activated T cells, as well as activated B cells and platelets, and under inflammatory conditions it is also induced in monocytic cells, natural killer cells, mast cells, and basophils.

Because CD40 can activate both the innate and adaptive immune system, it has been recognized as a suitable target for tumor immunotherapy. Several reports have confirmed that CD40 stimulation can enhance anti-tumor immune responses by means of dendritic cell maturation. Activation of dendritic cells with agonists of CD40 results in their increased survival, secretion of IL-1, IL-6, IL-8, IL-12, TNF-α, and macrophage inflammatory protein-1α. Additionally, CD40 activation induces the upregulation of costimulatory molecules such as MHC class II, LFA-3, CD80, and CD86 and promotes antigen presentation, priming and cross-priming of T helper cells (Th) and cytotoxic T lymphocytes (CTL), respectively. Agonistic antibodies against CD40 have proved efficacious in preclinical murine tumor models. However, although their use in the clinic has shown some anti-tumor efficacy, clinical development of agonistic anti-CD40 antibodies has likely been hampered by dose-limiting toxicities and resulting low efficacies.

[2] Thus, there remains a need for new CD40-specific binding proteins, and for therapeutic and diagnostic approaches for the treatment and characterization of diseases, including cancer, benefitting from CD40-specific binding and activation. In particular, there is a need for new generation agonists that can effectively engage CD40 while avoiding undesired side effects.

SUMMARY ~~OF THE INVENTION~~

[3] Based on the disclosure provided herein, those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific ~~embodiment~~examples of the ~~invention~~disclosure described herein. Such equivalents are intended to be encompassed by the following ~~embodiment~~examples (E).

E1. A recombinant protein comprising a first ankyrin repeat domain that specifically binds fibroblast activation protein (FAP) and a second ankyrin repeat domain that specifically binds CD40.

E2. The recombinant protein of E1, further comprising a third ankyrin repeat domain that specifically binds CD40.

E3. The recombinant protein of E2, wherein said ankyrin repeat domains are arranged, from the N-terminus to C-terminus, according to the following formula: (FAP-binding domain) – (CD40 binding domain) – (CD40 binding domain).

E4 The recombinant protein of any one of E1-E3, further comprising a half-life extending moiety.

E5. The recombinant protein of E4, wherein said half-life extending moiety comprises a fourth ankyrin repeat domain that specifically binds serum albumin.

E148. The recombinant protein of any one of E1-E117 and E120-E122, or the nucleic acid of E118 or E119, or the pharmaceutical composition of E131 for use in the treatment of a medical condition in a subject.

E149. The recombinant protein for use of E148, wherein said medical condition is cancer.

E150. Use of the recombinant protein of any one of E1-E117 and E120-E122, the nucleic acid of E118 or E119, or the pharmaceutical composition of E131 in the manufacture of a medicament for treating cancer in a subject.

E151. Use of the recombinant protein of any one of E1-E117 and E120-E122, the nucleic acid of E118 or E119, or the pharmaceutical composition of E131 for treating a medical condition in a subject.

E152. The use of E151, wherein said medical condition is cancer.

E153. A kit comprising a container, a composition within the container comprising the recombinant protein of any one of E1-E117 and E120-E122, or the nucleic acid of E118 or E119, or the pharmaceutical composition of E131, and a package insert containing instructions for administering a therapeutically effective amount of the recombinant protein, the nucleic acid or the pharmaceutical composition for treatment of a patient in need thereof.

E154. A method of inducing an anti-tumor immunological memory in a mammal, including a human, the method comprising the step of administering to said mammal the recombinant protein of any one of E1-E117 and E120-E122, the nucleic acid of E118 or E119, or the pharmaceutical composition of E131.

E155. The method of E154, wherein the immunological memory is not limited to FAP-related antigens.

E156. The recombinant protein of any one of E1-E117 and E120-E122, wherein said recombinant protein is capable of preferentially localizing and/or accumulating in a tumor in a mammal, including a human.

E157. The recombinant protein of E156, wherein said tumor comprises cells that express FAP.

E158. The recombinant protein of any one of E1-E117, E120-E122 and E156-E157, wherein said recombinant protein is capable of inducing an anti-tumor immunological memory in a mammal, including a human.

E159. The recombinant protein of E158, wherein said immunological memory is not limited to FAP-related antigens.

[3a] In one aspect, the present disclosure refers to a recombinant protein comprising: a first ankyrin repeat domain that specifically binds serum albumin, a second ankyrin repeat domain that specifically binds fibroblast activation protein (FAP), a third ankyrin repeat domain that specifically binds CD40, and a fourth ankyrin repeat domain that specifically binds CD40, wherein said ankyrin repeat domains are arranged, from the N-terminus to the C-terminus, according to the following formula: (serum albumin binding domain) – (FAP-binding domain) – (CD40 binding domain) – (CD40 binding domain).

[3b] In one aspect, the present disclosure refers to a recombinant protein comprising an amino acid sequence that is at least 90% identical to SEQ ID NO: 5, wherein said recombinant protein binds human FAP, human CD40, and human serum albumin with a K_D value of or below 100 nM, preferably wherein said recombinant protein comprises the amino acid sequence of SEQ ID NO: 5 or SEQ ID NO: 6.

[3c] In one aspect, the present disclosure refers to a nucleic acid encoding any one of the recombinant proteins as disclosed herein or an ankyrin repeat domain as defined herein.

[3d] In one aspect, the present disclosure refers to a pharmaceutical composition comprising any one of the recombinant proteins as disclosed herein or the nucleic acid as disclosed herein, and optionally a pharmaceutically acceptable carrier or excipient.

[3e] In one aspect, the present disclosure refers to a host cell comprising the nucleic acid as disclosed herein.

[3f] In one aspect, the present disclosure refers to a method for producing any one of the recombinant proteins as disclosed herein, comprising the step of culturing the host cell as disclosed herein under conditions wherein said recombinant protein is expressed.

[3g] In one aspect, the present disclosure refers to use of any one of the recombinant proteins as disclosed herein, the nucleic acid as disclosed herein, or the pharmaceutical composition as disclosed herein, in the manufacture of a medicament for treating a medical condition in a subject, preferably a human, in need thereof, preferably wherein said medical condition is cancer, and preferably wherein said cancer is a solid tumor.

[4] The use of section headings herein is merely for the convenience of reading, and not intended to be limiting per se. The entire document is intended to be viewed as a unified disclosure, and it should be understood that all combinations of features described herein are contemplated.