



US012384822B2

(12) **United States Patent**  
**Kim et al.**

(10) **Patent No.:** US 12,384,822 B2  
(45) **Date of Patent:** Aug. 12, 2025

(54) **TAM RECEPTOR-BINDING FUSION MOLECULE HAVING NON-INFLAMMATORY PHAGOCYTOSIS INDUCING ACTIVITY**

(71) Applicant: **ILLIMIS THERAPEUTICS, INC.,**  
Seoul (KR)

(72) Inventors: **Chan Hyuk Kim**, Daejeon (KR); **Won Suk Chung**, Daejeon (KR); **Hyun Cheol Jung**, Daejeon (KR); **Se Young Lee**, Daejeon (KR)

(73) Assignee: **ILLIMIS THERAPEUTICS, INC.,**  
Seoul (KR)

(\*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **18/360,984**

(22) Filed: **Jul. 28, 2023**

(65) **Prior Publication Data**

US 2024/0018204 A1 Jan. 18, 2024

**Related U.S. Application Data**

(63) Continuation-in-part of application No. PCT/KR2022/001671, filed on Jan. 28, 2022.

(30) **Foreign Application Priority Data**

Jan. 29, 2021 (KR) ..... 10-2021-0013045

(51) **Int. Cl.**

**C07K 19/00** (2006.01)  
**A61P 25/28** (2006.01)

(Continued)

(52) **U.S. Cl.**

CPC ..... **C07K 14/4703** (2013.01); **A61P 25/28** (2018.01); **C07K 16/18** (2013.01);

(Continued)

(58) **Field of Classification Search**

None

See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

8,268,973 B2	9/2012	Schenk et al.
8,753,628 B2	6/2014	Lazar et al.

(Continued)

FOREIGN PATENT DOCUMENTS

WO 2010/130751 A1	11/2010
WO 2010/131733 A1	11/2010

(Continued)

OTHER PUBLICATIONS

Caberoy et al., Tubby and tubby-like protein 1 are new MerTK ligands for phagocytosis, The EMBO J. 29: 3898-3910, 2010.\*

(Continued)

*Primary Examiner* — Claire Kaufman

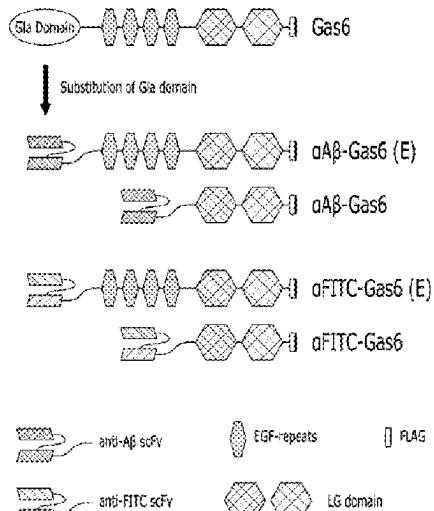
(74) *Attorney, Agent, or Firm* — Sughrue Mion, PLLC

(57) **ABSTRACT**

A fusion molecule having phagocytosis-inducing activity is disclosed. The fusion molecule contains a first region capable of binding a TAM receptor and a second region capable of binding to a target substance of which aberrant accumulation is associated with or characteristic of diseases. The fusion molecule effectively clears and/or reduces and/or suppresses accumulated abnormal proteins, such as beta-amyloid, tau, alpha-synuclein, huntingtin, or prion, or the like. Uses of the fusion molecule are disclosed. The fusion molecule can be used for prevention or treatment of proteinosis caused by the abnormal accumulation of substances.

**13 Claims, 35 Drawing Sheets**

**Specification includes a Sequence Listing.**



- (51) **Int. Cl.**
- C07K 14/47* (2006.01)
  - C07K 16/18* (2006.01)
  - C07K 16/46* (2006.01)
  - A61K 38/00* (2006.01)
- (52) **U.S. Cl.**
- CPC ..... *A61K 38/00* (2013.01); *C07K 2317/73* (2013.01); *C07K 2319/74* (2013.01)

(56) **References Cited**

## U.S. PATENT DOCUMENTS

9,283,271 B2	3/2016	Montrasio et al.
9,587,014 B2	3/2017	Nitsch et al.
10,882,902 B2	1/2021	Grimm et al.
10,961,306 B2	3/2021	Keane et al.
11,040,086 B2 *	6/2021	Zhang ..... <i>A61K 38/1709</i>
11,267,877 B2	3/2022	Salmans et al.
11,873,337 B2 *	1/2024	Takahashi ..... <i>A61P 25/00</i>
2018/0327465 A1	11/2018	Caberoy
2020/0181221 A1	6/2020	Kotenko et al.
2020/0390853 A1	12/2020	Zhang et al.
2021/0070870 A1	3/2021	Gardener et al.
2021/0079075 A1	3/2021	Heneka et al.
2022/0332808 A1	10/2022	Maier et al.
2022/0411485 A1	12/2022	Holtzman et al.

## FOREIGN PATENT DOCUMENTS

WO	WO-2011107591 A1 *	9/2011	..... <i>A61K 38/16</i>
WO	2011/159980 A1	12/2011	
WO	2012/088461 A2	6/2012	
WO	2012/130831 A1	10/2012	
WO	2012/175691 A1	12/2012	
WO	2015/193428 A1	12/2015	
WO	2015/193430 A1	12/2015	
WO	2016/005593 A1	1/2016	
WO	2016/097370 A2	6/2016	
WO	2016/106221 A1	6/2016	
WO	2016/166302 A1	10/2016	
WO	2016/166348 A1	10/2016	
WO	2017/009258 A1	1/2017	
WO	WO-2017083700 A1 *	5/2017	..... <i>A61K 38/00</i>
WO	2017/200493 A1	11/2017	
WO	2017/220695 A1	12/2017	
WO	2019/201970 A1	10/2019	
WO	2020/076799 A1	4/2020	
WO	2020/176497 A1	9/2020	

## OTHER PUBLICATIONS

- Burstyn-Cohen et al., TAM receptors in phagocytosis: Beyond the mere internalization of particles, *Immunological Rev.*, 139:7-26, 2023.\*
- Nomura et al., Activated Microglia Desialylate and Phagocytose Cells via Neuraminidase, Galectin-3, and Mer Tyrosine Kinase, *J. Immunol.* 198 (12): 4792-4801, 2017\*
- Sasaki et al., Crystal structure of a C-terminal fragment of growth arrest-specific protein Gas6, *J. Biol. Chem.* 277(46): 44164-44170, 2002.\*
- Van der Meer et al., TAM receptors, Gas6, and protein S: roles in inflammation and hemostasis, *Blood*. 123(16):2460-2469, 2014.\* International Search Report dated May 16, 2023 in International Application No. PCT/KR2022/001671.
- Written Opinion dated May 16, 2023 in International Application No. PCT/KR2022/001671.
- Kedage et al., "Harnessing MerTK agonism for targeted therapeutics", MABS, 2020, vol. 12, No. 1, pp. 1-8 (8 pages total).
- Tondo et al., "TAM Receptor Pathways at the Crossroads of Neuroinflammation and Neurodegeneration", Hindawi Disease Markers, 2019, vol. 2019, pp. 1-13 (13 pages total).
- Lew et al., "Differential TAM receptor-ligand-phospholipid interactions delimit differential TAM bioactivities", eLIFE, 2014, pp. 1-23 (23 pages total).

Hutchison et al., "A complete library of point substitution mutations in the glucocorticoid response element of mouse mammary tumor virus", *Proc. Natl. Acad. Sci. USA*, 1986, vol. 83, pp. 710-714, (5 pages total).

Higuchi, "Using PCR to Engineer DNA", *PCR Technology: Principles and Applications for DNA Amplification*, 1989, H. Erlich, ed., Stockton Press, 1989, Chapter 6, pp. 61-70, (10 pages total). Zheng et al., "Advances in aptamers against AB and applications in AB detection and regulation for Alzheimer's disease", *Theranostics*, 2022, vol. 12, No. 5, pp. 2095-2114, (20 pages total).

Donahue et al., "Rage, LRP-1, and amyloid-beta protein in Alzheimer's disease", *Acta Neuropathol.* 2006, vol. 112, pp. 405-415, (11 pages total).

Schwarzman et al., "Selection of peptides binding to the amyloid b-protein reveals potential inhibitors of amyloid formation", *Amyloid*, 2005, vol. 12, No. 4, pp. 199-209, (12 pages total).

Sambrook et al., "Molecular Cloning: A laboratory Manual", Cold Spring Harbor Laboratory Press, 1989, vol. 1, No. 4, (34 pages total).

Deuscher et al., "Guide to Protein Purification", *Methods Enzymology*, 1990, vol. 463, No. 2, (854 pages total).

Rowe et al., "Handbook of Pharmaceutical Excipients", American Pharmaceuticals Association, 2003, 4th Edition, (917 pages total).

Gennaro et al., "Remington: the Science and Practice of Pharmacy", Lippincott Williams & Wilkins, 2000, vol. 1, 20th Edition, (1053 pages total).

"Tyrosine-protein kinase receptor UFO isoform 1 precursor [*Homo sapiens*]", NCBI Reference Sequence: NP\_068713.2, cbi.nlm.nih.gov/protein/NP\_068713, last visited Aug. 15, 2023, pp. 1-5 (5 pages total).

"*Homo sapiens* AXL receptor tyrosine kinase (AXL), transcript variant 1, mRNA", NCBI Reference Sequence: NM\_021913.5, https://www.ncbi.nlm.nih.gov/nucleotide/NM\_021913, last visited Aug. 15, 2023, pp. 1-6 (6 pages total).

"AXL receptor tyrosine kinase [*Mus musculus*]", GenBank: AAH46618.1, https://www.ncbi.nlm.nih.gov/protein/AAH46618, last visited Aug. 15, 2023, pp. 1-4 (4 pages total).

"*Mus musculus* AXL receptor tyrosine kinase, mRNA (cDNA clone MGC:54698 Image:6494383), complete cds", GenBank: BC046618.1, https://www.ncbi.nlm.nih.gov/nucleotide/BC046618, last visited Aug. 15, 2023, pp. 1-3 (3 pages total).

"Tyrosine-protein kinase receptor UFO isoform 3 [*Homo sapiens*]", NCBI Reference Sequence: NP\_001265528.1, https://www.ncbi.nlm.nih.gov/protein/NP\_001265528.1 last visited Aug. 15, 2023, pp. 1-4 (4 pages total).

"Tyrosine-protein kinase receptor UFO isoform 2 precursor [*Homo sapiens*]", NCBI Reference Sequence: NP\_001690.2, https://www.ncbi.nlm.nih.gov/protein/NP\_001690.2 last visited Aug. 15, 2023, pp. 1-5 (5 pages total).

"AXL receptor tyrosine kinase, isoform CRA\_a [*Homo Sapiens*]", GenBank: EAW57022.1, https://www.ncbi.nlm.nih.gov/protein/EAW57022, last visited Aug. 15, 2023, pp. 1-2 (2 pages total).

"AXL receptor Tyrosine kinase, isoform CRA\_b [*Homo sapiens*]", GenBank: EAW57023.1, https://www.ncbi.nlm.nih.gov/protein/EAW57023.1, last visited Aug. 15, 2023, pp. 1-2 (2 pages total).

"AXL receptor tyrosine kinase [*Homo sapiens*]", GenBank: AAH32229.1 https://www.ncbi.nlm.nih.gov/protein/AAH32229.1 last visited Aug. 15, 2023, pp. 1-4 (4 pages total).

"RecName: Full=Tubby protein homolog", UniProtKB/Swiss-Prot: P50607.1, https://www.ncbi.nlm.nih.gov/protein/P50607 last visited Aug. 15, 2023, pp. 1-5 (5 pages total).

"Human tub homolog mRNA, complete cds" GenBank: U54644.1, https://www.ncbi.nlm.nih.gov/nucleotide/U54644.1 last visited Aug. 15, 2023, pp. 1-2 (2 pages total).

"Tub homolog [*Homo sapiens*]", GenBank: AAB53494.1, https://www.ncbi.nlm.nih.gov/protein/AAB53494.1, last visited Aug. 15, 2023, pp. 1-2 (2 pages total).

"Human tub homolog (Tub) mRNA, complete cds", GenBank: U82467.1, https://www.ncbi.nlm.nih.gov/nucleotide/U82467.1, last visited Aug. 15, 2023, pp. 1-2 (2 pages total).

"Tub homolog [*Homo sapiens*]", GenBank: AAB53699.1, https://www.ncbi.nlm.nih.gov/protein/AAB53699.1, last visited Aug. 15, 2023, pp. 1-2 (2 pages total).

(56)

**References Cited****OTHER PUBLICATIONS**

- “*Homo sapiens* 211000035833915 genomic scaffold, whole genome shotgun sequence” GenBank: CH471064.2, <https://www.ncbi.nlm.nih.gov/nuccore/CH471064.2>, last visited Aug. 15, 2023, pp. 1-8 (8 pages total).
- “Tubby homolog (mouse), isoform CRA\_b [*Homo sapiens*”, GenBank: EAW68634.1, <https://www.ncbi.nlm.nih.gov/protein/EAW68634.1>, last visited Aug. 15, 2023, pp. 1-3 (3 pages total).
- “*Homo sapiens* tubby homolog (mouse), mRNA (cDNA clone MGC: 104164 Image:30915625), complete cds”, GenBank: BC075031.2, <https://www.ncbi.nlm.nih.gov/nuccore/BC075031.2>, last visited Aug. 15, 2023, pp. 1-3 (3 pages total).
- “Tubby homolog (mouse) [*Homo sapiens*”, GenBank: AAH75031.1, <https://www.ncbi.nlm.nih.gov/protein/AAH75031.1>, last visited Aug. 15, 2023, pp. 1-2 (2 pages total).
- “*Homo sapiens* tubby homolog (mouse), mRNA (cDNA clone MGC: 104008 Image:30915418), complete cds”, GenBank: BC075032.2, <https://www.ncbi.nlm.nih.gov/nuccore/BC075032.2>, last visited Aug. 15, 2023, pp. 1-3 (3 pages total).
- “Tubby homolog (mouse) [*Homo sapiens*”, GenBank: AAH75032.1, <https://www.ncbi.nlm.nih.gov/protein/AAH75032.1>, last visited Aug. 15, 2023, pp. 1-2 (2 pages total).
- “Tubby protein homolog isoform a [*Homo sapiens*”, NCBI Reference Sequence: NP\_003311.2, [https://www.ncbi.nlm.nih.gov/protein/NP\\_003311.2](https://www.ncbi.nlm.nih.gov/protein/NP_003311.2), last visited Aug. 15, 2023, pp. 1-3 (3 pages total).
- “Tubby protein homolog isoform b [*Homo sapiens*”, NCBI Reference Sequence: NP\_813977.1, [https://www.ncbi.nlm.nih.gov/protein/NP\\_813977.1](https://www.ncbi.nlm.nih.gov/protein/NP_813977.1), last visited Aug. 15, 2023, pp. 1-3 (3 pages total).
- “Chain A, tubby isoform a”, PDB: 1S31\_A, [https://www.ncbi.nlm.nih.gov/protein/1S31\\_A](https://www.ncbi.nlm.nih.gov/protein/1S31_A), last visited Aug. 15, 2023, pp. 1-2 (2 pages total).
- “Tubby related protein 1 TULP1 [*Homo sapiens*”, GenBank: AAB53700.1, <https://www.ncbi.nlm.nih.gov/protein/AAB53700.1>, last visited Aug. 15, 2023, pp. 1-2 (2 pages total).
- “TULP1 protein [*Homo sapiens*”, GenBank: AAH32714.1, <https://www.ncbi.nlm.nih.gov/protein/AAH32714.1>, last visited Aug. 15, 2023, pp. 1-2 (2 pages total).
- “TULP1 protein [*Homo sapiens*”, GenBank: AAH65261.1, <https://www.ncbi.nlm.nih.gov/protein/AAH65261.1>, last visited Aug. 15, 2023, pp. 1-2 (2 pages total).
- “Tubby-related protein 1 isoform 2 [*Homo sapiens*”, NCBI Reference Sequence: NP\_001276324.1, [https://www.ncbi.nlm.nih.gov/protein/NP\\_001276324.1](https://www.ncbi.nlm.nih.gov/protein/NP_001276324.1), last visited Aug. 15, 2023, pp. 1-3 (3 pages total).
- “Tubby like protein 1 [*Homo sapiens*”, GenBank: AAB97966.1, <https://www.ncbi.nlm.nih.gov/protein/AAB97966.1>, last visited Aug. 15, 2023, pp. 1-2 (2 pages total).
- “Tubby like protein 1, isoform CRA\_b [*Homo sapiens*”, GenBank: EAX03840.1, <https://www.ncbi.nlm.nih.gov/protein/EAX03840.1>, last visited Aug. 15, 2023, pp. 1-2 (2 pages total).
- “Tubby like protein 1, isoform CRA\_a [*Homo sapiens*”, GeneBank: EAX03839.1, <https://www.ncbi.nlm.nih.gov/protein/EAX03839.1>, last visited Aug. 15, 2023, pp. 1-2 (2 pages total).
- “Tubby-related protein 1 [*Homo sapiens*”, GenBank: BAJ84064.1, <https://www.ncbi.nlm.nih.gov/protein/BAJ84064.1>, last visited Aug. 15, 2023, pp. 1-2 (2 pages total).
- “Tubby-related protein 1 [*Homo sapiens*”, GenBank: BAJ84063.1, <https://www.ncbi.nlm.nih.gov/protein/BAJ84063.1>, last visited Aug. 15, 2023, pp. 1-2 (2 pages total).
- “Tubby-like protein 1 [*Homo sapiens*”, GenBank: AKU84911.1, <https://www.ncbi.nlm.nih.gov/protein/AKU84911.1>, last visited Aug. 15, 2023, pp. 1-2 (2 pages total).
- “Galectin-3 isoform 1 [*Homo sapiens*”, NCBI Reference Sequence: NP\_002297.2, [https://www.ncbi.nlm.nih.gov/protein/NP\\_002297](https://www.ncbi.nlm.nih.gov/protein/NP_002297), last visited Aug. 15, 2023, pp. 1-4 (4 pages total).
- “Beta-amyloid, A beta-neuritic plaque amyloid [N-terminal] [human, familial Alzheimer’s disease patient, Peptide Partial, 30 aa]”, GenBank: AAB29908.1, <https://www.ncbi.nlm.nih.gov/protein/AAB29908.1>, last visited Aug. 15, 2023, p. 1 (1 page total).
- “Chain A, Amyloid Beta-Peptide”, PDB: 1BJC\_A, [https://www.ncbi.nlm.nih.gov/protein/1BJC\\_A](https://www.ncbi.nlm.nih.gov/protein/1BJC_A), last visited Aug. 15, 2023, p. 1 (1 page total).
- “Major prion protein preproprotein Prp precursor [*Homo sapiens*”, NCBI Reference Sequence: NP\_001073592.1, [https://www.ncbi.nlm.nih.gov/protein/NP\\_001073592.1](https://www.ncbi.nlm.nih.gov/protein/NP_001073592.1), last visited Aug. 15, 2023, pp. 1-4 (4 pages total).
- “Huntingtin isoform 1 [*Homo sapiens*”, NCBI Reference Sequence: NP\_001375421.1, [https://www.ncbi.nlm.nih.gov/protein/NP\\_001375421.1](https://www.ncbi.nlm.nih.gov/protein/NP_001375421.1), last visited Aug. 15, 2023, pp. 1-6 (6 pages total).
- “SOD1 [*Homo sapiens*”, GenBank: CAG46542.1, <https://www.ncbi.nlm.nih.gov/protein/CAG46542.1>, last visited Aug. 15, 2023, pp. 1-3 (3 pages total).
- “Serum amyloid A [*Homo sapiens*”, GenBank: AAB24060.1, <https://www.ncbi.nlm.nih.gov/protein/AAB24060.1>, last visited Aug. 15, 2023, p. 1 (1 page total).
- “Serum amyloid A [A *Homo sapiens*”, GenBank: AAA85338.1, <https://www.ncbi.nlm.nih.gov/protein/AAA85338.1>, last visited Aug. 15, 2023, p. 1 (1 page total).
- “Serum amyloid A-2 protein isoform a preproprotein [*Homo sapiens*”, NCBI Reference Sequence: NP\_001372595.1, [https://www.ncbi.nlm.nih.gov/protein/NP\\_001372595.1](https://www.ncbi.nlm.nih.gov/protein/NP_001372595.1), last visited Aug. 15, 2023, pp. 1-3 (3 pages total).
- “Serum amyloid A-2 protein isoform a preproprotein [*Homo sapiens*”, NCBI Reference Sequence: NP\_110381.2, [https://www.ncbi.nlm.nih.gov/protein/NP\\_110381.2](https://www.ncbi.nlm.nih.gov/protein/NP_110381.2), last visited Aug. 15, 2023, pp. 1-4 (4 pages total).
- “RecName: Full=Tyrosine-protein kinase receptor UFO; AltName: Full=AXL oncogene; Flags: Precursor”, UniProtKB/Swiss-Prot: P30530.4, <https://www.ncbi.nlm.nih.gov/protein/P30530.4>, last visited Aug. 15, 2023, pp. 1-14 (14 pages total).
- “RecName: Full=Alpha-synuclein; Altname: Full=Non-A beta component of AD amyloid; Altname: Full=Non-A4 component of amyloid precursor; Short=NACP”, UniProtKB/Swiss-Prot: P37840.1, <https://www.ncbi.nlm.nih.gov/protein/P37840.1>, last visited Aug. 15, 2023, pp. 1-17 (17 pages total).
- “RecName: Full=Mircotubule-associated protein tau; AltName: Full=Neurofibrillary tangle protein; AltName: Full=Paired helical filament-tau; Short=PHF-tau”, UniProtKB/Swiss-Prot P10636.5, <https://www.ncbi.nlm.nih.gov/protein/P10636.5>, last visited Aug. 15, 2023, pp. 1-33 (33 pages total).
- “RecName: Full=TAR DNA-binding protein 43; Short=TDP-43”, UniProtKB/Swiss-Prot: Q13148.1, <https://www.ncbi.nlm.nih.gov/protein/Q13148.1>, last visited Aug. 15, 2023, pp. 1-21 (21 pages total).
- “RecName: Full=Transthyretin; AltName: Full=ATTR; AltName: Full=Prealbumin; AltName: Full=TBPA; Flags: Precursor”, UniProtKB/Swiss-Prot: P02766.1, <https://www.ncbi.nlm.nih.gov/protein/P02766.1>, last visited Aug. 15, 2023, pp. 1-29 (29 pages total).
- “RecName: Full=Islet amyloid polypeptide; AltName: Full=Amylin; AltName: Full=Diabetes-associated peptide; Short=DAP; AltName: Full=Insulinoma amyloid peptide; Flags: Precursor”, UniProtKB/Swiss-Prot: P10997, <https://www.ncbi.nlm.nih.gov/protein/P10997>, last visited Aug. 15, 2023, pp. 1-6 (6 pages total).
- “RecName: Full=Apolipoprotein E; Short=Apo-E; Flags: Precursor”, UniProtKB/Swiss-Prot: P02649.1, <https://www.ncbi.nlm.nih.gov/protein/P02649.1>, last visited Aug. 15, 2023, pp. 1-23 (23 pages total).
- “RecName: Full=Apoptosis-associated speck-like protein containing a Card; Short=hASC; AltName: Full=Caspase recruitment domain-containing protein 5; AltName: Full=PYD and Card domain-containing protein; AltName: Full=Target of methylation-induced silencing 1”, UniProtKB/Swiss-Prot: Q9ULZ3.2, <https://www.ncbi.nlm.nih.gov/protein/Q9ULZ3.2>, last visited Aug. 15, 2023, pp. 1-16 (16 pages total).
- Picken, “The Pathology of Amyloidosis in Classification: A Review”, *Acta Haematologica*, 2020, pp. 1-13 (13 pages total).
- Kabat et al., “Sequences of Proteins of Immunological Interest”, National Institute of Health, 1991, vol. 1, No. 5, (1,243 pages total).
- Altschul et al., “Basic Local Alignment Search Tool”, *J. Mol. Biol.*, 1990, vol. 215, pp. 403-410, (8 pages total).
- Shpaer, “GeneAssist”, *Methods in Molecular Biology*, 1997, vol. 70, pp. 173-187 (15 pages total).

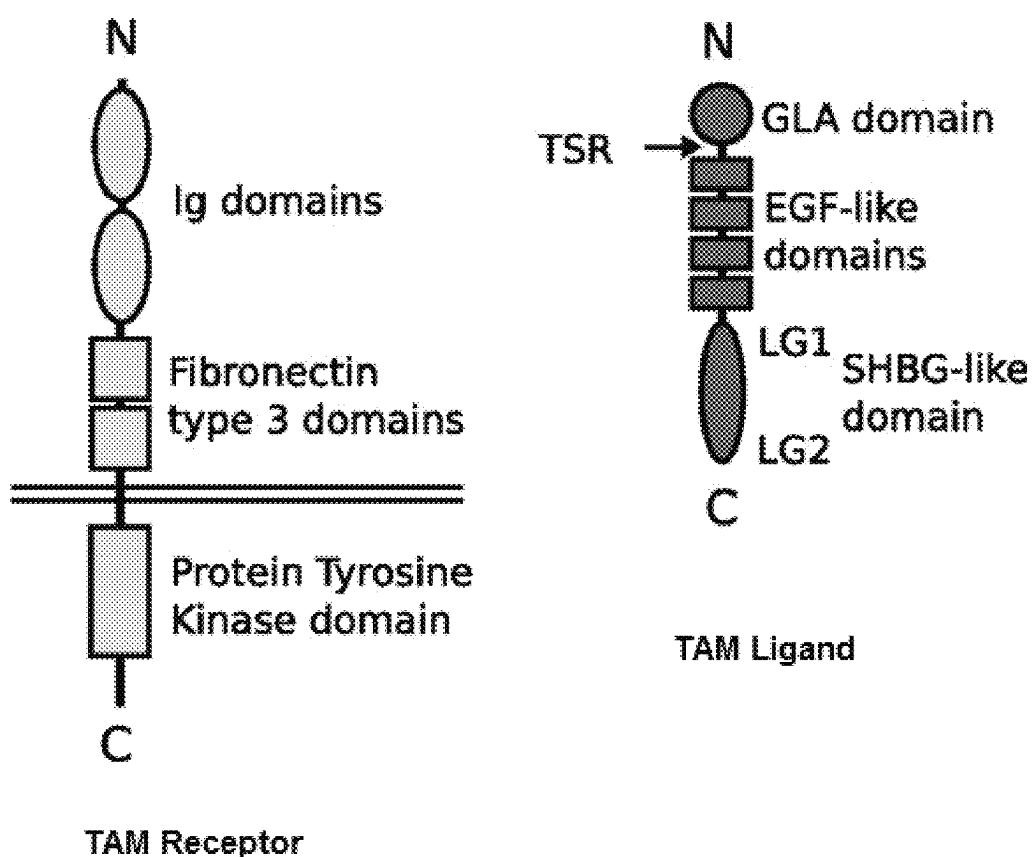
(56)

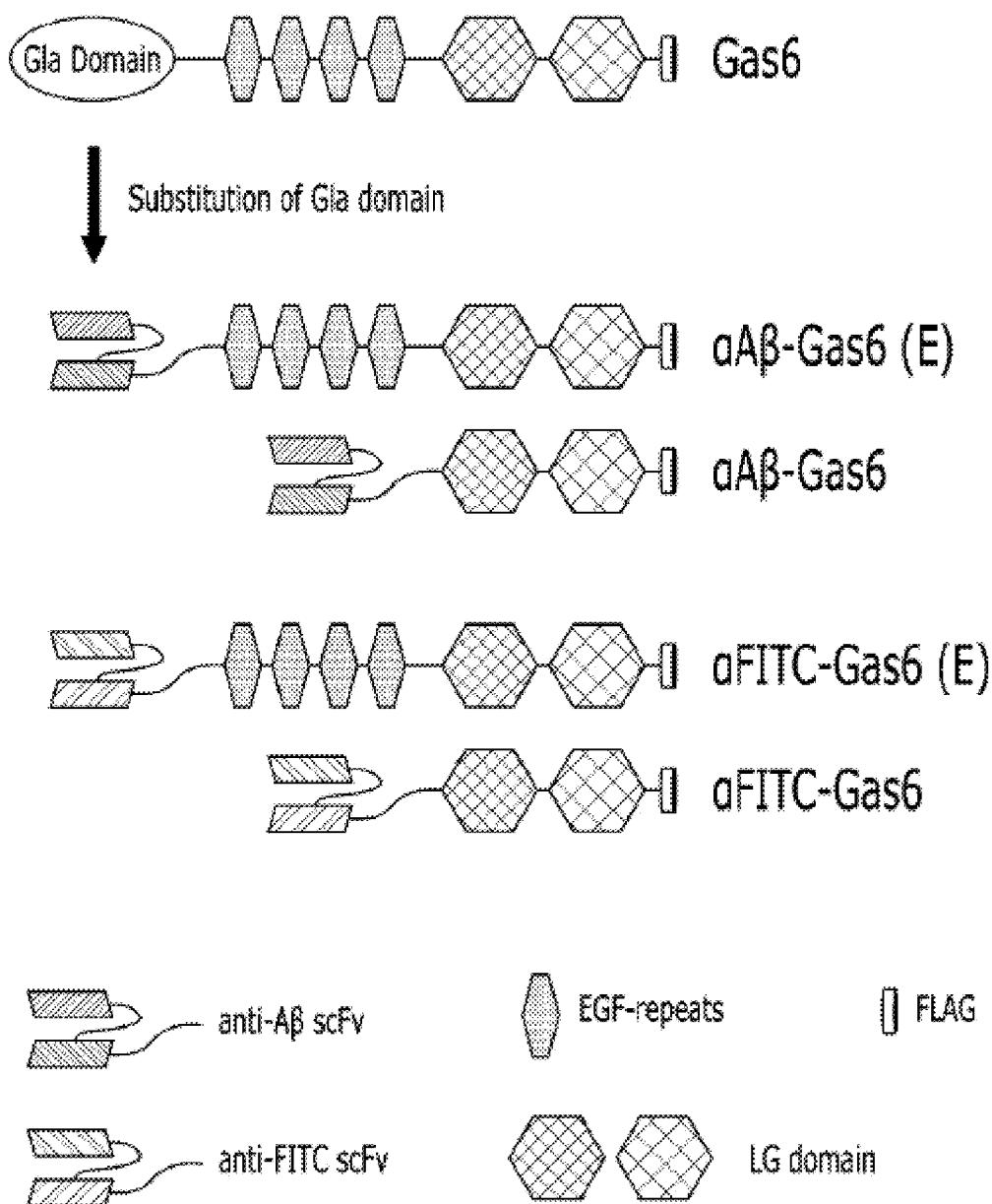
**References Cited****OTHER PUBLICATIONS**

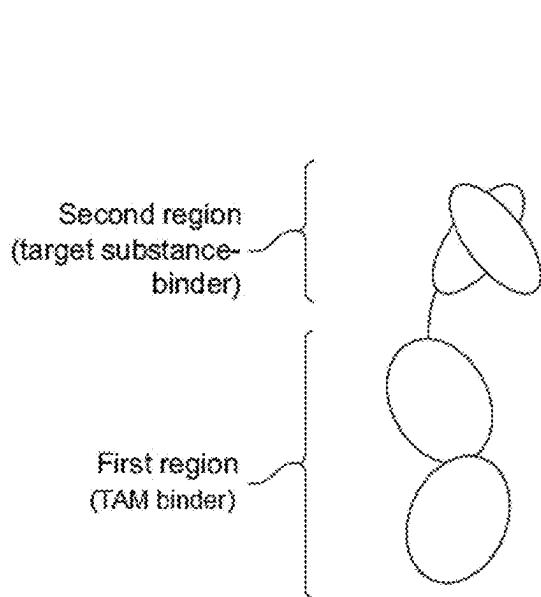
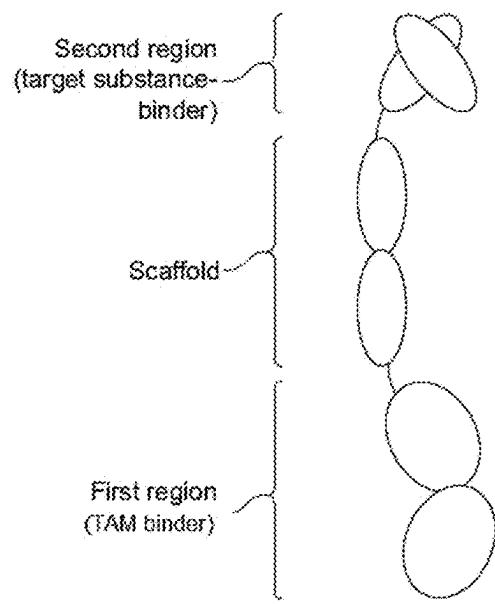
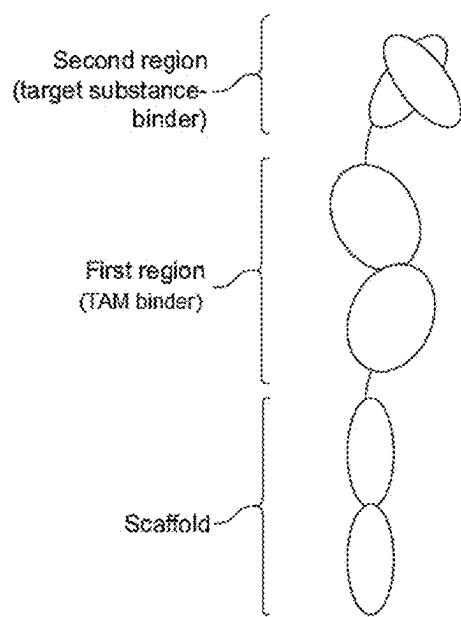
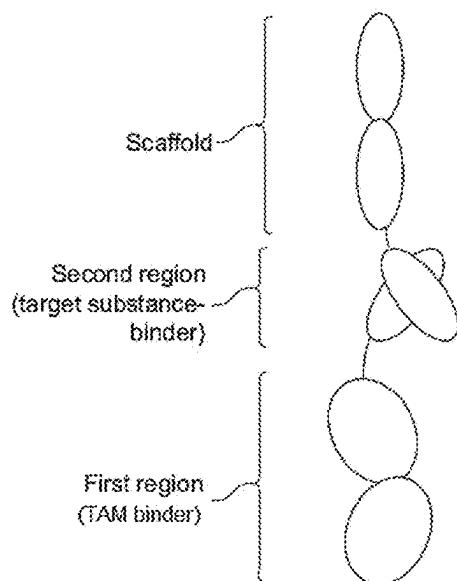
- Needleman et al., "A General Method Applicable to the Search for Similarities in the Amino Acid Sequence of Two Proteins", *J. Mol. Biol.*, 1970, vol. 48, pp. 443-453, (11 pages total).
- Hutchison et al., "Mutagenesis at a Specific Position in a DNA Sequence", *The Journal of Biological Chemistry*, 1978, vol. 253, No. 18, pp. 6551-6560, (10 pages total).
- Zoller et al., "Oligonucleotide-Directed Mutagenesis: A Simple Method Using Two Oligonucleotide Primers and a Single-Stranded DNA Template", *DNA*, 1984, vol. 3, No. 6, pp. 479-488, (10 pages total).
- Oliphant et al., "Cloning of random-sequence oligodeoxynucleotides", *Gene*, 1986, vol. 44, 177-183, (7 pages total).
- Geng et al., "Requirement of Gamma-Carboxyglutamic Acid Modification and Phosphatidylserine Binding for the Activation of Tyro3, Axl, and Merk Receptors by Growth Arrest-Specific 6", *Frontiers in Immunology*, vol. 8, Article 1521, Nov. 2017.
- Lew et al., "Differential TAM receptor-ligand-phospholipid interactions delimit differential TAM bioactivities", *eLife* 2014;3:e03385. DOI: 10.7554/eLife.03385.
- Hasanbasic et al., The role of  $\gamma$ -carboxylation in the anti-apoptotic function of gas6, *Journal of Thrombosis and Haemostasis*, 2005, pp. 2790-2797.
- Hall et al., "Gas6 Binding to Photoreceptor Outer Segments Requires  $\gamma$ -Carboxyglutamic Acid (Gla) and Ca<sup>2+</sup> and is Required for OS Phagocytosis by RPE Cells in vitro", *Exp. Eye Res.*, 2002, 75, pp. 391-400.
- Nakano et al., "Requirement of  $\gamma$ -carboxyglutamic acid residues for the biological activity of Gas6: contribution of endogenous Gas6 to the proliferation of vascular smooth muscle cells", *Biochem. J.*, 1997, 323, pp. 387-392.
- Rajotte et al., "Gas6-mediated signaling is dependent on the engagement of its gamma-carboxyglutamic acid domain with phosphatidylserine", *Biochemical and Biophysical Research Communications*, 376, 2008, pp. 70-73.
- Dransfield et al., "Mer receptor tyrosine kinase mediates both tethering and phagocytosis of apoptotic cells", *Cell Death and Disease*, 2015, 6, e1646; doi:10.1038/cddis.2015.18.
- Lemke, "Phosphatidylserine Is the Signal for TAM Receptors and Their Ligands", *Trends in Biochemical Sciences*, Sep. 2017, vol. 42, No. 9, pp. 738-748.
- Moon, "Curcumin in Cancer and Inflammation: An In-Depth Exploration of Molecular Interactions, Therapeutic Potentials, and the Role in Disease Management", *Int. J. Mol. Sci.* 2024, 25, 2911.
- Asadian et al., "The therapeutic effect of GAS6 in remyelination is dependent upon Tyro3", *Glia*. 2024; 1-10, DOI: 10.1002/glia.24534.
- Grondal et al., "Dynamic changes in immune cell populations by AXL kinase targeting diminish liver inflammation and fibrosis in experimental MASH", *Frontiers in Immunology*, 15:1400553. doi: 10.3389/fimmu.2024.1400553, May 16, 2024.
- Burstyn-Cohen et al., "TAM receptors in phagocytosis: Beyond the mere internalization of particles", *Immunological Reviews*, 2023;319, pp. 7-26.
- Tutusaus et al., "GAS6/TAM Axis as Therapeutic Target in Liver Diseases", *Seminars in Liver Disease*, vol. 44, No. Jan. 2024, 2024, pp. 99-114.
- Miao et al., "Therapeutic targeting of the functionally elusive TAM receptor family", *Nature Reviews Drug Discovery*, vol. 23, Mar. 2024, pp. 201-217.
- Zhuang et al., "Phosphatidylserine in the Nervous System: Cytoplasmic Regulator of the AKT and PKC Signaling Pathways and Extracellular "Eat-Me" Signal in Microglial Phagocytosis", *Molecular Neurobiology*, 2023, 60, pp. 1050-1066.
- Zhou et al., "An insight into the TAM system in Alzheimer's disease", *International Immunopharmacology*, 116, 2023, 109791.
- Prasad et al., "TAM receptor function in the retinal pigment epithelium", *Mol. Cell. Neurosci.*, 33, 2006, pp. 96-10.
- Burstyn-Cohen et al., "TAM receptors, Phosphatidylserine, inflammation, and Cancer", *Cell Communication and Signaling*, 2019, 17:156.
- McCloskey et al., "GAS6 Mediates Adhesion of Cells Expressing the Receptor Tyrosine Kinase Axl", *The Journal of Biological Chemistry*, vol. 272, No. 37, Sep. 12, 1997, pp. 23285-23291.
- Sasaki et al., "Structural basis for Gas6-Axl signaling", *The EMBO Journal*, vol. 25, No. 1, 2006, pp. 80-87.
- Owlett, Laura, "Modulation of acute inflammation and Alzheimer's disease pathology by Gas6-Axl interaction", Submitted in Partial Fulfillment of the Requirements for the Degree Neurobiology and Anatomy, University of Rochester, Rochester, New York, 2020.

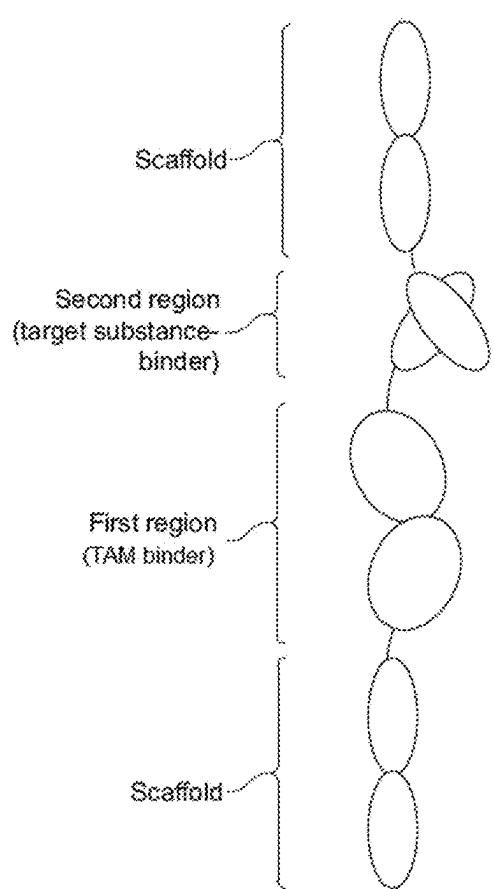
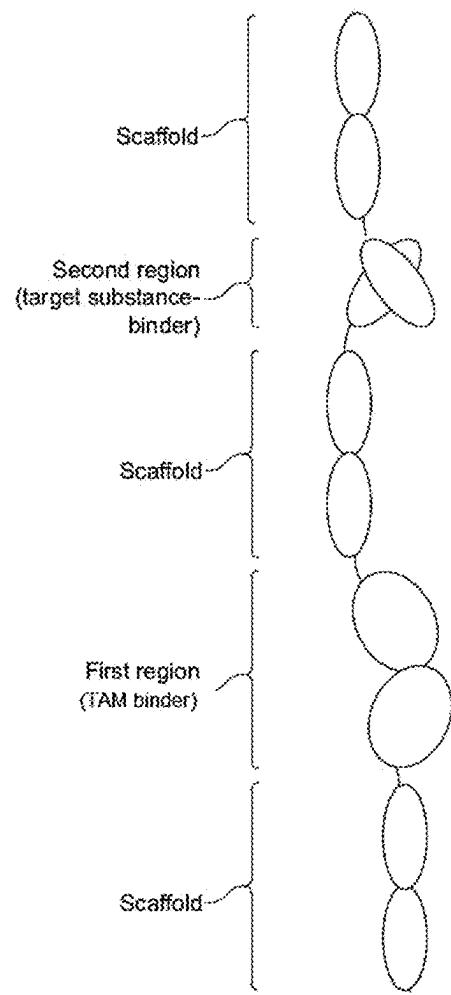
\* cited by examiner

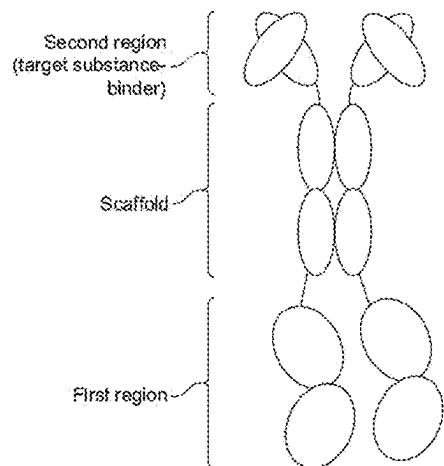
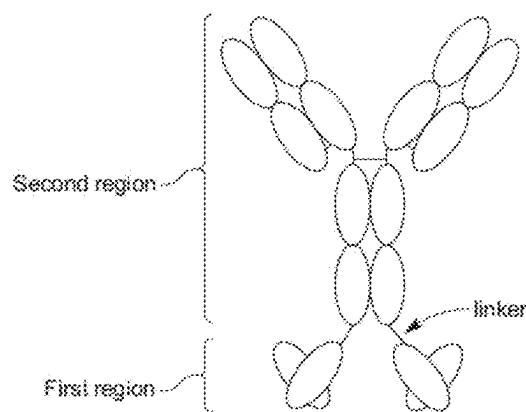
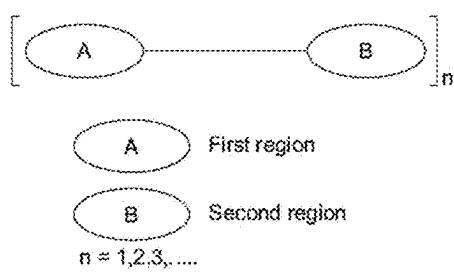
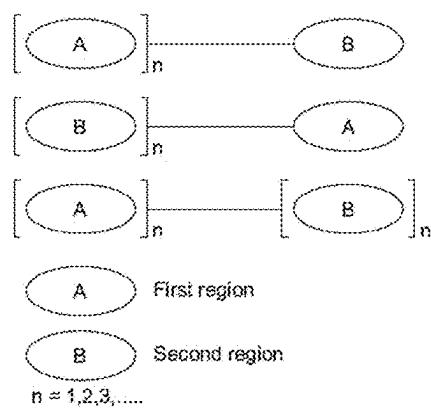
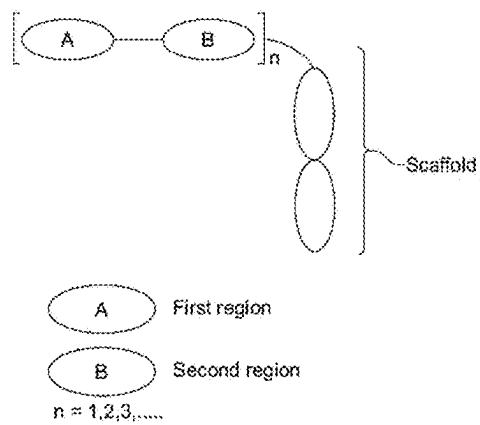
**FIG. 1A**  
**--Prior Art--**

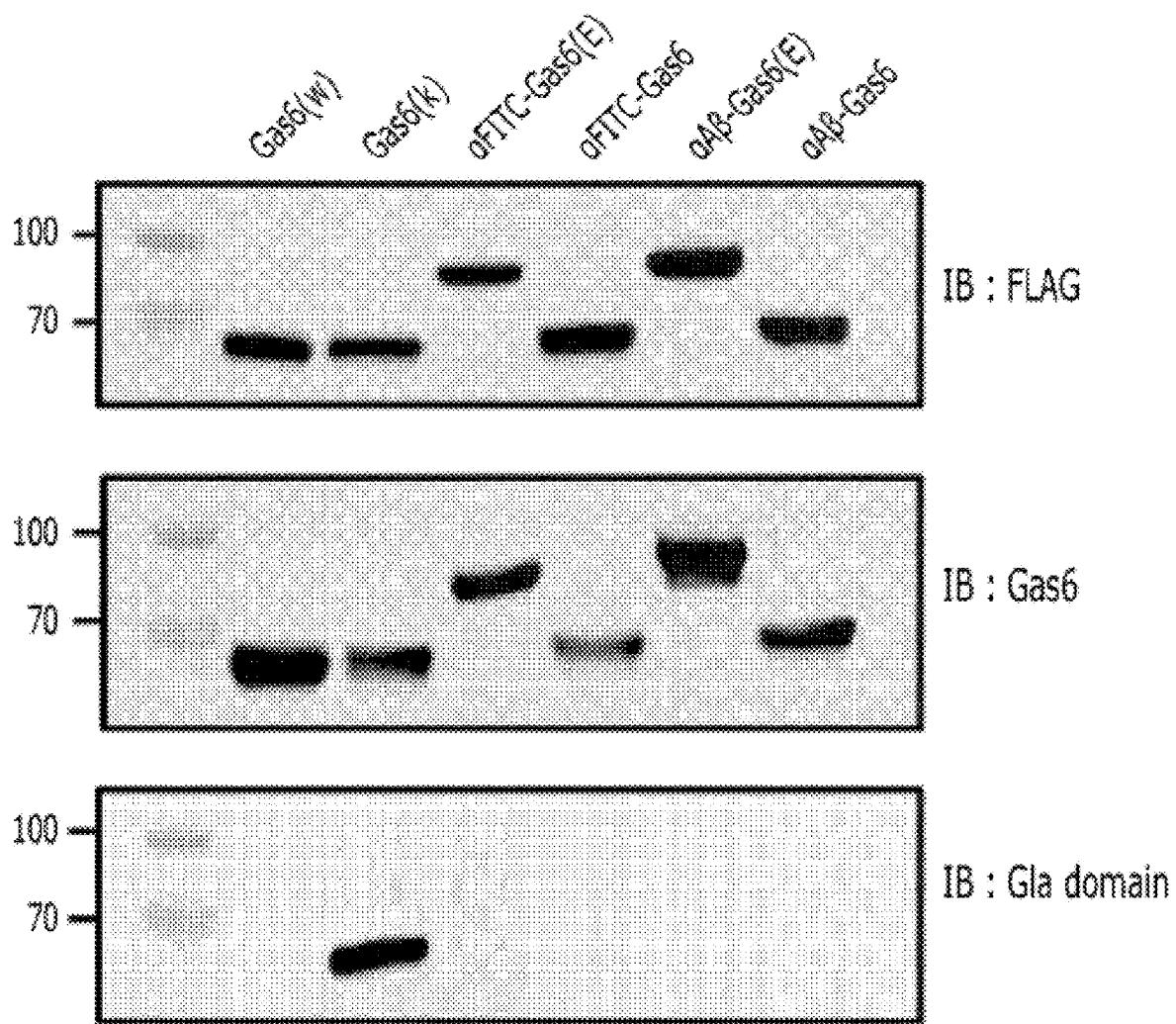


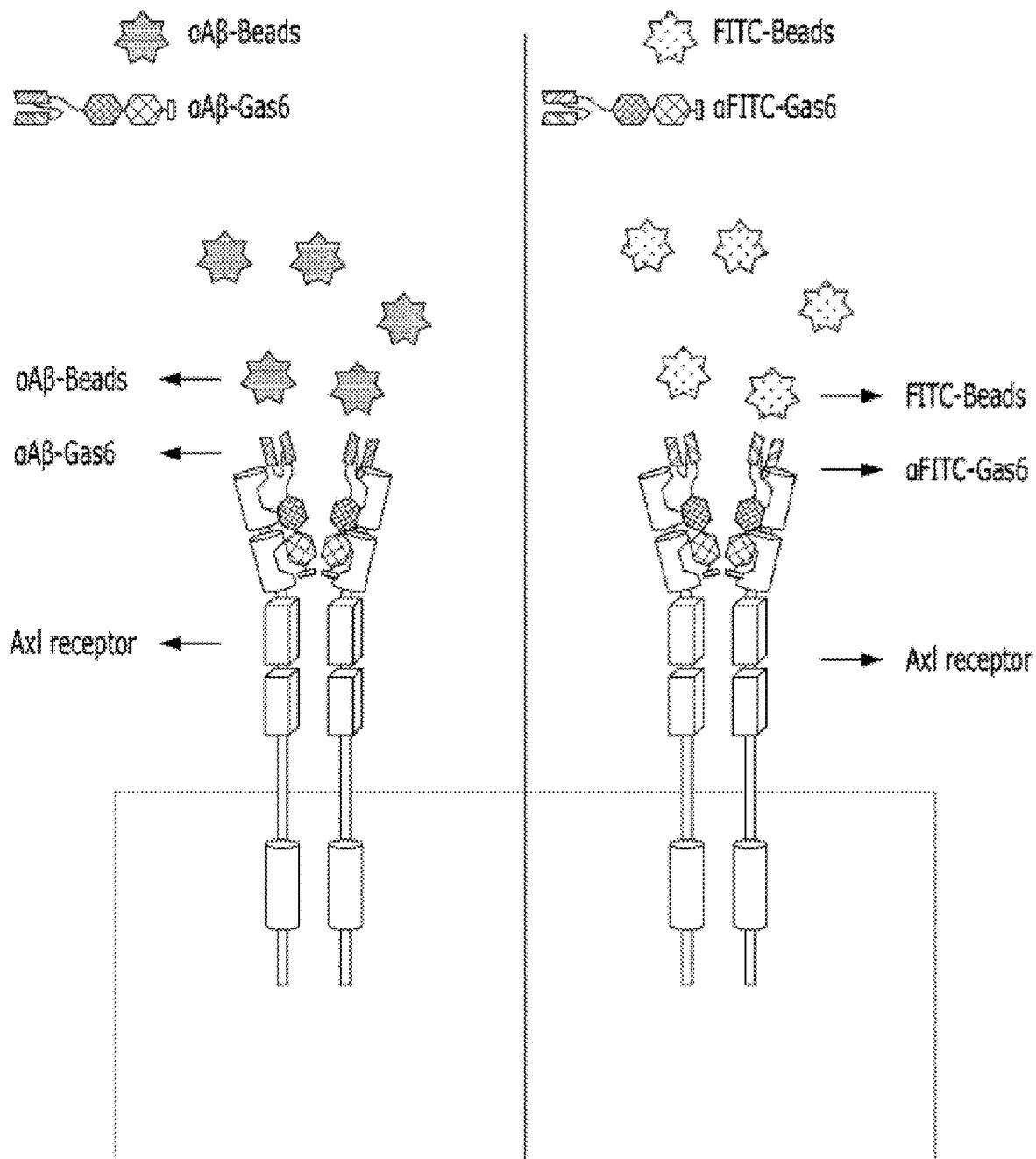
**FIG. 1B**

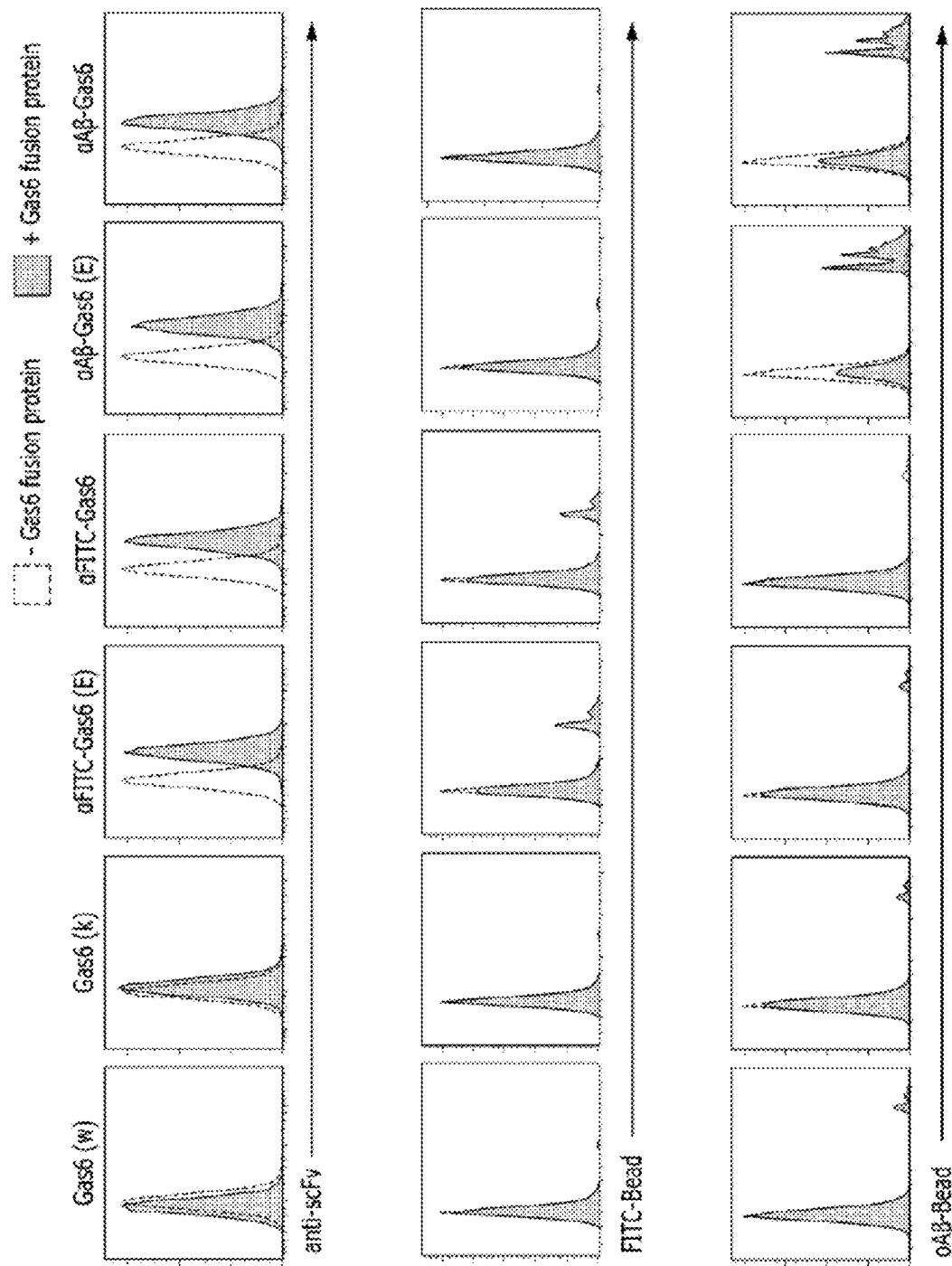
**FIG. 1C****FIG. 1D****FIG. 1E****FIG. 1F**

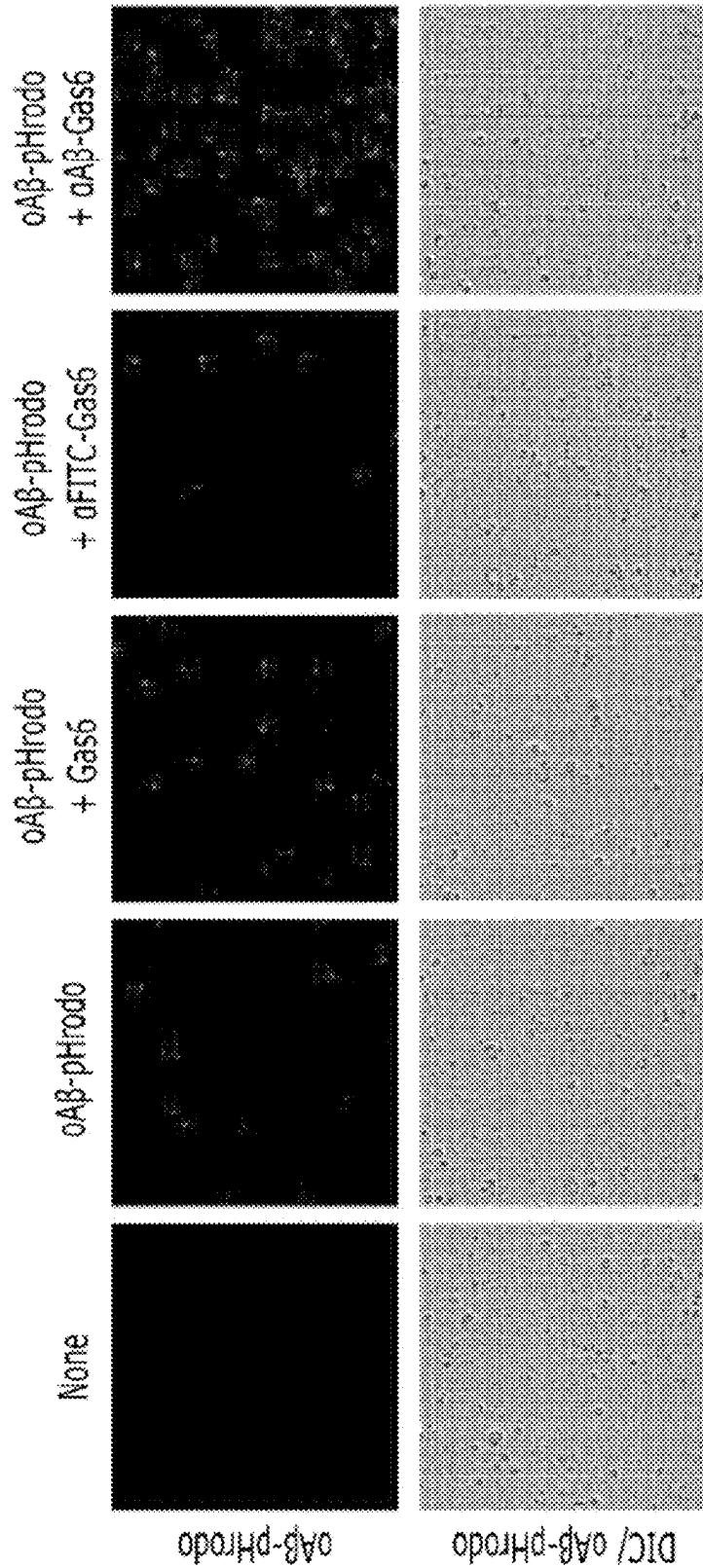
**FIG. 1G****FIG. 1H**

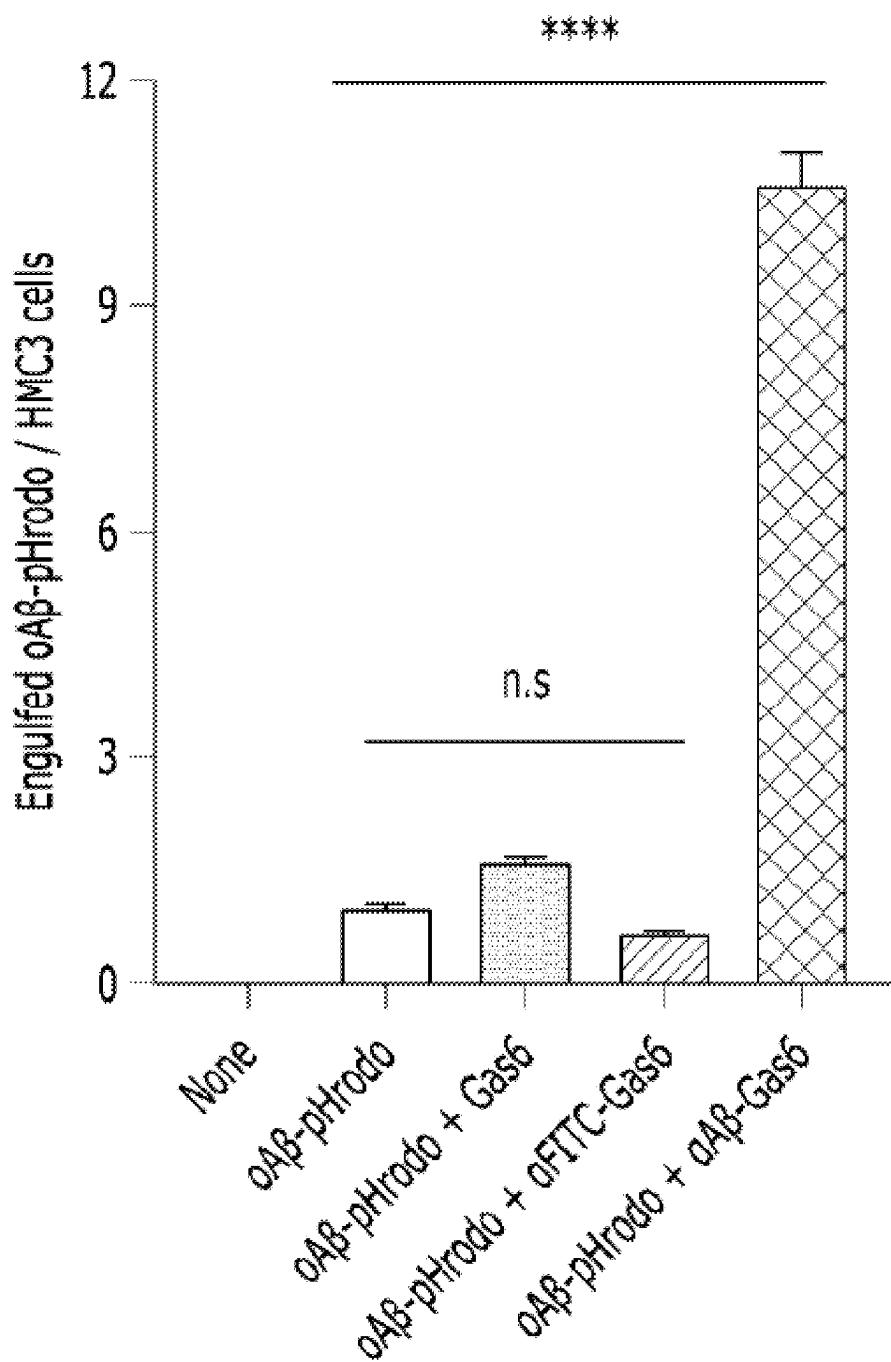
**FIG. 1I****FIG. 1J****FIG. 1K****FIG. 1L****FIG. 1M**

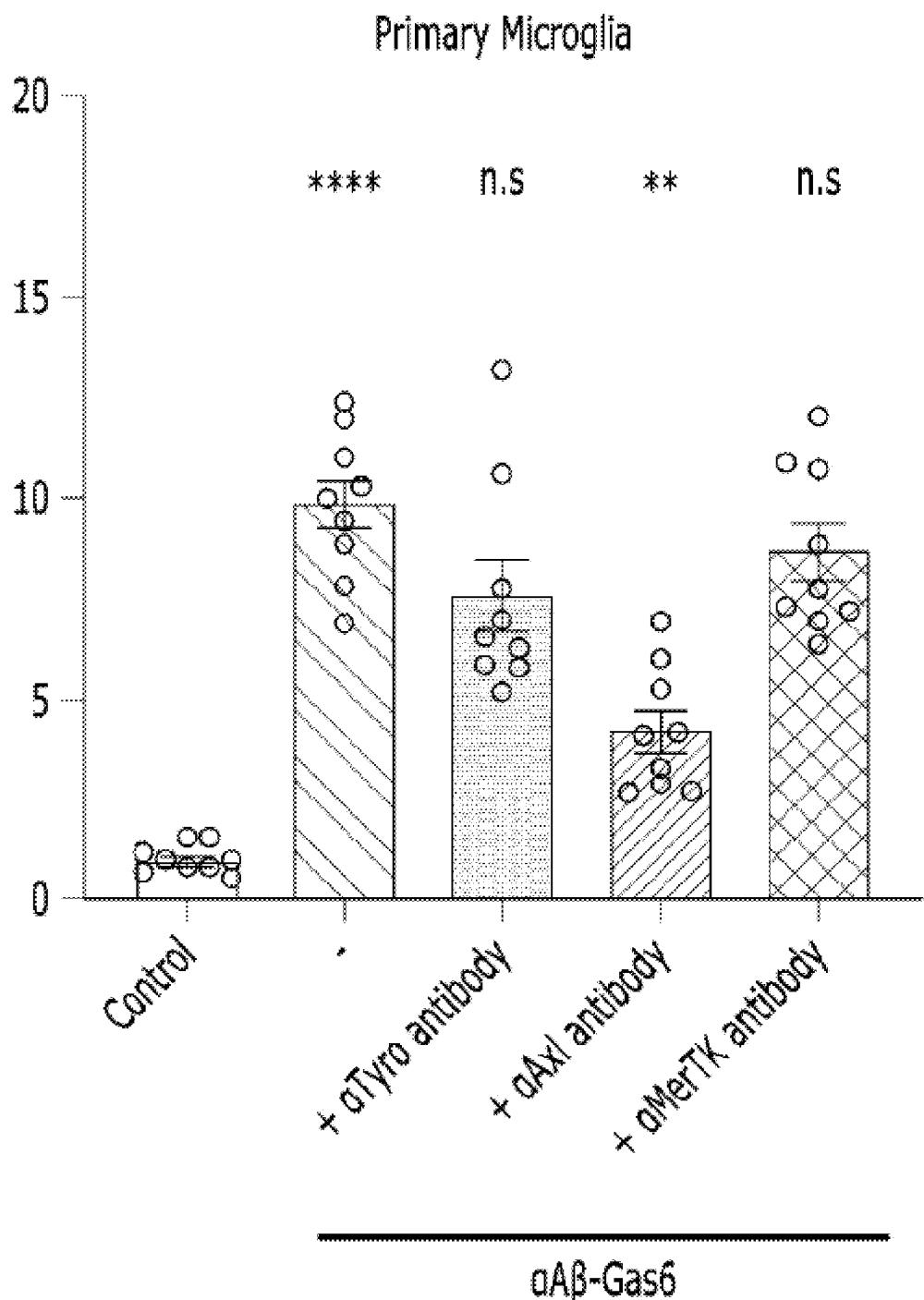
**FIG. 2**

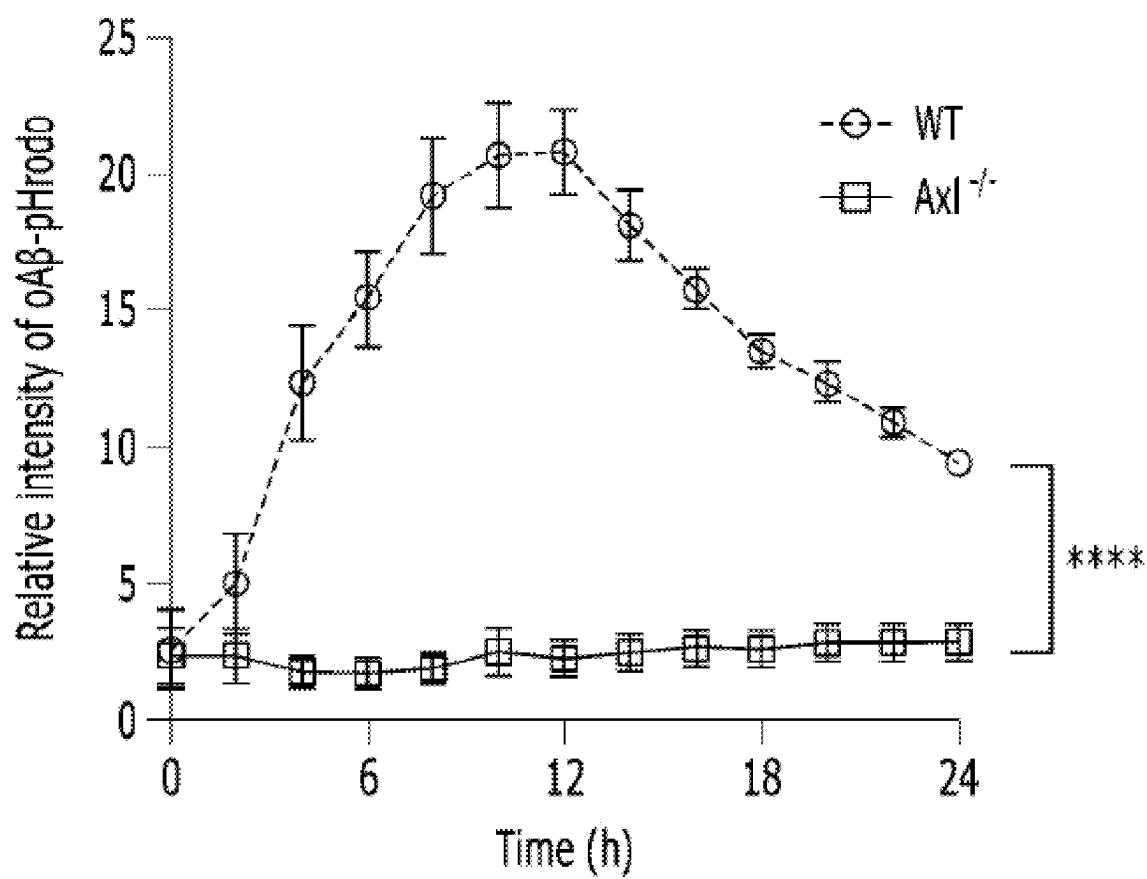
**FIG. 3**

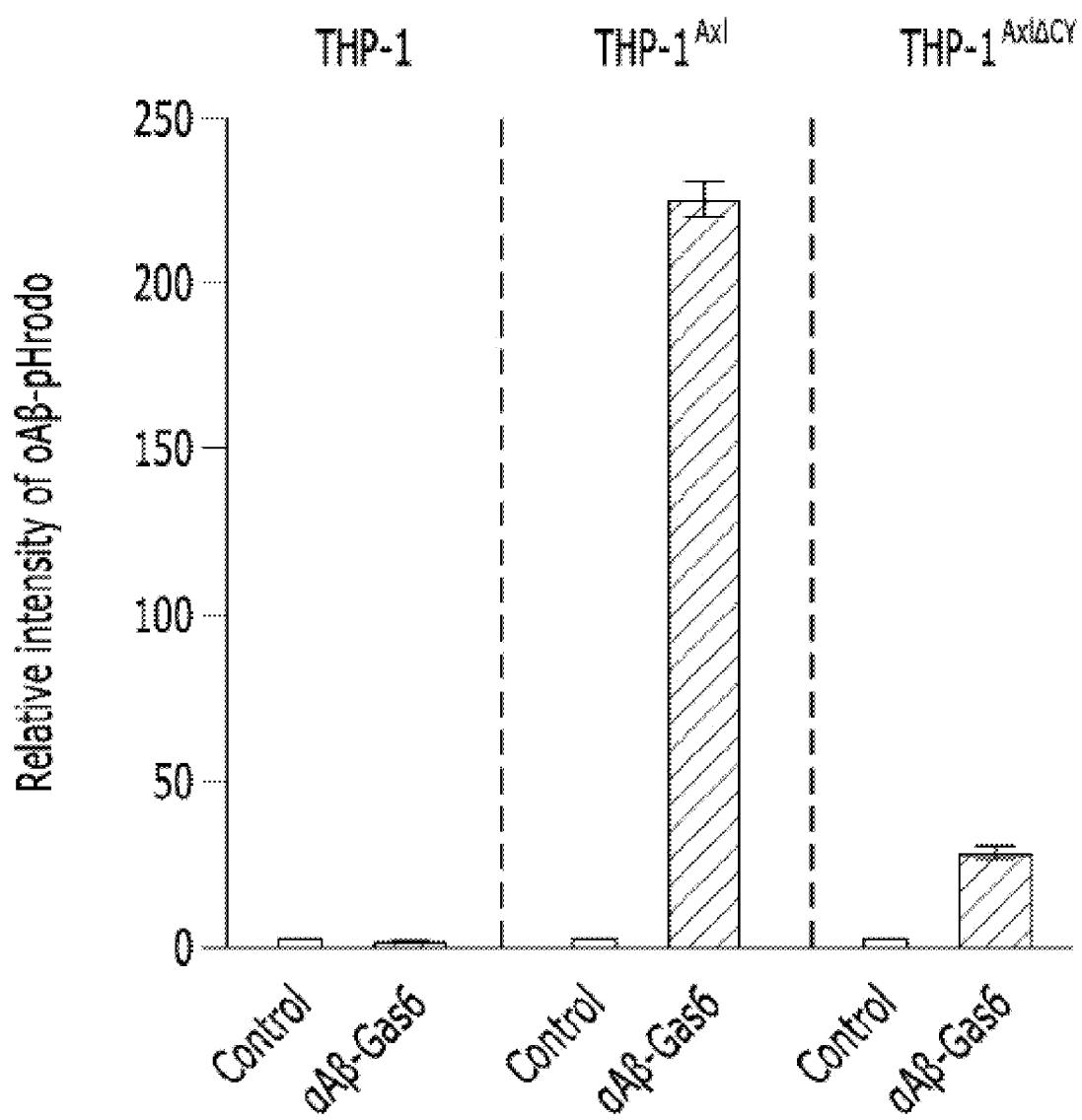
**FIG. 4**

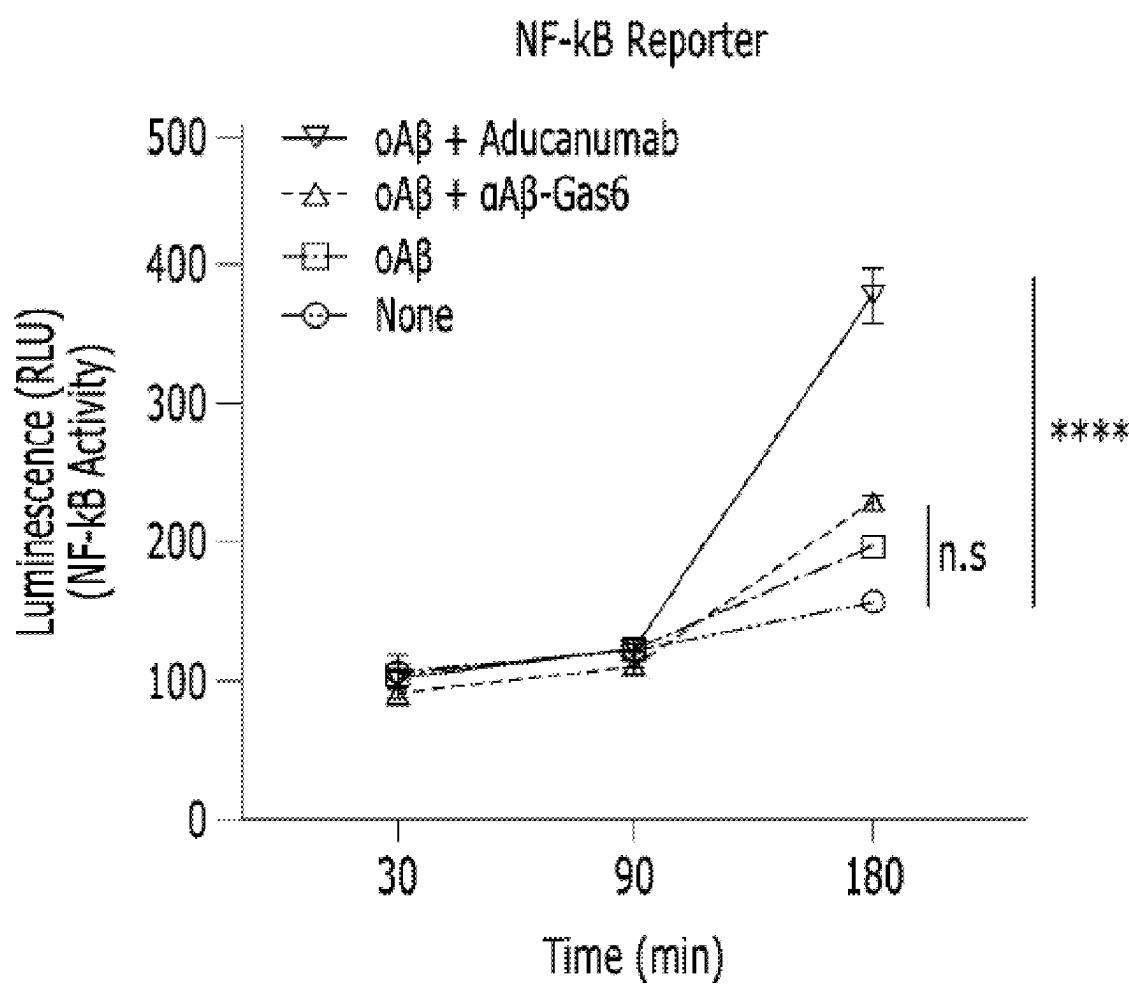
**FIG. 5**

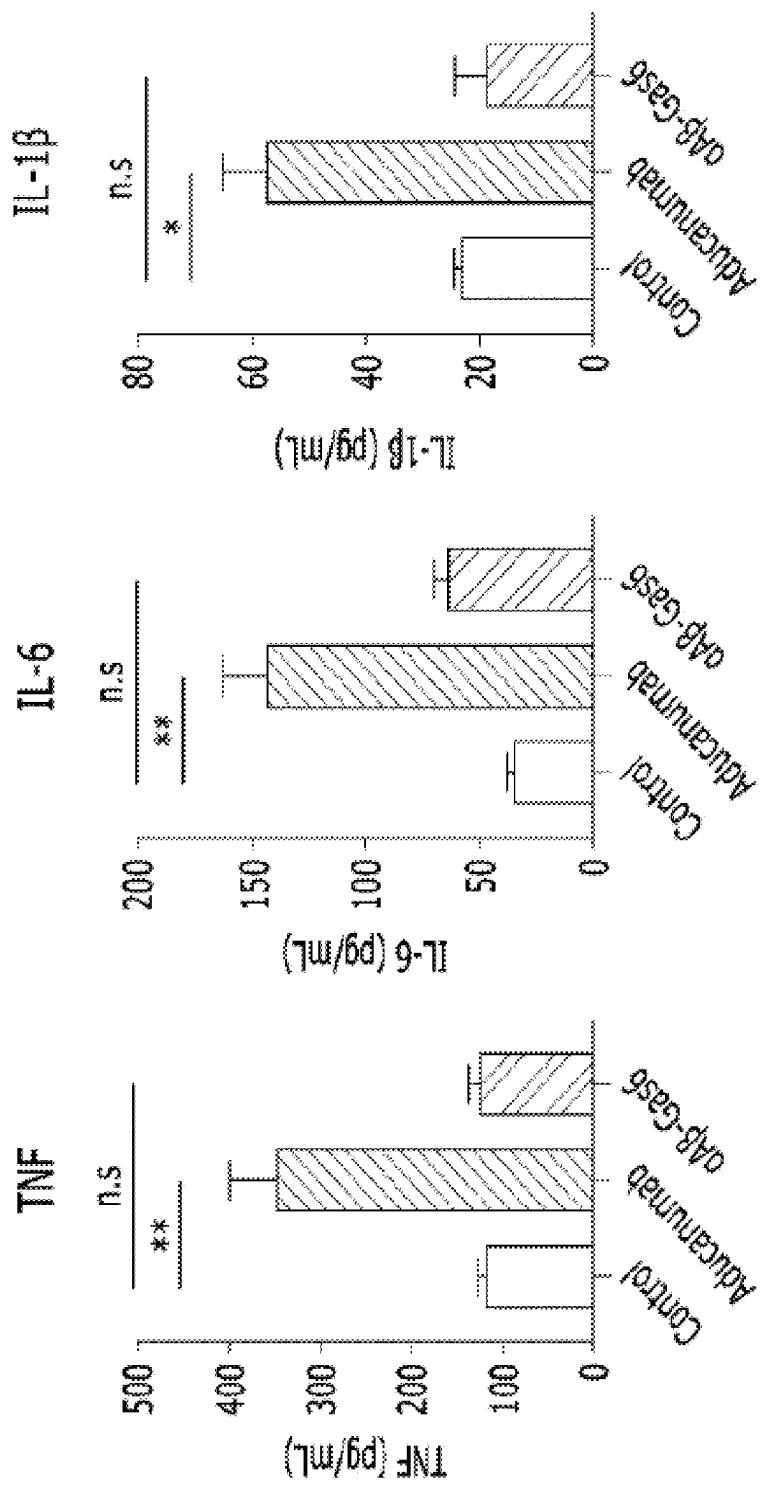
**FIG. 6**

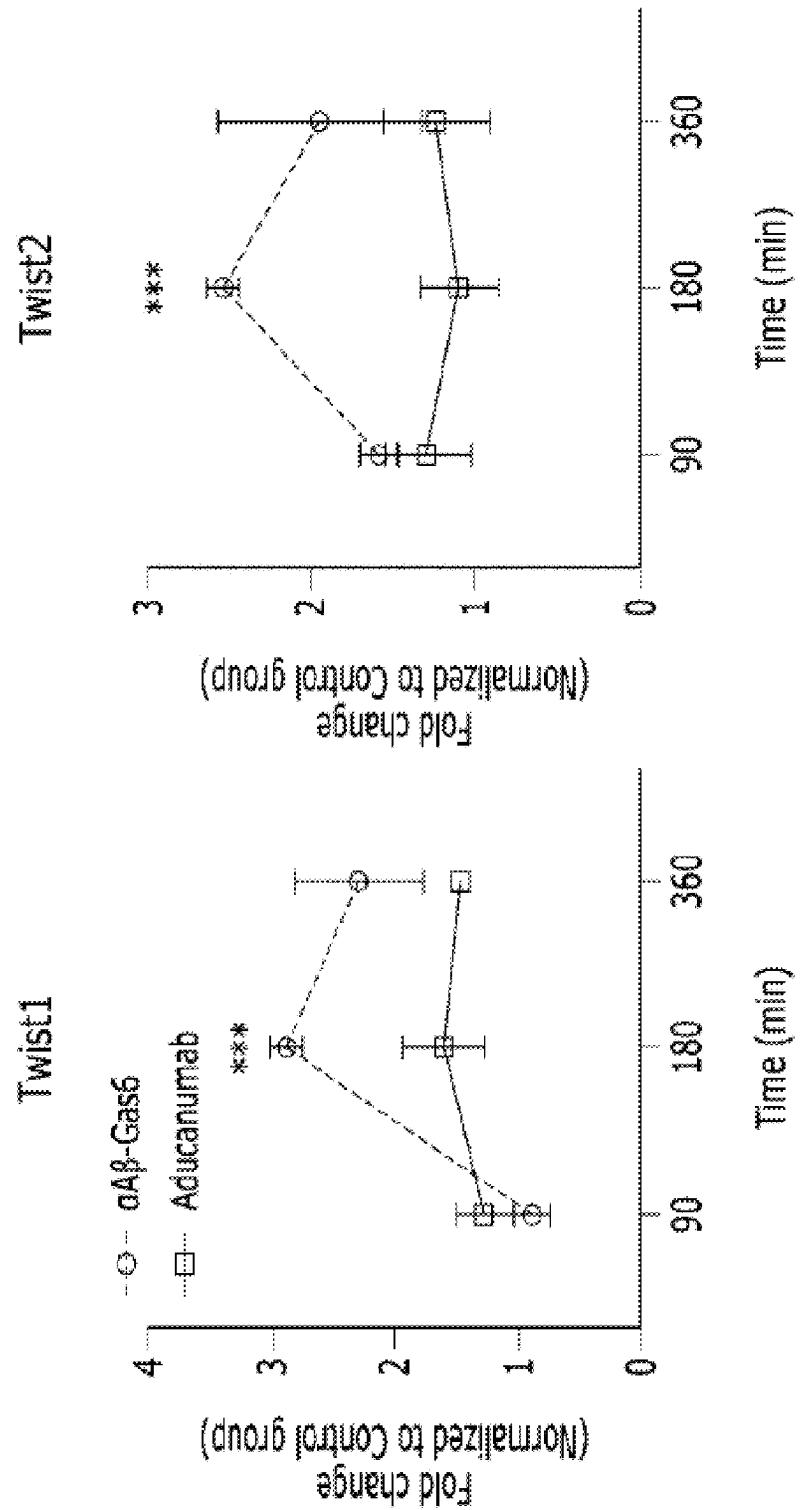
**FIG. 7**

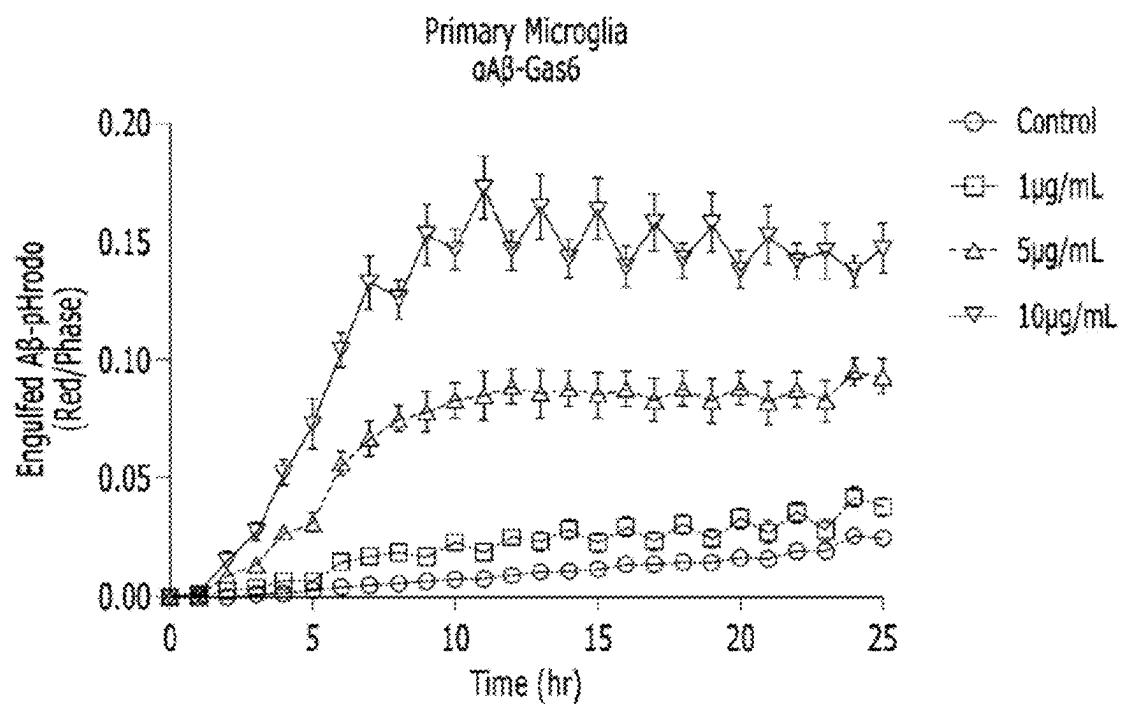
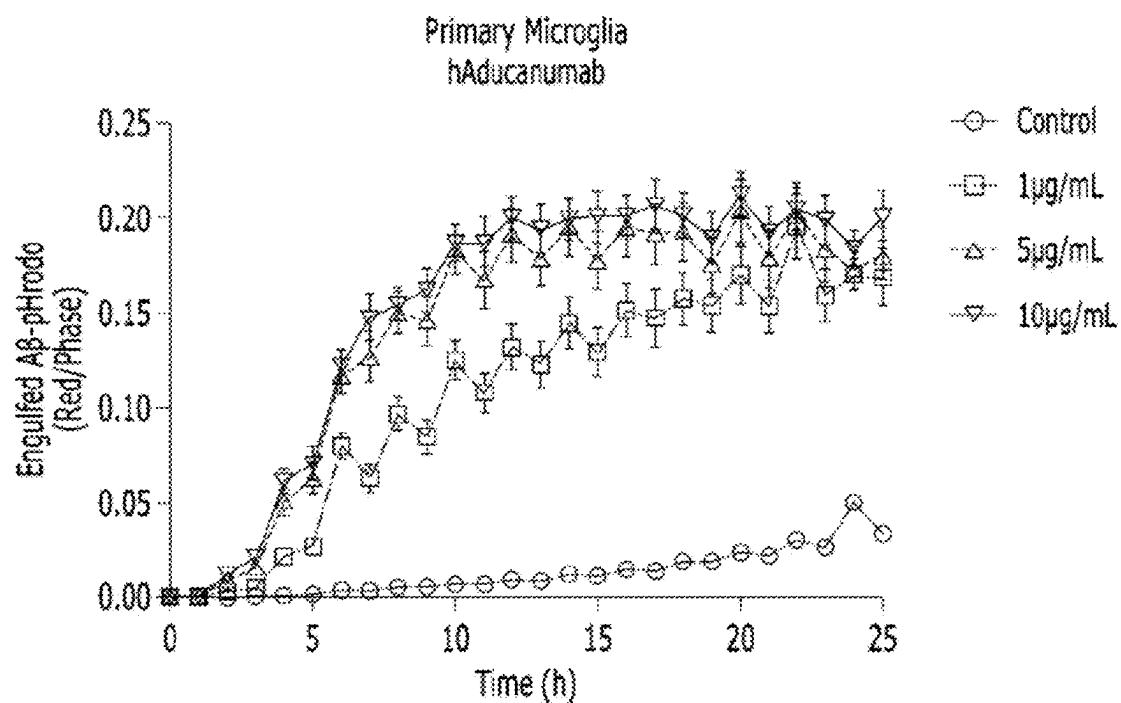
**FIG. 8****aA $\beta$ -Gas6**

**FIG. 9**

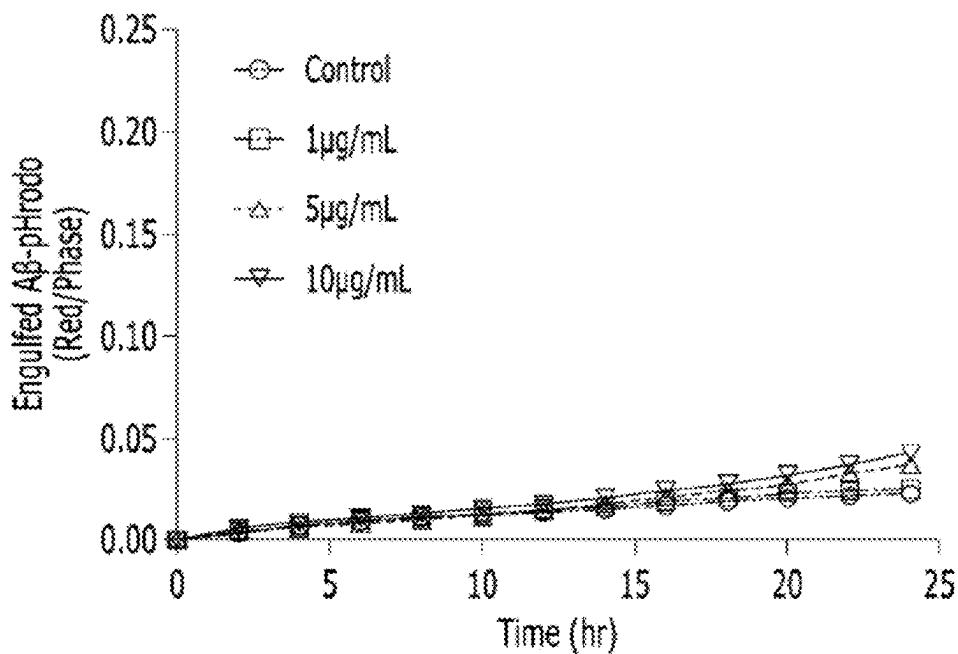
**FIG. 10**

**FIG. 11**

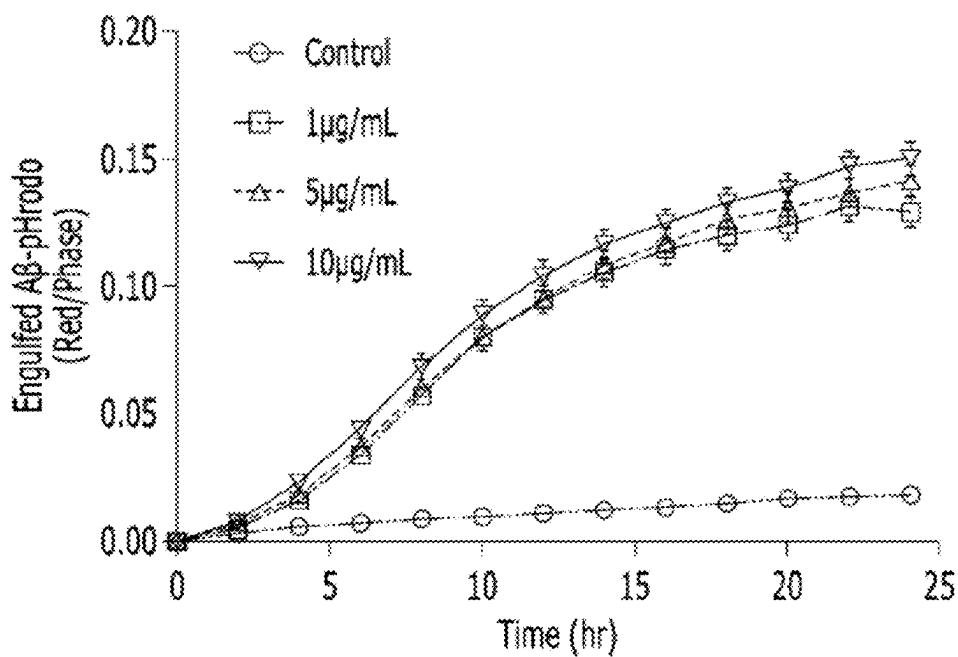
**FIG. 12**

**FIG. 13**

**FIG. 14**  
Primary Astrocyte  
hAducanumab

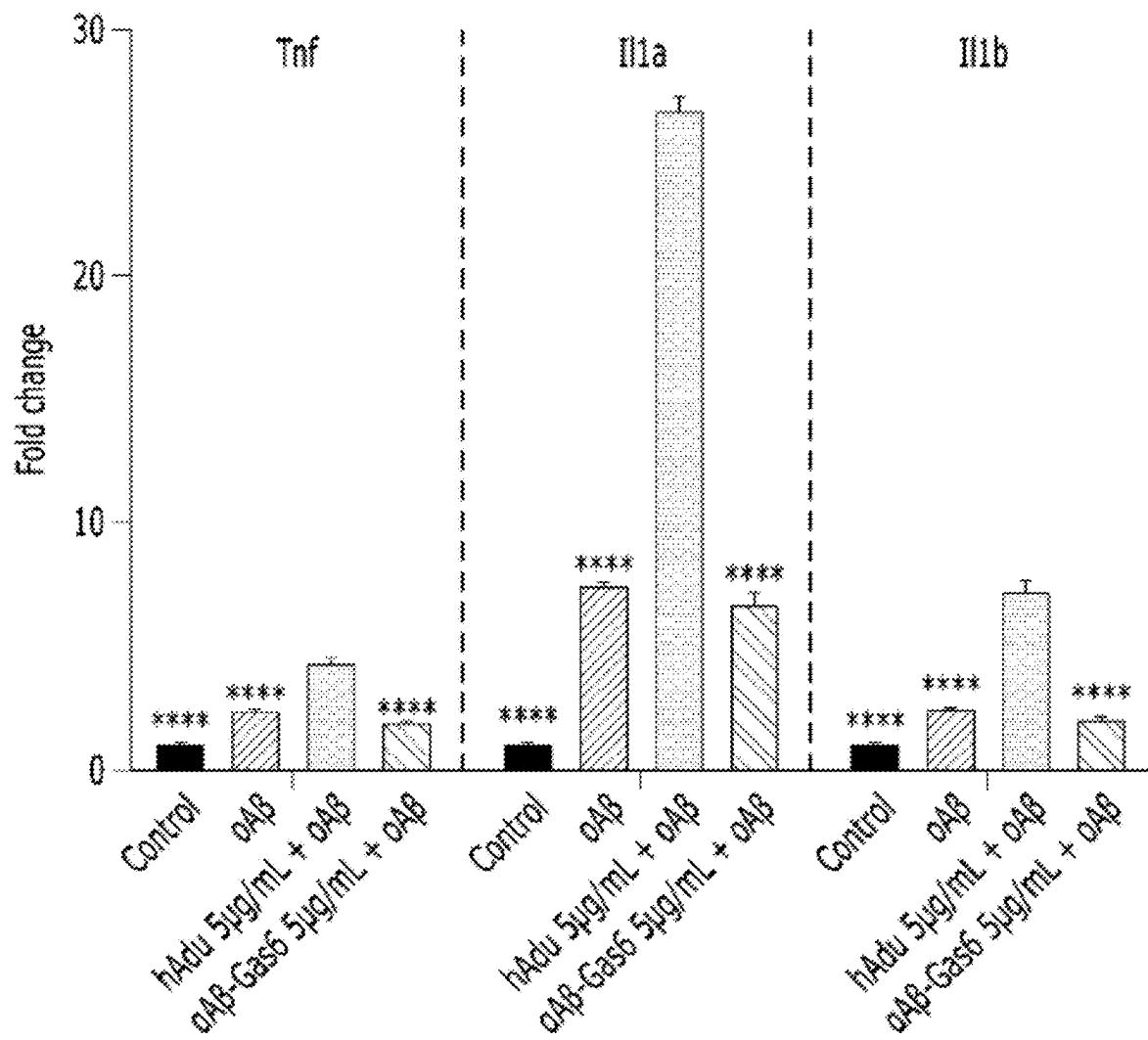


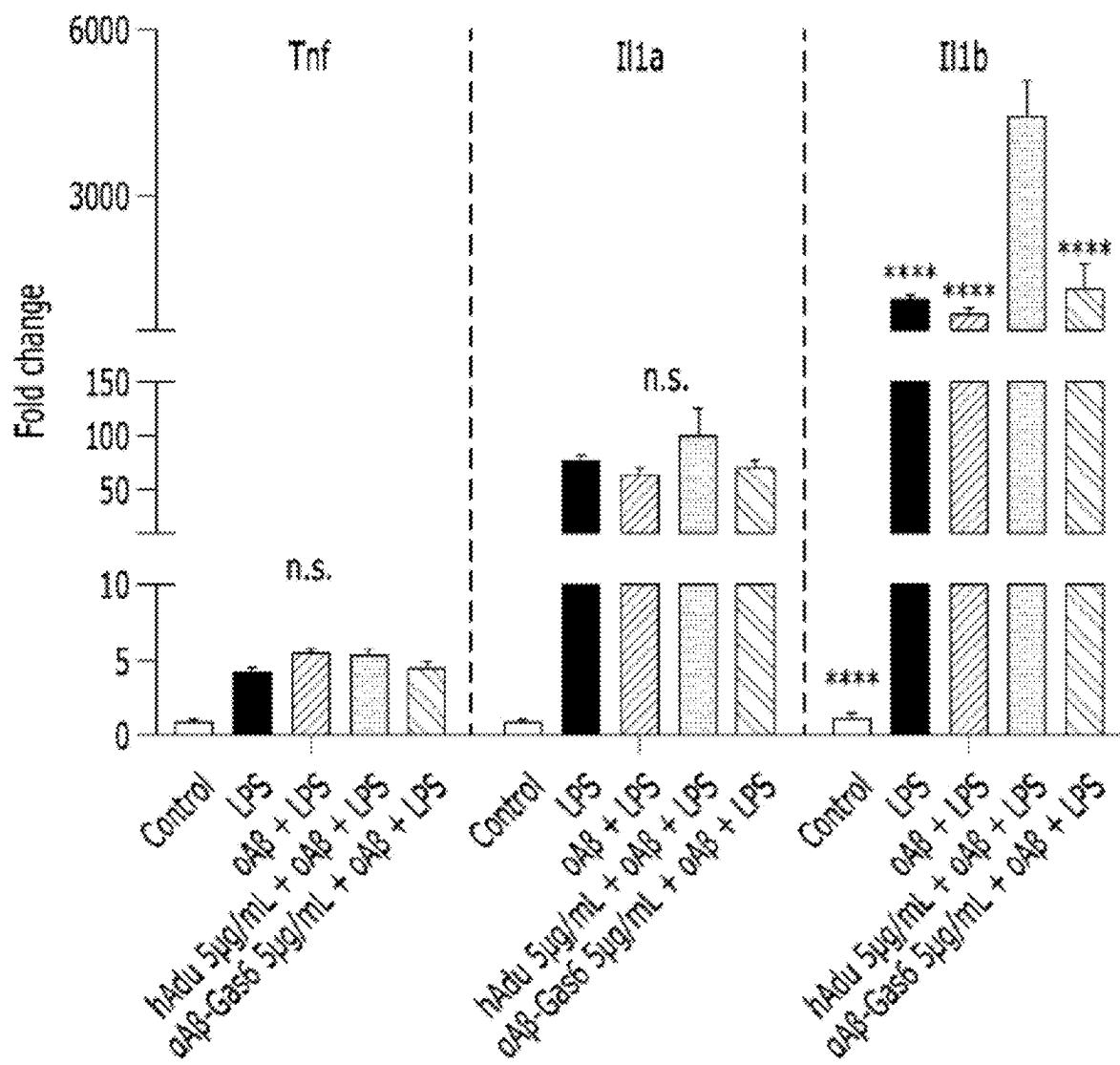
Primary Astrocyte  
oA $\beta$ -Gas6



**FIG. 15**

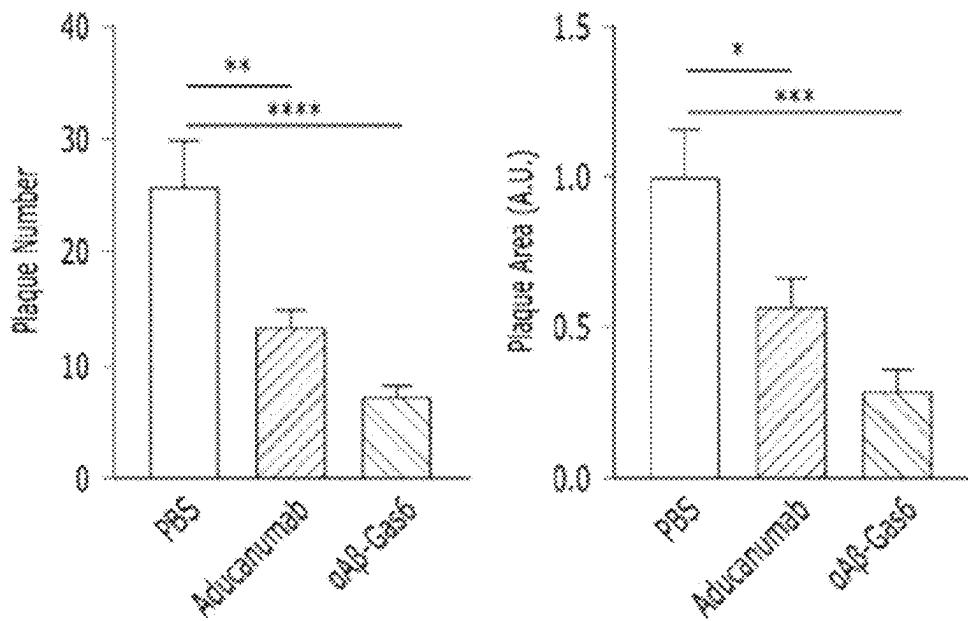
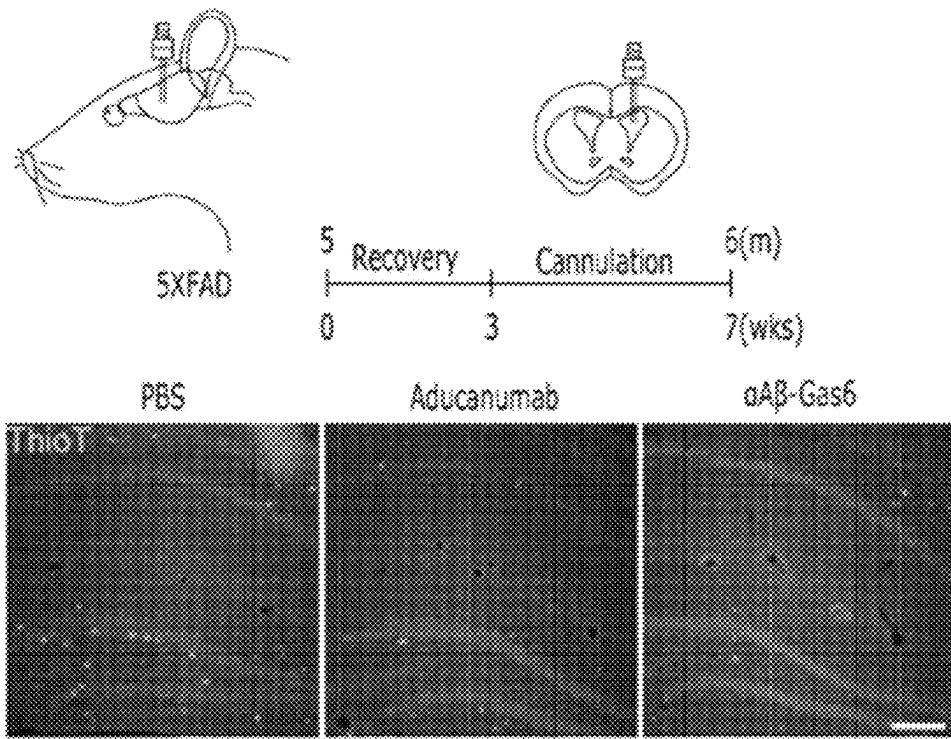
**Primary Astrocyte  
Inflammatory Cytokines**



**FIG. 16****BV2**  
**Inflammatory Cytokine**

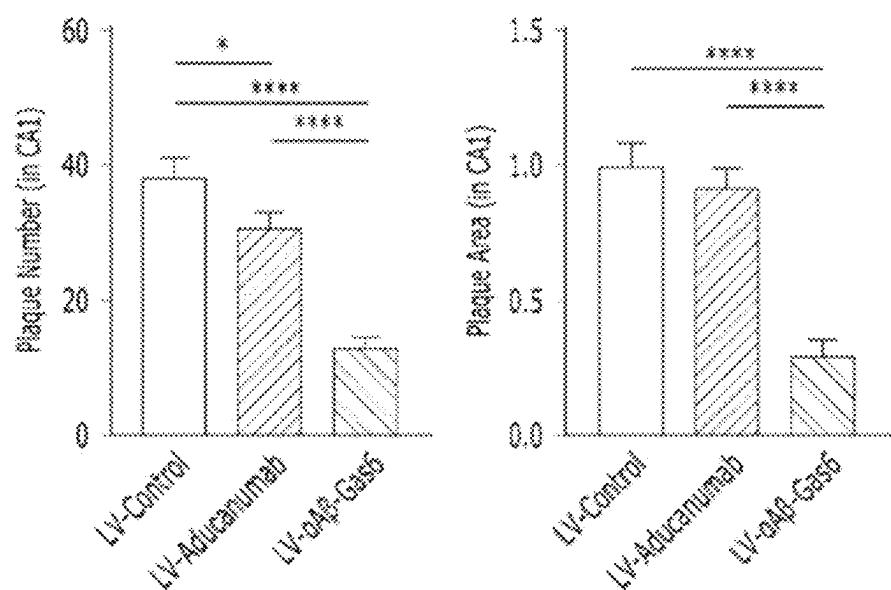
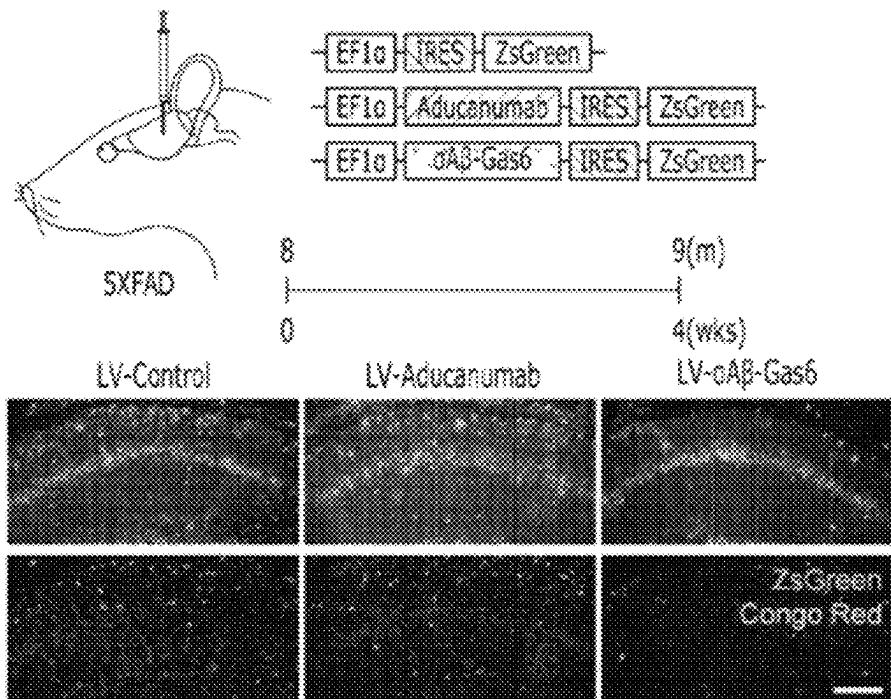
**FIG. 17**

Administration of  
 $\alpha\text{A}\beta\text{-Gas6}$  Fusion Protein



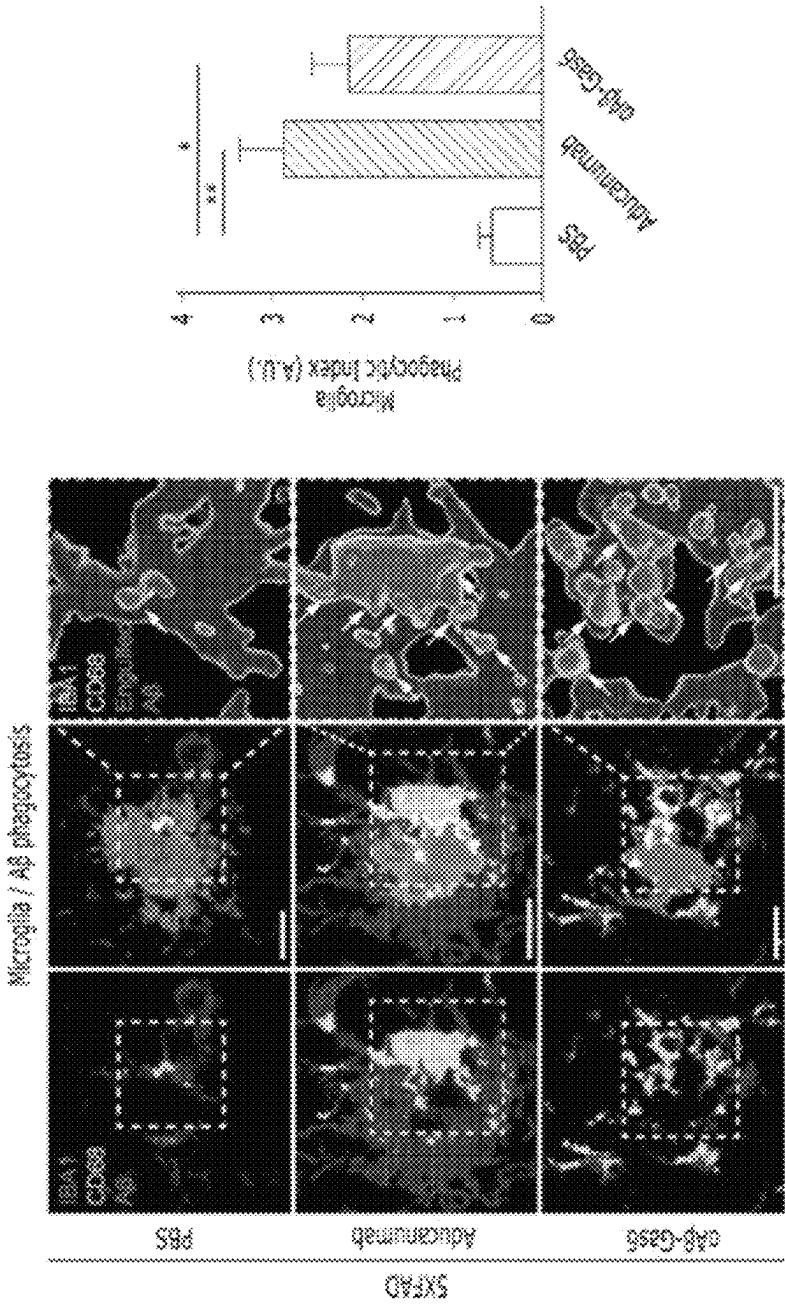
**FIG. 18**

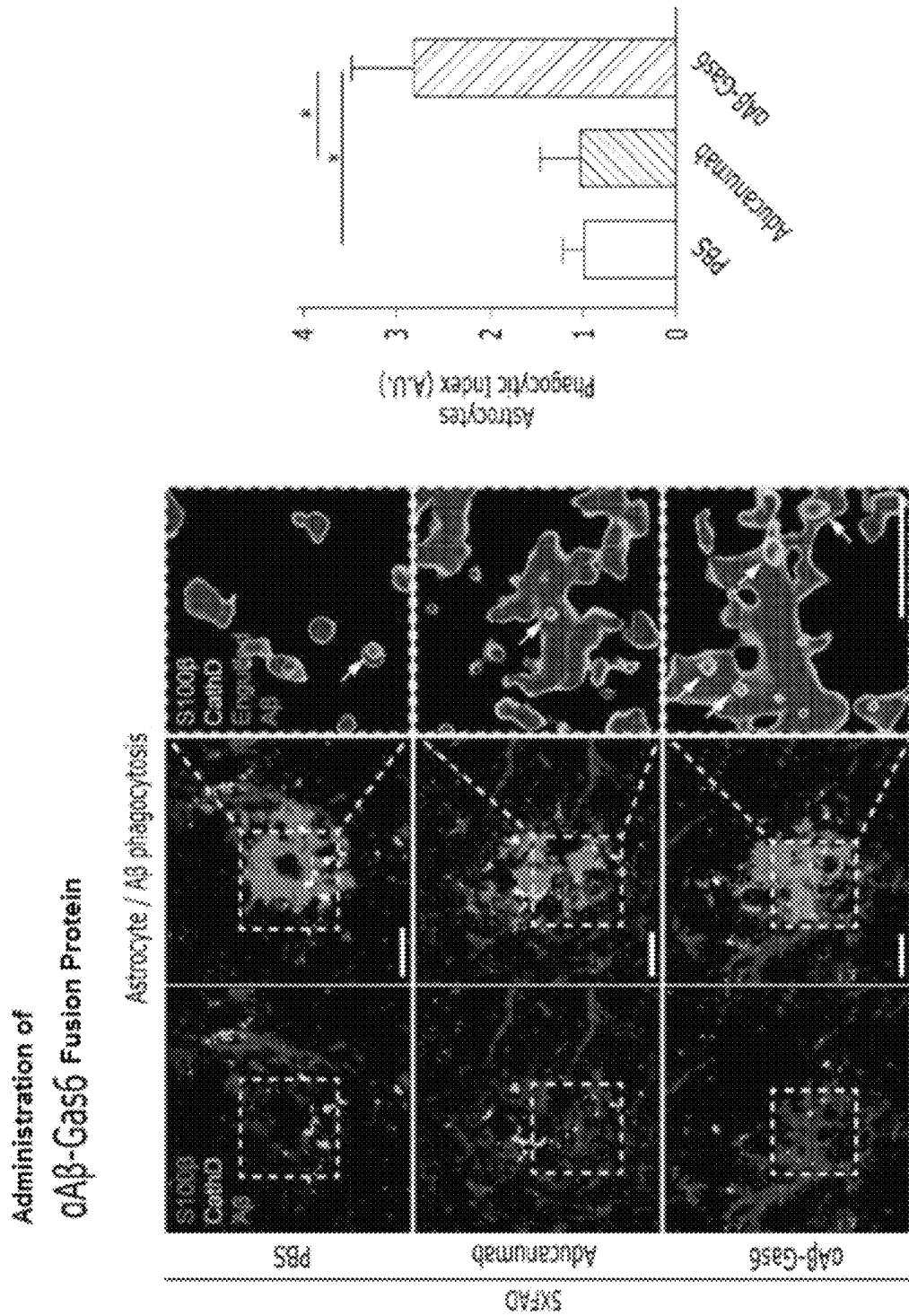
Administration of virus carrying  
 $\alpha\text{A}\beta\text{-Gas6}$  - encoding gene



**FIG. 19**

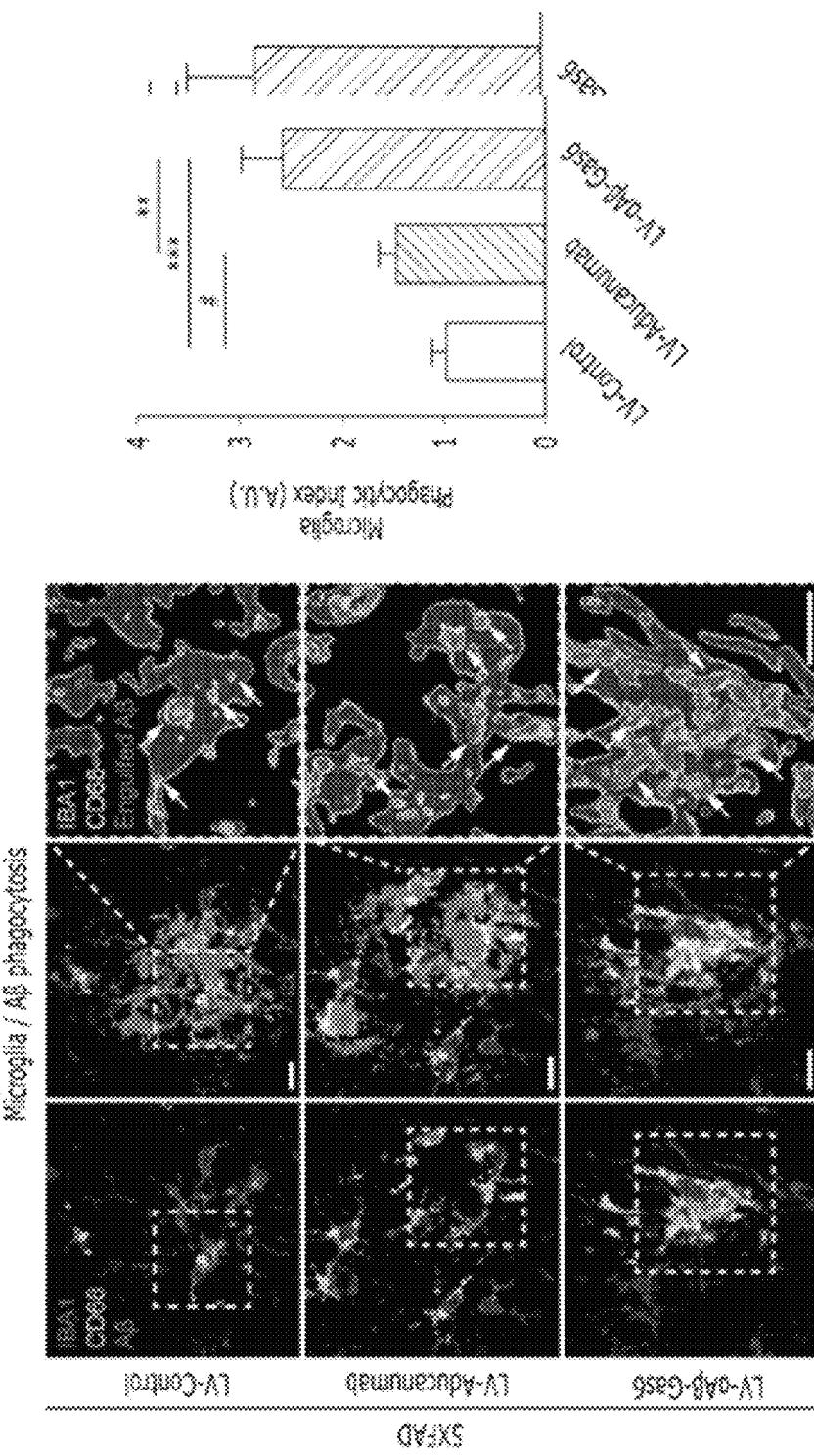
Administration of  
 $\alpha\beta$ -GAS6 Fusion Protein

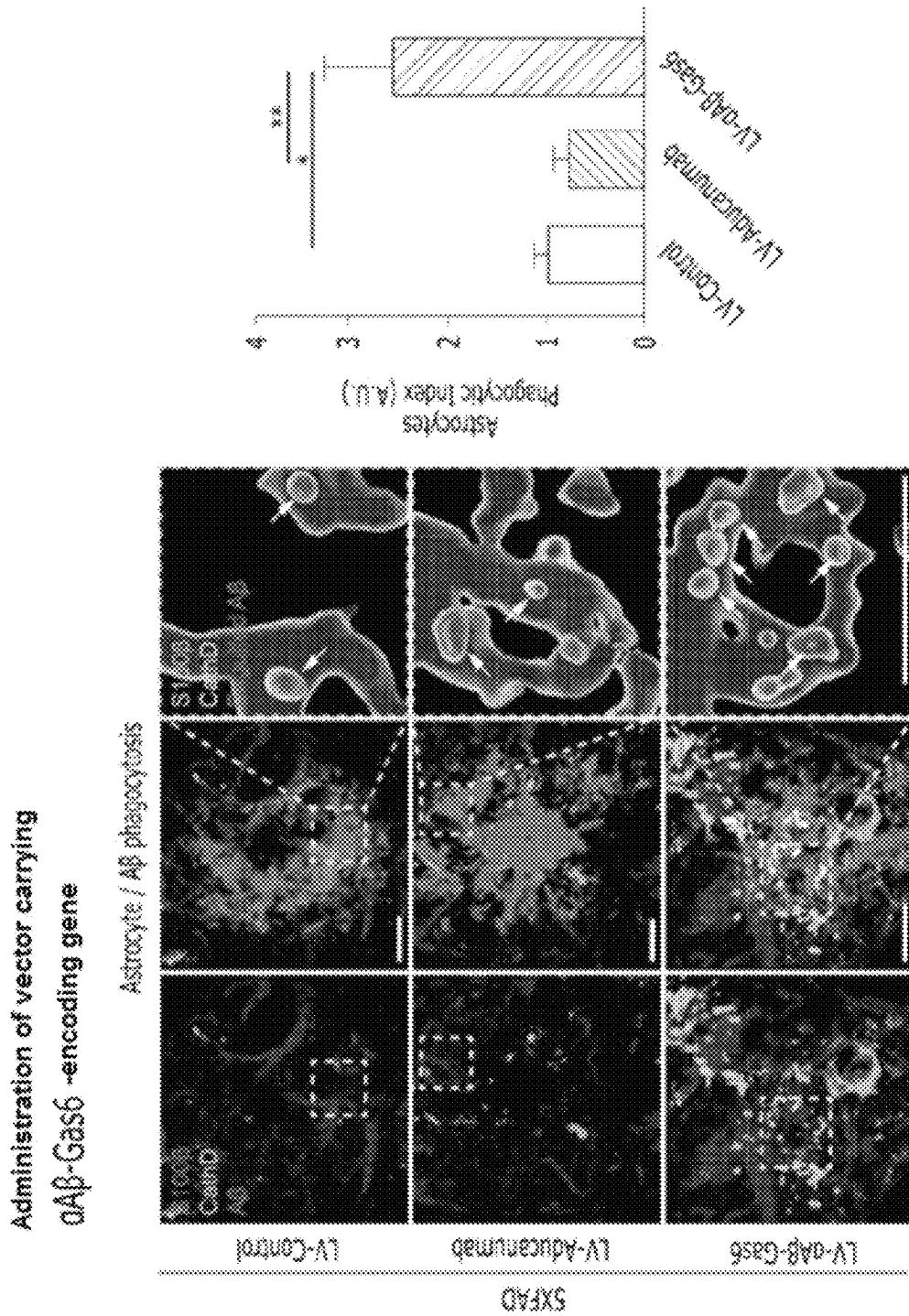


**FIG. 20**

**FIG. 21**

Administration of vector carrying  
cAP-Gas6 -encoding gene

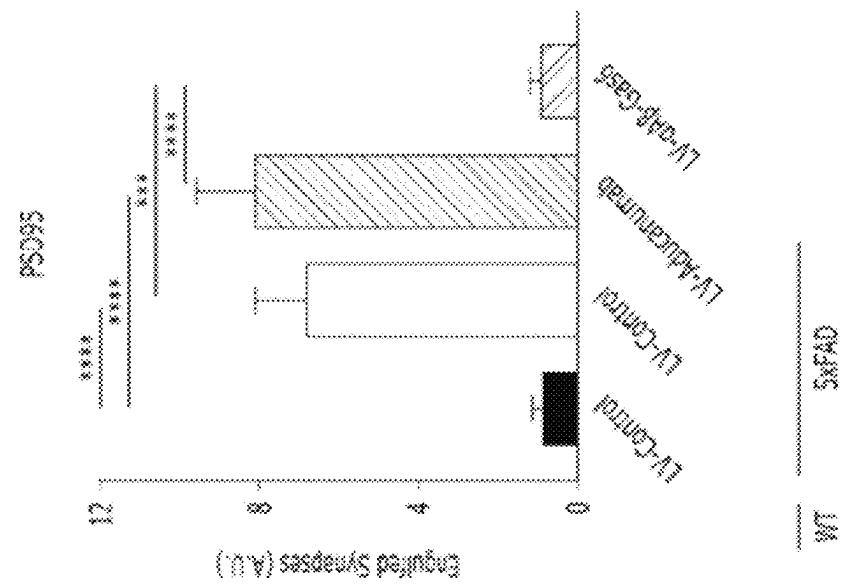
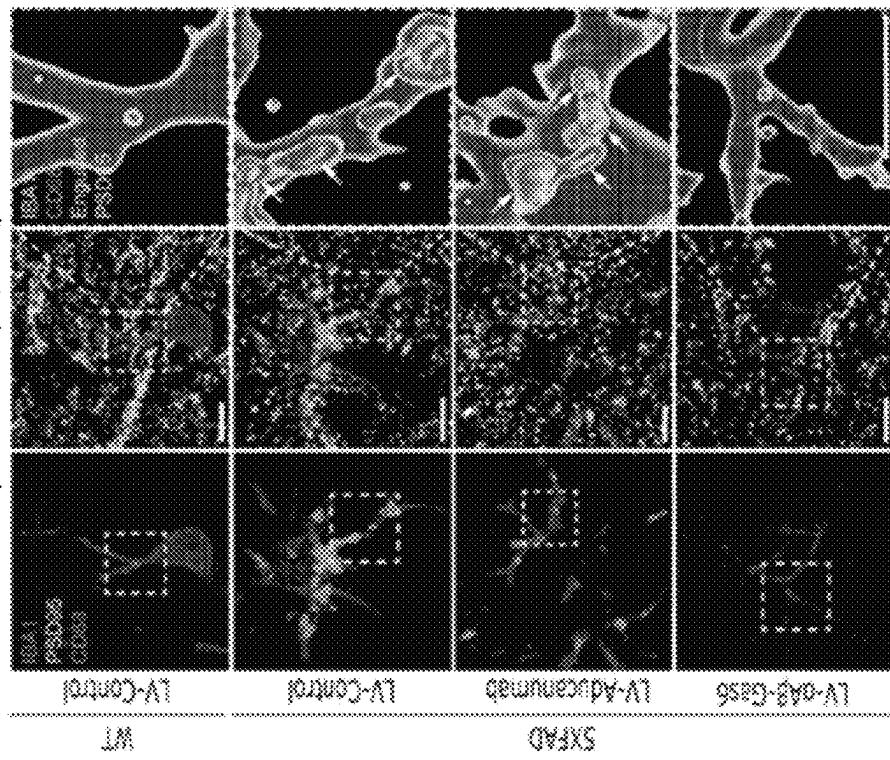


**FIG. 22**

**FIG. 23**

Administration of vector carrying  
GAP-G356 -encoding gene

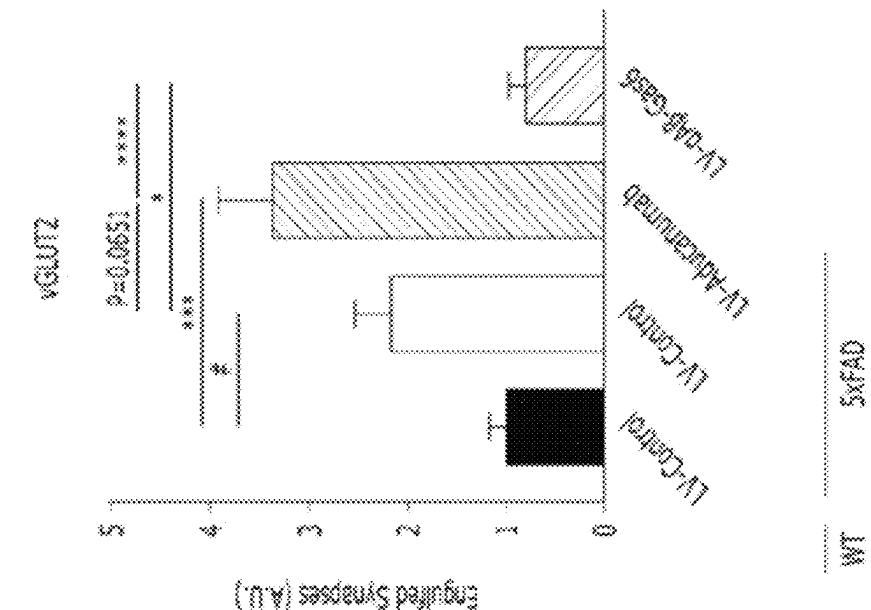
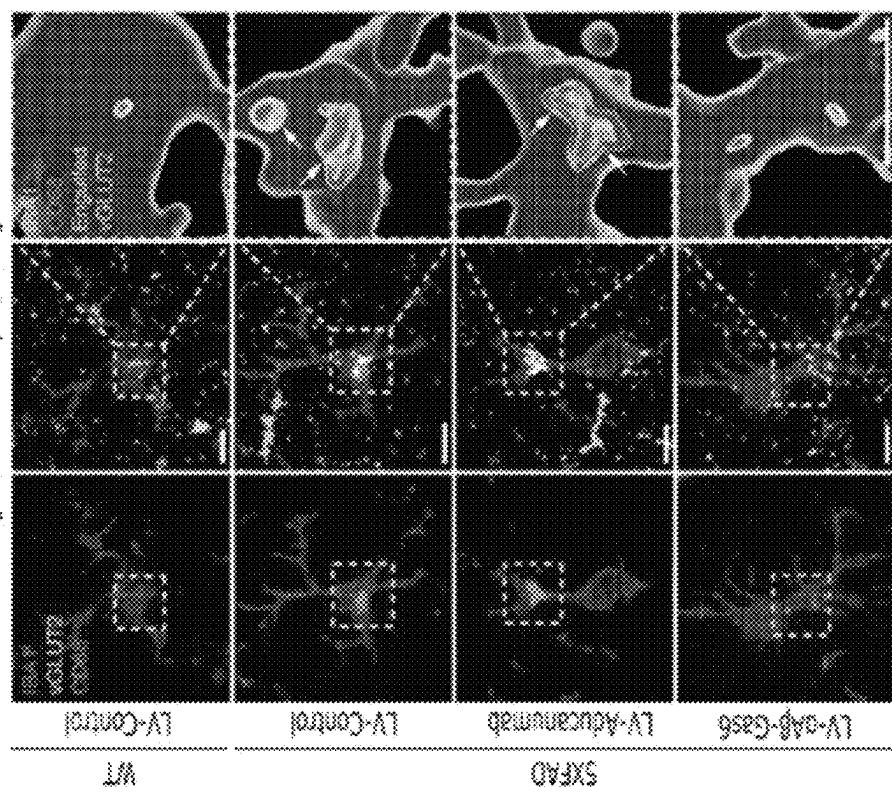
Microglia / G3565' Synapse Enrichment



**FIG. 24**

Administration of vector carrying  
 $\alpha\text{A}\beta$ -Gas6 -encoding gene

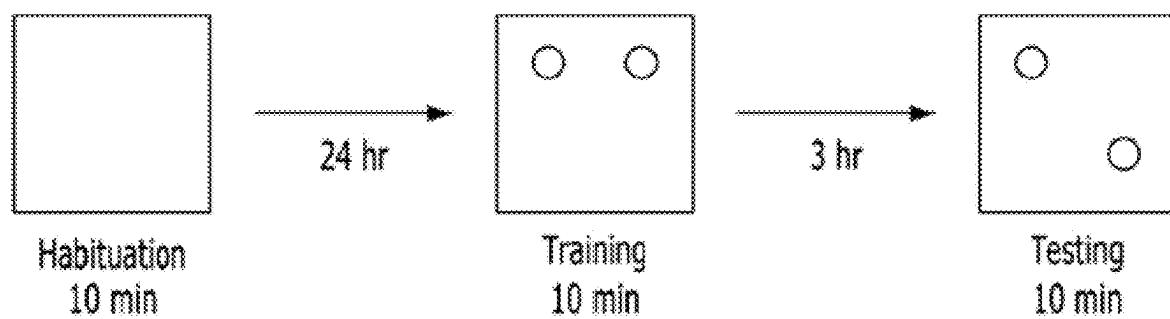
Mice / vGAT<sup>T2</sup> Synapse Enlargement



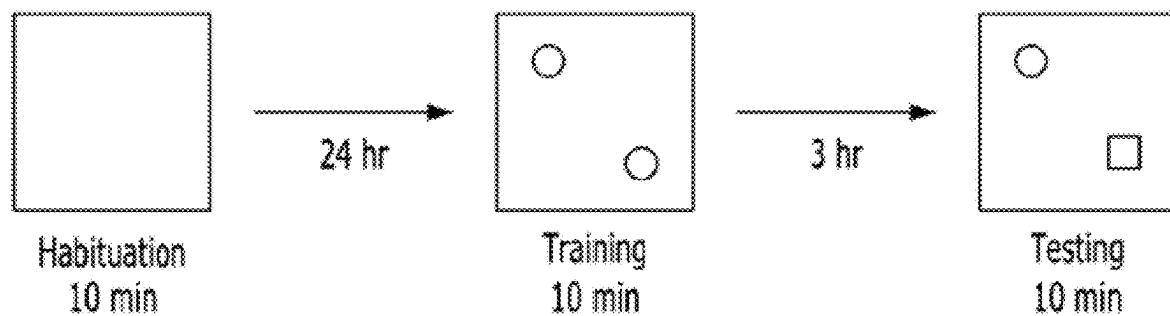
**FIG. 25**

Administration of vector carrying  
 $\alpha\text{A}\beta\text{-Gas6}$  -encoding gene

### Novel Object Location Test

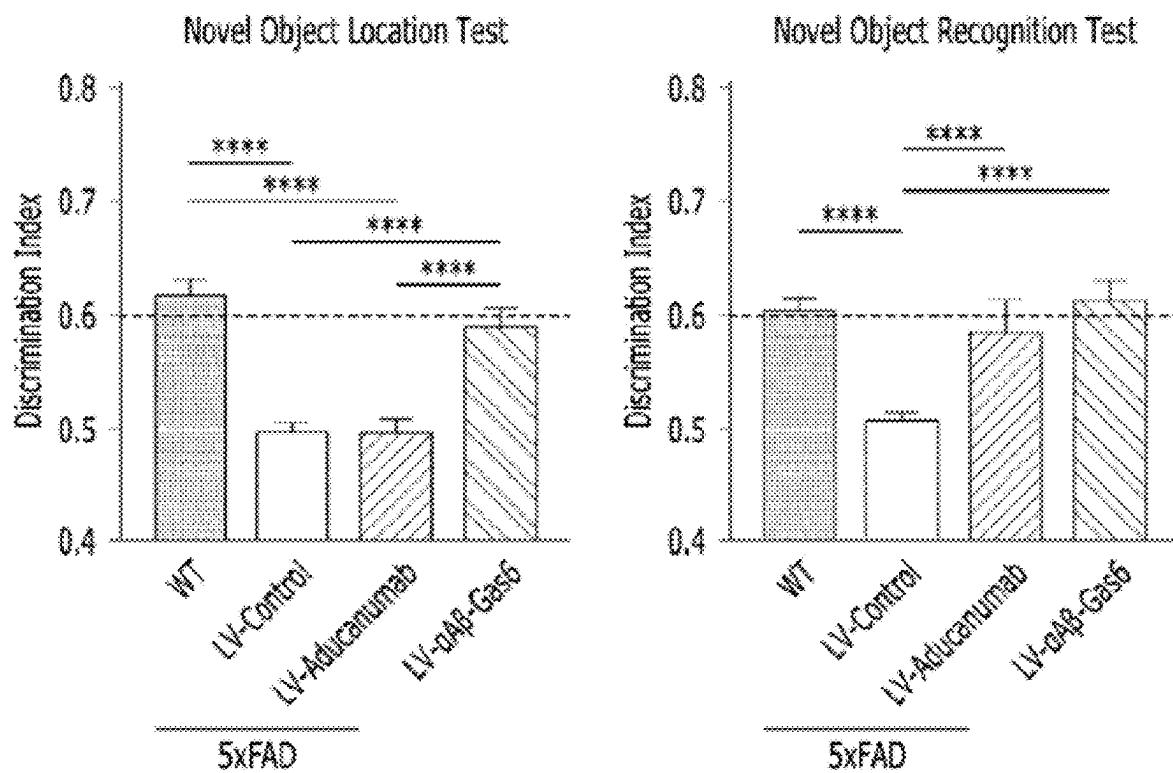


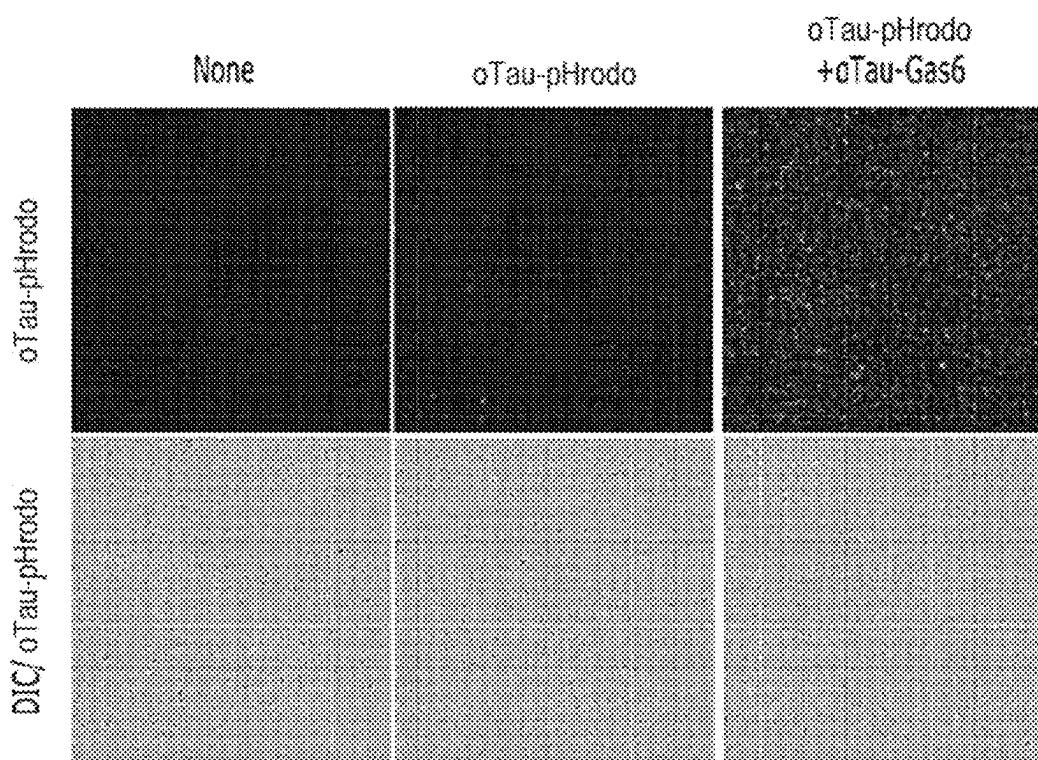
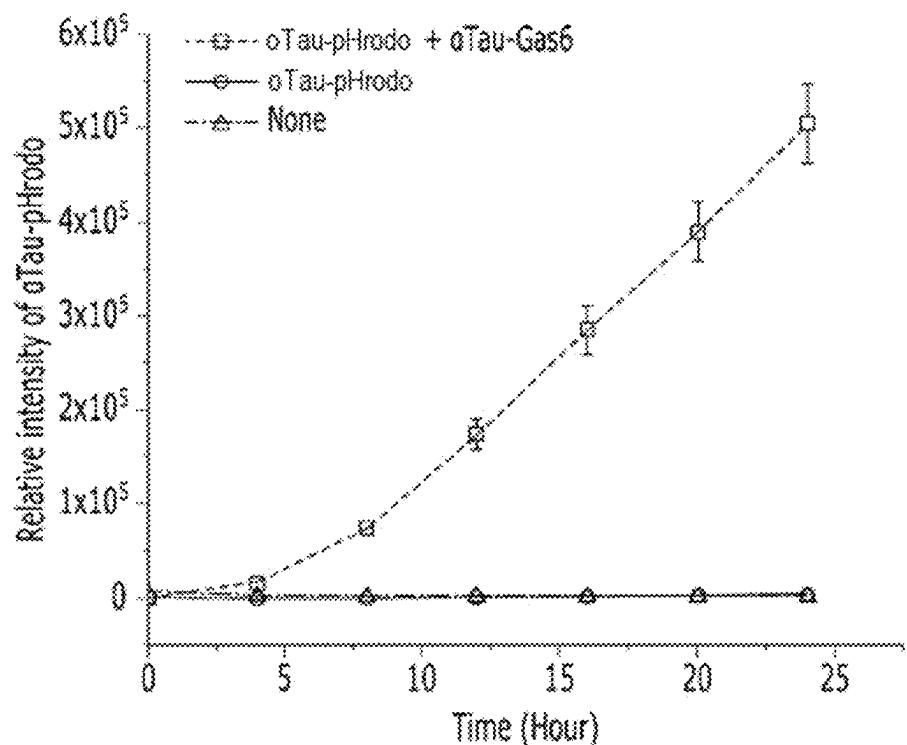
### Novel Object Recognition Test

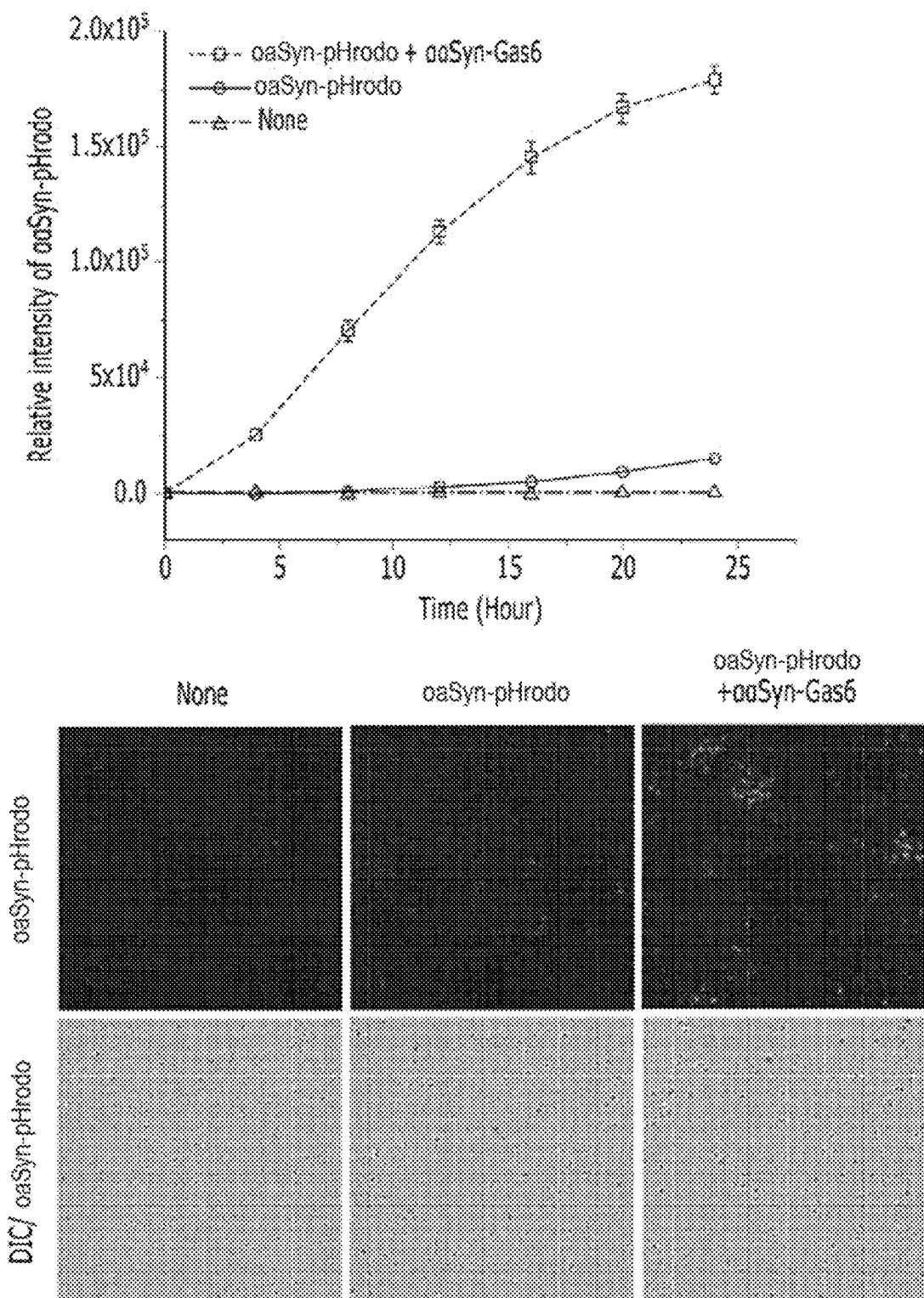


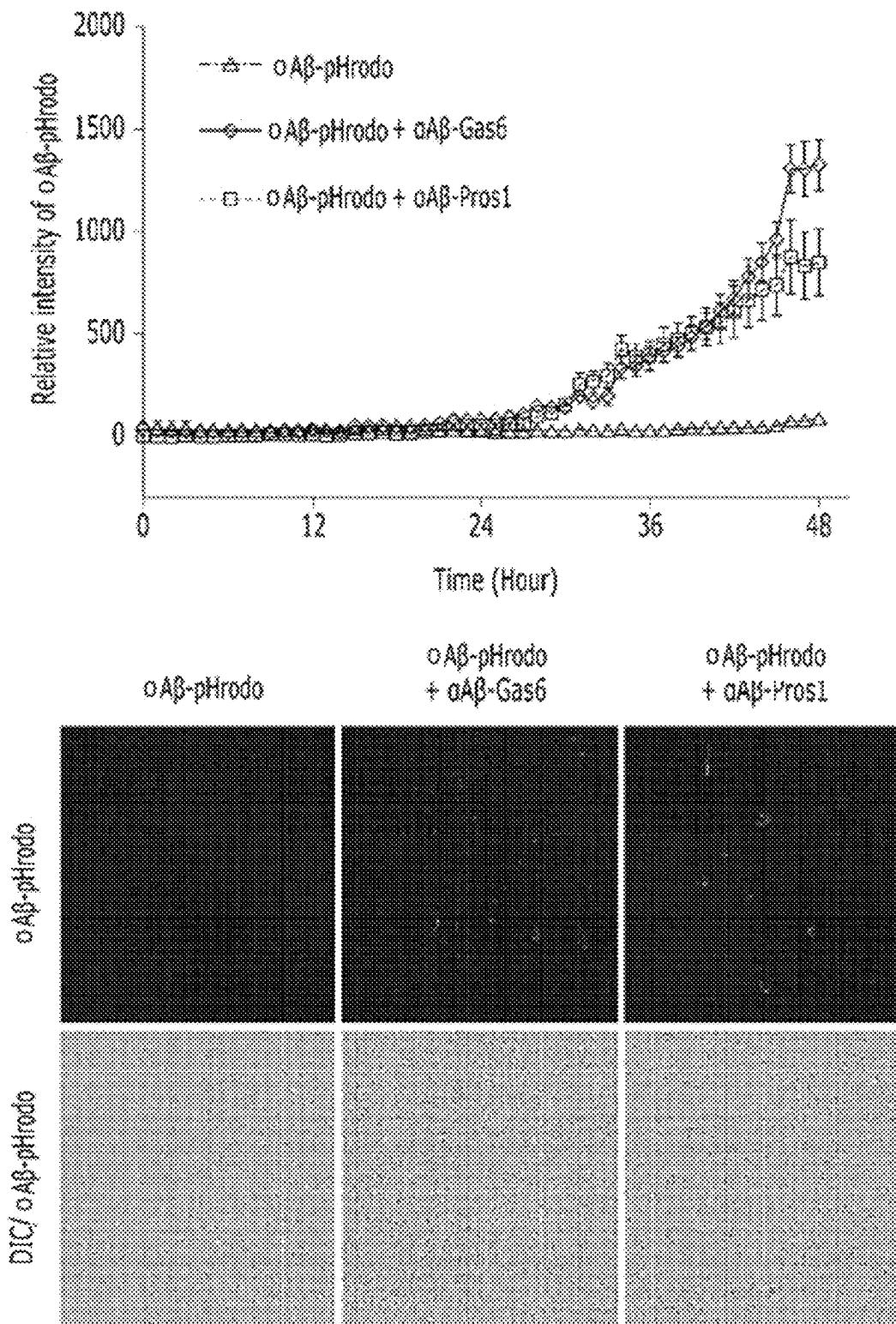
**FIG. 26**

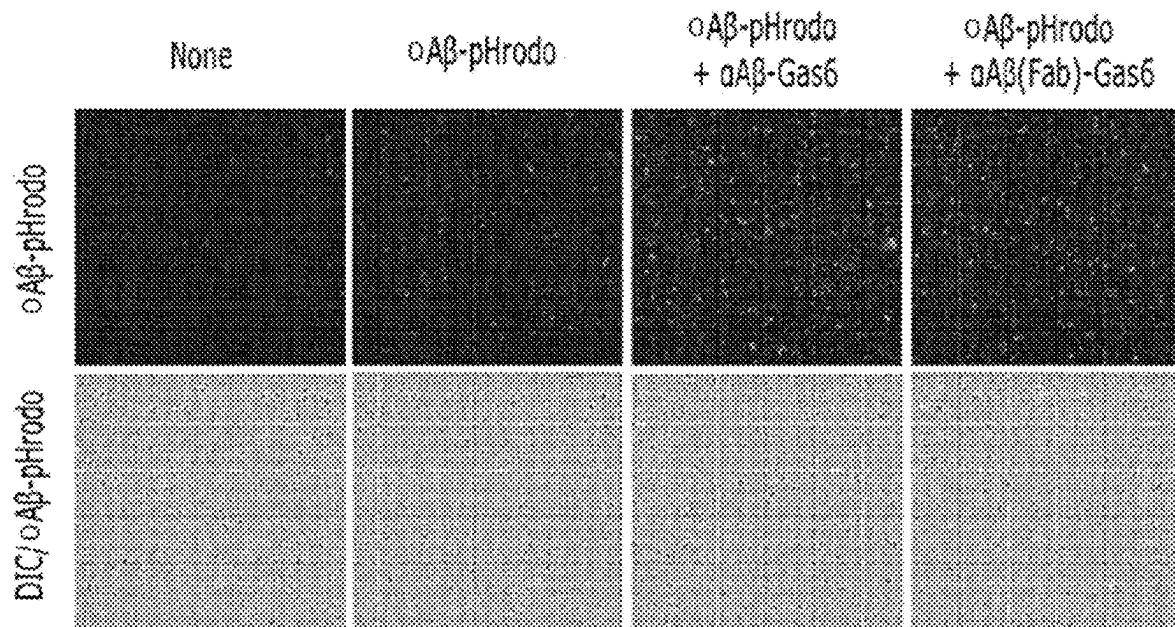
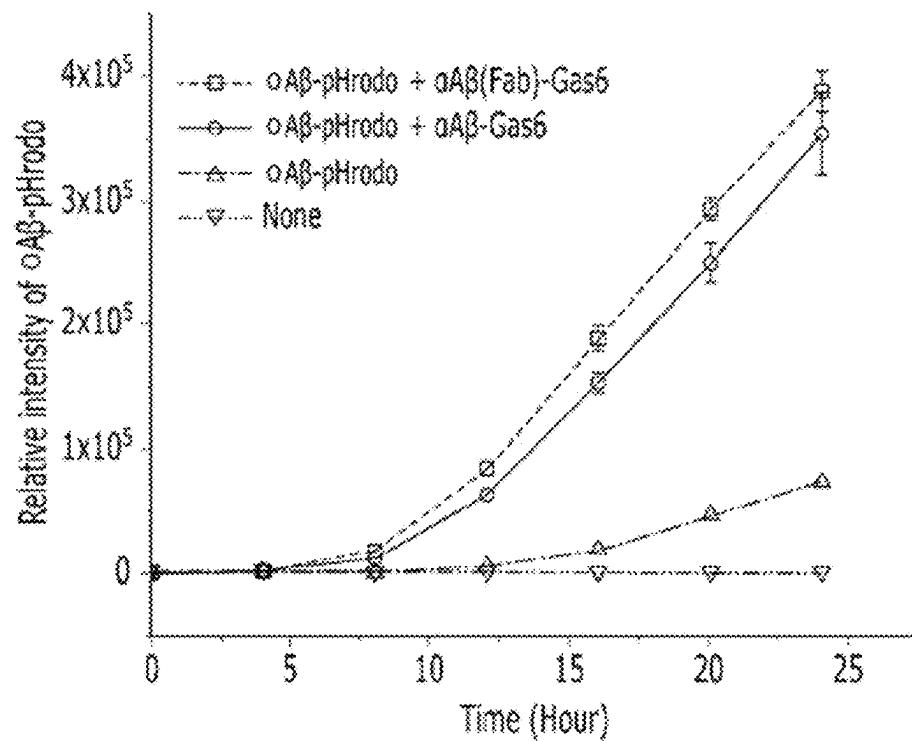
Administration of vector carrying  
 $\alpha\text{A}\beta$ -Gas6 -encoding gene

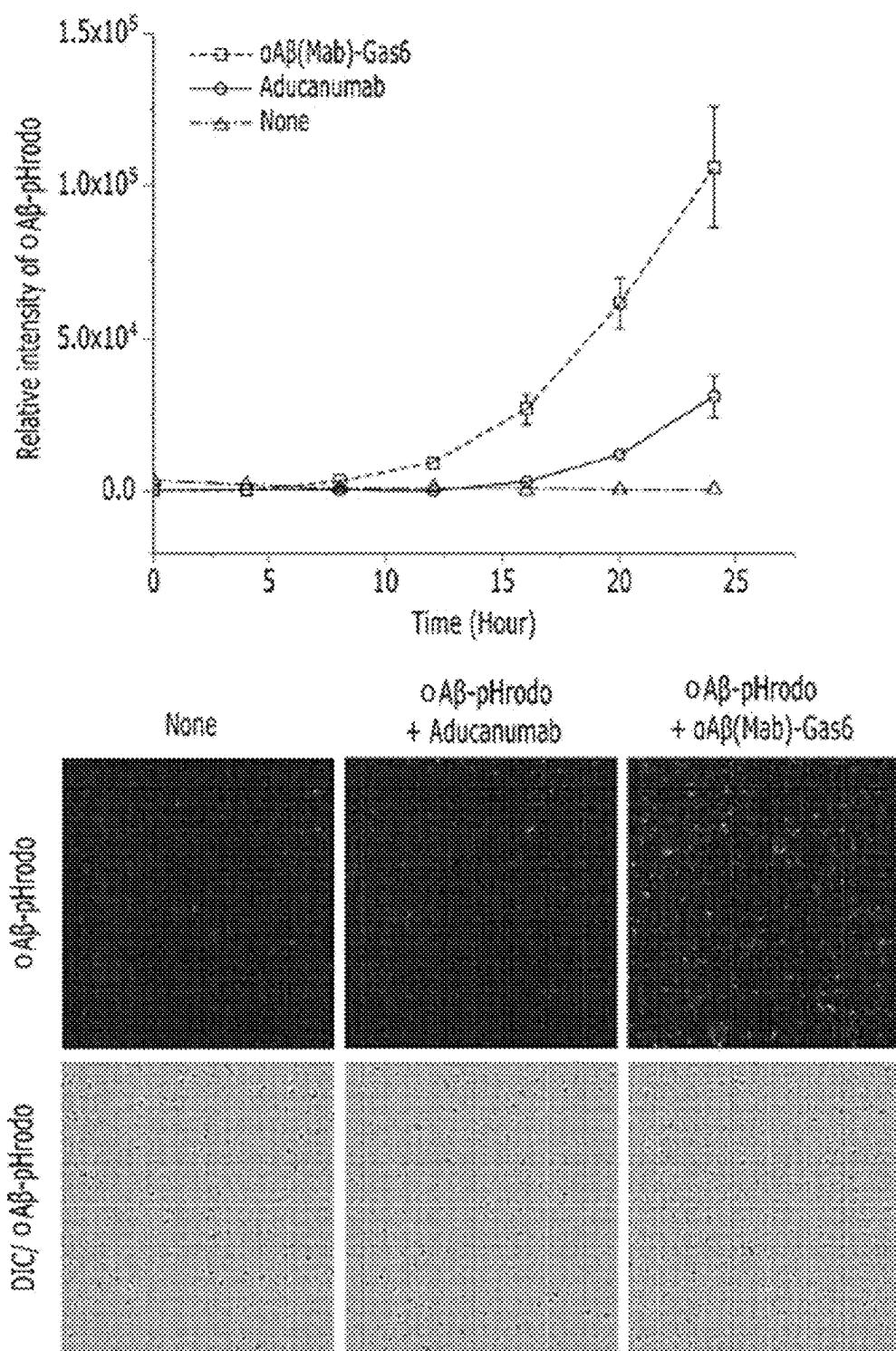


**FIG. 27**

**FIG. 28**

**FIG. 29**

**FIG. 30**

**FIG. 31**

1

**TAM RECEPTOR-BINDING FUSION  
MOLECULE HAVING  
NON-INFLAMMATORY PHAGOCYTOSIS  
INDUCING ACTIVITY**

**CROSS REFERENCE TO RELATED  
APPLICATIONS**

This application is a continuation-in-part of and claims the benefit of PCT Application No. PCT/KR2022/001671 filed Jan. 28, 2022, which claims priority based on Korean Patent Application No. 10-2021-0013056 filed Jan. 29, 2021, of which the entire contents are incorporated by reference herein.

**INCORPORATION BY REFERENCE OF  
SEQUENCE LISTING**

The content of the electronically submitted sequence listing, file name: Q289305\_SEQ\_LIST\_ST26.xml; size: 268,800 bytes; and date of creation: Jul. 16, 2023, filed herewith, is incorporated herein by reference in its entirety.

FILED

The present disclosure relates to fusion molecules that are capable of inducing phagocytosis without inducing inflammatory reaction, their uses, and manufacturing method. The fusion molecules are useful for prevention or treatment of diseases that are caused by or characterized by abnormal accumulation of substances in the body, such as proteopathy. The present disclosure also relates to nucleic acid molecules encoding the fusion molecules. The present disclosure further relates to methods of suppressing abnormal accumulation of substances, promoting clearance of aggregates of substances, and/or treating disorders or diseases that are caused by or characterized by abnormal accumulation of substances, without inducing inflammatory reaction.

**BACKGROUND**

Numerous degenerative diseases are characterized by aberrant folding, polymerization and accumulation of proteins. These proteopathies include various types of amyloidosis.

Amyloidosis is a disease in which abnormal proteins called amyloid accumulate in tissues. Amyloid is a protein aggregate that has a diameter of 7-13 nm and a beta-sheet structure and exhibits a fibrous morphology when viewed under a microscope, and it is characterized by being stained with Thioflavin T (ThioT) and Congo red. Amyloid is not normally found in the body, and to date, 36 proteins have been identified as being amyloidogenic (Picken, *Acta Haematol.* (2020), 143:322-334). Representative examples of amyloidosis diseases include neurological diseases such as Alzheimer's disease, Parkinson's disease, Huntington's disease and prion disease. In addition, there are a number of amyloid diseases having various aspects depending on amyloid-causing proteins and affected organs.

Alzheimer's disease is the biggest cause of dementia and is a fatal disease accompanied by learning and memory impairment. 130 million people are expected to suffer from Alzheimer's disease by 2050 worldwide, and 1 in 9 people among the population above 65 years old have already been diagnosed with Alzheimer's disease.

A hallmark of Alzheimer's disease is that beta-amyloid ( $\text{A}\beta$ ) protein caused by abnormal degradation of amyloid

2

precursor protein (APP), deposits and accumulates around the brain cell membrane. Another hallmark is abnormal hyperphosphorylation of microtubule-associated tau protein.

It has recently been reported that beta-amyloid oligomers and fibrils cause synaptic dysfunction and cytotoxicity through various pathways, and create a vicious cycle that adversely affects nerve cells through functional changes in astrocytes and microglia, which are responsible for immunity in the brain.

Therapeutic drugs for Alzheimer's disease approved by the FDA to date inhibit acetylcholine degradation or inhibit the activity of NMDA receptors, and, thus, provide temporary relief of symptoms, but do not treat the underlying cause or the disease itself. Therefore, there is a need for the development of new treatments for treating Alzheimer's disease and other diseases characterized by aberrant accumulation or deposit of beta-amyloid.

For a therapeutic treatment of Alzheimer's disease, drug development has been conducted for decades with a focus on inhibiting formation of and eliminating beta-amyloid. Unfortunately, however, most of the therapeutic drugs for Alzheimer's disease developed to inhibit formation of and eliminate beta-amyloid failed during the clinical stage due to ineffectiveness or insufficient efficacy. For example, in the case of BACE ( $\beta$ -site amyloid precursor protein cleaving enzyme) inhibitors for reducing beta-amyloid, strategies that prevent additional beta-amyloid production are largely ineffective, because in Alzheimer's patients with cognitive decline, beta-amyloid plaques have already accumulated and neuronal cell death is taking place.

Since the recent studies reporting that monoclonal antibodies which specifically bind to beta-amyloid oligomers and fibrils induced beta-amyloid clearance and restored cognitive function in Alzheimer's disease patients, a strategy to treat Alzheimer's disease through anti-beta-amyloid antibodies has emerged as a new hope.

The mechanisms of action of beta-amyloid monoclonal antibodies proposed to date include inhibition of aggregation of beta-amyloid oligomers and fibrils by binding thereto, or the induction of microglial phagocytosis of beta-amyloid through Fc receptors that recognize the monoclonal antibodies.

However, despite the advances in the development of therapeutic drugs for Alzheimer's disease, current immunotherapy using anti-beta-amyloid monoclonal antibodies shows amyloid-related imaging abnormalities (ARIAs) accompanied by severe edema in 55% of patients treated with the antibodies, and for this reason, about 35% of the ARIA patients were dropped from clinical trials. The ARIA phenomenon is known to be due to synaptotoxicity and cytotoxicity caused by inflammatory responses that are inevitably activated when anti-beta-amyloid monoclonal antibodies stimulate Fc receptors of microglia cells.

Since synapses and neurons in the brain respond sensitively to inflammatory cytokines, treatment using anti-beta-amyloid monoclonal antibodies has an inherent problem in that it inevitably causes damages to neurons and synapses, even if it clears beta-amyloid to some extent. In addition to monoclonal antibodies, companies such as Alektor and Denali presented strategies to improve the microglia's ability to clear beta-amyloid by activating targets such as TREM2 that regulate the immunological mechanism of microglia, and these strategies have received a lot of attention. However, even in these strategies, when microglia are excessively activated, synaptic damage due to an increase in overall phagocytic capacity is expected.

Therefore, an important task in the treatment of Alzheimer's disease is to develop therapeutic modalities to selectively clear only beta-amyloid oligomers and fibrils without causing inflammatory responses and synaptic damage, and these drugs are expected to make a significant contribution to the treatment of Alzheimer's disease.

Furthermore, there is a need to selectively clear only a substance of which abnormal accumulation causes disorders or accumulates thereof as a target, for example, abnormally accumulated proteins causing proteopathy, without causing inflammatory responses and consequent additional tissue damage reported in conventional experimental drugs. The present disclosure meets this need by providing therapeutic modalities for selectively clearing abnormally accumulated proteins that cause or characterize certain disease.

## SUMMARY

The present disclosure relates to fusion molecules having phagocytosis-inducing activity without inducing inflammatory responses. One aspect of the present disclosure provides a fusion molecule having phagocytosis-inducing activity, the fusion molecule comprising: a first region that is capable of binding to a TAM (Tyro3, Axl and MerTK) receptor; and a second region that specifically binds to a target substance to be cleared or decreased, and the fusion molecule does not induce inflammatory responses. In embodiments, the fusion molecule does not have an effector function and does not induce Fc-mediated inflammatory responses.

In some embodiments, the TAM receptor may be any one selected from the group consisting of Tyro3, Axl, MerTK, or a combination thereof, which are capable of inducing phagocytosis by binding to a laminin G-like domain (or LG domain) of a phagocytic cell including, but not limited to, macrophages or microglial cells. In embodiments, the TAM receptor may be Axl receptor.

In embodiments, the first region may comprise Gas6, ProS1, Tubby, Tulp1, Gal3, or an active fragment thereof, which each is capable of specifically binding to a TAM receptor. The first region may be selected from Gas6, ProS1, or an active fragment thereof, which each is capable of specifically binding to a TAM receptor. In embodiments, the first region may comprise or consist essentially of Gas6 or an active fragment thereof that is capable of binding to TAM receptor. In embodiments, the first region comprising or consisting essentially of Gas6 or an active fragment thereof is capable of binding to Axl receptor.

In certain embodiments, the first region may comprise a laminin G-like domain of Gas6 or ProS1, or an active fragment thereof, which contains a laminin G-like domain as a phagocytosis-related bridging molecule which is abundantly expressed in various tissue, and thus is able to induce phagocytosis through a TAM receptor. In embodiments, the laminin G-like domain may comprise an LG1 domain, an LG2 domain, or a combination thereof, and may preferably include both an LG1 domain and an LG2 domain, which are able to induce phagocytosis by binding to the TAM receptor.

Exemplary embodiments are directed to a binding molecule or fusion molecule comprising a first region capable of binding to a TAM receptor and a second region capable of specifically binding to a target substance, said target substance being a substance of which aberrant accumulation in a living tissue is characteristic of or associated with a disease, wherein the first region and the second region are coupled to each other directly or via a linker,

wherein the first region comprises

- (a) a TAM receptor ligand;
- (b) an anti-Axl antibody or an antigen-binding fragment thereof;
- (c) an anti-Tyro3 antibody or an antigen-binding fragment thereof; or
- (d) an anti-MerTK antibody or an antigen-binding fragment thereof, with proviso that when the first region comprises an anti-MerTK antibody or an antigen-binding fragment thereof, the molecule is not a bispecific antibody; or
- (e) combinations thereof.

According to some embodiments, the binding molecule may further comprise a scaffold bound to the first region, to the second, or to both of the first region and the second region at different positions.

In embodiments, the first region is a TAM receptor ligand and the TAM receptor ligand comprises a sequence selected from the group consisting of SEQ ID NOS: 1-113 or a sequence having at least 85% of sequence identity thereto.

In still some embodiments, the first region is capable of binding to an Axl receptor the first region capable of binding to an Axl receptor comprises one or more sequences selected from the group consisting of SEQ ID NO: 1, SEQ ID NO:

2, SEQ ID NO: 5, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 20, SEQ ID NO: 21, SEQ ID NO: 22, SEQ ID NO: 23, SEQ ID NO: 24, SEQ ID NO: 25, SEQ ID NO: 26, SEQ ID NO: 27, SEQ ID NO: 28, SEQ ID NO: 29, SEQ ID NO: 30, SEQ ID NO: 31, SEQ ID NO: 32, SEQ ID NO: 33, SEQ ID NO: 63, SEQ ID NO: 64, SEQ ID NO: 65, SEQ ID NO: 66, SEQ ID NO: 67, SEQ ID NO: 68, SEQ ID NO: 69, SEQ ID NO: 70, SEQ ID NO: 71, SEQ ID NO: 72, SEQ ID NO: 73, SEQ ID NO: 74, SEQ ID NO: 75, SEQ ID NO: 76, SEQ ID NO: 77, SEQ ID NO: 78, SEQ ID NO: 79, SEQ ID NO: 80, SEQ ID NO: 81, SEQ ID NO: 82, SEQ ID NO: 83, SEQ ID NO: 84, SEQ ID NO: 85, SEQ ID NO: 86, and SEQ ID NO: 87, or a sequence having at least 85% of sequence identity thereto.

In still some embodiments, the first region is capable of binding to an Axl receptor the first region capable of binding to an Axl receptor comprises the sequence of SEQ ID NO: 1 or a sequence having at least 85% of sequence identity thereto, and/or the sequence of SEQ ID NO: 2 or a sequence having at least 85% of sequence identity thereto.

In still another embodiment, the first region capable of binding to an Axl receptor the first region capable of binding to an Axl receptor comprises the sequence of SEQ ID NO: 5 or a sequence having at least 85% of sequence identity thereto.

In still some embodiments, the first region is capable of binding to an Axl receptor the first region capable of binding to an Axl receptor comprises one or more sequences selected from the group consisting of SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 35, SEQ ID NO: 36, SEQ ID NO: 37, SEQ ID NO: 38, SEQ ID NO: 39, SEQ ID NO: 40, SEQ ID NO: 41, SEQ ID NO: 42, SEQ ID NO: 43, SEQ ID NO: 44, SEQ ID NO: 45, SEQ ID NO: 46, SEQ ID NO: 47, SEQ ID NO: 48, SEQ ID NO: 49, SEQ ID NO: 50, SEQ ID NO: 51, SEQ ID NO: 52, SEQ ID NO: 53, SEQ ID NO: 54, SEQ ID NO: 55, SEQ ID NO: 56, SEQ ID NO: 57, SEQ ID NO: 58, SEQ ID NO: 59, SEQ ID NO: 60, SEQ ID NO: 61, SEQ ID NO: 62, SEQ ID NO: 88, SEQ ID NO: 89, SEQ ID NO: 90, SEQ ID NO: 91, SEQ ID NO: 92, SEQ ID NO: 93, SEQ ID NO: 94, SEQ ID NO: 95, SEQ ID NO: 96, SEQ ID NO: 97, SEQ ID NO: 98, SEQ ID NO: 99, SEQ ID NO:

100, SEQ ID NO: 101, SEQ ID NO: 102, SEQ ID NO: 103, SEQ ID NO: 104, SEQ ID NO: 105, SEQ ID NO: 106, SEQ ID NO: 107, SEQ ID NO: 108, SEQ ID NO: 109, SEQ ID NO: 110, SEQ ID NO: 111, SEQ ID NO: 112, and SEQ ID NO: 113, or a sequence having at least 85% of sequence identity thereto.

In still some embodiments, the first region is capable of binding to an Axl receptor the first region capable of binding to an Axl receptor comprises the sequence of SEQ ID NO: 3 or a sequence having at least 85% of sequence identity thereto, and/or the sequence of SEQ ID NO: 4 or a sequence having at least 85% of sequence identity thereto.

In still another embodiment, the first region capable of binding to an Axl receptor the first region capable of binding to an Axl receptor comprises the sequence of SEQ ID NO: 6 or a sequence having at least 85% of sequence identity thereto.

In embodiments, the fusion molecule (or binding molecule) may comprise the first region comprising the sequence of SEQ ID NO: 1, SEQ ID NO: 2, or a combination thereof, or a sequence having at least 85% sequence identity thereto. In an embodiment, the combination of the sequence of SEQ ID NO: 1 and SEQ ID NO: 2 may comprise the sequence of SEQ ID NO: 5 or a sequence having at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% to SEQ ID NO: 5.

In embodiments, the fusion molecule (or binding molecule) may comprise the first region comprising the sequence of SEQ ID NO: 3, SEQ ID NO: 4, or a combination thereof, or a sequence having at least 85% sequence identity thereto. In an embodiment, the combination of the sequence of SEQ ID NO: 3 and SEQ ID NO: 4 may comprise the sequence of SEQ ID NO: 6 or a sequence having at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% to SEQ ID NO: 6.

In embodiments, the fusion molecule (or binding molecule) may comprise the sequence of amino acid residues 31-871 of SEQ ID NO: 136, amino acid residues 31-687 of SEQ ID NO: 138, amino acid residues 31-697 of SEQ ID NO: 140, amino acid residues 31-684 of SEQ ID NO: 150, amino acid residues 31-676 of SEQ ID NO: 152, amino acid residues 25-673 of SEQ ID NO: 154, amino acid residues 22-662 of SEQ ID NO: 156, or amino acid residues 22-885 of SEQ ID NO: 158, amino acid residues 22-908 of SEQ ID NO: 162, amino acid residues 22-919 of SEQ ID NO: 163, amino acid residues 22-919 of SEQ ID NO: 165, or a sequence having at least 90% sequence identity thereto (wherein a different linker can be used in place the linkers as shown in Tables 3 and 5-10).

In embodiments, the first region comprising a laminin G-like domain of Gas6 or ProS1, or an active fragment thereof, does not comprise a Gla domain. Without being bound to a particular theory, it is expected that the lacking of Gla domain in the first region may make the fusion molecule not be able to recognize phosphatidylserine (PS) of TAM receptor, while the second region is able to induce phagocytosis by recognizing a target substance.

In some embodiments, the first region comprising a laminin G-like domain of Gas6 or ProS1, or an active fragment thereof, does not comprise a Gla domain and does not comprise an EGF domain. The lacking of EGF domain in the first region provides an advantage in the manufacturing process of the fusion molecule to increase the yield by suppressing an aggregation of the fusion molecule during the purification step. In some embodiments, the fusion molecule (or binding molecule) may form a homomultimer or a heteromultimer, or form a linear multimer as a single chain.

According to embodiments, the target substance that is to be cleared or decreased and to which the second region specifically binds, may be a substance that accumulates in living tissue, causing a disease. For example, it may be a substance accumulated in an affected (i.e., diseased) tissue of a patient or circulating in blood of a patient. The substance may be protein. That is, the disease may be, but not limited thereto, proteopathy. In certain embodiments, the target substance may be amyloid. That is, the proteopathy may be amyloidosis. The target substance may be one or more of the amyloid substances listed in Table 1 below or APOE or apoptosis-associated spec-like protein containing a caspase activating recruitment domain (ASC-speck), of which abnormal accumulation or deposit is associated with or characteristic of a disease, and in this case, the disease may be a disease in which each abnormally accumulated substance is detected. For example, the proteopathy may be Alzheimer's disease, Parkinson's disease, Huntington's disease, and Prion disease, and in this case, target substances may be  $\beta$ -amyloid, tau,  $\alpha$ -synuclein, huntingtin, and prion proteins, respectively, which are identified as proteins of which abnormal accumulation causes the diseases. Aberrant accumulation of APOE is associated with Alzheimer's disease, cerebral amyloid angiopathy, and/or cardiovascular disease. Aberrant accumulation of apoptosis-associated spec-like protein containing a caspase activating recruitment domain (ASC-speck) is associated with Alzheimer's Disease, Parkinson's Disease, Huntington's disease, Multiple System Atrophy, Amyotrophic Lateral Sclerosis, Spinocerebellar ataxia, Frontotemporal Dementia, Frontotemporal Lobar Degeneration, Mild Cognitive Impairment, Parkinson-plus syndromes, Pick disease, Progressive isolated aphasia, Grey-matter degeneration [Alpers], Subacute necrotizing encephalopathy, and Lewy body dementia.

TABLE 1

Target Substance	Abbreviation	Diseases associated with or characterized by aberrant accumulation of target substance
$\beta$ -Amyloid	A $\beta$	Alzheimer's disease, Hereditary cerebral haemorrhage with amyloidosis, etc.
Amyloid precursor protein-derived $\beta$ -amyloid	A $\beta$	Alzheimer's disease, Hereditary cerebral haemorrhage with amyloidosis, etc.
$\alpha$ -Synuclein	$\alpha$ -Syn	Parkinson's disease, Parkinson's dementia, dementia with Lewy bodies, multiple system atrophy, etc.

TABLE 1-continued

Target Substance	Abbreviation	Diseases associated with or characterized by aberrant accumulation of target substance
Prp <sup>Sc</sup>	PrP	Transmissible spongiform encephalopathy (fatal familial insomnia, Gerstmann-Straussler-Scheinker disease, Creutzfeldt-Jacob disease, new variant Creutzfeldt-Jacob disease, etc.), etc.
Microtubule-associated protein tau	Tau	Tauopathies (Pick's disease, progressive supranuclear palsy, corticobasal degeneration, frontotemporal dementia with parkinsonism linked to chromosome 17, argyrophilic grain disease, etc.), Alzheimer's disease, Parkinson's disease, etc.
Huntingtin exon 1	HTT exon 1	Huntington's disease, etc.
TAR DNA-binding protein 43	TDP43	Frontotemporal dementia, amyotrophic lateral sclerosis (ALS), etc.
Superoxide dismutase 1	SOD1	Amyotrophic lateral sclerosis (ALS), etc.
ABri peptide	bri	Familial British dementia
ADan peptide	dan	Familial Danish dementia
Immunoglobulin light-chain fragment	AL	Light-chain amyloidosis
Immunoglobulin heavy-chain fragment	AH	Heavy-chain amyloidosis
N-terminal fragment of serum amyloid A protein	AA	AA amyloidosis
Transthyretin	ATTR	Senile systemic amyloidosis, familial amyloid polyneuropathy, familial amyloid cardiomyopathy, leptomeningeal amyloidosis
β-2 microglobulin	Aβ2M	Dialysis-related amyloidosis, hereditary visceral amyloidosis
N-terminal fragment of apolipoprotein AI	AApoAI	ApoAI amyloidosis
C-terminally extended apolipoprotein AII	AApoAII	ApoAII amyloidosis
N-terminal fragment of apolipoprotein AIV	AApoAIV	ApoAIV amyloidosis
apolipoprotein C-II	AApoCII	ApoCII amyloidosis
apolipoprotein C-III	AApoCIII	ApoCIII amyloidosis
Gelsolin fragment	AGel	Familial amyloidosis, Finnish type, Hereditary gelsolin amyloidosis
Lysozyme	ALys	Hereditary non-neuropathic systemic amyloidosis
Fibrinogen alpha chain fragment	AFib	Fibrinogen amyloidosis
N-terminally truncated cystatin C	ACys	Hereditary cerebral hemorrhage with amyloidosis, Icelandic type
Amylin, IAPP	IAPP	Diabetes mellitus type 2, insulinoma
Calcitonin	Cal	Medullary carcinoma of the thyroid
Atrial natriuretic factor	AANF	Cardiac arrhythmias, isolated atrial amyloidosis
Prolactin	PRL	Pituitary prolactinoma
Insulin	AIns	Localized amyloidosis at insulin injection sites
Lactadherin or medin	AMed	Aortic medial amyloidosis
Lactotransferrin or lactoferrin	LTF	Gelatinous drop-like corneal dystrophy
Odontogenic ameloblast-associated protein	ODAM	Calcifying epithelial odontogenic tumors
pulmonary surfactant-associated protein C	SPC	Pulmonary alveolar proteinosis
Leukocyte cell-derived chemotaxin-2	ALECT2	Renal LECT2 amyloidosis
Galectin-7	Agal7	Lichen amyloidosis, macular amyloidosis
Corneodesmosin	Cor	Hypotrichosis simplex of the scalp
C-terminal fragment of TGFBI (or keratoepithelin)	Ker	Lattice corneal dystrophy; type I, 3A or Avellino
SGI (Semenogelin-1)	ASem1	Seminal vesicle amyloidosis
S100 protein (A8 or A9)	(no abbreviation)	Prostate cancer
Enfuvirtide	AEnv	Injection-localized amyloidosis
Apolipoprotein E	APOE	Alzheimer's disease, cerebral amyloid angiopathy, cardiovascular disease

TABLE 1-continued

Target Substance	Abbreviation	Diseases associated with or characterized by aberrant accumulation of target substance
Apoptosis-associated Spec-like protein containing a Caspase Activating Recruitment Domain	ASC	Alzheimer's Disease, Parkinson's Disease, Huntington's disease, Multiple System Atrophy, Amyotrophic Lateral Sclerosis, Spinocerebellar ataxia. Frontotemporal Dementia, Frontotemporal Lobar Degeneration, Mild Cognitive Impairment, Parkinson-plus syndromes, Pick disease, Progressive isolated aphasia, Grey-matter degeneration [Alpers], Subacute necrotizing encephalopathy, and Lewy body dementia

In embodiments, the present disclosure is directed to a nucleic acid or polynucleotide encoding the fusion proteins described above.

In embodiments, the present disclosure is directed to a vector containing the nucleic acid or polynucleotide.

Embodiments are directed to a host cell containing the vector.

Another aspect of the present disclosure provides a method of producing a therapeutic fusion molecule for treatment of a disease or disorder associated with or characterized by aberrant accumulation of substance in a subject, comprising expressing the fusion molecule by culturing a host cell under a condition for expressing the fusion molecule.

In embodiments, the present disclosure is directed to a method of reducing or enhancing a reduction of aberrant deposit of substance that causes or characterizes certain disorder or diseases in a subject, which method comprises administering to the subject an effective amount of a fusion molecule or a polynucleotide encoding the fusion molecule, wherein the fusion molecule comprises a first region that is capable of binding to a TAM (Tyro3, Axl and MerTK) receptor on surface of a cell in the subject; and a second region that specifically binds to the substance. In non-limiting embodiments, the substance and the disease or disorder may be one or more of those listed in Table 1. In non-limiting embodiments, the fusion molecule does not have an effector function and does not induce Fc-mediated inflammatory responses. For example, the fusion molecule does not comprise a moiety to bind to an Fc receptor, and preferably may comprise an Fc region variant that does not bind to an Fc receptor (particularly an Fcγ receptor).

In embodiments, the present disclosure is directed to a method of removing or clearing or enhancing clearance of aberrant deposit of substance that causes or characterizes certain disorder or diseases in a subject, which method comprises administering to the subject an effective amount of a fusion molecule or a polynucleotide encoding the fusion molecule, wherein the fusion molecule comprises a first region that is capable of binding to a TAM (Tyro3, Axl and MerTK) receptor on surface of a cell in the subject; and a second region that specifically binds to the substance. In non-limiting embodiments, the substance and the disease or disorder may be one or more of those listed in Table 1. In non-limiting embodiments, the fusion molecule does not have an effector function and does not induce inflammatory responses. For example, the fusion molecule does not comprise a moiety to bind to an Fc receptor, and may comprise an Fc region variant that does not bind to an Fc receptor (particularly an Fcγ receptor).

In embodiments, the present disclosure is directed to a method of suppressing formation of aberrant accumulations 20 of substance in a subject. The method comprises administering to the subject an effective amount of a fusion molecule or a polynucleotide encoding the fusion molecule, wherein the fusion molecule comprises a first region that is capable of binding to a TAM (Tyro3, Axl and MerTK) receptor on surface of a cell in the subject and a second region that specifically binds to the substance. In non-limiting embodiments, the substance and the disease or disorder may be one or more of those listed in Table 1. In non-limiting embodiments, the fusion molecule does not have an effector function and does not induce Fc-mediated inflammatory responses. For example, the fusion molecule does not comprise a moiety to bind to an Fc receptor, and preferably may comprise an Fc region variant that does not bind to an Fc receptor (particularly an Fcγ receptor).

In embodiments, the present disclosure is directed to a method of treating or preventing a disorder or disease in a subject, wherein the disorder or disease is characterized by or caused by aberrant accumulation of substance. The method comprises administering to the subject an effective amount of a fusion molecule or a polynucleotide encoding the fusion molecule, wherein the fusion molecule comprises a first region that is capable of binding to a TAM (Tyro3, Axl and MerTK) receptor on surface of a cell in the subject; and a second region that specifically binds to the substance. In non-limiting embodiments, the substance and the disease or disorder may be one or more of those listed in Table 1. In non-limiting embodiments, the fusion molecule does not have an effector function and does not induce Fc-mediated inflammatory responses. For example, the fusion molecule does not comprise a moiety to bind to an Fc receptor, and preferably may comprise an Fc region variant that does not bind to an Fc receptor (particularly an Fcγ receptor).

In embodiments, the present disclosure is directed to a method of delaying development of a symptom associated 55 with a disease that is characterized by, associated with, or caused by aberrant accumulation of substance, in a subject. The method comprises administering to the subject an effective amount of a fusion molecule or a polynucleotide encoding the fusion molecule, a vector comprising the polynucleotide, wherein the fusion molecule comprises a first region that is capable of binding to a TAM (Tyro3, Axl and MerTK) receptor on surface of a cell in the subject; and a second region that specifically binds to the substance. In non-limiting embodiments, the substance and the disease or disorder may be one or more of those listed in Table 1. In non-limiting embodiments, the fusion molecule does not have an effector function and does not induce Fc-mediated

**11**

inflammatory responses. For example, the fusion molecule does not comprise a moiety to bind to an Fc receptor, and preferably may comprise an Fc region variant that does not bind to an Fc receptor (particularly an Fcγ receptor).

In embodiments, the present disclosure provides a method of reducing a substance of which aberrant accumulation is associated with or characteristic of a disease or disorder, in a subject. The method comprises administering to the subject an effective amount of a fusion molecule or a polynucleotide encoding the fusion molecule, wherein the fusion molecule comprises a first region that is capable of binding to a TAM (Tyro3, Axl and MerTK) receptor on surface of a cell in the subject, and a second region that specifically binds to the substance. The substance may be soluble, oligomeric, or aggregated form. In some embodiments, the toxic effects of accumulated substance are inhibited and/or reduced. Thus, the method of the disclosure can be used to treat any disease in which accumulation of a substance is present or suspected. In non-limiting embodiments, the substance and the disease or disorder may be one or more of those listed in Table 1. In non-limiting embodiments, the fusion molecule does not have an effector function and does not induce Fc-mediated inflammatory responses. For example, the fusion molecule does not comprise a moiety to bind to an Fc receptor, and preferably may comprise an Fc region variant that does not bind to an Fc receptor (particularly an Fcγ receptor).

In the above methods, according to embodiments thereof, the aberrant deposits of substance are in the brain (brain tissue) of the subject. In some embodiments, the aberrant deposits of substance are in the cerebral vasculature. In some embodiments, the aberrant accumulation of substance is in the circulatory system. In some embodiments, the aberrant accumulation of substance is in various tissues such as heart, kidney, liver, and the like.

In embodiments, the present disclosure is directed to a pharmaceutical composition comprising an effective amount of any of the above-disclosed fusion molecule or polynucleotides encoding the fusion molecule, and a pharmaceutical acceptable excipient. In non-limiting embodiments, the fusion molecule does not have an effector function and does not induce Fc-mediated inflammatory responses. For example, the fusion molecule does not comprise a moiety to bind to an Fc receptor, and preferably may comprise an Fc region variant that does not bind to an Fc receptor (particularly an Fcγ receptor).

In embodiments, the present disclosure is directed to kits comprising an effective amount of any of the above-disclosed fusion molecule or polynucleotides encoding the fusion molecule. The kits are generally in suitable packaging and provided with appropriate instructions, are useful for any of the methods described herein.

These and other aspects, objects, features and advantages of the example embodiments will become apparent to those having ordinary skill in the art upon consideration of the following detailed description of illustrated example embodiments.

#### BRIEF DESCRIPTION OF DRAWINGS

FIG. 1A schematically illustrates the structure of TAM receptors and TAM ligands. In the structure of TAM receptors: the N-terminal starts with 2 Ig-like domains, followed by 2 fibronectin type 3 domains, followed by a single-pass transmembrane domain and a protein tyrosine kinase at the C-terminal. In the structure of the TAM ligands protein S (Pros1) and Gas6, the N-terminal contains a GLA domain,

**12**

followed by a thrombin-sensitive region (TSR), followed by 4 EGF-like domains, followed by a C-terminal (SHBG-like domain, consisting of 2 LG repeats. In FIG. 1A, EGF stands for epidermal growth factor, Ig stands for immunoglobulin, LG stands for laminin G, and SHBG stands for sex hormone-binding globulin.

FIG. 1B schematically shows beta-amyloid- and FITC-binding phagocytosis inducing fusion molecule comprising Gas6 as a non-limiting example of first region of the fusion molecule.

FIG. 1C through FIG. 1M schematically show non-limiting exemplary embodiments of the structure of the fusion molecules.

FIG. 2 shows the results of Western blot analysis of a non-limiting exemplary chimeric phagocytosis inducer comprising a FLAG Tag, produced according to Preparation Example 1.

FIG. 3 schematically shows an action of a non-limiting exemplary chimeric phagocytosis inducer, produced according to Preparation Example 1, on TAM receptor.

FIG. 4 shows the evaluation results for selective beta-amyloid clearing ability of αAβ-Gas6.

FIG. 5 shows the evaluation results for beta-amyloid clearing ability of αAβ-Gas6 in the HMC3 cell line by beta-amyloid engulfment assay in vitro.

FIG. 6 shows the evaluation results for beta-amyloid clearing ability of αAβ-Gas6 in the HMC3 cell line by beta-amyloid engulfment assay in vitro.

FIG. 7 shows results indicating that the beta-amyloid clearing ability of αAβ-Gas6 is associated with or dependent on Gas6 binding to Axl among TAM receptors.

FIG. 8 shows results indicating that the beta-amyloid clearing ability of αAβ-Gas6 is associated with or dependent on Gas6 binding to Axl among TAM receptors.

FIG. 9 shows results indicating that the beta-amyloid clearing ability of αAβ-Gas6 is associated with or dependent on Gas6 binding to Axl among TAM receptors.

FIG. 10 shows the results of comparative analysis of the activation of inflammatory response signaling by αAβ-Gas6 and aducanumab using THP-Axl cells.

FIG. 11 shows the results of comparative analysis of the levels of pro-inflammatory cytokine secretion by αAβ-Gas6 and aducanumab using THP-Axl cells.

FIG. 12 shows the evaluation results for anti-inflammatory activity of αAβ-Gas6.

FIG. 13 shows results indicating that the beta-amyloid clearing ability of microglia was significantly increased by αAβ-Gas6.

FIG. 14 shows results indicating that the beta-amyloid clearing ability of astrocytes was significantly increased by αAβ-Gas6.

FIG. 15 shows results indicating that the transcriptional levels of pro-inflammatory cytokines in astrocytes were changed by αAβ-Gas6 and aducanumab.

FIG. 16 shows results indicating that the transcriptional levels of pro-inflammatory cytokines in BV2 were changed by αAβ-Gas6 and aducanumab.

FIG. 17 shows the evaluation results for beta-amyloid plaque clearing ability of αAβ-Gas6 through administration of αAβ-Gas6 protein in 5xFAD Alzheimer's disease model mice.

FIG. 18 shows the evaluation results for beta-amyloid plaque clearing ability of αAβ-Gas6 through administration of αAβ-Gas6 virus in 5xFAD Alzheimer's disease model mice.

FIG. 19 shows results indicating that beta-amyloid contained in lysosomes were increased by microglia-mediated

13

clearance in 5xFAD Alzheimer's disease model mice upon administration of  $\alpha$ A $\beta$ -Gas6 protein.

FIG. 20 shows results indicating that beta-amyloid contained in lysosomes were increased by astrocyte-mediated clearance in 5xFAD Alzheimer's disease model mice upon administration of  $\alpha$ A $\beta$ -Gas6 protein.

FIG. 21 shows results indicating that beta-amyloid contained in lysosomes were increased by microglia-mediated clearance in 5xFAD Alzheimer's disease model mice upon administration of  $\alpha$ A $\beta$ -Gas6 virus.

FIG. 22 shows results indicating that beta-amyloid contained in lysosomes were increased by astrocyte-mediated clearance in 5xFAD Alzheimer's disease model mice upon administration of  $\alpha$ A $\beta$ -Gas6 virus.

FIG. 23 shows results indicating that microglia-mediated synapse engulfment that abnormally increased in 5xFAD Alzheimer's disease model mice due to the side effect of aducanumab was significantly restored upon administration of  $\alpha$ A $\beta$ -Gas6 virus.

FIG. 24 shows results indicating that microglia-mediated synapse engulfment that abnormally increased in 5xFAD Alzheimer's disease model mice due to the side effect of aducanumab was significantly restored upon administration of  $\alpha$ A $\beta$ -Gas6 virus.

FIG. 25 shows an experimental protocol for evaluating cognitive and memory abilities in 5xFAD Alzheimer's disease model mice upon administration of  $\alpha$ A $\beta$ -Gas6 virus.

FIG. 26 shows results indicating that cognitive and memory abilities in 5xFAD Alzheimer's disease model mice were more restored upon administration of  $\alpha$ A $\beta$ -Gas6 virus than administration of aducanumab.

FIG. 27 shows the evaluation results for tau clearing ability of  $\alpha$ Tau-Gas6 in the HMC3 cell line by in vitro tau engulfment assay.

FIG. 28 shows the evaluation results for alpha-synuclein clearing ability of  $\alpha$ Tau-Gas6 in the HMC3 cell line by in vitro tau engulfment assay.

FIG. 29 shows the evaluation results for beta-amyloid clearing ability of  $\alpha$ A $\beta$ -ProS1 in primary-cultured astrocytes by in vitro tau engulfment assay.

FIG. 30 shows the evaluation results for beta-amyloid clearing ability of  $\alpha$ A $\beta$ (Fab)-Gas6 in the HMC3 cell line by in vitro tau engulfment assay.

FIG. 31 shows the evaluation results for beta-amyloid clearing ability of  $\alpha$ A $\beta$ (Fab)-Gas6 in the HMC3 cell line by in vitro tau engulfment assay.

## DETAILED DESCRIPTION

Methods and compositions are provided for reducing or suppressing formation of or clearing a target substance of which accumulation is associated with or characteristic of a disorder or disease via a phagocytosis, preventing or treating an individual having a disease or disorder characterized by an aberrant accumulation of a substance, improving symptoms of a disease or disorder characterized by an aberrant accumulation of a substance, and/or a target substance of which accumulation is associated with or characteristic of a disorder or disease via a phagocytosis.

Where a range of values is provided, it is understood that each intervening value, to the tenth of the unit of the lower limit unless the context clearly dictates otherwise, between the upper and lower limits of that range is also specifically disclosed. Each smaller range between any stated value or intervening value in a stated range and any other stated or intervening value in that stated range is encompassed within the invention. The upper and lower limits of these smaller

14

ranges may independently be included or excluded in the range, and each range where either, neither or both limits are included in the smaller ranges is also encompassed within the invention, subject to any specifically excluded limit in the stated range. Where the stated range includes one or both of the limits, ranges excluding either or both of those included limits are also included in the invention.

## Definitions

10

As used herein, the singular forms "a," "an," and "the," refer to both the singular as well as plural, unless the context clearly indicates otherwise. Therefore, for example, reference to "a cell" includes a plurality of such cells and reference to "the peptide" includes reference to one or more peptides and equivalents thereof, e.g. polypeptides, known to those skilled in the art, and so forth.

As used herein, the terms "about" and "consisting essentially of" refers to a value or composition that is within an acceptable error range for the particular value or composition as determined by one of ordinary skill in the art, which will depend in part on how the value or composition is measured or determined, i.e., the limitations of the measurement system. For example, "about" or "consisting essentially of" can mean within 1 or more than 1 standard deviation per the practice in the art. Alternatively, "about" or "consisting essentially of" can mean a range of up to 10% (i.e.,  $\pm 10\%$ ). For example, "about 5 mg" can include any number between 4.5 mg and 5.5 mg (for 10%), between 4.75 mg and 6.25 mg (for 5%), between 4.8 mg and 6.2 mg (for 4%), between 4.85 mg and 6.15 mg (for 3%), between 4.9 mg and 6.1 mg (for 2%), or between 4.95 mg and 6.05 mg (for 1%). Furthermore, particularly with respect to biological systems or processes, the terms can mean up to an order of magnitude or up to 5-fold of a value. When particular values or compositions are provided in the application and claims, unless otherwise stated, the meaning of "about" or "consisting essentially of" should be assumed to be within an acceptable error range for that particular value or composition.

As used herein, "administration" or "administering" refers to the introduction of a composition into a subject by a chosen route. For example, if the chosen route is intravenous, the composition is administered by introducing the composition into a vein of the subject. In some examples, the peptides and antibodies disclosed herein are administered to a subject.

As used herein, "amino acid" refers to naturally occurring and synthetic amino acids, as well as amino acid analogs and amino acid mimetics that function in a manner similar to the naturally occurring amino acids. Naturally occurring amino acids are those encoded by the genetic code, as well as those amino acids that are later modified, e.g., hydroxyproline, gamma-carboxyglutamate, and O-phosphoserine. Amino acid analogs refers to compounds that have the same basic chemical structure as a naturally occurring amino acid, i.e., an .alpha. carbon that is bound to a hydrogen, a carboxyl group, an amino group, and an R group, e.g., homoserine, norleucine, methionine sulfoxide, methionine methyl sulfonium. Such analogs have modified R groups (e.g., norleucine) or modified peptide backbones, but retain the same basic chemical structure as a naturally occurring amino acid. Amino acid mimetics refers to chemical compounds that have a structure that is different from the general chemical structure of an amino acid, but that functions in a manner similar to a naturally occurring amino acid.

15

As used herein, "polypeptide," "oligopeptide," "peptide" and "protein" are used interchangeably herein to refer to a polymer of amino acid residues. The terms also apply to amino acid polymers in which one or more amino acid residue is an artificial chemical mimetic of a corresponding naturally occurring amino acid, as well as to naturally occurring amino acid polymers and non-naturally occurring amino acid polymer. The terms also encompass an amino acid polymer that has been modified naturally or by intervention; for example, disulfide bond formation, glycosylation, lipidation, acetylation, phosphorylation, or any other manipulation or modification, such as conjugation with a labeling component. Also included within the definition are, for example, polypeptides containing one or more analogs of an amino acid (including, for example, unnatural amino acids, etc.), as well as other modifications known in the art. It is understood that, because the polypeptides of this invention are based upon an antibody, the polypeptides can occur as single chains or associated chains.

As used herein, "polynucleotide," or "nucleic acid," as used interchangeably herein, refer to polymers of nucleotides of any length, and include DNA and RNA. The nucleotides can be deoxyribonucleotides, ribonucleotides, modified nucleotides or bases, and/or their analogs, or any substrate that can be incorporated into a polymer by DNA or RNA polymerase. A polynucleotide may comprise modified nucleotides, such as methylated nucleotides and their analogs. If present, modification to the nucleotide structure may be imparted before or after assembly of the polymer. The sequence of nucleotides may be interrupted by non-nucleotide components. A polynucleotide may be further modified after polymerization, such as by conjugation with a labeling component. Other types of modifications include, for example, "caps", substitution of one or more of the naturally occurring nucleotides with an analog, internucleotide modifications such as, for example, those with uncharged linkages (e.g., methyl phosphonates, phosphotriesters, phosphoramidates, carbamates, etc.) and with charged linkages (e.g., phosphorothioates, phosphorodithioates, etc.), those containing pendant moieties, such as, for example, proteins (e.g., nucleases, toxins, antibodies, signal peptides, poly-L-lysine, etc.), those with intercalators (e.g., acridine, psoralen, etc.), those containing chelators (e.g., metals, radioactive metals, boron, oxidative metals, etc.), those containing alkylators, those with modified linkages (e.g., alpha anomeric nucleic acids, etc.), as well as unmodified forms of the polynucleotide(s). Further, any of the hydroxyl groups ordinarily present in the sugars may be replaced, for example, by phosphonate groups, phosphate groups, protected by standard protecting groups, or activated to prepare additional linkages to additional nucleotides, or may be conjugated to solid supports. The 5 and 3 terminal OH can be phosphorylated or substituted with amines or organic capping group moieties of from 1 to 20 carbon atoms. Other hydroxyls may also be derivatized to standard protecting groups. Polynucleotides can also contain analogous forms of ribose or deoxyribose sugars that are generally known in the art, including, for example, 2'-O-methyl-, 2'-O-allyl, 2'-fluoro- or 2'-azido-ribose, carbocyclic sugar analogs, a-anomeric sugars, epimeric sugars such as arabinose, xyloses or lyxoses, pyranose sugars, furanose sugars, sedoheptulose, acyclic analogs and abasic nucleoside analogs such as methyl riboside. One or more phosphodiester linkages may be replaced by alternative linking groups. These alternative linking groups include, but are not limited to, embodiments wherein phosphate is replaced by P(O)S ("thiolate"), P(S)S ("dithioate"), "(O)NR<sub>2</sub>" ("amide"), P(O)R, P(O)OR', CO or CH<sub>2</sub> ("for-

16

macyl"), in which each R or R' is independently H or substituted or unsubstituted alkyl (1-20 C) optionally containing an ether (—O—) linkage, aryl, alkenyl, cycloalkyl, cycloalkenyl or araldyl. Not all linkages in a polynucleotide need be identical. The preceding description applies to all polynucleotides referred to herein, including RNA and DNA.

As used herein, "recipient", "individual", "subject", "host", and "patient", are used interchangeably herein and refer to any mammalian subject for whom diagnosis, treatment, or therapy is desired, particularly humans. "Mammal" for purposes of treatment refers to any animal classified as a mammal, including humans, domestic and farm animals, and zoo, sports, or pet animals, such as dogs, horses, cats, cows, sheep, goats, pigs, etc. In embodiments, the mammal is human.

As used herein, "antibody" refers to single chain, two-chain, and multi-chain proteins and glycoproteins belonging to the classes of polyclonal, monoclonal, chimeric and hetero immunoglobulins (monoclonal antibodies being preferred); it also includes synthetic and genetically engineered variants of these immunoglobulins.

As used herein, "specific binding," "specifically binds," and the like, refer to non-covalent or covalent preferential binding to a molecule relative to other molecules or moieties in a solution or reaction mixture (e.g., an antibody specifically binds to a particular polypeptide or epitope relative to other available polypeptides/epitopes). In some embodiments, the affinity of one molecule for another molecule to which it specifically binds is characterized by a KD (dissociation constant) of 10<sup>-5</sup> M or less (e.g., 10<sup>-6</sup> M or less, 10<sup>-7</sup> M or less, 10<sup>-8</sup> M or less, 10<sup>-9</sup> M or less, 10<sup>-10</sup> M or less, 10<sup>-11</sup> M or less, 10<sup>-12</sup> M or less, 10<sup>-13</sup> M or less, 10<sup>-14</sup> M or less, 10<sup>-15</sup> M or less, or 10<sup>-16</sup> M or less). "Affinity" refers to the strength of binding, increased binding affinity being correlated with a lower KD. As used herein, the "binding" and "specific binding" of the first region to TAM receptor and the second region to a target substance do not require modulating, changing, affecting, or modifying activity of the bound TAM receptor or the target substance.

As used herein, "variable" refers to the fact that certain portions of the variable domains differ extensively in sequence among antibodies and are used in the binding and specificity of each particular antibody for its particular antigen. However, the variability is not evenly distributed throughout the variable domains of antibodies. It is concentrated in three segments called complementarity-determining regions (CDRs) or hypervariable regions both in the light-chain and the heavy-chain variable domains. The more highly conserved portions of variable domains are called the framework (FR). The variable domains of native heavy and light chains each comprise four FR regions, largely adopting a b-sheet configuration, connected by three CDRs, which form loops connecting, and in some cases forming part of, the b-sheet structure. The CDRs in each chain are held together in close proximity by the FR regions and, with the CDRs from the other chain, contribute to the formation of the antigen-binding site of antibodies (see Kabat et al., Sequences of Proteins of Immunological Interest, Fifth Edition, National Institute of Health, Bethesda, Md. (1991)). The constant domains are not involved directly in binding an antibody to an antigen, but exhibit various effector functions, such as participation of the antibody in antibody-dependent cellular toxicity.

"Fv" is the minimum antibody fragment, which contains a complete antigen-recognition and -binding site. In a two-chain Fv species, this region consists of a dimer of one

heavy- and one light-chain variable domain in tight, non-covalent association. In a single-chain Fv species (scFv), one heavy- and one light-chain variable domain can be covalently linked by a flexible peptide linker such that the light and heavy chains can associate in a “dimeric” structure analogous to that in a two-chain Fv species. It is in this configuration that the three CDRs of each variable domain interact to define an antigen-binding site on the surface of the VH-VL dimer. Collectively, the six CDRs confer antigen-binding specificity to the antibody. However, even a single variable domain (or half of an Fv comprising only three CDRs specific for an antigen) has the ability to recognize and bind antigen, although at a lower affinity than the entire binding site.

The term “complementarity determining region” or “CDR,” as used herein, refers to the sequences of amino acids within antibody variable regions which confer antigen specificity and binding affinity. For example, in general, there are three CDRs in each heavy chain variable region (e.g., HCDR1, HCDR2, and HCDR3) and three CDRs in each light chain variable region (LCDR1, LCDR2, and LCDR3). The precise amino acid sequence boundaries of a given CDR can be determined using any of a number of well-known schemes, including those described by Kabat et al. (1991), “Sequences of Proteins of Immunological Interest,” 5th Ed. Public Health Service, National Institutes of Health, Bethesda, MD (“Kabat” numbering scheme), Al-Lazikani et al., (1997) JMB 273,927-948 (“Chothia” numbering scheme), or a combination thereof. Under the Kabat numbering scheme, in some embodiments, the CDR amino acid residues in the heavy chain variable domain (VH) are numbered 31-35 (HCDR1), 50-65 (HCDR2), and 95-102 (HCDR3); and the CDR amino acid residues in the light chain variable domain (VL) are numbered 24-34 (LCDR1), 50-56 (LCDR2), and 89-97 (LCDR3). Under the Chothia numbering scheme, in some embodiments, the CDR amino acids in the VH are numbered 26-32 (HCDR1), 52-56 (HCDR2), and 95-102 (HCDR3); and the CDR amino acid residues in the VL are numbered 26-32 (LCDR1), 50-52 (LCDR2), and 91-96 (LCDR3). In a combined Kabat and Chothia numbering scheme, in some embodiments, the CDRs correspond to the amino acid residues that are part of a Kabat CDR, a Chothia CDR, or both. For instance, in some embodiments, the CDRs correspond to amino acid residues 26-35 (HCDR1), 50-65 (HCDR2), and 95-102 (HCDR3) in a VH, e.g., a mammalian VH, e.g., a human VH; and amino acid residues 24-34 (LCDR1), 50-56 (LCDR2), and 89-97 (LCDR3) in a VL, e.g., a mammalian VL, e.g., a human VL.

The “Fab fragment” also contains the constant domain of the light chain and the first constant domain (CH1) of the heavy chain. Fab fragments differ from Fab fragments by the addition of a few residues at the carboxy terminus of the heavy chain CH1 domain including one or more cysteines from the antibody hinge region. Fab'-SH is the designation herein for Fab' in which the cysteine residue(s) of the constant domains bear a free thiol group. F(ab')2 antibody fragments originally were produced as pairs of Fab fragments which have hinge cysteines between them. Other chemical couplings of antibody fragments are also known.

As used herein, the term “antibody fragment” or “antigen-binding fragment” or “active fragment” is defined as a portion of an intact antibody comprising the antigen binding site or variable region of the intact antibody, wherein the portion is free of the constant heavy chain domains (i.e. CH2, CH3, and CH4, depending on antibody isotype) of the Fc region of the intact antibody. Examples of antibody fragments include Fab, Fab', Fab'-SH, F(ab')2, and Fv frag-

ments; diabodies; any antibody fragment that is a polypeptide having a primary structure consisting of one uninterrupted sequence of contiguous amino acid residues (referred to herein as a “single-chain antibody fragment” or “single chain polypeptide”), including without limitation (1) single-chain Fv (scFv) molecules, (2) single chain polypeptides containing only one light chain variable domain, or a fragment thereof that contains the three CDRs of the light chain variable domain, without an associated heavy chain moiety, (3) single chain polypeptides containing only one heavy chain variable region, or a fragment thereof containing the three CDRs of the heavy chain variable region, without an associated light chain moiety, (4) nanobodies comprising single Ig domains from non-human species or other specific single-domain binding modules; and multispecific or multivalent structures formed from antibody fragments. In an antibody fragment comprising one or more heavy chains, the heavy chain(s) can contain any constant domain sequence (e.g. CH1 in the IgG isotype) found in a non-Fc region of an intact antibody, and/or can contain any hinge region sequence found in an intact antibody, and/or can contain a leucine zipper sequence fused to or situated in the hinge region sequence or the constant domain sequence of the heavy chain(s), and (5) an isolated complementarity determining region (CDR).

The terms “phagocytic cells” and “phagocytes” are used interchangeably herein to refer to a cell that is capable of phagocytosis. There are four main categories of phagocytes: macrophages, mononuclear cells (histiocytes and monocytes), polymorphonuclear leukocytes (neutrophils), and dendritic cells.

As used herein “chimeric” refers to a molecule that includes sequences derived from two different molecules.

The term “Fc region” is used to define a C-terminal region of an immunoglobulin heavy chain. The “Fc region” may be a native sequence Fc region or a variant Fc region. Although the boundaries of the Fc region of an immunoglobulin heavy chain might vary, the human IgG heavy chain Fc region is usually defined to stretch from an amino acid residue at position Cys226, or from Pro230, to the carboxyl-terminus thereof. The numbering of the residues in the Fc region is that of the EU index as in Kabat. Kabat et al., Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, Md., 1991. The Fc region of an immunoglobulin generally comprises two constant domains, CH2 and CH3, and when the Fc region is employed as a scaffold according to embodiments of the present disclosure, the Fc region may comprise CH2, CH3, or combinations thereof. The Fc region as a scaffold or in a heavy chain of an antibody may contain mutations. For example, heavy chain constant region or Fc region may contain substitutions selected from T250Q/M428L; M252Y/S254T/T256E+H433K/N434F; E233P/L234V/L235A/G236A+A327G/A330S/P331S; E333A; S239D/A330L/I332E; P257I/Q311; K326W/E333S; S239D/I332E/G236A; N297A; L234A/L235A; N297A+M252Y/S254T/T256E; K322A and K444A, wherein the numbering is according to the EU numbering (Edelman, G. M. et al., Proc. Natl. Acad. USA, 63, 78-85 (1969); [www.imgt.org/IMGTScientificChart/Numbering/HuIGHGnber.html#refs](http://www.imgt.org/IMGTScientificChart/Numbering/HuIGHGnber.html#refs)).

As used herein, “Fc receptor” and “FcR” describe a receptor that binds to the Fc region of an antibody. The preferred FcR is a native sequence human FcR. Moreover, a preferred FcR is one which binds an IgG antibody (a gamma receptor) and includes receptors of the Fc<sub>Y</sub>RI, Fc<sub>Y</sub>RII, and Fc<sub>Y</sub>RIII subclasses, including allelic variants and alternatively spliced forms of these receptors. Fc<sub>Y</sub>RII receptors

19

include Fc<sub>γ</sub>RIIA (an “activating receptor”) and Fc<sub>γ</sub>RIM (an “inhibiting receptor”), which have similar amino acid sequences that differ primarily in the cytoplasmic domains thereof.

A “native sequence Fc region” or “wild-type Fc region” comprises an amino acid sequence identical to the amino acid sequence of an Fc region found in nature. A “variant Fc region” comprises an amino acid sequence which differs from that of a native sequence Fc region by virtue of at least one amino acid modification, yet retains at least one effector function of the native sequence Fc region. Preferably, the variant Fc region has at least one amino acid substitution compared to a native sequence Fc region or to the Fc region of a parent polypeptide, e.g. from about one to about ten amino acid substitutions, and preferably from about one to about five amino acid substitutions in a native sequence Fc region or in the Fc region of the parent polypeptide. The variant Fc region herein will preferably possess at least about 80% sequence identity with a native sequence Fc region and/or with an Fc region of a parent polypeptide, and most preferably at least about 90% sequence identity therewith, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99% sequence identity therewith.

A polynucleotide or polypeptide having a certain percent “sequence identity” to another polynucleotide or polypeptide, means that, when aligned, that percentage of bases or amino acids are the same, and in the same relative position, when comparing the two sequences. Sequence similarity can be determined in a number of different manners. To determine sequence identity, sequences can be aligned using the methods and computer programs, including BLAST, available over the world wide web ([www.ncbi.nlm.nih.gov/BLAST](http://www.ncbi.nlm.nih.gov/BLAST)). See, e.g., Altschul et al. (1990), J. Mol. Biol. 215:403-10. Another alignment algorithm is FASTA, available in the Genetics Computing Group (GCG) package. See also at [ebi.ac.uk/Tools/ss3/fasta/](http://ebi.ac.uk/Tools/ss3/fasta/). Other techniques for alignment are described in Methods in Enzymology, vol. 266: Computer Methods for Macromolecular Sequence Analysis (1996), ed. Doolittle, Academic Press, Inc., a division of Harcourt Brace & Co., San Diego, Calif., USA. Of particular interest are alignment programs that permit gaps in the sequence. The Smith-Waterman is one type of algorithm that permits gaps in sequence alignments. See Meth. Mol. Biol. 70:173-187 (1997). Also, the GAP program using the Needleman and Wunsch alignment method can be utilized to align sequences. See J. Mol. Biol. 48:443-453 (1970), doi: 10.1016/0022-2836 (70) 90057-4.

As used herein, an “effective dosage” or “effective amount” drug, compound, or pharmaceutical composition is an amount sufficient to effect beneficial or desired results. For prophylactic use, beneficial or desired results include results such as eliminating or reducing the risk, lessening the severity, or delaying the onset of the disease, including biochemical, histological and/or behavioral symptoms of the disease, its complications and intermediate pathological phenotypes presenting during development of the disease. For therapeutic use, beneficial or desired results include clinical results such as inhibiting, suppressing or reducing the formation of substance accumulation (non-limiting example may include amyloid plaques), reducing, removing, clearing amyloid plaques, improving cognition, reversing or slowing cognitive decline, sequestering or increasing soluble substance circulating in biological fluids, decreasing one or more symptoms resulting from the disease (biochemical, histological and/or behavioral), including its complica-

20

tions and intermediate pathological phenotypes presenting during development of the disease, increasing the quality of life of those suffering from the disease, decreasing the dose of other medications required to treat the disease, enhancing effect of another medication, delaying the progression of the disease, and/or prolonging survival of patients. An effective dosage can be administered in one or more administrations. For purposes of this invention, an effective dosage of drug, compound, or pharmaceutical composition is an amount sufficient to accomplish prophylactic or therapeutic treatment either directly or indirectly. As is understood in the clinical context, an effective dosage of a drug, compound, or pharmaceutical composition may or may not be achieved in conjunction with another drug, compound, or pharmaceutical composition. Thus, an “effective dosage” may be considered in the context of administering one or more therapeutic agents, and a single agent may be considered to be given in an effective amount if, in conjunction with one or more other agents, a desirable result may be or is achieved.

As used herein, “treatment” or “treating” is an approach for obtaining beneficial or desired results including clinical results. For purposes of this invention, beneficial or desired clinical results include, but are not limited to, one or more of the following: inhibiting, suppressing or reducing the formation of deposit of substance, reducing, removing, or clearing amyloid deposits, improving cognition, reversing or slowing cognitive decline, sequestering soluble substance circulating in biological fluids, reducing a substance (including soluble, oligomeric and deposited) in a tissue, inhibiting, slowing and/or reducing accumulation of substance in the tissue, inhibiting, slowing and/or reducing toxic effects of a substance peptide in a tissue, decreasing symptoms resulting from the disease, increasing the quality of life of those suffering from the disease, decreasing the dose of other medications required to treat the disease, delaying the progression of the disease, and/or prolonging survival of patients. The tissue may include brain of an individual.

The term “development” of a disease means the onset and/or progression of the disease within an individual. A disease development can be detectable using standard clinical techniques as described herein. However, development also refers to disease progression that may be initially undetectable. For purposes of this invention, progression refers to the biological course of the disease state, in this case, as determined by a standard neurological examination, patient interview, or may be determined by more specialized testing. A variety of these diagnostic tests include, but not limited to, neuroimaging, detecting alterations of levels of specific proteins in the serum or cerebrospinal fluid (e.g., amyloid peptides and Tau), computerized tomography (CT), and magnetic resonance imaging (MRI). “Development” includes occurrence, recurrence, and onset. As used herein “onset” or “occurrence” of a disease includes initial onset and/or recurrence.

As used herein, “delaying” development of a disease means to defer, hinder, slow, retard, stabilize, and/or postpone development of the disease. This delay can be of varying lengths of time, depending on the history of the disease and/or individual being treated. As is evident to one skilled in the art, a sufficient or significant delay can, in effect, encompass prevention, in that the individual does not develop the disease. For example, a method that delays development of a disease is a method that reduces probability of disease development in a given time frame and/or reduces extent of the disease in a given time frame, when compared to not using the method. Such comparisons are

21

typically based on clinical studies, using a statistically significant number of subjects.

As used herein, "vector" means a construct, which is capable of delivering, and preferably expressing, one or more gene(s) or sequence(s) of interest in a host cell. Examples of vectors include, but are not limited to, viral vectors, naked DNA or RNA expression vectors, plasmid, cosmid or phage vectors, DNA or RNA expression vectors associated with cationic condensing agents, DNA or RNA expression vectors encapsulated in liposomes, and certain eukaryotic cells, such as producer cells.

A "host cell" includes an individual cell or cell culture that can be or has been a recipient for vector(s) for incorporation of polynucleotide inserts. Host cells include progeny of a single host cell, and the progeny may not necessarily be completely identical (in morphology or in genomic DNA complement) to the original parent cell due to natural, accidental, or deliberate mutation. A host cell includes cells transfected in vivo with a polynucleotide(s) of this invention.

As used herein, "expression control sequence" means a nucleic acid sequence that directs transcription of a nucleic acid. An expression control sequence can be a promoter, such as a constitutive or an inducible promoter, or an enhancer. The expression control sequence is operably linked to the nucleic acid sequence to be transcribed.

As used herein, "pharmaceutically acceptable carrier" includes any material which, when combined with an active ingredient, allows the ingredient to retain biological activity and is non-reactive with the subject's immune system. Examples include, but are not limited to, any of the standard pharmaceutical carriers such as a phosphate buffered saline solution, water, emulsions such as oil/water emulsion, and various types of wetting agents. Preferred diluents for aerosol or parenteral administration are phosphate buffered saline or normal (0.9%) saline. Compositions comprising such carriers are formulated by well-known conventional methods.

#### TAM Receptor

TAM receptors (Tyro3, Axl, and Mer) belong to a family of receptor tyrosine kinases that have important effects on homeostasis and inflammation. Also, they affect cell proliferation, survival, adhesion, and migration. TAM receptors comprise 2 immunoglobulin-like and 2 fibronectin type III repeats in their extracellular domains in tandem. This is connected to a single-pass transmembrane domain and a cytoplasmic protein tyrosine kinase. Left figure of FIG. 1A.

TAM receptors enhance phagocytosis of apoptotic cells, also known as efferocytosis.

The Axl protein contains 894 amino acids with a glycine-rich loop (Gly543-Gly548), a catalytic loop (His670-Asn677), and a DFG motif (Asp690-Phe691-Gly692). Although the molecular weight of the full-length Axl is 104 kDa, post-translational modifications of the extracellular domains give rise to two modified forms with molecular weights 120 and 140 kDa. Potential N-linked glycosylation sites include Asn43, Asn157, Asn198, Asn339, Asn345, and Asn401. In various embodiments of the present disclosure, the term "Axl" or "Axl receptor" or "Axl protein" includes the full-length Axl of 104 kDa, post-translational modified Axl, and glycosylated Axl. In some embodiments, the human Axl polypeptide corresponds to Genbank accession no. NP\_068713 or NP\_068713.2 (isoform 1 precursor), SEQ ID NO: 114, or UniProt accession no. P30530.4, Q8N5L2, or Q9UD27, or their mature forms. Amino acid residues

22

1-32 of SEQ ID NO: 114 is reported as signal sequence, and regions ranging amino acid residues 26 to 92 of SEQ ID NO: 114 is reported as interaction with Gas6. In one embodiment, the nucleic acid encoding the human Axl polypeptide corresponds to Genbank accession no. NM\_021913, version no. NM\_021913.5. Murine Axl refers to the Axl member of the murine TAM family of receptor tyrosine kinases. In some embodiments, the murine Axl polypeptide corresponds to Genbank accession no. AAH46618, version no. AAH46618.1, SEQ ID NO: 115. In one embodiment, the nucleic acid encoding the murine Axl polypeptide corresponds to Genbank accession no. BC046618, version no. BC046618.1. Various natural variants and mutations, and posttranslational variants and mutants of Axl as well as orthologues of Axl have been reported. For example, human Axl proteins under accession nos. NP\_001265528.1 (626 amino acid residues), NP\_001690.2 (885 amino acid residues, isoform 2 precursor), EAW57022 (885 amino acid residues, isoform CRA\_a), EAW57023.1 (894 amino acid residues, isoform CRA\_b), AAH32229.1 (894 amino acid residues), AAH32229.1 (885 amino acid residues), and the like are considered as "Axl" or "Axl receptor" or "Axl protein" according to the embodiments of the present disclosure.

The cells expressing the TAM receptor(s) may be at least one type of professional phagocytes, at least one type of non-professional phagocytes, or a combination thereof. Here, the professional phagocytes refer to cells whose main role is to remove dead cells and accumulated debris through phagocytosis, and examples thereof include macrophages, neutrophils, dendritic cells, and mast cells. Macrophages usually stay in each tissue that can become a path of infection, and in many cases, they are called different names for tissues, including, for example, adipose tissue macrophages, bone marrow or blood monocytes, hepatic Kupffer cells, lymph node sinus histiocytes, alveolar macrophages, connective tissue histiocytes or giant cells, microglia of the central nervous system, placental Hofbauer cells, renal intraglomerular mesangial cells, bone osteoclasts, epithelioid cells of granulomas, red pulp macrophages of the spleen, peritoneal macrophage of the peritoneal cavity, LysoMac of Peyer's patch, and the like. On the other hand, the non-professional phagocytes refer to cells that mainly perform functions specific to the tissue in which the phagocytes reside, but can perform phagocytosis when necessary, and examples thereof are epithelial cells, endothelial cells, fibroblasts, mesenchymal cells, some tissue-specific cells, for example, astrocytes or oligodendrocyte of the central nervous system, retinal Muller glia, hepatocytes, muscular satellite cells, testicular Sertoli cells, etc., and some lymphocytes such as natural killer cells, large granular lymphocytes, eosinophils, basophils, B cells, etc. The fusion molecule according to the present disclosure is able to induce phagocytosis in phagocytes specific to a tissue in which a target substance to be cleared accumulates. For example, when abnormal proteins accumulated in the brain are to be cleared, the phagocytosis may be induced in astrocytes, microglia, oligodendrocytes, or combinations thereof. It may be induced, for example, by topically administering the fusion molecule according to the present disclosure to this tissue or by manipulating cells in the tissue to express and secrete the fusion molecule.

#### First Region Comprising a Sequence Capable of Binding to TAM Receptor

TAM receptors can be activated via their ligands, growth arrest specific 6 protein (Gas6) and Protein S (Pros1), which are members of the family of vitamin K-dependent proteins.

23

In exemplary embodiments, the first region that is capable of binding to TAM receptors may comprise, consist of, or consist essentially of one or more TAM ligands.

A TAM ligand, protein S contains an amino terminal  $\gamma$  carboxyglutamic acid (GLA) domain, followed by a thrombin-sensitive loop region and 4 epidermal growth factor-like domains ending with the carboxy-terminal (C-terminal), consisting of 2 laminin G repeats that together comprise the sex hormone-binding globulin domain (right figure of FIG. 1A). The C-terminal region is sufficient for TAM receptor binding and phosphorylation. Gas6 is a 75-kDa vitamin K-dependent protein and has high structural homology (~42%) with protein S and the modular composition is the same as shown in FIG. 1A.

In addition to Gas6 (SEQ ID NO: 7) and ProS1 (SEQ ID NO: 34), tubby (accession nos. P50607, U54644.1, AAB53494.1, U82467.1, AAB53699.1, CH471064.2, EAW68634.1, BC075031.2, AAH75031.1, BC075032.2, AAH75032.1, NP\_003311.2, NP\_813977.1, 1S31\_A), tubby-like protein 1 (Tulp1) (accession nos. AAB53700.1, AAH32714.1, AAH65261.1, NP\_001276324.1, AAB97966.1, EAX03840.1, EAX03839.1, BAJ84064.1, BAJ84063.1, AKU84911.1, NP\_813977.1, NP\_003311.2), and galectin-3 (Gal3) (accession nos. NP\_002297, NP\_002297.1) are reported as TAM receptor ligands. Tubby and Gal3 specifically bind to Mer, whereas Tulp1 can activate all 3 of the TAM receptors.

Gas6, one of the ligands for TAM receptors, is reported to show the highest affinity for Axl compared to Tyro3 or Mer. Human Gas6 contains 678 amino acids (SEQ ID NO: 7), with gamma-carboxyglutamic acid (Gla) domains, four epidermal growth factor (EGF)-like domains, and two laminin G-like (LG) domains (FIG. 1A, right figure). Various isoforms of GAS6 are reported. For example, S6L, G8R, G8V, R14H, L18Q isoforms have been reported and these isoforms are included in the present disclosure.

In embodiments, the first region that is capable of binding to TAM receptor may comprise, consist of, or consist essentially of Gas6 protein or an active fragment thereof. The term "active fragment" as used herein denotes a fragment that is capable of binding to TAM receptor, in particular, Axl receptor. For example, an active fragment of Gas6 protein may comprise, consist of, or consist essentially of the sequence of SEQ ID NO: 1, 2, 5, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, or 87. For example, an active fragment of ProS protein may comprise, consist of, or consist essential of the sequence of SEQ ID NO: 3, 4, 6, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, or 113. The present disclosure encompass the sequences having sequence identity of at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% to the sequence of any one of SEQ ID NOS. Sequences of SEQ ID NOS: 8-23 show sequence identity of at least 85% to SEQ ID NO: 1 (LG-1 domain of Gas6). Sequences of SEQ ID NOS: 24-33 show sequence identity of at least 85% to SEQ ID NO: 2 (LG-2 domain of Gas6). Sequences of SEQ ID NOS: 35-45 show sequence identity of at least 85% to SEQ ID NO: 3 (LG-1 domain of ProS). Sequences of SEQ ID NOS: 46-62 show sequence identity of at least 85% to SEQ ID NO: 4 (LG-2

24

domain of ProS). Sequences of SEQ ID NOS: 63-87 show sequence identity of at least 85% to SEQ ID NO: 5 (LG domains of Gas6). Sequences of SEQ ID NOS: 88-113 show sequence identity of at least 84% to SEQ ID NO: 6 (LG domains of ProS).

In other embodiments, the first region may comprise, consist, or consist essentially of variable region or CDRs of an anti-Axl antibody or a full-length anti-Axl antibody of which the effector function, in particular, Fc receptor-binding function is abolished or removed. The antibody or antigen-binding fragments may bind to extracellular domain of Axl, for example expressed on surface of phagocytic cells and induce internalization and phagocytosis without involving inflammatory reaction, in particular Fc-mediated inflammatory reaction. Non-limiting examples of anti-Axl antibody may include those described in, for example, WO2017200493A1, WO2015193430A1, WO2011159980A1, WO2016097370A1, WO2012175691A1, WO2015193428A1, WO2010131733A1, WO2017220695A1, WO2010130751A1, WO2016166302A1, WO2017009258A1, WO2016005593A1, and the like, all of which the contents are incorporated by reference herein in their entireties. According to embodiments of the present disclosure, whole antibody, variable region, CDRs, or scFv, F(ab), or F(ab') of those anti-Axl antibodies may be employed as the first region of the fusion molecule. In certain embodiments, anti-Axl antibody may be anti-Axl agonistic antibodies or antigen-binding fragments thereof. The antibody or an antigen-binding fragment thereof may be selected from among, for example, i) immunoglobulins such as IgG1, IgG2, IgG3 and IgG4; ii) native antibody fragments such as Fv, Fab, Fab', F(ab')2, VH, VNAR, etc.; and iii) engineered antibodies such as scFv, dsFv, ds-scFv, (scFv)2, diabody, triabody, tetrabody, pentabody, etc. The antibody or antigen-binding fragment thereof may be, for example, a Mab, Fab, or single-chain variable fragment (scFv) based on an antibody that specifically binds to a corresponding target substance, or six complementarity-determining regions (CDRs) derived from the antibody.

In other embodiments, the first region may comprise, consist, or consist essentially of variable region or CDRs of an anti-MerTK (Mer Tyrosine Kinase) antibody or a full-length anti-MerTK antibody of which the effector function, in particular, Fc receptor-binding function is abolished or removed. The antibody or antigen-binding fragments may bind to extracellular domain of MerTK, for example expressed on surface of phagocytic cells and induce internalization and phagocytosis without involving inflammatory reaction, in particular Fc-mediated inflammatory reaction. Non-limiting examples of anti-MerTK antibody may include those described in, for example, WO2016106221A1, WO2020076799A1, WO2020176497A1, and the like, all of which the contents are incorporated by reference herein in their entireties. According to embodiments of the present disclosure, whole antibody, variable region, CDRs, or scFv, F(ab), or F(ab') of those anti-MerTK antibodies may be employed as the first region of the fusion molecule. The antibody or an antigen-binding fragment thereof may be selected from among, for example, i) immunoglobulins such as IgG1, IgG2, IgG3 and IgG4; ii) native antibody fragments such as Fv, Fab, Fab', F(ab')2, VH, VNAR, etc.; and iii) engineered antibodies such as scFv, dsFv, ds-scFv, (scFv)2, diabody, triabody, tetrabody, pentabody, etc. The antibody or antigen-binding fragment thereof may be, for example, a Mab, Fab, or single-chain variable fragment (scFv) based on an antibody

that specifically binds to a corresponding target substance, or six complementarity-determining regions (CDRs) derived from the antibody.

In other embodiments, the first region may comprise, consist, or consist essentially of variable region or CDRs of an anti-Tyro3 antibody or a full-length anti-Tyro3 antibody of which the effector function, in particular, Fc receptor-binding function is abolished or removed. The antibody or antigen-binding fragments may bind to extracellular domain of Tyro3, for example expressed on surface of phagocytic cells and induce internalization and phagocytosis without involving inflammatory reaction, in particular Fc-mediated inflammatory reaction. Non-limiting examples of anti-Tyro3 antibody may include those described in, for example, WO2016166348A1, and the like, all of which the contents are incorporated by reference herein in their entirieties. According to embodiments of the present disclosure, whole antibody, variable region, CDRs, or scFv, F(ab), or F(ab') of those anti-Tyro3 antibodies may be employed as the first region of the fusion molecule. The antibody or an antigen-binding fragment thereof may be selected from among, for example, i) immunoglobulins such as IgG1, IgG2, IgG3 and IgG4; ii) native antibody fragments such as Fv, Fab, Fab', F(ab')2, VH, VNAR, etc.; and iii) engineered antibodies such as scFv, dsFv, ds-scFv, (scFv)2, diabody, triabody, tetrabody, pentabody, etc. The antibody or antigen-binding fragment thereof may be, for example, a Mab, Fab, or single-chain variable fragment (scFv) based on an antibody that specifically binds to a corresponding target substance, or six complementarity-determining regions (CDRs) derived from the antibody.

The peptide comprising the sequence of any one of SEQ ID Nos above includes not only the amino acid sequence of the peptide but also an amino acid sequence variant thereof. The term "sequence variant" refers to a protein having a sequence in which one or more amino acid residues differ from the amino acid sequence. As long as the activity of the fusion molecule is maintained, any truncation, deletion, insertion, substitution, or a combination thereof in the final structure of the protein is possible. One example of the sequence variant is a form in which amino acid residues at sites not essential for activity are truncated or deleted, or amino acid residues at sites important for autoinhibition are substituted. In some cases, it may also be modified by phosphorylation, glycosylation, methylation, farnesylation, or the like. These sequence variations and modifications are more preferable when the function and/or stability (thermal stability, pH stability, structural stability, etc.) and/or solubility of the protein are increased by mutation in the amino acid sequence.

The method for mutagenesis of the amino acid sequence is based on a method of producing a nucleic acid molecule comprising a nucleotide sequence corresponding to the amino acid sequence to be mutated by mutating a nucleotide sequence encoding the protein, and a method for obtaining the gene encoding the protein may be performed in vivo or in vitro using any mutagenesis technique well known in the art, for example, site-directed mutagenesis (Hutchinson et al., *J. Biol. Chem.*, 253:6551, 1978; Zoller and Smith, *DNA*, 3:479-488, 1984; Oliphant et al., *Gene*, 44:177, 1986; Hutchinson et al., Proc. Natl. Acad. Sci. U.S.A., 83:710, 1986), TAB linker (Pharmacia), PCR technique (Higuchi, 1989, "Using PCR to Engineer DNA" in *PCR Technology: Principles and Applications for DNA Amplification*, H. Erlich, ed., Stockton Press, Chapter 6, pp. 61-70), or the like.

Amino acid sequence insertions include amino- and/or carboxyl-terminal fusions ranging in length from one resi-

due to polypeptides containing a hundred or more residues, as well as intrasequence insertions of single or multiple amino acid residues. Examples of terminal insertions include an antibody with an N-terminal methionyl residue or the antibody fused to an epitope tag. Other insertional variants of the antibody molecule include the fusion to the N- or C-terminus of the antibody of an enzyme or a polypeptide which increases the serum half-life of the antibody.

Examples of modified polypeptides include polypeptides with conservative substitutions of amino acid residues, one or more deletions or additions of amino acids which do not significantly deleteriously change the functional activity, or use of chemical analogs.

Substitution variants have at least one amino acid residue in the antibody molecule removed and a different residue inserted in its place. The sites of greatest interest for substitutional mutagenesis include the hypervariable regions, but FR alterations are also contemplated. Conservative substitutions are shown in Table 2 under the heading of "conservative substitutions". If such substitutions result in a change in biological activity, then more substantial changes, denominated "exemplary substitutions" in Table 2, or as further described below in reference to amino acid classes, may be introduced and the products screened.

TABLE 2

Amino acid substitutions			
	Original Residue	Conservative Substitutions	Exemplary Substitutions
35	Ala (A)	Val	Val; Leu; Ile
	Arg (R)	Lys	Lys; Gln; Asn
	Asn (N)	Gln	Gln; His; Asp, Lys; Arg
	Asp (D)	Glu	Glu; Asn
	Cys (C)	Ser	Ser; Ala
	Gln (Q)	Asn	Asn; Glu
	Glut (E)	Asp	Asp; Gln
	Gly (G)	Ala	Ala
	His (H)	Arg	Asn; Gln; Lys; Arg
	Ile (I)	Leu	Leu; Val; Met; Ala; Phe; Norleucine
40	Leu (L)	Ile	Norleucine; Ile; Val; Met; Ala; Phe
	Lys (K)	Arg	Arg; Gln; Asn
	Met (M)	Leu	Leu; Phe; Ile
	Phe (F)	Tyr	Leu; Val; Ile; Ala; Tyr
	Pro (P)	Ala	Ala
	Ser (S)	Thr	Thr
	Thr (T)	Ser	Ser
	Trp (W)	Tyr	Tyr; Phe
	Tyr (Y)	Phe	Trp; Phe; Thr; Ser
	Val (V)	Leu	Ile; Leu; Met; Phe; Ala; Norleucine
45			

Substantial modifications in the biological properties of the antibody are accomplished by selecting substitutions that differ significantly in their effect on maintaining (a) the structure of the polypeptide backbone in the area of the substitution, for example, as a sheet or helical conformation, (b) the charge or hydrophobicity of the molecule at the target site, or (c) the bulk of the side chain. Naturally occurring residues are divided into groups based on common side-chain properties:

Non-polar: Norleucine, Met, Ala, Val, Leu, Ile;  
 Polar without charge: Cys, Ser, Thr, Asn, Gln;  
 Acidic (negatively charged): Asp, Glu;  
 Basic (positively charged): Lys, Arg;  
 Residues that influence chain orientation: Gly, Pro; and  
 Aromatic: Trp, Tyr, Phe, His.

Non-conservative substitutions are made by exchanging a member of one of these classes for another class. Any

cysteine residue not involved in maintaining the proper conformation of the antibody also may be substituted, generally with serine, to improve the oxidative stability of the molecule and prevent aberrant cross-linking. Conversely, cysteine bond(s) may be added to the antibody to improve its stability, particularly where the antibody is an antibody fragment such as an Fv fragment.

Amino acid modifications can range from changing or modifying one or more amino acids to complete redesign of a region, such as the variable region. Changes in the variable region can alter binding affinity and/or specificity. In some embodiments, no more than one to five conservative amino acid substitutions are made within a CDR domain. In other embodiments, no more than one to three conservative amino acid substitutions are made within a CDR domain. In still other embodiments, the CDR domain is CDR H3 and/or CDR L3.

#### Target Substances and Diseases Characterized by Aberrant Accumulation or Deposit of Target Substances

The target substance may be a substance that accumulates in living tissue, causing a disease. For example, it may be a substance accumulated in an affected (i.e., diseased) tissue of a patient. The substance accumulated in a disease may be protein. That is, the disease may be proteopathy, without being limited thereto. For example, the target substance may be amyloid. That is, the proteopathy may be amyloidosis. The target substance may be selected from abnormally accumulated substances listed in Table 1 above, and in this case, the disease may be a disease in which each abnormally accumulated substance is detected. In some embodiments, the target substance, of which aberrant accumulation is associated with proteopathy and which is desired to be cleared or reduced or suppressed, may be APOE or apoptosis-associated spec-like protein containing a caspase activating recruitment domain (ASC-speck). For example, the proteopathy may be selected from Alzheimer's disease, Parkinson's disease, Huntington's disease, and Prion disease, and in this case, target substances may be abnormally accumulated proteins that cause the diseases. That is, the target substances may be  $\beta$ -amyloid, tau,  $\alpha$ -synuclein, huntingtin, and prion proteins, respectively.

Aberrant accumulation of APOE is associated with Alzheimer's disease, cerebral amyloid angiopathy, and/or cardiovascular disease. Aberrant accumulation of apoptosis-associated spec-like protein containing a caspase activating recruitment domain (ASC-speck) is associated with Alzheimer's Disease, Parkinson's Disease, Huntington's disease, Multiple System Atrophy, Amyotrophic Lateral Sclerosis, Spinocerebellar ataxia, Frontotemporal Dementia, Frontotemporal Lobar Degeneration, Mild Cognitive Impairment, Parkinson-plus syndromes, Pick disease, Progressive isolated aphasia, Grey-matter degeneration [Alpers], Subacute necrotizing encephalopathy, and Lewy body dementia.

#### Second Region of Fusion Molecule

The second region that specifically binds to the target substance may be selected from among an antibody, an antigen-binding fragment thereof, an antibody-like protein, a peptide, an aptamer, and a soluble receptor, and is not particularly limited as long as it specifically binds to the target substance.

Here, the antibody or an antigen-binding fragment thereof may be selected from among, for example, i) immunoglobulins such as IgG1, IgG2, IgG3 and IgG4; ii) native antibody fragments such as Fv, Fab, Fab', F(ab')2, VH, VNAR, etc.; and iii) engineered antibodies such as scFv, dsFv, ds-scFv, (scFv)2, diabody, triabody, tetrabody, pentabody, etc. The antibody or antigen-binding fragment thereof may be, for example, a Mab, Fab, or single-chain variable fragment (scFv) based on an antibody that specifically binds to a corresponding target substance, or six complementarity-determining regions (CDRs) derived from the antibody. That is, the protein or antigen-binding fragment thereof that specifically binds to the target substance comprises a portion necessary for an activity that specifically binds to the target substance, and the type or range thereof is not particularly limited as long as the protein or antigen-binding fragment thereof is linked to the first region and does not cause an inflammatory response and synaptic damage. For example, the target substance may be beta-amyloid, and in this case, the protein or antigen-binding fragment thereof that specifically binds to the target substance may comprise aducanumab or a single-chain variable fragment thereof. The second region comprise a Mab, Fab, or single-chain variable fragment based on based on six complementarity determining regions (CDRs) derived from commercially available antibodies such as aducanumab, semorinemab, and cintapanemab.

In non-limiting exemplary embodiments, the sequence information of the target substance can be obtained from public database and the target substance-binding sequences can be obtained from the publications or public database. By way of exemplary embodiments, some sequences from the public database are exemplified below. One skilled art should understand that sequences of target substance or a second region capable of binding to the target substance are not limited to the specific sequences exemplified below, but encompass isomers, orthologues, variants, and mutants. For example, when Amyloid precursor protein-derived  $\beta$ -amyloid is a target substance, the target subject may have the sequence available under GenBank accession no. AAB29908.1 or a fragment thereof (e.g., beta-amyloid (29-40) or a Chain A (Accession No. 1BJC\_A)), and the second region that is capable of binding to the target substance can have a light chain variable region of SEQ ID NO: SEQ ID NO: 161 and a heavy chain variable region of SEQ ID NO: 162. When the target substance is  $\alpha$ -Synuclein, it can have the sequence available under UniProtKB/Swiss-Prot: P37840.1 or a fragment thereof, and the second region capable of binding to the target substance may have light chain variable region of SEQ ID NO: 163 and a heavy chain variable region of SEQ ID NO: 164. When the target substance is Microtubule-associated protein tau, it can have the sequence available under UniProtKB/Swiss-Prot: P10636.5 or a fragment thereof, and the second region capable of binding to the target substance may have light chain variable region of SEQ ID NO: 165 and a heavy chain variable region of SEQ ID NO: 166. When the target substance is PrP<sup>Sc</sup>, it can have the sequence available under GenBank Accession No. NP\_001073592.1 or a fragment thereof, and the second region capable of binding to the target substance may be the sequences disclosed in US 2021/0070870 A1. When the target substance is Huntingtin exon 1, it can have the sequence available under GenBank Accession No. NP\_001375421.1 or a fragment thereof, and the second region capable of binding to the target substance may be the sequences disclosed in US 2022/0332808 A1. When the target substance is TAR DNA-binding protein 43

(TDP43), it can have the sequence available under UniProtKB/Swiss-Prot: Q13148.1 or a fragment thereof, and the second region capable of binding to the target substance may be the sequences disclosed in U.S. Pat. No. 9,587,014 B2. When the target substance is superoxide dismutase 1 (SOD1), it can have the sequence available under GenBank: CAG46542.1 or a fragment thereof, and the second region capable of binding to the target substance may be the sequences disclosed in U.S. Pat. No. 9,283,271 B2. When the target substance is an immunoglobulin light-chain fragment, it can have the sequence available under PDB: 6Z1O\_A or a fragment thereof, and the second region capable of binding to the target substance may be the sequences disclosed in U.S. Pat. No. 8,268,973 B2. When the target substance is an N-terminal fragment of serum amyloid A protein, it can have the sequence available under GenBank: AAB24060.1, GenBank: AAA85338.1, NCBI NP\_001372595.1, or NCBI Reference Sequence: NP\_110381.2 or a fragment thereof, and the second region capable of binding to the target substance may be the sequences disclosed in U.S. Pat. No. 8,268,973 B2. When the target substance is a transthyretin, it can have the sequence available under UniProtKB/Swiss-Prot: P02766.1 or a fragment thereof, and the second region capable of binding to the target substance may be the sequences disclosed in U.S. Pat. No. 11,267,877 B2. When the target substance is an amylin, IAPP (AIAPP), it can have the sequence available under UniProtKB/Swiss-Prot:P10997 or a fragment thereof, and the second region capable of binding to the target substance may be the sequences disclosed in U.S. Pat. No. 10,882,902. When the target substance is an APOE, it can have the sequence available under UniProtKB/Swiss-Prot:P02649.1 or a fragment thereof, and the second region capable of binding to the target substance may be the sequences disclosed in US 2022/0411485A. When the target substance is an Apoptosis-associated Spec-like protein containing a Caspase Activating Recruitment Domain (ASC-speck), it can have the sequence available under UniProtKB/Swiss-Prot:Q9ULZ3.2 or a fragment thereof (e.g., US 2021/0079075A), and the second region capable of binding to the target substance may be the sequences disclosed in US No. 10,961,3-6 B22021/0079075A.

The antibody or antigen-binding fragment thereof may not comprise an Fc region, and preferably may comprise an Fc region variant that does not bind to an Fc receptor (particularly an Fc $\gamma$  receptor). This Fc region variant may serve to improve properties such as purification. Fc variants with a reduced affinity to the human Fc $\gamma$ RIIA and/or Fc $\gamma$ RIIA and/or Fc $\gamma$ RI compared to a IgG Fc region by way of amino acid substitution are disclosed for example, WO2012130831 and U.S. Pat. No. 8,753,628, of which entire content is incorporated by reference herein. Fc regions may be aglycosylated or deglycosylated.

The antibody-like protein refers to a protein scaffold capable of specifically binding to a target substance, like an antibody. Antibody-like proteins may be designed to have a size of about 2 to 20 kDa, which is smaller than antibodies (about 150 kDa on average), and thus target a binding site that antibodies cannot reach. It is known that antibody-like proteins are more stable at high temperatures than antibodies and are much easier to synthesize using non-mammalian cells such as viruses and yeast or synthesize chemically, compared to antibodies.

As used herein, the term "aptamer" refers to a single-stranded DNA (ssDNA) or RNA having high specificity and affinity for a specific substance. Aptamers have a very high affinity for specific substances, are stable, may be synthe-

sized in a relatively simple way, may be modified in various ways to increase the binding affinity thereof, and can target cells, proteins, and even small organic substances. Thus, the aptamers are characterized by having very high specificity and stability compared to antibodies that have already been developed. In addition, the aptamer may be produced through a known SELEX (Systematic Evolution of Ligands by Exponential enrichment) method. As this aptamer, an aptamer that specifically binds to, for example, beta-amyloid, tau, or alpha-synuclein, may be produced through a known SELEX (Systematic Evolution of Ligands by Exponential enrichment) method and then linked to the first region, thereby producing the fusion molecule according to the present invention.

The aptamer of the present disclosure is not limited as long as it is able to specifically bind to beta-amyloid, tau, or alpha-synuclein, and bases that are used for the aptamer may be selected from among A, G, C, U, and deoxy forms thereof, unless otherwise specified.

In addition, the aptamer may be modified by linkage of at least one, selected from the group consisting of polyethylene glycol (PEG), inverted deoxythymidine (idT), locked nucleic acid (LNA), 2'-methoxy nucleoside, 2'-amino nucleoside, 2'F-nucleoside, amine linker, thiol linker, and cholesterol, at the 5'-end region, intermediate region, 3'-end region, or both ends thereof in order to increase the stability thereof. Inverted deoxythymidine (idT) is a molecule that is generally used to prevent nuclease degradation of an aptamer having weak nuclease resistance. In the case of a nucleic acid unit, the 3'-OH of the previous nucleotide is attached to the 5'-OH of the next nucleotide to form a chain, but in the case of idT, the 3'-OH of the previous nucleotide is attached to the 3'-OH of the next unit so that 5'-OH, not 3'-OH, is exposed. Thus, idT is a molecule that has the effect of inhibiting degradation by 3' exonuclease, a type of nuclease. In exemplary embodiments, aptamers against beta-amyloid include, but are not limited to, those reported in Yan Zheng, Advances in aptamers against A $\beta$  and applications in A $\beta$  detection and regulation for Alzheimer's disease, Theranostics, 2022; 12(5): 2095-2114, of which the content is incorporated by reference herein in its entirety.

The soluble receptor of the present disclosure comprises a domain having an activity capable of binding to a target substance, that is, an endogenous ligand, wherein the domain may be one derived from an endogenous membrane receptor or an intracellular receptor, or a derivative thereof. In this case, the soluble receptor comprised in the second region of the fusion molecule of the present disclosure may preferably be one in which regions having activities other than binding to a target substance have been removed from the endogenous receptor. Exemplary soluble receptors that bind to beta-amyloid are reported by John E. Donahue et al., RAGE, LRP-1, and amyloid-beta protein in Alzheimer's disease, Acta Neuropathol (2006) 112:405-415, of which the content is incorporated by reference herein in its entirety.

In the embodiments, the peptide as a second region, means an entity other than the antibody or an active fragment thereof, antibody-like protein or soluble receptor among polypeptides having amino acids as monomers capable of binding specifically to a target substance. Various peptides that bind to beta amyloid are reported in, for example, Alexander L. Schwarzman, Selection of peptides binding to the amyloid b-protein reveals potential inhibitors of amyloid formation, Amyloid, December 2005; 12(4): 199-209, of which the content is incorporated by reference herein in its entirety.

Since the fusion molecule according to the present disclosure induces phagocytosis through interaction with the TAM receptor(s), the phagocytosis may be induced in cells expressing the TAM receptor(s). Phagocytosis generally means ingestion of cells or particles of 0.5 μm or more in size, and includes a process of tethering, engulfing, and degrading the cells or particles. In this case, phagocytosis forms a phagosome that surrounds the internalized cell or particle, and includes degradation within the phagolysosome by fusion of the phagosome and the lysosome. In phagocytosis, the process of cell death by apoptosis or necrosis is also referred to as efferocytosis.

#### Fusion Molecule or Binding Molecule

The induction of phagocytosis by the fusion molecule according to the present disclosure may not involve an inflammatory response. This enables clearance of the target substance without inducing an inflammatory response and tissue damage caused by an inflammatory response to be suppressed so that tissue dysfunction caused by accumulation of the target substance can be treated more safely than conventional techniques.

According to the embodiments, the fusion molecule or the binding molecule does not contain the target substance or a fragment thereof, to which the first region binds.

The first region and the second regions, described above, are coupled to each other directly or via a linker, to form a fusion molecule. Embodiments of the fusion molecule according to the present disclosure encompass monomers of a polypeptide comprising the first region and the second region in a single chain as well as multimers composed of two or more polypeptide chains. Multimers encompass various forms of multimers such as homo-multimers and hetero-multimers. Therefore, according to the embodiments, the fusion molecule may have a monovalent first region (i.e., having one binding site to a single TAM receptor) or a multivalent first region(s) (i.e., having multiple first regions or having one single first region capable of binding to two or more TAM receptors). Embodiments of the fusion molecule according to the present disclosure may have a monovalent second region (i.e., having one binding site to a single target substance) or a multivalent second region(s) (i.e., having multiple second regions each binding different target substances or having one single second region capable of binding to two or more target substances). Embodiments of the fusion molecule according to the present disclosure may a monovalent first region and a monovalent second region; a monovalent first region and a multivalent second region; or a multivalent first region and a multivalent second region.

Schematic depiction of non-limiting exemplary embodiments of the fusion molecules are shown in FIGS. 1C through 1M.

FIG. 1C depicts fusion molecules comprising a first region and a second region coupled to each other. The first region of FIG. 1C may be any one of the first region described above, which is capable of binding to a TAM receptor. The first region may be a single TAM ligand or an antibody or antigen-binding fragment thereof. The first region may be of a plurality of same or different TAM binders. Similarly, the second region of FIG. 1C may be any one of the second region described above, which is capable of binding to a target substance. The second region may be a single target substance binder. The second region may be of a plurality of same or different target substance binders. A fusion molecule may comprise a scFv, Fab, nanobody, or

antibody as a first region and a scFv, Fab, nanobody, or antibody as a second region, a TAM ligand or a fragment thereof as a first region and a scFv, Fab, nanobody, or antibody as a second region, a scFv, Fab, nanobody, or antibody as a first region and a ligand or receptor or an aptamer as a second region, and the like. For example, a scFv, Fab, or nanobody as a first region or a second region may be a part of an antibody as a second region or a first region, forming a bispecific or multispecific antibody as a fusion molecule. A single or tandem of a scFv, Fab, or nanobody as a first or a second region may be linked to a whole antibody as a second or a first region. When the fusion molecule is a form of bispecific antibody, the first region is not an anti-MerTK antibody or a fragment thereof. The fusion molecule may be of a monomeric structure, a tandem structure where the first region, the second region, or the entire fusion molecule are repeated, or a multimeric structure containing two or more peptide chains. In case of multimeric fusion molecules, individual peptide chain may have a same sequence (homomultimer) or different sequences (heteromultimer). For heteromultimeric fusion molecules, the first region and the second region may present in all of the plural peptide chains forming the multimeric structure, or in different peptide chains, respectively, or a part of the plural peptide chains has both the first and the second region and the other(s) of the plural peptide chains has only either of the first region or the second region. While not shown in FIG. 1C, the fusion molecule may comprise one or more linker to couple the first region and the second region.

FIGS. 1D-1M depict fusion molecules comprising a first region and a second region as well as a scaffold. The first region, second region, and scaffold are as those described in this disclosure. As depicted in FIGS. 1D-1M, the scaffold may be bond to the first region and/or second region at different positions. The first region of FIGS. 1D-1M may be any one of the first region described above, which is capable of binding to a TAM receptor. The first region may be a single TAM ligand or an antibody or antigen-binding fragment thereof. The first region may be of a plurality of same or different TAM binders. Similarly, the second region of FIGS. 1C-1M may be any one of the second region described above, which is capable of binding to a target substance. The second region may be a single target substance binder. The second region may be of a plurality of same or different target substance binders. A fusion molecule may comprise a scFv, Fab, nanobody, or antibody as a first region and a scFv, Fab, nanobody, or antibody as a second region, a TAM ligand or a fragment thereof as a first region and a scFv, Fab, nanobody, or antibody as a second region, a scFv, Fab, nanobody, or antibody as a first region and a ligand or receptor or an aptamer as a second region, and the like. For example, a scFv, Fab, or nanobody as a first region or a second region may be a part of an antibody as a second region or a first region, forming a bispecific or multispecific antibody as a fusion molecule. A single or tandem of a scFv, Fab, or nanobody as a first or a second region may be linked to a whole antibody as a second or a first region. When the fusion molecule is a form of bispecific antibody, the first region is not an anti-MerTK antibody or a fragment thereof. The fusion molecule may be of a monomeric structure, a tandem structure, or a multimeric structure containing two or more peptide chains. In case of multimeric fusion molecules, individual peptide chains may have a same sequence (homomultimer) or different sequences (heteromultimer). In case of heteromultimeric fusion molecules, the first region and the second region may present in all of the plural peptide

chains forming the multimeric structure, or in different peptide chains, respectively, or a part of the plural peptide chains has both the first and the second region and the other(s) of the plural peptide chains has only either of the first region or the second region. While not shown in FIGS. 1D-1M, the fusion molecule may comprise one or more linker to couple the first region, the second region, and/or the scaffold.

The fusion molecule may further comprise a tag. When such a label is added to the fusion molecule, it may be used to check the purification, expression, action or mechanism of action of the fusion molecule.

Examples of the tag include, but are not limited to, His-tag, T7-tag, S-tag, FLAG-tag, Strep-tag, thioredoxin (Trx)-tag, His-patch thioredoxin-tag, lacZ (L-galactosidase)-tag, chloramphenicol acetyltransferase-tag, trpE-tag, avidin/streptavidin/Strep-tag, T7gene10-tag, staphylococcal protein A-tag, streptococcal protein G-tag, glutathione-S-transferase (GST)-tag, dihydrofolate reductase (DHFR)-tag, cellulose binding domains (CBDs)-tag, maltose binding protein (MBP)-tag, galactose-binding protein-tag, calmodulin binding protein (CBP)-tag, hemagglutinin influenza virus (HAI)-tag, HSV-tag, B-(VP7 protein region of bluetongue virus)-tag, polycysteine-tag, polyphenylalanine-tag, (Ala-Trp-Trp-Pro),-tag, polyaspartic acid-tag, c-myc-tag, lac repressor-tag, and the like. The tag may be located at the N-terminus, C-terminus or internally of the target protein.

The fusion molecule may further comprise a signal peptide or leader sequence at the N-terminus. It is known that a signal peptide is a short peptide present at the N-terminus at the initial stage of protein synthesis toward the secretory pathway, and directs the intracellular localization of the corresponding protein, membrane topology (in the case of a membrane protein), and the like. The signal peptide may be cleaved during expression and extracellular secretion of the fusion molecule.

The above-mentioned first region, second region, tag, signal peptide, or regions having minimal functionality (e.g., LG1 and LG2 regions or scFv heavy chain variable region and light chain variable region) included in the fusion molecule may be linked together directly or by a linker comprising a short oligopeptide or polypeptide. In general, the linker may comprise 2 to 500 amino acid residues. The length or type of the linker is not particularly limited as long as the linker can link the above-described regions together so as to have the intended activity, thereby forming the fusion molecule. An example of the linker may be the commonly used oligopeptide linker (GGGGS)n (SEQ ID NO: 116), that is, a linker in which one or more Gly-Gly-Gly-Gly-Ser (SEQ ID NO: 117) units are repeated. Other examples of the linker include, but are not limited to, (GSSGGS)n (SEQ ID NO: 118), KESGSVSSE-QLAQFRSLD (SEQ ID NO: 119), EGKSSGSGSESKEST (SEQ ID NO: 120), GSAGSAAGSGEF (SEQ ID NO: 121), (EAAAK)n (SEQ ID NO: 122), CRRRRRREAEAC (SEQ ID NO: 123), A(EAAAK)<sub>4</sub>ALEA(EAAAK)<sub>4</sub>A (SEQ ID NO: 124), GGGGGGGGG (SEQ ID NO: 125), GGGGGG (SEQ ID NO: 126), AEAAAKEAAAATA (SEQ ID NO: 127), PAPAP (SEQ ID NO: 128), (Ala-Pro)n, VSQTSKL-TRAETVFPDV (SEQ ID NO: 129), PLGLWA (SEQ ID NO: 130), TRHRQPRGWE (SEQ ID NO: 131), AGNRVRRSVG (SEQ ID NO: 132), RRRRRRRR (SEQ ID NO: 133), GFLG (SEQ ID NO: 134), and GSSGGSGSSGGSGGGDEADGSRGSQKAGVDE (SEQ ID NO: 135). Other suitable linkers comprise the sequences described in WO2012/088461A, of which the content is incorporated by reference herein in its entirety.

The fusion molecule according to embodiments of the present disclosure may further comprise a scaffold bound to the first region, to the second, or to both of the first region and the second region at different positions of the scaffold, as schematically depicted in FIGS. 1D-1D-1M. The scaffold refers to a protein or peptide, when incorporated into a protein or peptide of interest, improves properties of the total protein such as PK, enhances stability and/or in vivo half-life, or enhances productivity of the protein. In some embodiments, blood-brain barrier (BBB) permeable scaffold may optimize BBB permeability and/or optimizing distribution of the protein of interest (e.g., the fusion molecules according to the present disclosure) in the brain.

The scaffold may include, but not limited thereto, a single chain Fc region with reduced or abolished Fc receptor binding affinity, a multimer Fc region with reduced or abolished Fc receptor binding affinity, an antibody without variable region, or an Fc-hinge region with reduced or abolished Fc receptor binding affinity. In some embodiments, the scaffold may include albumin. The first region may be linked or fused to one position of the scaffold and the second region may be linked or fused to another position of the scaffold. The link or fusion between the first/the second region and the scaffold may be a direct bond or via a linker described above. It is known that heavy chain constant region or Fc region may contain mutations selected among T250Q/M428L; M252Y/S254T/T256E+H433K/N434F; E233P/L234V/L235A/G236A+A327G/A330S/P331S; E333A; S239D/A330L/1332E; P257I/Q311; K326W/E333S; S239D/1332E/G236A; N297A; L234A/L235A; N297A+M252Y/S254T/T256E; K322A and K444A, wherein the numbering is according to the EU numbering (Edelman, G. M. et al., Proc. Natl. Acad. USA, 63, 78-85 (1969); [imgt.org/IMGTScientificChart/Numbering/HuIGHGnber.html](http://imgt.org/IMGTScientificChart/Numbering/HuIGHGnber.html) #refs).

The fusion molecules according to aspects of the present disclosure may have a structure as schematically shown in non-limiting exemplary illustrations of, for example, FIG. 1B and FIGS. 1C through 1D-1M.

Structures of non-limiting exemplary fusion molecules (including signal sequences, optional linkers, and tags) are illustrated in Tables 3 and 5-13 and SEQ ID NOs: 136, 138, 140, 142, 150, 152, 154, 156, 158, 162-169. Non-limiting exemplary fusion molecules may comprise, consist of, or consist essentially of the fusion molecule (or binding molecule) of the sequence of amino acid residues 31-871 of SEQ ID NO: 136, amino acid residues 31-687 of SEQ ID NO:138, amino acid residues 31-697 of SEQ ID NO:140, amino acid residues 31-684 of SEQ ID NO: 150, amino acid residues 31-676 of SEQ ID NO: 152, amino acid residues 25-673 of SEQ ID NO: 154, amino acid residues 22-662 of SEQ ID NO: 156, or amino acid residues 22-885 of SEQ ID NO: 158, or a sequence having at least 90% sequence identity thereto, wherein a different linker can be used in place the linkers as shown in Tables 3 and 5-Another aspect of the present disclosure provides a nucleic acid molecule encoding the fusion molecule, and an expression vector containing the same.

As described above, the nucleic acid molecule sequence encoding the fusion molecule may be mutated by substitution, deletion, insertion, or a combination thereof, of one or more nucleotide residues, as long as it encodes a protein having an activity equivalent thereto. The nucleic acid molecule sequence encoding the fusion molecule may be isolated from nature or artificially produced through synthesis or genetic recombination. The nucleic acid molecule

35

sequence encoding the fusion molecule is operatively linked to an expression vector capable of expressing the same.

The term "expression vector" is a vector capable of expressing a protein or RNA of interest by introducing a nucleic acid sequence encoding a gene of interest into a suitable host cell, and refers to a gene construct containing essential regulatory elements operably linked to express the gene insert. Such expression vectors include all vectors such as plasmid vectors, cosmid vectors, bacteriophage vectors, and viral vectors.

A suitable expression vector has expression control elements such as a promoter, a start codon, a stop codon, a polyadenylation signal and an enhancer. The start codon and the stop codon are generally considered to be part of a nucleic acid sequence encoding a protein, and the sequence encoding the protein is designed to be in frame so as to be operable in the vector. The promoter may be constitutive or inducible. In addition, a conventional expression vector contains a selectable marker. Operational linkage with the expression vector can be performed using genetic recombination techniques well known in the art, and site-specific DNA cleavage and ligation can be performed using enzymes generally known in the art.

The expression vector may preferably be configured to express the fusion molecule in a host cell for isolation and purification of the fusion molecule or such that the vector may be introduced into a cell *in vivo* and the corresponding cell may express and secrete the fusion molecule. For the purpose of introducing into cells *in vivo*, the vector may preferably be a non-integrating vector, that is, a vector that is not integrated into the genome of a host cell.

Still another aspect of the present disclosure provides a cell expressing the fusion molecule.

The cells may be transformed to contain the nucleic acid molecule or an expression vector containing the same, and the "transformation" may be performed using suitable standard techniques selected depending on the host cell as known in the art, including any method of introducing the nucleic acid molecule into an organism, cell, tissue, or organ. These methods include, but are not limited to, electroporation, protoplast fusion, calcium phosphate ( $\text{CaPO}_4$ ) precipitation, calcium chloride ( $\text{CaCl}_2$ ) precipitation, agitation using silicon carbide fibers, agrobacterium-mediated transformation, PEG-, dextran sulfate-, lipofectamine-, and desiccation/inhibition-mediated transformation methods.

Examples of the host cells include, but are not limited to, prokaryotic host cells such as *Escherichia coli*, *Bacillus subtilis*, *Streptomyces*, *Pseudomonas* (e.g., *Pseudomonas putida*), *Proteus mirabilis*, or *Staphylococcus* (e.g., *Staphylococcus carnosus*). Other examples of the host cell include fungal cells such as *Aspergillus*, yeast cells, including *Pichia pastoris*, *Saccharomyces cerevisiae*, *Schizosaccharomyces*, and *Neurospora crassa*, lower eukaryotic cells, or cells derived from higher eukaryotes including insect cells, plant cells, or mammalian cells.

After the fusion molecule is expressed in the cells, it may be isolated and purified using conventional biochemical isolation techniques, such as treatment with a protein precipitating agent (salting out method), centrifugation, sonication, ultrafiltration, dialysis, or various chromatography such as molecular sieve chromatography (gel filtration), adsorption chromatography, ion exchange chromatography, and affinity chromatography, which are generally used in combination in order to isolate proteins with high purity (Sambrook et al., Molecular Cloning: A laboratory Manual, 2nd Ed., Cold Spring Harbor Laboratory Press(1989); Deus-

36

cher, M., Guide to Protein Purification Methods Enzymology, Vol. 182. Academic Press. Inc., San Diego, CA (1990)).

#### Pharmaceutical Composition

Yet another aspect of the present disclosure provides a pharmaceutical composition for preventing or treating a disease caused by accumulation of the target substance in living tissue, the pharmaceutical composition containing the fusion molecule or the expression vector. Here, the composition may be administered topically to a site where the substance that causes the disease, that is, the target substance, accumulates.

A further aspect of the present disclosure provides the use of the fusion molecule for manufacture of a medicament for preventing or treating proteopathy.

The fusion molecule, which is an active ingredient in the pharmaceutical composition, is contained in a "pharmaceutically effective amount".

The pharmaceutical composition may be administered orally or parenterally, preferably parenterally. More preferably, it may be administered topically to a tissue in which the target substance to be cleared accumulates.

As used herein, the term "parenteral administration" includes subcutaneous injection, intravenous, intramuscular, intrasternal injection or infusion techniques.

When the pharmaceutical composition is prepared as an injectable formulation, it may be prepared as the injectable formulation a conventional method known in the art. The injectable formulation may be in a form dispersed in a sterile medium so that it may be administered directly to a patient or may be in a form that may be administered after being dispersed in distilled water for injection at an appropriate concentration.

When the pharmaceutical composition is formulated for oral administration, it may contain one or more carriers selected from among diluents, lubricants, binders, disintegrants, sweeteners, stabilizers, and preservatives, and may contain one or more additives selected from among flavorings, vitamins, and antioxidants.

Techniques necessary for formulation of the pharmaceutical composition, and pharmaceutically acceptable carriers, additives, etc. are widely known to those skilled in the art (see, for example, the Handbook of Pharmaceutical Excipients, 4<sup>th</sup> edition, Rowe et al., Eds., American Pharmaceuticals Association (2003); Remington: the Science and Practice of Pharmacy, 20<sup>th</sup> edition, Gennaro, Ed., Lippincott Williams & Wilkins (2000); Remington's Pharmaceutical Sciences (19<sup>th</sup> ed., 1995)).

The appropriate dosage of the pharmaceutical composition may vary depending on factors such as formulation method, administration mode, patient's age, weight, sex, medical condition, diet, administration time, administration route, excretion rate, and response sensitivity. The dosage of the pharmaceutical composition of the present disclosure is 0.0001 to 1,000  $\mu\text{g}/\text{kg}$  body weight for an adult.

#### Advantageous Effects

The present disclosure relates to a fusion molecule having phagocytosis-inducing activity, which can solve the problem of tissue damage caused by activation of an inflammatory response, which occurs in the prior art. Accordingly, the fusion molecule is able to effectively clear abnormally accumulated substances such as beta-amyloid, tau, alpha-synuclein, huntingtin or prion protein, and thus may be used to prevent or treat diseases caused by these abnormally

accumulated substances, for example, Alzheimer's disease, Parkinson's disease, Huntington's disease, or prion disease. The fusion molecule may be administered to a patient in the form of a purified fusion molecule or a gene therapy vector capable of expressing and secreting the fusion molecule when introduced into a cell.

However, it should be understood that effects of the present disclosure are not limited to the above effects, and include all effects that may be inferred from the configuration of the invention described in the detailed description or claims.

### EXAMPLES

Hereinafter, the present disclosure will be described in more detail with reference to examples and experimental examples. However, the following examples and experimental examples are illustrative only, and the scope of the invention is not limited thereto.

#### Preparation Example 1. Preparation of Gas6-Based Fusion Molecule Having Beta-Amyloid Clearance Activity (I): Beta-Amyloid Binding Region in the Form of scFv

To prepare a beta-amyloid (A $\beta$ )-specific chimeric phagocytosis inducer based on Gas6 protein, the Gla domain,

which recognizes PS (phosphatidylserine) in apoptotic cells, was first removed, and a single-chain variable fragment (scFv) of aducanumab, an amyloid-specific antibody, was introduced at that position [ $\alpha$ A $\beta$ -Gas6(E)].

In addition, for the efficiency of protein production, the EGF repeat domain present in the internal residues of the Gas6 protein was also removed and an scFv of aducanumab was introduced at that position, thereby preparing  $\alpha$ A $\beta$ -Gas6 (FIG. 1B).

In addition, as controls for verifying beta-amyloid-specific binding of the scFv of aducanumab,  $\alpha$ FITC-Gas6(E) and  $\alpha$ FITC-Gas6, each introduced with an E2 scFv that selectively recognizes FITC, instead of the scFv of aducanumab, were prepared.

Table 3 below shows amino acid sequences related to the preparation of the fusion molecules, and Table 4 below shows nucleotide sequences related to the preparation of the fusion molecules (the underlined sequences are flag tags). In

Table 3, information for sequences constituting the final binding molecules are included within parenthesis. The full length sequences contain, from the N-terminal to the C-terminal direction, as an example, signal sequence (SS), first region, linker (when applicable), second region, and flag or his tags, which are linked consecutively. The sequence identifiers are intended for the full length sequences.

TABLE 3

1. $\alpha$ A $\beta$ -Gas6 (E) (FLAG tag, Gla delete, G-/-) SEQ ID NO: 136 MAPSLSPGPALRRAPOQLLAAECALA (SS) DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGV PSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPLTFGGGTKEIKRGGGGSGGG GSGGGGSEVOLVESGGVVQPGRLRSRLSCAASGFAFSSYGMHWVRQAPGKGLEWV AVIWFDTGTTKYYTDSVKGRFTISRDNSKNTLYLQMNTLRAEDTAVYYCARDRIGA RRGPPYYMDVWGKGTIVTVSS (Adu-scFv) GGGGGGGGGG (Linker) CINKYGSPTYKNSGFATCVQNLPDQCTPNPCDRKGTCACQDLMGNFFCLCKAGWG GRLCDKDNECSQEENGGCLQICHNKPGSFHCSCHSGFELSSDRTCDIDECADSEA CGEARCKNLPGSYSCLCDEGFAYSSQEAKCRDVDECILQGRCEQVCVNSPGSYTCHC DGRGGLKLSDQMDTCEDEDLPCVPFSVAKSVKSLYLGRCMFGSTPVIRLRFKRLQPTRL VAEEDFRTFDPEGILLFAGGHQDSTWIVLALRAGRLELQLRYYNGVGRVTSSGPVINH GMWQTISVEELARNLVIKVNRDAVMKIAVAGDLFQPERGLYHNLNTVGGIPFHEKD LVQPINPRLDGCMRSWNWLNGEDTTIQTBTVKVNTRMCFSTVERGSYPGSGFAYF SLDMYRTPLDVGTESTWEVEVVAHIRPAADTGVLFALWAPDLRAVPLSVALVDYH STKKLKKQLVLAVENTHALALMEIKVCDGQEHVVTVSLRDGEATLEVGDGTRGQSE VSAAQLQERLAVLERHLRSPVLTFAAGGLPDVPTSAVTAFYRCMTLEVNRLLD LDEAAYKHSIDTAHSCPVEPAAA(Gas6-Gla deleted) QGSRADYKDHDGYKDHDIDYKDDDK* (FLAG)
2. $\alpha$ FITC-Gas6 (E) (FLAG tag, Gla delete, G-/-) SEQ ID NO: 137 MAPSLSPGPALRRAPOQLLAAECALA (SS) QVQLVESGGNVLQPQGGLSRLSCAASGFTFGSFSMSWVRQAPGGGLEWVAGLSARSS LTHYADSVKGRFTISRDNAKNSVYLQMQNSLRSVQEDTAVYYCARRSYDSGGWGHFY SYMDVWGGTQLTVGG NIGNNYVSWYQQHPGKAPKLMIVDVSKRPGSVPDFRSGSKSGNSASLDISGLQSEDE ADYYCAAWDDSLSEFLFGTGTKLTVLG (aFITC-scFv) GGGGGGGGGG (Linker) CINKYGSPTYKNSGFATCVQNLPDQCTPNPCDRKGTCACQDLMGNFFCLCKAGWG GRLCDKDNECSQEENGGCLQICHNKPGSFHCSCHSGFELSSDRTCDIDECADSEA CGEARCKNLPGSYSCLCDEGFAYSSQEAKCRDVDECILQGRCEQVCVNSPGSYTCHC DGRGGLKLSDQMDTCEDEDLPCVPFSVAKSVKSLYLGRCMFGSTPVIRLRFKRLQPTRL VAEEDFRTFDPEGILLFAGGHQDSTWIVLALRAGRLELQLRYYNGVGRVTSSGPVINH GMWQTISVEELARNLVIKVNRDAVMKIAVAGDLFQPERGLYHNLNTVGGIPFHEKD LVQPINPRLDGCMRSWNWLNGEDTTIQTBTVKVNTRMCFSTVERGSYPGSGFAYF SLDMYRTPLDVGTESTWEVEVVAHIRPAADTGVLFALWAPDLRAVPLSVALVDYH STKKLKKQLVLAVENTHALALMEIKVCDGQEHVVTVSLRDGEATLEVGDGTRGQSE VSAAQLQERLAVLERHLRSPVLTFAAGGLPDVPTSAVTAFYRCMTLEVNRLLD LDEAAYKHSIDTAHSCPVEPAAA(Gas6-Gla deleted) QGSRADYKDHDGYKDHDIDYKDDDK* (FLAG)
3. $\alpha$ A $\beta$ -Gas6 (FLAG tag, Gla EGF delete, GE-/-) SEQ ID NO: 138 MAPSLSPGPALRRAPOQLLAAECALA (SS) DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGV PSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPLTFGGGTKEIKRGGGGSGGG

TABLE 3 -continued

GSGGGGSEVQLVESGGGVQPGRSRLSCAASGFAFSSYGMHWVRQAPGKGLEWV  
 AVIWFDFGTKKYTDVKGRFTISRDNSKNTLYLQMNTLRAEDTAVYYCARDRGIGA  
 RRGPYYYMDVWGKTTVTVSS (Adu-scFv)  
 GGGGGGGGS (Linker)  
 DILPCVPFSVAKSVKSLYLGRMFSGTPVIRLFKRLQPTRLVAEFDRTFDPEGILLFA  
 GHQDSTWIVLALRAGRLELQLRYNGVGRVTSGPVINHGMWQTISVEELARNLVI  
 KVNRAVMKIAVAGDLFQPERGLYHNLNTVGGIPFHEKDLVQPINPRLDGCMRSWN  
 WLNGEDTTIQETVKVNTRMOCFSVTERGSFYPGSGFAFYSLDYMRTPLDVGTESTW  
 EVEVVAHIRPAADTGVLFALWAPDLRAVPLSVALVDYHSTKLLKKQLVVLAVENT  
 ALALMEIKVCDQEHHVTVTSLRDGEATLEVDGTRGQSEVSAAQLQERLAVLERHLR  
 SPVLTFAAGGLPDVPTSAVPTAFYRGCMTLEVNRRLLDLEAAAYKHSIDTAHSCPPV  
 EPAAA (Gas6-Gla EGF deleted)  
 QGSRADYKDHDGYKDHDIDYKDDDK\* (FLAG)

4. αFITC-Gas6 (FLAG tag, Gla EGF delete, GE-/-) SEQ ID NO: 139  
 MAPSLSPCPAALRAPQPLLLLAAECALA (SS)  
 QVQLVESGGNVLQPGGSRLSCAASGFTFGFSMSWVRQAPGGLEWVAGLSARSS  
 LTHYADSVKGRTISRDNAKNSVYLQMNSLRVEDTAVYYCARRSYDSSGYWGHFY  
 SYMDVWGQGTLVTSGGGGGGGGGGSSVLTQPSVSAAPGQKVТИSCSGSTS  
 NIGNNYWSWYQQHPGKAPKLMYDVSKRPSGVPDFRGSGSKSGNSASLDISGLQSEDE  
 ADYYCAAWDDSLSEFLFGTGTKLTVLG (αFITC-scFv)  
 GGGGGGGGS (Linker)  
 DILPCVPFSVAKSVKSLYLGRMFSGTPVIRLFKRLQPTRLVAEFDRTFDPEGILLFA  
 GHQDSTWIVLALRAGRLELQLRYNGVGRVTSGPVINHGMWQTISVEELARNLVI  
 KVNRAVMKIAVAGDLFQPERGLYHNLNTVGGIPFHEKDLVQPINPRLDGCMRSWN  
 WLNGEDTTIQETVKVNTRMOCFSVTERGSFYPGSGFAFYSLDYMRTPLDVGTESTW  
 EVEVVAHIRPAADTGVLFALWAPDLRAVPLSVALVDYHSTKLLKKQLVVLAVENT  
 ALALMEIKVCDQEHHVTVTSLRDGEATLEVDGTRGQSEVSAAQLQERLAVLERHLR  
 SPVLTFAAGGLPDVPTSAVPTAFYRGCMTLEVNRRLLDLEAAAYKHSIDTAHSCPPV  
 EPAAA (Gas6-Gla EGF deleted)  
 QGSRADYKDHDGYKDHDIDYKDDDK\* (FLAG)

5. αAβ-Gas6 (HA tag, Gla EGF delete, GE-/-) SEQ ID NO: 140  
 MAPSLSPCPAALRAPQPLLLLAAECALA (SS)  
 DIQMTQSPSSLSASVGDRTVITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGV  
 PSRFSGSGSGTDFTLTISSLQPEDFATYYCQSYSTPLTFGGTKVEIKRGGGGGGG  
 GSGGGGSEVQLVESGGGVQPGRSRLSCAASGFAFSSYGMHWVRQAPGKGLEWV  
 AVIWFDFGTKKYTDVKGRFTISRDNSKNTLYLQMNTLRAEDTAVYYCARDRGIGA  
 RRGPYYYMDVWGKTTVTVSS (Adu-scFv)  
 GGGGGGGGS (Linker)  
 DILPCVPFSVAKSVKSLYLGRMFSGTPVIRLFKRLQPTRLVAEFDRTFDPEGILLFA  
 GHQDSTWIVLALRAGRLELQLRYNGVGRVTSGPVINHGMWQTISVEELARNLVI  
 KVNRAVMKIAVAGDLFQPERGLYHNLNTVGGIPFHEKDLVQPINPRLDGCMRSWN  
 WLNGEDTTIQETVKVNTRMOCFSVTERGSFYPGSGFAFYSLDYMRTPLDVGTESTW  
 EVEVVAHIRPAADTGVLFALWAPDLRAVPLSVALVDYHSTKLLKKQLVVLAVENT  
 ALALMEIKVCDQEHHVTVTSLRDGEATLEVDGTRGQSEVSAAQLQERLAVLERHLR  
 SPVLTFAAGGLPDVPTSAVPTAFYRGCMTLEVNRRLLDLEAAAYKHSIDTAHSCPPV  
 EPAAA (Gas6-Gla EGF deleted)  
 GSGSGSGSGSGSYPYDVPDYA\* (HA)

6. Lentiviral Aducanumab IgG\_IRES Zsgreen deleted SEQ ID NO: 141  
 MGWSCIILFLVATATG (SS)  
 DIQMTQSPSSLSASVGDRTVITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGV  
 PSRFSGSGSGTDFTLTISSLQPEDFATYYCQSYSTPLTFGGTKVEIKRKRTVAAPSV  
 FIFPPSDEQLKSGTAGSVCLNNFYPREAKVQWVDNALQSGNSQESVTEQDSKDST  
 YSLSLSTTLSKADYEHKVKYACEVTHQGLSSPVTKSFRGEC (Adu-Light chain)  
 RRKRGSCEGRGSLLTTCGDNVEENPGP (T2A)  
 MGWSCIILFLVATATG (SS)  
 EVQLVESGGVVQPGRSRLSCAASGFAFSSYGMHWVRQAPGKGLEWVAVIWFDG  
 TKKYTYDSVKGRTFISR  
 DNSKNTLYLQMNTLRAEDTAVYYCARDRGIGARRGPYMDVWGKTTVTVSSA  
 STKGPSPVPLSPSSKSTGGTAALGCLVKDYFPEPVTVWNNSGALTSGVHTFPABL  
 QSSGLYSLSSVVTVPSLSSLGTQTYICNVNHPSENKVDKVKVEPKNSDKTHTSPPCPA  
 PELLGGPSVFLFPPKPDKTLMISRTPEVTCVVVDVSHEDPEVFKFNWYVDGVEVHN  
 AKTKPREEQYNSTYRVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTIISKAG  
 QPREPQVYTLPLPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPPV  
 LDSDGSFFPLYSKLTVDKSRWQQGNVFCSCVMEALHNHYTOKSLSLSPGK\* (Adu-  
 Heavy chain)

7. Endogenous full sequence human Gas6 protein SEQ ID NO: 142  
 MAPSLSPCPAALRAPQPLLLLAAECALAALLPAREATQFLPRQRRAFQVFEAK  
 QGHLERECVEELCSREEAREREVENDPETDYFPRYLDCCINKYGSPTKNSGFATCVQ  
 NLDPQCTPNPCDRKGTAQCDLMGNFFCLCKAGWGGRLCDKDVNECSQENGCL  
 QICHNKPGSFHCSCHSGFELSSDGRTCQDIDECAADCSEACGEARCKNLPGSYSCLCDE  
 GFAYSSQEKAIRDVDECLQGRCEQVCVNSPGSYTCHCDGRGGLKLSQDMDTCEDIL  
 PCVPFSVAKSVKSLYLGRMFSGTPVIRLFKRLQPTRLVAEFDRTFDPEGILLFAGG  
 HQDSTWIVLALRAGRLELQLRYNGVGRVTSSGPVINHGMWQTISVEELARNLVIK  
 NRDAMKIAVAGDLFQPERGLYHNLNTVGGIPFHEKDLVQPINPRLDGCMRSWNW  
 WLNGEDTTIQETVKVNTRMOCFSVTERGSFYPGSGFAFYSLDYMRTPLDVGTESTWE  
 EVEVVAHIRPAADTGVLFALWAPDLRAVPLSVALVDYHSTKLLKKQLVVLAVENTA

TABLE 3 -continued

LALMEIKVCDGQEHVVTVSLRGEATLEVDGTRGQSEVSAAQLQERLAVLERHLRS  
 PVLTFAAGGLPDVPVTSAPVTAFYRGCMLEVNRRLLDLDEAAYKHSDTAHSCPPVE  
 PAAA (full-length human Gas6)  
 QGSRADYKDHDGDYKDHDIDYKDDDK\* (FLAG)

TABLE 4

1.  $\alpha$ A $\beta$ -Gas6 (E) (FLAG tag, Gla delete, G-/-) SEQ ID NO: 143  
 ATGGCCCCCTCGCTCTGCCCGGGCCGCCCTGCCGCCGCCAGCTGC  
 TGGTGTGCTGCTGCTGGCGCGGGATGGCGCTTGCC (ss)  
 GACATTCAAGATGACTCAATCTCTAGCTCTGAGCGCCTCCGTTGGAGATAGAG  
 TCACTTACCTTCGAGAGCCAAATCCATCAGCTCTTATCTAAATTGGTACCA  
 ACAGAACGGGCAAAGCCTGCTCATCAGCTGCAAGCTCCTTACA  
 GAGCGGAGTACCCAGCAGATTCTCAGGCAGTGGCAGTGGGACTGACTTCACATT  
 GACGATTAGCTCTGCAGCCTGAAGACTTGGCCACATACTATTGTCAGCAGAGC  
 TATAGCACCCCTGAGCTTGGAGGGGAACTAAGGTGGAATTAAGAGAGG  
 AGGGGGGGCTCGGGGGGGCTGGCTGGGGGGAGGGCTCAGAGGTTTACG  
 TTGTCGAGTCTGGGGGGAGTCGTTCAGCAGGTTAGAAGCTTCAAGACTGAGCT  
 GTGCCGCAAGTGGGTTGCTTTTACATCTTACGGTATGCACTGGGTGAGACAGGC  
 TCCCTGGCAAAGGAACTCAGGTGAGCTGAGCT (Adu-scFv)  
 GGCGGGGGCGGCAAGCGGGGGCTGGCAGC (Linker)  
 TGCAACAAACTATGGGTCTCGTACACAAAAACTCAGGCTTCGCCACCTGC  
 GTGCAAAACCTCGCTGACCAGTCAGCAGCCAAACCCCTCGCATAGGAAGGGGACC  
 CAAGCCTGCCAGGACCTCATGGCAACTTCTCTGCTGTGTTAAAGCTGGCTGGG  
 GGGGGGGCTCTGGCAGAACAGGTCAACGAACTGCAAGGAGAACGGGGC  
 TGCTCCAGATCTGCCAACAAAGCCGGTAGCTTCAACTGTTCTGCCACAGCG  
 GCTTCGAGCTCTCTGATGGCAGGACCTGCAAGACATAGACGAGTGCAGCAG  
 ACTCGGGAGGCTCGGGGGAGGGCGCTGCAAGAACCTGCCCAGCTCTACTCT  
 GCCTCTGGTACAGGGGCTTGGCTACAGCTTCCAGGAGAACGGCTTGGCAGAGATG  
 TGGACGAGTGTCTGCAGGGCCCTGTCAGCAGGTCTCGTGAACCTCCAGGGA  
 GCTACACCTGCACTGTGACGGGCGTGGGGGCTCAAGCTGTCAGGACATGG  
 AACACCTGTGAGGACATCTTGGCTGCGCTGCCCTCAGCGTGGCCAAGAGTGTGA  
 AGTCCTGTGACTCTGGCGGATGTTCAAGTGGGACCCCGTGTGACTCGACTGCGCTT  
 CAAGAGGCTGCAAGCCCACAGGCTGGTAGCTGAGTTTGACTTCCGGACCTTGA  
 CCCCAGGGCATCTCTCTTGGCGAGGCCACAGGACAGCACCTGGATCGT  
 GCTGGCCCTGAGAGCCGGCCGCTGGAGCTGCAAGCTGCGTACAACGGGTGTCGG  
 CGCTGACCGACAGCGGCCGCTCATCAACCATGCGATGTGCAAGACAACTCTC  
 TGTTGAGGAGCTGGCGCGGAATCTGGTCAACAGGTCAACAGGGATGCTGT  
 GAAACATCGGGTGGGGAGGTATTCCCTTCCATGAGAAGGACCTCGTGCAGCTAT  
 AAACCTGACCGTGGGAGGTATTCCCTTCCATGAGAAGGACCTCGTGCAGCTAT  
 CACCCACATCCAGAAACGGTGAAGAGTGAACAGGAGATGCACTGTTCTCGGT  
 GACGGAGAGGGCTTTCTACCCGGAGGGCTTGCCTTCAAGCTGCGTGA  
 CTACATCGGGACCCCTCTGGACGTCGGGACTGAATCAACCTGGAAAGTAGAAAGT  
 CGTGGCTACACTCGCCAGCAGCACAGGGTGTGCTGTTGGCTCTGGC  
 CCCCGACCTCCGGCGCTCTCTGTCAGTGGTACAGTACTACTCCACG  
 AAGAAACTCAAGAAGCAGCTGGTGGCTCTGGCCGTGGAGCATACGCCCTTGGC  
 CTAATGGAGATCAAGGTCTGCAGGGCAAGAGCACGTGGTACCGTCTCGCTG  
 AGGGAGCGTGGGCCACCCCTGGAGGGTGACGGCAGGGGCCAGAGCAGG  
 GAGCGCCGCGCAGTCAGGAGAGGCTGGCGCTGCTGGAGGGCACCTGCGGA  
 GCCCCGTCCTACCTTGTGGCGGCTTGCCAGATGTGCGGTGACTTCAAGGCC  
 AGTCACCGCCTTCAACCGGGCTGCACTGAGGTCACCGGAGGTGCT  
 GAACACTGGAGGCGTCAAGGACAGCACGGGACATCACGCCACTCCTGCC  
 CCCCGTGGAGGCCGCCAGCC (Gas6-Gla deleted)  
 caagGATCCCGGGCTGACTACAAAGACCATGACGGTGATTATAAGATCATGACA  
 TCGACTACAAGGATGACGATGACAAGtga (FLAG)

2.  $\alpha$ FITC-Gas6 (E) (FLAG tag, Gla delete, G-/-) SEQ ID NO: 144  
 ATGGCCCCCTCGCTCTGCCCGGGCCGCCCTGCCGCCGCCAGCTGC  
 TGGTGTGCTGCTGCTGGCGCGGGATGGCGCTTGCC (ss)  
 CAGGTTCAAGCTGGTTGAGAGCGGAGGAATCTGGTCAAGCCGGTGGTAGCTG  
 CGTCTGTTGTGCGGGCTCAGGGTTACTTCGGTAGTTTCATGAGCTGGG  
 TCCGTCAGGCACCCAGGGCTGGGAATGGTGGCAGGTCGCTGCACTG  
 GCTCCCTGACCCACTATGCAAGATAGTGTAAAGGGGGTTACAATTCACGCG  
 AACACGCTAAGAATAGCGTCACTGCCAAATGAACTCCCTGGGGTCAAGGGATA  
 CGCAGTGTATTACTGCGCTGCCGTTCTATGACTCTAGTGGATACTGGGGCA  
 TTTTATAGCTACATGGATGTTGGGGACAGGGACTCTGGTGAACGGTTCTGACC  
 GGCGGTGGCTGGAGGGGGTGGAGTGGAGGGGGTCAAGCGTTCTGACC  
 CAGCCGCTCTGTCAAGGCCGCCAGGCCAGAAAGTGACAATTCTGTTCTG  
 GAAGTACTTCAACATCGGCAACATTGTTCTGGTATCAGCAGCACCCGG

TABLE 4 -continued

GCAAAGGCCAAGCTGATGATTATGATGTCTAACGTCAGTGGTGTCC  
 TGACCGGTTCAAGGGTCTCAACTCTGGAAATAGTGCCTCACTGGACATCTCAGG  
 CCTGCAAAGCGAAGATGAGGCCGACTATTACTGCGCAGCTGGGATGACGCT  
 GTCGAATTCTGTTCGCACGGGACAAGCTGACCGTGTGGG (aFITC-scFv)  
 GCGGGGGCGGAGCGGGCGG (Linker)  
 TGCATCAACAAGTATGGGCTCCGACACCAAAACTCAGGCTTCGCCACCTGC  
 GTGCAAAACCTGCTGACCAGTCAGGCCAACCCCTGCGATAGGAAGGGGACC  
 CAAGCGCTGCCAGGACCTCATGGCAACTTCTCTGCGCTGTAAAGCTGGCTGGG  
 GGGCGCGCTCTGCACAAAGATGTCAGGAAGCTGGCAGGAGAACGGGGGC  
 TGCTCCAGATCTGCCACAAACAGCCGGTAGCTTCCACTGTCTGCCACAGCG  
 GCTTCAGACTCTCTGATGGCAGGACCTGCCAAGACATAGACGAGTGCGCAG  
 ACTCGGAGGCTCGGGAGGGCTGCAAGAACCTGCCGGCTCTACTCT  
 GCCTCTGACGGGGCTTGCACAGCTCCAGGAGAACGGCTTGCGCAGATG  
 TGGACGAGTGTGACGGCCCTGAGCAGGTCTGCGTAAGTCCCAGGGA  
 GCTACACCTGCCACTGTGACGGGCGTGGGGCCTCAAGCTGTCCCAGGACATGG  
 ACACCTTGAGGACATCTTGGCTGCGCTGCCCTCAGCGTGCCAAAGAGTGTGA  
 AGTCCTTGACTGGGGGATGTTAGCTGGGACCCCCGTTGATCCGACTGCCCT  
 CAAGAGGCTGACGCCAACAGGCTGGTAGCTGAGTTGACTTCCGACCTTGA  
 CCCGAGGGCATCTCTCTTGGAGGACCCAGGACAGCACCTGGATCGT  
 GCTGGGCTGAGGAGGCTGGGGGACTTGTCAACCGGAGGAGACTGTATCATCT  
 GAAACCTGCGGGCTGGGGGACTTGTCAACCGGAGGAGACTGTATCATCT  
 GAAACCTGACCGCTGGGGGATATTCCCTCCATGAGAAGGACCTCGTGCAGCTT  
 AAACCCCTGCTGGATGGCTGACGGAGCTGGAACTGCTGAAACGGAGAAGA  
 CACCAACATCAGGAAACGGTGAAGAGCACCGAGGATGAGTGCCTCTGGT  
 GACGGAGAGGGCTTCTACCCGGGAGCGGCTTCGCCCTACAGCTGGA  
 CTACATGGGACCCCTGAGCTGGGACTGAACTCAACCTGGGAAGTAAAGT  
 CGTGGCTCACATGCCAGCCAGCGCAGACAGCGTGTCTGGG  
 CCCCGACCTCTGGCTGCCCTCTCTGTGCACTGGTAGACTATCACTCACG  
 AAGAAAATCAAGAAGCAGCTGGTGGCTGGCGAGCATCGCCCTGGCC  
 CTAATGGAGATCAAGGTCTGACGGGCAAGAGCAGTGGTACCGTCTCGCTG  
 AGGGAGGAGGGCTTCTACCCGGGAGCGGCTTCGCCCTACAGCTGGA  
 CTACATGGGACCCCTGAGCTGGGACTGAACTCAACCTGGGAAGTAAAGT  
 CGTGGCTCACATGCCAGCCAGCGCAGACAGCGTGTCTGGG  
 AGTCACCGCTTCTACCGCGCTGCACTGGAGGTCAACCGGAGGCTGCT  
 GGACCTGGACAGGGCGCTGCAAGCACAGGCCACATCACGCCACTCCTGCC  
 CCCCGTGGAGGCCGCCAGCC (Gas6-Gla deleted)  
 caagGATCCGGCTGACTAAAGACCATGACGGTGATTAAAGATCATGACA  
 TCAGACTACAAGGATGACGATGACAAGtga (FLAG)

3. αβ-Gas6 (FLAG tag, Gla EGF delete, GE-/-) SEQ ID NO: 145

ATGCCCTTCCTCTGCCGGGCCCTGCCGCGAGCTGC (ss)  
 TGCTGCTGCTGCTGGCCGCGAGTGCCTGCGCTTGCC (ss)  
 GACATTAGATGACTAAATCTCTAGCTCTGAGGCTCCGTTGGAGATAAGAG  
 TCACTATTACCTGCAAGGCCAACAGCTGCTCATCTACGCTCAAGCTCTTACA  
 ACAGAAGCCGCAAAGCGCAAAGCTGCTCATCTACGCTCAAGCTCTTACA  
 GAGCGGAGTACCCAGCAGATTCTCAGGAGTGGCAGTGGACTGACTTACATT  
 GAGGATAGCTCTGAGCTGAAGACTTGGCACATACTATTGTGAGAG  
 TATAGCACCCGCTGACGTTGGAGGGAACATAAGGTGAAATCAAGAGAG  
 AGGGGGGGCTGGCGGGGGGGCTGGCTGGGGGGAGGGGCTCAGAGGTTGAGC  
 TTGTCAGACTGGGGGGAGTCGTTAGGGCTAGGCTAGACTGAGCT  
 GTGCCAGGTGGGTTGCTTTTCATCTTACGGTATGCACTGGGTGAGACAGGC  
 TCCCTGGCAAAGGACTCGAGTGGGCTGCTGTAATATGGTTGAGTGGTACAAGAA  
 ATACTATACCGATAGTGTGAAGGAAGATTACCCATTCAAGAGACAAGTAA  
 AAATACCTTGACCTTCAGATGAAACACCCCTGAGAGCAGAGACACAGCGTGA  
 CTACTGCCAGAGATAGAGGTATCGAGGAGCAGGGCTGGTCCATTATATGGA  
 TGTGTGGGGAGGAAACACAGTGAATGTGAGAGCT (Adu-scFv)  
 GGGGGGGCGGAGCGGGCGGTGGCAG (Linker)  
 GACATCTTGGCGTGCCTCAGCGTGGCCAAGAGTGTGAAGTCCTTGAC  
 TGGGCCGATGTTCACTGGGACCCCCGTGACTCGCCTGCGCTCAAGAGGGCTG  
 AGGCCACAGGCTGGTAGCTGAGCTTGGGACTTCGGGACCTTGGACCCGGAGGG  
 TCCCTCTTTGGCGGAGGCCAGGAGCACGACCTGGATGCTGCTGGCCCTGAG  
 AGCGGGGGCTGGAGCTGCGCTACAACCGTGTGGCGCTGTACCCAG  
 CAGCGGGGGCTGGATGCTGAGCTGGAGACAATCTGTGAGGAGCT  
 GGCGGGAATCTGGTCAAGGAGTGTGAGTGGTCAAGGAGGCTGAGGAG  
 GGGCGGGAGCTTCTAACCGGAGCGAGGACTGTATCATGAGAACCTGACCGT  
 GGGAGGTATTCCCTCATGAGAAGGACCTGTCAGGCTATAAACCTCGTCTG  
 GATGGCTGATGAGGAGCTGGGACTGGCTGAGCGAGAACGACCCACATC  
 GGAAACGGTGAAGTGAACACAGGAGATGAGCTCTGGTGAAGGGAGAG  
 GCTCTTCTACCCGGGAGCGCTTCCCTCTACAGCCCTGAGACTACATGCC  
 CCCTCTGAGCTGGGACTGAACTCAACCTGGGAGTAGAAGTGTGGCTCACAT  
 CGCCCGAGCCGAGACACAGGGCTGTTGCGCTTGGGCCCGACCTCCGT  
 GCCGTGCTCTCTGTGGCAGTGGTAGACTATCCTACGCCACAGAAACTCAAG  
 AAGCAGCTGGTGTCTGGCGTGGAGCATAGGGCTTGGCCCTAATGGGAGATC  
 AAGGTCTGCGACGGCAAGAGCACGCTGAGCTGAGGAGGCTGAGGAG  
 GCCACCCCTGGAGGTGGACGGGACCAAGGGGAGGAGGAGGAGGAG  
 GCTGAGGAGAGGGCTGGCGTCTGAGAGGGACCTGCGGAGGAGGAG  
 CTTTGTGGCGGCTGCCCAGATGTGCGCTGACTTCAAGGCCAGTCACCG  
 TACCGCGGCTGCACTGGAGGCTACAACCGGAGGCTGAGGAG

TABLE 4-continued

GCGGCGTACAAGCACAGCGACATCACGGCCCCTCCTGCCCGCCGCGCAGCTGC  
 GCGGCAGCC (Gas6-Gla EGF deleted)  
 caaGGATCCCGGGCTGACTACAAAGACCATGACGGTGAATTAAAGATCATGACA  
 TCGACTACAAGGATGACGATGACAAGTGA (FLAG)

4.  $\alpha$ FITC-Gas6 (FLAG tag, Gla EGF delete, GE-/-) SEQ ID NO: 146  
 ATGGCCCCCTCGCTCGCCCGGGCCGCCGCGCTGCCGCCGCGCAGCTGC  
 TGCTGCTGCTGCTGGCGGGAGTGGCGCGCTGG (SS)  
 CAGGTTCAAGCTTGAGAGCGGAGGCAATCTGGTCAGCCCCGGTGGTAGTCG  
 CGTCTGTTGCGCGCTCAGGGTTCACTTCGGTAGTTTCATGAGCTGG  
 TCCGTAGGCACCAGGGCGTGGGCTGGAATGGGTGGCAGGTCTGCTGCAGTA  
 GTCTCCGTACCCACTATGCAAGTAGTGTAAAGGGGGTTACAATTCACCGC  
 ACAACGCTAAGAATAGCGTCACTGCAAAATGAACTCCCTGCGGGTGAAGGATA  
 CCCAGTGTATTACTGGCTCCCGTTTATGACTCTAGTGGATACTGGGGCA  
 TTTTATAGCTACATGGATGTTGGGGACAGGGCACTCTGGTACCGTTCCGGA  
 GGGGGGGTCTGGAGGGGGGGGGAGTGGAGCGGGTGGGTCAAGGGTTCTGACC  
 CAGCCGCTCTGTGAGCGCCGCCAGGGCAAGGGTACAATTTCTGTTCTG  
 GAAGTACTTCAAACATCGGAACAAATTATGTTCTGGTATCAGCAGCACCCGG  
 GCAAAGCGCCAAGCTGATGATTATGATGTTCTAAACGTCCAAGTGGTGTCC  
 TGACCGGTTACGGGTTCAAAGTCTGGGAATAGTGCCTCACTGGACATCTCAGG  
 CCTGCAAAGCGAAGATGAGGGGGACTATTACTGCGCAGCTGGGATGACAGCCT  
 GTCCGAATTCTGTTCGCACGGGACAAGCTGACCGTGTGGG (aFITC-scFv)  
 GCGGGGGCGGCAGCGGGCGGTGGCAGC (Linker)  
 GACATCTTGGCTGCGCTTCAGGTGGCCAAGAGTGTGAAGTCTTGTACC  
 TGGGCGGATGTCAGTGGGACCCCGTGAATGGCTTCAAGAGGCTG  
 AGGCCACAGGCTGGTAGCTGAGTTGACTTCGGACCTTGGACCCGAGGGCA  
 TCCTCCTTTGCGGGAGGCCCCCAGACGACCTGGATCGTGTGGCCCTGAG  
 AGCGGGCGGCTGGAGCTGCACTGGCAGCTAACACGGTGTGGCCGTGACCCAG  
 CAGCGGGAGTGGCATGACACGGGATGTTGAGGAGCTGATGAGGAGCT  
 GGGCGGAATCTGGTATCAGGTCACAGGGATGCTGTGATGAAAATCGGGT  
 GGGCGGGACTTGTCAACCGGAGCGAGGACTGATCATGAACTCACCGT  
 GGGAGGTATTCCCTCATGAGAAGGACCTGTGCAAGCTATAAACCTCTGCTG  
 GATGGCTGATGAGGAGCTGGAACCGGAGCTGAGCGAGAACACCCATC  
 GGAACACGGTAAAGTGAACACGAGGATGCACTGCTTCCTCGTGACGGAGAG  
 GCTCTTCTACCCGGAGGGCTCGCCTTACAGCCTGGACTACATCGGAC  
 CCCTCTGGACGTGGGACTGAATCAACCTGGGAAGTAGAAGTCGTGGCTCACAT  
 CGCCACGGCAGACAGGGCTGTTGCGCTTGGGCCCCGACCTCCGT  
 GCGGTGCGCTCTGTGGCAGCTGGTAGACTACACTCCACGAAGAAACTCAAG  
 AACAGCTGGTGGCTCTGGCGTGGAGCATACGGCCTTGGCCATTGGGATC  
 AAGGTCTGCGACGGCAAGAGCACGCTGGTACCGTCTCGTGAGGGACGGTGA  
 GCCACCTGGAGGTGGACGGCACAGGGGCAAGGGAGGTGAGGGCCGGCA  
 GCTGAGGAGAGGCTGGCGTCTGAGAGGACCTGTGCGGGAGGCGTGT  
 CTTTGCGCGGCGCTGCCAGATGTCGGGTGACTTCAGGCCAGTCACCGGTT  
 TACCGCGCTGCACTGACACTGGAGGTCAACCGGAGGCTGCTGGACCTGGACGAG  
 GCGCGTACAACGACAGCGACATCACGGCCACTCTGGCCCCCGTGGAGGCC  
 GCGCACCC (Gas6-Gla EGF deleted)  
 caaGGATCCCGGGCTGACTACAAAGACCATGACGGTGAATTAAAGATCATGACA  
 TCGACTACAAGGATGACGATGACAAGTGA (FLAG)

5.  $\alpha$ A $\beta$ -Gas6 HA tag (Gla EGF delete, GE-/-) SEQ ID NO: 147  
 ATGGCCCCCTCGCTCGCCCGGGCCGCCGCGCTGCCGCCGCGCAGCTGC  
 TGCTGCTGCTGCTGGCGCGGGAGTGGCGCTTG (SS)  
 GACATTCAAGATGACTCAATCTCTGAGGCGCTCCGGTGGAGATAGAG  
 TCACTATTACCTGAGGCCAGGCAATCCATGAGCTTATCTAAATTGGTACCA  
 ACAGAACGCCGCAAAGCGGAAAGCTGCTCATCTACGCTGCAAGCTCTTACA  
 GAGCGGAGTACCCAGCAGATTCTCAGGAGTGGCAGTGGACTGGACTTCACATT  
 GAGGATTAGCTCTGCAAGCTGAAGACTTTGCCACATATAATTGTCAGCAGAGC  
 TATAGCACCCCGCTGACGTTGGAGGCGGAACTAAGGTGAAATCAAGAGAGG  
 AGGGGGGGCTCGGGGGGGGGCTGGCTGGGGGGAGGGAGGCTCAGAGGTTGAGC  
 TTGCGAGTCTGGGGGGGGAGTCGTTAGGGCTAGGAGGCTAGAGCTCAGACTGAGCT  
 GTGCCGAAGTGGTTGCTTTCATCTTCAAGGTATGCACTGGGTGAGACAGGC  
 TCTGGCAAGGAGGAGGAGGAGGAGGAGGAGGAGGAGGAGGAGGAGGAGG  
 ATACTATACCGATAGTGTGAAGGAAGATTACCCATTCAAGAGAACAGTAA  
 AAATACCTTGATCCTTCAGATGAACACCCCTGAGAGCAGAAGACACAGCGTGA  
 CTACTGCCCAAGAGATAGAGGTATCGGAGCAAGGGCTGGTCCCTATTATGG  
 TGTGTGGGGGGAGGGAGAACACACAGTGAATGAGCT (Adu-scFv)  
 GGGGGGGCGGCAGCGGGCGGTGGCAGC (Linker)  
 GACATCTTGGCGTGTGCGCTTCAGCGTGGCCAAGAGTGTGAAGTCTTGTACC  
 TGGGCGGATGTCAGTGGGACCCCGTGAATGGCAGCTGGCTTCAAGAGGCTG  
 AGCGCGCAACAGGCTGGTAGCTGAGTTGACTTCGGACCTTGTGACCCGGAGGGCA  
 TCCTCCTTTGCGGGAGGCCCCCAGGAGCAGACCTGGATCGTGTGGCCCTGAG  
 AGCGGGCGGCTGGAGCTGCACTGGCAGCTAACACGGTGTGGCCGTGACCCAG  
 CAGCGGGCCGGCTCATCAACCTGGCATGTCAGGAGAACATCTGTGAGGGAGCT  
 GGCGCGGAATCTGGTATCAAGGTCAACAGGGATGCTGATGAAAATCGCGGT  
 GGCGGGGGACTTGTCAACCGGAGGGAGGACTGATCATGAACTGACCGT  
 GGGAGGTATTCCCTCATGAGAAGGACCTGTGCAAGCTATAAACCTCTGCTG  
 GATGGCTGCACTGAGGAGACTGGCTGAACGGAGAACACCCATC  
 GGAAACGGTAAAGTGAACACGAGGATGCACTGCTTCCTCGGTGACGGAGAGAG  
 GCTCTTCTACCCGGAGGGCTCGCCTTACAGCCTGGACTACATCGGAC  
 CCCTCTGGACGTGGGACTGAATCAACCTGGGAAGTAGAAGACTGTGGCTCACAT

TABLE 4 -continued

CCGCCCAGCGCAGACACAGGGTGTGTTGCCTCTGGCCCCGACCTCCGT  
 GCCGTGCTCTCTGTGGCACTGGTAGACTATCCTCCAGAAACTCAAG  
 AAGCAGCTGGTGGTCTGGCGTGGAGCATACGCCCTGGCCAATGGAGATC  
 AAGGTCTCGCACGGCAAGAGCACGTCGTCAGCTCGTGAGGGACGTTGAG  
 GCCACCTGGAGGGTGGACGGCACCAGGGCCAGAGCAGGGTGGAGCGCGCA  
 GCTGCAGGAGAGGCTGGCGTCTGAGAGGCACCTGCGGAGCCCGTGTCA  
 CTTGCTGGCGGCTGCCAGATGTGCGGTAACCTCAGCGCAGTCACCGCGTT  
 TACCGCGCTGATGACACTGGAGGTCAACCGGAGGCTGCTGAGCTGGAGAG  
 GCGCGTACAACAGCGACATCACGGCCACTCTGCCCCCGTGGAGCCC  
 GCGCAGCC (Gas6-Gla EGF deleted)  
 GGCAGCGCAGCGGAGCGGCAGCGGAGCAGCTACCCATAACGATGTTCC  
 AGATTACGCTTGA (HA)

6. Lentiviral Aducanumab IgG\_IRES Zsgreen deleted SEQ ID NO: 148  
 GGATCCATGGGCTGGTCTGCATCATCCTGTTCTGGTGGCCACCGCCACCGC  
 (SS)

GACATTAGATGACTCAATCTCTAGCTCTGAGCGCCTCCGGTGGAGATAGAG  
 TCACTATTACCTGCAAGGCCAACCTCATCAGCTCTTATCTAAATTGGTACCA  
 ACAGAAGCCCGAAAGCGCAAAGCTGCTCATCTACGCTGCAAGCTCCTTACA  
 GAGCGGAGTACCCAGCAGATTCTCAGCCAGTGGCAGTGGGACTGACTTCACATT  
 GAGCATTAGCTCTGCAAGCTGAGCTTGGCACATACTATTGTCAGCAGAGC  
 TATAGCACCCCGTGCAGTTGGAGGGAACTAAGGTGAAATCAAGAGAAA  
 ACGAACTGTGGCTGCACCATCTGCTTATCTCCCGCATCTGATGAGCAGTTG  
 AAATCTGGAACCTGCCATCTGCTGTGCTGTGAATAACTCTATCCAGAGAGG  
 CCAAAGTACAGTGGAAAGGTGGATAACGCCCTCAATGGTAACCTCCAGGAGA  
 GTGTCACAGAGCAGGACAGCAAGGACAGCCTACAGCCTCAGCAGCACCTG  
 ACGCTGAGCAAAGCAGACTACAGAGAAACACAAGTCAACGCTGCAAGTCA  
 CCATCAGGGCCTGCTCGCCGTACAAGAGCTAACAGGGAGAGTGT  
 (Adu-Light chain)  
 CGCAGAAAAGCGGAAGCGGAGAGGGCAGAGGAAGTCTTAAACATGCGGTGA  
 CGTGGAGGAGAATCCGGCCCT (T2A)  
 ATGGGCTGTCCTGCATCATCTGTTCTGGCCACCGCCACCGC (SS)  
 GAGGCTCAGCTGTGCAAGTCTGGGAGGACTCGTTAGCCAGGTAGAACGCTC  
 AGACTGAGCTGTGCCAGTGGGTTTGCTTTTATCTTACGGTATGCACTGGG  
 TGAGACAGGCTCTGGCAAAGGACTCGAGTGGTCGCTGTAATATGGTCATG  
 GTACAAAGAAATACTATACCGTAGTGTGAAAGGAAGATTACCAATTACGAG  
 AACACAGTAAATACCTTGACCTTCAAGATGAACACCCCTGAGGAGCAAGACA  
 CAGCCGTGACTACTGCGCCAGAGATAGGGTATCGGAGCAAGGCGTGGTCCCT  
 ATTATATGGATGTGTTGGGGAGGGAAACAACAGTACTGTGAGCTGCTCTCA  
 CCAAGGGCCATCGGTCTTCCCCCTGGCACCCCTCCAAGAGCACCTCTGGGG  
 CAAGCGCCCTGGCTGCCAGGACTACTCCCGAACCGGTGACGGT  
 GTCGTGGAACTCAGGCGCCCTGACCGAGCGCGTGACACCTTCCCGCTGTCCT  
 ACAGTCTCAGGACTCTACTCCCTCAGCGCTGGTACTGTGCTCTAGCAGC  
 TTGGGCACCCAGACACTATCTGAAACGTGAATCACAAGCCAGAACACCAAG  
 GTGAGAAAGAAGTGTGAGCCAAATCTAGCGACAAGAAACTCACACAGGCCAAC  
 GTGCCACAGCCTGAACTCTGGGGGACCTCAGTCTTCTCTTCCCCCAAAA  
 CCAAAGGACACCTCATGATCTCCGGACCCCTGAGGTCAATGCGTGGTGTG  
 GACGTGAGCCACGAAGACCTGAGGTCAAGTCAACTGGTACGTGGACGGCGTG  
 GAGGTGATAATGCCAAGACAAGCCGGGGAGGAGCAGTACAACAGCAGCTA  
 CGTGTGGTCACTGCTCACCGTCTGACCCAGGACTGGTGAATGGCAAGGA  
 GTACAAGTGAAGGTCTCAACAAAGCCCTCCAGCCCCATCGAGAAAACCAT  
 CTCCAAGGCAAAGGGCAGCCCCGAGAACACAGGTGTACACCCCTGCCCCATC  
 CCGGAGTGGCTGACCAAGAACAGGCTCAGCTGACCTGCTGGTCAAAGGCTT  
 CTATCCCAGCAGCATCGCCGTGGAGTGGAGGAGCAATGGGAGCCGGAGAAC  
 ACTACAAGACCAAGCCTCCCGTGTGACTCGACGGCTCTTCTCTACAG  
 CAAGCTCACCGTGGACAAGAGCAGGGCAGCAGGGAAACGTTCTCATGTC  
 CGTGATGATGAGGCTCTGCAACACCAACTACAGCAGAAGAGCCTCCCTGTC  
 CCCGGTAAAtga (Adu-Heavy chain)

7. Endogenous full sequence human Gas6 protein SEQ ID NO: 149

ATGGCCCCCTCGCCGGCCGCGCCCTGCGCCCGCGCAGCTGC  
 TCTGCTCTGCTGCGCCGGAGTGGCGCTTGGCGCGCTGTGCGCCGGCG  
 AGGCCACCGAGCTCTGCGCCAGGCAGGCCGCGCTTTCAGGTCTTCAGGG  
 AGGCCAAGCAGGGCACCTGGAGAGGGAGTGCCTGAGGGACTGTGCAAGCGC  
 GAGGGAGGGGGAGGAGGTGTCAGAGAACGACCCCGAGACGGATTATTTTACCA  
 AGATACTTAGACTGATCAACAAAGTATGGGCTCCGTACACCAAAACTCAGGC  
 TTGCCCACCTGCTGCAAACCTGCTGACAGGTGACGCCAACCCCTGGAT  
 AGGAAGGGACCAAGCTGCCAGGACCTCATGGCAACTTCTCTGCTGTG  
 AAAGCTGCTGGGGGGCCGGCTCTGCGACAAGAGATGTCACAGAATGCAAGCA  
 GGAGAACGGGGCTCCAGATCTGCCACACAAGCCGGTAGCTTCCACTG  
 TTCTGCCCACAGGGCTTCGAGCTCTCTGATGGCAGGACTGCGAACACATA  
 GACGAGTGGCGAGACTGGAGGGCTGCGGGAGGGCGCGTGCAGAACCTGCG  
 CGGCTCTACTCTGCTCTGACAGGGCTTGTGCTACAGCTCCAGGAGAAG  
 GCTTGGCGAGATGTTGGACGAGTGTCTGCAAGGGCCGCTGTGAGCAGGTCTGCG  
 AACTCCCCAGGGAGCTACACCTGCCACTGTGACGGCGTGGGGGCTCAAGCTG  
 TCCCAGGACATGGACACCTGTGAGGACATCTGCGCTGCGTCCCTCAGCGTG  
 GCGAAGAGTGTGAGGTCTTGTACCTGCGGAGGATGTTCAAGGGACCCCGTG  
 ATCCGACTGCGCTCAAGAGGCTGAGGCCACAGGCTGAGCTGAGTTGAC  
 TTCCGGACCTTTGACCCGGAGGGCATCCTCTTTGCGGAGGCCACAGGACA  
 GCACCTGGATGCTGCTGGCCCTGAGAGCGGCCGGCTGAGCTGAGCTGCGCT

TABLE 4-continued

---

```

ACAAACGGTGTGGCCCGTGTCAACCAGCAGCGGGCCGGTCATCAACCATGGCATGT
GGCAGACAATCTGTTGAGGAGCTGGCGCGGAATCTGGTCATCAAGGTCAACA
GGGATGCTGTATGAAAATCGCGTGCGGGGACTTGTCCAACCGGAGCGAG
GACTGTATCATCTGAACCTGACCGTGCGGGAGGTATTCCCTCCATGAGAAGGACCT
CGTGAGCCTATAAACCTCGTCTGGATGGCTGCATGAGGAGCTGGAACTGGCT
GAACGGAGAACACACCATCCAGGAAACCGTGAAGGTAAACACAGGAGATGC
AGTGCTTCGCGTGACGGAGAGAGGCTTTTACACCGGGAGCGGCTTCGCGCTT
CTACAGCTGCGGACTACATGCGGACCCCTCGGACGTGGGACTGAATCAACCTG
GGAACTAGAAGCTGTGGCTCACATCCGCCAGCGCGAGACACAGGCTGCTGTT
TGGGCTCTGGGCCCCGACCTCCGTGCCTCTCTGTGGCACTGGTAGAC
TATCACTCCACAGAAGAAACTCAAGAAGCAGCTGGTGGTCTCGCCGTGGAGCAT
ACCGCCTGGGCTTAATGGAGATCAAGGTCTCGCACGGCAAGAGCACGTGTC
ACCGTCTCGTGGGGACCCCTGGAGGTGGACGGCAGAGGGCCAGGG
CCAGAGCGAGGTGAGGCCCGCCAGTCAGGAGAGGCTGCCGTCTCGAGA
GGCACCTCGGGAGCCCCGTCTACCTTGTGGCGGCTGCCAGATGTGCCGT
GACTTCAGCAGCTGGGCTTACCGGCGCTGCATGACACTGGAGGTCAA
CCGGAGGCTGCTGGACCTGGAGGGCGTACAAGCACAGGACATCACGG
CCCACTCTGCCCGCCCGTGGAGCCCCCGCAGCC (full-length human Gas6)
caaGGATCCCAGGCTGACTACAAAGACCATGACGGTGATTATAAAAGATCATGACA
TCGACTACAAGGATGACGATGACAAGTGA (FLAG)

```

---

20

**Preparation Example 2. Gas6-Based Fusion Molecule Targeting Tau**

To prepare a tau-specific chimeric phagocytosis inducer based on Gas6 protein, the Gla domain and the EGF repeat

domain were first removed, and a single-chain variable fragment (scFv) of semorinemab, a tau-specific antibody fragment; scFv), was introduced at that position ( $\alpha$ Tau-Gas6). Table 5 below shows the amino acid sequence and nucleotide sequence of the chimeric phagocytosis inducer.

TABLE 5

---

1.  $\alpha$ Tau-Gas6 (Tau-VL-G4Sx3-VH-LG-HA-T2A-EGFP, amino acid sequence) SEQ ID NO: 150  
MAPSLSPGPAALRRAPOLLLLLAAECALA (ss)  
DDVLTQPLSLPVPQGPASISCRSSQSVHSNGNTYLEWYLQKPGQSPQLLIYKVSN  
RFSGVPDFSGSGSDFTLKRISLVEAEDEVGVVYCPQGSVPWTFQGQTKVEIKGG  
GSGGGGGGSEVQLVESGGVLQPQGSSLRLSCAASGLIFRSYGMWSVRQAPKG  
LEWVATINSGGTYTYYPDVSVKGRFTIISRDNSKNTLYLQMNSLRAEDTAVYYCANSYS  
GAMDYWQGQTLTVSS (aTau-scFv)  
GGGGSGGGGS (Linker)  
DILPCVPFSVAKSVKSLYLGMRFSGTPVIRLFKRLQPTRLVAEFDRTFDPEGILLFAG  
GHQDSTWIVLRLAGRILELQLRYNGVGRVTSSGPVINHGMWQTISVEELARNLVK  
VNRDAVMKIAVAGDLFQPERGLYHLNLTVGGIPFHEKDLVQPINPRLDGCMRSWNW  
LNGEDDTIQTETVKVNTRMOCFVSTERPGFVPGSFAFYPSLDYMRTPLDVGTESTWEV  
EVVAHIRPAADTGVLFALWAPDLRAVPLSVALDVYHSTKKLKQLVVLAHEHTALAL  
MEIKVCDQEHVVTVSLRDGEATLEVDTGTRQSEVSAQLQERLAVLERHLSRSPVLL  
TFAGGLPDVPVTSAPVTAFYRGCMTLEVNRRLLDLDEAAYKHSIDTAHSCPPVEPAA  
A (Gas6-Gla EGF deleted)  
GSGSGSGSGSGSYPYDVPDYA (HA)  
EGRGSLLTTCGDVEENPGP (T2A)  
VSKGEELFTGVVPILVLEDGVNGHKFSVSGECEGDATYGKLTFLKFICTTGKLPVWP  
PTLVTTITYGVQCFSRVPDHMKQHDFFKSAMPEGYVQERTIFFKDGNYKTRAEVK  
FEGDTLVNRIELKGIDEPKEDGNILGHKLEYNNNSHNVYIMADKQKNGIKVNFKIRHN  
IEDGSVQLADHYQQNTPIGDGPVLLPDNHYLSTQSALSKDNEKRDHMVLLEFVTA  
AGITLGMDELYK\* (EGFP)

2.  $\alpha$ Tau-Gas6 (Tau-VL-G4Sx3-VH-LG-HA-T2A-EGFP, nucleotide sequence) SEQ ID NO: 151  
ATGGCCCCCTCGCTCGCCGGCCGGCCGCGCTGCGCCGCGCGCCGAGCTGC  
TGCCTGCTGCTGCTGGCCCGGGAGTGGCGCGCTTGCC (ss)  
GACGATGTTAACACAAACTCCCTATCATGGCGGTGACCCGGGCAACCA  
GCTCTCGATCAGCTGGCGTAGCTTCAGAGCATCGTCACAGCAACGGTAATACC  
TACCTGGAATGTTATTGCAAAACCGGGTAATCCCGCAGTTCTGCTGATTATA  
AAGTTTCAATGTTTCAAGCTGAGGAGATCAGTCCGCTGGATCGTTAGCGGCTCTGGCTCCGG  
CACCGATTTCAAGCTGAGGAGATCAGTCCGCTGGATCGTTAGCGGCTCTGGCTCCGG  
CTACTGCTTCAAGCTGAGGAGATCAGTCCGCTGGATCGTTAGCGGCTCTGGCTCCGG  
GAATTAAGGGTGGGGGATCAGTGGAGGGTGGTCAAGCTGAGGAGATCAGTGG  
CGAGGTACAACACTAGTTGAATCAGTGGAGGGTGGTCAAGCTGAGGAGATCAGTGG  
GGCTGCTGAGTTGCGGCAAGGGTCTGGCTGGAGTGGGTGGCAGGACATTAACCTGGC  
GTTCTGAGGCGCCGGCAAGGGTCTGGCTGGAGTGGGTGGCAGGACATTAACCTGGC  
GCCACGTACACCTACTATCCCGACTCCGTAAAGGCCGTTTACCATCTCCCG  
ACAATAGAAAAACACCCGTATTCAGTGAAGTGAACCTGGCTCCGCGCAGAGGACA  
CCGCTGTTACTACTGGCCAACTTCTACAGCGGTGCTATGGATTATGGGTC  
GGGACATTGGTGACTGAGCAGC (aTau-scFv)  
GGGGGGGGCGCAGCGGGCGGTGGCAGC (Linker)  
GACATCTTGGCGTGCCTGCGCTTCAAGCTGAGGAGATCAGTGGCTTCAAGAGGCTGC  
TGGGCGGAGATGTCAGTGGGACCCCGTGAATCCGACTGGCCTTCAAGAGGCTGC  
AGCCCACCCAGGCTGGTAGCTGAGTTGACTCCGGACCTTGACCCGAGGGCA  
TCCTCCTTTGGCGGAGGGCACCAGGACAGCACCTGGATCAGTGGCTGCCCTGAG

TABLE 5-continued

AGCCGGCGGCTGGAGTCAGCTCGCTAACACGGTGTGGCGGTGTCAACAG  
CAGCGGCCCGCTCATACCATGGCATGGCAGACAACTCTCTGAGGAGCT  
GGCGCGGAATCTGGCATCAAGGTCAACGGGATGCTGTGATGAAATCGCGGT  
GGCGCGGAGACTGTGTCACCGGAGGAGGACTGTATCATCTGACACCTGACCGT  
GGGAGGTATTCCCTTCCATAGAAGGACCTCGTGAGCTATAACACCTCGTCTG  
GATGGCTGCATGAGGAGCTGGAACTGGCTGAACCGGAGAACACCCACATCCA  
AGAACGGCTTAAAGTGAACACAGGATGCGATGCTCTCGGTGAGGAGAG  
GCTCTTCTACCCCGGGAGGCGCTTCGCTCTACAGCGGACTATCATGCGGAC  
CCCTCTGGACGCTGGGAGCTGAATCAACCTGGGAGTAGAAAGTGTGGCTCACAT  
CGGCCAGCGGACAGACACGGCTGTGTTGCGCTCTGGCCCCCGACCTCCGT  
GGCGTCTCTCTCTGTGGCACTGGTAGACTATCATCTGGAGAACAACTCAAG  
AAGCGCTGGTGTCTGGGCGGGAGCATACGGCTCTGGCCCCTAATGGAGATC  
AAGGTCTGCGACGGCCAAGAGCACGCTGGTCAACCGTCTCGTGAGGGACGGTGAG  
GCCACCCCTGGAGGTGGACGCCACAGGGGCGAGACGAGGTGAGGCCCGCGCA  
GCTGAGGAGAGGCTGGCCGTGCTGAGAGGGACTCTGGGAGGCCCCGTGTCAC  
CTTGTGGGCCCTGGCAAGATGTCGGTGAATTCTGGCCAGTCAGCGGTC  
TACCGCGGCTGCATGACACTGGAGGTCAACCGGAGGCTGTGGACCTGGACAGAG  
GGGGCGTACAAGCACAGCGACATCACGGCCCACTCTGGCCCCCGTGGAGGCC  
GCCGAGC (Gass-Gla EGF deleted)  
GGCGAGGGCAGCGGAGCGGCAGCGGAGCGCAGaccatacgatgttcca  
gattacgt (HA)  
GAGGGCAGAGGAAGTCTGCTAACATCGGTGACGTGAGGAGAATCTGGCC  
A (T2A)  
TGAGACAGGGCAGGGAGCTTACCGGGGTGGTGCCTACCTGGTCAAGCTG  
GACGGCGACGTTAACCGGCCAACAGTCAGCGTGTCCGGGAGGGCAGGGCGA  
TGCCACCTACGGCAAGCTGACCTGAAAGTTCATCTGCACCCACGGCAAGCTGCC  
CGTGGCCTGGCCCAACCTCTGGACACCCCTGACCTACGGCTGAGCTTCAGC  
CGCTACCCGGCACACATGAAGCAGCACGACTCTTCAGGGCTGAGCTGGCC  
GGCTACGTCCAGGAGCGCACCATCTTCAAGGAGCAGCGCAACTACAAGACC  
CGCGCCGAGGTGAAGTTCAGGGCGACACCTGGTGAACGGGATCGAGCTGAAG  
GGCATGCTACCTCAAGGAGGAGGGCACACATCTGGGCAACAGCTGGAGTACA  
CTACACAGGCCAACAGCTATATCATGGGCCAACAGGAGAACAGCGCATCAA  
GGTGAACCTCAAGATCGCCACAAACATCAGGGAGCGCACGGTGCAGCTGGCC  
CCACTACAGAGAACACCCCATGGCGAGGGCCCGTGTGCTGCGGCCAACAA  
CCACTACCTGAGCACCCAGCTCGCCCTGACCAAAGACCCCCAACAGAGAGCGGA  
TCACATGGTCTGCTGGAGTTCTGACCGCCGGGATCACTCTGGCATGGAC  
GAGCTACAAAGtaa (EGFP)

### Preparation Example 3. Gas6-Based Fusion Molecule Targeting Alpha-Synuclein

To prepare an alpha-synuclein-specific chimera phagocytosis inducer based on Gas6 protein, the Gla domain and the

35 EGF repeat domain were first removed, and a single-chain variable region (scFv) of cипанемаб, an alpha-synuclein-specific antibody, was introduced at that position ( $\alpha$ Syn-Gas6). Table 6 below shows the amino acid sequence and nucleotide sequence of the chimeric phagocytosis inducer.

TABLE 6

1. aaSyn-Gas6 (Cinpanemab (aaSyn)\_VL-G4Sx3-VH-LG-HA-T2A-EGFP, amino acid sequence) SEQ ID NO: 152  
MAPSLSPGPAAALRQAPOLLALLLAEECALA (SS)  
SYELTQPPSVSVPQGQKARITCSEALPMQFAHWYQQRPGKPQKAVIVVYKDSERPNSGV  
PERFSGSSGGTTATLITIGVQAEDEADYYCQSPDSTNTYEVFGGGTQLTVLGGS  
GGGSGGGGSEVQLVESGGGLVEPGGSLRLSCAVSGFDPEKAWMSWVRQAPGQGLQ  
WVARIKSTADGGTTSYAAPVEGRFIISRDDSRNMLYQLMNSLKTEDTAVYCYCTSAH  
WGQGLTJVTVSS (aaSyn-aaFc)  
GGGGSGGGGS (Linker)  
DILPCVPFSVAKSVKSLYLRGMFSGTPVIRLRFKRLQPTRLVAEFDERTFDPEGILFA  
GGHQDSTWIVLALRAGRLEIQLRYNGVGRVTSVSGPVINHGMWQTI SVEELARNLVI  
KVNRDAVMKIAVGDLFQPERGLYHLNTWVGGPFFHEKDLLQVNPRLDCMRCSRWN  
WLNGDETTIQTETVKVNTRMCGFSVTTERGSFYPGSGFAFYSLDYMTPLDVGTESTW  
EVEVVAHPIRAPDATGVLFALWAPDRLAVPLSVALVDYHSTKLKKQLVVLAAEHT  
ALALMEIKVCDGQEHVVTVSLRDGEATLEVDTGTRGQSEVSAQLQERLAVLERHRL  
SPVLTFTAGGLPDVPVTSAPVTAFYRCMTLEVNRRLLDLEAAYKHSIDTAHSCPPV  
EPAAA (Gas6-G1a EGF deleted)  
GSGSGSGSGSGSPYVPDPYA (HA)  
EGRGSLLTCGDVEENPPG (T2A)  
VSKGEELFTGVVPILVELDGDVNGHKFSVSGEGEGDATYGKLTLKFICTTGKLPWPW  
PTLVITLTGYQCFCSRYPDMHKQHDFFKSAMPEGVYQERTIFFKDDGNYKTRAEVK  
FEGDFTLVRIELKGIDFKEDGNILGHKLEYNNSHNVYIMADKQKNGIKVNFKIRHN  
IEDGSQVOLADHYQQNTPIGDGPVLLPDNDHYLSTQSLSKDPNEKRDHMVLLEFVTA  
AGITLGMDELYK\*

2. aaSyn-Gas6 (Cinpanemab (aaSyn)\_VL-G4Sx3-VH-LG-HA-T2A-EGFP, nucleotide sequence) SEQ ID NO: 153  
ATGGCCCCCTCGCTCTGCCCGGGCCGCCGCCTCGGCCGCGCCGCAGCTGC  
TCTGCTGCTGCTGCTGGCCGGAGGTGCGCGCTTGCC (SS)  
TCCTATGAGCTGACTCAGCGCACCCCTCGGTCACTGTCAGTGTCCCAACAGACGGCC  
AGGATCACCTGCTCTGGAGAGCATTCGCACTGGTCAATTGTCATGGTACCAAC

TABLE 6 -continued

AGAGGCCAGGCAAGGCCCAAGTGATAGTGGGTACAAAGACAGTGAGAGACCG  
 TCAGGTCTCCCTGAGCGATTCTGGCTCCAGCTCAGGGCACACGCCACCGTG  
 ACCATCACTGGAGTCAGGCAGAACAGTGAGGTGACTATTACTGCCAGTCGCCA  
 GACAGCACTAACACTTATGAAGTCTTCGGCGGAGGACCAAGCTGACCGTCTA  
 GGTGGTGGGGATCAGGTGGCGGGCAGCGCGGGTGGCGGGAGCGAGGTGCA  
 GCTGGTGGAGTCTGGGGAGGTCTGGTCGAGCCGGGGGCTCCCTAACAGCTCTC  
 CTGTGCGAGTCTCGGATTGATTTGAAAAGCCTGGATGAGTTGGTCCGCCA  
 GGCCTGAGGCAAGGGCTACAGTGGGTGCCCCGATCAAGAGCACAGCTGATGG  
 TGGGACACAAAGTACGCCGCCCTGGAGGCAAGGTCATCATCTCAAGAGA  
 TGATTCGAGAACATGTTATCTGAAATGAACAGTCTGAAACAGTGAAGACAC  
 AGCGCTATTATGTACATCAGCCACTGGGCCAGGGAACCCCTGGTCACCGTC  
 TCTCG (aaSyn-scFv)  
 GGCGGGGCGGCAGCGGGGGTGGCAGC (Linker)  
 GACATCTGGCTTGTGCTTCAGGTGGCAAGAGTGAGTCAGGCTTGTACCC  
 TGGGCGGATGTTCAAGTGGGACCCCGTGATCGACTGCGCTCAAGAGGCTGC  
 AGGCCACAGGCTGGAGCTGAGTTGACTTCGGACCTTGTGACCCCGAGGGCA  
 TCCTCCTTTGGGGGAGGCCCCAGGACAGCACCTGGATCGTGGCCCTGAG  
 AGCGGGCGGCTGGAGCTGAGCTGGCTAACAGCGTGTGGCCGTGACCCAG  
 CAGCGGGCCGGTCAACCAGTGGCATGGCAGAACATCTGTGAGGAGCT  
 GGGCGGAATCTGGTCAAGGTCAACAGGGATGCTGTGAGTCAAATCGGGT  
 GGCGGGGACTTCCAACCGGAGGCGAGGACTGTGATCATCTGAACCTGACCGT  
 GGGAGGTATTCCCTCATGAGAAGGACCTCTGAGCCCTATAAACCTCGTCTG  
 GATGGCTGCATGAGGAGCTGAAACTGGCTGAACGGAGAACACACCACATCCA  
 GAAACCGTGAAGTGAACACAGGAGTCACTGCTTCGGTGACGGAGAG  
 GCTCTTCTACCCGGGAGCGCTTCAGCTGGACTACATCGGAC  
 CCCCCTGGACGTGGGACTGAATCAACCTGGGAAGTAGAAGTCGTGGCTCACAT  
 CCGCCCGAGCCAGACACAGGGTGTGTTGCGCTCTGGCCCCCGACCTCCGT  
 GCGGTGCTCTCTGTGGCACTGGTAGACTATCACTCCACGAAGAACACTAAG  
 AAGCAGCTGGTGTCTGGCGACTGGGAGCATACGGCCTTGGCCCTAATGGAGATC  
 AAGGTCTCGACGCCAAGGACAGTGTGACCGTCTCGTGAGGGACGGTGA  
 GCCACCTGGAGGTGGACGGCACCGGGGAGGGAGCTGAGGCCGCGC  
 GCTGAGGAGGGCTGGCGTCTCGAGAGGGACCTGCGGAGGCCGTGCTCAC  
 CTTTGCCGCTGCATGACACTGGAGGTCAACGGGAGGCTGCTGGACCTGGAG  
 GCGCGTACAAGCACAGCGACATCACGGCCACTCTGGCCCCCGTGGAGCC  
 GCCGAGCC (Gas6-Gla EGF deleted)  
 GGCAGCGCAGGGCAGCGCAGCGCAGCGCAGCTACCCATACGATGTTCC  
 AGATTACGCT (HA)  
 GAGGGCAGGAAAGTCTGTAACATCGGTGACGTCGAGGAGAACCTGGCC  
 A (T2A)  
 GTGAGCAAGGGGAGGAGCTTCACGGGGGGTCCACATCTGGTCAGCTG  
 GACGGCGACGTAACAGGCCAACAGTTCAAGCTGAGCTCATCTGACCC  
 CGTGGCCCTGGCCACCCCTCGTGAACACCGTACGGCGTGCAGTGCCTCAGC  
 CGCTAACCTGGCCACCATGAAGCAGCACGACTCTCAAGTGGCCATGCCGAA  
 GGCCTACCTCAAGGGAGGCCAACATCTGGGACAAGCTGGAGTACA  
 CGGGCGAGGTGAAGTTGAGGGGAGCACCTGGGACAAGCTGGAGTACA  
 GGCATCGACTCAAGGGAGGCCAACATCTGGGACAAGCTGGAGTACA  
 CTACAAAGGCCAACAGCTATCATGGCCACAAGCAGAAAGAACGGCATCAA  
 GGTGAACCTCAAGGATCCGCCAACATCGAGGACGGCAGCGTGCAGTGC  
 CCACTACCGAGAACACCCCCATCGCGACGGCCCCGTGCTGCTGCCGACAA  
 CCACATGAGCACCCAGTCCGCCCCGAGCAAAGACCCAACGAGAACGGCA  
 TACATGTCCTGCTGGAGTTGTCGACCGCCGGGATCATCTCGGATGGAC  
 GAGCTGTACAAGTAA (EGFP)

Preparation Example 4. ProS1-Based Fusion  
 Molecule Targeting Beta-Amyloid

To prepare a beta-amyloid (A $\beta$ )-specific chimeric phagocytosis inducer based on ProS1 protein, the Gla domain and

the EGF repeat domain were first removed, and a single-chain variable fragment (scFv) of aducanumab, a beta-amyloid-specific antibody, was introduced at that position ( $\alpha$ A $\beta$ -ProS1). Table 7 below shows the amino acid sequence and nucleotide sequence of the chimeric phagocytosis inducer.

TABLE 7

1.  $\alpha$ A $\beta$ -ProS1 ( $\alpha$ A $\beta$ -ProS1(GE)-FLAG, amino acid sequence)  
 SEQ ID NO: 154  
 MRVLGGRCGALLACLLVLPVSEA (SS)  
 DIQMTQSPSSLSASVGRVTITCRASQSISSYLNWYQQPKPGKAPKLLIYAASSLQSGV  
 PSRFSGSQSGTDFTLTISSLQPEDFATYYCQSYSTPLTFGGGTKVEIKRGGGGSGGG  
 GSGGGGSEVQLVESGGVVPQGRSLRLSCAASGFAFSSYGMHWVRQAPGKLEWV  
 AVIWFDTCKYTDHSVGRFTISRDNSKNTLYQMNTRAEDEAVYYCARDRGIGA  
 RRGPYMDVWGKTTTVTSS (Adu-scFv)  
 GGGGGGGG (Linker)  
 VVSVCPLNLDTKYELLYLAEQFAGVVLYLKFLRPEISRFSAEFDRTYDSEGVLYA  
 ESIDHSAWLIALRGKIEVQLKNEHTSKITGGDVINNGLWNMVSVEELEHSISIKIA  
 KEAVMDINKPGLFKPENGLLETKVYFAGFPRKVESELIKPINPRLDGICRSWNLMK

TABLE 7-continued

QGASGIKEIIIQEKQNKHCLVTVEKGSYPPGSGLAQFHDYNNVSSAEGWHVNVTLNI  
RPTSTGTGVMLALVSGNNTVPFAVSLVDSTSKEKSDILLSEVENTVIYRIQALSCLSDQQ  
SHLEFRVRNRNNLELSTPLKIEI SHEDLQRQLAVLDKAMAKVATYLGGLPDVPPFA  
TPVNAFYNGCMEVNINGVQLDLDEAISKHNDIRAHSCPSWKTKNS (ProS1 (GE-))  
QGSRADYKDHDGDYKDHDIDYKDDDK\* (FLAG)

2.  $\alpha$ A $\beta$ -ProS1 ( $\alpha$ A $\beta$ -ProS1 (GE-) -FLAG, nucleotide sequence)  
SEQ ID NO: 155  
ATGAGGGTCTCTGGCTGGGGCTCGGGGCGCTGCTGGCGTGCTCCTCTAGTG  
CTTCCTGCTCAAGGGCA (SS)  
GACATTCAAGATGACTCAATCTCTAGCTCTGAGCGCCTCCGTTGGAGATAGAG  
TCACTTACCTGCAGGCCAACCTCATCAGCTCTTATCTAAATTGGTACCA  
ACAGAAGCCGGCAAAGGCCAACAGCTGCTCATCAGCTGCAAGCTCCTTACA  
GAGCGGAGTACCCAGCAGATTCTCAGGCAGTGGCAGTGGGACTGACTTCACATT  
GACGATTAGCTCTGCAGCCTGAAGACTTGGCCACATACTATTGTCAGCAGAGC  
TATAGCACCCCCCTGACGTTGGAGGGGAACTAAGGTGGAATTAAGAGAGG  
AGGCGGGGCTCGGGGGGGCTGGCTGGGGGAGGGGCTCAGAGGTTTACG  
TTGTCGAGTCTGGGGGGAGTCGTTCAAGCAGGTAGAAGCCTCAGACTGAGCT  
GTGCCGCAAGTGGGTTGCTTTTACATCTACGGTATGCACTGGGTGAGACAGGC  
TCCCTGCAAAGGAACTCGAGTGGCTGTAATATGTTGATGGTACAAAGAA  
ATACTATACCGATAGTGTGAAAGGAAGATTACCCATTTCACGAGACAACAGTAA  
AAATACCTTGATACCTCAGATGAACACCCCTGAGAGCAGAACAGCCGTGTA  
CTACTGCCAGAGATAGAGGTATCGGAGCAAGGCGTGGTCCCTATTATATGGA  
TGTGTGGGGAAAGGAAACAACAGTGAATGTGAGCT (Adu-scFv)  
GCCGGGGCGGGCAGCGGGCGGTGCAGC (Linker)  
GTGTTTCAGTGTGCTTCCCCTGAACTTGCACAAAAGTATGAATTACTTACTT  
GGCGGAGCAGTTGCAAGGGTTGTTTATATTAAATTCGTTGCAAGAAATC  
AGCAGATTTCAGCAGATTGATTCGGGACATATGATTCAAGAAGGGTGTATA  
CTGTACCGAGAATCTATCGACTCAGCTGGCTCTGATTGCACTTCGTGGTG  
GAAAGATTGAACTTCAGCTTAAGAATGAACATACATCCAATCACAACTCGAG  
GTGATGTTATAATAATGGTCTATGGAATATGGTCTGTGGAAGAATTAGAAC  
ATAGTATTAGCATTAATAATAGCTAAAGAAGCTGTGATGGATATAAATAAACCTG  
GACCCCTTTAAGCGGAAATGGATTGCTGGAAACCAAAAGTATACCTTGCAG  
GATTCCCTCGGAAAGTGGAAAGTGAACTCATTAAACCGATTAACCTCTGCTAG  
ATGGATGTATACGAAGCTGGATTGATGAAGCAAGGAGCTCTGGAAATAAGG  
AAATTATTCAAGAAAAACAAAAGCATTGCTGGTACTGTGGAGAAGGGCT  
CCTACTATCCTGTTCTGGAATTGCTCAATTTCACATAGATTATAATAATGTATC  
CAGTGTGAGGGTGGCATGTAATGTGACCTGTAATATTGTCATCCACGGGC  
ACTGGTGTATGCTTGTGCTGGTTCTGGTAACAACACAGTGGCTTGTGTTG  
CTTGGTGGACTCCACCTCTGAAAATCACAGGATATTGTTATCTGTTGAAAAT  
ACTGTAATATATCGGATACAGGCCCTAAGTCATGTCGATCAACAATCTCATC  
TGGAAATTAGAGTCACAGAAACAATCTGGAGTTGTCGACACCACTTAAATAG  
AAACCATCTCCATGAAGACCTCAAAAGACAACCTTGCCTCTGGACAAAGCAA  
TGAAAGCAAAGTGGCCACATACCTGGGTGGCTTCCAGATGTTGATTACAGTG  
CCACACAGTGAATGCTTATAATGCTGATGGAAGTGAATTTAAATGTTG  
ACAGTTGGATCTGGATGAAGCCATTCTAAACATAATGATATTAGAGCTCACTCA  
TGTCATCAGTTGGAAAAGACAAAGAATTCT (ProS1 (GE-))  
CAAGGATCCCAGGCTGACTACAAAGACCATGACGGTGATTATAAAAGATCATGAC  
ATCGACTACAAGGATGACGATGACAAGtga (FLAG)

Preparation Example 5. Gas6-Based Fusion  
Molecules Targeting Beta-Amyloid (II):  
Beta-Amyloid-Binding Regions in the Form of Fab  
or Mab

To prepare gas6 protein-based beta-amyloid (A $\beta$ )-specific chimera phagocytosis inducer, the Gla domain, which rec-

ognizes PS (phosphatidylserine) in apoptotic cells, was first removed, and an antigen-binding fragment (Fab) or monoclonal antibody (Mab) of the beta-amyloid-specific antibody aducanumab was introduced at that position ( $\alpha$ A $\beta$ [Fab]-Gas6, and  $\alpha$ A $\beta$ [Mab]-Gas6). Tables 8-10 below show the amino acid sequences and nucleotide sequences of the two chimeric phagocytosis inducers.

TABLE 8

Second Region Light Chain (SEQ ID NO: 161) (the light chain which is capable of specifically binding to beta-amyloid can form a dimer with the peptide of sequence of SEQ ID NO: 156 or SEQ ID NO: 158 to form Fab Adu-Gas6 or Mab Adu-Gas6, respectively):  
MGWSCIILFLVLATATG (SS)  
DIQMTQSPSSLASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGV  
PSRFSGSGSGTDFTLTISLQPEDFATYYCQQSYSTPLTFGGGTKEIKRKRTVAAPSV  
FIFPPSDEQLKSGTASVCLLNNFYPREAKVQWVKVDNALQSGNSQESTVQDSKDST  
YSLSTLTLKADYEHKVVYACEVTHQGLSSPVTKSFNRGEC\* (Adu Light Chain)

1.  $\alpha$ A $\beta$ [Fab]-Gas6 (Aducanumab VH-CH1 (Fab) -Gas6-FLAG, amino acid sequence) SEQ ID NO: 156  
METDTLLLWVLLLWVPGSTGD (SS)  
EVQLVESGGVVQPGRSRLSRAASGFSSYGMHWVRQAPGKGLEWVAIVFDG  
TKYIYTDSVKGRFTISRDNSKNTLYLQMNTLRAEDTAVYYCARDRGIGARRGPYY

TABLE 8-continued

MDVWGKGTTVSSASTKGPSVPLAPSSKSTSGGTAALGCLVKDYLPEPVTVSWN  
 SGALTSGVHTFPAVLQSSGLYSLSSVTPSSSLGTQTYICNVNHPNSNTKVDKKVE  
 PKSCDKTH (Adu-VH-CH1)  
 GGGGSGGGGS (Linker)  
 DILPCVPFSVAKSVKSLYLGRCMFSGTPVIRLFKRLQPTRLVAEFDRTFDPEGILLFA  
 GHQDSTWIVLALARGLRLELQLRYNGVGRVTSGPVINHGMWQTISVEELARNLVI  
 KVRDAVMKIAVAGDLFQPERGLYHHLNTVGGIPFHEKDLVQPINPRLDGCMRSWN  
 WLNGEDTTIQTETKVNVTRMQCFSVTERGSFYPGSGFAFYSLDYMRTPLDVGTESTW  
 EEEVVAHIRPAFDLWAPDLRAVPLSVALVDYHSTKLLKKQLVVLAVEHT  
 AALALMEIKVCDQEHVVTVSLRDGEATLEVDGTRGSEVSAAQLQERLAVLERHLR  
 SPVLTFAAGGLPDVPVTSAPVTAFYRGCMTELEVNRRLLDDEAAYKHSDITAHCSCP  
 EPAAA (Gas6-Gla EGF deleted)  
 DYKDHDGDYKDHDIDYKDDDK\* (FLAG)

2.  $\alpha\beta$ [Fab]-Gas6 (Aducanumab (Fab) -Gas6-FLAG, nucleotide sequence) SEQ ID NO: 157  
 ATGGAGACAGACACACTCCTGCTATGGTACTGCTCTGGTTCCAGGTTCCA  
 CTGGTGAC (SS)  
 GAGGTTCAGCTTCAGTCTGGGGGGAGTCGTTCAAGCCAGGTAGAACGCTC  
 AGACTGAGCTGTCGCCAAGTGGGTTGCCTTCACTCTAACGGTATGCACTGGG  
 TGAGACAGGCTTCGGCAAAGGACTCGAGTGGCTCGCTGTAATATGGTTCGATG  
 GTACAAAGAAATACTATACCGATAGTGTGAAGGAAGATTACCACTTCAAGAG  
 ACAACAGTAAAAATACCTTGACCTTCAGATGAACACCCCTGAGAGCAGAACAGA  
 CAGCCGTGTACTACTGCCAGAGATAGAGGATATCGGAGCAAGGCGTGGTCCCT  
 ATTATACTGGATGTCGGGGAAAGGGAAACAACAGTACTGAGCTTCGCTTCA  
 CAAGGGCCCATGGCTTCCCCCTGGCACCTCTCAAGAGCACCTCTGGGG  
 CACAGCGCCCTGGCTGCCTGGTCAAGGACTACTTCCCAGACCCCTGGCTGAGCGT  
 GTCTGGAACTAGGGCCCTGACCAGCGGCGTGACACCTTCCCAGCTGCT  
 ACAGTCCTCAGGACTCTACTCCCTCAGCAGCTGGTACTGTGCCCCTAGCAGC  
 TTGGCAACCCAGGACTCATCTGCAACTGATGAAATACAAGCCAGAACACCAAG  
 GTGGACAAGAAAGTTGAGCCAAATCTGTGACAAACACTCAC (Adu-VH-CH1)  
 GCGGGAGGTGGAAGCGGAGGGCTGGAAGC (Linker)  
 GACATCTGGCTGCGCCTTCAGCGTGGCAAGAGGTGTGAAGTCTTGACCC  
 TGGGCCGATGTCAGTGGGACCCCGTAGCTGACTGCGCTCAAGAGGCTGC  
 AGCCCACCAAGGCTGGTAGCTGAGTTGACTTCGGACCTTGACCCGAGGGCA  
 TCCCTCTTTGCGGGAGGCCACCAGGACAGCACCTGGATCGTGTGGCCCTGAG  
 AGCCGGCGGCGTGCAGCTGCGCTAACAGCGTGTGGCCCTGTACACAG  
 CAGCGGGCCGGTCAACACCGGAGATGCACTGCTCTCGTGGAGGAGCT  
 GGGCGGAATCTGGTCAAGGTCACAGGGATGTCATGAAATCGGGT  
 GGCGGGGACTTGTCAACCGGAGCGAGGACTGTATCATGCAACCTCACCGT  
 GGGAGGATTCTGGCTTCAAGGACCTCGTGCAGCTTCAACACCTCTGCT  
 GATGGCTGATGAGGAGCTGGAACCTGGCTGAACGGAGAAAGACACCATCCA  
 GGAACACGGTGAAGTGAACACCGGAGATGCACTGCTCTCGTGGAGGAGAG  
 GCTCTTCTACCCGGAGCGGCTTCGCTTCAAGCCTGGACTACATGCGGAC  
 CCTCTGGACACTGGGACTGAATCAACCTGGGAGTAGAACTCGTGTGCTCACAT  
 CCGCCCAAGCCGCAACAGGGCTGCTGCTGCGCTTGGGCCCCGACCTCCGT  
 GCGGTGCGCTCTCTGTGGCAGCTGGTAGACTATCACTCCACGAAGAAACTCAAG  
 AACGAGCTGGTGGTCTGGCCCTGGAGCATACGGCTTGGCCATTGGAGATC  
 AAGGTCTGCGACGCCAAGAGCACGTTGACCGTCTCGTGTGAGGGACGGTGA  
 GCCACCCCTGGAGGTGGACGCCAACGGGAGGGAGGGAGGTGAGGCCGCC  
 GCTGCGAGGAGGCTGGCCCTGCTCGAGAGGGACCTCGCGAGGCCCCGTCTCAC  
 CTTTGCGCCGCGCTGCGAGATGTGCGGGTACTTCAGCGCAAGTCACCGCGTT  
 TACCGCGCTGCGATGACTGGAGGTCAACCGGAGGCTGCTGGACCTGGAG  
 GCGCGTACAAGCACAGCGACATCACGCCACTCTGCCCGTGGAGGCC  
 GCGCAGCC (Gas6-Gla EGF deleted)  
 GACTACAAAGACCATGACGGTATTATAAGATCATGACATCGACTACAAGGAT  
 GACGATGACAAGTga (FLAG)

TABLE 9

1.  $\alpha\beta$ [Mab]-Gas6 (Aducanumab heavy chain (Mab) -Gas6-FLAG, amino acid sequence) SEQ ID NO: 158  
 METDTLLLWVLLLWVPGSTGD (SS)  
 EVQLVESGGVVQPGRLRLSAAASGPFAFSSYGMHWVRQAPGKLEWVAIWF  
 TKYYTDVVKGFTISRDNKNTLYLQMNTLRAEDTAVYYCARDIGIARRGPPY  
 MDVWGKGTTVSSASTKGPSVPLAPSSKSTSGGTAALGCLVKDYLPEPVTVSWN  
 SGALTSGVHTFPAVLQSSGLYSLSSVTPSSSLGTQTYICNVNHPNSNTKVDKKVE  
 PKSCDKTHTCPPCPAPEELLGGPSVFLPPPKPDTLMISRTPEVTCVVVDVSHEDPEVK  
 FNWYVDGVEVHNNAKTKPREEQYNSTYRVVSLTVLHQDWLNGKEYCKVSNKAL  
 PAPIEKTIKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQ  
 PENNYKTPPPVLDSDGSSFLYSKLTVDSRWRQQGNVFSCVMHEALHNHYTQKSL  
 LSPGK (Adu-Heavy chain)  
 GGGGSGGGGS (Linker)  
 DILPCVPFSVAKSVKSLYLGRCMFSGTPVIRLFKRLQPTRLVAEFDRTFDPEGILLFA  
 GHQDSTWIVLALARGLRLELQLRYNGVGRVTSGPVINHGMWQTISVEELARNLVI  
 KVRDAVMKIAVAGDLFQPERGLYHHLNTVGGIPFHEKDLVQPINPRLDGCMRSWN  
 WLNGEDTTIQTETKVNVTRMQCFSVTERGSFYPGSGFAFYSLDYMRTPLDVGTESTW

TABLE 9-continued

EVEVVAHIRPAADTGVLFALWAPDLRAVPLSVALVDYHSTKKLKQLVVLA  
ALALMEIKVCDQEHVVTVSLRGEATLEVDGTRGQSEVSAAQLQERLAVLERHLR  
SPVLTFAAGGLPDVPVTSAVTAFYRCMTLEVNRLLLDDEAAYKHSIDTAHSCPPV  
EPAAA (Gas6-Gla EGF deleted)  
DYKDHDGDYKDHDIDYKDDDK\* (FLAG)

2.  $\alpha$ A $\beta$ [Mab]-Gas6 (Aducanumab (Mab) -Gas6-FLAG, nucleotide sequence) SEQ ID NO: 159

ATGGAGACAGACACACTCCTGCTATGGGTACTGCTGCTCTGGGTTCCAGGTTCCA  
CTGGTGCAC (SS)  
GAGGTTCACTGTCGAGTCTGGGGGGAGTCGTTCAAGCCAGGTAGAACCTC  
AGACTGAGCTGTGCCAAGTGGTTGCTTTTCACTCTACGGTATGCACTGG  
TGAGACAGGCTCTGGCAAAGGACTCGAGTGGGTGCTGTAATATGGTTGATG  
GTACAAAGAAATACTATACCGATAGTGTGAAAGGAAGATTCAACATTCA  
ACAACAGTAAAAATACTTGTACCTTCAAGATGAACACCCCTGAGAGCAGAAC  
CAGCCGTACTACTGCCAGAGATAGAGGTATCGAGCAAGGCTGGTCC  
ATTATATGGATGTTGGGGAAAGGAACACAGTACTGTGAGCTGCTGCC  
CCAAGGGCCCCTGGCTTCCCTGGCACCTCCCAAGAGCACCTCTGGGG  
CACAGGCCCTGGCTGCCCTGCAAGGACTACTCCCCAACCGTGACGGT  
GTCGTGAACTCAGGCCCTGACCAGCGGCGTGACACCTTCCGGCTGTCC  
ACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTACTGTGCCCTAGCAGC  
TTGGGCACCCAGACACTACATCTGCAACGTGAATCACAAGCCCAGAACACCAAG  
GTGGACAAGAAAGTTGAGCCAAATCTTGTGACAAAACCTCACACATGCC  
TGCCACACTGAACCTCTGGGGGACCGTCAGTCTCTCCCCAAC  
CCAAGGACACCCATGATCTCCGGACCCCTGAGGTACATGCGTGGTGG  
ACGTGAGCCAGGAAGACCCCTGAGGTCAAGTCAACTGGTACGTGGACGGCG  
AGGTGCAATAGCCAAGACAAAGCCGGGGAGGAGCAGTACACAGCACGTAC  
CGTGTGGTCAGGCTCTCACCCTGCAACAGGACTGGCTGAATGCAAGGAG  
TACAAGTCAAGGCTCTCAACAAGGCCCTCCAGGCCCCATCGAGAAAACCATC  
TCCAAAGCCAAGGGCAGCCCCGAGAACACAGGTGACACCTGCCCCCATCC  
CGGGATGAGCTGACCAAGAACAGGCTGAGCTGACCTGCTGGTCAAAGGCTC  
TATCCCAGCGACATCGCGTGGAGTGGAGAGCAATGGCAGCCGGAGAACAA  
CTACAAGGACACCCTCCCGTGTGGACTCGACGGCTCTTCTCTACAGC  
AAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGAACGTCTCATGCTCC  
GTGATGCATGAGGCTCTGCACAAACACTACACGCAGAAGAGCCTCTCC  
CCGGTAAA (Adu-Heavy chain)  
GGCGGAGGTGGAAGCGGAGGGGGTGGAAAGC (Linker)  
GACATCTTGGCGTGCCTCAGCGTGGCCAAGAGTGTGAAGTCCTGTACC  
TGGGCCGGATGTTCACTGGGACCCCGTGATCGACTCGCCTCAAGAGGCTG  
AGCCCACCAAGGCTGGTAGCTGAGTTGACTTCGGACCTTGACCCCGAGGGCA  
TCCTCCTTTGCCGGAGGCCACCAGGACAGCACCTGGATCGTGTGGCCCTGAG  
AGCCGGCGGCTGGAGCTGCAGCTGCCTACAACGGTGTGGCGTGTGAC  
CAGCGGCCGGTCAACCATGGCATGTGGAGACAATCTGTGAGGAGCT  
GGCGCGGAATCTGTGATCAAGGTCAACAGGGATGCTGTGATGAAATCGCGT  
GGCGGGGACTTGTCAACCGGAGCGAGGACTGTATCATGTAACCTCACCGT  
GGGAGGTATTCCCTCATGAGAAGGACCTCGCAGCCATATAAACCTCGCTG  
GATGGCTGATGAGGAGCTGGAACCTGGCTGAAACGGAGAAGACACCCATCCA  
GGAAACGGTGAAGTGAACACAGGAGATGCACTGGCTCTCGGTGACGGAGAG  
GCTCTTCTACCCGGAGCGGCTCGCCTCTACGGCTGGACTACATGCGGAC  
CCCTCTGGACGCTGGGACTGAATCAACCTGGGAAGTAGAAGTGTGGCTACAT  
CCGCCCAGCGCAGACACAGGCGTGTGTTGCGCTCTGGGCCCCGACCTCC  
GCCGTGCGCTCTCTGTGGCACTGGTAGACTATCACTCCACGAAGAAACTCAAG  
AAGCAGCTGGTGTCTGGCCCTGGAGCATACGGCTTGGCCCTAATGGAGATC  
AAGGTCTCGACGGCCAAGAGCACGTGTCACCGTCTCGTGAGGGACGGTGA  
GCCACCTGGAGGTGGACGGCACCAAGGGGCAAGGGCAGAGCGAGGTGAGGCC  
GCTGCAGGAGAGGCTGGCCGTGCTCGAGAGGCACCTGCGGAGCCCCGTGCTC  
CTTGCGCCGGCCTGCCAGATGTGCGGTGACTTCAGCGCCAGTCACCGCGTTC  
TACCGCGCCTGCGATGACACTGGAGGTCAACCGGAGGCTGCTGGACCTGGAG  
GCCCGTACAAGCACAGCGACATCACGGCCACTCTGCCCGGGAGGCC  
GCCGCAGCC (Gas6-Gla EGF deleted)  
GACTACAAAGACCATGACGGTATTAAAGATCATGACATGACTACAAGGAT  
GACGATGACAAG (FLAG)  
TGA

**61**

## Preparation Examples 6-8

As non-limiting exemplary embodiment of the binding molecule containing a scaffold protein between the first region and the second region, wherein the Gas6 and anti-amyloid antibody scFv (in this example, aducanumab scFv) are employed as the first region and the second region, respectively, a single chain Fc region with reduced or abolished Fc receptor binding affinity are manufactured. The sequences employed in the construction are shown in Table 10.

As another non-limiting exemplary embodiment of the binding molecule containing a scaffold protein between the first region and the second region, wherein the Gas6 and

**62**

anti-amyloid antibody scFv (in this example, aducanumab scFv) are employed as the first region and the second region, respectively, a heterodimeric binding molecule is manufactured. The first polypeptide of the heterodimeric binding molecule comprises anti-amyloid antibody scFv, Fc region (DD), and Gas6, and the second polypeptide of the heterodimeric binding molecule comprises anti-amyloid antibody scFv region and Fc region (KK). Still another non-limiting exemplary embodiment of the binding molecule containing a scaffold protein between the first region and the second region, a homodimer comprising two polypeptides which each comprise anti-amyloid antibody scFv (as second region), Fc region (scaffold), and Gas6 is manufactured. The peptide sequences are shown in Table 10

TABLE 10

<p><b>Preparation Example 6: Single polypeptide fusion molecule:</b>  <b>anti-amyloid antibody-MFc-Gas6-His (SEQ ID NO: 162)</b>  <b>METDTLLLWVLLLWVPGSTGD (SS)</b>  <b>DIQMTQSPSSLSASVGDRVITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGV</b>  <b>PSRFSGSGSGTDFTLTISSLQPEDFATYYCQSYSTPLTFGGGTKEIKGGGGSGGGG</b>  <b>SGGGGSEVQLVESGGVVQPGRSRLSRAAAGFAFSSYGMHWVRQAPGKGLEWVA</b>  <b>VIWFDTKKYTDTSVKGRFTISRDNSKNTLYLQMNTLRAEDTAVYYCARDRGIGAR</b>  <b>RGPYYMDWKGKTTVTVSS (anti-amyloid antibody-scFv)</b>  <b>GGGGSGGGGS (linker)</b>  <b>APEFLGGPSVFLFPPPKDFTLTYITREPEVTCVVVDVSQEDPEVQFNWYVDGVVEHNA</b>  <b>KTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPR</b>  <b>EPQVYTPPEQEEMTKNQVSLRCLVKGFYPSDIAVEWESNGQPENN</b>  <b>YKTTKPVLDSDGFSRLESRLTVDKSRWQEGNVESCSVHMHEACSWHLCKSLSLSLGK</b>  <b>(Monomeric Fc with reduced or abolished Fc gamma receptor binding affinity)</b>  <b>GGGGSGGGGS (linker)</b>  <b>DILPCVPFSVAKSVKSLYLGRMESGTPVIRLRFKRLQPTRLVAEFDRTFDPEGILLFA</b>  <b>GGHQDSTWIVLALRAGRLELQLRYNGVGRVTSSGPVINHGMWQTI SVEELARNLVI</b>  <b>KVNRDAVMKIAVAGDLQPQPERGLYHNLNTVGGIPFHEKDLVQPINPRLDGCMRSWN</b>  <b>WLNGEDTTIQETVKVNTRMOCFSVTERGSFYPGSGFAFYFSLDYMTPLDVGTESTW</b>  <b>EVEVVAHIRPAADTGVLFALWAPDLRAVPLSVALVDYHSTKLLKKQLVVLAVENTH</b>  <b>ALALMEIKVCDGQEHVVTVSLRGEATLEVDGTRGQSEVSAAQLQERLAVLERHLR</b>  <b>SPVLTFAAGGLPDVPVTSAPVTAFYRCMTLEVNRLLLDDEAAYKHSIDTAHSCPPV</b>  <b>EPAAA (Gas6)</b>  <b>HHHHHH (His)</b> </p>
<p><b>Preparation Example 7: Heterodimeric fusion molecule comprising monovalent first region and monovalent second region: First polypeptide comprising anti-amyloid antibody-Fc (DD)-Gas6-His (SEQ ID NO: 163)</b>  <b>METDTLLLWVLLLWVPGSTGD (SS)</b>  <b>DIQMTQSPSSLSASVGDRVITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGV</b>  <b>PSRFSGSGSGTDFTLTISSLQPEDFATYYCQSYSTPLTFGGGTKEIKGGGGSGGGG</b>  <b>SGGGGSEVQLVESGGVVQPGRSRLSRAAAGFAFSSYGMHWVRQAPGKGLEWVA</b>  <b>VIWFDTKKYTDTSVKGRFTISRDNSKNTLYLQMNTLRAEDTAVYYCARDRGIGAR</b>  <b>RGPYYMDWKGKTTVTVSS (anti-amyloid antibody-scFv)</b>  <b>GGGGSGGGGS (linker)</b>  <b>DKTHTCPPCPAPEELLGGPSVFLFPPPKDFTLTYITREPEVTCVVVDVSQEDPEVQFNW</b>  <b>YVDGVEVHNAKTKPREQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPI</b>  <b>EKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPEN</b>  <b>NYDTPVLDSDGSFFLYSDLTVDKSRWQQGNVFSCSVHMHEALHNHTQKSLSLSP</b>  <b>GK (Fc (DD))</b>  <b>GGGGSGGGGS (linker)</b>  <b>DILPCVPFSVAKSVKSLYLGRMESGTPVIRLRFKRLQPTRLVAEFDRTFDPEGILLFA</b>  <b>GGHQDSTWIVLALRAGRLELQLRYNGVGRVTSSGPVINHGMWQTI SVEELARNLVI</b>  <b>KVNRDAVMKIAVAGDLQPQPERGLYHNLNTVGGIPFHEKDLVQPINPRLDGCMRSWN</b>  <b>WLNGEDTTIQETVKVNTRMOCFSVTERGSFYPGSGFAFYFSLDYMTPLDVGTESTW</b>  <b>EVEVVAHIRPAADTGVLFALWAPDLRAVPLSVALVDYHSTKLLKKQLVVLAVENTH</b>  <b>ALALMEIKVCDGQEHVVTVSLRGEATLEVDGTRGQSEVSAAQLQERLAVLERHLR</b>  <b>SPVLTFAAGGLPDVPVTSAPVTAFYRCMTLEVNRLLLDDEAAYKHSIDTAHSCPPV</b>  <b>EPAAA (Gas6)</b>  <b>HHHHHH (His)</b>  <b>Second polypeptide comprising anti-amyloid antibody-Fc (KK)-Gas6-His (SEQ ID NO: 164)</b>  <b>METDTLLLWVLLLWVPGSTGD (SS)</b>  <b>DIQMTQSPSSLSASVGDRVITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGV</b>  <b>PSRFSGSGSGTDFTLTISSLQPEDFATYYCQSYSTPLTFGGGTKEIKGGGGSGGGG</b>  <b>SGGGGSEVQLVESGGVVQPGRSRLSRAAAGFAFSSYGMHWVRQAPGKGLEWVA</b> </p>

TABLE 10-continued

VIWFDGTTKYYTDSVKGRFTISRDNSKNTLYLQMNTLRAEDTAVYYCARDRGIGAR  
 RGPyYMDVWGKGTTVTVSS (anti-amyloid antibody-scFv)  
 GGGGSGGGGS (linker)  
 DKTHTCPCPAPELLGGPSVFLFPPPKDFTLYITREPEVTCVVVDVSHEDEPKFNW  
 YVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPI  
 EKTISKAKGQPREPQVYTLPPSRKEMTKNQVSLTCLVKGFYPSDIAVEWESNGOPEN  
 NYKTPPVLSKSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHTQKSLSLSP  
 GK (Fc (KK))

**Preparation Example 8:** Single polypeptide fusion molecule comprising monovalent first region, scaffold, and monovalent second region: Anti-amyloid antibody-Fc-Gas6-His  
 (SEQ ID NO: 165)

METDTLLLWVLLWVPGSTGD (ss)  
 DIQMTQS PSSLSASVGDRVTITCRASQSISSYLWYQQKPGKAPKLLIYAASSLQSGV  
 PSRFSGSGSGTDTLTISSLQPEDFATYYCQGSYSTPLTFGGGTKEIKGGGGSGGG  
 SGGGGSEVQLVESGGGVVQPGRSLRLSCAASGFYPSDIAVEWESNGOPEN  
 VIWFDGTTKYYTDSVKGRFTISRDNSKNTLYLQMNTLRAEDTAVYYCARDRGIGAR  
 RGPyYMDVWGKGTTVTVSS (anti-amyloid antibody-scFv)  
 GGGGSGGGGS (linker)  
 DKTHTCPCPAPELLGGPSVFLFPPPKDFTLYITREPEVTCVVVDVSHEDEPKFNW  
 YVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPI  
 EKTISKAKGQPREPQVYTLPPSRKEMTKNQVSLTCLVKGFYPSDIAVEWESNGOPEN  
 NYKTPPVLSKSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHTQKSLSLSP  
 GK (Fc region with reduced or abolished Fc gamma receptor binding affinity)  
 GGGGSGGGSGGGGS (linker)  
 DLPCVPFSVAKSVKSLYLGMRMSGTVPVIRLRFKRLQPTRLVAEFDRTFDPEGILLFA  
 GHQDSTWIVLARAGRLELQLRNYNGVGRVTSSGPVINHGMWQTISVEELARNLVI  
 KVRDAVMKIAVAGDLQPERGLYHLNLTVGGIPFHEKDLVQPINPRLDGMRSWN  
 WLNGEDTTIQETVKNTRMOCFSVTERGSFVPGSGFAFYSLDYMRTPLDVGTESTW  
 EVEVVAHIRPAADTGVLFALWAPDLRAVPLSVALVDYHSTKKLKQLVVLAVEHT  
 ALALMEIKVCDQEHVVTVSLRDGEATLEVDGTRGQSEVSAAQLQERLAVLERHLR  
 SPVLTFAAGGLPDVPVTSAPVTAFYRCMTLEVNRRLLDLEAAKYHSDITAHSCPPV  
 EPAAA (Gas6)  
 HHHHHH (His)

**Preparation Example 9**

As non-limiting exemplary embodiment of the binding molecule containing a scaffold protein between the first region and the second region, a bispecific antibody, wherein a scFv of anti-Axl antibody and anti-amyloid antibody are employed as the first region and the second region, respectively, is manufactured. See, FIG. 1J. A heavy chain of the bispecific antibody has the following sequence of Table 11 and the light chain of anti-amyloid antibody light chain has the sequence of SEQ ID NO: 161. The Fc region of the heavy chain contains NA mutation to reduced or abolish Fc gamma receptor binding affinity.

TABLE 11

Bispecific Antibody fusion molecule: Anti-amyloid Ab-anti-Axl ScFv (first polypeptide)  
 (SEQ ID NO: 166)  
 METDTLLLWVLLWVPGSTGD (ss)  
 EVQLVESGGVVVQPGRSLRLSCAASGFYAFSSYGMHWVRQAPGKGLEWVA  
 VIWFDGTTKYYTDSVKGRFTISRDNSKNTLYLQMNTLRAEDTAVYYCAR  
 DRGI GAR GRGPYVMDVWGKGTTVTSSASTKGPSPVFLAPSSKSTSGGTA  
 ALGCLVKDYFPPEVTVWSNNSGALTGVHTFPAVLQSSGLYSLSSVVTVP  
 SSSLGTQTYICNVNHPSNTKVDKVKEPKSCKDKTHCPCPAPELLGGP  
 SVFLFPPPKDFTLMISRTPEVTCVVVDVSHEDEPKFNWYVDGVEVHNA  
 KTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTI  
 SKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNG  
 QPENNYKTPPVLSKSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHN  
 HYTQKSLS  
 LSPGK (anti-amyloid-antibody heavy chain)  
 GGGGSGGGGS (Linker)  
 EVKLVESGGDLVKPGGSLKLSAACSGTFSSYGMWSVRQTPDKRLEWVA  
 TISSGGSYTYPDSVKGRFTISRDNAKNTLYLQMSSLKSEDТАMYYCAR  
 HPIYYTYDDTMYWGQGQTSVTVSSGGGGSGGGGGSDIVLTQSPAI

35 MAASPGEKVTMTCASSSSVSSGNFHWWYQQKPGTSPKLWIYRTSNLASGV  
 PARFGSGSGTYSLTISMEAEDAATYYCQQWSGYPWTFGGGTKLEIK  
 (anti-Axl scFv)

**Preparation Example 10**

As non-limiting exemplary embodiment of the binding molecule containing a scaffold protein between the first region and the second region, a homodimeric bispecific antibody, wherein a scFv of anti-Axl antibody and a scFv region of an anti-amyloid antibody are employed as the first region and the second region, respectively, is manufactured. See FIG. 11. The bispecific antibody comprises a first 40 polypeptide and a second polypeptide, which are identical to each other and each comprises the sequence of SEQ ID NO: 167. The structure of the first/second polypeptide is illustrated in Table 12, and the Fc region scaffold contains N—A mutation to reduced or abolish Fc gamma receptor binding affinity.

TABLE 12

Bispecific homodimeric comprising two polypeptides: anti-amyloid Ab-anti-Axl ScFv (SEQ ID NO: 167)  
 60 METDTLLLWVLLWVPGSTGD (ss)  
 EVQLVESGGVVVQPGRSLRLSCAASGFYAFSSYGMHWVRQAPGKGLEWVAI  
 WFDGTTKYYTDSVKGRFTISRDNSKNTLYLQMNTLRAEDTAVYYCARDRG  
 I GAR GRGPYVMDVWGKGTTVTSSASTKGPSPVFLAPSSKSTSGGTAALGCLV  
 KDYFPEPPTVWSNNSGALTGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQ  
 YICNVNHPSNTKVDKVKEPKSCKDKTHCPCPAPELLGGPSVFLFPPPKP  
 K 65 DTLMISRTPEVTCVVVDVSHEDEPKFNWYVDGVEVHNAKTKPREEQYAST  
 YRVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTI SKAKGQPREPQVY

TABLE 12-continued

LPPSRDELTKNQVSLTCLVKGPYPSDIAVEWESNGQPENNYKTTPPVLDS  
GSFFFLYSKLTVDKSRWQQGNFSCSVMHEALHNHYTQKSLSLSPGK  
(anti-amyloid-antibody heavy chain)  
GGGGSGGGGS (Linker)  
EVKLVESGGDLVKPGGLSLKLSAACASGTFSSYGMWSVRQTPDKRLEWVATI  
SSGGSYTYPDPSVKGRFTISRDNAKNTLYLQMSLKS ETDAMYYCARHPIY  
YTYYDDTMDYWGQGTSVTVS SGGGGSGGGSGGGSDIVLTQSPAIMAASP  
EKVTMTCASASSVSSGNFHWWYQOKPGTSPKLVWYRTSNLASGVPARFSGSG  
SGTSYSLTISSMEAEDAATYYCQQWSGYWPWTFGGGTKLEIK (anti-Axl  
scFv)

## Preparation Example 11

As another non-limiting exemplary embodiment of the binding molecule containing a scaffold protein between the first region and the second region, a heterodimeric bispecific antibody, wherein a scFv of anti-Axl antibody and an anti-amyloid antibody are employed as the first region and the second region, respectively, is manufactured. The first polypeptide of a heavy chain of the bispecific antibody has the following sequence of SEQ ID NO: 168 of Table 13 below, the second polypeptide of a heavy chain of the bispecific antibody comprises the sequence of SEQ ID NO: 169 of Table 13 below, and the light chain of anti-amyloid antibody has the sequence of SEQ ID NO: 161. The Fc region contains NA mutation to reduce or abolish Fc gamma receptor binding affinity and the polypeptides of the Fc region form a hetero dimer (DD-KK).

TABLE 13

Bispecific heterodimeric comprising bivalent second region and bivalent first region: first polypeptide of heavy chain of anti-amyloid Ab-anti-Axl ScFv (with Fc region DD) (SEQ ID NO: 168)  
METDTLLLWVLLWVPGSTGD (SS)  
EVQLVESGGVVQPGRSRLSLKAACGAFSSYGMHWVRQAPGKGLEWVAI  
WFDGTTKKYTDPSVKGRFTISRDNAKNTLYLQMSLKS ETDAMYYCARHPIY  
GARRGPYMDVWGKTTVTVSSASTKGPSVFP LAPSSKSTSGGTAALGCLV  
KDYFPEPPTVSVNSGAL TSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQT  
YICNVNHPKNSNTKVDKKVEPKSCDKTHTCPPCPAPAEELLGGPSVFLFPPPKP  
DTLMISRPTEVCTVVVDVSHEDPEVKFNWYDVGVEVHNAKTKPREEQYAST  
YRVS VSLTVLHQDWLNGKEYCKVSNKALPAPIEKTISKAKGQPREPVQVYT  
LPPSRDELTKNQVSLTCLVKGPYPSDIAVEWESNGQPENNYKTTPPVLDS  
GSFFFLYSKLTVDKSRWQQGNFSCSVMHEALHNHYTQKSLSLSPGK  
(anti-amyloid antibody heavy chain (DD))  
GGGGSGGGGS (Linker)  
EVKLVESGGDLVKPGGLSLKLSAACASGTFSSYGMWSVRQTPDKRLEWVATI  
SSGGSYTYPDPSVKGRFTISRDNAKNTLYLQMSLKS ETDAMYYCARHPIY  
YTYYDDTMDYWGQGTSVTVS SGGGGSGGGSGGGSDIVLTQSPAIMAASP  
EKVTMTCASASSVSSGNFHWWYQOKPGTSPKLVWYRTSNLASGVPARFSGSG  
SGTSYSLTISSMEAEDAATYYCQQWSGYWPWTFGGGTKLEIK (anti-Axl  
scFv)  
Second polypeptide of heavy chain of anti-amyloid Ab (with Fc region KK) (SEQ ID NO: 169)  
METDTLLLWVLLWVPGSTGD (SS)  
EVQLVESGGVVQPGRSRLSLKAACGAFSSYGMHWVRQAPGKGLEWVAI  
WFDGTTKKYTDPSVKGRFTISRDNAKNTLYLQMSLKS ETDAMYYCARHPIY  
GARRGPYMDVWGKTTVTVSSASTKGPSVFP LAPSSKSTSGGTAALGCLV  
KDYFPEPPTVSVNSGAL TSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQT  
YICNVNHPKNSNTKVDKKVEPKSCDKTHTCPPCPAPAEELLGGPSVFLFPPPKP  
DTLMISRPTEVCTVVVDVSHEDPEVKFNWYDVGVEVHNAKTKPREEQYAST  
YRVS VSLTVLHQDWLNGKEYCKVSNKALPAPIEKTISKAKGQPREPVQVYT  
LPPSRKELTKNQVSLTCLVKGPYPSDIAVEWESNGQPENNYKTTPPVLDS  
GSFFFLYSKLTVDKSRWQQGNFSCSVMHEALHNHYTQKSLSLSPGK  
(anti-amyloid antibody heavy chain (KK))

## Experimental Example 1. Gas6-Based Fusion Molecule Targeting Beta-Amyloid (I): Beta-Amyloid Binding Domain in scFv Form

## 5 1-1. Analysis of Expression of Fusion Molecule in Transfected Cells

After plasmid transfection into HEK293 cells, the expression of the fusion molecule containing the Flag tag according to Preparation Example 1 analyzed by Western blot analysis using the Flag tag, and the results are shown in FIG. 2.

## 15 1-2. Analysis of Beta-Amyloid Specific Binding Affinity of Prepared Fusion Molecules

To verify whether each of  $\alpha$ A $\beta$ -Gas6(E),  $\alpha$ A $\beta$ -Gas6,  $\alpha$ FITC-Gas6(E), and  $\alpha$ FITC-Gas6 can selectively recognize beta-amyloid and FITC, the culture broth secreted from the 20 HEK293 transfected with each plasmid was collected and subjected to an experiment using beta-amyloid oligomer and FITC-conjugated beads. The results showed that  $\alpha$ A $\beta$ -Gas6 (E) and  $\alpha$ A $\beta$ -Gas6 recognized only beta-amyloid oligomer beads, and  $\alpha$ FITC-Gas6 (E) and  $\alpha$ FITC-Gas6 recognized only FITC beads, thereby inducing phagocytosis, as shown in FIG. 4.

Although  $\alpha$ A $\beta$ -Gas6 (E) and  $\alpha$ A $\beta$ -Gas6 were shown to exhibit similar activities, it was found that  $\alpha$ A $\beta$ -Gas6 obtained by additionally removing the EGF domain of Gas6 30 could be obtained in high yield without aggregation in the protein purification process. Thus,  $\alpha$ A $\beta$ -Gas6 was used in subsequent experiments.

## 35 1-3. Analysis of Mechanism of Action of Prepared Fusion Molecule

## (1) Analysis Using Cell Line

An in vitro A $\beta$  engulfment assay was developed, in which beta-amyloid oligomers are conjugated with a pH indicator 40 and hence can emit red fluorescence in intracellular lysosomes when they are taken up by phagocytosis.

As a result of performing the in vitro A $\beta$  engulfment assay with HMC3 cells, a human microglial cell line expressing TAM receptors, it was shown that beta-amyloid oligomers 45 were selectively cleared by  $\alpha$ A $\beta$ -Gas6 (FIGS. 5 and 6).

In particular, in an experiment where cells were treated additionally with an antibody that interferes with the function of TAM receptors, it was confirmed that  $\alpha$ A $\beta$ -Gas6 cleared beta-amyloid oligomers mainly through Axl among 50 Tyro3, MerTK, and Axl (FIGS. 7 to 9). In fact, when Axl was removed from HMC3 cells, the activity of  $\alpha$ A $\beta$ -Gas6 significantly decreased. In addition, THP-1, which is a human monocyte cell line that does not express TAM receptors, did not show an increase in beta-amyloid clearance 55 by  $\alpha$ A $\beta$ -Gas6, while THP-Axl cells overexpressing Axl exhibited a significantly increased ability to clear beta-amyloid fibrils in a manner dependent on  $\alpha$ A $\beta$ -Gas6.

Next, since THP-Axl cells express both Axl and Fc receptors, the degree of inflammatory response induced 60 upon beta-amyloid uptake by each of  $\alpha$ A $\beta$ -Gas6 and aducanumab was analyzed in those cells. To this end, the NF- $\kappa$ B reporter was first expressed in THP-Axl cells, and each of a control,  $\alpha$ A $\beta$ -Gas6 and aducanumab was added to the cells together with beta-amyloid oligomers. As a result, it was 65 confirmed that, when aducanumab was added, the expression of the NF- $\kappa$ B reporter significantly increased, but when  $\alpha$ A $\beta$ -Gas6 was added, the NF- $\kappa$ B reporter was expressed at

or below the control level (FIG. 10). In addition, as a result of measuring the secreted protein levels of IL-1b, IL-6 and TNF, which are the three most representative inflammatory cytokines, it was shown that, when THP-Axl cells were treated with aducanumab, the protein levels of the inflammatory cytokines in the treated cells significantly increased compared to those in the control group (FIG. 11). In contrast, importantly, the levels of these inflammatory cytokines in the cells treated with  $\alpha$ A $\beta$ -Gas6 did not increase compared to those in the control group. This is a key result that, as our hypothesis suggests, the  $\alpha$ A $\beta$ -Gas6 fusion phagocytosis-inducing protein does not induce an inflammatory response when phagocytosing a target substance through a TAM receptor, which is similar to recognition and efferocytosis of naturally apoptotic cells.

In addition, unlike aducanumab,  $\alpha$ A $\beta$ -Gas6 increased the expression of Twist1/2 gene, which is known as a mechanism of suppressing inflammatory responses (FIG. 12).

#### (2) Analysis Using Astrocytes and Microglia

To examine whether astrocytes and microglia, which are cells expressing TAM receptors in the brain, can clear beta-amyloid through  $\alpha$ A $\beta$ -Gas6, primary astrocytes and microglia obtained from mouse brains were separately purified and then cultured. Then, each of purified  $\alpha$ A $\beta$ -Gas6 and aducanumab was added to the cells together with beta-amyloid fibrils, and the degree of clearance of beta-amyloid fibrils was measured in real time.

The results showed that  $\alpha$ A $\beta$ -Gas6 increased the beta-amyloid clearing ability of microglia in a concentration-dependent manner, which is similar to the results obtained in HMC3 which is a cell line expressing Axl (FIG. 13). Importantly, it was shown that, when aducanumab was added, the beta-amyloid clearing ability of astrocytes did not change at all, but when  $\alpha$ A $\beta$ -Gas6 was added, the beta-amyloid clearing ability of astrocytes significantly increased in a concentration-dependent manner (FIG. 14). This suggests that  $\alpha$ A $\beta$ -Gas6 significantly enhances the beta-amyloid clearing ability of astrocytes, which was previously insignificant, because astrocytes do not express Fc receptors but express TAM receptors.

Each of  $\alpha$ A $\beta$ -Gas6 and aducanumab was added to astrocytes and the microglia cell line BV2 together with beta-amyloid fibrils to increase beta-amyloid uptake, and then the mRNA levels of TNF, IL-1a and IL-1b in each cell line were measured to determine the degree of inflammatory responses (FIGS. 15 and 16). As a result, similar to the results obtained in the cell lines, it was shown that, when the cells were treated with aducanumab, the levels of transcripts and proteins of the above inflammatory cytokines in the astrocytes and BV2 cells significantly increased compared to those in the control group, but when the cells were treated with  $\alpha$ A $\beta$ -Gas6, the levels of these inflammatory cytokines in the cells did not increase compared to those in the control group.

As described above, it has been found that the use of the  $\alpha$ A $\beta$ -Gas6 fusion phagocytosis inducer may be a ground-breaking method of effectively clearing beta-amyloid plaques accumulated in the patient's brain, through astrocytes and microglia without causing an inflammatory response, which is a serious side effect of existing monoclonal antibody therapeutics. This could be a very encouraging result that can significantly improve current treatment strategies.

#### 1-4. Evaluation of In Vivo Efficacy

##### (1) Efficacy According to Introduction of Fusion Molecule or Expression Vector Containing the Same

5  $5\times$ FAD mice were used as Alzheimer's disease model mice. Since  $5\times$ FAD mice simultaneously express 5 genes with mutations, the onset at which beta-amyloid plaques are generated in the mice is early, and pathological symptoms 10 caused by beta-amyloid plaques can be studied from 3 to 4 months of age regardless of aging.

To verify the effect of  $\alpha$ A $\beta$ -Gas6 in vivo through the 15  $5\times$ FAD model,  $\alpha$ A $\beta$ -Gas6 was delivered to the brain in two different ways. Through previous studies, it is known that aducanumab is not delivered well to the brain by intravascular injection or intraperitoneal injection even in Alzheimer's disease model mice. Thus, to accurately compare and analyze the effects of  $\alpha$ A $\beta$ -Gas6 with aducanumab, 1) direct 20 cannulation was performed in the mouse brain, and each of purified  $\alpha$ A $\beta$ -Gas6 and aducanumab was injected once a day for 25 into the ventricle of the brain for 3 weeks, and 2) each of  $\alpha$ A $\beta$ -Gas6 and aducanumab was made in lentiviral form to be expressed in the hippocampus of the mouse through stereotaxic injection. Importantly, it was found that the number of beta-amyloid plaques significantly decreased both when the purified  $\alpha$ A $\beta$ -Gas6 protein was added and when the gene was expressed in lentiviral form (FIGS. 17 30 and 18).

In addition, by quantifying the levels of beta-amyloid in lysosomes of microglia and astrocytes after  $\alpha$ A $\beta$ -Gas6 was delivered to the brain in the form of protein or virus, it was 35 shown that the ability to clear beta-amyloid significantly increased in both types of cells (FIGS. 19 to 22).

This suggests that, since TAM receptors are expressed in 40 both microglia and astrocytes, microglia and astrocytes can recognize and clear beta-amyloid when  $\alpha$ A $\beta$ -Gas6 is introduced therein, which is similar to the results of the in vitro studies.

##### (2) Comparison of Effects of Antibody Therapeutics and 45 Fusion Molecule of the Present Invention

It is known that, in Alzheimer's disease, synapses are 50 indiscriminately removed by microglia, resulting in a decrease in the number of synapses. Surprisingly, this phenomenon was aggravated when aducanumab was delivered to Alzheimer's model mice, but when  $\alpha$ A $\beta$ -Gas6 was expressed in a viral form, abnormal removal of synapses by 55 microglia was restored to a normal level (FIGS. 23 and 24).

In addition, as in the results from a cognitive and memory test for remembering the shape or location of a new object 55 in Alzheimer's model mice according to the protocol shown in FIG. 25, it was confirmed that the expression of  $\alpha$ A $\beta$ -Gas6 exhibited significantly superior cognitive and memory recovery effects compared to aducanumab (FIG. 26).

60 In addition, to verify whether the chimeric phagocytic protein of the present disclosure is effective in clearing various target substances, phagocytosis-inducing proteins specific for tau and alpha-synuclein ( $\alpha$ Syn) in addition to beta-amyloid were prepared as described in Preparation 65 Examples 2 and 3, and the target substance clearing effects thereof were tested following protocols in Experimental Examples 2 and 3.

69

## 1-5. Assay of Fusion Molecules of Preparation Examples 6-11

By following the procedure of Example 1-1 through 1-4, the properties and in vivo efficacy of clearing amyloids are evaluated for the fusion molecules of Preparation Examples 6-11.

## Experimental Example 2. Gas6-Based Fusion Molecule Targeting Tau

An in vitro tau engulfment assay was developed, in which tau oligomers are conjugated with a pH indicator and hence can emit red fluorescence in intracellular lysosomes when they are taken up by phagocytosis. HMC3 cells, a human microglial cell line expressing TAM receptors, were treated with a culture medium expressing the phagocytosis-inducing protein [ $\alpha$ Tau-Gas6] according to Preparation Example 2, and in vitro tau engulfment assay was performed. As the result shown in FIG. 27, it was confirmed that tau oligomers were selectively cleared by  $\alpha$ Tau-Gas6.

## Experimental Example 3. Gas6-Based Fusion Molecule Targeting Alpha-Synuclein

An in vitro  $\alpha$ Syn engulfment assay was developed, in which alpha-synuclein ( $\alpha$ Syn) oligomers are conjugated with a pH indicator and hence can emit red fluorescence in intracellular lysosomes when they are taken up by phagocytosis. HMC3 cells, a human microglial cell line expressing TAM receptors, were treated with a culture medium expressing the phagocytosis-inducing protein [ $\alpha$  $\alpha$ Syn-Gas6] according to Preparation Example 3, and in vitro tau engulfment assay was performed. As the result shown in FIG. 27, it was confirmed that  $\alpha$ Syn oligomers were selectively cleared by  $\alpha$  $\alpha$ Syn-Gas6.

## Experimental Example 4. ProS1-Based Fusion Molecule Targeting Beta-Amyloid

Next, to verify whether the chimeric phagocytosis-inducing protein prepared using a ligand for TAM receptor other than Gas6 is also effective,  $\alpha$ A $\beta$ -ProS1 was prepared as described in Preparation Example 4 using the ProS1 ligand, and the efficacy thereof was evaluated. To this end, primary-cultured mouse astrocytes expressing TAM receptors were treated with a culture medium expressing  $\alpha$ A $\beta$ -ProS1, and

70

the in vitro A $\beta$  engulfment assay used in Experimental Example 1-3 was performed. As the result shown in FIG. 29, it was confirmed that beta-amyloid oligomers were selectively cleared by  $\alpha$ A $\beta$ -ProS1.

## Experimental Example 5. Gas6-Based Fusion Molecule Targeting Beta-Amyloid (II): Beta-Amyloid Binding Regions in the Forms of Fab and Mab

Next, to verify whether various target-binding regions other than scFv may be used as target protein-binding domains in the preparation of chimeric phagocytosis-inducing proteins, phagocytosis-inducing proteins were prepared according to Preparation Example 5 using an antigen-binding fragment (Fab) or a complete-form monoclonal antibody (Mab) instead of an scFv and were subjected to an experiment ( $\alpha$ A $\beta$ [Fab]-Gas6 and  $\alpha$ A $\beta$ [Mab]-Gas6). To this end, HMC3 cells, a human microglial cell line expressing TAM receptors, were treated with a culture medium expressing each of  $\alpha$ A $\beta$ [Fab]-Gas6 and  $\alpha$ A $\beta$ [Mab]-Gas6, and the in vitro A $\beta$  engulfment assay used in Experimental Example 1-3 was performed. As the results shown in FIGS. 30 and 31, it was confirmed that beta-amyloid oligomers were selectively cleaved by each of  $\alpha$ A $\beta$ [Fab]-Gas6 and  $\alpha$ A $\beta$ [Mab]-Gas6.

The scope of the present disclosure is defined by the appended claims, and all changes or modifications derived from the meaning and scope of the claims and equivalents thereto should be construed as being included in the scope of the present invention.

The fusion molecules having phagocytosis-inducing activity according to the embodiment of the present disclosure can solve the problem of tissue damage caused by activation of an inflammatory response, which occurs in the prior art. Accordingly, the fusion molecules could effectively clear abnormally accumulated substances such as beta-amyloid, tau, alpha-synuclein, huntingtin or prion protein, and thus may be used to prevent or treat diseases caused by these abnormally accumulated substances, for example, Alzheimer's disease, Parkinson's disease, Huntington's disease, or prion disease. Therefore, it may be used in the therapeutics industry for treatment of the above diseases.

All publications, patent applications, patents, and other references mentioned herein are expressly incorporated herein by reference in their entireties.

## SEQUENCE LISTING

```

Sequence total quantity: 169
SEQ ID NO: 1      moltype = AA  length = 173
FEATURE          Location/Qualifiers
REGION           1..173
note = TAM(Ax1)-binding sequence
source            1..173
mol_type = protein
organism = synthetic construct

SEQUENCE: 1
GRMFSGTPVII RLRFKRLQPT RLVAEFDVRT FDPEGILLFA GGHQDSTWIV LALRAGRLEL 60
QLRYNGVGRV TSSGPVINHG MWQTISVEEL ARNLVIKVNR DAVMKIAVAG DLFQPERGLY 120
HNLNTVGGIP FHEKDLVQPI NPLRDGCMRS WNWLNGEDTT IQETVKVNTR MQC 173

SEQ ID NO: 2      moltype = AA  length = 194
FEATURE          Location/Qualifiers
REGION           1..194
note = TAM(Ax1)-binding sequence
source            1..194
mol_type = protein

```

-continued

organism = synthetic construct

SEQUENCE: 2  
 GSFYPGSGFA FYSLDYMRTP LDVGTESTWE VEVVAHIRPA ADTGVLFLAW APDLRAVPLS 60  
 VALVDYHSTK KLKKQLVVLA VEHTALALME IKVCDGQEHV VTVPVLRGEA TLEVDGTRGQ 120  
 SEVSAALQQE RLAVLERHLR SPVLTFFAGGL PDVPVTSAPV TAFYRGCMTL EVNRRLLDLD 180  
 EAAYKHSDIT AHSC 194

SEQ ID NO: 3            moltype = AA length = 177  
 FEATURE                Location/Qualifiers  
 REGION                1..177  
 note = TAM(Axl)-binding sequence  
 source                1..177  
 mol\_type = protein  
 organism = synthetic construct

SEQUENCE: 3  
 LLYLAEQFAG VVLYLKFRLP EISRFSAEFD FRTYDSEGVVI LYAESIDHSA WLLIALRGKG 60  
 IEVQLNEHT SKITTGKVVI NNGLWNMVSV EELEHSISIK IAKEAVMDIN KPGPLFKPEN 120  
 GLLETKVKYFA GFPRKVESEL IKPINPRLDG CIRSWNLMKQ GASGIKEIIQ EKQNKHIC 177

SEQ ID NO: 4            moltype = AA length = 183  
 FEATURE                Location/Qualifiers  
 REGION                1..183  
 note = TAM(Axl)-binding sequence  
 source                1..183  
 mol\_type = protein  
 organism = synthetic construct

SEQUENCE: 4  
 YYPGSGIAQF HIDYNNVSSA EGWHVNVTLN IRPSTGTGVM LALVSGNNTV PFAVSLVDST 60  
 SEKSQDILLS VENTVIYRIQ ALSLCSDQQS HLEFRVNRRN LELSTPLKIE TISHEDLQRQ 120  
 LAVLDKAMKA KVATYLGGLP DVPPFSATPVN AFYNGCMEVN INGVQLDLDE AISKHNDIRA 180  
 HSC 183

SEQ ID NO: 5            moltype = AA length = 400  
 FEATURE                Location/Qualifiers  
 REGION                1..400  
 note = TAM(Axl)-binding sequence  
 source                1..400  
 mol\_type = protein  
 organism = synthetic construct

SEQUENCE: 5  
 DLPCVPPSV AKSVKSLYLG RMFGSTPVR LRFKRLQPTR LVAEFDVRTF DPEGILLFAG 60  
 GHQDSTWIVL ALRAGRLELQ LRYNGVGRVT SSGPVINHGM WQTISVEELA RNLVIKVNRD 120  
 AVMKIAVAGD LFQPERGLYH LNLTVGPIP HEKDLVQPIN PRLDGCMRSW NWLNGEDTTI 180  
 QETVKVNTRM QCFSVTERGS FYPGSGFAFY SLDDYMRPLD VGTESTWEVE VVAHIRPAAD 240  
 TVGLFALWAP DLRAVPLSVA LVVDYHSTKLL KKQLVVLA VEHTALALMEIK VCDGQEHVVT 300  
 VSLRDGEATL EVDGTRGQSE VSAAQLQERL AVLERHLRSP VLTFAGGLPD VPVTSAPVTA 360  
 FYRGCMTLEV NRRLLLDEA AYKHSDITAH SCPPVEPAAA 400

SEQ ID NO: 6            moltype = AA length = 393  
 FEATURE                Location/Qualifiers  
 REGION                1..393  
 note = TAM(Axl)-binding sequence  
 source                1..393  
 mol\_type = protein  
 organism = synthetic construct

SEQUENCE: 6  
 VVSVCLPLNL DTKYELLYLA EQFAGVVLYL KFRLPEISRFA SAEFDVRTYD SEGVILYAES 60  
 IDHSAWLIA LRGGKIEVQL KNEHTSKIT GGDIVINNGLW NMVSVEELAH SISIKIAKEA 120  
 VMDINKPGPL FKPGNGLLET KVYFAGPVRK VESELIKPIN PRLDGCIWSW NLMKQGASGI 180  
 KEIIQEKKN HCLVTEVKGS YYPGSGIAQF HIDYNNVSSA EGWHVNVTLN IRPSTGTGVM 240  
 LALVSGNNTV PFAVSLVDST SEKSQDILLS VENTVIYRIQ ALSLCSDQQS HLEFRVNRRN 300  
 LELSTPLKIE TISHEDLQRQ LAVLDKAMKA KVATYLGGLP DVPPFSATPVN AFYNGCMEVN 360  
 INGVQLDLDE AISKHNDIRA HSCPSSWKKT KNS 393

SEQ ID NO: 7            moltype = AA length = 678  
 FEATURE                Location/Qualifiers  
 REGION                1..678  
 note = GAS6 protein  
 source                1..678  
 mol\_type = protein  
 organism = Homo sapiens

SEQUENCE: 7  
 MAPSLSPGPA ALRRAPQLL LLLAAECALA ALLPAREATQ FLRPRQRRAF QVFEEAKQGH 60  
 LERECCVEELC SREEAREVFE NDPETDYFYP RYLDCKINKY SPYTKNSGFA TCVQNLDPQC 120  
 TPNPBCDRKGT QACQDLMGNF FCLCKAGWGG RLCDKDVNEC SQENGGLQI CHNPGPSFHC 180  
 SCHSGFELSS DGRTQCDIDE CADSEACGEA RCKNLPGSYS CLCDEGFAYS SQEKACRDVD 240  
 ECLQGRCEQV CVNSPGSYTC HCDGRGGLKL SQDMDTCEDI LPCVPFSVAK SVKSLYLGRM 300  
 FSGBTPIVRL FKRLQFTRLV AEFDFRTFDP EGILLFAGGH QDSTWIVLAL RAGRLELQLR 360  
 YNGVGRVTSS GPVINHGMWQ TISVEELARN LVIKVNRAV MKIAVAGDLF QPERGLYHNL 420

-continued

---

LTVGIGIPFHE KDLVQPINPR LDGCMRSWNW LNGEDTTIQC TVKVNTRMQC FSVTERGSFY 480  
 PGSGFAFYSL DYMRTPLDVG TESTWEVEVV AHIRPAADTG VLFalWAPDL RAVPLSVALV 540  
 DYHSTKKLKK QLVVLAVEHT ALALMEIKVC DGQEHHVVTVS LRDGEATLEV DGTRGQSEVS 600  
 AAQLQERLAV LERHLRSPVL TFAGGLPDVP VTSAPVTAFY RGCMTLEVNR RLLLDDEAAY 660  
 KHSIDTAHSC PPVEPAAA 678

SEQ ID NO: 8 moltype = AA length = 173  
 FEATURE Location/Qualifiers  
 REGION 1..173  
 note = TAM(Axl)-binding sequence  
 source 1..173  
 mol\_type = protein  
 organism = synthetic construct  
 SEQUENCE: 8  
 GRMFSGTPVI RLRFKRLQPT RLVAEFDFT FDPEGILLFA GGHQDSTWIV LALRAGRREL 60  
 QLRYNGVGRV TSSGPVINHG MWQTISVEEL ARNLVIKVNR DAVMKIAVAG DLFQPERGLY 120  
 HLNLTVGPIP FHEKDLVQPI NPrLDGCMRS WNWLNGEDTT IQETVKANTK MQC 173

SEQ ID NO: 9 moltype = AA length = 173  
 FEATURE Location/Qualifiers  
 REGION 1..173  
 note = TAM(Axl)-binding sequence  
 source 1..173  
 mol\_type = protein  
 organism = synthetic construct  
 SEQUENCE: 9  
 GRMFSGTPVI RLRFKRLQPT RLVAEFDFT FDPEGILLFA GGHQDSTWIV LALRAGRREL 60  
 QLRYNGVGRV TSSGPVINHG MWQTISVEEL ARNLVIKVNR DAVMKIAVAG DLFQPERGLY 120  
 HLNLTVGPIP FHEKDLVQPI NPrLDGCMRS WNWLNGEDTT IQETVKANTK MQC 173

SEQ ID NO: 10 moltype = AA length = 172  
 FEATURE Location/Qualifiers  
 REGION 1..172  
 note = TAM(Axl)-binding sequence  
 source 1..172  
 mol\_type = protein  
 organism = synthetic construct  
 SEQUENCE: 10  
 GRMFSGTPVI RLRFKRLQPT RLVAEFDFT FDPEGILLFA GGHQDSTWIV LALRAGRREL 60  
 QLRYNGVGRV TSSGPVINHG MWQTISVEEL ARNLVIKVNR DAVMKIAVAG DLFQPERGLY 120  
 HLNLTVGPIP FHEKDLVQPI NPrLDGCMRS WNWLNGEDTT IQETVKANTR MQC 172

SEQ ID NO: 11 moltype = AA length = 173  
 FEATURE Location/Qualifiers  
 REGION 1..173  
 note = TAM(Axl)-binding sequence  
 source 1..173  
 mol\_type = protein  
 organism = synthetic construct  
 SEQUENCE: 11  
 GRMFSGTPVI RLRFKRLQPT RLVAEFDFT FDPEGVLFFA GGHQDSTWIV LALRAGRREL 60  
 QLRYNGIGRV TSSGPVINHG MWQTISVEEL ERNLVIKVNR DAVMKIAVAG DLFQDRGLY 120  
 HLNLTVGPIP FKEKDLIQPI NPrLDGCLRS WNWLNGEDTT IQETVKVNTR MQC 173

SEQ ID NO: 12 moltype = AA length = 173  
 FEATURE Location/Qualifiers  
 REGION 1..173  
 note = TAM(Axl)-binding sequence  
 source 1..173  
 mol\_type = protein  
 organism = synthetic construct  
 SEQUENCE: 12  
 GRMFSGTPVI RLRFKRLQPT RLVAEFDFT FDPEGILLFA GGHQDSTWIV LALRAGRREL 60  
 QLRYNGVGRV TSSGPVINHG MWQTISVEEL ARNLVIKVNR DAVMKIAVAG DLFQPERGLY 120  
 HLNLTVGPIP FHEKDLVQPI NPrLDGCMRS WNWLNGEDTT IQETVKANAK MQC 173

SEQ ID NO: 13 moltype = AA length = 173  
 FEATURE Location/Qualifiers  
 REGION 1..173  
 note = TAM(Axl)-binding sequence  
 source 1..173  
 mol\_type = protein  
 organism = synthetic construct  
 SEQUENCE: 13  
 GRMFSGTPVI RLRFKRLQPT RLVAEFDFT FDPEGILLFA GGHQDSTWIV LALRAGRREL 60  
 QLRYSGVGRV TSSGPVINHG MWQTISVEEL ARNLVIKVNR DAVMKIAVAG DLFQPERGLY 120  
 HLNLTVGPIP FHEKDLVQPI NPrLDGCMRS WNWLNGEDTT IHEAVKVNAR MQC 173

SEQ ID NO: 14 moltype = AA length = 171

-continued

---

FEATURE Location/Qualifiers  
REGION 1..171  
note = TAM(Axl)-binding sequence  
source 1..171  
mol\_type = protein  
organism = synthetic construct

SEQUENCE: 14  
GRMFSGTPVI RLRFKRLQPT RLVAEFDERT FDPEGVLFFA GGHQDSAWIV LGLRAGRREL 60  
QLRYHGSRV TSSGPVINHG MWQTISVEEL DRNLVVKVNR DAVMKIAVAG DLFQLDRGLY 120  
HNLNTVGGIP FKERDLVQPI NPrLDGCVRS WNWLNGEDTT IQETVKANPK M 171

SEQ ID NO: 15 moltype = AA length = 173  
FEATURE Location/Qualifiers  
REGION 1..173  
note = TAM(Axl)-binding sequence  
source 1..173  
mol\_type = protein  
organism = synthetic construct

SEQUENCE: 15  
GRMFSGTPVI RLRFKRLQPT RLVAEFDERT FDPEGVLFFA GGHQDSTWIV LALRAGRREL 60  
QLRYGGGRV TSSGPVINHG TWQTISVEEL ERNVVVKVNR DAVMKIAVAG DLFQRDRGLY 120  
HNLNTVGGIP FKEKDLVQPI NPrLDGCMRS WNWLNGEDSA IQETVRANAR MQC 173

SEQ ID NO: 16 moltype = AA length = 173  
FEATURE Location/Qualifiers  
REGION 1..173  
note = TAM(Axl)-binding sequence  
source 1..173  
mol\_type = protein  
organism = synthetic construct

SEQUENCE: 16  
GRMFSGTPVI RLRFKRLQPT RLLAEFDERT FDPEGVLFFA GGHQDSAWIV LGLRAGRREL 60  
QLRYGGGRV TSSGPVINHG TWQTISVEEL DRNLVVKVNR DAVMKIAVAG DLFQLDRGLY 120  
HNLNTVGGIP FKEKDLVQPI NPrLDGCMRS WNWLNGEDSA IQETVKANSK MQC 173

SEQ ID NO: 17 moltype = AA length = 173  
FEATURE Location/Qualifiers  
REGION 1..173  
note = TAM(Axl)-binding sequence  
source 1..173  
mol\_type = protein  
organism = synthetic construct

SEQUENCE: 17  
GRMFSGTPVI RLRFKRLQPT RLVAEFDERT FDPEGVLFFA GGHQDSTWIV LALRAGRREL 60  
QLRYGGGRV TSSGPVINHG TWQTISVEEL ERNVVVKVNR DAVMKIAVAG DLFQRDRGLY 120  
HNLNTVGGIP FKEKDLVQPI NPrLDGCMRS WNWLNGEDSA IQETVRANAR MQC 173

SEQ ID NO: 18 moltype = AA length = 173  
FEATURE Location/Qualifiers  
REGION 1..173  
note = TAM(Axl)-binding sequence  
source 1..173  
mol\_type = protein  
organism = synthetic construct

SEQUENCE: 18  
GRMFSGTPVI RLRFKRLQPT RLVAEFDERT FDPEGVLFFA GGHQDSTWIV LGLRAGRREL 60  
QLRYQGVGRV TSSGPVINHG MWQTISVEEL ERNLVIKVNR DAVMKIAVAG DLFQLDRGLY 120  
HNLNTVGGIP FKEKDLVQPM NPrLDGCMRS WNWLNGEDTT IQETVKVNPK MQC 173

SEQ ID NO: 19 moltype = AA length = 173  
FEATURE Location/Qualifiers  
REGION 1..173  
note = TAM(Axl)-binding sequence  
source 1..173  
mol\_type = protein  
organism = synthetic construct

SEQUENCE: 19  
GRMFSGTPVI RLRFKRLQPT RLVAEFDERT FDPEGVLFFA GGHQDGTVWM LALRAGRREL 60  
QLHYNGVGRV TSSGPVINHG AWQTISVEEM ARSLVIKVNR DAVMKIAVAG DLFQPERGMF 120  
HNLNTVGGIP FHEKDLVQPI NPrLDGCIRS WNWMNGEDTT IQETVKVNPK MQC 173

SEQ ID NO: 20 moltype = AA length = 173  
FEATURE Location/Qualifiers  
REGION 1..173  
note = TAM(Axl)-binding sequence  
source 1..173  
mol\_type = protein  
organism = synthetic construct

SEQUENCE: 20

-continued

---

GRMFSGTPVI RLRFKRLQPT RLVAEFDVRT FDPEGVLFFA GGHQDSTWIV LGLRAGRLEL 60  
 QLRYQGVGRV TSSGPVINHG MWQTISVEEL ERNLVIKVNK DAVMKIAVAG DLFQLDRGLY 120  
 HLNLTVGIP FKEKDLVQPM NPrLDGCMRS WNWLNGEDTT IQETVKVNPK MQC 173

SEQ ID NO: 21 moltype = AA length = 163  
 FEATURE Location/Qualifiers  
 REGION 1..163  
 note = TAM(Axl)-binding sequence  
 source 1..163  
 mol\_type = protein  
 organism = synthetic construct

SEQUENCE: 21 RLRFKRLQPT RLVAEFDVRT FDPEGVLFFA GGHQDSTWIV LGLRAGRLEL QLRYQGVGRV 60  
 TSSGPVINHG MWQTISVEEL ERNLVIKVNK DAVMKIAVAG DLFQLDRGLY HLNLTVGIP 120  
 FKEKDLVQPM NPrLDGCMRS WNWLNGEDTT IQETVKVNPK MQC 163

SEQ ID NO: 22 moltype = AA length = 170  
 FEATURE Location/Qualifiers  
 REGION 1..170  
 note = TAM(Axl)-binding sequence  
 source 1..170  
 mol\_type = protein  
 organism = synthetic construct

SEQUENCE: 22 FSCTPVPVRLR FKRLQPTRLV AEFDFRTFDP EGVLFFAGH QDGTWVMLAL RAGRLELQLH 60  
 YNGVGRVTSS GPVINHGAQ QTISVEEMARS LVIKVNRDAV MKIAVAGDLF QPERGMFHNL 120  
 LTVGIGIPHE KDLVQPINPR LDGCIRSWN MNGEDTTIQE TVKVNTKMOC 170

SEQ ID NO: 23 moltype = AA length = 171  
 FEATURE Location/Qualifiers  
 REGION 1..171  
 note = TAM(Axl)-binding sequence  
 source 1..171  
 mol\_type = protein  
 organism = synthetic construct

SEQUENCE: 23 MSCTPVPVRLR FKRLQPTRLV VAEFDFRTFD PEGVLFFAGH HQDSTWIVLG LRAGRLELQL 60  
 RYQGVGRVTSS SGPVINHGMW QTISVEELER NLVIKVNKDA VMKIAVAGDLF FQLDRGLYHL 120  
 NLTVGGIPFK EKDLVQPMNP RLDGCMRSWN WLNGEDTTIQ ETVKVNPKMQ C 171

SEQ ID NO: 24 moltype = AA length = 194  
 FEATURE Location/Qualifiers  
 REGION 1..194  
 note = TAM(Axl)-binding sequence  
 source 1..194  
 mol\_type = protein  
 organism = synthetic construct

SEQUENCE: 24 GSFPYPGSGFA FYSLDYMRTP LDIGTESTWE IEVVAHIRPA ADTGVLFALW VPDLRAVPLS 60  
 VALVDYHSTK KLKKQLVVLA VEHVALALME IKVCDGQEHH VTISLREGEA TLEVGDTRGQ 120  
 SEVSAAQLQE RLAVLERHLR SPVLTFAAGGL PDVPVTSAPV TAFYRGCMTL EVNRRLLDLD 180  
 EAAYKHSDIT AHSC 194

SEQ ID NO: 25 moltype = AA length = 194  
 FEATURE Location/Qualifiers  
 REGION 1..194  
 note = TAM(Axl)-binding sequence  
 source 1..194  
 mol\_type = protein  
 organism = synthetic construct

SEQUENCE: 25 GSFPYPGSGFA FYSLDYMRTP LDIGTESTWE IEVVAHIRPA ADTGVLFALW VPDLRAVPLS 60  
 VALVDYHSTK KLKKQLVVLA VEHVALALME IKVCDGQEHH VTVSLRDSEA TLEVGDTRGQ 120  
 SEVSATQLQE RLAVLERHLR SPVLTFAAGGL PDVPVTSAPV TAFYRGCMTL EVNRRLLDLD 180  
 EAAYKHSDIT AHSC 194

SEQ ID NO: 26 moltype = AA length = 189  
 FEATURE Location/Qualifiers  
 REGION 1..189  
 note = TAM(Axl)-binding sequence  
 source 1..189  
 mol\_type = protein  
 organism = synthetic construct

SEQUENCE: 26 GSFPYPGSGFA FYSLDYMRTP LDIGTESTWE IEVVAHIRPA ADTGVLFALW VPDLRAVPLS 60  
 VALVDYHSTK KLKKQLVVLA VEHVALALME IKVCDGQEHH VTVSLRDSEA TLEVGDTRGQ 120  
 SEVSATQLQE RLAVLERHLR SPVLTFAAGGL PDVPVTSAPV TAFYRGCMTL EVNRRLLDLD 180  
 EAAYKHSDI 189

-continued

SEQ ID NO: 27  
**FEATURE**  
**REGION**  
**source**  
**SEQUENCE:** 27  
**moltype = AA length = 194**  
**Location/Qualifiers**  
**1..194**  
**note = TAM(Ax1)-binding sequence**  
**1..194**  
**mol\_type = protein**  
**organism = synthetic construct**

SEQ ID NO: 28  
**FEATURE**  
**REGION**  
**source**  
**SEQUENCE:** 28  
**moltype = AA length = 194**  
**Location/Qualifiers**  
**1..194**  
**note = TAM(Ax1)-binding sequence**  
**1..194**  
**mol\_type = protein**  
**organism = synthetic construct**

SEQ ID NO: 29  
**FEATURE**  
**REGION**  
**source**  
**SEQUENCE:** 29  
**moltype = AA length = 194**  
**Location/Qualifiers**  
**1..194**  
**note = TAM(Ax1)-binding sequence**  
**1..194**  
**mol\_type = protein**  
**organism = synthetic construct**

SEQ ID NO: 30  
**FEATURE**  
**REGION**  
**source**  
**SEQUENCE:** 30  
**moltype = AA length = 190**  
**Location/Qualifiers**  
**1..190**  
**note = TAM(Ax1)-binding sequence**  
**1..190**  
**mol\_type = protein**  
**organism = synthetic construct**

SEQ ID NO: 31  
**FEATURE**  
**REGION**  
**source**  
**SEQUENCE:** 31  
**moltype = AA length = 191**  
**Location/Qualifiers**  
**1..191**  
**note = TAM(Ax1)-binding sequence**  
**1..191**  
**mol\_type = protein**  
**organism = synthetic construct**

SEQ ID NO: 32  
**FEATURE**  
**REGION**  
**source**  
**SEQUENCE:** 32  
**moltype = AA length = 195**  
**Location/Qualifiers**  
**1..195**  
**note = TAM(Ax1)-binding sequence**  
**1..195**  
**mol\_type = protein**  
**organism = synthetic construct**

SEQ ID NO: 33  
**moltype = AA length = 194**

-continued

---

FEATURE REGION	Location/Qualifiers 1..194 note = TAM(Axl)-binding sequence
source	1..194 mol_type = protein organism = synthetic construct
SEQUENCE: 33	
GSFYPGNGFA FYSLNYMRTP LDVGTESTWE IEVVAHIRPA ADTGVLFALW AADLRAVPLS VALVDYHSTK KKKQLVVLA VERVERALALME IKVCDGQEHV VTVSREGEA TLAVDGTGQ SEVSAAQQLQE RLATLHRHLQ SPVLTFFAGGL PDVPVTSAPV TAFYRGCMTL EVNRRLLDLD EAAYKHGDIT SHSC	60 120 180 194
SEQ ID NO: 34	moltype = AA length = 676
FEATURE REGION	Location/Qualifiers 1..676 note = Pro S protein
source	1..676 mol_type = protein organism = Homo sapiens
SEQUENCE: 34	
MRLVGGRCGA PLACLLLVLV PSEANLLSKQ QASQVLRKR RANSLEETK QGNLERECIE ELCNKEEARE VFENDPETY FYPKLVCLR SFQTGLFTAA RQSTNAYPDL RSCVNAIPDQ CSPLPCNEDG YMCKDGKAS FTCTCKPGWQ GEKCEFDINE CKDPSNINGG CSQICDNTPG SYHCSCCKNGF VMLSNNKKDKC DVDECSLKP ICCTAVCKNI PGDFECECP EYRYNLKSKS CEDIDECSEN MCAQLCVNYI GGYTCYCDGK KGPKLAQDQK SCEVSVVCLP LNLDTKYELL YLAEQFAGVV YLKFRPEI SRFSAEFD FRYSSEGVI LIAESIDHSA WFLIALRGGK 60 VQLKNEHTSK ITTGGDVINN GLWNMVSVEE LEHSISIKIA IAKEAVMDIN KPGPLFKPEN 120 LETKVYFAGF PRKVESELIC PINPRLDGC RSWNLMKQGA SGIKEIIQEK QNKHCLVTVE 180 KGSSYYPGSGI AOFHIDYNNV SSAEGWHVNV TLNIRPSTGT GVMLALVSGN NTVPPAVSLV 240 DSTSEKSQDI LLSVENTVI RIQALSLCSD QQSHLEFRVN RNNLELSTPL KIETISHEDL 300 QRQLAVLDKA MKAKVATYLG GLPDVFSAT PVNAFYNGCM EVNINGVQLD LDEAISKHND 360 IRAHSCPSVW KKTNS	300 360 420 480 540 600 660 676
SEQ ID NO: 35	moltype = AA length = 177
FEATURE REGION	Location/Qualifiers 1..177 note = TAM(Axl)-binding sequence
source	1..177 mol_type = protein organism = synthetic construct
SEQUENCE: 35	
LLYLAEQFAG VVLYLKFRLP EISRFSAEFD FRTYDSQGVI LYAESIDHSA WFLIALRGGK IEIQLKNEHT SKITTGGDVI NNGLWNMVS EEELEHSISIKIA IAKEAVMDIN KPGPLFKPEN GLLETKVYFA GFPRKVESEL IKPINPRLDG CIRSWNLMKQ GASGIKEIIQ EKQNKHC	60 120 177
SEQ ID NO: 36	moltype = AA length = 177
FEATURE REGION	Location/Qualifiers 1..177 note = TAM(Axl)-binding sequence
source	1..177 mol_type = protein organism = synthetic construct
SEQUENCE: 36	
LLYLAEQFAG VVLYLKFRLP EISRFSAEFD FRTYDSQGVI LYAESIDHSA WLLIALRGGK IEVQLKNEHT SKITTGGDII NNGLWNMVS EEELEHSISIKIA IAKEAVMDIN KPGPLFKPEN GLLETKVYFA GFPRKVESEL IKPINPRLDG CIRSWNLMKQ GASGIKEIIQ EKQNKHC	60 120 177
SEQ ID NO: 37	moltype = AA length = 177
FEATURE REGION	Location/Qualifiers 1..177 note = TAM(Axl)-binding sequence
source	1..177 mol_type = protein organism = synthetic construct
SEQUENCE: 37	
LLYLAEQFAG VVLYLKFRLP EISRFSAEFD FRTYDSQGVI LYAESIDHSA WFLIALRGGK IEIQLKNEHT SKITTGGDVI NNGLWNMVS EEELEHSISIKIA IAKEAVMDIN KPGPLFKPEN GLLETKVYFA GFPRKVESEL IKPINPRLDG CIRSWNLMKQ GASGIKEIIQ EKQNKHC	60 120 177
SEQ ID NO: 38	moltype = AA length = 177
FEATURE REGION	Location/Qualifiers 1..177 note = TAM(Axl)-binding sequence
source	1..177 mol_type = protein organism = synthetic construct
SEQUENCE: 38	
LLYLAEQFAG VVLYLKFRLP EISRFSAEFD FRTYDSQGVI LYAESIDHSA WLLIALRGGK IEVQLKNEHT SKITTGGDII NNGLWNMVS EEELEHSISIKIA IAKEAVMDIN KPGPLFKPEN	60 120

---

-continued

GLLETKVYFA GFPRKVESEL IKPINPRLDG CIRSWNLMKQ GASGIKEIIQ EKQNKHC 177

SEQ ID NO: 39 moltype = AA length = 177  
 FEATURE Location/Qualifiers  
 REGION 1..177  
 note = TAM(Ax1)-binding sequence  
 source 1..177  
 mol\_type = protein  
 organism = synthetic construct

SEQUENCE: 39  
 LLYLAEQFAG VVLYLKFRLP EISRFTAEFD FRTYDSEGVY LYAESIDHSA WLLIALRGKK 60  
 IEVQLKNEHT SKITGGAIY NNGLWNMVSV EELEHSISIK IAKEAVMDIN KPGPLFKPEN 120  
 GLLETKVYFA GFPRKVESEL IKPINPRLDG CIRSWNLMKQ GASGIKEIIQ EKQNKHC 177

SEQ ID NO: 40 moltype = AA length = 177  
 FEATURE Location/Qualifiers  
 REGION 1..177  
 note = TAM(Ax1)-binding sequence  
 source 1..177  
 mol\_type = protein  
 organism = synthetic construct

SEQUENCE: 40  
 LLYLAEQFAG VVLYLKFRLP EISRFTAEFD FRTYDSEGVY LYAESIDHSA WILIAVRDGK 60  
 FEVQLKNEQT SKITGGGII NNGVWHTSVV EELEHSVSLK IAKEAVMNIN KLGPLFKPEH 120  
 GFLETKVYFA GFPRKVESQF IKPINPRLDG CIRGWNLMKQ GASGVKEIIQ EKQNKHC 177

SEQ ID NO: 41 moltype = AA length = 177  
 FEATURE Location/Qualifiers  
 REGION 1..177  
 note = TAM(Ax1)-binding sequence  
 source 1..177  
 mol\_type = protein  
 organism = synthetic construct

SEQUENCE: 41  
 LLYLAEQFVG VVLYLKFRLP EISRFTAEFD FRTYDSEGVY LYAESLDHSA WFLVALRDGK 60  
 IEIQFKNEHT TKITGGKVI SNGLWNMVSV EELEHSISVK IAKEAVMNIN KPGSLFNPTN 120  
 GFLETKVYFA GFPRKVENAL IKPINPRLDG CIRGWNLMNQ GASGVKEIIQ EKQNKHC 177

SEQ ID NO: 42 moltype = AA length = 177  
 FEATURE Location/Qualifiers  
 REGION 1..177  
 note = TAM(Ax1)-binding sequence  
 source 1..177  
 mol\_type = protein  
 organism = synthetic construct

SEQUENCE: 42  
 LLYLAEQFAG VVLYLKFRLP EISRFTAEFD FRTYDSEGVY LYAESIDHSA WILIAVRDGK 60  
 FEVQLKNEQT SKITGGGII NNGVWHTSVV EELEHSVSLK IAKEAVMNIN KLGPLFKPEH 120  
 GFLETKVYFA GFPRKVESQF IKPINPRLDG CIRGWNLMKQ GASGVKEIIQ EKQNKHC 177

SEQ ID NO: 43 moltype = AA length = 177  
 FEATURE Location/Qualifiers  
 REGION 1..177  
 note = TAM(Ax1)-binding sequence  
 source 1..177  
 mol\_type = protein  
 organism = synthetic construct

SEQUENCE: 43  
 LLYLAEQFAG VVLYLKFRLP EISRFTAEFD FRTYDSEGVY LYAESLDHSA WILIAVRDGK 60  
 FEVQLQNEQT SRITGGVV NNGVWHTSVV EELEHSVSLK IAKEAVMNIN KLGPLFKPEH 120  
 GFLETKVYFA GFPRQVESQF IKPINPRLDG CIRGWNLMKQ GASGVKEIIQ EKQNKHC 177

SEQ ID NO: 44 moltype = AA length = 182  
 FEATURE Location/Qualifiers  
 REGION 1..182  
 note = TAM(Ax1)-binding sequence  
 source 1..182  
 mol\_type = protein  
 organism = synthetic construct

VARIANT 42  
 note = X can be any amino acid

SEQUENCE: 44  
 LLYLAEQISG VVLYLKHFHP EISRFTAEFH FWTYDSEGMV LXAESVNHSW WLLIALRGKK 60  
 IEVQLKNEHT SKITTEGDVI NNGLWNELST SQVSVEELEH SISIKIAKEA VMDIDKPGPL 120  
 FKPENLLET KVFAGFPQK VESELIKPIN PCLDGCIRGW NLMKQGASGI KEIIQEKGK 180  
 HC 182

SEQ ID NO: 45 moltype = AA length = 177  
 FEATURE Location/Qualifiers

-continued

REGION 1..177  
note = TAM(Axl)-binding sequence

source 1..177  
mol\_type = protein  
organism = synthetic construct

SEQUENCE: 45  
LYLAEQFVG VVLYLKFRLP EITRFSAEFD FRTYDSEGVY LYAESDHSA WFLIALRDGK 60  
IEIQFKNEHT TKITTGGRVI NDGLWNMVSV EELEQSISVK IAKEAVMNIN KPESLFKPTN 120  
GFLETKVYFA GLPRKVENAL IKPINPRLDG CIRGWNLMNQ GASGVKEIIQ EKQNKH 177

SEQ ID NO: 46 moltype = AA length = 183  
FEATURE Location/Qualifiers  
REGION 1..183  
note = TAM(Axl)-binding sequence

source 1..183  
mol\_type = protein  
organism = synthetic construct

SEQUENCE: 46  
YYPGSGIAQF HIDYNNVSSA EGWHVNVTLN IRPSTGTGVM LALVSGNNTV PFAVSLVDST 60  
SEKSQDILLS VENTVIYRIQ ALSLCSDQQS HLEFRVNRNN LELSTPLKIE TISHEDLQRQ 120  
LAVLDKAMKA KVATYLGGLP DVPFSATPVN AFYNGCMEVN INGVQLDLDE AISKHNDIRA 180  
HSC 183

SEQ ID NO: 47 moltype = AA length = 183  
FEATURE Location/Qualifiers  
REGION 1..183  
note = TAM(Axl)-binding sequence

source 1..183  
mol\_type = protein  
organism = synthetic construct

SEQUENCE: 47  
YYPGSGIAQF HIDYNNVSSA EGWHVNVTLN IRPSTGTGVM LALVSGNNTV PFAVSLVDST 60  
SEKSQDILLS VENTVIYRIQ ALSLCSDQQS HLEFRVNRNN LELSTPLKIE TISHEDLQRQ 120  
LAVLDKAMKA KVATYLGGLP DVPFSATPVN AFYNGCMEVN INGVQLDLDE AISKHNDIRA 180  
HSC 183

SEQ ID NO: 48 moltype = AA length = 183  
FEATURE Location/Qualifiers  
REGION 1..183  
note = TAM(axl)-binding sequence

source 1..183  
mol\_type = protein  
organism = synthetic construct

SEQUENCE: 48  
YYPGSGIAQF HIDYNNVSSA EGWHINVTLN IRPSMGTGVM LALVSGNNTV PFAVSLVDST 60  
SEKSQDILLS VENTVIYRIQ ALSLCSDQQS HLEFRVNRNN LELSTPLKIE TISHEDLQRQ 120  
LAVLDKAMKA KVATYLGGLP DVPFSATPVN AFYNGCMEVN INGVQLDLDE AISKHNDIRA 180  
HSC 183

SEQ ID NO: 49 moltype = AA length = 183  
FEATURE Location/Qualifiers  
REGION 1..183  
note = TAM(axl)-binding sequence

source 1..183  
mol\_type = protein  
organism = synthetic construct

SEQUENCE: 49  
YYPGSGIAQF HIDYNNVSSA EGWHVNVTLN IRPSTGTGVM LALVSGNNTV PFAVSLVDST 60  
SEKSQDILLS VENTVIYRIQ APSLCSDQQS HLEFRVNRNN LELSTPLKIE TISHEDLQRQ 120  
LAVLDKAMKA KVATYLGGLP DVPFSATPVN AFYNGCMEVN INGVQLDLDE AISKHNDIRA 180  
HSC 183

SEQ ID NO: 50 moltype = AA length = 183  
FEATURE Location/Qualifiers  
REGION 1..183  
note = TAM(axl)-binding sequence

source 1..183  
mol\_type = protein  
organism = synthetic construct

SEQUENCE: 50  
YYPGSGIAQF HIDYNNVSSA EGWHINVTLN IRPSMGTGVM LALVSGNSTV PFAVSLVDST 60  
SEKSQDILLS VENTVIYRIQ ALSLCSDQQS HLEFRVNRNN LELSTPLKIE TISHEDLQRQ 120  
LAVLDKAMKA KVATYLGGLP DVPFSATPVN AFYNGCMEVN INGVQLDLDE AISKHNDIRA 180  
HSC 183

SEQ ID NO: 51 moltype = AA length = 183  
FEATURE Location/Qualifiers  
REGION 1..183  
note = TAM(Axl)-binding sequence

-continued

---

source                    1..183  
                         mol\_type = protein  
                         organism = synthetic construct

SEQUENCE: 51  
 YYPGSGIAEF HIDYNNNGSNA EGWHINVTLN IRPSMGTGVM LALVSSNNTV PFAVSLVDST 60  
 SEKSQDIVLS VENTVIYRIQ ALSLCSNQRS HLEFRVNRRN LELLTPLKIE TISQEELQTQ 120  
 LAILDKAMKG KVATYLGGLP DVPFSATPVN AFYNGCMEVN VNGVELLDDE AISKHNDIRA 180  
 HSC                      183

SEQ ID NO: 52            moltype = AA length = 183  
 FEATURE                  Location/Qualifiers  
 REGION                  1..183  
                         note = TAM(Ax1)-binding sequence  
 source                  1..183  
                         mol\_type = protein  
                         organism = synthetic construct  
 VARIANT                 80  
                         note = X can be any amino acid

SEQUENCE: 52  
 YYPGFGIAQF HVDPYNNVSSA EGWHINVTLN IHPSMGTGVM LALVSGNNTV PFAVSLVDST 60  
 SEKSQDIVLS VENTVIYRIX ALSLCSDQOS HLEFRVNRRN LELLPLKIE TISHEDLQRQ 120  
 LAILDKAMKA KVATYLGGLP DVPFSATPVN AFYNGCMEVN INGVQLLDDE AISKHNDIRA 180  
 HSC                      183

SEQ ID NO: 53            moltype = AA length = 183  
 FEATURE                  Location/Qualifiers  
 REGION                  1..183  
                         note = TAM(Ax) -binding sequence  
 source                  1..183  
                         mol\_type = protein  
                         organism = synthetic construct

SEQUENCE: 53  
 YYPGSGIAQF HIDYNNNGSNA EGWHINVTLN IRPSMGTGVM LALVSSNNTV PFAVSLVDST 60  
 SEKSQDIVLS VENTVIYRIQ ALSLCSNQRS HLEFRVNRRN LELLTPLKIE TISHEELQRQ 120  
 LAILDKAMTG KVATYLGGLP DVPFSATPVN AFYNGCMEVN INGVQLLDDE AISKHNDIRA 180  
 HSC                      183

SEQ ID NO: 54            moltype = AA length = 183  
 FEATURE                  Location/Qualifiers  
 REGION                  1..183  
                         note = TAM(Ax1)-binding sequence  
 source                  1..183  
                         mol\_type = protein  
                         organism = synthetic construct

SEQUENCE: 54  
 YYPGSGIAQF HIDYNNNGSNA EGWHINVTLN IRPSMGTGVM LALVSGNNTV PFAVSLVDST 60  
 SEKSQDIVLS VENTVIYRIQ ALSLCSNQRS HLEFRVNRRN LELLTPLKIE TISDEELRRQ 120  
 LAILDKAMTG KVATYLGGLP DVPFSATPVN AFYNGCMEVN INDVQLLDDE AISKHNDIRA 180  
 HSC                      183

SEQ ID NO: 55            moltype = AA length = 183  
 FEATURE                  Location/Qualifiers  
 REGION                  1..183  
                         note = TAM(Ax1)-binding sequence  
 source                  1..183  
                         mol\_type = protein  
                         organism = synthetic construct

SEQUENCE: 55  
 YYPGSGIAEF HIDYNNNGSNA EGWHINVTLN IRPSMGTGVM LALVSSNNTV PFAVSLVDST 60  
 SEKSQDIVLS VENTVIYRIQ ALSLCSNQRS HLEFRVNRRN LELLTPLKIE TISQEELQTQ 120  
 LAILDKAMKG KVATYLGGLP DVPFSATPVN AFYNGCMEVN VNGVELLDDE AISKHNDIRA 180  
 HSC                      183

SEQ ID NO: 56            moltype = AA length = 183  
 FEATURE                  Location/Qualifiers  
 REGION                  1..183  
                         note = TAM(Ax1)-binding sequence  
 source                  1..183  
                         mol\_type = protein  
                         organism = synthetic construct  
 VARIANT                 80  
                         note = X can be any amino acid

SEQUENCE: 56  
 YYPGSGIAQF RIDYNNVSSV EGWHINVTLN IHPSMGTGVM LALVSGNNTV PFAVSLVDST 60  
 SEKSQDIVLS VENTVIYLIK ALSLCSDQOS HLEFIVNRRN LELLPLKIE TISHEDLQRQ 120  
 LAILDKAMKA KVATYLGGLP DVPFSATPVN ALYKGCMEVN INGVQLLDDE AISKHNDIIA 180  
 HSC                      183

SEQ ID NO: 57            moltype = AA length = 183

-continued

---

FEATURE Location/Qualifiers  
REGION 1..183  
note = TAM(Axl)-binding sequence  
source 1..183  
mol\_type = protein  
organism = synthetic construct

SEQUENCE: 57  
YYPGSGIAKF IVDYNNVSSA EGWYVNVLN IRPSKGTGVM LALVSHNNTV PFAVSLVDST 60  
SEKLQDILLS VEKTVIYRIQ ALSLCSDQQF HLEFKVNRHN LEVSTPLKME TISHEDLQKQ 120  
LAILDKAMQG EVVTVLGGLP DVPPSATPVN AFYNGCMEVN INGVLLDLDE AISKHNDIRA 180  
HSC 183

SEQ ID NO: 58 moltype = AA length = 183  
FEATURE Location/Qualifiers  
REGION 1..183  
note = TAM(Axl)-binding sequence  
source 1..183  
mol\_type = protein  
organism = synthetic construct

SEQUENCE: 58  
YYPGSGIAKF IIDYNNNASNA EGWYVNVLN IRPSTGTGVM LALVSRNNNTV PFAVSLVDST 60  
SEKLQDILLS VEKTVVCRIQ ALSLCSDQQS HLEFKVNRHN LEVLTPLKME TISHEDLQKQ 120  
LAILDKAMQG DVVTVLGGLP DVPPSATPVN AFYNGCMEVN INGVLLDLDE AISKHNDIRA 180  
HSC 183

SEQ ID NO: 59 moltype = AA length = 183  
FEATURE Location/Qualifiers  
REGION 1..183  
note = TAM(Axl)-binding sequence  
source 1..183  
mol\_type = protein  
organism = synthetic construct

SEQUENCE: 59  
YYPGSGIAKF IIDYNNVSSA EGWHVNVLN IRPSMGTGVM LALVSRNNNTV PFAVSLVDST 60  
SEKLQDILLS VEKTVIYRIE ALSLCSDQQS HLELKVNRS LEVSTPLKME TVSHEDIQKE 120  
LAILDKAMQG EVVTVLGGLP DVPPSATPVN AFYNGCMEVN MNGVLLDLDE AISKHNDIRA 180  
HSC 183

SEQ ID NO: 60 moltype = AA length = 176  
FEATURE Location/Qualifiers  
REGION 1..176  
note = TAM(Axl)-binding sequence  
source 1..176  
mol\_type = protein  
organism = synthetic construct

SEQUENCE: 60  
SGIAQFHIDY NNVSSAEGWH VNVTLNIRPS TGTGVMLALV SGNNTVPFAV SLVDSTSEKS 60  
QDILLSVENT VIYRIQALSL CSDQQSHLEF RVNMRNNLELS TPLKIE TISHEDLQRLAVL 120  
DKAMAKAVAT YLGGLPDVFP SATPVNAFYIN GCMEVNINGV QLDLDEAISK HNDIRA 176

SEQ ID NO: 61 moltype = AA length = 173  
FEATURE Location/Qualifiers  
REGION 1..173  
note = TAM(Axl)-binding sequence  
source 1..173  
mol\_type = protein  
organism = synthetic construct

SEQUENCE: 61  
HIDYNNVSSA EGWHVNVTLN IRPSTGTGVM LALVSGNNNTV PFAVSLVDST SEKSQDILLS 60  
VENTVIYRIQ ALSLCSDQQS HLEFRVNRNN LELSTPLKIE TISHEDLQRQ LAVIDKAMKA 120  
KVATVYLGGLP DVPPSATPVN AFYNGCMEVN INGVQLDLDE AISKHNDIRA HSC 173

SEQ ID NO: 62 moltype = AA length = 173  
FEATURE Location/Qualifiers  
REGION 1..173  
note = TAM(Axl)-binding sequence  
source 1..173  
mol\_type = protein  
organism = synthetic construct

SEQUENCE: 62  
YYPGSGIAQF HIDYNNVSSA EGWHVNVTLN IRPSTGTGVM LALVSGNNNTV PFAVSLVDST 60  
SEKSQDILLS VENTVIYRIQ ALSLCSDQQS HLEFRVNRNN LELSTPLKIE TISHEDLQRQ 120  
LAVIDKAMKA KVATVYLGGLP DVPPSATPVN AFYNGCMEVN INGVQLDLDE AIS 173

SEQ ID NO: 63 moltype = AA length = 395  
FEATURE Location/Qualifiers  
REGION 1..395  
note = TAM(Axl)-binding sequence  
source 1..395

-continued

---

```

mol_type = protein
organism = synthetic construct

SEQUENCE: 63
VPFHSVAKSVK SLYLGRMFSG TPVIRLRFKR LQPTRLVAE DFRTFDPEGI LLFAGGHQDS 60
TWIVVLALRAG RLELQLRQPV INHGMWQTIS VEELARNLVI KVNRAVMKI 120
AVAGDLFQPE RGGLYHNLTV GGIPFHEKDL VQPINPRLDG CMRSWNWLNG EDTTIQETVK 180
VNTRMQCSV TERGSFYPPGS GFAYFSLDM RTPLDVGTES TWEVEVVAHT RPAADTGVLF 240
ALWAPDLRAV PLSVALVDYH STKKLKQLV VLAVEHTALA LMEIKVCDGQ EHVVTVSLRD 300
GEATLVEVDGT RGQSEVSAAQ LQERLAVLER HLRSVPVLTFA GLLPDVPPVTS APVTAFYRG 360
MTLEVNRLL DLDEAAYKHS DITAHKSCPPV EPAAA 395

SEQ ID NO: 64      moltype = AA length = 390
FEATURE          Location/Qualifiers
REGION           1..390
note = TAM(Axl)-binding sequence
source            1..390
mol_type = protein
organism = synthetic construct

SEQUENCE: 64
DILPCVPFSV AKSVKSLYLG RMFSGTPVIR LRFKRLQPTR LVAEFDRTF DPEGILLFAG 60
GHQDSTWIVL ALRAGRLELQ LRYNGVGRVT SSGPVINHGM WQTISVEELA RNLVIKVNRD 120
AVMKIAVAGD LFQPERGLYH LNLTGGIIPF HEKDLVQPIN PRDGCMSRW NWLNGEDTTI 180
QETVKVNTRM QCFSVTERGS FYPGSGFAYF SLDDYMRTPLD VGTESTWEVE VVAHIRPAAD 240
TGVLFALWAP DLRAVPLSVA LVVDYHSTKKL KKQLVVLAVE HTALALMEIK VCDGQEHVVT 300
VSLRDGEATL EVDGTRGQSE VSAAQLQERL AVLERHLRSP VLTFAGGLPD VPVTSAPVTA 360
FYRGCMTEV NRRLLDLDEA AYKHSDITAH 390

SEQ ID NO: 65      moltype = AA length = 400
FEATURE          Location/Qualifiers
REGION           1..400
note = TAM(Axl)-binding sequence
source            1..400
mol_type = protein
organism = synthetic construct

SEQUENCE: 65
DILPCVPFSV AKSVKSLYLG RMFSGTPVIR LRFKRLQPTR LVAEFDRTF DPEGILLFAG 60
GHQDSTWIVL ALRAGRLELQ LRYNGVGRVT SSGPVINHGM WQTISVEELA RNLVIKVNRD 120
AVMKIAVAGD LFQPERGLYH LNLTGGIIPF HEKDLVQPIN PRDGCMSRW NWLNGEDTTI 180
QETVKVNTRM QCFSVTERGS FYPGSGFAYF SLDDYMRTPLD IGTESTWEIE VVAHIRPAAD 240
TGVLFALWVP DLRAVPLSVA LVVDYHSTKKL KKQLVVLAVE HVALALMEIK VCDGQEHVVT 300
VSLRDGEATL EVDGTRGQSE VSAAQLQERL AVLERHLRSP VLTFAGGLPD VPVTSAPVTA 360
FYRGCMTEV NRRLLDLDEA AYKHSDITAH 400

SEQ ID NO: 66      moltype = AA length = 400
FEATURE          Location/Qualifiers
REGION           1..400
note = TAM(Axl)-binding sequence
source            1..400
mol_type = protein
organism = synthetic construct

SEQUENCE: 66
DILPCVPFSV AKSVKSLYLG RMFSGTPVIR LRFKRLQPTR LVAEFDRTF DPEGILLFAG 60
GHQDSTWIVL ALRAGRLELQ LRYNGVGRVT SSGPVINHGM WQTISVEELA RNLVIKVNRD 120
AVMKIAVAGD LFQPERGLYH LNLTGGIIPF HEKDLVQPIN PRDGCMSRW NWLNGEDTTI 180
QETVKVNTRM QCFSVTERGS FYPGSGFAYF SLDDYMRTPLD VGTESTWEIE VVAHIRPAAD 240
TGVLFALWVP DLRAVPLSVA LVVDYHSTKKL KKQLVVLAVE HVALALMEIK VCDGQEHVVT 300
VSLRDGEATL EVDGTRGQSE VSAAQLQERL AVLERHLRSP VLTFAGGLPD VPVTSAPVTA 360
FYRGCMTEV NRRLLDLDEA AYKHSDITAH 400

SEQ ID NO: 67      moltype = AA length = 380
FEATURE          Location/Qualifiers
REGION           1..380
note = TAM(Axl)-binding sequence
source            1..380
mol_type = protein
organism = synthetic construct

SEQUENCE: 67
RMFSGTPVIR LRFKRLQPTR LVAEFDRTF DPEGILLFAG GHQDSTWIVL ALRAGRLELQ 60
LRYNGVGRVT SSGPVINHGM WQTISVEELA RNLVIKVNRD AVMKIAVAGD LFQPERGLYH 120
LNLTGGIIPF HEKDLVQPIN PRDGCMSRW NWLNGEDTTI QETVKVNTRM QCFSVTERGS 180
FYPGSGFAYF SLDDYMRTPLD VGTESTWEVE VVAHIRPAAD TGVLFALWAP DLRAVPLSVA 240
LVVDYHSTKKL KKQLVVLAVE HTALALMEIK VCDGQEHVVT VSLRDGEATL EVDGTRGQSE 300
VSAAQLQERL AVLERHLRSP VLTFAGGLPD VPVTSAPVTA FYRGCMTEV NRRLLDLDEA 360
AYKHSDITAH SCPPVEPAAA 380

SEQ ID NO: 68      moltype = AA length = 400
FEATURE          Location/Qualifiers
REGION           1..400
note = TAM(Axl)-binding sequence

```

---

-continued

---

source 1..400  
mol\_type = protein  
organism = synthetic construct

SEQUENCE: 68  
DILPCVPFSV AKSVKSLYLG RMFSGTPVIR LRFKRLQPTR LVAEFDERTF DPEGILLFAG 60  
GHQDSTWIVL ALRAGRLELQ LRYNGVGRVT SSGPVINHGM WQTISVEELA RNLVIKVNRD 120  
AVMKIAVAGD LFQPERGLYH LNLTGGIIPF HEKDLVQPIN PRLDGCMRSW NWLNGEDTTI 180  
QETVKVNTRM QCFSVTERGS FYPGSGFAFY SLIDYMRPLD VGTESAWIE VVAHIRPAAD 240  
TGVLFALWVP DLRAVPLSVA LVDYHSTKKL KKQLVVLAVE HVALALMEIK VCDGQEHHVT 300  
VSLRDGEATL EVDGTRGQSE VSAAQLQERL AVLERHLRSP VLTFAGGLPD VPVTSAPVTA 360  
FYRGCMTEV NRRLLDLDEA AYKHSDITAH SCPPVEPAAA 400

SEQ ID NO: 69 moltype = AA length = 400  
FEATURE Location/Qualifiers  
REGION 1..400  
note = TAM(Axl)-binding sequence  
source 1..400  
mol\_type = protein  
organism = synthetic construct

SEQUENCE: 69  
DILPCVPFSV AKSVKSLYLG RMFSGTPVIR LRFKRLQPTR LVAEFDERTF DPEGILLFAG 60  
GHQDSTWIVL ALRAGRLELQ LRYNGVGRVT SSGPVINHGM WQTISVEELA RNLVIKVNRD 120  
AVMKIAVAGD LFQPERGLYH LNLTGGIIPF HEKDLVQPIN PRLDGCMRSW NWLNGEDTTI 180  
QETVKANTRM QCFSVTERGS FYPGSGFAFY SLIDYMRPLD IGTESTWEIE VVAHIRPAAD 240  
TGVLFALWVP DLRAVPLSVA LVDYHSTKKL KKQLVVLAVE HVALALMEIK VCDGQEHHVT 300  
VSLRDSEATL EVDGTRGQSE VSAAQLQERL AVLERHLRSP VLTFAGGLPD VPVTSAPVTA 360  
FYRGCMTEV NRRLLDLDEA AYKHSDITAH SCPPVEPAAA 400

SEQ ID NO: 70 moltype = AA length = 400  
FEATURE Location/Qualifiers  
REGION 1..400  
note = TAM(Axl)-binding sequence  
source 1..400  
mol\_type = protein  
organism = synthetic construct

SEQUENCE: 70  
DILPCVPFSV AKSVKSLYLG RMFSGTPVIR LRFKRLQPTR LVAEFDERTF DPEGILLFAG 60  
GHQDSTWIVL ALRAGRLELQ LRYNGVGRVT SSGPVINHGM WQTISVEELA RNLVIKVNRD 120  
AVMKIAVAGD LFQPERGLYH LNLTGGIIPF HEKDLVQPIN PRLDGCMRSW NWLNGEDTTI 180  
QETVKVNTRM QCFSVTERGS FYPGSGFAFY SLIDYMRPLD IGTESTWEIE VVAHIRPAAD 240  
TGVLFALWVP DLRAVPLSVA LVDYHSTKKL KKQLVVLAVE HVALALMEIK VCDGQEHHVT 300  
VSLRDGEATL EVDGTRGQSE VSAAQLQERL AVLERHLRSP VLTFAGGLPD VPVTSAPVTA 360  
FYRGCMTEV NRRLLDLDEA AYKHSDITAH SCPPVEPTTA 400

SEQ ID NO: 71 moltype = AA length = 395  
FEATURE Location/Qualifiers  
REGION 1..395  
note = TAM(Axl)-binding sequence  
source 1..395  
mol\_type = protein  
organism = synthetic construct

SEQUENCE: 71  
LPCVPFSVAK SVKSLYLGRM FSGTPVIRLR FKRLQPTRLV AEFDERTFDP EGILLFAGGH 60  
QDSTWIVL RAGRLELQLR YNGVGRVT SGPVINHGMWQ TISVEELARN LVIKVNRDAV 120  
MKIAVAGDLF PERGLYHNL LTGGVTFHE KDLVQPINPR LDGCMRSWNW LNGEDTTIQE 180  
TVKVNTRMOC FSUTERGSFY PGSGFAFYSL DMRTPLDVG TESTWEVEVV AHIRPAADTG 240  
VLFALWAPDL RAVPLSVALV DYHSTKKLKK QLVVLAVEHT ALALMEIKVC DGQEHHVT 300  
LRDGEATLEV DGTRGQSEVS AAQQLQERLAV LERHLRSPVLFAGGLPDVP VTSAPVAFY 360  
RCMTLEVNR RLLDLDEAAY KHSDITAHSC PPVEP 395

SEQ ID NO: 72 moltype = AA length = 400  
FEATURE Location/Qualifiers  
REGION 1..400  
note = TAM(Axl)-binding sequence  
source 1..400  
mol\_type = protein  
organism = synthetic construct

SEQUENCE: 72  
DILPCVPFSM AKSVKSLYLG RMFSGTPVIR LRFKRLQPTR LVAEFDERTF DPEGILLFAG 60  
GHQDSTWIVL ALRAGRLELQ LRYNGVGRVT SSGPVINHGM WQTISVEELA RNLVIKVNRD 120  
AVMKIAVAGD LFQPERGLYH LNLTGGIIPF HEKDLVQPIN PRLDGCMRSW NWLNGEDTTI 180  
QETVKANTKM QCFSVTERGS FYPGSGFAFY SLIDYMRPLD IGTESTWEIE VVAHIRPAAD 240  
TGVLFALWVP DLRAVPLSVA LVDYHSTKKL KKQLVVLAVE HVALALMEIK VCDGQEHHVT 300  
ISLREGEATL EVDGTRGQSE VSAAQLQERL AVLEKHLRSP VLTFAGGLPD VPVTSAPVTA 360  
FYRGCMTEV NRRLLDLDEA AYKHSDITAH SCPPVEPAAA 400

SEQ ID NO: 73 moltype = AA length = 400  
FEATURE Location/Qualifiers  
REGION 1..400

-continued

---

source note = TAM(Axl)-binding sequence  
1..400  
mol\_type = protein  
organism = synthetic construct

SEQUENCE: 73  
DILPCVPFSM AKSVKSLYLG RMFSGTPVIR LRFKRLQPTR LVAEFDRTF DPEGILLFAG 60  
GHODSSWIVL ALRAGRLELQ LRYNGVGRVT SSGPVINHGM WQTISVEELA RNLVIKVNRD 120  
AVMKIAVAGD LFQPERGLYH LNLTGGIPF HEKDLVQPIN PRLDGCMRSW NWLNGEDTTI 180  
QETVKANTKM QCFSVTERGS FYPGSGFAFY SLNDMRTPLD IGTTESTWEIE VVAHIRPAAD 240  
TGVLFALWVP DLRAVPLSVA LVVDYHSTKKL KKQLVVVLAVE HVALALMEIK VCDGQEHHMVT 300  
ISLREGEATL EVDGTRGQSE VSAAQLQERL AVLEKHLRSP VLTFAGGLPD VPVTSAPVTA 360  
FYRGCMTEV NRRLLDLDEA AYKHSDITAH SCPPVEPAAA 400

SEQ ID NO: 74 moltype = AA length = 400  
FEATURE Location/Qualifiers  
REGION 1..400  
source note = TAM(Axl)-binding sequence  
1..400  
mol\_type = protein  
organism = synthetic construct

SEQUENCE: 74  
DILPCVPFSM AKSVKSLYLG RMFSGTPVIR LRFKRLQPTR LVAEFDRTF DPEGILLFAG 60  
GHODSTWIVL ALRAGRLELQ LRYNGVGRVT SSGPVINHGM WQTISVEELA RNLVIKVNRD 120  
AVMKIAVAGD LFQPERGLYH LNLTGGIPF HEKDLVQPIN PRLDGCMRSW NWLNGEDTTI 180  
QETVKANAKM QCFSVTERGS FYPGSGFAFY SLNDMRTPLD IGTTESTWEIE VVAHIRPAAD 240  
TGVLFALWVP DLRAVPLSVA LVVDYHSTKKL KKQLVVVLAVE HVALALMEIK VCDGQEHHMVT 300  
ISLREGEATL EVDGTRGQSE VSAAQLQERL AVLEKHLQSP VLTFAGGLPD VPVTSAPVTA 360  
FYRGCMTEV NRRLLDLDEA AYKHSDITAH SCPPVEPTAA 400

SEQ ID NO: 75 moltype = AA length = 340  
FEATURE Location/Qualifiers  
REGION 1..340  
source note = TAM(Axl)-binding sequence  
1..340  
mol\_type = protein  
organism = synthetic construct

SEQUENCE: 75  
DILPCVPFSL AKSVKSLYLG RMFSGTPVIR LRFKRLQPTR LVAEFDRTF DPEGILLFAG 60  
GHODSTWIVL ALRAGRLELQ LRYNGVGRVT SSGPVINHGM WQTISVEELA RNLVIKVNRD 120  
QETVKANAKM QCFSVTERGS FYPGSGFAFY SLNDMRTPLD IGTTESTWEIE VVAHIRPAAD 180  
TGVLFALWVP DLRAVPLSVA LVVDYHSTKKL KKQLVVVLAVE HVALALMEIK VCDGQEHHMVT 240  
ISLREGEATL EVDGTRGQSE VSAAQLQERL AVLEKHLQSP VLTFAGGLPD VPVTSAPVTA 300  
FYRGCMTEV NRRLLDLDEA AYKHSDITAH SCPPVEPATA 340

SEQ ID NO: 76 moltype = AA length = 400  
FEATURE Location/Qualifiers  
REGION 1..400  
source note = TAM(Axl)-binding sequence  
1..400  
mol\_type = protein  
organism = synthetic construct  
VARIANT 100  
note = X can be A or T

SEQUENCE: 76  
DILPCVPFSV AKSVKSLYLG RMFSGTPVIR LRFKRLQPTR LVAEFDRTF DPEGVLLFAG 60  
GHODGTWML ALRAGRLELQ LHYNGVGRVT SSGPVINHGX WQTISVEEMA RSLVIKVNRD 120  
AVMKIAVAGD LFQPERGMFH LNLTGGIPF HEKDLVQPIN PRLDGCIWSW NWMNGEDTTI 180  
QETVKVNTKM QCFSVTERGS FYPGNGFAFY SLNYMRTPLD VGTESTWEIE VVAHIRPAAD 240  
TGVLFALWAA DLRAVPLSVA LVVDYHSTKKL KKQLVVVLAVE RVALALMEIK VCDGQEHHVVT 300  
VSLSREGEATL AVDGTRGQSE VSAAQLQERL ATLERHLQSP VLTFAGGLPD VPVTSAPVTA 360  
FYRGCMTEV NRRLLDLDEA AYKHGDITSH SCPTVEPAAA 400

SEQ ID NO: 77 moltype = AA length = 400  
FEATURE Location/Qualifiers  
REGION 1..400  
source note = TAM(Axl)-binding sequence  
1..400  
mol\_type = protein  
organism = synthetic construct

SEQUENCE: 77  
DILPCVPFSM AKSVKSLYLG RMFSGTPVIR LRYRRLQPTR LVAEFDRTF DPEGVLLFAG 60  
GHODGTWML ALRAGRLELQ LRYNGVGRIT SSGPVINHGT WQTISVEELA RSLVIKVNRD 120  
AVMKIAVAGD LFQPERGMFH LNLTGGIPF HEEDLVQPIN PRLDGCIWSW NWMNGEDTTI 180  
QETVKVNNSM QCFSVTERGS FYPGNGFAFY SLNYMRTPLD VGTESTWEIE VVAHIRPAAD 240  
TGVLFALWAA DLRAVPLSVA LVVDYHSTKKL KKQLVVVLAVE RVALALMEIK VCDGQEHHVVT 300  
VSLSREGEATL AVDGTRGQSE VSAAQLQERL ATLERHLQSP VLTFAGGLPD VPVTSAPVTA 360  
FYRGCMTEV NRRLLDLDEA AYKHGDITSH SCPTVEPAAA 400

SEQ ID NO: 78 moltype = AA length = 399

-continued

---

FEATURE REGION	Location/Qualifiers 1..399 note = TAM(Axl)-binding sequence
source	1..399 mol_type = protein organism = synthetic construct
SEQUENCE: 78	
DILPCVPFSV AKSLKSLYLG RMFSGTPVIR LRFKRLQPTR LVAEFDRTF DPEGILFFAG 60 GRHDSTWVL ALRAGRLELQ LLFNGVGRVT SSGPVINHGM WQTISVEELE RNLVVKVNKD 120 AVMKIAVAGD LFQLDRGLYH LNLTVGGLPF KEKDLVQPIN PRLDGCMRSW NWLNGEDTTI 180 QETVKANAKM QCFSLTEKGGS FFPGGAFAFY SLGYVRTSLD VGTETTWEIE VEARIRPAAD 240 TGVLALLWAP DHRAVPLSVA LVVDYHSTKKL KKQLVVLAVE SVALALMEIK VCDGQEHHVS 300 VSVRDEATL EVDGTRGQSE VSAAQLQERL AALGRHLRDP VLTFAGGLPE VPVTSAPVTA 360 YRGCMTELEV NRRPLLDSEA SYKHSDITAH SCPPVEPAA 399	
SEQ ID NO: 79	moltype = AA length = 399
FEATURE REGION	Location/Qualifiers 1..399 note = TAM(Axl)-binding sequence
source	1..399 mol_type = protein organism = synthetic construct
SEQUENCE: 79	
DILPCVPFGV AKSVKSLYLG RMFSGTPVIR LRFKRLQPTR LVAEFDRTF DPEGVLFFAG 60 GRQDSTWVL ALRAGRLELQ LRYNGVGRVT SSGPVINHGT WQTISVEELE RNLVVKVNKD 120 AVMKIAVAGD LFQRDRGLYH LNLTVGGLPF KEKELVQPIN PRLDGCMRSW NWLNSEDTTI 180 QETVKVNTKM QCFSVTEKGGS FYPGTGFAFY SLNYMRRTSLD VGTETTWEIK VMARIRPATD 240 TGVLALLCAP DHRTVPLSVA LVVDYHSTKKL KKQLVVLAVE SVVLALVEIK ACDGQEHEVS 300 VSLKEGEATL EVDGTRGWE ASATQLQERL DTLRRHLLHDP VLTFAGGLPD VPVTAAPVTA 360 YRGCMTELEV NRRLLDLDEA AYKHSDITSH SCPPVEPTA 399	
SEQ ID NO: 80	moltype = AA length = 399
FEATURE REGION	Location/Qualifiers 1..399 note = TAM(Axl)-binding sequence
source	1..399 mol_type = protein organism = synthetic construct
SEQUENCE: 80	
DILPCVPFSV AKSVKSLYLG RMFSGTPVIR LRFKRLQPTR LVAEFDRTF DPEGILLFAG 60 GHQDSTWVL ALRAGRLELQ LRYNGVGRVT SSGPVINHGM WQTISVEEELA RNLVIKVNRD 120 AVMKIAVAGD LFQPERGLYH LNLTVGGLPF HEKDLVQPIN PRLDGCMRSW NWLNGEDTTI 180 QETVKVNTRM QCFSVTERGS FYPGNGLAIY SLNYSRTPPD VGTTESTWEVE VVAHIRPAAD 240 TGVLFALWAP DLRAVPLSVA LVVDYHSTKKL KKQLVVLAVE HTALALMEIK VCDGQEHHVT 300 VSLRDGEATL EVDGTRGQSE VSAAQLQERL AVLERHLSRP VLTFAGGLPD VPVTSAPVTA 360 YRGCMTELEV NRRLLDLDEA AYKHSDITAH SCPPVEPAA 399	
SEQ ID NO: 81	moltype = AA length = 398
FEATURE REGION	Location/Qualifiers 1..398 note = TAM(Axl)-binding sequence
source	1..398 mol_type = protein organism = synthetic construct
SEQUENCE: 81	
DILPCVPFSV AKSMKSLYLG RMFSGTPVIR LRFKRLQPTR LVAEFDRTF DPEGVLFFAG 60 GHQDSTWVL ALRAGRLELQ LHNGVGRVT SSGPVINHGM WQTISVEELE RNVVIKVND 120 AVMKIAVAGD LFQLDRGLYH LNLTVGGLPF KEKHLVQPIN PRLDGCMRSW SWLNGEDTTI 180 QETVKVNTRM QCFSVTERGS FYPGNGLAIY SLNYSRTPPD VGTTESTWEVE VVARIRPATD 240 TGVLALLVGD GHTVPLSVAL VDHYHSTKKL KQLVVLAVEG MALALMEIKV CDGQEHHVAV 300 SLKAGEASLE VDGTKGQSEV SAAQLQERLA VLGRHLQGP LTFIGGLPDV PVTSAAPVAF 360 YRGCMTELEV QKRLDLDEAT YKHSDITSHS CPPVEHAA 398	
SEQ ID NO: 82	moltype = AA length = 397
FEATURE REGION	Location/Qualifiers 1..397 note = TAM(Axl)-binding sequence
source	1..397 mol_type = protein organism = synthetic construct
SEQUENCE: 82	
DILPCVPFTM AKSVKSLYLG RMFSGTPVIR LRFKRLQPTR LLAEFDRTF DPEGVLFFAG 60 GRSDSTWVL GLRAGRLELQ LRYNGVGRIT SSGPVINHGM WQTISVEELE RNLVIKVND 120 AVMKIAVAGE LFQLERGLYH LNLTVGGLPF KEQDLVQPIN PRLDGCMRSW NWLNGEDSAI 180 QETVKANTKM QCFSVTERGS FFPGGAFAFY SLNYTRTSLD VGTETTWEVE IVAWIRPATD 240 TGVLALLVGD NHVVPPLSVAL VDHYHSTKKL KQLVVLAVED VALALMEIKV CDSQEHVVTV 300 SLRDGEATL VDGTKGQSEV SAAQLQERLD TLGEHLQGTV LTFVGGLPDV PVTSAAPVAF 360 YRGCMTELEV QKTLDDLDEAS YKHSDITSHS CPPVEHA 397	

---

## US 12,384,822 B2

99

100

-continued

---

SEQ ID NO: 83      moltype = AA length = 398  
 FEATURE      Location/Qualifiers  
 REGION      1..398  
 note = TAM(Ax1)-binding sequence  
 source      1..398  
 mol\_type = protein  
 organism = synthetic construct

SEQUENCE: 83  
 DILPCVPFSV AKSVKSLYLG RMFSGTPVIR LRFKRLQPTR LVAEFDRTF DPEGILLFAG 60  
 GHQDSTWIVL ALRAGRLELQ LRYHGVGRVT SSGPVINHGM WQTISVEELA RNLVIKVNRD 120  
 AVMKIAVAGD LFQPERGLYH LNLTGGIIPF HEKDLVQPIN PRLDGCMRSW NWLNGEDTTI 180  
 QETVKVNTRM QCFSVTERGS FYPGSGFAFY SLDDYMRTPLD VGTESTWEVE VVAHIRPAAD 240  
 TGVLFLALWAP DLRAVPLSVA LVDYHSTKKL KKQLVVLAVE HTALALMEIK VCDGQEHVV 300  
 VSLRDGEATL EVDGTRGQSE VSAAQLQERL AVLERHLRSP VLTFAGGLPD VPVTSAPVTA 360  
 YRGCMTLEV NRRLLDLDEA AYKHSDITAH SCPPVEPA 398

SEQ ID NO: 84      moltype = AA length = 398  
 FEATURE      Location/Qualifiers  
 REGION      1..398  
 note = TAM(Ax1)-binding sequence  
 source      1..398  
 mol\_type = protein  
 organism = synthetic construct

SEQUENCE: 84  
 DILPCVPFNV AKSVKSLYLG RMFSGTPVIR LRFKRLQPTR LLAEFDRTF DPEGVLFAG 60  
 GRQDSTWIVL ALRAGRLELQ LRYHGVGRVT SSGPVINHGM WQTISVEELD RNLVIKVND 120  
 AVMKIAVAGD LFQLDRLGLYH LNLTGGIIPF KEKDLVQPIN PRLDGCMRSW NWLNGEDTTI 180  
 QETVKANSKM QCFSVTERGS FYPGTTGFAY SLDDYTRTSTA VGTEATWEIE VVAQIRPATD 240  
 TGVLFLALVAG DHVVALSVAL VDYZHSTKKL KKQLVVLAVE VTLALMEIK CDGQEHHRVAV 300  
 SVRKGEATL EVDGTRGQSE TAAGLQESLA VLGRHLQASV LTFVGGLPDV PVTSAVTA 360  
 YRGCMTLEVN QQALDLDEAA YKHSDITSHS CPPVEQAG 398

SEQ ID NO: 85      moltype = AA length = 395  
 FEATURE      Location/Qualifiers  
 REGION      1..395  
 note = TAM(Ax1)-binding sequence  
 source      1..395  
 mol\_type = protein  
 organism = synthetic construct

SEQUENCE: 85  
 DILPCVPFSV AKSVKSLYLG RMFSGTPVIR LRFKRLQPTR LVAEFDRTF DPEGILLFAG 60  
 GHQDSTWIVL ALRAGRLELQ LRYHGVGRVT SSGPVINHGM WQTISVEELA RNLVIKVNRD 120  
 AVMKIAVAGD LFQPERGLYH LNLTGGIIPF HEKDLVQPIN PRLDGCMRSW NWLNGEDTTI 180  
 QETVKVNTRM QCFSVTERGS FYPGSGFAFY SLDDYMRTPLD VGTESTWEVE VVAHIRPAAD 240  
 TGVLFLALWAP DLRAVPLSVA LVDYHSTKKL KKQLVVLAVE HTALALMEIK VCDGQEHVV 300  
 VSLRDGEATL EVDGTRGQSE VSAAQLQERL AVLERHLRSP VLTFAGGLPD VPVTSAPVTA 360  
 YRGCMTLEV NRRLLDLDEA AYKHSDITAH SCPPV 395

SEQ ID NO: 86      moltype = AA length = 394  
 FEATURE      Location/Qualifiers  
 REGION      1..394  
 note = TAM(Ax1)-binding sequence  
 source      1..394  
 mol\_type = protein  
 organism = synthetic construct

SEQUENCE: 86  
 DILPCVPFNV AKSVKSLYLG RMFSGTPVIR LRFKRLQPTR LVAEFDRTF DPEGVLFAG 60  
 GHQDSTWIVL ALRAGRLELQ LHYHGGIGRVT SSGSVINHGM WQTISVEELA RNLVIKINKD 120  
 AVMKIAVAGD LFQLDRLGLYH LNLTGGIIPF KDKDLVQPIN PRLDGCMRSW NWLNGEDSTI 180  
 QDTVKVNTRM QCFSVTEKGS FYPGNGFAFY SLNYVRTEA VGTEMTWEIE VIARIRPATD 240  
 TGVLFLALVAK NHTIPLSVAL VDYZHSTKKL KQLVILAIEN VALSLMEIKV CDGQEHVVTV 300  
 SVKEGEATLV VDGTRGQSE SPTQLQERL A VLKRHLQDSV HTFVGGLPDV PVTSAVTA 360  
 YHGCMTLEVN KKALDLDEAV YKHSDITSHS CPPI 394

SEQ ID NO: 87      moltype = AA length = 398  
 FEATURE      Location/Qualifiers  
 REGION      1..398  
 note = TAM(Ax1)-binding sequence  
 source      1..398  
 mol\_type = protein  
 organism = synthetic construct

SEQUENCE: 87  
 DILPCVPFNV AKSVKSLYLG RMFSGTPVIR LRFKRLQPTR LLAEFDRTF DPEGVLFAG 60  
 GHQDSAWIVL CLRAGRLELQ LRYHGGVGRVT SSGPVINHGT WQTISVEELD RNLVIKVNRD 120  
 AVMKIAVAGD LFQLDRLGLYH LNLTGGIIPF KEKDLVQPIN PRLDGCMRSW NWLNGEDTTI 180  
 QETVKANSKM QCFSVTERGS FYPGTTGFAY SLDDYTRTSA VGTEAAWEIE VVAWIRPATD 240  
 TGVLFLALVGG DRVVALSVAL VDYZHSTKKL KQLVVLAVEG VTLALMEIKV CDGQEHHRVAV 300  
 SVRKGEVTL EVDGTRGQSE SAAGLQESLA VLERHLQGSV LTFVGGLPDV PVTSAVTA 360  
 YRGCMTLEVN QQTLDLDEAA YKHSDITSHS CPPVEQAS 398

-continued

---

SEQ ID NO: 88            moltype = AA length = 392  
 FEATURE                Location/Qualifiers  
 REGION                1..392  
 note = TAM(Axl)-binding sequence  
 source                1..392  
 mol\_type = protein  
 organism = synthetic construct  
 SEQUENCE: 88  
 VSVCLPLNLD TKYELLYLAE QFAGVVVLYL KFRPEISRFS AEFDFRTYDS EGVILYAESI 60  
 IDHSAWLLIAL RGGKIEVQLK NEHTSKITTG GGDVINNGLWN NMVSVEELEH SISIKIAKEAV 120  
 MDINKPGPLF KPENGLLETK KVYFAGFPRKV VESELIKPINP RLDGCIRSWN LMKQGASGIK 180  
 KEIIQEKKH CLVTVEKGSY YPGSGIAQFH HIDYNNVSSA EGWHVNVTLN RPSTGTGVM 240  
 ALVSGNNTVP PFAVSLVDST SEKSQDILLS VENTVIYRIQ ALSLCSDQQS HLEFRVNRRNNL 300  
 LELSTPLKIE TISHEDLQRQL AVLKDAMKAK KVATYLGGLP DVPPFSATPVN AFYNGCMEVNI 360  
 NGVQLDLDE AISKHNDIRAH SCPSVWKTK NS 392

SEQ ID NO: 89            moltype = AA length = 388  
 FEATURE                Location/Qualifiers  
 REGION                1..388  
 note = TAM(Axl)-binding sequence  
 source                1..388  
 mol\_type = protein  
 organism = synthetic construct  
 SEQUENCE: 89  
 LPLNLDTKYE LLYLAEQFAG VVLYLKFRLP EISRFSAEFD FRTYDSEGVII LYAESIDHSA 60  
 WLLIALRGGK IEVQLKNEHT SKITGGDVII NNGLWNMVSS EELEHSISIK IAKEAVMDIN 120  
 KPGPLFKPEN GLLETKVYFA GFPRKVESEL IKPINPRLDG CIRSWNLMKQ GASGIKEIIQ 180  
 EKONKHKCLVT VEKGSYYPGS GIAQPHIDYN NVSSAEGWHV NVTLNRPST GTGVMALVS 240  
 GNNTVFPFAVSLVDST SEKSQDILLS VENTVIYRIQ ALSLCSDQQS HLEFRVNRRNNL 300  
 PLKETIESHE DLQRQLAVLKDAMKAK KVATYLGGLP DVPPFSATPVN AFYNGCMEVQ 360  
 LDLDEAISKH NDIRAHSCPS VWKTKNS 388

SEQ ID NO: 90            moltype = AA length = 392  
 FEATURE                Location/Qualifiers  
 REGION                1..392  
 note = TAM(Axl)-binding sequence  
 source                1..392  
 mol\_type = protein  
 organism = synthetic construct  
 SEQUENCE: 90  
 VVSVCPLNLD DTKYELLYLA EQFAGVVLYL KFRPEISRF SAEFDFRTYD SEGVILYAES 60  
 IDHSAWLLIA RGGKIEVQL KNEHTSKITT GGDVINNGLW NMVSVEELEH SISIKIAKEA 120  
 VMDINKPGPL FPKPENGLLET KVYFAGFPRK VESELIKPIN PRLDGCIWSN LMKQGASGI 180  
 KEIIQEKKH CLVTVEKGGS YPGSGIAQFH HIDYNNVSSA EGWHVNVTLN IRPSTGTGVM 240  
 ALVSGNNTVP PFAVSLVDST SEKSQDILLS VENTVIYRIQ ALSLCSDQQS HLEFRVNRRNN 300  
 LELSTPLKIE TISHEDLQRQ LAVLKDAMKA KVATYLGGLP DVPPFSATPVN AFYNGCMEVN 360  
 NGVQLDLDE AISKHNDIRAH HSCPSVWKKT NS 392

SEQ ID NO: 91            moltype = AA length = 390  
 FEATURE                Location/Qualifiers  
 REGION                1..390  
 note = TAM(Axl)-binding sequence  
 source                1..390  
 mol\_type = protein  
 organism = synthetic construct  
 SEQUENCE: 91  
 VVSVCPLNLD DTKYELLYLA EQFAGVVLYL KFRPEISRF SAEFDFRTYD SEGVILYAES 60  
 IDHSAWLLIA RGGKIEVQL KNEHTSKITT GGDVINNGLW NMVSVEELEH SISIKIAKEA 120  
 VMDINKPGPL FPKPENGLLET KVYFAGFPRK VESELIKPIN PRLDGCIWSN LMKQGASGI 180  
 KEIIQEKKH CLVTVEKGGS YPGSGIAQFH HIDYNNVSSA EGWHVNVTLN IRPSTGTGVM 240  
 ALVSGNNTVP PFAVSLVDST SEKSQDILLS VENTVIYRIQ ALSLCSDQQS HLEFRVNRRNN 300  
 LELSTPLKIE TISHEDLQRQ LAVLKDAMKA KVATYLGGLP DVPPFSATPVN AFYNGCMEVN 360  
 NGVQLDLDE AISKHNDIRAH HSCPSVWKKT 390

SEQ ID NO: 92            moltype = AA length = 393  
 FEATURE                Location/Qualifiers  
 REGION                1..393  
 note = TAM(Axl)-binding sequence  
 source                1..393  
 mol\_type = protein  
 organism = synthetic construct  
 SEQUENCE: 92  
 VVSVCPLNLD DTKYELLYLA EQFAGVVLYL KFRPEISRF SAEFDFRTYD SEGVILYAES 60  
 IDHSAWLLIA RGGKIEIQL KNEHTSKITT GGDVINNGLW NMVSVEELEH SISIKIAKEA 120  
 VMDINKPGPL FPKPENGLLET KVYFAGFPRK VESELIKPIN PRLDGCIWSN LMKQGASGI 180  
 KEIIQEKKH CLVTVEKGGS YPGSGIAQFH HIDYNNVSSA EGWHVNVTLN IRPSTGTGVM 240  
 ALVSGNNTVP PFAVSLVDST SEKSQDILLS VENTVIYRIQ ALSLCSDQQS HLEFRVNRRNN 300  
 LELSTPLKIE TISHEDLQRQ LAILDKAMKA KVATYLGGLP DVPPFSATPVN AFYNGCMEVN 360

-continued

INGVQLDLDE AISKHNDIRA HSCPSVWKKT KNS 393

SEQ ID NO: 93 moltype = AA length = 393  
 FEATURE Location/Qualifiers  
 REGION 1..393  
 note = TAM(Ax1)-binding sequence  
 source 1..393  
 mol\_type = protein  
 organism = synthetic construct

SEQUENCE: 93  
 VVSVCLPLNL DTKYELLYLA EQFAGVVLYL KFRLPEISRF SAEFDERTYD SEGVILYAES 60  
 IDHSAWLLIA LRGGKIEVQL KNEHTSKITT GGDVINNGLW NMVSVEELEH SISIKIAKEA 120  
 VMDINKPGPL FKPKPENGLLET KVFYFAGFPKR VESELIKPIN PRLDGCIKRW NLMKQGASGI 180  
 KEIIQEQQNK HCLITVEKGS YYPGSGIAQF HIDYNNVSSA EGWHVNVTLN IRPSTGTGVM 240  
 LALVSGNNTV PFAVSLVDST SEKSQDILLS VENTVIYRIQ ALSLCSDQQS HLEFRVNRNN 300  
 LELSTPLKIE TISHEDLQRQ LAILDKAMKA KVATYLGGLP DVPPFSATPVN AFYNGCMEVN 360  
 INGVQLDLDE AISKHNDIRA HSCPSVWKKT KNS 393

SEQ ID NO: 94 moltype = AA length = 393  
 FEATURE Location/Qualifiers  
 REGION 1..393  
 note = TAM(Ax1)-binding sequence  
 source 1..393  
 mol\_type = protein  
 organism = synthetic construct

SEQUENCE: 94  
 VVSVCLPLNL DTKYELLYLA EQFAGVVLYL KFRLPEISRF SAEFDERTYD SEGVILYAES 60  
 IDHSAWFLIA LRGGKIEIQL KNEHTSKITT GGDVINNGLW NMVSVEELEH SISIKIAKEA 120  
 VMDINKPGPL FKPKPENGLLET KVFYFAGFPKR VESELIKPIN PRLDGCIKRW NLMKQGASGI 180  
 KEIIQEQQNK HCLITVEKGS YYPGSGIAQF HIDYNNVSSA EGWHVNVTLN IRPSTGTGVM 240  
 LALVSGNNTV PFAVSLVDST SEKSQDILLS VENTVIYRIQ ALSLCSDQQS HLEFRVNRNN 300  
 LELSTPLKIE TISHEDLQRQ LAILDKAMKA KVATYLGGLP DVPPFSATPVN AFYNGCMEVN 360  
 INGVQLDLDE AISKHNDIRA HSCPSVWKKT KNS 393

SEQ ID NO: 95 moltype = AA length = 393  
 FEATURE Location/Qualifiers  
 REGION 1..393  
 note = TAM(Ax1)-binding sequence  
 source 1..393  
 mol\_type = protein  
 organism = synthetic construct

SEQUENCE: 95  
 VVSVCLPLNL DTKYELLYLA EQFAGVVLYL KFRLPEISRF SAEFDERTYD SEGVILYAES 60  
 IDHSAWLLIA LRGGKIEVQL KNEHTSKITT GGDVINNGLW NMVSVEELEH SISIKIAKEA 120  
 VMDINKPGPL FKPKPENGLLET KVFYFAGFPKR VESELIKPIN PRLDGCIKRW NLMKQGASGI 180  
 KEIIQEQQNK HCLITVEKGS YYPGSGIAQF HIDYNNVSSA EGWHVNVTLN IRPSTGTGVM 240  
 LALVSGNNTV PFAVSLVDST SEKSQDILLS VENTVIYRIQ ALSLCSDQQS HLEFRVNRNN 300  
 LELSTPLKIE TISHEDLQRQ LAILDKAMKA KVATYLGGLP DVPPFSATPVN AFYNGCMEVN 360  
 INGVQLDLDE AISKHNDIRA HSCPSVWKKT KNS 393

SEQ ID NO: 96 moltype = AA length = 393  
 FEATURE Location/Qualifiers  
 REGION 1..393  
 note = TAM(Ax1)-binding sequence  
 source 1..393  
 mol\_type = protein  
 organism = synthetic construct

SEQUENCE: 96  
 VVSVCLPLNL DTKYELLYLA EQFAGVVLYL KFRLPEISRF SAEFDERTYD SEGVILYAES 60  
 IDHSAWFLIA LRGGKIEIQL KNEHTSKITT GGDVINNGLW NMVSVEELEH SISIKIAKEA 120  
 VMDINKPGPL FKPKPENGLLET KVFYFAGFPKR VESELIKPIN PRLDGCIKRW NLMKQGASGI 180  
 KEIIQEQQNK HCLITVEKGS YYPGSGIAQF HIDYNNVSSA EGWHVNVTLN IRPSTGTGVM 240  
 LALVSGNNTV PFAVSLVDST SEKSQDILLS VENTVIYRIQ ALSLCSDQQS HLEFRVNRNN 300  
 LELSTPLKIE TISHEDLQRQ LAILDKAMKA KVATYLGGLP DVPPFSATPVN AFYNGCMEVN 360  
 INGVQLDLDE AISKHNDIRA HSCPSVWKKT KNS 393

SEQ ID NO: 97 moltype = AA length = 393  
 FEATURE Location/Qualifiers  
 REGION 1..393  
 note = TAM(Ax1)-binding sequence  
 source 1..393  
 mol\_type = protein  
 organism = synthetic construct

SEQUENCE: 97  
 VVSVCLPLNL DTKYELLYLA EQFAGVVLYL KFRLPEISRF SAEFDERTYD SEGVILYAES 60  
 IDHSAWFLIA LRGGKIEIQL KNEHTSKITT GGDVINNGLW NMVSVEELEH SISIKIAKEA 120  
 VMDINKPGPL FKPKPENGLLET KVFYFAGFPKR VESELIKPIN PRLDGCIKRW NLMKQGASGI 180  
 KEIIQEQQNK HCLITVEKGS YYPGSGIAQF HIDYNNVSSA EGWHVNVTLN IRPSTGTGVM 240  
 LALVSGNNTV PFAVSLVDST SEKSQDILLS VENTVIYRIQ ALSLCSDQQS HLEFRVNRNN 300

-continued

---

LELSTPLKIE TISHEDLQRQ LAILDKAMKA KVATYLGGLP DVPPFSATPVN AFYNGCMEVN 360  
INGVQLDLDE AISKHNDIRA HSCPSVWKKT KNS 393

SEQ ID NO: 98 moltype = AA length = 393  
FEATURE Location/Qualifiers  
REGION 1..393  
note = TAM(Ax1)-binding sequence  
source 1..393  
mol\_type = protein  
organism = synthetic construct

SEQUENCE: 98  
VVSVCLPLNL DTKYELLYLA EQFAGVVLYL KFRLPEISRF SAEFDERTYD SEGVILYAES 60  
IDHSAWLLIA LRGGKIEVQL KNEHTSKITT GGDVINNGLW NMVSVEELEH SISIKIAKEA 120  
VMDINKPGPL FKPENGLLET KVFAGFPKR VESELIKPIN PRLDGCIKRSW NLMKQGASGI 180  
KEIIQEKGK HCLVTVEKGS YYPGSGIAQF HIDYNNVSSA EGWHVNVTLN IRPSTGTGVM 240  
LALVSGNNTV PFAVSLVDST SEKSQDILLS VENTVIYRIQ APSLCSDQQS HLEFRVNRRNN 300  
LELSTPLKIE TISHEDLQRQ LAILDKAMKA KVATYLGGLP DVPPFSATPVN AFYNGCMEVN 360  
INGVQLDLDE AISKHNDIRA HSCPSVWKKT KNS 393

SEQ ID NO: 99 moltype = AA length = 393  
FEATURE Location/Qualifiers  
REGION 1..393  
note = TAM(Ax1)-binding sequence  
source 1..393  
mol\_type = protein  
organism = synthetic construct

SEQUENCE: 99  
VVSVCLPLNL DTKYELLYLA EQFAGVVLYL KFRLPEISRF SAEFDERTYD SEGVILYAES 60  
IDHSAWLLIA LRGGKIEVQL KNEHTSKITT GGDVINNGLW NMVSVEELEH SISIKIAKEA 120  
VMDINKPGPL FKPENGLLET KVFAGFPKR VESELIKPIN PRLDGCIKRSW NLMKQGASGI 180  
KEIIQEKGK HCLVTVEKGS YYPGSGIAQF HIDYNNVSSA EGWHVNVTLN IRPSTGTGVM 240  
LALVSGNNTV PFAVSLVDST SEKSQDILLS VENTVIYRIQ ALSLCSDQQS HLEFRVNRRNN 300  
LELSTPLKIE TISHEDLQRQ LAILDKAMKA KVATYLGGLP DVPPFSATPVN AFYNGCMEVN 360  
INGVQLDLDE AISKHNDIRA HSCPSVWKKT KNS 393

SEQ ID NO: 100 moltype = AA length = 393  
FEATURE Location/Qualifiers  
REGION 1..393  
note = TAM(Ax1)-binding sequence  
source 1..393  
mol\_type = protein  
organism = synthetic construct

SEQUENCE: 100  
VVSVCLPLNL NTKYELLYLA EQFAGVVLYL KFRLPEISRF SAEFDERTYD SEGVILYAES 60  
IDHSAWLLIA LRGGKIEVQL KNEHTSKITT GGDVINNGLW NMVSVEELEH SISIKIAKEA 120  
VMDINKPGPL FKPENGLLET KVFAGFPKR VESELIKPIN PRLDGCIKRSW NLMKQGASGI 180  
KEIIQEKGK HCLVTVEKGS YYPGSGIAQF HIDYNNVSSA EGWHVNVTLN IRPSTGTGVM 240  
LALVSGNNTV PFAVSLVDST SEKSQDILLS VENTVIYRIQ ALSLCSDQQS HLEFRVNRRNN 300  
LELSTPLKIE TISHEDLQRQ LAILDKAMKA KVATYLGGLP DVPPFSATPVN AFYNGCMEVN 360  
INGVQLDLDE AISKHNDIRA HSCPSVWKKT KNS 393

SEQ ID NO: 101 moltype = AA length = 393  
FEATURE Location/Qualifiers  
REGION 1..393  
note = TAM(Ax1)-binding sequences  
source 1..393  
mol\_type = protein  
organism = synthetic construct

SEQUENCE: 101  
AVSVCLPLNL DTKYELLYLA EQFAGVVLYL KFRLPEISRF SAEFDERTYD SQGVILYAES 60  
IDHSAWLLIA LRGGKIEVQL KNEHTSKITT GGDINNGLW NMVSVEELEH SISIKIAKEA 120  
VMDINKPGPL FKPENGLLET KVFAGFPKR VESELIKPIN PRLDGCIKRSW NLMKQGASGI 180  
KEIIQEKGK HCLVTVEKGS YYPGSGIAQF HIDYNNNGSSA EGWHVNVTLN IRPSTGTGVM 240  
LALVSSNNTV PFAVSLVDST SEKSQDIVLS VENTVIYRIQ ALSLCSNQRS HLEFRVNRRNN 300  
LELLTPLKIE TISHEELQRQ LAILDKAMTG KVATYLGGLP DVPPFSATPVN AFYNGCMEVN 360  
INGVQLDLDE AISKHNDIRA HSCPSVWKKT KNS 393

SEQ ID NO: 102 moltype = AA length = 393  
FEATURE Location/Qualifiers  
REGION 1..393  
note = TAM(Ax1)-binding sequence  
source 1..393  
mol\_type = protein  
organism = synthetic construct

SEQUENCE: 102  
AVSVCLPLNL DTKYELLYLA EQFAGVVLYL KFRLPEISRF SAEFDERTYD SQGVILYAES 60  
IDHSAWLLIA LRGGKIEVQL KNEHTSKITT GGDINNGLW NMVSVEELEH SISIKIAKEA 120  
VMDINKPGPL FKPENGLLET KVFAGFPKR VESELIKPIN PRLDGCIKRSW NLMKQGASGI 180  
KEIIQEKGK HCLVTVEKGS YYPGSGIAQF HIDYDNGSSA EGWHVNVTLN IRPSTGTGVM 240

-continued

LALVSSNNNTV PFAVSLVDST SEKSQDIVLS VENTVIYRIQ ALSLCSNQRS HLEFRVNRRNN	300
IELLTPLKIE TISHEELQRQ LAILDKAMTG KVATYLGGLP DVPPFSATPVN AFYNGCMEVN	360
INGVQLDDDE AISKHNDIRA HSCPSPWKKT KNS	393

SEQ ID NO: 103      moltype = AA length = 393  
 FEATURE                Location/Qualifiers  
 REGION                1..393  
 note = TAM(Axl)-binding sequence  
 source                1..393  
 mol\_type = protein  
 organism = synthetic construct

SEQUENCE: 103  
 AVSVCLPLNL DTKYELLYLA EQFAGVVLYL KFRLPEISRF SAEFDERTYD SQGVILYAES 60  
 IDHSAWLIA LRGGKIEVQL KNEHTSKITT GGGIINNGLW NMVSVEELEH SISIKIAKEA 120  
 VMDINKPGPL FKPENGLLET KVFAGFPKR VESELIKPIN PRLDGCIKSW NLMKQGASGI 180  
 KEIIQECKNK HCLVTVEKGS YYPGSGIAEF HIDYNNGNSNA EGWHINVTLN IRPSMGTGVM 240  
 LALVSSNNTV PFAVSLVDST SEKSQDIVLS VENTVIYRIQ ALSLCSNQRS HLEFRVNRRNN 300  
 IELLTPLKIE TISQUEELQTQ LAILDKAMKG KVATYLGGLP DVPPFSATPVN AFYNGCMEVN 360  
 INGVELLDDE AISKHNDIRA HSCPSPWKKT KNS 393

SEQ ID NO: 104      moltype = AA length = 393  
 FEATURE                Location/Qualifiers  
 REGION                1..393  
 note = TAM(Axl)-binding sequence  
 source                1..393  
 mol\_type = protein  
 organism = synthetic construct

SEQUENCE: 104  
 AVSVCLPLNL DTKYELLYLA EQFAGVVLYL KFRLPEISRF SAEFDERTYD SQGVILYAES 60  
 IDHSAWLIA LRGGKIEVQL KNEHTSKITT GGGIINNGLW NMVSVEELEH SISIKIAKEA 120  
 VMDINKPGPL FKPENGLLET KVFAGFPKR VESELIKPIN PRLDGCIKSW NLMKQGASGI 180  
 KEIIQECKNK HCLVTVEKGS YYPGSGIAEF HIDYNNGNSNA EGWHINVTLN IRPSMGTGVM 240  
 LALVSSNNTV PFAVSLVDST SEKSQDIVLS VENTVIYRIQ ALSLCSNQRS HLEFRVNRRNN 300  
 IELLTPLKIE TISQUEELQTQ LAILDKAMKG KVATYLGGLP DVPPFSATPVN AFYNGCMEVN 360  
 INGVELLDDE AISKHNDIRA HSCPSPWKKT KNS 393

SEQ ID NO: 105      moltype = AA length = 393  
 FEATURE                Location/Qualifiers  
 REGION                1..393  
 note = TAM(Axl)-binding sequence  
 source                1..393  
 mol\_type = protein  
 organism = synthetic construct

SEQUENCE: 105  
 AVSVCLPLNL DTKYELLYLA EQFAGVVLYL KFRLPEISRF SAEFDERTYD SQGVILYAES 60  
 IDHSAWLIA LRGGKIEVQL KNEHTSKITT GGGIINNGLW NMVSVEELEH SISIKIAKEA 120  
 VMDINKPGPL FKPENGLLET KVFAGFPKR VESELIKPIN PRLDGCIKSW NLMKQGASGI 180  
 KEIIQECKNK HCLVTVEKGS YYPGSGIAEF HIDYNNGNSNA EGWHINVTLN IRPSMGTGVM 240  
 LALVSSNNTV PFAVSLVDST SEKSQDIVLS VENTVIYRIQ ALSLCSNQRS HLEFRVNRRNN 300  
 IELLTPLKIE TISQUEELQTQ LAILDKAMKG KVATYLGGLP DVPPFSATPVN AFYNGCMEVN 360  
 INGVELLDDE AISKHNDIRA HSCPSPWKKT KNS 393

SEQ ID NO: 106      moltype = AA length = 393  
 FEATURE                Location/Qualifiers  
 REGION                1..393  
 note = TAM(Axl)-binding sequence  
 source                1..393  
 mol\_type = protein  
 organism = synthetic construct

SEQUENCE: 106  
 AVSVCLPLNL DTKYELLYLA EQFAGVVLYL KFRLPEISRF SAEFDERTYD SQGVILYAES 60  
 IDHSAWLIA LRGGKIEVQL KNEHTSKITT GGGIINNGLW NMVSVEELEH SISIKIAKEA 120  
 VMDINKPGPL FKPENGLLET KVFAGFPKR VESELIKPIN PRLDGCIKSW NLMKQGASGI 180  
 KEIIQECKNK HCLVTVEKGS YYPGSGIAEF HIDYNNGNSNA EGWHINVTLN IRPSMGTGVM 240  
 LALVSSNNTV PFAVSLVDST SEKSQDIVLS VENTVIYRIQ ALSLCSNQRS HLEFRVNRRNN 300  
 IELLTPLKIE TISQUEELQTQ LAILDKAMKG KVATYLGGLP DVPPFSATPVN AFYNGCMEVN 360  
 INGVELLDDE AISKHNDIRA HSCPSPWKKT KNS 393

SEQ ID NO: 107      moltype = AA length = 393  
 FEATURE                Location/Qualifiers  
 REGION                1..393  
 note = TAM(Axl)-binding sequence  
 source                1..393  
 mol\_type = protein  
 organism = synthetic construct

SEQUENCE: 107  
 AVSVCLPLDL DTKYELLYLA EQFAGVVLYL KFRLPEISRF SAEFDERTYD SQGVILYAES 60  
 IDHSAWLIA LRGGKIEVQL KNEHTSKITT GGAIINNGLW NMVSVEELEH SISIKIAKEA 120  
 VMDINKPGPL FKPENGLLET KVFAGFPKR VESELIKPIN PRLDGCIKSW NLMKQGASGI 180

-continued

---

KEIIQEKGK HCLVTVEKGS YYPGSGIAEF HIDYNNNGSNA EGWHINVTLN IRPSMGTGVM 240  
 VNHSAWLLIA VRDGKPEVQL SEKSQDIVLS VENTVIYRIQ ALSLCSNQRS HLEFRVNRRN 300  
 LELLTPLKIE TISQEELOQTQ LAILDKAMKG KVATYLGGLP DVPPFSATPVN AFYNGCMEVN 360  
 INGVLLDDE AISKHNDIRA HSCPSVWKKT KNS 393

SEQ ID NO: 108 moltype = AA length = 398  
 FEATURE Location/Qualifiers  
 REGION 1..398  
 note = TAM(Axl)-binding sequence  
 source 1..398  
 mol\_type = protein  
 organism = synthetic construct  
 VARIANT 57  
 note = X can be any amino acid  
 VARIANT 285  
 note = X can be any amino acid  
 SEQUENCE: 108  
 VVSVCPLNL DTQYELLYLA EQISGVVLYL KFHLPEISRF SAEFHFWTYD SEGMLXAES 60  
 VNHSAWLLIA LRGGKIEVQL KNEHTSKTTT EGDVINNGLW NELSTSQSVV EELEHSISIK 120  
 IAKEAVMDID KPGPLPKPEN GLLETKVYFA GYPQKVESEL IKPINPCLDG CIRGWNLMKQ 180  
 GASGIKEIIO EKQNQHCLVT VEKGYYPPGF GIAQFHVDYN NVSSAEGWHI NVTLNIHPSM 240  
 GTGVMLALVS GNNNTVPAVS LVDSTSEKSQ DILLSVENTVY IYRIXALSLC SDQOSHLEFR 300  
 VNRNNLLELLI PLKIELTSH DLQRQLAILD KAMKAKVATY LGGLPDVPFS ATPVNAFYNG 360  
 CMEVNINGVQ LDLDEAISKH NDIAHSCPS FWKKTNS 398

SEQ ID NO: 109 moltype = AA length = 393  
 FEATURE Location/Qualifiers  
 REGION 1..393  
 note = TAM(Axl)-binding sequence  
 source 1..393  
 mol\_type = protein  
 organism = synthetic construct  
 SEQUENCE: 109  
 AVPVCLPLNL DTKSELLYLA EQFAGGVVLYL KFRLPEISRF TAEFDFRTYD SEGVVLYAES 60  
 IDHSAWLLIA VRDGKPEVQL KNEQTSKITT GGGIINNNGVW HTVSVEELEH SVSLKIAKEA 120  
 VMNINKLGPL FKPEHGFLET KVFAGFPKR VESQFIKPIN PRDGICRGW NLMKQGASGV 180  
 KEIIQEKGK HCLVTVEKGS YYPGSGIAKF IIDYNNVSSA EGWYVNVSBN IRPSMGTGVM 240  
 LALVSHNNTV PFAVSLVDST SEKSQDILLS VEKTVVYRIQ ALSLCSDQQS HLEFRVNRRN 300  
 LEVSTPLKME TISHEDLQKQ LAILDKAMQG EVVTYLGGLP DVPPFSAAPAN AFYNGCMEVN 360  
 INGVLLDDE AISKHNDIRA HSCPSVWKKT KSS 393

SEQ ID NO: 110 moltype = AA length = 416  
 FEATURE Location/Qualifiers  
 REGION 1..416  
 note = TAM(Axl)-binding sequence  
 source 1..416  
 mol\_type = protein  
 organism = synthetic construct  
 VARIANT 57  
 note = X can be any amino acid  
 VARIANT 303  
 note = X can be any amino acid  
 SEQUENCE: 110  
 VVSVCPLNL DTQYELFYLA EQFAGGVVLYL KFHLPEISRF SAEFHFWTYD SEGMLXAES 60  
 VNHSAWLLIA LRGGKIEVQL ENEHTSKITT GGDVINNGLW NVFKIITFLK NVMNAKIVQQ 120  
 IFCVYVSVEE LEHSISIKIA KEAVMDINKP GPLFKPENGLET KVFAGFPAGF PQKAEGELIK 180  
 PINPCLDCGI RGWNLMKQGA SGIKEIIQEK QNKHCLVTVE KGSYYPFGI AQFRIDYNNV 240  
 SSVEGWHINV TLNIHPSMT GVMLALVSGN NTVPPFAVSLV DSTSEKSQDI LLSVENTVYI 300  
 LIXALSLCSD QQSHLEFIVN RNNLELLTPL KIETISHEDL QRQLAILDKA MKAKVATYLG 360  
 GLPDVPPFSAT PVNALYKGCM EVNINGVQLD LDEAISKHND IIAHSCPSFW KTKNS 416

SEQ ID NO: 111 moltype = AA length = 393  
 FEATURE Location/Qualifiers  
 REGION 1..393  
 note = TAM(Axl)-binding sequence  
 source 1..393  
 mol\_type = protein  
 organism = synthetic construct  
 SEQUENCE: 111

AVPVCLLNL DTKSELLYLA EQFAGGVVLYL KFRLPEISRF TAEFDFRTYD SEGVVLYAES 60  
 IDHSAWLLIA VRDGKPEVQL KNEQTSKITT GGGIINNNGVW HTVSVEELEH SVSLKIAKEA 120  
 VMNINKLGPL FKPEHGFLET KVFAGFPKR VESQFIKPIN PRDGICRGW NLMKQGASGV 180  
 KEIIQEKGK HCLVTVEKGS YYPGSGIAKF IIDYNNNASNA EGWYVNVSBN IRPSTGTGVM 240  
 LALVSRNNTV PFAVSLVDST SEKLQDILLS VEKTVVYRIQ ALSLCSDQQS HLEFKVNRRN 300  
 LEVSTPLKME TISHEDLQKQ LAILDKAMQG DVVTYLGGLP DVPPFSATPVN AFYNGCMEVN 360  
 INGVLLDDE AISKHNDIRA HSCPSVWKKT KSS 393

SEQ ID NO: 112 moltype = AA length = 393  
 FEATURE Location/Qualifiers

-continued

---

REGION	1..393
source	note = TAM(Ax1)-binding sequence
	1..393
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 112	
AIPVCLPLNL DTKSELLYLA EQFAGVVLYL KFRLPEISR TAEFDRTYD SEGVVLYAES	60
LDHSAWILIA VRDGKFEVQL QNEQTSRITT GGGVVNNNGVW HTVSVEELEH SVSLKIAKEA	120
VMNINKLGPL FPKPERHGFL ET KVFAGFPKRQ VESQFIKPIN PRLDGCIKGW NLMKQGASGV	180
KEIIQEKGKQNK HCLVTVEKGS YYPGSGIAKF IIDYNNNVSSA EGWHVNVLIN IRPSMGTGVM	240
LALVSRNNTV PFAVSLVDST SEKLDQILLS VEKTVIYRIE ALSLCSDQQS HLELKVNRHNS	300
LEVSTPLKME TVSHEDIQKE LAILDKAMQG EVVTYLGGLP DVFSATPVN AFYNGCMEVN	360
INGVQLLDDE AISKHNDIRA HSCPSVWRKT KSS	393
SEQ ID NO: 113	moltype = AA length = 388
FEATURE	Location/Qualifiers
REGION	1..388
source	note = TAM(Ax1)-binding sequence
	1..388
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 113	
VVSVCLPLNL DTKEYELLYLA EQFAGVVLYL KFRLPEISR SAEFDRTYD SEGVVLYAES	60
IDHSAWILLIA LRGGKIEVQL KNEHTSKITT GGDVINNGLW NMVSVEELEH SISIKIAKEA	120
VMDDINKPGPL FPKPENGLLET KVFAGFPKRQ VESELIKPIN PRLDGCIKGW NLMKQGASGV	180
KEIIQEKGKQNK HCLVTVEKGS YYPGSGIAKF HIDYNNNVSSA EGWHVNVLIN IRPSMGTGVM	240
LALVSGNNTV PFAVSLVDST SEKSDQILLS VENTVYRIE ALSLCSDQQS HLELKVNRHNS	300
LELSTPLKIE TISHEDLQRQ LAVLDKAMKA KVATYLGGLP DVFSATPVN AFYNGCMEVN	360
INGVQLLDDE AISKHNDIRA HSCPSVWK	388
SEQ ID NO: 114	moltype = AA length = 894
FEATURE	Location/Qualifiers
source	1..894
	mol_type = protein
	organism = Homo sapiens
SEQUENCE: 114	
MAWRCPRMGR VPLAWCLALC GWACMAPRGT QAEESPFGN PGNIITGARGL TGTLRCQLQV	60
QGEPPHEVHL RDGQILEAD STQTQVPLGE DEQDDWIVVNS QLRITSLQLS DTGQYQCLVF	120
LGHQTFVSPQ GVVGLEGLPY FLEEPEPRTV AANTPFNLSC QAQGPPEPVD LLWLQDAVPL	180
ATAPGHPGPR SLHVPGLNKT SSFSCEAHNA KGVTTSRAT ITVLPQQPRN LHLVSRQPTE	240
LEVAWTPLGS GIYPLTHCTL QAVLSDDGMG IQAGEPDPP EPLTSQASVP PHQLRLGSLH	300
PHTPYHIRVA CTSSQGPSSW THWLPVETPE GPVPLGPENI SATRNGSQAF VHWOEPRAPL	360
QGTLLQGYRLA YQGQDTPEVL MDIGLRLQEVIT LELVQGDGSNS NLTVCAVAYT AAGDGPWSLP	420
VPLEAWRPQQ AQPVHQLVKE PSTPAFSPWPW WYVLLGAVVA AACVLILALF LVHRRKKETR	480
YGEVFEPTVE RGEVLVVRVYRV RKSYSRRTT ATLNSLGLISE ELKEKLDRDV MDRHKVALGK	540
TIGEGERGAV MEGQLNQODDS ILKVAVKTMK IAICTRSELE DFLSEAVCMK EFDHPNVMLR	600
IGVCFQGSER ESFPAPVVL FPMKHMDFLHS FLLYSRQLGDQV PVYLPTQMLV KFMADIASGM	660
EYLSTKRFIH RDLAARNCMU NENMSVCVAD FGLSKKLYNG DYYRQGRIAK MPVKWIAES	720
LADRHYTSTS DVWSFGVTMW EIATRGQTPY PGVENSEIYD YLRQGNRLKQ PADCLDGLYA	780
LMSRCWELNP QDRPSPTELE EDLLENLTKAL PPAQEPDEIL YVNMDEGGGY PEPPGAAGGA	840
DPPTCPDPDK SCSCLTAAEV HPAGRYVLCPS STTPSPAQPA DRGSPAAGQ EDGA	894
SEQ ID NO: 115	moltype = AA length = 888
FEATURE	Location/Qualifiers
source	1..888
	mol_type = protein
	organism = Mus musculus
SEQUENCE: 115	
MGRVPLAWL ALCCWGCAAH KDTQTEAGSP FVGNPGNITG ARGLTGLR C ELQVQGEPP	60
VVWLRDQCIL ELADNTQTQV PLGEDWQDEW KVSQLRISA LQLSDAGEYQ CMVHLEGRFT	120
VSQPGFVGLE GLPYFLEEPE DKAVPANTPF NLSCQAQGPV EPVTLWLQD AVPLAPVTGH	180
SSQHSLOTPG LNKTSSFSCE AHNAKGVTTS RTATITVLPQ RPHHLHVSSR QPTELEVAVT	240
PGLSGIYPLQ HCNLQAVLSD DPPEDPLTLQ VSVPVPHQLRL EKLLPHTPYH	300
IRISCSSQPLG PSPWTHWLVP ETTEGVPLGP PENVSAMRNG SQVLRVRQEP RVPLQGTLLG	360
YRLAYRGQDT PEVLMIDIGLT REVTLERGD RPVANLTVSV TAYTSGADGP WSLPVPLEW	420
RPGQGQPLHH LVSEPPPRAF SWPWWYVLLG ALVAAACVLI LALFLVHRK KTRYGEVFE	480
PTVERGELVV RYRVRKSYSR RTTEATLNSL GISEELKEKL RDVMVDRHKV ALGKTLGEGE	540
FGAVMEGQLN QDDSIKLKAV KMCKIAICL SELEDFLSEA VCMKEDHPPN VMRLIGVCFQ	600
GSREGFPPEP VVILPFPKMG DLHFSFLLYSR LGDQPVFLPT QMLVKFMADI ASGMELYLSTK	660
RFIHRDLAAR NCMLNENMSV CVADFGLSKK IYNGDYYRQG RIAKMPVKWI AIESLADRKY	720
TSKSDVWSFG VTMWEIATRG QTPYPGVENS EIIDYLRQGN RLKQPVDCLD GLYALMSRCW	780
EINPRDRPSF AELREDLENT LKALPPAQEP DEILYVNMDG GGSHLEPRGA AGGADPPTQP	840
DPKDSCSCLT AADVHSAGR VLCPSTAPGP TLSADRGCPA PPGQEDGA	888
SEQ ID NO: 116	moltype = AA length = 5
FEATURE	Location/Qualifiers
source	1..5
	mol_type = protein
	organism = synthetic construct

---

-continued

---

REGION	1..5 note = The entire sequence of amino acids 1-5 can be repeated one or more times	
SEQUENCE: 116	GGGGS	5
SEQ ID NO: 117	moltype = length =	
SEQUENCE: 117	000	
SEQ ID NO: 118	moltype = AA length = 6	
FEATURE	Location/Qualifiers	
source	1..6	
	mol_type = protein	
	organism = synthetic construct	
REGION	1..6 note = The entire sequence of amino acids 1-6 can be repeated one or more times	
SEQUENCE: 118	GSSGGS	6
SEQ ID NO: 119	moltype = AA length = 18	
FEATURE	Location/Qualifiers	
source	1..18	
	mol_type = protein	
	organism = synthetic construct	
SEQUENCE: 119	KESGSVSSEQ LAQFRSLD	18
SEQ ID NO: 120	moltype = AA length = 14	
FEATURE	Location/Qualifiers	
source	1..14	
	mol_type = protein	
	organism = synthetic construct	
SEQUENCE: 120	EGKSSGSGSE SKST	14
SEQ ID NO: 121	moltype = AA length = 12	
FEATURE	Location/Qualifiers	
source	1..12	
	mol_type = protein	
	organism = synthetic construct	
SEQUENCE: 121	GSAGSAAGSG EF	12
SEQ ID NO: 122	moltype = AA length = 5	
FEATURE	Location/Qualifiers	
source	1..5	
	mol_type = protein	
	organism = synthetic construct	
REGION	1..5 note = The entire sequence of amino acids 1-5 can be repeated one or more times	
SEQUENCE: 122	EAAAK	5
SEQ ID NO: 123	moltype = AA length = 12	
FEATURE	Location/Qualifiers	
source	1..12	
	mol_type = protein	
	organism = synthetic construct	
SEQUENCE: 123	CRRRRRREAE AC	12
SEQ ID NO: 124	moltype = AA length = 46	
FEATURE	Location/Qualifiers	
source	1..46	
	mol_type = protein	
	organism = synthetic construct	
SEQUENCE: 124	AEAAAKEAAA KEAAAKEAAA KALEAEAAAK EAAAKEAAAK EAAAKA	46
SEQ ID NO: 125	moltype = AA length = 8	
FEATURE	Location/Qualifiers	
source	1..8	
	mol_type = protein	
	organism = synthetic construct	
SEQUENCE: 125	GGGGGGGG	8

-continued

SEQ ID NO: 126 FEATURE source	moltype = AA length = 6 Location/Qualifiers 1..6 mol_type = protein organism = synthetic construct	
SEQUENCE: 126 GGGGGG		6
SEQ ID NO: 127 FEATURE source	moltype = AA length = 13 Location/Qualifiers 1..13 mol_type = protein organism = synthetic construct	
SEQUENCE: 127 AEEAAKEAAA AKA		13
SEQ ID NO: 128 FEATURE source	moltype = AA length = 5 Location/Qualifiers 1..5 mol_type = protein organism = synthetic construct	
SEQUENCE: 128 PAPAP		5
SEQ ID NO: 129 FEATURE source	moltype = AA length = 17 Location/Qualifiers 1..17 mol_type = protein organism = synthetic construct	
SEQUENCE: 129 VSQTSKLRRA ETVFPDV		17
SEQ ID NO: 130 FEATURE source	moltype = AA length = 6 Location/Qualifiers 1..6 mol_type = protein organism = synthetic construct	
SEQUENCE: 130 PLGLWA		6
SEQ ID NO: 131 FEATURE source	moltype = AA length = 10 Location/Qualifiers 1..10 mol_type = protein organism = synthetic construct	
SEQUENCE: 131 TRHRQPRGWE		10
SEQ ID NO: 132 FEATURE source	moltype = AA length = 10 Location/Qualifiers 1..10 mol_type = protein organism = synthetic construct	
SEQUENCE: 132 AGNRVRRSVG		10
SEQ ID NO: 133 FEATURE source	moltype = AA length = 8 Location/Qualifiers 1..8 mol_type = protein organism = synthetic construct	
SEQUENCE: 133 RRRRRRRR		8
SEQ ID NO: 134 FEATURE source	moltype = AA length = 4 Location/Qualifiers 1..4 mol_type = protein organism = synthetic construct	
SEQUENCE: 134 GFLG		4
SEQ ID NO: 135 FEATURE source	moltype = AA length = 31 Location/Qualifiers 1..31 mol_type = protein organism = synthetic construct	
SEQUENCE: 135		

-continued

GSSGGSGSSG GSGGGDEADG SRGSQKAGVD E

31

SEQ ID NO: 136      moltype = AA length = 898  
 FEATURE                Location/Qualifiers  
 source                1..898  
 mol\_type = protein  
 organism = synthetic construct  
 SIGNAL                1..30  
 SEQUENCE: 136  
 MAPSLSPGPA ALRRAPQLL LLLAAECALA DIQMTQSPSS LSASVGDRVT ITCRASQSI 60  
 SYLNWYQQKP GKAPKLLIYA ASSLQSGVPS RFSGSGSGTD FTLTISLQP EDFATYYCQQ 120  
 SYSTPLTFGG GTKVEIKRGG GGSGGGSGG GGSEVQLVES GGGVVQPGRS LRLSCAASGF 180  
 AFSSYGMHWV RQAPGKGLEW VAVIWFDTK KYYTDHSVGR FTISRDNSKN TLYLQMNTLR 240  
 AEDTAVYCYCA RDRTGIGARRG PYYMDVWGKG TTIVTSSGGG GS CGGGGSCIN KYGSPYTKNS 300  
 GFATCVQNLQ DQCTPNPCD KGTQACQDLM GNPFCLCKAG WGGRLCDKDV NECSQENGGC 360  
 LQICHNKPGS FHCSCHSGFE LSSDGRTCQD IDECADSEAC GEARCKNLPG SYSCLCDEGF 420  
 AYSSQEKA CR DVDECLQGRC EQVCPNSPGS YTCHCDGRGG LKLSQDMDTC EDILPCVPFS 480  
 VAKSVKSLYL RMFSGTPVI RLRFKRLQPT RLVAEFDFTP FDPEGLLFA GGHQDSTWIV 540  
 LAIRAGRLEL QLRYNGVGRV TSSGPVINHG MWQTISVEEL ARNLVIKVNR DAVMKIAVAG 600  
 DLFQPERGLY HLNLTVGGIP FHEKDLVQPI NPLRDGCMRS WNWLNGEDTT IQETVKVNTR 660  
 MQCFSVTERG SFYPGSGFAF YSLDYMRTPL DVGTESTWEV EVVAHIRPAA DTGVLFALWA 720  
 PDLRAVPLSV AVSDYHSTKK LKLQLVVLAV EHTALALMEI KVCDFQEHVV TVSLRDGEAT 780  
 LEVDGTRQES EVSAQLQER LAVLERHLRS PVLTFAAGLPL DPVPTSAVPT AFYRCMTLE 840  
 VNRRLLLDDE AAYKHSDITA HSCPPVEPAA AQGSRADYKD HDGDYKDHD 898  
 DYKDDDDK  
 SEQ ID NO: 137      moltype = AA length = 902  
 FEATURE                Location/Qualifiers  
 source                1..902  
 mol\_type = protein  
 organism = synthetic construct  
 SEQUENCE: 137  
 MAPSLSPGPA ALRRAPQLL LLLAAECALA QVQLVESGGN LVQPGGSLRL SCAASGFTFG 60  
 SFMSMWRQA PGGGLEWVAG LSARSSLTHY AD SVKGRFTI SRDNAKNSVY LQMNSLRVED 120  
 TAVYYCARRS YDSSGYWGHF YSYMDVWGQG TLTVTSSGGG SG GGGGSGGGG SSVLQPSV 180  
 SAAPGQKVTI SC SGS TSNIG NNYVSWYQOH PGKAPKLMY DVSKRPSGVP DR FSGSKSGN 240  
 SASLDISGLQ SEDEADYYCA AW DDSLSEFL FGTGKLTBLV GGGGGSGGGG SCINKYGS 300  
 TKNSGFATCV QNLPDQCTPN PC DRKGTQAC QDLMGNFCL CKAGWGGRCL DKDVNECSQE 360  
 NGGCLQICHN KPGSFHCSCH SG FELSSDGR TC QDIDE CAD SEACGEARCK NLPGSYSCLC 420  
 DEGFAYSSQE KACRDVDEC L QGRCEQVCVN SPGSYTC HCD GRGGLKLSQD MDTCEDILPC 480  
 VPFSVAKSVK SLYLGRMFSG TPVIRLRFKR LQPTRLVAEF DFRTFDPEGI LLFAGGHQDS 540  
 TWIVLALRAG RLELQLRYNG VGRVITSSGPV INHGMWQTIS VEELARNL VKNRDAVMKI 600  
 AVAGDLPQPE RGLYHNLNTV GGIPFHEKDL VOPINPRLDG CMRSWNWLNG EDTTIQETVK 660  
 VNTRMQCSV T ERGSFYPGS GF AFYSLDM RTPLDVGTES T RVEVVAHI RPAADTGVL 720  
 ALWAPDLRAV PL SVALVDYH STKLLKKQLV VL AVEHTAL LMEIKVCDQ EHVVTVSLRD 780  
 GEATLEVDGT RGQSEVSAAQ LQERLAVLER HLRSPVLTFA GGLPDVPTVS APVTAFYRGC 840  
 MTLEVNRLL DLD EAYKHS DITA HSCPPV EPAAAQGSRA DYKDHDGYK DHDIDYKDD 900  
 DK  
 902  
 SEQ ID NO: 138      moltype = AA length = 714  
 FEATURE                Location/Qualifiers  
 source                1..714  
 mol\_type = protein  
 organism = synthetic construct  
 SIGNAL                1..30  
 SEQUENCE: 138  
 MAPSLSPGPA ALRRAPQLL LLLAAECALA DIQMTQSPSS LSASVGDRVT ITCRASQSI 60  
 SYLNWYQQKP GKAPKLLIYA ASSLQSGVPS RFSGSGSGTD FTLTISLQP EDFATYYCQQ 120  
 SYSTPLTFGG GTKVEIKRGG GGSGGGSGG GGSEVQLVES GGGVVQPGRS LRLSCAASGF 180  
 AFSSYGMHWV RQAPGKGLEW VAVIWFDTK KYYTDHSVGR FTISRDNSKN TLYLQMNTLR 240  
 AEDTAVYCYCA RDRTGIGARRG PYYMDVWGKG TTIVTSSGGG GS CGGGGSCIN KYGSPYTKNS 300  
 VKSLYLGRMF SGTPVIRLRF KRLQPTRLVA EFD FRTFDPE GILLFAGGHQ DSTWIVLALR 360  
 AGRLELQLRY NGVGRVTTSSGPV PVINHGMWQT ISVEELARNL VIKVN RDAVM KIAVAGD LFO 420  
 PERGLYHNLN T VGGIPFHEK DLVQPINPRL DGCMRSWNWL NGEDTTI QETVK VKNTRM QCF 480  
 SVTERGSFYP GS GFAF YSLD YMRTPL DVGTE ESTWEVVA HIRPAADTGV LFALWAPDLR 540  
 AVPLSVALVD YHSTKLLKKQ LVVLA VETA LALMEIKVCDQ QE HVVTVS LRDGEATLEVD 600  
 GTRGQSEVSA AQLQERLAVL ERHLLRSPVLT FAGGLPDVPTV TSAPVTAFYR GCMTLEVNRR 660  
 LLDLDEAAYK HS DITA HSCPPV EPAAAQGSRA DYKDHDGYK DHDIDYKDD 714  
 DDDK  
 SEQ ID NO: 139      moltype = AA length = 718  
 FEATURE                Location/Qualifiers  
 source                1..718  
 mol\_type = protein  
 organism = synthetic construct  
 SEQUENCE: 139  
 MAPSLSPGPA ALRRAPQLL LLLAAECALA QVQLVESGGN LVQPGGSLRL SCAASGFTFG 60  
 SFMSMWRQA PGGGLEWVAG LSARSSLTHY AD SVKGRFTI SRDNAKNSVY LQMNSLRVED 120  
 TAVYYCARRS YDSSGYWGHF YSYMDVWGQG TLTVTSSGGG SG GGGGSGGGG SSVLQPSV 180  
 SAAPGQKVTI SC SGS TSNIG NNYVSWYQOH PGKAPKLMY DVSKRPSGVP DR FSGSKSGN 240  
 SASLDISGLQ SEDEADYYCA AW DDSLSEFL FGTGKLTBLV GGGGGSGGGG SDILPCVPFS 300

-continued

---

VAKSVKSLYL GRMFSGTPVI RLRFKRLQPT RLVAEFDERT FDPEGILLFA GGHQDSTWIV 360  
 LALRAGRLEL QLRYNGVGRV TSSGPVINHG MWQTISVEEL ARNLVIVKVR DAVMKIAVAG 420  
 DLFQPERGLY HLNLTVGPIP FHEKDLVQPI NPLRDGCMRS WNWLNGEDTT IQETVKVNTR 480  
 MQCFSVTTERG SFYPGSGFAF YSLDYMRPTL DVGTESTWEV EVVAHIRPAA DTGVLFALWA 540  
 PDLRAVPLSV ALVDYHSTKK LKKQLVVLAV EHTALALMEI KVCDCQEHHVV TVSLRDGEAT 600  
 LEVDGTRGQS EVSAAQLQER LAVLERHLRS PVLTFAAGGLP DVPTVSAPVT AFYRCMTLE 660  
 VNRRLLLDDE AAYKHSITAHSCP HSCPPVEPAA AQGSRADYKD HDGDKDHDI DYKDDDDK 718

SEQ ID NO: 140 moltype = AA length = 708  
 FEATURE Location/Qualifiers  
 source 1..708  
 mol\_type = protein  
 organism = synthetic construct  
 SIGNAL 1..30  
 SEQUENCE: 140  
 MAPSLSPGPA ALRRAPQLLL LLLAECALA DIQMTQSPSS LSASVGDRVT ITCRASQSI 60  
 SYLNWYQOKP GKAPKLLIYA ASSLSQSGPS RFGSGSGSTD FTTLTISSLQP EDFATYYCQQ 120  
 SYSTPLTFGG GTKVEIKRGG GGSGGGSGG GGSEVQLVES GGGVQPGRS LRLSCAASGF 180  
 AFSSYGMHW RQAPGKGLEW VAVIWFDTK KYYTDSVKGR FTISRDNSKN TLYQMNTRL 240  
 AEDTAVYYCA RDRGIGARRG PYYMDVWGKG TTVTVSSGGG GSGGGGSDIL PCVPFSVAKS 300  
 VIKSLYLRMF SGTPVIRLVA KRLQPTRLVA EFDFTFDPF GILLFAGGHQ DSTWIVLALR 360  
 AGRLELQLRY NGVGRVTSSG PVINHGMWQT ISVEELARN VIKVNDRAVM KIAVAGDLFQ 420  
 PERGLYHLNL TVGGIFPHE DLVQPINPLR DGCMRSNWJL NGEDTTIQTET VKVNTRMQCF 480  
 SVTERGSFYP GSGFAFYSLD YMRTPLDVT ESTWEVEVVA HIRPAADTGV LFALWAPDLR 540  
 AVPLSVALVD YHSTKLLKKQ LVVLLAVEHTA LALMEIKVCD QGEHVVTVSL RDGEATLEVD 600  
 GTRGQSEVSA AQLQERLAVL ERHLLRSPVLT FAGGLPDVVP TSAPVTAFYR GCMTLEVNR 660  
 LLLDLEAAAYK HSITAHSCP PVEPAAAGSG SGSGSGSGSY PYDVPDYA 708

SEQ ID NO: 141 moltype = AA length = 727  
 FEATURE Location/Qualifiers  
 source 1..727  
 mol\_type = protein  
 organism = synthetic construct  
 SEQUENCE: 141  
 MGWSCIILFL VATATGDIQM TQSPSSLSAS VGDRVTITCR ASQSISSYLN WYQQKPGKAP 60  
 KLLIYAASSL QSGVPSRFSG SGSGTDFLT ISSLQPEDFA TYTYCQQSYST PLTFGGTKV 120  
 EIKRKRTVAA PSVFIPPPSD EQLKSGTAVS VCLLNNFYPY EAKVQWKVDN ALQSGNSQES 180  
 VTEQDSKDT YSLSSLTLS KADYFLHKVY ACEVTHQGLS SPVTKSFNRG ECRRKRGSGE 240  
 GRGSLLTCGD VEENPGPMW SCIIFLHKVAT ATGEVQLVES GGGVQPGRS LRLSCAASGF 300  
 AFSSYGMHW RQAPGKGLEW VAVIWFDTK KYYTDSVKGR FTISRDNSKN TLYQMNTRL 360  
 AEDTAVYYCA RDRGIGARRG PYYMDVWGKG TTVTVSSAST KGPSVFLAP SSKSTSGGTA 420  
 ALGCLVLDYF PEPVTPWSN GALTSGVHTF PAVLQSSGLY SLSSVVTVPS SSSLQTYYIC 480  
 NVNHKPSNTK DVKKVEPKSS DKHTKSPCP APELLGGPSV FLFPPKPKDT LMISRTPEVT 540  
 CVVVDVSHED PEVKFNWYVD GVEVHNNAKTK PREEQYNSTY RVVSVLTVLH QDWLNGKEYK 600  
 CKVSNKALPA PIEKTISKAK GQPREPQVYT LPSSRDELTK NQVSLTCLVK GFYPSDIAVE 660  
 WESNGQPEENN YTTPPVLDL DGSFFFLYSKL TVDKSRWQOG NVFSCSVMHE ALHNHYTQKS 720  
 LSLSPGK 727

SEQ ID NO: 142 moltype = AA length = 705  
 FEATURE Location/Qualifiers  
 source 1..705  
 mol\_type = protein  
 organism = synthetic construct  
 SEQUENCE: 142  
 MAPSLSPGPA ALRRAPQLLL LLLAECALA ALLPAREATQ FLRPRQRRAF QVFEEAKQGH 60  
 LERECEVEELC SREEAREVFE NDPETDYFYP RYLDCKINKY SPYTKNSGFA TCVQNLPDQC 120  
 TPNPCDRKGT QACQDLMGNF FCLCKAGWGG RLCDKDVNEC SQENGGCLQI CHNKPGSFHC 180  
 SCHSGFELSS DGRCTQDIDE CADSEACGEA RCKNLPGSYS CLCDEGFAYS SQEKACRDVD 240  
 ECLQGRCEQV CVNSPGSYTC HCDGRGGLKL SQDMDTCED1 LPPCPVFSVAK SVKSLYLGGM 300  
 FSCTPVIIRL FKRLQPTRLV AEFDFRTFDP EGILLFAGGHQ DSTWIVLAL RAGRELELQLR 360  
 YNGVGRVTSS GPVINHGMWQ TISVEELARN LVIKVNRDAV MKIAVAGDLF QPERGLYHLN 420  
 LTVGGIFPHE KDLVQPINR LDGCMRSWNW LNGEDTTIQTET TVKVNTRMQC FSVTERGSFY 480  
 PGSGFAFYSL DMYRTPDVG TESTWEVEVVA AHIRPAADTG VLFLWAPDL RAVPLSVALV 540  
 DYHSTKLLKKQ QLVVLLAVEHTA ALALMEIKVCD QGEHVVTVSL RDGEATLEVD DGTRGQSEVS 600  
 AQLQERLAVL LERHLLRSPVLT TFAGGLPDVVP TSAPVTAFYR GCMTLEVNR RLLDLEAAAY 660  
 HSITAHSCP PPVEPAAAQG SRADYKDHDG DYKDHIDYK DDDDK 705

SEQ ID NO: 143 moltype = DNA length = 2697  
 FEATURE Location/Qualifiers  
 source 1..2697  
 mol\_type = other DNA  
 organism = synthetic construct  
 SEQUENCE: 143  
 atggccctt cgctctcgcc cgggcccgc gcccgtcgcc ggcgcggcga gctgtgtcg 60  
 ctgctgtgg ccgcggagtg cgcgttgcgacattcaga tgactcaatc tccttagctct 120  
 ctgagcgcct ccgttggaga tagactcaactt accacgtca gagccgcataccatcagc 180  
 tcttatctaa attggatcca acagaagccc ggcaaagcgc caaagctgtcatctacgt 240  
 gcaagctct tacagagcgg agtaccacccg agattctcaag gcagtgccag tggactgac 300  
 ttcacattga cgattagctc tctgcagcct gaagactttt ccacatacta ttgtcagcag 360

-continued

actatagca	ccccgtgac	gttggaggc	ggaactaagg	tggaaatcaa	gagaggaggc	420
gggggctccg	cggggggtgg	ctcgggggg	ggaggctcg	aggttcagct	tgtcgagtct	480
gggggggggg	tcgttccagg	aggtagaa	ctcacgacta	gtgtgcggcc	aatgggggtt	540
gcttttcat	cttaacggtat	gactcggtg	agacagctc	ctggcaaaa	actcgagtgg	600
tcgtcgtaa	tatggttcga	tggataaca	aaatactact	cctggatgtt	gaaaggaga	660
ttcaccatt	cacgagacaa	cagtaaaaat	accttgtacc	ttcagatgaa	caccctgaga	720
gcagaagaca	caggcgctt	ctactgcgc	agagatagag	gtatccggac	aaggcgttgt	780
cccttataat	tggatgttg	ggggaaaggga	acaacatgt	ctgtgagetc	tggggggggc	840
ggcgcggcgc	ggcggtggac	ctgcatac	aagtatgggt	cttgcacac	caaaaactca	900
ggettogcc	cctgegtgc	aaacctgcct	gaccagtgea	cggccaaaccc	ctgcatagg	960
aagggggaccc	aaggctgc	ggacccatcg	ggcaactctt	tctgcgtgt	taaagctggc	1020
tggggggggc	ggcttcgtc	caaagatgtc	aaacgtatgea	cgccaggagaa	cgggggtgc	1080
ctccagatct	gccacaacaa	ggccgggtac	tccactgtt	cctgcacac	cggttcetag	1140
ctctctctgt	atggcaggac	ctgccaagac	atagacgagt	gceagactc	ggagggctgc	1200
ggggggggcgc	gctgcaagaa	cctgccccgc	tcctactctt	gcctctgtga	cgagggttt	1260
gcgtacatcg	cccaggagg	gggttgcgca	gatgtggacg	agtgttctga	ggggcgtgt	1320
gagcggatct	gcgttgcacte	cccaggggc	taacatccgc	actgtgcgg	gcgtggggcc	1380
ctcaagctgt	cccaggacat	ggacaccctgt	gaggacatct	tgccgtggct	gccttcacg	1440
gtggccaaga	gtgtgaagtc	cttgcac	ggccggatgt	tcagttggac	cccccgtatc	1500
cgactcgctc	tcaagagggt	gcagccacc	agggtgttag	ctgtgtttga	cttccggacc	1560
tttgcaccc	aggggatct	cctttgcgc	ggggccacc	aggacacac	cttgatctgt	1620
ctggccctga	gagccggcc	gctggagct	cagtcgcgt	aaacgggtgt	cggccgtgtc	1680
accagcagcg	gccccgtcat	caaccatgc	atgtggcaga	caatctctgt	tgaggagctg	1740
gcccggaaat	ttgttcatca	ggtaacagg	gatgtgtca	tggaaatccg	gggtggccgg	1800
gacttgttcc	aaccggagcc	aggactgtat	catctgaacc	tgaccgtgg	aggttattccc	1860
ttccatgaga	aggacttcgt	gcacgcata	aaccctcgt	tggatgtgt	catggaggac	1920
tggaaactggc	tgaacggaga	agacaccacc	atccaggaaa	cgtgtaaaagt	gaacacgagg	1980
atgcgtatcg	tctcggtgc	ggagagaggc	tcttttctacc	ccggggagegg	cttcgcctt	2040
tacagcgttg	actacatgc	ggccctctgt	gacgtcggt	ctgaatcaac	ctgggaagta	2100
gaagtctgg	ctcacatcc	cccgccggca	gacacaggcg	tgcgttgc	gtcttggcc	2160
cccgaccc	gtgcgtgtc	tctctctgt	gcactgttag	actatcactc	cacgaagaaa	2220
ctcaagaaggc	agctgtgtgtt	cctggccgt	gagcatacgg	ctttgcctt	aatggagatc	2280
aaggctcgcc	acggccaa	gcacgtgtc	accgtctcg	tgaggacgcg	tgaggccac	2340
ctgggggtgc	acggccacc	ggggccagac	gagggtgacg	ccgcgcacgt	gcaggagagg	2400
ctggccgtgc	tcagaggaca	cctggggac	ccctgtgtca	cctttgtcg	cggccgtcc	2460
gatgtgcgg	tgacttcage	gccagtcac	gcgttctacc	gcggctgcat	gacactggag	2520
gtcaacccgg	ggctgtgtga	cctggacag	gcggccatca	agacacaggca	cataccacggc	2580
cacttcgtcc	ccccctgtga	ggccggccca	gcccacaggat	ccggggctga	ctaaaaagac	2640
catgacgtgt	attataaaga	tcatgcacat	gactacaagg	atgacatgt	caatgtca	2697

```

SEQ ID NO: 144 moltype = DNA length = 2709
FEATURE Location/Qualifiers
source 1..2709
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 144
atggccctt cgtcttcgccc cggggccgcgc gcccgcgcgc gcgccgcga gctgtgtgtg 60
ctgtgtgtgg ccggggagggt cgccgttgc cagggtttagc tggttgagag cggaggcaat 120
ctgggttacgc cccgggtttagt tctgtgtctg tcttgtgtgg cgttgcgggtt cacttccgtt 180
agtttttcaat tgatgtgtgtt ccgttcaggca ccaggccgggtt gctgtgtgtt gggtggcgtt 240
ctgtgtgtccgat gtatgtgtgtt gcatgtatgtt aatgggggggtt gttccataat 300
tcacggcaca acgtcaagaat tagcgttctac ctgcataatgtt actccctgtt ggttgcggat 360
accggcgtgtt attactgtgtc tcgcgttctt tatgactcta ttggatactgtt gggccatttt 420
tatagtcata tggatgtgtgtt gggacagggtt actctgtgtt ccgttccggg aggccgttggg 480
tctgggggggtt gttgggggttggg agccgggtttt ccgttcagggtt tgaccacgggtt gtcctgtgtt 540
aggccggcgcgc caggccggaa atgttacatgtt tcctgtgtgtt gaaatgttcccaatccggc 600
aacaattatgtt tttctgtgtt tcacggcac ccggggcaaaatcgcccaatgtt gatgtatttt 660
gtatgtgttcaaaacgttcaag tgggtgttctt gacccgttca ggggttccaa gttctggaaat 720
agtgccttcaat tggacatcttcc acggctgttcc aacggaaatgtt agggccggactt ttactgtgtt 780
gttctggatgttcc acacgttccgtt cgaatattttt ttcggccacccgg gacaaatgtt gacccgttgc 840
ggccgggggggtt gccggcagccgg cggccgggttcc agtgcataatca acaagttatgg gttctccgtt 900
accaaaaaaatc cagggttccgtt caccgttccgtt caaaaacttgc ctgcacccgtt caccggccaaat 960
ccctgtgtgttcaaaatgggggttcc acggccgttccgtt cggggccaaactt tttctgtgtt 1020
ttgtttttttttt gttttttttttt gttttttttttt gttttttttttt gttttttttttt gttttttttttt 1080
aacgggggggttcc gcttccaaatgtt ctggccacaaatcc aaggccgggttcc gtttccactgtt tttctgtgttcc 1140
agccggccgttcc agtcttccgtt tgatgtgtgttcc acctgttccaaatgtt acatagacgtt gttccgttcc 1200
tcgggggggttcc gccgggggggttcc ggcgttccgttcc aaccttgcggccgttcc gtttccactgttcc 1260
gacgggggttcc ttgtgttccgttcc cttccggaggatcc aagggttccgttcc gatgtgtgttcc cggatgtgttcc 1320
caggccgggttcc ttgtgtgttccgttcc cttccggaggatcc gtttccactgttcc acactgttccgttcc 1380
ggccgggggttcc gcttccaaatgtt ccgttccgttcc acggccgggttcc gtttccactgttcc acactgttccgttcc 1440
gttccgttcc gcttccaaatgtt ccgttccgttcc acggccgggttcc gtttccactgttcc acactgttccgttcc 1500
acccggccgttcc tccgttccgttcc acggccgggttcc gtttccactgttcc acactgttccgttcc 1560
gactttccgttcc cttttccgttcc acggccgggttcc gtttccactgttcc acactgttccgttcc 1620
accttccgttcc tccgttccgttcc acggccgggttcc gtttccactgttcc acactgttccgttcc 1680
gttccgttccgttcc tccgttccgttcc acggccgggttcc gtttccactgttcc acactgttccgttcc 1740
gttccgttccgttcc tccgttccgttcc acggccgggttcc gtttccactgttcc acactgttccgttcc 1800
ggccgggggttcc ggggggttcc gtttccactgttcc acactgttccgttcc 1860
gggggggttcc ggggggttcc gtttccactgttcc acactgttccgttcc 1920
ttgtgtgttcc gtttccactgttcc acactgttccgttcc 1980

```

-continued

---

gtgaacacga ggtgcagtg ctttcgggtg acggagagag gctttctca cccggggagc 2040  
 ggcttcgcct tctacgcct ggactacatg cgacccttc tggacgtcg gactaatca 2100  
 acctggaaag tagaagtctgt ggctcacatc cgcccagccg cagacacagg cgtgtt 2160  
 ggcgtctggg ccccgacct ccgtgcgtg ctctctctg tggactgtt agactatcac 2220  
 tccacgaaga aactcaagaa gcacgtgtg gtctggccg tggagcatac ggccttgcc 2280  
 ctaatggaga tcaaggctcg cgacggccaa gacacgtgg tcaccgttc gctgaggggac 2340  
 ggtgaggcoca ccttgagggt ggacggcaco agggccaga gcgagggtgag cgccgcgcag 2400  
 ctgcaggaga ggctggccgt gctcgagagg cacctgcggg gccccgtgt caccttgc 2460  
 ggccgcgtgc cagatgtgcg ggtgactca cgccgttcta ccgcgttgc 2520  
 atgacactcg aggtaacccg gaggtgtcg gacctggacg aggccgcata caagcacac 2580  
 gacatcaccc cccactctcg ccccccgtg gagccgcgcg cagcccaagg atccgggt 2640  
 gactacaag accatgacgg tgattataaa gatcatgaca tcgactacaa ggtgacgat 2700  
 gacaagtga 2709

SEQ ID NO: 145 moltype = DNA length = 2145  
 FEATURE Location/Qualifiers  
 source 1..2145  
 mol\_type = other DNA  
 organism = synthetic construct

SEQUENCE: 145  
 atggccctt cgcttcgcg cggccgcgc gcccgtgc ggcgcgcga gctgtgtcg 60  
 ctgctgtcg ccggggagtg cgccgttgcg gacatcgaa tgactcaatc ttctagct 120  
 ctgagcgcct cgggtggaga tagactactt attacctgcg gacccggca atccatcagc 180  
 tcttatctaa attggatcca acagaagccc ggcaagcgc caaagctgt catctacgt 240  
 gcaagctct tacagacggg agtaccgg agattctcg gcaactggcag tggactgac 300  
 ttcacattga cggatgtc tctgcgtcg gaaacttgcg ccacatacta ttgtcagcag 360  
 agctatagca ccccggtac gtttggggd ggaactaagg tggaaatcaa gagaggaggc 420  
 gggggctccg cgggggggtgg ctgggggggaa ggaggctcg aggttcagct tgtegagct 480  
 gggggggggag tctgttgcgc aggttagaagg ctcaagactga gctgtgcgc aagtgggtt 540  
 gcttttcatt ttacggat gcaactgggtg agacagggtc ctggcaaaagg actcgagtgg 600  
 gtcgctgtaa tatggatcg tggatcaaa agataatataa ccgatgtgt gaaaggaaaga 660  
 ttcaccattt caccggacaa cgtaaaaat accttgtacc ttcaatgtaa caccctgaga 720  
 gcaagaagaca cagccgtgtc ctactgcgc agagatagag gtatcgagc aaggcgttgc 780  
 cccattttt tggatgtgtg ggggaaaggaa acaacagttca ctgtgagctc tggcgggggc 840  
 ggccggccgc gggggggcagc ccacatctg cctgtgcgtc ctttcagctg ggccaaaggt 900  
 gtaaaggctct tggacttggg ccggatgttc agtggggacc ccgtgtatccg actcggttc 960  
 aagaggctgc agccccaccag gctgttagct gagtttactt tccggaccct tgaccccgag 1020  
 ggatccctcc tctttggccg aggccaccag gacaggaccc ggatgtgtcg ggccttgaga 1080  
 gccggccggc tggagctca gctgcgtac aacgggtcg gccgtgtc ac cagccggc 1140  
 ccggcatca accatggcat tggcagaca atctctgttgg agaggctggc gccgaatctg 1200  
 gtcatcaagg tcaacaggga tgcgtgtcatg aaaatcgccg tggccgggggaa cttgttccaa 1260  
 ccggggccgg gactgtatca tctgcgtcc accgtggggag gtatccctt ccatgagaag 1320  
 gacccgtcgac agccctaaa ccctcggtcg gatggatcgca tgaggactg gaactggctg 1380  
 aacggggaaag acaccacccat ccaggaaacg gtgaaatgtg acacggatg gcaactggctc 1440  
 tcgggtacgg agagaggctc ttcttacccc gggagccgtc tgccttcata cagccgtggac 1500  
 tacatcgccg ccccttggaa cgtggggat gaaatcaactt gggaaatgaa agtgcgtggct 1560  
 cacatccgcg cccggcaga ccacgggtg ctgttgcgc tctggccccc cgacccctcg 1620  
 gccgtgcctc tctctgtgc actgttagac tatactccca cgaagaaact caaaggccag 1680  
 ctgggtgtcc tggccgtggaa gcatcgcc tttggccctaa tggagatcaa ggtctgcgac 1740  
 ggccaaggagg acgtgtgtcg cgtgtgtcg aggacgggtc aggccaccc ggagggtggac 1800  
 ggccaccaggc gggaggccg ggtggggcc ggcggccgtc aggaggatg ggccgtgtc 1860  
 gagaggccac tggccggccccc cgtgttccccc gctggccaga tggccgggtg 1920  
 acttcagccg cagtccaccgc ttcttaccgc ggtgtcatgaa cactggaggt caaccggagg 1980  
 ctgggtggacc tggacggaggc ggccgtacaag cacacgtccca tcaacggccca ctccctggccc 2040  
 cccgtggcgc cccggccgc ccaaggatcg acaaaaggatca tggccgtgt 2100  
 tataaaggatc atgacatcgatc tcaaaaggat gacgtgaca agtga 2145

SEQ ID NO: 146 moltype = DNA length = 2157  
 FEATURE Location/Qualifiers  
 source 1..2157  
 mol\_type = other DNA  
 organism = synthetic construct

SEQUENCE: 146  
 atggccctt cgcttcgcg cggccgcgc gcccgtgc ggcgcgcga gctgtgtcg 60  
 ctgctgtcg ccggggagtg cgccgttgcg cagggttcg tggatggagag cggaggcaat 120  
 ctgggttgcg ccgggtgttag tctgtgtcg tcttggcg gtcagggtt cactttcggt 180  
 agttttcaaa tgatgtgtgg ccgtcgaggta ccaggccgtg ggctggaaatg ggtggcagg 240  
 ctgtctgtcgac gtagctccctt gacccactt gcatgtatgg tttaaaggccg gttcaatatt 300  
 tcaacgcaca agcctaagaa tagctgtac ctgcataatgaa actccctgcg ggtcgaggat 360  
 acccgactgtt attactgcgc tcgcgttct tatgactcta gtggatactg gggccatattt 420  
 tataatgtaca tggatgtgtg gggacaggcc actctgtgtc ccgtttccgg aggccgtggg 480  
 tcggggccg gtggggatgg aggccgtggg tcaacgcgttgc tgacccaggcc gtccttcgtc 540  
 agccggccgcg caggccaggaa agtgcataatttctg gatgtacttcc aaacatccgc 600  
 aacaattatg tttctgtgttgc tcaacgcaca ccggccaaatg cgcccaatgt gatgttatt 660  
 gatgtgtctca aacgttcaag tggatgtgtcc gacccgttca ggggttccaa gtcgtggaaat 720  
 agtgcctcactc tggacatctc aggccgtccaa agcgttgcgtt gggccgtgttccgc 780  
 gctggggatgc acggccgttc cgaatttctg ttcggccaccg ggacaaatgt gacccgtgtc 840  
 ggccggccggg gggccggccgg cggccgtggc agccgttccgc gtcgtggcc 900  
 gtggccaaaga gtgtgaatgtc ttgttacccgtt gggccgtgttccgc 960

-continued

gcactgcgtc	tcaagaggct	gcageccacc	aggctggtag	ctgagttga	cttcggacc	1020
tttgaccccg	agggcatct	cctttgcc	ggaggccacc	aggacagcac	ctggatctgt	1080
ctggccctga	gagccggccg	gctggagctg	cagctggctg	acaacggct	ctggccgtgc	1140
accaggcagc	gccccgtcat	caaccatcg	atgtggcaga	caatctctgt	tgaggagctg	1200
gcgcggaaatc	tggtcatcaa	ggtcaaacagg	gatgtgtca	ttaaaatcg	ggtgccgggg	1260
gacttgttcc	aaccggagcg	aggactgtat	catctgaacc	tcacccgtggg	aggatattccc	1320
ttccatcgatg	aggacacctg	gcagectata	aaccctcgto	tggatggctg	tatgaggagcc	1380
ttggaaatggc	tgaaaggaga	agacacccac	atccaggaaa	ctggtaaaagt	gaacacgggg	1440
atgcagtgtc	tctcggtgac	ggagagagge	tctttctacc	ccgggaggegg	cttcgccttc	1500
taacagctgg	actacatgctg	gaccctctg	gacgtcgggg	ctgaatcaac	ctgggaagta	1560
gaagtgtgtt	ctcaatcccg	ccccacggcc	gacacaggcg	tgtgttttcg	gtctggggcc	1620
cccgacatcc	gtgcgcgtcc	tcttcgtgt	gcactgttag	atactatcc	caacggaaaa	1680
ctcaagaaggc	agctgggtt	cctggccgtg	gagcatacgg	ccttggccct	aatggagatc	1740
aaggcttcgc	acggccaaag	gcacggtgtc	accgtctcg	tgaggacgg	tgaggccacc	1800
ctggggatgt	acggccacca	ggggccagac	gggtgtggcg	ccgcgcacgt	gcaggagagg	1860
ctggccgtgc	tcgagaggcc	cctggggagg	ccctgtgtca	cttttgcggg	ccgcgtccca	1920
gatgtggccgg	tgacttcagc	gccagtcaacc	gcgttctacc	cgccgtcgtat	gacactggag	1980
gtcaacccgg	ggctgtgtga	cctggggagg	gcgggtacaa	agacacggca	catcacggcc	2040
cactctgtcc	ccccctgtga	gccccggcc	gccaaggat	ccccggctga	ctacaaagac	2100
catqacgggt	attataaaaq	tcatqacatc	gactacaagg	atqacatqa	caatgtqa	2157

```
SEQ ID NO: 148          moltype = DNA    length = 2190
FEATURE                  Location/Qualifiers
source                   1..2190
mol_type = other DNA
organism = synthetic construct
```

-continued

gagagtgtca cagagcagga cagcaaggac agcacctaca gcctcagcg caccctgacg 600  
ctgagcaaag cagactacga gaaacacaaa gtctacgcgt gcgaagtac ccatcaggcg 660  
ctgtctccgc ccgtcacaaa gagtttcaac agggggaggt gtgcgacaaaa acggcggaa 720  
ggagaggcga gaggaaatct tctaaccatg ggtgacgttg aggagaatcc cggccatctg 780  
ggctgttcct gcatcatctt gttctgtgc gcaaccgcga cccggcgagg tcaacctgtc 840  
gagtctgggg ggggagtcgt tcagccaggta agaagcctca gactgagctg tgccgcaagt 900  
gggtttgtct ttcatcttca cggatgtaccc tggtgtggagc aggttctggc caaaggact 960  
gagtgggtcg ctgtatataatg gttcgatgtg aaaaaaaatctt atataccga tagtgtgaaa 1020  
ggaagattca ccatttcacg agacaaacagt aaaaataccct tgtaacctca gatgaacacc 1080  
ctgagagcag aagacacacgc cgtgtactac tgccgcacag atagaggatg tggagcaagg 1140  
cgtaggttcctt attatatgtt gttgtgggg aaggggaaacaa cgtgtactgt gaggctgtc 1200  
tccaccaaaagg gccccatcggt cttcccccttgc gcacccctt ccaaggacac ctctggggcc 1260  
acagcgcccccc tggggctgcgt ggtcaaggac tacttcccccg aaccgggtgac ggtgtctgg 1320  
aactcaggcg ccctgaccatg cggcgctgcac accttcccccg ctgtctcttca gtcctcagg 1380  
ctctactccccc tcagcagcgt ggtgtactgtg cccttctatgeca gtttggccac ccgacactac 1440  
atctgcacacg tgaatcacaaa gccccacaaac accaaaggcttgg acaaaaggaaatg tgaccacaaa 1500  
tctatgegaca aaactcaccac aagccacccg tgcccaagcac ctgaaactctt ggggggaccc 1560  
tcagtttcctcc tttcccccccaaaaacccaaag gacacccctca tgatctcccg gacccttgcg 1620  
gtcaccatgcg tgggtgttggc cgtgagccac gaaaggccctg aggttcaaggat caactgtgtt 1680  
tgggacggccg tggagggttca taatgtccaa acaaaaggccg gggaggacca tgatcacacgc 1740  
acgttacccgtg tggtcagcgt cctcaccgtc ctgcaccagg actggctgaa tggcaaggag 1800  
tacaatgtca aggttcccaa caaaggccctc ccagccccca tggaaaaaaatcattccaaa 1860  
gccaaggccg agcccccggc accacaggatc tacacccttc cccatcccg ggatgagctg 1920  
accaaaacccg aggttacccgt gacccgtccgt gtcacccatgg tttatcccg cgacatccgc 1980  
gtggagtggg agagcaatgg gcacccggag aacaactaca agaccacccg tccctgtctg 2040  
gactcccgacg gctcttctt ccttacacgc aagctccacccg tggacaaagag cagttggcag 2100  
caggggaaatg ttttttcatgt cttccgtatg catggggctc tgcacaaacca ctacacccgc 2160  
aaqaqcttc ccccttccccc qqqqtaatqaa 2190

SEQ ID NO: 149 moltype = DNA length = 2118  
 FEATURE Location/Qualifiers  
 source 1..2118  
 mol\_type = other DNA  
 organism = synthetic construct  
 SEQUENCE: 149  
 atggccccctt cgctctcgcc cgggccccgc gcctcgccgc gcgcgcgcga gctgtctgtc 60  
 ctgtgtctgg ccgcggagggt cgcgttgc ggcgtttgc cggcgccgca ggccacgcag 120  
 ttccctggcc ccaggcagcg cgcgcgtt caggcttcg aggagggcca gcaggccac 180  
 ctggaggggg agtgcggttggaa ggagctgtgc agccgcgagg aggccgcggga ggtttcag 240  
 aacgaccggcc agacggat ttttttacca agatacttag actgcataca caaatatggg 300  
 ttcctgttaca caaaaaaactc agggcttcgc acctgtgtc aaaacatgc tgacggatgtc 360  
 acggccaaacc cctcgatag gaaggggccaa caagctgcg aggactcat gggcaacttc 420  
 ttctgttgtt gttaaagctgg ctgggggggc cggtctgcg acaaagatgt caacgaatgc 480  
 agccaggaggaa acggggggctg cttccagatc tgccacaaca agccgggtatg ctccactgt 540  
 tcttcacaca gggggcttcg gcttcctct gatggcaggatc cttgcagaatc catagacgag 600  
 tgcgcgacact cggaggccctg cggggaggcg cgctgcagaatc acctggcccg ctctactcc 660  
 tgccttgtgt acgagggttgc tgcgtacage tcccaggaga aggctgtgcg agatgtggac 720  
 gagttgttgc agggccgttgc tgagcagtc tgctgtacta ccccaaggaggatc acacttcgc 780  
 cacttgtgaccc gggccgttgc cttcaagatc tcccaggaca tggcacactgc tgaggacatc 840  
 ttccgttgcg tggcccttcgatc cttccatcgatc agtgtgttgcggttacttggccggatg 900  
 ttcagtggaa ccccggtatcc cggactgcgc ttcaaggaggc tgccggccac caggctgtta 960  
 gtcgttggttt acttcggac ctttgcaccc gaggccatc tccctttgc cggaggccac 1020  
 caggacacca ctttgatctg gtcggccctg agacccggcc ggttggatgtc gcatgtgcgc 1080  
 tacaacccgtt cttccgggttgc cttccatcgatc gggccgttca tcaacatcgatc catgtggcag 1140  
 acaatctctg ttgaggagatc ggcggggaaatc ctgttcatca aggtcaacacggatgtc 1200  
 atgaaaatctcg cgggtggccgg gggatgttgc caacccggac gaggactgtatc tcatgtgac 1260  
 ctggatgttgc gaggattttcc cttccatcgatc aaggacttcg tgccggccatc aaacctctgt 1320  
 ctggatgtgtc gcatggaggatc cttccatcgatc ctggccatgtc ctggccatc catccggaa 1380  
 acggtgaaatc tgaacacggatc gatgtgttc ttctcggttgc cggagagagg ctcttctac 1440  
 cccggccggatc gtttccgggttgc cttccatcgatc gactatcgatc ggccggccatc ggatgtgg 1500  
 actgtatcaatc cttccatcgatc agaaatcgatc gtcacatcc gcccggccgc agacacaggc 1560  
 tgctgttttgc cgtctgggc ccccgacttc cgtgcgttgc ctcttcgttgc ggcactgtta 1620  
 gactatcaatc ccacgaagaa actcaagaatc cagctggatgttgc tccctggccatc ggacgtatcg 1680  
 gctttggccatc taatggatgttgc caaggatcgttgc gacggccatc agacatgttgc caccgttgc 1740  
 ctggatgtgtc gttggggccatc cttccatcgatc gatgtgttgc gacggccatc gggccatc cggatgttgc 1800  
 ggcggccatc tggccggatc gttggatgttgc cttccatcgatc gacggccatc gggccatc cggatgttgc 1860  
 acctttgtgttgc gccggccatc agatgttgcgttgc gtcacttcgatc cggccatc cggatgttgc 1920  
 cggccatc tggccggatc gttggatgttgc cttccatcgatc gacggccatc gggccatc cggatgttgc 1980  
 aacggccatc acatccatcgatc ccacttcgttgc cccctggatgttgc agccggccatc agcccaatcg 2040  
 tccctggccatc actatcaatc cttccatcgatc gttggatgttgc cttccatcgatc gacggccatc 2100  
 gatgtatcgatc acaatcgatc gttggatgttgc cttccatcgatc gacggccatc gggccatc cggatgttgc 2118

```
SEQ ID NO: 150          moltype = AA  length = 961
FEATURE                Location/Qualifiers
source                 1..961
                       mol_type = protein
                       organism = synthetic construct
SIGNAL                1..30
SEQUENCE: 150
```

-continued

MAPSLSPGPA	ALRRAPQLLL	LLLAAECALA	DDVLTQTPLS	LPVTPGQPAS	ISCRSSQSIV	60
HNSGNTYLEW	YLQKPGQSPQ	LLIYKVSNRF	SGVPDRFSGS	GSGTDFTLKI	SRVEAEDVGV	120
YYCFQGLVP	WTFGQGTKVE	IKGGGGSGGG	GSGGGGSEVQ	LVESGGGLVQ	PGGSLRLSCA	180
ASGLIFRSYG	MSWVRQAPGK	GLEWVATINS	GGTYTYYPPDS	VKGRFTISRD	NSKNLTLQMQ	240
NSLRAEDTAV	YYCANSYSGA	MDYWGQGTLV	TVSSGGGGSG	GGGSIDLPCV	PFSVAKSVKS	300
LYLGRMFSGT	PVIRLRFKRL	QPTRLVAEFD	FRTFDPEGIL	LFAGGHQDST	WIVLALRAGR	360
LELQLRYNGV	GRVTSSGPVI	NHGMWQTISV	EELARNLVIK	VNRDAVMKIA	VAGDLFQPER	420
GLYHLNLNTVG	GIPFHEKDLV	QPINPRLDGC	MRSWNWLNGE	DTTIQETVKV	NTRMQCFSVT	480
ERGSFYPGSG	FAFYSLDYMP	TPLDVGTEST	WEVEVVVAHIR	PAADTGVLFA	LWAPDPLRAVP	540
LSVALVDYHS	TKKLKKLQLVV	LAVEHTALME	MEIKVCDGQE	HVTVTSLRDG	EATLEVGDGTR	600
GQSEVSAQQL	QERLAVLERL	LRSPVLTFA	GLPDVPTISA	PVTAFYRCM	TLEVNRLLD	660
LDEAAYKHSD	IAHSCPVE	PAAAGSGSGS	GSGSGSYPYD	VPDYAEGRGS	LLTCGDVEEN	720
PGFVSKGEEL	FTGVFSRILVE	LDGDNVNGHKF	SVSGEGEGDAA	TYGKLTLKFI	CTTGKLPVWP	780
PTLVTTILTYG	TCQFSRYPDH	MQHQDPPKSA	MPEGYVQBERT	IFFKDDGNYK	TRAEVKFEGD	840
TIVNRIELKG	IDFKEDGNIL	GHKLEYNNYS	HNVYIMADQK	KNGIKVNFKI	RHNIEDGSVQ	900
LADHYQQNTP	IGDGPVLLPD	NHYLSTQSL	SKDPNEKRDH	MVLLEFVTA	GITLGMDELY	960
K						961

SEQ ID NO: 151	moltype = DNA length = 2886					
FEATURE	Location/Qualifiers					
source	1..2886					
	mol_type = other DNA					
	organism = synthetic construct					
SEQUENCE: 151						
atggccctt	cgctctcgcc	cggccccccc	gccctgcgccc	ggcgccccca	gctgctgtcg	60
ctgctgtcg	ccgcggagt	cgcggttgc	gacgatgttat	taacacaaac	tccctatca	120
ttgccgttgc	cccgccggca	accaggcttc	atcagctccg	gtagcttca	gagcatcg	180
cacagcaacg	gtaataccta	cctggaatgg	tatttgc当地	aaccgggtca	atcccccgag	240
tttgttgcattt	ataaaatgttc	gaatcggttc	agcgggtgttc	cggtatcg	cagcggtct	300
gtgtccggca	cggatgttc	gtgttgc当地	agtgccgtgg	aaggccggga	ctgtgggtgtc	360
tactactgt	tttgcggtag	tttgcggcc	tggaccctttgc	gtcgggttac	taagggtggaa	420
attaagggtt	gtgggggatc	agggtggccgc	ggcagccggc	gtggccgggg	cgagggtacaa	480
ctagttgtat	cagggtggagg	gttgggttgc	ccagggtgtt	cgctgcgtc	gagttgtgc	540
gcaaggcggtt	tgatcttcgc	cagctgtgtt	atgagctgg	ttcgtcaggc	gcccggccaa	600
gggtctggagg	gggtggccgc	cattaaacttc	ggccggccact	acacactata	tcccgactcc	660
gtgaaaggccc	gttttccat	ctcccgccac	aatagcaaaa	acacccctgt	tttgcagatg	720
aactcgtcc	gcgcagagga	caccgcgtgt	tactactgcg	ccaattccca	cagcggtgtc	780
atggatttttgc	gggggttgcgg	cacatgttgc	actgttaaagg	ggccgggggg	ccgcagccgc	840
ggcggtggca	gcaacatctt	ggccgtcggt	cccttcaggg	tggccaaagag	tgtgaatgc	900
ttgttacccgg	gcccgtatgtt	cagtggggacc	cccggtatcc	gactgcgtt	caagaggctg	960
cageccacca	ggctgttgc	tgagtttgc	ttccggacct	ttgaccccg	gggcacatctc	1020
ctcttgcgcg	ggggccggcc	ggacggccac	tggatctgtc	tggccctgag	agccggccgg	1080
ctggaggtgc	agctgcgtca	caacgggtgc	ggccgtgtca	ccaggcgggg	cccggttac	1140
aaccatgcga	tgtggcagac	aatctctgtt	gaggagctgg	cgccggaaatct	ggtcatcaag	1200
gtcaacacggg	atgtgttcat	gaaaatcgcg	gtggccgggg	acttgc当地	accggagcga	1260
ggactgtatc	atctgc当地	gaccgtggga	ggtattccct	tccatgc当地	ggacccctgt	1320
cagectataaa	acccctgtct	ggatgggtt	atggaggatc	ggaaatgttgc	gaacggagaa	1380
gacaccacca	ttccaggaaac	gggttgc当地	aacacggagg	tgcagttgc	ctcggtgc	1440
gagagaggct	ttttctaccc	cgggagccgg	ttcgc当地	acagctgg	ctacatgcgg	1500
accctctgg	acgtcgccgg	tgaatcaac	tggaaatgttgc	aagtctgtgc	tcacatccgc	1560
ccagccgc当地	acacaggcg	gttgc当地	ccatgc当地	ccatgc当地	ccatgc当地	1620
cttctctgtgg	cactgttgc	ctatcacttc	acaaaggaaa	tcaaggaa	gtctgggtgc	1680
ctggccgtgg	agcatacgcc	cttggccata	atggagatca	aggctgtc	cgcccaagag	1740
cacgtgttca	ccgttgc当地	gaggccatgt	gaggccatcc	tggagggtgg	ccgc当地	1800
ggccgacaggg	agggtggccgc	cgccgc当地	caggaggac	tggccgtgt	cgaggaggac	1860
cttgc当地	ccgtgttca	cttgc当地	ggccgtccac	atgtggccgt	gacttc当地	1920
ccagtc当地	cggttctacc	cggttgc当地	acactggagg	tcaaccggag	gtctgtggac	1980
ctggacggcc	acgttaaacgg	cccaaaatgc	acgcgtgtcc	ggggggccga	ggggccatgt	2040
acctacggca	agctgc当地	gaagggttcat	tgc当地	accatgttgc	cccccgtgg	2100
cccaaccctcg	tggaccatct	gaccatcgcc	gtgc当地	tcaggccgtca	ccccggaccac	2160
atgaaggcgc	acgacttctt	caagtc当地	atgccc当地	gtacatgtca	ggaggccacc	2240
atcttcttca	aggacgacgg	caactacaag	accggccccc	aggtaaggat	cgaggccgac	2520
accctgttgc	accgc当地	gctgttgc当地	atgc当地	tttgc当地	tttgc当地	2580
gggcacaaggc	ttgggttcaaa	ctacaacgc	cacaacgtt	atatcatgc	ccgacaaggc	2640
aagaacggca	tcaagggttca	cttcaaggatc	cgcccaacaa	tccaggaggcc	cagctgtc	2700
ctggccgacc	actaccaggca	gaacacccc	atcgccgac	ggccccc当地	gtctgtggac	2760
aaccactacc	tgagcacc	gtccgc当地	agcaaaaggacc	ccaacggagaa	gccc当地	2820
atgttctgc	ttgggttgc	gaccgc当地	gggatcttc	tcggcatgga	cgagctgtac	2880
aagtaa						2886

SEQ ID NO: 152	moltype = AA length = 953
FEATURE	Location/Qualifiers
source	1..953
	mol_type = protein
	organism = synthetic construct

-continued

---

SIGNAL	1..30
SEQUENCE: 152	
MAPSLSPGPA ALRRAPQLL LLLAAECALA SYELTQPPSV SVSPGQTARI TCSGEALPMQ	60
FAHWYQQRPG KAPVIVVYKD SERPSGVPER FSGSSSGTTA TLITITGVQAE DEADYYCQSP	120
DSTNTYEVFG CGTKLTVLGG GGSGGGSGG GGEVQLVES GGGLVPEPGS LRLSCAVSGF	180
DFEKAWMSWV RQAPGQGLQW VARIKSTADG GTTSYAAPR GRFIISRDDS RNMLYLQMNS	240
LKTEDTAVYY CTSAHWGQGT LVTVSSGGG SGGGSDILP CVPFSVAKSV KSLYLGRMFS	300
GTPVIRLRFK RLQPTRLVAE FDFRTFDPEG ILLFAGGHQD STWIVLALRA GRLELQLRYN	360
GVGRVTSSG VVINHGMWQTT SVEELARNLV IKVNNDAMV TAVAGDLFQP ERGLYHLNL	420
VGGIPFHEKD NQQPINPRLD GCMRSWNWLN GEDTTIQETV KVNRDQCFES VTERGSFYPG	480
SGFAFYSLDY MRTPLDVGTE STWEVEVVAH IRPAADTGVF FALWAPDLRA VPLSVALVDY	540
HSTKKLKQQL VVLAVENTAL ALMEIKVCDG QEHVVTVSLR DGEATLEVVG TRGQSEVSAA	600
QLQERLAVL RHLRSPVLTE AGGLPDPVT SAPVTAFYRG CMTLEVNRLL LDLDEAAYKH	660
SDITAHCSPP VEPAAAEGSGS GSGSGSGSYPT YDVPDYAECR GSLLTCGDVE ENPGPVSKGE	720
ELFTGVVPL VELDGDVNGH KFVSVGELEG DATYGKLTLK FICTTGKLPV PWPTLVTLT	780
YGVQCFSRYP DHMKQHDFFK SAMPEGYVQE RTIFFKDDGN YKTRAEVKFE GDTLVNRIEL	840
KGIDFKEDGN ILGHKLEYNN NSHNVYIMAD KQKNGIKVNF KIRHNIEDGS VQLADHYQQN	900
TPIGDGPVLL PDNHYLSTQS ALSKDPNEKR DHMVLLFVT AAGITLGMDE LYK	953
SEQ ID NO: 153	moltype = DNA length = 2862
FEATURE	Location/Qualifiers
source	1..2862
	mol_type = other DNA
	organism = synthetic construct
SEQUENCE: 153	
atggccccctt cgcttcgcgc cggggccgcg gcccgtcgcc ggcgcgcgca gctgtgtctg	60
ctgctgtctgg cccgcggagtg cgcgcgttgcg tccatgtacg tgactcagcc accctcggtg	120
tcagtgccccc caggacagac ggccaggatc acctgtctg gagaaggcatt gccaatgca	180
tttgtcattt ggttaccaaca gaggccggc aaggccccca gttatgtgtt gtacaaagac	240
agtggagagac cgttcggatc ccctggcgatc ttctctggct ccaggcggcgg gacaacagcc	300
acgttgcattt ctaactggatc ccaggcggatc gatggggctg actattactg ccagtccgca	360
gacagcacta acactttatga agtcttcggc ggagggaccg agctgacccgt ccttagtgg	420
ggggggatccatc gtggccggcg cagccggcggt ggccggggccg aggtgcacgt ggtggaggt	480
ggggggggatccatc ttgttcggatc ggggggggtt ctaagactct cttgtgcacgt ctccggattc	540
gatttcggaaa aagccgttatc gatggggccg cggccggctc caggccgggg gctacagtgg	600
gttgcggatc tcaagagcac agctgtatgtt gggacaacaa gctacgcgcg ccccccgtggaa	660
ggcaggatc tcatctcaag agatgatttcg agaaacatgc ttatctgcg aatgaacagt	720
ctgaaactatc aagacacacgc cgttcttattatc ttgtacatcgcc cccacttggg ccaggaaacc	780
ctgggtcaccgc ttcctccggg cggggggccgc atggccggcg gtggcggccg catttggcc	840
tgcgtgcgcct tcagcgatcgc caagatgtgtt aatctggccg gatgttcagt	900
ggggccccccg tgatccgact ggcgttcaag aggctgcggc ccaccaggct ggttagctgg	960
tttgatcttc ggacccatgc ccccccggggg atctcccttc ttgcggggg ccaccaggac	1020
agcaccatgcg ttcgtgtccgc ccttagatcgcc ggcggccgttggcggccg agtgcacgt ggcgttacaa	1080
gggtgtccgcg gtgttaccatc cggccggccg gtcataacc atggcatgtg gcagacaatc	1140
tctgttgggg agctggccgcg gaatctggccg atcaaggatca acagggatgc tgcgtatggaa	1200
atccgggtgg cccggggactt gttcccaaccg gaggccggatc tgcgtatcatc gaaacctgacc	1260
gtggggggatca ttccttcataa tgagaaggac ctgcgtccgcgcttccatccatc tgcgttggat	1320
gggtgtccgcg ggagatggaa ctgggttgcacccatc ggagaagacca ccaccatccca ggaaacgggt	1380
aaagtgaaca cggatgtca gttgttctcg gtgcggatcc gaggctttt ctaccctggg	1440
agccggatccgc ctttccatcg cttgtggactatc atggccggacc ctctggacgtt cggggactgaa	1500
tcaacccatgcg aagtagaaatc cttgtggatc atccggccgcg ccggccggatc aggccgtctg	1560
tttgcgtcttccatccatc gttgttccatc ttgtggactt ctgtggactt ggttagactat	1620
cactccacgcg aaagaaactcaa gaaggccggatc gtggccatcg ccgtggatcc tacggccctt	1680
gccttaatgg agatcaatgg ctggccatcg ccggccatcg ccggccatcg tggccatcg tgcgttgg	1740
gacggatccgc cccatccatcg cttgtggatcc atggccggacc ccggccatcg tggccatcg	1800
caatccatgcg aagggatccgc cttgtggatcc atccggccgcg ccggccatcg gggcccccgt gtcacccatc	1860
gttggccgcg tggccatcg tggccatcg tggccatcg tggccatcg tggccatcg tggccatcg	1920
tgcgtatcgatcg tggccatcg tggccatcg tggccatcg tggccatcg tggccatcg tggccatcg	1980
agccggatccgc cccatccatcg tggccatcg tggccatcg tggccatcg tggccatcg tggccatcg	2040
ggcggccgcg gggccatcg tggccatcg tggccatcg tggccatcg tggccatcg tggccatcg	2100
ggaagtctgc taacatgcgg tgacgtcgatcg gagaatcttcgatcg gcccggatcg gacggccatcg	2160
gacgtgttca cccggggatcg tggccatcg tggccatcg tggccatcg tggccatcg tggccatcg	2220
aagttcggatcg tggccatcg tggccatcg tggccatcg tggccatcg tggccatcg tggccatcg	2280
tttcatctgcgca cccatccatcg tggccatcg tggccatcg tggccatcg tggccatcg tggccatcg	2340
tacggccatcg agtgcgttccatcg ccgttccatcg gaccatcgatcg agcggccatcg tttcttcataa	2400
tccggccatcg ccggatccatcg cttgtggatcc atccggccatcg tggccatcg tggccatcg tggccatcg	2460
tacaaggatccgc gggccatcgatcg tggccatcg tggccatcg tggccatcg tggccatcg tggccatcg	2520
aaggccatcgatcg acttcaatcgatcg tggccatcg tggccatcg tggccatcg tggccatcg tggccatcg	2580
aacaggccatcgatcg tggccatcg tggccatcg tggccatcg tggccatcg tggccatcg tggccatcg	2640
aagatccgcg acaacatcgatcg tggccatcg tggccatcg tggccatcg tggccatcg tggccatcg	2700
acccccattcgatcg tggccatcg tggccatcg tggccatcg tggccatcg tggccatcg tggccatcg	2760
gccctggatcgatcg aagccatcgatcg tggccatcg tggccatcg tggccatcg tggccatcg tggccatcg	2820
ggccggatcgatcg tggccatcg tggccatcg tggccatcg tggccatcg tggccatcg tggccatcg	2882
SEQ ID NO: 154	moltype = AA length = 701
FEATURE	Location/Qualifiers
source	1..701
	mol_type = protein
	organism = synthetic construct

-continued

---

SIGNAL 1..24  
 SEQUENCE: 154  
 MRVLGGRCGA LLACLLLVP VSEADIQMTO SPSSLSASVG DRVTITCRAS QSISSYLNWY 60  
 QQKPGKAPKL LIYAASSLQS GPVPSRSGSG SGTDFTLTIS SLQPEDFATY YCQQSYSTPL 120  
 TFGGGTKEI KRGGGGSGGG GSFGGGSEVQ LVESSGGVVQ PGRSRLRSCA ASGFAFSSYG 180  
 MHWVRQAPGK GLEWWAVIWF DGTKKYYTDS VKGRFTISRD NSKNTLYLQM NTLRAEDTAV 240  
 YYCARDRGIG ARRGPYYMDV WGKTTTVTS SGGGGSGGG SVSVCLPLN LDTKYELLYL 300  
 AEQFAGVVLY LKFRLPEISR FSAEFDERTY DSEGVIYAE SIDHSAWLLI ALRGKIEVQ 360  
 LINNEHTSKIT TGGDVINNGL WNMVSVEELE HSISIKIAKE AVMDINKPGP LFKPENGLLE 420  
 TKVYFAGFPR KVESELKPI NPLRDQGPR WNLMKQGASG IKEIIQEKGQ KHCLVTEVKG 480  
 SYYPGSGIAQ PHIDYNNVSS AEGWHVNVTL NIRPSTGTGV MLALVSGNNT VPFAVSLVDS 540  
 TSEKSQDILL SVENTVIYRI QALSLCSDQQ SHLEFRVNRN NLELSTPLKI ETISHEDLQR 600  
 QLAVALDKAMK AKVATYLGGL PDVPFSAATPV NAFYNGCMEV NINGVQLDD EAISKHNDIR 660  
 AHSCPSPWKK TNNSQGSRAD YKDHDGDKD HDIDYKDDDD K 701

SEQ ID NO: 155 moltype = DNA length = 2106  
 FEATURE Location/Qualifiers  
 source 1..2106  
 mol\_type = other DNA  
 organism = synthetic construct  
 SEQUENCE: 155  
 atgaggggtcc tgggtggcg ctggggggc ctgtggcgct gtctccctct agtgtttccc 60  
 gtctcaggagg cagacattca gatgactaa ttccttagct ctctgaggcgc ctcccttgga 120  
 gatagagtca ctattacctg cagagccago caatccatca gctttatct aaattggtag 180  
 caacagaaacg cccggaaacgc gccaaagctg ctcatctacg ctgcaagctc cttacagagc 240  
 ggagtaccca cgcgattctc aggcaactggc agtgggactg acttcacatt gacgatttgc 300  
 ttctctgcgc ctgaagactt tgccacatac tatttgtcgc agagctatac caccggctg 360  
 acgtttggag gcggaactaa ggtggaaatc aagagaggag gggggggcgc cgggggggt 420  
 gggtctggggg gaggaggcgc agagggtcag ctgttcgcgt ctgggggggg agtcttcag 480  
 ccaggtagaa gctctcagaact gactgtgcgc gcaagttggc ttgtcttttc atcttacgg 540  
 atgcactggg tgagacggc tcctggcaaa ggactcgcgt ggttcgcgtgt aatatggttc 600  
 gatggtacaca aaaaatacta taccatgtt gtaaaaggaa gattcacat ttccacggac 660  
 aacagaaaaaa atacccgttgc ccttccatgtt aacaccctgtc gaggcagaaga cacaggctg 720  
 tactactcgcc cccggatgtt ggttgcgtt gttttttttt tatggatgtg 780  
 tggggggaaagg gaacaacatc gactgtgcgc tctggggggg gggcggcggc cggcggggc 840  
 agcgttgtttt cagttgtgcct tcccttgcac ctggacacaa agtataattt actttacttg 900  
 gcgaggcagt ttgcagggtt tggtttat taaaatttc gtttgcaga aatcggcaga 960  
 tttcacggc aattttgttcc cccggatcat gttttttttt gtttgcgtat gtacccggaa 1020  
 tctatcgtcgtt gttttttttt gttttttttt gttttttttt gttttttttt taaaccgtt 1080  
 ctttccatgtt aacccatcatac cccggatcatc gttttttttt gttttttttt taaaccgtt 1140  
 tggaaatattt gttttttttt gttttttttt gttttttttt gttttttttt gttttttttt 1200  
 gctgtgtatgg atataatataa accttgcggcc cttttttttt gttttttttt gttttttttt 1260  
 accaaatgttcc aattttgttcc cccggatcat gttttttttt gttttttttt gttttttttt 1320  
 aaccctcgcc tttttttttt gttttttttt gttttttttt gttttttttt gttttttttt 1380  
 ataaaggaaa ttatttcaaga aaaaacaaaat aacccatgttcc gttttttttt gttttttttt 1440  
 tccctactatc tttttttttt gttttttttt gttttttttt gttttttttt gttttttttt 1500  
 gctgggggtt ggtttttttt gttttttttt gttttttttt gttttttttt gttttttttt 1560  
 atgtttttttt gttttttttt gttttttttt gttttttttt gttttttttt gttttttttt 1620  
 acctctgtttt aatccatgttcc tttttttttt gttttttttt gttttttttt gttttttttt 1680  
 caggccctaa gttttttttt gttttttttt gttttttttt gttttttttt gttttttttt 1740  
 aatcttggat gttttttttt gttttttttt gttttttttt gttttttttt gttttttttt 1800  
 caacttgcgc tttttttttt gttttttttt gttttttttt gttttttttt gttttttttt 1860  
 ccagatgttc tttttttttt gttttttttt gttttttttt gttttttttt gttttttttt 1920  
 aatattttttt gttttttttt gttttttttt gttttttttt gttttttttt gttttttttt 1980  
 gcttactcat gttttttttt gttttttttt gttttttttt gttttttttt gttttttttt 2040  
 tacaaggacc atgacgggtt gttttttttt gttttttttt gttttttttt gttttttttt 2100  
 aagtga 2106

SEQ ID NO: 156 moltype = AA length = 684  
 FEATURE Location/Qualifiers  
 source 1..684  
 mol\_type = protein  
 organism = synthetic construct  
 SIGNAL 1..21  
 SEQUENCE: 156  
 METDTLLLWV LLLWVPGSTG DEVQLVESGG GVQPGRSLR LSCAAASGF AF SSYGMHWVRQ 60  
 APGKGLEWA VIWFDFGKTY YTDSVKGRT ISRDNNSKNTL YLQMNNTLRAE DTAVYYCARD 120  
 RGIGARRGPY SWNWLNGEDT TIQETVKVNT RMQCFSVTER GSFYPGSGFA FYSLDYMRTP 180  
 PVTVWSNSGA LTSGVHTFPV VLQSSGLYSL SSVVTPSSS LGTQTYICNV NHKPSNTKVD 240  
 KKVPEPKSCDK THGGGGSGGG GSDILPCVPF SVAKSVKSLY LGRMFSGTPV IRLRFKRLQP 300  
 TRLVAEFDTR TFDPEGILLF AGGHQDSTWI VLALRAGRLE LQLRYNGVGR VTSSGPVINH 360  
 GMWQTISVEE LARNLVIKVN RDAVMKIAVA GDLFQPERGL YHNLNTVGGI PFHEKDLVQP 420  
 INPRLDGCML SWNWLNGEDT TIQETVKVNT RMQCFSVTER GSFYPGSGFA FYSLDYMRTP 480  
 LDVGTESTWE VEVVAHIRPA ADTGVLFALW APDLRAVPLS VALVDYHSTK KLKKQLVVL 540  
 VEHTALALME IKVCDGQEHV TVVSLRDGEA TLEVDGTRQG SEVSAAQLE RLAVLERHL 600  
 SPVLTTFAGGL PDVPPVTSAPV TAFYRCMML EVNRRLLDID EAAYKHSIDT AHSCPVEPA 660  
 AAADYKDHDGD YKDHDIDYKD DDDK 684

SEQ ID NO: 157 moltype = DNA length = 2055

-continued

FEATURE source	Location/Qualifiers
	1..2055
	mol_type = other DNA
	organism = synthetic construct
SEQUENCE: 157	
atggagacag acacactcct gctatggta ctgctgtct gggttccagg ttccactgg 60	
gacgagggtc agcttgtcga gtctgggggg ggagtcgttc agccaggtag aagcctcaga 120	
ctgagctgtg ccgcgaagtgg gtttgccttt tcatcttacg gtatgcactg ggtgagacag 180	
gctcctggca aaggactcga gtgggtcgct gtaatatggt tcatgtgtac aaagaaatac 240	
tataccgata gtgtgaaagg aagattcacc atttcacgag acaacagtaa aaataccttg 300	
taccttcaga tgaacaccct gagacgagaa gacacagccg tgtactactg cgccagagat 360	
agaggtatcg gagcaaggcg tggtccctat tataatggat tggggggaa gggacaaca 420	
gtgactgtga gtcgtgcctc cacaaggggc ccatcggtct tccccctggc acccccttcc 480	
aagaggacactt tggggggcac agccggccctg ggtgtcgctg tcaaggacta cttcccgaa 540	
cgggtgacgg tgcgtggaa ctcaaggccc ctgaccaggccg gcgtgcacac cttcccggt 600	
gtcctacagt ctcaggact ctactccctc agcagcgtgg tgactgtgcc ctctagcagc 660	
ttggggcaccc agacccatcat ctgcacacgg aatcacaacg ccagcaaac acagggtggac 720	
aagaaaatgg agcccaatc tggtgacaaa actcacggcg gagggtggaa cggaggccgt 780	
ggaaggacaca tcttgcgtg cgtccctc agcggtggca agagtgtgaa qtccctgtac 840	
ctggggccgga tgttcagtgg gacccctgtg atccgactgc gttcaagag gtcgagccc 900	
accaggctgg tagctgagggt tgacttcegg acctttgacc cccggggcat cctctcttt 960	
gccccggggc accaggacag cacctggatc gtgtcgccct tgagagccg cccggctggag 1020	
ctgcagctgc gtcataacacgg tgcgtggcg tgcaccaggca gggcccccgt catcaacat 1080	
ggcatgtggc agacaatctc tggtgaggag ctggcgccgaa atctggatc caaggtaac 1140	
agggtatgtc tcataaaaat cgggtggcc ggggacttgt tccaaacggg gcgaggactg 1200	
tatcatgtga accttcacggt gggggatgtt cccttcatc agaaggact cgtgtcgccct 1260	
ataaaccctc gtctggatgg ctgtatgggg agtggaaactt ggtgtggccg agaaagacacc 1320	
accatccagg aaacgggtgaa agtgaacacgg aggtatgcactg gtttctcggt gacggagaga 1380	
ggtcttctt accccggggag cgggttcgc ttcacagccg tggactacat ggggaccct 1440	
ctggacgtcg ggactgaataa aacctggggaa gtgaaggatcg tggctcacat ccggccacggc 1500	
gcagacacag gctgtgtt tgcgtgttgg gccccccggc tccgtggccgt gcctctct 1560	
gttgcactgg tagactatca ctccacgaaag aaactcaaga agcagctgg tggctggcc 1620	
gtggagcatc cggccctggc ctaatgggg atcaagggtt ggcacggcca agagcacgtg 1680	
gtcaccgtct cgcgtggggg cgggtggggcc accctggggg tggacggccac caggggccag 1740	
aggcgaggatc ggcggccgcg cgtcgaggag aggctggccg tgcgtcgagag gacactcgcc 1800	
agccccctgc tcaccttgc cggccgttgc ccagatgtc cgggtgacttc agcggcagtc 1860	
accgcgttct accgcggctg catgacactg gaggtcaacc ggaggctgtt ggacctggac 1920	
gaggccggctg acaagcacag cgacatcagc gcccactctt gccccccctg ggagccggcc 1980	
gcagccgact acaaagacca tgacgggtat tataaagatc atgacatcga ctacaaggat 2040	
gacgatgaca agtga 2055	
SEQ ID NO: 158	moltype = AA length = 907
FEATURE source	Location/Qualifiers
	1..907
	mol_type = protein
	organism = synthetic construct
SIGNAL	1..21
SEQUENCE: 158	
METDTLLLWV LLLWVPGSTG DEVQLVESGG GVVQPGRLR LSCAASGFAF SSYGMHWVRQ 60	
APGKGLEWVA VIWFDFGTKY YTDSVKGRT ISRDNSKNTL YLQMNTLRAE DTAVYVCARD 120	
RGIGARRGPY YMDVWGKGTT VTVSSASTKG PSVFPPLAPS KSTSGGTAAL GCLVKDVFPE 180	
PVTVSWNSGA LTSGVHTFPV VLQSSGLYSL SSVVTVPSSS LGTQTYICNV NHKPSNTKV 240	
KKVEPKSCDK THTCPCCPAP ELLGGGPSVFL FPPPKPKDTLM ISRTPEVTCV VVDVSCHEDPE 300	
VKEPNWYDVGV EVHNAKTKPVE EEQYNSTYRV VSVLTVLHQD WLNGKEYKCK VSNKALPAPI 360	
EKTISKAKQ PREPVQYTLR PSRDELTKNQ VSLTCLVKGF YPSDIAVEWE SNGQPENNYK 420	
TTPPVLDSDG SFFLYSKLTV DKSRRQQGNV FSCSVMHEAL NHYHDTQKSLN LSPGKGGGS 480	
GGGGSDILPC VPFSVAKSVK SLYLGRMFSG TPVIRLRFK LQPTRLVAEF DFRTFDPEGI 540	
LIFAGGHQDS TWIVLALRAG RLELQLRYNG VGRVTSSGPV INHGMQQTIS VEELARNLVI 600	
KVNRDAVMKI AVAGDLFQPE RGLYHNLNTV GGIPFHEKDL VQPINPRLDG CMRSWNWLNG 660	
EDTTIQETVK VNTRMQCFSV TERGSFYPGGS GFAFYSLDYM RTPLDVGTES TWEVVAHI 720	
RPAADTGVLF ALWAPDLRAV PLSVALVDYH STKLLKKQLV VLAVEHTALA LMEIKVCDGQ 780	
EHVVTVSLRD GEATLEVVDGT RGQSEVSAQ LQERLAVLER HLRSPVLTFA GGLPDVPTVS 840	
APVTAFYRG C MTLEVNRLL DLDEAAYKHS DITAHCSPPV EPAAADYKDH DGDYKDHDID 900	
YKDDDDK 907	
SEQ ID NO: 159	moltype = DNA length = 2724
FEATURE source	Location/Qualifiers
	1..2724
	mol_type = other DNA
	organism = synthetic construct
SEQUENCE: 159	
atggagacag acacactcct gctatggta ctgctgtct gggttccagg ttccactgg 60	
gacgagggtc agcttgtcga gtctgggggg ggagtcgttc agccaggtag aagcctcaga 120	
ctgagctgtg ccgcgaagtgg gtttgccttt tcatcttacg gtatgcactg ggtgagacag 180	
gctcctggca aaggactcga gtgggtcgct gtaatatggt tcatgtgtac aaagaaatac 240	
tataccgata gtgtgaaagg aagattcacc atttcacgag acaacagtaa aaataccttg 300	
taccttcaga tgaacaccct gagacgagaa gacacagccg tgtactactg cgccagagat 360	
agaggtatcg gagcaaggcg tggtccctat tataatggat tggggggaa gggacaaca 420	
gtgactgtga gtcgtgcctc cacaaggccc ccatcggtct tccccctggc acccccttcc 480	

-continued

aagagcacct	ctgggggcac	agcggccctg	ggctgcctgg	tcaaggacta	cttccccgaa	540
ccggtgacgg	tgtcgtaaa	ctcaggcgcc	ctgaccagcg	cgctgcacac	cttcccgct	600
gtcctacagt	cctcaggact	ctactccctc	agcagcgtgg	tgactgtgcc	ctctagcagc	660
ttgggcaccc	agacctacat	ctgcaacgtg	aatcacaagc	ccagcaacac	caaggctggac	720
aagaaaagtg	agcccaaata	ttgtgacaaa	actcacacat	gcccacccgt	cccacccact	780
gaactccctgg	ggggaccgtc	agtttcctc	ttccccccaa	aacccaaga	caccctcatg	840
atctcccgga	cccctgaggt	cacatgcgtg	gttgtggacg	tgagccacga	agacccttag	900
gtcaagtta	actggtagt	ggacggcggt	gagggtgcata	atgccaagac	aaagccgcgg	960
gaggagcagt	acaacagcgt	gtacggctgg	gtcagcgtcc	tcacccgtc	gcaccaggac	1020
tggctgaatg	tcaaggatg	caagtcaag	gtctccaa	aagccctccc	agccccatc	1080
gagaaaaacc	tctccaaagc	caaaggccag	ccccgagaac	cacagggtga	caccctggcc	1140
catecccggy	atgagctgac	caagaaccag	gtcagcgtg	cctgcgtgt	caaaggcttc	1200
tatcccacgg	acatecccgct	ggatgggag	agcaatgggc	agccggagaa	caactacaag	1260
accacgcctc	cctgtgttga	ctccacggc	tccttcttc	tctacagca	gctaccctgt	1320
gacaagagca	ggtggcagca	ggggaaacgtc	ttctcatgtc	ccgtgtatc	tgaggctctg	1380
cacaaccact	acacgcagaa	gacectctcc	ctgtccccgg	gtaaaggccg	aggtggaaagc	1440
ggaggccgtg	gaagcgtatg	cttgcgtgt	gtgccttc	gctgtggccaa	gagtgtgaag	1500
tccttgcgtt	ttggccggat	gttcgtgtt	accccccgtg	tecgactcg	cttcagagg	1560
ctgcagccca	ccaggctgtt	agctgagtt	gacttccgg	cctttgaccc	cgaggccatc	1620
ctctcttttgc	ccggaggccca	ccaggacago	acctggatcg	tgctggccct	gagagccg	1680
cggtctggagc	tgcagctgtcg	cttacacccgt	gtcggccctg	tcaccacgag	cgccccggtc	1740
atcaaccatc	gcatgtggc	gacaatcttca	gttgcgtgt	tcttgcgtt	tttgcgtatc	1800
aaggtaaca	gggtatgtt	catggaaatc	gctgtggcc	ggacttgg	ccaaccggag	1860
cgaggactgt	atcatctgaa	ccttcacccgt	ggaggtattt	ccttccatga	gaaggacttc	1920
gtgcagccca	taaacccctcg	tctggatgg	tgatgagga	gtgtggactg	gtgtggactg	1980
gaagagacca	ccatccaggaa	aacgtgttga	gtgaacacg	ggatgcgtg	tttgcgtgt	2040
acggagagag	gtctttctca	ccccccggag	ggtttcgcct	tctacagct	ggactacatc	2100
cgaccacccctc	tggacgtcg	gactgaatca	acctggaaag	tagaagtctg	gtgtcacatc	2160
cgtccacggc	cagacacagg	cgtgtgtt	ggctctgtgg	ccccccact	ccgtgcgtgt	2220
cctctctctgt	ttggcaactgtt	agactatac	tccacgaaga	aactcaagaa	gcagctgtgt	2280
gtccttgcgtt	ttggagccat	ggcccttggcc	ctaattggaa	tcaaggctcg	cgacggccaa	2340
gagcacgtgg	tcacccgtctc	gctgagggac	ggtgaggcc	ccctggaggt	ggacggccacc	2400
agggggccaga	ycgaggtgtag	cgccgcgcag	ctgcaggaga	ggctggccgt	gtctcgaggg	2460
cacctcggtt	gccccgtgt	cacccgttcc	ggccgcgttcc	cagatgttcc	gtgtacttca	2520
gcgcgcgttca	ccgcgttctc	ccgcgcgtt	atgacatgg	aggtaacccg	gaggctgtgt	2580
gacactggacg	aggccggcgta	caagcacago	gacatcacgg	cccactctg	ccccccctgt	2640
gagcccgccg	cagccgacta	caaagaccat	gacgggtattt	ataaaagatca	tgacatcgac	2700
tacaaggatg	acgtatgacaa	gtga				2724

SEQ ID NO: 160            moltype = AA   length = 5  
 FEATURE                    Location/Qualifiers  
 source                    1..5  
 mol\_type = protein  
 organism = synthetic construct

SEQUENCE: 160  
 GGGGS

5

SEQ ID NO: 161            moltype = AA   length = 232  
 FEATURE                    Location/Qualifiers  
 source                    1..232  
 mol\_type = protein  
 organism = synthetic construct  
 SIGNAL                    1..16  
 SEQUENCE: 161  
 MGWSCIILFL VATATGDIQM TQSPSSLSAS VGDRVTITCR ASQSISSYLN WYQQKPGKAP 60  
 KLLIYAASSL QSGVPSRFSG SGSGTDFLT ISSLQPEDFA TYYCQOQSYST PLTFGGTKV 120  
 EIKRKRVAAS PSVFIFPPSD EQLKSGTAVS VCLNNFYPR EAKVQWKVDN ALQSGNSQES 180  
 VTEQDSKDST YSLSSTLTLK KADYEKHKV ACEVTHQGLS SPVTKSFNRG EC 232

SEQ ID NO: 162            moltype = AA   length = 914  
 FEATURE                    Location/Qualifiers  
 source                    1..914  
 mol\_type = protein  
 organism = synthetic construct  
 SIGNAL                    1..21  
 SEQUENCE: 162  
 MDTDTLLWW LLLWVPGSTG DDIQMTQSPS SLSASVGDRV TITCRASQSI SSYLNWYQQK 60  
 PGKAPKLLIY AASSLQSGVP SRFGSGSGT DFTLTISLQ PEDFATYYCQ QSYSTPLTGF 120  
 GGTKVEIKGG CGSGGGGGSGG GGSEVQLVES GGGVVQPGRS LRLSCAASGF AFSSYGMHWV 180  
 RQAPGKGLEW VAVIWFDGTT KYYTDHSVGR FTISRDNSKN TLYLQMNTLR AEDTAVYYCA 240  
 RDRGIGARRG PYYMDVWGKG TTIVTVSSGGG GSCTGGGSAPE FLGGGPSVFLF PPKPKDLYI 300  
 TREPEVTCVV DVSVSQDPEV QFNWYVDGVE VHNAKTKPRE EQFNSTYRRV SVLTVLHQDW 360  
 LNGKEYKCKV SNKGLPSSIE KTISKAKGQP REPQVYTFPP EQEEMTKNQV SLRCLVKGFY 420  
 PSDIAVEWES NGQPENNYKT TKPVLDSDGS FRLESRLTVD KSRWQECNVV SCSVMEAC 480  
 WHLCKSLSLSLGKGGGGSGG GGSGGGGSDI LPCVPPFSVAK SVKSLYLGMR FSGTPVIRL 540  
 FKLQPTRLV AEFDFRTFDP EGILLFAGGH QDSTWIVLAL RAGRLELQLR YNGVGRVTSS 600  
 GPVINHGMWQ TISVEELARN LVIVKVNRAV MKIAVAGDLF QPERGLYHNL LTVGGIPFHE 660  
 KDLVQPINPR LDGCMRSWNW LNGEDTTIQE TVKVNRMCQ FSVTERGSFY PGSGFAFYSL 720  
 DYMRTPLDVG TESTWEVEVV AHIRPAADTG VLPALWAPDL RAVPLSVALV DYHSTKKLKK 780

-continued

---

QLVVLAVEHT ALALMEIKVC DGQEHHVTVS LRDGEATLEV DGTRGQSEVS AAQLQERLAV 840  
 LERHLRSPVL TFAAGGLPDVP VTSAPVTAFY RGCMTLEVNR RLLDLDEAAY KHSIDTAHSC 900  
 CPPVEPAAAH HHHHH 914

SEQ ID NO: 163            moltype = AA length = 925  
 FEATURE                    Location/Qualifiers  
 source                    1..925  
                           mol\_type = protein  
                           organism = synthetic construct  
 SIGNAL                    1..21  
 SEQUENCE: 163  
 METDTLLLWV LLLWVPGSTG DDIQMTQSPS SLSASVGDRV TITCRASQSI SSYLNWYQQK 60  
 PGKAPKLLIY AASSLQSGVP SRFSGSSGSGT DFTLTISSLQ PEDFATYCYCQ QSYSTPLTFG 120  
 GGTKVEIKGG GGSGGGGGGG GGSEVOLVES GGGVVQPGRS LRLSCAASGF AFSSYGMHWV 180  
 RQAPGKGLEW VAVIWPDGTK KYTDNSKRN TLYLQMTLRA EADTAVYYCA 240  
 RDRGIGARRG PYYMDVWGKG TTIVTSSGGG GSggggSDKT HTCPCPAPE LLGGPSVFLF 300  
 PPKPKDTLYI TREPEVTCVV VDVSHEDEPV KFNWYVDGVE VHNAKTPRE EQYASTYRVV 360  
 SVLTVLHQDW LNGKEYKCKV SNKALPAPIE KTISAKGQP REPQVYTLPP SREEMTKNQV 420  
 SLTCLVKGFY PSDIAVEWES NGQPENNYKT TPPVLDSDGS FFLYSKLTVD KSRWQQGNVF 480  
 SCSCVMHEALH NHYTQKSLSL SPGKGGGGSG GGGSGGGGSD ILPCVPFSA KSVKSLYLG 540  
 MFSGTPVIRL RPKRLQPTRL VAEFDFTFDP PEGILLFAGG HQDSTWIVLA LRAGRLELQL 600  
 RYNGVGRVTS SGPVINHGWM QTISVEELAR NLVIKVNRDA VMKIAVAGDL FQPERGLYHL 660  
 NLTVGGIPFH EKDLVQPINP RLDGCMRSWN WLNGEDTTIQ ETVKVNTRMQ CFSVTERGSF 720  
 YPGSGFAFYS LDYMRTPLDV GTESTWEVEV VAHIRPAADT GVLFALWAPD LRAPVLSVAL 780  
 VDYZHSTKKL KQLVVLAVEH TALALMEIKV CDQEHVVTV SLRDGEATLE VDGTRGQSEV 840  
 SAAQLQERLA VLERHLRSPV LTFAGGLPDV PVTSAVTAF YRGCMTEVN RRLLDLDEAA 900  
 YKHSDITAHs CPPVEPAAAH HHHHH 925

SEQ ID NO: 164            moltype = AA length = 504  
 FEATURE                    Location/Qualifiers  
 source                    1..504  
                           mol\_type = protein  
                           organism = synthetic construct  
 SIGNAL                    1..21  
 SEQUENCE: 164  
 METDTLLLWV LLLWVPGSTG DDIQMTQSPS SLSASVGDRV TITCRASQSI SSYLNWYQQK 60  
 PGKAPKLLIY AASSLQSGVP SRFSGSSGSGT DFTLTISSLQ PEDFATYCYCQ QSYSTPLTFG 120  
 GGTKVEIKGG GGSGGGGGGG GGSEVOLVES GGGVVQPGRS LRLSCAASGF AFSSYGMHWV 180  
 RQAPGKGLEW VAVIWPDGTK KYTDNSKRN TLYLQMTLRA EADTAVYYCA 240  
 RDRGIGARRG PYYMDVWGKG TTIVTSSGGG GSggggSDKT HTCPCPAPE LLGGPSVFLF 300  
 PPKPKDTLYI TREPEVTCVV VDVSHEDEPV KFNWYVDGVE VHNAKTPRE EQYASTYRVV 360  
 SVLTVLHQDW LNGKEYKCKV SNKALPAPIE KTISAKGQP REPQVYTLPP SREEMTKNQV 420  
 SLTCLVKGFY PSDIAVEWES NGQPENNYKT TPPVLDSDGS FFLYSKLTVD KSRWQQGNVF 480  
 SCSCVMHEALH NHYTQKSLSL SPGK 504

SEQ ID NO: 165            moltype = AA length = 925  
 FEATURE                    Location/Qualifiers  
 source                    1..925  
                           mol\_type = protein  
                           organism = synthetic construct  
 SIGNAL                    1..21  
 SEQUENCE: 165  
 METDTLLLWV LLLWVPGSTG DDIQMTQSPS SLSASVGDRV TITCRASQSI SSYLNWYQQK 60  
 PGKAPKLLIY AASSLQSGVP SRFSGSSGSGT DFTLTISSLQ PEDFATYCYCQ QSYSTPLTFG 120  
 GGTKVEIKGG GGSGGGGGGG GGSEVOLVES GGGVVQPGRS LRLSCAASGF AFSSYGMHWV 180  
 RQAPGKGLEW VAVIWPDGTK KYTDNSKRN TLYLQMTLRA EADTAVYYCA 240  
 RDRGIGARRG PYYMDVWGKG TTIVTSSGGG GSggggSDKT HTCPCPAPE LLGGPSVFLF 300  
 PPKPKDTLYI TREPEVTCVV VDVSHEDEPV KFNWYVDGVE VHNAKTPRE EQYASTYRVV 360  
 SVLTVLHQDW LNGKEYKCKV SNKALPAPIE KTISAKGQP REPQVYTLPP SREEMTKNQV 420  
 SLTCLVKGFY PSDIAVEWES NGQPENNYKT TPPVLDSDGS FFLYSKLTVD KSRWQQGNVF 480  
 SCSCVMHEALH NHYTQKSLSL SPGKGGGGSG GGGSGGGGSD ILPCVPFSA KSVKSLYLG 540  
 MFSGTPVIRL RPKRLQPTRL VAEFDFTFDP PEGILLFAGG HQDSTWIVLA LRAGRLELQL 600  
 RYNGVGRVTS SGPVINHGWM QTISVEELAR NLVIKVNRDA VMKIAVAGDL FQPERGLYHL 660  
 NLTVGGIPFH EKDLVQPINP RLDGCMRSWN WLNGEDTTIQ ETVKVNTRMQ CFSVTERGSF 720  
 YPGSGFAFYS LDYMRTPLDV GTESTWEVEV VAHIRPAADT GVLFALWAPD LRAPVLSVAL 780  
 VDYZHSTKKL KQLVVLAVEH TALALMEIKV CDQEHVVTV SLRDGEATLE VDGTRGQSEV 840  
 SAAQLQERLA VLERHLRSPV LTFAGGLPDV PVTSAVTAF YRGCMTEVN RRLLDLDEAA 900  
 YKHSDITAHs CPPVEPAAAH HHHHH 925

SEQ ID NO: 166            moltype = AA length = 730  
 FEATURE                    Location/Qualifiers  
 source                    1..730  
                           mol\_type = protein  
                           organism = synthetic construct  
 SEQUENCE: 166  
 METDTLLLWV LLLWVPGSTG DEVQLVESGG GVVPGRSLR LSCAASGFSSYGMHWVRQ 60  
 APGKGLEWVA VIWFDTGKTY YTDSVKGRFT ISRDNSKNTL YLQMNTLRAE DTAVYYCARD 120  
 RIGIGARRGPY YMDVWGKGTT VTVSSASTKG PSVFPLAPSS KSTSGGTAAL GCLVKDYFPE 180  
 PVTVSWNSGA LTSGVHTFPA VLQSSGLYSL SSVVTVPSSS LGTQTYICNV NHKPSNTKVD 240

-continued

---

KKVEPKSCDK THTCPPCPAP ELLGGPSVFL FPPKPKDLM ISRTPEVTCV VVDVSHEDPE 300  
 VKPNWYDGV EVHNAKTKPR EEQYASTYRV VSVLTVLHQD WLNGKEYKCK VSNKALPAPI 360  
 EKTISKAKGQ PREPVQVTLP PSRDELTKNQ VSLTCLVKGF YPSDIAVEWE SNGOPENNYK 420  
 TPPVLDSDG SFFLYSKLTV DKSRWQQGNV FSCSVMHEAL HNHYTQKSLS LSPGKGGS 480  
 GGGGSEVKLV ESGGDLVKPG GSLKLSCAAS GFTFSSYGMWS WRQTPDKRL EWVATISSGG 540  
 SYTYYPDHSV KRGFTISRDNA KNTLYLQMSS LKSEDTAMYY CARHPIYYTY DDTMDYWGQG 600  
 TSVTVSSGGG GSGGGGSSGG GSDIVLTQSP AIMAASPGEK VTMTCSASSS VSSGNFHWFQ 660  
 QKPGTSPKRW IYRTSNLASG VPARFSGSGS GTSYSLTIISS MEAEDAATYY CQQWSGPWT 720  
 FGGGTKEIK 730

SEQ ID NO: 167 moltype = AA length = 730  
 FEATURE Location/Qualifiers  
 source 1..730  
 mol\_type = protein  
 organism = synthetic construct

SEQUENCE: 167  
 METDTLLLWV LLLWVPGSTG DEVQLVESGG GVVQPGRSR LSCAASGF AF SSYGMHWVRQ 60  
 APGKGLEWVA VIWFDTKYY YTDSVKGRFT ISRDNSKNTL YLQMNTRAE DTAVYYCARD 120  
 RGIGARRGPY YMDVWKGKTT VTVSSASTKG PSVPLAPSS KSTSGGTAAL GCLVKDVFPE 180  
 PVTVSWNSGA LTSGVHTFPV VLQSSGLYSL SSVTVPPSSS LGTQTYICNV NHKPSNTKVD 240  
 KKVEPKSCDK THTCPPCPAP ELLGGPSVFL FPPKPKDLM ISRTPEVTCV VVDVSHEDPE 300  
 VKFNWYDGV EVHNAKTKPR EEQYASTYRV VSVLTVLHQD WLNGKEYKCK VSNKALPAPI 360  
 EKTISKAKGQ PREPVQVTLP PSRDELTKNQ VSLTCLVKGF YPSDIAVEWE SNGOPENNYK 420  
 TPPVLDSDG SFFLYSKLTV DKSRWQQGNV FSCSVMHEAL HNHYTQKSLS LSPGKGGS 480  
 GGGGSEVKLV ESGGDLVKPG GSLKLSCAAS GFTFSSYGMWS WRQTPDKRL EWVATISSGG 540  
 SYTYYPDHSV KRGFTISRDNA KNTLYLQMSS LKSEDTAMYY CARHPIYYTY DDTMDYWGQG 600  
 TSVTVSSGGG GSGGGGSSGG GSDIVLTQSP AIMAASPGEK VTMTCSASSS VSSGNFHWFQ 660  
 QKPGTSPKRW IYRTSNLASG VPARFSGSGS GTSYSLTIISS MEAEDAATYY CQQWSGPWT 720  
 FGGGTKEIK 730

SEQ ID NO: 168 moltype = AA length = 730  
 FEATURE Location/Qualifiers  
 source 1..730  
 mol\_type = protein  
 organism = synthetic construct

SEQUENCE: 168  
 METDTLLLWV LLLWVPGSTG DEVQLVESGG GVVQPGRSR LSCAASGF AF SSYGMHWVRQ 60  
 APGKGLEWVA VIWFDTKYY YTDSVKGRFT ISRDNSKNTL YLQMNTRAE DTAVYYCARD 120  
 RGIGARRGPY YMDVWKGKTT VTVSSASTKG PSVPLAPSS KSTSGGTAAL GCLVKDVFPE 180  
 PVTVSWNSGA LTSGVHTFPV VLQSSGLYSL SSVTVPPSSS LGTQTYICNV NHKPSNTKVD 240  
 KKVEPKSCDK THTCPPCPAP ELLGGPSVFL FPPKPKDLM ISRTPEVTCV VVDVSHEDPE 300  
 VKFNWYDGV EVHNAKTKPR EEQYASTYRV VSVLTVLHQD WLNGKEYKCK VSNKALPAPI 360  
 EKTISKAKGQ PREPVQVTLP PSRDELTKNQ VSLTCLVKGF YPSDIAVEWE SNGOPENNYD 420  
 TPPVLDSDG SFFLYSKLTV DKSRWQQGNV FSCSVMHEAL HNHYTQKSLS LSPGKGGS 480  
 GGGGSEVKLV ESGGDLVKPG GSLKLSCAAS GFTFSSYGMWS WRQTPDKRL EWVATISSGG 540  
 SYTYYPDHSV KRGFTISRDNA KNTLYLQMSS LKSEDTAMYY CARHPIYYTY DDTMDYWGQG 600  
 TSVTVSSGGG GSGGGGSSGG GSDIVLTQSP AIMAASPGEK VTMTCSASSS VSSGNFHWFQ 660  
 QKPGTSPKRW IYRTSNLASG VPARFSGSGS GTSYSLTIISS MEAEDAATYY CQQWSGPWT 720  
 FGGGTKEIK 730

SEQ ID NO: 169 moltype = AA length = 475  
 FEATURE Location/Qualifiers  
 source 1..475  
 mol\_type = protein  
 organism = synthetic construct

SEQUENCE: 169  
 METDTLLLWV LLLWVPGSTG DEVQLVESGG GVVQPGRSR LSCAASGF AF SSYGMHWVRQ 60  
 APGKGLEWVA VIWFDTKYY YTDSVKGRFT ISRDNSKNTL YLQMNTRAE DTAVYYCARD 120  
 RGIGARRGPY YMDVWKGKTT VTVSSASTKG PSVPLAPSS KSTSGGTAAL GCLVKDVFPE 180  
 PVTVSWNSGA LTSGVHTFPV VLQSSGLYSL SSVTVPPSSS LGTQTYICNV NHKPSNTKVD 240  
 KKVEPKSCDK THTCPPCPAP ELLGGPSVFL FPPKPKDLM ISRTPEVTCV VVDVSHEDPE 300  
 VKFNWYDGV EVHNAKTKPR EEQYASTYRV VSVLTVLHQD WLNGKEYKCK VSNKALPAPI 360  
 EKTISKAKGQ PREPVQVTLP PSRKELTKNQ VSLTCLVKGF YPSDIAVEWE SNGOPENNYK 420  
 TPPVLDSDG SFFLYSKLTV DKSRWQQGNV FSCSVMHEAL HNHYTQKSLS LSPGK 475

---

The invention claimed is:

1. A binding molecule comprising a first region capable of binding to a TAM (Tyro3, Axl, MerTK) receptor and a second region capable of specifically binding to a target substance, said target substance being a substance of which aberrant accumulation in a living tissue is characteristic of or associated with a disease, wherein the first region and the second region are coupled to each other directly or via a linker,  
 wherein the first region comprises a Gas6 protein comprising (i) the sequence of SEQ ID NO: 5 or (ii) a

sequence having sequence identity of at least 85% to the sequence of SEQ ID NO: 5 and comprising a sex hormone-binding globulin (SHBG)-like domain of Gas6 protein,  
 wherein the first region does not comprise N-terminal gamma carboxyglutamic acid (GLA) domain and epidermal growth factor (EGF)-like domain, and  
 wherein the binding molecule induces phagocytosis.  
 2. The binding molecule according to claim 1, wherein the Gas6 protein comprises the amino acid sequence of SEQ ID NO: 1 and the amino acid sequence of SEQ ID NO: 2.

**143**

**3.** The binding molecule according to claim **1**, wherein the Gas6 protein comprises one or more sequences selected from the group consisting of SEQ ID NO: 5, SEQ ID NO: 63, SEQ ID NO: 64, SEQ ID NO: 65, SEQ ID NO: 66, SEQ ID NO: 67, SEQ ID NO: 68, SEQ ID NO: 69, SEQ ID NO: 71, SEQ ID NO: 72, SEQ ID NO: 74, SEQ ID NO: 75, SEQ ID NO: 76, SEQ ID NO: 77, SEQ ID NO: 78, SEQ ID NO: 79, SEQ ID NO: 80, SEQ ID NO: 81, SEQ ID NO: 82, SEQ ID NO: 83, SEQ ID NO: 84, SEQ ID NO: 85, SEQ ID NO: 86, and SEQ ID NO: 87.

**4.** The binding molecule according to claim **1**, which is a monomer or multimer.

**5.** The binding molecule according to claim **1**, wherein the target substance is  $\beta$ -amyloid.

**6.** The binding molecule according to claim **1**, wherein the target substance is soluble amyloid, oligomeric amyloid, aggregated amyloid, or combinations thereof.

**7.** The binding molecule according to claim **1**, wherein the second region that specifically binds to the target substance is selected from the group consisting of an antibody or an antigen-binding fragment thereof, an antibody-like protein, a peptide, an aptamer, and a soluble receptor, which each specifically bind to the target substance.

**144**

**8.** A pharmaceutical composition comprising the binding molecule of claim **1** and a pharmaceutically acceptable carrier.

**9.** The binding molecule according to claim **1**, which further comprises an immunoglobulin Fc domain.

**10.** The binding molecule according to claim **9**, wherein the immunoglobulin Fc domain has a reduced or abolished Fc receptor binding affinity, compared to wild-type immunoglobulin Fc domain.

**11.** The binding molecule according to claim **1**, wherein the second region is an antibody or an antigen-binding fragment thereof that specifically binds to amyloid.

**12.** The binding molecule according to claim **1**, wherein the first region comprises the sequence of SEQ ID NO: 5 or a sequence having at least 95% sequence identity thereto, and wherein the second region is an antibody or an antigen-binding fragment thereof that specifically binds to soluble amyloid, oligomeric amyloid, and/or aggregated amyloid.

**13.** The binding molecule according to claim **3**, which further comprises an immunoglobulin Fc domain.

\* \* \* \* \*