSTVWY), W502(-ACDEFGILMPQSTVY), 502.5(ADEFGHILMNPQSTVWY), T503(-ADEFGILMNPQVWY), 503.5(ADEFGILMNPQSTVW), G504(-ACDEFHILMNPQSTVWY), 504.5(ACDEFGHILMNPQSTVWY), A505(-CDEFGHILMNPQSTVWY), 505.5(ACDEFGILMPQSTVWY), T506(-AFGILMNPQV), 506.5(ACIPSTVW), K507(-ACEFHILMNQRSTVWY), Y508(-DS), H509(CEFNQ), 509.5(K), L510(I), 510.5(K), N511(ACDEGLMQSWY), 512.5(S), R513(CHIV), D514(ACEFGILMQSTV), S515(V), L516(ACIMSTV), V517(CIL), 517.5(C), N518(IQR), P521(FMNS), 521.5(MS), A522(CV), M523(CLV), 523.5(A), A524(GPS), 524.5(ACGHSTW), S525(ACGHMNP), 525.5(ACDEFGHILMNPQSTVWY), H526(-ACDEFGIKLMNPQSTVWY), 526.5(ACDEFGHILMNPQSTVWY), K527(-DEFGHILMPQRSTVWY), 527.5(ACDEFGHILMPQSTVWY), D528(AEFMPQSVW), 528.5(DEPT), D529(S), 529.5(ADEGLMNPQTV), E530(NPVW), 530.5(ACDEFGHIKLMNQRSTVWY), E531(ACFGHILMNPQSTVY), 531.5(ADEFGIKLMNPQRSTVY), K532(-ACDEFGHILMNPQRSTVWY), 532.5(ACDEFGHIKLMNPQSTVWY), F533(ACDEGHILMNQSTVW), 533.5(ACDEFGHILNPQSTVWY), F534(ILMVWY), 534.5(F), P535(-AF), Q536(-ACDEFGHNPTVWY), 536.5(ACILTV), S537(-ADFGNQY), 537.5(T), G538(-), V539(AHLMQST), 540.5(KMN), I541(-DGPT), 541.5(Q), F542(GP), 542.5(QY), G543(P), 543.5(ACDIKPQRTVY), K544(-FGMNPQ), 544.5(ADEFGHIKLMRVWY), Q545(-FK),	

545.5(ACFILMNPQSVWY), G546(DEHLPTVWY), 546.5(ACEGHILMNPQSTVWY), S547(-DHIMQY), 547.5(ADGHNTVWY), E548(FNY), 548.5(ACDEFGHLMNPTWY), K549(-DFHILTWY), 549.5(ADFHLMQSTV), T550(CW), 550.5(AIKMNPRSTV), N551(ACDEHIKLPQRTV), 551.5(ACDEHILMNS), V552(N), D553(AGST), I554(EHMPQS), E555(AGHNSTVY), 555.5(N), K556(ACDEFGHMQTW), V557(L), M558(ADNSTV), 558.5(E), I559(C), 559.5(A), T560(AV), 560.5(A), D561(EFLY), E562(AD), E563(FITVY), I565(T), R566(ACDEFGHILMNQSTVWY), T567(Q), 567.5(E), T568(PV), 569.5(M), P570(CQS), 570.5(M), V571(ACDEFHLMQSTY), 571.5(G), A572(CGSY), 572.5(VWY), T573(ACDGINSVW), 573.5(MT), E574(ADLMQS), 574.5(DV), Q575(-CDGIKLMNSTVWY), 575.5(AFWY), Y576(ACFGHIMSV), 576.5(EFWY), G577(DW), 577.5(ACDEHIMNQSTV), S578(DEFGHILNVWY), 578.5(ACDEFGHILNSTVY), V579(ACDEFGHLMNQSTWY), 579.5(ACDEFGILMNPQSTVWY), S580(-DEFHILMNPQTVWY), 580.5(ACDEFGKLMNPQRSTVWY), T581(-CDEFGHKLNPWY), 581.5(ACDEFGILMNPQTVWY), N582(-ACDEFGHIKLMPQRSTVWY), 582.5(DFGHNPSTVW), L583(-ADEGIPQST), 583.5(DEGIMNPQSTVY), Q584(-ADEFGHILMNPSTVWY), 584.5(ACDEFGHILMNPQSTVWY), R585(-ACDEFGHIKLMNPQSTVWY), 585.5(ADEFGHILMNPQSTVWY), G586(-DEFHLMNSVWY), 586.5(ACDEFGHILMNPQSTVY), N587(-DEFGHILMPQSTVY), 587.5(ADEFGILMNPQSTVWY), R588(-ACDEFGHIKLMNPQSTVWY), 588.5(ADEFGHILMNPQSTVY), Q589(-DEIPRW), 589.5(ACDEFGHIKLMNPQSTVWY), A590(DEFHIKLMNQTWY), 590.5(ACDEFGIKLMNPQSTVWY), A591(-CDEFGILMNPTVWY), 591.5(ACDEFGHILMNPQSTVWY), T592(-ACDEFGHLMNPQSVY), 592.5(ACDEFGILMNPQSTVWY), A593(-DEP), 593.5(ACDEFGHILMNPQSTVWY), D594(ELT), 594.5(ACDEFGHILMNPQSTVWY), V595(ACDEFGHLMNPQSTWY), 595.5(ACDEFGHILMNQSTVW), N596(ACDEGIMPQTW), 596.5(DENY), T597(DEHINPQV), 597.5(F), Q598(ACEFGHILMNSTVY), G599(CSW), 600.5(F), L601(WY), P602(MQ), M604(AS), 605.5(N), 606.5(P), 607.5(P), D608(W), R609(D), D610(Y), 610.5(F), Y612(R), 613.5(Y), Q614(T), I617(K), 617.5(I), K620(HMN), H623(L), F628(HIM), P630(GHI), L633(FHY), F637(Y), K640(W), 640.5(N), P644(W), I646(M), L647(I), N650(L), P652(S), 657.5(C), S658(CE), 658.5(CKR), T659(K), 659.5(CNQY), T660(CHP), 660.5(CFIW), F661(EQT), 661.5(CP), S662(W), 662.5(FHLMPQW), 663.5(CIMW), 664.5(C), K665(I), 665.5(NW), 666.5(V), A667(C), 667.5(HY), S668(N), T671(R), Q672(E), S674(G), V678(T), S679(EGIKY), E681(M), E683(H), E685(ALS), L686(T), Q687(I), 697.5(N), 701.5(A), N703(D), 703.5(EHLTY), Y704(H), 704.5(ADILNS), N705(DEK), 705.5(EQY), K706(DEGRST), S707(DEH), 707.5(MY), V708(CER), 708.5(I), N709(DER), 709.5(CGP), V710(EMNP), 710.5(D), D711(GN), 711.5(Y), T716(C), 720.5(N), E722(D), P723(CEQ), R724(W), P725(M)	
A2(C), 3.5(DNTV), 4.5(DGHY), G5(Y), D9(G), W10(Y), 10.5(HI), E12(HIK), L15(H), S16(Q), I19(T), R20(GINQ), Q21(GK), 21.5(F), 22.5(Y), W23(DFKM), 23.5(F), K24(C), 24.5(DIN), L25(GR), 25.5(CVW), P27(T), 28.5(AEGINV), P29(ACEF), P30(Y), 30.5(GIKN), P31(H), 31.5(AY), P32(CIKS), P34(Q), 34.5(CV), A35(PY), 35.5(CGHNY), E36(CQ), 36.5(K), R37(F), 37.5(EMP), H38(ADE), 38.5(ADEFGKVY), K39(-AEPV), 39.5(DEHN), D40(-PY), 40.5(DEST), D41(A), 41.5(NQ), S42(-EHLQV), 42.5(KY), R43(GW), 43.5(DVY), 45.5(M), G49(HMQY), Y50(H), 50.5(N),	0.9-fold

Y52(D), 53.5(R), P55(Y), 55.5(E), F56(AV), G58(CT), 58.5(F), L59(CIR), 59.5(H), D60(NY), K61(C), 61.5(K), G62(Q), E63(CMV), E67(PV), A70(I), A71(NTY), L73(KNVY), E74(DFI), A78(CKQ), 78.5(AQ), Y79(-), R81(K), Q82(-HKM), 82.5(DK), L83(N), 83.5(DHNY), D84(IT), 84.5(N), S85(D), 85.5(HK), G86(-DH), 86.5(Q), D87(EKQ), 87.5(AHQ), N88(AI), 90.5(Y), L91(QY), K92(N), 92.5(D), Y93(G), N94(Q), D97(-), A98(N), 98.5(E), E99(DK), 99.5(K), Q101(DY), L104(C), 104.5(E), K105(MV), 105.5(HRW), E106(HN), 106.5(WY), D107(-QW), 107.5(EP), 108.5(W), S109(FKY), 109.5(D), F110(VY), 112.5(C), N113(CDW), 113.5(FN), L114(HNQ), G115(M), 115.5(A), 116.5(DEP), A117(NQY), 117.5(CKW), V118(K), F119(QY), 119.5(H), Q120(N), 120.5(K), 121.5(K), K122(-DFR), 122.5(EIKP), K123(CENW), 123.5(N), R124(-), 124.5(EK), 125.5(C), 126.5(A), E127(-F), 127.5(DIY), P128(F), 128.5(T), L129(CKW), G130(C), 130.5(D), L131(NV), 131.5(EHR), E133(FW), E134(K), 134.5(A), P135(Q), 135.5(DM), V136(Y), 136.5(CM), 137.5(Q), 139.5(R), P140(H), 140.5(N), G141(CK), 141.5(Q), K142(CH), 142.5(CEGW), 143.5(K), R144(NW), 144.5(RY), P145(AR), 145.5(KMY), 146.5(N), 147.5(EH), H148(CNW), 148.5(EMN), S149(W), 149.5(HM), P150(-M), 150.5(CDM), V151(D), E152(-DH), 152.5(CHK), P153(W), S156(T), 156.5(T), S157(EKNY), 157.5(CNPQ), G158(D), T159(C), 159.5(V), G160(C), 160.5(CDN), K161(CDHNTWY), 161.5(EHN), A162(-H), 162.5(ACSVY), G163(CFNPT), 163.5(CN), Q164(DM), 164.5(CEY), Q165(HW), 165.5(ITV), P166(AILS), 166.5(GN), N172(Y), 173.5(FI), G174(CFHS), Q175(DKT), 175.5(CILPRTW), T176(CGNRS), 176.5(GN), G177(-EQ), 177.5(IP), D178(NQW), 178.5(DGINW), 179.5(CDN), D180(CM), 180.5(ACM), S181(QRWY), 181.5(EIKLNPWY), V182(CGNW), 182.5(CFLPRW), P183(CS), 183.5(EIMY), D184(HNVY), 184.5(MY), P185(-DEIV), 185.5(D), Q186(NP), 186.5(CIK), P187(-CHK), 187.5(V), 188.5(Y), G189(-), 189.5(MQ), Q190(MTW), 190.5(DFMN), P191(CQ), 191.5(W), P192(CKMQW), 192.5(CMN), A193(CDFLM), 193.5(DGHLMNPW), A194(CKMRW), 194.5(CDM), P195(AKMNQR), 195.5(EMQY), S196(-HW), G197(AT), L198(-CDGINRV), G199(V), 199.5(CFHW), T200(IQV), N201(DHV), T202(NS), M203(ACDPR), A204(D), T205(IKR), G206(DEF), S207(D), G208(E), A209(ENP), P210(KQS), D213(LTW), N214(CEILY), N215(DFIM), E216(A), G217(CEFHLMVY), A218(PQ), G220(CNT), V221(I), N223(CHMY), S225(CQR), N227(D), H229(DSTV), D231(C), T233(DHL), M235(V), G236(V), 236.5(D), D237(C), 237.5(DGHKNQS), R238(CH), 238.5(FT), I240(CRW), T242(R), T244(C), A248(V), L249(V), P250(Q), T251(LV), N254(CGQ), H255(ANT), L256(ACGHMNQRSV), K258(LQ), Q259(CGHKPRS), I260(M), 260.5(ACDEMQST), S261(CDG), 261.5(S), S262(T), 262.5(DEGINST), Q263(-ADFGHWY), 263.5(DG), S264(-DEFGHLWY), 264.5(D), G265(-), 265.5(ADET), 266.5(AE), S267(ENT), 267.5(E), N268(ADEQ), 268.5(E), 269.5(D), N270(ACDGHQSY), H271(EFIN), F273(HMWY), S276(ACT), G280(A), Y281(F), F282(WY), F287(Y), H288(N), C289(A), D295(AE), R307(CNST), 307.5(K), P308(-W), K309(ACQS), R310(FILW), L311(AFIY), N312(LM), F313(CI), K314(CGHLMQSVWY), I318(F), T324(CL), 324.5(CKR), Q325(CHIKRV), 325.5(I), N326(CDLM), 326.5(M), D327(T), G328(AHNS), T329(ACI), T330(KQ), T331(ALY), I332(ACS), 332.5(K), A333(CD), N334(Q), T339(C), V342(AIL), T344(DFILM), S346(FIPW), Y348(ADMNRS), Q349(AGS), V353(CT), L354(AHT), G355(AS), S356(A), Q359(EGHM), F365(W), A367(P), V369(P), F370(Y), M371(AFS), V372(C), Q374(N), Y375(W), Y377(F), L378(A), T379(ACGV), 379.5(DE), L380(ENQTY), 380.5(E), N381(ACDGMQS), N382(CDE), 382.5(D), 383.5(E), 384.5(D), Q385(ENPRSTW), 385.5(AEHPT), A386(EHLNPRTVW), 386.5(CDEP),	

V387(CDELM), 387.5(EGKP), G388(IM), R389(AGILMPQSTVY), 389.5(N), S390(DGNT), S391(A), 394.5(N), Y397(AN), P399(EIMQ), Q401(CDIMRVW), L403(M), R404(K), 404.5(N), T405(S), G406(DEN), N408(DGHLM), 408.5(CN), F409(CHY), T410(H), F411(LQSTV), S412(CEFGILW), Y413(MW), T414(FGQ), 414.5(D), 415.5(ADGHMNQS), E416(AGP), 416.5(CEGMNR), D417(EFHILMNS), 417.5(ACEHKLMQRT), V418(GIMQST), P419(DEGHIKLNQVWY), F420(L), Y424(CT), 424.5(F), A425(-GQV), H426(N), S427(ACD), Q428(EHNS), S429(CPY), L430(IM), D431(FM), 431.5(Y), R432(-I), L433(DIQV), 433.5(F), M434(A), L437(ACHMNSTY), I438(GKNT), D439(HKNPSTY), 441.5(M), L442(CFIT), Y444(FH), 444.5(CLM), L445(CFMVY), 445.5(ACDEGHILMNQSTVY), S446(-CDEGHIKLMNQTV), 446.5(ACDEFGHILMNPQSTVWY), R447(-ACDEFGHILMNPQSTVWY), 447.5(ACDEFGHILMNPQSVWY), T448(-ACDEFGHILMNPQSVWY), 448.5(ACDEFGHILMNPQSWY), N449(-ACDEFGILMPQSTVWY), 449.5(AEGHLMNPSTVY), T450(-CDEGHPQW), 450.5(ADEFGHLMPQSTV), P451(-I), 451.5(GNP), S452(-DEFHILNPQVW), 452.5(AILPV), G453(-ADEFHIKLMNPQSTV), 453.5(FILMNTVY), T454(-DEFHILMNPV), 454.5(ADEFGLMPSTY), T455(-ADEILMNPQVY), 455.5(AFHLNPQSTY), T456(-DEFGHIKLMNPQ), 456.5(ADEGHILMNPQSV), Q457(-ADEFGHILP), 457.5(ADEFGHILMNPSVWY), S458(-CDEFHMNTVWY), 458.5(CDEFGHILMNPSTVWY), R459(-ACDEFGHILMNPQSTVWY), 459.5(DEP), L460(ACFHIMNPSTVWY), 460.5(W), Q461(CDEIKTVW), F462(Y), 462.5(N), S463(ACDGKNQRTV), 463.5(F), Q464(AFILRSTV), 464.5(SY), A465(CGP), G466(CQ), 466.5(E), A467(DFGHIKLMRVY), S468(CDEFLMQRV), D469(V), 469.5(DE), I470(FLM), R471(ACDEGKMQSTV), D472(LMY), Q473(FHMSY), S474(IY), R475(H), 475.5(SW), N476(CSTW), 476.5(L), W477(Y), 477.5(L), L478(FI), 478.5(L), P479(GIT), 479.5(D), G480(Y), P481(ACV), 481.5(GHY), C482(FGIMNQTWY), 482.5(FM), Y483(ACFHIMTVW), 483.5(FQV), R484(EFGHIKLMNQSTVY), 484.5(N), Q485(ACFGHILMNSTVY), 485.5(EIKMQY), Q486(ACDEFGILMNPSTVWY), 486.5(CFV), R487(-ACDEFGHIKLMNPQSTVWY), 487.5(FW), V488(ACEFGHLMNQTWY), 488.5(ACDEFGILMPQSVWY), S489(-ACDEFGHIKLMNPQTVWY), 489.5(ACDEGLMPQRSTVWY), K490(-ACDEFGHILMNPQRSTVWY), 490.5(ACDEFGHILMNPQRSTVWY), T491(-ADEGPSWY), 491.5(ACDEFGHIKLMNPQSTVWY), S492(-CDEFGILMNQ), 492.5(ADEGHILMPQSTVY), A493(-DEFHILNPQRVWY), 493.5(ADEFGHIKLMNPQSTVWY), D494(EFR), 494.5(ADEGHILMNPSTVWY), N495(-ADEFGHILMPQSTVWY), 495.5(ACDEFGILMPQSTVWY), N496(-ACDEFGHILMPQSTVWY), 496.5(ADEFGHILMPQSTVWY), N497(-ACEFGHILMPSTVWY), 497.5(ADEFGILMPQTVY), S498(-CDEFGILMNPQRTVWY), 498.5(ADEFGILMNPQSTVWY), E499(CDIPQS), 499.5(ACDEGHILMNPQRSTVWY), Y500(-ACDEGHIKLMNPQSTV), 500.5(ADEFGHILMNPQSTVWY), S501(-ACDEFGILMNPQRTVWY), 501.5(ACDEFGHILMNQRSTVWY), W502(-ACDEFGILMPQSTVY), 502.5(ADEFGHILMNPQSTVWY), T503(-ADEFGHILMNPQVWY), 503.5(ADEFGILMNPQSTVW), G504(-ACDEFHILMNPQSTVWY), 504.5(ACDEFGHILMNPQSTVWY), A505(-CDEFGHILMNPQSTVWY), 505.5(ACDEFGILMPQSTVWY), T506(-ACFGILMNPQV), 506.5(ACIPSTVW), K507(-ACEFHILMNQRSTVWY), Y508(-DMST), H509(CEFNQ), 509.5(K), L510(I), 510.5(K), N511(ACDEGLMQSWY), 512.5(S), R513(CHIV), D514(ACEFGILMQSTV), S515(CV),	

L516(ACIMSTV), V517(CIL), 517.5(C), N518(CILQRTV), P521(CFLMNST), 521.5(MS), A522(CV), M523(CLQV), 523.5(A), A524(CGPST), 524.5(ACGHSTW), S525(ACGHMNPT), 525.5(ACDEFGHILMNPQSTVWY), H526(-ACDEFGIKLMNPQSTVWY), 526.5(ACDEFGHILMNPQSTVWY), K527(-DEFGHILMPQRSTVWY), 527.5(ACDEFGHILMPQSTVWY), D528(AEFMPQSVW), 528.5(DEPT), D529(ES), 529.5(ADEGLMNPQTV), E530(DNPVW), 530.5(ACDEFGHIKLMNQRSTVWY), E531(ACFGHILMNPQSTVY), 531.5(ADEFGIKLMNPQRSTVY), K532(-ACDEFGHILMNPQRSTVWY), 532.5(ACDEFGHIKLMNPQSTVWY), F533(ACDEGHILMNQSTVW), 533.5(ACDEFGHILNPQSTVWY), F534(ILMVWY), 534.5(F), P535(-AF), Q536(-ACDEFGHIMNPSTVWY), 536.5(ACILTV), S537(-ACDFGNQTY), 537.5(T), G538(-), V539(AHILMNQST), L540(IM), 540.5(EKMN), I541(-ADEFGPQRTVY), 541.5(DEGPQST), F542(GKP), 542.5(QY), G543(FPS), 543.5(ACDHIKLMPQRSTVY), K544(-ACFGHILMNPQSTVY), 544.5(ACDEFGHIKLMRSTVWY), Q545(-ADFKLPVW), 545.5(ACDFGHILMNPQSTVWY), G546(ACDEFHILMNPQSTVWY), 546.5(ACDEFGHILMNPQSTVWY), S547(-DEFGHILMPQWY), 547.5(ACDEFGHILMNPQSTVWY), E548(FILNPQY), 548.5(ACDEFGHILMNPSTWY), K549(-DFGHILPQSTVWY), 549.5(ADEFGHLMNQSTV), T550(-ACDRW), 550.5(ADIKMNPRSTV), N551(ACDEGHIKLMPQRSTVY), 551.5(ACDEHILMNPSTV), V552(ACELNST), 552.5(VW), D553(AGST), I554(ACEFHLMPQSTW), E555(AGHNSTVY), 555.5(N), K556(ACDEFGHLMQSTVW), 556.5(Q), V557(L), M558(ACDINQSTVWY), 558.5(E), I559(CQV), 559.5(A), T560(ACSV), 560.5(A), D561(AEFLQRY), E562(AD), E563(AFHIMRTVY), I565(T), R566(ACDEFGHILMNQSTVWY), T567(PQ), 567.5(E), T568(PV), 569.5(M), P570(CQS), 570.5(M), V571(ACDEFHILMQSTY), 571.5(G), A572(CGSY), 572.5(VWY), T573(ACDGHINSVW), 573.5(MT), E574(ACDFLMQSW), 574.5(DV), Q575(-ACDFGHIKLMNSTVWY), 575.5(AFWY), Y576(ACFGHIMSVW), 576.5(EFWY), G577(DW), 577.5(ACDEHIMNQSTV), S578(DEFGHILNQVWY), 578.5(ACDEFGHILNSTVY), V579(ACDEFGHLMNQSTWY), 579.5(ACDEFGILMNPQSTVWY), S580(-DEFHILMNPQTVWY), 580.5(ACDEFGHIKLMNPQRSTVWY), T581(-CDEFGHKLNPWY), 581.5(ACDEFGILMNPQTVWY), N582(-ACDEFGHIKLMPQRSTVWY), 582.5(DFGHNPSTVW), L583(-ADEGIPQSTVW), 583.5(DEGIMNPQSTVY), Q584(-ADEFGHILMNPSTVWY), 584.5(ACDEFGHILMNPQSTVWY), R585(-ACDEFGHIKLMNPQSTVWY), 585.5(ADEFGHILMNPQSTVWY), G586(-DEFHLMNQSTVWY), 586.5(ACDEFGHILMNPQSTVY), N587(-DEFGHILMPQSTVY), 587.5(ADEFGILMNPQSTVWY), R588(-ACDEFGHIKLMNPQSTVWY), 588.5(ADEFGHILMNPQSTVY), Q589(-ADEFIPRSTVW), 589.5(ACDEFGHIKLMNPQSTVWY), A590(DEFGHIKLMNQTWY), 590.5(ACDEFGIKLMNPQSTVWY), A591(-CDEFGILMNPQTVWY), 591.5(ACDEFGHILMNPQSTVWY), T592(-ACDEFGHLMNPQSVY), 592.5(ACDEFGILMNPQSTVWY), A593(-DELPY), 593.5(ACDEFGHILMNPQSTVWY), D594(ELT), 594.5(ACDEFGHILMNPQSTVWY), V595(ACDEFGHLMNPQSTWY), 595.5(ACDEFGHILMNQSTVW), N596(ACDEFGIMPQSTWY), 596.5(DENY), T597(DEGHINPQRVW), 597.5(F), Q598(ACEFGHILMNSTVY), G599(CSW), 600.5(F), L601(VWY), P602(CMQ), M604(AQS), V605(N), 605.5(N), 606.5(P), 607.5(P), D608(W), R609(D), D610(Y), 610.5(F), Y612(R), 613.5(Y), Q614(CT), I617(K), 617.5(I), A619(CG), K620(ACHMNQS), I621(AHLR), H623(EKL), D625(S), G626(A), H627(VY), F628(HILM),	

P630(AGHIQSTV), 630.5(C), S631(N), L633(FHMY), M634(C), F637(IWY), L639(V), K640(FPVW), 640.5(N), H641(C), P644(WY), Q645(ILMTV), I646(MT), L647(I), I648(AC), N650(LTV), P652(AS), V653(T), 655.5(IW), N656(FT), 657.5(CDHIS), S658(CEFKMQ), 658.5(CFGHKLMQRW), T659(DKRS), 659.5(CELMNQRY), T660(-CFHKLP), 660.5(CEFHIPRW), F661(AEILQT), 661.5(CDELPQRSW), S662(NPW), 662.5(ACDFHKLMPQTVW), A663(HY), 663.5(CDEGIMNW), A664(CEHK), 664.5(CDGPRTV), K665(CGILSVWY), 665.5(HIMNPRVW), F666(C), 666.5(IVY), A667(CP), 667.5(HQY), S668(N), F669(Y), I670(V), T671(R), Q672(EL), S674(G), T675(AL), Q677(C), V678(AIT), S679(EFGHIKMRY), V680(L), E681(LMNT), I682(MV), E683(HILM), E685(ADLST), L686(CT), Q687(FIKMW), E697(-DLPR), 697.5(CGHNPSW), I698(V), 699.5(E), Y700(F), T701(S), 701.5(A), S702(CNV), 702.5(Q), N703(D), 703.5(AEHLTY), Y704(H), 704.5(ADEILNST), N705(CDEKMPW), 705.5(ENQY), K706(DEGRST), S707(CDEFH), 707.5(MY), V708(CEFGHMNRW), 708.5(I), N709(CDEGPR), 709.5(CGPQ), V710(EMNPQ), 710.5(D), D711(AGNP), 711.5(QY), T713(C), T716(CEFMPRVWY), N717(ER), V719(CFIKNR), 720.5(N), S721(FKLMQRTVW), E722(DQ), P723(CDEQSV), R724(FHSW), P725(ALMQ), I726(V), L735(CI), 735.5(LMV)	

Table 9: Amino acid alterations that reduce delivery to blood.

Amino acid alteration	Fold increase of efficiency
S264(W), 444.5(M), S446(D), R471(G), P479(G), 479.5(D), C482(Y), Y483(ACHV), Q485(AGS), 485.5(K), 487.5(F), 488.5(W), 502.5(Y), 504.5(NW), A505(Y), 505.5(AQTVW), T506(FL), 506.5(AV), N518(R), 524.5(S), 525.5(ANQTY), 526.5(FHMY), 527.5(HW), Q536(-), S537(-), G538(-), V539(H), A572(Y), T573(G), Y576(ACGH), V579(G), V595(DGHNQY), 595.5(H), Q598(GNY), L601(W)	0.1-fold
S264(W), 266.5(E), 268.5(E), 379.5(E), 444.5(M), S446(D), N449(C), 454.5(E), R459(C), F462(Y), 469.5(E), R471(AEGQSTV), 475.5(W), P479(GT), 479.5(D), G480(Y), C482(GY), Y483(ACHIQTV), R484(K), 484.5(N), Q485(AGNST), 485.5(K), 487.5(F), V488(G), 488.5(PW), 491.5(W), S492(C), 498.5(DE), 499.5(ADLMNPQ), 500.5(LNQST), 501.5(ACHNS), W502(-AE), 502.5(AGMNPTY), 503.5(AGILMNQT), G504(W), 504.5(AGHMNQVWY), A505(HLY), 505.5(AGLMQTVW), T506(FGILMP), 506.5(ACISV), K507(HIW), H509(E), D514(GIV), N518(R), P521(M), 523.5(A), 524.5(AS), S525(H), 525.5(AFHILNQSTY), H526(IPV), 526.5(AFHMNQSTY), 527.5(CFHIMQVWY), 530.5(C), 531.5(I), 532.5(P), F534(VY), P535(-F), Q536(-P), S537(-DFQ), G538(-), V539(H), P570(Q), A572(Y), T573(AG), E574(F), Q575(L), Y576(ACGHS), S578(D), V579(EGMNQ), S580(Q), N582(F), Q589(P), V595(DEGHLMNPQTWY), 595.5(ADHIQSTW), 596.5(N), T597(GLP), Q598(CEFGNSY), G599(C), L601(W), 640.5(N)	0.2-fold
S264(W), 266.5(E), 267.5(E), 268.5(E), N270(AGHSY), 379.5(E), 380.5(E), 431.5(Y), 433.5(F), 444.5(CLM), L445(Y), 445.5(ACLMSTY), S446(DEIL), 446.5(ALPQ), R447(I), 447.5(PW), T448(ILPQW), 448.5(CP), N449(CP), S452(D), 454.5(DE), T455(E), Q457(E), S458(D), 458.5(CW), R459(CDV), 460.5(W), Q461(D), F462(Y), D469(M), 469.5(E), R471(ACEGMQSTV), Q473(Y), S474(I), 475.5(SW), 477.5(L), P479(GT), 479.5(D), G480(Y), C482(FGY), 482.5(M), Y483(ACHIQTV), 483.5(Q), R484(K), 484.5(N),	0.3-fold

Q485(ACGNSTV), 485.5(KQY), 487.5(F), V488(FGY), 488.5(MPQW), S489(FQY), K490(DEFGHNQWY), 490.5(CPQ), 491.5(W), S492(C), 495.5(W), N496(M), S498(DE), 498.5(DE), 499.5(ADEGLMNPQST), Y500(-NP), 500.5(AGLMNPQST), S501(-CIL), 501.5(ACGHILNQSTVY), W502(-ACEV), 502.5(AFGILMNPSTVY), T503(EP), 503.5(AGILMNPQSTVW), G504(-IPW), 504.5(AFGHILMNPQSVWY), A505(FHILMPWY), 505.5(AGILMPQSTVWY), T506(FGILMNP), 506.5(ACISTV), K507(ACHINQSW), H509(EFN), N511(E), R513(C), D514(AGIV), L516(AST), 517.5(C), N518(R), P521(M), 523.5(A), 524.5(AS), S525(HM), 525.5(ACFHILMNQSTVWY), H526(-EGIKMPQV), 526.5(ACFGHLMNQSTVY), 527.5(ACDEFGHILMPQSTVWY), 528.5(DE), 529.5(DP), E530(P), 530.5(CILM), 531.5(IV), 532.5(P), F533(T), F534(VY), P535(-F), Q536(-DPW), S537(-DFGNQY), G538(-), V539(H), 559.5(A), T568(P), P570(Q), 570.5(M), V571(AHQS), A572(Y), T573(ACDG), E574(FLW), Q575(DGL), 575.5(W), Y576(ACGHS), 576.5(W), 577.5(HS), S578(DEFGL), 578.5(L), V579(EGHMNQ), S580(Q), N582(FWY), 585.5(A), 586.5(P), Q589(P), 593.5(P), V595(ACDEGHLMNPQTWY), 595.5(ADFHILMQSTW), 596.5(DN), T597(EGILMPV), Q598(CEFGNSTY), G599(C), L601(WY), L633(FY), 640.5(N)	
D180(M), 183.5(M), L256(S), S261(D), Q263(V), S264(W), 265.5(DE), 266.5(E), S267(E), 267.5(E), 268.5(E), 269.5(D), N270(ACDGHSY), H271(E), 379.5(DE), L380(E), 380.5(E), N382(D), 382.5(D), 383.5(E), 386.5(D), Q428(E), D431(M), 431.5(Y), R432(I), L433(D), 433.5(F), L437(Y), Y444(FH), 444.5(CLM), L445(FY), 445.5(ACGHLMQSTVY), S446(DEILV), 446.5(AFILPQSTVWY), R447(CEGILMQTV), 447.5(CFGIMPWY), T448(FGILNPQVWY), 448.5(CFLPW), N449(CDEFP), T450(CE), S452(D), 454.5(DE), T455(E), 456.5(D), Q457(DE), 457.5(D), S458(CDEW), 458.5(CDEMWY), R459(ACDEILMPQSTV), L460(NSTWY), 460.5(W), Q461(DE), F462(Y), S463(G), 463.5(F), Q464(KSV), 464.5(S), A465(CGP), A467(GY), S468(C), D469(CEMQRSV), 469.5(E), I470(FL), R471(ACDEGMQSTV), Q473(FMY), S474(I), 475.5(SW), N476(TW), 477.5(L), L478(F), P479(GT), 479.5(D), G480(Y), 481.5(Y), C482(FGY), 482.5(FM), Y483(ACHILMQTV), 483.5(FQ), R484(K), 484.5(N), Q485(ACGHILNSTVY), 485.5(EKQY), Q486(FIV), 487.5(FW), V488(EFGHLNWY), 488.5(FILMPQW), S489(FGILQVY), 489.5(DP), K490(ACDEFGHILMNQSTVWY), 490.5(CIPQV), T491(E), 491.5(FIMW), S492(CE), 492.5(DL), A493(DE), 493.5(KP), N495(AFLQTVY), 495.5(FILPVW), N496(AFGHILMW), N497(-I), 497.5(DE), S498(-DELMR), 498.5(DEGLQ), E499(I), 499.5(ADEGHILMNPQSTV), Y500(-ACEGKLNPQS), 500.5(AFGHILMNPQST), S501(-CILNV), 501.5(ACFGHILMNQRSTVWY), W502(-ACEGILMQSVY), 502.5(AFGHILMNPQSTVWY), T503(-ADEP), 503.5(AFGILMNPQSTVW), G504(-CILNPSVWY), 504.5(AFGHILMNPQSVWY), A505(EFHILMNPQVWY), 505.5(ACFGILMPQSTVWY), T506(FGILMNPV), 506.5(ACISTV), K507(ACHILMNQSVW), Y508(-), H509(EFN), L510(I), N511(DELMW), 512.5(S), R513(CIV), D514(ACGILMQTV), L516(ACSTV), V517(L), 517.5(C), N518(LR), P521(CFLMNS), 521.5(S), 523.5(A), 524.5(ACST), S525(HMP), 525.5(ACFGHILMNQSTVWY), H526(-ACDEFGIKMNPQSTVWY), 526.5(ACDEFGHLMNPQSTVY), K527(-), 527.5(ACDEFGHILMPQSTVWY), 528.5(DEPT), 529.5(ADEMNPTV), E530(P), 530.5(CDEFGHILMNQSTVWY), 531.5(ADFGINPQTVY), 532.5(HPSTW), F533(ACILQSTV), 533.5(Y), F534(ILVY), 534.5(F),	0.5-fold

P535(-AF), Q536(-DPWY), S537(-CDFGNQTY), G538(-), V539(H), 542.5(Y), G543(S), 543.5(Y), K544(FNQY), S547(-), K549(IW), 549.5(E), T550(CD), N551(DE), 551.5(DE), V552(NS), I554(E), V557(L), 558.5(E), 559.5(A), R566(ADEFGILMNTVWY), 567.5(E), T568(P), 569.5(M), P570(Q), 570.5(M), V571(ACHMQS), 571.5(G), A572(CY), T573(ACDGNSV), 573.5(M), E574(DFLMW), 574.5(V), Q575(DGKLMNV), 575.5(AWY), Y576(ACGHIS), 576.5(FWY), 577.5(AHMNS), S578(DEFGILWY), 578.5(AGHLNST), V579(ACEFGHMNQST), 579.5(L), S580(-MNQ), T581(ENP), N582(FILWY), 585.5(AGIMPQSTVY), 586.5(AGPQ), 587.5(MNQV), 588.5(LMV), Q589(APV), 589.5(PV), 590.5(CP), A591(DT), 591.5(FILP), T592(-DGN), 592.5(CGMS), A593(-D), 593.5(APSW), D594(E), 594.5(AGQST), V595(ACDEFGHLMNPQSTWY), 595.5(ADEFHILMQSTW), N596(CETW), 596.5(DEN), T597(DEGIKLMPQRV), Q598(ACEFGHNSTY), G599(C), L601(WY), P602(M), M604(A), 605.5(N), 607.5(P), 610.5(F), L633(FHY), 640.5(N), 662.5(W)	
D41(H), 41.5(D), S42(E), R43(T), 43.5(DT), 45.5(M), K51(Y), G58(ET), K61(-), E63(M), 107.5(E), D180(M), 180.5(M), 183.5(M), L256(ACS), 260.5(AEM), S261(D), S262(T), 262.5(DE), Q263(VW), S264(DEW), 264.5(D), 265.5(DE), 266.5(E), S267(E), 267.5(E), N268(ADEQ), 268.5(E), 269.5(D), N270(ACDGHQSY), H271(E), R307(MN), P308(M), 324.5(C), 326.5(M), Q359(DET), 379.5(DE), L380(E), 380.5(E), N381(D), N382(DE), 382.5(D), 383.5(E), 384.5(D), A386(E), 386.5(CDE), V387(E), 387.5(P), G388(E), 394.5(N), 408.5(C), 424.5(F), Q428(EH), S429(Y), D431(M), 431.5(Y), R432(I), L433(D), 433.5(F), L437(HY), L442(FI), Y444(FH), 444.5(CLM), L445(CFMY), 445.5(ACGHLMNQSTVY), S446(CDEGHILMTV), 446.5(AFHILNPQSTVWY), R447(ACEFGILMNQSTV), 447.5(CFGIMPVWY), T448(CFGILMNPQVWY), 448.5(CEFILPWY), N449(ACDEFGIMPSVW), T450(CE), S452(DE), T454(DEFI), 454.5(DE), T455(DE), T456(D), 456.5(D), Q457(DEIL), 457.5(DE), S458(CDEFMPVW), 458.5(CDEFIMWY), R459(-ACDEFGHILMNPQSTVWY), L460(ANSTVWY), 460.5(W), Q461(DEGK), F462(Y), S463(CDGNQ), 463.5(F), Q464(ACIKLSTV), 464.5(S), A465(CGP), G466(AQ), A467(DFGPQY), S468(CP), D469(ACEMQRSTV), 469.5(DE), I470(FLM), R471(ACDEGKMQSTV), D472(Y), Q473(FHMY), S474(I), R475(K), 475.5(SW), N476(TW), W477(Y), 477.5(L), L478(FI), P479(GIT), 479.5(D), G480(Y), P481(A), 481.5(HY), C482(FGY), 482.5(FM), Y483(ACHILMQTV), 483.5(FQ), R484(K), 484.5(N), Q485(ACFGHILNSTVY), 485.5(EKQY), Q486(FGINSVWY), 486.5(F), R487(H), 487.5(FW), V488(AEFGHLMNQTWY), 488.5(CFGILMPQVWY), S489(-ACFGHIKLPQTVY), 489.5(DEP), K490(-ACDEFGHILMNQRSTVWY), 490.5(ACFHINPQTV), T491(DE), 491.5(ACFILMPQTVWY), S492(CDELM), 492.5(ADEGILV), A493(DELV), 493.5(IKLMPV), D494(R), 494.5(GIPV), N495(-AFLMPQSTVY), 495.5(AFGILPSVWY), N496(-ACFGHILMQSVW), N497(-EITV), 497.5(DEGLM), S498(-ADEFGILMPQRVWY), 498.5(DEFGLMQY), E499(I), 499.5(ADEGHILMNPQRSTVWY), Y500(-ACDEGIKLNPQST), 500.5(AEFGHILMNPQSTW), S501(-ACILMNPTVW), 501.5(ACFGHILMNQRSTVWY), W502(-ACEGILMPQSVY), 502.5(AFGHILMNPQSTVWY), T503(-ADEFGIPV), 503.5(AFGILMNPQSTVW), G504(-ACFILMNPSTVWY), 504.5(ACFGHILMNPQSVWY), A505(-EFHILMNPQTVWY), 505.5(ACFGILMPQSTVWY), T506(ACFGILMNPQV),	0.7-fold

506.5(ACIPSTVW), K507(ACHILMNQSTVW), Y508(-D), H509(CEFN), 509.5(K), L510(I), N511(DELMQWY), 512.5(S), R513(CIV), D514(ACEGILMQSTV), L516(ACIMSTV), V517(L), 517.5(C), N518(ILQRTV), P521(CFLMNS), 521.5(S), A522(CV), 523.5(A), A524(CGP), 524.5(ACST), S525(ACHMP), 525.5(ACFGHILMNQSTVWY), H526(-ACDEFGIKLMNPQRSTVWY), 526.5(ACDEFGHILMNPQSTVY), K527(-HR), 527.5(ACDEFGHILMPQSTVWY), 528.5(DEPT), 529.5(ADEGLMNPTV), E530(P), 530.5(ACDEFGHILMNQRSTVWY), 531.5(ADEFGILMNPQSTVY), K532(R), 532.5(FHPSTVWY), F533(ACGHILMNQSTV), 533.5(FY), F534(ILMVWY), 534.5(F), P535(-AF), Q536(-CDNPWY), S537(-CDFGNQTY), G538(-), V539(AHLMNQS), 540.5(M), 541.5(D), F542(P), 542.5(Y), G543(APS), 543.5(ACDILPSY), K544(-ACFGHILMNPQSTVY), Q545(D), 546.5(E), S547(-DEIMQ), 547.5(CDV), 548.5(CDE), K549(CDFGILMPQTVWY), 549.5(DE), T550(CDE), 550.5(DE), N551(CDE), 551.5(CDEN), V552(AELMNST), I554(CEHPQSTW), 555.5(N), K556(ADEGMNQTV), V557(LM), M558(ADTV), 558.5(E), I559(C), 559.5(A), T560(AV), 560.5(A), D561(AFMQVY), E562(AD), R566(ACDEFGHILMNTVWY), T567(Q), 567.5(E), T568(P), 569.5(M), P570(QS), 570.5(M), V571(ACHLMQS), 571.5(G), A572(CGSY), T573(ACDGINSV), 573.5(MT), E574(DFLMQW), 574.5(V), Q575(DGIKLMNTV), 575.5(AFWY), Y576(ACGHIS), 576.5(EFWY), 577.5(ACHIMNQSTV), S578(DEFGHILNVWY), 578.5(AFGHLNST), V579(ACEFGHLMNQST), 579.5(FL), S580(-MNPQ), T581(CENP), N582(FILMTVWY), 584.5(NT), R585(K), 585.5(AFGILMPQSTVY), 586.5(AGPQS), N587(GILMQTV), 587.5(AIMNQV), 588.5(ILMV), Q589(APSTV), 589.5(AFPV), A590(MQV), 590.5(ACPQT), A591(CDHIT), 591.5(AFGILMNPTV), T592(-CDGMNP), 592.5(ACFGILMPSTY), A593(-DE), 593.5(AFGNPSTW), D594(E), 594.5(AGQSTW), V595(ACDEFGHILMNPQSTWY), 595.5(ADEFHILMQSTVW), N596(CDEFGMPTW), 596.5(DEN), T597(CDEGHIKLMPQRV), Q598(ACEFGHINSTVY), G599(C), L601(WY), P602(M), M604(ACS), V605(F), 605.5(N), 607.5(P), 610.5(F), F628(I), L633(FHMY), 640.5(N), S658(C), 658.5(C), T660(C), 662.5(W), N703(D), N705(DE), K706(EST), S707(D), V708(C), N709(DE), P723(E), R724(FHNTWY)	
.5(D), P30(D), E36(N), 38.5(K), 40.5(D), D41(AHQW), 41.5(D), S42(EGQ), R43(T), 43.5(DHPSTV), 45.5(M), V46(I), G49(H), 50.5(N), K51(AY), G58(ET), K61(-), 61.5(K), E63(M), E74(H), 107.5(E), 135.5(M), 137.5(M), K142(I), 145.5(M), 150.5(M), 179.5(D), D180(M), 180.5(M), 183.5(M), 190.5(F), P192(M), 193.5(W), A194(C), H229(V), H255(N), L256(ACS), 260.5(ACDEMT), S261(D), S262(T), 262.5(DE), Q263(VW), 263.5(D), S264(DEFLW), 264.5(D), 265.5(DE), 266.5(E), S267(E), 267.5(E), N268(ADEQ), 268.5(E), 269.5(D), N270(ACDGHQSY), H271(E), R307(DMN), P308(GM), T324(C), 324.5(C), Q325(C), 326.5(M), T330(Q), G355(AS), Q359(ADEHTV), F370(Y), T379(A), 379.5(DE), L380(EY), 380.5(E), N381(CD), N382(DE), 382.5(D), 383.5(E), 384.5(D), Q385(CGW), 385.5(DP), A386(E), 386.5(CDEP), V387(E), 387.5(EGP), G388(E), R389(ALMPSTY), S390(DT), 394.5(N), 404.5(N), G406(M), 408.5(C), 415.5(Q), 417.5(M), Y424(C), 424.5(F), Q428(EHS), S429(Y), D431(M), 431.5(Y), R432(I), L433(D), 433.5(F), L437(AHNY), I438(CGNT), D439(K), L442(FI), Y444(FH), 444.5(CLM), L445(CFMVY), 445.5(ACGHLMNQSTVY), S446(CDEGHILMNTV), 446.5(AFGHILMNPQSTVWY), R447(ACEFGHILMNQSTV), 447.5(CFGILMNPVWY), T448(CFGILMNPQVWY),	0.8-fold

448.5(CEFILMPWY), N449(ACDEFGILMPSVW), 449.5(PY), T450(CDE), S452(DEFLV), 452.5(I), G453(L), 453.5(I), T454(DEFILM), 454.5(DEF), T455(DEL), T456(D), 456.5(DE), Q457(ADEILMV), 457.5(DEW), S458(CDEFMPVWY), 458.5(CDEFILMWY), R459(-ACDEFGHILMNPQSTVWY), L460(ACFHINPSTVWY), 460.5(W), Q461(CDEGKNTV), F462(Y), S463(ACDGNQV), 463.5(F), Q464(ACIKLMSTV), 464.5(S), A465(CGP), G466(ACDNQ), A467(CDFGHMPQY), S468(CEFLPQY), D469(ACEHMNQRSTV), 469.5(DE), I470(CFLM), R471(ACDEGKMQSTV), D472(Y), Q473(FHMSY), S474(I), R475(K), 475.5(SW), N476(STW), W477(Y), 477.5(L), L478(FI), P479(GIT), 479.5(D), G480(Y), P481(A), 481.5(HY), C482(FGQY), 482.5(FM), Y483(ACFHILMQTV), 483.5(FQ), R484(K), 484.5(N), Q485(ACFGHILNSTVY), 485.5(EKQY), Q486(FGINSVWY), 486.5(FV), R487(H), 487.5(FW), V488(ACEFGHLMNQTWY), 488.5(ACFGILMPQVWY), S489(-ACFGHIKLMPQTVY), 489.5(CDEPY), K490(-ACDEFGHILMNPQRSTVWY), 490.5(ACFGHIMNPQSTV), T491(ADEM), 491.5(ACFILMPQTVWY), S492(CDEILMT), 492.5(ADEGILMPSV), A493(DEILPRV), 493.5(DIKLMPV), D494(R), 494.5(GIMPTV), N495(-AFILMPQSTVY), 495.5(AFGILMPSTVWY), N496(-ACFGHILMQSTVW), 496.5(FT), N497(-EITV), 497.5(ADEGILMQT), S498(-ADEFGILMPQRVWY), 498.5(DEFGLMPQY), E499(I), 499.5(ADEGHILMNPQRSTVWY), Y500(-ACDEGIKLMNPQST), 500.5(AEFGHILMNPQSTVW), S501(-ACEGILMNPTVWY), 501.5(ACFGHILMNPQRSTVWY), W502(-ACEGILMPQSVY), 502.5(AFGHILMNPQSTVWY), T503(-ADEFGIPSV), 503.5(AFGILMNPQSTVW), G504(-ACFILMNPQSTVWY), 504.5(ACFGHILMNPQSVWY), A505(-CEFGHILMNPQSTVWY), 505.5(ACFGILMPQSTVWY), T506(-ACFGILMNPQSV), 506.5(ACIPSTVW), K507(ACHILMNQSTVW), Y508(-DIMV), H509(CEFN), 509.5(K), L510(I), N511(ACDELMQWY), 512.5(S), R513(CHIV), D514(ACEGILMQSTV), S515(CIV), L516(ACIMSTV), V517(IL), 517.5(C), N518(CHILMQRTVY), P521(CFLMNST), 521.5(S), A522(CPV), M523(LV), 523.5(A), A524(CGPST), 524.5(ACHSTW), S525(ACGHMNP), 525.5(ACFGHILMNQSTVWY), H526(-ACDEFGIKLMNPQRSTVWY), 526.5(ACDEFGHILMNPQSTVY), K527(-HR), 527.5(ACDEFGHILMPQSTVWY), 528.5(DEPT), 529.5(ADEGLMNPTV), E530(P), 530.5(ACDEFGHIKLMNQRSTVWY), 531.5(ADEFGILMNPQSTVY), K532(-HRW), 532.5(FHIPSTVWY), F533(ACGHILMNQSTVW), 533.5(FHY), F534(ILMVWY), 534.5(F), P535(-AF), Q536(-CDFNPWY), 536.5(L), S537(-ACDFGNQTY), G538(-), V539(AHLMNQST), 540.5(KM), I541(DPY), 541.5(DGH), F542(P), 542.5(Y), G543(APS), 543.5(ACDHILPQSTVY), K544(-ACFGHILMNPQSTVY), 544.5(DE), Q545(-DEP), 545.5(W), G546(DE), 546.5(EILMT), S547(-CDEFGHILMNPQV), 547.5(ACDHNPVY), 548.5(CDEMP), K549(-ACDEFGHILMNPQSTVWY), 549.5(DE), T550(CDE), 550.5(DEG), N551(CDELY), 551.5(CDEN), V552(ACELMNST), I554(CEHPQSTW), 555.5(N), K556(ACDEGLMNQSTVWY), 556.5(Q), V557(LM), M558(ACDHINQSTVW), 558.5(E), I559(CV), 559.5(A), T560(AV), 560.5(A), D561(AEFGHILMNQTVY), E562(AD), E563(D), I565(T), R566(ACDEFGHILMNQSTVWY), T567(Q), 567.5(E), T568(PV), 569.5(M), P570(CQS), 570.5(M), V571(ACHLMQST), 571.5(G), A572(CGSY), T573(ACDGINSV), 573.5(MT), E574(CDFLMQW), 574.5(DV), Q575(DFGIKLMNTVW), 575.5(AFWY), Y576(ACGHIS), 576.5(EFWY), 577.5(ACHIMNQSTV), S578(DEFGHILNVWY), 578.5(AEFGHILNST), V579(ACEFGHLMNQST), 579.5(FLY), S580(-	

GMNPQ), T581(CEGKNP), N582(FILMTVWY), 583.5(Q), Q584(V), 584.5(FLNT), R585(K), 585.5(AFGILMPQSTVY), 586.5(AGMPQS), N587(GILMQTV), 587.5(AFIMNQV), 588.5(ILMV), Q589(APSTV), 589.5(AFPV), A590(GMPQV), 590.5(ACGPQST), A591(CDHIT), 591.5(AFGILMNPSTV), T592(-ACDGMNP), 592.5(ACFGILMNPSTY), A593(-DEN), 593.5(AFGNPSTW), D594(E), 594.5(AGHINQSTVWY), V595(ACDEFGHILMNPQSTWY), 595.5(ADEFHILMQSTVW), N596(CDEFGMPTW), 596.5(DEN), T597(CDEGHIKLMNPQRV), Q598(ACEFGHILMNSTVY), G599(CSW), L601(IWY), P602(M), M604(ACQS), V605(F), 605.5(N), 607.5(P), 610.5(F), K620(N), G626(A), F628(IM), P630(HIQ), L633(FHMY), 640.5(N), 657.5(C), S658(CE), 658.5(CQ), T660(C), 660.5(E), F661(LQ), S662(C), 662.5(FMW), A663(Y), 663.5(DM), 664.5(DE), A667(C), S674(E), 697.5(GN), N703(D), 703.5(E), N705(DE), K706(DEGST), S707(D), 707.5(Y), V708(CE), N709(DE), V710(E), 711.5(Y), T716(CE), N717(E), 720.5(N), S721(TV), E722(D), P723(CE), R724(FHNSTWY), 735.5(M)	
3.5(DT), 4.5(N), Y6(I), D9(AV), R20(Q), K24(G), P27(T), P30(D), 32.5(L), P34(L), 34.5(V), 35.5(IN), E36(N), R37(Q), H38(L), 38.5(FK), K39(-LPWY), 39.5(DP), D40(P), 40.5(DY), D41(AHKQTW), 41.5(DNV), S42(EGLQ), 42.5(AKNSTY), R43(AGPSTW), 43.5(DHPRSTV), 45.5(M), V46(IK), L47(F), P48(L), G49(HM), 50.5(N), K51(AMNY), P55(Y), 55.5(K), F56(V), G58(CEST), L59(AIQ), D60(N), K61(-Q), 61.5(K), G62(E), E63(CM), E67(DTV), A71(IT), L73(N), E74(DH), K77(Y), 78.5(Q), Q82(FM), 83.5(H), D84(I), D87(EQ), L91(W), K92(Y), A98(N), E99(K), Q101(IV), E102(QY), E106(H), D107(Q), 107.5(E), S109(N), F110(VY), R116(M), A117(N), A121(IL), L126(C), E127(F), L129(C), V132(AES), E133(-), 133.5(CFLPRSW), E134(-K), 134.5(W), 135.5(DEMW), 136.5(CNY), K137(L), 137.5(IM), 139.5(ADGT), P140(DHIT), 140.5(EN), G141(I), K142(CDEFHIT), 142.5(C), K143(-), P145(AY), 145.5(M), V146(NW), 146.5(DFNY), 147.5(DE), H148(DGNW), 148.5(E), 149.5(E), P150(DM), 150.5(DMP), V151(D), 151.5(WY), 152.5(M), S157(WY), K161(W), A162(H), T176(N), 177.5(IV), 178.5(D), 179.5(DN), D180(M), 180.5(M), S181(DF), 181.5(TWY), V182(W), P183(C), 183.5(LMY), P185(W), L188(Y), 188.5(EY), 189.5(Q), Q190(EW), 190.5(F), 191.5(W), P192(CMQW), 192.5(CDHM), A193(D), 193.5(DEPW), A194(CMW), P195(A), 195.5(TY), S196(FH), L198(C), N201(SV), 202.5(F), G206(E), G208(ET), A209(M), M211(V), N215(DI), G217(V), H229(DV), D231(C), S232(T), M235(V), T251(S), H255(N), L256(ACS), K258(LQ), 260.5(ACDEMQT), S261(DG), S262(T), 262.5(DEINT), Q263(EVW), 263.5(D), S264(DEFLMTW), 264.5(D), G265(-), 265.5(ADET), 266.5(AE), S267(ENT), 267.5(E), N268(ADEQ), 268.5(E), 269.5(D), N270(ACDGHQSY), H271(EIN), S276(T), H288(N), R307(-CDFMNS), 307.5(K), P308(-GMW), L311(I), N312(M), L315(I), T324(CL), 324.5(CL), Q325(CHIK), 325.5(I), 326.5(M), 327.5(P), G328(AHS), T329(CN), T330(Q), T331(L), I332(V), 332.5(K), L354(HT), G355(ACS), S356(N), Q359(ACDEGHNSTV), F370(Y), T379(ACV), 379.5(DE), L380(EY), 380.5(E), N381(CDGMQ), N382(DE), 382.5(D), 383.5(E), 384.5(D), Q385(CGSW), 385.5(ADEPTV), A386(CEFHNP), 386.5(CDEP), V387(DELM), 387.5(EGKP), G388(E), R389(ALMPQSTY), 389.5(N), S390(DT), 394.5(N), P399(EMQ), Q401(R), R404(K), 404.5(N), G406(M), 407.5(H), N408(HW), 408.5(C), F409(Y), T410(DHNY), S412(H), 412.5(Q), Y413(FW), T414(DK), 415.5(DQ), 416.5(EN), D417(NS), 417.5(KM), V418(IM), Y424(C), 424.5(F), A425(FGQ), S427(D), Q428(EHS), S429(CY), L430(I), D431(FM), 431.5(Y), R432(I), L433(ADMT), 433.5(F), L437(AHMNSY), I438(ACGHLNST), D439(K), L442(CFIV), Y443(F),	0.9-fold

Y444(FH), 444.5(CLM), L445(CFMVY), 445.5(ACGHILMNQSTVY), S446(ACDEGHILMNTV), 446.5(AFGHILMNPQSTVWY), R447(ACEFGHIKLMNQSTV), 447.5(CFGILMNPVWY), T448(ACFGILMNPQVWY), 448.5(ACEFILMPWY), N449(ACDEFGILMPSTVW), 449.5(PY), T450(CDEI), S452(DEFLV), 452.5(IV), G453(EL), 453.5(I), T454(DEFILM), 454.5(DEFL), T455(ADEL), T456(DP), 456.5(DEGLP), Q457(ADEILMSTV), 457.5(DEPW), S458(ACDEFMNPTVWY), 458.5(CDEFILMPTWY), R459(-ACDEFGHILMNPQSTVWY), L460(ACFHIMNPSTVWY), 460.5(W), Q461(CDEFGKMNTV), F462(Y), S463(ACDGMNQTV), 463.5(F), Q464(ACIKLMSTV), 464.5(S), A465(CGP), G466(ACDNQ), 466.5(E), A467(CDFGHIMPQSVY), S468(CEFILNPQVY), D469(ACEHMNQRSTV), 469.5(DE), I470(CFLMV), R471(ACDEGKMQSTV), D472(Y), Q473(ACFHMSY), S474(CI), R475(K), 475.5(SW), N476(STW), W477(Y), 477.5(L), L478(FI), P479(GIT), 479.5(D), G480(Y), P481(AV), 481.5(HY), C482(FGIQVY), 482.5(FM), Y483(ACFHILMQTV), 483.5(FQ), R484(K), 484.5(N), Q485(ACFGHILNSTVY), 485.5(EKQY), Q486(FGIMNSTVWY), 486.5(FV), R487(-H), 487.5(FW), V488(ACEFGHILMNQTWY), 488.5(ACFGILMPQVWY), S489(-ACFGHIKLMPQTVY), 489.5(CDEPQY), K490(-ACDEFGHILMNPQRSTVWY), 490.5(ACFGHILMNPQSTVWY), T491(ADEILMPQSVW), 491.5(ACFGILMPQTVWY), S492(ACDEILMNQTV), 492.5(ADEGILMPQSV), A493(DEILPRV), 493.5(ADGIKLMPV), D494(R), 494.5(GILMPTV), N495(-AFGILMPQSTVY), 495.5(AFGILMNPSTVWY), N496(-ACFGHILMQSTVWY), 496.5(FLNT), N497(-EILTV), 497.5(ADEGILMQTV), S498(-ADEFGILMPQRVWY), 498.5(ADEFGLMPQY), E499(DI), 499.5(ADEGHILMNPQRSTVWY), Y500(-ACDEFGIKLMNPQSTV), 500.5(AEFGHILMNPQSTVWY), S501(-ACEFGILMNPTVWY), 501.5(ACFGHILMNPQRSTVWY), W502(-ACEFGILMPQSTVY), 502.5(AFGHILMNPQSTVWY), T503(-ADEFGIPQSVY), 503.5(AFGILMNPQSTVW), G504(-ACFHILMNPQSTVWY), 504.5(ACFGHILMNPQSVWY), A505(-CDEFGHILMNPQSTVWY), 505.5(ACFGILMPQSTVWY), T506(-ACFGILMNPQSV), 506.5(ACIPSTVW), K507(ACHILMNQRSTVWY), Y508(-DIMSTV), H509(CEFNQ), 509.5(K), L510(I), 510.5(K), N511(ACDEGLMQSWY), 512.5(S), R513(CHIV), D514(ACEGILMQSTV), S515(CITV), L516(ACIMSTV), V517(CIL), 517.5(C), N518(CHILMQRTVY), P521(CFLMNSTV), 521.5(MS), A522(CPSV), M523(LV), 523.5(A), A524(CGPST), 524.5(ACHSTW), S525(ACGHMNP), 525.5(ACFGHILMNPQSTVWY), H526(-ACDEFGIKLMNPQRSTVWY), 526.5(ACDEFGHILMNPQSTVWY), K527(-FHR), 527.5(ACDEFGHILMPQSTVWY), 528.5(DEPT), 529.5(ADEGLMNPTV), E530(DP), 530.5(ACDEFGHIKLMNQRSTVWY), E531(C), 531.5(ADEFGILMNPQSTVY), K532(-HRW), 532.5(FHIPSTVWY), F533(ACGHILMNQSTVW), 533.5(FHLY), F534(ILMVWY), 534.5(F), P535(-AF), Q536(-CDEFGNPTVWY), 536.5(L), S537(-ACDFGHNQTY), G538(-), V539(AHILMNQST), L540(M), 540.5(KMN), I541(-ACDGHPQTY), 541.5(DEGHMQST), F542(KP), 542.5(Y), G543(APS), 543.5(ACDHILMPQSTVY), K544(-ACFGHILMNPQRSTVY), 544.5(ADEV), Q545(-DEFHLPVY), 545.5(CDNPTW), G546(ACDEMNPS), 546.5(CDEGILMPQSTV), S547(-CDEFGHILMNPQVY), 547.5(ACDFGHLNPQSTVWY), 548.5(CDELMPW), K549(-ACDEFGHILMNPQSTVWY), 549.5(ADELQTV), T550(ACDEGLNQ), 550.5(ADEGPST), N551(CDEFLMQSY), 551.5(CDENV), V552(ACEILMNST), 552.5(V),	

I554(ACEFHLMPQSTVW), 555.5(N), K556(ACDEGLMNQSTVWY), 556.5(Q), V557(ILM), M558(ACDHINQSTVWY), 558.5(E), I559(CFMQV), 559.5(A), T560(ACSV), 560.5(A), D561(AEFGHILMNQSTVY), E562(AD), E563(DG), I565(T), 565.5(Y), R566(ACDEFGHILMNQSTVWY), T567(AGPQS), 567.5(E), T568(PV), 569.5(M), P570(CQS), 570.5(M), V571(ACHLMQST), 571.5(G), A572(CGSY), 572.5(V), T573(ACDGINSVW), 573.5(MT), E574(CDFLMQW), 574.5(DV), Q575(-DFGIKLMNTVWY), 575.5(AFWY), Y576(ACFGHIS), 576.5(EFWY), 577.5(ACHIMNQSTV), S578(ADEFGHILNVWY), 578.5(ACEFGHILNST), V579(ACDEFGHILMNQST), 579.5(FGILMY), S580(-GMNPQT), T581(CEGKNP), N582(FILMSTVWY), 583.5(Q), Q584(AV), 584.5(FLNQT), R585(K), 585.5(AFGILMPQSTVY), G586(LMQ), 586.5(AGMPQST), N587(GILMQTV), 587.5(AFILMNQV), 588.5(ILMV), Q589(APSTV), 589.5(AFPV), A590(GILMNPQV), 590.5(ACGPQST), A591(CDHILMT), 591.5(AFGILMNPSTV), T592(-ACDEGMNPS), 592.5(ACFGILMNPSTVY), A593(-DEFNPY), 593.5(AFGMNPQSTVW), D594(E), 594.5(AFGHINQSTVWY), V595(ACDEFGHILMNPQSTWY), 595.5(ADEFHILMNQSTVW), N596(ACDEFGMPQTW), 596.5(DEN), T597(CDEGHIKLMNPQRVY), Q598(ACEFGHILMNSTVY), G599(CSW), V600(C), L601(FIMVWY), P602(M), M604(ACQS), V605(F), 605.5(N), 607.5(P), 610.5(F), Y612(F), Q614(N), P616(Q), A619(C), K620(ACMN), I621(AKL), H623(P), T624(V), D625(S), G626(A), F628(HIM), P630(CGHIQTV), 630.5(CHV), L633(FHMY), M634(C), 640.5(N), H641(M), Q645(LM), 655.5(IW), N656(FQ), 657.5(CH), S658(CEHMQ), 658.5(CEFGMQ), T659(CDHMS), 659.5(DEHPQY), T660(CDM), 660.5(DEF), F661(ELQTW), 661.5(LPS), S662(CDGP), 662.5(CDEFHMPW), A663(DEFNY), 663.5(CDEMW), A664(DEG), 664.5(ADEGNS), K665(P), 665.5(NP), F666(H), 666.5(V), A667(C), 667.5(Q), F669(Y), S674(E), E681(M), E697(M), 697.5(GNPW), I698(V), 699.5(E), Y700(F), 701.5(A), S702(N), N703(D), 703.5(E), N705(DEM), 705.5(E), K706(DEGST), S707(D), 707.5(Y), V708(CE), N709(CDE), V710(E), 711.5(QY), T716(CEM), N717(DE), V719(C), 720.5(N), S721(CIMQTV), E722(D), P723(ACEHIQTV), R724(FHNSTWY), P725(L), L735(IV), 735.5(LMV)	

[0062] The preceeding describes a wide range of individual amino acid mutations that are tolerated and affect viral tropism, positively or negatively. It is specifically comtemplated herein that combinations of these various mutations can be made to further alter viral tropism, or other properties. In one embodiment, for example, at least 2 of the single amino acid mutations described herein are introduced in combination. For example, 2 mutations that influence tropism for liver can be combined. It is anticipated that the resulting virus will also have increased tropism for liver. In further embodiments, at least 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, or more mutations described herein are introduced in combination. We have demonstrated herein that a wide range of mutations are tolerated, however, no more than 40% of the amino acids should change relative to a reference sequence (e.g., SEQ ID NO: 1). In certain embodiments, no more than 35%, 30%, 25%, 24%, 23%, 22%, 21%, 20%, 19%, 18%, 17%, 16%, 15%, 14%, 13%, 12%, 11%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1% of amino acids, or fewer, are changed relative to a reference sequence (e.g., SEQ ID NO: 1).

[0063] Mutations that are at equivalent positions in other homologous viruses can be made and used for improving virus packaging and virus infectivity. Examples of other homologous viruses include any of AAV serotypes 1, and 3-12, as well as other natural isolates or synthetic sequences. Corresponding positions in homologous viruses can be inferred from sequence homology to AAV2. In one embodiment, the mutations described herein are introduced into the corresponding amino acid sequence of an AAV1, AAV3, AAV3B, AAV4, AAV5, AAV6, AAV7, AAV8, AAV9, AAV10, AAV11, AAV12, and AAV13 capsid polypeptide.

[0064] Site-directed mutagenesis is known in the art and can be used to introduce a point mutation(s) (e.g., amino acid substitutions, insertions, or deletations) or other mutations or combinations thereof to a viral capsid polypeptide. Site-directed mutatgenesis is further described in, e.g., Li B, et al. *Hum Gene Ther Methods.* 2015 Dec: 26(6):2l 1-20, and Bachman, J. *Methods Enzymol.* 2013; 529:241-248, which are incorporated herein by reference in their entirety.

[0065] Combinations of mutations can be used to achieve a particular vector targeting goal. For example, it may be desirable to use a virus that has improved nucleic acid delivery in a first tissue and reduced nucleic acid delivery in one or more second tissues. Such a virus, whether achieved through a single mutation or multiple mutations, can have increased tissue specificity.

[0066] *Mutatable subregions of AAV2 capsid protein*

[0067] It was found herein that particular regions of AAV2 capsid protein tolerate amino acid alterations, e.g., deletion, insertion, or substitution better than others, and that changes to certain regions that tolerate such change have pronounced impact on viral vector tropism. The region of the AAV2 capsid polypeptide of SEQ ID NO: 1 from amino acids 440 to 600 is identified herein as both tolerant of a variety of changes and highly influential for viral tropism, with certain mutations influencing tropism towards or away from certain tissues or cell types, as indicated in the Tables herein. Within this region, sub-regions including amino acids 440-460, 475-505, 518-532 and 560-590 are seen, for example, in the heat maps provided herein, to be particularly important for changes in viral tropism, and one of these sub-regions, from amino acids 561-588 is shown herein to tolerate extensive mutation. This region, which was found in single amino acid mutation studies to be important for tropism, was selected for initial studies of the effect of combinations of mutations. It was found that combinations of two to at least 8 different single amino acid mutations within this region were well tolerated, and further influenced tropism, as shown in the SEQ ID Nos: 3-20.

[0068] SEQ ID NO: 2 is an amino acid sequence encoding the amino acid region between amino acids 440-600 of SEQ ID NO: 1.

QYLYYLSRTNTPSGTTTQSRLQ FSQAGASDIRDQSRNWLPGPCYRQQRVSKT SADNNNSEYSWTG ATKYHLNGRDSLVNPGPAMASHKDDEEKFFPQSGVL I FGKQGSEKTNVDI EKVMITDEEE IRTTN PVATEQYGSVSTNLQRGNRQAATADVNTQGV (SEQ ID NO: 2)

Table 10: Amino acid alterations between amino acids 440-600 of SEQ ID NO: 1 conferring more

efficient delivery to blood.	
Amino acid alteration	Fold increase of efficiency
445.5(D), S446(-), 446.5(DE), R447(-PWY), 447.5(DEHQ), T448(-DEH), 448.5(D), N449(H), T450(FS), 452.5(P), G453(V), T454(APQ), T455(GMS), T456(A), 456.5(A), 457.5(MT), Q464(R), 464.5(Y), S468(M), C482(MSW), Y483(W), R484(ILQV), 485.5(M), Q486(DE), R487(ACDEFGILMNPQSTVWY), 488.5(DE), S489(DE), 490.5(DE), T491(FN), 491.5(DE), A493(FS), 493.5(ENST), 494.5(E), N495(DEW), 495.5(DE), N496(DE), 496.5(DE), N497(AMP), 498.5(ST), 500.5(D), S501(D), 501.5(DE), 502.5(DE), 503.5(DE), G504(DE), 504.5(E), 505.5(E), K507(-EF), P521(I), M523(C), S525(T), 525.5(DE), K527(PQW), D528(Q), E531(DGMN), K532(ADEFGILMNPQSTVY), 532.5(DEMN), F533(DEY), 533.5(CDEGSV), 536.5(V), V539(C), V571(DE), Q575(A), Y576(M), 577.5(E), V579(VV), 579.5(CDEN), S580(ADE), 580.5(DEILMPY), T581(DSWY), 581.5(DEFILMPQV), N582(-ACDEPQ), 582.5(GP), L583(-DEGPT), 583.5(DEIPV), Q584(-DEFLNTY), 584.5(ADEIMVY), R585(-ADEFGHILMNPQSTVWY), 585.5(DE), G586(-DEP), 586.5(DEFHINVY), N587(-DE), 587.5(DEGPY), R588(-ACDEFGHILMNPQSTVWY), 588.5(DEFQTY), Q589(DEFMNY), 589.5(DEGINS), A590(DEW), 590.5(DEFY), A591(EFPQSY), 591.5(CDEQWY), T592(FY), 592.5(DEQ), A593(GLMTVW), 593.5(CDEILY), 594.5(CDEP), 595.5(C), N596(S), T597(AS), V600(AILST)	1.1-fold
445.5(D), S446(-), 446.5(DE), R447(-P), 447.5(DEHQ), T448(-DE), N449(H), T454(P), 464.5(Y), C482(M), R484(ILQV), 485.5(M), Q486(DE), R487(ACDEFGILMNPQSTVWY), 488.5(E), S489(DE), 490.5(DE), T491(N), N495(DEW), 495.5(DE), N496(DE), 496.5(DE), S501(D), 501.5(D), 502.5(DE), 503.5(DE), G504(DE), K507(-E), 525.5(D), E531(GMN), K532(ADEFGILMNPSTVY), 532.5(DEM), F533(DE), 533.5(CDEGSV), V571(DE), 577.5(E), V579(V), 579.5(CDE), S580(DE), 580.5(DEILMY), T581(W), 581.5(DEFILMPQV), N582(-ACDEP), 582.5(GP), L583(-DEPT), 583.5(DEIPV), Q584(-DEFLTY), 584.5(DEIV), R585(-ADEFGHILMNPQSTVWY), 585.5(DE), G586(-DE), 586.5(DEFHY), N587(-DE), 587.5(DEP), R588(-ACDEFGHILMNPQSTVWY), 588.5(DEFY), Q589(DEFY), 589.5(DEIN), A590(DEW), 590.5(DE), A591(PY), 591.5(CDEY), T592(FY), 592.5(DE), 593.5(CDE), 594.5(CDE), 595.5(C), N596(S)	1.5-fold
445.5(D), S446(-), 446.5(DE), R447(-P), 447.5(EHQ), T448(D), T454(P), 464.5(Y), R484(ILQV), 485.5(M), Q486(DE), R487(ACDEFGILMNPQSTVWY), 488.5(E), S489(DE), 490.5(D), N495(DEW), 495.5(DE), N496(DE), 496.5(DE), S501(D), 501.5(D), 502.5(E), 503.5(DE), G504(DE), K507(-), K532(ADEGILMNPSTV), 532.5(DE), F533(DE), 533.5(CDEGSV), V571(DE), 577.5(E), 579.5(DE), S580(DE), 580.5(DEILMY), T581(W), 581.5(DEFILMPQV), N582(-DEP), 582.5(GP), L583(-DEP), 583.5(DEIPV), Q584(-DEFY), 584.5(DEIV), R585(-ADEFGHILMNPQSTVWY), 585.5(DE), G586(-DE), 586.5(DEY), N587(-DE), 587.5(DEP), R588(-ACDEFGHILMNPQSTVWY), 588.5(DE), Q589(DE), 589.5(DEIN), A590(DEW), 590.5(DE), A591(PY), 591.5(DE), T592(FY), 592.5(DE), 593.5(DE), and 594.5(CDE)	2-fold
N496(DE), S501(D), G504(D), K532(DE), 581.5(DEIPV), N582(DE), 582.5(G), L583(-DE), 583.5(DEP), Q584(-DE), 584.5(DE), R585(-ADEFGHILMNPQSTVWY), 585.5(DE), G586(-D), 586.5(DE), N587(-DE),	5-fold

587.5(DEP), R588(-ACDEFGHILMNPQSTVY), 588.5(DE), 589.5(DE), A590(DE), 590.5(D), 593.5(E), and 594.5(E)	
R585(D)	10-fold

Table 11: Amino acid alterations between amino acids 440-600 of SEQ ID NO: 1 conferring more efficient delivery to heart.

Amino acid alteration	Fold increase of efficiency
Y444(F), 448.5(S), N449(A), T450(M), S452(M), T454(LQ), 455.5(A), T456(AV), Q457(DLV), S458(AP), 458.5(Q), R459(FH), Q464(AI), A467(CGNPQ), S468(ADG), D469(AENQST), I470(LMV), R471(CKM), C482(M), Q486(N), R487(ACGIMQSTV), S489(AD), 490.5(N), T491(FLW), 492.5(M), A493(M), N496(DHSY), N497(PV), S498(FM), Y500(M), T506(S), V517(I), S525(AG), H526(CNST), E531(D), K532(ADEFGILMNQRST), I541(C), K544(CGTVY), Q545(E), K549(Q), N551(Y), V552(Q), K556(DNY), D561(Q), R566(ASV), T567(S), S578(TV), V579(V), S580(A), T581(WY), 581.5(IV), N582(DE), L583(DE), 584.5(EIV), R585(-ADFGHILMNQSTVWY), G586(DE), N587(DE), 587.5(D), R588(ACDEFHILMNQSTVY), 588.5(DE), Q589(M), A590(P), A591(ETY), 591.5(CDE), T592(F), 594.5(D), T597(ANSW), Q598(L), V600(AS)	1.1-fold
D469(AQS), I470(LM), R471(K), R487(A), S489(D), 490.5(N), T491(W), N496(D), S498(M), K532(ADEL), D561(Q), N582(DE), L583(E), 584.5(V), R585(-AGHIMNQSTVWY), N587(DE), R588(ADEFILMNQSTVY), 588.5(DE), Q589(M), 591.5(D), T597(W), and V600(A)	1.5-fold
R471(K), K532(D), N582(D), L583(E), R585(Q), N587(DE), R588(MQTV), and 588.5(E)	2-fold

Table 12: Amino acid alterations between amino acids 440-600 of SEQ ID NO: 1 conferring more efficient delivery to kidney.

Amino acid alteration	Fold increase of efficiency
446.5(D), 447.5(HQ), N449(ACGS), T456(AG), 456.5(G), R459(HK), Q464(A), A467(GNP), S468(AG), D469(AEQST), I470(LMV), R471(K), C482(M), Q486(D), R487(P), S489(E), 490.5(N), T491(F), A493(FI), N495(E), 495.5(DE), N496(EHS), 496.5(D), N497(P), S498(M), Y500(M), S501(D), 501.5(D), G504(D), N518(S), H526(CS), K532(DER), 532.5(D), F533(Y), K544(ILTV), T550(G), K556(N), D561(Q), R566(AV), S578(TV), V579(V), S580(A), 580.5(IMY), 581.5(EFILMPQV), N582(-ACDEP), 582.5(GP), L583(-DEIP), 583.5(DEIPV), Q584(-EFY), 584.5(DEILV), R585(-DEINPQVW), 585.5(D), G586(-), 586.5(DEIY), N587(-D), 587.5(DEP), R588(-ACDEGHLNPQTV), 588.5(DE), Q589(MP), 589.5(DE), A590(DEPV), 590.5(DE), A591(PST), 591.5(C), A593(M), 593.5(CE), T597(ASW), Q598(L), V600(A)	1.1-fold
D469(AQ), I470(L), R471(K), 490.5(N), 495.5(DE), N496(EHS), S498(M), S501(D), K532(D), 580.5(I), 581.5(EILMPV), N582(-D), 582.5(GP), L583(DE), 583.5(DEIPV), Q584(-EFY), 584.5(IL), R585(-IP), G586(-), N587(-), 587.5(P), R588(-CDGV), 588.5(D), 589.5(DE), A591(P), 591.5(C), 593.5(C), T597(W), and V600(A)	1.5-fold

R471(K), K532(D), 581.5(IM), L583(DE), 583.5(D), 584.5(L), G586(-), N587(-), 587.5(P), R588(-), 591.5(C), and 593.5(C)	2-fold

Table 13: Amino acid alterations between amino acids 440-600 of SEQ ID NO: 1 conferring more efficient delivery to liver.

Amino acid alteration	Fold increase of efficiency
Y444(F), N449(S), T450(IV), S452(A), 455.5(A), T456(V), Q457(T), S458(AP), R459(HKT), L460(CN), A467(CGPQ), S468(G), D469(AENQST), I470(LMV), R471(CKM), C482(IM), Y483(M), Q486(N), 490.5(N), T491(DE), A493(MP), N496(HS), S498(AFLM), Y500(M), T503(V), T506(ACV), K507(S), V517(I), S525(G), H526(ACNST), K532(HINQWY), F533(Y), K544(C), 545.5(D), T550(E), I554(L), K556(ENY), M558(F), D561(Q), E563(D), R566(ACGNSTV), T567(S), S578(DEIT), V579(V), S580(A), T581(DM), L583(I), A590(IP), A591(DEQS), T592(S), A593(DET), N596(C), T597(ACDHLNQW), Q598(ILMV), V600(AST)	1.1-fold
R459(H), L460(N), A467(CGPQ), D469(AEQST), I470(LM), R471(K), C482(I), Q486(N), N496(H), S498(M), H526(CNS), K532(N), K544(C), T550(E), K556(Y), R566(AGTV), A590(P), A591(E), A593(DE), T597(HNQ)	1.5-fold
A467(G), D469(AEQS), I470(L), R471(K), Q486(N), N496(H), S498(M), H526(S), T550(E), A593(DE), and T597(N)	2-fold

Table 14: Amino acid alterations between amino acids 440-600 of SEQ ID NO: 1 conferring more efficient delivery to lung.

Amino acid alteration	Fold increase of efficiency
Y444(F), N449(Q), T450(I), S452(M), T454(IQ), T455(G), S458(AP), 458.5(Q), R459(F), Q461(G), A467(CGNPQ), S468(G), D469(AENQST), I470(LMV), R471(K), 490.5(N), T491(QW), N497(P), N518(M), P521(V), F533(Y), V539(C), K544(C), Q545(N), T550(A), K556(N), D561(Q), S578(T), S580(A), Q589(M), A590(P), A593(T), T597(AS), V600(A),	1.1-fold
S264(G), A467(G), D469(AQT), I470(M), R471(K), 490.5(N), and V600(A)	1.5-fold

Table 15: Amino acid alterations between amino acids 440-600 of SEQ ID NO: 1 conferring more efficient delivery to spleen.

Amino acid alteration	Fold increase of efficiency
L445(I), S458(A), R459(K), S468(G), D469(Q), T491(LQ), Y500(W), F533(Y), I541(C), M558(F), V579(V), S580(A), Q589(MN), A590(P), A591(S), A593(MT), T597(AMY), V600(AIT)	1.1-fold
Q589(M), and V600(A)	1.5-fold

[0069] Interestingly, when combinations of mutations were examined, it was found that if a single mutation identified to be beneficial, e.g., for a change in tropism, is introduced, the resulting polypeptide tends to tolerate further mutation to include other single amino acid changes found to be beneficial. This is illustrated in, e.g., Figure 3, which shows fitness at first mutation versus the number of mutations away from wild-type that will be tolerated before the virus is no longer viable. On the x-axis is the fitness at first mutation, i.e., whether a single mutation is neutral, deleterious, or beneficial. On the y-axis, is the number of mutations tolerated before the virus is no longer viable. The figure shows that if a virus has a first mutation that is beneficial, it will tolerate significantly more mutations, as compared to a virus with a first mutation that is neutral or deleterious. Thus, it is anticipated that combinations of mutations that do not interfere with viral fitness will be well tolerated.

[0070] Further identified herein are sub-regions (e.g., regions within the full length polypeptide) within the viral capsid polypeptide that are more likely to tolerate an amino acid change. One aspect herein is an AAV2 capsid polypeptide comprising a mutation in the sub-region of amino acids selected the group consisting of: 440-460 of SEQ ID NO: 1, 475-505 of SEQ ID NO: 1, 518-532 of SEQ ID NO: 1, and 560-590 of SEQ ID NO: 1 that alters tissue tropism of a virus comprising the viral capsid polypeptide. In further embodiments, at least 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, or more mutations described herein are introduced in combination into a sub-region. Though a wide range of mutations are tolerated, no more than 40% of the amino acids within a sub-region should change relative to a reference sequence (e.g., SEQ ID NO: 1). In certain embodiments, no more than 35%, 30%, 25%, 24%, 23%, 22%, 21%, 20%, 19%, 18%, 17%, 16%, 15%, 14%, 13%, 12%, 11%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1% of amino acids within a sub-region, or fewer, are changed relative to a reference sequence (e.g., SEQ ID NO: 1).

[0071] In one embodiment, a mutation described herein more efficiently increases viral tropism when introduced into a particular sub-region of the viral capsid polypeptide. In one embodiment, delivery is at least 1.1-fold more efficient as compared to a wild-type viral capsid polypeptide. In another embodiment, the delivery of a nucleic acid is at least 1.5-fold, at least 2-fold, at least 4-fold, at least 5-fold, at least 10-fold, or more, more efficient as compared to a virus comprising the wildtype SEQ ID NO: 1 capsid polypeptide.

[0072] One aspect of the technology is a method of altering tropism of a virus comprising modifying a capsid polypeptide corresponding to the polypeptide of SEQ ID NO: 1 to introduce a mutation in at least 2 regions selected from the group consisting of: amino acids 440-460 of SEQ ID NO: 1, amino acids 475-505 of SEQ ID NO: 1, amino acids 518-532 of SEQ ID NO: 1, and amino acids 560-590 of SEQ ID NO: 1.

[0073] One aspect is an AAV2 capsid polypeptide comprising a mutation in the region of amino acids 561-588 of SEQ ID NO: 1 that increases tissue tropism of a virus to the kidney, wherein the mutated region of amino acid 561-588 of SEQ ID NO: 1 has a sequence selected from the group consisting of: DEEEIATTNPVATEQYGDVSENLMHFQN (SEQ ID NO: 3);
DEEEIRQTNPVATEGYGEVSTNLMHGNK (SEQ ID NO: 4);
DEEEIRTTNPVATEQYGIVnStTNLNEGNR (SEQ ID NO: 5);
DEEEIRTTNPVATECYGSVSTDLQSGNL (SEQ ID NO: 6);

DENEIRTTNPVATEIYGSVSTeNLQNnGdNR (SEQ ID NO: 7);
DEEEIRTTNPVATEQYGSVSeTNpLvQNGdDR (SEQ ID NO: 8);
DEEEIRTTNPVATEQYGDVSENLMHFQN (SEQ ID NO: 9).

[0074] An AAV2 capsid polypeptide comprising a mutation in the region of amino acids 561-588 of SEQ ID NO: 1 that increases tissue tropism of a virus to the liver, wherein the mutated region of amino acid 561-588 of SEQ ID NO: 1 has a sequence selected from the group consisting of:
DEEEIRTTNPVATEQYGVVSDNLQRGNR (SEQ ID NO: 10);
DECEIRTTNPVATEQYGSVGENLQRGNR (SEQ ID NO: 11);
DEEEIRTTNPVATEQYGVVSENLQRGNR (SEQ ID NO: 12);
DESEITTTNPVATEQYGWVSTNQQRGNR (SEQ ID NO: 13);
HELEIATTNPVATEQYGSASTNIQRGNR (SEQ ID NO: 14);
DEEEIATTNPVATEQYGGVSTNLQRGNR (SEQ ID NO: 15).

[0075] An AAV2 capsid polypeptide comprising a mutation in the region of amino acids 561-588 of SEQ ID NO: 1 that increases tissue tropism of a virus to the lung, wherein the mutated region of amino acid 561-588 of SEQ ID NO: 1 has a sequence selected from the group consisting of:
DEEEIVTTNPVATEQYGNVSTNLQRGNR (SEQ ID NO: 16);
DEDEISTTNPVATEQYGSCSTNLQRGNR (SEQ ID NO: 17);
QEEEIRTTNPVATEQYGSVSTNLQRGDR (SEQ ID NO: 18);
NEEEIRTTNPCATEVYGSVSTNLQRGNR (SEQ ID NO: 19);
DEQEIVTTNPVATEVYGTVSTNLQRGNR (SEQ ID NO: 20).

[0076] One aspect of the technology described herein is a nucleic acid encoding any of the viral capsid polypeptides described herein.

[0077] Another aspect of the technology described herein is a viral particle comprising any of the viral capsid polypeptides described herein.

Corresponding mutations

[0078] Mutations at corresponding locations in, for example homolgous viral capsid polypeptides, would be expected to have similar effects on viral tropism. Corresponding locations can include, for example, a location relative to the full length capsid polypeptide (e.g., SEQ ID NO: 1), or for that matter, a location relative to a sub-domain or sub-region of the the full length capsid polypeptide (e.g., SEQ ID NO: 2). In one aspect, a viral capsid polypeptide is provided herein that bears a mutation that corresponds to a mutation of the polypeptide of SEQ ID NO: 1 as described herein or selected from the group consisting of the mutations in Tables 1-9 relative to SEQ ID NO: 1. In one embodiment, a homologous viral capsid polypeptide has at least 70%, at least 75%, at least 80%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or more sequence identity to wild-type AAV2 capsid protein (e.g., SEQ ID NO: 1). In another embodiment, the viral capid polypeptides of AAV serotypes 1, and 3-13 are homolgous to a AVV2 capsid polypeptide.

[0079] One aspect described herein is a viral capsid polypeptide comprising a region corresponding to the amino acid sequence of SEQ ID NO: 2, wherein the region corresponding to the amino acid sequence of SEQ ID NO: 2 comprises a mutation relative to SEQ ID NO: 2 that alters tissue tropism of a virus comprising the viral capsid polypeptide, wherein the mutation is selected from the mutations in any one of Tables 10-15. In one embodiment, a homologous viral capsid polypeptide has at least 70%, at least 75%, at least 80%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or more sequence identity to SEQ ID NO: 2.

[0080] As noted elsewhere herein, the identification of amino acid sites or regions of amino acid sequence in the AAV2 capsid polypeptide of SEQ ID NO: 1 that tolerate change in general, i.e., that permit packaging and infection by viral particles, as well as regions that influence tropism and/or packaging, either positively or negatively, can be used to guide changes in the capsid polypeptides of other AAV serotypes to similarly influence function or provide for modified properties. Thus, through use of sequence alignment, a mutation or set of mutations that provides a desired change in tropism and/or packaging for the AAV2 capsid polypeptide of SEQ ID NO: 1 can be introduced to the corresponding location of the capsid polypeptide of another AAV serotype to similarly influence those properties in that serotype. As but one example, it was determined herein that the region from amino acids 440 to 600 of the AAV2 capsid polypeptide of SEQ ID NO: 1 is important in determining viral tropism, and indeed, that there are sub-regions within that region, e.g., amino acids 561-588, that robustly influence tropism. It is contemplated that the introduction of changes identified herein in this amino acid 440 to 600 region, or in the amino acid 561-588 sub-region of the AAV2 capsid polypeptide to the corresponding region or sub-region of another AAV serotype capsid polypeptide will influence tropism of that AAV serotype in a similar manner.

Viral Packaging

[0081] One embodiment of the technology described herein relates to a method of increasing viral packaging by modification of an AAV2 capsid polypeptide to comprise at least one mutation in the region of amino acids selected the group consisting of: 34-38 of SEQ ID NO: 1, 133-152 of SEQ ID NO: 1, 188-194 of SEQ ID NO: 1, and 654-662 of SEQ ID NO: 1.

[0082] One embodiment of the technology described herein relates to a method of increasing viral packaging efficiency by modification of an AAV2 capsid polypeptide comprising any non-positive amino acid insertion, substitution, or deletion in the region of amino acids selected from the group consisting of: 442-452 of SEQ ID NO: 1, 489-506 of SEQ ID NO: 1, 541-551 of SEQ ID NO: 1, and 577-596 of SEQ ID NO: 1. In another embodiment, packaging efficiency is increased by the mutation of a plurality of amino acids to any non-positive amino acid insertion, substitution, or deletion in the region of amino acids selected from the group consisting of: 442-452 of SEQ ID NO: 1, 489-506 of SEQ ID NO: 1, 541-551 of SEQ ID NO: 1, and 577- 596 of SEQ ID NO: 1.

Table 16: Amino acid alterations conferring more efficient viral packaging.

Amino acid alteration	Fold increase of efficiency
D13(N), T14(HQ), I19(AV), Q21(F), W22(Y), W23(EFHIKLNQTVY), K24(M), L25(CI), K26(H), 28.5(AV), P29(ADFGIVY), P31(HIKNQT), 32.5(Q), K33(AFILNPQRST), P34(A), 34.5(AY), A35(-E), 35.5(CKPQSTVW), E36(GV), 36.5(ADGLV), R37(G), 37.5(ADEGNPQRV), H38(ADEGKPQVY), 38.5(ADE), K39(A), R43(T), P48(Y), E63(DHIP), V65(NS), N66(D), E67(A), A70(KQ), L73(N), K77(E), A78(K), D80(EHNQ), R81(H), D84(ET), S85(QT), N88(FV), K92(ACFLT), A98(Q), E99(DKQTV), Q101(HN), E102(Y), R103(AT), K105(DHN), E106(DTW), 108.5(H), S109(A), F110(K), L114(F), G115(A), R116(AFGIKLQST), A117(FLQSTW), V118(CFGILSTWY), Q120(EN), K123(C), R124(ADEHKNQT), V125(CFGILT), L126(ACDFGHNSTVY), E127(ADFGHIMNPSTY), L129(AFGHNPSWY), 129.5(P), G130(DHQ), L131(ACFGHQRWY), V132(CHY), 132.5(DE), 133.5(EKNT), E134(AHIKLNPQSTV), 134.5(ADEGHIKLNPQRSTVY), P135(-ACDEFGHKNQRSTVWY), 135.5(CEFKMY), V136(ACDEFGHIKNPQRSTWY), 136.5(ADEFGNPSTW), K137(ET), 137.5(AKT), T138(-DHY), 138.5(ADEGINPQSTWY), A139(-DEGNPVW), 139.5(ACDEFGHILNPQSTVWY), P140(-ADEFNQSTVW), 140.5(ACDEFGHILNPSTVWY), G141(-ACDEFLNPQSTVWY), 141.5(ADFGHILPQSTVY), K142(-AEFGHILNQRSTVY), 142.5(FT), K143(-), P145(CFHLQT), 145.5(ACFGHILNPSVWY), V146(FGINPQWY), 146.5(DEGINQTVY), E147(DI), 147.5(ACDEFGHILNPQSTVY), H148(-ACDEFGLNPQSTVWY), 148.5(CDEGLNPQSTVY), 149.5(PS), P150(FINWY), 150.5(ACEFGHIKLPQRSTVWY), V151(IQY), 151.5(ACDEHILPQRVWY), E152(LSWY), 152.5(F), S157(TWY), T159(FILQVY), K161(CF), A162(CIKNQSTVW), Q164(ACDFHKLNPRVWY), P166(H), Q175(WY), 175.5(D), 177.5(CFW), A179(P), D180(W), 180.5(S), S181(DEQ), 181.5(CST), V182(CIW), Q186(IVWY), 188.5(DST), G189(DENY), 189.5(CDEFGHINSTY), Q190(-CDENSTW), 190.5(ADEFGIKLNPQSTVW), P191(-CDEFGHIKLMNQSTVWY), 191.5(ADEFGHILMNPQSTVY), P192(-ADEFQRSTY), 192.5(AGKQST), A193(EFKP), 193.5(AEP), A194(ST), 194.5(EY), P195(-D), S196(A), T200(CY), T202(CW), T205(AH), A209(S), E216(D), 237.5(D), 262.5(D), Q263(G), S267(T), N270(CDS), Y275(W), S276(A), R310(K), T324(S), 324.5(R), T344(AEHS), S346(DEKN), L354(IV), H358(ACQS), Q359(DE), L362(F), F370(Y), M371(LTV), V372(I), G376(A), L380(V), N381(C), N382(D), Q385(W), V387(L), P399(A), N408(T), T410(N), T414(Y), V418(M), Y424(F), A425(C), L433(TV), I438(ACLNTV), L442(F), Y443(F), Y444(F), L445(CMV), 445.5(ACDIMNQSTV), S446(-ACEHMNQTV), 446.5(ACDEFILMNPQSTVW), R447(-ACDEFGHILMNPQSTVWY), 447.5(CDEFGHILMNPQVWY), T448(-DEFHILMNPQVWY), 448.5(ADEFLMPY), N449(ACDEFGILMPQSVW), T450(EIS), 450.5(E), S452(DFL), 452.5(P), G453(EL), T454(EIM), 454.5(DE), T455(ADE), T456(D), 456.5(DG), Q457(ADELSV), 457.5(DE), S458(DENPTW), 458.5(DEFMWY), R459(-ACDEFGHILMNPQSTV), L460(ACIMNPSTV), Q461(E), S463(N), Q464(AIV), A467(GMNPS), S468(AGHMQ), D469(AEST), I470(CLMV), R471(ACKMQST), D472(Y), Q473(FH), C482(M), Y483(CIMVW), R484(IKLQV), 484.5(N), Q485(ACFIV),	1.1-fold

Q486(DEGNSTV), R487(ACDEFGHILMNPQSTVWY), V488(ACFILMWY), 488.5(DEP), S489(ADEGHMPQW), K490(-ACDEFGHILMNPQRSTVWY), 490.5(DFGIMNQTVWY), T491(ADEFGMQSWY), 491.5(ADEFILNPQTV), S492(DEHMT), 492.5(ADEGILMQV), A493(DEFILMV), 493.5(DEINSV), 494.5(DEM), N495(ADEFILMPQVWY), 495.5(DEFGWY), N496(ACDEFGHILMQSVWY), 496.5(DE), N497(-AEILMTV), 497.5(DEGIMQST), S498(-ADEFGLMQTWY), 498.5(ADFGLMQS), E499(D), 499.5(ADELMNPQSTV), Y500(-ADEGLMNPQSTVW), 500.5(ADEFGLMNPQST), S501(-CDEFGILMNPQTV), 501.5(ACDEGHILMNQSTVWY), W502(P), 502.5(ADEFGHILMNPQSTVWY), T503(AFIPVY), 503.5(ADEFILMNSTVW), G504(ACDEFILMNPVWY), 504.5(ACEFILMQSTVWY), A505(EGLSY), 505.5(CEFILMV), T506(ACILMNPV), 506.5(ACIV), K507(-CFHILMNQSTVWY), 510.5(K), N511(ACDM), R513(V), S515(TV), L516(ACIMSTV), V517(I), N518(QT), P521(ILT), A522(P), M523(CQ), A524(G), 524.5(T), S525(CG), H526(-ACDEGILMNPQRSTVW), K527(FHR), E531(DM), K532(-ADEFGHILMNPQRSTVWY), 532.5(AE), F533(ACDEGHILMNQSTV), 533.5(CDEGS), F534(MW), P535(-), Q536(-CDEFPTVY), 536.5(CV), S537(-ACDFGNQTY), G538(-), V539(CMST), I541(CH), K544(AILMQT), 544.5(D), Q545(EM), 545.5(E), G546(H), 546.5(D), K549(CNQT), 549.5(E), T550(AD), N551(DEMY), I554(QV), K556(DE), M558(N), D561(Q), R566(ACGMNSTVW), V571(ACES), A572(G), T573(CG), E574(D), Q575(GILMNTV), Y576(CM), 577.5(E), S578(DEGILNWY), 578.5(A), V579(ACEGIMNSTWY), 579.5(DEN), S580(-DEGINPQT), 580.5(DEL), T581(-DEMNPSWY), 581.5(DEILPQ), N582(-ACDEFILMPQSTVWY), 582.5(GP), L583(DEGIPTV), 583.5(DEPQV), Q584(DEGILTV), 584.5(ADEFGILMQSTVY), R585(-ADEFGHIKLMNPQSTVWY), 585.5(ADEFGILMNPQSTVY), G586(-DELMP), 586.5(ADEFGHILMNPQSTV), N587(-DEGILMPQTV), 587.5(ADEFILMNPQSTVY), R588(-ACDEFGHILMNPQSTVWY), 588.5(DEILMQTVY), Q589(ADEFMNPSTVY), 589.5(ADEFNPSTV), A590(DEGIMPSV), 590.5(ADEFGPST), A591(DEFILMPTVY), 591.5(ACDEFGILMNPQSTVY), T592(-ACDEFGLMNPQSY), 592.5(ACDEFGILMNQSTVWY), A593(-DEFL), 593.5(ACDEFGILMNPQSTVWY), D594(E), 594.5(ACDEFGHILMPQSTVWY), V595(ACEGHILMNPQTW), 595.5(CDEILMTV), N596(CDE), T597(CDEGHILNQSVW), Q598(ACEFHILMSTVY), V600(L), L601(FIMVY), V605(I), W606(F), Q607(M), D608(N), P616(Q), H627(C), P630(ACM), H641(ENT), I646(V), L647(M), N656(A), S658(FNQ), 658.5(NT), T659(NS), T660(H), 660.5(T), F661(Y), S662(M), 662.5(FGSW), A663(CGHIQT), 663.5(DEQ), A664(QT), 664.5(EH), K665(HR), F666(MW), A667(FS), S679(M), V708(W), T716(A), N734(C)	
W23(EN), P29(AFGIV), P31(NT), P34(A), 34.5(A), E36(V), 36.5(AG), R37(G), 37.5(ADEGV), H38(ADEGQV), 38.5(AE), R43(T), N66(D), A78(K), Q101(H), K105(N), A117(W), R124(DN), V125(T), L126(FHNY), E127(D), L129(HSY), L131(Y), 132.5(E), 133.5(EN), 134.5(ADEIKNT), P135(ADEFHKNQTW), V136(DEHKPST), 136.5(ADE), 137.5(KT), 138.5(AE), A139(E), 139.5(AEFLNPQSTY), P140(-), 140.5(CDFIPY), G141(-DE), K142(-EGILQSTVY), K143(-), V146(GW), 146.5(DN), H148(-DEQW), 148.5(EY), 149.5(P), P150(FWY), 150.5(ACEFILQVY), 151.5(CPQY), T159(IY), A162(VW), Q164(Y), Q175(Y), 177.5(W), 180.5(S), 181.5(T), V182(W), Q186(VW), G189(DE), 189.5(C), Q190(D),	1.5-fold

190.5(EQW), P191(DEFLSWY), 191.5(ILTY), P192(EFT), 192.5(T), T205(H), N270(CD), V372(I), G376(A), N382(D), Q385(W), T410(N), A425(C), I438(AV), Y444(F), L445(C), 445.5(DMNQST), S446(-CNQV), 446.5(ADEFILNPSTVW), R447(-ACDEFGILMNPQSTVWY), 447.5(DEFHILMNPQVWY), T448(-DEFHILMNPQVWY), 448.5(DEP), N449(ACDEFIMP), T450(E), S452(DF), T454(IM), 454.5(DE), T455(DE), 456.5(D), Q457(DE), 457.5(DE), S458(DE), 458.5(DEFW), R459(ACDEGLNPQSTV), L460(ACNSV), Q461(E), S463(N), Q464(AIV), A467(M), D469(E), I470(LM), R471(ACKMQST), D472(Y), Q473(H), C482(M), Y483(V), R484(IKLQ), Q485(C), Q486(DEN), R487(ACDEFGHILMNPQSTVWY), V488(CFMWY), 488.5(D), S489(ADEGMPQW), K490(ACDEFGHILNPQSTVWY), 490.5(DV), T491(DEMQW), 491.5(DEINPQT), S492(E), 492.5(DELQV), A493(EM), 493.5(DN), 494.5(DE), N495(ADEILPQVW), 495.5(DEFWY), N496(ACDEFGHILMVWY), 496.5(DE), N497(-ELV), 497.5(DEMQ), S498(ADEFGLMQWY), 498.5(DFGLMQS), 499.5(ADELMNPQSTV), Y500(-AELNPQSW), 500.5(EGLMNQST), S501(-CDEILMNPTV), 501.5(ACDEGHILMNSTVW), 502.5(ADEFILMSTVWY), T503(PV), 503.5(DEILMNTVW), G504(ACDEFIMVWY), 504.5(CEFILMSTVW), A505(E), 505.5(EIMV), T506(ACILMNV), 506.5(ACV), K507(-CFHILMNQSTVWY), 510.5(K), N511(D), R513(V), L516(ACSTV), V517(I), H526(ACDEGILMNPQSTV), K527(FHR), K532(-AFGILMNPQSTVWY), 532.5(E), F533(ACDEGILMNSTV), 533.5(D), Q536(-CPY), 536.5(CV), S537(-CDGNTY), G538(-), T550(D), N551(E), R566(ACGNSTVW), V571(ES), Q575(GIL), 577.5(E), S578(DEILWY), V579(ACGSY), 579.5(DE), S580(-DENPQ), 580.5(DE), T581(-DENP), 581.5(DEQ), N582(-ACDEFILMPQTVWY), 582.5(GP), L583(DEGIP), 583.5(DPQV), Q584(DEIV), 584.5(ADEFGILMQSTVY), R585(-ADEFGHILMNPQSTVWY), 585.5(ADEFGILMNPQSTVY), G586(-M), 586.5(ADEFGILMNPQSTV), N587(-DEGILMPQTV), 587.5(ADEFILMNQSTVY), R588(-ACDEFGHILMNPQSTVWY), 588.5(DEILMTV), Q589(ADEPSTV), 589.5(ADEFNPTV), A590(DEGIPV), 590.5(ADEGPST), A591(DEFILMTVY), 591.5(ACDEFGILMNPQSTV), T592(-ACDEGNPSY), 592.5(ACDEFGILMNQSTVWY), A593(-DE), 593.5(ACDEFGILMNPQSTVWY), D594(E), 594.5(ADEFHILMPQTVWY), V595(ACEGHLMNPT), 595.5(CDEILV), N596(CDE), T597(DEGHINQVW), Q598(ACEFVY), V600(L), L601(IMY), 662.5(F), 663.5(Q), V708(W)	
P29(AV), 34.5(A), 37.5(AEGV), H38(AEGV), 38.5(A), Q101(H), R124(N), P135(DW), 138.5(E), A139(E), P140(-), K142(I), P150(Y), 150.5(Y), 181.5(T), V182(W), Q186(W), 191.5(Y), N270(D), 445.5(DQ), 446.5(DEN), R447(ACDEILMNPQSTVW), 447.5(DEFHILMNPQWY), T448(-DEFHILPQW), 448.5(DE), N449(ADEF), T450(E), T454(M), 454.5(DE), T455(E), Q457(DE), S458(DE), 458.5(DEW), R459(ACDEPQTV), L460(NS), Q461(E), D469(E), R471(ACKMQST), Y483(V), R484(ILQ), Q485(C), Q486(DEN), R487(ACDEGHILMNPQSTVWY), V488(FMWY), S489(DEGW), K490(ACDEGHLNPQSTVWY), T491(Q), 491.5(DE), S492(E), 492.5(DEQ), A493(E), 493.5(D), 494.5(DE), N495(DEIP), 495.5(DEFWY), N496(DEFGHIMW), 496.5(DE), N497(EV), 497.5(DEMQ), S498(DEFGLMWY), 498.5(DFLMQ), 499.5(ADEMNPQS), Y500(-AELNPQS), 500.5(EGMNQST), S501(ILMNTV), 501.5(ACDEGHILNSTVW), 502.5(ADEFVWY), T503(PV), 503.5(DELTV), G504(DEFMW), 504.5(FIVW), A505(E), 505.5(EI), T506(ILMNV), 506.5(V), K507(-CFHILMNQSTVWY), 510.5(K), R513(V), L516(AST), H526(ACEGIMNQTV), K527(FH),	2-fold

K532(AFGILMPQSTVWY), F533(ACDEGISTV), Q536(-P), 536.5(V), S537(-DNY), G538(-), R566(ACW), V571(E), Q575(IL), 577.5(E), S578(DEIWY), V579(A), 579.5(DE), S580(DENQ), 580.5(DE), T581(-DEN), 581.5(DEQ), N582(-DEFILMPTVWY), L583(D), 583.5(DQ), Q584(DEV), 584.5(ADEFILMQSTVY), R585(-ADFGHILMNPQSTVWY), 585.5(ADEFIMNPQSTVY), 586.5(ADEFGILMPQSTV), N587(DEGILMPQTV), 587.5(ADEFILMQTV), R588(-ACDEFGHILMNPQSTVWY), 588.5(DEILMV), Q589(ADEPSTV), 589.5(ADEFNPTV), A590(DEGP), 590.5(ADEGPS), A591(DEFILMTVY), 591.5(ADEFGILMNPQSTV), T592(DEGY), 592.5(ACDEFGILMNSTVWY), A593(-DE), 593.5(ACDEFGILMNSTWY), 594.5(ADEFILMPQTVWY), V595(AGHLMN), 595.5(CDIV), N596(DE), T597(DEINQVW), Q598(CFVY), L601(Y)	
448.5(D), S458(E), R471(AMST), R484(ILQ), Q486(E), R487(CGILPQSTVY), V488(Y), K490(E), N495(E), 495.5(D), N496(DEF), 496.5(DE), 497.5(E), S498(D), 498.5(Q), S501(IL), 501.5(DE), K507(CFHILMSTVWY), Q536(-), S537(-), 577.5(E), S578(DE), 579.5(DE), S580(E), 580.5(E), T581(DE), N582(FIPW), Q584(DE), 584.5(D), R585(FIVWY), 585.5(ADNY), 586.5(EILMPV), N587(M), 587.5(DILV), R588(ADFHILMNPSTVWY), 588.5(DE), Q589(DP), 589.5(P), A590(DE), 590.5(DEGP), A591(DE), 591.5(DEFILMV), T592(DE), 592.5(DEFNSW), A593(DE), 593.5(DE), 594.5(DEFV), 595.5(CV), N596(D)	5-fold
R471(AMS), R487(I), K507(CIVWY), S578(D), 580.5(E), T581(DE), N582(F), R588(FL), 590.5(D), 591.5(DE), T592(DE), 592.5(D), 593.5(D), 594.5(D)	10-fold

[0083] In one embodiment, a mutation in the viral capsid polypeptide that alters viral tropism as described herein, is combined with a mutation or mutations that increase viral packaging (e.g., any mutation of Table 16).

[0084] In another embodiment, a mutation in the viral capsid polypeptide that alters viral tropism as described herein, is combined with a mutation in the region of amino acids selected the group consisting of: 34-38 of SEQ ID NO: 1, 133-152 of SEQ ID NO: 1, 188-194 of SEQ ID NO: 1, and 654-662 of SEQ ID NO: 1 that increases viral packaging.

[0085] In yet another embodiment, a mutation in the viral capsid polypeptide that alters viral tropism, as described herein, is combined with any non-positive amino acid insertion, substitution, or deletion in the region of amino acids selected the group consisting of: 442-452 of SEQ ID NO: 1, 489-506 of SEQ ID NO: 1, 541-551 of SEQ ID NO: 1, and 577-596 of SEQ ID NO: 1 that increases viral packaging.

[0086] Any region is the packaging heat map that tolerates change, e.g, neutral or posistive regions, can potentially tolerate the insertion of additional functional peptide sequences, e.g., an eptitope, a tag, a ligand, or other structural sequence that would not necessarily interrupt packaging of a virus.

Methods for delivering nucleic acid

[0087] Provide herein is a method of delivering a nucleic acid to a cell comprising contacting a cell with a viral particle comprising any of the viral capsid polypeptides described herein. In one embodiment, the contacting occurs *in vitro.* In one embodiment, the contacting occurs *ex vivo.* In another embodiment, the contacting occurs *in vivo,* e.g., via local or systemic administration.

[0088] In one embodiment, the delivering of a nucleic acid is at least 1.1-fold more efficient as compared to a wild-type viral capsid polypeptide. In one embodiment, the the delivering of a nucleic acid is at least 1.5-fold, at least 2-fold, at least 4-fold, at least 5-fold, at least lO-fold, or more, more efficient as compared to a wild-type viral capsid polypeptide. Methods for measuring tropism are described herein above.

[0089] In one aspect, a nucleic acid is delivered to a blood cell by contacting a blood cell with a viral particle comprising a viral capsid polypeptide comprising a mutation of Table 1. The cell can be any type blood cell. Exemplary blood cells include, but are not limited to, red blood cells, platelets, neutrophils, eosinophils, basophils, lymphocytes, or monocytes.

[0090] In one aspect, a nucleic acid is delivered to a heart cell by contacting a heart cell with a viral particle comprising a viral capsid polypeptide comprising a mutation of Table 2. Exemplary heart cells include, but are not limited to, cardiomyocyte, endocardial cells, or cardiac smooth muscle cells.

[0091] In one aspect, a nucleic acid is delivered to a kidney cell by contacting a kidney cell with a viral particle comprising a viral capsid polypeptide comprising a mutation of Table 3. Exemplary kidney cells include, but are not limited to, kidney glomerulus parietal cells, kidney glomerulus podocytes, kidney proximal tubule brush border cells, loop of Henle thin segment cells, thick ascending limb cells, kidney distal tubule cells, collecting duct principal cells, collecting duct intercalated cells, and interstitial kidney cells.

[0092] In one aspect, a nucleic acid is delivered to a liver cell by contacting a liver cell with a viral particle comprising a viral capsid polypeptide comprising a mutation of Table 4. Exemplary liver cells include, but are not limited to, parenchymal cells, non-parenchymal cells, sinusoidal endothelial cells, phagocytic Kupffer cells, hepatic stellate cells, and intrahepatic lymphocytes.

[0093] In one aspect, a nucleic acid is delivered to a lung cell by contacting a lung cell with a viral particle comprising a viral capsid polypeptide comprising a mutation of Table 5. Exemplary lung cells include, but are not limited to, bronchioles, lung epithelial cells, lung smooth muscle cells, and alveoli.

[0094] In one aspect, a nucleic acid is delivered to a spleen cell by contacting a spleen cell with a viral particle comprising a viral capsid polypeptide comprising a mutation of Table 6. Exemplary spleen cells include, but are not limited to, splenic endothelial cells and splenic fibroblasts.

Method for reducing viral tropism

[0095] One aspect of the technology described herein is a method for reducing tissue tropism of a virus comprising modifying a viral capsid polypeptide corresponding to the viral capsid polypeptide of

SEQ ID NO: 1 by introducing a mutation set out in any of Tables 7-9. In one embodiment, the viral tropism for liver, spleen, or blood is reduced.

[0096] In one embodiment, the method for reducing viral tropism further comprises any mutation, or combination thereof, as described herein, that increases tropism for a tissue other than the tissue for which the tropism is reduced. For example, a viral capsid polypeptide bearing a mutation which reduces tropism for liver is combined a mutation that increases tropism for kidney. In this example, it is contemplated that this combination of mutations will result in increased tropism for kidney.

[0097] Further, one aspect provides a method of increasing delivery of a nucleic acid to a cell of a kidney, heart, or lung, comprising contacting a cell of a kidney, heart, or lung with a viral particle comprising a viral capsid polypeptide comprising a mutation that reduces delivery of a nucleic acid to a cell of a liver, blood, or spleen. In one embodiment, the mutation that reduces delivery of a nucleic acid to a cell of a liver, blood, or spleen is selected from any of Tables 7-9. In one embodiment, the contacting is performed *in vivo,* e.g., via local or systemic administration.

[0098] Another aspect provides a method of delivering a nucleic acid to a lung cell comprising contacting a lung cell with a viral particle comprising a viral capsid polypetide comprising a mutation of Table 5 and a mutation selected from any of Tables 7-9. In one embodiment, the contacting is performed *in vivo,* e.g., via local or systemic administration.

[0099] Another aspect provides a method of delivering a nucleic acid to a heart cell, the method comprising contacting a heart cell with a viral particle comprising a viral capsid polypetide comprising a mutation of Table 2 and a mutation selected from any of Tables 7-9. In one embodiment, the contacting is performed *in vivo,* e.g., via local or systemic administration.

[00100] Yet another aspect provides a method of delivering a nucleic acid to a kidney cell comprising contacting a kidney cell with a viral particle comprising a viral capsid polypetide comprising a mutation of Table 3 and a mutation selected from any of Tables 7-9. In one embodiment, the contacting is performed *in vivo,* e.g., via local or systemic administration.

[00101] The above disclosure generally describes the present invention. All references disclosed herein are expressly incorporated by reference. A more complete understanding can be obtained by reference to the following specific examples which are provided herein for purposes of illustration only, and are not intended to limit the scope of the invention.

[00102] Some embodiments of the technology described herein can be defined according to any of the following numbered paragraphs:

1. A viral capsid polypeptide bearing a mutation relative to SEQ ID NO: 1 (WT AAV2) that alters tissue tropism of a virus comprising the viral capsid polypeptide, wherein the mutation is selected from the mutations in any one of Tables 1-9.
2. The viral capsid polypeptide of paragraph 1, wherein the tissue is heart, kidney, liver, lung, spleen, or blood.

3. The viral capsid polypeptide of any of the proceeding paragraphs, wherein the tropism to the tissue is increased.
4. The viral capsid polypeptide of any of the proceeding paragraphs, wherein the tropism to the tissue is decreased.
5. A nucleic acid encoding the viral capsid polypeptide of any of the proceeding paragraphs.
6. A viral particle comprising a viral capsid polypeptide of any of the proceeding paragraphs.
7. A viral capsid polypeptide bearing a mutation that corresponds to a mutation of the polypeptide of SEQ ID NO: 1, the mutation selected for the group consisting of the mutations in Tables 1-9 relative to SEQ ID NO: 1.
8. A viral capsid polypeptide comprising a region corresponding to the amino acid sequence of SEQ ID NO: 2, wherein the region corresponding to the amino acid sequence of SEQ ID NO: 2 comprises a mutation relative to SEQ ID NO: 2 that alters tissue tropism of a virus comprising the viral capsid polypeptide, wherein the mutation is selected from the mutations in any one of Tables 10-15
9. The viral capsid polypeptide of any of the proceeding paragraphs, wherein the tissue is heart, kidney, liver, lung, spleen, or blood.
10. The viral capsid polypeptide of any of the proceeding paragraphs, wherein the tropism to the tissue is increased.
11. The viral capsid polypeptide of any of the proceeding paragraphs, wherein the tropism to the tissue is decreased.
12. A nucleic acid encoding the viral capsid polypeptide of any of the proceeding paragraphs.
13. A viral particle comprising a viral capsid polypeptide of any of the proceeding paragraphs.
14. A method of delivering a nucleic acid to a cell, the method comprising; contacting the cell with a viral particle comprising a viral capsid polypeptide of any of the proceeding paragraphs.
15. A method of delivering a nucleic acid to a blood cell, the method comprising; contacting a blood cell with a viral particle comprising a viral capsid polypeptide comprising a mutation of Table 1.
16. A method of delivering a nucleic acid to a heart cell, the method comprising; contacting a heart cell with a viral particle comprising a viral capsid polypeptide comprising a mutation of Table 2.

17. A method of delivering a nucleic acid to a kidney cell, the method comprising; contacting a kidney cell with a viral particle comprising a viral capsid polypeptide comprising a mutation of Table 3.
18. A method of delivering a nucleic acid to a liver cell, the method comprising; contacting a liver cell with a viral particle comprising a viral capsid polypeptide comprising a mutation of Table 4.
19. A method of delivering a nucleic acid to a lung cell, the method comprising; contacting a lung cell with a viral particle comprising a viral capsid polypeptide comprising a mutation of Table 5.
20. A method of delivering a nucleic acid to a spleen cell, the method comprising; contacting a spleen cell with a viral particle comprising a viral capsid polypeptide comprising a mutation of Table 6.
21. The method of any of the proceeding paragraphs, wherein the delivering is at least 1.1-fold more efficient as compared to a wild-type viral capsid polypeptide.
22. A method of reducing tissue tropism of a virus comprising a viral capsid polypeptide corresponding to the viral capsid polypeptide of SEQ ID NO: 1, the method comprising introducing a mutation set out in any of Tables 7-9.
23. A method of increasing delivery of a nucleic acid to a cell of a kidney, heart, or lung, the method comprising; contacting a cell of a kidney, heart, or lung with a viral particle comprising a viral capsid polypeptide comprising a mutation that reduces delivery of a nucleic acid to a cell of a liver, blood, or spleen.
24. The method of paragraph 23, wherein the mutation that reduces delivery of a nucleic acid to a cell of a liver, blood, or spleen is selected from any of Tables 7-9.
25. A method of delivering a nucleic acid to a lung cell, the method comprising; contacting a lung cell with a viral particle comprising a viral capsid polypetide comprising a mutation of Table 5 and a mutation selected from any of Tables 7-9.
26. A method of delivering a nucleic acid to a heart cell, the method comprising; contacting a heart cell with a viral particle comprising a viral capsid polypetide comprising a mutation of Table 2 and a mutation selected from any of Tables 7-9.
27. A method of delivering a nucleic acid to a kidney cell, the method comprising; contacting a kidney cell with a viral particle comprising a viral capsid polypetide comprising a mutation of Table 3 and a mutation selected from any of Tables 7-9.
28. An AAV2 capsid polypeptide comprising a mutation in the region of amino acids selected the group consisting of: 440-460 of SEQ ID NO: 1, 475-505 of SEQ ID NO: 1, 518-532 of SEQ ID NO: 1, and 560-590 of SEQ ID NO: 1 that alters tissue tropism of a virus comprising the viral capsid polypeptide.

29. The AAV2 capsid polypeptide of paragraph 28, wherein the tissue is kidney, liver, or lung.
30. The AAV2 capsid polypeptide of paragraph 28, wherein the tropism is increased.
31. An AAV2 capsid polypeptide comprising a mutation in the region of amino acids 561-588 of SEQ ID NO: 1 that increases tissue tropism of a virus to the kidney, wherein the mutated region of amino acid 561-588 of SEQ ID NO: 1 has a sequence selected from the group consisting of: DEEEIATTNPVATEQYGDVSENLMHFQN (SEQ ID NO: 3); DEEEIRQTNPVATEGYGEVSTNLMHGNK (SEQ ID NO: 4); DEEEIRTTNPVATEQYGIVnStTNLNEGNR (SEQ ID NO: 5); DEEEIRTTNPVATECYGSVSTDLQSGNL (SEQ ID NO: 6); DENEIRTTNPVATEIYGSVSTeNLQNnGdNR (SEQ ID NO: 7); DEEEIRTTNPVATEQYGSVSeTNpLvQNGdDR (SEQ ID NO: 8); DEEEIRTTNPVATEQYGDVSENLMHFQN (SEQ ID NO: 9).
32. An AAV2 capsid polypeptide comprising a mutation in the region of amino acids 561-588 of SEQ ID NO: 1 that increases tissue tropism of a virus to the liver, wherein the mutated region of amino acid 561-588 of SEQ ID NO: 1 has a sequence selected from the group consisting of: DEEEIRTTNPVATEQYGVVSDNLQRGNR (SEQ ID NO: 10); DECEIRTTNPVATEQYGSVGENLQRGNR (SEQ ID NO: 11); DEEEIRTTNPVATEQYGVVSENLQRGNR (SEQ ID NO: 12); DESEITTTNPVATEQYGWVSTNQQRGNR (SEQ ID NO: 13); HELEIATTNPVATEQYGSASTNIQRGNR (SEQ ID NO: 14); DEEEIATTNPVATEQYGGVSTNLQRGNR (SEQ ID NO: 15).
33. An AAV2 capsid polypeptide comprising a mutation in the region of amino acids 561-588 of SEQ ID NO: 1 that increases tissue tropism of a virus to the lung, wherein the mutated region of amino acid 561-588 of SEQ ID NO: 1 has a sequence selected from the group consisting of: DEEEIVTTNPVATEQYGNVSTNLQRGNR (SEQ ID NO: 16); DEDEISTTNPVATEQYGSCSTNLQRGNR (SEQ ID NO: 17); QEEEIRTTNPVATEQYGSVSTNLQRGDR (SEQ ID NO: 18); NEEEIRTTNPCATEVYGSVSTNLQRGNR (SEQ ID NO: 19); DEQEIVTTNPVATEVYGTVSTNLQRGNR (SEQ ID NO: 20).
34. A method of altering tropism of a virus comprising a capsid polypeptide corresponding to the polypeptide of SEQ ID NO: 1, the method comprising introducing a mutation in at least 2 regions selected from the group consisting of: amino acids 440-460 of SEQ ID NO: 1, amino acids 475-505 of SEQ ID NO: 1, amino acids 518-532 of SEQ ID NO: 1, and amino acids 560-590 of SEQ ID NO: 1.

35. A viral capsid polypeptide bearing a mutation relative to SEQ ID NO: 1 (WT AAV2) that alters packaging efficiency of a virus comprising the viral capsid polypeptide, wherein the mutation is selected from the mutations in Table 16.

[00103] ***References***

1. Adachi, Kei, Enoki, Tatsuji, Kawano, Yasuhiro, Veraz, Michael, and Nakai Hiroyuki, *Drawing a high-resolution functional map of adeno-associated virus capsid by massively parallel sequencing.* Nature Communications 5, 3075 (2014)

2. Grimm, D. and Zolotukhin, S. *EPluribus Unum: 50 Years of Research, Millions of Viruses, and One Goal-Tailored Acceleration of AAV Evolution.* Molecular Therapy 23, 1819—1831 (2015).

CLAIMS

1. A viral capsid polypeptide bearing a mutation relative to SEQ ID NO: 1 (WT AAV2) that alters tissue tropism of a virus comprising the viral capsid polypeptide, wherein the mutation is selected from the mutations in any one of Tables 1-9.
2. The viral capsid polypeptide of claim 1, wherein the tissue is heart, kidney, liver, lung, spleen, or blood.
3. The viral capsid polypeptide of claim 1, wherein the tropism to the tissue is increased.
4. The viral capsid polypeptide of claim 1, wherein the tropism to the tissue is decreased.
5. A nucleic acid encoding the viral capsid polypeptide of any of claims 1-4.
6. A viral particle comprising a viral capsid polypeptide of any of claims 1-4.
7. A viral capsid polypeptide bearing a mutation that corresponds to a mutation of the polypeptide of SEQ ID NO: 1, the mutation selected for the group consisting of the mutations in Tables 1-9 relative to SEQ ID NO: 1.
8. A viral capsid polypeptide comprising a region corresponding to the amino acid sequence of SEQ ID NO: 2, wherein the region corresponding to the amino acid sequence of SEQ ID NO: 2 comprises a mutation relative to SEQ ID NO: 2 that alters tissue tropism of a virus comprising the viral capsid polypeptide, wherein the mutation is selected from the mutations in any one of Tables 10-15
9. The viral capsid polypeptide of claim 1, wherein the tissue is heart, kidney, liver, lung, spleen, or blood.
10. The viral capsid polypeptide of claim 8, wherein the tropism to the tissue is increased.
11. The viral capsid polypeptide of claim 8, wherein the tropism to the tissue is decreased.
12. A nucleic acid encoding the viral capsid polypeptide of any of claims 8-11.
13. A viral particle comprising a viral capsid polypeptide of any of claims 8-11.
14. A method of delivering a nucleic acid to a cell, the method comprising; contacting the cell with a viral particle comprising a viral capsid polypeptide of claims 1-4, or 8-11.
15. A method of delivering a nucleic acid to a blood cell, the method comprising; contacting a blood cell with a viral particle comprising a viral capsid polypeptide comprising a mutation of Table 1.
16. A method of delivering a nucleic acid to a heart cell, the method comprising; contacting a heart cell with a viral particle comprising a viral capsid polypeptide comprising a mutation of Table 2.
17. A method of delivering a nucleic acid to a kidney cell, the method comprising; contacting a kidney cell with a viral particle comprising a viral capsid polypeptide comprising a mutation of Table 3.
18. A method of delivering a nucleic acid to a liver cell, the method comprising; contacting a liver cell with a viral particle comprising a viral capsid polypeptide comprising a mutation of Table 4.
19. A method of delivering a nucleic acid to a lung cell, the method comprising; contacting a lung cell with a viral particle comprising a viral capsid polypeptide comprising a mutation of Table 5.

20. A method of delivering a nucleic acid to a spleen cell, the method comprising; contacting a spleen cell with a viral particle comprising a viral capsid polypeptide comprising a mutation of Table 6.
21. The method of any of claims 14-20, wherein the delivering is at least 1.1-fold more efficient as compared to a wild-type viral capsid polypeptide.
22. A method of reducing tissue tropism of a virus comprising a viral capsid polypeptide corresponding to the viral capsid polypeptide of SEQ ID NO: 1, the method comprising introducing a mutation set out in any of Tables 7-9.
23. A method of increasing delivery of a nucleic acid to a cell of a kidney, heart, or lung, the method comprising; contacting a cell of a kidney, heart, or lung with a viral particle comprising a viral capsid polypeptide comprising a mutation that reduces delivery of a nucleic acid to a cell of a liver, blood, or spleen.
24. The method of claim 23, wherein the mutation that reduces delivery of a nucleic acid to a cell of a liver, blood, or spleen is selected from any of Tables 7-9.
25. A method of delivering a nucleic acid to a lung cell, the method comprising; contacting a lung cell with a viral particle comprising a viral capsid polypetide comprising a mutation of Table 5 and a mutation selected from any of Tables 7-9.
26. A method of delivering a nucleic acid to a heart cell, the method comprising; contacting a heart cell with a viral particle comprising a viral capsid polypetide comprising a mutation of Table 2 and a mutation selected from any of Tables 7-9.
27. A method of delivering a nucleic acid to a kidney cell, the method comprising; contacting a kidney cell with a viral particle comprising a viral capsid polypetide comprising a mutation of Table 3 and a mutation selected from any of Tables 7-9.
28. An AAV2 capsid polypeptide comprising a mutation in the region of amino acids selected the group consisting of: 440-460 of SEQ ID NO: 1, 475-505 of SEQ ID NO: 1, 518-532 of SEQ ID NO: 1, and 560-590 of SEQ ID NO: 1 that alters tissue tropism of a virus comprising the viral capsid polypeptide.
29. The AAV2 capsid polypeptide of claim 28, wherein the tissue is kidney, liver, or lung.
30. The AAV2 capsid polypeptide of claim 28, wherein the tropism is increased.
31. An AAV2 capsid polypeptide comprising a mutation in the region of amino acids 561-588 of SEQ ID NO: 1 that increases tissue tropism of a virus to the kidney, wherein the mutated region of amino acid 561-588 of SEQ ID NO: 1 has a sequence selected from the group consisting of:
    DEEEIATTNP VATEQY GDV SENLMHFQN (SEQ ID NO: 3);
    DEEEIRQTNPVATEGY GEV STNLMHGNK (SEQ ID NO: 4);
    DEEEIRTTNPVATEQY GIVnStTNLNEGNR (SEQ ID NO: 5);
    DEEEIRTTNPVATECY GSV STDLQSGNL (SEQ ID NO: 6);
    DENEIRTTNPVATEIY GSV STeNLQNnGdNR (SEQ ID NO: 7);

DEEEIRTTNPVATEQYGSVSeTNpLvQNGdDR (SEQ ID NO: 8);

DEEEIRTTNPVATEQYGDVSENLMHFQN (SEQ ID NO: 9).

32. An AAV2 capsid polypeptide comprising a mutation in the region of amino acids 561-588 of SEQ ID NO: 1 that increases tissue tropism of a virus to the liver, wherein the mutated region of amino acid 561-588 of SEQ ID NO: 1 has a sequence selected from the group consisting of:
DEEEIRTTNPVATEQYGVVSDNLQRGNR (SEQ ID NO: 10);
DECEIRTTNPVATEQYGSVGENLQRGNR (SEQ ID NO: 11);
DEEEIRTTNPVATEQYGVVSENLQRGNR (SEQ ID NO: 12);
DESEITTTNPVATEQYGWVSTNQQRGNR (SEQ ID NO: 13);
HELEIATTNPVATEQYGSASTNIQRGNR (SEQ ID NO: 14);
DEEEIATTNPVATEQYGGVSTNLQRGNR (SEQ ID NO: 15).

33. An AAV2 capsid polypeptide comprising a mutation in the region of amino acids 561-588 of SEQ ID NO: 1 that increases tissue tropism of a virus to the lung, wherein the mutated region of amino acid 561-588 of SEQ ID NO: 1 has a sequence selected from the group consisting of:
DEEEIVTTNPVATEQYGNVSTNLQRGNR (SEQ ID NO: 16);
DEDEISTTNPVATEQYGSCSTNLQRGNR (SEQ ID NO: 17);
QEEEIRTTNPVATEQYGSVSTNLQRGDR (SEQ ID NO: 18);
NEEEIRTTNPCATEVYGSVSTNLQRGNR (SEQ ID NO: 19);
DEQEIVTTNPVATEVYGTVSTNLQRGNR (SEQ ID NO: 20).

34. A method of altering tropism of a virus comprising a capsid polypeptide corresponding to the polypeptide of SEQ ID NO: 1, the method comprising introducing a mutation in at least 2 regions selected from the group consisting of: amino acids 440-460 of SEQ ID NO: 1, amino acids 475-505 of SEQ ID NO: 1, amino acids 518-532 of SEQ ID NO: 1, and amino acids 560-590 of SEQ ID NO: 1.

35. A viral capsid polypeptide bearing a mutation relative to SEQ ID NO: 1 (WT AAV2) that alters packaging efficiency of a virus comprising the viral capsid polypeptide, wherein the mutation is selected from the mutations in Table 16.

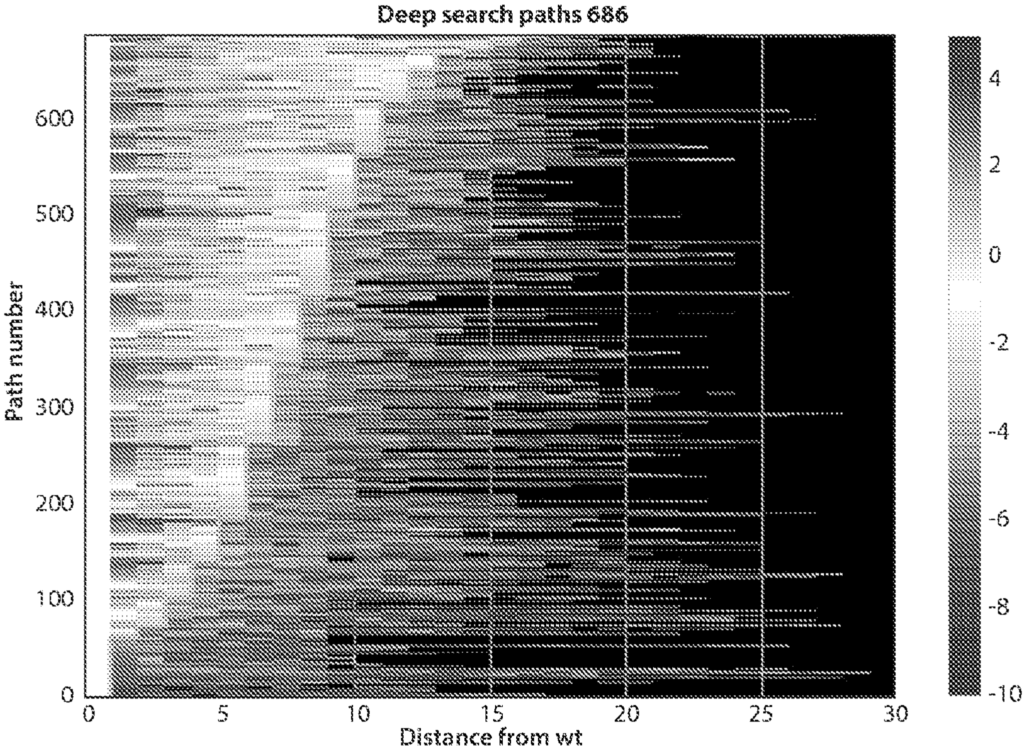
Deep search paths 686
Path number
0
100
200
300
400
500
600
Distance from wt
0
5
10
15
20
25
30
4
2
0
-2
-4
-6
-8
-10

FIG. 1

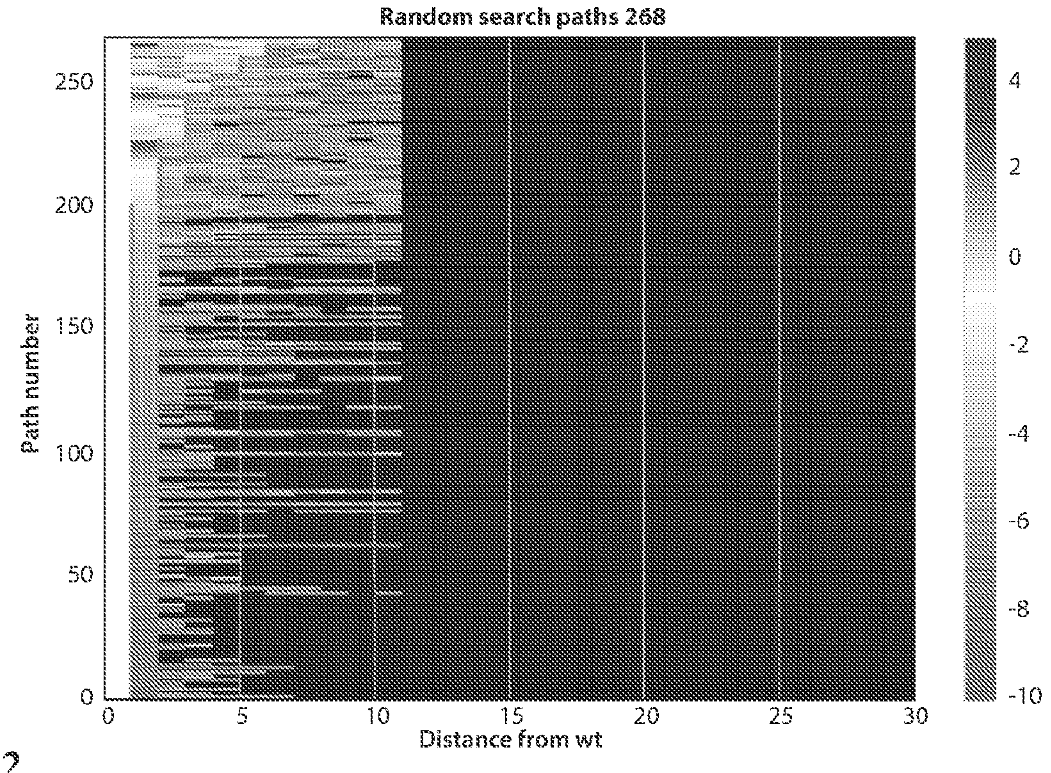
Random search paths 268
Path number
250
200
150
100
50
0
Distance from wt
0
5
10
15
20
25
30
4
2
0
-2
-4
-6
-8
-10

FIG. 2

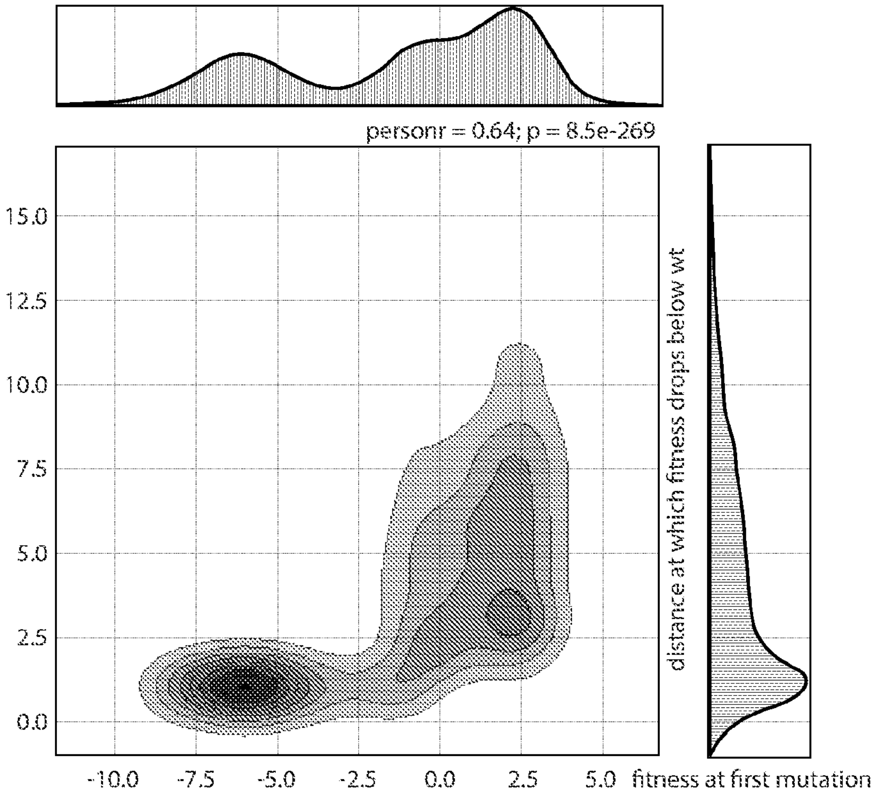
personr = 0.64; p = 8.5e-269
15.0
12.5
10.0
7.5
5.0
2.5
0.0
-10.0
-7.5
-5.0
-2.5
0.0
2.5
5.0
fitness at first mutation
distance at which fitness drops below wt

FIG. 3

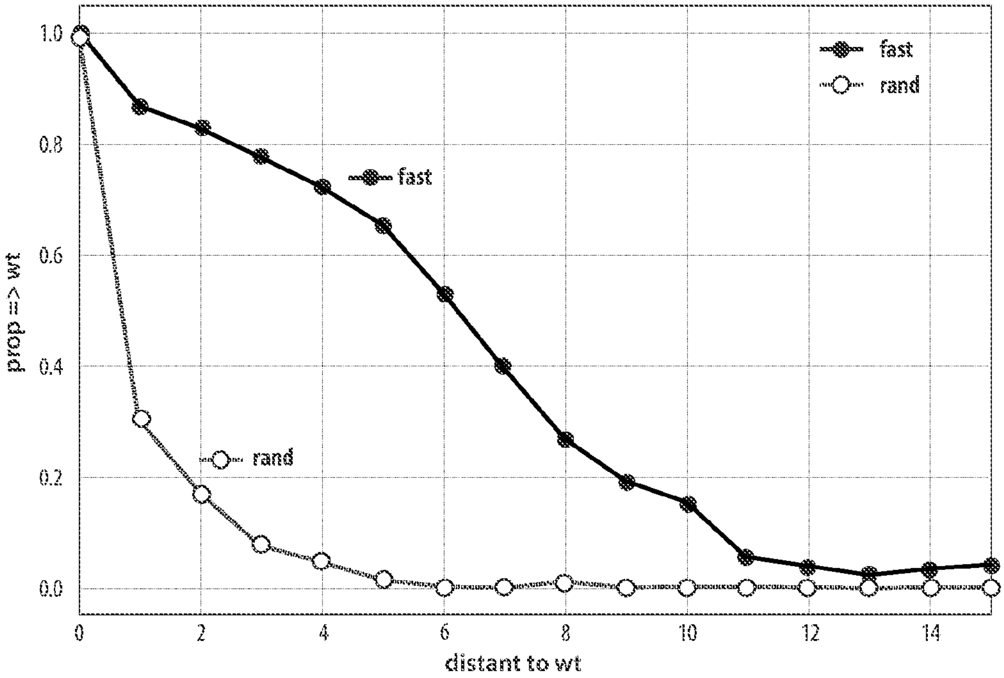
fast
rand
fast
rand
1.0
0.8
0.6
0.4
0.2
0.0
prop => wt
0
2
4
6
8
10
12
14
distant to wt

FIG. 4

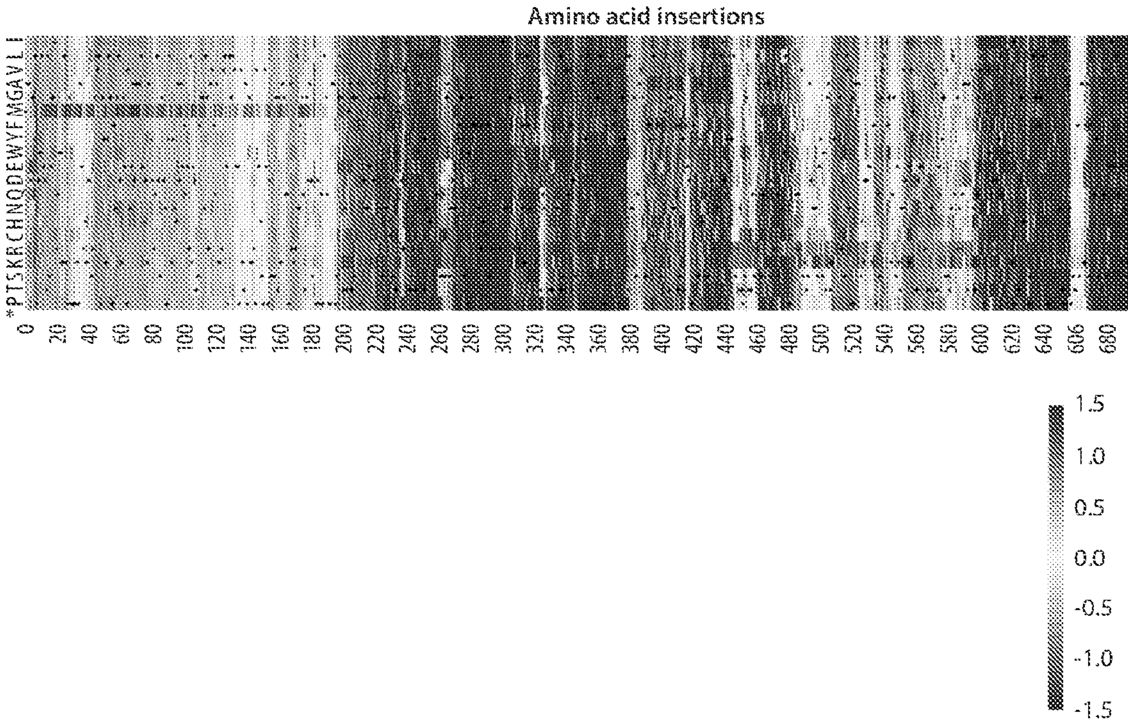
Amino acid insertions

FIG. 5

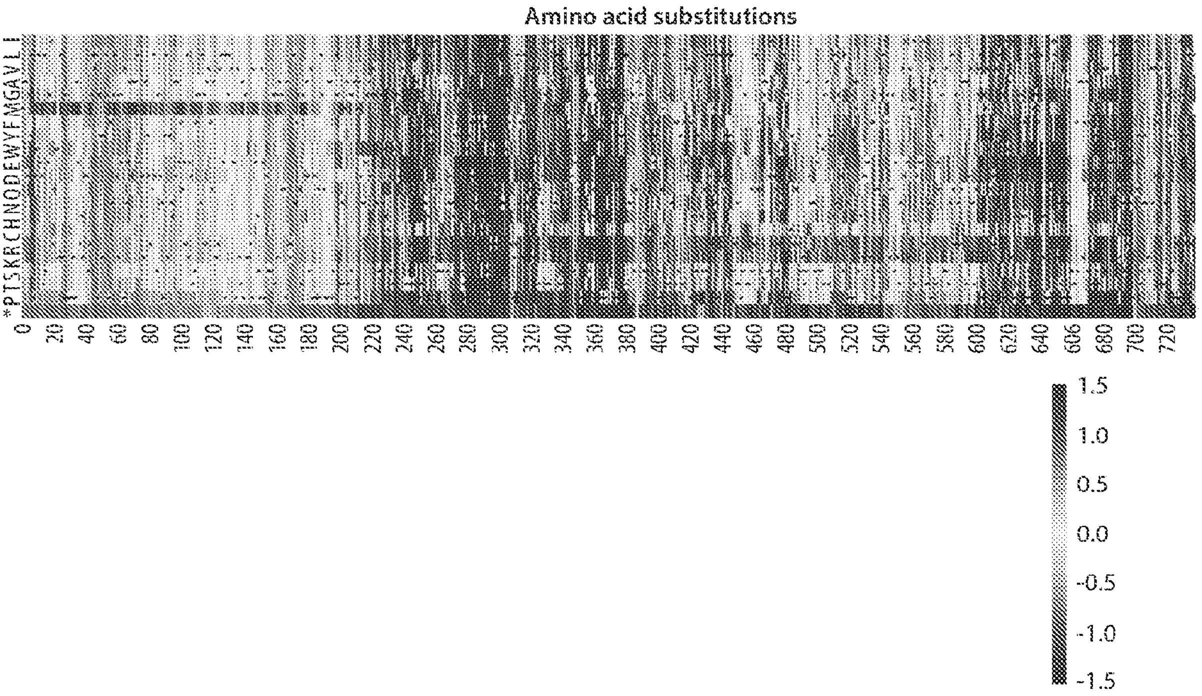
Amino acid substitutions
* P T S K R C H N Q D E W Y F M G A V L I
0
20
40
60
80
100
120
140
160
180
200
220
240
260
280
300
320
340
360
380
400
420
440
460
480
500
520
540
560
580
600
620
640
606
680
700
720
1.5
1.0
0.5
0.0
-0.5
-1.0
-1.5

FIG. 6

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 19/31307

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 31/7088, C07K 14/00 (2019.01)
CPC - A61K 31/7088, A61K 2039/525, C07K 14/005

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
See Search History Document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
See Search History Document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
See Search History Document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X ------ Y	WU et al. Mutational analysis of the adeno-associated virus type 2 (AAV2) capsid gene and construction of AAV2 vectors with altered tropism. Journal of Virology, 15 September 2000, Vol 74, No 18, pp. 8635-8647. entire document, especially abstract; p. 8643, col 1, para 2; p. 8645, col 2, para 2; p. 8636, col 1, para 5 to col 2, para 2; Tables 1 and 3	1-3, 5/(1-3), 6/(1-3), 7 ------ 4, 5/2, 6/2
Y	US 2009/0215879 A1 (DIPRIMIO et al.) 27 August 2009 (27.08.2009) abstract; para [0091]	4, 5/2, 6/2

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search 18 September 2019	Date of mailing of the international search report 10 OCT 2019
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 19/31307

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 14, 21
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

--continued on first extra sheet--

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-7 limited to D4(F) relative to SEQ ID NO: 1

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

--continued from Box III: Observations where unity of invention is lacking--

Group I+, claims 1-13, 28-33, 35, directed to a viral capsid polypeptide bearing a mutation, a nucleic acid encoding the viral capsid polypeptide, and a viral particle comprising a viral capsid polypeptide. The viral capsid will be searched to the extent that the mutation encompasses D4(F) relative to SEQ ID NO: 1 (the first mutation listed in Table 1). It is believed that claims 1-7 encompass this first named invention, and thus these claims will be searched without fee to the extent that the viral capsid encompass D4(F) relative to SEQ ID NO: 1. Additional viral capsid(s) will be searched upon the payment of additional fees. Applicants must specify the claims that encompass any additionally elected viral capsid(s). Applicants must further indicate, if applicable, the claims which encompass the first named invention, if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be searched. An exemplary election would be viral capsid comprising D13(HQ) relative to SEQ ID NO: 1 (the second mutation listed in Table 1), (claims 1-7).

[note, SEQ ID NO: 2 comprises residues 440-590 of SEQ ID NO: 1; Tables 2-16 do not comprise mutation D4(F); only Tables 1 and 3 have mutation D13(HQ)]

Group II+, claims 14-21, 23-27, directed to a method of delivering a nucleic acid to a cell, or of increasing delivery of a nucleic acid to a cell. Group II+ will be searched upon payment of additional fees. The method may be searched, for example, to encompass D4(F) relative to SEQ ID NO: 1 for an additional fee and election as such. It is believed that claims 14(in part), 15, 21(in part), 23 read on this exemplary invention. Additional variant(s) will be searched upon the payment of additional fees. Applicants must specify the claims that encompass any additionally elected variant(s). Failure to clearly identify how any paid additional invention fees are to be applied to the"+" group(s) will result in only the first claimed invention to be searched. Another exemplary election would be D13(HQ) relative to SEQ ID NO: 1 (claims 14(in part), 15, 17, 21(in part), 23).

Group III, claims 22 and 34, directed to a method of altering tissue tropism of a virus.

The inventions listed as Groups I+, II+ and III do not relate to a single special technical feature under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

Special technical features

Group I+ has the special technical feature of a viral capsid polypeptide bearing a mutation, a nucleic acid encoding the viral capsid polypeptide, or a viral particle comprising a viral capsid polypeptide, that is not required by Group II+ or III.

Group II+ has the special technical feature of contacting a cell with a viral particle comprising a viral capsid polypeptide, that is not required by Group I+ or III.

Group III has the special technical feature of altering tropism of a virus comprising a capsid polypeptide, the method comprising introducing a mutation, that is not required by Group I+ or II+.

The inventions of Group I+ and II+ each include the special technical feature of a unique amino acid sequence and mutation. Each amino acid sequence encodes a unique peptide, and is considered a distinct technical feature.

Common technical features

The inventions of Group I+, II+ and Group III share the common technical feature of an AAV2 viral capsid polypeptide bearing a mutation relative to wild type that alters tissue tropism of a virus comprising the viral capsid polypeptide.

No technical features are shared between the viral capsid polypeptide amino acid sequences of Group I+ or II+ and, accordingly, these groups lack unity a priori.

Additionally, even if Group I+ were considered to share the technical features of including: a viral capsid polypeptide bearing a mutation, a nucleic acid encoding the viral capsid polypeptide, and a viral particle comprising a viral capsid polypeptide, these shared technical features are previously taught by US 2009/0215879 A1 to Diprimio et al., (hereinafter Diprimio).

Additionally, even if Group II+ were considered to share the technical features of including: a method of increasing delivery of a nucleic acid to a cell of a kidney, heart, or lung, the method comprising; contacting a cell of a kidney, heart, or lung with a viral particle comprising a viral capsid polypeptide comprising a mutation that reduces delivery of a nucleic acid to a cell of a liver, blood, or spleen, these shared technical features are previously taught by Diprimio.

Diprimio teaches an AAV2 viral capsid polypeptide bearing a mutation relative to wild type that alters tissue tropism of a virus comprising the viral capsid polypeptide (para [0088] "the RGD sequence is substituted at amino acids 658 to 660, amino acids 660 to 662, or amino acids 662 to 664 of the native AAV2 capsid protein"; [0091] "a targeting sequence can be substituted into the HI loop (substitutions are as described hereinabove), e.g., to direct the tropism of the virus to a desired target tissue(s). Any suitable targeting sequence can be incorporated into the HI loop of the AAV capsid protein. Alternatively or additionally, a targeting sequence can be added at an orthogonal position (outside of the HI loop) to target the vector. For example, in embodiments of the invention, virus capsids and virus vectors comprising the modified AAV capsid proteins are detargeted from the liver").

--continud on next sheet--

--continued from previous sheet--

Diprimio teaches a viral capsid polypeptide bearing a mutation (para [0106]-[0109] "the AAV capsid protein to be modified can be derived from a naturally occurring AAV but further comprise one or more foreign sequences (e.g., that are exogenous to the native virus) that are inserted and/or substituted into the capsid protein"), a nucleic acid encoding the viral capsid polypeptide (para [0123] "The invention also provides nucleic acids (optionally, isolated nucleic acids) encoding the modified AAV virus capsids and capsid proteins of the invention"), and a viral particle comprising a viral capsid polypeptide (para [0067] "The virus vectors of the invention can also be duplexed parvovirus particles...genomes can be packaged into the virus capsids of the invention").
Diprimio teaches a method of increasing delivery of a nucleic acid to a cell of a kidney, heart, or lung, the method comprising; contacting a cell of a liver, kidney, heart, or lung with a viral particle comprising a viral capsid polypeptide comprising a mutation that reduces delivery of a nucleic acid to a cell of a liver, blood, or spleen (para [0012] "a method of administering a nucleic acid to a cell comprising contacting the cell with a virus vector or pharmaceutical formulation of this invention"; [0091] "Alternatively or additionally, a targeting sequence can be added at an orthogonal position (outside of the HI loop) to target the vector. For example, in embodiments of the invention, virus capsids and virus vectors comprising the modified AAV capsid proteins are detargeted from the liver"; [0121] "For example, the inventive capsids can be delivered to block cellular receptors on liver cells and a delivery vector can be administered subsequently or concurrently, which may reduce transduction of liver cells, and enhance transduction of other targets (e.g., skeletal muscle)").

As the technical features were known in the art at the time of the invention, they cannot be considered special technical features that would otherwise unify the groups.

Therefore, Group I+, II+ and III inventions lack unity under PCT Rule 13 because they do not share the same or corresponding special technical feature.