CLAIMS

1. A TNF-alpha variant comprising a polypeptide that specifically binds to TNFR2, wherein the polypeptide comprises an amino acid sequence of SEQ ID NO: 10 or SEQ ID NO: 9.

2. The TNF-alpha variant of claim 1, wherein the polypeptide comprises an amino acid sequence of SEQ ID NO: 10.

3. A TNF-alpha variant molecule comprising one or more TNF-alpha variants of any one of claims 1-2.

4. The TNF-alpha variant molecule of claim 3, wherein the TNF-alpha variant molecule comprises a plurality of TNF-alpha variants, optionally at least three TNF-alpha variants;

   optionally wherein each TNF-alpha variant comprises three TNF-alpha variants, wherein one of the three TNF-alpha variants comprises a polypeptide comprising an amino acid sequence of SEQ ID NO: 9 and two of the three TNF-alpha variants comprise a polypeptide of an amino acid sequence of SEQ ID NO: 10.

5. The TNF-alpha variant molecule of claim 3 or claim 4, wherein the TNF-alpha variant molecule comprises a linker between the TNF-alpha variants, optionally a linker comprising an amino acid sequence of SEQ ID NO: 16;

   optionally wherein the TNF-alpha variant molecule comprises more than one linker.

6. The TNF-alpha variant molecule of any one of claims 3-5, wherein the TNF-alpha variant molecule comprises the amino acid sequence of SEQ ID NO: 15.

7. A TNF-alpha variant fusion molecule comprising the TNF-alpha variant molecule of any one of claims 3-6 and an Fc domain.

8. A TNF-alpha variant fusion molecule comprising from N-terminus to C-terminus:
   a) a first TNF-alpha variant of any one of claims 1-2;
   b) a first linker;
   c) a second TNF-alpha variant of any one of claims 1-2;
   d) a second linker;
   e) a third TNF-alpha variant of any one of claims 1-2;

f) a third linker; and

g) an Fc domain.

9. The TNF-alpha variant fusion molecule of claim 7 or claim 8, wherein the Fc domain:
(i) is a human IgG1 isotype, optionally wherein the human IgG1 isotype Fc domain comprises:
(a) a L234A mutation and a L235A mutation; and/or
(b) a P331S mutation;
(ii) has:
a) reduced or eliminated binding to FcγRI, FcγRII, FcγRIII, or C1q;
b) reduced or eliminated antibody-dependent cellular cytotoxicity (ADCC) and/or reduced complement binding activity; or
c) any combination of a) and b);
(iii) comprises the amino acid sequence of SEQ ID NO: 17;
(iv) is located at a C-terminus of the TNF-alpha variant fusion molecule; and/or
(v) comprises the amino acid sequence of SEQ ID NO: 23.

10. The TNF-alpha variant, TNF-alpha variant molecule, or TNF-alpha variant fusion molecule of any one of claims 1-9, wherein the TNF-alpha variant, TNF-alpha variant molecule, or TNF-alpha variant fusion molecule:
a) binds to TNFR2 with over a 20 fold affinity compared to TNFR1, optionally as determined by bio-layer interferometry;
b) binds to and activates TNFR2 with an EC50 of at least about 5 ng/mL, optionally as determined by flow cytometry using human TNFR2 expressing (HEK293-NF-kB/Luc-TNFR2) cells and human TNFR2 non-expressing HEK293-NF-kB/Luc) cells;
c) has increased Tm compared to SEQ ID NO: 21 or SEQ ID NO: 22, optionally as determined by differential scanning fluorimetry (DSF);
d) has increased serum stability compared to SEQ ID NO: 21 or SEQ ID NO: 22, optionally as determined by Size Exclusion Chromatography; or
e) any combination of a)-d).

11. An isolated nucleic acid or an expression vector comprising an isolated nucleic acid, wherein the isolated nucleic acid comprises a nucleic acid sequence that encodes the TNF-alpha variant, TNF-alpha variant molecule, or TNF-alpha variant fusion molecule of

any one of claims 1-10, optionally wherein the isolated nucleic acid encodes an amino acid sequence of SEQ ID NO: 23.

12. A host cell:
(a) comprising the isolated nucleic acid of claim 11 or the expression vector of claim 11; or
(b) that expresses the TNF-alpha variant, TNF-alpha variant molecule, or TNF-alpha variant fusion molecule of any one of claims 1-10.

13. A method of manufacturing the TNF-alpha variant, TNF-alpha variant molecule, or TNF-alpha variant fusion molecule of any one of claims 1-10.

14. A pharmaceutical composition comprising the TNF-alpha variant, TNF-alpha variant molecule, or TNF-alpha variant fusion molecule of any one of claims 1-10 and a pharmaceutically acceptable carrier.

15. Use of the TNF-alpha variant, TNF-alpha variant molecule, or TNF-alpha variant fusion molecule of any one of claims 1-10 or the pharmaceutical composition of claim 14 in the manufacture of a medicament for:
(a) treating an inflammatory disease or disorder, optionally wherein the inflammatory disease or disorder is selected from the group consisting of inflammatory bowel disease (IBD), ulcerative colitis, Crohn's disease, primary sclerosing cholangitis, celiac disease, atopic dermatitis, alopecia areata, vitiligo, dermatomyositis, hidradenitis suppurativa, systemic lupus erythematosus, rheumatoid arthritis, ankylosing spondylitis, multiple sclerosis, myasthenia gravis, Behcet's disease, and type I diabetes;
(b) treating a disease or disorder associated with dysregulation of Treg cells, autoreactive T cells, or HLA-associated susceptibility; or
(c) selectively activating TNFR2 in an individual.

16. The TNF-alpha variant, TNF-alpha variant molecule, or TNF-alpha variant fusion molecule of any one of claims 1-10 or the pharmaceutical composition of claim 14, for use in therapy.