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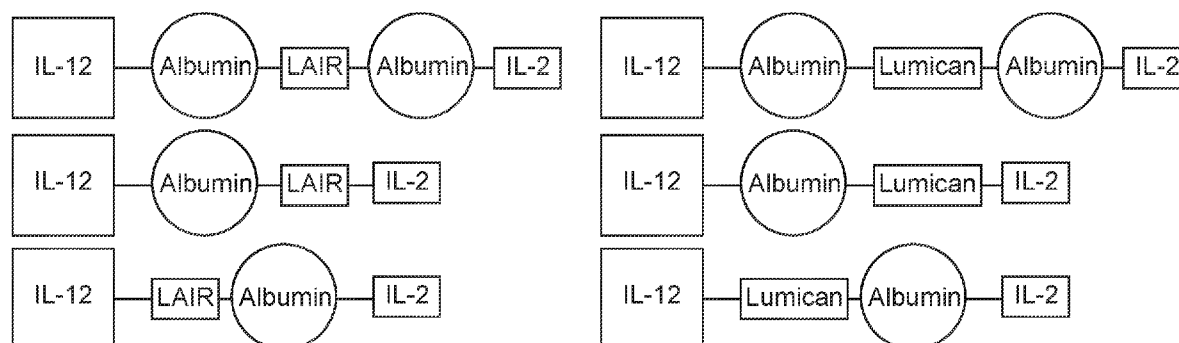


FIG. 1

(57) Abstract: Disclosed herein are immunomodulatory fusion proteins comprising an IL-2; an IL-12, a collagen-binding domain, and a linear polypeptide spacer, methods of making and using the same. The immunomodulatory fusion proteins disclosed herein are useful for the treatment of cancer.



## BI-FUNCTIONAL LINEAR FUSION COLLAGEN-LOCALIZED IMMUNOMODULATORY MOLECULES AND METHODS THEREOF

### CROSS-REFERENCE TO RELATED APPLICATION

- 5   **[0001]**   The present application claims the benefit of and priority to U.S. Provisional Patent Application No. 63/127,995, filed December 18, 2020, the disclosures of which are hereby incorporated by reference in their entireties for all purposes.

### BACKGROUND

- 10   **[0002]**   While immunotherapy has transformed oncology with durable curative responses in a minority of patients, immune-related adverse events (irAEs) limit its broadest application (Michot et al. 2016, Eur J Cancer, 54: 139-148). It is desired to restrict the most potent immune activation events to tumor tissue, while sparing non-tumor healthy tissue. Various tumor-localization approaches have been proposed: linking immunomodulatory agents to tumor-targeting modules in immunocytokines (Hutmacher and Neri 2018, Adv Drug Deliv Rev); masking agent activity  
15   systemically, with tumor-localized proteolytic activation (Thomas and Daugherty 2009, Protein Sci 18:2053-2059); intratumoral injection of the agents (Singh and Overwijk 2015, Nat Commun 8:1447; Ager et al. 2017, Cancer Immunol Res 5:676-684; Bommarreddy et al. 2017, Cancer J 23:40-47; Milling et al. 2017, Adv Drug Deliv Rev 114:79-101; Singh et al. 2017, Nat Commun 8:1447; Sagiv-Barfi et al. 2018, Sci Transl Med 10:eaan4488); peritumoral injection of a solid  
20   biomaterial to entrap the agent (Park et al. 2018, Sci Transl Med, 10:eaar1916); conjugation to a solid particle (Kwong et al. 2013, Cancer Res 73:1547- 1558) or conjugation of basic charged peptides to drive some nonspecific sticking of the agent to tumor extracellular matrix (Ishihara et al. 2017, Sci Transl Med 9:eaan0401; Ishihara et al. 2018, Mol Cancer Ther 17:2399-2411). A related but distinct approach is to localize growth factors in tissue to drive tissue regeneration  
25   (Nishi et al. 1998, Proc Natl Acad Sci 95:7018-7023; Martino et al. 2014, Science 343:885-888; Mitchell et al. 2016, Acta Biomater 30:1-12).

- 30   **[0003]**   Significant problems exist with each of the current approaches above. Immunocytokines systemically expose immune cells to the immunomodulatory agent (Tzeng et al. 2015, Proc Natl Acad Sci 112:3320-3325). Masking agents may be unmasked outside target tissues, and the masking agent may complicate manufacturing and immunogenicity. Intratumoral injection often leads to rapid diffusion out of the tumor compartment. Conjugation of peptides at random sites is difficult to reproduce, can negatively impact specific activity, doesn't fully prevent tumor exit, and

creates significant CMC issues due to the heterogeneous products of random conjugation methods.

**[0004]** Accordingly, there remains a need for novel immunotherapy approaches to promote tumor-localization and increase efficacy, while preventing systemic toxicity.

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## SUMMARY

**[0005]** Described herein are compounds, compositions, and methods for treating cancer. The compounds include a fusion protein including each of an IL-2, an IL-12, a collagen-binding domain, and a linear polypeptide spacer. When administered to a subject, the compounds have a favorable residence time in the tumor and can provide in some embodiments treatments with acceptable toxicity an enhanced therapeutic index. In some embodiments, the collagen-binding domain binds to the collagen in the tumor to maintain localization of the compound in the tumor for an extended period of time.

**[0006]** Disclosed herein is an immunomodulatory fusion protein comprising: (i) an IL-2; (ii) an IL-12; (iii) a collagen-binding domain, and (iv) a linear polypeptide spacer.

**[0007]** In various embodiments, the immunomodulatory fusion protein is linear. In various embodiments, the immunomodulatory fusion protein is a continuous chain. In various embodiments, the immunomodulatory fusion protein is a continuous polypeptide chain.

**[0008]** In various embodiments, the IL-2 is at the N-terminus of the immunomodulatory fusion protein. In various embodiments, the IL-12 is at the C-terminus of the immunomodulatory fusion protein. In various embodiments, the IL-2 is at the N-terminus of the immunomodulatory fusion protein and the IL-12 is at the C-terminus of the immunomodulatory fusion protein.

**[0009]** In various embodiments, the linear polypeptide spacer is positioned in between the IL-2 and the collagen-binding domain. In various embodiments, the collagen-binding domain is positioned in between the IL-12 and the linear polypeptide spacer.

**[0010]** In various embodiments, the C-terminus of the IL-2 is operably linked to the N-terminus of the linear polypeptide spacer. In various embodiments, the C-terminus of the IL-2 is operably linked by a linker to the N-terminus of the linear polypeptide spacer.

**[0011]** In various embodiments, the C-terminus of the linear polypeptide spacer is operably linked to the N-terminus of the collagen-binding domain. In various embodiments, the C-terminus of the linear polypeptide spacer is operably linked by a linker to the N-terminus of the collagen-binding domain.

[0012] In various embodiments, the C-terminus of the collagen-binding domain is operably linked to the N-terminus of the the IL-12. In various embodiments, the C-terminus of the collagen-binding domain is operably linked by a linker to the N-terminus of the the IL-12.

[0013] In various embodiments, the collagen-binding domain is positioned in between the IL-2 and the linear polypeptide spacer. In various embodiments, the linear polypeptide spacer is positioned in between the IL-12 and the collagen-binding domain. In various embodiments, the C-terminus of the IL-2 is operably linked to the N-terminus of the collagen-binding domain.

[0014] In various embodiments, the C-terminus of the IL-2 is operably linked by a linker to the N-terminus of the collagen-binding domain. In various embodiments, the C-terminus of the collagen-binding domain is operably linked to the N-terminus of the linear polypeptide spacer.

[0015] In various embodiments, the C-terminus of the collagen-binding domain is operably linked by a linker to the N-terminus of the linear polypeptide spacer. In various embodiments, the C-terminus of the linear polypeptide spacer is operably linked to the N-terminus of the the IL-12. In various embodiments, the C-terminus of the linear polypeptide spacer is operably linked by a linker to the N-terminus of the the IL-12.

[0016] In various embodiments, the IL-2 is at the C-terminus of the immunomodulatory fusion protein. In various embodiments, the IL-12 is at the N-terminus of the immunomodulatory fusion protein. In various embodiments, the IL-2 is at the C-terminus and the IL-12 is at the N-terminus of the immunomodulatory fusion protein.

[0017] In various embodiments, the N-terminus of the IL-2 is operably linked to the C-terminus of the linear polypeptide spacer. In various embodiments, the N-terminus of the IL-2 is operably linked by a linker to the C-terminus of the linear polypeptide spacer.

[0018] In various embodiments, the N-terminus of the linear polypeptide spacer is operably linked to the C-terminus of the collagen-binding domain. In various embodiments, the N-terminus of the linear polypeptide spacer is operably linked by a linker to the C-terminus of the collagen-binding domain.

[0019] In various embodiments, the N-terminus of the collagen-binding domain is operably linked to the C-terminus of the the IL-12. In various embodiments, the N-terminus of the collagen-binding domain is operably linked by a linker to the C-terminus of the the IL-12.

[0020] In various embodiments, the collagen-binding domain is positioned in between the IL-2 and the linear polypeptide spacer. In various embodiments, the linear polypeptide spacer is positioned in between the IL-12 and the collagen-binding domain.

[0021] In various embodiments, the N-terminus of the IL-2 is operably linked to the C-terminus of the collagen-binding domain. In various embodiments, the N-terminus of the IL-2 is operably linked by a linker to the C-terminus of the collagen-binding domain.

[0022] In various embodiments, the N-terminus of the collagen-binding domain is operably linked to the C-terminus of the linear polypeptide spacer. In various embodiments, the N-terminus of the collagen-binding domain is operably linked by a linker to the C-terminus of the linear polypeptide spacer.

[0023] In various embodiments, the N-terminus of the linear polypeptide spacer is operably linked to the C-terminus of the IL-12. In various embodiments, the N-terminus of the linear polypeptide spacer is operably linked by a linker to the C-terminus of the IL-12.

[0024] In various embodiments, one or more of the linkers are the same. In various embodiments, one or more of the linkers are the different.

[0025] In various embodiments, the IL-12 is at the C terminus of the immulatory fusion protein and is operably linked to the collagen binding domain, which is operably linked to a linear polypeptide spacer, which is operably linked to the IL-2 at the N terminus of the protein, and wherein the protein is linear.

[0026] In various embodiments, the IL-12 is at the N terminus of the immulatory fusion protein and is operably linked to the collagen binding domain, which is operably linked to a linear polypeptide spacer, which is operably linked to the IL-2 at the C terminus of the protein, and wherein the protein is linear.

[0027] In various embodiments, the IL-12 is at the C terminus of the immulatory fusion protein and is operably linked to the linear polypeptide spacer, which is operably linked to collagen binding domain, which is operably linked to the IL-2 at the N terminus of the protein, and wherein the protein is linear.

[0028] In various embodiments, the IL-12 is at the N terminus of the immulatory fusion protein and is operably linked to the linear polypeptide spacer, which is operably linked to collagen binding domain, which is operably linked to the IL-2 at the C terminus of the protein, and wherein the protein is linear.

[0029] In various embodiments, the immulatory fusion protein further comprises a second linear polypeptide spacer.

[0030] In various embodiments, the IL-12 is at the N terminus of the immulatory fusion protein and is operably linked to the first linear polypeptide spacer, which is operably linked to the collagen binding domain, which is operably linked to the second linear polypeptide spacer,

which is operably linked to the IL-2 at the C terminus of the protein, and wherein the protein is linear.

**[0031]** In various embodiments, the IL-12 is at the C terminus of the immunomodulatory fusion protein and is operably linked to the first linear polypeptide spacer, which is operably linked to the collagen binding domain, which is operably linked to the second linear polypeptide spacer, which is operably linked to the IL-2 at the N terminus of the protein, and wherein the protein is linear.

**[0032]** In various embodiments, the immunomodulatory fusion protein is a continuous chain. In various embodiments, the immunomodulatory fusion protein is a continuous polypeptide chain.

**[0033]** In various embodiments, the collagen-binding domain comprises (i) a leucine-rich repeat from a human proteoglycan Class II member of the small leucine-rich proteoglycan (SLRP) family which comprises lumican; or (ii) a human type I glycoprotein having an Ig-like domain selected from LAIR1 and LAIR2.

**[0034]** In various embodiments, the collagen-binding domain comprises lumican. In various embodiments, the lumican comprises at least about 80% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 11.

**[0035]** In various embodiments, the collagen-binding domain comprises LAIR 1. In various embodiments, the LAIR1 comprises at least about 80% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 13. In various embodiments, the LAIR1 comprises at least 80% identity to the amino acid as set forth in SEQ ID NO: 14.

**[0036]** In various embodiments, the collagen-binding domain comprises LAIR 2. In various embodiments, the LAIR2 comprises at least 80% identity to the amino acid sequence as set forth in SEQ ID NO: 15.

**[0037]** In various embodiments, the IL-2 comprises human IL-2. In various embodiments, the IL-2 comprises human wild-type IL-2. In various embodiments, the IL-2 comprises at least about 80% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 1. In various embodiments, the IL-2 comprises at least about 80% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 2.

**[0038]** In various embodiments, the IL-12 comprises human IL-12. In various embodiments, the IL-12 comprises human wild-type IL-12. In various embodiments, the IL-12 comprises at least about 80% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 5. In various embodiments, the IL-12 comprises at least about 80% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 6.

[0039] In various embodiments, the linear polypeptide spacer is an albumin. In various embodiments, the linear polypeptide spacer is an albumin binding domain. In various embodiments, the albumin comprises human albumin.

[0040] In various embodiments, the albumin comprises at least about 80% sequence identity to the amino acid sequence as set forth in SEQ ID NOs: 16-18. In various embodiments, the albumin binding domain comprises at least about 80% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 19.

[0041] In various embodiments, the immunomodulatory fusion protein molecular weight is at least about 100-1000 kDa..

[0042] Additionally disclosed herein is an pharmaceutical composition comprising an immunomodulatory fusion protein of any one of the immunomodulatory fusion proteins disclosed herein, and a pharmaceutically acceptable carrier.

[0043] Additionally disclosed herein is a method for activating, enhancing or promoting a response by an immune cell in a subject or inhibiting, reducing or suppressing a response by an immune cell in a subject, comprising administering to a subject in need thereof, an effective amount of the pharmaceutical composition of any one of the pharmaceutical composition disclosed herein.

[0044] Additionally disclosed herein is a method for treating cancer, or reducing or inhibiting tumor growth, comprising administering to a subject in need thereof, an effective amount of the pharmaceutical composition of any one of the pharmaceutical composition disclosed herein.

[0045] In various embodiments, the subject has at least one tumor. In various embodiments, the composition is administered intratumorally (i.tu) or peritumorally (peri.tu) to the at least one tumor. In various embodiments, the at least one tumor size is reduced or substantially identical to a reference standard. In various embodiments, the reference standard is the size of the tumor prior to administration.

[0046] In various embodiments, the composition is administered by injection.

[0047] In various embodiments, the composition has an intratumoral retention  $t_{1/2}$  of more than 24 hours.

[0048] In various embodiments, twelve hours after intratumoral injection less than 25% of the injected dose is detected in the serum.

[0049] In various embodiments, the at least one tumor has stromal CD8<sup>+</sup> cytotoxic T cells (CTL)  $\leq 50$  cells/mm<sup>2</sup>. In various embodiments, the at least one tumor has stromal CD8<sup>+</sup> cytotoxic T cells (CTL)  $\geq 50$  cells/mm<sup>2</sup> and intraepithelial compartment CD8<sup>+</sup> cytotoxic T cells

(CTL)  $\leq 500$  cells/mm<sup>2</sup>. In various embodiments, the at least one tumor has intraepithelial compartment CD8<sup>+</sup> cytotoxic T cells (CTL)  $\geq 500$  cells/mm<sup>2</sup>.

**[0050]** In various embodiments, the method does not result in cytokine release syndrome in the subject. In various embodiments, the subject does not experience grade 4 cytokine release syndrome.

**[0051]** Additionally disclosed herein is a method for reducing or inhibiting tumor growth or treating cancer in a subject, the method comprising administering to a subject in need thereof, an effective amount of the pharmaceutical composition of any one of the pharmaceutical composition disclosed herein, and an effective amount of a second composition comprising (i) a tumor antigen-targeting antibody, (ii) a cancer vaccine, (iii) an immune checkpoint inhibitor, or (iv) an adoptive cell therapy, thereby reducing or inhibiting tumor growth or treating cancer in the subject.

**[0052]** In various embodiments, the tumor antigen is a tumor-associated antigen (TAA), a tumor specific antigen (TSA), or a tumor neoantigen and/or wherein the tumor antigen-targeting antibody specifically binds human HER-2/neu, EGFR, VEGFR, CD20, CD33, CD38 or antigen-binding fragment thereof. In various embodiments, the cancer vaccine is a peptide comprising one or more tumor-associated antigens, or a population of cells immunized in vitro with a tumor antigen and administered to the subject. In various embodiments, the immune checkpoint inhibitor is an antibody or antigen binding fragment thereof which binds PD-1, PD-L1, CTLA-4, LAG3, or TIM3. In various embodiments, the immune effector cell comprises a chimeric antigen receptor (CAR) molecule which binds to a tumor antigen.

In certain aspects, described herein is an immunomodulatory fusion protein comprising: an IL-2; an IL-12; a LAIR2 collagen-binding domain, wherein LAIR2 comprises at least 80% identity to the amino acid sequence as set forth in SEQ ID NO: 15; and an albumin; wherein the albumin comprises at least about 80% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 16-18.

### BRIEF DESCRIPTION OF THE DRAWINGS

**[0053]** **FIG. 1** illustrates exemplary bi-functional linear fusion collagen-localized immunomodulatory constructs comprising an IL-12, a collagen-binding domain, an albumin, and an IL-2.

**[0054]** **FIGs. 2A-2F** are graphs showing recombinant proteins purified with NiNTA resin and evaluated for product quality using analytical size exclusion chromatography (SEC). **FIG. 2A** shows the SEC profile of the 12-MSA-Lum-MSA-2 construct (HMW = 19%; Main = 79%; LMW = 2%). **FIG. 2B** shows the SEC profile of the 12-Lum-MSA-2 construct (HMW = 9%; Main =

90%; LMW = 1%). **FIG. 2C** shows the SEC profile of the 12-MSA-Lum-2 construct (HMW = 34%; Main = 64%; LMW = 2%). **FIG. 2D** shows the SEC profile of the 12-MSA-LAIR-MSA-2 construct (HMW = 11%; Main = 89%; LMW = 0%). **FIG. 2E** shows the SEC profile of the 12-LAIR-MSA-2 construct (HMW = 11%; Main = 89%; LMW = 1%). **FIG. 2F** shows the SEC profile of the 12-MSA-LAIR-2 construct (HMW = 16%; Main = 84%; LMW = 0%).

**[0055]** **FIG. 3** is a bar graph showing the production yield and product quality of various constructs. The production yield and product quality (percentage of the Main peak) are highest when only a single MSA is present in the construct and such MSA was placed between the collagen binding domain (Lumican or LAIR) and IL-2

**[0056]** **FIGs. 4A-4B** are graphs showing binding of bi-functional linear fusion immunomodulatory constructs comprising a collagen-binding domain to collagen as a function of concentration. Binding was determined by ELISA. **FIG. 4A** shows a construct comprising LAIR (e.g., 12-MSA-LAIR-MSA-2 construct) effected higher affinity binding to collagen compared to a construct comprising Lumican (e.g., 12-MSA-Lum-MSA-2 construct). Furthermore, placing Lumican between MSA and IL-2 (e.g., 12-MSA-Lum-2 construct) enabled higher affinity binding to collagen than placing Lumican between MSA and IL-2. **FIG. 4B** shows three constructs comprising LAIR, each comprising a different spacer between LAIR and IL-2, MSA, ABD, and MSA\_Mut1-2, effected comparable level of collagen binding. The MSA\_Mut1-2 comprises an H464Q mutation which abrogates FcRn binding.

**[0057]** **FIGs. 5A-5B** are graphs showing IL-2 cytokine activity of various constructs is maintained in the presence of collagen. IL-2 bioactivity was measured for: (1) IL-2 alone, (2) IL-12 alone, (3) a combination of an IL-2 mono-functional linear construct comprising a collagen-binding domain and an IL-12 mono-functional linear construct comprising a collagen-binding domain, and (4) two bi-functional linear constructs each comprising a collagen-binding domain: 12-Lum-MSA-2 and 12-LAIR-MSA-2. **FIG. 5A** shows absorbance readings of the constructs on normal tissue-culture plates. **FIG. 5B** shows absorbance readings of the constructs on collagen I (Corning) coated plates.

**[0058]** **FIGs. 5C-5D** are graphs showing IL-2 cytokine activity of various constructs is maintained in the presence of collagen. IL-2 bioactivity was measured for three bi-functional linear constructs comprising a collagen-binding domain: (1) 12-LAIR-MSA-2, (2) 12-LAIR-MSA-2, and (3) 12-LAIR-MSA\_H464Q-2 which comprises an H464Q mutation which abrogates FcRn binding. **FIG. 5C** shows absorbance readings of the constructs on normal tissue-culture plates. **FIG. 5D** shows absorbance readings of the constructs on collagen I (Corning) coated plates.

**[0059]** **FIGs. 6A-6B** are graphs showing IL-12 activity of various constructs is maintained in the presence of collagen. IL-12 bioactivity was measured for: (1) IL-2 alone, (2) IL-12 alone, (3) a combination of an IL-2 mono-functional linear construct comprising a collagen-binding domain and an IL-12 mono-functional linear construct comprising a collagen-binding domain, and (4) two bi-functional linear constructs each comprising a collagen-binding domain: 12-Lum-MSA-2 and 12-LAIR-MSA-2. **FIG. 6A** shows absorbance readings of the constructs on normal tissue-culture plates. **FIG. 6B** shows absorbance readings of the constructs on collagen I (Corning) coated plates.

**[0060]** **FIG. 7A** is a graph of a tumor growth curve (mean tumor volume over time) showing the tumor volume growth of C57BL/6 mice inoculated with B16F10 cells and subsequently treated with intratumoral injections on days 0 and 6 with 100 pmol of: (1) PBS, (2) a combination of an IL-2 mono-functional linear construct comprising an MSA (MSA-2) and an IL-12 mono-functional linear construct comprising an MSA (12-MSA), (3) a combination of an IL-2 mono-functional linear construct comprising an MSA and a collagen-binding domain (LAIR-MSA-2) and an IL-12 mono-functional linear construct comprising an MSA and collagen-binding domain (12-MSA-LAIR), (4) a bi-functional linear constructs comprising MSA and a collagen-binding domain 12-Lum-MSA-2, and (5) a bi-functional linear constructs comprising MSA and a collagen-binding domain 12-LAIR-MSA-2.

**[0061]** **FIG. 7B** is a graph showing the percent change in body weight of C57BL/6 mice inoculated with B16F10 cells and subsequently treated with intratumoral injections on days 0 and 6 with 100 pmol of: (1) PBS, (2) a combination of an IL-2 mono-functional linear construct comprising an MSA (MSA-2) and an IL-12 mono-functional linear construct comprising an MSA (12-MSA), (3) a combination of an IL-2 mono-functional linear construct comprising an MSA and a collagen-binding domain (LAIR-MSA-2) and an IL-12 mono-functional linear construct comprising an MSA and collagen-binding domain (12-MSA-LAIR), (4) a bi-functional linear constructs comprising MSA and a collagen-binding domain 12-Lum-MSA-2, and (5) a bi-functional linear constructs comprising MSA and a collagen-binding domain 12-LAIR-MSA-2.

**[0062]** **FIGS. 8A-8B** is a graph of a tumor growth curve (mean tumor volume over time) showing the dose-response therapeutic efficacy of a bi-functional linear constructs comprising MSA and a collagen-binding domain, 12-LAIR-MSA-2, in a dual-flank inoculated subcutaneous B16F10 melanoma syngeneic model in C57BL/6 mice. The bi-functional linear constructs 12-LAIR-MSA-2, at all dose levels tested, effected significantly tumor growth inhibition, both in the treated tumor (FIG. 8A) and the untreated tumor (FIG. 8B), demonstrating abscopal effect.

[0063] **FIGs. 9A-9C** show the efficacy and toxicity various bi-functional constructs in the B16F10 mouse model. C57BL/6 mice were inoculated with B16F10 cells and treated with intratumoral injections of 400 pmol of (1) PBS control, (2) 12-LAIR-MSA-2, (3) 12-LAIR-MSA\_H464Q-2, (4) 12-LAIR-ABD-2, and (5) 12-Lum-MSA-2. **FIG. 9A** is a graph of a tumor growth curve (mean tumor volume over time) showing all bi-functional constructs tested effected significant tumor growth inhibition compared to the PBS control group. **FIG. 9B** is a graph of survival showing extended survival of the animals treated with intratumoral injections of bi-functional constructs compared to PBS control group. **FIG. 9C** is a graph of percent change in body weight showing all bi-functional constructs tested demonstrated good safety profile reflected by the lack of body weight loss.

[0064] **FIGs. 10A-10C** show the efficacy and toxicity of 12-LAIR-MSA-2 in combination with checkpoint inhibitors anti-PD1 or anti-CTLA. C57BL/6 mice were inoculated with B16F10 cells and treated with intratumoral (IT) injections of PBS or 400 pmol of 12-LAIR-MSA-2 and intraperitoneal (IP) injections of isotype control (Rat IgG2a), anti-PD1 (clone RMP1-14), or anti-CTLA4 (9D9) as indicated. **FIGs. 10A-10B** show treatment with either anti-PD1 or anti-CTLA4 alone did not affect tumor growth inhibition, treatment with bi-functional construct 12-LAIR-MSA-2 alone resulted in significant tumor growth inhibition, and the anti-tumor activity of 12-LAIR-MSA-2 was further enhanced by the combination with either anti-PD1 or anti-CTLA4. **FIG. 10C** shows the addition of either anti-PD1 or anti-CTLA4 to bi-functional construct 12-LAIR-MSA-2 did not result in additional weight loss compared to treatment with 12-LAIR-MSA-2 alone.

[0065] **FIG. 11A** is a graph of a tumor growth curve (mean tumor volume over time) showing the tumor volume growth of C57BL/6 mice inoculated with MC38 cells and subsequently treated with intratumoral injections on days 0 and 6 with PBS or 12-LAIR-MSA-2.

[0066] **FIG. 11B** is a graph showing the percent change in body weight of C57BL/6 mice inoculated with MC38 cells and subsequently treated with intratumoral injections on days 0 and 6 with PBS or 12-LAIR-MSA-2.

[0067] **FIG. 12A** is a graph of a tumor growth curve (mean tumor volume over time) showing the tumor volume growth of C57BL/6 mice inoculated with MC38 cells and subsequently treated with intratumoral injections on days 0 and 6 with intratumoral injections of indicated doses of test articles (PBS, 12-LAIR-MSA-2, 12-LAIR-ABD-2, and 12-Lum-MSA-2) on days 0 and 6. Mice were treated with intraperitoneal injections of isotype control (Rat IgG2a) or anti-PD1 (clone RMP1-14) BIW for three weeks if indicated.

[0068] FIG. 12B is a graph showing the percent change in body weight of C57BL/6 mice inoculated with MC38 cells and subsequently treated with intratumoral injections on days 0 and 6 intratumoral injections of indicated doses of test articles (PBS, 12-LAIR-MSA-2, 12-LAIR-ABD-2, and 12-Lum-MSA-2) on days 0 and 6. Mice were treated with intraperitoneal injections of isotype control (Rat IgG2a) or anti-PD1 (clone RMP1-14) BIW for three weeks if indicated.

[0069] FIG. 13A is a graph of a tumor growth curve (mean tumor volume over time) showing the tumor volume growth of BALB/c mice inoculated with CT6 cells and subsequently treated with intratumoral injections on days 0 and 6 with PBS or 12-LAIR-MSA-2.

[0070] FIG. 13B is a graph showing the percent change in body weight of BALB/c mice inoculated with CT26 cells and subsequently treated with intratumoral injections on days 0 and 6 with PBS or 12-LAIR-MSA-2.

[0071] FIG. 14A is a graph of a tumor growth curve (mean tumor volume over time) showing the tumor volume growth of BALB/c mice inoculated with CT26 cells and subsequently treated with intratumoral injections on days 0 and 6 with intratumoral injections of indicated doses of test articles (PBS, 12-LAIR-MSA-2, 12-LAIR-ABD-2, and 12-Lum-MSA-2) on days 0 and 6. Mice were treated with intraperitoneal injections of isotype control (Rat IgG2a) or anti-PD1 (clone RMP1-14) BIW for three weeks if indicated.

[0072] FIG. 14B is a graph showing the percent change in body weight of BALB/c mice inoculated with CT26 cells and subsequently treated with intratumoral injections on days 0 and 6 intratumoral injections of indicated doses of test articles (PBS, 12-LAIR-MSA-2, 12-LAIR-ABD-2, and 12-Lum-MSA-2) on days 0 and 6. Mice were treated with intraperitoneal injections of isotype control (Rat IgG2a) or anti-PD1 (clone RMP1-14) BIW for three weeks if indicated.

[0073] FIG. 15A is a graph showing levels of 12-LAIR-MSA-2 in the serum of C57BL/6 mice that were inoculated on the right rear flank with B16F10 cells. 7 days post-inoculation (day 0), mice were randomized into treatment groups (n=10), and the mice were treated with either intraveunous or intratumoral injections of 400 pmol of PBS control or 12-LAIR-MSA-2. Two hours or 24 hours after administration, the amount of 12-LAIR-MSA-2 in the serum was measured.

[0074] FIG. 15B is a graph showing levels of interferon gamma (INF- $\gamma$ ) either 2 h or 24 h after administration of the 12-LAIR-MSA-2 fusion protein by IT or IV admininitration.

[0075] FIG. 15C is a graph showing levels of IP-10 either 2 h or 24 h after administration of the 12-LAIR-MSA-2 fusion protein by IT or IV admininitration.

[0076] FIG. 15D is a graph showing levels of MCP-1 either 2 h or 24 h after administration of the 12-LAIR-MSA-2 fusion protein by IT or IV admininitration.

[0077] **FIG. 15E** Is a graph showing the efficacy of treatment, as measured by survival, in mice that were administered the 12-LAIR-MSA-2 fusion protein by IT administration as compared to IV administration.

5

## DETAILED DESCRIPTION

[0078] Cytokines that amplify and coordinate immune cell responses for tumor control can robustly synergize with other immunotherapies. Two such cytokines are interleukin-2 (IL-2) and IL-12, which expand and stimulate T cells and natural killer (NK) cells to mediate antitumor immunity. Despite their promising therapeutic effects, in some embodiments, dose-limiting toxicity curbs the efficacy and the clinical translation of these cytokine therapies.

[0079] Ultimately, a cytokine's therapeutic index could be improved by localizing its effects to the tumor and away from healthy tissue. However, even when administered directly into a tumor, cytokines rapidly escape and enter systemic circulations, thus failing to fully address issues of toxicity and limited efficacy. The compounds described herein, in some embodiments, when injected into the tumor imiting systemic dissemination while prolonging and localizing their therapeutic antitumor activity, thereby improving efficacy while improving safety profile. In some embodiments, the compounds bind to the collagen, which is abundantly expressed and present in many tumor types.

20

### Bi-Functional Linear Fusion Construct

[0080] To devise collagen-binding cytokines, IL-2 and IL-12 were combined in a single fusion protein with a collagen-binding protein.

[0081] When administered intratumorally, bi-functional linear immodulatory fusion proteins with a collagen-binding domain, an IL-2, and an IL-12 demonstrated reduced systemic exposure and improved therapeutic index compared to the administration of either a linear immodulatory fusion proteins with a collagen-binding domain and an IL-2, or a linear immodulatory fusion proteins with a collagen-binding domain and an IL-12. In some embodiments, the reduced systemic exposure results in a reduced toxicity or an improved therapeutic index. When administered intratumorally, bi-functional linear immodulatory fusion proteins with a collagen-binding domain, an IL-2, and an IL-12 demonstrated reduced systemic exposure compared to the combined administration of either immodulatory fusion proteins with a collagen-binding domain and a IL-2, and immodulatory fusion proteins with a collagen-binding domain and an IL-12. In

some embodiments, the reduced systemic exposure results in a reduced toxicity or an improved therapeutic index.

### **Intratumoral Retention**

5 **[0082]** Several factors dictate the intratumoral retention of a cytokine fusion protein: collagen-binding affinity, collagen concentration, size-dependent escape by diffusion or convection, and cytokine receptor-mediated consumption. Affinity to collagen and increased molecular weight contribute the intratumoral retention and systemic distribution of collagen binding fusion proteins. In some embodiments, increasing the affinity to collagen or increasing the molecular weight of a  
10 collagen-binding immunomodulatory molecule will increase intratumoral retention and decrease systemic distribution, thereby providing a therapeutic effect of a composition comprising the immunomodulatory fusion protein administered to a subject.

**[0083]** Accordingly, provided herein are immunomodulatory fusions to domains with specific affinity for collagen, in some embodiments, leading to greater retention within the particular  
15 collagen-rich tumors. In some aspects described herein, the immunomodulatory fusion proteins comprise an IL-2, an IL-12, and a collagen-binding domain, wherein the collagen-binding domain increases tumor retention and reduces systemic exposure to IL-2 and IL-12 following intratumoral administration in a subject, thereby reducing treatment-related toxicity.

**[0084]** Unless the context indicates otherwise, it is specifically intended that the various  
20 features described herein can be used in any combination. Moreover in some embodiments, any feature or combination of features set forth herein can be excluded or omitted. To illustrate, if the specification states that a complex comprises components A, B, and C, it is specifically intended that any of A, B, or C, or a combination thereof, can be omitted and disclaimed singularly or in any combination.

25

### **Definitions**

**[0085]** As used in the present specification, the following words and phrases are generally intended to have the meanings as set forth below, except to the extent that the context in which they are used indicates otherwise.

30 **[0086]** It is to be noted that as used herein and in the claims, the singular forms “a,” “an” and “the” include plural referents unless the context clearly dictates otherwise.

**[0087]** As used herein, “and/or” refer to and encompasses any and all possible combinations of one or more of the associated listed items, as well as the lack of combinations when interpreted in

the alternative (“or”). Moreover, any feature or combination of features set forth herein can be excluded or omitted.

[0088] The term “about” as used herein when referring to a measurable value such as an amount of a compound or agent, dose, time, temperature, and the like, is meant to encompass variations of  $\pm 10\%$ ,  $\pm 5\%$ ,  $\pm 1\%$ ,  $\pm 0.5\%$ , or even  $\pm 0.1\%$  of the specified amount.

[0089] The terms “polypeptide,” “protein” or “peptide” refer to any chain of amino acid residues, regardless of its length or post-translational modification (e.g., glycosylation or phosphorylation).

[0090] The term “fusion protein” as used herein, refers to a protein that is created by joining two or more elements, components, or domains and/or polypeptides to create a larger polypeptide. As used herein, the terms “linked,” “operably linked,” “fused” or “fusion”, are used interchangeably, and refers to the joining together of two or more elements, components, domains and/or polypeptides within a fusion protein that allow for at least one element, component, domain and/or polypeptide to have at least a portion of the biological function or cellular activity when expressed in the fusion protein as when expressed in its natural state and/or without the linkage. The joining together of the two more elements or components or domains can be performed by whatever means known in the art including chemical conjugation, noncovalent complex formation or recombinant means. Methods of chemical conjugation (e.g., using heterobifunctional crosslinking agents) are known in the art. Thus, the elements, components, domains and/or polypeptides can be joined by covalent bonds (e.g., peptide bonds) or non-covalent bonds. The elements, components, domains and/or polypeptides can be joined by peptide bond formation in the ribosome during translation or post-translationally.

[0091] Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art. The terminology used in the description herein is for the purpose of describing particular embodiments only and is not intended to be limiting.

### **Immunomodulatory Fusion Protein**

[0092] As used herein, the term “immunomodulatory fusion protein” refers to a polypeptide comprising a collagen-binding domain operably linked to an IL-2 and IL-12. In some embodiments, the collagen binding domain is operably linked to the IL-2 and IL-12 by a linear polypeptide spacer. In some embodiments, the collagen binding domain is operably linked to the IL-2 and IL-12 by a linear polypeptide spacer. In some embodiments, the collagen binding domain is operably linked to the IL-2 and IL-12 by a linker.

[0093] In some aspects, the disclosure provides an immunomodulatory fusion protein comprising a collagen-binding domain is operably linked to an IL-2 and IL-12. In some aspects, the disclosure provides an immunomodulatory fusion protein comprising a collagen-binding domain is operably linked to an IL-2 and IL-12 by a linear polypeptide spacer. In some  
5   embodiments, the immunomodulatory fusion protein further comprises a linker. In some  
embodiments, the immunomodulatory fusion protein further comprises a plurality of linkers.

### **I. Collagen-Binding Domains**

[0094] In some embodiments, the disclosure provides immunomodulatory fusion proteins  
10   comprising a collagen-binding domain. In some embodiments, the collagen-binding domain has a  
MW of about 5-1,000kD, about 5-100 kDa, about 10-80 kDa, about 20-60 kDa, about 30-50 kDa,  
or about 10 kDa, about 20 kDa, about 30 kDa, about 40 kDa, about 50 kDa, about 60 kDa, about  
70 kDa, about 80 kDa, about 90 kDa or about 100 kDa. In some embodiments, the collagen-  
binding domain is about 5 kDa, about 10 kDa, about 20 kDa, about 30 kDa, about 40 kDa, about  
15   50 kDa, about 60 kDa, about 70 kDa, about 80 kDa, about 90 kDa, about 100 kDa, about 150kDa,  
about 200kDa, about 300kDa, about 400kDa, about 500kDa, about 600kDa, about 700kDa, about  
800kDa, about 900kDa or about 1,000kDa. In some embodiments, the collagen-binding domain is  
about 30 kDa. In some embodiments, the collagen-binding domain is about 40 kDa.

[0095] In some embodiments, the collagen-binding domain is about 10-350, about 10-300,  
20   about 10-250, about 10-200, about 10-150, about 10-100, about 10-50, or about 10-20 amino  
acids in length. In some embodiments, the collagen-binding domain is about 10 amino acids in  
length. In some embodiments, the collagen-binding domain is about 15 amino acids in length. In  
some embodiments, the collagen- binding domain is about 20 amino acids in length. In some  
embodiments, the collagen-binding domain is about 30 amino acids in length. In some  
25   embodiments, the collagen-binding domain is about 40 amino acids in length. In some  
embodiments, the collagen-binding domain is about 50 amino acids in length. In some  
embodiments, the collagen- binding domain is about 60 amino acids in length. In some  
embodiments, the collagen-binding domain is about 70 amino acids in length. In some  
embodiments, the collagen- binding domain is about 80 amino acids in length. In some  
30   embodiments, the collagen-binding domain is about 90 amino acids in length. In some  
embodiments, the collagen- binding domain is about 100 amino acids in length. In some  
embodiments, the collagen-binding domain is about 120 amino acids in length. In some  
embodiments, the collagen-binding domain is about 150 amino acids in length. In some  
embodiments, the collagen-binding domain is about 200 amino acids in length. In some

embodiments, the collagen-binding domain is about 250 amino acids in length. In some embodiments, the collagen-binding domain is about 300 amino acids in length. In some embodiments, the collagen-binding domain is about 350 amino acids in length.

**[0096]** In some embodiments, the collagen-binding domain comprises one or more (e.g., two, three, four, five, six, seven, eight, nine, ten or more) leucine-rich repeats which bind collagen. In some embodiments, the collagen-binding domain comprises a proteoglycan. In some embodiments, the collagen-binding domain comprises a proteoglycan, wherein the proteoglycan is selected from the group consisting of: decorin, biglycan, testican, bikunin, fibromodulin, lumican, chondroadherin, keratin, ECM2, epiphykan, asporin, PRELP, keratocan, osteoadherin, opticon, osteoglycan, nyctalopin, Tsukushi, podocan, podocan-like protein 1 versican, perlecan, nidogen, neurocan, aggrecan, and brevican.

**[0097]** In some embodiments, the collagen-binding domain comprises a class I small leucine-rich proteoglycan (SLRP). In some embodiments, the collagen-binding domain comprises a class II SLRP. In some embodiments, the collagen-binding domain comprises a class III SLRP. In some embodiments, the collagen-binding domain comprises a class IV SLRP. In some embodiments, the collagen-binding domain comprises a class V SLRP. Further description of SLRP classes is disclosed in Schaefer & Iozzo (2008) J Biol Chem 283(31):21305-21309, which is incorporated herein by reference in its entirety.

**[0098]** In some embodiments, the collagen-binding domain comprises one or more leucine-rich repeats from a human proteoglycan Class II member of the small leucine-rich proteoglycan (SLRP) family. In some embodiments, the SLRP is selected from lumican, decorin, biglycan, fibromodulin, keratin, epiphykan, asporin and osteoglycin.

**[0099]** The term " $k_d$ " ( $\text{sec}^{-1}$ ), as used herein, refers to the dissociation rate constant of a particular protein-protein interaction. This value is also referred to as the  $k_{\text{off}}$  value.

**[00100]** The term " $k_a$ " ( $\text{M}^{-1} \times \text{sec}^{-1}$ ), as used herein, refers to the association rate constant of a particular protein-protein interaction. This value is also referred to as the  $k_{\text{on}}$  value.

**[00101]** The term " $K_D$ " (M), as used herein, refers to the dissociation equilibrium constant of a particular protein-protein interaction.  $K_D = k_d/k_a$ . In some embodiments, the affinity of a protein (e.g., binding domain) is described in terms of the  $K_D$  for an interaction between two proteins.

For clarity, as known in the art, a smaller  $K_D$  value indicates a higher affinity interaction, while a larger  $K_D$  value indicates a lower affinity interaction.

**[00102]**

In some embodiments, the collagen-binding domain binds collagen (e.g., collagen type 1 or type 3) with a binding affinity  $K_D$  value of 0.1-1,000 nM as measured by a suitable method known in

the art for determining protein binding affinity, e.g., by ELISA, surface plasmon resonance (BIAcore), FACS analysis, etc. In some embodiments, the collagen-binding domain binds collagen with a binding affinity  $K_D$  value of 0.1-1.0 nM, 1.0-10 nM, 10-20 nM, 20-30 nM, 30-40 nM, 40-50 nM, 50-60 nM, 70-80 nM, 90-100 nM, 10-50 nM, 50-100nM, 100-1,000, or 1,000-10,000 nM as determined by a suitable method known in the art. In some embodiments, the immunomodulatory fusion protein binds collagen with a binding affinity  $K_D$  value of 0.1-1.0 nM, 1.0-10 nM, 10-20 nM, 20-30 nM, 30-40 nM, 40-50 nM, 50-60 nM, 70-80 nM, 90-100 nM, 10-50 nM, 50-100nM, 100-1,000, or 1,000-10,000 nM as determined by a suitable method known in the art. In some embodiments, the collagen-binding domain binds trimeric peptides containing repeated GPO triplets. In some embodiments, the collagen-binding domain binds common collagen motifs in a hydroxyproline-dependent manner.

#### A. Lumican

**[00103]** Lumican, also known as LUM, is an extracellular matrix protein that, in humans, is encoded by the LUM gene on chromosome 12 (Chakravarti et al., (1995) Genomics 27(3):481-488). Lumican is a proteoglycan Class II member of the small leucine-rich proteoglycan (SLRP) family that includes decorin, biglycan, fibromodulin, keratocan, epiphykan, and osteoglycin (Iozzo & Schaefer (2015) Matrix Biology 42: 11-55). Lumican is a stable protein that binds specifically to collagen types I and IV.

**[00104]** Lumican has a molecular weight of about 40 kDa and has four major intramolecular domains: 1) a signal peptide of 16 amino acid residues, 2) a negatively-charged N-terminal domain containing sulfated tyrosine and disulfide bond(s), 3) ten tandem leucine-rich repeats allowing lumican to bind to collagen, and 4) a carboxyl terminal domain of 50 amino acid residues containing two conserved cysteines 32 residues apart. Kao et al., (2006) Experimental Eye Research 82(1):3-4). There are four N-linked sites within the leucine-rich repeat domain of the protein core that can be substituted with keratan sulfate. The core protein of lumican (like decorin and fibromodulin) is horseshoe shaped. This enables it bind to collagen molecules within a collagen fibril, thus helping keep adjacent fibrils apart Scott (1996) Biochemistry 35(27): 8795-8799.

**[00105]** In some embodiments, the collagen-binding domain comprises a class II small leucine-rich proteoglycan (SLRP). Further description of SLRP classes is disclosed in Schaefer & Iozzo (2008) J Biol Chem 283(31):21305-21309, which is incorporated herein by reference in its entirety. In some embodiments, the collagen-binding domain comprises one or more leucine-rich repeats from a human proteoglycan Class II member of the small leucine-rich proteoglycan (SLRP) family. In some embodiments, the SLRP is lumican. In some embodiments, the lumican

is human lumican. In some embodiments, lumican comprises an amino acid sequence having 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%, at least 99%, or 100% identity to the amino acid sequence as set forth in SEQ ID NO: 11, or a portion thereof.

**[00106]** In some embodiments, the lumican is a variant comprising one or more amino acid substitutions, additions or deletions, optionally two, three, four, five, six, seven, eight, nine, ten or more amino acid substitutions, additions or deletions relative to a lumican protein comprising the amino acid sequence of SEQ ID NO: 11. In some embodiments, the lumican variant has increased binding affinity to collagen relative to a collagen binding affinity of a lumican protein comprising the amino acid sequence of SEQ ID NO: 11. In some embodiments, the lumican variant has decreased binding affinity to collagen relative to a collagen binding affinity of a lumican protein comprising the amino acid sequence of SEQ ID NO: 11.

## B. LAIR1 and LAIR2

### **[00107]** Leukocyte-Associated Immunoglobulin-Like Receptors (LAIR- and LAIR-2)

Leukocyte-associated Ig-like receptor (LAIR)-1 is a collagen-receptor that inhibits immune cell function upon collagen binding. Next to LAIR-I, the human genome encodes LAIR-2, a soluble homolog. Human (h) LAIR-I is expressed on the majority of PBMC and thymocytes (Maasho et al., (2005) *Mal Immunol* 42: 1521-1530). Cross-linking of LAIR-1 by mAbs in vitro delivers a potent inhibitory signal that is capable of inhibiting immune cell function. Collagens are known to be natural, high-affinity ligands for the LAIR molecules. Interaction of hLAIR-1 with collagens directly inhibits immune cell activation in vitro (Meyaard et al., (1997) *Immunity* 7:283-290; Poggi (1998) *Eur J Immunol* 28:2086-2091; Van der Vuurst de Vries et al., (1999) *Eur J Immunol* 29:3160-3167; Lebbink et al., (2006) *J Exp Med* 203:1419-1425).

**[00108]** In some embodiments, the collagen-binding domain comprises a human type I glycoprotein having an Ig-like domain, or an extracellular portion thereof which binds collagen. In some embodiments, the type I glycoprotein competes with lumican for binding for binding to collagen type I. In some embodiments, the human type I glycoprotein is selected from LAIR, LAIR1, and LAIR2.

**[00109]** In some embodiments, the human type I glycoprotein is LAIR1. In some embodiments, the LAIR1 comprises an amino acid sequence having 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%, at least 99%, or 100% identity to the amino acid sequence as set forth in SEQ ID NO: 13, or a portion thereof. In some embodiments, the human type I glycoprotein is LAIR1 and the collagen-binding domain comprises an amino acid sequence having 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%,  
5 at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to amino acid residues 22-122 of the amino acid sequence as set forth in SEQ ID NO: 13, or a portion thereof.

**[00110]** In some embodiments, the human type I glycoprotein is LAIR1. In some embodiments, the LAIR1 comprises an amino acid sequence having 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  
10 at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to the amino acid sequence as set forth in SEQ ID NO: 14, or a portion thereof.

**[00111]** . In some embodiments, the LAIR comprises an amino acid sequence having at least  
15 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%, at least 99%, or 100% identity to the amino acid sequence as set forth in SEQ ID NO: 12, or a portion thereof.

**[00112]** In some embodiments, the LAIR1 is a variant comprising one or more amino acid  
20 substitutions, additions or deletions, optionally two, three, four, five, six, seven, eight, nine, ten or more amino acid substitutions, additions or deletions relative to a LAIR1 protein comprising the amino acid sequence of SEQ ID NO: 13. In some embodiments, the LAIR1 variant has increased binding affinity to collagen relative to a collagen binding affinity of a LAIR1 protein comprising the amino acid sequence of SEQ ID NO: 13. In some embodiments, the LAIR1 variant has  
25 decreased binding affinity to collagen relative to a collagen binding affinity of a LAIR1 protein comprising the amino acid sequence of SEQ ID NO: 13.

**[00113]** In some embodiments, the LAIR1 is a variant comprising one or more amino acid  
substitutions, additions or deletions, optionally two, three, four, five, six, seven, eight, nine, ten or more amino acid substitutions, additions or deletions relative to a LAIR1 protein comprising the  
30 amino acid sequence of SEQ ID NO: 14. In some embodiments, the LAIR1 variant has increased binding affinity to collagen relative to a collagen binding affinity of a LAIR1 protein comprising the amino acid sequence of SEQ ID NO: 14. In some embodiments, the LAIR1 variant has decreased binding affinity to collagen relative to a collagen binding affinity of a LAIR1 protein comprising the amino acid sequence of SEQ ID NO: 14.

**[00114]** In some embodiments, the LAIR is a variant comprising one or more amino acid substitutions, additions or deletions, optionally two, three, four, five, six, seven, eight, nine, ten or more amino acid substitutions, additions or deletions relative to a LAIR protein comprising the amino acid sequence of SEQ ID NO: 12. In some embodiments, the LAIR1 variant has increased binding affinity to collagen relative to a collagen binding affinity of a LAIR protein comprising the amino acid sequence of SEQ ID NO: 12. In some embodiments, the LAIR variant has decreased binding affinity to collagen relative to a collagen binding affinity of a LAIR protein comprising the amino acid sequence of SEQ ID NO: 12.

**[00115]** In some embodiments, the human type I glycoprotein is LAIR2. In some embodiments, the LAIR2 comprises an amino acid sequence having 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%, at least 99%, or 100% identity to the amino acid sequence as set forth in SEQ ID NO: 15, or a portion thereof.

**[00116]** In some embodiments, the LAIR2 is a variant comprising one or more amino acid substitutions, additions or deletions, optionally two, three, four, five, six, seven, eight, nine, ten or more amino acid substitutions, additions or deletions relative to a LAIR2 protein comprising the amino acid sequence of SEQ ID NO: 15. In some embodiments, the LAIR2 variant has increased binding affinity to collagen relative to a collagen binding affinity of a LAIR2 protein comprising the amino acid sequence of SEQ ID NO: 15. In some embodiments, the LAIR2 variant has decreased binding affinity to collagen relative to a collagen binding affinity of a LAIR2 protein comprising the amino acid sequence of SEQ ID NO: 15.

Table 1. Exemplary sequences for collagen-binding domains

| SEQ ID NO: | Description      | Sequence                                                                                                                                                                                                                                                                                                                                                                    |
|------------|------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 11         | Lumican          | MSLSAFTLFLALIGGTSGQYYDYDFPLSIYGQSSPNCAPCNCPE<br>ESYPSAMYCDELKLKSVPMVPPGIKYLYLRNNQIDHIDEKAFE<br>NVTDLQWLILDHNLLENSKIKGRVFSKLKQLKKLHINHNLT<br>ESVGPLPKSLEDLQLTHNKITKLGSFEGLVNLTFIHLQHNRLKE<br>DAVSAAFKGLKSLEYLDLSFNQIARLPGLPVSLLTLYLDNNK<br>ISNIPDEYFKRFNALQYLRLSHNELADSGIPGNSFNVSSVELD<br>LSYNKLKNIPTVNENLENYYLEVNQLEKFDIKSFCKILGPLSYS<br>KIKHLRLDGNRISETSLPPDMYECLRVANEVTLN |
| 12         | LAIR<br>(murine) | MSLHPVILLVLVLCLGWKINTQEGSLPDITIFPNSSLMISQGTFF<br>TVVCSYSDKHDLYNMVRLEKDGSTFMEKSTEPYKTEDEFEIG<br>PVNETITGHYSCIYSKGITWSERSKTLELKVIKENVIQTPAPGPT<br>SDTSWLKTYSIYIFTVVSIVIFLLCLSALLFCFLRHRQKKQGLPN                                                                                                                                                                               |

|    |                  |                                                                                                                                                                                                                                                                                                                         |
|----|------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|    |                  | NKRQQQRPEERLNLATNGLEMPDIVADDRLPEDRWTTETWTP<br>VAGDLQEVTYIQLDHHSLTQRAVGAVTSQSTDMAESSTYAAII<br>RH                                                                                                                                                                                                                         |
| 13 | LAIR1<br>(human) | MSPHPTALLGLVLCLAQTIHTQEEDLPRPSISAEPGTVIPLGSH<br>VTFVCRGPVGVQTFRLERESRSTYNDTEDVSQASPESEARFRI<br>DSVSEGNAGPYRCIYYKPPKWSEQSDYLELLVKETSGGPDSPD<br>TEPGSSAGPTQRPSDNSHNEHAPASQGLKAEHLYILIGVSVVF<br>LFCLLLLVLFLHRQNQIKQGPPRSKDEEQKPQQRPD LAVDVL<br>ERTADKATVNGLPKEDRETDT SALAAGSSQEVTYAQLDHW A<br>LTQRTARAVSPQSTKPMASITYAAVARH |
| 14 | ECD of<br>LAIR1  | QEEDLPRPSISAEPGTVIPLGSHVTFVCRGPVGVQTFRLERESR<br>STYNDTEDVSQASPESEARFRIDSVSEGNAGPYRCIYYKPPK<br>WSEQSDYLELLVKETSGGPDSPDTEPGSSAGPTQRPSDNSHNE<br>HAPASQGLKAEHLY                                                                                                                                                             |
| 15 | LAIR2<br>(human) | MSPHLTALLGLVLCLAQTIHTQEGALPRPSISAEPGTVISPGSH<br>VTFMCRGPVGVQTFRLEREDRAKYKDSYNVFR LGPSESEARF<br>HIDSVSEGNAGLYRCLYYKPPGWSEHSDFLELLVKESGGPDS<br>PDTEPGSSAGTVPGTEASGFDAP                                                                                                                                                    |

## II. Immunomodulatory Domain

[00117] The immunomodulatory fusion proteins disclosed herein comprises at least one IL-2 and at least one IL-12. In certain embodiments, the immunomodulatory fusion proteins disclosed herein comprises an IL-2, an IL-12, and a collagen-binding domain. In certain embodiments, the immunomodulatory fusion proteins disclosed herein comprises an IL-2, an IL-12, a collagen-binding domain, and at least one linear polypeptide spacer. In some embodiments, the IL-2 is operably linked to a collagen-binding domain. In some embodiments, the IL-2 is operably linked to a linear polypeptide spacer. In some embodiments, the IL-12 is operably linked to a collagen-binding domain. In some embodiments, the IL-12 is operably linked to a linear polypeptide spacer.

### A. IL-2

[00118] As used herein, "interleukin (IL)-2," (IL-2) refers to a pleiotropic cytokine that activates and induces proliferation of T cells and natural killer (NK) cells. The biological activity of IL-2 is mediated through a multi-subunit IL-2 receptor complex (IL-2R) of three polypeptide subunits that span the cell membrane: p55 (IL-2R $\alpha$ , the alpha subunit, also known as CD25 in humans), p75 (IL-2R $\beta$ , the beta subunit, also known as CD122 in humans) and p64 (IL-2R $\gamma$ , the gamma subunit, also known as CD132 in humans).

[00119] In some embodiments, the immunomodulatory fusion protein comprises an IL-2. In some embodiments, the IL-2 is operably linked to a collagen binding domain. In some embodiments, the immunomodulatory fusion protein comprises a member of the IL-2 family operably linked to a collagen binding domain.

5 [00120] T cell response to IL-2 depends on a variety of factors, including: (1) the concentration of IL-2; (2) the number of IL-2R molecules on the cell surface; and (3) the number of IL-2R occupied by IL-2 (i.e., the affinity of the binding interaction between IL-2 and IL-2R (Smith, "Cell Growth Signal Transduction is Quanta!" In Receptor Activation by Antigens, Cytokines, Hormones, and Growth Factors 766:263-271, 1995)).

10 [00121] In some embodiments, the IL-2 is wild-type IL-2 (e.g., human IL-2 in its precursor form or mature IL-2. In some embodiments, the IL-2 is human IL-2. In some embodiments, the IL-2 comprises an amino acid sequence having 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%, at least 99%, or 100% identity to the amino acid sequence as set forth in SEQ ID NOs: 1 or 2, or a portion thereof. In some embodiments, the IL-2 comprises an amino acid sequence having 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%, at least 99%, or 100% identity to the amino acid sequence as set forth in SEQ ID NOs: 3 or 4, or a portion thereof.

20 [00122] In other embodiments, the IL-2 is a mutant human IL-2. The term "IL-2 mutant" or "mutant IL-2 polypeptide" as used herein is intended to encompass any mutant forms of various forms of the IL-2 molecule including full-length IL-2, truncated forms of IL-2 and forms where IL-2 is linked to another molecule such as by fusion or chemical conjugation. The various forms of IL-2 mutants are characterized in having a at least one amino acid mutation affecting the interaction of IL-2 with CD25. This mutation may involve substitution, deletion, truncation or modification of the wild-type amino acid residue normally located at that position. Mutants obtained by amino acid substitution are preferred. Unless otherwise indicated, an IL-2 mutant may be referred to herein as an IL-2 mutant peptide sequence, an IL-2 mutant polypeptide, IL-2 mutant protein or IL-2 mutant analog.

30 [00123] In some embodiments, IL-2 mutants comprise an amino acid sequence that is at least 80% identical to SEQ ID NOs: 1 or 2 that bind CD25. For example, some embodiments an IL-2 mutant has at least one mutation (e.g., a deletion, addition, or substitution of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or more amino acid residues) that increases the

affinity for the alpha subunit of the IL-2 receptor relative to wild-type IL-2. It should be understood that mutations identified in mouse IL-2 may be made at corresponding residues in full length human IL-2 (nucleic acid sequence (accession: NM000586); amino acid sequence (accession: P60568) or human IL-2 without the signal peptide. Accordingly, in some

5 embodiments, the IL-2 is human IL-2. In other embodiments, the IL-2 is a mutant human IL-2. The amino acid sequence of human IL-2 (SEQ ID NO:1; full length) is found in Genbank under accession locator NP\_000577.2. The amino acid sequence of mature human IL-2 is depicted in SEQ ID NO:2 (human wild-type mature). The murine (*Mus musculus*) IL-2 amino acid sequence is found in Genbank under accession locator (SEQ ID NO:3). The amino acid sequence of mature

10 murine IL-2 is depicted in SEQ ID NO:4.

**[00124]** In certain embodiments, IL-2 is mutated such that it has an altered affinity (e.g., a lower affinity) for the IL-2R alpha receptor compared with unmodified IL-2. Site-directed mutagenesis can be used to isolate IL-2 mutants that exhibit decreased affinity binding to CD25, i.e., IL-2Ra, as compared to wild-type IL-2. Increasing the affinity of IL-2 for IL-2Ra at the cell surface will

15 increase receptor occupancy within a limited range of IL-2 concentration, as well as raise the local concentration of IL-2 at the cell surface.

**[00125]** In some embodiments, the amino acid substitutions increasing IL-2R $\beta$  binding affinity include: L80F, R81D, L85V, I86V, and I92F. In some embodiments, the amino acid substitutions that increase IL-2R $\beta$  binding affinity include: L80F, R81D, L85V, I86V, and I92F.

Table 2. Exemplary sequences for IL-2

| SEQ ID NO: | Description                 | Sequence                                                                                                                                                                                 |
|------------|-----------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1          | Human IL-2                  | MYRMQLLSIALSLALVTNSAPTSSSTKKTQLQLEHLL<br>LDLQMILNGINNYKNPKLTRMLTFKFYMPKKATELKH<br>LQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVL<br>ELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT                     |
| 2          | Human wild-type mature IL-2 | APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTR<br>MLTFKFYMPKKATELKHLLQCLEEELKPLEEVLNLAQS<br>KNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATI<br>VEFLNRWITFCQSIISTLT                                       |
| 3          | Murine IL-2                 | MYSMQLASCVTTLTVLLVNSAPTSSSTSSSTAEAAQQQQ<br>QQQQQQQQHLEQLLMDLQELLSRMENYRNKLPRML<br>TFKFYLPKQATELKDLQCLEDELGPLRHVLDLTQSKSF<br>QLEDAENFISNIRVTVVKLKGSDNTFECQ<br>FDDESATVVDLRRWIAFCQSIISTSPQ |
| 4          | Murine mature IL-2          | APTSSSTSSSTAEAAQQQQQQQQQQQQHLEQLLMDLQE<br>LLSRMENYRNKLPRMLTFKFYLPKQATELKDLQCLE                                                                                                           |

|  |  |                                                                                  |
|--|--|----------------------------------------------------------------------------------|
|  |  | DELGPLRHVLDLTQSKSFQLEDAENFISNIRVTVVKLK<br>GSDNTFECQFDDESATVVDFLRRWIAFCQ SIISTSPQ |
|--|--|----------------------------------------------------------------------------------|

## B. IL-12

**[00126]** Interleukin-12 (IL-2) plays an important role in innate and adaptive immunity. Gately, MK et al., Annu Rev Immunol. 16: 495-521 (1998). IL-12 functions primarily as a 70 kDa heterodimeric protein consisting of two disulfide-linked p35 and p40 subunits. The precursor form of the IL-12 p40 subunit (NM\_002187; P29460; also referred to as IL-12B, natural killer cell stimulatory factor 2, cytotoxic lymphocyte maturation factor 2) is 328 amino acids in length, while its mature form is 306 amino acids long. The precursor form of the IL-12 p35 subunit (NM\_000882; P29459; also referred to as IL-12A, natural killer cell stimulatory factor 1, cytotoxic lymphocyte maturation factor 1) is 219 amino acids in length and the mature form is 197 amino acids long.

**[00127]** In some embodiments, the immunomodulatory fusion protein comprises an IL-12. In some embodiments, the immunomodulatory fusion protein comprises an IL-12 operably linked to a collagen binding domain.

**[00128]** In some embodiments, the IL-12 comprises IL-12A (e.g., SEQ ID NO: 6). In some embodiments, the IL-12 comprises an amino acid sequence having 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%, at least 99%, or 100% identity to the amino acid sequence of IL-12A as set forth in SEQ ID NO: 6, or a portion thereof.

**[00129]** In some embodiments, the IL-12 comprises IL-12A (e.g., SEQ ID NO: 8). In some embodiments, the IL-12 comprises an amino acid sequence having 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%, at least 99%, or 100% identity to the amino acid sequence of IL-12A as set forth in SEQ ID NO: 8, or a portion thereof.

**[00130]** In some embodiments, the IL-12 comprises an amino acid sequence having 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%, at least 99%, or 100% identity to the amino acid sequence of IL-12A as set forth in SEQ ID NO: 10, or a portion thereof.

**[00131]** In some embodiments, the IL-12 comprises IL-12B (e.g., SEQ ID NOs: 5). In some embodiments, the IL-12 comprises an amino acid sequence having 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%, at least 99%, or 100% identity to the amino acid sequence of IL-12B as set forth in SEQ ID NO: 5, or a portion thereof.

**[00132]** In some embodiments, the IL-12 comprises IL-12B (e.g., SEQ ID NO: 7). In some embodiments, the IL-12 comprises an amino acid sequence having 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%, at least 99%, or 100% identity to the amino acid sequence of IL-12B as set forth in SEQ ID NOs: 7, or a portion thereof. In some embodiments, the IL-12 comprises IL-12B (e.g., SEQ ID NO: 7).

**[00133]** In some embodiments, the IL-12 comprises an amino acid sequence having 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%, at least 99%, or 100% identity to the amino acid sequence of IL-12B as set forth in SEQ ID NO: 9, or a portion thereof.

**[00134]** In some embodiments, the IL-12 comprises both IL-12A and IL-12B. In some embodiments, the IL-12 comprises both IL-12A and IL-12B and a linker. In some embodiments, the immunomodulatory fusion protein comprises an IL-12 comprising the amino acid sequences set forth in SEQ ID NOs: 5-10. In some embodiments, the IL-12 comprises an amino acid sequence having 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%, at least 99%, or 100% identity to the amino acid sequence of IL-12A and IL-12B as set forth in SEQ ID NOs: 5-10, or a portion thereof.

**[00135]** The term “IL-12 mutant” or “mutant IL-12 polypeptide” as used herein is intended to encompass any mutant forms of various forms of the IL-12 molecule including full-length IL-12, truncated forms of IL-12 and forms where IL-12 is linked to another molecule such as by fusion or chemical conjugation. The various forms of IL-12 mutants are characterized in having a at least one amino acid mutation. This mutation may involve substitution, deletion, truncation or modification of the wild-type amino acid residue normally located at that position. Mutants obtained by amino acid substitution are preferred. Unless otherwise indicated, an IL-12 mutant

may be referred to herein as an IL-12 mutant peptide sequence, an IL-12 mutant polypeptide, IL-12 mutant protein or IL-12 mutant analog.

Table 3: Exemplary sequences for IL-12

| SEQ ID NO: | Protein                                                        | Sequence                                                                                                                                                                                                                                                                                                                                                                |
|------------|----------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 5          | Human IL-12 p40 wild-type<br><br>(IL-12 subunit beta; IL-12B)  | MHPQQQLVVSWSFLVLLASPIVAIWELEKNVYVVELDW<br>YPDAPGETVVLTCDTPEEDGITWTSDQSSEVLGSGKTLT<br>IQVKEFGDAGQYTCHKGGGEALSRSLLLLHKKEDGIWST<br>DILKDQKEPKAKSFLKCEAKDYSGHFTCWWLTAISTDL<br>KFSVKSSRGSSDPRGVTCEAASLSAEKVSVDHREYNKY<br>TVECQEGSTCPAAEESLLIEVVVEAVHKLKYENYTSSFF<br>IRDIIKPDPPKNLQLKPLKNSRQVEVSWEYPDTWSTPHS<br>YFSLTFCVQVQGKNKREKKLFMDQTSKVTCHKDANV<br>RVQARDRYSSFWSEWASVSCS |
| 6          | Human IL-12 p35 wild-type<br><br>(IL-12 subunit alpha; IL-12A) | MSPLRKCLLLTSLVLLVSCSLARNLPRASPAPVTEPVQC<br>FNHSQTLLRAVNSELHKAIQMLAVYSCTPEEIDHEDITK<br>DKTSTVKACVPLELVKNESCLASGHISFTTNGSCLASGK<br>TSFMMALCLNSIYEDLKLYQLEFKNMNAQLLMDPQRQ<br>IFLDQNMLSAIDELIQALNGSDVTVPQKLSLEEPDFYKIK<br>MKLCILLHAFRIRAVTIDRVMSYLTSS                                                                                                                       |
| 7          | Human IL-12B without signal peptide                            | IWELKKDVYVVELDWYPDAPGEMVVLTCDTPEEDGIT<br>WTLDQSSEVLGSGKTLTIQVKEFGDAGQYTCHKGGEV<br>LSHLLLLHKKEDGIWSTDILKDQKEPKNKTLRCEAK<br>NYSGRFTCWWLTTISTDLTFSVKSSRGSSDPQGVTCGA<br>ATLSAERVRGDNKEYEYSVECQEDSACPAAEESLPIEV<br>MVDAVHKLKYENYTSSFFIRDIIKPDPPKNLQLKPLKNS<br>RQVEVSWEYPDTWSTPHSYFSLTFCVQVQGKSKREKK<br>DRVFTDKTSATVICRKNASISVRAQDRYSSSWSEWAS<br>VPCS                         |
| 8          | Human IL-12A without signal peptide                            | RNLPVATPDPMFPCLLHHSQNLLRAVSNMLQKARQTL<br>EFYPCTSEEIDHEDITKDKTSTVEACLPLELTKNESCLNS<br>RETSFITNGSCLASRKTSFMMALCLSSIYEDLKMYQVEF<br>KTMNAKLLMDPKRQIFLDQNMLAVIDELMQALNFNSE<br>TVPQKSSLEEPDFYKTKIKLCILLHAFRIRAVTIDRVMSY<br>LNAS                                                                                                                                               |
| 9          | Murine IL-12 subunit beta                                      | MWELEKDVYVVEVDWTPDAPGETVNLTCDTPEEDDIT<br>WTSDQRHGVIGSGKTLTITVKEFLDAGQYTCHKGGGETL<br>SHSHLLLLHKKENGIWSTEILKNFNKNTFLKCEAPNYSGR<br>FTCSWLVRNMDLKFNKSSSSSPDSRAVTCGMASLSA<br>EKVTLQDRDYEKYSVSCQEDVTCPTAEETLPIELALEAR<br>QQNKYENYSTSFFIRDIIKPDPPKNLQMKPLKNSQVEVS<br>WEYPDSWSTPHSYFSLKFFVRIQRKKEKMKETEEGCNQ<br>KGAFLVEKTSTEVQCKGGNVCVQAQDRYNNSSCSKW<br>ACVPCRVR                |

|    |                               |                                                                                                                                                                                                                |
|----|-------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 10 | Murine IL-12 subunit<br>alpha | RVIPVSGPARCLSQSRNLLKTTDDMVKTAREKLKHYSCTAEDIDHEDITRDQTSTLKTCLPLELHKNESCLATRETSS<br>TTRGSCLPQKTSMMTLCLGSIYEDLKMYQTEFQAIN<br>AALQNHNHQIILDKGMLVAIDELMQSLNHNGETLRQ<br>KPPVGEADPYRVKMKLCILLHAFSTRVVTINRVMGYLS<br>SA |
|----|-------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

### III. Linear Polypeptide Spacer

**[00136]** In some embodiments, the linear polypeptide spacer is a polypeptide comprising "N" amino acids in length, wherein N=1-1000, 50-800, 100-600, or 200-500. In some embodiments, the linear polypeptide spacer comprises about 1 to about 100 amino acid residues. In some  
5       embodiments, the linear polypeptide space comprises more than 100 amino acid residues. In certain embodiments, the linear polypeptide spacer comprises about 1 to about 100 amino acid residues.

**[00137]** In some embodiments, the linear polypeptide spacer is a soluble polypeptide. In some  
10       embodiments, the linear polypeptide spacer has a molecular weight between 1 and 200 kDa. In some embodiments, the linear polypeptide spacer has a molecular weight 1-10 kDa, 10-20 kDa, 20-30 kDa, 30-40 kDa, 40-50 kDa, 50-60 kDa, 60-70 kDa, 70-80 kDa, 80-90 kDa, 90-100 kDa, 100-110 kDa, 110-120 kDa, 120-130 kDa, 130-140 kDa, 140-150 kDa, 150-160 kDa, 160-170 kDa, 170-180 kDa, 180-190 kDa, 190-200kDa, 10-100, 100-200kDa, 200-300kDa, 300-400kDa,  
15       400-500kDa, 500-1,000kDa, or 100-1,000 kDa.

**[00138]** In certain embodiments, the linear polypeptide spacer provides a steric separation between one element of the fusion protein to another. In certain embodiments, the linear polypeptide spacer provides a steric separation between one domain of the fusion protein to another. In some embodiments, the linear polypeptide spacer between the IL-2 and the collagen-binding protein provides a steric separation such that the IL-2 retains its activity (e.g., promote  
20       receptor/ligand engagement). In some embodiments, the linear polypeptide spacer between the IL-12 and the collagen-binding protein provides a steric separation such that the IL-12 retains its activity (e.g., promote receptor/ligand engagement). In certain embodiments, the linear polypeptide spacer between the IL-2 and the collagen-binding protein and/or the IL-12 and the  
25       collagen-binding protein provides a steric separation wuch that the IL-2 and/or the IL-12 binds to to receptors on the same cell. In certain embodiments, the linear polypeptide spacer between the IL-2 and the collagen-binding protein and/or the IL-12 and the collagen-binding protein provides a steric separation wuch that the IL-2 and/or the IL-12 binds to to receptors on different cells.

**[00139]** In some embodiments, the linear polypeptide spacer between IL-2 and the collagen-binding protein is of sufficient length or mass to reduce adsorption of the immunomodulatory  
30

domain onto collagen fibrils. In some embodiments, the linear polypeptide spacer between IL-12 and the collagen-binding protein is of sufficient length or mass to reduce adsorption of the immunomodulatory domain onto collagen fibrils. Methods for measuring adsorption are known to those of skill in the art. For example, adsorption can be measured by ellipsometry (ELM), surface plasmon resonance (SPR), optical waveguide lightmode spectroscopy (OWLS), attenuated total internal reflectance-infrared spectroscopy (ATR-IR), circular dichroism spectroscopy (CD), total internal reflectance infrared spectroscopy (TIRF), and other high resolution microscopy techniques. In some embodiments, these methods show the spatial arrangement between the domains of the immunomodulatory fusion protein.

**[00140]** In certain embodiments, the linear polypeptide spacer provides one of several functional benefits, including but not limited to: i) separation of IL2 and IL12 to allow both cytokines to access their receptors either on the same cell or separate cells; ii) separation of collagen from IL2 to improve the geometries of their interactions in vivo; iii) increased hydrodynamic radius of the fusion construct, thereby utilizing size exclusion to slow down the rate of burst release upon administration; and/or iv) stabilization and/or improved solubilization of domains that are relatively insoluble. In certain embodiments, the linear polypeptide spacer improves retention of the fusion product at the target tissue when administered to a subject.

**[00141]** In some embodiments, the linear polypeptide spacer between IL-2 and the collagen-binding protein provides sufficient molecular weight to slow or reduce diffusion from the tissue.

In some embodiments, the linear polypeptide spacer between IL-12 and the collagen-binding protein provides sufficient molecular weight to slow or reduce diffusion from the tissue. Methods for measuring diffusion from the tissue are known to those of skill in the art. For example, diffusion can be measured by in vivo imaging, or via microscopy of tissue sections over time. Exemplary methods are described in at least Schmidt & Wittrup, Mol. Canc. Ther. 2009' and Wittrup et al., Methods in Enzymol 2012, each of which is herein incorporated by reference in their entirety.

#### Albumin

**[00142]** The term "albumin" refers to a protein having the same, or very similar three dimensional structure as human albumin (SEQ ID NO: 16) and having a long serum half-life. Exemplary albumin proteins include human serum albumin (HSA; SEQ ID NOs: 17 and 18), primate serum albumin (such as chimpanzee serum albumin), gorilla serum albumin or macaque serum albumin, rodent serum albumin (such as hamster serum albumin), guinea pig serum albumin, mouse serum albumin and rat serum albumin, bovine serum albumin (such as cow serum

albumin), equine serum albumin (such as horse serum albumin or donkey serum albumin), rabbit serum albumin, goat serum albumin, sheep serum albumin, dog serum albumin, chicken serum albumin and pig serum albumin.

**[00143]** In some embodiments, the linear polypeptide spacer is an albumin, an albumin binder, an albumin binding domain, or an albumin mutation. In some embodiments, the linear polypeptide spacer comprises albumin, or fragments thereof. In some embodiments, the linear polypeptide spacer is human albumin. In some embodiments, the albumin is a serum albumin, for example, a human serum albumin (SEQ ID NO: 17). In some embodiments, the linear polypeptide spacer is an albumin binding domain.

**[00144]** In some embodiments, the linear polypeptide spacer comprises an amino acid sequence having 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%, at least 99%, or 100% identity to the amino acid sequence of human albumin as set forth in SEQ ID NO: 16, or a portion thereof.

**[00145]** In some embodiments, the linear polypeptide spacer comprises an amino acid sequence having 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%, at least 99%, or 100% identity to the amino acid sequence of human serum albumin as set forth in SEQ ID NO: 17, or a portion thereof.

**[00146]** In some embodiments, the linear polypeptide spacer comprises an amino acid sequence having 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%, at least 99%, or 100% identity to the amino acid sequence of human serum albumin as set forth in SEQ ID NO: 18, or a portion thereof.

**[00147]** In some embodiments, the albumin is a variant comprising one or more amino acid substitutions, additions or deletions, optionally two, three, four, five, six, seven, eight, nine, ten or more amino acid substitutions, additions or deletions relative to an albumin protein comprising the amino acid sequence of SEQ ID NOs: 16-18. In some embodiments, the albumin mutation comprises at least one amino acid mutation compared to wild-type albumin. This mutation may involve substitution, deletion, truncation or modification of the wild-type amino acid residue normally located at that position.

**[00148]** In certain embodiments, the linear polypeptide is a serum protein binding domain. In some embodiments, the linear polypeptide spacer is an albumin binding domain. In some embodiments, the linear polypeptide spacer comprises an amino acid sequence having 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%, at least 99%, or 100% identity to the amino acid sequence of albumin binding domain as set forth in SEQ ID NO: 19, or a portion thereof. In some embodiments, the albumin binding domain non-covalently binds to serum albumin once administered to a subject. In some embodiments, the albumin binding domain demonstrates a non-covalent means of enhancing the hydrodynamic radius of the fusion construct in situ. In certain embodiments, the albumin binding domain improves retention of the fusion construct at the target tissue when administered to a subject.

Table 4. Exemplary Sequences for Albumin

| SEQ ID NO: | Description         | Sequence                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|------------|---------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 16         | Human albumin       | MKWVTFISLLFLFSSAYS RGVFRRDAHKSEVAHRFKDLGEEN<br>FKALVLIAFAQYLQQCPFEDHVKLVNEVTEFAKTCVADESAE<br>NCDKSLHTLFGDKLCTVATLRETYGEMADCCAKQEPERNECF<br>LQHKDDNP NLPRLVRPEVDVMCTAFHDNEETFLKKYLYEIAR<br>RHPYFYAPELLFFAKRYKAAFTECCQAADKAACLLPKLDEL R<br>DEGKASSAKQRLK CASLQKFGERAFAKAWAVARLSQRFPKAE<br>FAEVSKLVTDLT KVHTECCHGDLLECADDRADLAKYICENQD<br>SISSKLKECCEKPLLEKSHCIAEVENDEMPADLPSLAADFVESK<br>DVCKNYAEAKDVFLGMFLY EYARRHPDYSV VLLLRLAKTYE<br>TTLEKCCAAADPHECYAKVFDEFKPLVEEPQNLIKQNC ELF EQ<br>LGEYKFQNAL LVRYTKKVPQVSTPTLVEVSRNLGKVGSKCCK<br>HPEAKRMPCAEDYLSVVLNQLCVLHEKTPVSDRVTKCCTESL<br>VNRPCFSALEVDETYVPKEFNAETFTFHADICTLSEKERQIKK<br>QTALVELVKHKPKATKEQLKAVMDDFAAFVEKCKADDKET<br>CFAEEGKKLV AASQAALGL |
| 17         | Human serum albumin | MDMRVPAQLLGLLLLWLP GARCADAHKSEVAHRFKDLGEEN<br>FKALVLIAFAQYLQQCPFEDHVKLVNEVGEFAKTCVADESAE<br>NCDKSLHTLFGDKLCTVATLRETYGEMADCCAKQEPERNECF<br>LQHKDDNP NLPRLVRPEVDVMCTAFHDNEETFLKKYLYEIAR<br>HPYFYAPELLFFAKRYKAAFTECCQAADKAACLLPKLDEL RD<br>EGKASSAKQRLK CASLQKFGERAFAKAWAVARLSQRFPKAEF<br>AEVSKLVTDLT KVHTECCHGDLLECADDRADLAKYICENQDS<br>ISSKLKECCEKPLLEKSHCIAEVENDEMPADLPSLAADFVESK<br>DVCKNYAEAKDVFLGMFLY EYARRHPDYSW LLLLRLAKTYET<br>TLEKCCAAADPHECYAKVFDEFKPLVEEPQNLIKQNC ELF EQ<br>GEYKFQNAL LVRYTKKVPQVSTPTLVEVSRNLGKVGSKCCK<br>HPEAKRMPCAEDYLSWLNQLCVLHEKTPVSDRVTKCCTESLV<br>NRRPCFSALEVDEGYVPKEFNAETFTFHADICTLSEKERQIKK                                                                        |

|    |                           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|----|---------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|    |                           | QTALVELVKHKPKATKEQLKAVMDDFAAFVEKCKKADDKET<br>CFAEEGKKLVAAASQAALGLGGGSAPTSSSTKKTQLQLEHLLL<br>DLQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEE<br>ELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMC<br>EYADETATIVEFLNRWITFCQSIISTLGGGS                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| 18 | Mature HSA                | DAHKSEVAHRFKDLGEENFKALVLIAFAQYLQQCPFEDHVKL<br>VNEVTEFAKTCVADESAENCDKSLHTLFGDKLCTVATLRETY<br>GEMADCCAKQEPERNECFLQHKDDNPNLPRLVRPEVDVMCT<br>AFHDNEETFLKKYLYEIAARRHPYFYAPELFFAKRYKAAFTEC<br>CQAADKAACLLPKLDELDEGKASSAKQRLKASLQKFGER<br>AFKAWAVARLSQRFPKAEFAEVSKLVTDLTKVHTECCHGDL<br>LECADDRADLAKYICENQDSISSKLKECCEKPLLEKSHCIAEV<br>ENDEMPADLPSLAADFVESKDVCKNYAEAKDVFLGMFLY<br>ARRHPDYSVVLRLAKTYETTLKCCAAADPHECYAKVFDE<br>FKPLVEEPQNLKQNCLEFEQLGEYKFQNALLVRYTKKVPQVS<br>TPTLVEVSRNLGKVGSKCKHPEAKRMPCAEYLSVVLNQLC<br>VLHEKTPVSDRVTKCCTESLVNRRPCFSALEVDETYVPKEFNA<br>ETFTFHADICTLSEKERQIKKQTALVELVKHKPKATKEQLKAV<br>MDDFAAFVEKCKKADDKETCFAEEGKKLVAAASQAALGLGGG<br>SAPTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTF<br>KFYMPKKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRD<br>LISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIIS<br>TLTGGGS |
| 19 | Albumin<br>binding domain | KVQLVESGGGLVQPGGSLRLSCAASGFTSSFGMTWVRQAPG<br>KGLEWVSSISGSGSDTLYADSVRGRFTISRDNKNTLYLQMNS<br>LRAEDTAVYYCTIGGSLSPSSQGTLVTVSS                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| 20 | HSA domain I              | DAHKSEVAHRFKDLGEENFKALVLIAFAQYLQQCPFEDHVKL<br>VNEVTEFAKTCVADESAENCDKSLHTLFGDKLCTVATLRETY<br>GEMADCCAKQEPERNECFLQHKDDNPNLPRLVRPEVDVMCT<br>AFHDNEETFLKKYLYEIAARRHPYFYAPELFFAKRYKAAFTEC<br>CQAADKAACLLPKLDELDEGKASSAKQR                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| 21 | HSA domain II             | GKASSAKQRLKASLQKFGERAFKAWAVARLSQRFPKAEFA<br>EVSKLVTDLTKVHTECCHGDLLECADDRADLAKYICENQDSI<br>SSKLKECCEKPLLEKSHCIAEVENDEMPADLPSLAADFVESKD<br>VCKNYAEAKDVFLGMFLYEYARRHPDYSWLLRLAKTYETT<br>LEKCCAAADPHECYAKVFDEFKPLVEEPQ                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| 22 | HSA domain<br>III         | NLIKQNCLEFEQLGEYKFQNALLVRYTKKVPQVSTPTLVEVSR<br>NLGKVGSKCKHPEAKRMPCAEYLSVVLNQLCVLHEKTPV<br>SDRVTKCCTESLVNRRPCFSALEVDETYVPKEFNAETFTFHAD<br>ICTLSEKERQIKKQTALVELVKHKPKATKEQLKAVMDDFAAF<br>VEKCKKADDKETCFAEEGKKLVAAASQAALGL                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |

#### IV. Linkers

[00149] In certain embodiments, the fusion proteins described herein comprise one or more linkers. In certain embodiments, the linker connects one element of the fusion protein to another.

5 In certain embodiments, the linker connects one domain of the fusion protein to another. In certain

embodiments, the fusion proteins described herein comprise one, two, three, four, five or more linkers. In some embodiments, the linker is “short,” e.g., consists of 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 amino acid residues. Thus, in certain instances, the linker consist of about 12 or fewer amino acid residues. In the case of 0 amino acid residues, the linker is a peptide bond. In some  
 5 embodiments, the linker consists of about 3 to about 50, for example 8, 9 or 10 contiguous amino acid residues. In some embodiments, the linker comprises 0 to about 100 amino acid residues. In some embodiments, the linker comprises about 5 to about 50 amino acid residues. In some embodiments, the linker comprises about 5 to about 15 amino acid residues. In certain  
 10 embodiments, the linker is a non-peptide linker. In certain embodiments, the linker connects one element of the fusion protein to another via a covalent bond. In certain embodiments, the linker connects one element of the fusion protein to another via a non-covalent bond. In certain  
 embodiments, the fusion proteins described herein comprise more than one type of linker, and/or more than one linker of the same or different lengths (e.g., number of amino acid residues).

#### 15 Peptide linkers

**[00150]** Exemplary linkers include gly-ser polypeptide linkers, glycine-praline polypeptide linkers, and praline-alanine polypeptide linkers. In certain embodiments, the linear polypeptide spacers is a gly-ser polypeptide linker, i.e., a peptide that consists of glycine and serine residues.

**[00151]** In some embodiments, the linker is a peptide linker comprising one or more amino acids, typically about 2-20 amino acids, that are described herein or are known in the art. Suitable, non-immunogenic linker peptides include, for example,  $(G_4S)_n$ ,  $(SG_4)_n$  or  $G_4(SG_4)_n$  linker peptides, wherein n is generally a number between 1 and 10, typically between 2 and 4.

**[00152]** Exemplary gly-ser polypeptide linkers comprise the amino acid sequence  $Ser(Gly_4Ser)_n$ .

In certain embodiments,  $n=1$ . In certain embodiments,  $n=2$ . In certain embodiments,  $n=3$ , i.e.,  
 25  $Ser(Gly_4Ser)_3$ . In certain embodiments,  $n=4$ , i.e.,  $Ser(Gly_4Ser)_4$ . In certain embodiments,  $n=5$ . In certain embodiments,  $n=6$ . In certain embodiments,  $n=7$ . In certain embodiments,  $n=8$ . In certain  
 embodiments,  $n=9$ . In certain embodiments,  $n=10$ . Another exemplary gly-ser polypeptide linker comprises the amino acid sequence  $Ser(Gly_4Ser)_n$ . In certain embodiments,  $n=1$ . In certain  
 30 embodiments,  $n=2$ . In certain embodiments,  $n=3$ . In certain embodiments,  $n=4$ . In certain  
 embodiments,  $n=5$ . In certain embodiments,  $n=6$ . Another exemplary gly-ser polypeptide linker comprises  $(Gly_4Ser)_n$ . In certain embodiments,  $n=1$ . In certain embodiments,  $n=2$ . In certain  
 embodiments,  $n=3$ . In certain embodiments,  $n=4$ . In certain embodiments,  $n=5$ . In certain  
 embodiments,  $n=6$ . Another exemplary gly-ser polypeptide linker comprises  $(Gly_3Ser)_n$ . In certain

embodiments, n=1. In certain embodiments, n=2. In certain embodiments, n=3. In certain embodiments, n=4. In certain embodiments, n=5. In certain embodiments n=6.

[00153] In some embodiments, the IL-2 is operably linked to a collagen-binding domain by a linker, e.g., a gly-ser linker. In some embodiments, the IL-2 is operably linked to a linear peptide spacer by a linker, e.g., a gly-ser linker. In some embodiments, the IL-12 is operably linked to a collagen-binding domain by a linker, e.g., a gly-ser linker. In some embodiments, the IL-12 is operably linked to a linear polypeptide spacer by a linker, e.g., a gly-ser linker. In some embodiments, the collagen-binding domain is operably linked to a linear polypeptide spacer by a linker, e.g., a gly-ser linker.

## V. Exemplary Immunomodulatory Fusion Proteins

[00154] The disclosure provides immunomodulatory fusion proteins comprising an immunomodulatory domain and a collagen-binding domain. The immunomodulatory fusion proteins of the disclosure are modular and can be configured to incorporate various individual domains.

### A. IL-2 and IL-12 Fusion Proteins

[00155] In some embodiments, the immunomodulatory fusion protein comprises IL-2, IL-12, lumican and a linear polypeptide space, wherein IL-2 is operably linked to lumican. In some embodiments, the immunomodulatory fusion protein comprises IL-2, IL-12, lumican and a linear polypeptide space, wherein IL-2 is operably linked to the linear polypeptide spacer. In some embodiments, the immunomodulatory fusion protein comprises IL-2, IL-12, lumican, and a linear polypeptide spacer wherein IL-12 is operably linked to lumican. In some embodiments, the immunomodulatory fusion protein comprises IL-2, IL-12, lumican, and a linear polypeptide spacer wherein IL-12 is operably linked to the linear polypeptide spacer.

[00156] In some embodiments, the immunomodulatory fusion protein comprises IL-2, IL-12, LAIR1 and a linear polypeptide space, wherein IL-2 is operably linked to LAIR1. In some embodiments, the immunomodulatory fusion protein comprises IL-2, IL-12, LAIR1 and a linear polypeptide space, wherein IL-2 is operably linked to the linear polypeptide spacer. In some embodiments, the immunomodulatory fusion protein comprises IL-2, IL-12, LAIR1, and a linear polypeptide spacer wherein IL-12 is operably linked to LAIR1. In some embodiments, the immunomodulatory fusion protein comprises IL-2, IL-12, LAIR1, and a linear polypeptide spacer wherein IL-12 is operably linked to the linear polypeptide spacer.

[00157] In some embodiments, the immunomodulatory fusion protein comprises IL-2, IL-12, LAIR2 and a linear polypeptide space, wherein IL-2 is operably linked to LAIR2. In some embodiments, the immunomodulatory fusion protein comprises IL-2, IL-12, LAIR2 and a linear polypeptide space, wherein IL-2 is operably linked to the linear polypeptide spacer. In some  
5   embodiments, the immunomodulatory fusion protein comprises IL-2, IL-12, LAIR2, and a linear polypeptide spacer wherein IL-12 is operably linked to LAIR2. In some embodiments, the immunomodulatory fusion protein comprises IL-2, IL-12, LAIR2, and a linear polypeptide spacer wherein IL-12 is operably linked to the linear polypeptide spacer.

[00158] In some embodiments, the immunomodulatory fusion protein comprises an amino acid  
10   sequence having 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%, at least 99%, or 100% identity to the amino acid sequence as set forth in SEQ ID NOs: 23-70, or a portion thereof.

[00159] In some embodiments, the immunomodulatory fusion protein comprises an amino acid  
15   sequence having a leader sequence as set forth in SEQ ID NO: 71:

MRVPAQLLGLLLLWLPGARCA.

[00160] In some embodiments, the immunomodulatory fusion protein comprises an amino acid sequence having a His tag sequence as set forth in SEQ ID NO: 72: HHHHHHHHHH.

[00161] In some embodiments, the immunomodulatory fusion protein comprises an amino acid  
20   sequence having at least 80% identity to the amino acid sequence set forth in SEQ ID NOs: 23-70 or a portion thereof, wherein the immunomodulatory fusion protein excludes the leader sequence of SEQ ID NO: 71: MRVPAQLLGLLLLWLPGARCA.

[00162] In some embodiments, the immunomodulatory fusion protein comprises an amino acid sequence having at least 80% identity to the amino acid sequence set forth in SEQ ID NOs: 23-70  
25   or a portion thereof, wherein the the immunomodulatory fusion protein excludes the His tag sequence of SEQ ID NO: 72: HHHHHHHHHH.

[00163] In some embodiments, the immunomodulatory fusion protein comprises an amino acid sequence having at least 80% identity to the amino acid sequence set forth in SEQ ID NOs: 23-70 or a portion thereof, wherein the immunomodulatory fusion protein excludes the leader sequence  
30   of SEQ ID NO: 71: MRVPAQLLGLLLLWLPGARCA. and the His tag sequence of SEQ ID NO: 72: HHHHHHHHHH.

[00164] In some embodiments, the immunomodulatory fusion protein comprises an amino acid sequence having at least 80% identity to a portion of the amino acid sequence set forth in SEQ ID

NOs: 23-70, wherein the portion excludes the leader sequence having an amino acid sequence set forth in SEQ ID NO: 71.

**[00165]** In some embodiments, the immunomodulatory fusion protein comprises an amino acid sequence having at least 80% identity to a portion of the amino acid sequence set forth in SEQ ID

5 NOs: 23-70, wherein the portion excludes the His tag sequence having an amino acid sequence set forth in SEQ ID NO: 72.

**[00166]** In some embodiments, the immunomodulatory fusion protein comprises an amino acid sequence having at least 80% identity to a portion of the amino acid sequence set forth in SEQ ID

10 NOs: 23-70, wherein the portion excludes the leader sequence having an amino acid sequence set forth in SEQ ID NO: 71 and the portion further excludes the His tag sequence having an amino acid sequence set forth in SEQ ID NO: 72.

**[00167]** In some embodiments, the immunomodulatory fusion protein comprises an amino acid sequence having at least 80% identity to a portion of the amino acid sequence set forth in SEQ ID NO: 73. In some embodiments, the immunomodulatory fusion protein comprises an amino acid

15 sequence having at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identity to the amino acid sequence set forth in SEQ ID NO: 73.

Table 5. Exemplary murine bi-functional linear constructs

| SEQ ID NO: | Construct Name   | Sequence                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|------------|------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 23         | 12-MSA-Lum-MSA-2 | MWELEKDVYVVEVDWTPDAPGETVNLTCDTPEEDDITWTSDQ<br>RHGVIGSGKTLTITVKEFLDAGQYTCHKGGETLSHSHLLLHKK<br>ENGIWSTEILKNFKNKTFLKCEAPNYSGRFTCSWLVRQNMMDLK<br>FNIKSSSSSPDSRAVTCGMASLSAEKVTLDQRDYEKYSVSCQE<br>DVTCPAEETLPIELALEARQQNKYENYSTSFFIRDIKPDPPKN<br>LQMKPLKNSQVEVSWEYPDSWSTPHSYFSLKFFVRIQRKKEK<br>MKETEEGCNQKGAFLVEKTSTEVQCKGGNVCVQAQDRYYNS<br>SCSKWACVPCRVRSGGSGGGSGGGSGGGSRVIPVSGPARCLSQ<br>SRNLLKTTDDMVKTAREKLKHYSCTAEDIDHEDITRDQTSTLK<br>TCLPLELHKNESCLATRETSSTTRGSCLPPQKTSLLMMTLCLGSI<br>YEDLKMYQTEFQAINAALQNHNHQQIILDKGMLVAIDELMQS<br>LNHNGETLRQKPPVGEADPYRVKMKLCILLHAFSTRVVTINRV<br>MGYLSSAGSGGGSEAHKSEIAHRYNDLGEQHFGLVLIASFQY<br>LQKCSYDEHAKLVQEVTDFAKTCVADESAANCDKSLHTLFGD<br>KLCAIPNLRENYGELADCCTKQEPERNECFQHKDDNPSLPPFE<br>RPEAEAMCTSFKENPTTFMGHYLHEVARRHPYFYAPELLYYAE<br>QYNEILTQCCAEADKESCLTPKLDGVKEKALVSSVRQRMKCSS<br>MQKFGERAFAKAWAVARLSQTFPNADFAEITKLATDLTKVNKE<br>CCHGDLLECADDRAELAKYMCENQATISSKLQTCCDKPLLKKA<br>AHCLSEVEHDTMPADLPAIAADFVEDQEVCKNYAEAKDVFLG<br>TFLYEYSRRHPDYSVSLLLRLAKKYEATLEKCCAEANPPACYG<br>TVLAEFQPLVEEPKNLVKTNCDLYEKLGEYGFQNAILVRYTQK<br>APQVSTPTLVEAARNLGRVGTKCCTLPEDQRLPCVEDYLSAIL<br>NRVCLLHEKTPVSEHVTKCCSGSLVERRPCFSALTVEDETYVPK<br>EFKAETFTFHSIDICTLPEKEKQIKKQTALAELVKHKPKATAEQL<br>KTVMDDDFAQFLDTCCAADKDTCFSTEGPNLVTRCKDALAGG<br>GSGGGSSQYYDYDIPLFMYGQISPNCAPCNCPSYPTAMYCD<br>DLKLKSVPMVPPGIKYLRLNQNIDHIDEKAFENVTDLQWLIL<br>DHNLENSKIKGKVFSLKQLKKLHINYNNLTESVGPLPKSLQ<br>DLQLTNNKISKLGSDGLVNLTFIYLQHNQLKEDAVSASLKG<br>KSLEYLDLSFNQMSKLPAGLPTSLTLYLDNNKISNIPDEYFKR<br>FTGLQYLRLSHNELADSGVPGNSFNISLLELDLSYNKLKSIPTV<br>NENLENYYLEVNELEKFDVKSFCKILGPLSYSKIKHLRLDGNPL<br>TQSSLPPDMECLRVANEITVNGGGSGGGSEAHKSEIAHRYND<br>LGEQHFGLVLIASFQYLQKCSYDEHAKLVQEVTDFAKTCVA<br>DESAANCDKSLHTLFGDKLCAIPNLRENYGELADCCTKQEPER<br>NECFQHKDDNPSLPPFERPEAEAMCTSFKENPTTFMGHYLHE<br>VARRHPYFYAPELLYYAEQYNEILTQCCAEADKESCLTPKLDG<br>VKEKALVSSVRQRMKCSSMQKFGERAFAKAWAVARLSQTFPN<br>ADFAEITKLATDLTKVNKECCHGDLLECADDRAELAKYMCEN<br>QATISSKLQTCCDKPLLKKAHCLSEVEHDTMPADLPAIAADFV<br>EDQEVCKNYAEAKDVFLGTFLYEYSRRHPDYSVSLLLRLAKK<br>YEATLEKCCAEANPPACYGTVLAEFQPLVEEPKNLVKTNCDLY<br>EKLGEYGFQNAILVRYTQKAPQVSTPTLVEAARNLGRVGTKCC<br>TLPEDQRLPCVEDYLSAILNRVCLLHEKTPVSEHVTKCCSGSLV<br>ERRPCFSALTVEDETYVPKEFKAETFTFHSIDICTLPEKEKQIKKQT<br>ALAELVKHKPKATAEQLKTVMDDDFAQFLDTCCAADKDTCF<br>TEGPNLVTRCKDALAGGGSAPTSSSTSSSTAQAQQQQQQQQQ<br>QQHLEQLLMDLQELLSRMENYRNKLPRMLTFKFYLPKQATE<br>LKDLQCLEDELGPLRHVLDLTQSKSFQLEDAENFISNIRVTVVK |

|    |              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|----|--------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|    |              | LKGS DNTFECQFDDESATVVDLRRWIAFCQSIISTSPQH HHHH HHHH                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| 24 | 12-Lum-MSA-2 | MWELEKDVYVVEVDWTPDAPGETVNLTCDTPEEDDITWTS DQ<br>RHGVIGSGKTLTITVKEFLDAGQYTCHKGGETLSHSHLLLHKK<br>ENGIWSTEILKNFKNKTF LKCEAPNYSGRFTCSWL VQRNMDLK<br>FNIKSSSSSPDSRAVTCGMASLSAEKVTL DQRDYEKYSVSCQE<br>DVTCP TAEETLPIELALEARQQNKYENYSTSFFIRDI IKPDPPKN<br>LQMKPLKNSQVEVSWEYPDSWSTPHSYFSLKFFVRIQRKKEK<br>MKETE EGCNQKGAFLVEKTSTEVQCKGGNVCVQAQDRYNS<br>SCSKWACVPCRVRSGGSGGGSGGGSGGGSRVIPVSGPARCLSQ<br>SRNLLKTTDDMVKTAREKLKHYSCTAEDIDHEDITRDQTSTLK<br>TCLPLELHKNESCLATRETSSTTRGSCLPPQKTSLM MTLCLGSI<br>YEDLKMYQTEFQAINAALQNH NHQQIILDKGMLVAIDELMQS<br>LNHNGETLRQKPPVGEADPYRVKMKLCILLHAFSTRVVTINRV<br>MGYLSSAGGGSGGGSSQYYDYDIPLFMYGQISPNC APECNCPH<br>SYPTAMYCDDLK LKSVPMVPPGIKYLYLRNNQIDHIDEKAFEN<br>VTDLQWLILDHNLLENSKIKGKVFSKLKQLK LKHINYNNLTES<br>VGPLPKSLQDLQLTNNKISKLG SFDGLVNLTFIYLQHNQLKEDA<br>VSASLKGLKSLEYLDLSFNQMSKLPAGLP TSLTLYLDNNKISN<br>IPDEYFKRFTGLQYLR LSHNELADSGVPGNSFNISLLELDLSYN<br>KLKSIPTVNENLENYYLEVNELEKFDVK SFCKILGPLSYSKIKHL<br>RLDGNPLTQSSLPPDMECLRVANEITVNGGGSGGGSEAHKSE<br>IAHRYNDLGEQHF KGLVLIAFSQYLQKCSYDEHAKLVQEVTDF<br>AKTCVADESAANCDKSLHTLFGDKLCAIPNLRENYGELADCCT<br>KQEPERNECF LQHKDDNPSLPPFERPEAEAMCTSFKENPTTFM<br>GHY LHEVARRHPYFYAPELLYYAEQYNEILTQCCA EADKESCL<br>TPKLDGVKEKALVSSVRQRMKCSSMQKFGERAFKAWAVARL<br>SQTFPNADFAEITKLATDLTKVNKECCHGDLLECADDRAELAK<br>YMCENQATISSKLQTCCDKPLLKKAHCLSEVEHDTMPADLPAI<br>AADFVEDQEVCKNYAEAKDVFLGTFLYEYSRRHPDYSVSLLL<br>RLAKKYEATLEKCCAEANPPACYGTVLAEFQPLVEEPKNLVKT<br>NCDLYEKLGEYGFQNAILVRYTQKAPQVSTPTLVEAARNLGR<br>VGTKCCTLPEDQRLPCVEDYLSAILNRVCLLHEKTPVSEHVTK<br>CCSGSLVERRPCFSALTVD ETYVPKEFKAETFTFHSDICTLPEKE<br>KQIKKQTALAE LVKHKPKATAEQLKTVMD DFAQFLDTCKKAA<br>DKDTCFSTEGPNLVTRCKDALAGGGSAPTSSSTSSSTA EAAQQQ<br>QQQQQQQQQHLEQLLMDLQELLSRMENYRN LKLPRLMTFKF<br>YLPKQATELKD LQCLEDELGPLRHVLDLTQSKSFQLEDAENFIS<br>NIRVTVVKLKGS DNTFECQFDDESATVVDLRRWIAFCQSIISTSPQH<br>HHHHHHHHHHH |
| 25 | 12-MSA-Lum-2 | MWELEKDVYVVEVDWTPDAPGETVNLTCDTPEEDDITWTS DQ<br>RHGVIGSGKTLTITVKEFLDAGQYTCHKGGETLSHSHLLLHKK<br>ENGIWSTEILKNFKNKTF LKCEAPNYSGRFTCSWL VQRNMDLK<br>FNIKSSSSSPDSRAVTCGMASLSAEKVTL DQRDYEKYSVSCQE<br>DVTCP TAEETLPIELALEARQQNKYENYSTSFFIRDI IKPDPPKN<br>LQMKPLKNSQVEVSWEYPDSWSTPHSYFSLKFFVRIQRKKEK<br>MKETE EGCNQKGAFLVEKTSTEVQCKGGNVCVQAQDRYNS<br>SCSKWACVPCRVRSGGSGGGSGGGSGGGSRVIPVSGPARCLSQ<br>SRNLLKTTDDMVKTAREKLKHYSCTAEDIDHEDITRDQTSTLK<br>TCLPLELHKNESCLATRETSSTTRGSCLPPQKTSLM MTLCLGSI<br>YEDLKMYQTEFQAINAALQNH NHQQIILDKGMLVAIDELMQS<br>LNHNGETLRQKPPVGEADPYRVKMKLCILLHAFSTRVVTINRV<br>MGYLSSAGSGGGSEAHKSEIAHRYNDLGEQHF KGLVLIAFSQY                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |

|    |                       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|----|-----------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|    |                       | <p> LQKCSYDEHAKLVQEVTDFAKTCVADESAANCDKSLHTLFGD<br/> KLCAIPNLRENYGELADCCTKQEPERNECFLQHKDDNPSLPPFE<br/> RPEAEAMCTSFKENPTTFMGHYLHEVARRHPYFYAPELLYYAE<br/> QYNEILTQCCAEADKESCLTPKLDGVKEKALVSSVRQRMKCSS<br/> MQKFGERAFAKAWAVARLSQTFPNADFAEITKLATDLTKVNKE<br/> CCHGDLLECADDRAELAKYMCENQATISSKLQTCCDKPLLKK<br/> AHCLSEVEHDTMPADLPAIAADFVEDQEVCKNYAEAKDVFLG<br/> TFLYEYSRRHPDYSVSLLLRLAKKYEATLEKCCAEANPPACYG<br/> TVLAEFQPLVEEPKNLVKTNCDLYEKLGEYGFQNAILVRYTQK<br/> APQVSTPTLVEAARNLGRVGTKCCTLPEDQRLPCVEDYLSAIL<br/> NRVCLLHEKTPVSEHVTKCCSGSLVERRPCFSALTVDETYVPK<br/> EFKAETFTFHSICTLPEKEKQIKKQTALAELVKHKPKATAEQL<br/> KTVMD DFAQFLDTCKAADKDTCFSTEGPNLVTRCKDALAGG<br/> GSGGGSSQYYDYDIPLFMYGQISPNCAPCNCPSHYPTAMYCD<br/> DLKLKSVPMVPPGIKYLRLRNNQIDHIDEKAFENVTDLQWLIL<br/> DHNLENSKIKGKVFSKLLKQLKLLHINYNNLTESVGPLPKSLQ<br/> DLQLTNNKISKLG SFDGLVNLTFIYLQHNQLKEDAVSASLKGL<br/> KSLEYLDLSFNQMSKLPAGLPTSLLTYLDNNKISNIPDEYFKR<br/> FTGLQYLR LSHNELADSGVPGNSFNISLLELDLSYNKLKSIPTV<br/> NENLENYYLEVNELEKFDVKSFCILGPLSYKIKHLRLDGNPL<br/> TQSSLPPDMECLRVANEITVNGGGSGGGSAPTSSSTSSSTAEA<br/> QQQQQQQQQQQHLEQLLMDLQELLSRMENYRNKLPRMLT<br/> FKFYLPKQATELKDLCLEDELGPLRHVLDLTQSKSFQLEDAE<br/> NFISNIRVTVVKLKGSDNTFECQFDDESATVVDLRRWIAFCQS<br/> IISTSPQH HHHHHHHHHH </p>                                                                                                                                                                                                                                  |
| 26 | 12-MSA-<br>LAIR-MSA-2 | <p> MWELEKDVYVVEVDWTPDAPGETVNLTCDTPEEDDITWTSDQ<br/> RHGVIGSGKTLTITVKEFLDAGQYTCHKGGETLSHSHLLLHKK<br/> ENGIWSTEILKNFKNKTFLKCEAPNYSGRFTCSWLVRNMDLK<br/> FNIKSSSSSPDSRAVTCGMASLSAEKVTL DQRDYEKYSVSCQE<br/> DVTCP TAEETLPIELALEARQQNKYENYSTSFIRDIIKPDPPKN<br/> LQMKPLKNSQVEVSWEYPDSWSTPHSYFSLKFFVRIQRKKEK<br/> MKETEEGCNQKGAFLVEKTSTEVQCKGGNVCVQAQDRYYNS<br/> SCSKWACVPCRVRSGGSGGGSGGGSGGGSRVIPVSGPARCLSQ<br/> SRNLLKTDDMVKTAREKLKHYSCTAEDIDHEDITRDQTSTLK<br/> TCLPLELHKNESCLATRETSSTTRGSCLPPQKTSLMMTLCLGSI<br/> YEDLKMYQTEFQAINAALQNHNHQQIILDKGMLVAIDELMQS<br/> LNHNGETLRQKPPVGEADPYRVKMKLCILLHAFSTRVVTINRV<br/> MGYLSSAGSGGGSEAHKSEIAHRYNDLGEQHFGLVLIASFQY<br/> LQKCSYDEHAKLVQEVTDFAKTCVADESAANCDKSLHTLFGD<br/> KLCAIPNLRENYGELADCCTKQEPERNECFLQHKDDNPSLPPFE<br/> RPEAEAMCTSFKENPTTFMGHYLHEVARRHPYFYAPELLYYAE<br/> QYNEILTQCCAEADKESCLTPKLDGVKEKALVSSVRQRMKCSS<br/> MQKFGERAFAKAWAVARLSQTFPNADFAEITKLATDLTKVNKE<br/> CCHGDLLECADDRAELAKYMCENQATISSKLQTCCDKPLLKK<br/> AHCLSEVEHDTMPADLPAIAADFVEDQEVCKNYAEAKDVFLG<br/> TFLYEYSRRHPDYSVSLLLRLAKKYEATLEKCCAEANPPACYG<br/> TVLAEFQPLVEEPKNLVKTNCDLYEKLGEYGFQNAILVRYTQK<br/> APQVSTPTLVEAARNLGRVGTKCCTLPEDQRLPCVEDYLSAIL<br/> NRVCLLHEKTPVSEHVTKCCSGSLVERRPCFSALTVDETYVPK<br/> EFKAETFTFHSICTLPEKEKQIKKQTALAELVKHKPKATAEQL<br/> KTVMD DFAQFLDTCKAADKDTCFSTEGPNLVTRCKDALAGG<br/> GSGGGSQEGSLPDITIFPNSSLMISQGTFTVTVVCSYSDKHDLYN<br/> MVRLEKDGSTFMEKSTEPYKTEDEFEIGPVNETITGHYSCIYSK<br/> GITWSERSKTLELKVIKENVIQTPAPGPTSDTSWLKTYSIYGGGS </p> |

|    |                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
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|    |                   | GGGSEAHKSEIAHRYNDLGEQHFGLVLIASFQYLQKCSYDEH<br>AKLVQEVTDFAKTCVADESAANCDKSLHTLFGDKLCAIPNLRE<br>NYGELADCCTKQEPERNECFLQHKDDNPSLPPFERPEAEAMCT<br>SFKENPTTFMGHYLHEVARRHPYFYAPELLYYAEQYNEILTQC<br>CAEADKESCLTPKLDGVKEKALVSSVRQRMKCSSMQKFGERA<br>FKAWAVARLSQTFPNADFAEITKLATDLTKVNKECCHGDLLEC<br>ADDRAELAKYMCENQATISSKLQTCCDKPLLKKAHCLSEVEH<br>DTMPADLPAIAADFVEDQEVCKNYAEAKDVFLGTFLYEYSRR<br>HPDYSVSLLLRLAKKYEATLEKCCAANPPACYGTVLAEFQPL<br>VEEPKNLVKTNCDLYEKLGEYGFQNAILVRYTQKAPQVSTPTL<br>VEAARNLGRVGTKCCTLPEDQRLPCVEDYLSAILNRVCLLHEK<br>TPVSEHVTKCCSGSLVERRPCFSALTVDETYVPKEFKAETFTFH<br>SDICTLPEKEKQIKKQTALAELVKHKPKATAEQLKTVMDDFAQ<br>FLDTCKAADKDTCFSTEGPNLVTRCKDALAGGGSAPTSSSTS<br>SSTAEEAQQQQQQQQQQQHLQQLMDLQELLSRMENYRNK<br>LPRMLTFKFYLPKQATELKDLQCLEDELGPLRHVLDLTQSKSF<br>QLEDAENFISNIRVTVVKLKGSNDTFECQFDDESATVVDFLRR<br>WIAFCQSIISTSPQH HHHHHHHHHH                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| 27 | 12-LAIR-<br>MSA-2 | MWELEKDVYVVEVDWTPDAPGETVNLTCDTPEEDDITWTSQ<br>RHGVIGSGKTLTITVKEFLDAGQYTCHKGGETLSHSHLLLHKK<br>ENGIWSTEILKNFKNKTFLKCEAPNYSGRFTCSWLVRNMDLK<br>FNIKSSSSSPDSRAVTCGMASLSAEKVTLQDRDYEKYSVSCQE<br>DVTCPAEETLPIELALEARQQNKYENYSTSFIRDIKPDPPKN<br>LQMKPLKNSQVEVSWEYPDSWSTPHSYFSLKFFVRIQRKKEK<br>MKETEEGCNQKGAFLVEKTSTEVQCKGGNVCVQAQDRYNS<br>SCSKWACVPCRVRSGGSGGGSGGGSGGGSRVIPVSGPARCLSQ<br>SRNLLKTDDMVKTAREKLKHYSCTAEDIDHEDITRDQTSTLK<br>TCLPLELHKNESCLATRETSSTTRGSCLPPQKTSLMMTLCLGSI<br>YEDLKMYQTEFQAINAALQNHNHQQIILDKGMLVAIDELMQS<br>LNHNGETLRQKPPVGEADPYRVKMKLCILLHAFSTRVVTINRV<br>MGYLSSAGGSGGGSGGSLPDITIFPNSSLMISQGTFTVTVCS<br>YSDKHDLYNMVRLEKDGSTFMEKSTEPYKTEDEFEIGPVNETI<br>TGHYSCIYSKGITWSERSKTLELKVIKENVIQTPAPGPTSSTSWL<br>KTYSIYGGGSGGGSEAHKSEIAHRYNDLGEQHFGLVLIASFQ<br>YLQKCSYDEHAKLVQEVTDFAKTCVADESAANCDKSLHTLFG<br>DKLCAIPNLRENYGELADCCTKQEPERNECFLQHKDDNPSLPPF<br>ERPEAEAMCTSFKENPTTFMGHYLHEVARRHPYFYAPELLYYA<br>EQYNEILTQCCAADKESCLTPKLDGVKEKALVSSVRQRMKCS<br>SMQKFGERAFAKAWAVARLSQTFPNADFAEITKLATDLTKVNK<br>ECCHGDLLECADDRAELAKYMCENQATISSKLQTCCDKPLLK<br>KAHCLSEVEHDTMPADLPAIAADFVEDQEVCKNYAEAKDVFL<br>GTFLYEYSRRHPDYSVSLLLRLAKKYEATLEKCCAANPPACY<br>GTVLAEFQPLVEEPKNLVKTNCDLYEKLGEYGFQNAILVRYTQ<br>KAPQVSTPTLVEAARNLGRVGTKCCTLPEDQRLPCVEDYLSAI<br>LNRVCLLHEKTPVSEHVTKCCSGSLVERRPCFSALTVDETYVP<br>KEFKAETFTFHSDICTLPEKEKQIKKQTALAELVKHKPKATAEQ<br>LKTVMDDFAQFLDTCKAADKDTCFSTEGPNLVTRCKDALAG<br>GGSAPTSSSTSSTAEEAQQQQQQQQQQQHLQQLMDLQELLS<br>RMENYRNKLPRLMLTFKFYLPKQATELKDLQCLEDELGPLRH<br>VLDLTQSKSFQLEDAENFISNIRVTVVKLKGSNDTFECQFDDES<br>ATVVDFLRRWIAFCQSIISTSPQH HHHHHHHHHH |
| 28 | 12-MSA-<br>LAIR-2 | MWELEKDVYVVEVDWTPDAPGETVNLTCDTPEEDDITWTSQ<br>RHGVIGSGKTLTITVKEFLDAGQYTCHKGGETLSHSHLLLHKK                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |

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|    |                  | <p> ENGIWSTEILKNFKNKTFLKCEAPNYSGRFTCSWLVRNMDLK<br/> FNIKSSSSSPDSRAVTCGMASLSAEKVTLDQRDYEKYSVSCQE<br/> DVTCPAEETLPIELALEARQQNKYENYSTSFFIRDIIKPDPPKN<br/> LQMKPLKNSQVEVSWEYPDSWSTPHSYFSLKFFVRIQRKKEK<br/> MKETEEGCNQGAFLEKTSTEVQCKGGNVCVQAQDRYYNS<br/> SCSKWACVPCRVRSGGSGGGSGGGSGGGSRVIPVSGPARCLSQ<br/> SRNLLKTDDMVKTAREKLKHYSCTAEDIDHEDITRDQTSTLK<br/> TCLPLELHKNESCLATRETSSTTRGSCLPQKTSMLMTLCLGSI<br/> YEDLKMYQTEFQAINAALQNHNHQQIILDKGMLVAIDELMQS<br/> LNHNGETLRQKPPVGEADPYRVKMKLCILLHAFSTRVVTINRV<br/> MGYLSSAGSGGGSEAHKSEIAHRYNDLGEQHFGLVLIASFQY<br/> LQKCSYDEHAKLVQEVTDFAKTCVADESAANCDKSLHTLFGD<br/> KLCAIPNLRENYGELADCCTKQEPERNECFLOHKDDNPSLPPFE<br/> RPEAEAMCTSFKENPTTFMGHYLHEVARRHPYFYAPELLYYAE<br/> QYNEILTQCCAEADKESCLTPKLDGVKEKALVSSVRQRMKCSS<br/> MQKFGERAFAKAWAVARLSQTFPNADFAEITKLATDLTKVNKE<br/> CCHGDLLECADDRAELAKYMCENQATISSKLQTCCKPLLKK<br/> AHCLSEVEHDTMPADLPAIAADFVEDQEVCKNYAEAKDVFLG<br/> TFLYEYSRRHPDYSVSLLLRLAKKYEATLEKCCAEANPPACYG<br/> TVLAEFQPLVEEPKNLVKTNCDLYEKLGEYGFQNAILVRYTQK<br/> APQVSTPTLVEAARNLGRVGTKCCTLPEDQRLPCVEDYLSAIL<br/> NRVCLLHEKTPVSEHVTKCCSGSLVERRPCFSALTVDETYVPK<br/> EFKAETFTFHSICTLPEKEKQIKKQTALAELVKHKPKATAEQL<br/> KTVMDDDFAQFLDTCKAADKDTCFSTEGPNLVTRCKDALAGG<br/> GGGGSGQESLPDITIFPNSSLMISQGTFTVTVCSYSDKHDLN<br/> MVRLEKDGSTFMEKSTEPYKTEDEFEIGPVNETITGHYSCIYSK<br/> GITWSERSKTLELKVIKENVIQTPAPGPTSDTSWLKTYSIYGGGS<br/> GGGSAPTSSSTSSSTAEEAQQQQQQQQQQQHLQLLMDLQEL<br/> LSRMENYRNKLPRMLTFKFYLPKQATELKDLQCLEDELGPLR<br/> HVLDTQSKSFQLEDAENFISNIRVTVVKLKGSNDTFECQFDDE<br/> SATVVDLRRWIAFCQSIISTSPQHSHHHHHHHHHH </p> |
| 29 | 12-Lum-<br>ABD-2 | <p> MRVPAQLLGLLLLWLPGARCAMWELEKD VYVVEVDWTPDAP<br/> GETVNLTCDTPEEDDITWTS DQRHGVIGSGKTLTITVKEFLDAG<br/> QYTCHKGGETLSHSHLLLHKKENGIWSTEILKNFKNKTFLKCE<br/> APNYSGRFTCSWLVRNMDLKFNKSSSSSPDSRAVTCGMASL<br/> SAEKVTLDQRDYEKYSVSCQEDVTCPTAEETLPIELALEARQQ<br/> NKYENYSTSFFIRDIIKPDPPKNLQMKPLKNSQVEVSWEYPDSW<br/> STPHSYFSLKFFVRIQRKKEKMKETEEGCNQGAFLEKTSTE<br/> VQCKGGNVCVQAQDRYYNSSCSKWACVPCRVRSGGSGGGSG<br/> GGSGGSRVIPVSGPARCLSQSRNLLKTDDMVKTAREKLKHYS<br/> CTAEDIDHEDITRDQTSTLKTCCLPLELHKNESCLATRETSSTTR<br/> GSCLPQKTSMLMTLCLGSIYEDLKMYQTEFQAINAALQNHNH<br/> QQIILDKGMLVAIDELMQSLNHNGETLRQKPPVGEADPYRVK<br/> MKLCILLHAFSTRVVTINRVMGYLSSAGSGGGSSQYYDYDI<br/> PLFMYGQISPNCAPECNCPHSYPTAMYCDDLKLSVPMVPPGI<br/> KYLYLRNNQIDHIDEKAFENVTDLQWLILDHNLLENSKIKGKV<br/> FSKLKQLKKLHINYNNLTESVGPLPKSLQDLQLTNNKISKLGFS<br/> DGLVNLTFIYLQHNQLKEDAVSASLKGLKSLEYLDLSFNQMSK<br/> LPAGLPTSLTLYLDNNKISNIPDEYFKRFTGLQYLRLSHNELA<br/> DSGVPGNSFNISLLELDLSYNKLKSIPTVNENLENYYLEVNEL<br/> EKFDVKSFCILGPLSYSKIHLRLDGNPLTQSSLPPDMYECLR<br/> VANEITVNGGGSGGGSKVQLVESGGGLVQPGGSLRLSCAASGF<br/> TFSSFGMTWVRQAPGKGLEWVSSISGSGSDTLYADSVRGRFTIS<br/> RDNSKNTLYLQMNSLRAEDTAVYYCTIGGSLSPSSQGTLVTVS </p>                                                                                                                                                                                                                                                                                                                                                                                           |

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|    |                            | SGGGSAPTSSSTSSSTAEEAQQQQQQQQQQQQHLEQLLMDLQEL<br>LSRMENYRNLKLPRMLTFKFYLPKQATELKDLCLEDELGPLR<br>HVLDLTQSKSFQLEDAENFISNIRVTVVKLKGSDNTFECQFDDE<br>SATVVDFLRRWIAFCQSIISTSPQH HHHHHHHHHH                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| 30 | 12-LAIR-<br>ABD2           | MRVPAQLLGLLLLWLPGARCAMWELEKDVYVVEVDWTPDAP<br>GETVNLTCDTPEEDDITWTSQQRHGVIGSGKTLTITVKEFLDAG<br>QYTCHKGGETLSHSHLLLHKKENGIWSTEILKNFKNKTFKCE<br>APNYSGRFTCSWLVRNMDLKFNIKSSSSSPDSRAVTCGMASL<br>SAEKVTLDQRDYEKYSVSCQEDVTCPTAEETLPIELALEARQQ<br>NKYENYSTSFFIRDIIKPDPPKNLQMKPLKNSQVEVSWEYPDSW<br>STPHSYFSLKFFVRIQRKKEKMKETEEGCNQKGAFLVEKTSTE<br>VQCKGGNVCVQAQDRYNNSSCSKWACVPCRVRSGGSGGGSG<br>GGSGGGSRVIPVSGPARCLSQSRNLLKTTDDMVKTAREKLKHY<br>SCTAEDIDHEDITRDQTSTLKTCLPLELHKNESCLATRETSSTTR<br>GSCLPPQKTSMMTLCLGSIYEDLKMYQTEFQAINAALQNHNH<br>QQIILDKGMLVAIDELMQSLNHNGETLRQKPPVGEADPYRVK<br>MKLCILLHAFSTRVVTINRVMGYLSSAGGGSGGGSSQEGSLPDIT<br>IFPNSSLMISQGTFTVTVCSYSDKHDLYNMVRLEKDGSTFMEK<br>STEPYKTEDEFEIGPVNETITGHYSCIYSGKITWSERSKTLELKVI<br>KENVIQTPAPGPTSDTSWLKTYSIYGGGSGGGSKVQLVESGGG<br>LVQPGGSLRLSCAASGFTFSSFGMTWVRQAPGKGLEWVSSISG<br>SGSDTLYADSVRGRFTISRDN SKNTLYLQMNSLRAEDTAVYYC<br>TIGGSLSPSSQGT LVTVSSGGGSAPTSSSTSSSTAEEAQQQQQQQ<br>QQQQQHLEQLLMDLQELLSRMENYRNLKLPRMLTFKFYLPKQ<br>ATELKDLCLEDELGPLRHVLDTQSKSFQLEDAENFISNIRVT<br>VVKLKGSDNTFECQFDDESATVVDFLRRWIAFCQSIISTSPQH<br>HHHHHHHHH                                                                                                                                                                      |
| 31 | 12-Lum-<br>MSA_H464Q<br>-2 | MRVPAQLLGLLLLWLPGARCAMWELEKDVYVVEVDWTPDAP<br>GETVNLTCDTPEEDDITWTSQQRHGVIGSGKTLTITVKEFLDAG<br>QYTCHKGGETLSHSHLLLHKKENGIWSTEILKNFKNKTFKCE<br>APNYSGRFTCSWLVRNMDLKFNIKSSSSSPDSRAVTCGMASL<br>SAEKVTLDQRDYEKYSVSCQEDVTCPTAEETLPIELALEARQQ<br>NKYENYSTSFFIRDIIKPDPPKNLQMKPLKNSQVEVSWEYPDSW<br>STPHSYFSLKFFVRIQRKKEKMKETEEGCNQKGAFLVEKTSTE<br>VQCKGGNVCVQAQDRYNNSSCSKWACVPCRVRSGGSGGGSG<br>GGSGGGSRVIPVSGPARCLSQSRNLLKTTDDMVKTAREKLKHY<br>SCTAEDIDHEDITRDQTSTLKTCLPLELHKNESCLATRETSSTTR<br>GSCLPPQKTSMMTLCLGSIYEDLKMYQTEFQAINAALQNHNH<br>QQIILDKGMLVAIDELMQSLNHNGETLRQKPPVGEADPYRVK<br>MKLCILLHAFSTRVVTINRVMGYLSSAGGGSGGGSSQYYDYDI<br>PLFMYGQISPNCAPCNCPSYPTAMYCDDLKLSVPMVPPGI<br>KYLYLRNNQIDHIDEKAFENVTDLQWLILDHNLLENSKIKGKV<br>FSKLLQLKKLHINYNNLTESVGPLPKSLQDLQLTNNKISKLSGF<br>DGLVNLTFIY LQHNQLKEDAVSASLKGKLSLEYLDLSFNQMSK<br>LPAGLPTSLLTYLDNNKISNIPDEYFKRFTGLQYLRLSHNELA<br>DSGVPGNSFNISLLELDLSYNKLKSIPTVNENLENYYLEVNEL<br>EKFDVKSFCILGPLSYSKIKHLRLDGNPLTQSSLPPDMECLR<br>VANEITVNGGGSGGGSEAHKSEIAHRYNDLGEQHFGLVLI AF<br>SQYLQKCSYDEHAKLVQEVTDFAKTCVADESAANCDKSLHTL<br>FGDKLCAIPNLRENYGELADCC TKQEPERNECFLQHKDDNPSL<br>PPFERPEAEAMCTSFKENPTTFMGHYLHEVARRHPYFYAPELL<br>YYAEQYNEILTQCCA EADKESCLTPKLDGVKEKALVSSVRQR<br>MKCSSMQKFGERAFKAWAVARLSQTFPNADFAEITKLATDLT |

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|    |                             | KVNKECCHGDLLECADDRAELAKYMCENQATISSKLQTCCDK<br>PLLKKAHCLSEVEHDTMPADLPAIAADFVEDQEVCKNYAEAK<br>DVFLGTFLYEYSRRHPDYSVSLLLRLAKKYEATLEKCCAEANP<br>PACYGTVLAEFQPLVEEPKNLVKTNCDLYEKLGEYGFQNAILV<br>RYTQKAPQVSTPTLVEAARNLGRVGTKCCTLPEDQRLPCVEDY<br>LSAILNRVCLLQEKTPVSEHVTKCCSGSLVERRPCFSALTVD<br>YVPKEFKAETFTFHSIDICTLPEKEKQIKKQTALAEKVHKPKAT<br>AEQLKTVMD DFAQFLDTCCKAADKDTCFSTEGPNLVTRCKDA<br>LAGGGSAPTSSSTSSSTAEEAQQQQQQQQQQQHLEQLLMDLQ<br>ELLSRMENYRNKLPRMLTFKFYLPKQATELKDLQCLEDELGP<br>LRHVLDLTQSKSFQLEDAENFISNIRVTTVVKLGSDNTFECQFD<br>DESATVVDFLRRWIAFCQSIISTSPQH HHHHHHHHHH                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| 32 | 12-LAIR-<br>MSA_H464Q<br>-2 | MRVPAQLLGLLLLWLPGARCAMWELEKD VYVVEVDWTPDAP<br>GETVNLTC DTPEEDDITWTS DQRHGVIGSGKLTITVKEFLDAG<br>QYTCHKGGETLSHSHLLLHKKENGIWSTEILKNFKNKTFLKCE<br>APNYSGRFTCSWL VQRNMDLKFNKSSSSSPDSRAVTCGMASL<br>SAEKVTL DQRDYEKYSVSCQEDVTCPTAEETLPIELALEARQQ<br>NKYENYSTSFFIRDIIKPDPPKNLQMKPLKNSQVEVSWEYPDSW<br>STPHSYFSLKFFVRIQRKKEKMKETEEGCNQKGAFLVEKTSTE<br>VQCKGGNVCVQAQDRYNNSSCSKWACVPCRVRSGSGGGSG<br>GGSGGGSRVIPVSGPARCLSQSRNLLKTDDMVKTAREKLKHY<br>SCTAEDIDHEDITRDQTSTLKTCLPLELHKNESCLATRETSSTR<br>GSCLPQKTSLMMTLCLGSIYEDLKMYQTEFQAINAALQNHNH<br>QQIILDKGMLVAIDELMQSLNHNGETLRQKPPVGEADPYRVK<br>MKLCILLHAFSTRVVTINRVMGYLSSAGGSGGGSGQEGSLPDIT<br>IFPNSSLMISQGTFTVTVCSYSDKHDLYNMVRLEKDGSTFMEK<br>STEPYKTEDEFEIGPVNETITGHYSCIYSGKITWSERSKTLELKI<br>KENVIQTPAPGPTSDTSWLKTYSIYGGSGGGSEAHKSEIAHRY<br>NDLGEQHFGLVLIASFQYLQKCSYDEHAKLVQEVTDFAKTC<br>VADESAANCDKSLHTLFGDKLCAIPNLRENYGELADCCTKQEP<br>ERNECFLQHKDDNPSLPPFERPEAEAMCTSFKENPTTFMGHYL<br>HEVARRHPYFYAPELLYAEQYNEILTQCCAEADKESCLTPKL<br>DGVKEKALVSSVRQRMKCSSMQKFGERAFAKAWAVARLSQTF<br>PNADFAEITKLATDLTKVNKECCHGDLLECADDRAELAKYMC<br>ENQATISSKLQTCCDKPLLKKAHCLSEVEHDTMPADLPAIAAD<br>FVEDQEVCKNYAEAKDVFLGTFLYEYSRRHPDYSVSLLLRLAK<br>KYEATLEKCCAEANPPACYGTVLAEFQPLVEEPKNLVKTNCDL<br>YEKLGEYGFQNAILVRYTQKAPQVSTPTLVEAARNLGRVGTK<br>CCTLPEDQRLPCVEDYLSAILNRVCLLQEKTPVSEHVTKCCSGS<br>LVERRPCFSALTVDETYVPKEFKAETFTFHSIDICTLPEKEKQIKK<br>QTALAEKVHKPKATAEQLKTVMD DFAQFLDTCCKAADKDT<br>CFSTEGPNLVTRCKDALAGGGSAPTSSSTSSSTAEEAQQQQQQQ<br>QQQQQHLEQLLMDLQELLSRMENYRNKLPRMLTFKFYLPKQ<br>ATELKDLQCLEDELGPLRHVLDLTQSKSFQLEDAENFISNIRVT<br>VVKLGSDNTFECQFDDESATVVDFLRRWIAFCQSIISTSPQH<br>HHHHHHHHH |
| 33 | 2-LAIR-<br>MSA-12           | MRVPAQLLGLLLLWLPGARCAAPTSSSTSSSTAEEAQQQQQQQ<br>QQQQQHLEQLLMDLQELLSRMENYRNKLPRMLTFKFYLPKQ<br>ATELKDLQCLEDELGPLRHVLDLTQSKSFQLEDAENFISNIRVT<br>VVKLGSDNTFECQFDDESATVVDFLRRWIAFCQSIISTSPQGG<br>GGGGSGEGSLPDITIFPNSSLMISQGTFTVTVCSYSDKHDLYN<br>MVRLEKDGSTFMEKSTEPYKTEDEFEIGPVNETITGHYSCIYSG<br>KITWSERSKTLELKI KENVIQTPAPGPTSDTSWLKTYSIYGGGS                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |

|    |                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
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|    |                   | GGGSEAHKSEIAHRYNDLGEQHFGLVLIASFQYLQKCSYDEH<br>AKLVQEVTDFAKTCVADESAANCDKSLHTLFGDKLCAIPNLRE<br>NYGELADCCTKQEPERNECFLQHKDDNPSLPPFERPEAEAMCT<br>SFKENPTTFMGHYLHEVARRHPYFYAPELLYYAEQYNEILTQC<br>CAEADKESCLTPKLDGVKEKALVSSVRQRMKCSSMQKFGERA<br>FKAWAVARLSQTFPNADFAEITKLATDLTKVNKECCHGDLLEC<br>ADDRAELAKYMCENQATISSKLQTCCDKPLLKKAHCLSEVEH<br>DTMPADLPAIAADFVEDQEVCKNYAEAKDVFLGTFLYEYSRR<br>HPDYSVSLLLRLAKKYEATLEKCCAEANPPACYGTVLAEFQPL<br>VEEPKNLVKTNCDLYEKLGEYGFQNAILVRYTQKAPQVSTPTL<br>VEAARNLGRVGTKCCTLPEDQRLPCVEDYLSAILNRVCLLHEK<br>TPVSEHVTKCCSGSLVERRPCFSALTVEDETYVPKEFKAETFTFH<br>SDICTLPEKEKQIKKQTALAELVKHKPKATAEQLKTVMDDFAQ<br>FLDTCCAADKDTCFSTEGPNLVTRCKDALAGGGSMWELEKD<br>VYVVEVDWTPDAPGETVNLTCDTPEEDDITWTSQDRHGVIGS<br>GKTLTITVKEFLDAGQYTCHKGGETLSHSHLLLHKKENGWST<br>EILKNFKNKTFLKCEAPNYSGRFTCSWLVRNMDLKFNIKSSSS<br>SPDSRAVTCGMASLSAEKVTLQDRDYEKYSVSCQEDVTCPTAE<br>ETLPIELALEARQQNKYENYSTSFIRDIKPDPPKNLQMKPLKN<br>SQVEVSWEYPDSWSTPHSYFSLKFFVRIQRKKEKMKETEEGCN<br>QKGAFLVEKTSTEVQCKGGNVCVQAQDRYNNSSCSKWACVP<br>CRVRSGGSGGGSGGGSGGSRVIPVSGPARCLSQSRNLLKTTD<br>DMVKTAREKLKHYSCTAEDIDHEDITRDQTSTLKTCLPLELHK<br>NESCLATRETSSSTRGSCLPQKTSMLMTLCLGSIYEDLKMYQT<br>EFQAINAALQNHNHQQIILDKGMLVAIDELMQSLNHNGETLRQ<br>KPPVGEADPYRVKMKLCILLHAFSTRVV TINRVMGYLSSAHHH<br>HHHHHHH                                                                                         |
| 34 | 2-MSA-<br>LAIR-12 | MRVPAQLLGLLLLWLPGARCAAPTSSSTSSSTAEEAQQQQQQQ<br>QQQQQHLEQLLMDLQELLSRMENYRNLKLPRMLTFKFYLPKQ<br>ATELKDLQCLEDELGPLRHVLDLTQSKSFQLEDAENFISNIRVT<br>VVKLKGSDNTFECQFDDDESATVVDFLRRWIAFCQSIISTSPQGG<br>GSEAHKSEIAHRYNDLGEQHFGLVLIASFQYLQKCSYDEHAK<br>LVQEVTDFAKTCVADESAANCDKSLHTLFGDKLCAIPNLRENY<br>GELADCCTKQEPERNECFLQHKDDNPSLPPFERPEAEAMCTSF<br>KENPTTFMGHYLHEVARRHPYFYAPELLYYAEQYNEILTQCCA<br>EADKESCLTPKLDGVKEKALVSSVRQRMKCSSMQKFGERAFK<br>AWAVARLSQTFPNADFAEITKLATDLTKVNKECCHGDLLECA<br>DDRAELAKYMCENQATISSKLQTCCDKPLLKKAHCLSEVEHD<br>TMPADLPAIAADFVEDQEVCKNYAEAKDVFLGTFLYEYSRRHP<br>DYSVSLLLRLAKKYEATLEKCCAEANPPACYGTVLAEFQPLVE<br>EPKNLVKTNCDLYEKLGEYGFQNAILVRYTQKAPQVSTPTLVE<br>AARNLGRVGTKCCTLPEDQRLPCVEDYLSAILNRVCLLHEKTP<br>VSEHVTKCCSGSLVERRPCFSALTVEDETYVPKEFKAETFTFHSD<br>ICTLPEKEKQIKKQTALAELVKHKPKATAEQLKTVMDDFAQFL<br>DTCCAADKDTCFSTEGPNLVTRCKDALAGGGSGGGSGEGSL<br>PDITIFPNSSLMISQGTFTVTVCSYSDKHDLYNMVRLEKDGSTF<br>MEKSTEPYKTEDEFEIGPVNETITGHYSCIYSKGITWSERSKTLE<br>LKVIKENVIQTPAPGPTSDTSWLKTYSIYGGSGGGSMWELEK<br>DVYVVEVDWTPDAPGETVNLTCDTPEEDDITWTSQDRHGVIG<br>SGKTLTITVKEFLDAGQYTCHKGGETLSHSHLLLHKKENGWST<br>TEILKNFKNKTFLKCEAPNYSGRFTCSWLVRNMDLKFNIKSSS<br>SSPDSRAVTCGMASLSAEKVTLQDRDYEKYSVSCQEDVTCPTA<br>EETLPIELALEARQQNKYENYSTSFIRDIKPDPPKNLQMKPLK<br>NSQVEVSWEYPDSWSTPHSYFSLKFFVRIQRKKEKMKETEEGC<br>NQKGAFLVEKTSTEVQCKGGNVCVQAQDRYNNSSCSKWACV |

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|    |                   | <p>PCRVRSGSGGGSGGGSGGGSRVIPVSGPARCLSQSRNLLKTT<br/>DDMVKTAREKLKHYSCTAEDIDHEDITRDQTSTLKTCLPLELH<br/>KNESCLATRETSSSTRGSCLPQKTSMMTLCLGSIYEDLKMY<br/>QTEFQAINAALQNHNHQQIILDKGMLVAIDELMQSLNHNGETL<br/>RQKPPVGEADPYRVKMKLCILLHAFSTRVVTINRVMGYLSSAH<br/>HHHHHHHHH</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| 35 | 2-LAIR-<br>ABD-12 | <p>MRVPAQLLGLLLLWLPGARCAAPTSSSTSSSTAEAAQQQQQQQ<br/>QQQQQHLEQLLMDLQELLSRMENYRNKLPRMLTFKFYLPKQ<br/>ATELKDLQCLEDELGPLRHVLDLTQSKSFQLEDAENFISNIRVT<br/>VVKLKGSDNTEFCQFDDDESATVVDFLRRWIAFCQSIISTSPQGG<br/>GSGGGSQEGSLPDITIFPNSSLMISQGTFTVTVVCSYSDKHDLYN<br/>MVRLEKDGSTFMEKSTEPYKTEDEFEIGPVNETITGHYSCIYSK<br/>GITWSERSKTLELKVIKENVIQTPAPGPTSDTSWLKTYSIYGGGS<br/>GGGSKVQLVESGGGLVQPGGSLRLSCAASGFTFSSFGMTWVR<br/>QAPGKGLEWVSSISGSGSDTLYADSVRGRFTISRDN SKNTLYLQ<br/>MNSLRAEDTAVYYCTIGGSLSPSSQGT LTVVSSGGGSMWELEK<br/>DVYVVEVDWTPDAPGETVNLTCDTPEEDDITWTS DQRHGVIG<br/>SGKTLTITVKEFLDAGQYTCHKGGETLSHSHLLLHKKENGIWS<br/>TEILKNFKNKTF LKCEAPNYSGRFTCSWL VQRNMDLKFNIKSSS<br/>SSPDSRAVTCGMASLSAEKVTL DQRDYEKYSVSCQEDVTCPTA<br/>EETLPIELALEARQQNKYENYSTSFFIRDIKPDPPKNLQMKPLK<br/>NSQVEVSWEYPDSWSTPHSYFSLKFFVRIQRKKEKMKETEEGC<br/>NQKGAFLVEKTSTEVQCKGGNVCVQAQDRYYNSSCSKWACV<br/>PCRVRSGSGGGSGGGSGGGSRVIPVSGPARCLSQSRNLLKTT<br/>DDMVKTAREKLKHYSCTAEDIDHEDITRDQTSTLKTCLPLELH<br/>KNESCLATRETSSSTRGSCLPQKTSMMTLCLGSIYEDLKMY<br/>QTEFQAINAALQNHNHQQIILDKGMLVAIDELMQSLNHNGETL<br/>RQKPPVGEADPYRVKMKLCILLHAFSTRVVTINRVMGYLSSAH<br/>HHHHHHHHH</p>  |
| 36 | 2-ABD-<br>LAIR-12 | <p>MRVPAQLLGLLLLWLPGARCAAPTSSSTSSSTAEAAQQQQQQQ<br/>QQQQQHLEQLLMDLQELLSRMENYRNKLPRMLTFKFYLPKQ<br/>ATELKDLQCLEDELGPLRHVLDLTQSKSFQLEDAENFISNIRVT<br/>VVKLKGSDNTEFCQFDDDESATVVDFLRRWIAFCQSIISTSPQGG<br/>GSKVQLVESGGGLVQPGGSLRLSCAASGFTFSSFGMTWVRQAP<br/>GKGLEWVSSISGSGSDTLYADSVRGRFTISRDN SKNTLYLQMN<br/>SLRAEDTAVYYCTIGGSLSPSSQGT LTVVSSGGGSGGGSGEGSL<br/>PDITIFPNSSLMISQGTFTVTVVCSYSDKHDLYNMVRLEKDGSTF<br/>MEKSTEPYKTEDEFEIGPVNETITGHYSCIYSK GITWSERSKTLE<br/>LKVIKENVIQTPAPGPTSDTSWLKTYSIYGGGSGGGSMWELEK<br/>DVYVVEVDWTPDAPGETVNLTCDTPEEDDITWTS DQRHGVIG<br/>SGKTLTITVKEFLDAGQYTCHKGGETLSHSHLLLHKKENGIWS<br/>TEILKNFKNKTF LKCEAPNYSGRFTCSWL VQRNMDLKFNIKSSS<br/>SSPDSRAVTCGMASLSAEKVTL DQRDYEKYSVSCQEDVTCPTA<br/>EETLPIELALEARQQNKYENYSTSFFIRDIKPDPPKNLQMKPLK<br/>NSQVEVSWEYPDSWSTPHSYFSLKFFVRIQRKKEKMKETEEGC<br/>NQKGAFLVEKTSTEVQCKGGNVCVQAQDRYYNSSCSKWACV<br/>PCRVRSGSGGGSGGGSGGGSRVIPVSGPARCLSQSRNLLKTT<br/>DDMVKTAREKLKHYSCTAEDIDHEDITRDQTSTLKTCLPLELH<br/>KNESCLATRETSSSTRGSCLPQKTSMMTLCLGSIYEDLKMY<br/>QTEFQAINAALQNHNHQQIILDKGMLVAIDELMQSLNHNGETL<br/>RQKPPVGEADPYRVKMKLCILLHAFSTRVVTINRVMGYLSSAH<br/>HHHHHHHHH</p> |

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| 37 | 12-LAIR-MSA-2<br>(normal linkers) | MRVPAQLLGLLLLWLPGARCAMWELEKDVYVVEVDWTPDAP<br>GETVNLTCDTPEEDDITWTSDQRHGVIGSGKTLTITVKEFLDAG<br>QYTCHKGGETLSHSHLLLHKKENGIWSTEILKNFKNKTFKCE<br>APNYSGRFTCSWLVRQNMMDLKFNIKSSSSSPDSRAVTCGMASL<br>SAEKVTLDQRDYEKYSVSCQEDVTCPTAEETLPIELALEARQQ<br>NKYENYSTSFFIRDIIKPDPPKNLQMKPLKNSQVEVSWEYPDSW<br>STPHSYFSLKFFVRIQRKKEKMKETEEGCNQKGAFLVEKTSTE<br>VQCKGGNVCVQAQDRYYNSSCSKWACVPCRVRSGGSGGGSG<br>GGSGGGSRVIPVSGPARCLSQSRNLLKTDDMVKTAREKLKHY<br>SCTAEDIDHEDITRDQTSTLKTCLPLELHKNESCLATRETSSTTR<br>GSCLPPQKTSMLMTLCLGSIYEDLKMYQTEFQAINAALQNHNH<br>QQIILDKGMLVAIDELMQSLNHNGETLRQKPPVGEADPYRVK<br>MKLCILLHAFSTRVVTINRVMGYLSSAGGGGSGGGSGEGSLPD<br>ITIFPNSSLMISQGTFTVTVCSYSDKHDLNVMVRLEKDGSTFME<br>KSTEPYKTEDEFEIGPVNETITGHYSCIYSKGITWSERSKTLELK<br>VIKENVIQTPAPGPTSDTSWLKTYSIYGGGGSGGGSEAHKSEIA<br>HRYNDLGEQHFGLVLIAFSQYLQKCSYDEHAKLVQEVTDFAK<br>KTCVADESAANCDKSLHTLFGDKLCAIPNLRENYGELADCCTK<br>QEPERNECFLQHKDDNPSLPPFERPEAEAMCTSFKENPTTFMG<br>HYLHEVARRHPYFYAPELLYYAEQYNEILTQCCAEADKESCLT<br>PKLDGVKEKALVSSVRQRMKCSSMQKFGERAFAKAWAVARLS<br>QTFPNADFAEITKLATDLTKVNKECCHGDLLECADDRAELAKY<br>MCENQATISSKLQTCCDKPLLKKAHCLSEVEHDTMPADLPAIA<br>ADFVEDQEVCKNYAEAKDVFLGTFLYEYSRRHPDYSVSLLLRL<br>AKKYEATLEKCCAEANPPACYGTVLAEFQPLVEEPKNLVKTN<br>CDLYEKLGEYGFQNAILVRYTQKAPQVSTPTLVEAARNLGRV<br>GTKCCTLPEDQRLPCVEDYLSAILNRVCLLHEKTPVSEHVTKC<br>CSGSLVERRPCFSALTVDETYVPKEFKAETFTFHSICTLPEKEK<br>QIKKQTALAEVLKHKPKATAEQLKTVMDFAQFLDTCKAAD<br>KDTCFSTEGPNLVTRCKDALAGGGGSGGGSAPTSSSTSSSTA<br>EAQQQQQQQQQQQHLEQLLMDLQELLSRMENYRNKLPRMLT<br>FKFYLPKQATELKDLCLEDELGPLRHVLDLTQSKSFQLEDAE<br>NFISNIRVTVVKLKGSNTFECQFDDSATVVDLRRWIAFCQS<br>IISTSPQHHHHHHHHHH |
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Table 6. Exemplary human bi-functional linear constructs

| SEQ ID NO: | Construct Name | Sequence                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
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| 38         | 12-LAIR1-HSA-2 | MRVPAQLLGLLLLWLPGARCAIWELKKDVYVVELDWYPDAP<br>GEMVVLTCDTPEEDGITWTLQSSSEVLGSGKTLTIQVKEFGDA<br>GQYTCHKGGEVLSHSLLLLHKKEDGIWSTDILKDQKEPKNKT<br>LRCEAKNYSGRFTCWLLTTISTDLTFSVKSSRGSSDPQGVTCG<br>AATLSAERVVRGDNKEYEYSVEQEDSACPAAEESLPIEVMVDA<br>VHKLKYENYTSSFFIRDIIKPDPPKNLQLKPLKNSRQVEVSWEY<br>PDTWSTPHSYFSLTFCVQVQGKSKREKKDRVFTDKTSATVICR<br>KNASISVRAQDRYYSSSWSEWASVPCSGGSGGGSGGGSGGG<br>RNLPVATPDPGMFPCPLHHSQNLLRAVSNMLQKARQTLEFYPT<br>SEEIDHEDITDKTSTVEACLPLELTKNESCLNSRETSFITNGSCL<br>ASRKTSFMMALCLSSYEDLKMYQVEFKTMNAKLLMDPKRQI<br>FLDQNMALVIDELMQALNFNSETVPQKSSLEEPDFYKTKIKLCI<br>LLHAFRIRAVTIDRVMSYLNASGGGSGGGSGEEDLPRPSISAEP<br>GTVIPLGSHVTFVCRGPVGVQTFRLERESRSTYNDTEDVSQASP<br>SESEARFRIDSVSEGNAGPYRCIYYKPPKWSEQSDYLELLVKET |

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|    |                | SGGPDSPDTEPGSSAGPTQRPSDNSHNEHAPASQGLKAEHLYG<br>GSGGGS DAHKSEVAHFRKDLGEENFKALVLIAFAQYLQQCPF<br>EDHVKL VNEVTEFAKTCVADESAENCDKSLHTLFGDKLCTVA<br>TLRETYGEMADCCAKQEPERNECFLQHKDDNP NLPRLVRPEV<br>DVMCTAFHDNEETFLKKYLYE IARRHPYFYAPELLFFAKRYKA<br>AFTECCQAADKAACLLPKLDEL RDEGKASSAKQRLKCASLQK<br>FGERAFKAWAVARLSQRFPKAEFAEVSKLVTDLT KVHTECCH<br>GDLLECADDRADLAKYICENQDSISSKLKECCEKPLLEKSHCIA<br>EVENDEMPADLPSLAADFVESKDVCKNYAEAKDVFLGMFLYE<br>YARRHPDYSVVLRLAKTYETTLEKCCAAADPHECYAKVFD<br>EFKPLVEEPQNLIKQNC ELFELGEYKFQNALLVRYTKKVPQV<br>STPTLVEVSRNLGKVGSKCKHPEAKRMPCAEDYLSVVLNQL<br>CVLHEKTPVSDRVT KCCTESLVNRRPCFSALEVDETYVPKEFN<br>AETFTFHADICTLSEKERQIKKQTALVELVKHKPKATKEQLKA<br>VMDDFAAFVEKCKADDKETCFAEEGKKLVAASQAALGLGG<br>GSAPTSSSTKKTQLQLEHLLDLQMILNGINNYKNPKLTRMLTF<br>KFYMPKKATELKHLCLEELKPLEEVLNLAQSKNFHLRPRDL<br>ISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIIST<br>LTHHHHHHHHHH                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| 39 | 12-LAIR2-HSA-2 | MRVPAQLLGLLLLWLPGARCAIWELKKDVYVVELDWYPDAP<br>GEMVVLTCDTPEEDGITWTL DQSSEVLGSGKTLTIQVKEFGDA<br>GQYTCHKGGEVLSHSLLLHKKEDGIWSTDILKDQKEPKNKTF<br>LRCEAKNYSGRFTCWWT TISTDLTFSVKSSRGSSDPQGVTCG<br>AATLSAERVGRDNKEYEYSVE CQEDSACPAAEESLPIEVMVDA<br>VHKLKYENYTSSFFIRDI IKPDPPKNLQLKPLKNSRQVEVSWEY<br>PDTWSTPHSYFSLTFCVQVQ GKSKREKKDRVFTDKTSATVICR<br>KNASISVRAQDRYYSSSWSEWASVPCSGSGGSGGSGGSGGGS<br>RNLVPATPDPMFPCLHHSQNLLRAVSNMLQKARQTLEFYPTCT<br>SEEIDHEDITKDKTSTVEACLPLELTKNESCLNSRETSFITNGSCL<br>ASRKTSFMMALCLSSIYEDL KMYQVEFKTMNAKLLMDPKRQI<br>FLDQNMLAVIDELMQALNF NSETVPQKSSLEEPDFYKTKIKLCI<br>LLHAFRIRAVTIDRVMSYLNASGGGSGGGSQEGALPRPSISAEP<br>GTVISPGSHVTFMCRGPVG VQTFRLEREDRAKYKDSYNVFRLG<br>PSESEARFHIDSVSEGNAGLYRCLYYKPPGWSEHSDFLELLVKE<br>SSGGPDSPDTEPGSSAGT VPGTEASGFDAPGGGSGGGS DAHKS<br>EVAHFRKDLGEENFKALVLIAFAQYLQQCPFEDHVKL VNEVTE<br>FAKTCVADESAENCDKSLHTLFGDKLCTVATLRETYGEMADC<br>CAKQEPERNECFLQHKDDNP NLPRLVRPEVDVMCTAFHDNEE<br>TFLKKYLYE IARRHPYFYAPELLFFAKRYKAAFTTECCQAADKA<br>ACLLPKLDEL RDEGKASSAKQRLKCASLQKFGERAFKAWAVA<br>RLSQRFPKAEFAEVSKLVTDLT KVHTECCHGDLLECADDRADL<br>AKYICENQDSISSKLKECCEKPLLEKSHCIAEVENDEMPADLPS<br>LAADFVESKDVCKNYAEAKDVFLGMFLYEYARRHPDYSVVL<br>LRLAKTYETTLEKCCAAADPHECYAKVDEFKPLVEEPQNLIK<br>QNC ELFELGEYKFQNALLVRYTKKVPQVSTPTLVEVSRNLGK<br>VGSKCKHPEAKRMPCAEDYLSVVLNQLCVLHEKTPVSDRVT<br>KCCTESLVNRRPCFSALEVDETYVPKEFNAETFTFHADICTLSE<br>KERQIKKQTALVELVKHKPKATKEQLKAVMDDFAAFVEKCK<br>ADDKETCFAEEGKKLVAASQAALGLGGGSAPTSSSTKKTQLQL<br>EHLLDLQMILNGINNYKNPKLTRMLTFK FYMPKKATELKHLC<br>CLEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELKGSETT<br>FMCEYADETATIVEFLNRWITFCQSIISTLTHHHHHHHHHH |

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| 40 | 12-Lum-HSA-2   | <p>MRVPAQLLGLLLLWLPGARCAIWELKKDVYVVELDWYPDAP<br/> GEMVVLTCDTPEEDGITWTLDSSEVLGSGKTLTIQVKEFGDA<br/> GQYTCHKGGEVLSHSLLLLHKKEDGIWSTDILKDQKEPKNKTF<br/> LRCEAKNYSGRFTCWWTITSTDLTFSVKSSRGSSDPQGVTCG<br/> AATLSAERVGRDNKEYEYSVEQCEDSACPAAEESLPIEVMVDA<br/> VHKLKYENYTSSFFIRDIKPDPPKNLQLKPLKNSRQVEVSWEY<br/> PDTWSTPHSYFSLTFCVQVQGKSKREKKDRVFTDKTSATVICR<br/> KNASISVRAQDRYYSSSWSEWASVPCSGGSGGGSGGGSGGGGS<br/> RNLPAVATPDPMFPC LHHSQNLLRAVSNMLQKARQTLEFYPTCT<br/> SEEIDHEDITKDKTSTVEACLPLELTKNESCLNSRETSFITNGSCL<br/> ASRKTSFMMALCLSSIYEDLKMYQVEFKTMNAKLLMDPKRQI<br/> FLDQNMLAVIDELMQALNFNSETVPQKSSLEEDFYKTKIKLCI<br/> LLHAFRIRAVTIDRVMSYLNASGGGSGGGSGGGSGQYYDYDFPLSI<br/> YGQSSPNCAPCNCPEPSYPSAMYCDELKLSVPMVPPGIKYLY<br/> LRNNQIDHIDEKAFENVTDLQWLILDHNLLENKIKGRVFSKLLK<br/> QLKKLHINHNNLTESVGPLPKSLEDLQLTHNKITKLGSFEGLVN<br/> LTFIHLQHNRLKEDAVSAAFKGLKSLEYLDLSFNQIARLPGLP<br/> VSLTLYLDNNKISNIPDEYFKRFNALQYLRLSHNELADSGIPG<br/> NSFNVSSLVELDLSYNKLNKNIPTVNENLENYYLEVNQLEKFDIK<br/> SFCKILGPLSYSKIKHLRLDGNRISETSLPPDMYECLRVANEVTL<br/> NGGGSGGGSDAHKSEVAHRFKDLGEENFKALVLIAFAQYLQQ<br/> CPFEDHVKLNVNEVTEFAKTCVADESAENCDSLHTLFGDKLCT<br/> VATLRETYGEMADCCAKQEPERNECFQLQHKDDNPPLRVRP<br/> EVDVMCTAFHDNEETFLKKYLYEIARRHPYFYAPELLFFAKRY<br/> KAAFECCQAADKAACLLPKLDELDEGKASSAKQRLKCASL<br/> QKFGERAFAKAWAVARLSQRFPKAEFAEVSKLVTDLTKVHTEC<br/> CHGDLLECADDRADLAKYICENQDSISSKLKECCEKPLEKSH<br/> CIAEVNDEMPADLPSLAADFVESKDVCKNYAEAKDVFLGMF<br/> LYEYARRHPDYSVVLRLAKTYETTLEKCCAAADPHECYAK<br/> VFDEFKPLVEEPQNLKQNCLEFEQLGEYKFQNALLVRYTKKV<br/> PQVSTPTLVEVSRNLGKVGSKCKHPEAKRMPCAEDYLSVVL<br/> NQLCVLHEKTPVSDRVTKCCTESLVNRRPCFSALEVDETYVPK<br/> EFNAETFTFHADICTLSEKERQIKKQATALVELVKHKPKATKEQL<br/> KAVMDDFAAFVEKCKKADDKETCFAEEGKKLVAASQAALGL<br/> GGGSAPTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRM<br/> LTFKFYMPKKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRP<br/> RDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSI<br/> ISTLTHHHHHHHHHH</p> |
| 41 | 12-LAIR1-ABD-2 | <p>MRVPAQLLGLLLLWLPGARCAIWELKKDVYVVELDWYPDAP<br/> GEMVVLTCDTPEEDGITWTLDSSEVLGSGKTLTIQVKEFGDA<br/> GQYTCHKGGEVLSHSLLLLHKKEDGIWSTDILKDQKEPKNKTF<br/> LRCEAKNYSGRFTCWWTITSTDLTFSVKSSRGSSDPQGVTCG<br/> AATLSAERVGRDNKEYEYSVEQCEDSACPAAEESLPIEVMVDA<br/> VHKLKYENYTSSFFIRDIKPDPPKNLQLKPLKNSRQVEVSWEY<br/> PDTWSTPHSYFSLTFCVQVQGKSKREKKDRVFTDKTSATVICR<br/> KNASISVRAQDRYYSSSWSEWASVPCSGGSGGGSGGGSGGGGS<br/> RNLPAVATPDPMFPC LHHSQNLLRAVSNMLQKARQTLEFYPTCT<br/> SEEIDHEDITKDKTSTVEACLPLELTKNESCLNSRETSFITNGSCL<br/> ASRKTSFMMALCLSSIYEDLKMYQVEFKTMNAKLLMDPKRQI<br/> FLDQNMLAVIDELMQALNFNSETVPQKSSLEEDFYKTKIKLCI<br/> LLHAFRIRAVTIDRVMSYLNASGGGSGGGSGQEEEDLPRPSISAEP<br/> GTVIPLGSHVTFVCRGPVGVTFRLERESRSTYNDTEDVSQASP<br/> SESEARFRIDSVSEGNAGPYRCIYYKPPKWSEQSDYLELLVKET<br/> SGGPDSPDTEPGSSAGPTQRPSDNSHNEHAPASQGLKAEHLYG</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |

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|    |                    | GGSGGGSKVQLVESGGGLVQPGGSLRLSCAASGFTFSSFGMT<br>WVRQAPGKGLEWVSSISGSGSDTLYADSVRGRFTISRDN SKNT<br>LYLQMNSLRAEDTAVYYCTIGGSLSPSSQGT LVT VSSGGGSAP<br>TSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFY<br>MPKKATELKH LQCLEELKPLEEVLNLAQSKNFHLRPRDLISNI<br>NVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLTH<br>HHHHHHHHH                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| 42 | 12-LAIR2-<br>ABD-2 | MRVPAQLLGLLLLWLPGARCAIWELKKDVYVVELDWYPDAP<br>GEMVVLTC DTPEEDGITWTLDQSSEVLGSGKTLTIQVKEFGDA<br>GQYTCHKGGEVLSHSLLLHKKEDGIWSTDILKDQKEPKNKTF<br>LRCEAKNYSGRFTCWWLT TISTDLTFSVKSSRGSSDPQGVTCG<br>AATLSAERVGRDNKEYEYSVEQCEDSACPAAEESLPIEVMVDA<br>VHKLKYENYTSSFFIRDIKPDPPKNLQLKPLKNSRQVEVSWEY<br>PDTWSTPHSYFSLTFCVQVQGKSKREKKDRVFTDKTSATVICR<br>KNASISVRAQDRYYSSSWSEWASVPCSGSGGSGGSGGSGGGS<br>RNLPVATPDPGMFPC LHHSQNLLRAVSNMLQKARQTLEFY PCT<br>SEEIDHEDITKDKTSTVEACLPLELTKNESCLNSRETSFITNGSCL<br>ASRKTSFMMALCLSSIEDLKMYQVEFKTMNAKLLMDPKRQI<br>FLDQNMLAVIDELMQALNFNSETVPQKSSLEEPDFYKTKIKLCI<br>LLHAFRIRAVTIDRVMSYLNASGGGSGGGSQEGALPRPSISAEP<br>GTVISPGSHVTFMCRGPVG VQTFRLEREDRAKYKDSYNVFR LG<br>PSESEARFHIDSVSEGNAGLYRCLYYKPPGWSEHSDFLELLVKE<br>SSGGPDSPDTEPGSSAGTVPGTEASGFDAPGGGSGGGSKVQLV<br>ESGGGLVQPGGSLRLSCAASGFTFSSFGMTWVRQAPGKGLEW<br>VSSISGSGSDTLYADSVRGRFTISRDN SKNTLYLQMNSLRAEDT<br>AVYYCTIGGSLSPSSQGT LVT VSSGGGSAPTSSSTKKTQLQLEH<br>LLLDLQMILNGINNYKNPKLTRMLTFKFYMPKKATELKH LQC<br>LEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELKGSETTFM<br>CEYADETATIVEFLNRWITFCQSIISTLTHHHHHHHHHH                                                                                                   |
| 43 | 12-Lum-<br>ABD-2   | MRVPAQLLGLLLLWLPGARCAIWELKKDVYVVELDWYPDAP<br>GEMVVLTC DTPEEDGITWTLDQSSEVLGSGKTLTIQVKEFGDA<br>GQYTCHKGGEVLSHSLLLHKKEDGIWSTDILKDQKEPKNKTF<br>LRCEAKNYSGRFTCWWLT TISTDLTFSVKSSRGSSDPQGVTCG<br>AATLSAERVGRDNKEYEYSVEQCEDSACPAAEESLPIEVMVDA<br>VHKLKYENYTSSFFIRDIKPDPPKNLQLKPLKNSRQVEVSWEY<br>PDTWSTPHSYFSLTFCVQVQGKSKREKKDRVFTDKTSATVICR<br>KNASISVRAQDRYYSSSWSEWASVPCSGSGGSGGSGGSGGGS<br>RNLPVATPDPGMFPC LHHSQNLLRAVSNMLQKARQTLEFY PCT<br>SEEIDHEDITKDKTSTVEACLPLELTKNESCLNSRETSFITNGSCL<br>ASRKTSFMMALCLSSIEDLKMYQVEFKTMNAKLLMDPKRQI<br>FLDQNMLAVIDELMQALNFNSETVPQKSSLEEPDFYKTKIKLCI<br>LLHAFRIRAVTIDRVMSYLNASGGGSGGGSQYYDYDFPLSI<br>YGQSSPNCAPCNCPE SYPSAMYCDELKLKSVPMVPPGIKYLY<br>LRNNQIDHIDEKAFENVTDLQWLILDHNLLENSKIKGRVFSKLK<br>QLKKLHINHNNLTESVGPLPKSLEDLQLTHNKITKLGSFEGLVN<br>LTFIHLQHNRLKEDAVSAAFKGLKSLEYLDLSFNQIARLP SGLP<br>VSLLTLYLDNNKISNIPDEYFKRFNALQYLR LSHNELADSGIPG<br>NSFNVSSLVELDLSYNKLKNIPTVNENLENYYLEVNQLEKFDIK<br>SFCKILGPLSYSKIKHLRLDGNRISETSLPPDMECLRVANEVTL<br>NGGGSGGGSKVQLVESGGGLVQPGGSLRLSCAASGFTFSSFGM<br>TWVRQAPGKGLEWVSSISGSGSDTLYADSVRGRFTISRDN SKN<br>TLYLQMNSLRAEDTAVYYCTIGGSLSPSSQGT LVT VSSGGGSA<br>PTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFY |

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|----|-------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|    |                                           | MPKKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNI<br>NVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLTH<br>HHHHHHHHH                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| 44 | 12-LAIR1-<br>HSA-2<br>(normal<br>linkers) | MRVPAQLLGLLLLWLPGARCAIWELKKDVYVVELDWYPDAP<br>GEMVVLTCDTPEEDGITWTLDQSSEVLGSGKTLTIQVKEFGDA<br>GQYTCHKGGEVLSHSLLLLHKKEDGIWSTDILKDQKEPKNKTF<br>LRCEAKNYSGRFTCWWLTTISTDLTFSVKSSRGSSDPQGVTCG<br>AATLSAERVGRDNKEYEYSVEQCEDSACPAAEESLPIEVMVDA<br>VHKLKYENYTSSFFIRDIIKPDPPKNLQLKPLKNSRQVEVSWEY<br>PDTWSTPHSYFSLTFCVQVQGKSKREKKDRVFTDKTSATVICR<br>KNASISVRAQDRYYSSSWSEWASVPCSGSGSGSGSGSGSGGS<br>RNLPVATPDPGMFPC LHHSQNLLRAVSNMLQKARQTLEFYPCT<br>SEEIDHEDITKDKTSTVEACLPLELTKNESCLNSRETSFITNGSCL<br>ASRKTSFMMALCLSSIEDLKMYQVEFKTMNAKLLMDPKRQI<br>FLDQNMLAVIDELMQALNFNSETVPQKSSLEEPDFYKTKIKLCI<br>LLHAFRIRAVTIDRVMSYLNASGGGGSGGGSGQEE DLPRPSISAE<br>PGTVIPLGSHVTFVCRGPVGVQTFRLERESRSTYNDTEDVSQAS<br>PSESEARFRIDSVSEGNAGPYRCIYYKPPKWSEQSDYLELLVKE<br>TSGGPDSPTDEPGSSAGPTQRPSDNSHNEHAPASQGLKAEHLY<br>GGGGSGGGSDAHKSEVAHRFKDLGEENFKALVLIAFAQYLQQ<br>CPFEDHVKL VNEVTEFAKTCVADESAENCDKSLHTLFGDKLCT<br>VATLRETYGEMADCCAQKEPERNECF LQHKDDNP NLPRLVRP<br>EVDVMCTAFHDNEETFLKKYLYEIARRHPYFYAPELLFFAKRY<br>KAAFECCQAADKAACLLPKLDEL RDEGKASSAKQRLK CASL<br>QKFGERAFAKAWAVARLSQRFPKAEFAEVSKLVTDLTKVHTEC<br>CHGDLLECADDRADLAKYICENQDSISSKLKECCEKPLLEKSH<br>CIAEVENDEMPADLPSLAADFVESKDVCKNYAEAKDVF LGMF<br>LYEYARRHPDY SVVLLLRLAKTYETTLEKCCAAADPHECYAK<br>VFDEFKPLVEEPQNLIKQNCELFEQLGEYKFQNALLVRYTKKV<br>PQVSTPTLVEVSRNLGKVGSKCKHPEAKRMPCAEDYLSVVL<br>NQLCVLHEKTPVSDRVTKCCTESLVNRRPCFSALEVDETYVPK<br>EFNAETFTFHADICTLSEKERQIKKQTALVELVKHKPKATKEQL<br>KAVMDDFAAFVEKCKKADDKETCFAEEGKKLVAASQAALGL<br>GGGGSGGGSAPTSSSTKKTQLQLEHLLLDLQMILNGINNYKNP<br>KLTRMLTFKFYMPKKATELKHLQCLEEELKPLEEVLNLAQSKN<br>FHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWI<br>TFCQSIISTLTHHHHHHHHHH |
| 45 | 12-LAIR2-<br>HSA-2<br>(normal<br>linkers) | MRVPAQLLGLLLLWLPGARCAIWELKKDVYVVELDWYPDAP<br>GEMVVLTCDTPEEDGITWTLDQSSEVLGSGKTLTIQVKEFGDA<br>GQYTCHKGGEVLSHSLLLLHKKEDGIWSTDILKDQKEPKNKTF<br>LRCEAKNYSGRFTCWWLTTISTDLTFSVKSSRGSSDPQGVTCG<br>AATLSAERVGRDNKEYEYSVEQCEDSACPAAEESLPIEVMVDA<br>VHKLKYENYTSSFFIRDIIKPDPPKNLQLKPLKNSRQVEVSWEY<br>PDTWSTPHSYFSLTFCVQVQGKSKREKKDRVFTDKTSATVICR<br>KNASISVRAQDRYYSSSWSEWASVPCSGSGSGSGSGSGSGGS<br>RNLPVATPDPGMFPC LHHSQNLLRAVSNMLQKARQTLEFYPCT<br>SEEIDHEDITKDKTSTVEACLPLELTKNESCLNSRETSFITNGSCL<br>ASRKTSFMMALCLSSIEDLKMYQVEFKTMNAKLLMDPKRQI<br>FLDQNMLAVIDELMQALNFNSETVPQKSSLEEPDFYKTKIKLCI<br>LLHAFRIRAVTIDRVMSYLNASGGGGSGGGSGEGALPRPSISAE<br>PGTVISPGSHVTFMCRGPVGVQTFRLEREDRAKYKDSYNV FRL<br>GPSESEARFHIDSVSEGNAGLYRCLYYKPPGWSEHSDFLELLVK<br>ESSGGPDSPTDEPGSSAGTVPGTEASGFDAPGGGGSGGGSDAH                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |

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|    |                                         | <p>KSEVAHRFKDLGEENFKALVLIAFAQYLQQCPFEDHVKLVNEV<br/>TEFAKTCVADESAENCDKSLHTLFGDKLCTVATLRETYGEMA<br/>DCCAKQEPERNECFLQHKDDNPNLPRLVREVDVMCTAFHDN<br/>EETFLKKYLYEIAARRHPYFYAPELLFFAKRYKAAFTECCQAAD<br/>KAACLLPKLDEL RDEGKASSAKQRLK CASLQKFGERAFKAWA<br/>VARLSQRFPKAEFAEVSKLVTDLT KVHTECCHGDLLECADDR<br/>ADLAKYICENQDSISSKLKECCEKPLLEKSHCIAEVENDEMPAD<br/>LPSLAADFVESKDVCKNYAEAKDVFLGMFLY EYARRHPDYSV<br/>VLLLRLAKTYETTLEKCCAAADPHECYAKVFDEFKPLVEEPQN<br/>LIKQNC ELFELGEYKFQNALLVRYTKKVPQVSTPTLVEVSRN<br/>LGKVGSKCKHPEAKRMPCAEDYLSVVLNQLCVLHEKTPVSD<br/>RVTKCCTESLVNRRPCFSALEVDETYVPKEFNAETFTFHADICT<br/>LSEKERQIKKQTALVELVKHKPKATKEQLKAVMDDFAAFVEK<br/>CKKADDKETCFAEEGKKLVAASQAALGLGGGSGGGGSAPTSS<br/>STKKTQLQLEHLLLDLQMLNGINNYKNPKLTRMLTFKFYMPK<br/>KATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVI<br/>VLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLTHHHH<br/>HHHHHH</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| 46 | 12-Lum-<br>HSA-2<br>(normal<br>linkers) | <p>MRVPAQLLGLLLLWLPGARCAIWELKKDVYVVELDWYPDAP<br/>GEMVVLTCDTPEEDGITWTL DQSSEVLGSGKTLTIQVKEFGDA<br/>GQYTCHKGGEVLSHSLLLHKKEDGIWSTDILKDQKEPKNKTF<br/>LRCEAKNYSGRFTCWWT TISTDLTFSVKSSRGSSDPQGVTCG<br/>AATLSAERVGRDNKEYEYSVEQCEDSACPAAEESLPIEVMVDA<br/>VHKLKYENYTSSFFIRDIIPDPK NLQLKPLKNSRQVEVSWEY<br/>PDTWSTPHSYFSLTFCVQVQGKSKREKKDRVFTDKTSATVICR<br/>KNASISVRAQDRYYSSSWSEWASVPCSGSGGGSGGGSGGGGS<br/>RNLPVATPDPMFPCLHHSQNL LRAVSNMLQKARQTLEFYPTCT<br/>SEEIDHEDITKDKTSTVEACLPLELTKNESCLNSRETSFITNGSCL<br/>ASRKTSFMMALCLSSIEDLKMYQVEFKTMNAKLLMDPKRQI<br/>FLDQNM LAVIDELMQALNFNSETVPQKSSLEEPDFYKTKIKLCI<br/>LLHAFRIRAVTIDRVMSYLNASGGGGSGGGSSGQYYDYDFPLS<br/>IYGQSSPNCAPCNCPE SYPSAMYCDELKLKSVPMVPPGIKYLY<br/>LRNNQIDHIDEKAFENVTDLQWLILDHNLLENSKIKGRVFSKLK<br/>QLKKLHINHNNLTESVGPLPKSLEDLQLTHNKITKLGSFEGLVN<br/>LTFIHLQHNRLKEDAVSAAFGLKSLEYLDLSFNQIARLP SGLP<br/>VSLLTLYLDNNKISNIPDEYFKRFNALQYLRLSHNELADSGIPG<br/>NSFNVSSLVELDLSYNKLKNIPTVNENLENYYLEVNQLEKFDIK<br/>SFCKILGPLSYSKIKHLRLDGNRISETSLPPDMECLRVANEVTL<br/>NGGGGSGGGSDAHKSEVAHRFKDLGEENFKALVLIAFAQYLQ<br/>QCPFEDHVKLVNEVTEFAKTCVADESAENCDKSLHTLFGDKLC<br/>TVATLRETYGEMADCCAKQEPERNECFLQHKDDNPNLPRLV<br/>PEVDVMCTAFHDNEETFLKKYLYEIAARRHPYFYAPELLFFAKR<br/>YKAAFTECCQAADKAACLLPKLDEL RDEGKASSAKQRLK CAS<br/>LQKFGERAFKAWAVARLSQRFPKAEFAEVSKLVTDLT KVHTE<br/>CCHGDLLECADDRADLAKYICENQDSISSKLKECCEKPLLEKS<br/>HCIAEVENDEMPADLPSLAADFVESKDVCKNYAEAKDVFLGM<br/>FLY EYARRHPDYSVLLLRLAKTYETTLEKCCAAADPHECYA<br/>KVFDEFKPLVEEPQNLIKQNC ELFELGEYKFQNALLVRYTKK<br/>VPQVSTPTLVEVSRNLGKVGSKCKHPEAKRMPCAEDYLSV<br/>LNQLCVLHEKTPVSDRVTKCCTESLVNRRPCFSALEVDETYVP<br/>KEFNAETFTFHADICTLSEKERQIKKQTALVELVKHKPKATKEQ<br/>LKAVMDDFAAFVEKCKKADDKETCFAEEGKKLVAASQAALG<br/>LGGGSGGGGSAPTSSSTKKTQLQLEHLLLDLQMLNGINNYKN<br/>PKLTRMLTFKFYMPKKATELKHLQCLEEELKPLEEVLNLAQSK</p> |

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|    |                                           | NFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNR<br>WITFCQSIISTLTHHHHHHHHHH                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| 47 | 12-LAIR1-<br>ABD-2<br>(normal<br>linkers) | MRVPAQLLGLLLLWLPGARCAIWELKKDVYVVELDWYPDAP<br>GEMVVLTCDTPEEDGITWTLDSSEVLGSGKTLTIQVKEFGDA<br>GQYTCHKGGEVLSHSLLLHKKEDGIWSTDILKDQKEPKNKTF<br>LRCEAKNYSGRFTCWWLTTISTDLTFSVKSSRGSSDPQGVTCG<br>AATLSAERVVRGDNKEYEYSVEQCEDSACPAAEESLPIEVMVDA<br>VHKLKYENYTSSFFIRDIIKPDPPKNLQLKPLKNSRQVEVSWEY<br>PDTWSTPHSYFSLTFCVQVQGKSKREKKDRVFTDKTSATVICR<br>KNASISVRAQDRYYSSSWSEWASVPCSGGSGGGSGGGSGGGGS<br>RNLPVATPDPGMFPC LHHSQNLLRAVSNMLQKARQTLEFYPC<br>SEEIDHEDITKDKTSTVEACLPLELTKNESCLNSRETSFITNGSCL<br>ASRKTSFMMALCLSSIEDLKMYQVEFKTMNAKLLMDPKRQI<br>FLDQNMLAVIDELMQALNFNSETVPQKSSLEEDFYKTKIKLCI<br>LLHAFRIRAVTIDRVMSYLNASGGGGSGGGSGQEDLPRPSISAE<br>PGTVIPLGSHVTFVCRGPVGVQTFRLERESRSTYNDTEDVSQAS<br>PSESEARFRIDSVSEGNAGPYRCIYYKPPKWSEQSDYLELLVKE<br>TSGGPDSPDTEPGSSAGPTQRPSDNSHNEHAPASQGLKAEHLY<br>GGGGSGGGSKVQLVESGGGLVQPGGSLRLSCAASGFTFSSFGM<br>TWVRQAPGKGLEWVSSISGSGSDTLYADSVRGRFTISRDN SKN<br>TLYLQMNSLRAEDTAVYYCTIGGSLSPSSQGT LVTVSSGGGGGS<br>GGGSAPTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRM<br>LTFKFYMPKKATELKHLCLEELKPLEEVLNLAQSKNFHLRP<br>RDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSI<br>ISTLTHHHHHHHHHH |
| 48 | 12-LAIR2-<br>ABD-2<br>(normal<br>linkers) | MRVPAQLLGLLLLWLPGARCAIWELKKDVYVVELDWYPDAP<br>GEMVVLTCDTPEEDGITWTLDSSEVLGSGKTLTIQVKEFGDA<br>GQYTCHKGGEVLSHSLLLHKKEDGIWSTDILKDQKEPKNKTF<br>LRCEAKNYSGRFTCWWLTTISTDLTFSVKSSRGSSDPQGVTCG<br>AATLSAERVVRGDNKEYEYSVEQCEDSACPAAEESLPIEVMVDA<br>VHKLKYENYTSSFFIRDIIKPDPPKNLQLKPLKNSRQVEVSWEY<br>PDTWSTPHSYFSLTFCVQVQGKSKREKKDRVFTDKTSATVICR<br>KNASISVRAQDRYYSSSWSEWASVPCSGGSGGGSGGGSGGGGS<br>RNLPVATPDPGMFPC LHHSQNLLRAVSNMLQKARQTLEFYPC<br>SEEIDHEDITKDKTSTVEACLPLELTKNESCLNSRETSFITNGSCL<br>ASRKTSFMMALCLSSIEDLKMYQVEFKTMNAKLLMDPKRQI<br>FLDQNMLAVIDELMQALNFNSETVPQKSSLEEDFYKTKIKLCI<br>LLHAFRIRAVTIDRVMSYLNASGGGGSGGGSGEGALPRPSISAE<br>PGTVISPGSHVTFMCRGPVGVQTFRLEREDRAKYKDSYNVFR<br>LPSESEARFHIDSVSEGNAGLYRCLYKPPGWSEHSDFLELLVK<br>ESSGGPDSPDTEPGSSAGTVPGTEASGFDAPGGGGSGGGSKVQ<br>LVESGGGLVQPGGSLRLSCAASGFTFSSFGMTWVRQAPGKGLE<br>WVSSISGSGSDTLYADSVRGRFTISRDN SKNTLYLQMNSLRAE<br>DTAVYYCTIGGSLSPSSQGT LVTVSSGGGGSGGGSAPTSSSTKK<br>TQLQLEHLLLDLQMILNGINNYKNPKLTRMLTTFKFYMPKKATE<br>LKHLCLEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELKG<br>SETTFMCEYADETATIVEFLNRWITFCQSIISTLTHHHHHHHH<br>HH                |
| 49 | 12-Lum-<br>ABD-2<br>(normal<br>linkers)   | MRVPAQLLGLLLLWLPGARCAIWELKKDVYVVELDWYPDAP<br>GEMVVLTCDTPEEDGITWTLDSSEVLGSGKTLTIQVKEFGDA<br>GQYTCHKGGEVLSHSLLLHKKEDGIWSTDILKDQKEPKNKTF<br>LRCEAKNYSGRFTCWWLTTISTDLTFSVKSSRGSSDPQGVTCG                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |

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|    |                                 | AATLSAERVVRGDNKEYEYSVEQCQEDSACPAAEESLPIEVMVDA<br>VHKLKYENYTSSFFIRDIIKPDPPKNLQLKPLKNSRQVEVSWEY<br>PDTWSTPHSYFSLTFCVQVQVGKSKREKKDRVFTDKTSATVICR<br>KNASISVRAQDRYYSSSWSEWASVPCSGGSGGGSGGGSGGGSGG<br>RNLVPVATPDPMFPCLLHHSQNLLRAVSNMLQKARQTLEFYPC<br>SEEIDHEDITKDKTSTVEACLPLELTKNESCLNSRETSFITNGSCL<br>ASRKTSFMMALCLSSIEDLKMYQVEFKTMNAKLLMDPKRQI<br>FLDQNMMLAVIDELMQALNFNSETVPQKSSLEEDFYKTKIKLCI<br>LLHAFRIRAVTIDRVMSYLNASGGGGSGGGSSGQYYDYDFPLS<br>IYGQSSPNCAPCNCPEPSAMYCDELKLSVPMVPPGIKYLY<br>LRNNQIDHIDEKAFENVTDLQWLILDHNLLENSKIKGRVFSKLK<br>QLKKLHINHNNLTESVGPLPKSLEDLQLTHNKITKLGSFEGLVN<br>LTFIHLQHNRLKEDAVSAAFGLKSLEYLDLSFNQIARLPSPGLP<br>VSLTLYLDNNKISNIPDEYFKRFNALQYLRLSHNELADSGIPG<br>NSFNVSSLVELDLSYNKLKNIPTVNNENLENYYLEVNQLEKFDIK<br>SFCKILGPLSYSKIKHLRLDGNRISETSLPPDMYECLRVANEVTL<br>NGGGSGGGSGKVQLVESGGGLVQPGGSLRLSCAASGFTFSSFG<br>MTWVRQAPGKGLEWVSSISGSGSDTLYADSVRGRFTISRDNK<br>NTLYLQMNSLRAEDTAVYYCTIGGSLSPSSQGTLLTVSSGGGG<br>SGGGSAPTSSSTKKTQLQLEHLLLDLQMLNGINNYKNPKLTR<br>MLTFKFYMPKKATELKHLQCLEEELKPLEEVLNLAQSKNFHLR<br>PRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQ<br>SIISTLTHHHHHHHHHH                                                                                                                                                                                                                                                                                                                                                                                                |
| 50 | 2-LAIR1-HSA-12 (normal linkers) | MRVPAQLLGLLLLWLPGARCAAPTSSSTKKTQLQLEHLLLDLQ<br>MILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKP<br>LEEVLNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYAD<br>ETATIVEFLNRWITFCQSIISTLTGGGGSGGGSQEEDLPRPSISAE<br>PGTVIPLGSHVTFVCRGPVGVQTFRLERESRSTYNDTEDVSQAS<br>PSESEARFRIDSVSEGNAGPYRCIYYKPPKWSEQSDYLELLVKE<br>TSGGPDSPDTEPGSSAGPTQRPSDNSHNEHAPASQGLKAEHLY<br>GGGGSGGGSDAHKSEVAHRFKDLGEENFKALVLIAFAQYLQ<br>CPFEDHVKLNVNEVTEFAKTCVADESAENCDKSLHTLFGDKLCT<br>VATLRETYGEMADCCAKQEPERNECFQHKDDNPNLRLVRP<br>EVDVMCTAFHDNEETFLKKYLYEIARRHPYFYAPELLFFAKRY<br>KAAFTECCQAADKAACLLPKLDELDEGKASSAKQRLKCASL<br>QKFGERAFAKAWAVARLSQRFPKAEFAEVSKLVTDLTKVHTEC<br>CHGDLLECADDRADLAKYICENQDSISSKLKECCEKPLLEKSH<br>CIAEVENDEMPADLPSLAADFVESKDVCKNYAEAKDVFLGMF<br>LYEYARRHPDYSVVLRLAKTYETTLEKCCAAADPHECYAK<br>VFDEFKPLVEEPQNLIKQNCLEFEQLGEYKFQNALLVRYTKKV<br>PQVSTPTLVEVSRNLGKVGSKCKHPEAKRMPCAEDYLSVVL<br>NQLCVLHEKTPVSDRVTKCCTESLVNRRPCFSALEVDETYVPK<br>EFNAETFTFHADICTLSEKERQIKKQTALVELVKHKPKATKEQL<br>KAVMDDFAAFVEKCKADDKETCFEEGKKLVAASQAALGL<br>GGGGSGGGSIWELKKDVYVVELDWYPDAPGEMVVLTCDTPE<br>EDGITWTLDSSEVLGSGKTLTIQVKEFGDAGQYTCHKGGEVL<br>SHSLLLHKKEDGIWSTDILKDQKEPKNTFLRCEAKNYSGRF<br>TCWWLTISTDLTFSVKSSRGSSDPQGVTCGAATLSAERVVRG<br>DKEYEYSVEQCQEDSACPAAEESLPIEVMVDAVHKLKYENYTSS<br>FFIRDIIKPDPPKNLQLKPLKNSRQVEVSWEYPTWSTPHSYFSL<br>TFCVQVQVGKSKREKKDRVFTDKTSATVICRKNASISVRAQDRY<br>YSSSWSEWASVPCSGGSGGGSGGGSGGGSGGGSRNLVPVATPDPMF<br>PCLHHSQNLLRAVSNMLQKARQTLEFYPCSEEIDHEDITKDKT<br>STVEACLPLELTKNESCLNSRETSFITNGSCLASRKTSFMMALC |

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|    |                                           | LSSIIYEDLKMYQVEFKTMNAKLLMDPKRQIFLDQNMLAVIDEL<br>MQALNFNSETVPQKSSLEEPDFYKTKIKLCILLHAFRIRAVTIDR<br>VMSYLNASHHHHHHHHHH                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| 51 | 2-LAIR2-<br>HSA-12<br>(normal<br>linkers) | MRVPAQLLGLLLLWLPGARCAAPTSSSTKKTQLQLEHLLLDLQ<br>MILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKP<br>LEEVLNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYAD<br>ETATIVEFLNRWITFCQSIISTLTGGGGSGGGSGEGALPRPSISAE<br>PGTVISPGSHVTFMCRGPVGVQTFRLEREDRAKYKDSYNVFR<br>GPSESEARFHIDSVSEGNAGLYRCLYYKPPGWSEHSDFLELLVK<br>ESSGGPDSPDTEPGSSAGTVPGTEASGFDAPGGGGSGGGSDAH<br>KSEVAHRFKDLGEENFKALVLIAFAQYLQQCPFEDHVKL VNEV<br>TEFAKTCVADESAENCDKSLHTLFGDKLCTVATLRETYGEMA<br>DCCAKQEPERNECFLQHKDDNPPLRLVRPEVDVMCTAFHDN<br>EETFLKKYLYEIAARRHPYFYAPELLFFAKRYKAAFTTECCQAAD<br>KAACLLPKLDEL RDEGKASSAKQRLKCASLQKFGERAFKAWA<br>VARLSQRFPKAEFAEVSKLVTDLT KVHTECCHGDLLECADDR<br>ADLAKYICENQDSISSKLKECCEKPLLEKSHCIAEVENDEMPAD<br>LPSLAADFVESKDVCKNYAEAKDVFLGMFLY EYARRHPDYSV<br>VLLRLAKTYETTLEKCCAAADPHECYAKVFDEFKPLVEEPQN<br>LIKQNCLEFEQLGEYKFQNALLVRYTKKVPQVSTPTLVEVSRN<br>LGKVGSKCKHPEAKRMPCAEDYLSVVLNQLCVLHEKTPVSD<br>RVTKCCTESLVNRRPCFSALEVDETYVPKEFNAETFTFHADICT<br>LSEKERQIKKTALVELVKHKPKATKEQLKAVMDDFAAFVEK<br>CKADDKETCFAEEGKKLVAASQAALGLGGGGSGGGSIWELK<br>KDVYVVELDWYPDAPGEMVVLTCDTPEEDGITWTL DQSSEVL<br>GSGKTLTIQVKEFGDAGQYTCHKGGEVLSHSLLLHKKEDGIW<br>STDILKDQKEPKNKTFLRCEAKNYSGRFTCWWT TISTDLTFSV<br>KSSRGSSDPQGVTCGAATLSAERV RGDNKEYEYSVECQEDSAC<br>PAAEESLPIEVMVDAVHKLKYENYTSSFFIRDIKPDPPKNLQLK<br>PLKNSRQVEVSWEYPDTWSTPHSYFSLTFCVQVQGKSKREKK<br>DRVFTDKTSATVICRKNASISVRAQDRYYSSSWSEWASVPCSG<br>GSGGGSGGGSGGGSRNLPVATPDPGMFPLHHSQNLLRAVSN<br>MLQKARQTLEFYPTSEEIDHEDITKDKTSTVEACLPLELTKNE<br>SCLNSRETSFITNGSCLASRKTSFMMALCLSSIIYEDLKMYQVEF<br>KTMNAKLLMDPKRQIFLDQNMLAVIDELMQALNFNSETVPQK<br>SSLEEPDFYKTKIKLCILLHAFRIRAVTIDRVMSYLNASHHHHH<br>HHHHH |
| 52 | 2-Lum-HSA-<br>12 (normal<br>linkers)      | MRVPAQLLGLLLLWLPGARCAAPTSSSTKKTQLQLEHLLLDLQ<br>MILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKP<br>LEEVLNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYAD<br>ETATIVEFLNRWITFCQSIISTLTGGGGSGGGSGQYYDYDFPLS<br>IYGQSSPNCAPCNCPEPSAMYCDELKLKSVPMVPPGIKYLY<br>LRNNQIDHIDEKAFENVTDLQWLILDHNLENSKIKGRVFSKLK<br>QLKKLHINHNNLTESVGPLPKSLEDLQLTHNKITKLGSFEGLVN<br>LTFIHLQHNRLKEDAVSAAFGLKSLEYLDLSFNQIARLP SGLP<br>VSLLTLYLDNNKISNIPDEYFKRFNALQYLR LSHNELADSGIPG<br>NSFNVSSLVELDLSYNKLKNIPTVNENLENYYLEVNQLEKFDIK<br>SFCKILGPLSYSKIKHLRLDGNRISETSLPPDMECLRVANEVTL<br>NGGGGSGGGSDAHKSEVAHRFKDLGEENFKALVLIAFAQYLQ<br>QCPFEDHVKL VNEVTEFAKTCVADESAENCDKSLHTLFGDKLC<br>TVATLRETYGEMADCCAKQEPERNECFLQHKDDNPPLRLVR<br>PEVDVMCTAFHDNEETFLKKYLYEIAARRHPYFYAPELLFFAKR<br>YKAAFTTECCQAADKAACLLPKLDEL RDEGKASSAKQRLKCAS                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |

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|----|-------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|    |                                           | <p>LQKFGERAFAKAWAVARLSQRFPKAEFAEVSKLVTDLTQVHTE<br/> CCHGDLLECADDRADLAKYICENQDSISSKLKECCEKPLLEKS<br/> HCIAEVENDEMPADLPSLAADFVESKDVCKNYAEAKDVFGLM<br/> FLYEYARRHPDYSVLLRLAKTYETTLEKCCAAADPHECYA<br/> KVFDEFKPLVEEPQNLIKQNCELFEQLGEYKFQNALLVRYTKK<br/> VPQVSTPTLVEVSRNLGKVGSKCCKHPEAKRMPCAEDYLSVV<br/> LNQLCVLHEKTPVSDRVTKCCTESLVNRRPCFSALEVDETYVP<br/> KEFNAETFTFHADICTLSEKERQIKKQTALVELVKHKPKATKEQ<br/> LKAVMDDFAAFVEKCCCKADDKETCFAEEGKKLVAASQAALG<br/> LGGGSGGGSIWELKKDVYVVELDWYPDAPGEMVVLTCDDTP<br/> EEDGITWTLTQSSSEVLGSGKTLTIQVKEFGDAGQYTCHKGGEV<br/> LSHSLLLLHKKEDGIWSTDILKDQKEPKNKTFRLCEAKNYSGR<br/> FTCWWLTISTDLTFSVKSSRGSSDPQGVTCGAATLSAERVGR<br/> DNKEYEYSVEQEDSACPAAEESLPIEVMVDAVHKLKYENYTS<br/> SFFIRDIHKPDPPKNLQKPLKNSRQVEVSWEYPDTWSTPHSYFS<br/> LTFCVQVQGKSKREKKDRVFTDKTSATVICRKNASISVRAQDR<br/> YYSSSWSEWASVPCSGGSGGGSGGGSGGGSRNLPVATPDPGM<br/> FPCLHHSQNLLRAVSNMLQKARQTLEFYPTSEEIDHEDITKDK<br/> TSTVEACLPLELTKNESCLNSRETSFITNGSCLASRKTSFMMAL<br/> CLSSIYEDLKMYQVEFKTMNAKLLMDPKRQIFLDQNMLAVIDE<br/> LMQALNFNSETVPQKSSLEEPDFYKTKIKLCILLHAFRIRAVTID<br/> RVMSYLNASHHHHHHHHHH</p>                                                           |
| 53 | 2-LAIR1-<br>ABD-12<br>(normal<br>linkers) | <p>MRVPAQLLGLLLLWLPGARCAAPTSSSTKKTQLQLEHLLLDLQ<br/> MILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKP<br/> LEEVLNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYAD<br/> ETATIVEFLNRWITFCQSIISTLTGGGGSGGGSQEEDLPRPSISAE<br/> PGTVIPLGSHVTFVCRGPVGVQTFRLERESRSTYNDTEDVSQAS<br/> PSESEARFRIDSVSEGNAGPYRCIYYKPPKWSEQSDYLELLVKE<br/> TSGGPDSPDTEPGSSAGPTQRPSDNSHNEHAPASQGLKAEHLY<br/> GGGGSGGGSKVQLVESGGGLVQPGGSLRLSCAASGFTFSSFGM<br/> TWVRQAPGKGLEWVSSISGSGSDTLYADSVRGRFTISRDN SKN<br/> TLYLQMNSLRAEDTAVYYCTIGGSLSPSSQGT LVTVSSGGGGS<br/> GGGSIWELKKDVYVVELDWYPDAPGEMVVLTCDDTP EEDGITW<br/> TLDQSSSEVLGSGKTLTIQVKEFGDAGQYTCHKGGEVLSHSLLL<br/> LHKKEDGIWSTDILKDQKEPKNKTFRLCEAKNYSGRFTCWWL<br/> TTISTDLTFSVKSSRGSSDPQGVTCGAATLSAERVGRDNKEYEY<br/> SVEQEDSACPAAEESLPIEVMVDAVHKLKYENYTSSFFIRDIHK<br/> PDPPKNLQKPLKNSRQVEVSWEYPDTWSTPHSYFSLTFCVQV<br/> QGKSKREKKDRVFTDKTSATVICRKNASISVRAQDRYYSSWS<br/> EWASVPCSGGSGGGSGGGSGGGSRNLPVATPDPGMFPCLHHS<br/> QNLLRAVSNMLQKARQTLEFYPTSEEIDHEDITKDKTSTVEA<br/> CLPLELTKNESCLNSRETSFITNGSCLASRKTSFMMALCLSSIYE<br/> DLKMYQVEFKTMNAKLLMDPKRQIFLDQNMLAVIDELMQAL<br/> NFNSETVPQKSSLEEPDFYKTKIKLCILLHAFRIRAVTIDRVMSY<br/> LNASHHHHHHHHHH</p> |
| 54 | 2-LAIR2-<br>ABD-12<br>(normal<br>linkers) | <p>MRVPAQLLGLLLLWLPGARCAAPTSSSTKKTQLQLEHLLLDLQ<br/> MILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKP<br/> LEEVLNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYAD<br/> ETATIVEFLNRWITFCQSIISTLTGGGGSGGGSQEGALPRPSISAE<br/> PGTVISPGSHVTFMCRGPVGVQTFRLEREDRAKYKDSYNVFR<br/> GPSESEARFHIDSVSEGNAGLYRCLYYKPPGWSEHSDFLELLVK<br/> ESSGGPDSPDTEPGSSAGTVPGTEASGFDAPGGGGSGGGSKVQ<br/> LVESGGGLVQPGGSLRLSCAASGFTFSSFGMTWVRQAPGKGLE</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |

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|----|---------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|    |                                 | <p>WVSSISGSGSDTLYADSVRGRFTISRDN SKNTLYLQMNSLRAE<br/> DTAVYYCTIGGSLSPSSQGLTVTVSSGGGGSGGGSIWELKKDV<br/> YVVELDWYPDAPGEMVVLTCDTPEEDGITWTL DQSSEVLGSG<br/> KTLTIQVKEFGDAGQYTCHKGGEVLSHSL LLLHKKEDGIWSTD<br/> ILKDQKEPKNKTF LRCEAKNYSGRFTCW WLTISTDLTFSVKSS<br/> RGSSDPQGVTCGAATLSAERV RGDNKEYEYSVEQCEDSACPA<br/> AEESLPIEVMVDAVHKLKYENYTSSFFIRDI IKPDPPKNLQLKPL<br/> KNSRQVEVSWEYPDTWSTPHSYFSLTFCVQVQGKSKREKKDR<br/> VFTDKTSATVICRKNASISVRAQDRYYSSSWSEWASVPCSGGS<br/> GGGSGGGSGGGSRNLPVATPDPMFPC LHHSQNLLRAVSNML<br/> QKARQTLEFYPTCTSEEIDHEDITKDKTSTVEACLPLELTKNESCL<br/> NSRETSFITNGSCLASRKTSFMMALCLSSIYEDLKMYQVEFKT<br/> MNAKLLMDPKRQIFLDQNM LAVIDELMQALNFNSETVPQKSS<br/> LEEPDFYKTKIKLCILLHAFRIRAVTIDRVMSYLNASHHHHHHH<br/> HHH</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| 55 | 2-Lum-ABD-12 (normal linkers)   | <p>MRVPAQLLGLLLLWLPGARCAAPTSSSTKKTQLQLEHLLDLQ<br/> MILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEELKP<br/> LEEVLNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYAD<br/> ETATIVEFLNRWITFCQSIISTLTGGGGSGGGSSGQYYDYDFPLS<br/> IYGQSSPNCAPCNCPE SYPSAMYCDELKLKSVPMVPPGIKYLY<br/> LRNNQIDHIDEKAFENVTDLQWLILDHNLLENSKIKGRVFSKLK<br/> QLKKLHINHNNLTESVGPLPKSLEDLQLTHNKITKLGSFEGLVN<br/> LTFIHLQHNRLKEDAVSAAFKGLKSLEYLDLSFNQIARLPGLP<br/> VSLTLYLDNNKISNIPDEYFKRFNALQYLRLSHNELADSGIPG<br/> NSFNVSSLVELDLSYNKLKNIPTVNENLENYYLEVNQLEKFDIK<br/> SFCKILGPLSYSKIHLRLDGNRISETSLPPDMECLRVANEVTL<br/> NGGGSGGGSGKVLVESGGGLVQPGGSLRLS CAASGFTFSSFG<br/> MTWVRQAPGKGLEWVSSISGSGSDTLYADSVRGRFTISRDN SK<br/> NTLYLQMNSLRAEDTAVYYCTIGGSLSPSSQGLTVTVSSGGGG<br/> SGGGSIWELKKDVYVVELDWYPDAPGEMVVLTCDTPEEDGIT<br/> WTL DQSSEVLGSGKTLTIQVKEFGDAGQYTCHKGGEVLSHSL<br/> LLHKKEDGIWSTDILKDQKEPKNKTF LRCEAKNYSGRFTCW<br/> LTTISTDLTFSVKSSRGSSDPQGVTCGAATLSAERV RGDNKEYE<br/> YSVEQCEDSACPAAEESLPIEVMVDAVHKLKYENYTSSFFIRDI<br/> KPDPPKNLQLKPLKNSRQVEVSWEYPDTWSTPHSYFSLTFCVQ<br/> VQGKSKREKKDRVFTDKTSATVICRKNASISVRAQDRYYSSSW<br/> SEWASVPCSGSGGGSGGGSGGGSRNLPVATPDPMFPC LHHS<br/> QNLLRAVSNMLQKARQTLEFYPTCTSEEIDHEDITKDKTSTVEA<br/> CLPLELTKNESCLNSRETSFITNGSCLASRKTSFMMALCLSSIYE<br/> DLKMYQVEFKTMNAKLLMDPKRQIFLDQNM LAVIDELMQAL<br/> NFNSETVPQKSSLEEPDFYKTKIKLCILLHAFRIRAVTIDRVMSY<br/> LNASHHHHHHHHHH</p> |
| 56 | 2-HSA-LAIR1-12 (normal linkers) | <p>MRVPAQLLGLLLLWLPGARCAAPTSSSTKKTQLQLEHLLDLQ<br/> MILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEELKP<br/> LEEVLNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYAD<br/> ETATIVEFLNRWITFCQSIISTLTGGGGSGGGSDAHKSEVAHRF<br/> KDLGEENFKALVLIAFAQYLQQCPFEDHVKL VNEVTEFAKTCV<br/> ADESAENCDKSLHTLFGDKLCTVATLRETYGEMADCCAKQEP<br/> ERNECFLQHKDDNPNLPR LVRPEVDVMCTAFHDNEETFLKKY<br/> LYEIARRHPYFYAPELFFAKRYKAAFTECCQAADKAACLLPK<br/> LDEL RDEGKASSAKQRLK CASLQKFGERAFKAWAVARLSQRF<br/> PKAEFAEVSKLVTDLT KVHTECCHGDLLECADDRADLAKYICE<br/> NQDSISSKLKECCEKPLLEKSHCIAEVENDEMPADLP SLAADFV</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |

|    |                                           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|----|-------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|    |                                           | <p>ESKDVCKNYAEAKDVFLGMFLY EYARRHPDYSVVLLLRLAKT<br/> YETTLKCCAAADPHECYAKVFDEFKPLVEEPQNLKQNCSELF<br/> EQLGEYKFQNALLVRYTKKVPQVSTPTLVEVSRNLGKVGSKC<br/> CKHPEAKRMPCAE DYLSVVLNQLCVLHEKTPVSDRVTKCCTE<br/> SLVNRRPCFSALEVDETYVPKEFNAETFTFHADICTLSEKERQIK<br/> KQTALVELVKHKPKATKEQLKAVMDDFAAFVEKCKKADDKE<br/> TCFAEEGKKLVAAASQAALGLGGGGSGGGSQEEDLPRPSISAEP<br/> GTVIPLGSHVTFVCRGPVGVQTFRLERESRSTYNDTEDVSQASP<br/> SESEARFRIDSVSEGNAGPYRCIYYKPPKWSEQSDYLELLVKET<br/> SGGPDSPDTEPGSSAGPTQRPSDNSHNEHAPASQGLKAEHLYG<br/> GGSGGGSIWELKKDVYVVELDWYPDAPGEMVVLTCDTPEE<br/> DGITWTLDSSEVLGSGKTLTIQVKEFGDAGQYTCHKGGEVLS<br/> HLLLLLHKKEDGIWSTDILKDQKEPKNKTFLRCEAKNYSGRFT<br/> CWWLTTISTDLTFSVKSSRGSSDPQGVTCGAATLSAERVGRDN<br/> KEYEYSVECQEDSACPAAEESLPIEVMVDAVHKLKYENYTSSF<br/> FIRDIKPDPPKNLQLKPLKNSRQVEVSWEYPDTWSTPHSYFSLT<br/> FCVQVQGKSKREKKDRVFTDKTSATVICRKNASISVRAQDRYY<br/> SSSWSEWASVPCSGSGGGSGGGSGGGSRNLPVATPDPGMFPC<br/> LHHSQNLLRAVSNMLQKARQTLEFYPCTSEEIDHEDITKDKTST<br/> VEACLPLELTKNESCLNSRETSFITNGSCLASRKTSFMMALCLS<br/> SIYEDLKMYQVEFKTMNAKLLMDPKRQIFLDQNMLAVIDELM<br/> QALNFNSETVPQKSSLEEPDFYKTKIKLCILLHAFRIRAVTIDRV<br/> MSYLNASHHHHHHHHHH</p>                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| 57 | 2-HSA-<br>LAIR2-12<br>(normal<br>linkers) | <p>MRVPAQLLGLLLLWLPGARCAAPTSSSTKKTQLQLEHLLLDLQ<br/> MILNGINNYKNPKLTRMLTFKFYMPKKATELKHLCLEELKP<br/> LEEVLNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYAD<br/> ETATIVEFLNRWITFCQSIISTLTGGGGSGGGSDAHKSEVAHRF<br/> KDLGEENFKALVLIAFAQYLQQCPFEDHVKL VNEVTEFAKTCV<br/> ADESAENC DKSLHTLFGDKLCTVATLRETYGEMADCCAKQEP<br/> ERNECFLQHKDDNPNL PRLVRPEVDVMCTAFHDNEETFLKKY<br/> LYEIARRHPYFYAPELFFAKRYKAAFTECCQAADKAAACLLPK<br/> LDEL RDEGKASSAKQRLK CASLQKFGERAFKAWAVARLSQRF<br/> PKAEFAEVSKLVTDLT KVHTECCHGDLLECADDRADLAKYICE<br/> NQDSISSKLKECCEKPLEKSHCIAEVENDEMPADLPSLAADFV<br/> ESKDVCKNYAEAKDVFLGMFLY EYARRHPDYSVVLLLRLAKT<br/> YETTLKCCAAADPHECYAKVFDEFKPLVEEPQNLKQNCSELF<br/> EQLGEYKFQNALLVRYTKKVPQVSTPTLVEVSRNLGKVGSKC<br/> CKHPEAKRMPCAE DYLSVVLNQLCVLHEKTPVSDRVTKCCTE<br/> SLVNRRPCFSALEVDETYVPKEFNAETFTFHADICTLSEKERQIK<br/> KQTALVELVKHKPKATKEQLKAVMDDFAAFVEKCKKADDKE<br/> TCFAEEGKKLVAAASQAALGLGGGGSGGGSQEGALPRPSISAEP<br/> GTVISPGSHVTFMCRGPVGVQTFRLEREDRAKYKDSYNVFR LG<br/> PSESEARFHIDSVSEGNAGLYRCLYYKPPGWSEHSDFLELLVKE<br/> SSGGPDSPDTEPGSSAGTPGTEASGFDAPGGGGSGGGSIWELK<br/> KDVYVVELDWYPDAPGEMVVLTCDTPEEDGITWTLDSSEVL<br/> GSGKTLTIQVKEFGDAGQYTCHKGGEVLSHLLLLLHKKEDGIW<br/> STDILKDQKEPKNKTFLRCEAKNYSGRFTCWWLTTISTDLTFSV<br/> KSSRGSSDPQGVTCGAATLSAERVGRDNKEYEYSVECQEDSAC<br/> PAAEESLPIEVMVDAVHKLKYENYTSSFIRDIKPDPPKNLQLK<br/> PLKNSRQVEVSWEYPDTWSTPHSYFSLTFCVQVQGKSKREKK<br/> DRVFTDKTSATVICRKNASISVRAQDRYYSSSWSEWASVPCSG<br/> SGGGSGGGSGGGSRNLPVATPDPGMFPC LHHSQNLLRAVSN<br/> MLQKARQTLEFYPCTSEEIDHEDITKDKTSTVEACLPLELTKNE<br/> SCLNSRETSFITNGSCLASRKTSFMMALCLSSIYEDLKMYQVEF</p> |

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|    |                                           | KTMNAKLLMDPKRQIFLDQNMLAVIDELMQALNFNSETVPQK<br>SSLEEPDFYKTKIKLCILLHAFRIRAVTIDRVMSYLNASHHHHH<br>HHHHH                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| 58 | 2-HSA-Lum-<br>12 (normal<br>linkers)      | MRVPAQLLGLLLLWLPGARCAAPTSSSTKKTQLQLEHLLLDLQ<br>MILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKP<br>LEEVLNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYAD<br>ETATIVEFLNRWITFCQSIISTLTGGGGSGGGSDAHKSEVAHRF<br>KDLGEENFKALVLIAFAQYLQQCPFEDHVKLNVNTEFAKTCV<br>ADESAENCDKSLHTLFGDKLCTVATLRETYGEMADCCAKQEP<br>ERNECFLQHKDDNPPLRLVRPEVDVMCTAFHDNEETFLKKY<br>LYEIARRHPYFYAPELLFFAKRYKAAFTECCQAADKAAACLLPK<br>LDELRDEGKASSAKQRLKCASLQKFGERAFKAWAVARLSQRF<br>PKAEFAEVSKLVTDLT KVHTECCHGDLLECADDRADLAKYICE<br>NQDSISSKLKECCEKPLLEKSHCIAEVENDEMPADLPSLAADFV<br>ESKDVCCKNYAEAKDVFLGMFLYFYARRHPDYSVVLRLAKT<br>YETTLKCCAAADPHECYAKVFDEFKPLVEEPQNLKQNCSELF<br>EQLGEYKFQNALLVRYTKKVPQVSTPTLVEVSRNLGKVGSKC<br>CKHPEAKRMPCAEDYLSVVLNQLCVLHEKTPVSDRVTKCCTE<br>SLVNRPCFSALEVDETYVPKEFNAETFTFHADICTLSEKERQIK<br>KQTALVELVKHKPKATKEQLKAVMDDFAAFVEKCKKADDKE<br>TCFAEEGKKLVAASQAALGLGGGGSGGGSSGQYYDYDFPLSIY<br>GQSSPNCAPCNCPEPSYPSAMYCDELKLSVPMVPPGIKYL<br>RNNQIDHIDEKAFENVTDLQWLILDHNLLENSKIKGRVFSKLK<br>QLKKLHINHNNLTESVGPLPKSLEDLQLTHNKITKLGSFEGLVN<br>LTFIHLQHNRLKEDAVSAAFKGLKSLEYLDLSFNQIARLPGLP<br>VSLLTLYLDNNKISNIPDEYFKRFNALQYLRLSHNELADSGIPG<br>NSFNVSSLVELDLSYNKLNKNIPTVNENLENYYLEVNQLEKFDIK<br>SFCKILGPLSYSKIKHLRLDGNRISETSLPPDMECLRVANEVTL<br>NGGGGSGGGSIWELKKDVYVVELDWYPDAPGEMVVLTCDDTP<br>EEDGITWTLTLDQSSEVLGSGKTLTIQVKEFGDAGQYTCHKGGEV<br>LSHSLLLLHKKEDGIWSTDILKDQKEPKNKTFLRCEAKNYSGR<br>FTCWWLTTISTDLTFSVKSSRGSSDPQGVTCGAATLSAERVGR<br>DNKEYEYSVECQEDSACPAAEESLPIEVMVDAVHKLKYENYTS<br>SFFIRDIKPDPPKNLQLKPLKNSRQVEVSWEYPDTWSTPHSYFS<br>LTFCVQVQGKSKREKKDRVFTDKTSATVICRKNASISVRAQDR<br>YYSSSWSEWASVPCSGGGSGGGSGGGSGGGSRNLPVATPDPGM<br>FPCLHHSQNLLRAVSNNMLQKARQTLEFYPTSEEIDHEDITKDK<br>TSTVEACLPLELTKNESCLNSRETSFITNGSCLASRKTSFMMAL<br>CLSSIEDLKMYQVEFKTMNAKLLMDPKRQIFLDQNMLAVIDE<br>LMQALNFNSETVPQKSSLEEPDFYKTKIKLCILLHAFRIRAVTID<br>RVMSYLNASHHHHHHHHHH |
| 59 | 2-ABD-<br>LAIR1-12<br>(normal<br>linkers) | MRVPAQLLGLLLLWLPGARCAAPTSSSTKKTQLQLEHLLLDLQ<br>MILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKP<br>LEEVLNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYAD<br>ETATIVEFLNRWITFCQSIISTLTGGGGSGGGSKVQLVESGGGL<br>VQPGGSLRLSCAASGFTFSSFGMTWVRQAPGKGLEWVSSISGS<br>GSDTLYADSVRGRFTISRDNKNTLYLQMNSLRAEDTAVYYCT<br>IGGSLSPSSQGTLVTVSSGGGGSGGGSQEEDLPRPSISAEPGTVIP<br>LGSHVTFVCRGPVGVQTFRLERESRSTYNDTEDVSQASPSESEA<br>RFRIDSVSEGNAGPYRCIYYKPPKWSEQSDYLELLVKETSGGPD<br>SPDTEPGSSAGPTQRPSPDNHNEHAPASQGLKAEHLYGGGGSG<br>GGSIWELKKDVYVVELDWYPDAPGEMVVLTCDDTP EEDGITWT<br>LDQSSEVLGSGKTLTIQVKEFGDAGQYTCHKGGEVLSHSLLLL                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |

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|    |                                    | HKKEDGIWSTDILKDQKEPKNKTFLRCEAKNYSGRFTCWWT<br>TISTDLTFSVKSSRGSSDPQGVTCGAATLSAERVGRDNKEYEYS<br>VECQEDSACPAAEESLPIEVMVDAVHKLKYENYTSSFFIRDIIKP<br>DPPKNLQLKPLKNSRQVEVSWEYPDTWSTPHSYFSLTFCVQVQ<br>GKSKREKKDRVFTDKTSATVICRKNASISVRAQDRYSSSSWSE<br>WASVPCSGGSGGGSGGGSGGGSRNLPVATPDPGMFPC LHHSQ<br>NLLRAVSNMLQKARQTLEFYPTSEEIDHEDITKDKTSTVEACL<br>PLELTKNESCLNSRETSFITNGSCLASRKTSFMMALCLSSIIYEDL<br>KMYQVEFKTMNAKLLMDPKRQIFLDQNMLAVIDELMQALNF<br>NSETVPQKSSLEEPDFYKTKIKLCILLHAFRIRAVTIDRVMSYLN<br>ASHHHHHHHHH                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| 60 | 2-ABD-LAIR2-12<br>(normal linkers) | MRVPAQLLGLLLLWLPGARCAAPTSSSTKKTQLQLEHLLDLQ<br>MILNGINNYKNPKLTRMLTFKFYMPKKATELKHLCLEELKP<br>LEEVLNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYAD<br>ETATIVEFLNRWITFCQSIISTLTGGGGSGGGSKVQLVESGGGL<br>VQPGGSLRLSCAASGFTFSSFGMTWVRQAPGKGLEWVSSISGS<br>GSDTLYADSVRGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCT<br>IGGSLPSSQGT LVTVSSGGGGSGGGSGQEGALPRPSISAEPTVI<br>SPGSHVTFMCRGPVGVQTFRLEREDRAKYKDSYNVFR LGPSES<br>EARFHIDSVSEGNAGLYRCLYKPPGWSEHSDFLELLVKESG<br>GPDSPDTEPGSSAGTVPGTEASGFDAPGGGGSGGGSIWELKGD<br>VYVVELDWYPDAPGEMVVLTCDTPEEDGITWTL DQSSEVLGS<br>GKTLTIQVKEFGDAGQYTCHKGGEVL SHSLLLHKKEDGIWST<br>DILKDQKEPKNKTFLRCEAKNYSGRFTCWWT TISTDLTFSVK<br>SSRGSSDPQGVTCGAATLSAERVGRDNKEYEYSVE CQEDSACP<br>AAESLPIEVMVDAVHKLKYENYTSSFFIRDIIKPDPPKNLQLK<br>P LKNSRQVEVSWEYPDTWSTPHSYFSLTFCVQVQ GKSKREKKD<br>RVFTDKTSATVICRKNASISVRAQDRYSSSSWSEWASVPCSGG<br>SGGGSGGGSGGGSRNLPVATPDPGMFPC LHHSQNLLRAVSNM<br>LQKARQTLEFYPTSEEIDHEDITKDKTSTVEACLPLELTKNESC<br>LNSRETSFITNGSCLASRKTSFMMALCLSSIIYEDLKMYQVEFKT<br>MNAKLLMDPKRQIFLDQNMLAVIDELMQALNFNSETVPQKSS<br>LEEPDFYKTKIKLCILLHAFRIRAVTIDRVMSYLNASHHHHHHHH<br>HHH |
| 61 | 2-ABD-Lum-12 (normal linkers)      | MRVPAQLLGLLLLWLPGARCAAPTSSSTKKTQLQLEHLLDLQ<br>MILNGINNYKNPKLTRMLTFKFYMPKKATELKHLCLEELKP<br>LEEVLNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYAD<br>ETATIVEFLNRWITFCQSIISTLTGGGGSGGGSKVQLVESGGGL<br>VQPGGSLRLSCAASGFTFSSFGMTWVRQAPGKGLEWVSSISGS<br>GSDTLYADSVRGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCT<br>IGGSLPSSQGT LVTVSSGGGGSGGGSSGQYYDYDFPLSIYGQS<br>SPNCAPECNCPESYPSAMYCDELKLKSVPMVPPGIKYLYLRNN<br>QIDHIDEKAFENVTDLQWLILDHNLLENSKIKGRVFSKLKQLKK<br>LHINHNNLTESVGPLPKSLEDLQLTHNKITKLGSFEGLVNLTFIH<br>LQHNRLKEDAVSAAFGLKSLEYLDLSFNQIARLP SGLPVSLT<br>LYLDNNKISNIPDEYFKRFNALQYLR LSHNELADSGIPGNSFNV<br>SSLVELDLSYNKLKNIPTVNENLENYYLEVNQLEKFDIKSFCKI<br>LGPLSYSKIKHLRLDGNRISETSLPPDMYECLRVANEVT LN GGG<br>GSGGGSIWELKGDVYVVELDWYPDAPGEMVVLTCDTPEEDGI<br>TWTL DQSSEVLGSGKTLTIQVKEFGDAGQYTCHKGGEVL SHS<br>LLLHKKEDGIWSTDILKDQKEPKNKTFLRCEAKNYSGRFTCW<br>WLT TISTDLTFSVKSSRGSSDPQGVTCGAATLSAERVGRDNKE<br>YEYSVE CQEDSACPAAEESLPIEVMVDAVHKLKYENYTSSFFIR                                                                                                                                                 |

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|    |                                       | <p> DIHKPDPPKNLQLKPLKNSRQVEVSWEYPDTWSTPHSYFSLTFC<br/> VQVQGKSKREKKDRVFTDKTSATVICRKNASISVRAQDRYYSS<br/> SWSEWASVPCSGGSGGGSGGGSGGGSRNLPVATPDPGMFPCL<br/> HHSQNLLRAVSNMLQKARQTLEFYPTCTSEEIDHEDITKDKTST<br/> VEACLPLELTKNESCLNSRETSFITNGSCLASRKTSFMMALCLS<br/> SIYEDLKMYQVEFKTMNAKLLMDPKRQIFLDQNMLAVIDELM<br/> QALNFNSETVPPQKSSLEEPDFYKTKIKLCILLHAFRIRAVTIDRV<br/> MSYLNASHHHHHHHHHH </p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| 62 | 12-LAIR1-HSA_H464Q-2 (normal linkers) | <p> MRVPAQLLGLLLLWLPGARCAIWELKKDVYVVELDWYPDAP<br/> GEMVVLTCDTPEEDGITWTLDQSSEVLGSGKTLTIQVKEFGDA<br/> GQYTCHKGGEVLSHSLLLLHKKEDGIWSTDILKDQKEPKNKTF<br/> LRCEAKNYSGRFTCWWTITSTDLTFSVKSSRGSSDPQGVTCG<br/> AATLSAERVRGDNKEYEYSVEQEDSACPAAEESLPIEVMVDA<br/> VHKLKYENYTSSFFIRDIIKPDPPKNLQLKPLKNSRQVEVSWEY<br/> PDTWSTPHSYFSLTFCVQVQGKSKREKKDRVFTDKTSATVICR<br/> KNASISVRAQDRYYSSSWSEWASVPCSGGSGGGSGGGSGGGGS<br/> RNLPVATPDPGMFPCLHHSQNLLRAVSNMLQKARQTLEFYPTCT<br/> SEEIDHEDITKDKTSTVEACLPLELTKNESCLNSRETSFITNGSCL<br/> ASRKTSFMMALCLSSIYEDLKMYQVEFKTMNAKLLMDPKRQI<br/> FLDQNMLAVIDELMQALNFNSETVPPQKSSLEEPDFYKTKIKLCI<br/> LLHAFRIRAVTIDRVMSYLNASGGGGSGGGSGGGSGGGSGGGGS<br/> PGTVIPLGSHVTFVCRGPVGVQTFRLERESRSTYNDTEDVSQAS<br/> PSESEARFRIDSVSEGNAGPYRCIYYKPPKWSEQSDYLELLVKE<br/> TSGGPDSPDTEPGSSAGPTQRPSDNSHNEHAPASQGLKAEHLY<br/> GGGGSGGGSDAHKSEVAHRFKDLGEENFKALVLIQAFQYLQO<br/> CPFEDHVKLNVNEVTEFAKTCVADESAENCCKSLHTLFGDKLCT<br/> VATLRETYGEMADCCAKQEPERNECFQHKDDNPPLRLVRP<br/> EVDVMCTAFHDNEETFLKKYLYEIARRHPYFYAPPELLFFAKRY<br/> KAAFTECCQAADKAACLLPKLDELDEGKASSAKQRLKCASL<br/> QKFGERAFAKAWAVARLSQRFPKAEFAEVSKLVTDLTKVHTEC<br/> CHGDLLECADDRAADLAKEYICENQDSISSKLKECCEKPLEKSH<br/> CIAEVENDEMPADLPSLAADFVESKDVCKNYAEAKDVFLGMF<br/> LYEYARRHPDYSVVLRLAKTYETTLEKCCAAADPHECYAK<br/> VFDEFKPLVEEPQNLKQNCLEFEQLGEYKFQNALLVRYTKKV<br/> PQVSTPTLVEVSRNLGKVGSKCKHPEAKRMPCAEDYLSVVL<br/> NQLCVLQEKTPVSDRVTKCCTESLVNRRPCFSALEVDETYVPK<br/> EFNAETFTFHADICTLSEKERQIKKQALVELVKHKPKATKEQL<br/> KAVMDDFAAFVEKCKKADDEKTCFAEKGKLVAAASQAALGL<br/> GGGGSGGGSAPTSSSTKKTQLQLEHLLLDLQMLNGINNYKNP<br/> KLTRMLTFKFYMPKKATELKHLCLEELKPLEEVLNLAQSKN<br/> FHLRPDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWI<br/> TFCQSIISTLTHHHHHHHHHH </p> |
| 63 | 12-LAIR2-HSA_H464Q-2 (normal linkers) | <p> MRVPAQLLGLLLLWLPGARCAIWELKKDVYVVELDWYPDAP<br/> GEMVVLTCDTPEEDGITWTLDQSSEVLGSGKTLTIQVKEFGDA<br/> GQYTCHKGGEVLSHSLLLLHKKEDGIWSTDILKDQKEPKNKTF<br/> LRCEAKNYSGRFTCWWTITSTDLTFSVKSSRGSSDPQGVTCG<br/> AATLSAERVRGDNKEYEYSVEQEDSACPAAEESLPIEVMVDA<br/> VHKLKYENYTSSFFIRDIIKPDPPKNLQLKPLKNSRQVEVSWEY<br/> PDTWSTPHSYFSLTFCVQVQGKSKREKKDRVFTDKTSATVICR<br/> KNASISVRAQDRYYSSSWSEWASVPCSGGSGGGSGGGSGGGGS<br/> RNLPVATPDPGMFPCLHHSQNLLRAVSNMLQKARQTLEFYPTCT<br/> SEEIDHEDITKDKTSTVEACLPLELTKNESCLNSRETSFITNGSCL<br/> ASRKTSFMMALCLSSIYEDLKMYQVEFKTMNAKLLMDPKRQI </p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |

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|    |                                                | <p>FLDQNMMLAVIDELMQALNFNSETVPQKSSLEEDFYKTKIKLCI<br/> LLHAFRIRAVTIDRVMSYLNASGGGGSGGGSGEGALPRPSISAE<br/> PGTVISPGSHVTFMCRGPVGVQTFRLEREDRAKYKDSYNVFR<br/> GPSESEARFHIDSVSEGNAGLYRCLYYKPPGWSEHSDFLELLVK<br/> ESSGGPDSPDTEPGSSAGTVPGTEASGFDAPGGGGSGGGSDAH<br/> KSEVAHRFKDLGEENFKALVLIAFAQYLQQCPFEDHVKL VNEV<br/> TEFAKTCVADESAENCDKSLHTLFGDKLCTVATLRETYGEMA<br/> DCCAKQEPERNECFLQHKDDNP NLPRLVRPEVDVMCTAFHDN<br/> EETFLKKYLYEIAARRHPYFYAPELLFFAKRYKAAFTTECCQAAD<br/> KAACLLPKLDEL RDEGKASSAKQRLK CASLQKFGERAFKAWA<br/> VARLSQRFPKAEFAEVSKLVTDLT KVHTECCHGDLLECADDR<br/> ADLAKYICENQDSISSKLKECCEKPLLEKSHCIAEVENDEMPAD<br/> LPSLAADFVESKDVCKNYAEAKDVFLGMFLY EYARRHPDYSV<br/> VLLLRLAKTYETTLEKCCAAADPHECYAKVFDEFKPLVEEPQN<br/> LIKQNCELFEQLGEYKFQNALLVRYTKKVPQVSTPTLVEVSRN<br/> LGKVGSKCCKHPEAKRMPCAEDYLSVVLNQLCVLQEKTPVSD<br/> RVTKCCTESLVNRRPCFSALEVDETYVPKEFNAETFTFHADICT<br/> LSEKERQIKKQTALVELVKHKPKATKEQLKAVMDDFAAFVEK<br/> CCKADDKETCFAEEGKKLVAASQAALGLGGGGSGGGSAPTSS<br/> STKKTQLQLEHLLLDLQMLNGINNYKNPKLTRMLTFKFYMPK<br/> KATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVI<br/> VLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLTHHHH<br/> HHHHHH</p>                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| 64 | 12-Lum-<br>HSA_H464Q<br>-2 (normal<br>linkers) | <p>MRVPAQLLGLLLLWLPGARCAIWELKKDVYVVELDWYPDAP<br/> GEMVVLTCDTPEEDGITWTLDSSEVLGSGKTLTIQVKEFGDA<br/> GQYTCHKGGEVLSHSLLLLHKKEDGIWSTDILKDQKEPKNKTF<br/> LRCEAKNYSGRFTCWWTITISTDLTFSVKSSRGSSDPQGVTCG<br/> AATLSAERVVRGDNKEYEYSVEQEDSACPAAEESLPIEVMVDA<br/> VHKLKYENYTSSFFIRDIIKPDPPKNLQLKPLKNSRQVEVSWEY<br/> PDTWSTPHSYFSLTFCVQVQGKSKREKKDRVFTDKTSATVICR<br/> KNASISVRAQDRYYSSSWSEWASVPCSGGSGGGSGGGSGGG<br/> RNLPVATPDPGMFPC LHHSQNLLRAVSNMLQKARQTLEFYPC<br/> SEEIDHEDITKDKTSTVEACLPLELTKNESCLNSRETSFITNGSCL<br/> ASRKTSFMMALCLSSIEDLKMYQVEFKTMNAKLLMDPKRQI<br/> FLDQNMMLAVIDELMQALNFNSETVPQKSSLEEDFYKTKIKLCI<br/> LLHAFRIRAVTIDRVMSYLNASGGGGSGGGSGGQYYDYDFPLS<br/> IYGQSSPNCAPCNCPEPSAMYCDELKLKSVPMVPPGIKYLY<br/> LRNNQIDHIDEKAFENVTDLQWLILDHNLLENSKIKGRVFSKLK<br/> QLKKLHINHNNLTESVGPLPKSLEDLQLTHNKITKLGSFEGLVN<br/> LTFIHLQHNRLKEDAVSAAFKGLKSLEYLDLSFNQIARLPSGLP<br/> VSLLTLYLDNNKISNIPDEYFKRFNALQYLRLSHNELADSGIPG<br/> NSFNVSSLVELDLSYNKLKNIPTVNENLENYYLEVNQLEKFDIK<br/> SFCKILGPLSYSKIKHLRLDGNRISETSLPPDMYECLRVANEVTL<br/> NGGGSGGGSDAHKSEVAHRFKDLGEENFKALVLIAFAQYLQ<br/> QCPFEDHVKL VNEVTEFAKTCVADESAENCDKSLHTLFGDKLC<br/> TVATLRETYGEMADCCAKQEPERNECFLQHKDDNP NLPRLVR<br/> PEVDVMCTAFHDNEETFLKKYLYEIAARRHPYFYAPELLFFAKR<br/> YKAAFTTECCQAADKAACLLPKLDEL RDEGKASSAKQRLK CAS<br/> LQKFGERAFKAWAVARLSQRFPKAEFAEVSKLVTDLT KVHTE<br/> CCHGDLLECADDRADLAKYICENQDSISSKLKECCEKPLLEKS<br/> HCIAEVENDEMPADLPSLAADFVESKDVCKNYAEAKDVFLGM<br/> FLY EYARRHPDYSVLLLRLAKTYETTLEKCCAAADPHECYA<br/> KVDEFKPLVEEPQNLIKQNCELFEQLGEYKFQNALLVRYTKK<br/> VPQVSTPTLVEVSRNLGKVGSKCCKHPEAKRMPCAEDYLSV</p> |

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|    |                                                  | LNQLCVLQEKTPVSDRVTKCTESLVNRRPCFSALEVDETYVP<br>KEFNAETFTFHADICTLSEKERQIKKQTALVELVKHKPKATKEQ<br>LKAVMDDFAAFVEKCKADDKETCFAEEGKKLVAASQAALG<br>LGGGSGGGSAPTSSTKKTQLQLEHLLLDLQMLNGINNYKN<br>PKLTRMLTFKFYMPKKATELKHLQCLEEELKPLEEVLNLAQSK<br>NFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNR<br>WITFCQSIISTLTHHHHHHHHHH                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| 65 | 2-LAIR1-<br>HSA_H464Q<br>-12 (normal<br>linkers) | MRVPAQLLGLLLLWLPGARCAAPTSSSTKKTQLQLEHLLLDLQ<br>MILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKP<br>LEEVLNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYAD<br>ETATIVEFLNRWITFCQSIISTLTGGGSGGGSGEEDLPRPSISAE<br>PGTVIPLGSHVTFVCRGPVGVQTFRLERESRSTYNDTEDVSQAS<br>PSESEARFRIDSVSEGNAGPYRCIYYKPPKWSEQSDYLELLVKE<br>TSGGPDSPTDEPGSSAGPTQRPSDNSHNEHAPASQGLKAEHLY<br>GGGSGGGSDAHKSEVAHRFKDLGEENFKALVLIIFAQYLQQ<br>CPFEDHVKLNVNEVTEFAKTCVADESAENCDSLHTLFGDKLCT<br>VATLRETYGEMADCCAKQEPERNECFLQHKDDNPPLRLVRP<br>EVDVMCTAFHDNEETFLKKYLYEIARRHPYFYAPELLFFAKRY<br>KAAFTECCQAADKAACLLPKLDELDEGKASSAKQRLKCASL<br>QKFGERAFAKAWAVARLSQRFPKAEFAEVSKLVTDLTKVHTEC<br>CHGDLLECADDRADLAKYICENQDSISSKLKECCEKPLEKSH<br>CIAEVENDEMPADLPSLAADFVESKDVCKNYAEAKDVFLGMF<br>LYEYARRHPDYSVVLRLAKTYETTLEKCCAAADPHECYAK<br>VFDEFKPLVEEPQNLKQNCLEFEQLGEYKFQNALLVRYTKKV<br>PQVSTPTLVEVSRNLGKVGSKCKHPEAKRMPCAEDYLSVVL<br>NQLCVLQEKTPVSDRVTKCTESLVNRRPCFSALEVDETYVPK<br>EFNAETFTFHADICTLSEKERQIKKQTALVELVKHKPKATKEQL<br>KAVMDDFAAFVEKCKADDKETCFAEEGKKLVAASQAALGL<br>GGGSGGGSIWELKKDVYVVELDWYPDAPGEMVVLTCDTPE<br>EDGITWTLDSSEVLGSGKTLTIQVKEFGDAGQYTCHKGGEVL<br>SHSLLLHKKEDGIWSTDILKDQKEPKNKTFLRCEAKNYSGRF<br>TCWWLTISTDLTFSVKSSRGSSDPQGVTCGAATLSAERVGRD<br>NKEYEYSVEQCEDSACPAEESLPIEVMVDAVHKLKYENYTSS<br>FFIRDIKPDPPKNLQLKPLKNSRQVEVSWEYPDTWSTPHSYFSL<br>TFCVQVQGKSKREKKDRVFTDKTSATVICRKNASISVRAQDRY<br>YSSSWSEWASVPCSGSGGGSGGGSGGGSRNLPVATPDPGMF<br>PCLHHSQNLLRAVSNMLQKARQTLEFYPTSEEIDHEDITKDKT<br>STVEACLPLELTKNESCLNSRETSFITNGSCLASRKTSFMMALC<br>LSSIEDLKMYQVEFKTMNAKLLMDPKRQIFLDQNMLAVIDEL<br>MQALNFNSETVPQKSSLEEPDFYKTKIKLCILLHAFRIRAVTIDR<br>VMSYLNASHHHHHHHHHH |
| 66 | 2-LAIR2-<br>HSA_H464Q<br>-12 (normal<br>linkers) | MRVPAQLLGLLLLWLPGARCAAPTSSSTKKTQLQLEHLLLDLQ<br>MILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKP<br>LEEVLNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYAD<br>ETATIVEFLNRWITFCQSIISTLTGGGSGGGSGEGALPRPSISAE<br>PGTVISPGSHVTFMCRGPVGVQTFRLEREDRAKYKDSYNVFR<br>GPSESEARFHIDSVSEGNAGLYRCLYYKPPGWSEHSDFLELLVK<br>ESSGGPDSPTDEPGSSAGTVPGTEASGFDAPGGGSGGGSDAH<br>KSEVAHRFKDLGEENFKALVLIIFAQYLQQCPFEDHVKLNVNEV<br>TEFAKTCVADESAENCDSLHTLFGDKLCTVATLRETYGEMA<br>DCCAKQEPERNECFLQHKDDNPPLRLVRPEVDVMCTAFHDN<br>EETFLKKYLYEIARRHPYFYAPELLFFAKRYKAAFTECCQAAD<br>KAACLLPKLDELDEGKASSAKQRLKCASLQKFGERAFAKAWA                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |

|    |                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|----|------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|    |                                                | <p>VARLSQRFPKAEFAEVSKLVTDLT KVHTECCHGDLLECADDR<br/>ADLAKYICENQDSISSKLKECCEKPLLEKSHCIAEVENDEMPAD<br/>LPSLAADFVESKDVCKNYAEAKDVFLGMFLYEYARRHPDYSV<br/>VLLRLAKTYETTLEKCCAAADPHECYAKVFDEFKPLVEEPQN<br/>LIKQNCLEFEQLGEYKFQNALLVRYTKKVPQVSTPTLVEVSRN<br/>LGKVGSKCCKHPEAKRMPCAEDYLSVVLNQLCVLQEKTPVSD<br/>RVTKCCTESLVNRRPCFSALEVDETYVPKEFNAETFTFHADICT<br/>LSEKERQIKKQTALVELVKHKPKATKEQLKAVMDDFAAFVEK<br/>CCKADDKETCFAEEGKKLVAASQAALGLGGGGSGGGSIWELK<br/>KDVYVVELDWYPDAPGEMVVLTCDTPEEDGITWTLDQSSEVL<br/>GSGKTLTIQVKEFGDAGQYTCHKGGEVLSHSLLLHKKEDGIW<br/>STDILKDQKEPKNKTFLRCEAKNYSGRFTCWWLTTISTDLTFSV<br/>KSSRGSSDPQGVTCGAATLSAERVGRDNKEYEYSVECQEDSAC<br/>PAAEESLPIEVMVDAVHKLKYENYTSSFFIRDIKPDPPKNLQLK<br/>PLKNSRQVEVSWEYPDTWSTPHSYFSLTFCVQVQGKSKREKK<br/>DRVFTDKTSATVICRKNASISVRAQDRYYSSSWSEWASVPCSG<br/>GSGGGSGGGSGGGSRNLPVATPDPGMFPCLHHSQNLLRAVSN<br/>MLQKARQTLEFYPTSEEIDHEDITKDKTSTVEACLPLELTKNE<br/>SCLNSRETSFITNGSCLASRKTSFMMALCLSSIEDLKMYQVEF<br/>KTMNAKLLMDPKRQIFLDQNMLAVIDELMQALNFNSETVPQK<br/>SSLEEPDFYKTKIKLCILLHAFRIRAVTIDRVMSYLNASHHHHH<br/>HHHHH</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| 67 | 2-Lum-<br>HSA_H464Q<br>-12 (normal<br>linkers) | <p>MRVPAQLLGLLLLWLPGARCAAPTSSSTKKTQLQLEHLLLDLQ<br/>MILNGINNYKNPKLTRMLTFKFYMPKKATELKHLCLEELKP<br/>LEEVLNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYAD<br/>ETATIVEFLNRWITFCQSIISTLTGGGGSGGGSSGQYYDYDFPLS<br/>IYGQSSPNCAPCNCPEPSAMYCDELKLSVPMVPPGIKYLY<br/>LRNNQIDHIDEKAFENVTDLQWLILDHNLLENSKIKGRVFSKLK<br/>QLKKLHINHNNLTESVGPLPKSLEDLQLTHNKITKLGSFEGLVN<br/>LTFIHLQHNRLKEDAVSAAFKGLKSLEYLDLSFNQIARLPSGLP<br/>VSLLTLYLDNNKISNIPDEYFKRFNALQYLRLSHNELADSGIPG<br/>NSFNVSSLVELDLSYNKLKNIPTVNENLENYYLEVNQLEKFDIK<br/>SFCKILGPLSYSKIKHLRLDGNRISETSLPPDMYECLRVANEVTL<br/>NGGGGSGGGSDAHKSEVAHRFKDLGEENFKALVLIAFAQYLQ<br/>QCPFEDHVKL VNEVTEFAKTCVADESAENCDSLHTLFGDKLC<br/>TVATLRETYGEMADCCAKQEPERNECFLQHKDDNPNLPRLV<br/>PEVDVMCTAFHDNEETFLKKYLYEIARRHPYFYAPELFFAKR<br/>YKAAFTECCQAADKAACLLPKLDEL RDEGKASSAKQRLKAS<br/>LQKFGERAFKAWAVARLSQRFPKAEFAEVSKLVTDLT KVHTE<br/>CCHGDLLECADDRADLAKYICENQDSISSKLKECCEKPLLEKS<br/>HCIAEVENDEMPADLPSLAADFVESKDVCKNYAEAKDVFLGM<br/>FLYEYARRHPDYSVLLRLAKTYETTLEKCCAAADPHECYA<br/>KVFDEFKPLVEEPQNLIKQNCLEFEQLGEYKFQNALLVRYTKK<br/>VPQVSTPTLVEVSRNLGKVGSKCCKHPEAKRMPCAEDYLSV<br/>LNQLCVLQEKTPVSDRVTKCCTESLVNRRPCFSALEVDETYVP<br/>KEFNAETFTFHADICTLSEKERQIKKQTALVELVKHKPKATKEQ<br/>LKAVMDDFAAFVEKCKADDKETCFAEEGKKLVAASQAALG<br/>LGGGGSGGGSIWELKKDVYVVELDWYPDAPGEMVVLTCDT<br/>EEDGITWTLDQSSEVLGSGKTLTIQVKEFGDAGQYTCHKGGEV<br/>LSHSLLLHKKEDGIWSTDILKDQKEPKNKTFLRCEAKNYSGR<br/>FTCWWLTTISTDLTFSVKSSRGSSDPQGVTCGAATLSAERVGR<br/>DNKEYEYSVECQEDSACPAAEESLPIEVMVDAVHKLKYENYT<br/>SFFIRDIKPDPPKNLQLKPLKNSRQVEVSWEYPDTWSTPHSYF<br/>LTFCVQVQGKSKREKKDRVFTDKTSATVICRKNASISVRAQDR<br/>YYSSSWSEWASVPCSGGGGGSGGGSGGGSRNLPVATPDPGM</p> |

|    |                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|----|-----------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|    |                                                     | FPCLHHSQNLLRAVSNMLQKARQTLEFYPTCTSEEDHEDITKDK<br>TSTVEACLPLELTKNESCLNSRETSFITNGSCLASRKTSFMMAL<br>CLSSIIYEDLKMYQVEFKTMNAKLLMDPKRQIFLDQNMLAVIDE<br>LMQALNFNSETVPQKSSLEEPDFYKTKIKLCILLHAFRIRAVTID<br>RVMSYLNASHHHHHHHHHH                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| 68 | 2-<br>HSA_H464Q<br>-LAIR1-12<br>(normal<br>linkers) | MRVPAQLLGLLLLWLPGARCAAPTSSSTKKTQLQLEHLLLDLQ<br>MILNGINNYKNPKLTRMLTFKFYMPKKATELKHLCLEELKP<br>LEEVNLNAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYAD<br>ETATIVEFLNRWITFCQSIISTLTGGGGSGGGSDAHKSEVAHRF<br>KDLGEENFKALVLIAFAQYLQQCFEDHVKL VNEVTEFAKTCV<br>ADESAENCDKSLHTLFGDKLCTVATLRETYGEMADCCAKQEP<br>ERNECFLQHKDDNPNLPRLVRPEVDVMCTAFHDNEETFLKKY<br>LYEIARRHPYFYAPELFFAKRYKAAFTECCQAADKAAACLLPK<br>LDEL RDEGKASSAKQRLK CASLQKFGERAFKAWAVARLSQRF<br>PKAEFAEVSKLVTDLT KVHTECCHGDLLECADDRADLAKYICE<br>NQDSISSKLKECCEKPLLEKSHCIAEVENDEMPADLPSLAADFV<br>ESKDVCKNYAEAKDVFLGMFLY EYARRHPDYSVVLRLAKT<br>YETTL EKCCAAADPHECYAKVFDEFKPLVEEPQNLKQNCSELF<br>EQLGEYKFQNALLVRYTKKVPQVSTPTLVEVSRNLGKVGSKC<br>CKHPEAKRMPCAEDYLSVVLNQLCVLQEKTPVSDRVTKCCTE<br>SLVNRRPCFSALEVDETYVPKEFNAETFTFHADICTLSEKERQIK<br>KQTALVELVKHKPKATKEQLKAVMDDFAAFVEKCKKADDKE<br>TCFAEEGKKLVAAASQAALGLGGGGSGGGSQEEDLPRPSISAEP<br>GTVIPLGSHVTFVCRGPVGVQTFRLERESRSTYNDTEDVSQASP<br>SESEARFRIDSVSEGNAGPYRCIYYKPPKWSEQSDYLELLVKET<br>SGGPDSPDTEPGSSAGPTQRPSDNSHNEHAPASQGLKAEHLYG<br>GGGSGGGSIWELKKDVYVVELDWYPDAPGEMVVLTCDTPEE<br>DGITWTLDQSSEVLGSGKTLTIQVKEFGDAGQYTCHKGGEVLS<br>HLLLLLHKKEDGIWSTDILKDQKEPKNKTFLRCEAKNYSGRFT<br>CWWLT TISTDLTFSVKSSRGSSDPQGVTCGAATLSAERVGRDN<br>KEYEYSVEQCEDSACPAAEESLPIEVMVDAVHKLKYENYTSSF<br>FIRDIKPDPPKNLQLKPLKNSRQVEVSWEYPTWSTPHSYFSLT<br>FCVQVQGKSKREKKDRVFTDKTSATVICRKNASISVRAQDRYY<br>SSSWSEWASVPCSGGSGGGSGGGSGGGSRNLPVATPDPMFPC<br>LHHSQNLLRAVSNMLQKARQTLEFYPTCTSEEDHEDITKDKTST<br>VEACLPLELTKNESCLNSRETSFITNGSCLASRKTSFMMALCLS<br>SIYEDLKMYQVEFKTMNAKLLMDPKRQIFLDQNMLAVIDELM<br>QALNFNSETVPQKSSLEEPDFYKTKIKLCILLHAFRIRAVTIDRV<br>MSYLNASHHHHHHHHHH |
| 69 | 2-<br>HSA_H464Q<br>-LAIR2-12<br>(normal<br>linkers) | MRVPAQLLGLLLLWLPGARCAAPTSSSTKKTQLQLEHLLLDLQ<br>MILNGINNYKNPKLTRMLTFKFYMPKKATELKHLCLEELKP<br>LEEVNLNAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYAD<br>ETATIVEFLNRWITFCQSIISTLTGGGGSGGGSDAHKSEVAHRF<br>KDLGEENFKALVLIAFAQYLQQCFEDHVKL VNEVTEFAKTCV<br>ADESAENCDKSLHTLFGDKLCTVATLRETYGEMADCCAKQEP<br>ERNECFLQHKDDNPNLPRLVRPEVDVMCTAFHDNEETFLKKY<br>LYEIARRHPYFYAPELFFAKRYKAAFTECCQAADKAAACLLPK<br>LDEL RDEGKASSAKQRLK CASLQKFGERAFKAWAVARLSQRF<br>PKAEFAEVSKLVTDLT KVHTECCHGDLLECADDRADLAKYICE<br>NQDSISSKLKECCEKPLLEKSHCIAEVENDEMPADLPSLAADFV<br>ESKDVCKNYAEAKDVFLGMFLY EYARRHPDYSVVLRLAKT<br>YETTL EKCCAAADPHECYAKVFDEFKPLVEEPQNLKQNCSELF<br>EQLGEYKFQNALLVRYTKKVPQVSTPTLVEVSRNLGKVGSKC                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |

|    |                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|----|---------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|    |                                                   | <p>CKHPEAKRMPCAEDYLSVVLNQLCVLQEKTPVSDRVTKCCTE<br/> SLVNRRPCFSALEVDETYVPKEFNAETFTFHADICTLSEKERQIK<br/> KQTALVELVKHKPKATKEQLKAVMDDFAAFVEKCKKADDKE<br/> TCFAEEGKKLVAAASQAALGLGGGGSGGGSSQEGALPRPSISAEP<br/> GTVISPGSHVTFMCRGPVGVQTFRLEREDRAKYKDSYNVFRLG<br/> PSESEARFIDSVSEGNAGLYRCLYYKPPGWSEHSDFLELLVKE<br/> SSGGPDSPDTEPGSSAGTVPGTASGFDAPGGGGSGGGSIWELK<br/> KDVYVVELDWYPDAPGEMVVLTCDTPEEDGITWTLDQSSEVL<br/> GSGKTLTIQVKEFGDAGQYTCHKGGEVLSHSLLLHKKEDGIW<br/> STDILKDQKEPKNKTFLRCEAKNYSGRFTCWWTITISTDLTFSV<br/> KSSRGSSDPQGVTCGAATLSAERVGRDNKEYEYSVEQEDSAC<br/> PAAEESLPIEVMVDAVHKLKYENYTSSFFIRDIKPDPPKNLQLK<br/> PLKNSRQVEVSWEYPDTWSTPHSYFSLTFCVQVQGKSKREKK<br/> DRVFTDKTSATVICRKNASISVRAQDRYSSSWSEWASVPCSG<br/> GSGGGSGGGSGGGSRNLPVATPDPGMFPC LHHSQNLLRAVSN<br/> MLQKARQTLEFYPTSEEIDHEDITKDKTSTVEACLPLELTKNE<br/> SCLNSRETSFITNGSCLASRKTSFMMALCLSSIEDLKMYQVEF<br/> KTMNAKLLMDPKRQIFLDQNMLAVIDELMQALNFNSETVPQK<br/> SSLEEPDFYKTKIKLCILLHAFRIRAVTIDRVMSYLNASHHHHH<br/> HHHHH</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| 70 | 2-<br>HSA_H464Q<br>-Lum-12<br>(normal<br>linkers) | <p>MRVPAQLLGLLLLWLPGARCAAPTSSSTKKTQLQLEHLLLDLQ<br/> MILNGINNYKNPKLTRMLTFKFYMPKKATELKHLCLEELKP<br/> LEEVLNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYAD<br/> ETATIVEFLNRWITFCQSIISTLTGGGGSGGGSDAHKSEVAHRF<br/> KDLGEENFKALVLIAFAQYLQQCPFEDHVKLVNEVTEFAKTCV<br/> ADESAENCDKSLHTLFGDKLCTVATLRETYGEMADCCAKQEP<br/> ERNECFLQHKDDNPPLRLVRPEVDVMCTAFHDNEETFLKKY<br/> LYEIARRHPYFYAPELFFAKRYKAAFTCECCQAADKAAACLLPK<br/> LDELRDEGKASSAKQRLKCASLQKFGERAFKAWAVARLSQRF<br/> PKAEFAEVSKLVTDLT KVHTECCHGDLLECADDRADLAKYICE<br/> NQDSISSKLKECCEKPLEKSHCIAEVENDEMPADLPSLAADFV<br/> ESKDVCKNYAEAKDVFLGMFLYFYARRHPDYSVVLRLAKT<br/> YETTLEKCCAAADPHECYAKVFDEFKPLVEEPQNLKQNCSELF<br/> EQLGEYKFQNALLVRYTKKVPQVSTPTLVEVSRNLGKVGSKC<br/> CKHPEAKRMPCAEDYLSVVLNQLCVLQEKTPVSDRVTKCCTE<br/> SLVNRRPCFSALEVDETYVPKEFNAETFTFHADICTLSEKERQIK<br/> KQTALVELVKHKPKATKEQLKAVMDDFAAFVEKCKKADDKE<br/> TCFAEEGKKLVAAASQAALGLGGGGSGGGSSGQYYDYDFPLSIY<br/> GQSSPNCAPCNCPEPSAMYCDELKLSVPMVPPGIKYL<br/> RNNQIDHIDEKAFENVTDLQWLILDHNLLENSKIKGRVFSKLK<br/> QLKKLHINHNNLTESVGPLPKSLEDLQLTHNKITKLGSFEGLVN<br/> LTFIHLQHNRLKEDAVSAAFKGLKSLEYLDLSFNQIARLPGLP<br/> VSLLTLYLDNNKISNIPDEYFKRFNALQYLRLSHNELADSGIPG<br/> NSFNVSSLVELDLSYNKLKNIPTVNENLENYYLEVNQLEKFDIK<br/> SFCKILGPLSYKIKHLRLDGNRISETSLPPDMYECLRVANEVTL<br/> NGGGSGGGSIWELKKDVYVVELDWYPDAPGEMVVLTCDT<br/> EEDGITWTLDQSSEVLGSGKTLTIQVKEFGDAGQYTCHKGGEV<br/> LSHSLLLHKKEDGIWSTDILKDQKEPKNKTFLRCEAKNYSGR<br/> FTCWWTITISTDLTFSVKSSRGSSDPQGVTCGAATLSAERVGR<br/> DNKEYEYSVEQEDSACPAAEESLPIEVMVDAVHKLKYENYT<br/> SFFIRDIKPDPPKNLQLKPLKNSRQVEVSWEYPDTWSTPHSYF<br/> LTFCVQVQGKSKREKKDRVFTDKTSATVICRKNASISVRAQDR<br/> YYSSSWSEWASVPCSGGGSGGGSGGGSGGGSRNLPVATPDPM<br/> FPCLHHSQNLLRAVSNMLQKARQTLEFYPTSEEIDHEDITKDK<br/> TSTVEACLPLELTKNESCLNSRETSFITNGSCLASRKTSFMMAL</p> |

|    |                                             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|----|---------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|    |                                             | CLSSIEDLKMYQVEFKTMNAKLLMDPKRQIFLDQNMLAVIDE<br>LMQALNFNSETVPQKSSLEEDFYKTKIKLCILLHAFRIRAVTID<br>RVMSYLNASHHHHHHHHHH                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| 73 | 12-LAIR2-<br>HSA-2 (no<br>Histidine<br>Tag) | MRVPAQLLGLLLLWLPGARCAIWELKKDVYVVELDWYPDAP<br>GEMVVLTCDTPEEDGITWTLDQSSEVLGSGKTLTIQVKEFGDA<br>GQYTCHKGGEVLSHLLLLHKKEDGIWSTDILKDQKEPKNKT<br>LRCEAKNYSGRFTCWWTITSTDLTFSVKSSRGSSDPQGVTCG<br>AATLSAERVVRGDNKEYEYSVEQEDSACPAAEESLPIEVMVDA<br>VHKLKYENYTSSFFIRDIIKPDPPKNLQLKPLKNSRQVEVSWEY<br>PDTWSTPHSYFSLTFCVQVQGKSKREKKDRVFTDKTSATVICR<br>KNASISVRAQDRYSSSWSEWASVPCSGSGSGSGSGSGSGGS<br>RNLPAVATPDPMFPCLLHHSQNLLRAVSNMLQKARQTLEFYPC<br>SEEIDHEDITDKTSTVEACLPLELTKNESCLNSRETSFITNGSCL<br>ASRKTSFMMALCLSSIEDLKMYQVEFKTMNAKLLMDPKRQI<br>FLDQNMLAVIDELMQALNFNSETVPQKSSLEEDFYKTKIKLCI<br>LLHAFRIRAVTIDRVMSYLNASGGGSGGGSGEGALPRPSISAEP<br>GTVISPGSHVTFMCRGPVGVQTFRLEREDRAKYKDSYNVFRLG<br>PSESEARFHDVSEGNAGLYRCLYYKPPGWSEHSDFLELLVKE<br>SSGGPDSPDTEPGSSAGTVPGTEASGFDAPGGGSGGGSDAHKS<br>EVAHRFKDLGEENFKALVLIAFAQYLQQCPFEDHVKLNVNEVTE<br>FAKTCVADESAENCCKSLHTLFGDKLCTVATLRETYGEMADC<br>CAKQEPERNECFLQHKKDDNPNLPRLVPEVDVMCTAFHDNEE<br>TFLKKYLYEIARRHPYFYAPELLFFAKRYKAAFTCECQAADKA<br>ACLLPKLDELDEGKASSAKQRLKCASLQKFGERAFAKAWAVA<br>RLSQRFPKAEFAEVSKLVTDLTGVHTECCHGDLLECADDRADL<br>AKYICENQDSISSKLKECCEKPLLEKSHCIAEVENDEMPADLPS<br>LAADFVESKDVCKNYAEAKDVFLGMFLYFYARRHPDYSVLL<br>LRLAKTYETTLEKCCAAADPHECYAKVFDEFKPLVEEPQNLIK<br>QNCLEFEQLGEYKFQNALLVRYTKKVPQVSTPTLVEVSRNLGK<br>VGSKCKKHPEAKRMPCAEDYLSVVLNQLCVLHEKTPVSDRVT<br>KCCTESLVNRRPCFSALEVDETYVPKEFNAETFTFHADICTLSE<br>KERQIKKQTALVELVKHKPKATKEQLKAVMDDFAAFVEKCKK<br>ADDKETCFAEEGKKLVAAASQAALGLGGGSAPTSSSTKKTQLQL<br>EHLLLDLQMLNGINNYKNPKLTRMLTFKFYMPKKATELKHLLQ<br>CLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELKGSETT<br>FMCEYADETATIVEFLNRWITFCQSIISTLT |

## VI. Methods for Making Immunomodulatory Fusion Proteins

[00168] The immunomodulatory fusion proteins of the present invention are made using recombinant DNA technology. In some aspects, the domains of the immunomodulatory fusion proteins described herein (e.g., collagen-binding domains, cytokines) are made in transformed host cells using recombinant DNA techniques. Methods of preparing such DNA molecules are well known in the art. For instance, sequences coding for the peptides could be excised from DNA using suitable restriction enzymes. Alternatively, the DNA molecule could be synthesized using chemical synthesis techniques, such as the phosphoramidate method. Also, a combination of these techniques could be used.

[00169] The immunomodulatory fusion proteins of the present invention are isolated and purified using one or more methods known in the art, including centrifugation, depth filtration, cell lysis, homogenization, freeze thawing, affinity purification, gel filtration, size exchange chromatography, ion exchange chromatography, hydrophobic interaction exchange chromatography, and mixed-mode chromatography. In certain embodiments, the fusion proteins described herein are purified by size exchange chromatography with a protein A resin. In certain embodiments, the fusion proteins described herein are purified by size exchange chromatography with Capto<sup>TM</sup>Blue resin. In certain embodiments, the fusion proteins described herein are purified by size exchange chromatography with CaptureSelect<sup>TM</sup> HSA resin. In certain embodiments, the purified fusion proteins described herein are concentrated by any suitable method known in the art. In certain embodiments, the purified fusion protein is concentrated to a concentration of 0.1-100 mg/ml, 1-50 mg/ml, or 10-30 mg/ml. In certain embodiments, the purified fusion protein is concentrated to a concentration of 0.1-100 mg/ml, 1-50 mg/ml, or 10-30 mg/ml without detectable aggregation of the fusion protein. In certain embodiments, the purified fusion protein is concentrated to a concentration of about 20 mg/ml without detectable aggregation of the fusion protein.

[00170] In one exemplary embodiment, codon-optimized DNA sequences encoding comprising IL-12, IL-2, a collagen-binding protein, and albumin were synthesized and cloned into a pD2610-v1 vector. Plasmids were transformed into DH10B competent cells for expansion. Purified expression vectors were transiently transfected into HEK293 cells. Recombinant proteins were purified via anion exchange using Q Sepharose resin and preparative size exclusion chromatography (SEC).

## VII. Pharmaceutical Compositions and Modes of Administration

[00171] As used herein, the term “pharmaceutical composition” refers to the combination of an active agent with a carrier, inert or active, making the composition especially suitable for diagnostic or therapeutic use *in vivo* or *ex vivo*.

[00172] As used herein, the term “pharmaceutically acceptable carrier” refers to any of the standard pharmaceutical carriers, such as a phosphate buffered saline solution, water, emulsions (e.g., such as an oil/water or water/oil emulsions), and various types of wetting agents. The compositions also can include stabilizers and preservatives. For examples of carriers, stabilizers and adjuvants, see e.g., Martin, Remington's Pharmaceutical Sciences, 15th Ed., Mack Publ. Co., Easton, PA [1975]

[00173] As used herein, the term “pharmaceutically acceptable salt” refers to any pharmaceutically acceptable salt (e.g., acid or base) of a compound of the present invention which, upon administration to a subject, is capable of providing a compound of this invention or an active metabolite or residue thereof. As is known to those of skill in the art, “salts” of the compounds of the present invention may be derived from inorganic or organic acids and bases. Exemplary acids include, but are not limited to, hydrochloric, hydrobromic, sulfuric, nitric, perchloric, fumaric, maleic, phosphoric, glycolic, lactic, salicylic, succinic, toluene-psulfonic, tartaric, acetic, citric, methanesulfonic, ethanesulfonic, formic, benzoic, malonic, naphthalene-2-sulfonic, benzenesulfonic acid, and the like. Other acids, such as oxalic, while not in themselves pharmaceutically acceptable, may be employed in the preparation of salts useful as intermediates in obtaining the compounds of the invention and their pharmaceutically acceptable acid addition salts. In certain embodiments, the disclosure provides for a pharmaceutical composition comprising an immunomodulatory fusion protein with a pharmaceutically acceptable diluent, carrier, solubilizer, emulsifier, preservative and/or adjuvant.

[00174] In certain embodiments, the disclosure provides for a pharmaceutical composition comprising an immunomodulatory fusion protein with a pharmaceutically acceptable diluent, carrier, solubilizer, emulsifier, preservative and/or adjuvant.

[00175] In certain embodiments, the effective amount of a pharmaceutical composition comprising immunomodulatory fusion protein to be employed therapeutically will depend, for example, upon the therapeutic context and objectives. One skilled in the art will appreciate that the appropriate dosage levels for treatment, according to certain embodiments, will thus vary depending, in part, upon the molecule delivered, the indication for which the immunomodulatory fusion protein is being used, the route of administration, and the size (body weight, body surface or organ size) and/or condition (the age and general health) of the patient. In certain embodiments, the clinician can titer the dosage and modify the route of administration to obtain the optimal therapeutic effect.

## VIII. Methods of Treating

[00176] The immunomodulatory fusion proteins and/or nucleic acids expressing them, described herein, are useful for treating a disorder associated with abnormal apoptosis or a differentiative process (e.g., cellular proliferative disorders (e.g., hyperproliferative disorders) or cellular differentiative disorders, such as cancer). Non-limiting examples of cancers that are amenable to treatment with the methods of the present disclosure are described below.

[00177] Examples of cellular proliferative and/or differentiative disorders include cancer (e.g., carcinoma, sarcoma, metastatic disorders or hematopoietic neoplastic disorders, e.g., leukemias). A metastatic tumor can arise from a multitude of primary tumor types, including but not limited to those of prostate, colon, lung, breast and liver. Accordingly, the compositions used herein, comprising, e.g., immunomodulatory fusion protein, can be administered to a patient who has cancer.

[00178] As used herein, the terms "cancer" (or "cancerous"), "hyperproliferative," and "neoplastic" refer to cells having the capacity for autonomous growth (i.e., an abnormal state or condition characterized by rapidly proliferating cell growth). Hyperproliferative and neoplastic disease states may be categorized as pathologic (i.e., characterizing or constituting a disease state), or they may be categorized as non-pathologic (i.e., as a deviation from normal but not associated with a disease state). The terms are meant to include all types of cancerous growths or oncogenic processes, metastatic tissues or malignantly transformed cells, tissues, or organs, irrespective of histopathologic type or stage of invasiveness. "Pathologic hyperproliferative" cells occur in disease states characterized by malignant tumor growth. Examples of non-pathologic hyperproliferative cells include proliferation of cells associated with wound repair.

[00179] The terms "cancer" or "neoplasm" are used to refer to malignancies of the various organ systems, including those affecting the lung, breast, thyroid, lymph glands and lymphoid tissue, gastrointestinal organs, and the genitourinary tract, as well as to adenocarcinomas which are generally considered to include malignancies such as most colon cancers, renal-cell carcinoma, prostate cancer and/or testicular tumors, non-small cell carcinoma of the lung, cancer of the small intestine and cancer of the esophagus.

[00180] The term "carcinoma" is art recognized and refers to malignancies of epithelial or endocrine tissues including respiratory system carcinomas, gastrointestinal system carcinomas, genitourinary system carcinomas, testicular carcinomas, breast carcinomas, prostatic carcinomas, endocrine system carcinomas, and melanomas. The immunomodulatory fusion proteins can be used to treat patients who have, who are suspected of having, or who may be at high risk for developing any type of cancer, including renal carcinoma or melanoma, or any viral disease. Exemplary carcinomas include those forming from tissue of the cervix, lung, prostate, breast, head and neck, colon and ovary. The term also includes carcinosarcomas, which include malignant tumors composed of carcinomatous and sarcomatous tissues. An "adenocarcinoma" refers to a carcinoma derived from glandular tissue or in which the tumor cells form recognizable glandular structures.

[00181] In certain embodiments, the immunomodulatory fusion proteins disclosed herein are used to treat cancer. In certain embodiments, the immunomodulatory fusion proteins disclosed herein are used to treat melanoma, leukemia, lung cancer, breast cancer, prostate cancer, ovarian cancer, colon cancer, and brain cancer.

5 [00182] In certain embodiments, the immunomodulatory fusion proteins disclosed herein inhibit the growth and/or proliferation of tumor cells. In certain embodiments, the immunomodulatory fusion proteins disclosed herein reduce tumor size. In certain embodiments, the immunomodulatory fusion proteins disclosed herein inhibit metastases of a primary tumor.

10 [00183] In certain embodiments, administration of the immunomodulatory fusion proteins disclosed herein to a subject do not result in cytokine release syndrome after administration to a subject. In certain embodiments, the subject does not experience grade 4 cytokine release syndrome. In certain embodiments, the subject does not experience one or more symptoms associated with grade 4 cytokine release syndrome selected from the group consisting of hypotension, organ toxicity, fever and/or respiratory distress resulting in a need for supplemental  
15 Oxygen.

[00184] In certain embodiments, the administration of the fusion proteins disclosed herein, when administered either intravenously or intratumorally in a subject with cancer, the level of cytokines is increased in the serum of the subject after administration compared to IV or IT administration of recombinant IL-2 and/or IL-12. In certain embodiments, the cytokines that are increased in the  
20 serum of the subject are selected from  $\text{INF}\gamma$ , IP-10 and MCP-1.

#### Combination Therapy

[00185] In some embodiments, the immunomodulatory fusion proteins are used in combination with other therapies. In some embodiments, the immunomodulatory fusion proteins are used in  
25 combination with additional therapeutic agents to treat cancer. For example, in some embodiments the immunomodulatory fusion proteins are used in combination with another immunotherapy. Exemplary immunotherapies include, but are not limited to, chimeric antigen receptor (CAR) T cell therapy, tumor-associated antigen targeting antibodies, immune checkpoint inhibitors, and cancer vaccines.

#### I. Tumor-Associated Antigen Targeting Antibodies

30 [00186] In some aspects, the disclosure provides immunomodulatory fusion proteins to be used or performed in conjunction with antibodies that target tumor antigens.

[00187] Therapeutic monoclonal antibodies have been conceived as a class of pharmaceutically active agents which should allow tumor selective treatment by targeting tumor selective antigens or epitopes.

[00188] Methods of producing antibodies, and antigen binding fragments thereof, are well

known in the art and are disclosed in, e.g., U.S. Pat. Nos. 7,247,301, 7,923,221, and U.S. Patent Application 2008/0138336, all of which are herein incorporated by reference in their entirety.

[00189] Therapeutic antibodies that can be used in the methods of the present disclosure include, but are not limited to, any of the art-recognized anti-cancer antibodies that are approved for use, in clinical trials, or in development for clinical use. In certain embodiments, more than one anticancer antibody can be included in the combination therapy of the present disclosure.

[00190] Non-limiting examples of anti-cancer antibodies include the following, without limitation: trastuzumab (HERCEPTIWM, by Genentech, South San Francisco, Calif.), which is used to treat HER-2/neu positive breast cancer or metastatic breast cancer; bevacizumab (AVASTIWM by Genentech), which are used to treat colorectal cancer, metastatic colorectal

cancer, breast cancer, metastatic breast cancer, non-small cell lung cancer, or renal cell carcinoma; rituximab (RITUXAWM by Genentech), which is used to treat non-Hodgkin's lymphoma or chronic lymphocytic leukemia; pertuzumab (OMNITARG™ by Genentech),

[00191] which is used to treat breast cancer, prostate cancer, non-small cell lung cancer, or ovarian cancer; cetuximab (ERBITUX™ by ImClone Systems Incorporated, New York, N.Y.),

which can be used to treat colorectal cancer, metastatic colorectal cancer, lung cancer, head and neck cancer, colon cancer, breast cancer, prostate cancer, gastric cancer, ovarian cancer, brain cancer, pancreatic cancer, esophageal cancer, renal cell cancer, prostate cancer, cervical cancer, or bladder cancer; IMC-1 Cl 1 (Im Clone Systems Incorporated), which is used to treat colorectal cancer, head and neck cancer, as well as other potential cancer targets; tositumomab and

tositumomab and iodine I 131 (BEXXAR XM by Corixa Corporation, Seattle, Wash.), which is used to treat non-Hodgkin's lymphoma, which can be CD20 positive, follicular, non-Hodgkin's lymphoma, with and without transformation, whose disease is refractory to Rituximab and has relapsed following chemotherapy; In111 ibirtumomab tiuxetan; Y90 ibirtumomab tiuxetan; In111

ibirtumomab tiuxetan and Y90 ibirtumomab tiuxetan (ZEVALIN™ by Biogen Idec, Cambridge, Mass.), which is used to treat lymphoma or non-Hodgkin's lymphoma, which can include relapsed follicular lymphoma; relapsed or refractory, low grade or follicular non-Hodgkin's lymphoma; or transformed B-cell non-Hodgkin's lymphoma; EMD 7200 (EMD Pharmaceuticals, Durham, N.C.), which is used for treating non-small cell lung cancer or cervical cancer; SGN-30 (a genetically engineered monoclonal antibody targeted to CD30 antigen by Seattle Genetics,

Bothell, Wash.), which is used for treating Hodgkin's lymphoma or non-Hodgkin's lymphoma; SGN-15 (a genetically engineered monoclonal antibody targeted to a Lewisy-related antigen that is conjugated to doxorubicin by Seattle Genetics), which is used for treating non-small cell lung cancer; SGN-33 (a humanized antibody targeted to CD33 antigen by Seattle Genetics), which is used for treating acute myeloid leukemia (AML) and myelodysplasia syndromes (MDS); SGN-40 (a humanized monoclonal antibody targeted to CD40 antigen by Seattle Genetics), which is used for treating multiple myeloma or non-Hodgkin's lymphoma; SGN-35 (a genetically engineered monoclonal antibody targeted to a CD30 antigen that is conjugated to auristatin E by Seattle Genetics), which is used for treating non-Hodgkin's lymphoma; SGN-70 (a humanized antibody targeted to CD70 antigen by Seattle Genetics), which is used for treating renal cancer and nasopharyngeal carcinoma; SGN-75 (a conjugate comprised of the SGN70 antibody and an Auristatin derivative by Seattle Genetics); and SGN-17/19 (a fusion protein containing antibody and enzyme conjugated to melphalan prodrug by Seattle Genetics), which is used for treating melanoma or metastatic melanoma.

## II. Immune Checkpoint Blockade

**[00192]** In some aspects, the disclosure provides immunomodulatory fusion proteins to be used or performed in conjunction with immune checkpoint inhibitors or immune checkpoint blockers.

**[00193]** T cell activation and effector functions are balanced by co-stimulatory and inhibitory signals, referred to as "immune checkpoints." Inhibitory ligands and receptors that regulate T cell effector functions are overexpressed on tumor cells. Subsequently, agonists of co-stimulatory receptors or antagonists of inhibitory signals, result in the amplification of antigen-specific T cell responses. In contrast to therapeutic antibodies which target tumor cells directly, immune checkpoint blocker enhances endogenous anti-tumor activity.

**[00194]** In certain embodiments, the immune checkpoint blocker suitable for use in the methods disclosed herein, is an antagonist of inhibitory signals, e.g., an antibody which targets, for example, PD-1, PD-L1, CTLA-4, LAG3, B7-H3, B7-H4, or TIM3. These ligands and receptors are reviewed in Pardoll, D., Nature. 12: 252-264, 2012.

**[00195]** In certain embodiments, the immune checkpoint blocker is an antibody or an antigen-binding portion thereof, that disrupts or inhibits signaling from an inhibitory immunoregulator. In certain embodiments, the immune checkpoint blocker is a small molecule that disrupts or inhibits signaling from an inhibitory immunoregulator.

## EXAMPLES

[00196] The invention now being generally described, will be more readily understood by reference to the following examples, which are included merely for purposes of illustration of certain aspects and embodiments of the present invention, and is not intended to limit the invention.

#### 5 **Example 1: Method of Preparation of Linear Constructs**

[00197] The proteins of the present invention are typically made using recombinant DNA technology. In one exemplary embodiment, codon-optimized DNA sequences encoding comprising IL-12, IL-2, a collagen-binding protein, and albumin were synthesized and cloned into a pD2610-v1 vector. Plasmids were transformed into DH10B competent cells for expansion.

10 Purified expression vectors were transiently transfected into HEK293 cells. Recombinant proteins were purified via anion exchange using Q Sepharose resin and preparative size exclusion chromatography (SEC). Concentrated protein was evaluated for product quality using analytical SEC. Proteins were subsequently polished with another round of preparative SEC prior to *in vitro* and *in vivo* evaluation

15 [00198] The proteins are isolated and purified using methods known in the art including centrifugation, depth filtration, cell lysis, homogenization, freeze thawing, affinity purification, gel filtration, ion exchange chromatography, hydrophobic interaction exchange chromatography, and mixed-mode chromatography.

#### **Example 2: Recombinant Collagen-Binding Fusion Proteins Bind Collagen In Vitro**

20 [00199] To evaluate the ability of collagen-binding immunomodulatory molecules to bind collagen, the collagen-binding fusion proteins expressed and purified as described in Example 1 were tested for their ability to bind to collagen I-coated plates by ELISA with linear fusion constructs and anti-His detection. Briefly, collagen I (Corning) coated 96-well plates were blocked at room temperature for 1 hour with 1% wt/vol bovine serum albumin (BSA). Hisx10-  
25 containing proteins were incubated on plates for 1.5 hours at increasing concentration. Wells were subsequently washed and incubated with an anti-His tag detection antibody (Abcam) for 1.5 hours. Bound Hisx10-tagged collagen-binding fusion proteins were visualized with TMB development followed by absorbance reads at 450 nm minus absorbance reads at 650 nm. As shown in FIG. 4A, LAIR-containing construct effected stronger binding to collagen compared to  
30 Lum-containing construct. Furthermore, placing Lumican between MSA and IL-2 enabled tighter binding to collagen than placing Lumican between MSA and IL-2. As shown in FIG. 4B, three

LAIR-containing constructs using different spacer between LAIR and IL-2 effected comparable level of collagen binding

[00200] LAIR fusions potently bind collagen. LAIR fusion binds with tighter affinity than lumican fusion. Optionality to select weak or strong binding pending in vivo data and biological activity.

### **Example 3: Recombinant Collagen-Binding Fusion Proteins Maintain IL-2 Cytokine Activity**

[00201] To evaluate the ability of collagen-binding immunomodulatory molecules to maintain IL-2 cytokine activity in the presence of collagen, samples were serially diluted in assay media and 50 µl diluted samples and 50 µl assay media added to either normal tissue-culture plates or collagen I (Corning) coated plates and incubated for 1 hour. About 25,000 CTLL-2 cells were subsequently transferred to each well in 100 µl assay media and incubated for 3 days. Following incubation, 20 µl Promega Substrate Cell Titer 96 Aqueous One Solution Reagent was added to each well, incubated at 37C, and absorbance read at 490 nm.

[00202] As shown in FIGs. 5A-5D, bi-functional constructs containing both IL-2 and IL-12 effected IL-2 activity at a level comparable to IL-2 alone. Furthermore, the IL-2 activity is not affected by collagen binding, and is independent of the choice of the spacer or the choice of the collagen binding domain.

### **Example 4: Recombinant Collagen-Binding Fusion Proteins Maintain IL-12 Cytokine Activity**

[00203] To evaluate the ability of collagen-binding immunomodulatory molecules to maintain IL-2 cytokine activity in the presence of collagen, samples were serially diluted in assay media and 50 µl diluted samples and 50 µl assay media were added to either normal tissue-culture plates or Corning collagen I-coated plates and incubated for 1hr. About 15,000 2D6 cells were subsequently transferred to each well in 100 µl assay media and incubated for 4 days. Following incubation, 20 µl Promega Substrate Cell Titer 96 Aqueous One Solution Reagent was added to each well, incubated at 37°C, and absorbance read at 490 nm.

[00204] As shown in FIGs. 6A-6B, bi-functional constructs containing both IL-2 and IL-12 effected IL-12 activity at a level comparable to IL-12 alone. Furthermore, the IL-12 activity is not affected by collagen binding, and is independent of the choice of the collagen binding domain.

### **Example 5: Synergistic Effect of Immunomodulatory Collagen-Binding Molecules and Anti-Tumor Antigen Antibody in Mouse Melanoma Tumor Model**

**[00205]** To evaluate efficacy and toxicity of by bi-functional constructs and the combination of mono-functional constructs, C57BL/6 mice were inoculated on the right rear flank with 200,000 B16F10 cells in 0.1 ml PBS. After 9 days post-inoculation (day 0), mice were randomized into treatment groups (n=10). Mice were treated with intratumoral injections of 100 pmol on days 0 and 6 with 100 pmol of: (1) PBS, (2) a combination of an IL-2 mono-functional linear construct comprising an MSA (MSA-2) and an IL-12 mono-functional linear construct comprising an MSA (12-MSA), (3) a combination of an IL-2 mono-functional linear construct comprising an MSA and a collagen-binding domain (LAIR-MSA-2) and an IL-12 mono-functional linear construct comprising an MSA and collagen-binding domain (12-MSA-LAIR), (4) a bi-functional linear constructs comprising MSA and a collagen-binding domain 12-Lum-MSA-2, and (5) a bi-functional linear constructs comprising MSA and a collagen-binding domain 12-LAIR-MSA-2. Mice were monitored for tumor outgrowth and body weight loss at least twice a week and were euthanized if found to be moribund, if body weight loss >20%, or if tumor volume >3,000 mm<sup>3</sup>.

**[00206]** As shown in FIGs. 7A-7B, the tumor growth and body weight upon treatment by bi-functional constructs or combinations of mono-functional constructs show that both bi-functional linear constructs 12-Lum-MSA-2 and 12-LAIR-MSA-2 demonstrated superior safety profile indicated by lack of body weight loss, illustrating toxicity associated with systemic exposure of cytokines, compared to combination of mono-functional constructs regardless of whether the mono-functional constructs contain a collagen binding domain. Both 12-Lum-MSA-2 and 12-LAIR-MSA-2 effected significant tumor growth inhibition.

### **Example 6: Linear Construct Monotherapy in B16F10 Model – abscopal effect and dual flank model**

**[00207]** To further evaluate the dose-response therapeutic efficacy of the bi-functional linear construct comprising MSA and a collagen-binding domain, 12-LAIR-MSA-2, was evaluated in a dual-flank inoculated subcutaneous B16F10 melanoma syngeneic model in C57BL/6 mice. Control C57BL/6 mice were inoculated with 200,000 B16F10 cells in 0.1 mL PBS on either the right rear flank (treated tumor plot) or on the left rear flank 10 days later (untreated tumor plot). Other mice on study were inoculated with 200,000 B16F10 cells in 0.1 mL PBS on the right rear flank and on the left rear flank 10d later. 8 days post-inoculation of the tumor on the right rear flank (day 0) , mice were randomized into treatment groups (n=15). Mice were treated with

intratumoral injections of indicated doses of 12-LAIR-MSA-2 on days 0, 6, and 12 in the right rear flank tumor. Mice were monitored for tumor outgrowth on both flanks and body weight loss at least twice a week and were euthanized if found to be moribund, if body weight loss >20%, or if total tumor volume >3,000 mm<sup>3</sup>.

- 5    **[00208]** As shown in FIGs. 8A-8B, the bi-functional linear constructs 12-LAIR-MSA-2, at all dose levels tested, effected significantly tumor growth inhibition, both in the treated tumor (FIG. 8A) and the untreated tumor (FIG. 8B), demonstrating abscopal effect.

#### **Example 7: Linear Constructs Comparison in B16F10 Model**

- 10    **[00209]** The efficacy and toxicity various bi-functional constructs were evaluated in a B16F10 mouse model. C57BL/6 mice were inoculated on the right rear flank with 200,000 B16F10 cells in 0.1 ml PBS. 7 days post-inoculation (day 0), mice were randomized into treatment groups (n=10). Mice were treated with intratumoral injections of 400 pmol of (1) PBS control, (2) 12-LAIR-MSA-2, (3) 12-LAIR-MSA\_H464Q-2, (4) 12-LAIR-ABD-2, and (5) 12-Lum-MSA-2 n days 0 and 6. Mice were monitored for tumor outgrowth and body weight loss at least twice a  
15    week and were euthanized if found to be moribund, if body weight loss >20%, or if tumor volume >3,000 mm<sup>3</sup>.

**[00210]** As shown in FIGs. 9A-9C, all bi-functional constructs tested effected significant tumor growth inhibition, demonstrated good safety profile reflected by the lack of body weight loss, and extended survival of the animals compared to PBS control group.

#### **20    Example 8: Linear Construct in B16F10 Model – Checkpoint Combination**

- [00211]** To evaluate 12-LAIR-MSA-2 in combination with checkpoint inhibitors anti-PD1 or anti-CTLA, C57BL/6 mice were inoculated on the right rear flank with 200,000 B16F10 cells in 0.1 ml PBS. 7 days post-inoculation (day 0), mice were randomized into treatment groups (n=10). Mice were treated with intratumoral (IT) injections of PBS or 400 pmol of 12-LAIR-MSA-2 and  
25    intraperitoneal (IP) injections of isotype control (Rat IgG2a), anti-PD1 (clone RMP1-14), or anti-CTLA4 (9D9) as indicated. IT injections were performed on days 0, 6, and 12 while IP injections were performed BIW until end of study. Mice were monitored for tumor outgrowth and body weight loss at least twice a week and were euthanized if found to be moribund, if body weight loss >20%, or if tumor volume >3,000 mm<sup>3</sup>.

- 30    **[00212]** As shown in FIGs. 10A-10B, treatment with either anti-PD1 or anti-CTLA4 alone did not affect tumor growth inhibition. Treatment with bi-functional construct 12-LAIR-MSA-2 alone resulted in significant tumor growth inhibition. The anti-tumor activity of 12-LAIR-MSA-2 was

further enhanced by the combination with either anti-PD1 or anti-CTLA4. As shown in FIG. 10C, the addition of either anti-PD1 or anti-CTLA4 to bi-functional construct 12-LAIR-MSA-2 did not result in additional weight loss compared to treatment with 12-LAIR-MSA-2 alone.

#### **Example 9: Linear Construct Monotherapy in MC38 Model – Safety and Efficacy**

[00213] The dose-response therapeutic efficacy of the bi-functional linear construct comprising MSA and a collagen-binding domain, 12-LAIR-MSA-2, was evaluated in an MC38 model in C57BL/6 mice. C57BL/6 mice were inoculated on the right rear flank with 1,000,000 MC38 cells in 0.1 ml PBS. After 6 days post-inoculation (day 0), mice were randomized into treatment groups (n=10). Mice were treated with intratumoral injections of indicated doses of 12-LAIR-MSA-2 on days 0 and 6. Mice were monitored for tumor outgrowth and body weight loss at least twice a week and were euthanized if found to be moribund, if body weight loss >20%, or if tumor volume >3,000 mm<sup>3</sup>.

[00214] As shown in FIG. 11A, treatment with 12-LAIR-MSA-2 at all dose levels resulted in significant tumor growth inhibition. Furthermore, dose response was observed with treatment at the highest dose level resulting in the highest complete response (CR) rate. As shown in FIG. 11B, none of the treatment groups showed significant body weight loss.

#### **Example 10: Linear Constructs Comparison in MC38 Model**

[00215] The efficacy and toxicity various bi-functional constructs were evaluated in a B16F10 mouse model. Mice were treated with intratumoral injections of indicated doses of PBS, 12-LAIR-MSA-2, 12-LAIR-ABD-2, and 12-Lum-MSA-2 on days 0 and 6. Mice were treated with intraperitoneal injections of isotype control (Rat IgG2a) or anti-PD1 (clone RMP1-14) BIW for three weeks if indicated. Mice were monitored for tumor outgrowth and body weight loss at least twice a week and were euthanized if found to be moribund, if body weight loss >20%, or if tumor volume >3,000 mm<sup>3</sup>.

[00216] As shown in FIG. 12A, bi-functional constructs containing different collagen binding domains or spacer between IL-2 and the collagen binding domain, all resulted in significant tumor growth inhibition and CR rate. In comparison, treatment with anti-PD1 in the same model did not effect comparable degree of tumor growth control and did not result in any cures. As shown in FIG. 12B, none of the treatment groups showed significant body weight loss.

#### **Example 11: Linear Construct Monotherapy in CT26 Model – Safety and Efficacy**

**[00217]** The dose-response therapeutic efficacy of the bi-functional linear construct comprising MSA and a collagen-binding domain, 12-LAIR-MSA-2, was evaluated in a CT26 model in BALB/c mice. BALB/c mice were inoculated on the right rear flank with 500,000 CT26 cells in 0.1 ml PBS. 6 days post-inoculation (day 0), mice were randomized into treatment groups (n=10).

5 Mice were treated with intratumoral injections of indicated doses of PBS or 12-LAIR-MSA-2, with treatments administered on days 0, 6, and 12. Mice were treated with intraperitoneal injections of isotype control (Rat IgG2a) or anti-PD1 (clone RMP1-14) BIW for three weeks if indicated. Mice were monitored for tumor outgrowth and body weight loss at least twice a week and were euthanized if found to be moribund, if body weight loss >20%, or if tumor volume  
10 >3,000 mm<sup>3</sup>.

As shown in FIGs. 13A-13B tumor growth inhibition and body weight change upon treatment with 12-LAIR-MSA-2 at various dose levels or dose frequencies. None of the treatment groups showed body weight loss, and dose-dependent anti-tumor activity was observed.

#### **Example 12: Linear Constructs Comparison in MC38 Model**

15 **[00218]** The efficacy and toxicity various bi-functional constructs were evaluated in a B16F10 mouse model. BALB/c mice were inoculated on the right rear flank with 500,000 CT26 cells in 0.1 ml PBS. 6 days post-inoculation (day 0), mice were randomized into treatment groups (n=10). Mice were treated with intratumoral injections of indicated doses of PBS, 12-LAIR-MSA-2, 12-LAIR-ABD-2, and 12-Lum-MSA-2 the indicated number of times, with treatments administered  
20 on days 0, 6, and 12. Mice were treated with intraperitoneal injections of isotype control (Rat IgG2a) or anti-PD1 (clone RMP1-14) BIW for three weeks if indicated. Mice were monitored for tumor outgrowth and body weight loss at least twice a week and were euthanized if found to be moribund, if body weight loss >20%, or if tumor volume >3,000 mm<sup>3</sup>.

**[00219]** As shown in FIGs. 14A-14B, bi-functional constructs containing different collagen  
25 binding domains or spacer between IL-2 and the collagen binding domain, all resulted in significant tumor growth inhibition. In comparison, treatment with anti-PD1 in the same model did not effect tumor growth inhibition. None of the treatment groups showed body weight loss.

#### **Example 13: Linear Construct in B16F10 Model – IT and IV administration**

**[00220]** The efficacy of intratumoral (IT) compared to intravenous (IV) administration of the 12-LAIR-MSA-2 construct was evaluated in a B16F10 mouse model. C57BL/6 mice were  
30 inoculated on the right rear flank with 200,000 B16F10 cells in 0.1 ml PBS. Seven days post-inoculation (day 0), mice were randomized into treatment groups (n=10). Mice were treated with

either intraveunous or intratumoral injections of 400 pmol of PBS control or 12-LAIR-MSA-2. Two hours or 24 hours after administration, the amount of 12-LAIR-MSA-2 in the serum was measured (Fig. 15A). After two hours, there was a significant reduction in serum levels of the fusion protein when delivered IT compared to IV. After 24 hours, there were very low levels of fusion protein detected in mice administered the fusion protein either by IT or IV. Cytokines interferon gama (INF- $\gamma$ ), interferon gamma inducible protein (IP-10) and monocyte chemoattractant protein-1 (MCP-1) were also measured either 2 h or 24 h after administration of the fusion protein by IT or IV admininistration (Fig. 15B-15D). The level of cytokines after 24 h was not significantly different when compared to mice that were administered the fusion protein by IT or IV. The efficacy of treatment, as measured by survival, however, was significantly improved in mice that were administered the fursion protein by IT aministration as compared to IV adminstration (Fig. 15E). These results confirm that the fusion proteins described herein are effective at reducing serum concentrations of the fusion protein and improving survival of subjects when the fusion proteins are adminsitared by intratumoral aministration.

#### INCORPORATION BY REFERENCE

**[00221]** The entire disclosure of each of the patent documents and scientific articles cited herein is incorporated by reference for all purposes.

#### EQUIVALENTS

**[00222]** The disclosure can be embodied in other specific forms with departing from the essential characteristics thereof. The foregoing embodiments therefore are to be considered illustrative rather than limiting on the disclosure described herein. The scope of the disclosure is indicated by the appended claims rather than by the foregoing description, and all changes that come within the meaning and range of equivalency of the claims are intended to be embraced therein.

## CLAIMS

## WHAT IS CLAIMED IS:

1. An immunomodulatory fusion protein comprising:
  - (i) an IL-2;
  - 5 (ii) an IL-12;
  - (iii) a collagen-binding domain, and
  - (iv) a linear polypeptide spacer.
2. The immunomodulatory fusion protein of claim 1, wherein the fusion protein is linear.
3. The immunomodulatory fusion protein of any one of claims 1-2, wherein the fusion
- 10 protein is a continuous chain.
4. The immunomodulatory fusion protein of any one of claims 1-3, wherein the fusion protein is a continuous polypeptide chain.
5. The immunomodulatory fusion protein of any one of claims 1-4, wherein the IL-2 is at the N-terminus.
- 15 6. The immunomodulatory fusion protein of any one of claims 1-5, wherein the IL-12 is at the C-terminus.
7. The immunomodulatory fusion protein of any one of claims 1-6, wherein the IL-2 is at the N-terminus and the IL-12 is at the C-terminus.
8. The immunomodulatory fusion protein of any one of claims 1-7, wherein the linear
- 20 polypeptide spacer is positioned in between the IL-2 and the collagen-binding domain.
9. The immunomodulatory fusion protein of any one of claims 1-8, wherein the collagen-binding domain is positioned in between the IL-12 and the linear polypeptide spacer.
10. The immunomodulatory fusion protein of any one of claims 1-9, wherein the C-terminus of the IL-2 is operably linked to the N-terminus of the linear polypeptide spacer.
- 25 11. The immunomodulatory fusion protein of claim 10, wherein the C-terminus of the IL-2 is operably linked by a linker to the N-terminus of the linear polypeptide spacer.
12. The immunomodulatory fusion protein of any one of claims 1-11, wherein the C-terminus of the linear polypeptide spacer is operably linked to the N-terminus of the collagen-binding domain.
- 30 13. The immunomodulatory fusion protein of claim 12, wherein the C-terminus of the linear polypeptide spacer is operably linked by a linker to the N-terminus of the collagen-binding domain.

14. The immunomodulatory fusion protein of any one of claims 1-13, wherein C-terminus of the collagen-binding domain is operably linked to the N-terminus of the IL-12.
15. The immunomodulatory fusion protein of claim 14, wherein C-terminus of the collagen-binding domain is operably linked by a linker to the N-terminus of the IL-12.
- 5 16. The immunomodulatory fusion protein of any one of claims 1-6, wherein the collagen-binding domain is positioned in between the IL-2 and the linear polypeptide spacer.
17. The immunomodulatory fusion protein of claim 16, wherein the linear polypeptide spacer is positioned in between the IL-12 and the collagen-binding domain.
18. The immunomodulatory fusion protein of any one of claims 16-17, wherein the C-terminus of the IL-2 is operably linked to the N-terminus of the collagen-binding domain.
- 10 19. The immunomodulatory fusion protein of claim 18, wherein the C-terminus of the IL-2 is operably linked by a linker to the N-terminus of the collagen-binding domain.
20. The immunomodulatory fusion protein of any one of claims 16-19, wherein the C-terminus of the collagen-binding domain is operably linked to the N-terminus of the linear polypeptide spacer.
- 15 21. The immunomodulatory fusion protein of claim 20, wherein the C-terminus of the collagen-binding domain is operably linked by a linker to the N-terminus of the linear polypeptide spacer.
22. The immunomodulatory fusion protein of any one of claims 16-21, wherein C-terminus of the linear polypeptide spacer is operably linked to the N-terminus of the the IL-12.
- 20 23. The immunomodulatory fusion protein of claim 22, wherein C-terminus of the linear polypeptide spacer is operably linked by a linker to the N-terminus of the the IL-12.
24. The immunomodulatory fusion protein of any one of claims 1-3, wherein the IL-2 is at the C-terminus.
- 25 25. The immunomodulatory fusion protein of claim 24, wherein the IL-12 is at the N-terminus.
26. The immunomodulatory fusion protein of any one of claims 24-25, wherein the IL-2 is at the C-terminus and the IL-12 is at the N-terminus.
27. The immunomodulatory fusion protein of any one of claims 24-27, wherein the N-terminus of the IL-2 is operably linked to the C-terminus of the linear polypeptide spacer.
- 30 28. The immunomodulatory fusion protein of claim 27, wherein the N-terminus of the IL-2 is operably linked by a linker to the C-terminus of the linear polypeptide spacer.

29. The immunomodulatory fusion protein of any one of claims 24-28, wherein the N-terminus of the linear polypeptide spacer is operably linked to the C-terminus of the collagen-binding domain.
30. The immunomodulatory fusion protein of claim 27, wherein the N-terminus of the linear polypeptide spacer is operably linked by a linker to the C-terminus of the collagen-binding domain.
31. The immunomodulatory fusion protein of any one of claims 24-30, wherein N-terminus of the collagen-binding domain is operably linked to the C-terminus of the the IL-12.
32. The immunomodulatory fusion protein of claim 31, wherein N-terminus of the collagen-binding domain is operably linked by a linker to the C-terminus of the the IL-12.
33. The immunomodulatory fusion protein of claim 26, wherein the collagen-binding domain is positioned in between the IL-2 and the linear polypeptide spacer.
34. The immunomodulatory fusion protein of claim 27, wherein the linear polypeptide spacer is positioned in between the IL-12 and the collagen-binding domain.
35. The immunomodulatory fusion protein of any one of claims 33-34, wherein the N-terminus of the IL-2 is operably linked to the C-terminus of the collagen-binding domain.
36. The immunomodulatory fusion protein of claim 35, wherein the N-terminus of the IL-2 is operably linked by a linker to the C-terminus of the collagen-binding domain.
37. The immunomodulatory fusion protein of any one of claims 33-36, wherein the N-terminus of the collagen-binding domain is operably linked to the C-terminus of the linear polypeptide spacer.
38. The immunomodulatory fusion protein of claim 37, wherein the N-terminus of the collagen-binding domain is operably linked by a linker to the C-terminus of the linear polypeptide spacer.
39. The immunomodulatory fusion protein of any one of claims 33-38, wherein N-terminus of the linear polypeptide spacer is operably linked to the C-terminus of the the IL-12.
40. The immunomodulatory fusion protein of claim 39, wherein N-terminus of the linear polypeptide spacer is operably linked by a linker to the C-terminus of the the IL-12.
41. The immunomodulatory fusion protein of any one of claims 11, 13, 15, 19, 21, 23, 28, 30, 32, 36, 38, 40, wherein one or more of the linkers are the same.
42. The immunomodulatory fusion protein of any one of claims 11, 13, 15, 19, 21, 23, 28, 30, 32, 36, 38, 40, wherein one or more of the linkers are the different.
43. The immunomodulatory fusion protein of claim 1, wherein the IL-12 is at the C terminus and is operably linked to the collagen binding domain, which is operably linked to a linear

polypeptide spacer, which is operably linked to the IL-2 at the N terminus of the protein, and wherein the protein is linear.

44. The immunomodulatory fusion protein of claim 1, wherein the IL-12 is at the N terminus and is operably linked to the collagen binding domain, which is operably linked to a linear polypeptide spacer, which is operably linked to the IL-2 at the C terminus of the protein, and wherein the protein is linear.

45. The immunomodulatory fusion protein of claim 1, wherein the IL-12 is at the C terminus and is operably linked to the linear polypeptide spacer, which is operably linked to collagen binding domain, which is operably linked to the IL-2 at the N terminus of the protein, and wherein the protein is linear.

46. The immunomodulatory fusion protein of claim 1, wherein the IL-12 is at the N terminus and is operably linked to the linear polypeptide spacer, which is operably linked to collagen binding domain, which is operably linked to the IL-2 at the C terminus of the protein, and wherein the protein is linear.

47. The immunomodulatory fusion protein of any one of claims 1-46, further comprising a second linear polypeptide spacer.

48. The immunomodulatory fusion protein of claim 47, wherein the IL-12 is at the N terminus and is operably linked to the first linear polypeptide spacer, which is operably linked to the collagen binding domain, which is operably linked to the second linear polypeptide spacer, which is operably linked to the IL-2 at the C terminus of the protein, and wherein the protein is linear.

49. The immunomodulatory fusion protein of claim 47, wherein the IL-12 is at the C terminus and is operably linked to the first linear polypeptide spacer, which is operably linked to the collagen binding domain, which is operably linked to the second linear polypeptide spacer, which is operably linked to the IL-2 at the N terminus of the protein, and wherein the protein is linear.

50. The immunomodulatory fusion protein of any one of claims 43-49, wherein the fusion protein is a continuous chain.

51. The immunomodulatory fusion protein of any one of claims 43-50, wherein the fusion protein is a continuous polypeptide chain.

52. The immunomodulatory fusion protein of any one of claims 1-51, wherein the collagen-binding domain comprises

- (i) a leucine-rich repeat from a human proteoglycan Class II member of the small leucine-rich proteoglycan (SLRP) family which comprises lumican; or
- (ii) a human type I glycoprotein having an Ig-like domain selected from LAIR1 and LAIR2.

53. The immunomodulatory fusion protein of claim 52, wherein the collagen-binding domain comprises lumican.
54. The immunomodulatory fusion protein of claim 53, wherein the lumican comprises at least about 80% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 11.
- 5 55. The immunomodulatory fusion protein of claim 52, wherein the collagen-binding domain comprises LAIR 1.
56. The immunomodulatory fusion protein of claim 55, wherein LAIR1 comprises at least about 80% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 13.
57. The immunomodulatory fusion protein of claim 55, wherein LAIR1 comprises at least  
10 80% identity to the amino acid sequence as set forth in SEQ ID NO: 14.
58. The immunomodulatory fusion protein of claim 52, wherein the collagen-binding domain comprises LAIR 2.
59. The immunomodulatory fusion protein of claim 58, wherein LAIR2 comprises at least 80% identity to the amino acid sequence as set forth in SEQ ID NO: 15.
- 15 60. The immunomodulatory fusion protein of any one of claims 1-59, wherein the IL-2 comprises human IL-2.
61. The immunomodulatory fusion protein of any one of claims 1-60, wherein the IL-2 comprises human wild-type IL-2.
62. The immunomodulatory fusion protein of any one of claims 1-61, wherein the IL-2  
20 comprises at least about 80% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 1.
63. The immunomodulatory fusion protein of any one of claims 1-62, wherein the IL-2 comprises at least about 80% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 2.
- 25 64. The immunomodulatory fusion protein of any one of claims 1-63, wherein the IL-12 comprises human IL-12.
65. The immunomodulatory fusion protein of any one of claims 1-64, wherein the IL-12 comprises human wild-type IL-12.
66. The immunomodulatory fusion protein of any one of claims 1-65, wherein the IL-12  
30 comprises at least about 80% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 5 or SEQ ID NO: 6.
67. The immunomodulatory fusion protein of any one of claims 1-66, wherein the linear polypeptide spacer is an albumin.

68. The immunomodulatory fusion protein of any one of claims 1-66, wherein the linear polypeptide spacer is an albumin binding domain.
69. The immunomodulatory fusion protein of claim 67, wherein the albumin comprises human albumin.
- 5 70. The immunomodulatory fusion protein of claim 67, wherein the albumin comprises human serum albumin.
71. The immunomodulatory fusion protein of claim 67, wherein the albumin comprises at least about 80% sequence identity to the amino acid sequence as set forth in SEQ ID NOs: 16-18.
72. The immunomodulatory fusion protein of claim 68, wherein the albumin binding domain  
10 comprises at least about 80% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 19.
73. The immunomodulatory fusion protein of any one of claims 1-72, wherein the molecular weight is at least 100-1000 kDa.
74. A pharmaceutical composition comprising an immunomodulatory fusion protein of any  
15 one of claims 1-73, and a pharmaceutically acceptable carrier.
75. A method for activating, enhancing or promoting a response by an immune cell in a subject or inhibiting, reducing or suppressing a response by an immune cell in a subject, comprising administering to a subject in need thereof, an effective amount of the pharmaceutical composition of claim 74.
- 20 76. A method for treating cancer, or reducing or inhibiting tumor growth, comprising administering to a subject in need thereof, an effective amount of the pharmaceutical composition of claim 74.
77. The method of claim 76, wherein the subject has at least one tumor.
78. The method of claim 77, wherein the composition is administered intratumorally (i.tu) or  
25 peritumorally (peri.tu) to the at least one tumor.
79. The method of claim 78, wherein the composition is administered by injection.
80. The method of of any one of claims 77-79, wherein the at least one tumor size is reduced or substantially identical to a reference standard.
81. The method of claim 80, wherein the reference standard is the size of the tumor prior to  
30 administration.
82. The method of of any one of claims 75-81, wherein the composition has an intratumoral retention  $t_{1/2}$  of more than 24 hours.
83. The method of claim 78, wherein twelve hours after intratumoral injection less than 25% of the injected dose is detected in the serum.

84. The method of any one of claims 77-83, wherein the at least one tumor has stromal CD8+ cytotoxic T cells (CTL)  $\leq 50$  cells/mm<sup>2</sup>.

85. The method of any one of claims 77-83, wherein the at least one tumor has stromal CD8+ cytotoxic T cells (CTL)  $\geq 50$  cells/mm<sup>2</sup> and intraepithelial compartment CD8+ cytotoxic T cells (CTL)  $\leq 500$  cells/mm<sup>2</sup>.

86. The method of any one of claims 77-83, wherein the at least one tumor has intraepithelial compartment CD8+ cytotoxic T cells (CTL)  $\geq 500$  cells/mm<sup>2</sup>.

87. The method of any one of claims 75-86, wherein the method does not result in cytokine release syndrome in the subject.

88. The method of any one of claims 75-87, wherein the subject does not experience grade 4 cytokine release syndrome.

89. A method for reducing or inhibiting tumor growth or treating cancer in a subject, the method comprising administering to a subject in need thereof, an effective amount of the pharmaceutical composition of claim 74, and an effective amount of a second composition

comprising (i) a tumor antigen-targeting antibody, (ii) a cancer vaccine, (iii) an immune checkpoint inhibitor, or (iv) an adoptive cell therapy, thereby reducing or inhibiting tumor growth or treating cancer in the subject.

90. The method of claim 89, wherein the tumor antigen is a tumor-associated antigen (TAA), a tumor specific antigen (TSA), or a tumor neoantigen and/or wherein the tumor antigen-targeting antibody specifically binds human HER-2/neu, EGFR, VEGFR, CD20, CD33, CD38 or antigen-binding fragment thereof.

91. The method of claim 89, wherein the cancer vaccine is a peptide comprising one or more tumor-associated antigens, or a population of cells immunized in vitro with a tumor antigen and administered to the subject.

92. The method of claim 89, wherein the immune checkpoint inhibitor is an antibody or antigen binding fragment thereof which binds PD-1, PD-L1, CTLA-4, LAG3, or TIM3.

93. The method of claim 89, wherein the immune effector cell comprises a chimeric antigen receptor (CAR) molecule which binds to a tumor antigen.

94. An immunomodulatory fusion protein comprising:

- (i) an IL-2;
- (ii) an IL-12;
- (iii) a LAIR2 collagen-binding domain,

wherein LAIR2 comprises at least 80% identity to the amino acid sequence as set forth in SEQ ID NO: 15; and

(iv) an albumin;

wherein the albumin comprises at least about 80% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 16-18.

5

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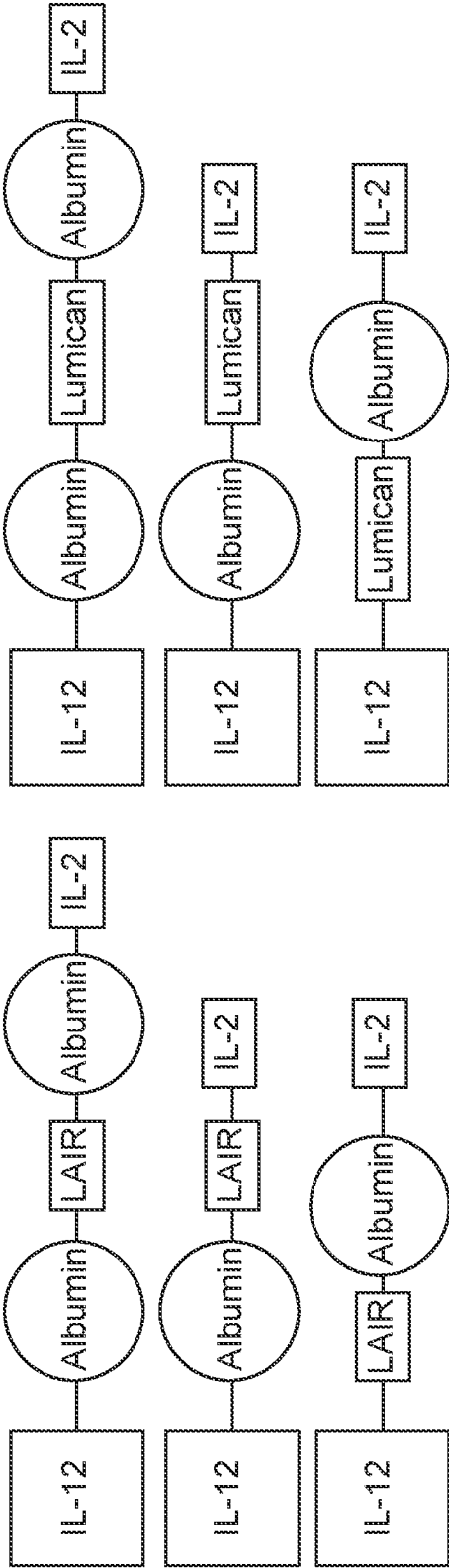


FIG. 1

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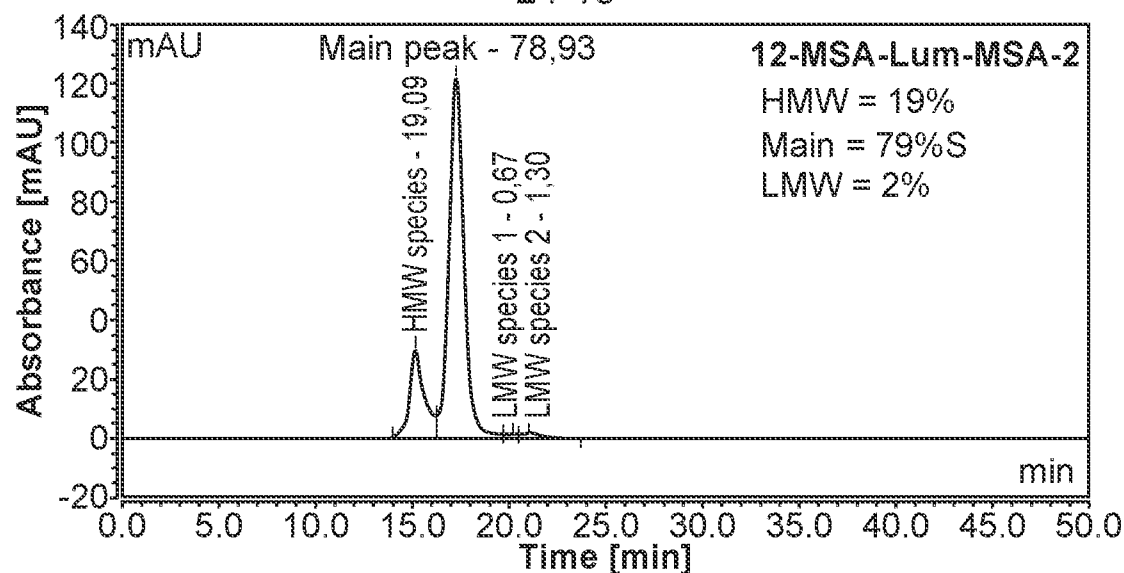


FIG. 2A

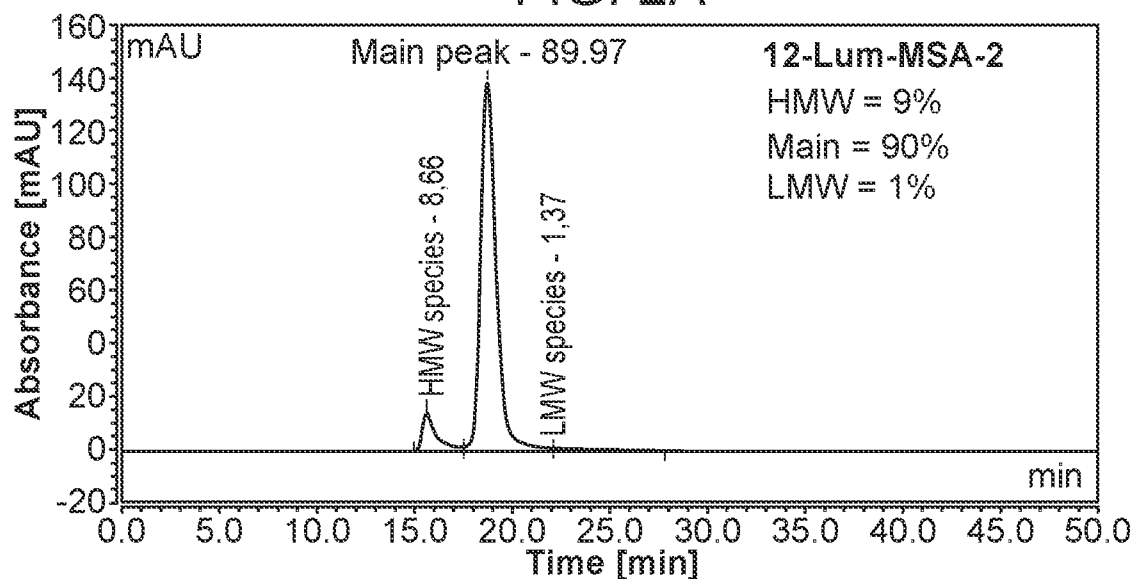


FIG. 2B

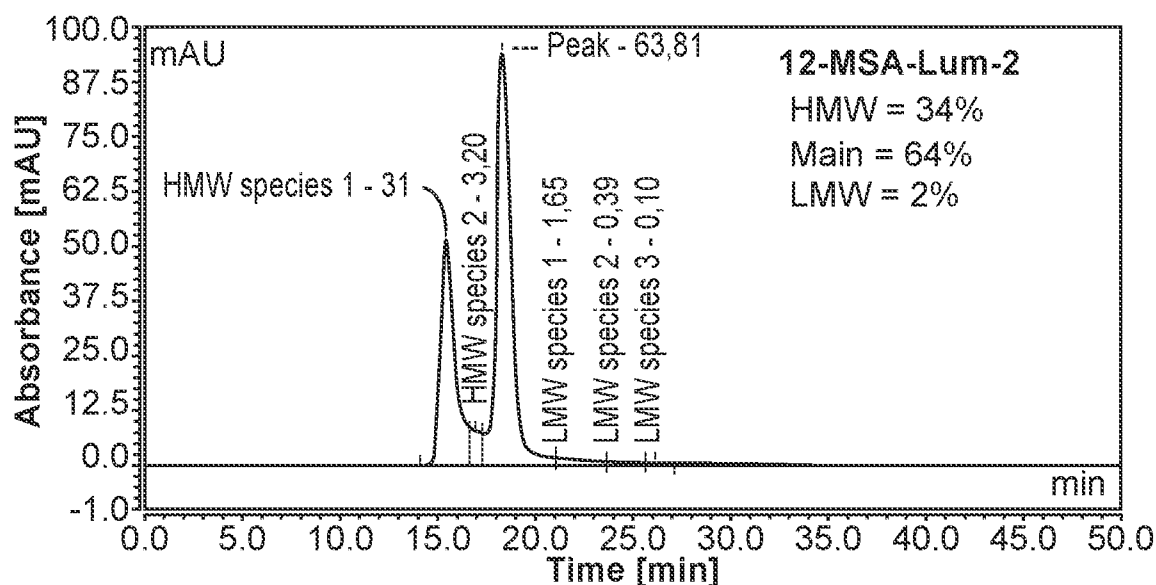


FIG. 2C

3 / 15

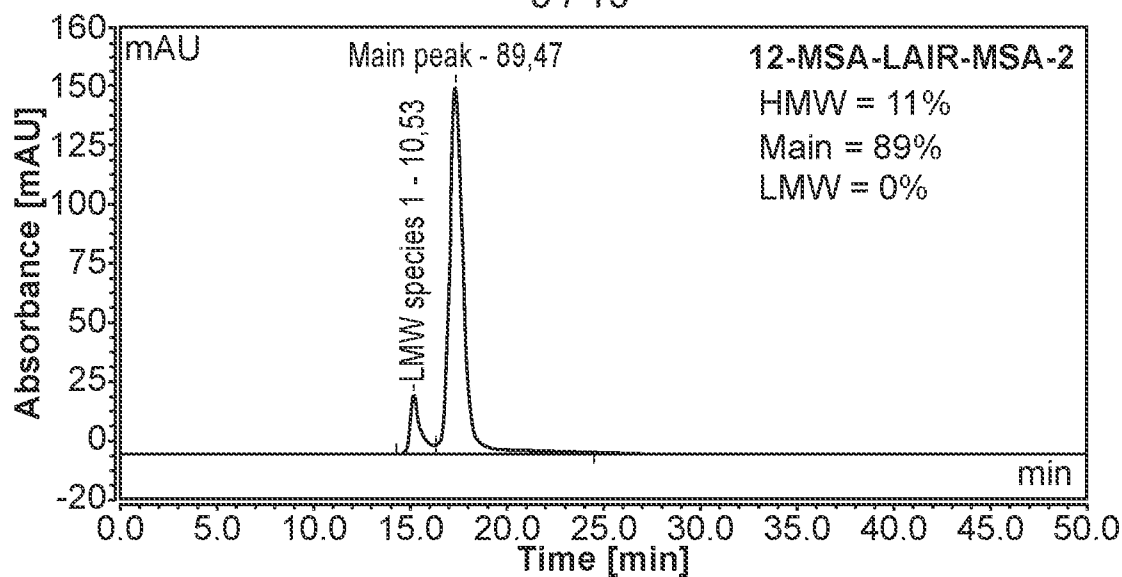


FIG. 2D

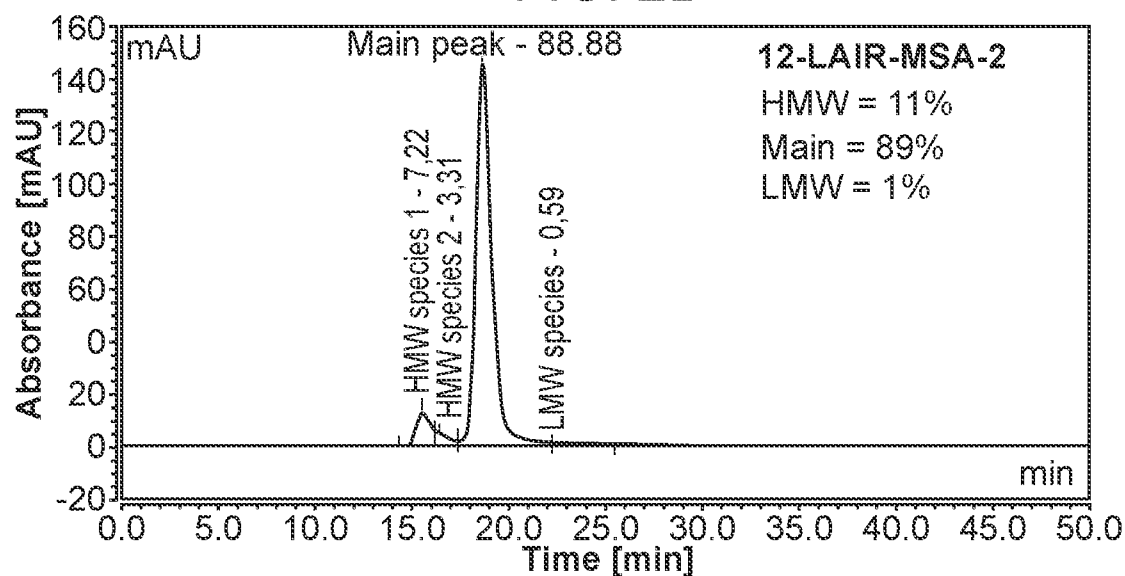


FIG. 2E

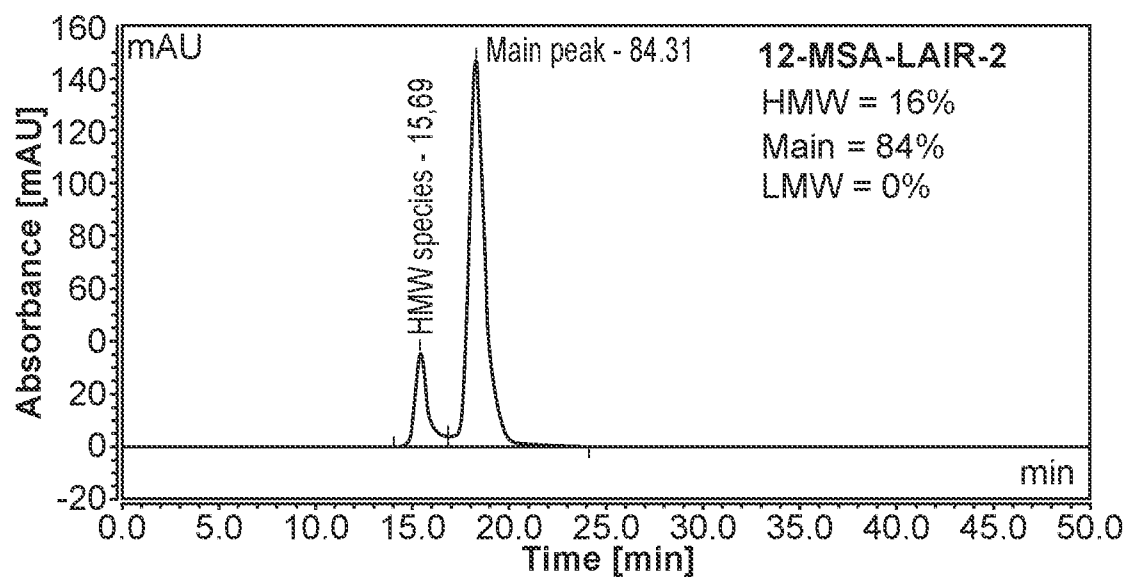


FIG. 2F

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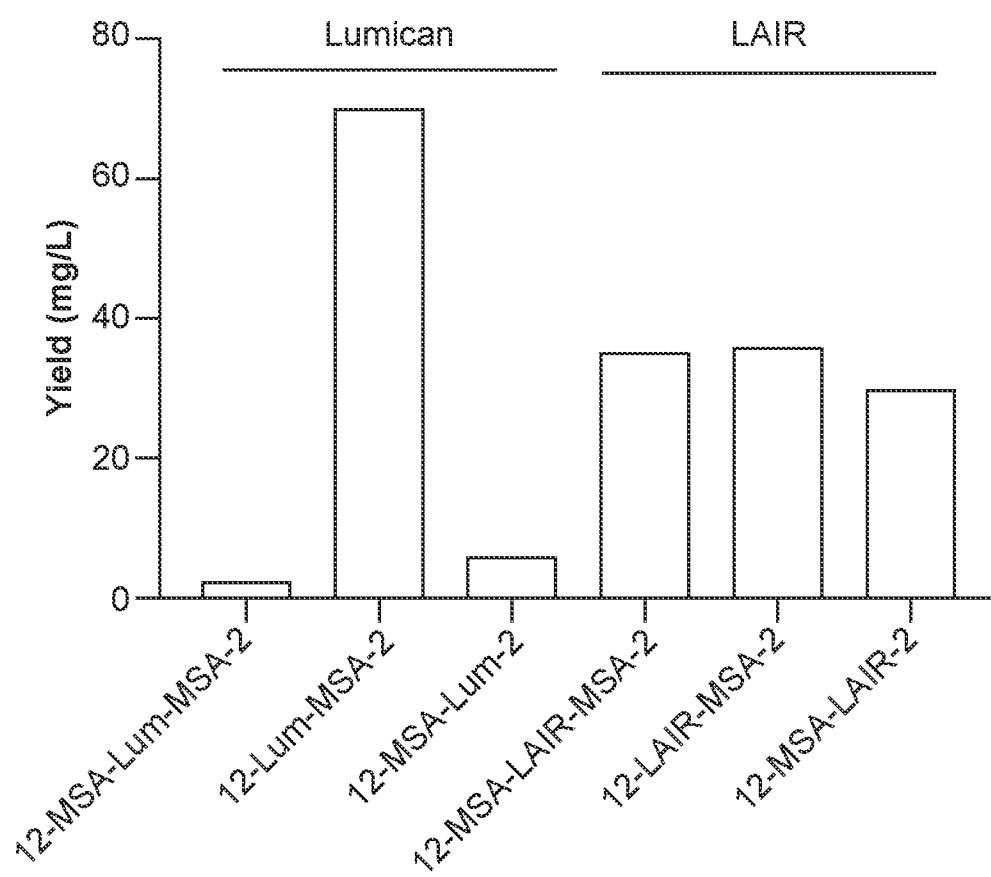


FIG. 3

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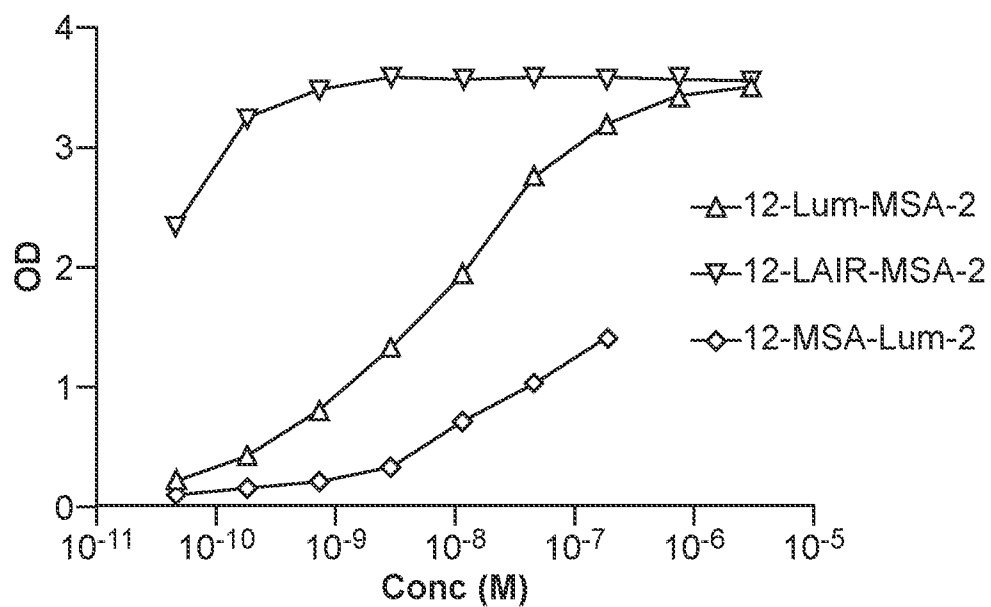


FIG. 4A

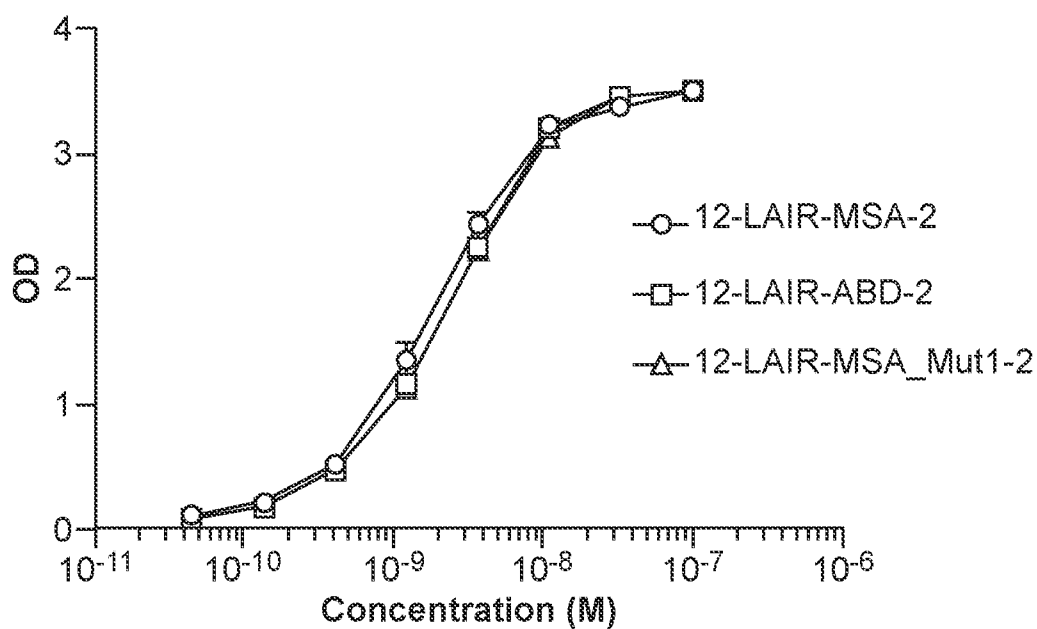


FIG. 4B

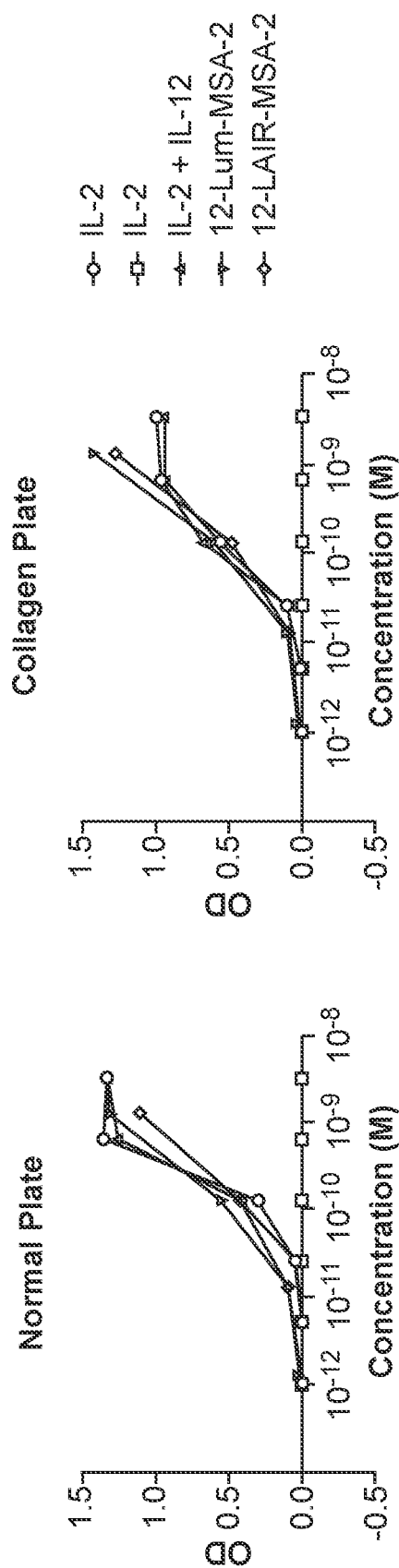


FIG. 5B

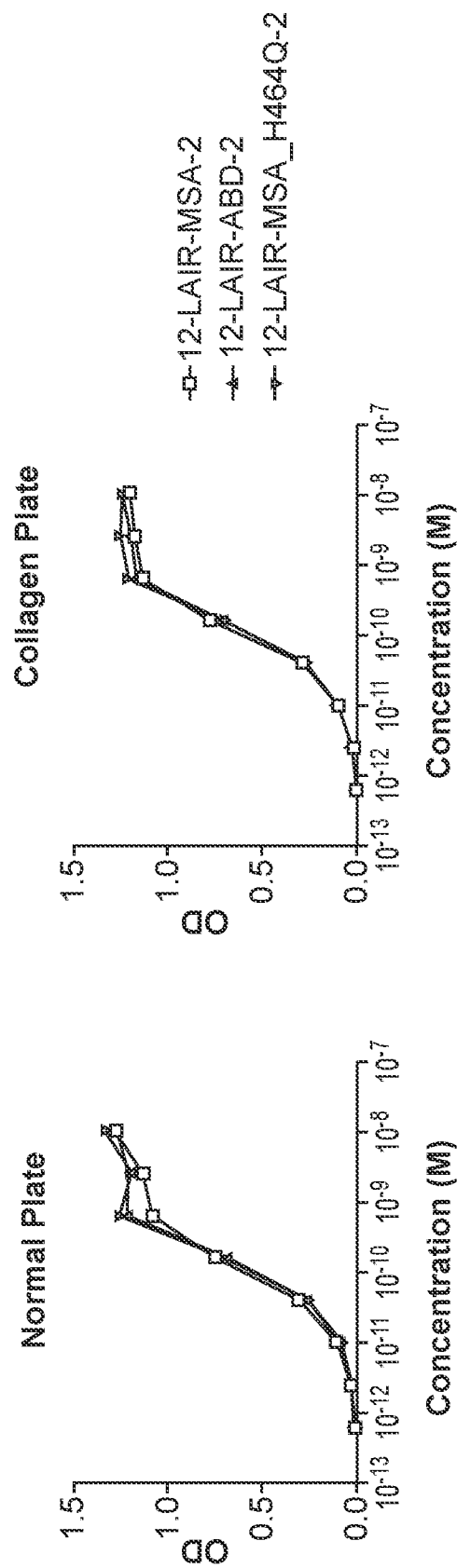


FIG. 5D

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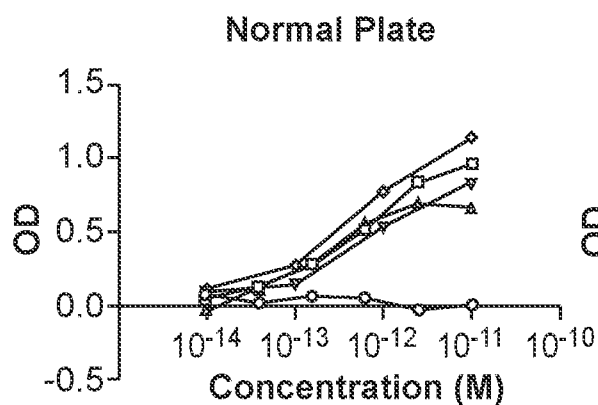


FIG. 6A

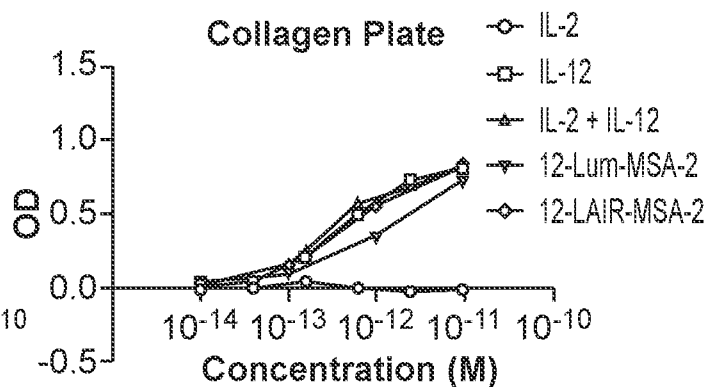


FIG. 6B

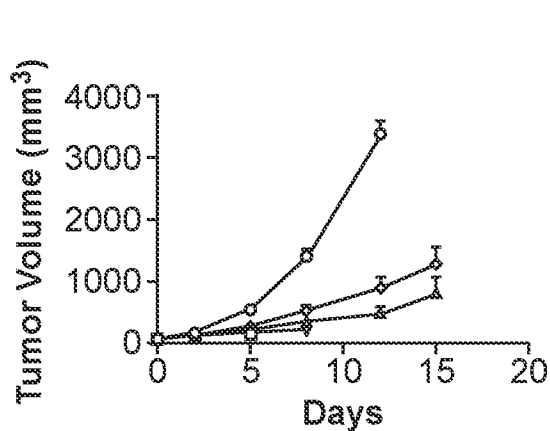


FIG. 7A

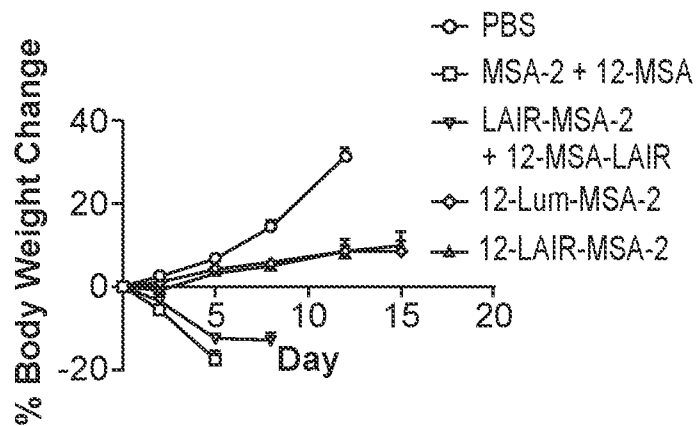


FIG. 7B

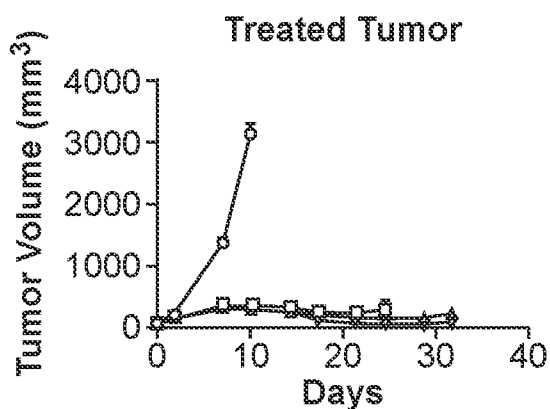


FIG. 8A

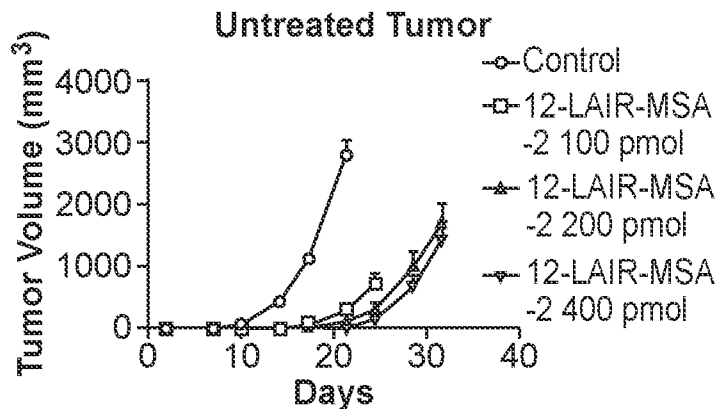


FIG. 8B

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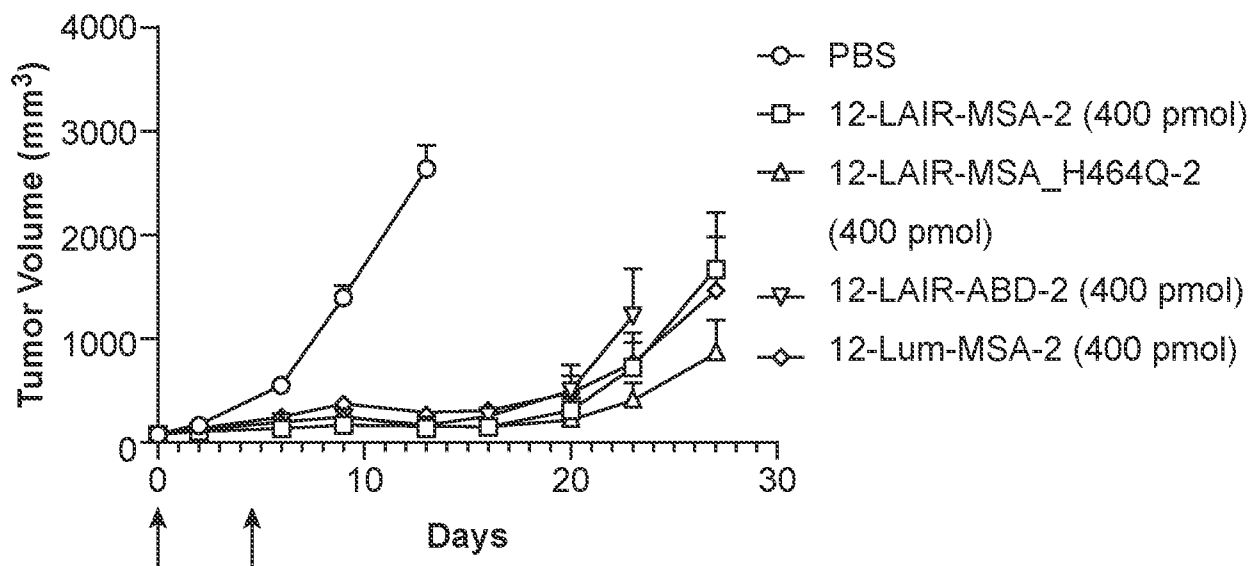


FIG. 9A

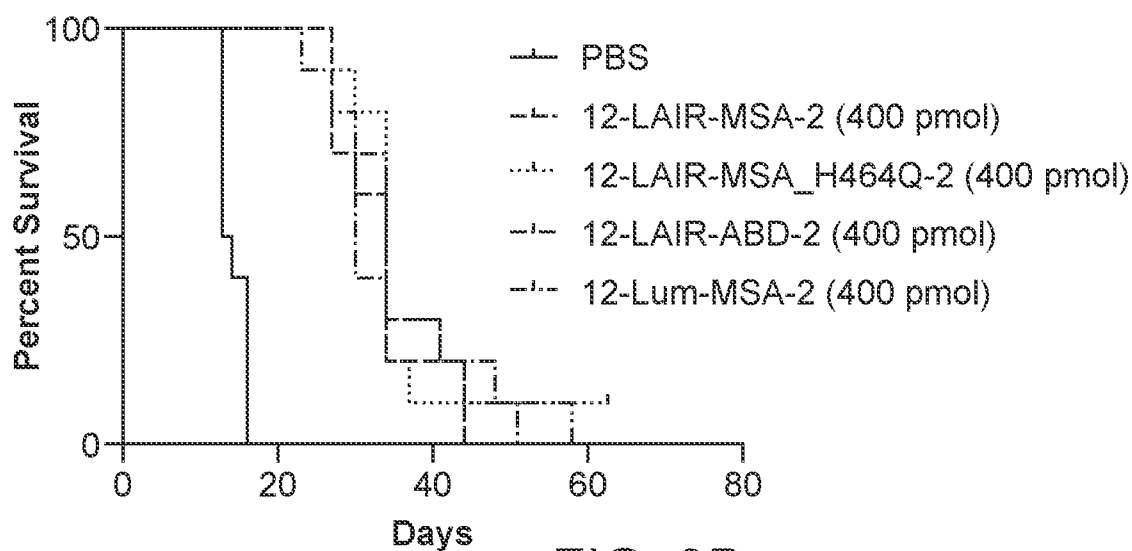


FIG. 9B

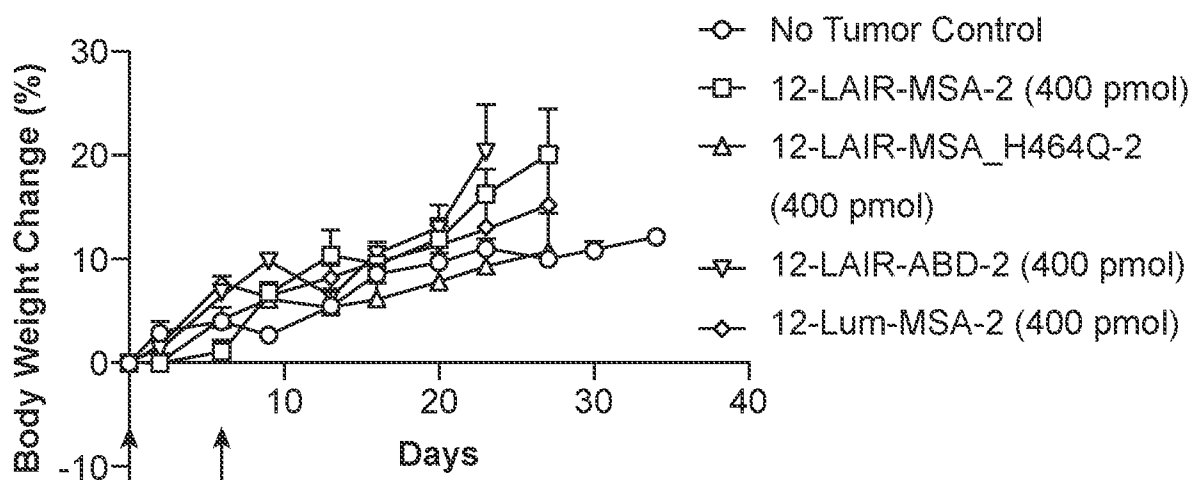


FIG. 9C

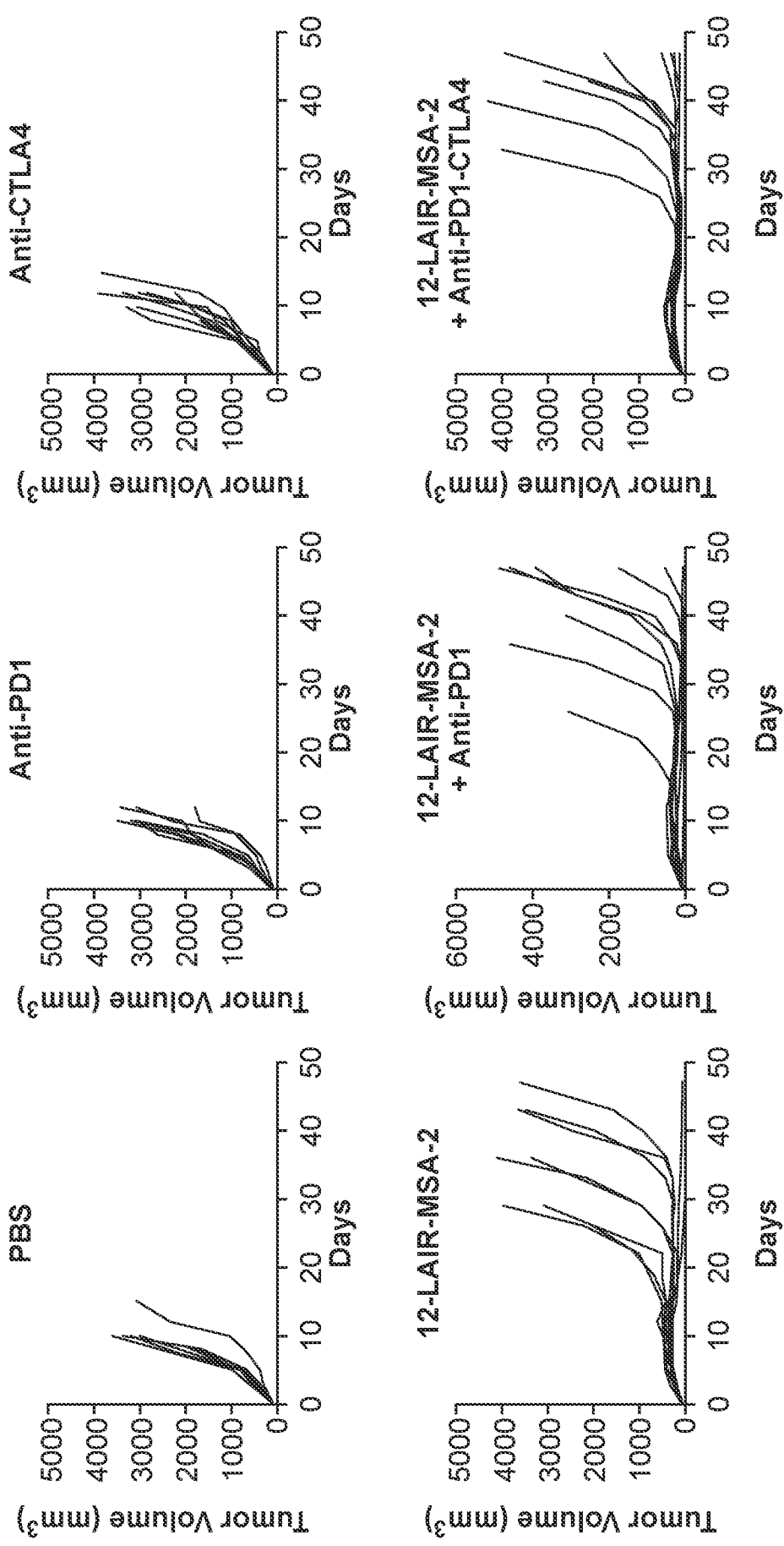


FIG. 10A

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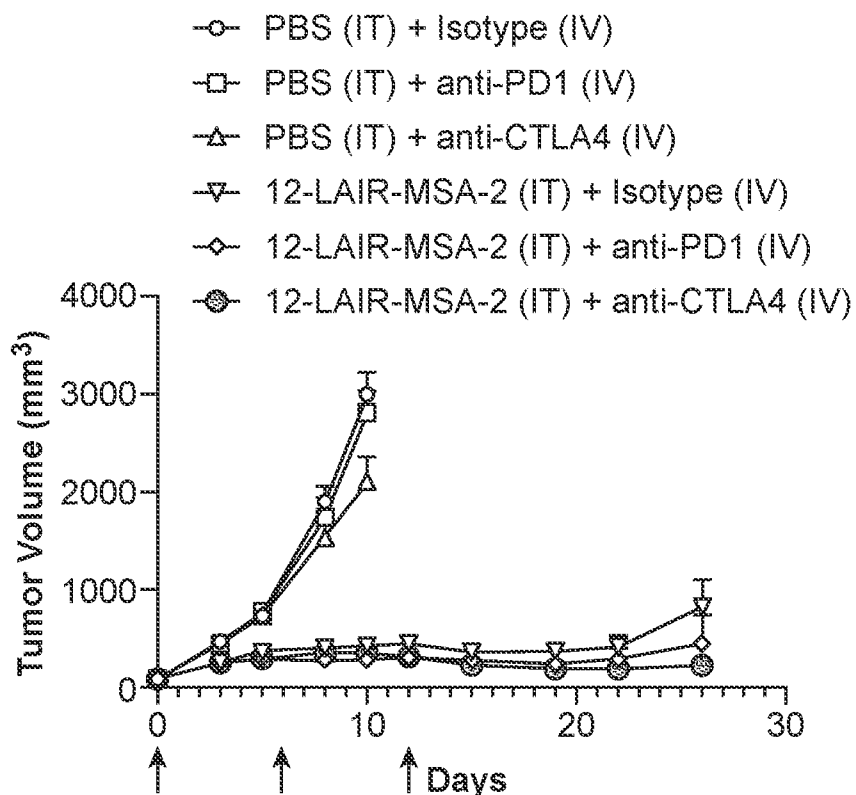


FIG. 10B

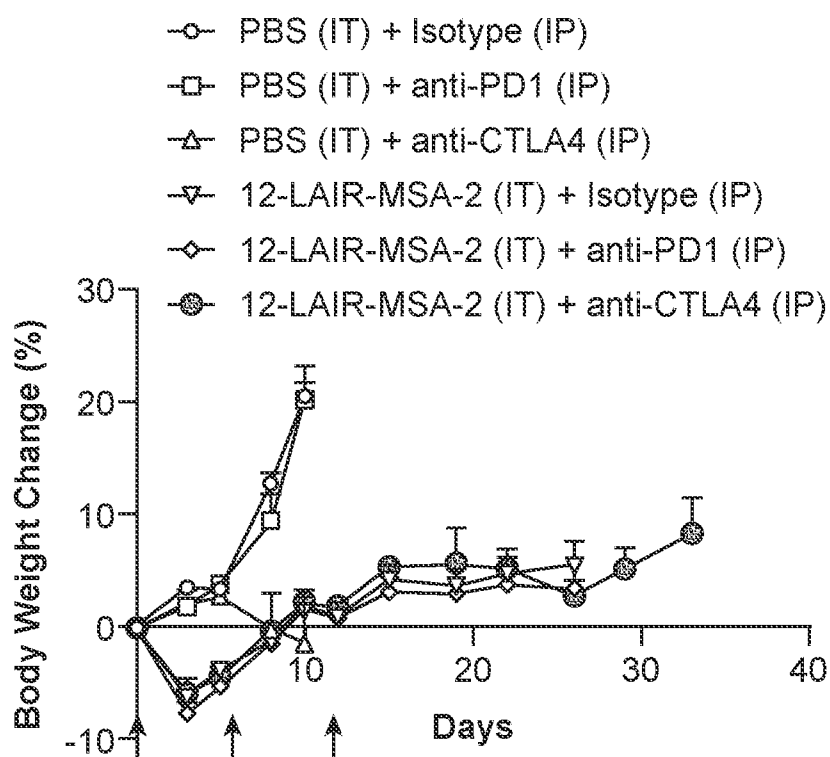


FIG. 10C

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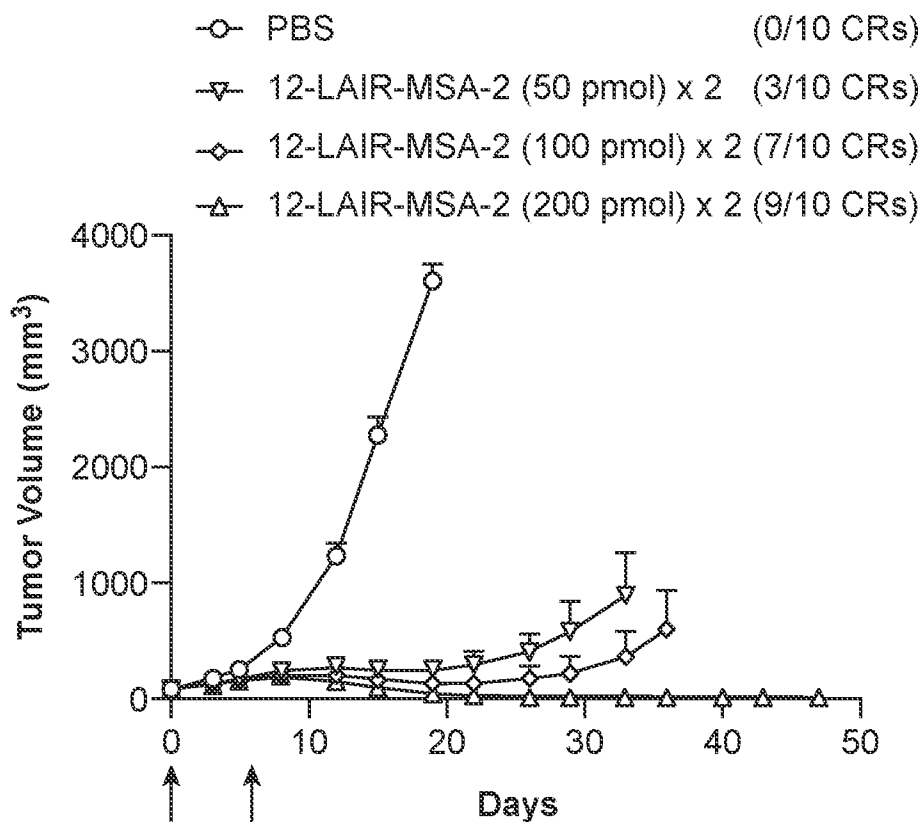


FIG. 11A

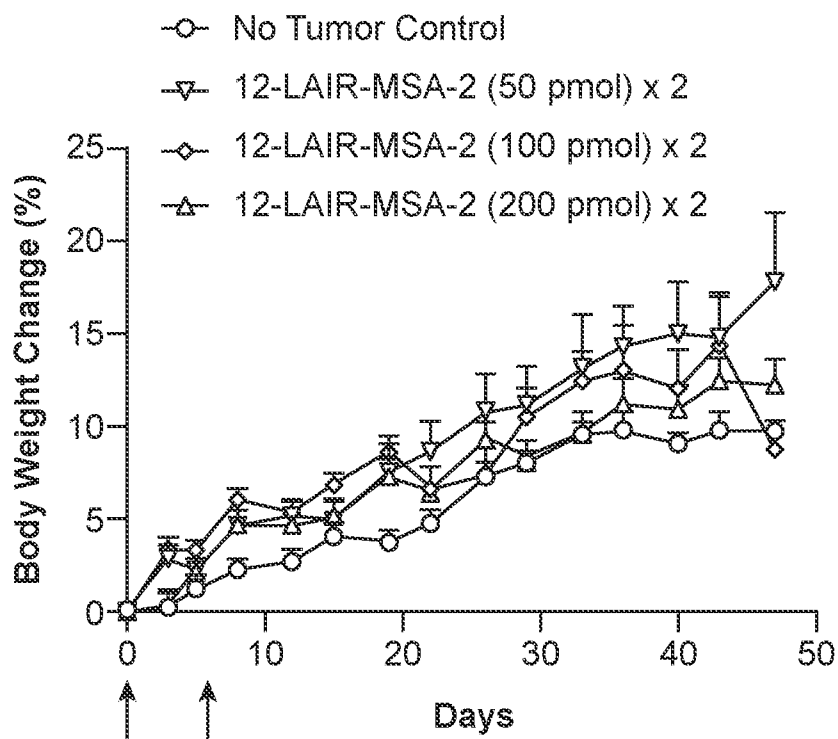


FIG. 11B

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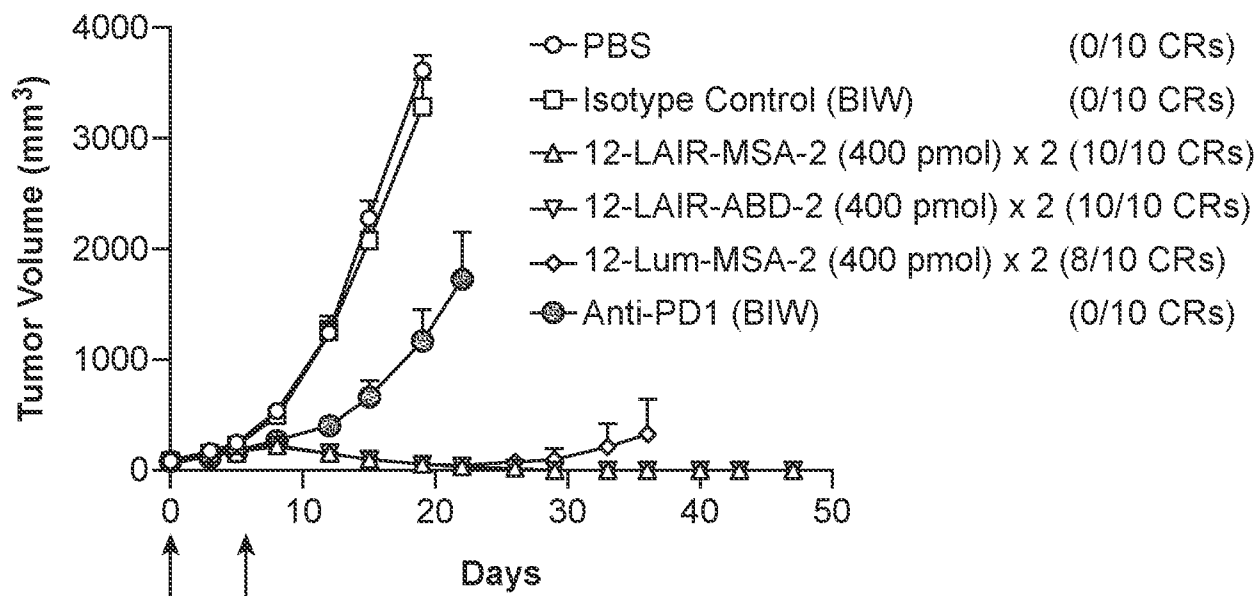


FIG. 12A

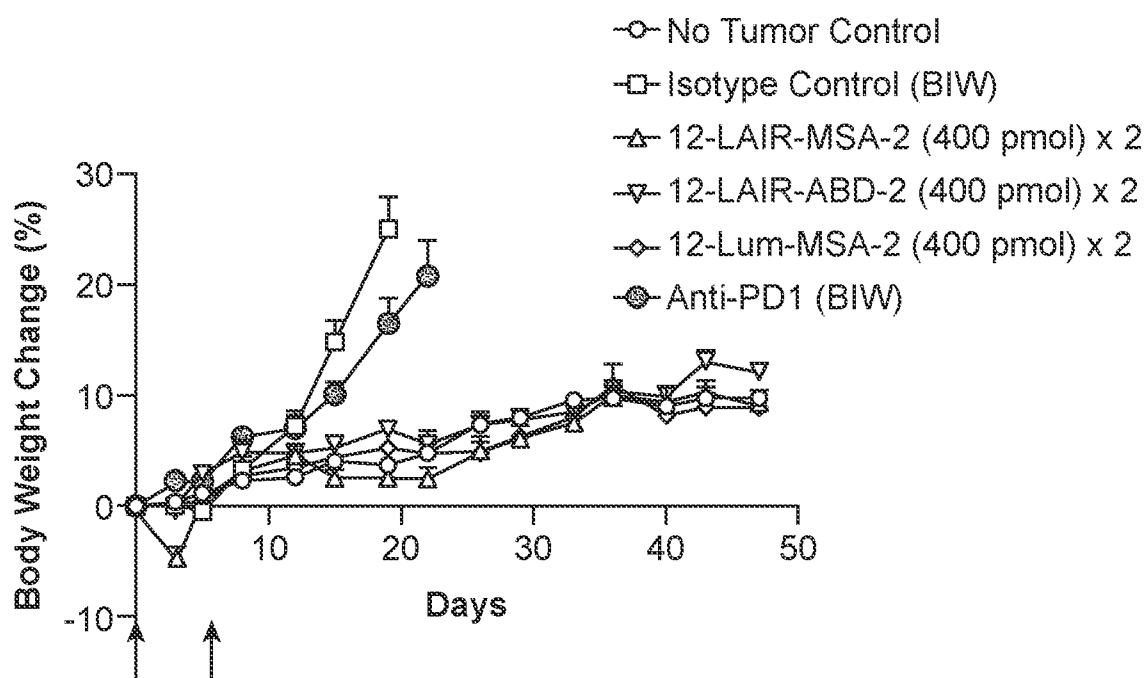


FIG. 12B

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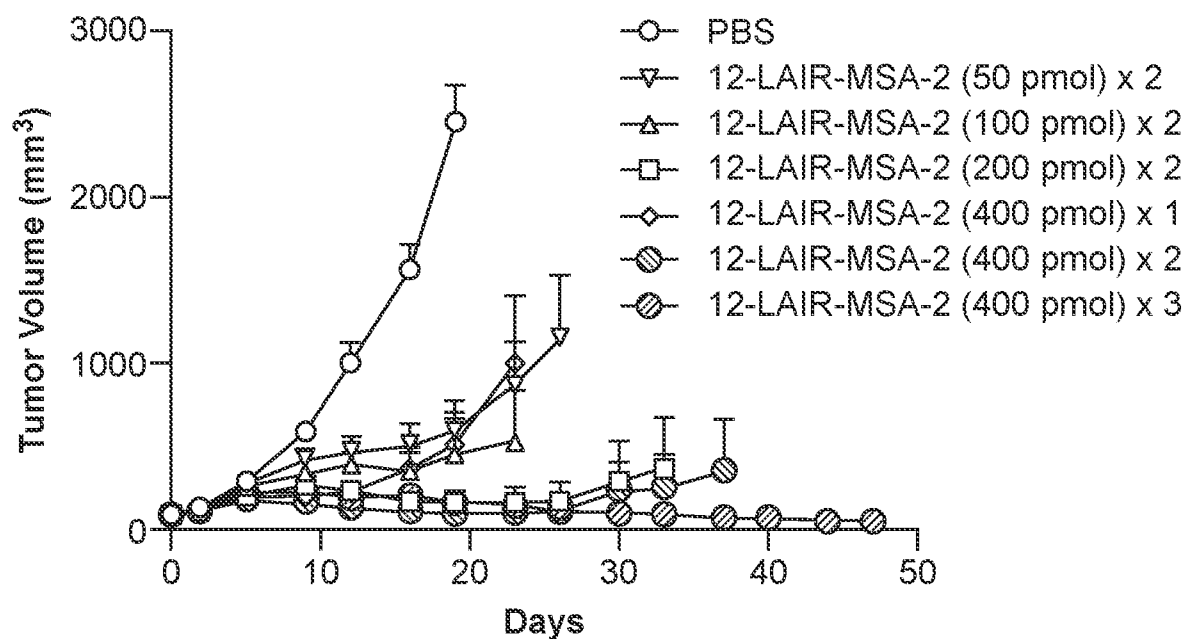


FIG. 13A

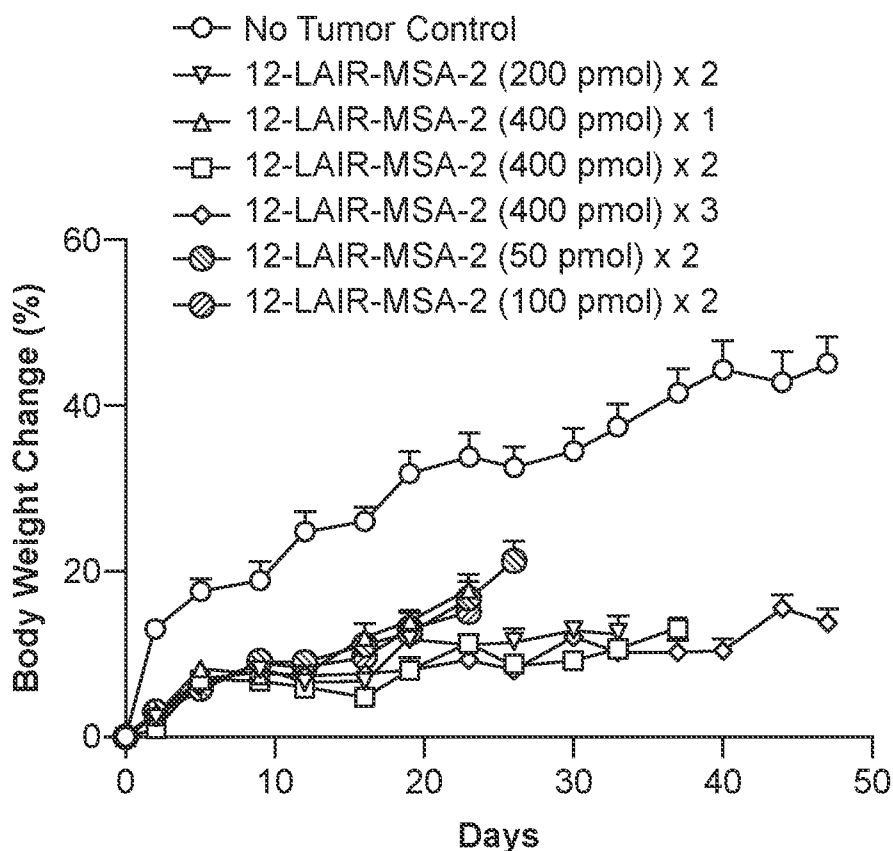


FIG. 13B

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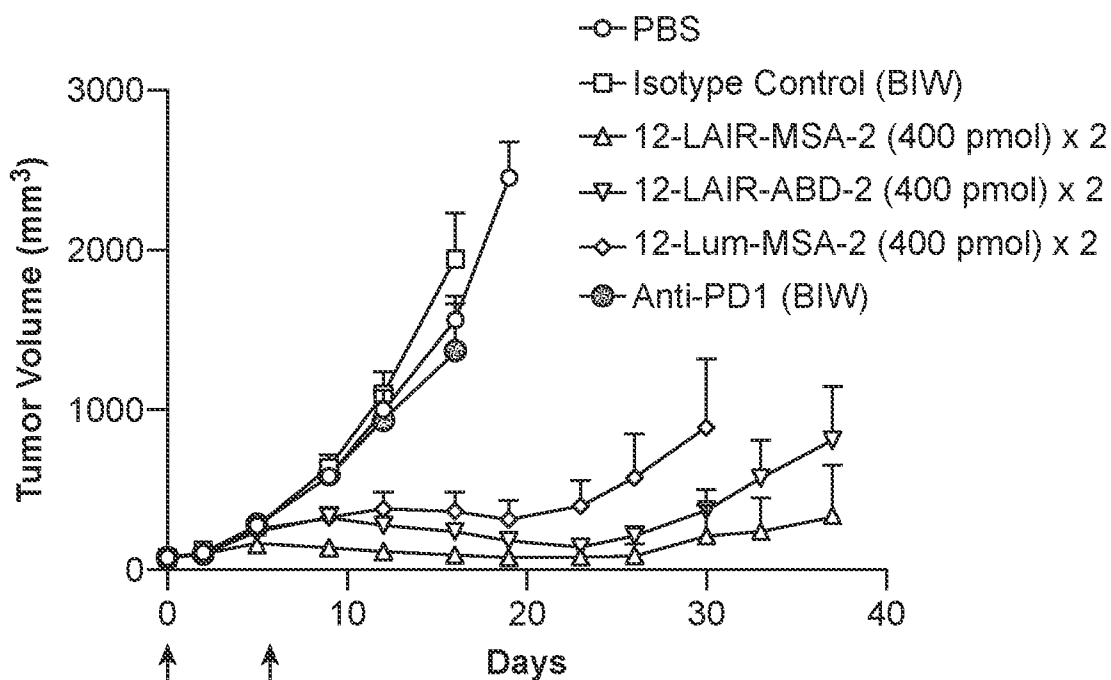


FIG. 14A

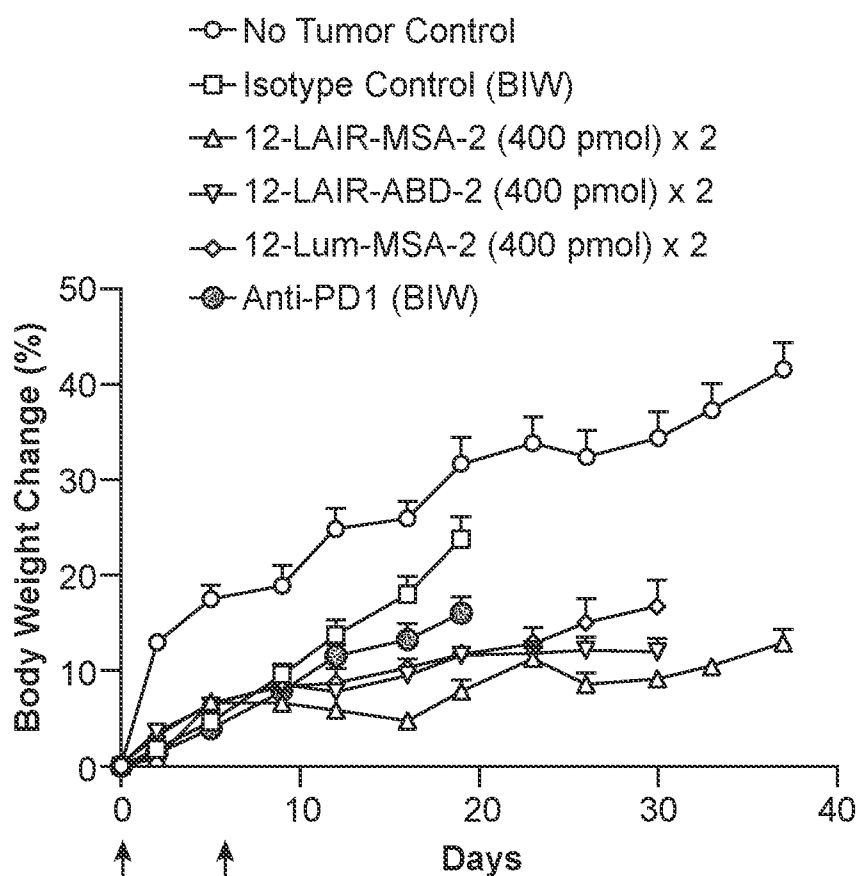


FIG. 14B

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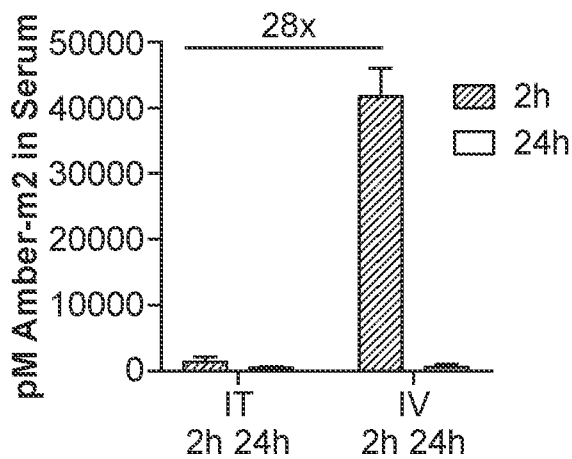


FIG. 15A

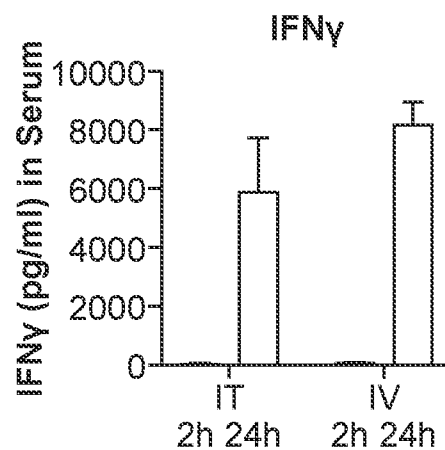


FIG. 15B

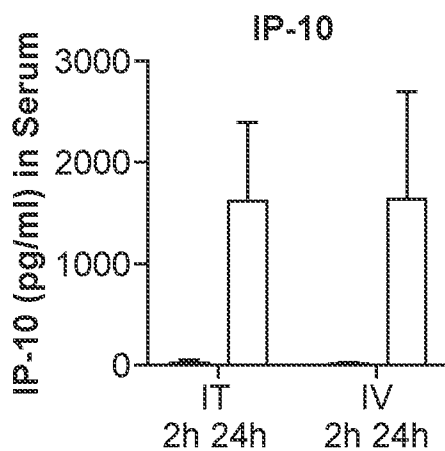


FIG. 15C

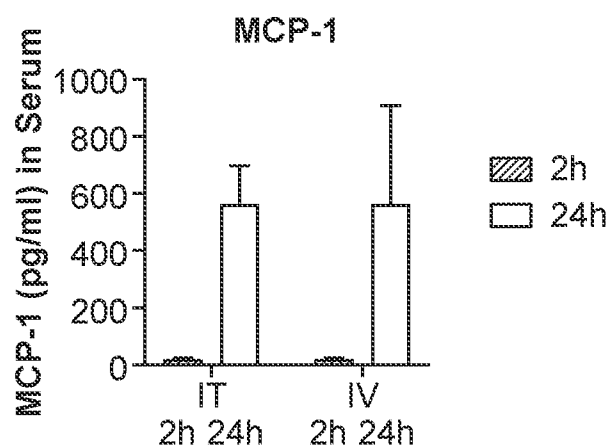


FIG. 15D

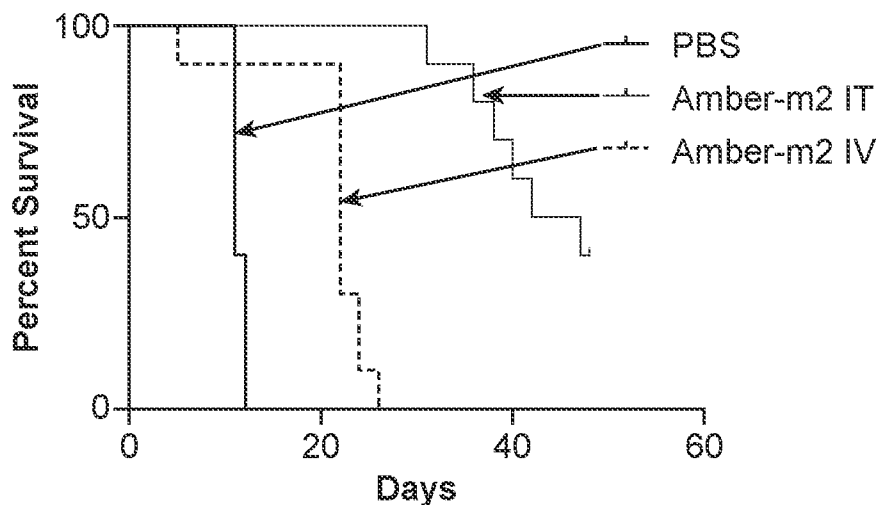


FIG. 15E

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2021/064224

## A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61K 38/00; A61K 38/19; A61K 38/20; C07K 14/52; C07K 14/54; C07K 14/55 (2022.01)

CPC - A61K 38/00; C07K 14/52; C07K 14/54; C07K 14/5434; C07K 14/55; C07K 2319/00 (2022.02)

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

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

see Search History document

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

see Search History document

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

see Search History document

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages                              | Relevant to claim No. |
|-----------|-----------------------------------------------------------------------------------------------------------------|-----------------------|
| Y         | US 2014/0316109 A1 (YANTAI ZHENGHAI BIO-TECHNOLOGY CO. LTD. et al) 23 October 2014 (23.10.2014) entire document | 1-3, 43-46            |
| Y         | US 2020/0283490 A1 (WEREWOLF THERAPEUTICS INC.) 10 September 2020 (10.09.2020) entire document                  | 1-3, 43-46, 94        |
| Y         | WO 2018/027039 A1 (NEXTCURE INC.) 08 February 2018 (08.02.2018) entire document                                 | 94                    |



Further documents are listed in the continuation of Box C.



See patent family annex.

\* Special categories of cited documents:

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

"D" document cited by the applicant in the international application

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

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

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

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

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

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

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

"&amp;" document member of the same patent family

Date of the actual completion of the international search

18 March 2022

Date of mailing of the international search report

MAR 30 2022

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US, Commissioner for Patents  
P.O. Box 1450, Alexandria, VA 22313-1450

Facsimile No. 571-273-8300

Authorized officer

Harry Kim

Telephone No. PCT Helpdesk: 571-272-4300

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2021/064224

## Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing:

- a. ☐ forming part of the international application as filed:
    - ☐ in the form of an Annex C/ST.25 text file.
    - ☐ on paper or in the form of an image file.
  - b. ☐ furnished together with the international application under PCT Rule 13ter.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.
  - c. ☒ furnished subsequent to the international filing date for the purposes of international search only:
    - ☒ in the form of an Annex C/ST.25 text file (Rule 13ter.1(a)).
    - ☐ on paper or in the form of an image file (Rule 13ter.1(b) and Administrative Instructions, Section 713).
2. ☒ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

SEQ ID NOs: 15-18 were searched

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2021/064224

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

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

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
  
2. ☐ Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
  
3. ☒ Claims Nos.: 4-42, 47-93  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
  
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

### Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.