polypeptide associate through the binding of the first domain and the second domain of the pair of affinity domains; and the first target-binding domain binds specifically to a ligand of TGF-β receptor II (TGF-βRII) and the second target-binding domain binds specifically to a ligand of TGF-βRII. In some examples of any of the methods described herein, the liver disease is selected from the group of: fatty liver disease, hepatic steatosis, acute hepatic porphyria, Alagille syndrome, alcohol-related liver disease, alpha-1 anti-trypsin deficiency, autoimmune hepatitis, benign liver tumors, cholangiocarcinoma, biliary atresia, Budd-Chiari syndrome, cirrhosis, Crigler-Najjar syndrome, galactosemia, Gilbert syndrome, hemochromatosis, hepatic encephalopathy, hepatitis A, hepatitis B, hepatitis C, hepatorenal syndrome, intrahepatic cholestasis of pregnancy (ICP), lysosomal acid lipase deficiency (LAL-D), liver cysts, liver cancer, newborn jaundice, non-alcoholic fatty liver disease, non-alcoholic steatohepatitis, primary biliary cholangitis (PBC), primary sclerosing cholangitis (PSC), progressive familial intrahepatic cholestasis (PFIC), Reye's syndrome, type 1 glycogen storage disease, and Wilson's disease. In some examples of any of the methods described herein, the metabolic syndrome is selected from the group of: coronary heart disease, pulmonary disease, gall bladder disease, dyslipidemia, hypertension, type 2 diabetes, dementia, cancer, gynecological abnormalities including polycystic ovarian syndrome, osteoarthritis, pancreatitis, idiopathic intracranial hypertension, stroke, and cataracts.

Also provided herein are methods of reducing one or more of the rate of: progression from non-alcoholic fatty liver disease (NAFL) to non-alcoholic steatohepatitis (NASH), progression from NASH to cirrhosis, and progression from cirrhosis to hepatocellular carcinoma, that include administering to a subject identified or diagnosed as having NAFL, NASH, or cirrhosis, a therapeutically effective amount of a multi-chain chimeric polypeptide comprising: (a) a first chimeric polypeptide comprising: (i) a first target-binding domain; (ii) soluble tissue factor domain; and (iii) a first domain of a pair of affinity domains; and (b) a second chimeric polypeptide comprising: (i) a second domain of a pair of affinity domains; and (ii) a second target-binding domain, where: the first chimeric polypeptide and the second chimeric polypeptide associate through the binding of the first domain and the second domain of the pair of affinity domains; and the first target-binding domain binds specifically to a

ligand of TGF-β receptor II (TGF-βRII) and the second target-binding domain binds specifically to a ligand of TGF-βRII. In some examples of any of the methods described herein, the method results in a decreasing in the rate of progression from NAFL to NASH. In some examples of any of the methods described herein, the method results in decreasing the rate of progression of NASH to cirrhosis. In some examples of any of the methods described herein, the method results in decreasing the rate of progression from cirrhosis to hepatocellular carcinoma.

Also provided herein are methods of reducing inflammation in a liver of a subject that include administering to the subject a therapeutically effective amount of a multi-chain chimeric polypeptide comprising: (a) a first chimeric polypeptide comprising: (i) a first target-binding domain; (ii) soluble tissue factor domain; and (iii) a first domain of a pair of affinity domains; and (b) a second chimeric polypeptide comprising: (i) a second domain of a pair of affinity domains; and (ii) a second target-binding domain, where: the first chimeric polypeptide and the second chimeric polypeptide associate through the binding of the first domain and the second domain of the pair of affinity domains; and the first target-binding domain binds specifically to a ligand of TGF-β receptor II (TGF-βRII) and the second target-binding domain binds specifically to a ligand of TGF-βRII. In one aspect, the present disclosure refers to use of a multi-chain chimeric polypeptide in the manufacture of a medicament for reducing inflammation in the liver of a subject, wherein the multi-chain chimeric polypeptide comprises: (a) a first chimeric polypeptide comprising: (i) a first target-binding domain; (ii) soluble tissue factor domain; and (iii) a first domain of a pair of affinity domains; (b) a second chimeric polypeptide comprising: (i) a second domain of a pair of affinity domains; and (ii) a second target-binding domain, wherein: the first chimeric polypeptide and the second chimeric polypeptide associate through the binding of the first domain and the second domain of the pair of affinity domains, wherein the pair of affinity domains comprises a soluble IL-15 and a sushi domain from an alpha chain of human IL-15 receptor (IL-15Rα); and wherein the first target-binding domain binds specifically to a ligand of TGF-β receptor II (TGF-βRII) and the second target-binding domain binds specifically to a ligand of TGF-βRII.

Also provided herein are methods of decreasing gluconeogenesis in a liver of a subject that include administering to the subject a therapeutically effective amount of a multi-chain chimeric polypeptide comprising: (a) a first chimeric polypeptide comprising: (i) a first target-binding domain; (ii) soluble tissue factor domain; and (iii) a first domain of a pair of affinity domains; and (b) a second chimeric polypeptide comprising: (i) a second domain of a pair of affinity domains; and (ii) a second target-binding domain, where: the first chimeric polypeptide and the second chimeric polypeptide associate through the binding of the first domain and the second domain of the pair of affinity domains; and the first target-binding domain binds specifically to a ligand of TGF-β receptor II (TGF-βRII) and the second target-binding domain binds specifically to a ligand of TGF-βRII.

Also provided herein are methods of decreasing lipogenesis in a liver of a subject that include administering to the subject a therapeutically effective amount of a multi-

chain chimeric polypeptide comprising: (a) a first chimeric polypeptide comprising: (i) a first target-binding domain; (ii) soluble tissue factor domain; and (iii) a first domain of a pair of affinity domains; and (b) a second chimeric polypeptide comprising: (i) a second domain of a pair of affinity domains; and (ii) a second target-binding domain, where: the first chimeric polypeptide and the second chimeric polypeptide associate through the binding of the first domain and the second domain of the pair of affinity domains; and the first target-binding domain binds specifically to a ligand of TGF-β receptor II (TGF-βRII) and the second target-binding domain binds specifically to a ligand of TGF-βRII.

Also provided herein are methods of decreasing hepatocytic senescence in a liver of a subject that include administering to the subject a therapeutically effective amount of a multi-chain chimeric polypeptide comprising: (a) a first chimeric polypeptide comprising: (i) a first target-binding domain; (ii) soluble tissue factor domain; and (iii) a first domain of a pair of affinity domains; and (b) a second chimeric polypeptide comprising: (i) a second domain of a pair of affinity domains; and (ii) a second target-binding domain, where: the first chimeric polypeptide and the second chimeric polypeptide associate through the binding of the first domain and the second domain of the pair of affinity domains; and the first target-binding domain binds specifically to a ligand of TGF-β receptor II (TGF-βRII) and the second target-binding domain binds specifically to a ligand of TGF-βRII.

In one aspect, the present disclosure refers to use of a multi-chain chimeric polypeptide in the manufacture of a medicament for decreasing chemical induced steatosis in a liver of a subject, wherein the multi-chain chimeric polypeptide comprises: (a) a first chimeric polypeptide comprising: (i) a first target-binding domain; (ii) soluble tissue factor domain; and (iii) a first domain of a pair of affinity domains; (b) a second chimeric polypeptide comprising: (i) a second domain of a pair of affinity domains; and (ii) a second target-binding domain, wherein: the first chimeric polypeptide and the second chimeric polypeptide associate through the binding of the first domain and the second domain of the pair of affinity domains, wherein the pair of affinity domains comprises a soluble IL-15 and a sushi domain from an alpha chain of human IL-15 receptor (IL-15Rα); and wherein the first target-binding domain binds specifically to a ligand of TGF-β receptor II (TGF-βRII) and the second target-binding domain binds specifically to a ligand of TGF-βRII.

Also provided herein are methods of rebalancing metabolic function in a liver of a subject that include administering to the subject a therapeutically effective amount of a multi-chain chimeric polypeptide comprising: (a) a first chimeric polypeptide comprising: (i) a first target-binding domain; (ii) soluble tissue factor domain; and (iii) a first domain of a pair of affinity domains; and (b) a second chimeric polypeptide comprising: (i) a second domain of a pair of affinity domains; and (ii) a second target-binding domain, where: the first chimeric polypeptide and the second chimeric polypeptide associate through the binding of the first domain and the second domain of the pair of affinity domains; and the first target-binding domain binds specifically to a ligand of TGF-β receptor II (TGF-βRII) and the second target-binding domain binds specifically to a ligand of TGF-βRII.

Also provided herein are methods of modulating expression of one or more genes in Tables 1-4 in a liver of a subject that include administering to the subject a therapeutically effective amount of a multi-chain chimeric polypeptide comprising: (a) a first chimeric polypeptide comprising: (i) a first target-binding domain; (ii) soluble tissue factor domain; and (iii) a first domain of a pair of affinity domains; and (b) a second chimeric polypeptide comprising: (i) a second domain of a pair of affinity domains; and (ii) a second target-binding domain, where: the first chimeric polypeptide and the second chimeric polypeptide associate through the binding of the first domain and the second domain of the pair of affinity domains; and the first target-binding domain binds specifically to a ligand of TGF-β receptor II (TGF-βRII) and the second target-binding domain binds specifically to a ligand of TGF-βRII. In some examples of any of the methods described herein, the administering results in a decrease in the expression of one or more genes in the liver of the subject selected from the group consisting of: ACSS1, RETN, SLC2A4, PDK4, PNPLA3, GADD45B, PPARGC1A, CAV1, ENDOD1, REG3G, IGHG3, IGHG2B, SCGB3A1, GLYCAM1, IGHG2C, IGKC, LTF, MS4A1, JCHAIN, CD19, IGHM, IFI27L2A, ACKR3, LSP1, PMEPA1, CORO1A, GPX3, MYH8, NPPA, TCAP, FLNC, SLC36A2, MYH6, ACTC1, ACTA2, and TPM2, as compared to the level of expression of the one or more genes in the subject prior to the administering. In some examples of any of the methods described herein, the administering results in an increase in the expression of one or more genes in the liver of the subject selected from the group consisting of: SLC34A2, and CISH, as compared to the level of expression of the one or more genes in the subject prior to the administering. In some examples of any of the methods described herein, the administering results in a decrease in the expression of one or more genes in the liver of the subject selected from the group consisting of: CSF3R, IFI27L2A, GM17066, GNL3, FABP1, GM14303, AURKA, RPL14-PS1, QTRT2, G6PC, C8B, DYNLL1, LCN2, LRG1, CEBPD, COL4A3, ST3GAL5, RSAD2, 9330162G02RIK, PINX1, SRA1, SPATA2L, PNRC1, MUP20, IL6RA, APOA1, IL1B, WDR54, CTCFLOS, GM16973, 4632427E13RIK, IGHG2B, TGFB1I1, SELENBP2, SEMA6B, NEXN, ZFP653, NOB1, PCK1, FAM25C, MAPK15, GM16551, ESM1, RPL37RT, FAM133B, PDE8B, TUT1, S100A11, PDILT, PPARD, IER2, GM15401, MX2, WNK4, G0S2, BC005561, AA986860, JDP2,

GM26982, NOP58, ACTB, GM14586, RPP38, GM13436, NT5DC2, IMPDH1, CYTIP, AI846148, CHKA, GM37963, NR0B2, CYP4A32, ALKBH2, FAU-PS2, PPP1R15A, KLF2, SLC25A22, GM13341, IGHM, SATB1, SNRPF, DNASE1L2, CD3EAP, GM2788, DANCR, ZFP612, NOP56, JUND, ID1, HSPB1, KLHDC8A, KLF10, ANGPT2, THBS1, GM44891, GM9752, ABLIM3, PTGES, GM28438, 2410002F23RIK, FOSL2, CRIP3, JUN, ALAS1, GM2000, RHOC, LMCD1, GM2061, GM42595, GM11478, IKZF2, PNLDC1, COMTD1, SNORA31, COL20A1, AKAP12, C1QTNF12, 1810032O08RIK, 2310033P09RIK, GM47528, SERPINE2, NPFF, SERPINA3K, RFXANK, IGKV5-39, NAB2, MAFF, CEP85, CSAD, LTB4R1, 1810012K08RIK, BCL7C, NRBP2, NLE1, ALKBH1, ARID5A, CFAP43, GM45767, CD8A, PPRC1, GM26870, TMC7, BCL6B, GM16348, GM26981, SLC16A3, TNFRSF12A, CYP2J9, NR4A2, MMP9, MIR17HG, TMEM191C, PCDH11X, HILPDA, RAPGEF4, GM17300, SLC25A47, KCNJ2, NYAP1, LAX1, RPS19-PS3, HES1, RGS16, DUSP1, GM43323, ASB4, MUC6, GM15502, UNG, FOXQ1, GM17936, UBE2C, SLC16A6, MIR7052, NLRP12, GM14286, FGF21, KLF5, GM37969, PF4, GM21738, HOTAIRM1, GM6493, LOR, MFSD2B, MATK, SYNE4, GM44694, TRBC1, GM37274, PLN, CXCR4, PHF24, SNORD104, SERPINA7, RGS4, TCIM, EGFR, GM37760, FBXL22, TEDC2, ENHO, GM26917, GM43775, 4833411C07RIK, GM45053, INHBB, OPN3, SNHG15, B230206H07RIK, KCNE3, GM43305, C530043K16RIK, KLF4, LEPR, JCHAIN, TSKU, LGALS4, PCP4L1, GM44829, DUSP8, GM44620, IGFBP1, JUNB, GM32017, GM2814, GM37144, MYADML2OS, GM37666, HDC, SLFN4, A530041M06RIK, GM43359, GM2602, GM10277, FAM222A, FOXA3, AOC2, SERPINA1E, CTXN1, RAPGEF4OS2, SOCS2, PPAN, PRKAG2OS1, GADD45B, HOXA5, GRHL1, EIF4EBP3, OSGIN1, GM28513, MAP3K6, SLC34A2, B630019A10RIK, IGKC, PLIN4, ANGPTL4, DUSP5, EGR1, GM42507, GM14257, APOLD1, IER3, ZBTB16, GM37033, IGLC1, GADD45G, IGLC3, GM45244, RGS1, CXCL1, RNF225, GM44005, ANKRD37, NR4A1, GM8893, GM26762, CDKN1A, 5330406M23RIK, IGLV1, IGKV3-2, FOS, GM43637, IGKV3-10, S100A9, GM15622, S100A8, MT1, RETNLG, MT2, IGKV19-93, GM45774, and SERPINA4-PS1, as compared to the level of expression of the one or more genes in the subject prior to the administering. In some examples of any of the methods described

COL15A1, PCDH12, IRS1, ASCC3, KIF16B, and MR1, as compared to the level of expression of the one or more genes in the subject prior to the administering.

In some examples of any of the methods described herein, the subject has been previously identified or diagnosed as having a liver disease or a metabolic syndrome. In some examples of any of the methods described herein, the subject has been previously identified or diagnosed as having a liver disease. In some examples of any of the metthods described herein, the liver disease is selected from the group of: fatty liver disease, hepatic steatosis, acute hepatic porphyria, Alagille syndrome, alcohol-related liver disease, alpha-1 anti-trypsin deficiency, autoimmune hepatitis, benign liver tumors, cholangiocarcinoma, biliary atresia, Budd-Chiari syndrome, cirrhosis, Crigler-Najjar syndrome, galactosemia, Gilbert syndrome, hemochromatosis, hepatic encephalopathy, hepatitis A, hepatitis B, hepatitis C, hepatorenal syndrome, intrahepatic cholestasis of pregnancy (ICP), lysosomal acid lipase deficiency (LAL-D), liver cysts, liver cancer, newborn jaundice, non-alcoholic fatty liver disease, non-alcoholic steatohepatitis, primary biliary cholangitis (PBC), primary sclerosing cholangitis (PSC), progressive familial intrahepatic cholestasis (PFIC), Reye's syndrome, type 1 glycogen storage disease, and Wilson's disease. In some examples of any of the methods described herein, the subject has been previously identified or diagnosed as having a metabolic syndrome. In some examples of any of the methods described herein, the metabolic syndrome is selected from the group consisting of: coronary heart disease, pulmonary disease, gall bladder disease, dyslipidemia, hypertension, type 2 diabetes, dementia, cancer, gynecological abnormalities including polycystic ovarian syndrome, osteoarthritis, pancreatitis, idiopathic intracranial hypertension, stroke, and cataracts.

In some examples of any of the methods described herein, the first target-binding domain and the soluble tissue factor domain directly abut each other in the first chimeric polypeptide. In some examples of any of the methods described herein, the first chimeric polypeptide further comprises a linker sequence between the first target-binding domain and the soluble tissue factor domain in the first chimeric polypeptide. In some examples of any of the methods described herein, the soluble tissue factor domain and the first domain of the pair of affinity domains directly abut each other in the first chimeric polypeptide. In some examples of any of the methods described herein,

the first chimeric polypeptide further comprises a linker sequence between the soluble tissue factor domain and the first domain of the pair of affinity domains in the first chimeric polypeptide.

In some examples of any of the methods described herein, the second domain of the pair of affinity domains and the second target-binding domain directly abut each other in the second chimeric polypeptide. In some examples of any of the methods described herein, the second chimeric polypeptide further comprises a linker sequence between the second domain of the pair of affinity domains and the second target-binding domain in the second chimeric polypeptide.

In some examples of any of the methods described herein, one or both of the first target-binding domain and the second target-binding domain is an antigen-binding domain. In some examples of any of the methods described herein, one or both of the first target-binding domain and the second target-binding domain is a soluble interleukin or cytokine receptor.

In some examples of any of the methods described herein, the first chimeric polypeptide further comprises one or more additional target-binding domain(s). In some examples of any of the methods described herein, the second chimeric polypeptide further comprises one or more additional target-binding domain(s).

In some examples of any of the methods described herein, the soluble tissue factor domain is a soluble human tissue factor domain. In some examples of any of the methods described herein, the soluble human tissue factor domain comprises a sequence that is at least 80% identical to SEQ ID NO: 1. In some examples of any of the methods described herein, the pair of affinity domains is a sushi domain from an alpha chain of human IL-15 receptor (IL-15Rα) and a soluble IL-15.

In some examples of any of the methods described herein, the first target-binding domain comprises a soluble TGF-βRII. In some examples of any of the methods described herein, the first target-binding domain comprises a first sequence that is at least 80% identical to SEQ ID NO: 2 and a second sequence that is at least 80% identical to SEQ ID NO: 2, wherein the first and second sequence are separated by a linker. In some examples of any of the methods described herein, the first target-binding domain comprises a first sequence that is at least 90% identical to SEQ ID NO: 2

and a second sequence that is at least 90% identical to SEQ ID NO: 2. In some examples of any of the methods described herein, the first target-binding domain comprises a first sequence of SEQ ID NO: 2 and a second sequence of SEQ ID NO: 2. In some examples of any of the methods described herein, the linker comprises a sequence of SEQ ID NO: 3. In some examples of any of the methods described herein, the first target-binding domain comprises a sequence that is at least 80% identical to SEQ ID NO: 4. In some examples of any of the methods described herein, the first target-binding domain comprises a sequence that is at least 90% identical to SEQ ID NO: 4. In some examples of any of the methods described herein, the first target-binding domain comprises a sequence of SEQ ID NO: 4. In some examples of any of the methods described herein, the first chimeric polypeptide comprises a sequence that is at least 80% identical to SEQ ID NO: 6. In some examples of any of the methods described herein, the first chimeric polypeptide comprises a sequence that is at least 90% identical to SEQ ID NO: 6. In some examples of any of the methods described herein, the first chimeric polypeptide comprises a sequence of SEQ ID NO: 6. In some examples of any of the methods described herein, the first chimeric polypeptide comprises a sequence of SEQ ID NO: 7.

In some examples of any of the methods described herein, the second target-binding domain comprises a soluble TGF-βRII. In some examples of any of the methods described herein, the second target-binding domain comprises a first sequence that is at least 80% identical to SEQ ID NO: 2 and a second sequence that is at least 80% identical to SEQ ID NO: 2, wherein the first and second sequence are separated by a linker. In some examples of any of the methods described herein, the second target-binding domain comprises a first sequence that is at least 90% identical to SEQ ID NO: 2 and a second sequence that is at least 90% identical to SEQ ID NO: 2. In some examples of any of the methods described herein, the second target-binding domain comprises a first sequence of SEQ ID NO: 2 and a second sequence of SEQ ID NO: 2. In some examples of any of the methods described herein, the linker comprises a sequence of SEQ ID NO: 3. In some examples of any of the methods described herein, the second target-binding domain comprises a sequence that is at least 80% identical to SEQ ID NO: 4. In some examples of any of the methods described

herein, the second target-binding domain comprises a sequence that is at least 90% identical to SEQ ID NO: 4. In some examples of any of the methods described herein, the second target-binding domain comprises a sequence of SEQ ID NO: 4. In some examples of any of the methods described herein, the second chimeric polypeptide comprises a sequence that is at least 80% identical to SEQ ID NO: 5. In some examples of any of the methods described herein, the first chimeric polypeptide comprises a sequence that is at least 80% identical to SEQ ID NO: 6. In some examples of any of the methods described herein, the second chimeric polypeptide comprises a sequence that is at least 90% identical to SEQ ID NO: 5. In some examples of any of the methods described herein, the second chimeric polypeptide comprises a sequence of SEQ ID NO: 5. In some examples of any of the methods described herein, the first chimeric polypeptide comprises a sequence of SEQ ID NO: 6. In some examples of any of the methods described herein, the second chimeric polypeptide comprises a sequence of SEQ ID NO: 8.

As used herein, the term "chimeric" refers to a polypeptide that includes amino acid sequences (e.g., domains) originally derived from two different sources (e.g., two different naturally-occurring proteins, e.g., from the same or different species). For example, a chimeric polypeptide can include domains from at least two different naturally occurring human proteins. In some examples, a chimeric polypeptide can include a domain that is a synthetic sequence (e.g., an scFv) and a domain that is derived from a naturally-occurring protein (e.g., a naturally-occurring human protein). In some examples, a chimeric polypeptide can include at least two different domains that are synthetic sequences (e.g., two different scFvs).

An "antigen-binding domain" is one or more protein domain(s) (e.g., formed from amino acids from a single polypeptide or formed from amino acids from two or more polypeptides (e.g., the same or different polypeptides) that is capable of specifically binding to one or more different antigen(s). In some examples, an antigen-binding domain can bind to an antigen or epitope with specificity and affinity similar to that of naturally-occurring antibodies. In some examples, the antigen-binding domain can be an antibody or a fragment thereof. In some examples, an antigen-binding domain can include an alternative scaffold. Non-limiting examples of antigen-binding domains

The term “antibody” is used herein in its broadest sense and includes certain types of immunoglobulin molecules that include one or more antigen-binding domains that specifically bind to an antigen or epitope. An antibody specifically includes, e.g., intact antibodies (e.g., intact immunoglobulins), antibody fragments, and multi-specific antibodies. One example of an antigen-binding domain is an antigen-binding domain formed by a VH -VL dimer. Additional examples of an antibody are described herein. Additional examples of an antibody are known in the art.

“Affinity” refers to the strength of the sum total of non-covalent interactions between an antigen-binding site and its binding partner (e.g., an antigen or epitope). Unless indicated otherwise, as used herein, “affinity” refers to intrinsic binding affinity, which reflects a 1:1 interaction between members of an antigen-binding domain and an antigen or epitope. The affinity of a molecule X for its partner Y can be represented by the dissociation equilibrium constant (K_D). The kinetic components that contribute to the dissociation equilibrium constant are described in more detail below. Affinity can be measured by common methods known in the art, including those described herein. Affinity can be determined, for example, using surface plasmon resonance (SPR) technology (e.g., BIACORE®) or biolayer interferometry (e.g., FORTEBIO®). Additional methods for determining the affinity for an antigen-binding domain and its corresponding antigen or epitope are known in the art.

A “multi-chain polypeptide” as used herein to refers to a polypeptide comprising two or more (e.g., three, four, five, six, seven, eight, nine, or ten) protein chains (e.g., at least a first chimeric polypeptide and a second polypeptide), where the two or more proteins chains associate through non-covalent bonds to form a quaternary structure.

The term “pair of affinity domains” is two different protein domain(s) that bind specifically to each other with a K_D of less than of less than 1×10^{-7} M (e.g., less than 1×10^{-8} M, less than 1×10^{-9} M, less than 1×10^{-10} M, or less than 1×10^{-11} M). In some examples, a pair of affinity domains can be a pair of naturally-occurring proteins. In some examples, a pair of affinity domains can be a pair of synthetic proteins. Non-limiting examples of pairs of affinity domains are described herein.

The term “epitope” means a portion of an antigen that specifically binds to an antigen-binding domain. Epitopes can, e.g., consist of surface-accessible amino acid

residues and/or sugar side chains and may have specific three-dimensional structural characteristics, as well as specific charge characteristics. Conformational and non-conformational epitopes are distinguished in that the binding to the former but not the latter may be lost in the presence of denaturing solvents. An epitope may comprise amino acid residues that are directly involved in the binding, and other amino acid residues, which are not directly involved in the binding. Methods for identifying an epitope to which an antigen-binding domain binds are known in the art.

An "immune effector cell" refers to a cell of the immune system of a mammal that is capable, directly or indirectly, of recognizing and/or causing cytostasis or cell death of a pathogenic cell (e.g., a cancer cell) in the mammal. Non-limiting examples of immune effector cells include macrophages, T-lymphocytes (e.g., cytotoxic T-lymphocytes and T-helper cells), natural killer cells, neutrophils, monocytes, and eosinophils. Additional examples of immune effector cells are known in the art.

The term "treatment" means to ameliorate at least one symptom of a disorder. In some examples, the disorder being treated is cancer and to ameliorate at least one symptom of cancer includes reducing aberrant proliferation, gene expression, signaling, translation, and/or secretion of factors. Generally, the methods of treatment include administering a therapeutically effective amount of composition that reduces at least one symptom of a disorder to a subject who is in need of, or who has been determined to be in need of such treatment.

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 to which this disclosure belongs. Methods and materials are described herein for use in the present disclosure; other, suitable methods and materials known in the art can also be used. The materials, methods, and examples are illustrative only and not intended to be limiting. All publications, patent applications, patents, sequences, database entries, and other references mentioned herein are incorporated by reference in their entirety. In case of conflict, the present specification, including definitions, will control.

Other features and advantages of the disclosure will be apparent from the following detailed description and figures, and from the claims.