SUMMARY

This summary is provided to introduce a selection of concepts in a simplified form that are further described below in the Detailed Description. This summary is not intended to identify key features of the claimed subject matter, nor is it intended to be used as an aid in determining the scope of the claimed subject matter.

In one example, the present disclosure provides targeted complement-activating molecules comprising a targeting or target-binding domain and a complement-activating serine protease effector domain. In one aspect, the present disclosure refers to a targeted complement-activating molecule comprising: (a) a target-binding domain; and (b) a complement-activating serine protease effector domain. In some examples, the target-binding domain is derived from an antibody. In some examples, the target-binding domain comprises an antigen-binding fragment of an antibody. In some examples, the complement-activating serine protease effector domain is catalytically active, while in other examples the complement-activating serine protease effector domain is in a zymogen form. In some examples, the target-binding domain binds to an antigen present on a cell, such as CD20, CD38, or CD52. In other examples, the target-binding domain binds to an antigen present on a microbial pathogen, such as a bacterial pathogen, a viral pathogen, a fungal pathogen, or a parasitic pathogen.

In some examples, the targeted complement-activating molecules comprise a fusion protein comprising the N-terminus of the serine protease effector domain fused to the C-terminus of the antibody heavy chain or fragment thereof or to the C-terminus of the antibody light chain or fragment thereof. In other examples, the fusion protein comprises the C-terminus of the serine protease effector domain fused to the N-terminus of the antibody heavy chain or fragment thereof or to the N-terminus of the antibody light chain or fragment thereof. In some examples, the targeted complement-activating molecules comprise such a fusion protein and a second antibody chain, which is a light chain or fragment thereof if the fusion protein comprises a heavy chain or fragment thereof and which is a heavy chain or fragment thereof if the fusion protein comprises a light chain or fragment thereof. In some examples, the targeted complement-activating molecules comprise a fusion protein comprising the N-terminus of the serine protease effector domain fused to the C-terminus of a single-chain antibody or fragment thereof, or a fusion protein comprising the C-terminus of the serine protease effector domain fused to the N-terminus of a single-chain antibody or fragment thereof.

In some examples, the serine protease effector domain comprises complement factor D or a fragment thereof, C1r or a fragment thereof, C1s or a fragment thereof, MASP-2 or a fragment thereof, MASP-3 or a fragment thereof, MASP-1 or a fragment thereof, C2a or a fragment thereof, or Bb or a fragment thereof.

Also provided herein are polynucleotides encoding targeted complement-activating molecules or portions thereof, and cloning vectors or expression cassettes comprising such polynucleotides. In one aspect, the present disclosure refers to a polynucleotide encoding the molecule as disclosed herein. In one aspect, the present disclosure refers to a polynucleotide encoding the fusion protein as disclosed herein. In another aspect, the present disclosure refers to a cloning vector or expression cassette comprising the polynucleotide as disclosed herein. In another aspect, the present disclosure refers to a cloning vector or expression cassette comprising a first polynucleotide encoding the fusion protein as disclosed herein and a second polynucleotide; wherein the second polynucleotide encodes an antibody heavy chain or fragment thereof if the fusion protein comprises an antibody light chain or fragment thereof, and the second polynucleotide encodes an antibody light chain or fragment thereof if the fusion protein comprises an antibody heavy chain or fragment thereof. In yet another aspect, the present disclosure refers to a first cloning vector or expression cassette comprising a first polynucleotide encoding the fusion protein as disclosed herein and a second cloning vector or expression cassette comprising a second polynucleotide; wherein the second polynucleotide encodes an antibody heavy chain or fragment thereof if the fusion protein comprises an antibody light chain or fragment thereof, and the second polynucleotide encodes an antibody light chain or fragment thereof if the fusion protein comprises an antibody heavy chain or fragment thereof.

Further provided herein are host cells expressing targeted complement-activating molecules and methods of producing targeted complement-activating molecules comprising culturing the host cells under conditions allowing for expression of the molecules and isolating the molecules. In one aspect, the present disclosure refers to a host cell expressing the molecule as disclosed herein, or comprising the cloning vector(s) or expression cassette(s) as disclosed herein. In one aspect, the present disclosure refers to a method of producing a molecule comprising: (a) a target-binding domain; and (b) a complement-activating serine protease effector domain; the method comprising culturing the host cell as disclosed herein under conditions allowing for expression of the molecule and isolating the molecule.

In one aspect, the present disclosure refers to a composition comprising the molecule as disclosed herein and one or more excipients.

Also provided herein are methods of activating at least one complement pathway in a mammalian subject using the targeted complement-activating molecules. In one aspect, the present disclosure refers to use of the molecule as disclosed herein or the composition as disclosed herein in the manufacture of a medicament for activating at least one complement pathway in a mammalian subject. In some examples, the targeted complement-activating molecules may be used to induce complement dependent cytotoxicity (CDC), complement-dependent cellular cytotoxicity (CDCC), or complement-dependent cellular phagocytosis (CDCP) in a target cell. In one aspect, the present disclosure refers to use of the molecule as disclosed herein or the composition as disclosed herein in the manufacture of a medicament for inducing complement dependent cell death (CDC), complement-dependent cell-mediated cytotoxicity (CDCC), or complement-dependent cellular phagocytosis (CDCP) in a target cell. In some examples, the targeted complement-activating molecules may be used to treat cancer, autoimmune disease, or a microbial infection, such as a bacterial infection, a viral infection, a fungal infection, or a parasitic infection. In one aspect, the present disclosure refers to use of the molecule as disclosed herein or the composition as disclosed herein in the manufacture of a medicament for treating cancer, autoimmune disease, or a microbial infection.

In one aspect, the present disclosure refers to a method of inducing complement-dependent cell-mediated cytotoxicity (CDCC) or complement-dependent cellular phagocytosis (CDCP) toward a target cell, comprising contacting the target cell with the molecule as disclosed herein or the composition as disclosed herein, wherein said contacting results in complement deposition on the target cell, thereby leading to complement-mediated cell death.

BRIEF DESCRIPTION OF THE DRAWINGS

The foregoing aspects and many of the attendant advantages of this invention will become more readily appreciated as the same become better understood by reference to the following detailed description, when taken in conjunction with the accompanying drawings, wherein:

FIGURE 1 is a diagram illustrating the classical, lectin, and alternative complement pathways.

FIGURE 2 graphically illustrates the surface levels of CD20, CD55, and CD59 on CD20+ cancer cell lines Ramos, Kasumi-2, and SU-DHL-8. Cells were stained with primary