67(5):741-8; Leitner et al., J. Immunol. 2015 195(2):477-87). CD2 is expressed on all T cells, but expression is greater on memory T cells as compared to naïve or regulatory T cells (Chamian et al., Proc. Natl. Acad. Sci. 2005 102(6):2075-80; Rigby et al., J. Clin. Invest. 2015 125(8):3285-96). In humans, CD2 is also expressed on NK cells and some dendritic cell populations. Interaction of CD2 on T cells or NK cells and LFA3 on accessory cells can deliver a costimulatory signal for both naïve lymphocytes and previously activated or memory lymphocytes. This costimulatory signal potentially involves increasing the avidity of cell-cell interaction and/or delivering a direct costimulatory signal through CD2 (Kaizuka et al. J. Cell Biol. 2009 185(3):521-34; Skanland et al., Biochem. J. 2014 460(3):399-410). As such, targeting CD2, *e.g.*, using soluble LFA3 molecules, may have therapeutic benefit for treating autoimmune diseases, such as Type 1 Diabetes (T1D) and/or psoriatic arthritis. Accordingly, in view of the prominent role of CD2 and LFA3 in mediating immune responses, the need exists for developing strategies for modulating the activity of CD2 as well as depleting CD2-expressing immune effector cells.

SUMMARY OF THE INVENTION

[0005a] In one aspect, provided herein is an isolated polypeptide molecule that specifically binds to CD2, wherein the polypeptide molecule comprises an amino acid sequence having at least about 95% identity to the amino acid sequence of SEQ ID NO: 69, and wherein the polypeptide molecule consists of one or more substitutions at residues 36, 38, 43, 45, 77, and 86 relative to SEQ ID NO: 3, numbered according to SEQ ID NO: 3.

[0005b] In another aspect, provided herein is an isolated polypeptide that specifically binds to CD2, comprising an LFA3 domain comprising an amino acid sequence having at least about 95% identity to an amino acid sequence selected from the group consisting of SEQ ID NOs: 17-41, wherein the LFA3 domain comprises one or more substitutions at residues 36, 38, 43, 45, 77, and 86 relative to SEQ ID NO: 3, numbered according to SEQ ID NO: 3.

[0005c] In another aspect, provided herein is an isolated polypeptide comprising an LFA3 domain, wherein the LFA3 domain comprises an amino acid sequence having at least 95% identity to the amino acid sequence of SEQ ID NO: 3 with one or more mutations at residues 36, 38, 43 and 86, numbered according to SEQ ID NO: 3.

[0005d] In another aspect, provided herein is a pharmaceutical composition comprising the polypeptide molecule as described herein and a pharmaceutically acceptable carrier or excipient.

[0005e] In yet another aspect, provided herein is a use of the pharmaceutical composition as described herein in the manufacture of a medicament for treating an immune disease, disorder or condition mediated by CD2 in a human subject in need thereof, wherein an effective amount of the pharmaceutical composition is to be administered to the subject, wherein said disease, disorder or condition is selected from the group consisting of: type 1 diabetes, psoriasis, plaque psoriasis, palmoplantaris pustulosis, pustular psoriasis of palms and soles, pustulosis palmaris et plantaris, pustulosis of palms and soles, atopic dermatitis, lichen planus, graft-versus-host disease (GVHD), vitiligo, Pityriasis rubra pilaris, transplantation, psoriatic arthritis, a disease, disorder, or condition requiring allogeneic hematopoietic stem cell transplantation, thalassemia, sickle cell disease, glanzmann thrombasthenia, Wiskott-Aldrich syndrome, chronic-granulomatous disease, severe congenital neutropenia, leukocyte adhesion deficiency, Schwachman-Diamond syndrome, Diamond-Blackfan anemia, Fanconi anemia, Dyskeratosis-congenita, Chediak-Higashi syndrome, aplastic anemia, alopecia areata, and T cell lymphoma.

[0005f] In yet another aspect, provided herein is the pharmaceutical composition as described herein for use in therapy.

[0006] The present disclosure provides, in part, the discovery that certain LFA3-Fc fusion polypeptides modulate the activity of CD2, as well as deplete CD2-expressing cells. Modulation of CD2-expressing cells may have beneficial effects in the treatment of autoimmune disease, such as diabetes and or psoriatic arthritis. This application discloses LFA3 polypeptide molecules, e.g., variant LFA3 polypeptide molecules, e.g., variant LFA3 fusion polypeptide molecules, e.g., variant LFA3-Fc fusion polypeptide molecules. In certain aspects, the LFA3 polypeptide molecules bind to CD2, modulate CD2-LFA3 interaction, and selectively deplete CD2-expressing memory T cells.

[0007] Without wishing to be bound by theory, the LFA3 polypeptide molecules disclosed herein, e.g., the variant LFA3-Fc fusion polypeptide molecules, e.g., M1d1 (also referred to herein as M1-d1, LFA3-Fc M1d1 and LFA3-Fc M1-d1), modulate the function of and selective depletion of CD2+ T_{EM} cells to rebalance the regulatory/T_{EM} cell numbers. In some embodiments, the LFA3 polypeptide molecules disclosed herein, e.g., the variant

LFA3-Fc fusion polypeptide molecules, e.g., M1d1, promote elimination and/or suppression of pathogenic T effector cells. In some embodiments, the LFA3 polypeptide molecules disclosed herein, e.g., the variant LFA3-Fc fusion polypeptide molecules, e.g., M1d1,