

CLAIMS

What is claimed is:

1. A fibroblast binding agent comprising a targeting moiety that targets F2 fibroblasts, wherein the fibroblast binding agent directly or indirectly alters a disease microenvironment comprising the F2 fibroblasts.
- 5 2. The fibroblast binding agent of claim 1, wherein the fibroblast binding agent directly or indirectly polarizes the F2 fibroblasts.
3. The fibroblast binding agent of claim 1 or 2, wherein the fibroblast binding agent targets a FAP marker.
4. The fibroblast binding agent of claim 3, comprising at least one targeting moiety that targets fibroblast activation protein (FAP) and comprises three complementarity determining regions (CDR1, CDR2, and CDR3), wherein:
 - 10 (a) CDR1 comprises an amino acid sequence of SEQ ID NO: 95 or having any one of SEQ ID NOS: 87 to 94 or SEQ ID NOS: 96 to 115 or having any one of SEQ ID NOS: 87 to 115 with one to five amino acid substitutions, deletions, or insertions;
 - (b) CDR2 comprises an amino acid sequence of SEQ ID NO: 121 or having any one of SEQ ID NOS: 116 to 120 or SEQ ID NOS: 122 to 144 or having any one of SEQ ID NOS: 116 to 144 with one to five amino acid substitutions, deletions, or insertions; and
 - 15 (c) CDR3 comprises an amino acid sequence of SEQ ID NO: 152 or having any one of SEQ ID NOS: 145 to 151 or SEQ ID NOS: 153 to 175 or having any one of SEQ ID NOS: 145 to 175 with one to five amino acid substitutions, deletions, or insertions.
5. The fibroblast binding agent of any one of claims 1-4, wherein the targeting moiety is a full-length antibody, a single-domain antibody, a recombinant heavy-chain-only antibody (VHH), a single-chain antibody (scFv), a shark heavy-chain-only antibody (VNAR), a microprotein, a darpin, an anticalin, an adnectin, an aptamer, a Fv, a Fab, a Fab', a F(ab')₂, a peptide mimetic molecule, a natural ligand for a receptor, or a synthetic molecule.
- 20 6. The fibroblast binding agent of claim 4, wherein the targeting moiety is a single-domain antibody.
7. The fibroblast binding agent of claim 6, wherein the targeting moiety comprises a VHH, a humanized VHH, or a camelized VHH.
- 25 8. The fibroblast binding agent of any one of claims 1 to 7, wherein the targeting moiety comprises an amino acid sequence having at least 90% sequence similarity with SEQ ID NO: 58 or any one of SEQ ID NOS: 2 to 42, 46 to 57, or 59 to 86.
9. The fibroblast binding agent of any one of claims 1 to 8, further comprising one or more signaling agents.
- 30 10. The fibroblast binding agent of claim 9, wherein the signaling agent is selected from one or more of an interferon, an interleukin, a tumor necrosis factor, and a modified form thereof.
11. The fibroblast binding agent of claim 10, wherein the signaling agent is a mutant interferon alpha 2 (IFNα2) comprising an amino acid sequence having at least 95% identity with SEQ ID NO: 176 or 177 and having one or more mutations at positions 144 to 154 with respect to SEQ ID NO: 176 or 177 or one or more of positions L15, A19, R22, R23,

L26, F27, L30, K31, D32, R33, H34, D35, Q40, H57, E58, Q61, F64, N65, T69, L80, Y85, Y89, D114, L117, R120, R125, K133, K134, R144, A145, A145, M148, R149, S152, L153, and N156 with respect to SEQ ID NO: 176 or 177.

12. The fibroblast binding agent of claim 11, wherein the mutant IFN α 2 has one or more mutations at position R149, M148, or L153.

5 13. The fibroblast binding agent of claim 12, wherein the mutation is one or more of L15A, A19W, R22A, R23A, L26A, F27A, L30A, L30V, K31A, D32A, R33K, R33A, R33Q, H34A, D35A, Q40A, H57Y, E58N, Q61S, F64A, N65A, T69A, L80A, Y85A, Y89A, D114R, L117A, R120A, R125A, K133A, K134A, R144A, A145G, A145M, M148A, R149A, S152A, L153A, and N156A, optionally M148A, R149A, or L153A with respect to SEQ ID NO: 176 or 177.

10 14. The fibroblast binding agent of any one of claims 1 to 13, wherein the fibroblast binding agent comprises one or more additional targeting moieties.

15 15. The fibroblast binding agent of claim 14, wherein the one or more additional targeting moieties recognize or functionally modulate a tumor antigen.

16. The fibroblast binding agent of claim 14, wherein the one or more additional targeting moieties recognize or functionally modulate an antigen on an immune cell.

15 17. The fibroblast binding agent of claim 16, wherein the immune cell is selected from a T cell, a B cell, a dendritic cell, a macrophage, neutrophil, and a NK cell.

18. The fibroblast binding agent of any of claims 1 to 17, wherein the fibroblast binding agent recruits cytotoxic T cells to tumor cells or to a tumor microenvironment.

20 19. The fibroblast binding agent of claim 14, wherein the one or more additional targeting moieties recognize or functionally modulate PD-1, PD-L1, PD-L2, CTLA4, OX40L, OX40, CD20, XCR1, and Clec9A.

20. The fibroblast binding agent of any of claims 1 to 19, wherein the fibroblast binding agent recognizes or binds FAP without substantially functionally modulating its activity.

25 21. A fibroblast activation protein (FAP) binding agent comprising at least one targeting moiety that targets fibroblast activation protein (FAP) and comprises three complementarity determining regions (CDR1, CDR2, and CDR3), wherein:

(a) CDR1 comprises an amino acid sequence of SEQ ID NO: 95 or having any one of SEQ ID NOS: 87 to 94 or SEQ ID NOS: 96 to 115 or having any one of SEQ ID NOS: 87 to 115 with one to five amino acid substitutions, deletions, or insertions;

30 (b) CDR2 comprises an amino acid sequence of SEQ ID NO: 121 or having any one of SEQ ID NOS: 116 to 120 or SEQ ID NOS: 122 to 144 or having any one of SEQ ID NOS: 116 to 144 with one to five amino acid substitutions, deletions, or insertions; and

(c) CDR3 comprises an amino acid sequence of SEQ ID NO: 152 or having any one of SEQ ID NOS: 145 to 151 or SEQ ID NOS: 153 to 175 or having any one of SEQ ID NOS: 145 to 175 with one to five amino acid substitutions, deletions, or insertions.

35 22. The FAP binding agent of claim 21, wherein the targeting moiety is a single-domain antibody, a recombinant heavy-chain-only antibody (VHH), a single-chain antibody (scFv), a shark heavy-chain-only antibody (VNAR), a

microprotein, a darpin, an anticalin, an adnectin, an aptamer, a Fv, a Fab, a Fab', a F(ab')₂, a peptide mimetic molecule, a natural ligand for a receptor, or a synthetic molecule.

23. The FAP binding agent of claim 21, wherein the targeting moiety is a single-domain antibody.

24. The FAP binding agent of claim 23, wherein the targeting moiety comprises a VHH, a humanized VHH, or
5 a camelized VHH.

25. The FAP binding agent of any one of claims 21 to 24, wherein the targeting moiety comprises an amino acid sequence having at least 90% sequence similarity with SEQ ID NO: 58 or any one of SEQ ID NOS: 2 to 42, 46 to 57, or 59 to 86.

26. The FAP binding agent of any one of claims 21 to 25, wherein the FAP binding agent comprises one or
10 more signaling agents.

27. The FAP binding agent of claim 26, wherein the signaling agent is selected from one or more of an interferon, an interleukin, a tumor necrosis factor, and a modified form thereof.

28. The FAP binding agent of claim 27, wherein the signaling agent is a mutant interferon alpha 2 (IFNα2) comprising an amino acid sequence having at least 95% identity with SEQ ID NO: 176 or 177 and having one or more
15 mutations at positions 144 to 154 with respect to SEQ ID NO: 176 or 177 or one or more of positions L15, A19, R22, R23, L26, F27, L30, L30, K31, D32, R33, H34, D35, Q40, H57, E58, Q61, F64, N65, T69, L80, Y85, Y89, D114, L117, R120, R125, K133, K134, R144, A145, A145, M148, R149, S152, L153, and N156 with respect to SEQ ID NO: 176 or 177.

29. The FAP binding agent of claim 28, wherein the mutant IFNα2 has one or more mutations at position R149, M148, or L153.

30. The FAP binding agent of claim 29, wherein the mutation is L15A, A19W, R22A, R23A, L26A, F27A, L30A, L30V, K31A, D32A, R33K, R33A, R33Q, H34A, D35A, Q40A, H57Y, E58N, Q61S, F64A, N65A, T69A, L80A, Y85A, Y89A, D114R, L117A, R120A, R125A, K133A, K134A, R144A, A145G, A145M, M148A, R149A, S152A, L153A, and N156A, optionally M148A, R149A, or L153A with respect to SEQ ID NO: 176 or 177.

31. The FAP binding agent of any one of claims 21 to 30, wherein the FAP binding agent comprises one or
25 more additional targeting moieties.

32. The FAP binding agent of claim 31, wherein the one or more additional targeting moieties recognize or functionally modulate a tumor antigen.

33. The FAP binding agent of claim 32, wherein the one or more additional targeting moieties recognize or functionally modulate an antigen on an immune cell.

34. The FAP binding agent of claim 33, wherein the immune cell is selected from a T cell, a B cell, a dendritic cell, a macrophage, neutrophil, and a NK cell.

35. The FAP binding agent of any one of claims 21 to 34, wherein the FAP binding agent recruits cytotoxic T cells to tumor cells or to the tumor environment.

36. The FAP binding agent of claim 31, wherein the one or more additional targeting moieties recognize or
35 functionally modulate PD-1, PD-L1, PD-L2, CTLA4, OX40L, OX40, CD20, XCR1, and Clec9A.

37. The FAP binding agent of any one of claims 21-36, wherein the FAP binding agent recognizes or binds FAP without substantially functionally modulating its activity.

38. A chimeric protein comprising:

at least one targeting moiety and one signaling agent,

5 wherein the targeting moiety targets disease-associated fibroblasts, and

wherein the chimeric protein directly or indirectly alters the disease-associated fibroblast's function and/or a disease microenvironment comprising the disease-associated fibroblast.

39. The chimeric protein of claim 38, wherein the chimeric protein directly or indirectly polarizes the disease-associated fibroblast.

10 40. The chimeric protein of claims 38 or 39, wherein the disease-associated fibroblast is associated with a disease selected from cancer, infections, immune disorders, autoimmune disease, fibrotic diseases, and cardiovascular disease.

41. The chimeric protein of any one of claims 38 to 40, wherein the targeting moiety targets F2 fibroblasts.

42. The chimeric protein of any one of claims 38 to 41, wherein the targeting moiety is a FAP binding agent.

15 43. The chimeric protein of claim 42, wherein the FAP binding agent comprises three complementarity determining regions (CDR1, CDR2, and CDR3), wherein

(a) CDR1 comprises an amino acid sequence of SEQ ID NO: 95 or having any one of SEQ ID NOS: 87 to 94 or SEQ ID NOS: 96 to 115 or having any one of SEQ ID NOS: 87 to 115 with one to five amino acid substitutions, deletions, or insertions;

20 (b) CDR2 comprises an amino acid sequence of SEQ ID NO: 121 or having any one of SEQ ID NOS: 116 to 120 or SEQ ID NOS: 122 to 144 or having any one of SEQ ID NOS: 116 to 144 with one to five amino acid substitutions, deletions, or insertions; and

(c) CDR3 comprises an amino acid sequence of SEQ ID NO: 152 or having any one of SEQ ID NOS: 145 to 151 or SEQ ID NOS: 153 to 175 or having any one of SEQ ID NOS: 145 to 175 with one to five amino acid substitutions, deletions, or insertions.

25 44. The chimeric protein of any one of claims 38 to 43, wherein the targeting moiety is a full-length antibody, a single-domain antibody, a recombinant heavy-chain-only antibody (VHH), a single-chain antibody (scFv), a shark heavy-chain-only antibody (VNAR), a microprotein, a darpin, an anticalin, an adnectin, an aptamer, a Fv, a Fab, a Fab', a F(ab')₂, a peptide mimetic molecule, a natural ligand for a receptor, or a synthetic molecule.

30 45. The chimeric protein of claim 44, wherein the targeting moiety is a single-domain antibody.

46. The chimeric protein of claim 45, wherein the targeting moiety comprises a VHH, a humanized VHH, or a camelized VHH.

47. The chimeric protein of any one of claims 38 to 46, wherein the targeting moiety comprises an amino acid sequence having at least 90% sequence similarity with SEQ ID NO: 58 or any one of SEQ ID NO: 2 to 42, 46 to 57, or 59 to 86.

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48. The chimeric protein of any one of claims 38 to 47, wherein the FAP binding agent comprises one or more signaling agents.
49. The chimeric protein of claim 48, wherein the signaling agent is selected from one or more of an interferon, an interleukin, and a tumor necrosis factor, and a modified form thereof.
- 5 50. The chimeric protein of claim 48, wherein the signaling agent is a mutant interferon alpha 2 (IFN α 2) comprising an amino acid sequence having at least 95% identity with SEQ ID NO: 176 or 177 and having one or more mutations at positions 144 to 154 with respect to SEQ ID NO: 176 or 177 or one or more of positions L15, A19, R22, R23, L26, F27, L30, L30, K31, D32, R33, H34, D35, Q40, H57, E58, Q61, F64, N65, T69, L80, Y85, Y89, D114, L117, R120, R125, K133, K134, R144, A145, A145, M148, R149, S152, L153, and N156 with respect to SEQ ID NO: 176 or 177.
- 10 51. The chimeric protein of claim 50, wherein the mutant IFN α 2 has one or more mutations at position R149, M148, or L153.
52. The chimeric protein of claim 51, wherein the mutation is L15A, A19W, R22A, R23A, L26A, F27A, L30A, L30V, K31A, D32A, R33K, R33A, R33Q, H34A, D35A, Q40A, H57Y, E58N, Q61S, F64A, N65A, T69A, L80A, Y85A, Y89A, D114R, L117A, R120A, R125A, K133A, K134A, R144A, A145G, A145M, M148A, R149A, S152A, L153A, and N156A,
- 15 optionally M148A, R149A, or L153A with respect to SEQ ID NO: 176 or 177.
53. The chimeric protein of any one of claims 38 to 52, wherein the FAP binding agent comprises one or more additional targeting moieties.
54. The chimeric protein of claim 53, wherein the one or more additional targeting moieties recognize or functionally modulate a tumor antigen.
- 20 55. The chimeric protein of claim 53, wherein the one or more additional targeting moieties recognize or functionally modulate an antigen on an immune cell.
56. The chimeric protein of claim 55, wherein the immune cell is selected from a T cell, a B cell, a dendritic cell, a macrophage, neutrophil, and a NK cell.
57. The chimeric protein of any of claims 38 to 56, wherein the chimeric protein recruits cytotoxic T cells to
- 25 tumor cells or to a tumor microenvironment.
58. The chimeric protein of claim 53, wherein the one or more additional targeting moieties recognize or functionally modulate PD-1, PD-L1, PD-L2, CTLA4, OX40L, OX40, CD20, XCR1, and Clec9A.
59. The chimeric protein of any of claims 38 to 58, wherein the chimeric protein recognizes or binds FAP without substantially functionally modulating its activity.
- 30 60. A chimeric protein comprising:
- (a) at least one targeting moiety that targets fibroblast activation protein (FAP) and comprises an amino acid sequence having at least 90% sequence similarity with SEQ ID NO: 58 or any one of SEQ ID NO: 2 to 42, 46 to 57, or 59 to 86; or three complementarity determining regions (CDR1, CDR2, and CDR3), wherein:
- (i) CDR1 comprises an amino acid sequence of SEQ ID NO: 95 or having any one of SEQ ID NOS: 87 to 94 or SEQ
- 35 ID NOS: 96 to 115 or having any one of SEQ ID NOS: 87 to 115 with one to five amino acid substitutions, deletions, or insertions;

(ii) CDR2 comprises an amino acid sequence of SEQ ID NO: 121 or having any one of SEQ ID NOS: 116 to 120 or SEQ ID NOS: 122 to 144 or having any one of SEQ ID NOS: 116 to 144 with one to five amino acid substitutions, deletions, or insertions; and

(iii) CDR3 comprises an amino acid sequence of SEQ ID NO: 152 or having any one of SEQ ID NOS: 145 to 151 or
 5 SEQ ID NOS: 153 to 175 or having any one of SEQ ID NOS: 145 to 175 with one to five amino acid substitutions, deletions, or insertions; and

(b) a modified signaling agent, wherein the signaling agent is a human IFN- α 2 having one or more mutations that confer improved safety as compared to a wild type IFN- α 2 having an amino acid sequence of SEQ ID NO: 176 or 177; and

wherein the targeting moiety and the modified signaling agent are optionally connected with one or more linkers.

10 61. The chimeric protein of claim 60, wherein the modified human IFN- α 2 comprises one or more mutations at positions R33, R120, R144, A145, M148, R149, and L153 in SEQ ID NO: 176 or 177.

62. The chimeric protein of claim 60, wherein the modified human IFN- α 2 comprises one or more mutations selected from R33A, R120E, R144X₁ A145X₂, M148A, R149A, and L153A, wherein X₁ is selected from A, S, T, Y, L, and I, and wherein X₂ is selected from G, H, Y, K, and D in SEQ ID NO: 176 or 177.

15 63. The chimeric protein of claim 60, wherein the modified human IFN- α 2 comprises a R149A mutation.

64. A chimeric protein comprising:

(a) at least one targeting moiety that targets fibroblast activation protein (FAP) and comprises an amino acid sequence having at least 90% sequence similarity with SEQ ID NO: 58 or any one of SEQ ID NO: 2 to 42, 46 to 57, or 59 to 86; or three complementarity determining regions (CDR1, CDR2, and CDR3), wherein:

20 (i) CDR1 comprises an amino acid sequence of SEQ ID NO: 95 or having any one of SEQ ID NOS: 87 to 94 or SEQ ID NOS: 96 to 115 or having any one of SEQ ID NOS: 87 to 115 with one to five amino acid substitutions, deletions, or insertions;

(ii) CDR2 comprises an amino acid sequence of SEQ ID NO: 121 or having any one of SEQ ID NOS: 116 to 120 or SEQ ID NOS: 122 to 144 or having any one of SEQ ID NOS: 116 to 144 with one to five amino acid substitutions, deletions,
 25 or insertions; and

(iii) CDR3 comprises an amino acid sequence of SEQ ID NO: 152 or having any one of SEQ ID NOS: 145 to 151 or SEQ ID NOS: 153 to 175 or having any one of SEQ ID NOS: 145 to 175 with one to five amino acid substitutions, deletions, or insertions; and

(b) a modified signaling agent, wherein the signaling agent is a modified human IFN- β having one or more mutations
 30 that confer improved safety as compared to a wild type IFN- β having an amino acid sequence of SEQ ID NO: 178; and

wherein the targeting moiety and the modified signaling agent are optionally connected with one or more linkers.

65. The chimeric protein of claim 64, wherein the modified human IFN- β comprises one or more mutations at positions W22, R27, L32, R35, V148, L151, R152, and Y155 of SEQ ID NO: 178.

66. The chimeric protein of claim 65, wherein the modified human IFN- β comprises one or more mutations
 35 selected from W22G, R27G, L32A, L32G, R35A, R35G, V148G, L151G, R152A, R152G of SEQ ID NO: 178.

67. A recombinant nucleic acid encoding the fibroblast binding agent of any one of claims 1 to 20.
68. A recombinant nucleic acid encoding the FAP binding agent of any one of claims 21 to 37.
69. A recombinant nucleic acid encoding the chimeric protein of any one of claims 38 to 66.
70. A host cell comprising a nucleic acid of claims 67, 68, or 69.
- 5 71. The fibroblast binding agent of any one of claims 1 to 20, wherein the fibroblast binding agent is suitable for use in a patient having one or more of: cancer, infections, immune disorders, fibrotic diseases, and autoimmune diseases.
72. The FAP binding agent of any one of claims 21 to 37, wherein the FAP binding agent is suitable for use in a patient having one or more of: cancer, infections, immune disorders, fibrotic diseases, and autoimmune diseases.
73. The chimeric protein of any one of claims 38 to 66, wherein the chimeric protein is suitable for use in a
10 patient having one or more of: cancer, infections, immune disorders, fibrotic diseases, and autoimmune diseases.
74. A method for treating or preventing cancer, comprising administering to a patient in need thereof an effective amount of a chimeric protein comprising:
- (a) at least one targeting moiety that targets fibroblast activation protein (FAP) and comprises an amino acid sequence having at least 90% sequence similarity with SEQ ID NO: 58 or any one of SEQ ID NO: 2 to 42, 46 to 57, or 59 to
15 86; or three complementarity determining regions (CDR1, CDR2, and CDR3), wherein:
- (i) CDR1 comprises an amino acid sequence of SEQ ID NO: 95 or having any one of SEQ ID NOS: 87 to 94 or SEQ ID NOS: 96 to 115 or having any one of SEQ ID NOS: 87 to 115 with one to five amino acid substitutions, deletions, or insertions;
- (ii) CDR2 comprises an amino acid sequence of SEQ ID NO: 121 or having any one of SEQ ID NOS: 116 to 120 or
20 SEQ ID NOS: 122 to 144 or having any one of SEQ ID NOS: 116 to 144 with one to five amino acid substitutions, deletions, or insertions; and
- (iii) CDR3 comprises an amino acid sequence of SEQ ID NO: 152 or having any one of SEQ ID NOS: 145 to 151 or SEQ ID NOS: 153 to 175 or having any one of SEQ ID NOS: 145 to 175 with one to five amino acid substitutions, deletions, or insertions; and
- 25 (b) or a signaling agent, wherein the signaling agent is a human IFN- α 2 or a human IFN- β ; and wherein the targeting moiety and the modified signaling agent are optionally connected with one or more linkers.
75. The method of claim 74, wherein the signaling agent is modified.
76. The method of claim 74, wherein the modified signaling agent is a modified human IFN- α 2 having one or more mutations that confer improved safety as compared to a wild type IFN- α 2 having an amino acid sequence of SEQ ID
30 NO: 176 or 177 or the modified signaling agent is a modified human IFN- β having one or more mutations that confer improved safety as compared to a wild type IFN- β having an amino acid sequence of SEQ ID NO: 178.
77. The method of claim 76, wherein the modified human IFN- β comprises one or more mutations at positions W22, R27, L32, R35, V148, L151, R152, and Y155 of SEQ ID NO: 178, optionally selected from W22G, R27G, L32A, L32G, R35A, R35G, V148G, L151G, R152A, R152G of SEQ ID NO: 178.

78. The method of claim 76, wherein the modified human IFN- α 2 comprises one or more mutations at positions L15, A19, R22, R23, L26, F27, L30, L30, K31, D32, R33, H34, D35, Q40, H57, E58, Q61, F64, N65, T69, L80, Y85, Y89, D114, L117, R120, R125, K133, K134, R144, A145, A145, M148, R149, S152, L153, and N156 in SEQ ID NO: 176 or 177.

5 79. The method of claim 78, wherein the modified human IFN- α 2 comprises one or more mutations selected from R33A, R120E, R144X₁, A145X₂, M148A, R149A, and L153A, wherein X₁ is selected from A, S, T, Y, L, and I, and wherein X₂ is selected from G, H, Y, K, and D in SEQ ID NO: 176 or 177.

80. The method of claim 79, wherein the modified human IFN- α 2 comprises a R149A mutation.

81. The method of any of any of claims 74 to 80, wherein the cancer is selected from one or more of basal
 10 cell carcinoma, biliary tract cancer; bladder cancer; bone cancer; brain and central nervous system cancer; breast cancer; cancer of the peritoneum; cervical cancer; choriocarcinoma; colon and rectum cancer; connective tissue cancer; cancer of the digestive system; endometrial cancer; esophageal cancer; eye cancer; cancer of the head and neck; gastric cancer (including gastrointestinal cancer); glioblastoma; hepatic carcinoma; hepatoma; intra-epithelial neoplasm; kidney or renal cancer; larynx cancer; leukemia; liver cancer; lung cancer (e.g., small-cell lung cancer, non-small cell lung cancer, adenocarcinoma of the
 15 lung, and squamous carcinoma of the lung); melanoma; myeloma; neuroblastoma; oral cavity cancer (lip, tongue, mouth, and pharynx); ovarian cancer; pancreatic cancer; prostate cancer; retinoblastoma; rhabdomyosarcoma; rectal cancer; cancer of the respiratory system; salivary gland carcinoma; sarcoma; skin cancer; squamous cell cancer; stomach cancer; testicular cancer; thyroid cancer; uterine or endometrial cancer; cancer of the urinary system; vulval cancer; lymphoma including Hodgkin's and non-Hodgkin's lymphoma, as well as B-cell lymphoma (including low grade/follicular non-Hodgkin's lymphoma
 20 (NHL); small lymphocytic (SL) NHL; intermediate grade/follicular NHL; intermediate grade diffuse NHL; high grade immunoblastic NHL; high grade lymphoblastic NHL; high grade small non-cleaved cell NHL; bulky disease NHL; mantle cell lymphoma; AIDS-related lymphoma; and Waldenstrom's Macroglobulinemia; chronic lymphocytic leukemia (CLL); acute lymphoblastic leukemia (ALL); Hairy cell leukemia; chronic myeloblastic leukemia; as well as other carcinomas and sarcomas; and post-transplant lymphoproliferative disorder (PTLD), as well as abnormal vascular proliferation associated with
 25 phakomatoses, edema (e.g., that associated with brain tumors), and Meigs' syndrome.

82. The method of any of any of claims 74 to 81, further comprising administering a DNA-intercalating agent chemotherapeutic agent, such as doxorubicin, cisplatin, daunorubicin, or epirubicin.

83. The method of any one of claims 74 to 82, wherein the chimeric protein directly or indirectly recruits immune cells to a tumor or tumor microenvironment.

30 84. A method for treating or preventing an autoimmune and/or neurodegenerative disease, comprising administering to a patient in need thereof an effective amount of a chimeric protein comprising:

(a) at least one targeting moiety that targets fibroblast activation protein (FAP) and comprises an amino acid sequence having at least 90% sequence similarity with SEQ ID NO: 58 or any one of SEQ ID NO: 2 to 42, 46 to 57, or 59 to 86; or three complementarity determining regions (CDR1, CDR2, and CDR3), wherein:

35 (i) CDR1 comprises an amino acid sequence of SEQ ID NO: 95 or having any one of SEQ ID NOS: 87 to 94 or SEQ ID NOS: 96 to 115 or having any one of SEQ ID NOS: 87 to 115 with one to five amino acid substitutions, deletions, or insertions;

(ii) CDR2 comprises an amino acid sequence of SEQ ID NO: 121 or having any one of SEQ ID NOS: 116 to 120 or SEQ ID NOS: 122 to 144 or having any one of SEQ ID NOS: 116 to 144 with one to five amino acid substitutions, deletions, or insertions; and

(iii) CDR3 comprises an amino acid sequence of SEQ ID NO: 152 or having any one of SEQ ID NOS: 145 to 151 or
5 SEQ ID NOS: 153 to 175 or having any one of SEQ ID NOS: 145 to 175 with one to five amino acid substitutions, deletions, or insertions; and

(b) or a signaling agent, wherein the signaling agent is a human IFN- α 2 or a human IFN- β ; and wherein the targeting moiety and the modified signaling agent are optionally connected with one or more linkers.

85. The method of claim 84, wherein the signaling agent is modified.

10 86. The method of claim 85, wherein the modified signaling agent is a modified human IFN- α 2 having one or more mutations that confer improved safety as compared to a wild type IFN- α 2 having an amino acid sequence of SEQ ID NO: 176 or 177 or the modified signaling agent is a modified human IFN- β having one or more mutations that confer improved safety as compared to a wild type IFN- β having an amino acid sequence of SEQ ID NO: 178.

87. The method of claim 86, wherein the modified human IFN- β comprises one or more mutations at positions
15 W22, R27, L32, R35, V148, L151, R152, and Y155 of SEQ ID NO: 178.

88. The method of claim 87, wherein the modified human IFN- β comprises one or more mutations selected from W22G, R27G, L32A, L32G, R35A, R35G, V148G, L151G, R152A, R152G of SEQ ID NO: 178.

89. The method of claim 86, wherein the modified human IFN- α 2 comprises one or more mutations at positions L15, A19, R22, R23, L26, F27, L30, L30, K31, D32, R33, H34, D35, Q40, H57, E58, Q61, F64, N65, T69, L80, Y85,
20 Y89, D114, L117, R120, R125, K133, K134, R144, A145, A145, M148, R149, S152, L153, and N156 in SEQ ID NO: 176 or 177.

90. The method of claim 89, wherein the modified human IFN- α 2 comprises one or more mutations selected from R33A, R120E, R144X₁ A145X₂, M148A, R149A, and L153A, wherein X₁ is selected from A, S, T, Y, L, and I, and wherein X₂ is selected from G, H, Y, K, and D in SEQ ID NO: 176 or 177.

25 91. The method of claim 90, wherein the modified human IFN- α 2 comprises a R149A mutation.

92. The method of claim 84, wherein the autoimmune and/or neurodegenerative disease is selected from multiple sclerosis, diabetes mellitus, lupus, celiac disease, Crohn's disease, ulcerative colitis, Guillain-Barre syndrome, scleroderms, Goodpasture's syndrome, Wegener's granulomatosis, autoimmune epilepsy, Rasmussen's encephalitis, Primary biliary sclerosis, Sclerosing cholangitis, Autoimmune hepatitis, Addison's disease, Hashimoto's thyroiditis, Fibromyalgia,
30 Menier's syndrome; transplantation rejection (e.g., prevention of allograft rejection) pernicious anemia, rheumatoid arthritis, systemic lupus erythematosus, dermatomyositis, Sjogren's syndrome, lupus erythematosus, myasthenia gravis, Reiter's syndrome, and Grave's disease.

93. The method of claim 92, wherein the autoimmune and/or neurodegenerative disease is multiple sclerosis.

94. The method of any one of claims 84 to 93, wherein the chimeric protein leads to immunosuppression in
35 the patient.

95. A method for treating or preventing a fibrotic disease, comprising administering to a patient in need thereof an effective amount of a chimeric protein comprising:

- (a) at least one targeting moiety that targets fibroblast activation protein (FAP) and comprises an amino acid sequence having at least 90% sequence similarity with SEQ ID NO: 58 or any one of SEQ ID NO: 2 to 42, 46 to 57, or 59 to 175; or three complementarity determining regions (CDR1, CDR2, and CDR3), wherein:
 - (i) CDR1 comprises an amino acid sequence of SEQ ID NO: 95 or having any one of SEQ ID NOS: 87 to 94 or SEQ ID NOS: 96 to 115 or having any one of SEQ ID NOS: 87 to 115 with one to five amino acid substitutions, deletions, or insertions;
 - (ii) CDR2 comprises an amino acid sequence of SEQ ID NO: 121 or having any one of SEQ ID NOS: 116 to 120 or SEQ ID NOS: 122 to 144 or having any one of SEQ ID NOS: 116 to 144 with one to five amino acid substitutions, deletions, or insertions; and
 - (iii) CDR3 comprises an amino acid sequence of SEQ ID NO: 152 or having any one of SEQ ID NOS: 145 to 151 or SEQ ID NOS: 153 to 175 or having any one of SEQ ID NOS: 145 to 175 with one to five amino acid substitutions, deletions, or insertions; and
 - (b) or a signaling agent, wherein the signaling agent is a human IFN- α 2 or a human IFN- β ; and wherein the targeting moiety and the modified signaling agent are optionally connected with one or more linkers.
96. The method of claim 95, wherein the signaling agent is modified.
97. The method of claim 96, wherein the modified signaling agent is a modified human IFN- α 2 having one or more mutations that confer improved safety as compared to a wild type IFN- α 2 having an amino acid sequence of SEQ ID NO: 176 or 177 or the modified signaling agent is a modified human IFN- β having one or more mutations that confer improved safety as compared to a wild type IFN- β having an amino acid sequence of SEQ ID NO: 178.
98. The method of claim 97, wherein the modified human IFN- β comprises one or more mutations at positions W22, R27, L32, R35, V148, L151, R152, and Y155 of SEQ ID NO: 178.
99. The method of claim 98, wherein the modified human IFN- β comprises one or more mutations selected from W22G, R27G, L32A, L32G, R35A, R35G, V148G, L151G, R152A, R152G of SEQ ID NO: 178.
100. The method of claim 97, wherein the modified human IFN- α 2 comprises one or more mutations at positions L15, A19, R22, R23, L26, F27, L30, L30, K31, D32, R33, H34, D35, Q40, H57, E58, Q61, F64, N65, T69, L80, Y85, Y89, D114, L117, R120, R125, K133, K134, R144, A145, A145, M148, R149, S152, L153, and N156 in SEQ ID NO: 176 or 177.
101. The method of claim 100, wherein the modified human IFN- α 2 comprises one or more mutations selected from R33A, R120E, R144X₁, A145X₂, M148A, R149A, and L153A, wherein X₁ is selected from A, S, T, Y, L, and I, and wherein X₂ is selected from G, H, Y, K, and D in SEQ ID NO: 176 or 177.
102. The method of claim 101, wherein the modified human IFN- α 2 comprises a R149A mutation.
103. The method of any of any of claims 95 to 102, wherein the fibrotic disease is selected from liver fibrosis, lung fibrosis, primary sclerosing cholangitis (PSC), chronic liver disease, nonalcoholic fatty liver disease (NAFLD),

nonalcoholic steatohepatitis (NASH), hepatitis C infection, alcoholic liver disease, liver damage, liver cirrhosis, and myelodysplastic syndrome.