CLAIMS

1. A chimeric protein comprising:

(a) at least one recombinant heavy-chain-only antibody (VHH) or a single-chain antibody (scFv) targeting moiety that is a fibroblast activation protein (FAP) binding agent and

(b) a modified human interferon alpha 2 (IFNα2) signaling agent comprising an amino acid sequence having at least 95% identity with SEQ ID NO: 176 or 177 and having one or more mutations selected from K133A, L153A, R149A, and M148A that confer lower toxicity, lessened or eliminated side effects, increased tolerability, lessened or eliminated adverse events, reduced or eliminated off-target effects, and/or increased therapeutic window, as compared to a wild type IFNα2 having an amino acid sequence of SEQ ID NO: 176 or 177;

wherein the one or more mutations confer reduced or ablated binding affinity and/or activity to the modified IFNα2 signaling agent that is restorable by the targeting moiety,

wherein the targeting moiety targets F2 fibroblasts, and

wherein the chimeric protein alters the F2 fibroblast's function and/or a disease microenvironment comprising the F2 fibroblast.

2. The chimeric protein of claim 1, wherein the FAP binding agent polarizes F2 fibroblasts.

3. The chimeric protein of claim 1, wherein the FAP binding agent recruits cytotoxic T cells to tumor cells or to a tumor microenvironment.

4. The chimeric protein of claim 1, wherein the FAP binding agent recognizes or binds FAP without modulating its activity.

5. The chimeric protein of claim 1, wherein the FAP binding agent comprises three complementarity determining regions (CDR1, CDR2, and CDR3), wherein

CDR1 comprises an amino acid sequence of SEQ ID NO: 95; CDR2 comprises an amino acid sequence of SEQ ID NO: 121; CDR3 comprises an amino acid sequence of SEQ ID NO: 152;

CDR1 comprises an amino acid sequence of SEQ ID NO: 87; CDR2 comprises an amino acid sequence of SEQ ID NO: 116; CDR3 comprises an amino acid sequence of SEQ ID NO: 145;

CDR1 comprises an amino acid sequence of SEQ ID NO: 89; CDR2 comprises an amino acid sequence of SEQ ID NO: 117; CDR3 comprises an amino acid sequence of SEQ ID NO: 146;

CDR1 comprises an amino acid sequence of SEQ ID NO: 90; CDR2 comprises an amino acid sequence of SEQ ID NO: 117; CDR3 comprises an amino acid sequence of SEQ ID NO: 147;

CDR1 comprises an amino acid sequence of SEQ ID NO: 91; CDR2 comprises an amino acid sequence of SEQ ID NO: 118; CDR3 comprises an amino acid sequence of SEQ ID NO: 148;

CDR1 comprises an amino acid sequence of SEQ ID NO: 92; CDR2 comprises an amino acid sequence of SEQ ID NO: 118; CDR3 comprises an amino acid sequence of SEQ ID NO: 149;

CDR1 comprises an amino acid sequence of SEQ ID NO: 93; CDR2 comprises an amino acid sequence of SEQ ID NO: 119; CDR3 comprises an amino acid sequence of SEQ ID NO: 146;

CDR1 comprises an amino acid sequence of SEQ ID NO: 94; CDR2 comprises an amino acid sequence of SEQ ID NO: 120; CDR3 comprises an amino acid sequence of SEQ ID NO: 150;

CDR1 comprises an amino acid sequence of SEQ ID NO: 94; CDR2 comprises an amino acid sequence of SEQ ID NO: 120; CDR3 comprises an amino acid sequence of SEQ ID NO: 151;

CDR1 comprises an amino acid sequence of SEQ ID NO: 96; CDR2 comprises an amino acid sequence of SEQ ID NO: 122; CDR3 comprises an amino acid sequence of SEQ ID NO: 153;

CDR1 comprises an amino acid sequence of SEQ ID NO: 97; CDR2 comprises an amino acid sequence of SEQ ID NO: 123; CDR3 comprises an amino acid sequence of SEQ ID NO: 154;

CDR1 comprises an amino acid sequence of SEQ ID NO: 98; CDR2 comprises an amino acid sequence of SEQ ID NO: 124; CDR3 comprises an amino acid sequence of SEQ ID NO:155;

CDR1 comprises an amino acid sequence of SEQ ID NO: 99; CDR2 comprises an amino acid sequence of SEQ ID NO: 125; CDR3 comprises an amino acid sequence of SEQ ID NO: 156;

CDR1 comprises an amino acid sequence of SEQ ID NO: 100; CDR2 comprises an amino acid sequence of SEQ ID NO: 126; CDR3 comprises an amino acid sequence of SEQ ID NO: 157;

CDR1 comprises an amino acid sequence of SEQ ID NO: 101; CDR2 comprises an amino acid sequence of SEQ ID NO: 127; CDR3 comprises an amino acid sequence of SEQ ID NO: 158;

CDR1 comprises an amino acid sequence of SEQ ID NO: 102; CDR2 comprises an amino acid sequence of SEQ ID NO: 128; CDR3 comprises an amino acid sequence of SEQ ID NO: 159;

CDR1 comprises an amino acid sequence of SEQ ID NO: 103; CDR2 comprises an amino acid sequence of SEQ ID NO: 129; CDR3 comprises an amino acid sequence of SEQ ID NO: 160;

CDR1 comprises an amino acid sequence of SEQ ID NO: 104; CDR2 comprises an amino acid sequence of SEQ ID NO: 129; CDR3 comprises an amino acid sequence of SEQ ID NO: 160;

CDR1 comprises an amino acid sequence of SEQ ID NO: 105; CDR2 comprises an amino acid sequence of SEQ ID NO: 130; CDR3 comprises an amino acid sequence of SEQ ID NO: 160;

CDR1 comprises an amino acid sequence of SEQ ID NO: 105; CDR2 comprises an amino acid sequence of SEQ ID NO: 131; CDR3 comprises an amino acid sequence of SEQ ID NO: 161;

CDR1 comprises an amino acid sequence of SEQ ID NO: 106; CDR2 comprises an amino acid sequence of SEQ ID NO: 132; CDR3 comprises an amino acid sequence of SEQ ID NO: 162;

CDR1 comprises an amino acid sequence of SEQ ID NO: 107; CDR2 comprises an amino acid sequence of SEQ ID NO: 133; CDR3 comprises an amino acid sequence of SEQ ID NO: 163;

CDR1 comprises an amino acid sequence of SEQ ID NO: 108; CDR2 comprises an amino acid sequence of SEQ ID NO: 132; CDR3 comprises an amino acid sequence of SEQ ID NO: 164;

CDR1 comprises an amino acid sequence of SEQ ID NO: 106; CDR2 comprises an amino acid sequence of SEQ ID NO: 134; CDR3 comprises an amino acid sequence of SEQ ID NO: 165;

CDR1 comprises an amino acid sequence of SEQ ID NO: 106; CDR2 comprises an amino acid sequence of SEQ ID NO: 135; CDR3 comprises an amino acid sequence of SEQ ID NO: 166;

CDR1 comprises an amino acid sequence of SEQ ID NO: 106; CDR2 comprises an amino acid sequence of SEQ ID NO: 136; CDR3 comprises an amino acid sequence of SEQ ID NO: 167;

CDR1 comprises an amino acid sequence of SEQ ID NO: 109; CDR2 comprises an amino acid sequence of SEQ ID NO: 137; CDR3 comprises an amino acid sequence of SEQ ID NO: 168;

CDR1 comprises an amino acid sequence of SEQ ID NO: 106; CDR2 comprises an amino acid sequence of SEQ ID NO: 138; CDR3 comprises an amino acid sequence of SEQ ID NO: 169;

CDR1 comprises an amino acid sequence of SEQ ID NO: 110; CDR2 comprises an amino acid sequence of SEQ ID NO: 139; CDR3 comprises an amino acid sequence of SEQ ID NO: 170;

CDR1 comprises an amino acid sequence of SEQ ID NO: 111; CDR2 comprises an amino acid sequence of SEQ ID NO: 140; CDR3 comprises an amino acid sequence of SEQ ID NO: 171;

CDR1 comprises an amino acid sequence of SEQ ID NO: 112; CDR2 comprises an amino acid sequence of SEQ ID NO: 141; CDR3 comprises an amino acid sequence of SEQ ID NO: 172;

CDR1 comprises an amino acid sequence of SEQ ID NO: 113; CDR2 comprises an amino acid sequence of SEQ ID NO: 142; CDR3 comprises an amino acid sequence of SEQ ID NO: 173;

CDR1 comprises an amino acid sequence of SEQ ID NO: 114; CDR2 comprises an amino acid sequence of SEQ ID NO: 143; CDR3 comprises an amino acid sequence of SEQ ID NO: 174; or

CDR1 comprises an amino acid sequence of SEQ ID NO: 115; CDR2 comprises an amino acid sequence of SEQ ID NO: 144; CDR3 comprises an amino acid sequence of SEQ ID NO: 175.

6. The chimeric protein of claim 1, wherein the targeting moiety comprises the amino acid sequence of SEQ ID NO: 58 or any one of SEQ ID NOS: 2 to 42, 46 to 57, or 59 to 86.

7. The chimeric protein of claim 1, wherein the mutation is one or more of K133A, M148A, R149A, or L153A with respect to SEQ ID NO: 176 or 177.

8. The chimeric protein of claim 1, wherein the FAP binding agent comprises one or more additional targeting moieties that recognize a tumor antigen or an antigen on an immune cell selected from a T cell, a B cell, a dendritic cell, a macrophage, neutrophil, and a NK cell.

9. The chimeric protein of claim 8, wherein the one or more additional targeting moieties recognize PD-1, PD-L1, PD-L2, CTLA4, OX40L, OX40, CD20, XCR1, and Clec9A.

10. The chimeric protein of claim 1, wherein the F2 fibroblast is associated with a disease selected from cancer, infections, immune disorders, autoimmune disease, fibrotic diseases, and cardiovascular disease.

11. A recombinant nucleic acid encoding the chimeric protein of claim 1, or a Fc-based component thereof.

12. A host cell comprising the nucleic acid of claim 11.

13. The chimeric protein of any one of claims 1-10 for use in treating cancer, infections, immune disorders, fibrotic diseases, and/or autoimmune diseases that are related to the FAP protein, comprising administering an effective amount of the chimeric protein to a patient in need thereof.

14. The chimeric protein of any one of claims 1-10, for use as a medicament.

15. Use of the chimeric protein of any one of claims 1-10 in the manufacture of a medicament for treating cancer, infections, immune disorders, fibrotic diseases, and/or autoimmune diseases that are related to the FAP protein.