

What is claimed is:

1. A polypeptide comprising a targeting moiety that binds to a target cell and an effector binding/modulating moiety, wherein the effector binding/modulating moiety is a IL-2 mutein polypeptide (IL-2 mutein).
2. The polypeptide of claim 1, wherein the targeting moiety comprises an antibody that binds to a target protein on the surface of a target cell.
3. The polypeptide of claim 1, wherein the antibody is an antibody that binds to MAdCAM, OAT1, OCT2, FXYP2, TSPAN7, DPP6, HEPACAM2, TMEM27, or GPR119.
4. The polypeptide of claim 1, wherein the targeting moiety comprises an anti-MAdCAM antibody.
5. The polypeptide of claim 1, wherein the IL-2 mutein comprises a IL-2 sequence of SEQ ID NO: 6, wherein peptide comprises a mutation at a position that corresponds to position 53, 56, 80, or 118 of SEQ ID NO: 6.
6. The polypeptide of claim 5, wherein the mutation is a L to I mutation at position 53, 56, 80, or 118.
7. The polypeptide of claim 5, further comprising a mutation at one or more positions of 29, 31, 35, 37, 48, 69, 71, 74, 88, and 125 in SEQ ID NO: 6.
8. The polypeptide of any one of the preceding claims, wherein the mutation in the mutein is one or more of E15Q, H16N, Q22E, D84N, E95Q, or Q126E.
9. The polypeptide of any one of the preceding claims, wherein the mutein comprises a N29S, Y31S, Y51H, K35R, T37A, K48E, V69A, N71R, Q74P, N88D, N88R, C125A, or C125S mutation in SEQ ID NO: 6.
10. The polypeptide of any of the preceding claims, wherein the IL-2 mutein is fused or linked to a Fc peptide.

11. The polypeptide of claim 10, wherein the Fc peptide comprises a mutation at one or more of positions of L234, L247, L235, L248, G237, and G250.
12. The polypeptide of claim 11, wherein the Fc peptide comprises a L234A mutation, a L235A mutation, and/or a G237A mutation.
13. The polypeptide of claim 1, wherein the polypeptide comprises a first chain and a second chain that form the polypeptide, wherein
the first chain comprises:
V_H-H_c-Linker-C₁, wherein V_H is a variable heavy domain that binds to the target cell with a V_L domain of the second chain; H_c is a heavy chain of antibody comprising CH1-CH2-CH3 domain, the Linker is a glycine/serine linker, and C₁ is a IL-2 mutein fused to a Fc protein in either the N-terminal or C-terminal orientation; and
the second chain comprises:
V_L-L_c, wherein V_L is a variable light chain domain that binds to the target cell with the V_H domain of the first chain, and the L_c domain is a light chain CK domain.
14. The polypeptide of claim 13, wherein the V_H and V_L domain are anti-MAdCAM variable domains that bind to MAdCAM expressed on a cell.
15. The polypeptide of claim 13, wherein the IL-2 mutein comprises a mutation at a position that corresponds to position 53, 56, 80, or 118 of SEQ ID NO: 6.
16. The polypeptide of claim 15, wherein the mutation is a L to I mutation at position 53, 56, 80, or 118.
17. The polypeptide of claim 15, wherein the mutein further comprises a mutation at a position that corresponds to position 69, 75, 88, or 125, or any combination thereof.
18. The polypeptide of claim 15, comprises a mutation selected from the group consisting of: at one of L53I, L56I, L80I, and L118I and the mutations of V69A, Q74P, N88D or N88R, and optionally C125A or C125S.
19. Use of the polypeptide of any one of claims 1 to 18 in the manufacture of a medicament for treatment of inflammatory bowel disease in a subject.

20. Use of the polypeptide of polypeptide of any of claims 1 to 18 in the manufacture of a medicament for the treatment of auto-immune hepatitis, primary sclerosing cholangitis, Type 1 diabetes, a transplant, or GVHD.