(12) STANDARD PATENT (11) Application No. **AU 2019369403 B2**
(19) AUSTRALIAN PATENT OFFICE

(54) Title
Compositions and methods for alpha-1-antitrypsin disorders

(51) International Patent Classification(s)
C07K 14/81 (2006.01) ***C12N 15/62*** (2006.01)
A61K 38/47 (2006.01)

(21) Application No: **2019369403** (22) Date of Filing: **2019.10.29**

(87) WIPO No: **WO20/092448**

(30) Priority Data

(31) Number	(32) Date	(33) Country
62/752,182	**2018.10.29**	**US**

(43) Publication Date: **2020.05.07**
(44) Accepted Journal Date: **2025.04.17**

(71) Applicant(s)
Spin Therapeutics, LLC

(72) Inventor(s)
SATO, Aaron;DESOUZA, Mark

(74) Agent / Attorney
K&L Gates, Level 25 South Tower 525 Collins Street, Melbourne, VIC, 3000, AU

(56) Related Art
WO 2013/003641 A2
WO 2016/069574 A1

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
07 May 2020 (07.05.2020)

WIPO | PCT

(10) International Publication Number
WO 2020/092448 A1

(51) International Patent Classification:
C07K 14/81 (2006.01) *A61K 38/47* (2006.01)
C12N 15/62 (2006.01)

(21) International Application Number:
PCT/US2019/058673

(22) International Filing Date:
29 October 2019 (29.10.2019)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
62/752,182 29 October 2018 (29.10.2018) US

(71) Applicant: **SPIN THERAPEUTICS, LLC** [US/US]; 2600 Tenth St., Suite 435, Berkeley, California 94710 (US).

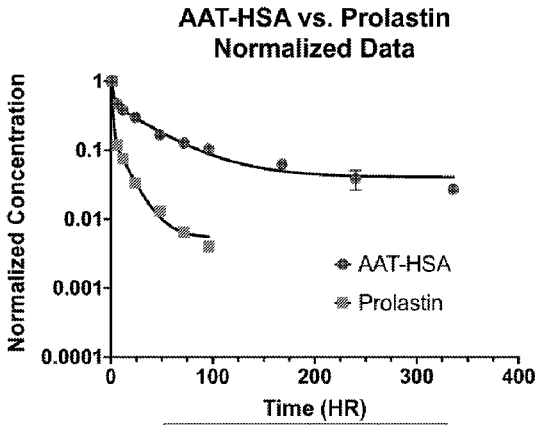
(72) Inventors: **SATO, Aaron**; c/o SPIN THERAPEUTICS, LLC, 2600 Tenth St., Suite 435, Berkeley, California 94710 (US). **DESOUZA, Mark**; c/o SPIN THERAPEUTICS, LLC, 2600 Tenth St., Suite 435, Berkeley, California 94710 (US).

(74) Agent: **ANDERTON, JR., H. Thomas** et al.; Squire Patton Boggs (US) LLP, 275 Battery Street, Suite 2600, San Francisco, California 94111 (US).

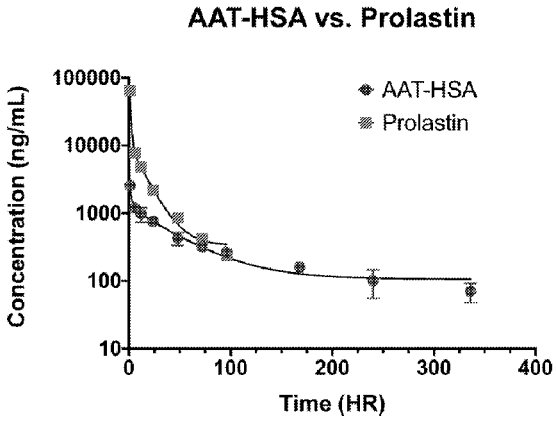
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS,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

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

(54) Title: COMPOSITIONS AND METHODS FOR ALPHA-1-ANTITRYPSIN DISORDERS



	AAT-HSA	Prolastin
Y0	1.339	2.291
Plateau	0.04047	0.005383
PercentFast	66.20	92.95
KFast	0.4832	0.9226
KSlow	0.02302	0.07099
Half Life (Slow)	30.12	9.764
Half Life (Fast)	1.435	0.7513
Tau (slow)	43.45	14.09
Tau (fast)	2.070	1.084
Rate constant ratio	20.99	13.00



	AAT-HSA	Prolastin
Y0	3493	145620
Plateau	105.7	332.7
PercentFast	66.50	92.90
KFast	0.5181	0.9002
KSlow	0.02354	0.07017
Half Life (Slow)	29.44	9.879
Half Life (Fast)	1.338	0.7700
Tau (slow)	42.48	14.25
Tau (fast)	1.930	1.111
Rate constant ratio	22.01	12.83

FIG. 12

(57) Abstract: Disclosed herein are compositions and methods useful for treating an alpha-1-antitrypsin deficiency.

[Continued on next page]

WO 2020/092448 A1

Declarations under Rule 4.17:

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

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

Published:

— *with international search report (Art. 21(3))*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

— *with sequence listing part of description (Rule 5.2(a))*

COMPOSITIONS AND METHODS FOR ALPHA-1-ANTITRYPSIN DISORDERS

BACKGROUND OF THE INVENTION

[0001] This application claims priority to 62/752,182 filed October 29, 2018, which is incorporated by reference herein.

[0002] Serpins are a superfamily of proteins with similar structures that were first identified for their ability to inhibit proteases. The name serpin was originally coined because the first serpins to be identified were found to act on chymotrypsin-like serine proteases. As a result, the acronym serpin was chosen to incorporate the first couple of letters of the word(s) serine protease inhibitors.

[0003] Serpins are interesting because of their unusual mechanism of action in which they irreversibly inhibit a target protease by undergoing a large conformational change to disrupt an active site on the target protease. Protease inhibition by serpins controls an array of biological processes, including coagulation and inflammation. The mechanism of protease inhibition confers certain advantages but also has drawbacks. One major drawback is that serpins are especially vulnerable to a mutation that can result in serpinopathies, such as protein misfolding and the formation of inactive long-chain polymers.

[0004] Alpha-1-antitrypsin or α_1-antitrypsin ("A1AT," "A1A," or "AAT") is a protein belonging to the serpin superfamily. It is encoded in humans by the *SERPINA1* gene, which has 4 coding exons and 3 untranslated exons and resides on chromosome 14 at q31-31.2. It is also known as alpha$_1$–proteinase inhibitor or alpha$_1$-antiproteinase because it inhibits various proteases, not just trypsin. It is a 52-kD glycoprotein that functions as an antiprotease. It has a single chain of 394 amino acids with a signal peptide of 24 amino acids in length attached. As a type of enzyme inhibitor, it protects tissues from enzymes of inflammatory cells, especially neutrophil elastase and proteinase 3 ("PR3"), and has a normal reference range in blood of 1.5–3.5 g/L. The concentration of alpha-1-antitrypsin can rise manyfold upon acute inflammation.

[0005] Neutrophil elastase is a serine protease that destroys elastase, the rubberlike macromolecule that provides elastic recoil to the lung. When the blood contains inadequate amounts of alpha-1-antitrypsin or functionally defective alpha-1-antitrypsin, neutrophil

elastase is excessively free to break down elastin, degrading the elasticity of the lungs. Degradation of elasticity results in respiratory complications, such as chronic obstructive pulmonary disease.

[0006] PR3 is a serine protease enzyme expressed mainly in neutrophil granulocytes. Its exact role in the function of the neutrophil is unknown, but, in human neutrophils, proteinase 3 contributes to the proteolytic generation of antimicrobial peptides.

[0007] Alpha-1-antitrypsin deficiency ("AATD") is a genetic disorder that causes defective production of alpha-1-antitrypsin. AATD is an autosomal recessive disorder caused by reduced serum levels of AATD. The disease leads to a decrease of alpha-1-antitrypsin. The disease often causes lung and liver disease and is referred to as hereditary pulmonary emphysema. AATD is one of the most common lethal hereditary disorders of caucasians of European descent.

[0008] There are several forms and degrees of alpha-1-antitrypsin deficiency and the form and degree depend on whether the sufferer has one or two copies of a defective allele. Severe alpha-1-antitrypsin deficiency can cause panacinar emphysema or COPD-like symptoms in adult life in many people with the condition, especially if they are exposed to cigarette smoke. The disorder can also lead to various liver diseases in children and adults, and occasionally can lead to problems that are more unusual. Alpha-1-antitrypsin deficiency usually produces some degree of disability and reduces life expectancy.

[0009] Alpha-1-antitrypsin deficiency is treated through avoidance of damaging inhalants and by intravenous infusions of alpha-1-antitrypsin or by transplantation of the liver or lungs. Recombinant versions of alpha-1-antitrypsin are also known but are currently used in medical research more than as treatment. Approved alpha-1-antitrypsin deficiency products are purified from human plasma and require frequent weekly infusion, with high doses (60-120 mg/kg) and have only limited efficacy. Alpha-1-antitrypsin augmentation therapy is not ideal due to poor pharmacokinetics, with peaks and troughs seen in circulating AAT levels, despite administration of high concentrations of plasma-derived AAT.

[0010] Some current research is focused on developing long-acting alpha-1-antitrypsin fusions through protein engineering. For example, AAT Fc has been expressed and developed by two groups: Soohyun Kim (Konkuk University, Seoul, Korea; licensed to OmniBio ("Kim/OmniBio molecule") (*See* Lee S, Lee Y, Hong K, Hong J, Bae S, Choi J, Jhun H, Kwak A, Kim E, Jo S, Dinarello CA, Kim S. Effect of recombinant α1-antitrypsin Fc-fused (AAT-

Fc) protein on the inhibition of inflammatory cytokine production and streptozotocin-induced diabetes. Mol Med. 2013 May 20;19:65-71. doi:10.2119/molmed.2012.00308. PubMed PMID: 23552726; PubMed Central PMCID:PMC3667213, which is incorporated by reference in its entirety herein, including any drawings.) and InhibRx ("InhibRx molecule") (*See*, for example, US 8,980,266 B2, Serpin Fusion Polypeptides and Methods and Use Thereof, which is incorporated in its entirety herein in its entirety, including any drawings.) Both molecules are N-terminal AAT fusions to IgG1 Fc. The Kim/OmniBio molecule does not inhibit human neutrophil elastase as well as plasma derived AAT, which may be a result of low-pH instability upon elution from protein A chromatography during purification. The InhibRx molecule is reported to inhibit human neutrophil elastase like plasma derived AAT.

[0011] Others have modified the glycosylation pattern of AAT by increasing the number of N-glycans (*See*, for example, Chung HS, Kim JS, Lee SM, Park SJ. Additional N-glycosylation in the N-terminal region of recombinant human alpha-1 antitrypsin enhances the circulatory half-life in Sprague-Dawley rats. Glycoconj J. 2016 Apr;33(2):201-8. doi: 10.1007/s10719-016-9657-3. Epub 2016 Mar 7. PubMed PMID: 26947874, which is incorporated by reference in its entirety herein, including any drawings) or adding polysialyation (*See*, for example, Lindhout T, Iqbal U, Willis LM, Reid AN, Li J, Liu X, Moreno M, Wakarchuk WW. Site-specific enzymatic polysialylation of therapeutic proteins using bacterial enzymes. Proc Natl Acad Sci U S A. 2011 May 3;108(18):7397-402. doi:10.1073/pnas.1019266108. Epub 2011 Apr 18. PubMed PMID: 21502532; PubMed Central PMCID: PMC3088639, which is incorporated by reference in its entirety herein, including any drawings.) Some have produced an aglycosylated AAT (*See*, for example, Cantin AM, Woods DE, Cloutier D, Héroux J, Dufour EK, Leduc R. Leukocyte elastase inhibition therapy in cystic fibrosis: role of glycosylation on the distribution of alpha-1-proteinase inhibitor in blood versus lung. J Aerosol Med. 2002 Summer;15(2):141-8. PubMed PMID: 12184864, which is incorporated by reference in its entirety herein, including any drawings.) Still others have developed a PEGylated aglycosylated AAT to extend half-life (*See,* for example, Cantin AM, Woods DE, Cloutier D, Dufour EK, Leduc R. Polyethylene glycol conjugation at Cys232 prolongs the half-life of alpha1 proteinase inhibitor. Am J Respir Cell Mol Biol. 2002 Dec;27(6):659-65. PubMed PMID: 12444025, which is incorporated by reference in its entirety herein, including any drawings.)

[0012] AAT is prone to Met oxidation in the lung and so some groups have constructed mutated AAT variants that are resistant to methionine oxidation but retain activity. In

particular, the M351V/M358V mutant is resistant to oxidation (*See*, for example, Taggart C, Cervantes-Laurean D, Kim G, McElvaney NG, Wehr N, Moss J, Levine RL. Oxidation of either methionine 351 or methionine 358 in alpha 1-antitrypsin causes loss of anti-neutrophil elastase activity. J Biol Chem. 2000 Sep 1;275(35):27258-65. PubMed PMID: 10867014, which is incorporated by reference in its entirety herein, including any drawings.) Baek et al. have introduced a disulfide bond (K168C–F189C) in AAT and substantially increased resistance to loop-sheet polymerization (*See* Baek JH, Im H, Kang UB, Seong KM, Lee C, Kim J, Yu MH. Probing the local conformational change of alpha1-antitrypsin. Protein Sci. 2007 Sep;16(9):1842-50. Epub 2007 Jul 27. PubMed PMID: 17660256; PubMed Central PMCID: PMC2206966m, which is incorporated by reference in its entirety herein, including any drawings.) Single point mutations (F51L, G117F, K331F, K335A) in AAT have also been created and show increases in stability and resistance to loop-sheet polymerization (*See,* Dafforn TR, Mahadeva R, Elliott PR, Sivasothy P, Lomas DA. A kinetic mechanism for the polymerization of alpha1-antitrypsin. J Biol Chem. 1999 Apr 2;274(14):9548-55. PubMed PMID: 10092640; Parfrey H, Mahadeva R, Ravenhill NA, Zhou A, Dafforn TR, Foreman RC, Lomas DA. Targeting a surface cavity of alpha 1-antitrypsin to prevent conformational disease. J Biol Chem. 2003 Aug 29;278(35):33060-6. Epub 2003 Jun 13. PubMed PMID: 12807889; Gilis D, McLennan HR, Dehouck Y, Cabrita LD, Rooman M, Bottomley SP. In vitro and in silico design of alpha1-antitrypsin mutants with different conformational stabilities. J Mol Biol. 2003 Jan 17;325(3):581-9. PubMed PMID: 12498804; and Im H, Seo EJ, Yu MH. Metastability in the inhibitory mechanism of human alpha1-antitrypsin. J Biol Chem. 1999 Apr 16;274(16):11072-7. PubMed PMID: 10196190, each of which is incorporated by reference herein including any drawings.)

[0013] However, despite the above-mentioned progress, additional treatment options are needed.

SUMMARY OF THE INVENTION

[0014] The invention described herein is based, in part, on a recombinant engineered alpha-1-antitrypsin serpin domain fused to a human serum albumin binding domain or human serum albumin domain.

[0015] Some embodiments comprise a recombinant protein comprising an alpha-1-antitrypsin serpin domain and a human serum albumin binding domain or a human serum albumin domain. In some embodiments, the aplha-1-antitrypsin serpin domain has a sequence comprising all or part of SEQ ID NO: 1. In some embodiments, the recombinant protein

comprises one or more linkers. In some embodiments, the C-terminus of the alpha-1-antitrypsin serpin domain is fused to the N-terminus of the human serum albumin or human serum albumin binding domain in the recombinant protein. Some embodiments comprise a recombinant protein comprising an alpha-1-antitrypsin serpin domain and a human serum albumin domain wherein the alpha-1-antitrypsin serpin domain and a human serum albumin domain are not both wild-type alpha-1-antitrypsin and a wild type human serum albumin.

[0016] In some embodiments, the alpha-1-antitrypsin serpin domain has one or more mutations. In some embodiments, the alpha-1-antitrypsin serpin domain retains activity compared to a wild type alpha-1-antitrypsin serpin domain. In some embodiments, the one or more mutations causes resistance to methionine oxidation as compared to wild type alpha-1-antitrypsin. In some embodiments, the one or more mutations comprises M351V and/or M358V with residues being numbered according to SEQ ID NO: 1. In some embodiments, the one or more mutations comprises K168C and F189C with residues being numbered according to SEQ ID NO: 1. In some embodiments, the one or more mutations confer a substantially increased resistance to loop-sheet polymerization as compared to wild type alpha-1-antitrypsin. In some embodiments, the one or more mutations are one or more point mutations selected from F51L, G117F, K331F, or K335A with residues being numbered according to SEQ ID NO: 1. In some embodiments, the alpha-1-antitrypsin serpin domain retains activity against human neutrophil elastase and/or PR3 compared to a wild type alpha-1-antitrypsin serpin domain.

[0017] In some embodiments, the one or more mutations comprises a mutation in at least one of the following residue positions according to SEQ ID NO 1: 51, 100, 114, 117, 163, 164, 165, 168, 169, 172, 173, 174, 183, 189, 232, 283, 300, 302, 303, 304, 306, 330, 331, 333, 335, 336, 337, 338, 339, 340, 351, 356, 358, or 361. In some embodiments, the one or more mutations comprises one or more of the following mutations according to SEQ ID NO 1: F51L, L100F, L100C, T114F, G117F, K163T, G164V, T165S, K168C, K168I, K168A, K169V, L172V, L172A, L172C, V173C, K174T, A183V, F189C, F189I, F189V, C232S, S283C, K300A, V302A, L303A, G304A, L306A, S330R, K331F, K331I, K331V, K331T, K331C, V333C, V333A, K335A, K331F, K335G, K335T, A336G, V337C, V337A, L338A, T339S, I340V, M351V, I356M, M358I, M358P, M358A, M358R, M358L, M358V, or P361C. In some embodiments, the one or more mutations comprises F51L, G117F, K168C, F189C, C232S, S283C, K331F, K335A, M351V, M358V, M358L, or P361C according to SEQ ID NO: 1. In some embodiments, the one or more mutations are both of K168C and F189C

according to SEQ ID NO: 1. In some embodiments, the one or more mutations are both of P361C and S283C according to SEQ ID NO: 1.

[0018] In some embodiments, the alpha-1-antitrypsin serpin domain has one or more mutations comprising C232S according to SEQ ID NO: 1. In some embodiments, the alpha-1-antitrypsin serpin domain has one or more mutations comprising M351V and M358V according to SEQ ID NO: 1. In some embodiments, the alpha-1-antitrypsin serpin domain has one or more mutations comprising M351V and M358L according to SEQ ID NO: 1. In some embodiments, the alpha-1-antitrypsin serpin domain has one or more mutations comprising C232S, M351V, and M358V according to SEQ ID NO: 1.

[0019] In some embodiments, the alpha-1-antitrypsin serpin domain has one or more mutations comprising F51L, C232S, M351V and M358L according to SEQ ID NO: 1. In some embodiments, the alpha-1-antitrypsin serpin domain has one or more mutations comprising G117F, C232S, M351V and M358L according to SEQ ID NO: 1. In some embodiments, the alpha-1-antitrypsin serpin domain has one or more mutations comprising C232S, K331F, M351V and M358L according to SEQ ID NO: 1. In some embodiments, the alpha-1-antitrypsin serpin domain has one or more mutations comprising C232S, K335A, M351V and M358L according to SEQ ID NO: 1. In some embodiments, the alpha-1-antitrypsin serpin domain has one or more mutations comprising K168C, F189C, C232S, M351V, and M358L according to SEQ ID NO: 1. In some embodiments, the alpha-1-antitrypsin serpin domain has one or more mutations comprising C232S, S283C, M351V, M358L, and P361C according to SEQ ID NO: 1. In some embodiments, the alpha-1-antitrypsin serpin domain has one or more mutations comprising F51L, G117F, C232S, M351V, and M358L according to SEQ ID NO: 1. In some embodiments, the alpha-1-antitrypsin serpin domain has one or more mutations comprising F51L, C232S, K331F, M351V, and M358L according to SEQ ID NO: 1. In some embodiments, the alpha-1-antitrypsin serpin domain has one or more mutations comprising F51L, C232S, K335A, M351V, and M358L according to SEQ ID NO: 1. In some embodiments, the alpha-1-antitrypsin serpin domain has one or more mutations comprising K51L, K168C, F189C, C232S, M351V, and M358L according to SEQ ID NO: 1. In some embodiments, the alpha-1-antitrypsin serpin domain has one or more mutations comprising F51L, C232S, S283C, M351V, M358L, and P361C according to SEQ ID NO: 1. In some embodiments, the alpha-1-antitrypsin serpin domain has one or more mutations comprising G117F, C232S, K331F, M351V, and M358L according to SEQ ID NO: 1. In some embodiments, the alpha-1-antitrypsin serpin domain has one or more mutations comprising

G117F, K335A, C232S, M351V, and M358L according to SEQ ID NO: 1. In some embodiments, the alpha-1-antitrypsin serpin domain has one or more mutations comprising G117F, K168C, F189C, C232S, M351V, and M358L according to SEQ ID NO: 1. In some embodiments, the alpha-1-antitrypsin serpin domain has one or more mutations comprising G117F, C232S, S283C, M351V, M358L, and P361C according to SEQ ID NO: 1. In some embodiments, the alpha-1-antitrypsin serpin domain has one or more mutations comprising C232S, K331F, K335A, M351V, and M358L according to SEQ ID NO: 1. In some embodiments, the alpha-1-antitrypsin serpin domain has one or more mutations comprising K168C, F189C, C232S, K331F, M351V, and M358L according to SEQ ID NO: 1. In some embodiments, the alpha-1-antitrypsin serpin domain has one or more mutations comprising C232S, S283C, K331F, M351V, M358L, and P361C according to SEQ ID NO: 1. In some embodiments, the alpha-1-antitrypsin serpin domain has one or more mutations comprising K168C, F189C, C232S, K335A, M351V, and M358L according to SEQ ID NO: 1. In some embodiments, the alpha-1-antitrypsin serpin domain has one or more mutations comprising C232S, S283C, K335A, M351V, M358L, and P361C according to SEQ ID NO: 1. In some embodiments, the alpha-1-antitrypsin serpin domain has one or more mutations comprising K168C, F189C, C232S, S283C, M351V, M358L, and P361C according to SEQ ID NO: 1.In some embodiments, the alpha-1-antitrypsin serpin domain comprises a point mutation K335A according to SEQ ID NO: 1. In some embodiments, the alpha-1-antitrypsin serpin domain comprises a point mutation K331F according to SEQ ID NO: 1. In some embodiments, the alpha-1-antitrypsin serpin domain comprises a point mutation G117F according to SEQ ID NO: 1. In some embodiments, the alpha-1-antitrypsin serpin domain comprises a point mutation S283C according to SEQ ID NO: 1. In some embodiments, the alpha-1-antitrypsin serpin domain comprises a point mutation P361C according to SEQ ID NO: 1.

[0020] In some embodiments, the human serum albumin is at least a portion of SEQ ID NO: 3 or SEQ ID NO: 5. In some embodiments, the human serum albumin binding domain is one of SEQ ID NOs: 22-36. In some embodiments, the human serum albumin binding domain comprises one or more CDRs selected from SEQ ID NOs: 6-21. In some embodiments, the human serum albumin or human serum albumin binding domain increases plasma half-life of the alpha-1-antitrypsin serpin domain as compared to wild type alpha-1-antitrypsin. In some embodiments, a number of N-glycans or polysialyation of the recombinant protein in the alpha-1-antitrypsin serpin domain is greater than a wild type alpha-1-antitrypsin serpin domain.

[0021] In some embodiments, the human serum albumin comprises one or more mutations. In some embodiments, the one or more mutations are one or more of residues 407, 408, 409, 410, 413, and 414, wherein the one or more residues are numbered according to SEQ ID NO: 5. In some embodiments, the one or more mutations are one or more of L407A, L408V, V409A, R410A, L413Q, and L414Q, wherein the one or more residues are numbered according to SEQ ID NO. 5. In some embodiments, the human serum albumin comprises a portion or a variant of human serum albumin.

[0022] In some embodiments, the human serum albumin binding protein comprises an amino acid sequence that is capable of binding to all or a part of human serum albumin protein having the sequence set forth in SEQ ID NO: 3 or SEQ ID NO: 5.

[0023] In some emodiments, the recombinant protein comprises or consists of a protein having any one of SEQ ID Nos: 64-68 or SEQ ID NO: 71. In some embodiments, the recombinant protein comprises or consists of a protein having SEQ ID NO: 64. In some embodiments, the recombinant protein comprises or consists of a protein having SEQ ID NO: 65. In some embodiments, the recombinant protein comprises or consists of a protein having SEQ ID NO: 66. In some embodiments, the recombinant protein comprises or consists of a protein having SEQ ID NO: 67. In some embodiments, the recombinant protein comprises or consists of a protein having SEQ ID NO: 68. In some embodiments, the recombinant protein comprises or consists of a protein having SEQ ID NO: 71.

[0024] In some embodiments, a nucleic acid is provided which encodes a recombinant protein as provided herein. In some embodiments, the nucleic acid comprises a vector. In some embodiments, the vector comprises a host cell.

[0025] Some embodiments are drawn to a method of making a recombinant protein comprising culturing the host cell with one of the nucleic acids provided herein and collecting the recombinant protein. In some embodiments, the host cell is a eukaryotic host cell. In some embodiments, the host cell is a mammalian host cell. In some embodiments, the mammalian host is a CHO cell. In some embodiments, the recombinant protein is collected using an alpha-1-antitrypsin-Fc capture select media at neutral pH.

[0026] Some embodiments are drawn to a method of treating an alpha-1-antitrypsin deficiency in a patient in need thereof comprising administering a recombinant protein, as provided herein, to the patient. In some embodiments, the recombinant protein comprises a pharmaceutical composition. In some embodiments, administration of the recombinant protein

is administered about once a week or at longer intervals than about once a week, about once every 10 days or at longer intervals than about once every ten days, about once every 15 days or at longer intervals than about once every 15 days, about once every 20 days or at longer intervals than about once every 20 days, about once every 25 days or at longer intervals than about once every 25 days, about once every month or at longer intervals than about once every month, or about once every two months or at longer intervals than about once every two months.

[0027] Some embodiments are drawn to a method of improving the pharmacokinetics of a protein comprising an alpha-1-antitrypsin serpin domain. In some embodiments, the protein is any of the recombinant proteins set forth herein. In some embodiments improved pharmacokinetics means an improvement with respect to Prolastin.

BRIEF DESCRIPTION OF THE DRAWINGS

[0028] FIG. 1 depicts the structure of the alpha-1-antitrypsin protein and gene. The top shows the normal protein in its linear form, a 394 amino acid single chain protein with three asparaginyl-linked complex carbohydrates side chains at residues 46, 83, and 247 according to SEQ ID NO: 1. The bottom shows the gene (SEQ ID NO: 69) and consists of three non-coding exons (IA, IB, and IC) and four coding exons (II-V). Alpha helices are shown with boxes and beta sheets are shown with squiggles. The start codon is in exon II followed by a 24 residue signal peptide. The carbohydrate attachment sites are shown in the figure as CHO.

[0029] FIG. 2 shows locations of mutations associated with alpha-1-antitrypsin gene associated with alpha-1-antitrypsin deficiency.

[0030] FIG. 3 shows alpha-1-antitrypsin secondary structure.

[0031] FIG. 4 depicts purified CE-SDS for constructs of the invention. FIG.4A depicts purified CE-SDS for PP11288. FIG.4B depicts purified CE-SDS for PP11289. FIG.4C depicts purified CE-SDS for PP11290. FIG.4D depicts purified CE-SDS for PP11291. FIG.4E depicts purified CE-SDS for PP11292. FIG.4F depicts purified CE-SDS for purified samples (reducued overlay.) FIG.4G depicts purified CE-SDS for purified samples (non-reducing conditions.)

[0032] FIG. 5 depicts the stability analysis of 5 AAT-Albumin fusions.

[0033] FIG. 6 depicts results for an hNE inhibition assay with 5 AAT-albumin fusions.

[0034] FIG. 7 depicts purified CE-SDS for constructs of the invention. FIG.7A depicts purified CE-SDS for PP13579. FIG.7B depicts purified CE-SDS for PP13580. FIG.7C depicts purified CE-SDS for PP13581. FIG.7D depicts purified CE-SDS for PP13582. FIG.7E depicts purified CE-SDS for PP13583. FIG.7F depicts purified CE-SDS for PP13584. FIG.7G depicts purified CE-SDS for PP13585. FIG.7H depicts purified CE-SDS for PP13586. FIG.7I depicts purified CE-SDS for PP13587. FIG.7J depicts purified CE-SDS for PP13588. FIG.7K depicts purified CE-SDS for PP13589. FIG.7L depicts purified CE-SDS for PP13590. FIG.7M depicts purified CE-SDS for PP13592. FIG.7N depicts purified CE-SDS for PP13593. FIG.7O depicts purified CE-SDS for PP13594. FIG.7P depicts purified CE-SDS for PP13595. FIG.7Q depicts purified CE-SDS for PP13596. FIG.7R depicts purified CE-SDS for PP13597. FIG.7S depicts purified CE-SDS for PP13598. FIG.7T depicts purified CE-SDS for PP13599. FIG.7U depicts purified CE-SDS for PP13600.

[0035] FIG. 8 depicts the stability analysis of 21 AAT-Albumin fusions.

[0036] FIG. 9 depicts IC50 analysis of AAT mutants. FIG. 9A depicts IC50 analysis of AAT mutants. FIG. 9B depicts IC50 analysis of AAT mutants. FIG. 9C depicts IC50 analysis of AAT mutants.

[0037] FIG. 10 depicts EpiMatrix protein scores normalized and plotted on a standardized scale.

[0038] FIG. 11 depicts stability analysis of AAT variant (K335A, S283C/P361C) on base (C232S,M351V, M351L).

[0039] FIG. 12 depicts cyno PK data.

[0040] FIG. 13 depicts that AAT-HSA and prolastin after PK in monkey after 10 mg/kg was 3 compartmental.

DETAILED DESCRIPTION OF THE INVENTION

Terminology

[0041] As used herein, the term “about” shall refer to an approximate mathematical quantity and can be used with respect to integer values as well as percentages. When an upper or lower bound limit comprises an integer value, the term about shall refer to a boundary that is approximate and the term shall also include everything above that boundary (with respect to a lower boundary) or below that boundary (with respect to an upper

boundary.) For example, a portion of a sequence that comprises "about" 20 residues of a 393 residue sequence shall include a boundary that is approximately 20 residues and all integer values above that value.

[0042] As used herein, "albumin" shall refer to an albumin protein or albumin fragment, portion, or variant having one or more functional activities of albumin or to a nucleic acid sequence encoding an albumin protein, fragment, portion, or variant thereof having one or more functional activities of albumin. Albumin may be derived from any vertebrate, especially any mammal. In some embodiments, the albumin is derived from human, cow, sheep, or pig. Non-mammalian albumins include, but are not limited to, hen and salmon. In some embodiments, an albumin derived from any vertebrate may be substituted for human albumin or human serum albumin.

[0043] The term "antibody" as used herein refers to a type of immunoglobulin molecule and is used in its broadest sense. An antibody specifically includes intact antibodies (e.g., intact immunoglobulins), and antibody fragments. Antibodies comprise at least one antigen-binding domain. One example of an antigen-binding domain is an antigen binding domain formed by a V_H-V_L dimer. Other examples of antibodies are set forth in the following sections.

[0044] The V_H and V_L regions may be further subdivided into regions of hypervariability ("hypervariable regions (HVRs);" also called CDRs, as defined herein) interspersed with regions that are more conserved. The more conserved regions are called framework regions (FRs). Each V_H and V_L generally comprises three CDRs and four FRs, arranged in the following order (from N-terminus to C-terminus): FR1 - CDR1 - FR2 - CDR2 - FR3 - CDR3 - FR4. The CDRs are involved in antigen binding, and confer antigen specificity and binding affinity to the antibody. See Kabat et al., *Sequences of Proteins of Immunological Interest* 5th ed. (1991) Public Health Service, National Institutes of Health, Bethesda, MD, incorporated by reference in its entirety.

[0045] The light chain from any vertebrate species can be assigned to one of two types, called kappa and lambda, based on the sequence of the constant domain.

[0046] The heavy chain from any vertebrate species can be assigned to one of five different classes (or isotypes): IgA, IgD, IgE, IgG, and IgM. These classes are also designated α, δ, ε, γ, and μ, respectively. The IgG and IgA classes are further divided into

subclasses on the basis of differences in sequence and function. Humans express the following subclasses: IgG1, IgG2, IgG3, IgG4, IgA1, and IgA2.

[0047] An "antibody fragment" comprises a portion of an intact antibody, such as the antigen binding or variable region of an intact antibody. Antibody fragments include, for example, Fv fragments, Fab fragments, $F(ab')_2$ fragments, Fab′ fragments, scFv (sFv) fragments, and scFv-Fc fragments.

[0048] "Fv" fragments comprise a non-covalently-linked dimer of one heavy chain variable domain and one light chain variable domain.

[0049] "Fab" fragments comprise, in addition to the heavy and light chain variable domains, the constant domain of the light chain and the first constant domain (C_{H1}) of the heavy chain. Fab fragments may be generated, for example, by papain digestion of a full-length antibody.

[0050] "$F(ab')_2$" fragments contain two Fab′ fragments joined, near the hinge region, by disulfide bonds. $F(ab')_2$ fragments may be generated, for example, by pepsin digestion of an intact antibody. The F(ab′) fragments can be dissociated, for example, by treatment with ß-mercaptoethanol.

[0051] "Single-chain Fv" or "sFv" or "scFv" antibody fragments comprise a V_H domain and a V_L domain in a single polypeptide chain linked by a peptide linker. *See* Plückthun A. (1994.) "scFv-Fc" fragments comprise an scFv attached to an Fc domain. For example, an Fc domain may be attached to the C-terminal of the scFv. The Fc domain may follow the V_H or V_L, depending on the orientation of the variable domains in the scFv (i.e., V_H-V_L or V_L-V_H). Any suitable Fc domain known in the art or described herein may be used.

[0052] "Humanized" forms of non-human antibodies are chimeric antibodies that contain minimal sequence derived from the non-human antibody. A humanized antibody is generally a human immunoglobulin (recipient antibody) in which residues from one or more CDRs are replaced by residues from one or more CDRs of a non-human antibody (donor antibody).

[0053] A "human antibody" is one which possesses an amino acid sequence corresponding to that of an antibody produced by a human or a human cell, or derived from a non-human source that utilizes a human antibody repertoire or human antibody-encoding sequences (e.g., obtained from human sources or designed *de novo*). Human antibodies specifically exclude humanized antibodies.

[0054] As used herein, a "single domain antibody" shall refer to an antibody whose CDRs are part of a single domain polypeptide. Examples include, but are not limited to, heavy chain antibodies, antibodies naturally devoid of light chains, single domain antibodies derived from conventional four chain antibodies and single domain scaffolds other than those derived from antibodies. Single domain antibodies may be derived from any species including, but not limited to, mouse, human, camel, llama, goat, rabbit, shark, and bovine. As an example, a single domain antibody may be raised in *Camelidae* species such as camel, dromedary, alpaca, and guanaco. In some embodiment, a single domain antibody comprises a sequence set forth in any one of SEQ ID NOs: 22-28 and SEQ ID NOs: 29-36.

[0055] As used herein, "complementary-determing regions" or "CDRs" are part of the variable chains in antibodies. The CDRs are responsible for specific antibodies. One skilled in the art would appreciate how to determine the location of CDRs within an antibody for specific antibodies and there are several systems determining CDR location. For the sake of clarity, in this application, CDRs for single domain antibodies shall be determined according to US 2010/011339, which is incorporated by reference in its entirety herein.

[0056] The term "epitope" means a portion of an antigen capable of specific binding to a binding protein, such as, for example, without limitation, an antibody. Epitopes frequently consist of surface-accessible amino acid residues and/or sugar side chains and may have specific three-dimensional structural characteristics, as well as specific charge characteristics. An epitope may comprise amino acid residues that are directly involved in the binding, and other amino acid residues, which are not directly involved in the binding. The epitope to which an antibody binds can be determined using known techniques for epitope determination.

[0057] As used herein, "human albumin" refers to a human albumin protein or human albumin fragment or variant or portion having one or more functional activities of human albumin or nucleic acid sequence encoding a human albumin, fragment, portion, or variant thereof having one or more functional activities of human albumin. Human albumin is a polypeptide sequence of 609 amino acids, the first 18 amino acids of which constitute the leader sequence not found in the final blood bourne product. A human albumin is set forth in SEQ ID NO: 3 in some embodiments.

[0058] As used herein, "human serum albumin" shall refer to the human serum albumin found in human blood, which is normally devoid of the initial 18 amino acid leader

sequence. In some embodiments, human serum albumin has the sequence set forth in SEQ ID NO: 5. A human serum albumin domain shall also refer to any human serum albumin protein or human serum albumin fragment or variant or portion having one or more functional activities of human serum albumin.

[0059] As used herein, "human serum albumin binding protein" or "human albumin binding domain" shall refer to any protein or protein fragment or variant having one or more binding activities to human albumin or human serum albumin.

[0060] As used herein, "alpha-1-antitrypsin" or "α_1-antitrypsin" (also "A1AT," "A1A," or "AAT") shall refer to an alpha-1-antitrypsin protein or an alpha-1-antitrypsin fragment or variant having one or more functional activities of alpha-1-antitrypsin or a nucleic acid sequence encoding an alpha-1-antitrypsin protein, fragment, or variant thereof having one or more functional activities of alpha-1-antitrypsin. In some embodiments, the alpha-1-antitrypsin protein has the sequence set forth in SEQ ID NO: 1.

[0061] As used herein, "alpha-1-antitrypsin serpin domain" or "α_1-antitrypsin serpin domain" (also "A1AT, domain" "A1A domain," or "AAT domain") shall refer to an alpha-1-antitrypsin serpin domain or an alpha-1-antitrypsin serpin domain fragment or variant having one or more functional activities of an alpha-1-antitrypsin protein or fragment or a nucleic acid sequence encoding an alpha-1-antitrypsin protein serpin domain or fragment, or variant thereof having one or more functional activities of alpha-1-antitrypsin protein.

[0062] As used herein, "alpha-1-antitrypsin deficiency" or "AATD" is a genetic disorder that causes defective production of alpha-1-antitrypsin. The disease leads to a decrease of alpha-1-antitrypsin and is also referred to as hereditary pulmonary emphysema and results in lung and liver disease. There are several forms and degrees of the deficiency. The form and degree depend on whether the sufferer has one or two copies of a defective allele. Severe alpha-1-antitrypsin deficiency causes panacinar emphysema or COPD in adult life in many people with the condition, especially if they are exposed to cigarette smoke. The disorder can also lead to various liver diseases in a minority of children and adults, and occasionally more unusual problems. Alpha-1-antitrypsin deficiency usually produces some degree of disability and reduces life expectancy.

[0063] An "effective amount" of a recombinant protein described herein or functional fragment or variant thereof refers to the amount of the polypeptide or functional fragment or variant thereof, when administered in an aggregate of multiple doses, or as part of any other

type of defined treatment regimen, produces a measureable statistical improvement in outcome or prophylaxis, as evidenced by at least one clinical parameter associated with the complication.

[0064] As used herein, “neutrophil elastase” shall refer to a serine protease that destroys elastase, the rubberlike macromolecule that provides elastic recoil to the lung. When the blood contains inadequate amounts of AAT, neutrophil elastase can break down elastin, degrading the elasticity of the lungs, which results in respiratory complications, such as chronic obstructive pulmonary disease.

[0065] The term “portion" as used herein shall mean a part of a whole or piece of something such as a protein or polypeptide.

[0066] As used herein, “recombinant” in reference to a protein or polypeptide molecule, refers to a protein or polypeptide molecule expressed utilizing isolated nucleic acid molecules or recombinant nucleic acid molecules.

[0067] The term “variant” or "variants" as used herein shall mean a different sequence of a protein including, for example, without limitation, insertions, deletions, and substitutions, either conservative or non-conservative, where such changes do not substantially alter one or more of the oncotic, useful ligand-binding, and non-immunogenic properties of an albumin or albumin binding domain or do not alter the serpin domain.

[0068] Variants of polypeptides described herein include polypeptides having at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98% or at least about 99% identity with the amino acid sequence of the human wild type polypeptides provided herein. For example, variants of alpha-1-antitrypsin include polypeptides having at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% identity with the amino acid sequence of SEQ ID NO: 1. For example, variants of human albumin include polypeptides having at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% identity with the amino acid sequence of SEQ ID NO: 3 or SEQ ID NO: 5. Calculations of “identity” or “sequence homology” between two sequences (the terms are used interchangeably herein) are performed by aligning for optimal comparison purposes (*e.g.*, gaps can be introduced in one or both of a first and a second amino acid or nucleic acid sequence for optimal alignment and non-

homologous sequences can be disregarded for comparison purposes). The amino acid residues or nucleotides at corresponding amino acid positions or nucleotide positions are then compared. When a position in the first sequence is occupied by the same amino acid residue or nucleotide as the corresponding position in the second sequence, then the molecules are identical at that position (as used herein amino acid or nucleic acid "identity" is equivalent to amino acid or nucleic acid "homology"). The percent identity between the two sequences is a function of the number of identical positions shared by the sequences. Variants include, but are not limited to, polypeptides that have been either chemically modified relative to the human wild type polypeptide and/or contain one or more amino acid sequence alterations relative to the human wild type polypeptide.

[0069] Variants of polypeptides described herein can be those having amino acid modifications (*e.g.,* deletions, additions, or substitutions, such as conservative substations) from the wild type amino acid sequence of the polypeptide. In some embodiments, a variant of AAT can differ by at least 1, 2, 3, 4, 5, or more resides from alpha-1-antitrypsin (SEQ ID NO: 1) and a variant of a human serum albumin can vary by at least 1, 2, 3, 4, or 5 residues from human serum albumin (SEQ ID NO: 5).

[0070] A "conservative amino acid substitution" is one in which the amino acid residue is replaced with an amino acid residue having a similar side chain. Families of amino acid residues having similar side chains have been defined in the art. These families include amino acids with basic side chains (*e.g.,* lysine, arginine, histidine), acidic side chains (*e.g.,* aspartic acid, glutamic acid), uncharged polar side chains (*e.g.,* glycine, asparagine, glutamine, serine, threonine, tyrosine, cysteine), nonpolar side chains (*e.g.,* alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, tryptophan), beta-branched side chains (*e.g.,* threonine, valine, isoleucine) and aromatic side chains (*e.g.,* tyrosine, phenylalanine, tryptophan, histidine). Recombinant proteins having conservative substitutions are intended to be within the scope of the current invention.

[0071] The term "fusion" or "fusion molecule" can refer to a polypeptide or a nucleic acid fusion, depending on the context. It may include a full-length sequence or a protein or nucleic acid or a fragment thereof. It may also include a recombinant protein with or without a linker molecule.

[0072] An "isolated" protein refers to a protein that is removed from at least about 90% of at least one component of a natural sample from which the isolated protein can be obtained.

Proteins can be "of at least about" a certain degree of purity if the species or population of species of interest is at least about 5, 25, 50, 75, 80, 90, 92, 95, 98, or 99% pure on a weight-weight basis.

[0073] As used herein, the term "oncotic" shall refer to oncotic pressure, or colloid osmotic pressure. It is a form of osmotic pressure exerted by proteins, notably albumin, in a blood vessel's plasma that pulls water into the circulatory system. It is the opposing force to hydrostatic pressure. It has a major effect on the pressure across the glomerular filter.

[0074] A "patient," "subject," or "host" (these terms are used interchangeably) to be treated by the subject method may mean either a human or non-human animal. Preferably, a patient, subject, or host refers to a human patient.

[0075] The term "prophylactically treating" a disease in a subject refers to subjecting the subject to a pharmaceutical treatment, *e.g.,* the administration of a drug, such that at least one symptom of the disease is prophylactically treated, that is, administered prior to clinical manifestation of the unwanted condition so that it protects the host against developing the unwanted condition. "Prohylactially treating" a disease may also be referred to as "prophylaxis." In some embodiments, prophylactic treatment prevents the disorder.

[0076] As used herein, "treating" a disorder associated with an alpha-1-antitrypsin deficiency in a subject in need or "treating" a subject having a disorder associated with an alpha-1-antitrypsin deficiency, refers to subjecting the subject to a pharmaceutical treatment, *e.g.,* the administration of a drug, such that at least one symptom of the disease is cured, alleviated, or decreased.

[0077] Any of the treatments described herein can be administered in combination with another agent or therapy. The term "combination" refers to the use of the two or more agents or therapies to treat the same patient, wherein the use or action of the agents or therapies overlap in time. The agents or therapies can be administered at the same time (*e.g.,* as a single formulation that is administered to a patient or as two separate formulations administered concurrently) or sequentially in any order.

Recombinant Protein

[0078] Some embodiments provide a recombinant protein comprising an alpha-1-antitrypsin serpin domain, or functional fragment or variant thereof, and a human serum albumin domain or functional fragment or variant thereof, or human serum albumin binding domain or functional fragment or variant thereof.

Alpha-1-antitrypsin Serpin Domain

[0079] In some embodiments, the alpha-1-antitrypsin serpin domain comprises a full-length alpha-1-antitrypsin. In some embodiments, the alpha-1-antitrypsin is a protein that comprises the sequence set forth in SEQ ID NO: 1.

[0080] In some embodiments, the alpha-1-antitrypsin serpin domain comprises one or more mutations. In some embodiments, the one or more mutations comprises a mutation in at least one of the following residue positions according to SEQ ID NO 1: 51, 100, 114, 117, 163, 164, 165, 168, 169, 172, 173, 174, 183, 189, 232, 283, 300, 302, 303, 304, 306, 330, 331, 333, 335, 336, 337, 338, 339, 340, 351, 356, 358, or 361. In some embodiments, the one or more mutations comprises one or more of the following mutations according to SEQ ID NO 1: F51L, L100F, L100C, T114F, G117F, K163T, G164V, T165S, K168C, K168I, K168A, K169V, L172V, L172A, L172C, V173C, K174T, A183V, F189C, F189I, F189V, C232S, S283C, K300A, V302A, L303A, G304A, L306A, S330R, K331F, K331I, K331V, K331T, K331C, V333C, V333A, K335A, K331F, K335G, K335T, A336G, V337C, V337A, L338A, T339S, I340V, M351V, I356M, M358I, M358P, M358A, M358R, M358L, M358V, or P361C. In some embodiments, the one or more mutations comprises F51L, G117F, K168C, F189C, C232S, S283C, K331F, K335A, M351V, M358V, M358L, or P361C according to SEQ ID NO: 1. In some embodiments, the one or more mutations are both of K168C and F189C according to SEQ ID NO: 1. In some embodiments, the one or more mutations are both of P361C and S283C according to SEQ ID NO: 1.

[0081] In some embodiments, the alpha-1-antitrypsin serpin domain has one or more mutations comprising C232S according to SEQ ID NO: 1. In some embodiments, the alpha-1-antitrypsin serpin domain has one or more mutations comprising M351V and M358V according to SEQ ID NO: 1. In some embodiments, the alpha-1-antitrypsin serpin domain has one or more mutations comprising M351V and M358L according to SEQ ID NO: 1. In some embodiments, the alpha-1-antitrypsin serpin domain has one or more mutations comprising C232S, M351V, and M358V according to SEQ ID NO: 1.

[0082] In some embodiments, the alpha-1-antitrypsin serpin domain has one or more mutations comprising F51L, C232S, M351V and M358L according to SEQ ID NO: 1. In some embodiments, the alpha-1-antitrypsin serpin domain has one or more mutations comprising G117F, C232S, M351V and M358L according to SEQ ID NO: 1. In some embodiments, the alpha-1-antitrypsin serpin domain has one or more mutations comprising C232S, K331F,

M351V and M358L according to SEQ ID NO: 1. In some embodiments, the alpha-1-antitrypsin serpin domain has one or more mutations comprising C232S, K335A, M351V and M358L according to SEQ ID NO: 1. In some embodiments, the alpha-1-antitrypsin serpin domain has one or more mutations comprising K168C, F189C, C232S, M351V, and M358L according to SEQ ID NO: 1. In some embodiments, the alpha-1-antitrypsin serpin domain has one or more mutations comprising C232S, S283C, M351V, M358L, and P361C according to SEQ ID NO: 1. In some embodiments, the alpha-1-antitrypsin serpin domain has one or more mutations comprising F51L, G117F, C232S, M351V, and M358L according to SEQ ID NO: 1. In some embodiments, the alpha-1-antitrypsin serpin domain has one or more mutations comprising F51L, C232S, K331F, M351V, and M358L according to SEQ ID NO: 1. In some embodiments, the alpha-1-antitrypsin serpin domain has one or more mutations comprising F51L, C232S, K335A, M351V, and M358L according to SEQ ID NO: 1. In some embodiments, the alpha-1-antitrypsin serpin domain has one or more mutations comprising K51L, K168C, F189C, C232S, M351V, and M358L according to SEQ ID NO: 1. In some embodiments, the alpha-1-antitrypsin serpin domain has one or more mutations comprising F51L, C232S, S283C, M351V, M358L, and P361C according to SEQ ID NO: 1. In some embodiments, the alpha-1-antitrypsin serpin domain has one or more mutations comprising G117F, C232S, K331F, M351V, and M358L according to SEQ ID NO: 1. In some embodiments, the alpha-1-antitrypsin serpin domain has one or more mutations comprising G117F, K335A, C232S, M351V, and M358L according to SEQ ID NO: 1. In some embodiments, the alpha-1-antitrypsin serpin domain has one or more mutations comprising G117F, K168C, F189C, C232S, M351V, and M358L according to SEQ ID NO: 1. In some embodiments, the alpha-1-antitrypsin serpin domain has one or more mutations comprising G117F, C232S, S283C, M351V, M358L, and P361C according to SEQ ID NO: 1. In some embodiments, the alpha-1-antitrypsin serpin domain has one or more mutations comprising C232S, K331F, K335A, M351V, and M358L according to SEQ ID NO: 1. In some embodiments, the alpha-1-antitrypsin serpin domain has one or more mutations comprising K168C, F189C, C232S, K331F, M351V, and M358L according to SEQ ID NO: 1. In some embodiments, the alpha-1-antitrypsin serpin domain has one or more mutations comprising C232S, S283C, K331F, M351V, M358L, and P361C according to SEQ ID NO: 1. In some embodiments, the alpha-1-antitrypsin serpin domain has one or more mutations comprising K168C, F189C, C232S, K335A, M351V, and M358L according to SEQ ID NO: 1. In some embodiments, the alpha-1-antitrypsin serpin domain has one or more mutations comprising C232S, S283C, K335A, M351V, M358L, and P361C according to SEQ ID NO: 1. In some

embodiments, the alpha-1-antitrypsin serpin domain has one or more mutations comprising K168C, F189C, C232S, S283C, M351V, M358L, and P361C according to SEQ ID NO: 1.In some embodiments, the alpha-1-antitrypsin serpin domain comprises a point mutation K335A according to SEQ ID NO: 1. In some embodiments, the alpha-1-antitrypsin serpin domain comprises a point mutation K331F according to SEQ ID NO: 1. In some embodiments, the alpha-1-antitrypsin serpin domain comprises a point mutation G117F according to SEQ ID NO: 1. In some embodiments, the alpha-1-antitrypsin serpin domain comprises a point mutation S283C according to SEQ ID NO: 1. In some embodiments, the alpha-1-antitrypsin serpin domain comprises a point mutation P361C according to SEQ ID NO: 1.

[0083] In some embodiments, glycan sites in an alpha-1-antitrypsin serpin domain are truncated and deleted. In some embodiments, the first residue of SEQ ID NO: 1 is mutated so that the glycan sites are deleted. In some embodiments, residues 1-46 of SEQ ID NO: 1 are deleted.

[0084] In some embodiments, the one or more mutations provide improved stability including improved stability to oxidation, retention of potency against human neutrophil elastase, resistance to polymerization, and ease of production, wherein the improved stability is measured against wild type.

[0085] In some embodiments, the one or more mutations are one or more mutations as set forth in Table 1 and in Tables 2-5 with residue positions being set forth according to SEQ ID NO: 1.

	AAT-Albumin Fusion
Base	WT
Base	C232S
Base	M351V, M358V
Base	M351V, M358L
Base	C232S, M351V, M358L

AAT Mutants

	Base	F51L	G117F	**K331F**	**K335A**	K168C/F189C	P361C – S283C
Base			**1**	**2**	**3**	**4**	**5**	**6**
F51L				**7**	**8**	**9**	**10**	**11**
G117F					**12**	**13**	**14**	**15**
K331F						**16**	**17**	**18**
K335A							**19**	**20**
K168C/F189C								**21**
P361C – S283C								

Table 1

[0086] In some embodiments, the alpha-1-antitrypsin serpin domain comprises a portion of the alpha-1-antitrypsin. In some embodiments, the portion of the alpha-1-antitrypsin serpin domain has an activity that is equal to or greater than a full length human alpha-1-antitrypsin such as, for example, without limitation, the alpha-1-antitrypsin serpin domain having the sequence set forth in SEQ ID NO: 1. In some embodiments, the portion is at least about 20 residues of an alpha-1-antitrypsin, at least about 30 residues of an alpha-1-antitrypsin, at least about 40 residues of an alpha-1-antitrypsin, at least about 50 residues of an alpha-1-antitrypsin, at least about 60 residues of an alpha-1-antitrypsin, at least about 70 residues of an alpha-1-antitrypsin, at least about 80 residues of an alpha-1-antitrypsin, at least about 90 residues of an alpha-1-antitrypsin, at least about 100 residues of an alpha-1-antitrypsin, at least about 110 residues of an alpha-1-antitrypsin, at least about 120 residues of an alpha-1-antitrypsin, at least about 130 residues of an alpha-1-antitrypsin, at least about 140 residues of an alpha-1-antitrypsin, at least about 150 residues of an alpha-1-antitrypsin, at least about 160 residues of an alpha-1-antitrypsin, at least about 170 residues of an alpha-1-antitrypsin, at least about 180 residues of an alpha-1-antitrypsin, at least about 190 residues of an alpha-1-antitrypsin, at least about 200 residues of an alpha-1-antitrypsin, at least about 210 residues of an alpha-1-antitrypsin, at least about 220 residues of an alpha-1-antitrypsin, at least about 230 residues of an alpha-1-antitrypsin, at least about 240 residues of an alpha-1-antitrypsin, at least about 250 residues of an alpha-1-antitrypsin, at least about 260 residues of an alpha-1-antitrypsin, at least about 270 residues of an alpha-1-antitrypsin, at least about 280 residues of an alpha-1-antitrypsin, at least about 290 residues of an alpha-1-antitrypsin, at least about 300 residues of an alpha-1-antitrypsin, at least about 310 residues of an alpha-1-antitrypsin, at least about 320 residues of an alpha-1-antitrypsin, at least about 330 residues of an alpha-1-antitrypsin, at least about 340 residues of an alpha-1-antitrypsin, at least about 350 residues of an alpha-1-antitrypsin, at least about 360 residues of an alpha-1-antitrypsin, at least about 370 residues of an alpha-1-antitrypsin, at least about 380 residues of an alpha-1-antitrypsin, or at least about 390 residues of an alpha-1-antitrypsin.

[0087] In some embodiments, the portion is at least about 20 residues of an alpha-1-antitrypsin having the sequence set forth in SEQ ID NO: 1, at least about 30 residues of an alpha-1-antitrypsin having the sequence set forth in SEQ ID NO: 1, at least about 40 residues of an alpha-1-antitrypsin having the sequence set forth in SEQ ID NO: 1, at least about 50 residues of an alpha-1-antitrypsin having the sequence set forth in SEQ ID NO: 1, at least about 60 residues of an alpha-1-antitrypsin having the sequence set forth in SEQ ID NO: 1, at least

about 70 residues of an alpha-1-antitrypsin having the sequence set forth in SEQ ID NO: 1, at least about 80 residues of an alpha-1-antitrypsin having the sequence set forth in SEQ ID NO: 1, at least about 90 residues of an alpha-1-antitrypsin having the sequence set forth in SEQ ID NO: 1, at least about 100 residues of an alpha-1-antitrypsin having the sequence set forth in SEQ ID NO: 1, at least about 110 residues of an alpha-1-antitrypsin having the sequence set forth in SEQ ID NO: 1, at least about 120 residues of an alpha-1-antitrypsin having the sequence set forth in SEQ ID NO: 1, at least about 130 residues of an alpha-1-antitrypsin having the sequence set forth in SEQ ID NO: 1, at least about 140 residues of an alpha-1-antitrypsin having the sequence set forth in SEQ ID NO: 1, at least about 150 residues of an alpha-1-antitrypsin having the sequence set forth in SEQ ID NO: 1, at least about 160 residues of an alpha-1-antitrypsin having the sequence set forth in SEQ ID NO: 1, at least about 170 residues of an alpha-1-antitrypsin having the sequence set forth in SEQ ID NO: 1, at least about 180 residues of an alpha-1-antitrypsin having the sequence set forth in SEQ ID NO: 1, at least about 190 residues of an alpha-1-antitrypsin having the sequence set forth in SEQ ID NO: 1, at least about 200 residues of an alpha-1-antitrypsin having the sequence set forth in SEQ ID NO: 1, at least about 210 residues of an alpha-1-antitrypsin having the sequence set forth in SEQ ID NO: 1, at least about 220 residues of an alpha-1-antitrypsin having the sequence set forth in SEQ ID NO: 1, at least about 230 residues of an alpha-1-antitrypsin having the sequence set forth in SEQ ID NO: 1, at least about 240 residues of an alpha-1-antitrypsin having the sequence set forth in SEQ ID NO: 1, at least about 250 residues of an alpha-1-antitrypsin having the sequence set forth in SEQ ID NO: 1, at least about 260 residues of an alpha-1-antitrypsin having the sequence set forth in SEQ ID NO: 1, at least about 270 residues of an alpha-1-antitrypsin having the sequence set forth in SEQ ID NO: 1, at least about 280 residues of an alpha-1-antitrypsin having the sequence set forth in SEQ ID NO: 1, at least about 290 residues of an alpha-1-antitrypsin having the sequence set forth in SEQ ID NO: 1, at least about 300 residues of an alpha-1-antitrypsin having the sequence set forth in SEQ ID NO: 1, at least about 310 residues of an alpha-1-antitrypsin having the sequence set forth in SEQ ID NO: 1, at least about 320 residues of an alpha-1-antitrypsin having the sequence set forth in SEQ ID NO: 1, at least about 330 residues of an alpha-1-antitrypsin having the sequence set forth in SEQ ID NO: 1, at least about 340 residues of an alpha-1-antitrypsin having the sequence set forth in SEQ ID NO: 1, at least about 350 residues of an alpha-1-antitrypsin having the sequence set forth in SEQ ID NO: 1, at least about 360 residues of an alpha-1-antitrypsin having the sequence set forth in SEQ ID NO: 1, at least about 370 residues of an alpha-1-antitrypsin having the sequence set forth in SEQ ID NO: 1, at least about 380 residues of an alpha-1-antitrypsin

having the sequence set forth in SEQ ID NO: 1, or at least about 390 residues of an alpha-1-antitrypsin having the sequence set forth in SEQ ID NO: 1.

[0088] In some embodiments, an alpha-1-antitrypsin serpin domain comprises a variant of a normal alpha-1-antitrypsin as set forth in SEQ ID NO: 1. In some embodiments, the variant comprises an active portion of the alpha-1-antitrypsin serpin domain.

Albumin

[0089] In some embodiments, the human serum albumin domain comprises a full-length human albumin. In some embodiments, the human serum albumin domain comprises the sequence set forth in SEQ ID NO: 3 or SEQ ID NO: 5. In some embodiments, the human serum albumin domain has a sequence comprising SEQ ID NO: 3 or SEQ ID NO: 5

[0090] In some embodiments, the human serum albumin domain comprises one or more mutations. In some embodiments, the one or more mutations comprises mutations in one or more of the following locations: 407, 408, 409, 410, 413, and 414, wherein the location numbers are with respect to SEQ ID NO. 5. In some embodiments, the one or more mutations comprises at least one of the following mutations: L407A, L408V, V409A, R410A, L413Q, and L414Q, wherein the position numbers are with respect to SEQ ID NO. 5 (*See*, e.g., International Publication No. WO95/23857, hereby incorporated in its entirety by reference herein.) In some embodiments, the one or more mutations comprises L407A, L408V, V409A, and R410A, wherein the position numbers are with respect to SEQ ID NO. 5. In some embodiments, the one or more mutations comprises R410A, L413Q, and L414Q, wherein the position numbers are with respect to SEQ ID NO. 5. In some embodiments, the one or more mutations improves stability and/or increases production of the recombinant protein.

[0091] In some embodiments, the human serum albumin domain comprises a portion of human albumin. In some embodiments, the portion is at least about 20 residues of a human serum albumin, at least about 30 residues of a human serum albumin, at least about 40 residues of a human serum albumin, at least about 50 residues of a human serum albumin, at least about 60 residues of a human serum albumin, at least about 70 residues of a human serum albumin, at least about 80 residues of a human serum albumin, at least about 90 residues of a human serum albumin, at least about 100 residues of a human serum albumin, at least about 110 residues of a human serum albumin, at least about 120 residues of a human serum albumin, at least about 130 residues of a human serum albumin, at least about 140 residues of a human serum albumin, at least about 150 residues of a human serum albumin, at least about 160

residues of a human serum albumin, at least about 170 residues of a human serum albumin, at least about 180 residues of a human serum albumin, at least about 190 residues of a human serum albumin, at least about 200 residues of a human serum albumin, at least about 210 residues of a human serum albumin, at least about 220 residues of a human serum albumin, at least about 230 residues of a human serum albumin, at least about 240 residues of a human serum albumin, at least about 250 residues of a human serum albumin, at least about 260 residues of a human serum albumin, at least about 270 residues of a human serum albumin, at least about 280 residues of a human serum albumin, at least about 290 residues of a human serum albumin, at least about 300 residues of a human serum albumin, at least about 310 residues of a human serum albumin, at least about 320 residues of a human serum albumin, at least about 330 residues of a human serum albumin, at least about 340 residues of a human serum albumin, at least about 350 residues of a human serum albumin, at least about 360 residues of a human serum albumin, at least about 370 residues of a human serum albumin, at least about 380 residues of a human serum albumin, at least about 390 residues of a human serum albumin, at least about 400 residues of a human serum albumin, at least about 410 residues of a human serum albumin, at least about 420 residues of a human serum albumin, at least about 430 residues of a human serum albumin, at least about 440 residues of a human serum albumin, at least about 450 residues of a human serum albumin, at least about 460 residues of a human serum albumin, at least about 470 residues of a human serum albumin, at least about 480 residues of a human serum albumin, at least about 490 residues of a human serum albumin, at least about 500 residues of a human serum albumin, at least about 510 residues of a human serum albumin, at least about 520 residues of a human serum albumin, at least about 530 residues of a human serum albumin, at least about 540 residues of a human serum albumin, at least about 550 residues of a human serum albumin, at least about 560 residues of a human serum albumin, at least about 570 residues of a human serum albumin, at least about 580 residues of a human serum albumin, at least about 590 residues of a human serum albumin, or at least about 600 residues of a human serum albumin.

[0092] In some embodiments, the portion is at least about 20 residues of a human serum albumin having the sequence set forth in SEQ ID NO: 3 or SEQ ID NO: 5, at least about 30 residues of a human serum albumin having the sequence set forth in SEQ ID NO: 3 or SEQ ID NO: 5, at least about 40 residues of a human serum albumin having the sequence set forth in SEQ ID NO: 3 or SEQ ID NO: 5, at least about 50 residues of a human serum albumin having the sequence set forth in SEQ ID NO: 3 or SEQ ID NO: 5, at least about 60 residues of a human

serum albumin having the sequence set forth in SEQ ID NO: 3 or SEQ ID NO: 5, at least about 70 residues of a human serum albumin having the sequence set forth in SEQ ID NO: 3 or SEQ ID NO: 5, at least about 80 residues of a human serum albumin having the sequence set forth in SEQ ID NO: 3 or SEQ ID NO: 5, at least about 90 residues of a human serum albumin having the sequence set forth in SEQ ID NO: 3 or SEQ ID NO: 5, at least about 100 residues of a human serum albumin having the sequence set forth in SEQ ID NO: 3 or SEQ ID NO: 5, at least about 110 residues of a human serum albumin having the sequence set forth in SEQ ID NO: 3 or SEQ ID NO: 5, at least about 120 residues of a human serum albumin having the sequence set forth in SEQ ID NO: 3 or SEQ ID NO: 5, at least about 130 residues of a human serum albumin having the sequence set forth in SEQ ID NO: 3 or SEQ ID NO: 5, at least about 140 residues of a human serum albumin having the sequence set forth in SEQ ID NO: 3 or SEQ ID NO: 5, at least about 150 residues of a human serum albumin having the sequence set forth in SEQ ID NO: 3 or SEQ ID NO: 5, at least about 160 residues of a human serum albumin having the sequence set forth in SEQ ID NO: 3 or SEQ ID NO: 5, at least about 170 residues of a human serum albumin having the sequence set forth in SEQ ID NO: 3 or SEQ ID NO: 5, at least about 180 residues of a human serum albumin having the sequence set forth in SEQ ID NO: 3 or SEQ ID NO: 5, at least about 190 residues of a human serum albumin having the sequence set forth in SEQ ID NO: 3 or SEQ ID NO: 5, at least about 200 residues of a human serum albumin having the sequence set forth in SEQ ID NO: 3 or SEQ ID NO: 5, at least about 210 residues of a human serum albumin having the sequence set forth in SEQ ID NO: 3 or SEQ ID NO: 5, at least about 220 residues of a human serum albumin having the sequence set forth in SEQ ID NO: 3 or SEQ ID NO: 5, at least about 230 residues of a human serum albumin having the sequence set forth in SEQ ID NO: 3 or SEQ ID NO: 5, at least about 240 residues of a human serum albumin having the sequence set forth in SEQ ID NO: 3 or SEQ ID NO: 5, at least about 250 residues of a human serum albumin having the sequence set forth in SEQ ID NO: 3 or SEQ ID NO: 5, at least about 260 residues of a human serum albumin having the sequence set forth in SEQ ID NO: 3 or SEQ ID NO: 5, at least about 270 residues of a human serum albumin having the sequence set forth in SEQ ID NO: 3 or SEQ ID NO: 5, at least about 280 residues of a human serum albumin having the sequence set forth in SEQ ID NO: 3 or SEQ ID NO: 5, at least about 290 residues of a human serum albumin having the sequence set forth in SEQ ID NO: 3 or SEQ ID NO: 5, at least about 300 residues of a human serum albumin having the sequence set forth in SEQ ID NO: 3 or SEQ ID NO: 5, at least about 310 residues of a human serum albumin having the sequence set forth in SEQ ID NO: 3 or SEQ ID NO: 5, at least about 320 residues of a human serum albumin having the sequence set forth in SEQ ID

NO: 3 or SEQ ID NO: 5, at least about 330 residues of a human serum albumin having the sequence set forth in SEQ ID NO: 3 or SEQ ID NO: 5, at least about 340 residues of a human serum albumin having the sequence set forth in SEQ ID NO: 3 or SEQ ID NO: 5, at least about 350 residues of a human serum albumin having the sequence set forth in SEQ ID NO: 3 or SEQ ID NO: 5, at least about 360 residues of a human serum albumin having the sequence set forth in SEQ ID NO: 3 or SEQ ID NO: 5, at least about 370 residues of a human serum albumin having the sequence set forth in SEQ ID NO: 3 or SEQ ID NO: 5, at least about 380 residues of a human serum albumin having the sequence set forth in SEQ ID NO: 3 or SEQ ID NO: 5, at least about 390 residues of a human serum albumin having the sequence set forth in SEQ ID NO: 3 or SEQ ID NO: 5, at least about 400 residues of a human serum albumin having the sequence set forth in SEQ ID NO: 3 or SEQ ID NO: 5, at least about 410 residues of a human serum albumin having the sequence set forth in SEQ ID NO: 3 or SEQ ID NO: 5, at least about 420 residues of a human serum albumin having the sequence set forth in SEQ ID NO: 3 or SEQ ID NO: 5, at least about 430 residues of a human serum albumin having the sequence set forth in SEQ ID NO: 3 or SEQ ID NO: 5, at least about 440 residues of a human serum albumin having the sequence set forth in SEQ ID NO: 3 or SEQ ID NO: 5, at least about 450 residues of a human serum albumin having the sequence set forth in SEQ ID NO: 3 or SEQ ID NO: 5, at least about 460 residues of a human serum albumin having the sequence set forth in SEQ ID NO: 3 or SEQ ID NO: 5, at least about 470 residues of a human serum albumin having the sequence set forth in SEQ ID NO: 3 or SEQ ID NO: 5, at least about 480 residues of a human serum albumin having the sequence set forth in SEQ ID NO: 3 or SEQ ID NO: 5, at least about 490 residues of a human serum albumin having the sequence set forth in SEQ ID NO: 3 or SEQ ID NO: 5, at least about 500 residues of a human serum albumin having the sequence set forth in SEQ ID NO: 3 or SEQ ID NO: 5, at least about 510 residues of a human serum albumin having the sequence set forth in SEQ ID NO: 3 or SEQ ID NO: 5, at least about 520 residues of a human serum albumin having the sequence set forth in SEQ ID NO: 3 or SEQ ID NO: 5, at least about 530 residues of a human serum albumin having the sequence set forth in SEQ ID NO: 3 or SEQ ID NO: 5, at least about 540 residues of a human serum albumin having the sequence set forth in SEQ ID NO: 3 or SEQ ID NO: 5, at least about 550 residues of a human serum albumin having the sequence set forth in SEQ ID NO: 3 or SEQ ID NO: 5, at least about 560 residues of a human serum albumin having the sequence set forth in SEQ ID NO: 3 or SEQ ID NO: 5, at least about 570 residues of a human serum albumin having the sequence set forth in SEQ ID NO: 3 or SEQ ID NO: 5, at least about 580 residues of a human serum albumin having the sequence set forth in SEQ ID NO: 3 or SEQ ID NO: 5, at least about 590 residues

of a human serum albumin having the sequence set forth in SEQ ID NO: 3 or SEQ ID NO: 5, or at least about 600 residues of a human serum albumin having the sequence set forth in SEQ ID NO: 3 or SEQ ID NO: 5.

[0093] In some embodiments, the portion of human serum albumin consists of or comprises at least one amino acid sequence, or a variant thereof, of the sequences set forth in amino acid residues 1-194 of SEQ ID NO: 5, amino acid residues 195-387 of SEQ ID NO: 5, amino acid residues 388-585 of SEQ ID NO: 5, 1-387 of SEQ ID NO: 5, 195-585 of SEQ ID NO: 5, or amino acid residues 1-194 of SEQ ID NO:5 and amino acid residues 388-585 of SEQ ID NO: 5. Each domain is itself made up of two homologous subdomains namely 1-105, 120-194, 195-291, 316-387, 388-491 and 512-585, with flexible inter-subdomain linker regions (*See*, for example, EP 2 090 589 A1, which is incorporated by reference herein, including any drawings.) In some embodiments, the portion consists of or comprises at least one subdomain.

[0094] In some embodiments, the portion of the human serum albumin domain has an activity that is equal to or greater than a full length human albumin such as. In some embodiments, the human serum albumin has a sequence comprising the sequence set forth in SEQ ID NO: 5.

[0095] In some embodiments, the human serum albumin domain comprises a variant of a wild type human serum albumin.

Albumin Binding Protein

[0096] In some embodiments, the human serum albumin binding domain comprises amino acid sequences that are capable of binding to human serum albumin. In some embodiments, the human serum albumin has the sequence set forth in SEQ ID NO: 3 or SEQ ID NO: 5. In some embodiments, human serum albumin comprises a portion of the human serum albumin set forth in SEQ ID NO: 5. In some embodiments, the portion of the human albumin comprises an epitope.

[0097] In some embodiments, the human serum albumin binding domain comprises an antibody. In some embodiments, the antibody is a monoclonal antibody. In some embodiments, the antibody is a humanized antibody. In some embodiments, the antibody is a human immunoglobulin ((*e.g.*, IgG (*e.g.*, IgG1, IgG2, IgG3, IgG4); IgE (*e.g.*, IgE1), IgA (*e.g.*, IgA1, IgA2), IgM (*e.g.*, IgM1), IgD (*e.g.*, IgD1)) or fragment, portion, or variant of a human immunoglobulin.

[0098] In some embodiments, the human serum albumin binding domain comprises a single domain antibody. In some embodiments, the single domain antibody comprises a CDR1 sequence comprising, consisting of, or consisting essentially of a sequence selected from SEQ ID NOs: 6-9. In some embodiments, the single domain antibody comprises a CDR2 sequence comprising, consisting of, or consisting essentially of a sequence selected from SEQ ID NOs: 10-16. In some embodiments, the single domain antibody comprises a CDR3 sequence comprising, consisting of, or consisting essentially of a sequence selected from SEQ ID NOs: 17-21. In some embodiments, the single domain antibody includes any one or more of the framework regions having a sequence comprising SEQ ID NOs: 37-62.

[0099] In some embodiments, the single domain antibody comprises a combination of one or more binding domains. In some embodiments, the single domain antibody comprises a combination of one or more of CDR1, CDR2, and CDR3. In some embodiments, the single domain antibody comprises a CDR1 sequence comprising, consisting of, or consisting essentially of a sequence selected from SEQ ID NOs: 6-9 and a CDR2 sequence comprising, consisting of, or consisting essentially of a sequence selected from SEQ ID NOs: 10-16. In some embodiments, the single domain antibody comprises a CDR1 sequence comprising, consisting of, or consisting essentially of a sequence selected from SEQ ID NOs: 6-9 and a CDR3 sequence comprising, consisting of, or consisting essentially of a sequence selected from SEQ ID NOs: 17-21. In some embodiments, the single domain antibody comprises a CDR2 sequence comprising, consisting of, or consisting essentially of a sequence selected from SEQ ID NOs: 10-16 and a CDR3 sequence comprising, consisting of, or consisting essentially of a sequence selected from SEQ ID NOs: 17-21. In some embodiments, the single domain antibody comprises a CDR1 sequence comprising, consisting of, or consisting essentially of a sequence selected from SEQ ID NOs: 6-9, a CDR2 sequence comprising, consisting of, or consisting essentially of a sequence selected from SEQ ID NOs: 10-16, and a CDR3 sequence comprising, consisting of, or consisting essentially of a sequence selected from SEQ ID NOs: 17-21.

[00100] In some embodiments, the single domain antibody comprises a sequence selected from SEQ ID NOs: 22-28.

[00101] In some embodiments, the single domain antibody comprises a humanized sequence selected from SEQ ID NOs: 29-36. In some embodiments, the single domain antibody comprises a humanized sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 29. In some embodiments, the single domain antibody comprises a humanized

sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 30. In some embodiments, the single domain antibody comprises a humanized sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 31. In some embodiments, the single domain antibody comprises a humanized sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 32. In some embodiments, the single domain antibody comprises a humanized sequence having SEQ ID NO: 33. In some embodiments, the single domain antibody comprises a humanized sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 34. In some embodiments, the single domain antibody comprises a humanized sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 35. In some embodiments, the single domain antibody comprises a humanized sequence comprising, consisting of, or consisting essentially of SEQ ID NO: 36.

[00102] In some embodiments, the single domain antibody comprises a variant of a humanized sequence selected from SEQ ID NOs: 29-36. Variants described herein include polypeptides having at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98% or at least about 99% identity with any sequence of the popypeptides provided herein. For example, variants of a humanized single domain antibody would have at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% identity with the amino acid sequence of any one of SEQ ID NOs: 29-36.

Nucleic Acids

[00103] Some embodiments comprise an isolated nucleic acid molecule encoding a recombinant protein comprising a nucleic acid encoding an alpha-1-antitrypsin serpin domain operatively linked to a nucleotide sequence encoding a human serum albumin or a human serum albumin binding domain. In some embodiments, the human serum albumin binding domain comprises an antibody. In some embodiments, the antibody comprises a single domain antibody.

[00104] In some embodiments, the disclosure features a nucleic acid molecule that includes a fragment of an alpha-1-antitrypsin serpin domain encoding sequence and a fragment of a human serum albumin binding domain or a human serum albumin domain encoding sequence. In some embodiments, the nucleotide sequence encodes a fragment or variant of the alpha-1-antitrypsin of SEQ ID NO: 1 and/or a fragment of a human serum albumin binding

domain or a human serum albumin domain encoding sequence of SEQ ID NO: 3 or SEQ ID NO: 5 or any of SEQ NOs: 22-36.

[00105] In some embodiments, the nucleic acid comprises a vector as will be set forth below.

Domains, Domain Order, and Linkers

[00106] In some embodiments, the recombinant proteins of the invention have one human serum albumin domain or one human serum albumin binding domain and one alpha1-antitrypsin serum domain. In some embodiments, multiple domains of each protein, however, may be used to make a recombinant protein of the invention. Similarly, more than one alpha-1-antitrypsin serum domain may be used to make a recombinant protein of the invention. For instance, an alpha-1-antitrypsin serum domain may be fused to both the N- and C-terminal ends of the human serum albumin domain or the human serum albumin binding domain.

[00107] In some embodiments, the recombinant proteins do not contain a linker between the fused portions of the polypeptides (*e.g.*, the portion of alpha-1-antitrypsin serpin domain is fused to the portion of the human serum albumin domain and/or human serum albumin binding domain). In some embodiments, the recombinant proteins include a linker peptide between the fused portions of the polypeptides. The linker can be a peptide linker. The linker can improve expression yield of the recombinant protein. The linker can improve and/or enhance biological activity of the alpha-1-antitrypsin serpin domain.

[00108] One skilled in the art will appreciate that there are a great number of linkers that can be used for the present invention (*See*, for example, Chen at al., Fusion Protein Linkers: Property, Design, and Functionality, *Adv Drug Deliv Rev.* 2013 October 15; 65(10): 1357-1369 (2012), which is incorporated by reference herein in its entirety.) In some embodiments, the linker is a peptide having a sequence comprising, consisting of or, or consisting essentially of the set forth in SEQ ID NO: 63.

Compositions

[00109] The disclosure provides a pharmaceutical composition comprising any of the recombinant proteins set forth herein. Pharmaceutical compositions may take the form of any acceptable pharmaceutical formulation. Pharmaceutical compositions can be formulated in a variety of different forms, such as liquid, semi-solid, and solid dosage forms, such as liquid solutions (*e.g.*, injectable and infusible solutions), dispersions or suspensions, tablets, pills,

powders, liposomes, and suppositories. The preferred form can depend on the intended mode of administration and therapeutic application.

[00110] Exemplary pharmaceutical compositions are described below. The pharmaceutical compositions include those suitable for parenteral (including intravenous, subcutaneous, intradermal, intramuscular, and intraarticular), topical (including dermal, transdermal, transmucosal, buccal, sublingual, and intraocular), and rectal administration, although the most suitable route may depend upon, for example, the condition and disorder of the recipient.

[00111] The pharmaceutical compositions described herein can be administered systemically, *e.g.,* parenteral (*e.g.,* intravenous, subcutaneous, intradermal, intramuscular, and intraarticular). The pharmaceutical compositions described herein can be administered locally, *e.g.,* administered to an area affected by the condition or disorder the pharmaceutical composition is being administered to treat.

[00112] Compositions for parenteral administration include aqueous and non-aqueous sterile injection solutions that may contain anti-oxidants, buffers, bacteriostats, and solutes that render the composition isotonic with the blood of the intended recipient and aqueous and non-aqueous sterile suspensions that may include suspending agents and thickening agents. The composition may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example saline or water-for-injection, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules, and tablets. Exemplary compositions for parenteral administration include injectable solutions or suspensions which can contain, for example, suitable non-toxic, parenterally acceptable diluents, or solvents, such as EDTA, mannitol, 1,3-butanediol, water, Ringer's solution, an isotonic sodium chloride solution, or other suitable dispersing or wetting and suspending agents. The compositions may contain pharmaceutically acceptable substances or adjuvants, including, but not limited to, EDTA, *e.g.,* 0.5mM EDTA; pH adjusting and buffering agents and/or tonicity adjusting agents, *e.g.,* sodium acetate, sodium lactate, sodium chloride, potassium chloride, calcium chloride, sorbitan monolaurate, minor amounts of non-toxic auxiliary substances, such as wetting, or emulsifying agents or preservatives.

Treatment

[00113] In some embodiments, the disclosure features a method of treating a disorder associated with an alpha-1 antitrypsin deficiency, the method comprising administering to a patient or subject in need thereof having a disorder associated with an alpha-1-antitrypsin deficiency an effective amount of a recombinant protein or pharmaceutical compositions provided herein. In some embodiments, the disclosure features a method of prophylactically treating a disorder associated with an alpha-1 antitrypsin deficiency, the method comprising administering to a patient or subject in need thereof having a disorder associated with an alpha-1-antitrypsin deficiency an effective amount of a recombinant protein or pharmaceutical compositions as set forth herein. In some embodiments, the recombinant protein or pharmaceutical compositions may be administered to a patient in need thereof alone or in combination with another compound.

[00114] In some embodiments, administration of the recombinant protein or pharmaceutical compositions is administered about once a week or at longer intervals than about once a week, about once every 10 days or at longer intervals than about once every 10 days, about once every 15 days or at longer intervals than about once every 15 days, about once every 20 days or at longer intervals than about once every 20 days, about once every 25 days or at longer intervals than about once every 25 days, about once every month or at longer intervals than about once a month, about once every two months or at longer intervals than about once every two months, or about once every three months or at longer intervals than about once every three months.

[00115] In some embodiments, the subject has been diagnosed with or is at risk of being diagnosed with an alpha-1-antitrypsin deficiency. In some embodiments, the alpha-1-antitrypsin deficiency shows evidence of liver disease or evidence of lung disease. In some embodiments, the alpha-1-antitrypsin deficiency occurs in a person that has no apparent cause of liver disease or lung disease. In some embodiments, the evidence of liver disease or evidence of lung disease is at least one selected from the group consisting of emphysema, hepatic failure, hepatitis, hepatomology, jaundice, cirrhosis, nephratic syndrome, autosomal recessive inheritance, COPD-like symptoms, dyspnea, elevated hepatic transaminases, and hepatocellular carcinoma.

[00116] In some embodiments, the alpha-1-antitrypsin deficiency is caused by deficiency mutations in the *SERPINA1* gene. More than 120 deficiency mutations in the

SERPINA1 gene have been identified and may be useful for diagnosis according to the invention. Some deficiency mutations do not affect the production of alpha-1 antitrypsin while others cause a shortage or deficiency of the protein. In some embodiments, the deficiency mutations in the *SERPINA1* gene replace the amino acid glutamic acid with the amino acid lysine at protein position 342 according to SEQ ID NO: 1.

[00117] Abnormal alpha-1 antitrypsin proteins may bind together to form a large molecule that cannot leave the liver. The accumulation of these polymers often results in liver damage. In addition, lung tissue is destroyed because not enough alpha-1 antitrypsin is available to protect against neutrophil elastase or PR3. Polymers of alpha-1 antitrypsin may also contribute to excessive inflammation, which may explain some of the other features of alpha-1 antitrypsin deficiency, such as a skin condition called panniculitis. Other *SERPINA1* deficiency mutations lead to the production of an abnormally small form of alpha-1 antitrypsin that is quickly broken down in the liver. As a result, little or no alpha-1 antitrypsin is available in the lungs. While the liver remains healthy in individuals with these deficiency mutations, the lungs are left unprotected from neutrophil elastase or PR3.

[00118] In some embodiments, the deficiency mutation is a loss-of-function mutation. In some embodiments, the deficiency mutation results in a stop codon. In some embodiments, the deficiency mutation results in an amino acid substitution. In some embodiments, the deficiency mutation is a point mutation, insertion, deletion, and/or substitution. In some embodiments, the deficiency mutation is a point mutation. In some embodiments, the deficiency mutation is a deletion. The deletion can involve only one or a few base pairs, multiple exons, or the entire gene. In some embodiments, the deficiency mutation is a whole gene deletion. In some embodiments, the deficiency mutation is a partial gene deletion. In some embodiments, the deficiency mutation results in intronic changes that affect splicing. In some embodiments, the deficiency mutation is an alteration of the 3' untranslated region of the gene. In some embodiments, the deficiency mutation is a gross chromosomal rearrangement. In some embodiments, the deficiency mutation results in truncation of the *SERPINA1* gene product.

[00119] In some embodiments, the subject has aberrant expression of the alpha-1-antitrypsin protein compared to a reference standard. In some embodiments, the reference standard is the level of expression of the alpha-1-antitrypsin protein in a subject who does not have the disorder associated with alpha-1-antitrypsin deficiency. In some embodiments, the subject has decreased or substantially no expression of the alpha-1-antitrypsin protein

compared to a reference standard. In some embodiments, the reference standard is the level of expression of the alpha-1-antitrypsin protein in a subject who does not have the disorder associated with alpha-1-antitrypsin deficiency.

[00120] In some embodiments, the alpha-1-antitrypsin serpin domain is a normal alpha-1-antitrypsin domain allele (*See* Crystal, R. G. The alpha-1-antitrypsin gene and its deficiency states. Trends Genet. 5: 411-417, 1989. [PubMed: 2696185], which is incorporated by reference in its entirety herein.) In some embodiments, the allele is an allele with a valine at position 213 (M1V; 107400.0002) and that with alanine at position 213 (M1A; 107400.0001) according to SEQ ID NO: 1 (*See* Nukiwa, T., Brantly, M. L., Ogushi, F., Fells, G. A., Crystal, R. G. Characterization of the gene and protein of the common alpha-1-antitrypsin normal M2 allele. Am. J. Hum. Genet. 43: 322-330, 1988. [PubMed: 2901226], which is incorporated by reference in its entirety herein.) In some embodiments, the allele is a deficiency allele or a null allele.

[00121] In some embodiments, the subject has been diagnosed with or is at risk of a disorder associated with an alpha-1-antitrypsin deficiency. In some embodiments, the subject has a mutation in the gene encoding an alpha-1-antitrypsin domain. In some embodiments, the mutation is a mutation in one of the exons of alpha-1-antitrypsin. In some embodiments, the mutation is a mutation in exon 1 of alpha-1-antitrypsin, the 5-prime coding region of exon 2 of alpha-1-antitrypsin, or the 3-prime portion of exon 5 of alpha-1-antitrypsin (*See* Long, G. L., Chandra, T., Woo, S. L. C., Davie, E. W., Kurachi, K. Complete sequence of the cDNA for human alpha-1-antitrypsin and the gene for the S variant. Biochemistry 23: 4828-4837, 1984. [PubMed: 6093867], which is incorporated by reference in its entirety herein.)

[00122] In some embodiments, the recombinant protein or pharmaceutical compositions is administered intravenously. In some embodiments, the recombinant protein or pharmaceutical compositions is administered intradermally. In some embodiments, the recombinant protein or pharmaceutical compositions is administered topically. In some embodiments, the recombinant protein or pharmaceutical compositions is administered subcutaneously. In some embodiments, the recombinant protein or pharmaceutical compositions is administered intrathecally. In some embodiments, the recombinant protein or pharmaceutical compositions is administered intrathecally.

Vectors and Host Cells and Expression of Polypeptides

[00123] In some embodiments, the nucleic acid is a vector. In some embodiments, the vector comprises a host cell. Some embodiments are drawn to a method of making a recombinant protein comprising culturing the host cell with one of the nucleic acids provided herein and collecting the recombinant protein. In some embodiments, the recombinant protein is collected using an alpha-1-antitrypsin-Fc capture select media at neutral pH.

[00124] The recombinant proteins described herein may be produced, *e.g.*, as recombinant molecules by secretion from any suitable host cell. Many expression systems are known and may be used, including bacteria (for example *E. coli* and *Bacillus subtilis*), yeasts (for example *Saccharomyces cerevisiae*, *Kluyveromyces lactis* and *Pichia pastoris*, filamentous fungi (for example Aspergillus), plant cells, animal cells, and insect cells.

[00125] In some embodiments, the host cell is a eukaryotic cell. In some embodiments, the host cell is a mammalian cell. In some embodiments, the host cell is selected from the group consisting of CHO cells, BHK cells, COS-7 cells, L cells, C127 cells, and 3T3 cells. In some embodiments, the host cell is a CHO cell.

[00126] In some embodiments, the host cell is a yeast cell. Exemplary genera of yeast which can be used as hosts described herein include but are not limited to *Pichia, Saccharomyces, Kluyveromyces, Aspergillus, Candida, Torulopsis, Torulaspora, Schizosaccharomyces, Citeromyces, Pachysolen, Zygosaccharomyces, Debaromyces, Trichoderma, Cephalosporium, Humicola, Mucor, Neurospora, Yarrowia, Metschunikowia, Rhodosporidium, Leucosporidium, Botryoascus, Sporidiobolus, Endomycopsis*, and the like. Examples of *Saccharomyces spp, are S. cerevisiae, S. italicus and S. rouxii*. Yeast strains suitable for the production of fusion polypeptides described herein can include, but are not limited to D88, DXY1 and BXP10.

[00127] In addition to the transformed host cells themselves, also described herein is a culture of those cells, preferably a monoclonal (clonally homogeneous) culture, or a culture derived from a monoclonal culture, in a nutrient medium. If the recombinant protein is secreted, the medium will contain the recombinant protein, with the cells, or without the cells if they have been filtered or centrifuged away.

[00128] The recombinant proteins can be produced in conventional ways, for example from a coding sequence inserted in the host chromosome or on a free plasmid. The host cells are transformed with a coding sequence for the recombinant protein by any method known in

the art, for example electroporation. Successfully transformed cells, i.e., cells that contain a DNA construct described herein, can be identified by techniques known to those of skill in the art. For example, cells resulting from the introduction of an expression construct can be grown to produce the recombinant protein. Cells can be harvested and lysed and their DNA content examined for the presence of the DNA using methods known in the art. The presence of the recombinant protein in the supernatant can be detected using any method known in the art (e.g. an antibody based detection method).

[00129] Also disclosed herein are plasmid vectors comprising the nucleic acids used to express the recombinant proteins described herein. In order to express the recombinant proteins described herein, the nucleotide sequence encoding the appropriate recombinant proteins, or a functional equivalent, can be inserted into a suitable vector. A suitable vector contains the necessary and appropriate transcriptional and translational control sequences for expression of the inserted nucleic acid sequence. Standard methods, known to those skilled in the art, may be used to construct the recombinant expression vectors containing the nucleic acid sequences described herein. These methods include, but are not limited to, *in vitro* recombinant techniques, synthetic techniques, and *in vivo* recombination/genetic recombination; the choice of method depends on the nature of the specific nucleotide fragments and may be determined by persons skilled in the art.

[00130] Suitable vectors for use herein may contain an origin of replication and a restriction endonuclease sequence site. Persons skilled in the art would have knowledge of suitable origin of replication and restriction endonuclease sequences for use in the host cell. Suitable vectors for use herein may contain sequence elements to aid transcription, including, but not limited to, promoter and enhancer elements. Persons skilled in the art would have knowledge of various transcriptional control elements, including but not limited to, promoters, inducible promoters, and enhancer elements, that would be suitable in the host cell.

[00131] Suitable vectors for use herein may also contain a selectable marker gene that encodes a product necessary for the host cell to grow and survive under specific conditions, aiding in the selection of host cells into which the vector has been introduced. Typical selection genes may include, but not be limited to, genes encoding a protein that confers resistance to an antibiotic, drug, or toxin (e.g. tetracycline, ampicillin, neomycin, hygromycin, etc). Persons skilled in the art would have knowledge of coding sequences for suitable selectable markers and reporter genes for use in the host cell.

[00132] Expression vectors described herein can be introduced into host cells via conventional transformation or transfection techniques. Transformation and transfection techniques include, but are not limited to, calcium phosphate or calcium chloride coprecipitation, DEAE-dextran-mediated transfection, lipofectamine, electroporation, microinjection, and viral mediated transfection (*See,* U.S. Pat No. 6,632,637, which is incorporated by reference herein in its entirety.) Persons skilled in the art would have knowledge of suitable transformation and transfection methods based on the host cell/vector combination. For long term, high yield production of recombinant proteins, stable expression of the recombinant protein may be preferred. Host cells that stably express the recombinant protein may be engineered. Yeast plasmid vectors can include but are not limited to pRS403-406, pRS413-416, pRS403, pRS404, pRS405, pRS406 , pRS413-416, pPPC0005, pScCHSA, pScNHSA, and pC4.

[00133] In another embodiment, the recombinant mammalian expression vector is capable of directing expression of the polypeptide preferentially in a particular cell type (*e.g.,* tissue-specific regulatory elements are used I to express the polypeptide). Tissue-specific regulatory elements are known in the art. Non-limiting examples of suitable tissue-specific promoters include the albumin promoter (liver-specific; Pinkert et al. (1987) Genes Dev. 1:268-277), lymphoid-specific promoters (Calame and Eaton (1988) Adv. Immunol. 43:235-275), T cell promoters (Winoto and Baltimore (1989) EMBO J. 8:729-733) and immunoglobulin promoters (Banerji et al. (1983) Cell 33:729-740 and Queen and Baltimore (1983) Cell 33:741-748), neuron-specific promoters (*e.g.,* the neurofilament promoter; Byrne and Ruddle (1989) Proc. Natl. Acad. Sci. USA 86:5473-5477), pancreas-specific promoters (Edlund et al. (1985) Science 230:912-916), and mammary gland-specific promoters (*e.g.,* milk whey promoter; U.S. Patent No. 4,873,316 and European Application Publication No. 264,166). Developmentally-regulated promoters are also encompassed, for example the murine hox promoters (Kessel and Gruss (1990) Science 249:374-379) and the alpha-fetoprotein promoter (Campes and Tilghman (1989) Genes Dev. 3:537-546). Each of the above-idenitified references are incorporated by reference in their entirety, including any drawings.

[00134] Recombinant proteins described herein can be recovered and purified from recombinant cell cultures by well-known methods including ammonium sulfate or ethanol precipitation, acid extraction, anion or cation exchange chromatography, phosphocellulose chromatography, hydrophobic interaction chromatography, affinity chromatography, hydroxylapatite chromatography, hydrophobic charge interaction chromatography, and lectin

chromatography. In some embodiments, high performance liquid chromatography ("HPLC") is employed for purification. Polypeptides produced and recovered by recombinant and molecular biology methods described herein may be purified according to standard protocols known in the art (*e.g.*, dialysis, ion exchange chromatography, affinity chromatography, SDS gel electrophoresis, etc). The polypeptides and/or fusion polypeptides described herein may be purified to homogeneity by ion exchange chromatography, hydrophobic interaction chromatography, reverse phase chromatography, or gel filtration. Depending upon the host employed in a recombinant production procedure, the polypeptides of the present invention may be glycosylated or may be non-glycosylated. In some embodiments, the recombinant protein will be purified with an alpha-1-antitrypisn-Fc capture select media at neutral pH.

[00135] In some embodiments, the nucleic acids encoding the recombinant protein described herein is optimized for expression in yeast. Exemplary genera of yeast which can be used as hosts for expressing the fusion polypeptides described herein include but are not limited to *Pichia, Saccharomyces, Kluyveromyces, Aspergillus, Candida, Torulopsis, Torulaspora, Schizosaccharomyces, Citeromyces, Pachysolen, Zygosaccharomyces, Debaromyces, Trichoderma, Cephalosporium, Humicola, Mucor, Neurospora, Yarrowia, Metschunikowia, Rhodosporidium, Leucosporidium, Botryoascus, Sporidiobolus, Endomycopsis*, and the like. Yeast strains suitable for the production of fusion polypeptides described herein can include, but are not limited to D88, DXY1 and BXP10. Yeast plasmid vectors can include but are not limied to pRS403-406, pRS413-416, pRS403, pRS404, pRS405, pRS406 , pRS413-416, pPPC0005, pScCHSA, pScNHSA, and pC4. Vectors for making albumin fusion proteins for expression in yeast include pPPC0005, pScCHSA, pScNHSA, and pC4:HSA.

[00136] In some embodiments, the nucleic acids encoding the recombinant protein described herein is expressed in Saccharomyces. Preferred exemplary species of Saccharomyces include *S. cerevisiae, S. italicus, S. diastaticus,* and *Zygosaccharomyces rouxii*. Preferred exemplary species of *Kluyveromyces* include *K. fragilis* and *K. lactis*. Preferred exemplary species of *Hansenula* include *H. polymorpha* (now Pichia angusta), *H. anomala* (now Pichia anomala) and *Pichia capsulata*.

[00137] Other organisms may be used for expression. Additional exemplary species of *Pichia* include *P. pastoris*. Exemplary species of *Aspergillus* include *A. niger* and *A. nidulans*. Preferred exemplary species of *Yarrowia* include *Y. lipolytica*. Many preferred yeast species are available from the ATCC® (American Type Culture Collection).

Table S. Sequences.

SEQ ID NO:	Region	Sequence
1	Alpha-1-antitrypsin	EDPQGDAAQKTDTSHHDQDHPTFNKITPNLAEFAFSLYRQLAHQ SNSTNIFFSPVSIATAFAMLSLGTKADTHDEILEGLNFNLTEIP EAQIHEGFQELLRTLNQPDSQLQLTTGNGLFLSEGLKLVDKFLE DVKKLYHSEAFTVNFGDTEEAKKQINDYVEKGTQGKIVDLVKEL DRDTVFALVNYIFFKGKWERPFEVKDTEEEDFHVDQVTTVKVPM MKRLGMFNIQHCKKLSSWVLLMKYLGNATAIFFLPDEGKLQHLE NELTHDIITKFLENEDRRSASLHLPKLSITGTYDLKSVLGQLGI TKVFSNGADLSGVTEEAPLKLSKAVHKAVLTIDEKGTEAAGAMF LEAIPMSIPPEVKFNKPFVFLMIEQNTKSPLFMGKVVNPTQK
2	Alpha-1-antitrypsin leader	MPSSVSWGILLLAGLCCLVPVSLA
3	Human Albumin	MKWVTFISLLFLFSSAYSRGVFRRDAHKSEVAHRFKDLGEENFK ALVLIAFAQYLQQCPFEDHVKLVNEVTEFAKTCVADESAENCDK SLHTLFGDKLCTVATLRETYGEMADCCAKQEPERNECFLQHKDD NPNLPRLVRPEVDVMCTAFHDNEETFLKKYLYEIARRHPYFYAP ELLFFAKRYKAAFTECCQAADKAACLLPKLDELRDEGKASSAKQ GLKCASLQKFGERAFKAWAVARLSQRFPKAEFAEVSKLVTDLTK VHTECCHGDLLECADDRADLAKYICENQDSISSKLKECCEKPLL EKSHCIAEVENDEMPADLPSLAADFVGSKDVCKNYAEAKDVFLG MFLYEYARRHPDYSVVLLLRLAKTYETTLEKCCAAADPHECYAK VFDEFKPLVEEPQNLIKQNCELFEQLGEYKFQNALLVRYTKKVP QVSTPTLVEVSRNLGKVGSKCCKHPEAKRMPCAEDCLSVFLNQL CVLHEKTPVSDRVT
4	Human Albumin Leader	MKWVTFISLLFLFSSAYS
5	Human Serum Albumin	RGVFRRDAHKSEVAHRFKDLGEENFKALVLIAFAQYLQQCPFED HVKLVNEVTEFAKTCVADESAENCDKSLHTLFGDKLCTVATLRE TYGEMADCCAKQEPERNECFLQHKDDNPNLPRLVRPEVDVMCTA FHDNEETFLKKYLYEIARRHPYFYAPELLFFAKRYKAAFTECCQ AADKAACLLPKLDELRDEGKASSAKQGLKCASLQKFGERAFKAW AVARLSQRFPKAEFAEVSKLVTDLTKVHTECCHGDLLECADDRA DLAKYICENQDSISSKLKECCEKPLLEKSHCIAEVENDEMPADL PSLAADFVGSKDVCKNYAEAKDVFLGMFLYEYARRHPDYSVVLL

SEQ ID NO:	Region	Sequence
		LRLAKTYETTLEKCCAAADPHECYAKVFDEFKPLVEEPQNLIKQ NCELFEQLGEYKFQNALLVRYTKKVPQVSTPTLVEVSRNLGKVG SKCCKHPEAKRMPCAEDCLSVFLNQLCVLHEKTPVSDRVT
6	CDR1	LNLMG
7	CDR1	INLLG
8	CDR1	SFGMS
9	CDR1	NYWMY
10	CDR2	TCITVGDSTNYADSVKG
11	CDR2	TITVGDSTSYADSVKG
12	CDR2	SISGSGSDTLYADSVKG
13	CDR2	SINGRGDDTRYADSVKG
14	CDR2	AISADSSTKNYADSVKG
15	CDR2	AISADSSDKRYADSVKG
16	CDR2	RDISTGGGYSYYADSVKG
17	CDR3	RRTWHSEL
18	CDR3	GGSLSR
19	CDR3	GRSVSRS
20	CDR3	GRGSP
21	CDR3	DREAQVDTLDFDY
22	SDA	AVQLVESGGGLVQGGGSLRLACAASERIFDLNLMGWYRQGPGNE RELVATCITVGDSTNYADSVKGRFTISMDYTKQTVYLHMNSLRP EDTGLYYCKIRRTWHSELWGQGTQVTVSS
23	SDA	EVQLVESGGGLVQEGGSLRLACAASERIWDINLLGWYRQGPGNE RELVATITVGDSTSYADSVKGRFTISRDYDKNTLYLQMNSLRPE DTGLYYCKIRRTWHSELWGQGTQVTVSS
24	SDA	AVQLVESGGGLVQPGNSLRLSCAASGFTFRSFGMSWVRQAPGKE PEWVSSISGSGSDTLYADSVKGRFTISRDNAKTTLYLQMNSLKP EDTAVYYCTIGGSLSRSSQGTQVTVSS

SEQ ID NO:	Region	Sequence
25	SDA	AVQLVDSGGGLVQPGGSLRLSCAASGFSFGSFGMSWVRQYPGKE PEWVSSINGRGDDTRYADSVKGRFSISRDNAKNTLYLQMNSLKP EDTAEYYCTIGRSVSRSRTQGTQVTVSS
26	SDA	AVQLVESGGGLVQPGGSLRLTCTASGFTFRSFGMSWVRQAPGKD QEWVSAISADSSTKNYADSVKGRFTISRDNAKKMLYLEMNSLKP EDTAVYYCVIGRGSPSSPGTQVTVSS
27	SDA	QVQLAESGGGLVQPGGSLRLTCTASGFTFGSFGMSWVRQAPGEG LEWVSAISADSSDKRYADSVKGRFTISRDNAKKMLYLEMNSLKS EDTAVYYCVIGRGSPASQGTQVTVSS
28	SDA	QVQLVESGGGLVQPGGSLRLSCAASGFTFSNYWMYWVRVAPGKG LERISRDISTGGGYSYYADSVKGRFTISRDNAKNTLYLQMNSLK PEDTALYYCAKDREAQVDTLDFDYRGQGTQVTVSS
29	hSDA	EVQLVESGGGLVQPGGSLRLSCAASGFTFRSFGMSWVRQAPGKE PEWVSSISGSGSDTLYADSVKGRFTISRDNAKTTLYLQMNSLKP EDTAVYYCTIGGSLSRSSQGTQVTVSS
30	hSDA	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSFGMSWVRQAPGKE PEWVSSISGSGSDTLYADSVKGRFTISRDNAKTTLYLQMNSLKP EDTAVYYCTIGGSLSRSSQGTQVTVSS
31	hSDA	EVQLVESGGGLVQPGGSLRLSCAASGFTFRSFGMSWVRQAPGKG LEWVSSISGSGSDTLYADSVKGRFTISRDNAKTTLYLQMNSLKP EDTAVYYCTIGGSLSRSSQGTQVTVSS
32	hSDA	EVQLVESGGGLVQPGNSLRLSCAASGFTFRSFGMSWVRQAPGKG LEWVSSISGSGSDTLYADSVKGRFTISRDNAKTTLYLQMNSLKP EDTAVYYCTIGGSLSRSSQGTLVTVSS
33	hSDA	EVQLVESGGGLVQPGNSLRLSCAASGFTFRSFGMSWVRQAPGKG LEWVSSISGSGSDTLYADSVKGRFTISRDNAKTTLYLQMNSLRP EDTAVYYCTIGGSLSRSSQGTLVTVSS
34	hSDA	EVQLVESGGGLVQPGNSLRLSCAASGFTFSSFGMSWVRQAPGKG LEWVSSISGSGSDTLYADSVKGRFTISRDNAKTTLYLQMNSLRP EDTAVYYCTIGGSLSRSSQGTLVTVSS

SEQ ID NO:	Region	Sequence
35	hSDA	EVQLVESGGGLVQPGNSLRLSCAASGFTFSSFGMSWVRQAPGKG LEWVSSISGSGSDTLYADSVKGRFTISRDNAKNTLYLQMNSLRP EDTAVYYCTIGGSLSRSSQGTLVTVSS
36	hSDA	EVQLVESGGGLVQPGNSLRLSCAASGFTFSSFGMSWVRQAPGKG LEWVSSISGSGSDTLYADSVKGRFTISRDNAKNTLYLQMNSLRP EDTAVYYCTIGGSLSRSGQGTLVTVSS
37	FR1	AVQLVESGGGLVQGGGSLRLACAASERIFD
38	FR1	EVQLVESGGGLVQEGGSLRLACAASERIWD
39	FR1	AVQLVESGGGLVQPGNSLRLSCAASGFTFR
40	FR1	AVQLVDSGGGLVQPGGSLRLSCAASGFSFG
41	FR1	AVQLVESGGGLVQPGGSLRLTCTASGFTFR
42	FR1	QVQLAESGGGLVQPGGSLRLTCTASGFTFG
43	FR1	QVQLVESGGGLVQPGGSLRLSCAASGFTFS
44	FR2	WYRQGPGNERELVA
45	FR2	WVRQAPGKEPEWVS
46	FR2	WVRQYPGKEPEWVS
47	FR2	WVRQAPGKDQEWVS
48	FR2	WVRQAPGEGLEWVS
49	FR2	WVRVAPGKGLERIS
50	FR3	RFTISMDYTKQTVYLHMNSLRPEDTGLYYCKI
51	FR3	RFTISRDYDKNTLYLQMNSLRPEDTGLYYCKI
52	FR3	RFTISRDNAKTTLYLQMNSLKPEDTAVYYCTI
53	FR3	RFSISRDNAKNTLYLQMNSLKPEDTAEYYCTI
54	FR3	RFTISRDNAKKMLYLEMNSLKPEDTAVYYCVI
55	FR3	RFTISRDNAKKMLYLEMNSLKSEDTAVYYCVI
56	FR3	RFTISRDNAKNTLYLQMNSLKPEDTALYYCAK
57	FR4	WGQGTQVTVSS
58	FR4	SSQGTQVTVSS
59	FR4	RTQGTQVTVSS
60	FR4	SSPGTQVTVSS

SEQ ID NO:	Region	Sequence
61	FR4	ASQGTQVTVSS
62	FR4	RGQGTQVTVSS
63	Linker	GGSGGSGGSGGSGG
64	AAT-linkerAlbumin Fusion	MPSSVSWGILLLAGLCCLVPVSLA_EDPQGDAAQKTDTSHHDQD HPTFNKITPNLAEFAFSLYRQLAHQSNSTNIFFSPVSIATAFAM LSLGTKADTHDEILEGLNFNLTEIPEAQIHEGFQELLRTLNQPD SQLQLTTGNGLFLSEGLKLVDKFLEDVKKLYHSEAFTVNFGDTE EAKKQINDYVEKGTQGKIVDLVKELDRDTVFALVNYIFFKGKWE RPFEVKDTEEEDFHVDQVTTVKVPMMKRLGMFNIQHCKKLSSWV LLMKYLGNATAIFFLPDEGKLQHLENELTHDIITKFLENEDRRS ASLHLPKLSITGTYDLKSVLGQLGITKVFSNGADLSGVTEEAPL KLSKAVHKAVLTIDEKGTEAAGAMFLEAIPMSIPPEVKFNKPFV FLMIEQNTKSPLFMGKVVNPTQKGGSGGSGGSGGSGGDAHKSEV AHRFKDLGEENFKALVLIAFAQYLQQCPFEDHVKLVNEVTEFAK TCVADESAENCDKSLHTLFGDKLCTVATLRETYGEMADCCAKQE PERNECFLQHKDDNPNLPRLVRPEVDVMCTAFHDNEETFLKKYL YEIARRHPYFYAPELLFFAKRYKAAFTECCQAADKAACLLPKLD ELRDEGKASSAKQRLKCASLQKFGERAFKAWAVARLSQRFPKAE FAEVSKLVTDLTKVHTECCHGDLLECADDRADLAKYICENQDSI SSKLKECCEKPLLEKSHCIAEVENDEMPADLPSLAADFVESKDV CKNYAEAKDVFLGMFLYEYARRHPDYSVVLLLRLAKTYETTLEK CCAAADPHECYAKVFDEFKPLVEEPQNLIKQNCELFEQLGEYKF QNALLVRYTKKVPQVSTPTLVEVSRNLGKVGSKCCKHPEAKRMP CAEDYLSVVLNQLCVLHEKTPVSDRVTKCCTESLVNRRPCFSAL EVDETYVPKEFNAETFTFHADICTLSEKERQIKKQTALVELVKH KPKATKEQLKAVMDDFAAFVEKCCKADDKETCFAEEGKKLVAAS QAALGL
65	Mutant AAT-linkerAlbumin Fusion (C232S)	MPSSVSWGILLLAGLCCLVPVSLA_EDPQGDAAQKTDTSHHDQD HPTFNKITPNLAEFAFSLYRQLAHQSNSTNIFFSPVSIATAFAM LSLGTKADTHDEILEGLNFNLTEIPEAQIHEGFQELLRTLNQPD SQLQLTTGNGLFLSEGLKLVDKFLEDVKKLYHSEAFTVNFGDTE

SEQ ID NO:	Region	Sequence
		EAKKQINDYVEKGTQGKIVDLVKELDRDTVFALVNYIFFKGKWE RPFEVKDTEEEDFHVDQVTTVKVPMMKRLGMFNIQHSKKLSSWV LLMKYLGNATAIFFLPDEGKLQHLENELTHDIITKFLENEDRRS ASLHLPKLSITGTYDLKSVLGQLGITKVFSNGADLSGVTEEAPL KLSKAVHKAVLTIDEKGTEAAGAMFLEAIPMSIPPEVKFNKPFV FLMIEQNTKSPLFMGKVVNPTQKGGSGGSGGSGGSGGDAHKSEV AHRFKDLGEENFKALVLIAFAQYLQQCPFEDHVKLVNEVTEFAK TCVADESAENCDKSLHTLFGDKLCTVATLRETYGEMADCCAKQE PERNECFLQHKDDNPNLPRLVRPEVDVMCTAFHDNEETFLKKYL YEIARRHPYFYAPELLFFAKRYKAAFTECCQAADKAACLLPKLD ELRDEGKASSAKQRLKCASLQKFGERAFKAWAVARLSQRFPKAE FAEVSKLVTDLTKVHTECCHGDLLECADDRADLAKYICENQDSI SSKLKECCEKPLLEKSHCIAEVENDEMPADLPSLAADFVESKDV CKNYAEAKDVFLGMFLYEYARRHPDYSVVLLLRLAKTYETTLEK CCAAADPHECYAKVFDEFKPLVEEPQNLIKQNCELFEQLGEYKF QNALLVRYTKKVPQVSTPTLVEVSRNLGKVGSKCCKHPEAKRMP CAEDYLSVVLNQLCVLHEKTPVSDRVTKCCTESLVNRRPCFSAL EVDETYVPKEFNAETFTFHADICTLSEKERQIKKQTALVELVKH KPKATKEQLKAVMDDFAAFVEKCCKADDKETCFAEEGKKLVAAS QAALGL
66	Mutant AAT-linkerAlbumin Fusion (M351V, M358V)	MPSSVSWGILLLAGLCCLVPVSLA_EDPQGDAAQKTDTSHHDQD HPTFNKITPNLAEFAFSLYRQLAHQSNSTNIFFSPVSIATAFAM LSLGTKADTHDEILEGLNFNLTEIPEAQIHEGFQELLRTLNQPD SQLQLTTGNGLFLSEGLKLVDKFLEDVKKLYHSEAFTVNFGDTE EAKKQINDYVEKGTQGKIVDLVKELDRDTVFALVNYIFFKGKWE RPFEVKDTEEEDFHVDQVTTVKVPMMKRLGMFNIQHCKKLSSWV LLMKYLGNATAIFFLPDEGKLQHLENELTHDIITKFLENEDRRS ASLHLPKLSITGTYDLKSVLGQLGITKVFSNGADLSGVTEEAPL KLSKAVHKAVLTIDEKGTEAAGAVFLEAIPVSIPPEVKFNKPFV FLMIEQNTKSPLFMGKVVNPTQKGGSGGSGGSGGSGGDAHKSEV AHRFKDLGEENFKALVLIAFAQYLQQCPFEDHVKLVNEVTEFAK

SEQ ID NO:	Region	Sequence
		TCVADESAENCDKSLHTLFGDKLCTVATLRETYGEMADCCAKQE PERNECFLQHKDDNPNLPRLVRPEVDVMCTAFHDNEETFLKKYL YEIARRHPYFYAPELLFFAKRYKAAFTECCQAADKAACLLPKLD ELRDEGKASSAKQRLKCASLQKFGERAFKAWAVARLSQRFPKAE FAEVSKLVTDLTKVHTECCHGDLLECADDRADLAKYICENQDSI SSKLKECCEKPLLEKSHCIAEVENDEMPADLPSLAADFVESKDV CKNYAEAKDVFLGMFLYEYARRHPDYSVVLLLRLAKTYETTLEK CCAAADPHECYAKVFDEFKPLVEEPQNLIKQNCELFEQLGEYKF QNALLVRYTKKVPQVSTPTLVEVSRNLGKVGSKCCKHPEAKRMP CAEDYLSVVLNQLCVLHEKTPVSDRVTKCCTESLVNRRPCFSAL EVDETYVPKEFNAETFTFHADICTLSEKERQIKKQTALVELVKH KPKATKEQLKAVMDDFAAFVEKCCKADDKETCFAEEGKKLVAAS QAALGL
67	Mutant AAT-linkerAlbumin Fusion (M351V, M358L)	MPSSVSWGILLLAGLCCLVPVSLA_EDPQGDAAQKTDTSHHDQD HPTFNKITPNLAEFAFSLYRQLAHQSNSTNIFFSPVSIATAFAM LSLGTKADTHDEILEGLNFNLTEIPEAQIHEGFQELLRTLNQPD SQLQLTTGNGLFLSEGLKLVDKFLEDVKKLYHSEAFTVNFGDTE EAKKQINDYVEKGTQGKIVDLVKELDRDTVFALVNYIFFKGKWE RPFEVKDTEEEDFHVDQVTTVKVPMMKRLGMFNIQHCKKLSSWV LLMKYLGNATAIFFLPDEGKLQHLENELTHDIITKFLENEDRRS ASLHLPKLSITGTYDLKSVLGQLGITKVFSNGADLSGVTEEAPL KLSKAVHKAVLTIDEKGTEAAGAVFLEAIPLSIPPEVKFNKPFV FLMIEQNTKSPLFMGKVVNPTQKGGSGGSGGSGGSGGDAHKSEV AHRFKDLGEENFKALVLIAFAQYLQQCPFEDHVKLVNEVTEFAK TCVADESAENCDKSLHTLFGDKLCTVATLRETYGEMADCCAKQE PERNECFLQHKDDNPNLPRLVRPEVDVMCTAFHDNEETFLKKYL YEIARRHPYFYAPELLFFAKRYKAAFTECCQAADKAACLLPKLD ELRDEGKASSAKQRLKCASLQKFGERAFKAWAVARLSQRFPKAE FAEVSKLVTDLTKVHTECCHGDLLECADDRADLAKYICENQDSI SSKLKECCEKPLLEKSHCIAEVENDEMPADLPSLAADFVESKDV CKNYAEAKDVFLGMFLYEYARRHPDYSVVLLLRLAKTYETTLEK

SEQ ID NO:	Region	Sequence
		CCAAADPHECYAKVFDEFKPLVEEPQNLIKQNCELFEQLGEYKF QNALLVRYTKKVPQVSTPTLVEVSRNLGKVGSKCCKHPEAKRMP CAEDYLSVVLNQLCVLHEKTPVSDRVTKCCTESLVNRRPCFSAL EVDETYVPKEFNAETFTFHADICTLSEKERQIKKQTALVELVKH KPKATKEQLKAVMDDFAAFVEKCCKADDKETCFAEEGKKLVAAS QAALGL
68	Mutant AAT-linkerAlbumin Fusion (C232S, M351V, M358L)	MPSSVSWGILLLAGLCCLVPVSLA_EDPQGDAAQKTDTSHHDQD HPTFNKITPNLAEFAFSLYRQLAHQSNSTNIFFSPVSIATAFAM LSLGTKADTHDEILEGLNFNLTEIPEAQIHEGFQELLRTLNQPD SQLQLTTGNGLFLSEGLKLVDKFLEDVKKLYHSEAFTVNFGDTE EAKKQINDYVEKGTQGKIVDLVKELDRDTVFALVNYIFFKGKWE RPFEVKDTEEEDFHVDQVTTVKVPMMKRLGMFNIQHSKKLSSWV LLMKYLGNATAIFFLPDEGKLQHLENELTHDIITKFLENEDRRS ASLHLPKLSITGTYDLKSVLGQLGITKVFSNGADLSGVTEEAPL KLSKAVHKAVLTIDEKGTEAAGAVFLEAIPLSIPPEVKFNKPFV FLMIEQNTKSPLFMGKVVNPTQKGGSGGSGGSGGSGGDAHKSEV AHRFKDLGEENFKALVLIAFAQYLQQCPFEDHVKLVNEVTEFAK TCVADESAENCDKSLHTLFGDKLCTVATLRETYGEMADCCAKQE PERNECFLQHKDDNPNLPRLVRPEVDVMCTAFHDNEETFLKKYL YEIARRHPYFYAPELLFFAKRYKAAFTECCQAADKAACLLPKLD ELRDEGKASSAKQRLKCASLQKFGERAFKAWAVARLSQRFPKAE FAEVSKLVTDLTKVHTECCHGDLLECADDRADLAKYICENQDSI SSKLKECCEKPLLEKSHCIAEVENDEMPADLPSLAADFVESKDV CKNYAEAKDVFLGMFLYEYARRHPDYSVVLLLRLAKTYETTLEK CCAAADPHECYAKVFDEFKPLVEEPQNLIKQNCELFEQLGEYKF QNALLVRYTKKVPQVSTPTLVEVSRNLGKVGSKCCKHPEAKRMP CAEDYLSVVLNQLCVLHEKTPVSDRVTKCCTESLVNRRPCFSAL EVDETYVPKEFNAETFTFHADICTLSEKERQIKKQTALVELVKH KPKATKEQLKAVMDDFAAFVEKCCKADDKETCFAEEGKKLVAAS QAALGL

SEQ ID NO:	Region	Sequence
69	Wild Type AAT Nucleic Acid	tgggcaggaactgggcactgtgcccagggcatgcactgcctcca cgcagcaaccctcagagtcctgagctgaaccaagaaggaggagg gggtcgggcctccgaggaaggcctagccgctgctgctgccagga attccaggttggaggggcggcaacctcctgccagccttcaggcc actctcctgtgcctgccagaagagacagagcttgaggagagctt gaggagagcaggaaaggacaatgccgtcttctgtctcgtggggc atcctcctgctggcaggcctgtgctgcctggtccctgtctccct ggctgaggatccccagggagatgctgcccagaagacagatacat cccaccatgatcaggatcacccaaccttcaacaagatcaccccc aacctggctgagttcgccttcagcctataccgccagctggcaca ccagtccaacagcaccaatatcttcttctccccagtgagcatcg ctacagcctttgcaatgctctccctggggaccaaggctgacact cacgatgaaatcctggagggcctgaatttcaacctcacggagat tccggaggctcagatccatgaaggcttccaggaactcctccgta ccctcaaccagccagacagccagctccagctgaccaccggcaat ggcctgttcctcagcgagggcctgaagctagtggataagttttt ggaggatgttaaaaagttgtaccactcagaagccttcactgtca acttcggggacaccgaagaggccaagaaacagatcaacgattac gtggagaagggtactcaagggaaaattgtggatttggtcaagga gcttgacagagacacagtttttgctctggtgaattacatcttct ttaaaggcaaatgggagagacccttgaagtcaaggacaccgag gaagaggacttccacgtggaccaggtgaccaccgtgaaggtgcc tatgatgaagcgtttaggcatgtttaacatccagcactgtaaga agctgtccagctgggtgctgctgatgaaatacctgggcaatgcc accgccatcttcttcctgcctgatgaggggaaactacagcacct ggaaaatgaactcacccacgatatcatcaccaagttcctggaaa atgaagacagaaggtctgccagcttacatttacccaaactgtcc attactggaacctatgatctgaagagcgtcctgggtcaactggg catcactaaggtcttcagcaatggggctgacctctccggggtca cagaggaggcacccctgaagctctccaaggccgtgcataaggct gtgctgaccatcgacgagaaagggactgaagctgctggggccat

SEQ ID NO:	Region	Sequence
		gtttttagaggccatacccatgtctatccccccgaggtcaagt tcaacaaaccctttgtcttcttaatgattgaacaaaataccaag tctcccctcttcatgggaaaagtggtgaatcccacccaaaaata actgcctctcgctcctcaacccctcccctccatccctggccccc tccctggatgaattaaagaagggttgagctggtccctgcctgca tgtgactgtaaatccctcccatgttttctctgagtctccctttg cctgctgaggctgtatgtgggctccaggtaacagtgctgtcttc gggcccctgaactgtgttcatggagcatctggctgggtaggca catgctgggcttgaatccaggggggactgaatcctcagcttacg gacctgggcccatctgtttctggagggctccagtcttccttgtc ctgtcttggagtccccaagaaggaatcacaggggaggaaccaga taccagccatgaccccaggctccaccaagcatcttcatgtcccc ctgctcatcccccactcccccccacccagagttgctcatcctgc cagggctggctgtgcccaccccaaggctgccctcctgggggccc cagaactgcctgatcgtgccgtggcccagttttgtggcatctgc agcaacacaagagagaggacaatgtcctcctcttgactcgggcc ctgcacctctcaggcacttctggaaaatgactgaggcagattct tcctgaagcccattctccatggggcaacaaggacacctattctg tccttgtccttccatcgctgccccagaaagcctcacatatctcc gtttagaatcaggtcccttctccccagatgaagaggagggtctc tgctttgttttctctatctcctcctcagacttgaccaggcccag caggccccagaagaccattaccctatatcccttctcctccctag tcacatggccataggcctgctgatggctcaggaaggccattgca aggactcctcagctatgggagaggaagcacatcacccattgacc cccgcaacccctccctttcctcctctgagtcccgactggggcca catgcagcctgacttctttgtgcctgttgctgtccctgcagtct tcagagggccaccgcagctccagtgccacggcaggaggctgttc ctgaatagcccctgtggtaagggccaggagagtccttccatcct ccaaggccctgctaaaggacacagcagccaggaagtcccctggg cccctagctgaaggacagcctgctccctccgtctctaccaggaa tggccttgtcctatggaaggcactgccccatcccaaactaatct

SEQ ID NO:	Region	Sequence
		aggaatcactgtctaaccactcactgtcatgaatgtgtacttaa aggatgaggttgagtcataccaaatagtgatttcgatagttcaa aatggtgaaattagcaattctacatgattcagtctaatcaatgg ataccgactgtttcccacacaagtctcctgttctcttaagctta ctcactgacagcctttcactctccacaaatacattaaagatatg gccatcaccaagccccctaggatgacaccagacctgagagtctg aagacctggatccaagttctgacttttccccctgacagctgtgt gaccttcgtgaagtcgccaaacctctctgagccccagtcattgc tagtaagacctgcctttgagttggtatgatgttcaagttagata acaaaatgtttatacccattagaacagagaataaatagaactac atttcttgca
70	Wild Type Human Serum Albumin Nucleic Acid	cctttcccagggacttctacaaggaaaaagctagagttggttac tgacttctaataaataatgcctacaatttctaggaagttaaaag ttgacataatttatccaagaaagaattattttcttaacttagaa tagtttctttttttctttcagatgtaggtttttctggctttaga aaaaatgcttgtttttcttcaatggaaaataggcacacttgttt tatgtctgttcatctgtagtcagaaagacaagtctggtatttcc tttcaggactcccttgagtcattaaaaaaaatcttcctatctat ctatgtatctatcatccatctagctttgatttttttcctcttctg tgctttattagttaattagtacccatttctgaagaagaaataac ataagattatagaaaataatttctttcattgtaagactgaatag aaaaaattttctttcattataagactgagtagaaaaaataatac tttgttagtctctgtgcctctatgtgccatgaggaaatttgact actggttttgactgactgagttatttaattaagtaaaataactg gcttagtactaattattgttctgtagtatcagagaaagttgttc ttcctactggttgagctcagtagttcttcatattctgagcaaaa gggcagaggtaggatagcttttctgaggtagagataagaacctt gggtagggaaggaagatttatgaaatatttaaaaaattattctt ccttcgctttgtttttagacataatgttaaatttatttttgaaat ttaaagcaacataaaagaacatgtgatttttctacttattgaaa

SEQ ID NO:	Region	Sequence
		gagagaaaggaaaaaaatatgaaacagggatggaaagaatcctatgcctggtgaaggtcaagggttctcataacctacagagaatttgggtcagcctgtcctattgtatattatggcaaagataatcatctctcatttgggtccattttcctctccatctctgcttaactgaagatcccatgagatatactcacactgaatctaaatagcctatctcagggcttgaatcacatgtgggccacagcaggaatgggaacatggaatttctaagtcctatcttacttgttattgttgctatgtcttttcttagtttgcatctgaggcaacatcagcttttcagacagaatggctttggaatagtaaaaaagacacagaagccctaaaatatgtatgtatgtatatgtgtgtgtgcatgcgtgagtacttgtgtgtaaatttttcattatctataggtaaaagcacacttggaattagcaatagatgcaatttgggacttaactctttcagtatgtcttatttctaagcaaagtatttagtttggttagtaattactaaacactgagaactaaattgcaaacaccaagaactaaaatgttcaagtgggaaattacagttaaataccatggtaatgaataaaaggtacaaatcgtttaaactcttatgtaaaatttgataagatgttttacacaactttaatacattgacaaggtcttgtggagaaaacagttccagatggtaaatatacacaagggatttagtcaaacaatttttttggcaagaatattatgaattttgtaatcggttggcagccaatgaaatacaaagatgagtctagttaataatctacaattattggttaaagaagtatattagtgctaatttccctccgtttgtcctagcttttctcttctgtcaacccacacgcctttggcacaatgaagtgggtaacctttatttcccttctttttctctttagctcggcttattccaggggtgtgtttcgtcgagatgcacgtaagaaatccatttttctattgttcaacttttattctattttcccagtaaaataaagttttagtaaactctgcatctttaaagaattattttggcatttatttctaaaatggcatagtattttgtatttgtgaagtcttacaaggttatcttattaataaaattcaaacatcctaggtaaaaaaaaaaaaaggtcagaattgtttagtgactgtaattttcttttgcgcactaaggaaagtgcaaagtaacttagagtgactgaaacttcacagaatagggttgaagattgaattcataactatcccaaagacctatccattgcactatgctttatttaaaaacc

SEQ ID NO:	Region	Sequence
		acaaaacctgtgctgttgatctcataaatagaacttgtatttat atttattttcattttagtctgtcttcttggttgctgttgataga cactaaaagagtattagatattatctaagtttgaatataaggct ataaatatttaataatttttaaaatagtattcttggtaattgaa ttattcttctgtttaaaggcagaagaaataattgaacatcatcc tgagtttttctgtaggaatcagagcccaatattttgaaacaaat gcataatctaagtcaaatggaaagaaatataaaaagtaacatta ttacttcttgttttcttcagtatttaacaatccttttttttctt cccttgcccagacaagagtgaggttgctcatcggtttaaagatt tgggagaagaaaatttcaaagccttgtaagttaaaatattgatg aatcaaatttaatgtttctaatagtgttgtttattattctaaag tgcttatatttccttgtcatcagggttcagattctaaaacagtg ctgcctcgtagagttttctgcgttgaggaagatattctgtatct gggctatccaataaggtagtcactggtcacatggctattgagta cttcaaatatgacaagtgcaactgagaaacaaaaacttaaattg tatttaattgtagttaatttgaatgtatatagtcacatgtggct aatggctactgtattggacagtacagctctggaacttgcttggt ggaaaggactttaatataggtttcctttggtggcttacccacta aatcttctttacatagcaagcattcctgtgcttagttgggaata tttaatttttttttttttttaagacagggtctcgctctgtcgcc caggctggagtgcagtggcgcaatctcggctcactgcaaactcc gctcccgggttcacgccattctcctgcctcagcctcccgagtag ctgggactacaggcgcccgccatcacgcccggctaatcttttgt atttttagtagagatggggtttcaccgtgtgccaggatggtctc aatctcctgacatcgtgatctgcccacctcggcctcccaaagtg ctgggattacaggagtgagtcaccgcgcccggcctatttaaatg ttttttaatctagtaaaaaatgagaaaattgtttttttaaaagt ctacctaatcctacaggctaattaaagacgtgtgtggggatcag gtgcggtggttcacacctgtaatcccagcactttggaaggctga tgcaggaggattgcttgagcccaggagtacaagaccagcctggg caagtctctttaaaaaaaacaaaacaaacaaacaaaaaaattag

SEQ ID NO:	Region	Sequence
		gcatggtggcacatgcctgtagtcctagctacttaggaggctga cgtaggaggatcgtttggacctgagaggtcaaggctacagtgag ccatgattgtgccactgcactccagcctgggtgacagagtgaga ctctgtctcaaaaaagaaaaaggaaatctgtggggtttgtttta gttttaagtaattctaaggactttaaaaatgcctagtcttgaca attagatctatttggcatacaatttgcttgcttaatctatgtgt gtgcatagatctactgacacacgcatacatataaacattaggga actaccattctctttgcgtaggaagccacatatgcctatctagg cctcagatcatacctgatatgaataggctttctggataatggtg aagaagatgtataaaagatagaacctatacccatacatgatttg ttctctagcgtagcaacctgttacatattaaagttttattatac tacatttttctacatcctttgtttcagggtgttgattgcctttg ctcagtatcttcagcagtgtccatttgaagatcatgtaaaatta gtgaatgaagtaactgaatttgcaaaaacatgtgttgctgatga gtcagctgaaaattgtgacaaatcacttgtaagtacattctaat tgtggagattctttcttctgtttgaagtaatcccaagcatttca aaggaatttttttaagttttctcaattattattaagtgtcctg atttgtaagaaacactaaaaagttgctcatagactgataagcca ttgtttcttttgtgatagagatgctttagctatgtccacagttt taaaatcatttctttattgagaccaaacacaacagtcatggtgt atttaaatggcaatttgtcatttataaacacctcttttaaaat ttgaggtttggtttcttttgtagaggctaatagggatatgata gcatgtatttatttatttatttatcttattttattatagtaaga acccttaacatgagatctaccctgttatatttttaagtgtacaa tccattattgttaactacgggtacactgttgtatagcttactca tcttgctgtattaaaactttgtgcccattgattagtaacccctc gtttcgtcctcccccagccactggcaaccagcattatactcttt gattctatgagtttgactactttagctaccttatataagtggta ttatgtactgtttatctttttatgactgacttatttcccttagc atagtgcattcaaagtccaaccatgttgttgcctattgcagaat ttccttcttttcaaggctgaataatattccagtgcatgtgtgta

SEQ ID NO:	Region	Sequence
		ccacattttctttatccattaatttgttgattgatagacattta ggttggttttctacatcttgactatcatgaatagtgttgcaatg aacacaggagagctactatctcttagagatgatatcatggtttt tatcatcagaaaacacccactgatttctatgctaattttgttac ctgggtggaataatagtacagctatatattcctcattttagata tctttgtatttctacatacaataaaaaagcagagtacttagtca tgttgaagaactttaaacttttagtatttccagatcaatcttca aaacaaggacaggtttatctttctctcaccactcaatctatata tacctcttgtgggcaaggccagttttatcactggagcctttcc ccttttttattatgtacctctccctcacagcagagtcaggacttt aactttacacaatactatggctctacatatgaaatcttaaaaat acataaaaattaataaattctgtctagagtagtatattttccct ggggttacgattactttcataataaaaattagagataaggaaag gactcatttattggaaagtgattttaggtaacatttctggaaga aaaatgtctatatcttaatagtcacttaatatatgatggattgt gttactcctcagttttcaatggcatatactaaaacatggccctc taaaaaggggggcaaatgaaatgagaaactctctgaatgtttttc tcccctaggtgaattcacctgctgcttagaagcttattttctct tgatttctgttataatgattgctcttaccctttagttttaagtt tcaaaataggagtcatataactttccttaaagctattgactgtc tttttgtcctgttttattcaccatgagttatagtgtgacagtta attcttatgaaaattatatagagatggttaaatcatcagaaact gtaaacctcgattgggaggggaagcggatttttaaatgatttcc tgaccaagcttaaccagtatattaaatcctttgtactgttcttt ggctataaagaaaaaaggtactgtccagcaactgaaacctgctt tcttccatttagcataccctttttggagacaaattatgcacagt tgcaactcttcgtgaaacctatggtgaaatggctgactgctgtg caaaacaagaacctgagagaaatgaatgcttcttgcaacacaaa gatgacaacccaaacctcccccgattggtgagaccagaggttga tgtgatgtgcactgcttttcatgacaatgaagagacattttga aaaagtaagtaatcagatgtttatagttcaaaattaaaaagcat

SEQ ID NO:	Region	Sequence
		ggagtaactccataggccaacactctataaaaattaccataaca aaaatattttcaacattaagacttggaagttttgttatgatgat tttttaaagaagtagtatttgataccacaaaattctacacagca aaaaatatgatcaaagatattttgaagtttattgaaacaggata caatctttctgaaaaatttaagatagacaaattatttaatgtat tacgaagatatgtatatatggttgttataattgatttcgtttta gtcagcaacattatattgccaaaatttaaccatttatgcacaca cacacacacacacacacacttaacccttttttccacatacttaa agaatgacagagacaagaccatcatgtgcaaattgagcttaatt ggttaattagatatctttggaatttggaggttctggggagaatg tcgattacaattatttctgtaatattgtctgctatagaaaagtg actgtttttctttttcaaaatttagatacttatatgaaattgcc agaagacatccttacttttatgccccggaactccttttctttgc taaaaggtataaagctgcttttacagaatgttgccaagctgctg ataaagctgcctgcctgttgccaaaggtattatgcaaaagaata gaaaaaaagagttcattatccaacctgattttgtccattttgtg gctagatttagggaacctgagtgtctgatacaaactttccgaca tggtcaaaaaagccttccttttatctgtcttgaaaatctttcat ctttgaaggcctacactctcgtttcttcttttaagatttgccaa tgatgatctgtcagaggtaatcactgtgcatgtgtttaaagatt tcaccacttttatggtggtgatcactatagtgaaatactgaaa cttgtttgtcaaattgcacagcaaggggacacagttcttgttta tcttttcatgataatttttagtagggagggaattcaaagtagag aattttactgcatctagatgcctgagttcatgcattcattccat aaatatatattatggaatgctttatttttcttttctgaggagttt actgatgttggtggaggagagactgaaatgaattatacacaaaa tttaaaaattagcaaaattgcagcccctgggatattagcgtact ctttctctgacttttctcccacttttaaggctctttttcctggc aatgtttccagttggtttctaactacatagggaattccgctgtg accagaatgatcgaatgatctttccttttcttagagagcaaaat cattattcgctaaagggagtacttgggaatttaggcataaatta

SEQ ID NO:	Region	Sequence
		tgccttcaaaatttaatttggcacagtctcatctgagcttatgg aggggtgtttcatgtagaatttttcttctaattttcatcaaatt attccttttgtagctcgatgaacttcgggatgaagggaaggct tcgtctgccaaacagagactcaagtgtgccagtctccaaaaatt tggagaaagagctttcaaagcatggtaaatacttttaaacatag ttggcatctttataacgatgtaaatgataatgcttcagtgacaa attgtacatttttatgtattttgcaaagtgctgtcaaatacatt tctttggttgtctaacaggtagaactctaatagaggtaaaaatc agaatatcaatgacaatttgacattatttttaatcttttctttt ctaaatagttgaataatttagaggacgctgtccttttgtccta aaaaaagggacagatatttaagttctatttatttataaaatctt ggactcttattctaatggttcattatttttatagagctgtaggc atggttctttatttaatttttaaagttatttttaatttttgtg gatacagagtaggtatacatatttacggggtatatgagatattt tgatataagtatacaacatatataatccctttatttaattttat cttccccccaatgatctaaaactatttgcttgtccttttatgtc ttatagttaaattcagtcaccaactaagttgaagttacttctta tttttgcatagctccagctctgatcttcatctcatgtttttgcc tgagcctctgttttcatattacttagttggttctgggagcatac tttaatagccgagtcaagaaaaatactagctgccccgtcaccca cactcctcacctgctagtcaacagcaaatcaacacaacaggaaa taaaatgaaaataatagacattatgcatgctctctagaaactgt caattgaactgtatttgctcatcattcctaccatctacaccacc aaaatcaaccaaatttatgaaaaaaaaacagccccaacataaaa ttatacacagataaacaggctatgattggttttgggaaagaagt caccttacctgatttaggcaactgtgaaatgactagagaatga agaaaattagacgtttacatcttgtcatagagtttgaagatagt gctggatctttctttttataagtaagatcaataaaaactccctc attctgtagaagttatgatttcttttctaagagacctttagaag tcagaaaaaatgtgtttcaattgagaaaaaagataactggagtt tgtgtagtacttcccagattataaaatgcttttgtatgtattat

SEQ ID NO:	Region	Sequence
		ctaatttaatcctcaaaacttcttcaatttagcatgttgtcatg acactgcagaggctgaagctcagagacgctgagccctctgctaa caagtcctactgctaacaagtgataaagccagagctggaagtca catctggactccaaacctgatgcttctcagcctgttgccccttt tagagttccttttaatttctgcttttatgacttgctagatttc tacctaccacacacactcttaaatggataattctgccctaagga taagtgattaccatttggttcagaactagaactaatgaatttta aaaattatttctgtatgtccattttgaattttcttatgagaaat agtatttgcctagtgttttcatataaaatatcgcatgataatac cattttgattggcgattttctttttagggcagtagctcgcctga gccagagatttcccaaagctgagtttgcagaagtttccaagtta gtgacagatcttaccaaagtccacacggaatgctgccatggaga tctgcttgaatgtgctgatgacagggtaaagagtcgtcgatatg ctttttggtagcttgcatgctcaagttggtagaatggatgcgtt tggtatcattggtgatagctgacagtgggttgagattgtcttct gtgctttcgtctgtcctatcttcaatctttccctgcctatggtg gtggtacctttctgtttttaacctgctataaattaccagataaa cccattcactgatttgtaactcctttcagtcatgctctaactgt aaatgaaggcttaaactgaagtagaacagttacaaggttttact tggcagaacatcttgcaaggtagatgtctaagaagatttttttt tctttttttaagacagagtttcgctcttgtttcccaggctgggg tgcaatggtgtgatcttggctcagcgcaacctctgcctcctggg ttcaagtgattttcatgcctcagcctcccaagtagctgggatta caggcatgcgccaccacacctggctaattttgtatttttagtag aggcggggtttcaccatattgtccagactggtctcgaactcctg acctcaggtgatccacccgccttggcctcccaaagtgctgggat tacaggcatgagccaccttgcccagcctaagaagatttttgag ggaggtaggtggacttggagaaggtcactacttgaagagatttt tggaaatgatgtatttttcttctctatattccttcccttaatta actctgtttgttagatgtgcaaatatttggaatgatatctcttt tctcaaaacttataatattttctttctccctttcttcaagatta

SEQ ID NO:	Region	Sequence
		aacttatgggcaaatactagaatcctaatctctcatggcacttt ctggaaaatttaaggcggttattttatatatgtaagcagggcct atgactatgatcttgactcatttttcaaaaatcttctatatttt atttagttatttggtttcaaaaggcctgcacttaattttggggg attatttggaaaaacagcattgagttttaatgaaaaaaacttaa atgccctaacagtagaaacataaaattaataaataactgagctg agcacctgctactgattagtctattttaattaagtgggaatgtt tttgtagtcctatctacatctccaggtttaggagcaaacagagt atgttcatagaaggaatatgtgtatggtcttagaatacaatgaa catgttctgccaacttaataaaggtctgaggagaaagtgtagca atgtcaattcgtgttgaacaatttccaccaacttacttataggc ggaccttgccaagtatatctgtgaaaatcaagattcgatctcca gtaaactgaaggaatgctgtgaaaaacctctgttggaaaaatcc cactgcattgccgaagtggaaaatgatgagatgcctgctgactt gccttcattagctgctgattttgttgaaagtaaggatgtttgca aaaactatgctgaggcaaaggatgtcttcctgggcatgtaagta gataagaaattattcttttatagctttggcatgacctcacaact taggaggatagcctaggcttttctgtggagttgctacaatttcc ctgctgcccagaatgtttcttcatccttccctttcccaggcttt aacaatttttgaaatagttaattagttgaatacattgtcataaa ataatacatgttcacggcaaagctcaacattccttactccttag gggtatttctgaaaatacgtctagaaacattttgtgtatatata aattatgtatacttcagtcattcattccaagtgtatttcttgaa catctataatatatgtgtgtgactatgtattgcctgtctatcta actaatctaatctaatctagtctatctatctaatctatgcaatg atagcaaagaagtataaaaagaaatatagagtctgacacaggtg ctttatatttggtgaaaagaccagaagttcagtataatggcaat atggtaggcaactcaattacaaaataaatgtttacgtattgtca gaagttgtggtgataaactgcattttttgttgttggattatgata atgcactaaataatatttcctaaaattatgtaccctacaagatt tcactcatacagagaagaaagagaatattttaagaacatatctc

SEQ ID NO:	Region	Sequence
		tgcccatctatttatcagaatccttttgagatgtagtttaaatc aaacaaaatgttaataaaaataacaagtatcattcatcaaagac ttcatatgtgccaagcagtgtgtgctttgtgtagattatgtcat atagttctcataatccaccttccgagacagatactatttatttt ttgagacagagttttactcttgttgcccaggctggagtgcaatg gtgccatctcggctcaccacaaccttcgcctcccaggttcaagc gattctcctgcctcagcctcctgggattacaggcatgcaccacc atgcctggctaattttgtatttttagtagagatggggtttcacc atgttggtcagactggtctcaaactcctgacctctggtgatatg cctgcctcagcctcctaaagtgctgggattacaggcatgagcca ctgtgcccagccgacagatactattattatttccattctaccga gaaggagactaaggctctgatcatttaaataagttgcctaaggt gatgcagtgatataagtagcagagctaggaattgagccttggta actttaactctggaccccaagtccttagctactaagctttactg catggggtttagtcaaattaagacttttggaatatgagttactt ttgagattagctttgtgatatttttgtgctcatttgtccaaca aagtctattttatttcatcttaattaggttttgtatgaatat gcaagaaggcatcctgattactctgtcgtgctgctgctgagact tgccaagacatatgaaaccactctagagaagtgctgtgccgctg cagatcctcatgaatgctatgccaaagtggtaggtttattgttg gaaaaaaatgtagttctttgactgatgattccaataatgagaaa gaaaaataatgcaagaatgtaaaatgatatacagtgcaatttag atcttttcttgagatggtttcaattctggaatcttaaacatgaa agaaaaagtagccttagaatgattaacaaaatttagactagtta gaatagaaagatctgaatagagcaatctctaaaaaattttgatc ttttttctctttttcacaatcctgagaacaaaaaaaaattaaa tttaaatgttaattagaagatatttaacttagatgtaaagtgag ttaacctgattccaggattaatcaagtactagaattagtatctt atggcaaattatagaacctatccctttagaatattttcaaatct ttttgaggatgtttaggaatagttttacaagaaattaagttagg agaggaaatctgttctggaggatttttagggttcccactagcat

SEQ ID NO:	Region	Sequence
		atgtaatggtttctgaactattcagaatcagagaaaactcattt ttcctgctttcaagaagctactgtatgccaggcaccatgcacaa acaatgaccaacgtaaaatctctcattttggagagcctggaatc taactggaaaggtgaactaataataataatatgtacaatcatag ccatcatttattaaacttttattatatgcaaggcactgtttaat ttcattagcttacctggtttacagagcagctctatgagatgagt gccatctttgcccctattttagggataaggattccgaaatgtgg agatggtaagtaaaattgcacaactgaagaatgagttacatgac ttggctcaaatactggtcattgaactccagagcctgaatattct taaccacttacatgatgcaagctcaccaaataaatagttcgaat gtattgtgacagagcggcattgatattcatctattcatgtggct ttgagtaggaagaagaaaggatatcattctgaccagaggggtga aaaacaacctgcatctgatcctgaggcataatactattaacaca attcttttatgtttcagttcgatgaatttaaacctcttgtggaa gagcctcagaatttaatcaaacaaaattgtgagcttttgagca gcttggagagtacaaattccagaatgcgtaagtaatttttattg actgatttttttatcaatttgtaattatttaagacttaatata tgagccacctagcatagaacttttaagaatgaaaatacattgca tatttctaatcactctttgtcaagaaagataggagaggagagat aaaatagttgatggggtggagaggtctatatttgaatgtagtct aaaaattgttctcttaagattggaagtatgtaggctgggagggt aaataccaaatcttggtatatcagaactgagcatgtcccttgaa ggttaagaaatagttaatgggcaaatagagcatggcaatatttt gtagagcagcaagtagtaggccttgaatagatgtcgctcaaaaa gtaatatgtaagctgaacacaaaaatgtaacaaatgaatttaga tacatatttgaatattaaattcaggttgtttgggagatgcacct agtctttgatggttaaacctttccctccatagaagagacagaga cagaatggcttgctggactaatgtcccaattcaatagagtctta tctacgaaggttaaaaacaagaagagacatattatacagtagat atttattgtgtggctcatacacatggtgctcttctgattatgga ttttagagataataacagtgaacaagacatagtttctttcctcg

SEQ ID NO:	Region	Sequence
		agtagattaaagtcatacattgacttttaatggtgactggcatt cttaatacatgattattatatattaggtaccatgtcagattaat tataatactttactatttttaatttaacccttgaactatcccta ttgagtcagatatatttccttccattttctacttgtatctttca agtttagcatatgctgatacatatgaagctctctccaggtttta ttgaaagaagaaattaataaatttattaatgtcactgaattagg caactcactttcccaagattatgcaagtggtacaggtggaactc aaagccaagtttaactagttgttcaggagaatgttttctaccct ccactaacccactactctgcagatggagataatatgatgaatgg aacatagcaacatcttagttgattccggccaagtgttctctgtt ttatctactatgttagacagtttcttgccttgctgaaaacacat gacttctttttttcaggctattagttcgttacaccaagaaagta ccccaagtgtcaactccaactcttgtagaggtctcaagaaacct aggaaaagtgggcagcaaatgttgtaaacatcctgaagcaaaaa gaatgccctgtgcagaagactatgtgagtctttaaaaaaatata ataaattaataatgaaaaaattttacctttagatattgataatg ctagctttcataagcagaaggaagtaatgtgtgtgtgtgcatgt ttgtgtgcatgtgtgtgtgcatgcacgtgtgtgtatgtgtgata ttggcagtcaaggccccgaggatgataatttttttttttttttt gagacggagtctcgctttgttgtccaggctggagtgcagtggtg ccatctcggctcactgcaacctccgcctcccaagttcaagccat tctcctgcctcagcctcccaagtagctgggactacaggtgcatg ccaccatgcctggctaatttttgtatttttagtagaaaatttt cagcttcacctcttttgaatttctgctctcctgcctgttcttta gctatccgtggtcctgaaccagttatgtgtgttgcatgagaaaa cgccagtaagtgacagagtcaccaaatgctgcacagaatccttg gtgaacaggcgaccatgcttttcagctctggaagtcgatgaaac atacgttcccaaagagtttaatgctgaaacattcaccttccatg cagatatatgcacactttctgagaaggagagacaaatcaagaaa caaacgtgaggagtatttcattactgcatgtgtttgtagtcttg atagcaagaactgtcaattcaagctagcaacttttcctgaagt

SEQ ID NO:	Region	Sequence
		agtgattatatttcttagaggaaagtattggagtgttgcccttattatgctgataagagtacccagaataaaatgaataacttttttaaagacaaaatcctctgttataatattgctaaaattattcagagtaatattgtggattaaagccacaatagaataacatgttagaccattcagtagaaaaagatgaacaattaactgataaatttgtgcacatggcaaattagttaatgggaaccataggagaatttatttctagatgtaaataattattttaagtttgccctatggtggccccacacatgagacaaaccccaagatgtgacttttgagaatgagacttggataaaaaacatgtagaaatgcaagccctgaagctcaactccctattgctatcacaggggttataattgcataaaatttagctatagaaagttgctgtcatctcttgtgggctgtaatcatcgtctaggcttaagagtaatattgcaaaacctgtcatgcccacacaaatctctccctggcattgttgtctttgcagatgtcagtgaaagagaaccagcagctcccatgagtttggatagccttattttctatagcctccccactgaagggagcaaagtttaagaaccaaatataaagtttctcatcttatagatgagaaaaatttaaataaagtccaagataattaaatttttaaggatcatttttagctctttaatagcaataaaactcaatatgacataatatggcacttccaaaatctgaataatatataattgcaatgacatacttcttttcagagatttactgaaaagaaatttgttgacactacataacgtgatgagtggtttatactgattgtttcagttggtcttcccaccaactccatgaaagtggattttattatcctcatcatgcagatgagaatattgagacttatagcggtatgcctggccaagtactcagagttgcctggctccaagatttataatcttaaatgatgggactaccatccttactctctccatttttctatacgtgagtaatgtttttctgtttttttttttctttttccattcaaactcagtgcacttgttgagctcgtgaaacacaagcccaaggcaacaaaagagcaactgaaagctgttatggatgatttcgcagcttttgtagagaagtgctgcaaggctgacgataaggagacctgctttgccgaggaggtactacagttctcttcattttaatatgtccagtattcatttttgcatgtttggttaggctagggcttagggatttatatatcaaaggaggctttgtacatgtgggacagggatcttattttacaaacaat

SEQ ID NO:	Region	Sequence
		tgtcttacaaaatgaataaaacagcactttgtttttatctcctg ctctattgtgccatactgttgaatgtttataatgcatgttctgt ttccaaatttgtgatgcttatgaatattaataggaatatttgta aggcctgaaatattttgatcatgaaatcaaaacattaatttatt taaacatttacttgaaatgtggtggtttgtgatttagttgattt tataggctagtgggagaatttacattcaaatgtctaaatcactt aaaatttccctttatggcctgacagtaacttttttttattcatt tggggacaactatgtccgtgagcttccatccagagattatagta gtaaattgtaattaaaggatatgatgcacgtgaaatcactttgc aatcatcaatagcttcataaatgttaattttgtatcctaatagt aatgctaatattttcctaacatctgtcatgtctttgtgttcagg gtaaaaaacttgttgctgcaagtcaagctgccttaggcttataa catcacatttaaaagcatctcaggtaactatattttgaattttt taaaaaagtaactataatagttattattaaaatagcaaagattg accatttccaagagccatatagaccagcaccgaccactattcta aactatttatgtatgtaaatattagcttttaaaattctcaaaat agttgctgagttgggaaccactattatttctattttgtagatga gaaaatgaagataaacatcaaagcatagattaagtaattttcca aagggtcaaaattcaaaattgaaaccaaggtttcagtgttgccc attgtcctgttctgacttatatgatgcggtacacagagccatcc aagtaagtgatggctcagcagtggaatactctgggaattaggct gaaccacatgaaagagtgctttatagggcaaaaacagttgaata tcagtgatttcacatggttcaacctaatagttcaactcatcctt tccattggagaatatgatggatctaccttctgtgaactttatag tgaagaatctgctattacatttccaatttgtcaacatgctgagc tttaataggacttatcttcttatgacaacatttattggtgtgtc cccttgcctagcccaacagaagaattcagcagccgtaagtctag gacaggcttaaattgttttcactggtgtaaattgcagaaagatg atctaagtaatttggcatttatttaataggtttgaaaaacaca tgccattttacaaataagacttatatttgtccttttgtttttca gcctaccatgagaataagagaaagaaaatgaagatcaaaagctt

SEQ ID NO:	Region	Sequence
		attcatctgtttttctttttcgttggtgtaaagccaacaccctg tctaaaaaacataaatttctttaatcattttgcctcttttctct gtgcttcaattaataaaaaatggaaagaatctaatagagtggta cagcactgttatttttcaaagatgtgttgctatcctgaaaattc tgtaggttctgtggaagttccagtgttctcttattccacttc ggtagaggatttctagtttcttgtgggctaattaaataaatcat taatactcttctaagttatggattataaacattcaaaataatat tttgacattatgataattctgaataaaagaacaaaaaccatggt ataggtaaggaatataaaacatggcttttaccttagaaaaaaca attctaaaattcatatggaatcaaaaaagagcctgcag
71	Mutant AAT-linkerAlbumin Fusion (S283C, K335A, P361C)	EDPQGDAAQKTDTSHHDQDHPTFNKITPNLAEFAFSLYRQLAHQ SNSTNIFFSPVSIATAFAMLSLGTKADTHDEILEGLNFNLTEIP EAQIHEGFQELLRTLNQPDSQLQLTTGNGLFLSEGLKLVDKFLE DVKKLYHSEAFTVNFGDTEEAKKQINDYVEKGTQGKIVDLVKEL DRDTVFALVNYIFFKGKWERPFEVKDTEEEDFHVDQVTTVKVPM MKRLGMFNIQHSKKLSSWVLLMKYLGNATAIFFLPDEGKLQHLE NELTHDIITKFLENEDRRCASLHLPKLSITGTYDLKSVLGQLGI TKVFSNGADLSGVTEEAPLKLSKAVHAAVLTIDEKGTEAAGAVF LEAIPLSICPEVKFNKPFVFLMIEQNTKSPLFMGKVVNPTQKGG SGGSGGSGGSGGDAHKSEVAHRFKDLGEENFKALVLIAFAQYLQ QCPFEDHVKLVNEVTEFAKTCVADESAENCDKSLHTLFGDKLCT VATLRETYGEMADCCAKQEPERNECFLQHKDDNPNLPRLVRPEV DVMCTAFHDNEETFLKKYLYEIARRHPYFYAPELLFFAKRYKAA FTECCQAADKAACLLPKLDELRDEGKASSAKQRLKCASLQKFGE RAFKAWAVARLSQRFPKAEFAEVSKLVTDLTKVHTECCHGDLLE CADDRADLAKYICENQDSISSKLKECCEKPLLEKSHCIAEVEND EMPADLPSLAADFVESKDVCKNYAEAKDVFLGMFLYEYARRHPD YSVVLLLRLAKTYETTLEKCCAAADPHECYAKVFDEFKPLVEEP QNLIKQNCELFEQLGEYKFQNALLVRYTKKVPQVSTPTLVEVSR NLGKVGSKCCKHPEAKRMPCAEDYLSVVLNQLCVLHEKTPVSDR VTKCCTESLVNRRPCFSALEVDETYVPKEFNAETFTFHADICTL SEKERQIKKQTALVELVKHKPKATKEQLKAVMDDFAAFVEKCCK ADDKETCFAEEGKKLVAASQAALGL

EXAMPLES

Example 1: Construction of AAT-Albumin

[00139] Wildtype alpha-1-antitrypsin (alpha-1-antitrypsin, SEQ ID: 1) and four variants (C232S, SEQ ID: 64; M351V, M358V, SEQ ID: 65; M351V, M358L, SEQ ID: 66; C232S, M351V, M358L, SEQ ID: 67) are fused to the N-terminus of human serum albumin via long glycine-serine linker (GGSGGSGGSGGSGG (SEQ ID NO: 63)). The gene encoding human AAT can be PCR amplified from human liver cDNA (Zyagen). Specific point mutations within the AAT gene are created by overlapping PCR (See, for example, *Higuchi R, Krummel B, Saiki R* (1988) "A general method of in vitro preparation and specific mutagenesis of DNA fragments: study of protein and DNA interactions". *Nucleic Acids Res.* 16 (15): 7351–67, which is incorproated by reference herein in its entirety, including any drawings.) The alpha-1-antitrypsin gene is cloned in frame with a gene encoding human serum albumand a linker, into a mammalian expression vector containing a mammalian secretion signal sequence up stream of the alpha-1-antitrypsin gene insertion site.

[00140] The initial AAT variants are chosen because they are either resistant to cysteine oxidation and/or methionine oxidation. Methionine oxidation is known to decrease the AAT inhibitory activity for human neutrophil elastase. Once expressed in Chinese Hamster Ovary (CHO) cells, each AAT-human serum albumin (WT or variant, SEQ ID:1-5) is purified using an anti-AAT resin (GE) and tested for inhibition of human neutrophil elastase (hNE). Each AAT-human serum albumin (WT or variant, SEQ ID:1-5) is also tested for overall protein stability using a dynamic light scattering (DLS) & dynamic scanning fluorimetry (DSF) instrument (UNcle, Unchained).

[00141] Overall AAT protein stability is known to correlate with resistance to self-polymerization of AAT. With this data, AAT-human serum albumins are chosen for further mutagenesis with at least one additional mutation (*See* Table 1 above). These mutations are known to further increase AAT stability and prevent self-polymerization. Each AAT-human serum albumin variant is expressed in CHO, purified, and tested for hNE inhibition and protein stability.

[00142] By combining multiple mutations together, unexpected synergistic increases in stability are observed with little to no loss in hNE inhibition.

[00143] Each gene sequence was cloned into proprietary high expression mammalian vectors. Each completed construct was sequence confirmed before proceeding to DNA scale up. Each DNA expression construct was scaled up to the appropriate amount for transfection. Plasmid DNA was run on agaraose gel for quality assessment and the sequence was confirmed before proceeding to transfection.

Example 2 Construction of AAT-Albumin Binding Domain

[00144] Preferred AAT domains are fused to an albumin binding single domain antibody instead of human serum albumin as set forth in Example 1. For example, single domain antibodies having any of respective sequences SEQ ID NOs 22-36 are fused to AAT as provided in Example 1. The AAT-albumin binding domain variant is expressed in CHO, purified, and tested for hNE inhibition and protein stability as set forth in Example 1.

[00145] Each gene sequence was cloned into proprietary high expression mammalian vectors. Each completed construct was sequence confirmed before proceeding to DNA scale up. Each DNA expression construct was scaled up to the appropriate amount for transfection. Plasmid DNA was run on agaraose gel for quality assessment and the sequence was confirmed before proceeding to transfection.

Example 3 CHO Transient Transfection

[00146] Suspension CHO cells were seeded in a shake flask and were expanded using serum-free chemically defined medium. On the day of transfection, expanded cells were seeded into a new flask with fresh medium. Each DNA construct was transiently transfected

into the CHO cells. Cells were maintained as a batch-fed culture (C1603 and C1604, Medna) until the end of the production run.

[00147] The results can be seen in Table 2 and in Table 4.

Name	V	Harvest	Titer	Final Yield	In Stock	PI
PP12288 - J1350 AAT	100 mL	50.99 mg	509.9 mg/L	28.14 mg	23.10 mg	5.6 (Calc.)
PP12289 - J1351 C232S	100 mL	43.64 mg	436.4 mg/L	25.74 mg	20.70 mg	5.6 (Calc.)
PP12290 - J1352 M351V, M358V	100 mL	43.65 mg	436.5 mg/L	25.58 mg	20.42 mg	5.6 (Calc.)
PP12291 - J1353 M351V, M358L	100 mL	46.94 mg	469.4 mg/L	20.98 mg	15.90 mg	5.6 (Calc.)
PP12292 - J1354 C232S, M351V, M358L	100 mL	47.73 mg	477.3 mg/L	28.89 mg	23.52 mg	5.6 (Calc.)

Table 2

Name	Harvest	V (L)	Titer (mg/L)	Final Yield	In-Stock	PI
F51L	37.44	0.1	374.4	21.35	21.35	5.6 (Calc.)
G117F	36.66	0.1	366.6	28.03	28.03	5.6 (Calc.)
K331F	33.82	0.1	338.2	21.51	21.51	5.5 (Calc.)
K335A	24.65	0.1	246.5	13.86	13.86	5.5 (Calc.)
K168C/F189C	48.03	0.1	480.3	32.82	32.82	5.5 (Calc.)
S283C/P361C	40.59	0.1	405.9	27.37	27.37	5.6 (Calc.)
F51L/G117F	32.48	0.1	324.8	22.06	22.06	5.6 (Calc.)
F51L/K331F	31.71	0.1	317.1	18.71	18.71	5.5 (Calc.)
F51L, K335A	39.21	0.1	392.1	22.45	16.41	5.5 (Calc.)
F51L/K168C/F189C	40.55	0.1	405.5	26.48	20.44	5.5 (Calc.)
F51L/S283C/P361C	45.31	0.1	453.1	35.17	29.14	5.6 (Calc.)
G117F/K331F	34.45	0.1	344.5	21.43	15.43	5.5 (Calc.)
G117F/K335A	40.87	0.1	408.7	27.58	21.42	5.5 (Calc.)
G117F/K168C/F189C	35.71	0.1	357.1	28.96	22.9	5.5 (Calc.)
G117F/S283C/P361C	42.52	0.1	425.2	31.57	25.54	5.6 (Calc.)
K331F/K335A	26.72	0.1	267.2	13.33	7.2	5.5 (Calc.)
K331F/K168C/F189C	28	0.1	280.0	17.75	11.68	5.5 (Calc.)
K331F/S283C/P361C	41.18	0.1	411.8	24.12	18.07	5.5 (Calc.)
K335A/K168C/F189C	39.16	0.1	391.6	19.23	13.13	5.5 (Calc.)
K335A/S283C/P361C	40.15	0.1	401.5	29.75	23.61	5.5 (Calc.)
K168C/F189C/S283C/P361C	41.3	0.1	413.0	32.41	26.35	5.5 (Calc.)

Table 4

Example 4 CHO Albumin Affinity Purification

[00148] Conditioned media from the transient production run was harvested and clarified by centrifugation and filtration. The supernatant was loaded over a column packed with alpha-1 antitrypsin select resin and pre-equilibrated with PBS, pH 7.4. The column was washed with PBS to remove impurities until OD280 (measured by NanoDrop, Thermo Scientific) dropped to around zero. Target protein was eluted with a high salt elution buffer (20 mM Tris, 2 M MgCl2, pH 7.4), fractions were collected and OD280 was measured and recorded. Fractions containing the target protein were pooled and dialyzed to final buffer to PBS, pH 7.4. The final product was filtered through 0.2 μm membrane filter. Protein concentration and final yield were calculated from OD280 value and calculated extinction coefficient after buffer exchange.

[00149] CE-SDS analysis of target protein was performed using LabChip GXII (Perkins Elmer).

[00150] The results can be seen in FIG. 4 and in FIG. 7.

Example 5: Stability Analysis

[00151] A sample was submitted to the UNcle system (Unchained Labs) for analysis. A temperature ramp of 1 °C/min was performed with monitoring from 25 °C to 95 °C for dynamic light scattering ("DSF") and static light scattering ("SLS"). UNcle measures SLS at 266 nm and 473 nm. DLS was measured at the beginning of thermal ramp. Tm, Tagg, and DLS measurements were calculated and analyzed by using the UNcle Analysis Software. The Tm as determined is indicated by a solid dropline in DSF graph.

[00152] The results can be seen in FIG. 5 and in FIG. 8.

Example 6: hNA Assay

[00153] A neutrophil elastase inhibitory assay was performed with the screening kit from Abcam (Cat#ab118971). Results are shown in FIG. 6.

Example 7: IC50

[00154] IC50 analysis of AAT mutants was also performed with the screening kit from Abcam (Cat#ab118971). 400 nM-98 pM was concentration range used for IC50 analysis and data obtained from two replicates was analyzed using GraphPad Prism.

[00155] Table 3 shows IC50s for base albumin-fusion.

Name	Titer	IC50 (nM)
PP12288 - J1350 AAT	509.9 mg/L	34.57
PP12289 - J1351 C232S	436.4 mg/L	45.32
PP12290 - J1352 M351V, M358V	436.5 mg/L	33.71
PP12291 - J1353 M351V, M358L	469.4 mg/L	31.12
PP12292 - J1354 C232S, M351V, M358L	477.3 mg/L	34.55
Plasma AAT	NA	59.12

Table 3

[00156] 21 AAT mutant proteins and 1AAT serum control were also used to generate IC50 analysis curves. Table 5 shows IC50s for mutant AAT.

BASE	Mutations	Titer (mg/L)	IC50 (nM)
C232S, M351V, M358L	K335A	247	5.96
C232S, M351V, M358L	K331F	338	7.05
AAT Serum Control	-	-	7.98
C232S, M351V, M358L	K335A/S283C/P361C	402	8.55
C232S, M351V, M358L	G117F/K335A	409	8.58
C232S, M351V, M358L	G117F/K331F	345	8.94
C232S, M351V, M358L	F51L/K331F	317	9.18
C232S, M351V, M358L	K331F/K335A	267	9.30
C232S, M351V, M358L	G117F	367	10.45
C232S, M351V, M358L	F51L/K335A	392	10.67
C232S, M351V, M358L	F51L	374	13.57
C232S, M351V, M358L	K331F/S283C/P361C	412	14.32
C232S, M351V, M358L	K335A/K168C/F189C	392	15.77
C232S, M351V, M358L	F51L/S283C/P361C	453	15.97
C232S, M351V, M358L	F51L/G117F	325	19.00
C232S, M351V, M358L	G117F/S283C/P361C	425	20.15
C232S, M351V, M358L	F51L/K168C/F189C	406	23.32
C232S, M351V, M358L	K168C/F189C	480	23.47
C232S, M351V, M358L	K331F/K168C/F189C	280	27.96
C232S, M351V, M358L	G117F/K168C/F189C	357	29.10
C232S, M351V, M358L	K168C/F189C/S283C/P361C	413	35.01
C232S, M351V, M358L	S283C/P361C	406	41.71

Table 5

[00157] FIG. 9 shows IC50 analysis of AAT mutants, with the x-axis showing log concentration of AAT proteins (nM) and the y-axis showing percent inhibition. Curves that have a higher slope show a very cooperative inhibition profile. Mutants G11F/K335A, G117F/K331F, F51L/K331F, and K331F/K335A all have a very cooperative inhibition profile.

Example 8: In-Silico Immunogencity

[00158] A proprietary screen was used to compare proteins with those already in clinical use (*See*, Jawa et al., T-cell dependent immunogenicity of protein therapeutics: Preclinical assessment and mitigation, 149 Clinical Immunoology, 534-555 (2013), which is incorporated by reference herein in its entirety, including any drawings). AAT-albumin fusions

("AAT_MLA"), AAT mutants ("AAT_Mutant"), and albumin proteins ("Albumin") were screened for the presence of putative T-cell epitopes. The AAT Mutant has the following mutations according to SEQ ID NO: 1: C232S, M351V, M358L, K335A, S283C, and P361C. The immunogenic potential of each T-cell epitope or AAT-albumin fusions, AAT mutants, and albumin proteins were compared to othes, normalized, and ranked.

[00159] Input sequences were parsed into overlapping 9-mer frames and each frame was evaluated with respect to a panel of eight common Class II HLA alleles. The alleles are called super-types. Each super type is functionally equivalent to, or nearly equivalent to, many additional family member alleles. Taken collectively, the eight super-type alleles, along with their respective family members, cover well over 95% of the human population. Each frame-by-allele assessment is a statement about predicted HLA binding affinity.

[00160] Assessment scores range from approximately -3 to +3. Assessment scores above 1.64 are defined as "hits" and are considered potentially immunogenic and worthy of further consideration. One can often expect about 5% of all assessments to score above 1.64. These peptides have a significant chance of binding to HLA molecules with moderate to high affinity and, therefore, have a significant chance of being presented on the surface of APCs, such as dendritic cells or macrophages, where they may be interrogated by passing T cells. The greater the burden of HLA ligands (i.e. hits) contained in a given protein, the more likely that protein is to induce an immune response.

[00161] The EpiMatrix Protein Score is the difference between the number of predicted T cell epitopes one would expect to find in a protein of a given size and the number of putative epitopes predicted by the EpiMatrix System. EpiMatrix Protein Scores are "normalized" and can be plotted on a standardized scale (*See*, for example, Figure 10). The EpiMatrix Protein Score of an "average" protein is zero. EpiMatrix Protein Scores above zero indicate the presence of excess MHC ligands and denote a higher potential for immunogenicity while scores below zero indicate the presence of fewer potential MHC ligands than expected and a lower potential for immunogenicity.

[00162] In analyzing the full AAT_MLA sequence, the algorithm performed a total of 7,880 frame-by-allele assessments. In analyzing the AAT_MUTANT domain, the algorithm performed a total of 3,088 frame-by-allele assessments. In analyzing the ALBUMIN domain, the algorithm performed a total of 4,616 frame-by-allele assessments. The results are shown in Table 6. Mutant AAT shows a marginally increased immunogenicity score compared to

wild type AAT. The fusion of high-scoring AAT_MUTANT domain to the low-scoring glycine-serine linker and low-scoring ALBUMIN domain lowers the overall epitope density of the ATT_MLA fusion. AAT, when fused to albumin (AAT_MLA), has a negative score, indicating reduced immunogenic potential compared to wild type or mutant AAT alone.

Protein Label	Length	Assessments	EpiMatrix Hits	EpiMatrix Score
AAT_MLA	993	7,880	384	-10.72
AAT_MUTANT	394	3,088	206	26.87
AAT_WT	394	3,088	202	21.01
ALBUMIN	585	4,616	178	-32.04

Table 6

[00163] 384 peptide-to-HLA hits were identified within the full fusion sequence AAT_MLA, resulting in an overall score of -10.72. 206 hits were identified within the full fusion sequence AAT_MUTANT, resulting in an overall score of 26.87. 202 hits were identified within the full fusion sequence AAT_WT, resulting in an overall score of 21.01. 178 hits were identified within the full fusion sequence AAT_MLA, resulting in an overall score of -32.04. The results are shown in FIG. 10.

Example 9: Stability Analysis of AAT Variant (K335A, S283C/P361C) on Base (C232S,M351V, M351L)

[00164] Sample was submitted to UNcle (Unchained Labs) for analysis. A temperature range of 1°C/mi was performed while being monitored from 25°C to 95°C for DSF and SLS. UNcle measures SLS aat 266 nm and 473 nm. DLS was measured at the beginning of the thermal ramp. Tm, Tagg, and DLS measurements were calculated and analyzed by usinbg the UNcle analysis software. Tm was determined as indictaed by a solid dropline in FIG. 11. As can be seen, the variant AAT albumin fusion is very stable.

[00165] **Example 10: Cyno PK** Potential toxicity of recombinant Alpha-1-antitrypsin (AAT) K335A/S283C/P361C fused to human serum albumin (AAT Albumin Fusion) when given once by intravenous bolus injection for to cynomolgus monkeys was determined. The cynomolgus monkey was chosen as the animal model for this study as it is an accepted nonrodent species for preclinical toxicity testing by regulatory agencies and most accurately reflects the pharmacokinetics and pharmacodynamics of the test agent expected in human

subjects. Pharmacokinetic characteristics of the AAT Albumin Fusion, compared to human plasma-derived AAT (Prolastin C) was also determined.

[00166] Table 7 provides the test articles and control article.

[00167]	Test Article -1	Test Article -2	Control Article
Identification	Recombinant AAT K335A/S283C/P361C fused to human	Human Plasma-Derived AAT (Prolastin C)	137mM NaCl 2.7mM KCl
Physical Description	Liquid	Powder	Liquid
Concentration	7.58mg/mL	1129 mg, dilute	Not applicable

Table 7

[00168] The control article was used for dilution of the test articles. Test article dosing formulations of 2 mg/mL were prepared to meet dose level requirements by diluting the test article stock (7.8 mg/mL), less than or equal to 4-fold serial dilution with the control article. Dose levels were selected based on the previous published studies (Journal of Chronic Obstructive Pulmonary Disease (2013) 10(6):687-95; Lancet (2015) 386(9991):360-8). Therapy with 60 mg/kg weekly as an intravenous (IV) infusion of human plasma-derived alpha-1 antitrypsin (AAT), is approved in individuals with alpha-1 antitrypsin deficiency. The safety and pharmacokinetic profile of weekly infusions of a 120 mg/kg dose AAT was considered to be safe and well tolerated in adults with AATD.

[00169] Animals were randomized and assigned to groups using a computer-based procedure prior to transfer to study. The experimental design used is provided in Table 8.

Group	Test Material	Dose Level	Dose	Dose	No. of
1	Recombinant AAT K335A/S283C/P361C	10	5	2	2
2	Human Plasma-Derived	10	0.2	50	2

Table 8

[00170] Test articles were administered to animals via intravenous (slow bolus) injection once on Day 1. The dose volume for each animal was based on the most recent body weight measurement. The animals were temporarily restrained for dose administration and were not be sedated

[00171] Blood was collected by venipuncture. Samples were collected according to Table 9.

Group Nos.	Time Point	Hematology	Clinical Chemistry
All animals	Pretreatment	X	X
1 and 2	Day 29	X	X

Table 9

[00172] Hematology was performed with a target volume of 1 mL and an anticoagulant of Potassium (K3) EDTA.A blood smear was prepared from each hematology sample. Smears were examined to assess an animal's health following. No animals were deemed unhealthy.

[00173] Clinical chemistry was performed with a target volume of 2 mL and without an anticoagulant.

[00174] Samples were collected according to Table 10.

Sample Collection Time Points		
Group No(s).	Study Day/Week	Time Points (Relative to Dosing)
All Animals	Pretreatment	-
1 to 2	Day 1	Day 1: 1, 6, and 12 hr post
	Day 2	Day 1: 24 hr post
	Day 3	Day 1: 48 hr post
	Day 4	Day 1: 72 hr post
	Day 5	Day 1: 96 hr post
	Day 8	Day 1: 168 hr post
	Day 11	Day 1: 240 hr post
	Day 15	Day 1: 336 hr post

Table 10

[00175] Plasma from the samples was analyzed for concentration of test articles Bronchoalveolar lavage samples were collected from anesthetized animals and will be analyzed (data not shown).

[00176] Plasma results are shown in FIG. 12 and were fitted to a 2 phase exponential decay model in Graphpad Prism. As can be seen from FIG. 12, the variant has a significantly longer terminal half life. The AAT-HSA variant (Test Article 1) half-life (beta phase, slow) was over 30 hours compared to less 10 hours for Prolastin (plasma AAT).

[00177] The plasma results were further analyzed by a three compartment model (Tables 11-13) and are also shown in FIG. 13. FIG. 13 shows median (lines), 5th and 95th

percentiles (areas) from 1000 simulated PK profiles together with the individual observations (symbols). Observations below limit of quantification (BLQ, crosses) were not included in the analysis.

[00178] As can be seen from above, monkey PK after 10 mg/kg was three compartmental. C_{max} of test article 2 was ~40-fold higher than the C_{max} of test article 1 for 10 mg/kg of compound. The central volume of distribution was 0.213 L for test article 2 and 8 L for test article 1. Total volumes of distribution were 1.45 L for test article 2 and 42 L for test article 1. Volume of distribution for Aralast (plasma derived AAT) in human was 5.6 L [https://www.drugbank.ca/drugs/DB00058]. Allometric scaling to NHP would predict a volume of distribution of 0.240 L, which is equivalent to test article 2 from this study.

[00179] Terminal HSA half-life in monkey is approximately 5 days. Test article 1 β and γ half-lives were 0.75 days and 5.8 days, respectively. Test article 2 β and γ half-lives were 0.36 days and 1.49 days, respectively. The test article 2 γ half-life is approximately 3.9 times longer than the γ half-life of test article 1. The γ terminal half-life of HSA (from the literature) and test article 1 are equivalent in monkey.

[00180] Table 11 shows PK parameters for test article 2 and test article 1.

Description	**Parameter**	**Test article 2**	**Test article 1**
Clearance	Cl (mL/h)	87.3	295
Central volume of distribution	V1 (mL)	213	8020
1st peripheral volume of distribution	V2 (mL)	749	23600
2nd peripheral volume of distribution	V3 (mL)	485	10800
1st inter-compartmental exchange coefficient	Q12 (mL/h)	18.2	320
2nd inter-compartmental exchange coefficient	Q13 (mL/h)	65.3	3’090
α half life	$T_{1/2,\alpha}$ (h)	0.80	0.97

β half life	$T_{1/2,\beta}$ (h)	8.64	18.1
γ half life	$T_{1/2,\gamma}$ (h)	35.7	134

Table 11

[00181] Table 12 shows population PK parameters for test article 2:

Parameter	**Parameter**	**Estimation (%CV)**	**RSE**
Fixed effects			
Clearance	Cl (mL/h)	87.3 (1)	2.36
Central volume of distribution	V1 (mL)	213 (0)	10.6
Inter-compartmental clearance	Q2 (mL/h)	18.2 (0)	9.1
Peripheral volume of distribution	V2 (mL)	749 (0)	5.71
2nd inter-compartmental clearance	Q3 (mL/h)	65.3 (0)	9.41
2nd peripheral volume of distribution	V3 (mL)	485 (0)	7.21
Standard deviations			
Clearance	ω_{Cl}	0.0128	65.1
Observational error			
Proportional error	b	0.0399	19.6

Table 12

[00182] Table 13 shows population PK parameters for test article 1:

Parameter	**Parameter**	**Estimation (%CV)**	**RSE**
Fixed effects			
Clearance	Cl (mL/h)	295 (12)	9.05
Central volume of distribution	V1 (mL)	8020 (0)	24.5
Inter-compartmental clearance	Q2 (mL/h)	320 (0)	20.6
Peripheral volume of distribution	V2 (mL)	23600 (0)	9.22

2nd inter-compartmental clearance	Q3 (mL/h)	3090 (0)	48.1
2nd peripheral volume of distribution	V3 (mL)	10800 (0)	20.3
Standard deviations			
Clearance	ω_{Cl}	0.122	53
Observational error			
Proportional error	b	0.0987	16.8

Table 13

2019369403 26 Mar 2025

Claims

1. A recombinant protein comprising:
   (a) an alpha-1-antitrypsin serpin domain; and
   (b) a human serum albumin domain
wherein the alpha-1-antitrypsin serpin domain has base mutations comprising C232S, M351V and M358L, and one or more further mutations according to SEQ ID NO 1: F51L, G117F, K168C, F189C, S283C, K331F, K335A, or P361C compared to a wild type alpha-1 antitrypsin.

2. The recombinant protein of claim1, wherein the human serum albumin domain is a wild-type human serum albumin.

3. The recombinant protein of any one of claims 1-2comprising a linker having a sequence set forth in SEQ ID NO: 63.

4. The recombinant protein of any one of claims 21-3, wherein the C-terminus of the alpha-1-antitrypsin serpin domain is fused to the N-terminus of the human serum albumin domain.

5. The recombinant protein of any one of claims1-4, wherein the human serum albumin domain increases plasma half-life of the alpha-1 -antitrypsin serpin domain as compared to wild type alpha-1-antitrypsin.

6. The recombinant protein of any one of claims 1-5, wherein a number of N glycans or polysialyation of the recombinant protein in the alpha-1-antitrypsin serpin domain is greater than a wild type alpha-1-antitrypsin serpin domain.

7. The recombinant protein of any one of claims 1-6, wherein the one or more mutations causes resistance to methionine oxidation compared to wild type alpha-1-antitrypsin.

8. The recombinant protein of any one of claims 1-7, wherein the one or more mutations comprises K168C and F189C, with residues being numbered according to SEQ ID NO:

1, and the one or more mutations confers a substantially increased alpha-1-antitrypsin resistance to loop-sheet polymerization, as compared to wild type alpha-1-antitrypsin.

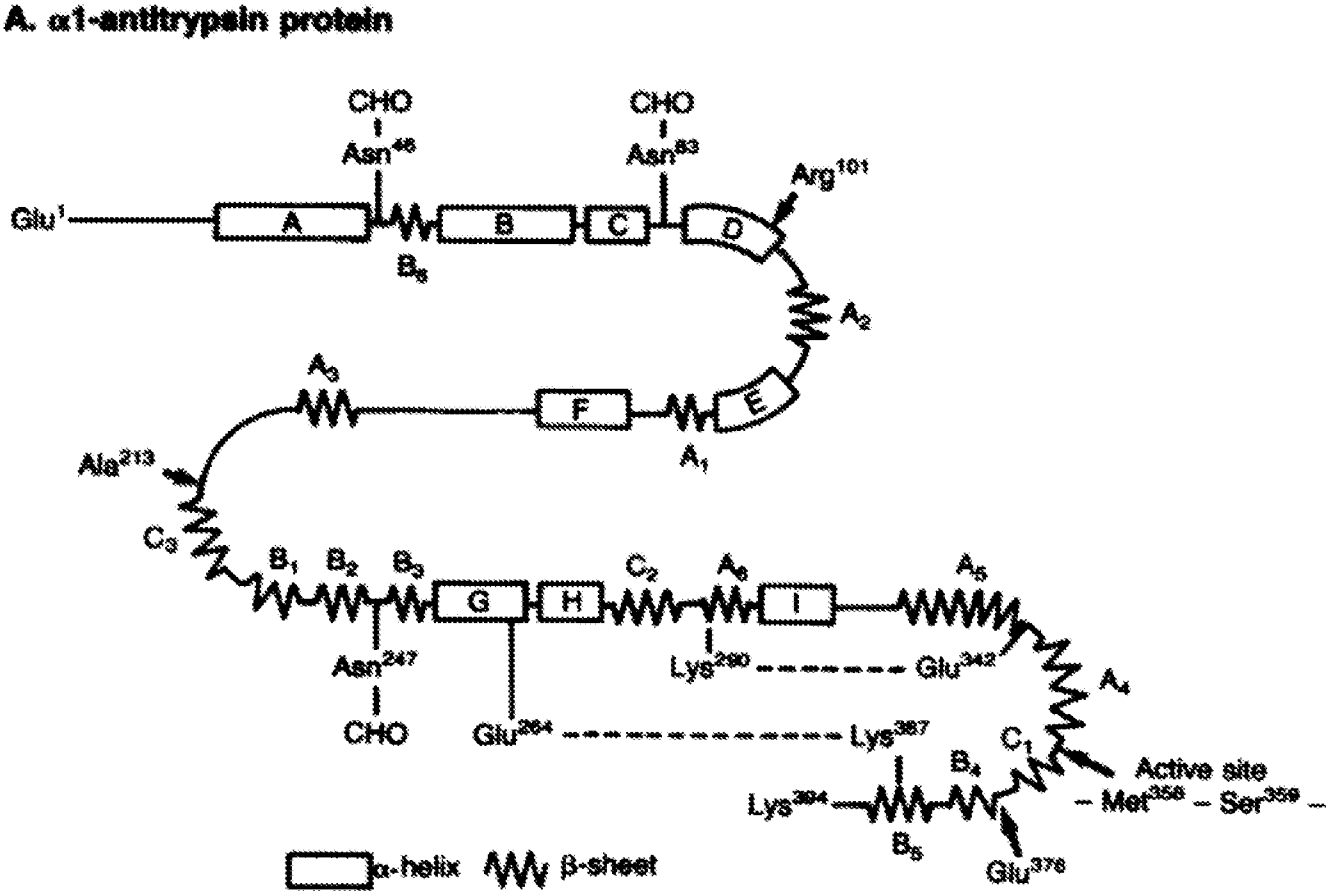
9. The recombinant protein of any one of claims 1-8, wherein the one or more mutations are one or more point mutations selected from F51L, G117F , S283C, K331F, K335A, or P361C with residues being numbered according to SEQ ID NO: 1.

10. The recombinant protein of any of claims 1-9, wherein the alpha-1 antitrypsin serpin domain has re mutations comprising F51L, C232S, M351V and M358L according to SEQ ID NO: 1, mutations comprising G117F, C232S, M351V and M358L according to SEQ ID NO: 1, mutations comprising C232S, K331F, M351V and M358L according to SEQ ID NO: 1, mutations comprising C232S, K335A, M351V and M358L according to SEQ ID NO: 1, mutations comprising K168C, F189C, C232S, M351V, and M358L according to SEQ ID NO: 1, mutations comprising C232S, S283C, M351V, M358L, and P361C according to SEQ ID NO: 1, mutations comprising F51L, G117F, C232S, M351V, and M358L according to SEQ ID NO: 1, mutations comprising F51L, C232S, K331F, M351V, and M358L according to SEQ ID NO: 1, mutations comprising F51L, C232S, K335A, M351V, and M358L according to SEQ ID NO: 1, mutations comprising K51L, K168C, F189C, C232S, M351V, and M358L according to SEQ ID NO: 1, mutations comprising F51L, C232S, S283C, M351V, M358L, and P361C according to SEQ ID NO: 1, mutations comprising G117F, C232S, K331F, M351V, and M358L according to SEQ ID NO: 1, mutations comprising G117F, K335A, C232S, M351V, and M358L according to SEQ ID NO: 1, mutations comprising G117F, K168C, F189C, C232S, M351V, and M358L according to SEQ ID NO: 1, mutations comprising G117F, C232S, S283C, M351V, M358L, and P361C according to SEQ ID NO: 1, mutations comprising C232S, K331F, K335A, M351V, and M358L according to SEQ ID NO: 1, mutations comprising K168C, F189C, C232S, K331F, M351V, and M358L according to SEQ ID NO: 1, mutations comprising C232S, S283C, K331F, M351V, M358L, and P361C according to SEQ ID NO: 1, comprising K168C, F189C, C232S, K335A, M351V, and M358L according to SEQ ID NO: 1, mutations comprising C232S, S283C, K335A, M351V, M358L, and P361C according to SEQ ID NO: 1, or mutations comprising K168C, F189C, C232S, S283C, M351V, M358L, and P361C according to SEQ ID NO: 1.

2019369403 26 Mar 2025

11. The recombinant protein of any one of claims 1-10, wherein the alpha-1 antitrypsin retains activity as compared to the wild type alpha-1-antitrypsin.

12. The recombinant protein of any one of claims 1-11, wherein the alpha-1 antitrypsin retains activity against human neutrophil elastase and/or PR3 compared to wild type alpha-1-antitrypsin.


A. α1-antitrypain protein
CHO
Asn46
CHO
Asn83
Arg101
Glu1
A
B
C
D
B6
A2
A3
F
E
A1
Ala213
C3
B1 B2 B3
G
H
C2
A6
I
A5
Asn247
CHO
Lys290
Glu342
A4
Glu264
Lys387
C1
B4
Active site
Lys394
– Met358 – Ser359 –
B5
Glu376
α-helix
β-sheet

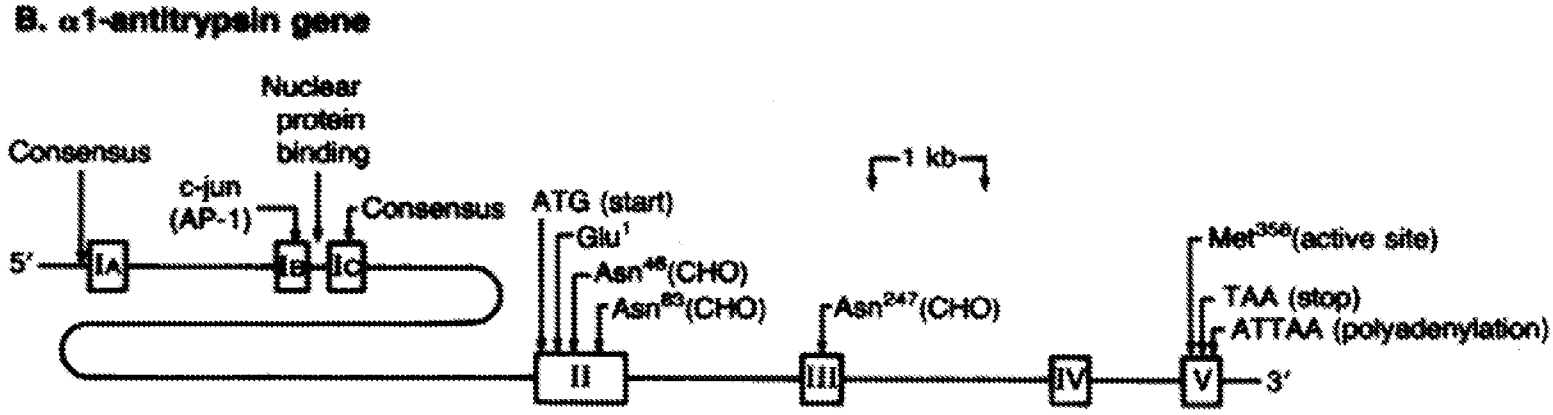

B. α1-antitrypain gene
Nuclear protein binding
Consensus
c-jun (AP-1)
Consensus
1 kb
ATG (start)
Glu1
Asn46(CHO)
Asn83(CHO)
Asn247(CHO)
Met358(active site)
TAA (stop)
ATTAA (polyadenylation)
5′
IA
IB
IC
II
III
IV
V
3′

FIG. 1

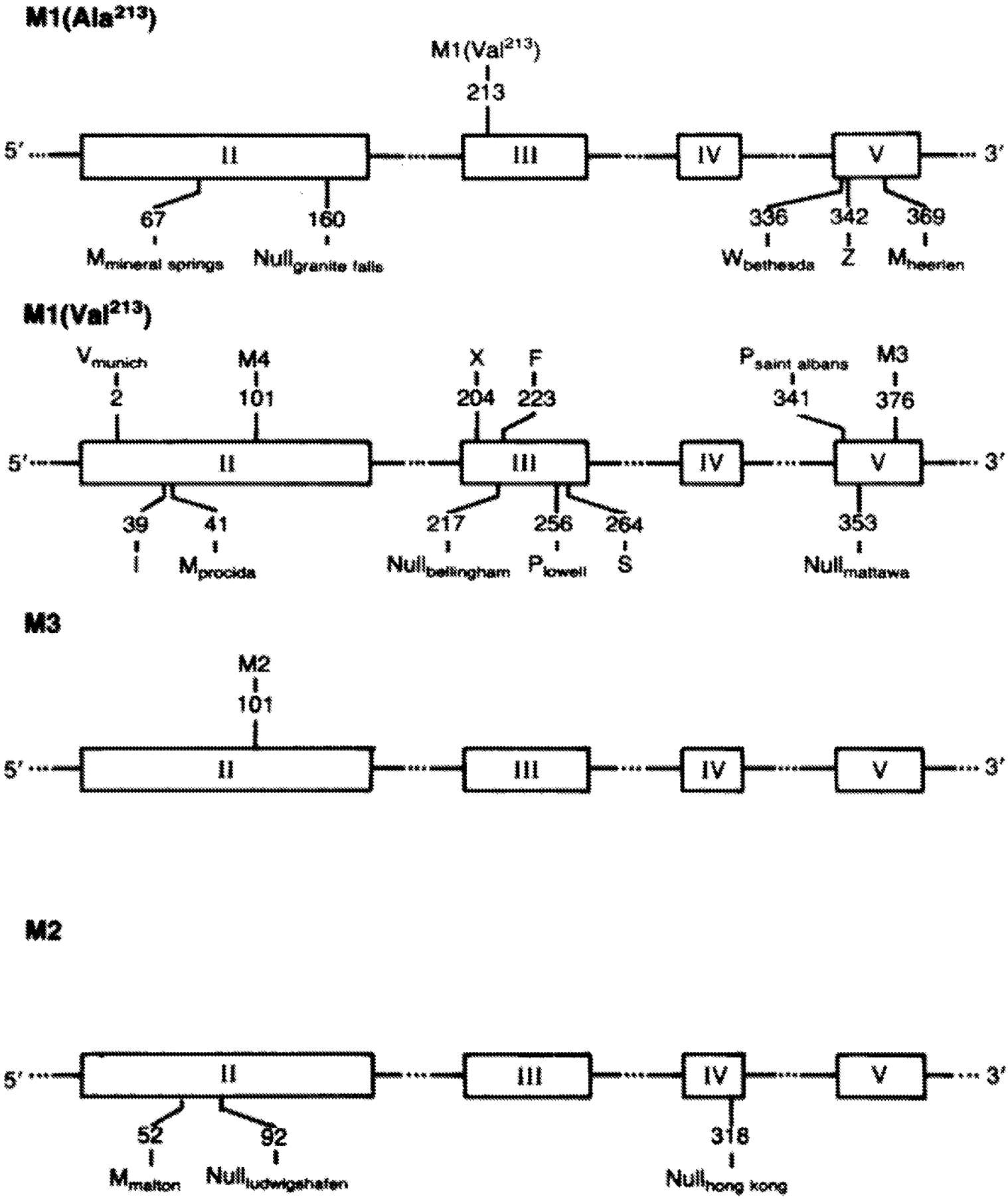

M1(Ala213)
M1(Val213)
213
5'
II
III
IV
V
3'
67
160
336
342
369
Mmineral springs
Nullgranite falls
Wbethesda
Z
Mheerlen
M1(Val213)
Vmunich
M4
X
F
Psaint albans
M3
2
101
204
223
341
376
39
41
217
256
264
353
I
Mprocida
Nullbellingham
Plowell
S
Nullmattawa
M3
M2
101
M2
52
92
318
Mmalton
Nullludwigshafen
Nullhong kong

FIG. 2

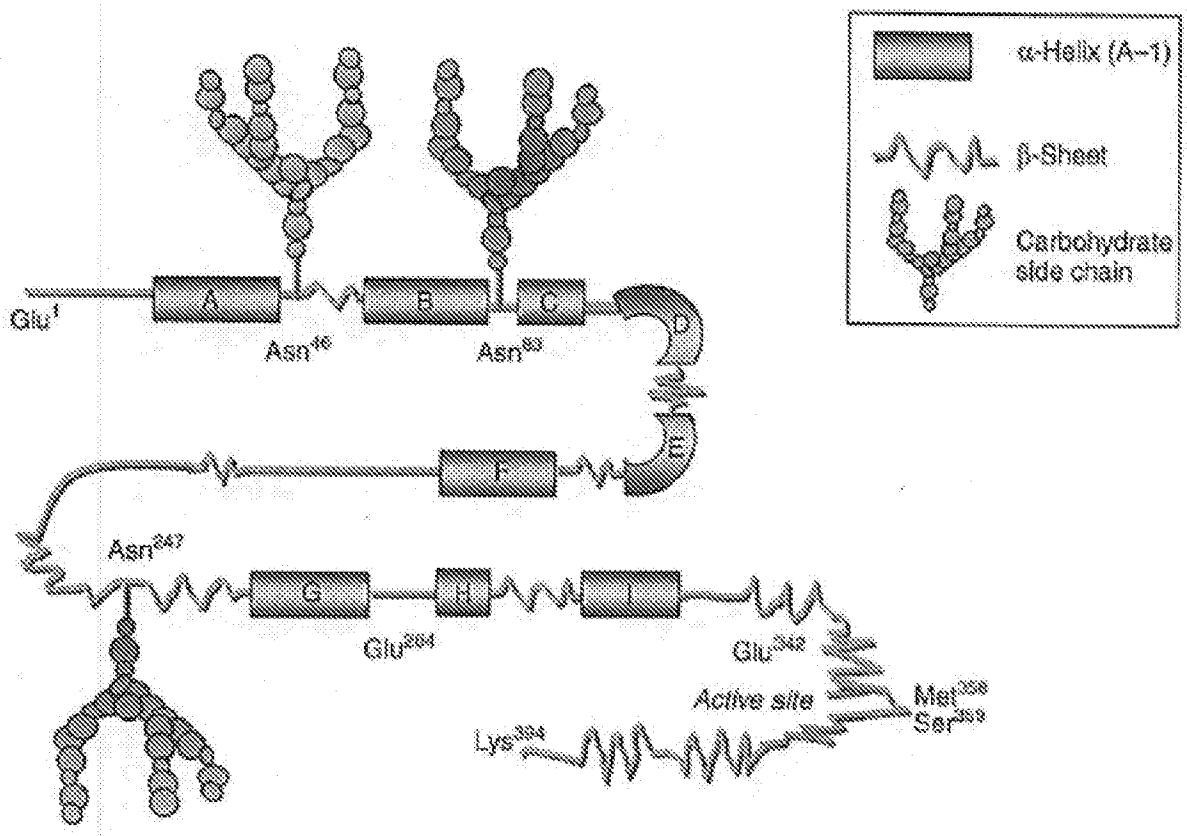

α-Helix (A–1)
β-Sheet
Carbohydrate side chain
Glu1
A
B
C
D
E
F
Asn46
Asn63
Asn247
G
H
I
Glu264
Glu340
Active site
Met358
Ser359
Lys384

FIG. 3

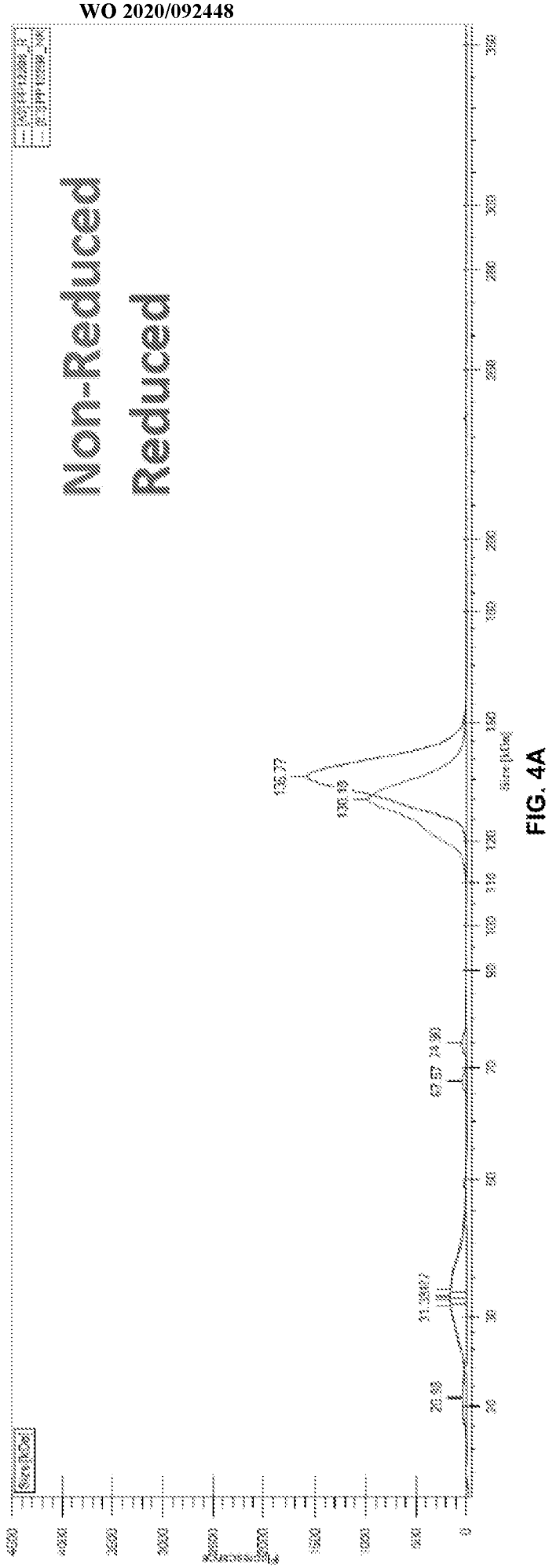


FIG. 4A

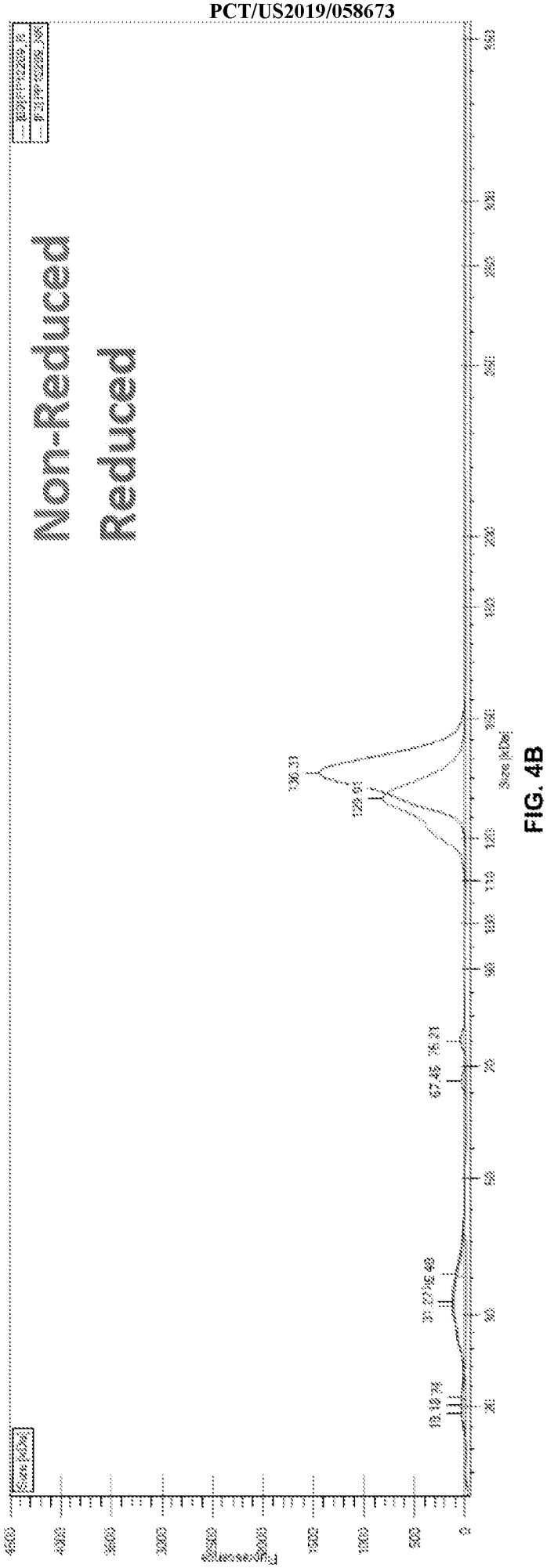


FIG. 4B

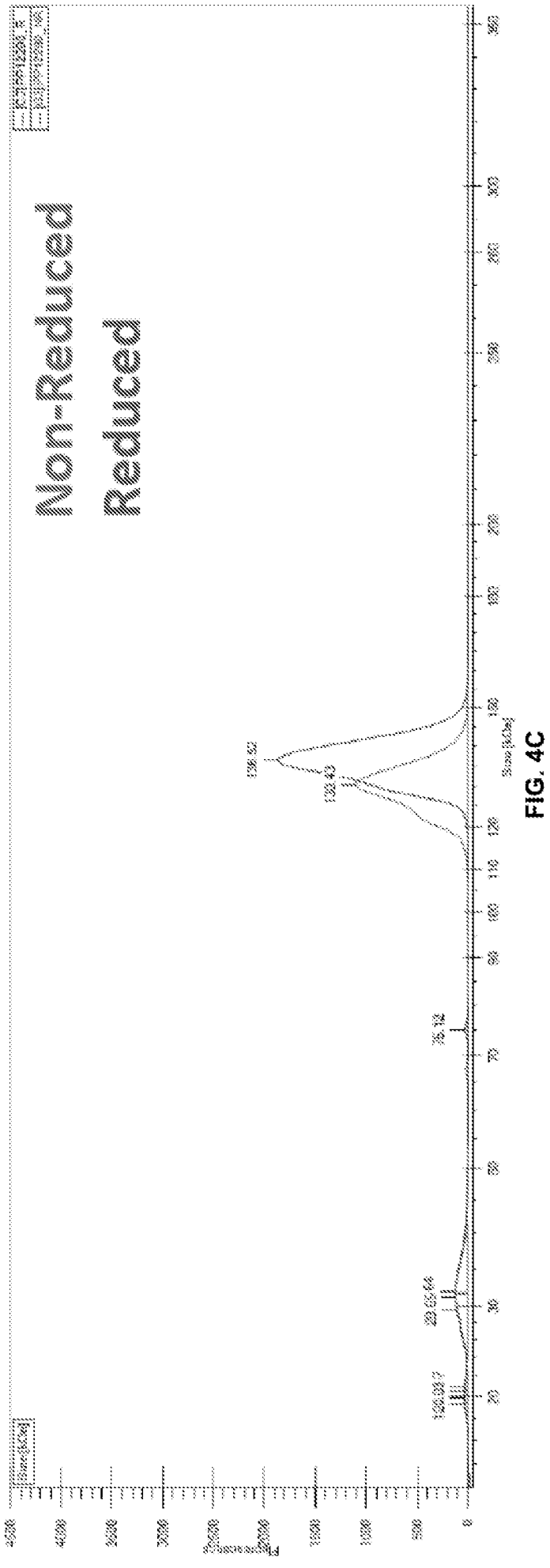


FIG. 4C

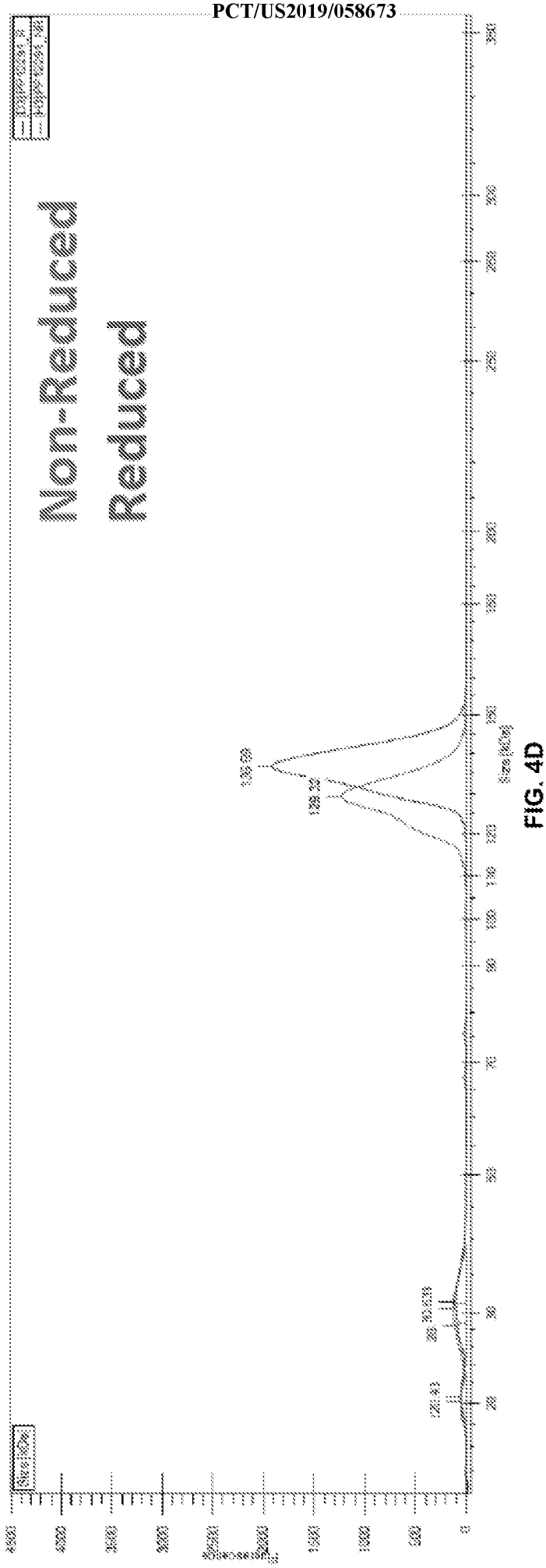


FIG. 4D

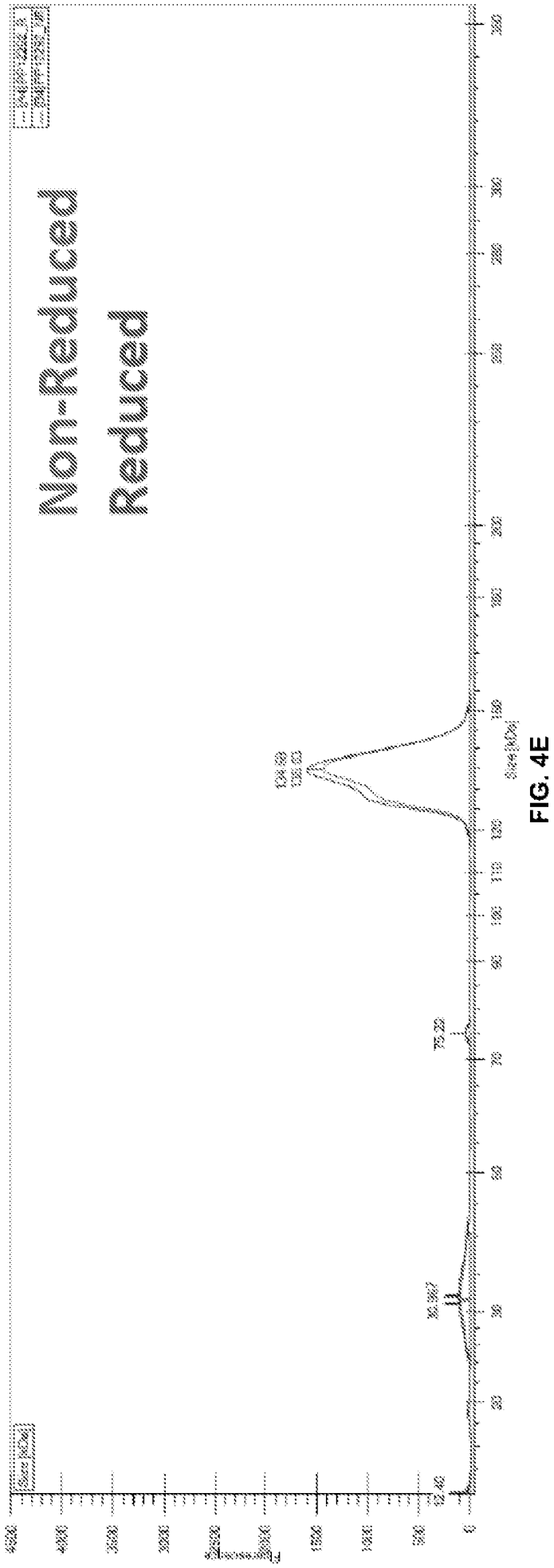

Non-Reduced
Reduced
Size [KDa]
Fluorescence

FIG. 4E

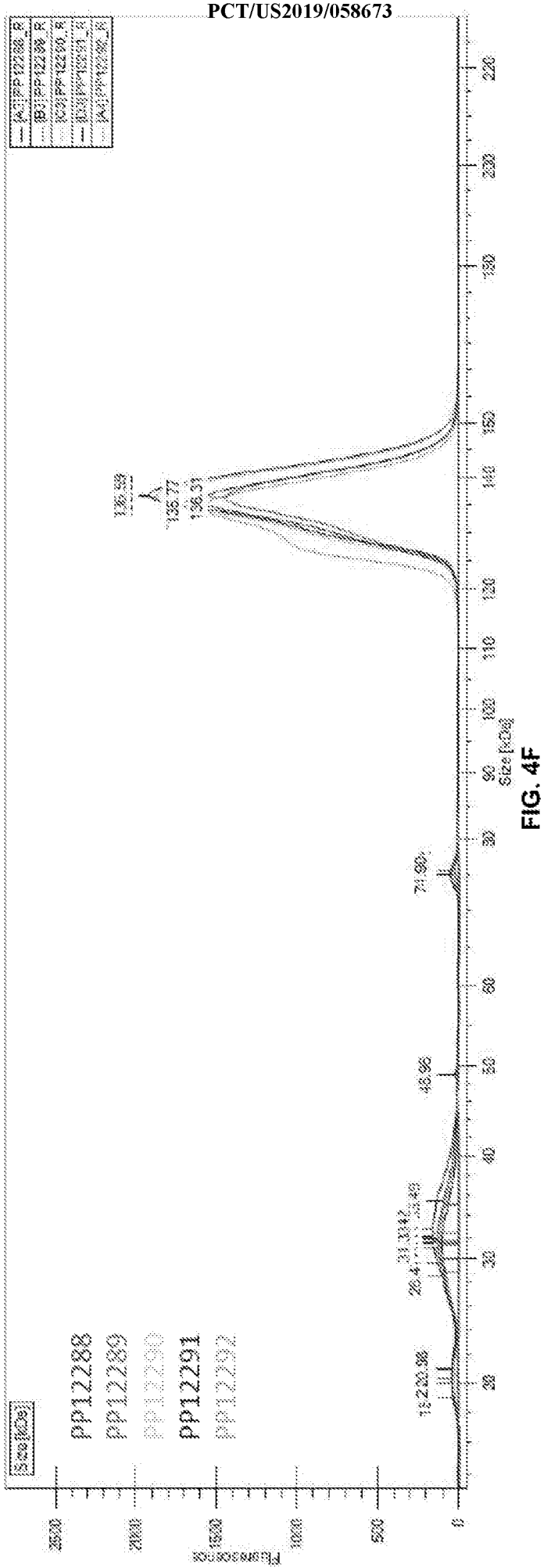

PP12288
PP12289
PP12290
PP12291
PP12292
Size [KDa]
Fluorescence

FIG. 4F

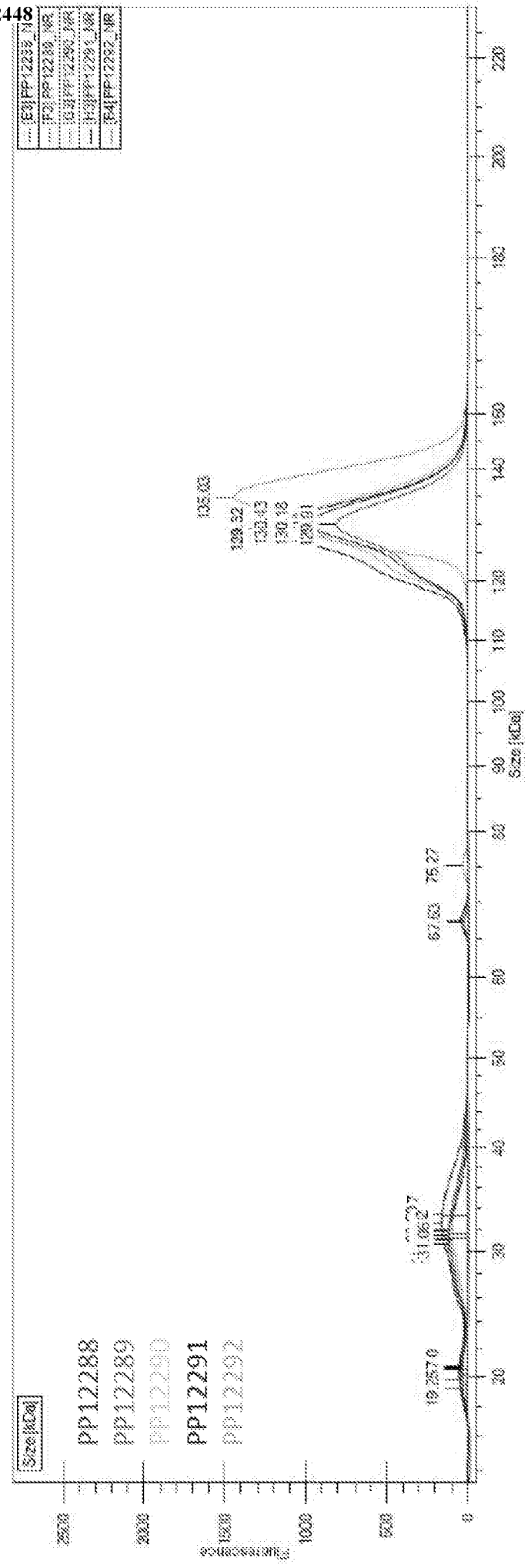

Size [kDa]
PP12288
PP12289
PP12290
PP12291
PP12292
Size [kDa]
Fluorescence
135.03
139.32
133.43
130.18
129.01
75.27
67.63
31.06
10.25

FIG. 4G

AAT

No.	Sample	Tm1 (°C)	Tm2 (°C)	Tm3 (°C)	Tm4 (°C)	Tm5 (°C)	Tagg 266 (°C)	Tagg 473 (°C)
1	AAT (PP122888)	49.3	60.3		76.3	87.2	55.2	48.2
2	C2325 (PP122889)	46.5	59.9	70.5	77.2		55.9	68.6
3	M351V, M358V (PP122890)	49.9	59.9		77.2		51.9	46.7
4	M351V, M358L (PP122891)	46.9	58.8	73.6	77.6		51.9	46.7
5	C2325, M351V, M358L (PP122892)	46.5	60.9		78.3		56.3	48.5

HSA

FIG. 5

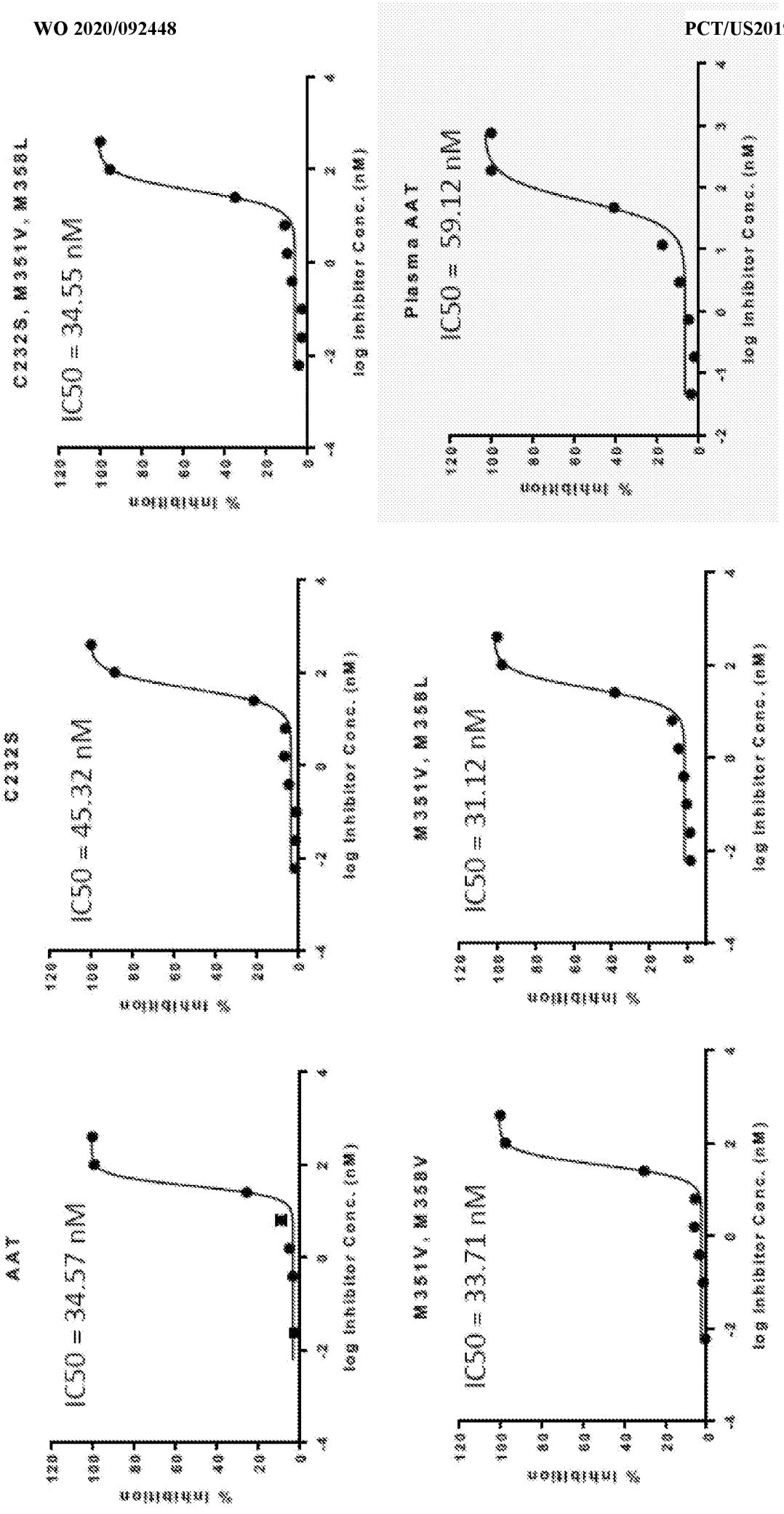

AAT
IC50 = 34.57 nM
C232S
IC50 = 45.32 nM
M351V, M358L
IC50 = 31.12 nM
M351V, M358V
IC50 = 33.71 nM
C232S, M351V, M358L
IC50 = 34.55 nM
Plasma AAT
IC50 = 59.12 nM
% Inhibition
log Inhibitor Conc. (nM)

FIG. 6

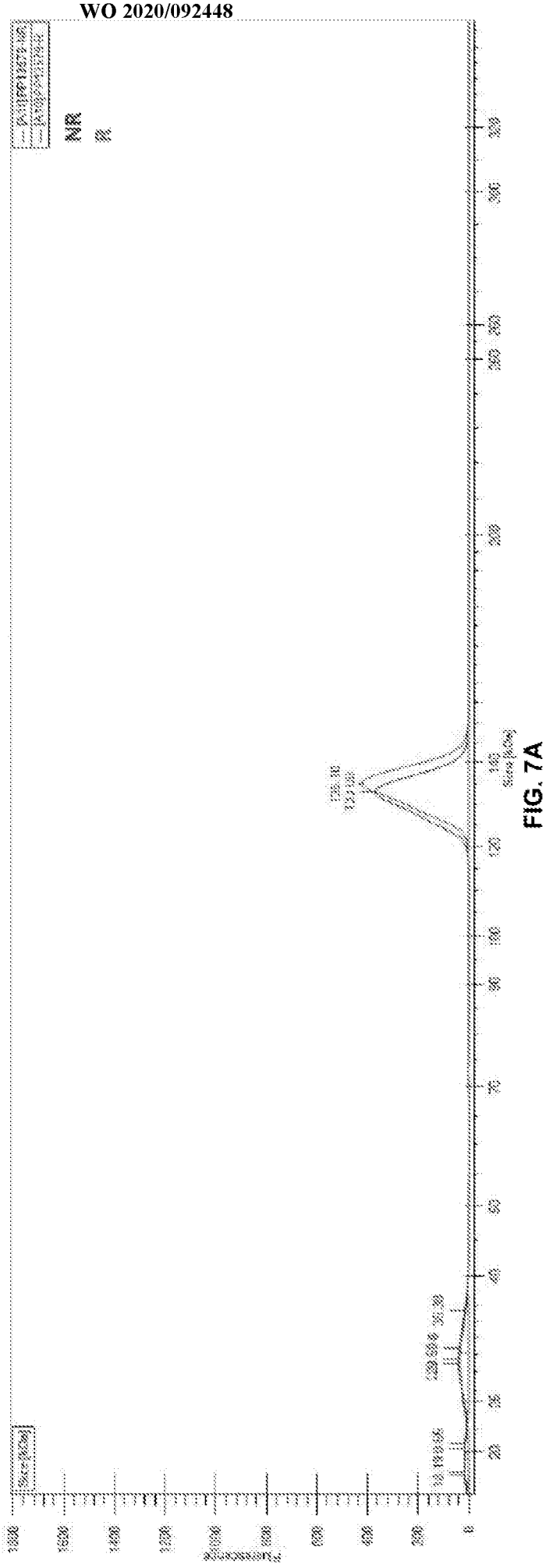


FIG. 7A

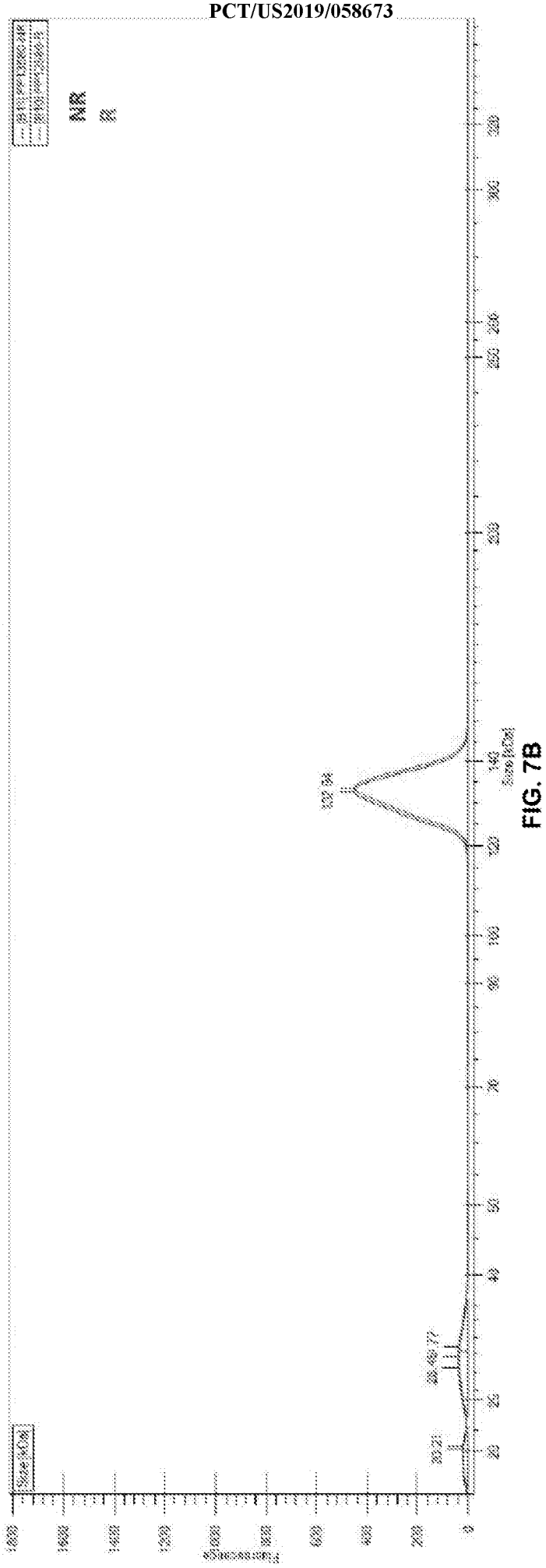


FIG. 7B

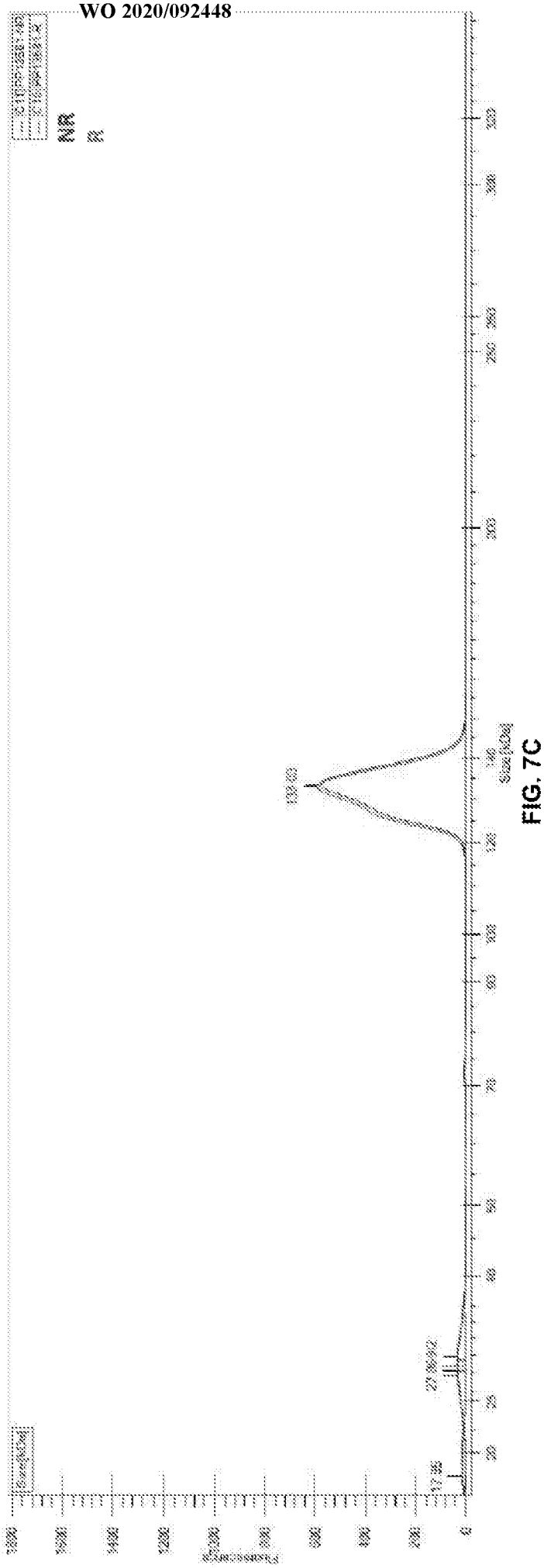


FIG. 7C

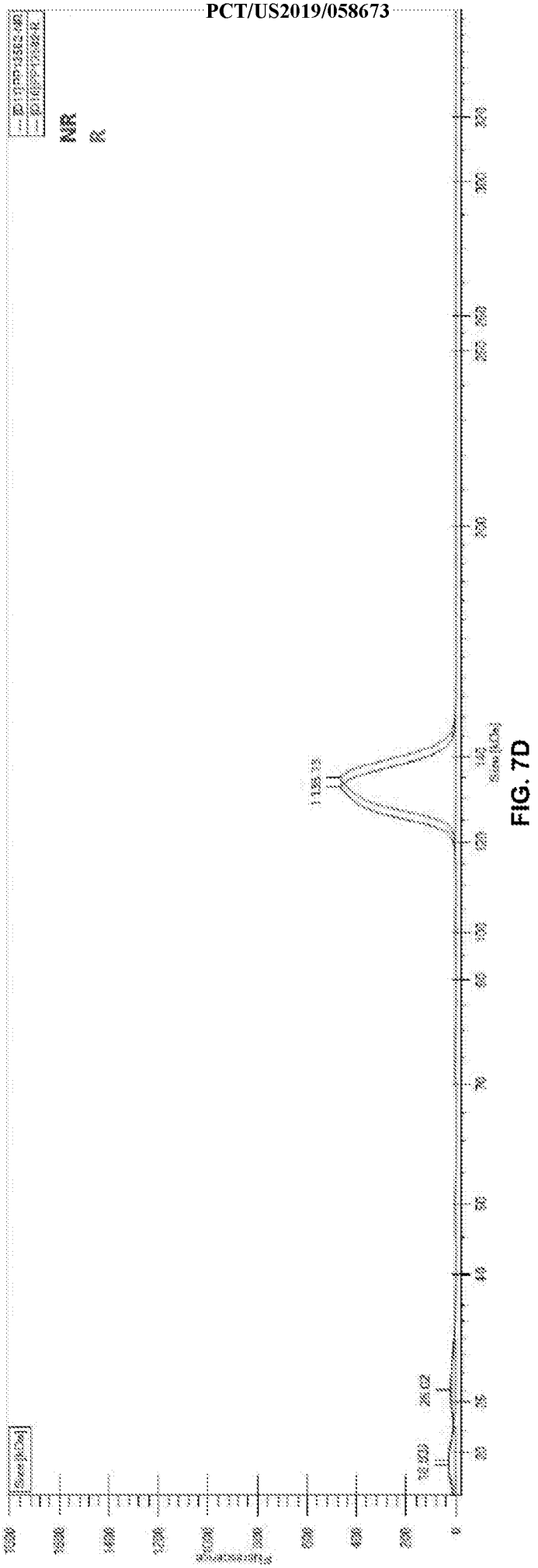


FIG. 7D

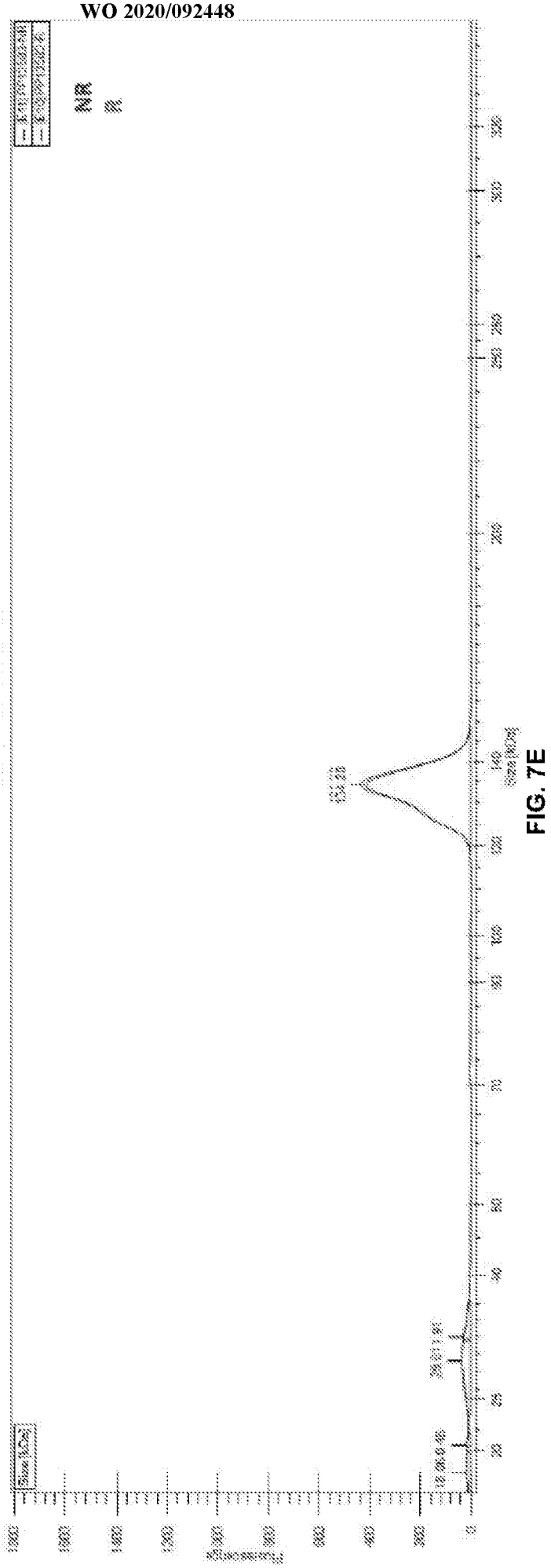


FIG. 7E

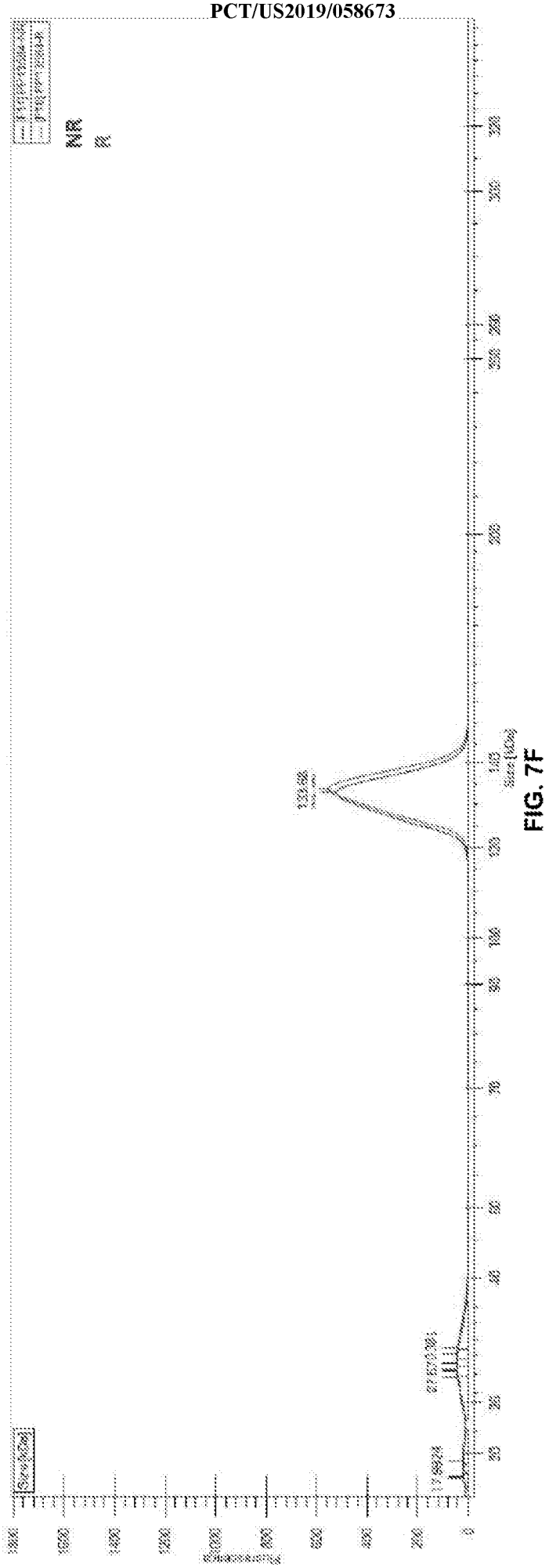


FIG. 7F

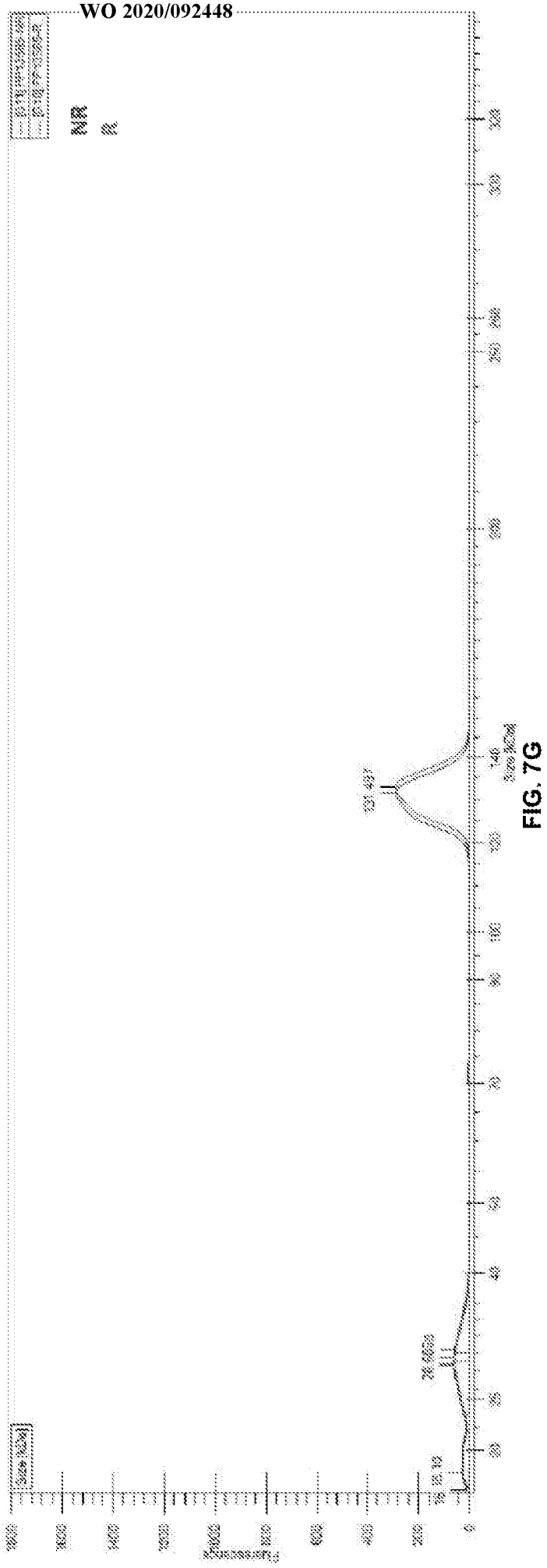


FIG. 7G

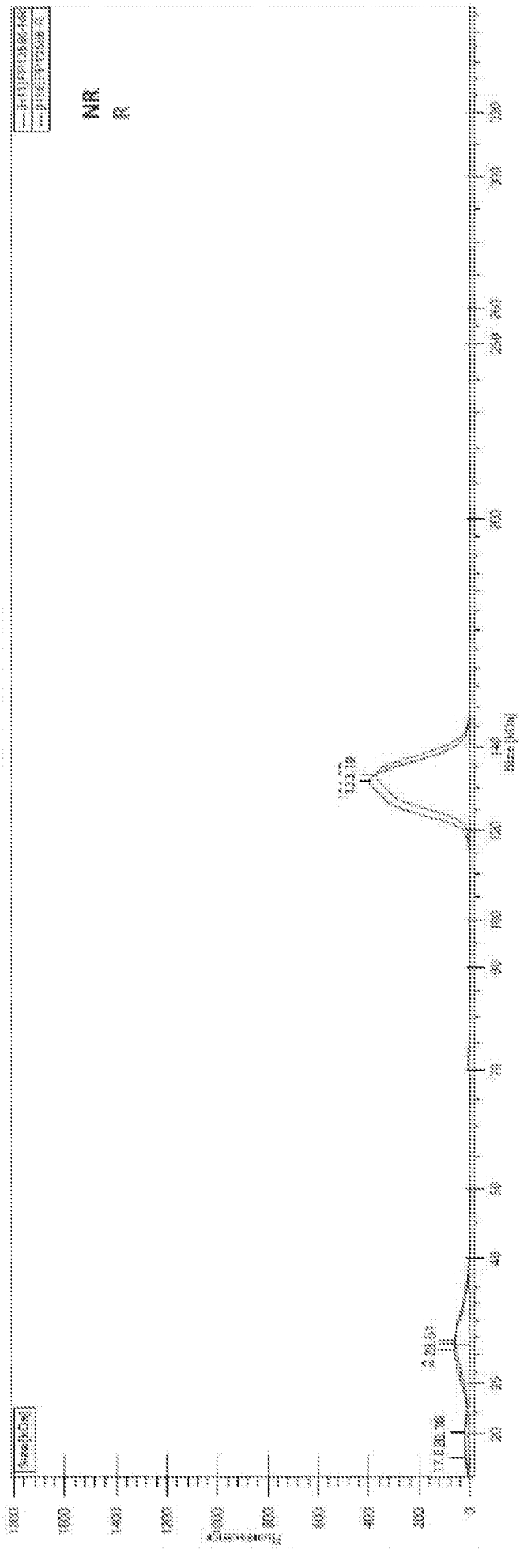


FIG. 7H

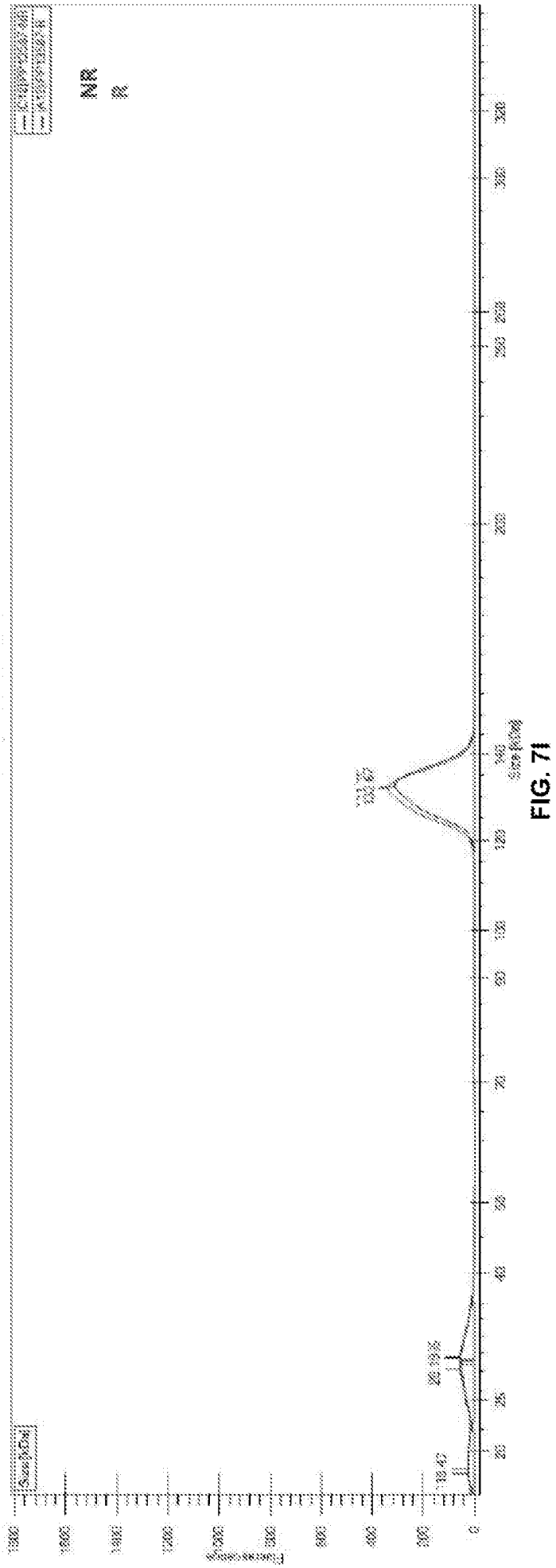


FIG. 7I

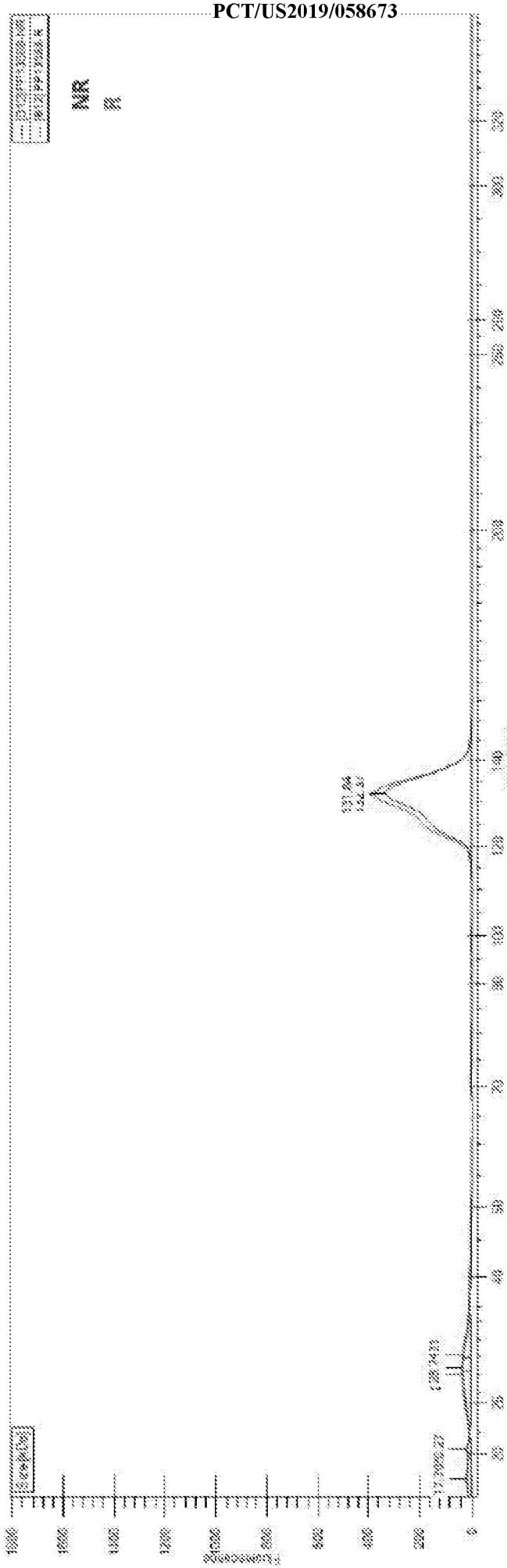


FIG. 7J

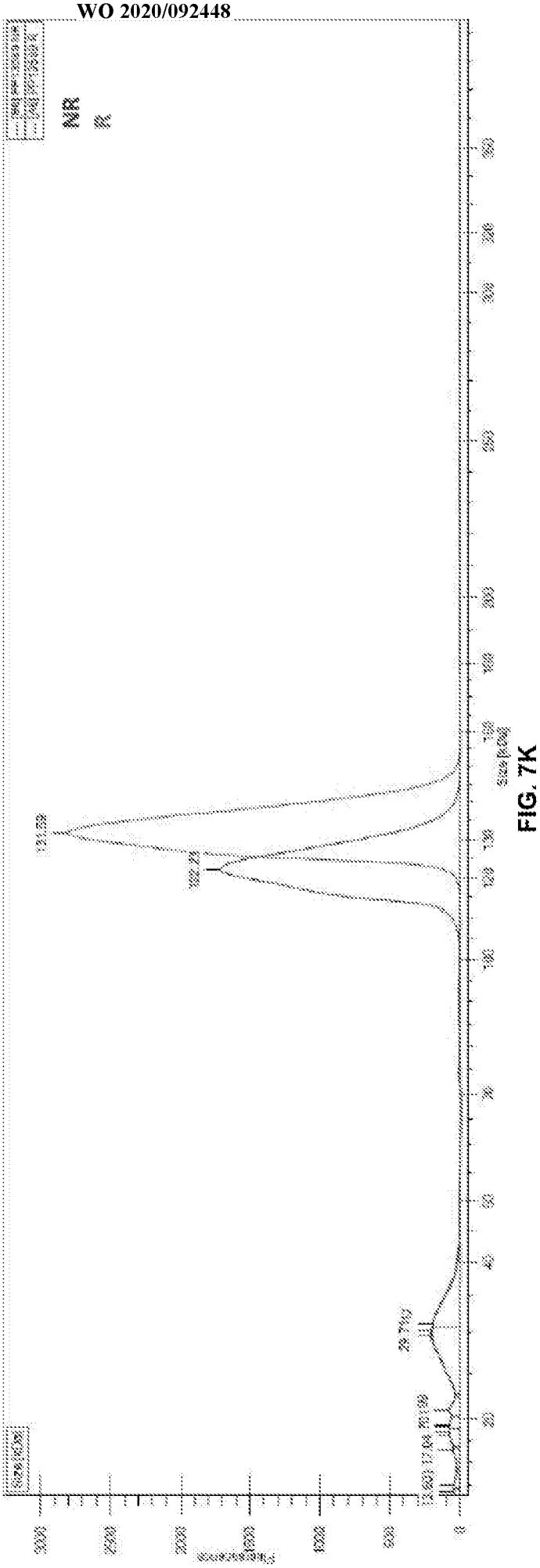

NR
%
Size [bp]
121.59
160.26
29.710
70.178

FIG. 7K

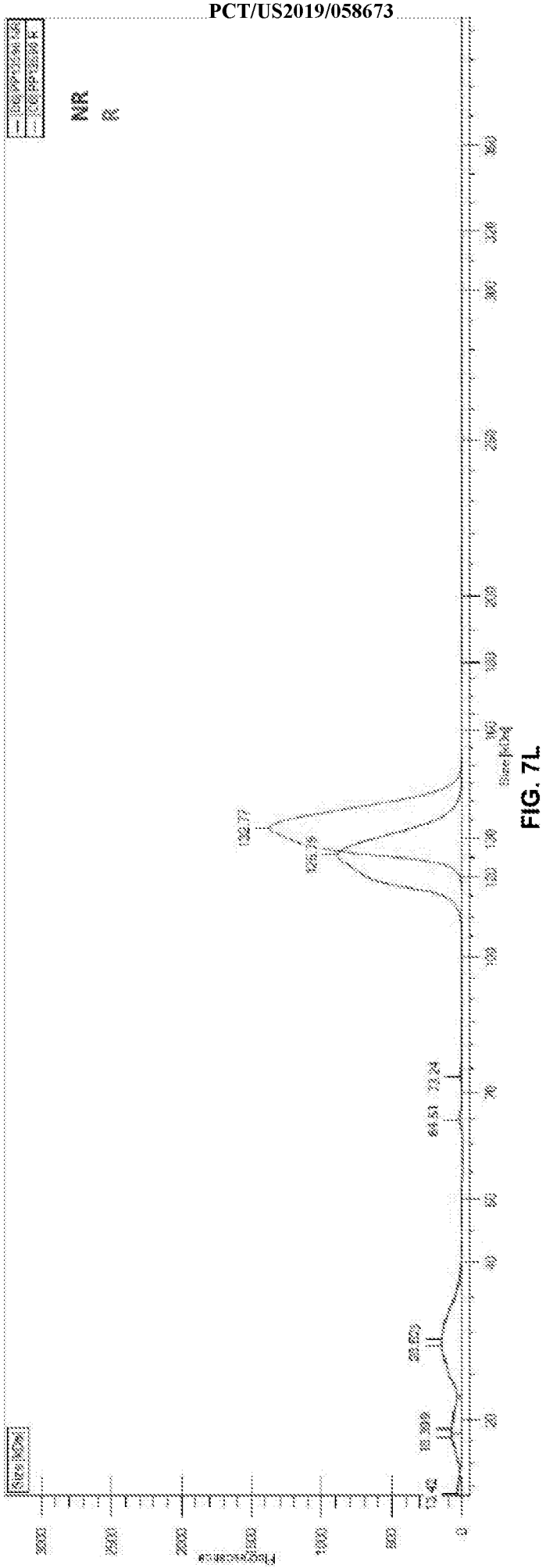

NR
%
Size [bp]
122.77
159.16
70.24
69.53
29.852
15.908
1.45

FIG. 7L

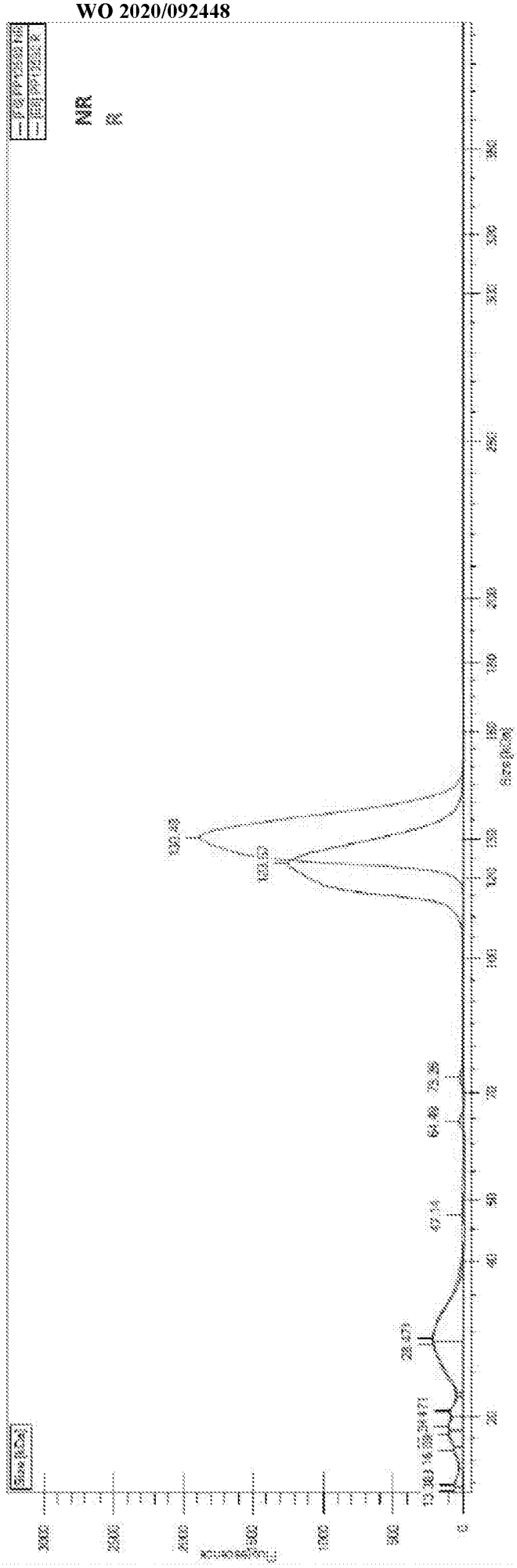


FIG. 7M

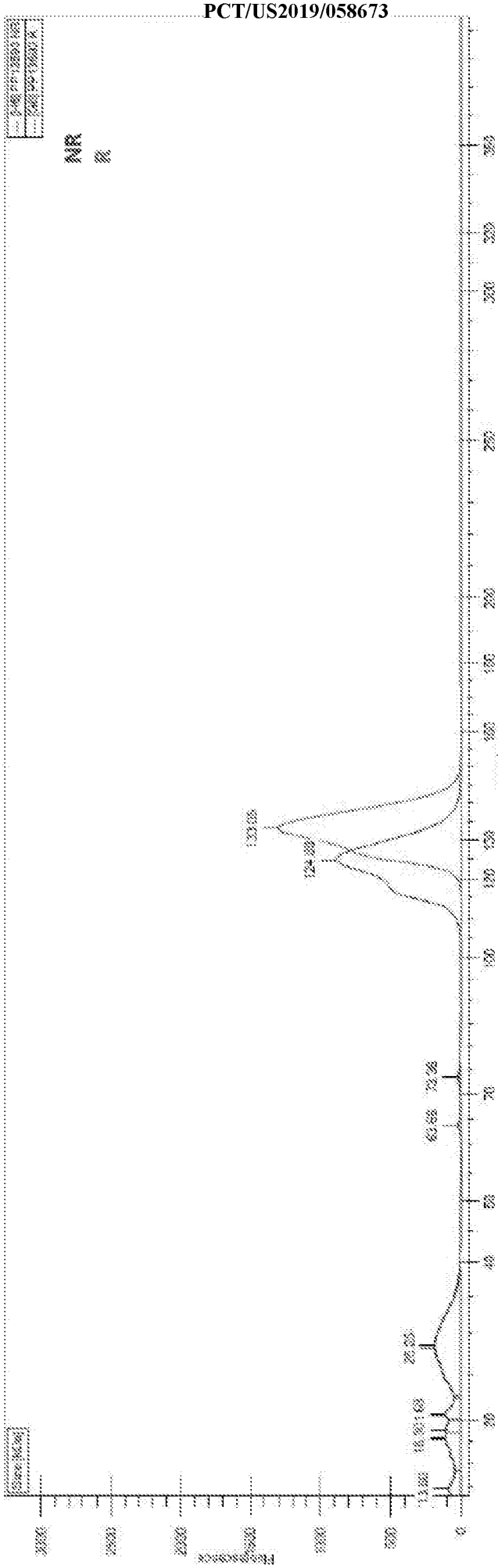


FIG. 7N

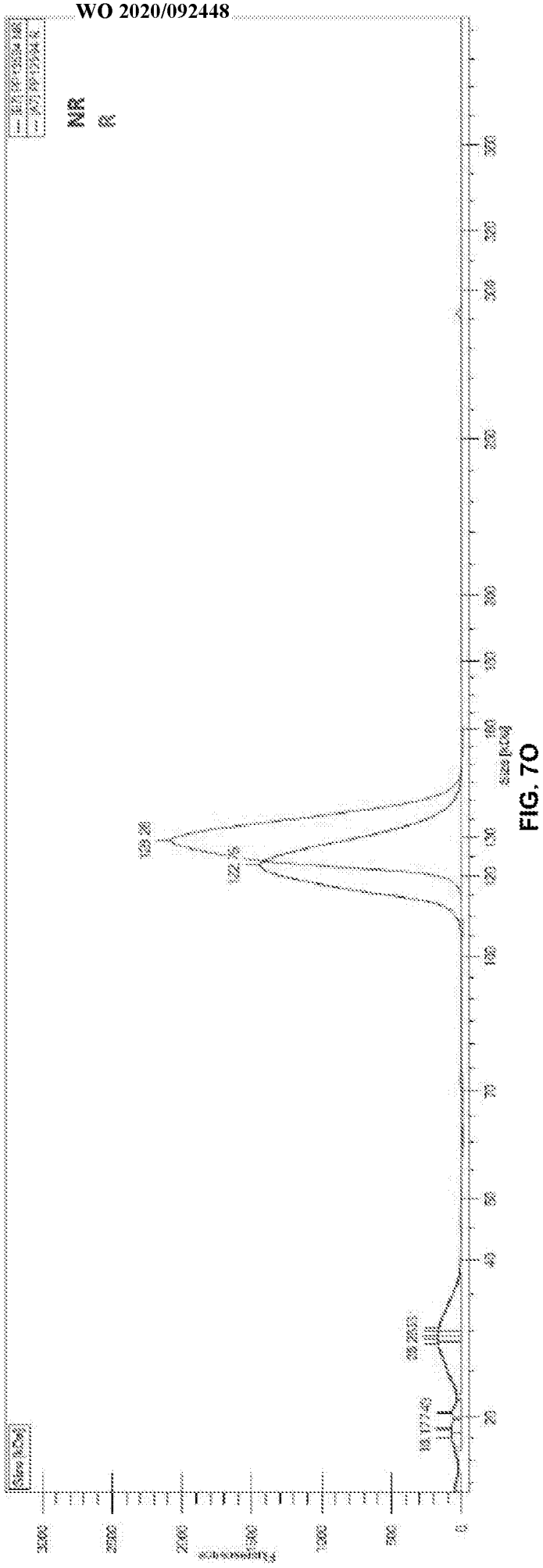


FIG. 7O

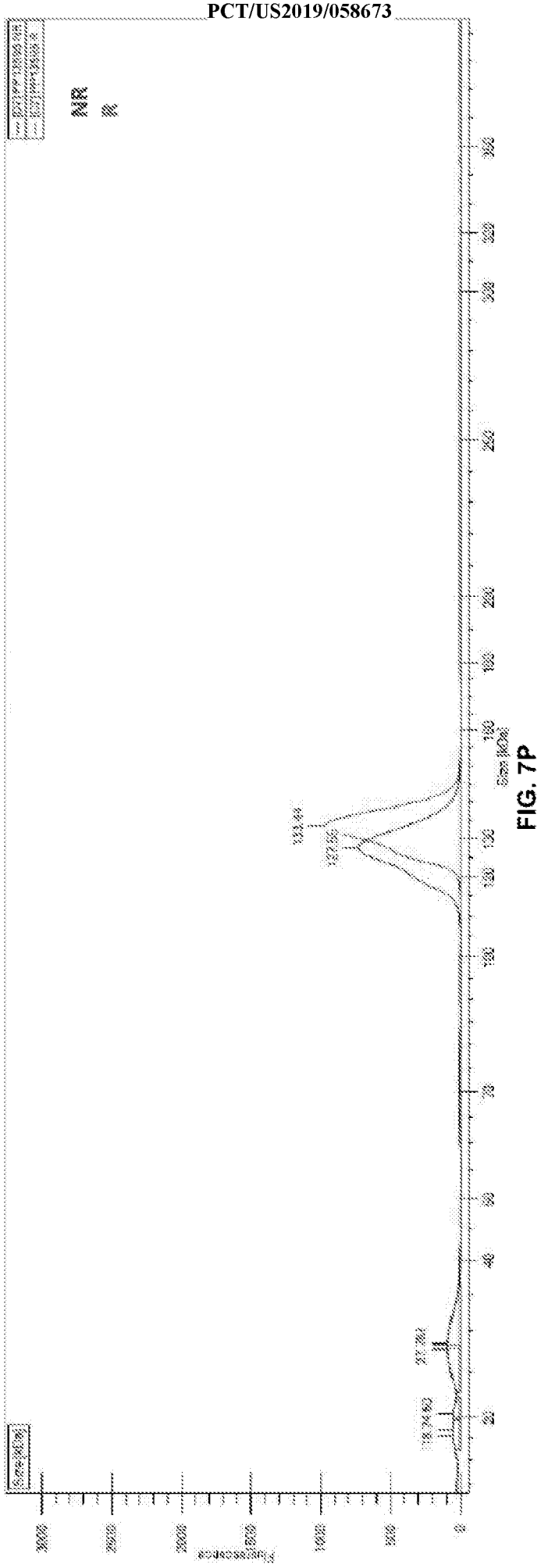


FIG. 7P

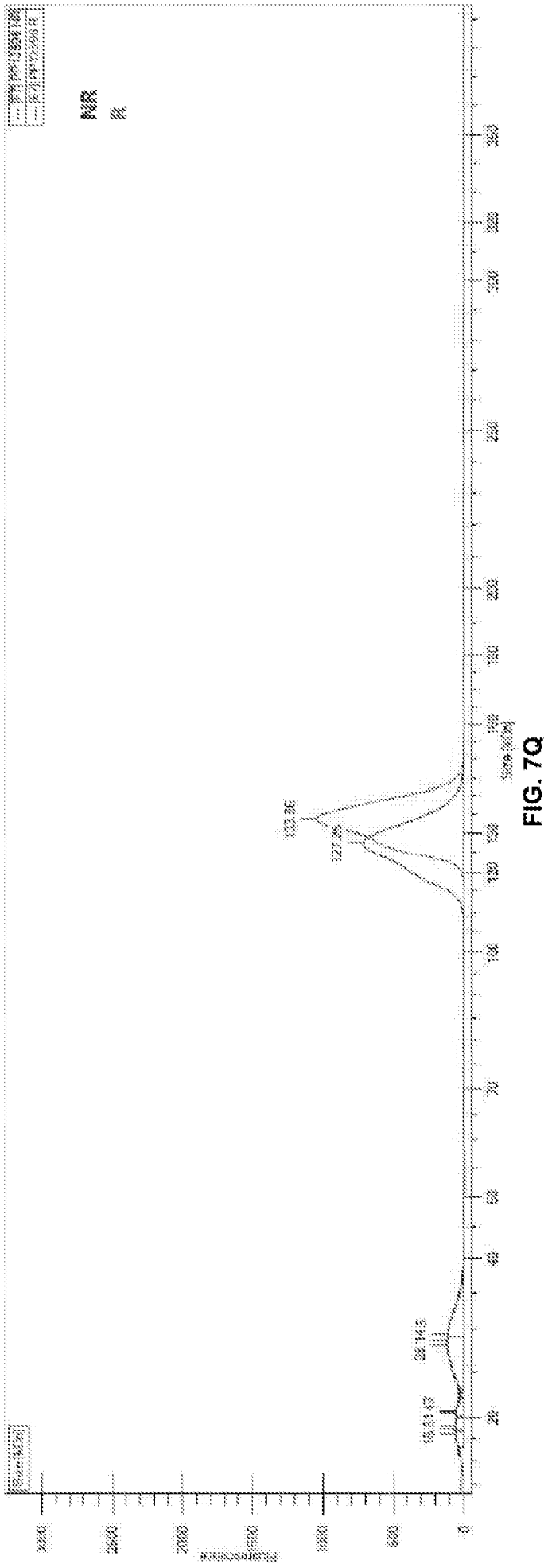

NR
%
Size [kDa]
130.86
127.96
29.745
18.817

FIG. 7Q

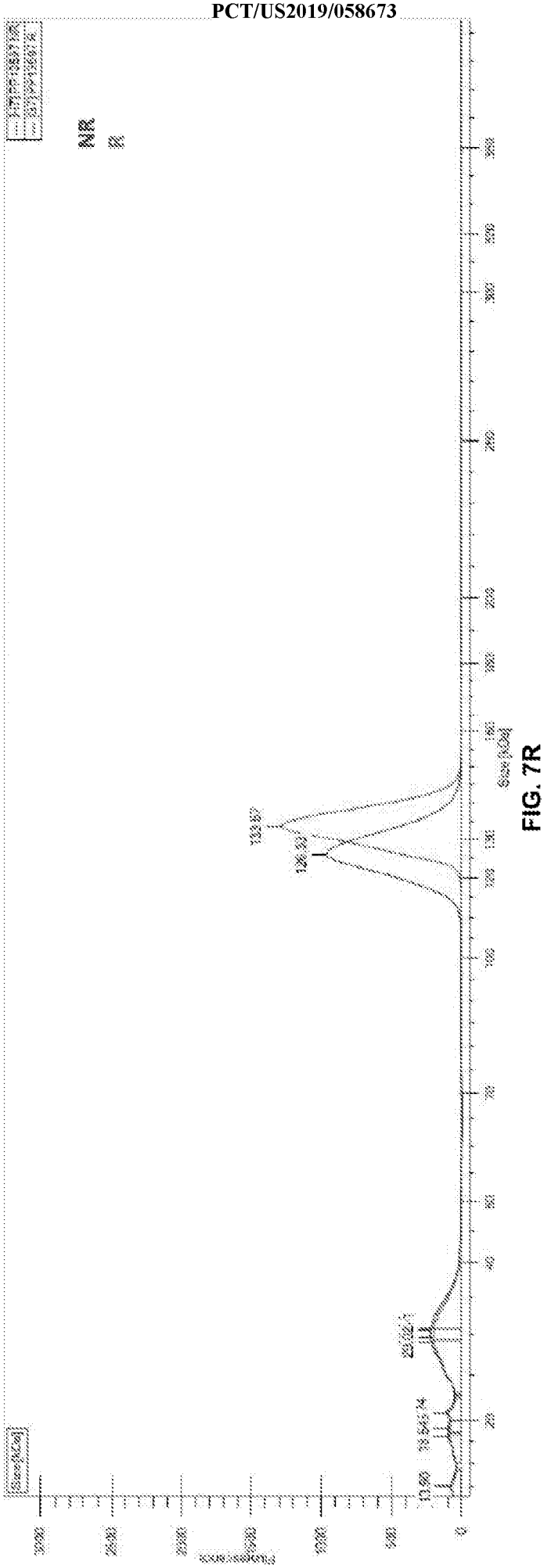

NR
%
Size [kDa]
130.67
126.30
29.702
13.640

FIG. 7R

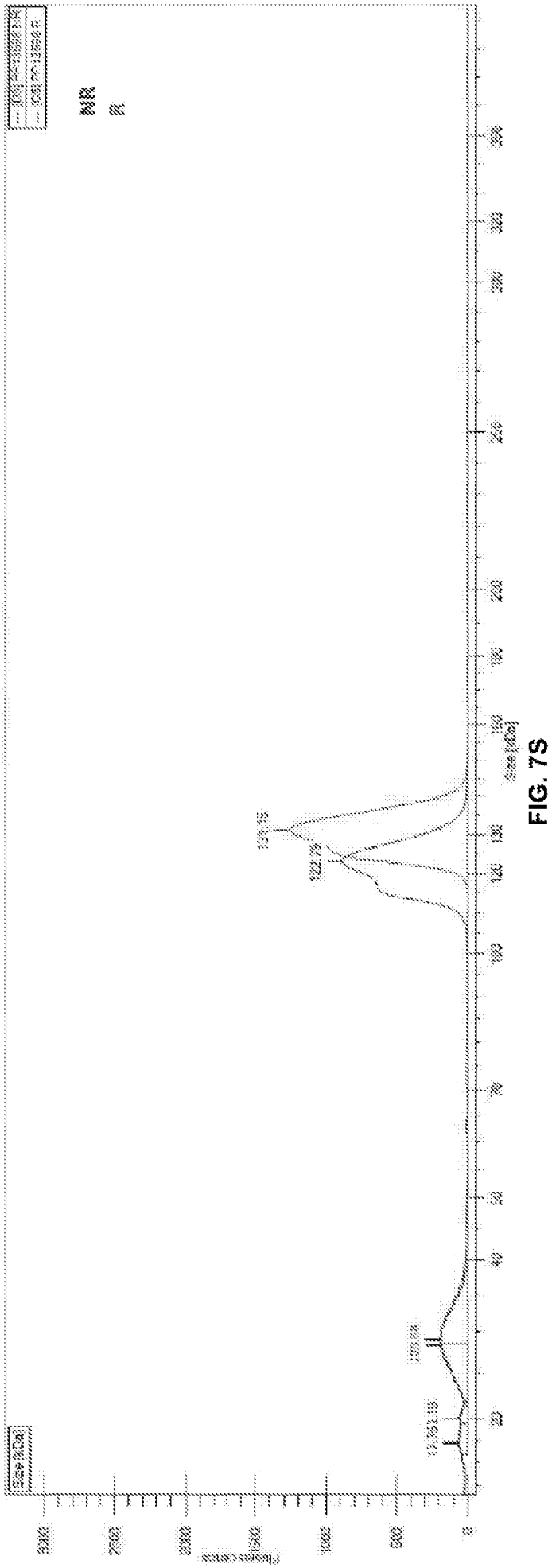

NR
IR
Size [kDa]
Size [kDa]
122.79
129.15
29.86
13.49
13.19

FIG. 7S

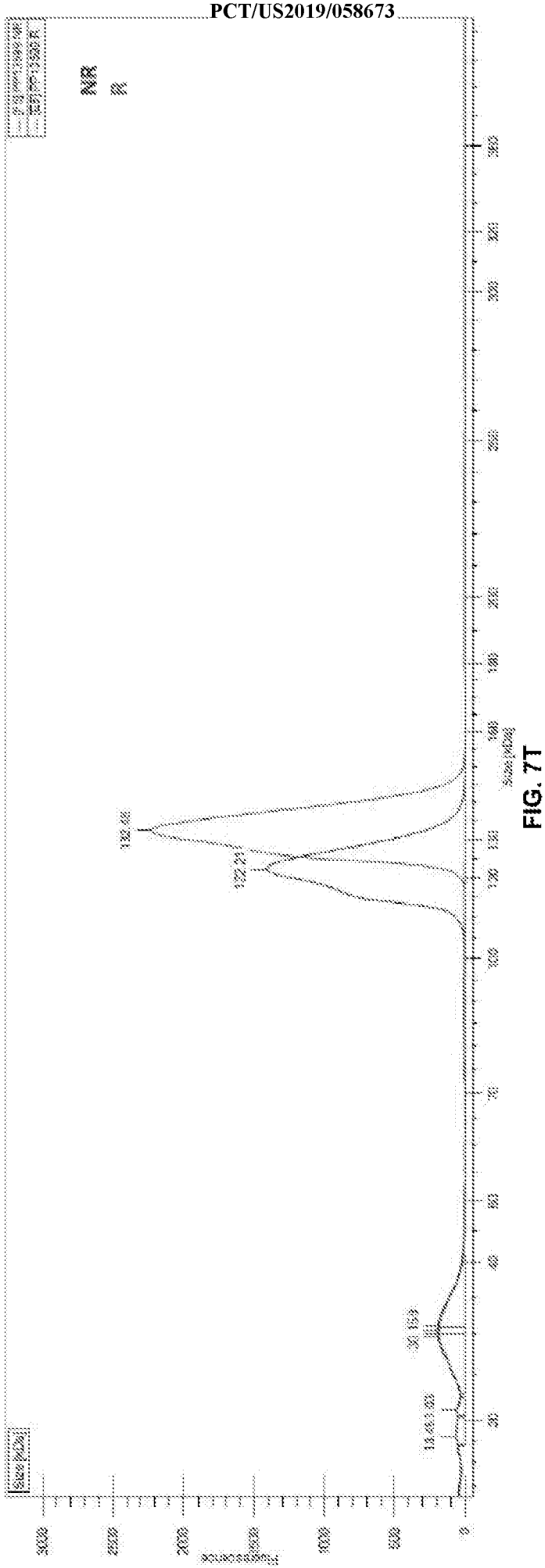

NR
IR
Size [kDa]
Size [kDa]
132.27
138.48
30.19
13.49
13.23

FIG. 7T

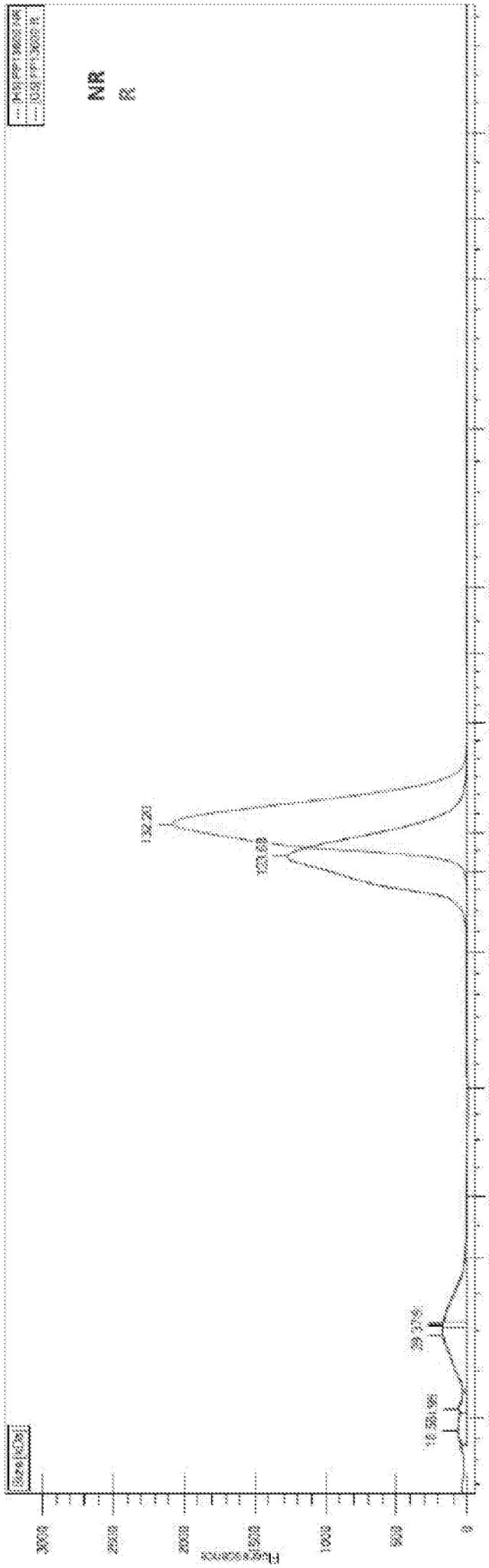
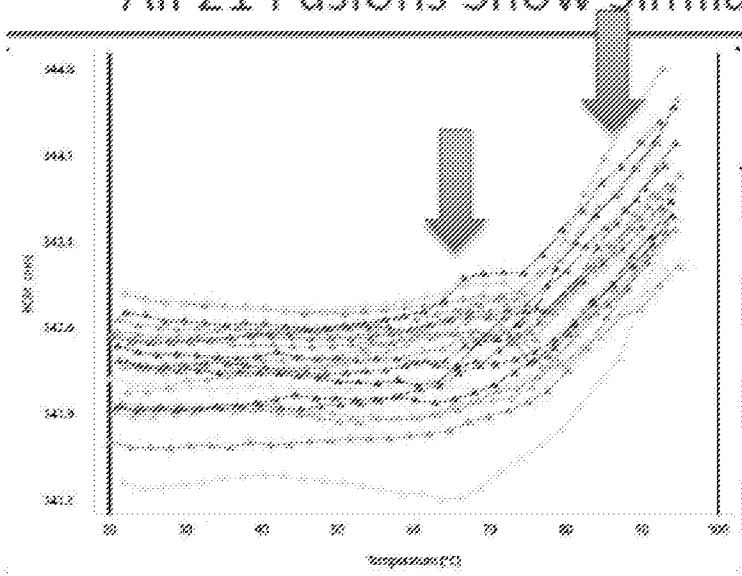

NIR
RT
132.20
120.08
89.17
80.58
Time [min]
Intensity
2000
1500
1000
500
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
220
230
240
250

FIG. 7U

Stability Analysis of 21 AAT-Albumin Fusions
All 21 Fusions Show Similar Stability



Client Name	FP#	Tm1 (°C)	Tm2 (°C)	Tm3 (°C)	Tm4 (°C)	Tagg 266 (°C)	Tagg 473 (°C)
FS1L	FP13579	35.9	45.2	61.7	82.9	46.6	50.2
G117F	FP13580	35.6	45.1	65.2	85.0	50.8	53.7
K331F	FP13581	35.8	54.3	70.3	84.9	52.4	49.9
K335A	FP13582	33.3	52.2	60.9	85.8	51.0	53.7
K168C/F189C	FP13583	30.3	49.8	58.2	81.7	44.4	44.3
S289C/P361C	FP13584	30.0	38.2	63.5	83.8	47.2	44.1
FS1L/G117F	FP13585	32.0	38.5	66	84.1	45.0	45.4
FS1L/K331F	FP13586	36.6	51.3	69.6	84.8	47.4	47.0
FS1L K335A	FP13587	32.6	51.4	64.1	85.0	48.9	46.7
FS1L/K168C/F189C	FP13588	32.4	38.8	61.7	83.6	48.3	47.2
FS1L/S289C/P361C	FP13589	35.2	58.7	67.0	80.5	46.4	49.5
G117F/K331F	FP13590	38.9	58.0	65.1	83.0	46.9	46.7
G117F/K335A	FP13592	34.1	48.3	67.4	84.5	48.1	48.3
G117F/K168C/F189C	FP13593	28.7	61.3	70.1	84.5	50.7	50.2
G117F/S289C/P361C	FP13594	32.4	45.1	69.0	86.9	47.7	47.5
K331F/K335A	FP13595	38.1	48.5	63.9	86.9	48.5	44.2
K331F/K168C/F189C	FP13596	34.9	51.1	62.6	85.4	50.8	49.9
K331F/S289C/P361C	FP13597	34.9	50.4	61.6	82.0	45.7	47.8
K335A/K168C/F189C	FP13598	30.1	46.9	62.3	85.0	46.2	47.6
K335A/S289C/P361C	FP13599	30.1	54.8	68.1	83.8	48.2	47.8
K168C/F189C/S289C/P361C	FP13600	28.9	48.6	71.0	81.3	45.8	44.4

FIG. 8

E392C/P393C
K168C/P169C
F51L/Q117F
F51L
G117F
K333A
K333F
F51L/K333F
Log Conc. of AAT Proteins (nM)

FIG. 9A

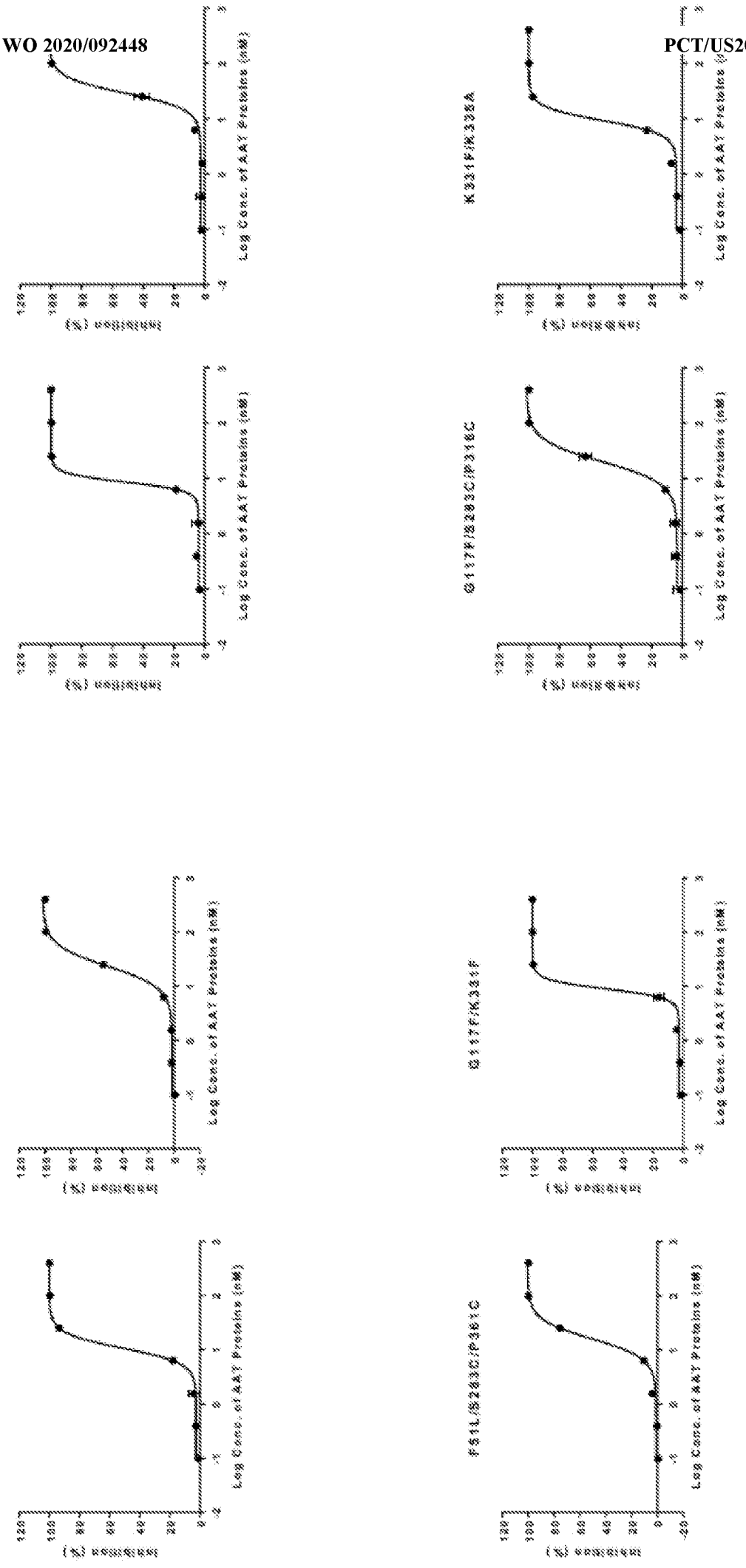
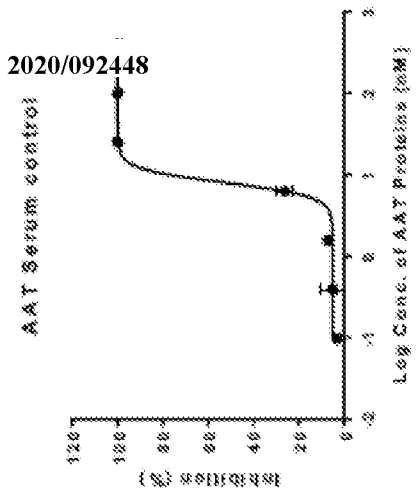
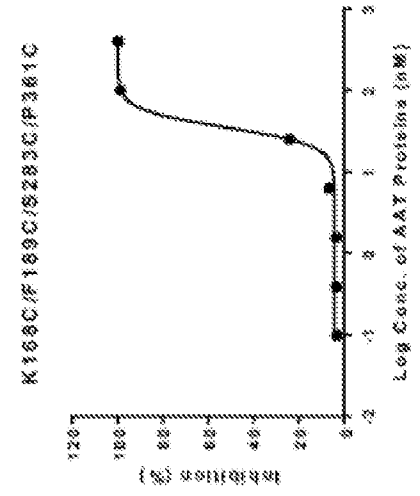
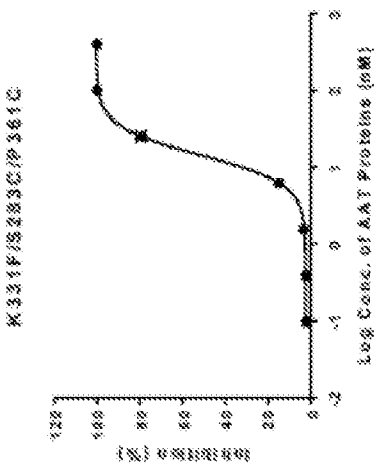
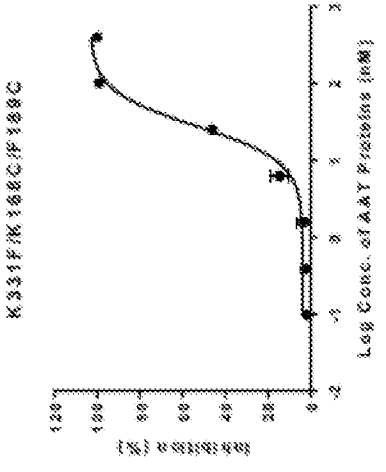


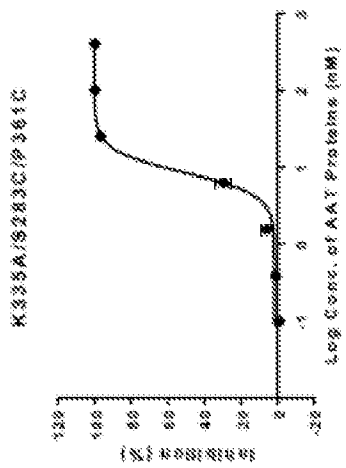
FIG. 9B


AAT Serum control
Inhibition (%)
Log Conc. of AAT Proteins (nM)


K168C/F189C/S283C/P361C
Inhibition (%)
Log Conc. of AAT Proteins (nM)


K331F/S283C/P361C
Inhibition (%)
Log Conc. of AAT Proteins (nM)


K331F/K168C/F189C
Inhibition (%)
Log Conc. of AAT Proteins (nM)


K335A/S283C/P361C
Inhibition (%)
Log Conc. of AAT Proteins (nM)

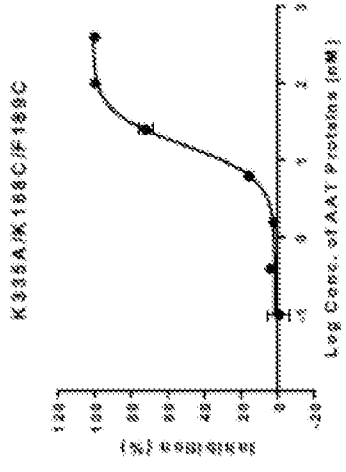

K335A/K168C/F189C
Inhibition (%)
Log Conc. of AAT Proteins (nM)

FIG. 9C

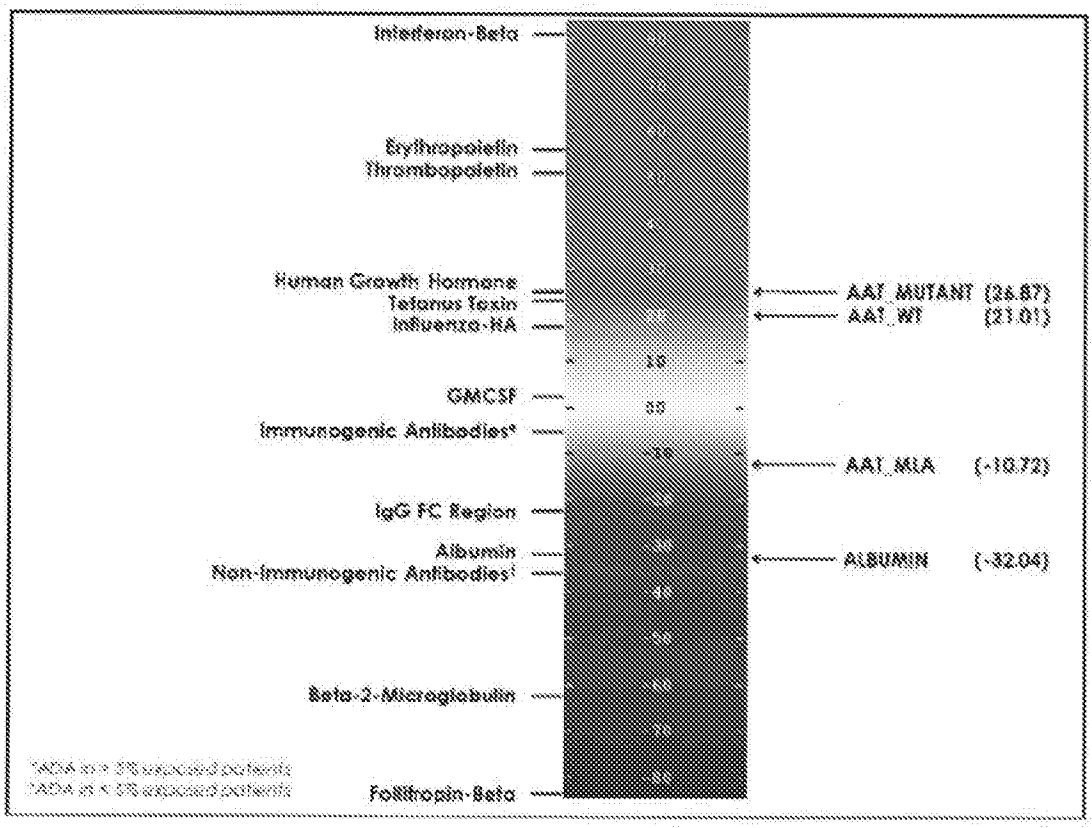
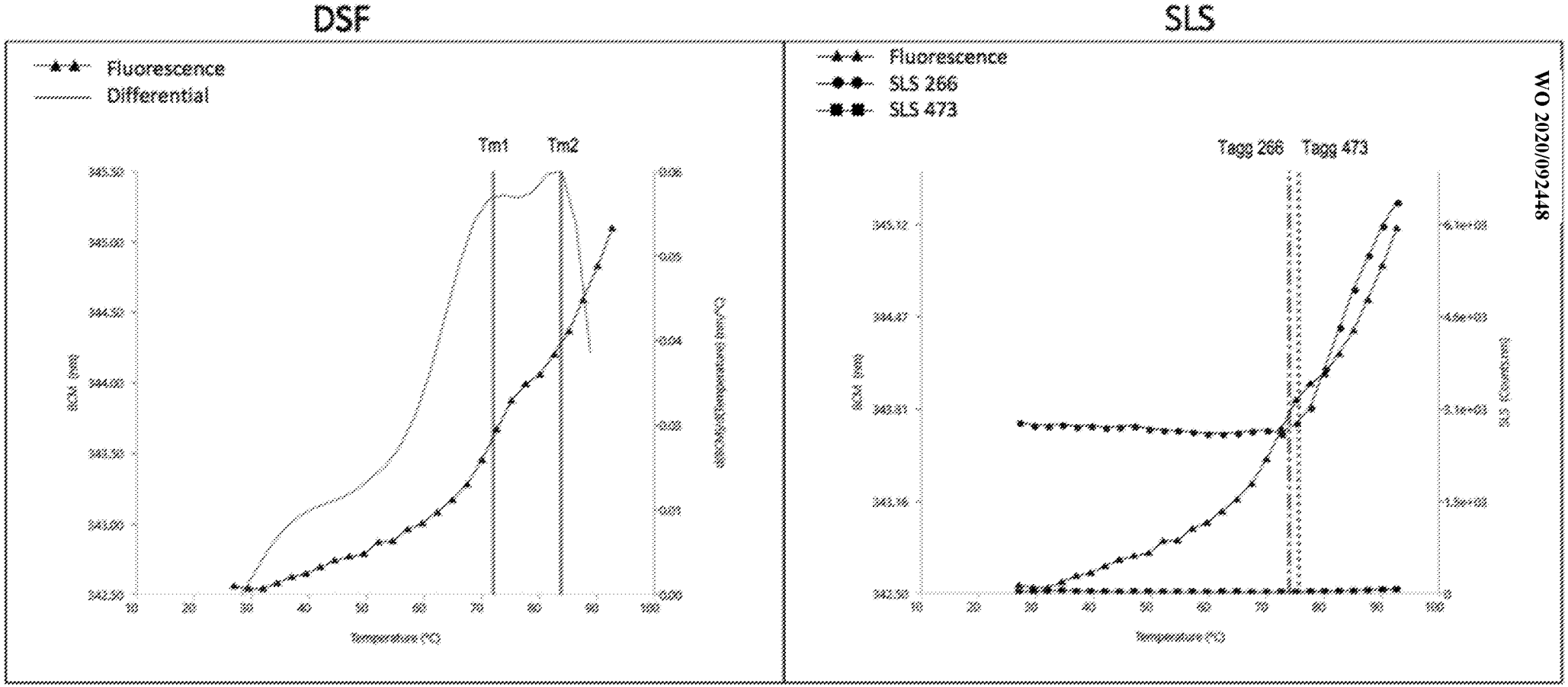
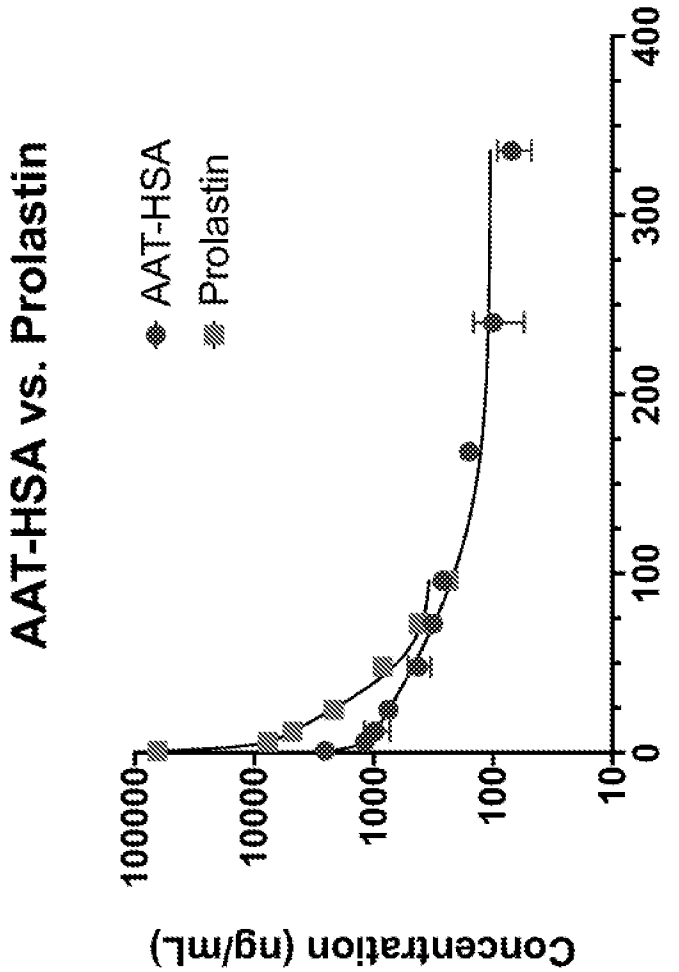

Interferon-Beta
Erythropoietin
Thrombopoietin
Human Growth Hormone
Tetanus Toxin
Influenza-HA
GMCSF
Immunogenic Antibodies*
IgG FC Region
Albumin
Non-Immunogenic Antibodies†
Beta-2-Microglobulin
Follitropin-Beta
AAT_MUTANT (26.87)
AAT_WT (21.01)
AAT_MIA (-10.72)
ALBUMIN (-32.04)

FIG. 10

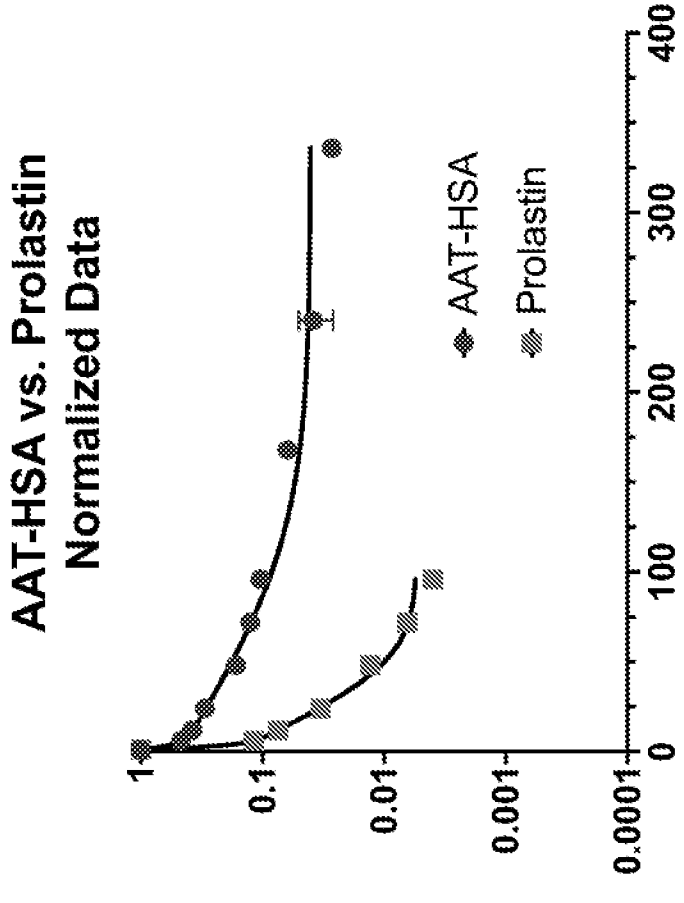


	DSF				SLS	
Temperature (°C)	Tm1	Tm2	Tm3	Tm4	Tagg 266	Tagg 473
	72.0	83.8			74.0	76.0

FIG. 11



	AAT-HSA	Prolastin
Y0	3493	145620
Plateau	105.7	332.7
PercentFast	66.50	92.90
KFast	0.5181	0.9002
KSlow	0.02354	0.07017
Half Life (Slow)	29.44	9.879
Half Life (Fast)	1.338	0.7700
Tau (slow)	42.48	14.25
Tau (fast)	1.930	1.111
Rate constant ratio	22.01	12.83



	AAT-HSA	Prolastin
Y0	1.339	2.291
Plateau	0.04047	0.005383
PercentFast	66.20	92.95
KFast	0.4832	0.9226
KSlow	0.02302	0.07099
Half Life (Slow)	30.12	9.764
Half Life (Fast)	1.435	0.7513
Tau (slow)	43.45	14.09
Tau (fast)	2.070	1.084
Rate constant ratio	20.99	13.00

FIG. 12

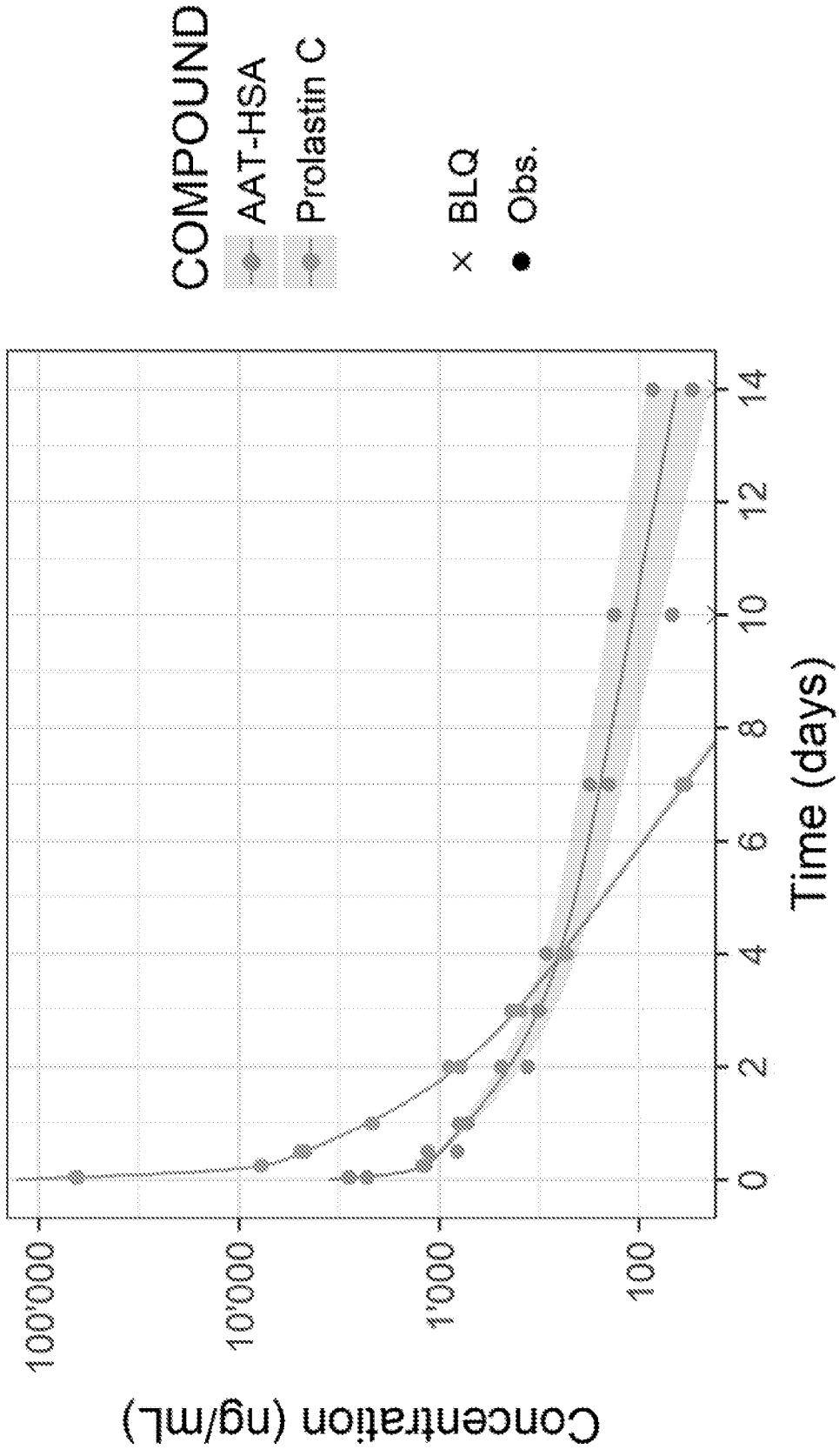

COMPOUND
AAT-HSA
Prolastin C
BLQ
Obs.
Concentration (ng/mL)
100'000
10'000
1'000
100
0
2
4
6
8
10
12
14
Time (days)

FIG. 13

SEQUENCE LISTING

<110> SPIN THERAPEUTICS LLC
SATO, Aaron
DESOUZA, Mark

<120> COMPOSITIONS AND METHODS FOR ALPHA-1-ANTITRYPSIN DISORDERS

<130> 118030.00008

<150> US 62/752,182
<151> 2018-10-29

<160> 71

<170> PatentIn version 3.5

<210> 1
<211> 394
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic: Alpha-1-antitrypsin

<400> 1

Glu Asp Pro Gln Gly Asp Ala Ala Gln Lys Thr Asp Thr Ser His His
1 5 10 15

Asp Gln Asp His Pro Thr Phe Asn Lys Ile Thr Pro Asn Leu Ala Glu
20 25 30

Phe Ala Phe Ser Leu Tyr Arg Gln Leu Ala His Gln Ser Asn Ser Thr
35 40 45

Asn Ile Phe Phe Ser Pro Val Ser Ile Ala Thr Ala Phe Ala Met Leu
50 55 60

Ser Leu Gly Thr Lys Ala Asp Thr His Asp Glu Ile Leu Glu Gly Leu
65 70 75 80

Asn Phe Asn Leu Thr Glu Ile Pro Glu Ala Gln Ile His Glu Gly Phe
85 90 95

```
Gln Glu Leu Leu Arg Thr Leu Asn Gln Pro Asp Ser Gln Leu Gln Leu
            100                 105                 110

Thr Thr Gly Asn Gly Leu Phe Leu Ser Glu Gly Leu Lys Leu Val Asp
        115                 120                 125

Lys Phe Leu Glu Asp Val Lys Lys Leu Tyr His Ser Glu Ala Phe Thr
    130                 135                 140

Val Asn Phe Gly Asp Thr Glu Glu Ala Lys Lys Gln Ile Asn Asp Tyr
145                 150                 155                 160

Val Glu Lys Gly Thr Gln Gly Lys Ile Val Asp Leu Val Lys Glu Leu
                165                 170                 175

Asp Arg Asp Thr Val Phe Ala Leu Val Asn Tyr Ile Phe Phe Lys Gly
            180                 185                 190

Lys Trp Glu Arg Pro Phe Glu Val Lys Asp Thr Glu Glu Glu Asp Phe
        195                 200                 205

His Val Asp Gln Val Thr Thr Val Lys Val Pro Met Met Lys Arg Leu
    210                 215                 220

Gly Met Phe Asn Ile Gln His Cys Lys Lys Leu Ser Ser Trp Val Leu
225                 230                 235                 240

Leu Met Lys Tyr Leu Gly Asn Ala Thr Ala Ile Phe Phe Leu Pro Asp
                245                 250                 255

Glu Gly Lys Leu Gln His Leu Glu Asn Glu Leu Thr His Asp Ile Ile
            260                 265                 270

Thr Lys Phe Leu Glu Asn Glu Asp Arg Arg Ser Ala Ser Leu His Leu
        275                 280                 285

Pro Lys Leu Ser Ile Thr Gly Thr Tyr Asp Leu Lys Ser Val Leu Gly
```

```
    290                 295                 300

Gln Leu Gly Ile Thr Lys Val Phe Ser Asn Gly Ala Asp Leu Ser Gly
305                 310                 315                 320

Val Thr Glu Glu Ala Pro Leu Lys Leu Ser Lys Ala Val His Lys Ala
                325                 330                 335

Val Leu Thr Ile Asp Glu Lys Gly Thr Glu Ala Ala Gly Ala Met Phe
            340                 345                 350

Leu Glu Ala Ile Pro Met Ser Ile Pro Pro Glu Val Lys Phe Asn Lys
        355                 360                 365

Pro Phe Val Phe Leu Met Ile Glu Gln Asn Thr Lys Ser Pro Leu Phe
    370                 375                 380

Met Gly Lys Val Val Asn Pro Thr Gln Lys
385                 390


<210>  2
<211>  24
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic: Alpha-1-antitrypsin leader

<400>  2

Met Pro Ser Ser Val Ser Trp Gly Ile Leu Leu Leu Ala Gly Leu Cys
1               5                   10                  15

Cys Leu Val Pro Val Ser Leu Ala
            20


<210>  3
<211>  498
<212>  PRT
<213>  Homo sapiens
```

<220>
<221> misc_feature
<223> Human Albumin

<400> 3

```
Met Lys Trp Val Thr Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1               5                   10                  15


Tyr Ser Arg Gly Val Phe Arg Arg Asp Ala His Lys Ser Glu Val Ala
            20                  25                  30


His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
        35                  40                  45


Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
    50                  55                  60


Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
65                  70                  75                  80


Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
                85                  90                  95


Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
            100                 105                 110


Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
        115                 120                 125


His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
    130                 135                 140


Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
145                 150                 155                 160


Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
                165                 170                 175
```

```
Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
            180                 185                 190

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
        195                 200                 205

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Gly Leu Lys Cys
    210                 215                 220

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225                 230                 235                 240

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
                245                 250                 255

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
            260                 265                 270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
        275                 280                 285

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
    290                 295                 300

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
305                 310                 315                 320

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Gly Ser
                325                 330                 335

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
            340                 345                 350

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
        355                 360                 365

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
```

```
    370                 375                 380

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
385                 390                 395                 400

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
                405                 410                 415

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
            420                 425                 430

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
        435                 440                 445

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
    450                 455                 460

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Cys Leu Ser Val Phe
465                 470                 475                 480

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
                485                 490                 495

Val Thr
```

<210> 4
<211> 18
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Human Albumin Leader

<400> 4

```
Met Lys Trp Val Thr Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1               5                   10                  15
```

Tyr Ser

<210> 5
<211> 480
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Human Serum Albumin

<400> 5

```
Arg Gly Val Phe Arg Arg Asp Ala His Lys Ser Glu Val Ala His Arg
1               5                   10                  15

Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu Ile Ala
            20                  25                  30

Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val Lys Leu
        35                  40                  45

Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp Glu Ser
    50                  55                  60

Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu
65                  70                  75                  80

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

Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys
            100                 105                 110

Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val Asp Val
        115                 120                 125

Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr
```

```
    130                 135                 140

Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu
145                 150                 155                 160

Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln
                165                 170                 175

Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg
            180                 185                 190

Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Gly Leu Lys Cys Ala Ser
        195                 200                 205

Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg
    210                 215                 220

Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser Lys Leu
225                 230                 235                 240

Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly Asp Leu
                245                 250                 255

Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu
            260                 265                 270

Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro
        275                 280                 285

Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp Glu Met
    290                 295                 300

Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Gly Ser Lys Asp
305                 310                 315                 320

Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Met Phe
                325                 330                 335
```

```
Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val Leu Leu
            340                 345                 350


Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala
        355                 360                 365


Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys
    370                 375                 380


Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu
385                 390                 395                 400


Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg
                405                 410                 415


Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val
            420                 425                 430


Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu
        435                 440                 445


Ala Lys Arg Met Pro Cys Ala Glu Asp Cys Leu Ser Val Phe Leu Asn
    450                 455                 460


Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg Val Thr
465                 470                 475                 480


<210>  6
<211>  5
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic: CDR1

<400>  6

Leu Asn Leu Met Gly
1               5
```

<210> 7
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic: CDR1

<400> 7

Ile Asn Leu Leu Gly
1 5

<210> 8
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic: CDR1

<400> 8

Ser Phe Gly Met Ser
1 5

<210> 9
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic: CDR1

<400> 9

Asn Tyr Trp Met Tyr
1 5

<210> 10
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic: CDR2

<400> 10

Thr Cys Ile Thr Val Gly Asp Ser Thr Asn Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 11
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic: CDR2

<400> 11

Thr Ile Thr Val Gly Asp Ser Thr Ser Tyr Ala Asp Ser Val Lys Gly
1 5 10 15

<210> 12
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic: CDR2

<400> 12

Ser Ile Ser Gly Ser Gly Ser Asp Thr Leu Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 13
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic: CDR2

<400> 13

Ser Ile Asn Gly Arg Gly Asp Asp Thr Arg Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 14
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic: CDR2

<400> 14

Ala Ile Ser Ala Asp Ser Ser Thr Lys Asn Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 15
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic: CDR2

<400> 15

Ala Ile Ser Ala Asp Ser Ser Asp Lys Arg Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 16
<211> 18
<212> PRT

<213> Artificial Sequence

<220>
<223> Synthetic: CDR2

<400> 16

Arg Asp Ile Ser Thr Gly Gly Gly Tyr Ser Tyr Tyr Ala Asp Ser Val
1 5 10 15

Lys Gly

<210> 17
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic: CDR3

<400> 17

Arg Arg Thr Trp His Ser Glu Leu
1 5

<210> 18
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic: CDR3

<400> 18

Gly Gly Ser Leu Ser Arg
1 5

<210> 19
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic: CDR3

<400> 19

Gly Arg Ser Val Ser Arg Ser
1 5

<210> 20
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic: CDR3

<400> 20

Gly Arg Gly Ser Pro
1 5

<210> 21
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic: CDR3

<400> 21

Asp Arg Glu Ala Gln Val Asp Thr Leu Asp Phe Asp Tyr
1 5 10

<210> 22
<211> 117
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic: SDA

<400> 22

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

Ser Leu Arg Leu Ala Cys Ala Ala Ser Glu Arg Ile Phe Asp Leu Asn

```
            20                  25                  30

Leu Met Gly Trp Tyr Arg Gln Gly Pro Gly Asn Glu Arg Glu Leu Val
        35                  40                  45

Ala Thr Cys Ile Thr Val Gly Asp Ser Thr Asn Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Met Asp Tyr Thr Lys Gln Thr Val Tyr
65                  70                  75                  80

Leu His Met Asn Ser Leu Arg Pro Glu Asp Thr Gly Leu Tyr Tyr Cys
                85                  90                  95

Lys Ile Arg Arg Thr Trp His Ser Glu Leu Trp Gly Gln Gly Thr Gln
            100                 105                 110

Val Thr Val Ser Ser
        115


<210>  23
<211>  116
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic: SDA

<400>  23

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Glu Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ala Cys Ala Ala Ser Glu Arg Ile Trp Asp Ile Asn
            20                  25                  30

Leu Leu Gly Trp Tyr Arg Gln Gly Pro Gly Asn Glu Arg Glu Leu Val
        35                  40                  45

Ala Thr Ile Thr Val Gly Asp Ser Thr Ser Tyr Ala Asp Ser Val Lys
```

50 55 60

Gly Arg Phe Thr Ile Ser Arg Asp Tyr Asp Lys Asn Thr Leu Tyr Leu
65 70 75 80

Gln Met Asn Ser Leu Arg Pro Glu Asp Thr Gly Leu Tyr Tyr Cys Lys
85 90 95

Ile Arg Arg Thr Trp His Ser Glu Leu Trp Gly Gln Gly Thr Gln Val
100 105 110

Thr Val Ser Ser
115

<210> 24
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic: SDA

<400> 24

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Arg Ser Phe
20 25 30

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

Ser Ser Ile Ser Gly Ser Gly Ser Asp Thr Leu Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Thr Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys

85 90 95

Thr Ile Gly Gly Ser Leu Ser Arg Ser Ser Gln Gly Thr Gln Val Thr
100 105 110

Val Ser Ser
115

<210> 25
<211> 116
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic: SDA

<400> 25

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ser Phe Gly Ser Phe
20 25 30

Gly Met Ser Trp Val Arg Gln Tyr Pro Gly Lys Glu Pro Glu Trp Val
35 40 45

Ser Ser Ile Asn Gly Arg Gly Asp Asp Thr Arg Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Ser Ile Ser Arg Asp Asn Ala Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Glu Tyr Tyr Cys
85 90 95

Thr Ile Gly Arg Ser Val Ser Arg Ser Arg Thr Gln Gly Thr Gln Val
100 105 110

Thr Val Ser Ser

115

<210> 26
<211> 114
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic: SDA

<400> 26

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

Ser Leu Arg Leu Thr Cys Thr Ala Ser Gly Phe Thr Phe Arg Ser Phe
20 25 30

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

Ser Ala Ile Ser Ala Asp Ser Ser Thr Lys Asn Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Lys Met Leu Tyr
65 70 75 80

Leu Glu Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Val Ile Gly Arg Gly Ser Pro Ser Ser Pro Gly Thr Gln Val Thr Val
100 105 110

Ser Ser

<210> 27
<211> 114
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic: SDA

<400> 27

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

Ser Leu Arg Leu Thr Cys Thr Ala Ser Gly Phe Thr Phe Gly Ser Phe
            20   25   30

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

Ser Ala Ile Ser Ala Asp Ser Ser Asp Lys Arg Tyr Ala Asp Ser Val
    50   55   60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Lys Met Leu Tyr
65   70   75   80

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

Val Ile Gly Arg Gly Ser Pro Ala Ser Gln Gly Thr Gln Val Thr Val
            100   105   110

Ser Ser

<210> 28
<211> 123
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic: SDA

<400> 28

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

```
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Tyr
            20                  25                  30


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


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


Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Leu
65                  70                  75                  80


Tyr Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Leu Tyr Tyr
                85                  90                  95


Cys Ala Lys Asp Arg Glu Ala Gln Val Asp Thr Leu Asp Phe Asp Tyr
            100                 105                 110


Arg Gly Gln Gly Thr Gln Val Thr Val Ser Ser
        115                 120


<210>  29
<211>  115
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic: hSDA

<400>  29

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


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Arg Ser Phe
            20                  25                  30


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

Ser Ser Ile Ser Gly Ser Gly Ser Asp Thr Leu Tyr Ala Asp Ser Val
    50   55   60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Thr Thr Leu Tyr
65   70   75   80

Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95

Thr Ile Gly Gly Ser Leu Ser Arg Ser Ser Gln Gly Thr Gln Val Thr
            100   105   110

Val Ser Ser
        115

<210> 30
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic: hSDA

<400> 30

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Phe
            20   25   30

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

Ser Ser Ile Ser Gly Ser Gly Ser Asp Thr Leu Tyr Ala Asp Ser Val
    50   55   60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Thr Thr Leu Tyr
65   70   75   80

```
Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95


Thr Ile Gly Gly Ser Leu Ser Arg Ser Ser Gln Gly Thr Gln Val Thr
            100                 105                 110


Val Ser Ser
        115


<210>  31
<211>  115
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic: hSDA

<400>  31

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


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Arg Ser Phe
            20                  25                  30


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


Ser Ser Ile Ser Gly Ser Gly Ser Asp Thr Leu Tyr Ala Asp Ser Val
    50                  55                  60


Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Thr Thr Leu Tyr
65                  70                  75                  80


Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95


Thr Ile Gly Gly Ser Leu Ser Arg Ser Ser Gln Gly Thr Gln Val Thr
            100                 105                 110
```

Val Ser Ser
        115

<210> 32
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic: hSDA

<400> 32

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Asn
1   5   10   15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Arg Ser Phe
            20   25   30

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

Ser Ser Ile Ser Gly Ser Gly Ser Asp Thr Leu Tyr Ala Asp Ser Val
    50   55   60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Thr Thr Leu Tyr
65   70   75   80

Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95

Thr Ile Gly Gly Ser Leu Ser Arg Ser Ser Gln Gly Thr Leu Val Thr
            100   105   110

Val Ser Ser
        115

<210> 33
<211> 115
<212> PRT

<213> Artificial Sequence

<220>
<223> Synthetic: hSDA

<400> 33

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Asn
1   5   10   15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Arg Ser Phe
            20   25   30

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

Ser Ser Ile Ser Gly Ser Gly Ser Asp Thr Leu Tyr Ala Asp Ser Val
    50   55   60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Thr Thr Leu Tyr
65   70   75   80

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

Thr Ile Gly Gly Ser Leu Ser Arg Ser Ser Gln Gly Thr Leu Val Thr
            100   105   110

Val Ser Ser
        115

<210> 34
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic: hSDA

<400> 34

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Asn

1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Phe
20 25 30

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

Ser Ser Ile Ser Gly Ser Gly Ser Asp Thr Leu Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Thr Thr Leu Tyr
65 70 75 80

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

Thr Ile Gly Gly Ser Leu Ser Arg Ser Ser Gln Gly Thr Leu Val Thr
100 105 110

Val Ser Ser
115

<210> 35
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic: hSDA

<400> 35

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Asn
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Phe
20 25 30

Gly Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val

```
        35                  40                  45

Ser Ser Ile Ser Gly Ser Gly Ser Asp Thr Leu Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Leu Tyr
65                  70                  75                  80

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

Thr Ile Gly Gly Ser Leu Ser Arg Ser Ser Gln Gly Thr Leu Val Thr
            100                 105                 110

Val Ser Ser
        115
```

<210> 36
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic: hSDA

<400> 36

```
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Asn
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Phe
            20                  25                  30

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

Ser Ser Ile Ser Gly Ser Gly Ser Asp Thr Leu Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Leu Tyr
```

65 70 75 80

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

Thr Ile Gly Gly Ser Leu Ser Arg Ser Gly Gln Gly Thr Leu Val Thr
100 105 110

Val Ser Ser
115

<210> 37
<211> 30
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic: FR1

<400> 37

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

Ser Leu Arg Leu Ala Cys Ala Ala Ser Glu Arg Ile Phe Asp
20 25 30

<210> 38
<211> 30
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic: FR1

<400> 38

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Glu Gly Gly
1 5 10 15

Ser Leu Arg Leu Ala Cys Ala Ala Ser Glu Arg Ile Trp Asp
20 25 30

<210> 39
<211> 30
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic: FR1

<400> 39

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Arg
            20   25   30

<210> 40
<211> 30
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic: FR1

<400> 40

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ser Phe Gly
            20   25   30

<210> 41
<211> 30
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic: FR1

<400> 41

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

Ser Leu Arg Leu Thr Cys Thr Ala Ser Gly Phe Thr Phe Arg
            20   25   30

<210> 42
<211> 30
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic: FR1

<400> 42

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

Ser Leu Arg Leu Thr Cys Thr Ala Ser Gly Phe Thr Phe Gly
            20   25   30

<210> 43
<211> 30
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic: FR1

<400> 43

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser
            20   25   30

<210> 44
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic: FR2

<400> 44

Trp Tyr Arg Gln Gly Pro Gly Asn Glu Arg Glu Leu Val Ala
1   5   10

<210> 45
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic: FR2

<400> 45

Trp Val Arg Gln Ala Pro Gly Lys Glu Pro Glu Trp Val Ser
1   5   10

<210> 46
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic: FR2

<400> 46

Trp Val Arg Gln Tyr Pro Gly Lys Glu Pro Glu Trp Val Ser
1   5   10

<210> 47
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic: FR2

<400> 47

Trp Val Arg Gln Ala Pro Gly Lys Asp Gln Glu Trp Val Ser
1   5   10

<210> 48
<211> 14
<212> PRT

<213> Artificial Sequence

<220>
<223> Synthetic: FR2

<400> 48

Trp Val Arg Gln Ala Pro Gly Glu Gly Leu Glu Trp Val Ser
1 5 10

<210> 49
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic: FR2

<400> 49

Trp Val Arg Val Ala Pro Gly Lys Gly Leu Glu Arg Ile Ser
1 5 10

<210> 50
<211> 32
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic: FR3

<400> 50

Arg Phe Thr Ile Ser Met Asp Tyr Thr Lys Gln Thr Val Tyr Leu His
1 5 10 15

Met Asn Ser Leu Arg Pro Glu Asp Thr Gly Leu Tyr Tyr Cys Lys Ile
20 25 30

<210> 51
<211> 32
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic: FR3

<400> 51

Arg Phe Thr Ile Ser Arg Asp Tyr Asp Lys Asn Thr Leu Tyr Leu Gln
1 5 10 15

Met Asn Ser Leu Arg Pro Glu Asp Thr Gly Leu Tyr Tyr Cys Lys Ile
20 25 30

<210> 52
<211> 32
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic: FR3

<400> 52

Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Thr Thr Leu Tyr Leu Gln
1 5 10 15

Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys Thr Ile
20 25 30

<210> 53
<211> 32
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic: FR3

<400> 53

Arg Phe Ser Ile Ser Arg Asp Asn Ala Lys Asn Thr Leu Tyr Leu Gln
1 5 10 15

Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Glu Tyr Tyr Cys Thr Ile
20 25 30

<210> 54
<211> 32
<212> PRT

<213> Artificial Sequence

<220>
<223> Synthetic: FR3

<400> 54

Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Lys Met Leu Tyr Leu Glu
1 5 10 15

Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys Val Ile
20 25 30

<210> 55
<211> 32
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic: FR3

<400> 55

Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Lys Met Leu Tyr Leu Glu
1 5 10 15

Met Asn Ser Leu Lys Ser Glu Asp Thr Ala Val Tyr Tyr Cys Val Ile
20 25 30

<210> 56
<211> 32
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic: FR3

<400> 56

Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Leu Tyr Leu Gln
1 5 10 15

Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Leu Tyr Tyr Cys Ala Lys
20 25 30

<210> 57
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic: FR4

<400> 57

Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser
1 5 10

<210> 58
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic: FR4

<400> 58

Ser Ser Gln Gly Thr Gln Val Thr Val Ser Ser
1 5 10

<210> 59
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic: FR4

<400> 59

Arg Thr Gln Gly Thr Gln Val Thr Val Ser Ser
1 5 10

<210> 60
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic: FR4

<400> 60

Ser Ser Pro Gly Thr Gln Val Thr Val Ser Ser
1 5 10

<210> 61
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic: FR4

<400> 61

Ala Ser Gln Gly Thr Gln Val Thr Val Ser Ser
1 5 10

<210> 62
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic: FR4

<400> 62

Arg Gly Gln Gly Thr Gln Val Thr Val Ser Ser
1 5 10

<210> 63
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic: Linker

<400> 63

Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
1 5 10

<210> 64

<211> 1017
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic: AAT-linkerAlbumin Fusion

<400> 64

Met Pro Ser Ser Val Ser Trp Gly Ile Leu Leu Leu Ala Gly Leu Cys
1 5 10 15

Cys Leu Val Pro Val Ser Leu Ala Glu Asp Pro Gln Gly Asp Ala Ala
20 25 30

Gln Lys Thr Asp Thr Ser His His Asp Gln Asp His Pro Thr Phe Asn
35 40 45

Lys Ile Thr Pro Asn Leu Ala Glu Phe Ala Phe Ser Leu Tyr Arg Gln
50 55 60

Leu Ala His Gln Ser Asn Ser Thr Asn Ile Phe Phe Ser Pro Val Ser
65 70 75 80

Ile Ala Thr Ala Phe Ala Met Leu Ser Leu Gly Thr Lys Ala Asp Thr
85 90 95

His Asp Glu Ile Leu Glu Gly Leu Asn Phe Asn Leu Thr Glu Ile Pro
100 105 110

Glu Ala Gln Ile His Glu Gly Phe Gln Glu Leu Leu Arg Thr Leu Asn
115 120 125

Gln Pro Asp Ser Gln Leu Gln Leu Thr Thr Gly Asn Gly Leu Phe Leu
130 135 140

Ser Glu Gly Leu Lys Leu Val Asp Lys Phe Leu Glu Asp Val Lys Lys
145 150 155 160

Leu Tyr His Ser Glu Ala Phe Thr Val Asn Phe Gly Asp Thr Glu Glu

```
                165                 170                 175

Ala Lys Lys Gln Ile Asn Asp Tyr Val Glu Lys Gly Thr Gln Gly Lys
            180                 185                 190

Ile Val Asp Leu Val Lys Glu Leu Asp Arg Asp Thr Val Phe Ala Leu
        195                 200                 205

Val Asn Tyr Ile Phe Phe Lys Gly Lys Trp Glu Arg Pro Phe Glu Val
    210                 215                 220

Lys Asp Thr Glu Glu Glu Asp Phe His Val Asp Gln Val Thr Thr Val
225                 230                 235                 240

Lys Val Pro Met Met Lys Arg Leu Gly Met Phe Asn Ile Gln His Cys
                245                 250                 255

Lys Lys Leu Ser Ser Trp Val Leu Leu Met Lys Tyr Leu Gly Asn Ala
            260                 265                 270

Thr Ala Ile Phe Phe Leu Pro Asp Glu Gly Lys Leu Gln His Leu Glu
        275                 280                 285

Asn Glu Leu Thr His Asp Ile Ile Thr Lys Phe Leu Glu Asn Glu Asp
    290                 295                 300

Arg Arg Ser Ala Ser Leu His Leu Pro Lys Leu Ser Ile Thr Gly Thr
305                 310                 315                 320

Tyr Asp Leu Lys Ser Val Leu Gly Gln Leu Gly Ile Thr Lys Val Phe
                325                 330                 335

Ser Asn Gly Ala Asp Leu Ser Gly Val Thr Glu Glu Ala Pro Leu Lys
            340                 345                 350

Leu Ser Lys Ala Val His Lys Ala Val Leu Thr Ile Asp Glu Lys Gly
        355                 360                 365
```

```
Thr Glu Ala Ala Gly Ala Met Phe Leu Glu Ala Ile Pro Met Ser Ile
    370                 375                 380

Pro Pro Glu Val Lys Phe Asn Lys Pro Phe Val Phe Leu Met Ile Glu
385                 390                 395                 400

Gln Asn Thr Lys Ser Pro Leu Phe Met Gly Lys Val Val Asn Pro Thr
                405                 410                 415

Gln Lys Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
            420                 425                 430

Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
        435                 440                 445

Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
    450                 455                 460

Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
465                 470                 475                 480

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
                485                 490                 495

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
            500                 505                 510

Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
        515                 520                 525

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu
    530                 535                 540

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
545                 550                 555                 560

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
```

```
                565                 570                 575

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
            580                 585                 590

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
        595                 600                 605

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
    610                 615                 620

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
625                 630                 635                 640

Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
                645                 650                 655

Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
            660                 665                 670

Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
        675                 680                 685

Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
    690                 695                 700

Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
705                 710                 715                 720

Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
                725                 730                 735

Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
            740                 745                 750

Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
        755                 760                 765
```

```
Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr
    770                 775                 780

Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
785                 790                 795                 800

Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
                805                 810                 815

Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
            820                 825                 830

Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
        835                 840                 845

Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
    850                 855                 860

Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
865                 870                 875                 880

Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
                885                 890                 895

Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
            900                 905                 910

Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr
        915                 920                 925

Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
    930                 935                 940

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
945                 950                 955                 960

Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
```

965 970 975

Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
980 985 990

Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val
995 1000 1005

Ala Ala Ser Gln Ala Ala Leu Gly Leu
1010 1015

<210> 65
<211> 1017
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic: Mutant AAT-linkerAlbumin Fusion (C232S)

<400> 65

Met Pro Ser Ser Val Ser Trp Gly Ile Leu Leu Leu Ala Gly Leu Cys
1 5 10 15

Cys Leu Val Pro Val Ser Leu Ala Glu Asp Pro Gln Gly Asp Ala Ala
20 25 30

Gln Lys Thr Asp Thr Ser His His Asp Gln Asp His Pro Thr Phe Asn
35 40 45

Lys Ile Thr Pro Asn Leu Ala Glu Phe Ala Phe Ser Leu Tyr Arg Gln
50 55 60

Leu Ala His Gln Ser Asn Ser Thr Asn Ile Phe Phe Ser Pro Val Ser
65 70 75 80

Ile Ala Thr Ala Phe Ala Met Leu Ser Leu Gly Thr Lys Ala Asp Thr
85 90 95

His Asp Glu Ile Leu Glu Gly Leu Asn Phe Asn Leu Thr Glu Ile Pro

```
            100                 105                 110

Glu Ala Gln Ile His Glu Gly Phe Gln Glu Leu Leu Arg Thr Leu Asn
        115                 120                 125

Gln Pro Asp Ser Gln Leu Gln Leu Thr Thr Gly Asn Gly Leu Phe Leu
    130                 135                 140

Ser Glu Gly Leu Lys Leu Val Asp Lys Phe Leu Glu Asp Val Lys Lys
145                 150                 155                 160

Leu Tyr His Ser Glu Ala Phe Thr Val Asn Phe Gly Asp Thr Glu Glu
                165                 170                 175

Ala Lys Lys Gln Ile Asn Asp Tyr Val Glu Lys Gly Thr Gln Gly Lys
            180                 185                 190

Ile Val Asp Leu Val Lys Glu Leu Asp Arg Asp Thr Val Phe Ala Leu
        195                 200                 205

Val Asn Tyr Ile Phe Phe Lys Gly Lys Trp Glu Arg Pro Phe Glu Val
    210                 215                 220

Lys Asp Thr Glu Glu Glu Asp Phe His Val Asp Gln Val Thr Thr Val
225                 230                 235                 240

Lys Val Pro Met Met Lys Arg Leu Gly Met Phe Asn Ile Gln His Ser
                245                 250                 255

Lys Lys Leu Ser Ser Trp Val Leu Leu Met Lys Tyr Leu Gly Asn Ala
            260                 265                 270

Thr Ala Ile Phe Phe Leu Pro Asp Glu Gly Lys Leu Gln His Leu Glu
        275                 280                 285

Asn Glu Leu Thr His Asp Ile Ile Thr Lys Phe Leu Glu Asn Glu Asp
    290                 295                 300
```

```
Arg Arg Ser Ala Ser Leu His Leu Pro Lys Leu Ser Ile Thr Gly Thr
305                 310                 315                 320

Tyr Asp Leu Lys Ser Val Leu Gly Gln Leu Gly Ile Thr Lys Val Phe
                325                 330                 335

Ser Asn Gly Ala Asp Leu Ser Gly Val Thr Glu Glu Ala Pro Leu Lys
            340                 345                 350

Leu Ser Lys Ala Val His Lys Ala Val Leu Thr Ile Asp Glu Lys Gly
        355                 360                 365

Thr Glu Ala Ala Gly Ala Met Phe Leu Glu Ala Ile Pro Met Ser Ile
    370                 375                 380

Pro Pro Glu Val Lys Phe Asn Lys Pro Phe Val Phe Leu Met Ile Glu
385                 390                 395                 400

Gln Asn Thr Lys Ser Pro Leu Phe Met Gly Lys Val Val Asn Pro Thr
                405                 410                 415

Gln Lys Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
            420                 425                 430

Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
        435                 440                 445

Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
    450                 455                 460

Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
465                 470                 475                 480

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
                485                 490                 495

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
```

```
            500                 505                 510

Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
        515                 520                 525

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu
    530                 535                 540

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
545                 550                 555                 560

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
                565                 570                 575

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
            580                 585                 590

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
        595                 600                 605

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
    610                 615                 620

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
625                 630                 635                 640

Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
                645                 650                 655

Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
            660                 665                 670

Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
        675                 680                 685

Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
    690                 695                 700
```

```
Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
705                 710                 715                 720


Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
                725                 730                 735


Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
            740                 745                 750


Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
        755                 760                 765


Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr
    770                 775                 780


Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
785                 790                 795                 800


Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
                805                 810                 815


Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
            820                 825                 830


Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
        835                 840                 845


Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
    850                 855                 860


Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
865                 870                 875                 880


Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
                885                 890                 895


Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
```

```
            900                 905                 910

Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr
        915                 920                 925

Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
    930                 935                 940

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
945                 950                 955                 960

Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
                965                 970                 975

Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
            980                 985                 990

Ala Asp Asp Lys Glu Thr Cys Phe  Ala Glu Glu Gly Lys  Lys Leu Val
        995                 1000                1005

Ala Ala  Ser Gln Ala Ala Leu  Gly Leu
    1010                1015
```

<210> 66
<211> 1017
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic: Mutant AAT-linkerAlbumin Fusion (M351V, M358V)

<400> 66

```
Met Pro Ser Ser Val Ser Trp Gly Ile Leu Leu Leu Ala Gly Leu Cys
1               5                   10                  15

Cys Leu Val Pro Val Ser Leu Ala Glu Asp Pro Gln Gly Asp Ala Ala
            20                  25                  30

Gln Lys Thr Asp Thr Ser His His Asp Gln Asp His Pro Thr Phe Asn
```

```
        35                  40                  45

Lys Ile Thr Pro Asn Leu Ala Glu Phe Ala Phe Ser Leu Tyr Arg Gln
    50                  55                  60

Leu Ala His Gln Ser Asn Ser Thr Asn Ile Phe Phe Ser Pro Val Ser
65                  70                  75                  80

Ile Ala Thr Ala Phe Ala Met Leu Ser Leu Gly Thr Lys Ala Asp Thr
                85                  90                  95

His Asp Glu Ile Leu Glu Gly Leu Asn Phe Asn Leu Thr Glu Ile Pro
            100                 105                 110

Glu Ala Gln Ile His Glu Gly Phe Gln Glu Leu Leu Arg Thr Leu Asn
        115                 120                 125

Gln Pro Asp Ser Gln Leu Gln Leu Thr Thr Gly Asn Gly Leu Phe Leu
    130                 135                 140

Ser Glu Gly Leu Lys Leu Val Asp Lys Phe Leu Glu Asp Val Lys Lys
145                 150                 155                 160

Leu Tyr His Ser Glu Ala Phe Thr Val Asn Phe Gly Asp Thr Glu Glu
                165                 170                 175

Ala Lys Lys Gln Ile Asn Asp Tyr Val Glu Lys Gly Thr Gln Gly Lys
            180                 185                 190

Ile Val Asp Leu Val Lys Glu Leu Asp Arg Asp Thr Val Phe Ala Leu
        195                 200                 205

Val Asn Tyr Ile Phe Phe Lys Gly Lys Trp Glu Arg Pro Phe Glu Val
    210                 215                 220

Lys Asp Thr Glu Glu Glu Asp Phe His Val Asp Gln Val Thr Thr Val
225                 230                 235                 240
```

```
Lys Val Pro Met Met Lys Arg Leu Gly Met Phe Asn Ile Gln His Cys
                245                 250                 255

Lys Lys Leu Ser Ser Trp Val Leu Leu Met Lys Tyr Leu Gly Asn Ala
            260                 265                 270

Thr Ala Ile Phe Phe Leu Pro Asp Glu Gly Lys Leu Gln His Leu Glu
        275                 280                 285

Asn Glu Leu Thr His Asp Ile Ile Thr Lys Phe Leu Glu Asn Glu Asp
    290                 295                 300

Arg Arg Ser Ala Ser Leu His Leu Pro Lys Leu Ser Ile Thr Gly Thr
305                 310                 315                 320

Tyr Asp Leu Lys Ser Val Leu Gly Gln Leu Gly Ile Thr Lys Val Phe
                325                 330                 335

Ser Asn Gly Ala Asp Leu Ser Gly Val Thr Glu Glu Ala Pro Leu Lys
            340                 345                 350

Leu Ser Lys Ala Val His Lys Ala Val Leu Thr Ile Asp Glu Lys Gly
        355                 360                 365

Thr Glu Ala Ala Gly Ala Val Phe Leu Glu Ala Ile Pro Val Ser Ile
    370                 375                 380

Pro Pro Glu Val Lys Phe Asn Lys Pro Phe Val Phe Leu Met Ile Glu
385                 390                 395                 400

Gln Asn Thr Lys Ser Pro Leu Phe Met Gly Lys Val Val Asn Pro Thr
                405                 410                 415

Gln Lys Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
            420                 425                 430

Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
```

```
        435                 440                 445

Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
    450                 455                 460

Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
465                 470                 475                 480

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
                485                 490                 495

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
            500                 505                 510

Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
        515                 520                 525

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu
    530                 535                 540

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
545                 550                 555                 560

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
                565                 570                 575

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
            580                 585                 590

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
        595                 600                 605

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
    610                 615                 620

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
625                 630                 635                 640
```

```
Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
               645                 650                 655

Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
            660                 665                 670

Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
        675                 680                 685

Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
    690                 695                 700

Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
705                 710                 715                 720

Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
               725                 730                 735

Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
            740                 745                 750

Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
        755                 760                 765

Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr
    770                 775                 780

Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
785                 790                 795                 800

Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
               805                 810                 815

Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
            820                 825                 830

Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
```

```
        835                 840                 845

Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
    850                 855                 860

Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
865                 870                 875                 880

Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
                885                 890                 895

Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
            900                 905                 910

Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr
        915                 920                 925

Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
    930                 935                 940

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
945                 950                 955                 960

Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
                965                 970                 975

Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
            980                 985                 990

Ala Asp Asp Lys Glu Thr Cys Phe  Ala Glu Glu Gly Lys  Lys Leu Val
        995                 1000                1005

Ala Ala  Ser Gln Ala Ala Leu  Gly Leu
    1010                1015
```

<210> 67
<211> 1017
<212> PRT

<213> Artificial Sequence

<220>
<223> Synthetic: Mutant AAT-linkerAlbumin Fusion (M351V, M358L)

<400> 67

```
Met Pro Ser Ser Val Ser Trp Gly Ile Leu Leu Leu Ala Gly Leu Cys
1               5                   10                  15


Cys Leu Val Pro Val Ser Leu Ala Glu Asp Pro Gln Gly Asp Ala Ala
            20                  25                  30


Gln Lys Thr Asp Thr Ser His His Asp Gln Asp His Pro Thr Phe Asn
        35                  40                  45


Lys Ile Thr Pro Asn Leu Ala Glu Phe Ala Phe Ser Leu Tyr Arg Gln
    50                  55                  60


Leu Ala His Gln Ser Asn Ser Thr Asn Ile Phe Phe Ser Pro Val Ser
65                  70                  75                  80


Ile Ala Thr Ala Phe Ala Met Leu Ser Leu Gly Thr Lys Ala Asp Thr
                85                  90                  95


His Asp Glu Ile Leu Glu Gly Leu Asn Phe Asn Leu Thr Glu Ile Pro
            100                 105                 110


Glu Ala Gln Ile His Glu Gly Phe Gln Glu Leu Leu Arg Thr Leu Asn
        115                 120                 125


Gln Pro Asp Ser Gln Leu Gln Leu Thr Thr Gly Asn Gly Leu Phe Leu
    130                 135                 140


Ser Glu Gly Leu Lys Leu Val Asp Lys Phe Leu Glu Asp Val Lys Lys
145                 150                 155                 160


Leu Tyr His Ser Glu Ala Phe Thr Val Asn Phe Gly Asp Thr Glu Glu
                165                 170                 175
```

```
Ala Lys Lys Gln Ile Asn Asp Tyr Val Glu Lys Gly Thr Gln Gly Lys
            180                 185                 190

Ile Val Asp Leu Val Lys Glu Leu Asp Arg Asp Thr Val Phe Ala Leu
        195                 200                 205

Val Asn Tyr Ile Phe Phe Lys Gly Lys Trp Glu Arg Pro Phe Glu Val
    210                 215                 220

Lys Asp Thr Glu Glu Glu Asp Phe His Val Asp Gln Val Thr Thr Val
225                 230                 235                 240

Lys Val Pro Met Met Lys Arg Leu Gly Met Phe Asn Ile Gln His Cys
                245                 250                 255

Lys Lys Leu Ser Ser Trp Val Leu Leu Met Lys Tyr Leu Gly Asn Ala
            260                 265                 270

Thr Ala Ile Phe Phe Leu Pro Asp Glu Gly Lys Leu Gln His Leu Glu
        275                 280                 285

Asn Glu Leu Thr His Asp Ile Ile Thr Lys Phe Leu Glu Asn Glu Asp
    290                 295                 300

Arg Arg Ser Ala Ser Leu His Leu Pro Lys Leu Ser Ile Thr Gly Thr
305                 310                 315                 320

Tyr Asp Leu Lys Ser Val Leu Gly Gln Leu Gly Ile Thr Lys Val Phe
                325                 330                 335

Ser Asn Gly Ala Asp Leu Ser Gly Val Thr Glu Glu Ala Pro Leu Lys
            340                 345                 350

Leu Ser Lys Ala Val His Lys Ala Val Leu Thr Ile Asp Glu Lys Gly
        355                 360                 365

Thr Glu Ala Ala Gly Ala Val Phe Leu Glu Ala Ile Pro Leu Ser Ile
```

```
    370                 375                 380

Pro Pro Glu Val Lys Phe Asn Lys Pro Phe Val Phe Leu Met Ile Glu
385                 390                 395                 400

Gln Asn Thr Lys Ser Pro Leu Phe Met Gly Lys Val Val Asn Pro Thr
                405                 410                 415

Gln Lys Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
            420                 425                 430

Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
        435                 440                 445

Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
    450                 455                 460

Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
465                 470                 475                 480

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
                485                 490                 495

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
            500                 505                 510

Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
        515                 520                 525

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu
    530                 535                 540

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
545                 550                 555                 560

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
                565                 570                 575
```

```
Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
            580                 585                 590

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
        595                 600                 605

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
    610                 615                 620

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
625                 630                 635                 640

Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
                645                 650                 655

Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
            660                 665                 670

Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
        675                 680                 685

Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
    690                 695                 700

Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
705                 710                 715                 720

Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
                725                 730                 735

Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
            740                 745                 750

Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
        755                 760                 765

Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr
```

```
    770                 775                 780

Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
785                 790                 795                 800

Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
                805                 810                 815

Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
            820                 825                 830

Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
        835                 840                 845

Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
    850                 855                 860

Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
865                 870                 875                 880

Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
                885                 890                 895

Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
            900                 905                 910

Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr
        915                 920                 925

Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
    930                 935                 940

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
945                 950                 955                 960

Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
                965                 970                 975
```

Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
980 985 990

Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val
995 1000 1005

Ala Ala Ser Gln Ala Ala Leu Gly Leu
1010 1015

<210> 68
<211> 1017
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic: Mutant AAT-linkerAlbumin Fusion (C232S, M351V, M358L)

<400> 68

Met Pro Ser Ser Val Ser Trp Gly Ile Leu Leu Leu Ala Gly Leu Cys
1 5 10 15

Cys Leu Val Pro Val Ser Leu Ala Glu Asp Pro Gln Gly Asp Ala Ala
20 25 30

Gln Lys Thr Asp Thr Ser His His Asp Gln Asp His Pro Thr Phe Asn
35 40 45

Lys Ile Thr Pro Asn Leu Ala Glu Phe Ala Phe Ser Leu Tyr Arg Gln
50 55 60

Leu Ala His Gln Ser Asn Ser Thr Asn Ile Phe Phe Ser Pro Val Ser
65 70 75 80

Ile Ala Thr Ala Phe Ala Met Leu Ser Leu Gly Thr Lys Ala Asp Thr
85 90 95

His Asp Glu Ile Leu Glu Gly Leu Asn Phe Asn Leu Thr Glu Ile Pro
100 105 110

```
Glu Ala Gln Ile His Glu Gly Phe Gln Glu Leu Leu Arg Thr Leu Asn
        115                 120                 125

Gln Pro Asp Ser Gln Leu Gln Leu Thr Thr Gly Asn Gly Leu Phe Leu
    130                 135                 140

Ser Glu Gly Leu Lys Leu Val Asp Lys Phe Leu Glu Asp Val Lys Lys
145                 150                 155                 160

Leu Tyr His Ser Glu Ala Phe Thr Val Asn Phe Gly Asp Thr Glu Glu
                165                 170                 175

Ala Lys Lys Gln Ile Asn Asp Tyr Val Glu Lys Gly Thr Gln Gly Lys
            180                 185                 190

Ile Val Asp Leu Val Lys Glu Leu Asp Arg Asp Thr Val Phe Ala Leu
        195                 200                 205

Val Asn Tyr Ile Phe Phe Lys Gly Lys Trp Glu Arg Pro Phe Glu Val
    210                 215                 220

Lys Asp Thr Glu Glu Glu Asp Phe His Val Asp Gln Val Thr Thr Val
225                 230                 235                 240

Lys Val Pro Met Met Lys Arg Leu Gly Met Phe Asn Ile Gln His Ser
                245                 250                 255

Lys Lys Leu Ser Ser Trp Val Leu Leu Met Lys Tyr Leu Gly Asn Ala
            260                 265                 270

Thr Ala Ile Phe Phe Leu Pro Asp Glu Gly Lys Leu Gln His Leu Glu
        275                 280                 285

Asn Glu Leu Thr His Asp Ile Ile Thr Lys Phe Leu Glu Asn Glu Asp
    290                 295                 300

Arg Arg Ser Ala Ser Leu His Leu Pro Lys Leu Ser Ile Thr Gly Thr
```

```
305                 310                 315                 320

Tyr Asp Leu Lys Ser Val Leu Gly Gln Leu Gly Ile Thr Lys Val Phe
                325                 330                 335

Ser Asn Gly Ala Asp Leu Ser Gly Val Thr Glu Glu Ala Pro Leu Lys
            340                 345                 350

Leu Ser Lys Ala Val His Lys Ala Val Leu Thr Ile Asp Glu Lys Gly
        355                 360                 365

Thr Glu Ala Ala Gly Ala Val Phe Leu Glu Ala Ile Pro Leu Ser Ile
    370                 375                 380

Pro Pro Glu Val Lys Phe Asn Lys Pro Phe Val Phe Leu Met Ile Glu
385                 390                 395                 400

Gln Asn Thr Lys Ser Pro Leu Phe Met Gly Lys Val Val Asn Pro Thr
                405                 410                 415

Gln Lys Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
            420                 425                 430

Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
        435                 440                 445

Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
    450                 455                 460

Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
465                 470                 475                 480

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
                485                 490                 495

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
            500                 505                 510
```

```
Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
        515                 520                 525

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu
    530                 535                 540

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
545                 550                 555                 560

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
                565                 570                 575

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
            580                 585                 590

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
        595                 600                 605

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
    610                 615                 620

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
625                 630                 635                 640

Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
                645                 650                 655

Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
            660                 665                 670

Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
        675                 680                 685

Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
    690                 695                 700

Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
```

```
705                 710                 715                 720

Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
                725                 730                 735

Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
            740                 745                 750

Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
        755                 760                 765

Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr
    770                 775                 780

Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
785                 790                 795                 800

Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
                805                 810                 815

Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
            820                 825                 830

Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
        835                 840                 845

Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
    850                 855                 860

Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
865                 870                 875                 880

Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
                885                 890                 895

Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
            900                 905                 910
```

```
Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr
        915                 920                 925


Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
    930                 935                 940


Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
945                 950                 955                 960


Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
                965                 970                 975


Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
            980                 985                 990


Ala Asp Asp Lys Glu Thr Cys Phe  Ala Glu Glu Gly Lys  Lys Leu Val
        995                 1000                1005


Ala Ala  Ser Gln Ala Ala Leu  Gly Leu
    1010                1015


<210>  69
<211>  3178
<212>  DNA
<213>  Homo sapiens


<220>
<221>  misc_feature
<223>  Wild Type AAT Nucleic Acid

<400>  69
tgggcaggaa ctgggcactg tgcccagggc atgcactgcc tccacgcagc aaccctcaga       60

gtcctgagct gaaccaagaa ggaggagggg gtcgggcctc cgaggaaggc ctagccgctg      120

ctgctgccag gaattccagg ttggaggggc ggcaacctcc tgccagcctt caggccactc      180

tcctgtgcct gccagaagag acagagcttg aggagagctt gaggagagca ggaaaggaca      240

atgccgtctt ctgtctcgtg gggcatcctc ctgctggcag gcctgtgctg cctggtccct      300
```

gtctccctgg ctgaggatcc ccagggagat gctgcccaga agacagatac atcccaccat 360

gatcaggatc acccaacctt caacaagatc acccccaacc tggctgagtt cgccttcagc 420

ctataccgcc agctggcaca ccagtccaac agcaccaata tcttcttctc cccagtgagc 480

atcgctacag cctttgcaat gctctccctg gggaccaagg ctgacactca cgatgaaatc 540

ctggagggcc tgaatttcaa cctcacggag attccggagg ctcagatcca tgaaggcttc 600

caggaactcc tccgtaccct caaccagcca gacagccagc tccagctgac caccggcaat 660

ggcctgttcc tcagcgaggg cctgaagcta gtggataagt ttttggagga tgttaaaaag 720

ttgtaccact cagaagcctt cactgtcaac ttcggggaca ccgaagaggc caagaaacag 780

atcaacgatt acgtggagaa gggtactcaa gggaaaattg tggatttggt caaggagctt 840

gacagagaca cagtttttgc tctggtgaat tacatcttct ttaaaggcaa atgggagaga 900

ccctttgaag tcaaggacac cgaggaagag gacttccacg tggaccaggt gaccaccgtg 960

aaggtgccta tgatgaagcg tttaggcatg tttaacatcc agcactgtaa gaagctgtcc 1020

agctgggtgc tgctgatgaa atacctgggc aatgccaccg ccatcttctt cctgcctgat 1080

gaggggaaac tacagcacct ggaaaatgaa ctcacccacg atatcatcac caagttcctg 1140

gaaaatgaag acagaaggtc tgccagctta catttaccca aactgtccat tactggaacc 1200

tatgatctga agagcgtcct gggtcaactg ggcatcacta aggtcttcag caatggggct 1260

gacctctccg gggtcacaga ggaggcaccc ctgaagctct ccaaggccgt gcataaggct 1320

gtgctgacca tcgacgagaa agggactgaa gctgctgggg ccatgttttt agaggccata 1380

cccatgtcta tccccccga ggtcaagttc aacaaaccct ttgtcttctt aatgattgaa 1440

caaaatacca agtctcccct cttcatggga aaagtggtga atcccaccca aaaataactg 1500

cctctcgctc ctcaacccct cccctccatc cctggccccc tccctggatg aattaaagaa 1560

gggttgagct ggtccctgcc tgcatgtgac tgtaaatccc tcccatgttt tctctgagtc 1620

tccctttgcc tgctgaggct gtatgtgggc tccaggtaac agtgctgtct tcgggccccc 1680

tgaactgtgt tcatggagca tctggctggg taggcacatg ctgggcttga atccaggggg 1740

gactgaatcc tcagcttacg gacctgggcc catctgtttc tggagggctc cagtcttcct 1800

tgtcctgtct tggagtcccc aagaaggaat cacaggggag gaaccagata ccagccatga 1860

ccccaggctc caccaagcat cttcatgtcc ccctgctcat cccccactcc cccccaccca 1920

gagttgctca tcctgccagg gctggctgtg cccaccccaa ggctgccctc ctgggggccc 1980

cagaactgcc tgatcgtgcc gtggcccagt tttgtggcat ctgcagcaac acaagagaga 2040

ggacaatgtc ctcctcttga ctcgggccct gcacctctca ggcacttctg gaaaatgact 2100

gaggcagatt cttcctgaag cccattctcc atggggcaac aaggacacct attctgtcct 2160

tgtccttcca tcgctgcccc agaaagcctc acatatctcc gtttagaatc aggtcccttc 2220

tccccagatg aagaggaggg tctctgcttt gttttctcta tctcctcctc agacttgacc 2280

aggcccagca ggccccagaa gaccattacc ctatatccct tctcctccct agtcacatgg 2340

ccataggcct gctgatggct caggaaggcc attgcaagga ctcctcagct atgggagagg 2400

aagcacatca cccattgacc cccgcaaccc ctccctttcc tcctctgagt cccgactggg 2460

gccacatgca gcctgacttc tttgtgcctg ttgctgtccc tgcagtcttc agagggccac 2520

cgcagctcca gtgccacggc aggaggctgt tcctgaatag cccctgtggt aagggccagg 2580

agagtccttc catcctccaa ggccctgcta aaggacacag cagccaggaa gtcccctggg 2640

cccctagctg aaggacagcc tgctccctcc gtctctacca ggaatggcct tgtcctatgg 2700

aaggcactgc cccatcccaa actaatctag gaatcactgt ctaaccactc actgtcatga 2760

atgtgtactt aaaggatgag gttgagtcat accaaatagt gatttcgata gttcaaaatg 2820

gtgaaattag caattctaca tgattcagtc taatcaatgg ataccgactg tttcccacac 2880

aagtctcctg ttctcttaag cttactcact gacagccttt cactctccac aaatacatta 2940

aagatatggc catcaccaag ccccctagga tgacaccaga cctgagagtc tgaagacctg 3000

gatccaagtt ctgacttttc cccctgacag ctgtgtgacc ttcgtgaagt cgccaaacct 3060

ctctgagccc cagtcattgc tagtaagacc tgcctttgag ttggtatgat gttcaagtta 3120

gataacaaaa tgtttatacc cattagaaca gagaataaat agaactacat ttcttgca 3178

<210> 70
<211> 19002
<212> DNA

<213> Homo sapiens

<220>
<221> misc_feature
<223> Wild Type Human Serum Albumin Nucleic Acid

<400> 70
cctttcccag ggacttctac aaggaaaaag ctagagttgg ttactgactt ctaataaata 60

atgcctacaa tttctaggaa gttaaaagtt gacataattt atccaagaaa gaattatttt 120

cttaacttag aatagtttct tttttctttt cagatgtagg tttttctggc tttagaaaaa 180

atgcttgttt ttcttcaatg gaaaataggc acacttgttt tatgtctgtt catctgtagt 240

cagaaagaca agtctggtat ttcctttcag gactcccttg agtcattaaa aaaaatcttc 300

ctatctatct atgtatctat catccatcta gctttgattt tttcctcttc tgtgctttat 360

tagttaatta gtacccattt ctgaagaaga aataacataa gattatagaa aataatttct 420

ttcattgtaa gactgaatag aaaaaatttt ctttcattat aagactgagt agaaaaaata 480

atactttgtt agtctctgtg cctctatgtg ccatgaggaa atttgactac tggttttgac 540

tgactgagtt atttaattaa gtaaaataac tggcttagta ctaattattg ttctgtagta 600

tcagagaaag ttgttcttcc tactggttga gctcagtagt tcttcatatt ctgagcaaaa 660

gggcagaggt aggatagctt ttctgaggta gagataagaa ccttgggtag ggaaggaaga 720

tttatgaaat atttaaaaaa ttattcttcc ttcgctttgt ttttagacat aatgttaaat 780

ttattttgaa atttaaagca acataaaaga acatgtgatt tttctactta ttgaaagaga 840

gaaaggaaaa aaatatgaaa cagggatgga aagaatccta tgcctggtga aggtcaaggg 900

ttctcataac ctacagagaa tttggggtca gcctgtccta ttgtatatta tggcaaagat 960

aatcatcatc tcatttgggt ccattttcct ctccatctct gcttaactga agatcccatg 1020

agatatactc acactgaatc taaatagcct atctcagggc ttgaatcaca tgtgggccac 1080

agcaggaatg ggaacatgga atttctaagt cctatcttac ttgttattgt tgctatgtct 1140

ttttcttagt ttgcatctga ggcaacatca gctttttcag acagaatggc tttggaatag 1200

taaaaaagac acagaagccc taaaatatgt atgtatgtat atgtgtgtgt gcatgcgtga 1260

gtacttgtgt gtaaattttt cattatctat aggtaaaagc acacttggaa ttagcaatag 1320

atgcaatttg ggacttaact ctttcagtat gtcttatttc taagcaaagt atttagtttg 1380

gttagtaatt actaaacact gagaactaaa ttgcaaacac caagaactaa aatgttcaag 1440

tgggaaatta cagttaaata ccatggtaat gaataaaagg tacaaatcgt ttaaactctt 1500

atgtaaaatt tgataagatg ttttacacaa ctttaataca ttgacaaggt cttgtggaga 1560

aaacagttcc agatggtaaa tatacacaag ggatttagtc aaacaatttt ttggcaagaa 1620

tattatgaat tttgtaatcg gttggcagcc aatgaaatac aaagatgagt ctagttaata 1680

atctacaatt attggttaaa gaagtatatt agtgctaatt tccctccgtt tgtcctagct 1740

tttctcttct gtcaacccca cacgcctttg gcacaatgaa gtgggtaacc tttatttccc 1800

ttctttttct ctttagctcg gcttattcca ggggtgtgtt tcgtcgagat gcacgtaaga 1860

aatccatttt tctattgttc aacttttatt ctattttccc agtaaaataa agttttagta 1920

aactctgcat ctttaaagaa ttattttggc atttatttct aaaatggcat agtattttgt 1980

atttgtgaag tcttacaagg ttatcttatt aataaaattc aaacatccta ggtaaaaaaa 2040

aaaaaaggtc agaattgttt agtgactgta attttctttt gcgcactaag gaaagtgcaa 2100

agtaacttag agtgactgaa acttcacaga atagggttga agattgaatt cataactatc 2160

ccaaagacct atccattgca ctatgcttta tttaaaaacc acaaaacctg tgctgttgat 2220

ctcataaata gaacttgtat ttatatttat tttcatttta gtctgtcttc ttggttgctg 2280

ttgatagaca ctaaaagagt attagatatt atctaagttt gaatataagg ctataaatat 2340

ttaataattt ttaaaatagt attcttggta attgaattat tcttctgttt aaaggcagaa 2400

gaaataattg aacatcatcc tgagtttttc tgtaggaatc agagcccaat attttgaaac 2460

aaatgcataa tctaagtcaa atggaaagaa atataaaaag taacattatt acttcttgtt 2520

ttcttcagta tttaacaatc ctttttttttc ttcccttgcc cagacaagag tgaggttgct 2580

catcggttta aagatttggg agaagaaaat ttcaaagcct tgtaagttaa aatattgatg 2640

aatcaaattt aatgtttcta atagtgttgt ttattattct aaagtgctta tatttccttg 2700

tcatcagggt tcagattcta aaacagtgct gcctcgtaga gttttctgcg ttgaggaaga 2760

tattctgtat ctgggctatc caataaggta gtcactggtc acatggctat tgagtacttc 2820

aaatatgaca agtgcaactg agaaacaaaa acttaaattg tatttaattg tagttaattt 2880

gaatgtatat agtcacatgt ggctaatggc tactgtattg gacagtacag ctctggaact 2940

tgcttggtgg aaaggacttt aatataggtt tcctttggtg gcttacccac taaatcttct 3000

ttacatagca agcattcctg tgcttagttg ggaatattta attttttttt ttttttaaga 3060

cagggtctcg ctctgtcgcc caggctggag tgcagtggcg caatctcggc tcactgcaaa 3120

ctccgctccc gggttcacgc cattctcctg cctcagcctc ccgagtagct gggactacag 3180

gcgcccgcca tcacgcccgg ctaatctttt gtatttttag tagagatggg gtttcaccgt 3240

gtgccaggat ggtctcaatc tcctgacatc gtgatctgcc cacctcggcc tcccaaagtg 3300

ctgggattac aggagtgagt caccgcgccc ggcctattta aatgtttttt aatctagtaa 3360

aaaatgagaa aattgttttt ttaaaagtct acctaatcct acaggctaat taaagacgtg 3420

tgtggggatc aggtgcggtg gttcacacct gtaatcccag cactttggaa ggctgatgca 3480

ggaggattgc ttgagcccag gagtacaaga ccagcctggg caagtctctt taaaaaaaac 3540

aaaacaaaca aacaaaaaaa ttaggcatgg tggcacatgc ctgtagtcct agctacttag 3600

gaggctgacg taggaggatc gtttggacct gagaggtcaa ggctacagtg agccatgatt 3660

gtgccactgc actccagcct gggtgacaga gtgagactct gtctcaaaaa agaaaaagga 3720

aatctgtggg gtttgtttta gttttaagta attctaagga ctttaaaaat gcctagtctt 3780

gacaattaga tctatttggc atacaatttg cttgcttaat ctatgtgtgt gcatagatct 3840

actgacacac gcatacatat aaacattagg gaactaccat tctctttgcg taggaagcca 3900

catatgccta tctaggcctc agatcatacc tgatatgaat aggctttctg gataatggtg 3960

aagaagatgt ataaaagata gaacctatac ccatacatga tttgttctct agcgtagcaa 4020

cctgttacat attaaagttt tattatacta catttttcta catcctttgt ttcagggtgt 4080

tgattgcctt tgctcagtat cttcagcagt gtccatttga agatcatgta aaattagtga 4140

atgaagtaac tgaatttgca aaaacatgtg ttgctgatga gtcagctgaa aattgtgaca 4200

aatcacttgt aagtacattc taattgtgga gattctttct tctgtttgaa gtaatcccaa 4260

gcatttcaaa ggaatttttt ttaagttttc tcaattatta ttaagtgtcc tgatttgtaa 4320

gaaacactaa aaagttgctc atagactgat aagccattgt ttcttttgtg atagagatgc 4380

tttagctatg tccacagttt taaaatcatt tctttattga gaccaaacac aacagtcatg 4440

gtgtatttaa atggcaattt gtcatttata aacacctctt tttaaaattt gaggtttggt 4500

ttctttttgt agaggctaat agggatatga tagcatgtat ttatttattt atttatctta 4560

ttttattata gtaagaaccc ttaacatgag atctaccctg ttatattttt aagtgtacaa 4620

tccattattg ttaactacgg gtacactgtt gtatagctta ctcatcttgc tgtattaaaa 4680

ctttgtgccc attgattagt aacccctcgt ttcgtcctcc cccagccact ggcaaccagc 4740

attatactct ttgattctat gagtttgact actttagcta ccttatataa gtggtattat 4800

gtactgttta tctttttatg actgacttat ttcccttagc atagtgcatt caaagtccaa 4860

ccatgttgtt gcctattgca gaatttcctt cttttcaagg ctgaataata ttccagtgca 4920

tgtgtgtacc acattttctt tatccattaa tttgttgatt gatagacatt taggttggtt 4980

ttctacatct tgactatcat gaatagtgtt gcaatgaaca caggagagct actatctctt 5040

agagatgata tcatggtttt tatcatcaga aaacacccac tgatttctat gctaattttg 5100

ttacctgggt ggaataatag tacagctata tattcctcat tttagatatc tttgtatttc 5160

tacatacaat aaaaaagcag agtacttagt catgttgaag aactttaaac ttttagtatt 5220

tccagatcaa tcttcaaaac aaggacaggt ttatctttct ctcaccactc aatctatata 5280

tacctcttgt gggcaaggcc agtttttatc actggagcct ttccccttttt tattatgtac 5340

ctctccctca cagcagagtc aggactttaa ctttacacaa tactatggct ctacatatga 5400

aatcttaaaa atacataaaa attaataaat tctgtctaga gtagtatatt ttccctgggg 5460

ttacgattac tttcataata aaaattagag ataaggaaag gactcattta ttggaaagtg 5520

attttaggta acatttctgg aagaaaaatg tctatatctt aatagtcact taatatatga 5580

tggattgtgt tactcctcag ttttcaatgg catatactaa aacatggccc tctaaaaagg 5640

gggcaaatga aatgagaaac tctctgaatg tttttctccc ctaggtgaat tcacctgctg 5700

cttagaagct tattttctct tgatttctgt tataatgatt gctcttaccc tttagtttta 5760

agtttcaaaa taggagtcat ataactttcc ttaaagctat tgactgtctt tttgtcctgt 5820

tttattcacc atgagttata gtgtgacagt taattcttat gaaaattata tagagatggt 5880

taaatcatca gaaactgtaa acctcgattg ggaggggaag cggattttta aatgatttcc 5940

tgaccaagct taaccagtat attaaatcct ttgtactgtt ctttggctat aaagaaaaaa 6000

ggtactgtcc agcaactgaa acctgctttc ttccatttag catacccttt ttggagacaa 6060

attatgcaca gttgcaactc ttcgtgaaac ctatggtgaa atggctgact gctgtgcaaa 6120

acaagaacct gagagaaatg aatgcttctt gcaacacaaa gatgacaacc caaacctccc 6180

ccgattggtg agaccagagg ttgatgtgat gtgcactgct tttcatgaca atgaagagac 6240

atttttgaaa aagtaagtaa tcagatgttt atagttcaaa attaaaaagc atggagtaac 6300

tccataggcc aacactctat aaaaattacc ataacaaaaa tattttcaac attaagactt 6360

ggaagttttg ttatgatgat tttttaaaga agtagtattt gataccacaa aattctacac 6420

agcaaaaaat atgatcaaag atattttgaa gtttattgaa acaggataca atctttctga 6480

aaaatttaag atagacaaat tatttaatgt attacgaaga tatgtatata tggttgttat 6540

aattgatttc gttttagtca gcaacattat attgccaaaa tttaaccatt tatgcacaca 6600

cacacacaca cacacacact taacccttttt ttccacatac ttaaagaatg acagagacaa 6660

gaccatcatg tgcaaattga gcttaattgg ttaattagat atctttggaa tttggaggtt 6720

ctggggagaa tgtcgattac aattatttct gtaatattgt ctgctataga aaagtgactg 6780

tttttctttt tcaaaattta gatacttata tgaaattgcc agaagacatc cttactttta 6840

tgccccggaa ctccttttct ttgctaaaag gtataaagct gcttttacag aatgttgcca 6900

agctgctgat aaagctgcct gcctgttgcc aaaggtatta tgcaaaagaa tagaaaaaaa 6960

gagttcatta tccaacctga ttttgtccat tttgtggcta gatttaggga acctgagtgt 7020

ctgatacaaa ctttccgaca tggtcaaaaa agccttcctt ttatctgtct tgaaaatctt 7080

tcatctttga aggcctacac tctcgtttct tcttttaaga tttgccaatg atgatctgtc 7140

agaggtaatc actgtgcatg tgtttaaaga tttcaccact ttttatggtg gtgatcacta 7200

tagtgaaata ctgaaacttg tttgtcaaat tgcacagcaa ggggacacag ttcttgttta 7260

tcttttcatg ataattttta gtagggaggg aattcaaagt agagaatttt actgcatcta 7320

gatgcctgag ttcatgcatt cattccataa atatatatta tggaatgctt tattttcttt 7380

tctgaggagt ttactgatgt tggtggagga gagactgaaa tgaattatac acaaaattta 7440

aaaattagca aaattgcagc ccctgggata ttagcgtact ctttctctga cttttctccc 7500

acttttaagg ctctttttcc tggcaatgtt tccagttggt ttctaactac atagggaatt 7560

ccgctgtgac cagaatgatc gaatgatctt tccttttctt agagagcaaa atcattattc 7620

gctaaaggga gtacttggga atttaggcat aaattatgcc ttcaaaattt aatttggcac 7680

agtctcatct gagcttatgg aggggtgttt catgtagaat ttttcttcta attttcatca 7740

aattattcct ttttgtagct cgatgaactt cgggatgaag ggaaggcttc gtctgccaaa 7800

cagagactca agtgtgccag tctccaaaaa tttggagaaa gagctttcaa agcatggtaa 7860

atacttttaa acatagttgg catctttata acgatgtaaa tgataatgct tcagtgacaa 7920

attgtacatt tttatgtatt ttgcaaagtg ctgtcaaata catttctttg gttgtctaac 7980

aggtagaact ctaatagagg taaaaatcag aatatcaatg acaatttgac attattttta 8040

atcttttctt ttctaaatag ttgaataatt tagaggacgc tgtccttttt gtcctaaaaa 8100

aagggacaga tatttaagtt ctatttattt ataaaatctt ggactcttat tctaatggtt 8160

cattattttt atagagctgt aggcatggtt ctttatttaa ttttttaaag ttatttttaa 8220

tttttgtgga tacagagtag gtatacatat ttacggggta tatgagatat tttgatataa 8280

gtatacaaca tatataatcc ctttatttaa ttttatcttc cccccaatga tctaaaacta 8340

tttgcttgtc cttttatgtc ttatagttaa attcagtcac caactaagtt gaagttactt 8400

cttatttttg catagctcca gctctgatct tcatctcatg tttttgcctg agcctctgtt 8460

ttcatattac ttagttggtt ctgggagcat actttaatag ccgagtcaag aaaaatacta 8520

gctgccccgt cacccacact cctcacctgc tagtcaacag caaatcaaca caacaggaaa 8580

taaaatgaaa ataatagaca ttatgcatgc tctctagaaa ctgtcaattg aactgtattt 8640

gctcatcatt cctaccatct acaccaccaa aatcaaccaa atttatgaaa aaaaaacagc 8700

cccaacataa aattatacac agataaacag gctatgattg gttttgggaa agaagtcacc 8760

tttacctgat ttaggcaact gtgaaatgac tagagaatga agaaaattag acgtttacat 8820

cttgtcatag agtttgaaga tagtgctgga tctttctttt tataagtaag atcaataaaa 8880

actccctcat tctgtagaag ttatgatttc ttttctaaga gacctttaga agtcagaaaa 8940

aatgtgtttc aattgagaaa aaagataact ggagtttgtg tagtacttcc cagattataa 9000

aatgcttttg tatgtattat ctaatttaat cctcaaaact tcttcaattt agcatgttgt 9060

catgacactg cagaggctga agctcagaga cgctgagccc tctgctaaca agtcctactg 9120

ctaacaagtg ataaagccag agctggaagt cacatctgga ctccaaacct gatgcttctc 9180

agcctgttgc ccctttaga gttccttttt aatttctgct tttatgactt gctagatttc 9240

tacctaccac acacactctt aaatggataa ttctgcccta aggataagtg attaccattt 9300

ggttcagaac tagaactaat gaattttaaa aattatttct gtatgtccat tttgaatttt 9360

cttatgagaa atagtatttg cctagtgttt tcatataaaa tatcgcatga taataccatt 9420

ttgattggcg attttctttt tagggcagta gctcgcctga gccagagatt tcccaaagct 9480

gagtttgcag aagtttccaa gttagtgaca gatcttacca aagtccacac ggaatgctgc 9540

catggagatc tgcttgaatg tgctgatgac agggtaaaga gtcgtcgata tgctttttgg 9600

tagcttgcat gctcaagttg gtagaatgga tgcgtttggt atcattggtg atagctgaca 9660

gtgggttgag attgtcttct gtgctttcgt ctgtcctatc ttcaatcttt ccctgcctat 9720

ggtggtggta cctttctgtt tttaacctgc tataaattac cagataaacc cattcactga 9780

tttgtaactc ctttcagtca tgctctaact gtaaatgaag gcttaaactg aagtagaaca 9840

gttacaaggt tttacttggc agaacatctt gcaaggtaga tgtctaagaa gatttttttt 9900

tctttttta agacagagtt tcgctcttgt ttcccaggct ggggtgcaat ggtgtgatct 9960

tggctcagcg caacctctgc ctcctgggtt caagtgattt tcatgcctca gcctcccaag 10020

tagctgggat tacaggcatg cgccaccaca cctggctaat tttgtatttt tagtagaggc 10080

ggggtttcac catattgtcc agactggtct cgaactcctg acctcaggtg atccacccgc 10140

cttggcctcc caaagtgctg ggattacagg catgagccac cttgcccagc ctaagaagat 10200

tttttgaggg aggtaggtgg acttggagaa ggtcactact tgaagagatt tttggaaatg 10260

atgtattttt cttctctata ttccttccct taattaactc tgtttgttag atgtgcaaat 10320

atttggaatg atatctcttt tctcaaaact tataatattt tctttctccc tttcttcaag 10380

attaaactta tgggcaaata ctagaatcct aatctctcat ggcactttct ggaaaattta 10440

aggcggttat tttatatatg taagcagggc ctatgactat gatcttgact cattttcaa 10500

aaatcttcta tattttattt agttatttgg tttcaaaagg cctgcactta attttggggg 10560

attatttgga aaaacagcat tgagttttaa tgaaaaaaac ttaaatgccc taacagtaga 10620

aacataaaat taataaataa ctgagctgag cacctgctac tgattagtct attttaatta 10680

agtgggaatg tttttgtagt cctatctaca tctccaggtt taggagcaaa cagagtatgt 10740

tcatagaagg aatatgtgta tggtcttaga atacaatgaa catgttctgc caacttaata 10800

aaggtctgag gagaaagtgt agcaatgtca attcgtgttg aacaatttcc accaacttac 10860

ttataggcgg accttgccaa gtatatctgt gaaaatcaag attcgatctc cagtaaactg 10920

aaggaatgct gtgaaaaacc tctgttggaa aaatcccact gcattgccga agtggaaaat 10980

gatgagatgc ctgctgactt gccttcatta gctgctgatt ttgttgaaag taaggatgtt 11040

tgcaaaaact atgctgaggc aaaggatgtc ttcctgggca tgtaagtaga taagaaatta 11100

ttcttttata gctttggcat gacctcacaa cttaggagga tagcctaggc ttttctgtgg 11160

agttgctaca atttccctgc tgcccagaat gtttcttcat ccttcccttt cccaggcttt 11220

aacaattttt gaaatagtta attagttgaa tacattgtca taaaataata catgttcacg 11280

gcaaagctca acattcctta ctccttaggg gtatttctga aaatacgtct agaaacattt 11340

tgtgtatata taaattatgt atacttcagt cattcattcc aagtgtattt cttgaacatc 11400

tataatatat gtgtgtgact atgtattgcc tgtctatcta actaatctaa tctaatctag 11460

tctatctatc taatctatgc aatgatagca aagaagtata aaaagaaata tagagtctga 11520

cacaggtgct ttatatttgg tgaaaagacc agaagttcag tataatggca atatggtagg 11580

caactcaatt acaaaataaa tgtttacgta ttgtcagaag ttgtggtgat aaactgcatt 11640

tttgttgttg gattatgata atgcactaaa taatatttcc taaaattatg taccctacaa 11700

gatttcactc atacagagaa gaaagagaat attttaagaa catatctctg cccatctatt 11760

tatcagaatc cttttgagat gtagtttaaa tcaaacaaaa tgttaataaa aataacaagt 11820

atcattcatc aaagacttca tatgtgccaa gcagtgtgtg ctttgtgtag attatgtcat 11880

atagttctca taatccacct tccgagacag atactattta ttttttgaga cagagtttta 11940

ctcttgttgc ccaggctgga gtgcaatggt gccatctcgg ctcaccacaa ccttcgcctc 12000

ccaggttcaa gcgattctcc tgcctcagcc tcctgggatt acaggcatgc accaccatgc 12060

ctggctaatt ttgtattttt agtagagatg gggtttcacc atgttggtca gactggtctc 12120

aaactcctga cctctggtga tatgcctgcc tcagcctcct aaagtgctgg gattacaggc 12180

atgagccact gtgcccagcc gacagatact attattattt ccattctacc gagaaggaga 12240

ctaaggctct gatcatttaa ataagttgcc taaggtgatg cagtgatata agtagcagag 12300

ctaggaattg agccttggta actttaactc tggaccccaa gtccttagct actaagcttt 12360

actgcatggg gtttagtcaa attaagactt ttggaatatg agttactttt gagattagct 12420

ttgtgatatt ttttgtgctc atttgtccaa caaagtctat tttattttca tcttaattag 12480

gtttttgtat gaatatgcaa gaaggcatcc tgattactct gtcgtgctgc tgctgagact 12540

tgccaagaca tatgaaacca ctctagagaa gtgctgtgcc gctgcagatc ctcatgaatg 12600

ctatgccaaa gtggtaggtt tattgttgga aaaaaatgta gttctttgac tgatgattcc 12660

aataatgaga aagaaaaata atgcaagaat gtaaaatgat atacagtgca atttagatct 12720

tttcttgaga tggtttcaat tctggaatct taaacatgaa agaaaaagta gccttagaat 12780

gattaacaaa atttagacta gttagaatag aaagatctga atagagcaat ctctaaaaaa 12840

ttttgatctt tttttctctt tttcacaatc ctgagaacaa aaaaaaatta aatttaaatg 12900

ttaattagaa gatatttaac ttagatgtaa agtgagttaa cctgattcca ggattaatca 12960

agtactagaa ttagtatctt atggcaaatt atagaaccta tccctttaga atattttcaa 13020

atctttttga ggatgtttag gaatagtttt acaagaaatt aagttaggag aggaaatctg 13080

ttctggagga tttttagggt tcccactagc atatgtaatg gtttctgaac tattcagaat 13140

cagagaaaac tcatttttcc tgctttcaag aagctactgt atgccaggca ccatgcacaa 13200

acaatgacca acgtaaaatc tctcattttg gagagcctgg aatctaactg gaaaggtgaa 13260

ctaataataa taatatgtac aatcatagcc atcatttatt aaacttttat tatatgcaag 13320

gcactgttta atttcattag cttacctggt ttacagagca gctctatgag atgagtgcca 13380

tctttgcccc tattttaggg ataaggattc cgaaatgtgg agatggtaag taaaattgca 13440

caactgaaga atgagttaca tgacttggct caaatactgg tcattgaact ccagagcctg 13500

aatattctta accacttaca tgatgcaagc tcaccaaata aatagttcga atgtattgtg 13560

acagagcggc attgatattc atctattcat gtggctttga gtaggaagaa gaaaggatat 13620

cattctgacc agaggggtga aaaacaacct gcatctgatc ctgaggcata atactattaa 13680

cacaattctt ttatgtttca gttcgatgaa tttaaacctc ttgtggaaga gcctcagaat 13740

ttaatcaaac aaaattgtga gctttttgag cagcttggag agtacaaatt ccagaatgcg 13800

taagtaattt ttattgactg attttttta tcaatttgta attatttaag acttaatata 13860

tgagccacct agcatagaac ttttaagaat gaaaatacat tgcatatttc taatcactct 13920

ttgtcaagaa agataggaga ggagagataa aatagttgat ggggtggaga ggtctatatt 13980

tgaatgtagt ctaaaaattg ttctcttaag attggaagta tgtaggctgg gagggtaaat 14040

accaaatctt ggtatatcag aactgagcat gtcccttgaa ggttaagaaa tagttaatgg 14100

gcaaatagag catggcaata ttttgtagag cagcaagtag taggccttga atagatgtcg 14160

ctcaaaaagt aatatgtaag ctgaacacaa aaatgtaaca aatgaattta gatacatatt 14220

tgaatattaa attcaggttg tttgggagat gcacctagtc tttgatggtt aaacctttcc 14280

ctccatagaa gagacagaga cagaatggct tgctggacta atgtcccaat tcaatagagt 14340

cttatctacg aaggttaaaa acaagaagag acatattata cagtagatat ttattgtgtg 14400

gctcatacac atggtgctct tctgattatg gattttagag ataataacag tgaacaagac 14460

atagtttctt tcctcgagta gattaaagtc atacattgac ttttaatggt gactggcatt 14520

cttaatacat gattattata tattaggtac catgtcagat taattataat actttactat 14580

ttttaattta acccttgaac tatccctatt gagtcagata tatttccttc cattttctac 14640

ttgtatcttt caagtttagc atatgctgat acatatgaag ctctctccag gttttattga 14700

aagaagaaat taataaattt attaatgtca ctgaattagg caactcactt tcccaagatt 14760

atgcaagtgg tacaggtgga actcaaagcc aagtttaact agttgttcag gagaatgttt 14820

tctaccctcc actaacccac tactctgcag atggagataa tatgatgaat ggaacatagc 14880

aacatcttag ttgattccgg ccaagtgttc tctgttttat ctactatgtt agacagtttc 14940

ttgccttgct gaaaacacat gacttctttt tttcaggcta ttagttcgtt acaccaagaa 15000

agtaccccaa gtgtcaactc caactcttgt agaggtctca agaaacctag gaaaagtggg 15060

cagcaaatgt tgtaaacatc ctgaagcaaa aagaatgccc tgtgcagaag actatgtgag 15120

tctttaaaaa aatataataa attaataatg aaaaaatttt acctttagat attgataatg 15180

ctagctttca taagcagaag gaagtaatgt gtgtgtgtgc atgtttgtgt gcatgtgtgt 15240

gtgcatgcac gtgtgtgtat gtgtgatatt ggcagtcaag gccccgagga tgataatttt 15300

ttttttttt ttgagacgga gtctcgcttt gttgtccagg ctggagtgca gtggtgccat 15360

ctcggctcac tgcaacctcc gcctcccaag ttcaagccat tctcctgcct cagcctccca 15420

agtagctggg actacaggtg catgccacca tgcctggcta atttttgta tttttagtag 15480

aaaattttca gcttcacctc ttttgaattt ctgctctcct gcctgttctt tagctatccg 15540

tggtcctgaa ccagttatgt gtgttgcatg agaaaacgcc agtaagtgac agagtcacca 15600

aatgctgcac agaatccttg gtgaacaggc gaccatgctt ttcagctctg gaagtcgatg 15660

aaacatacgt tcccaaagag tttaatgctg aaacattcac cttccatgca gatatatgca 15720

cactttctga gaaggagaga caaatcaaga aacaaacgtg aggagtattt cattactgca 15780

tgtgtttgta gtcttgatag caagaactgt caattcaagc tagcaacttt ttcctgaagt 15840

agtgattata tttcttagag gaaagtattg gagtgttgcc cttattatgc tgataagagt 15900

acccagaata aaatgaataa ctttttaaag acaaaatcct ctgttataat attgctaaaa 15960

ttattcagag taatattgtg gattaaagcc acaatagaat aacatgttag accatattca 16020

gtagaaaaag atgaacaatt aactgataaa tttgtgcaca tggcaaatta gttaatggga 16080

accataggag aatttatttc tagatgtaaa taattatttt aagtttgccc tatggtggcc 16140

ccacacatga gacaaacccc caagatgtga cttttgagaa tgagacttgg ataaaaaaca 16200

tgtagaaatg caagccctga agctcaactc cctattgcta tcacaggggt tataattgca 16260

taaaatttag ctatagaaag ttgctgtcat ctcttgtggg ctgtaatcat cgtctaggct 16320

taagagtaat attgcaaaac ctgtcatgcc cacacaaatc tctccctggc attgttgtct 16380

ttgcagatgt cagtgaaaga gaaccagcag ctcccatgag tttggatagc cttattttct 16440

atagcctccc cactgaaggg agcaaagttt aagaaccaaa tataaagttt ctcatcttta 16500

tagatgagaa aaattttaaa taaagtccaa gataattaaa tttttaagga tcatttttag 16560

ctctttaata gcaataaaac tcaatatgac ataatatggc acttccaaaa tctgaataat 16620

atataattgc aatgacatac ttcttttcag agatttactg aaaagaaatt tgttgacact 16680

acataacgtg atgagtggtt tatactgatt gtttcagttg gtcttcccac caactccatg 16740

aaagtggatt ttattatcct catcatgcag atgagaatat tgagacttat agcggtatgc 16800

ctggcccaag tactcagagt tgcctggctc caagatttat aatcttaaat gatgggacta 16860

ccatccttac tctctccatt tttctatacg tgagtaatgt tttttctgtt ttttttttt 16920

ctttttccat tcaaactcag tgcacttgtt gagctcgtga aacacaagcc caaggcaaca 16980

aaagagcaac tgaaagctgt tatggatgat ttcgcagctt ttgtagagaa gtgctgcaag 17040

gctgacgata aggagacctg ctttgccgag gaggtactac agttctcttc attttaatat 17100

gtccagtatt cattttgca tgtttggtta ggctagggct tagggattta tatatcaaag 17160

gaggctttgt acatgtggga cagggatctt attttacaaa caattgtctt acaaaatgaa 17220

taaaacagca ctttgttttt atctcctgct ctattgtgcc atactgttga atgtttataa 17280

tgcatgttct gtttccaaat ttgtgatgct tatgaatatt aataggaata tttgtaaggc 17340

ctgaaatatt ttgatcatga aatcaaaaca ttaatttatt taaacattta cttgaaatgt 17400

ggtggtttgt gatttagttg attttatagg ctagtgggag aatttacatt caaatgtcta 17460

aatcacttaa aatttccctt tatggcctga cagtaacttt tttttattca tttggggaca 17520

actatgtccg tgagcttcca tccagagatt atagtagtaa attgtaatta aaggatatga 17580

tgcacgtgaa atcactttgc aatcatcaat agcttcataa atgttaattt tgtatcctaa 17640

tagtaatgct aatattttcc taacatctgt catgtctttg tgttcagggt aaaaaacttg 17700

ttgctgcaag tcaagctgcc ttaggcttat aacatcacat ttaaaagcat ctcaggtaac 17760

tatattttga atttttaaa aaagtaacta taatagttat tattaaaata gcaaagattg 17820

accatttcca agagccatat agaccagcac cgaccactat tctaaactat ttatgtatgt 17880

aaatattagc ttttaaaatt ctcaaaatag ttgctgagtt gggaaccact attatttcta 17940

ttttgtagat gagaaaatga agataaacat caaagcatag attaagtaat tttccaaagg 18000

gtcaaaattc aaaattgaaa ccaaggtttc agtgttgccc attgtcctgt tctgacttat 18060

atgatgcggt acacagagcc atccaagtaa gtgatggctc agcagtggaa tactctggga 18120

attaggctga accacatgaa agagtgcttt atagggcaaa aacagttgaa tatcagtgat 18180

ttcacatggt tcaacctaat agttcaactc atcctttcca ttggagaata tgatggatct 18240

accttctgtg aactttatag tgaagaatct gctattacat ttccaatttg tcaacatgct 18300

gagctttaat aggacttatc ttcttatgac aacatttatt ggtgtgtccc cttgcctagc 18360

ccaacagaag aattcagcag ccgtaagtct aggacaggct taaattgttt tcactggtgt 18420

aaattgcaga aagatgatct aagtaatttg gcatttattt taataggttt gaaaaacaca 18480

tgccatttta caaataagac ttatatttgt ccttttgttt ttcagcctac catgagaata 18540

agagaaagaa aatgaagatc aaaagcttat tcatctgttt ttctttttcg ttggtgtaaa 18600

gccaacaccc tgtctaaaaa acataaattt ctttaatcat tttgcctctt ttctctgtgc 18660

ttcaattaat aaaaaatgga aagaatctaa tagagtggta cagcactgtt atttttcaaa 18720

gatgtgttgc tatcctgaaa attctgtagg ttctgtggaa gttccagtgt tctctcttat 18780

tccacttcgg tagaggattt ctagtttctt gtgggctaat taaataaatc attaatactc 18840

ttctaagtta tggattataa acattcaaaa taatattttg acattatgat aattctgaat 18900

aaaagaacaa aaaccatggt ataggtaagg aatataaaac atggctttta ccttagaaaa 18960

aacaattcta aaattcatat ggaatcaaaa aagagcctgc ag 19002

<210> 71
<211> 993
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic: Mutant AAT-linkerAlbumin Fusion (S283C, K335A, P361C)

<400> 71

```
Glu Asp Pro Gln Gly Asp Ala Ala Gln Lys Thr Asp Thr Ser His His
1               5                  10                  15

Asp Gln Asp His Pro Thr Phe Asn Lys Ile Thr Pro Asn Leu Ala Glu
            20                  25                  30

Phe Ala Phe Ser Leu Tyr Arg Gln Leu Ala His Gln Ser Asn Ser Thr
        35                  40                  45

Asn Ile Phe Phe Ser Pro Val Ser Ile Ala Thr Ala Phe Ala Met Leu
    50                  55                  60

Ser Leu Gly Thr Lys Ala Asp Thr His Asp Glu Ile Leu Glu Gly Leu
65                  70                  75                  80

Asn Phe Asn Leu Thr Glu Ile Pro Glu Ala Gln Ile His Glu Gly Phe
                85                  90                  95

Gln Glu Leu Leu Arg Thr Leu Asn Gln Pro Asp Ser Gln Leu Gln Leu
            100                 105                 110

Thr Thr Gly Asn Gly Leu Phe Leu Ser Glu Gly Leu Lys Leu Val Asp
        115                 120                 125

Lys Phe Leu Glu Asp Val Lys Lys Leu Tyr His Ser Glu Ala Phe Thr
    130                 135                 140

Val Asn Phe Gly Asp Thr Glu Glu Ala Lys Lys Gln Ile Asn Asp Tyr
145                 150                 155                 160

Val Glu Lys Gly Thr Gln Gly Lys Ile Val Asp Leu Val Lys Glu Leu
                165                 170                 175

Asp Arg Asp Thr Val Phe Ala Leu Val Asn Tyr Ile Phe Phe Lys Gly
            180                 185                 190
```

```
Lys Trp Glu Arg Pro Phe Glu Val Lys Asp Thr Glu Glu Glu Asp Phe
        195                 200                 205

His Val Asp Gln Val Thr Thr Val Lys Val Pro Met Met Lys Arg Leu
    210                 215                 220

Gly Met Phe Asn Ile Gln His Ser Lys Lys Leu Ser Ser Trp Val Leu
225                 230                 235                 240

Leu Met Lys Tyr Leu Gly Asn Ala Thr Ala Ile Phe Phe Leu Pro Asp
                245                 250                 255

Glu Gly Lys Leu Gln His Leu Glu Asn Glu Leu Thr His Asp Ile Ile
            260                 265                 270

Thr Lys Phe Leu Glu Asn Glu Asp Arg Arg Cys Ala Ser Leu His Leu
        275                 280                 285

Pro Lys Leu Ser Ile Thr Gly Thr Tyr Asp Leu Lys Ser Val Leu Gly
    290                 295                 300

Gln Leu Gly Ile Thr Lys Val Phe Ser Asn Gly Ala Asp Leu Ser Gly
305                 310                 315                 320

Val Thr Glu Glu Ala Pro Leu Lys Leu Ser Lys Ala Val His Ala Ala
                325                 330                 335

Val Leu Thr Ile Asp Glu Lys Gly Thr Glu Ala Ala Gly Ala Val Phe
            340                 345                 350

Leu Glu Ala Ile Pro Leu Ser Ile Cys Pro Glu Val Lys Phe Asn Lys
        355                 360                 365

Pro Phe Val Phe Leu Met Ile Glu Gln Asn Thr Lys Ser Pro Leu Phe
    370                 375                 380

Met Gly Lys Val Val Asn Pro Thr Gln Lys Gly Gly Ser Gly Gly Ser
```

```
385                 390                 395                 400

Gly Gly Ser Gly Gly Ser Gly Gly Asp Ala His Lys Ser Glu Val Ala
                405                 410                 415

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
            420                 425                 430

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
        435                 440                 445

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
    450                 455                 460

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
465                 470                 475                 480

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
                485                 490                 495

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
            500                 505                 510

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
        515                 520                 525

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
    530                 535                 540

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
545                 550                 555                 560

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
                565                 570                 575

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
            580                 585                 590
```

```
Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
        595                 600                 605

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
    610                 615                 620

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
625                 630                 635                 640

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
                645                 650                 655

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
            660                 665                 670

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
        675                 680                 685

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
    690                 695                 700

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
705                 710                 715                 720

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
                725                 730                 735

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
            740                 745                 750

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
        755                 760                 765

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
    770                 775                 780

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
```

```
785                 790                 795                 800

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
                805                 810                 815

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
            820                 825                 830

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
        835                 840                 845

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
    850                 855                 860

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
865                 870                 875                 880

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
                885                 890                 895

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
            900                 905                 910

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
        915                 920                 925

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
    930                 935                 940

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
945                 950                 955                 960

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
                965                 970                 975

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
            980                 985                 990
```

Leu