**CLAIMS**

1. A variant Adenosine Deaminase 2 (ADA2) protein or a catalytically active portion thereof, comprising a modification(s) in the sequence of amino acids of an unmodified ADA2 protein or a catalytically active portion thereof, wherein:

a) the catalytically active portion comprises the ADA domain that corresponds to residues 77-473 of the sequence of amino acids set forth in SEQ ID NO:5;

b) the unmodified ADA2 protein or catalytically active portion thereof is selected from among:

i) the sequence of amino acids set forth in any of SEQ ID NOS: 5, 326-334, 340, 375 and 380-383, or a catalytically active portion thereof;

ii) the sequence of amino acids set forth in any of SEQ ID NOS: 5, 326-334, 340, 375 and 380-383 or a catalytically active portion thereof, with all or a portion of the putative receptor binding (PRB) domain deleted, wherein the PRB domain consists of residues corresponding to residues 98-156 of SEQ ID NO:5; and

iii) the sequence of amino acids set forth in any of SEQ ID NOS: 5, 326-334, 340, 375 and 380-383 or a catalytically active portion thereof, with all or a portion of the PRB domain deleted, and comprising a linker in place thereof, wherein:

the PRB domain consists of residues 98-156 with reference to SEQ ID NO:5; and

the linker is $(GGGGS)_n$, where n = 1-5, or is $(Gly)_n$, where n = 2-20;

c) the variant ADA2 protein or catalytically active portion thereof has up to 2, 3, 4, 5, 6, 7, 8, 9 or 10 amino acid modifications, in addition to any deletion of all or a portion of the PRB domain, compared to the unmodified ADA2 protein or catalytically active portion thereof;

d) the amino acid modification(s) are selected from among amino acid replacement(s), deletion(s) and insertion(s);

e) the variant ADA2 protein or catalytically active portion thereof comprises an amino acid replacement at one or both of positions corresponding to amino acid residues 219 and 262, selected from among replacements corresponding to R219K, R219Q, R219N, S262M, and S262N, with reference to amino acid positions set forth in SEQ ID NO:5;

f) the variant ADA2 protein, when in dimer form, exhibits increased adenosine deaminase activity compared to the corresponding dimer form of the unmodified ADA2 protein of SEQ ID NO:5 or dimer form of the corresponding catalytically activity portion thereof; and

g) adenosine deaminase activity is catalysis of the conversion of adenosine to inosine.

2. The variant ADA2 protein or catalytically active portion thereof of claim 1, comprising amino acid modifications in addition to the replacements at positions R219 or S262, or R219 and S262, that confer increased adenosine deaminase activity, reduced heparin binding, longer serum half-life, altered pH optimum, or increased thermal stability, or that add a glycosylation site(s), compared to the unmodified ADA2 protein or to the catalytically active portion thereof, wherein:

replacements that confer increased adenosine deaminase activity are selected from among K11E, R20E, L221A, L221V, L221G, H264Q, H264G, R366D, R366E, K371D, K371E, K372A, K372D, K372E, K452D, K452E, K11A/R20A, and R20A/K371A, with reference to amino acid positions set forth in SEQ ID NO:5;

replacements that confer reduced heparin binding are selected from among R20A, R20D, R20E, S262N, R366A, R366D, R366E, K371A, K371D, K371E, K372A, K372D, K372E, K452E, K11A/R20A, K11A/R20A/K371A, R20A/K371A, K11A/K371A, S262N/K371D, S262N/K371E, R20E/S262N, R20E/S262N/K371D, and R20E/S262N/K371E, with reference to amino acid positions set forth in SEQ ID NO:5;

replacements that confer longer serum half-life are selected from among R20E and K371D, with reference to amino acid positions set forth in SEQ ID NO:5;

replacements that confer altered pH optimum are selected from among R20E, R219Q, S262N, K371D, K371E, R219Q/S262N, S262N/K371D, S262N/K371E, R20E/R219Q, R20E/S262N, R20E/S262N/K371D, R20E/S262N/K371E, R219Q/K371D, R219Q/K371E, R20E/R219Q/K371E, R20E/R219Q/K371D, R219Q/S262N/K371E, R219Q/S262N/K371D, R20E/R219Q/S262N, R20E/R219Q/S262N/K371E, and R20E/R219Q/S262N/K371D, with reference to amino acid positions set forth in SEQ ID NO:5;

the replacement K371E, with reference to amino acid positions set forth in SEQ ID NO:5, confers increased thermal stability; and

amino acid modifications that result in an additional glycosylation site(s) are selected from among --→N1/--→A2/--→S3, R20N/V22S, K371N/D373S, K372N/I374S, T403N/H405S, G404N/P406S, R125N/P126A, S127N/K129S, P126N/E128T, R112N/I114T, I134N/L135C/L136T, I134N/L135S/L136T, R142N/Q144S, E137N/Y139T, and P111N/G113S, with reference to amino acid positions set forth in SEQ ID NO:5.

3. The variant ADA2 protein or catalytically active portion thereof of claim 1 or claim 2, wherein the variant ADA2 protein does not contain a modification selected from among an amino acid replacement corresponding to H7R, G18A, G18R, G18V, I64T, A80D, H83Q, V90A, C108G, A120V, H121R, W133G, R125C, R140Q, K141R, R142W, P164L, P222L, W235S, H306R, E330G, W333G, V365L, Y424C, and F464S, or a deletion corresponding to R8-K14del→--, with numbering with reference to amino acid residues set forth in SEQ ID NO:5.

4. The variant ADA2 protein or catalytically active portion thereof of any of claims 1-3, wherein the variant ADA2 protein comprises one or more amino acid replacement(s) selected from among R20A, R20D, R20E, S262N, R366A, R366D, R366E, K371A, K371D, K371E, K372A, K372D, K372E and K452E, with reference to amino acid positions set forth in SEQ ID NO:5.

5. The variant ADA2 protein or catalytically active portion thereof of any of claims 1-3, comprising one or more amino acid replacement(s) corresponding to K11E; K371A; K371D; K371E; K372A; K372D; K372E; K452D; K452E; R20A; R20D; R20E; R366A; R366D; and R366E, with reference to amino acid positions set forth in SEQ ID NO:5.

6. The variant ADA2 protein or catalytically active portion thereof of any of claims 1-5, wherein the unmodified ADA2 protein or catalytically active portion thereof lacks all or a portion of the PRB domain.

7. The variant ADA2 protein or catalytically active portion thereof of claim 6, wherein the unmodified ADA2 protein consists of the sequence of amino acids set forth in any of SEQ ID NOS:548-550 and 579.

8. The variant ADA2 protein or catalytically active portion thereof of any of claims 1-6, wherein the unmodified ADA2 protein is a homodimer, and the monomer form comprises the sequence of amino acid residues set forth in any of SEQ ID NOS:5, 548-550 and 579.

9. A catalytically active portion of the variant ADA2 protein of any of claims 1-5, wherein the unmodified ADA2 protein is a homodimer of corresponding catalytically active portions of the polypeptide whose sequence is set forth in SEQ ID NO:5, wherein corresponding portions are determined by alignment.

10. The variant ADA2 protein or catalytically active portion thereof of any of claims 1-6, wherein the unmodified ADA2 protein comprises the sequence of amino acids set forth in any of SEQ ID NOS: 5, 326-330, 380-383, 548-550 and 579 or is a catalytically active portion thereof.

11. The variant ADA2 protein or catalytically active portion thereof of any of claims 1-6, wherein the unmodified ADA2 protein consists of the sequence of amino acids set forth in any of SEQ ID NOS: 5, 326-330, 380-383, 548-550 and 579 or is a catalytically active portion thereof.

12. The variant ADA2 protein or catalytically active portion thereof of any of claims 1-5, wherein the unmodified ADA2 protein comprises the sequence of amino acids set forth in SEQ ID NO: 5 or a catalytically active portion thereof.

13. The variant ADA2 protein or catalytically active portion thereof of any of claims 1-12, comprising the replacement corresponding to S262N, with reference to amino acid positions set forth in SEQ ID NO:5.

14. The variant ADA2 protein or catalytically active portion thereof of any of claims 1-12, comprising the replacement corresponding to R219K, R219Q, or R219N, with reference to amino acid positions set forth in SEQ ID NO:5.

15. The variant ADA2 protein or catalytically active portion thereof of any of claims 1-12, comprising the replacements corresponding to R219Q/S262N, with reference to amino acid positions set forth in SEQ ID NO:5.

16. The variant ADA2 protein or catalytically active portion thereof of any of claims 1-15, comprising the modifications selected from among any of R219Q/S262N/R20N/V22S, R219Q/S262N/K371N/D373S, R219Q/S262N/K372N/I374S, R219Q/S262N/T403N/H405S, R219Q/S262N/G404N/P406S, R219Q/S262N/C105-T147del→$(Gly)_{15}$, R219Q/S262N/C105-T147del→$(Gly)_{10}$, R219Q/S262N/C105-T147del→$(Gly)_7$, R219Q/S262N/C105-T147del→$(Gly)_5$, R219Q/S262N/C105-T147del→$(Gly)_3$, R219Q/S262N/R125N/P126A, R219Q/S262N/S127N/K129S, R219Q/S262N/P126N/E128T, R219Q/S262N/R112N/I114T, R219Q/S262N/I134N/L135C/L136T, R219Q/S262N/I134N/L135S/L136T, R219Q/S262N/R142N/Q144S, R219Q/S262N/E137N/Y139T, R219Q/S262N/P111N/G113S, R219Q/S262N/F119S, R219Q/S262N/F119K, R219Q/S262N/Y224R, R219Q/S262N/Y224N, R219Q/S262N/Y191S, R219Q/S262N/Y191D, R219Q/S262N/F183K, R219Q/S262N/Y191D/Y224R, R219Q/S262N/F109S, R219Q/S262N/F109A, R219Q/S262N/R118D, R219Q/S262N/R118A, R219Q/S262N/Y139T, R219Q/S262N/Y139A, R219Q/S262N/W133S, R219Q/S262N/W133T, R219Q/S262N/P124A, R219Q/S262N/P124S, R219Q/S262N/V99-Q144del→$(GGGGS)_1$, R219Q/S262N/V99-Q144del→$(GGGGS)_2$, R219Q/S262N/V99-Q144del→$(GGGGS)_3$, R219Q/S262N/C105-T147del→$(GGGGS)_1$, R219Q/S262N/C105-T147del→$(GGGGS)_2$, R219Q/S262N/C105-T147del→$(GGGGS)_3$, R219Q/S262N/K371D/V99-Q144del→$(GGGGS)_1$, R219Q/S262N/K371D/V99-Q144del→$(GGGGS)_2$, R219Q/S262N/K371D/V99-Q144del→$(GGGGS)_3$, R219Q/S262N/K371D/C105-T147del→$(GGGGS)_1$, R219Q/S262N/K371D/C105-T147del→$(GGGGS)_2$, R219Q/S262N/K371D/C105-T147del→$(GGGGS)_3$, R219Q/S262N/C105-T147del→$(Gly)_n$, wherein n is 2 to 20, R219Q/S262N/K11A, R219Q/S262N/K11D, R219Q/S262N/K11E, R219Q/S262N/K13A, R219Q/S262N/K13D, R219Q/S262N/V99-Q144del→$(GGGGS)_n$ wherein n = 1 to 5, R219Q/S262N/C105-T147del→$(GGGGS)_n$, wherein n = 1 to 5, R219Q/S262N/N98-N156del, R219Q/S262N/C105-E148del, R219Q/S262N/C105-T147del, R219Q/S262N/V99-Q144del, R219Q/S262N/K371D/C105-T147del→$(Gly)_n$, wherein n = 2 to 20, R219Q/S262N/K371D/C105-T147del→$(Gly)_{15}$, R219Q/S262N/K371D/C105-T147del→$(Gly)_{10}$, R219Q/S262N/K371D/C105-T147del→$(Gly)_7$, R219Q/S262N/K371D/C105-T147del→$(Gly)_5$, R219Q/S262N/K371D/C105-T147del→$(Gly)_3$, R219Q/S262N/K371D/V99-Q144del→$(GGGGS)_n$, wherein n = 1 to 5, R219Q/S262N/K371D/C105-T147del→$(GGGGS)_n$, wherein n = 1 to 5, R219Q/S262N/K371D/N98-N156del, R219Q/S262N/K371D/C105-E148del, R219Q/S262N/K371D/C105-T147del, R219Q/S262N/K371D/V99-Q144del, R219Q/S262N/K13E, R219Q/S262N/K371A, R219Q/S262N/K372A, R219Q/S262N/K372D, R219Q/S262N/K372E, R219Q/S262N/K452A, R219Q/S262N/K452D, R219Q/S262N/K452E, R219Q/S262N/R20A, R219Q/S262N/R20D,

R219Q/S262N/R366A, R219Q/S262N/R366D, R219Q/S262N/R366E, R219Q/S262N/H264A, R219Q/S262N/H264Q, R219Q/S262N/H264N, R219Q/S262N/H264G, R219K/S262N, R219N/S262N, R219Q/S262N/L221A, R219Q/S262N/L221V, R219Q/S262N/L221G, R219Q/S262N/E179D, R219Q/S262N/E179A, R219Q/S262N/E179S, R219Q/S262N/E179T, R219Q/S262N/E179V, R219Q/S262N/E179G, R219Q/S262N/K11A/R20A, R219Q/S262N/K11A/R20A/K371A, R219Q/S262N/R20A/K371A, R219Q/S262N/K11A/K371A, R219Q/S262N/K26A, R219Q/S262N/K26D, R219Q/S262N/K26E, R219Q/S262N/R217A, R219Q/S262N/R217D, R219Q/S262N/R217E, R219Q/S262N/K258A, R219Q/S262N/K258D, R219Q/S262N/K258E, R219Q/S262N/R277A, R219Q/S262N/R277D, R219Q/S262N/R277E, R219Q/S262N/R283A, R219Q/S262N/R283D, R219Q/S262N/R283E, R219Q/S262N/K309A, R219Q/S262N/K309D, R219Q/S262N/K309E, R219Q/S262N/K317A, R219Q/S262N/K317D, R219Q/S262N/K317E, R219Q/S262N/K321A, R219Q/S262N/K321D, R219Q/S262N/K321E, R219Q/S262N/R352A, R219Q/S262N/R352D, R219Q/S262N/R352E, R219Q/S262N/R441A, R219Q/S262N/R441D, R219Q/S262N/R441E, R219Q/S262N/K444A, R219Q/S262N/K444D, R219Q/S262N/K444E, R219Q/S262N/K461A, R219Q/S262N/K461D, R219Q/S262N/K461E, R219Q/S262N/K469A, R219Q/S262N/K469D, R219Q/S262N/K469E, R219Q/S262N/K470A, R219Q/S262N/K470D, R219Q/S262N/K470E, R219Q/S262N/D86A, R219Q/S262N/D86C, R219Q/S262N/D86E, R219Q/S262N/D86F, R219Q/S262N/D86G, R219Q/S262N/D86H, R219Q/S262N/D86I, R219Q/S262N/D86K, R219Q/S262N/D86L, R219Q/S262N/D86M, R219Q/S262N/D86N, R219Q/S262N/D86P, R219Q/S262N/D86Q, R219Q/S262N/D86R, R219Q/S262N/D86S, R219Q/S262N/D86T, R219Q/S262N/D86V, R219Q/S262N/D86W, R219Q/S262N/D86Y, R219Q/S262N/E179C, R219Q/S262N/E179F, R219Q/S262N/E179H, R219Q/S262N/E179I, R219Q/S262N/E179K, R219Q/S262N/E179L, R219Q/S262N/E179M, R219Q/S262N/E179N, R219Q/S262N/E179P, R219Q/S262N/E179Q, R219Q/S262N/E179R, R219Q/S262N/E179W, R219Q/S262N/E179Y, R219Q/S262N/L221C, R219Q/S262N/L221D, R219Q/S262N/L221E, R219Q/S262N/L221F, R219Q/S262N/L221H, R219Q/S262N/L221I, R219Q/S262N/L221K, R219Q/S262N/L221M, R219Q/S262N/L221N, R219Q/S262N/L221P, R219Q/S262N/L221Q, R219Q/S262N/L221R, R219Q/S262N/L221S, R219Q/S262N/L221T, R219Q/S262N/L221W, R219Q/S262N/L221Y, R219Q/S262N/H264C, R219Q/S262N/H264D, R219Q/S262N/H264E, R219Q/S262N/H264F, R219Q/S262N/H264I, R219Q/S262N/H264K, R219Q/S262N/H264L, R219Q/S262N/H264M, R219Q/S262N/H264P, R219Q/S262N/H264R, R219Q/S262N/H264S, R219Q/S262N/H264T, R219Q/S262N/H264V, R219Q/S262N/H264W, R219Q/S262N/H264Y, R219Q/S262N/S266A, R219Q/S262N/S266C, R219Q/S262N/S266D, R219Q/S262N/S266E, R219Q/S262N/S266F, R219Q/S262N/S266G, R219Q/S262N/S266H, R219Q/S262N/S266I, R219Q/S262N/S266K, R219Q/S262N/S266L, R219Q/S262N/S266M, R219Q/S262N/S266N, R219Q/S262N/S266P, R219Q/S262N/S266Q, R219Q/S262N/S266R, R219Q/S262N/S266T, R219Q/S262N/S266V, R219Q/S262N/S266W, R219Q/S262N/S266Y, R219Q/S262N/K267A, R219Q/S262N/K267C, R219Q/S262N/K267D, R219Q/S262N/K267E, R219Q/S262N/K267F, R219Q/S262N/K267G, R219Q/S262N/K267H, R219Q/S262N/K267I, R219Q/S262N/K267L, R219Q/S262N/K267M, R219Q/S262N/K267N, R219Q/S262N/K267P, R219Q/S262N/K267Q, R219Q/S262N/K267R, R219Q/S262N/K267S, R219Q/S262N/K267T, R219Q/S262N/K267V, R219Q/S262N/K267W, R219Q/S262N/K267Y, R219Q/S262N/V296A, R219Q/S262N/V296C, R219Q/S262N/V296D, R219Q/S262N/V296E, R219Q/S262N/V296F, R219Q/S262N/V296G, R219Q/S262N/V296H, R219Q/S262N/V296I, R219Q/S262N/V296K, R219Q/S262N/V296L, R219Q/S262N/V296M, R219Q/S262N/V296N, R219Q/S262N/V296P, R219Q/S262N/V296Q, R219Q/S262N/V296R, R219Q/S262N/V296S, R219Q/S262N/V296T, R219Q/S262N/V296W and R219Q/S262N/V296Y, with reference to amino acid positions set forth in SEQ ID NO:5.

17. The variant ADA2 protein or catalytically active portion thereof of any of claims 1-15, that comprises amino acid replacements selected from among R219Q/S262N/K371E,

R219Q/S262N/K371D, R219Q/S262N/R20E and R219Q/S262N/K371D/R20E, with reference to amino acid positions set forth in SEQ ID NO:5.

18. The variant ADA2 protein or catalytically active portion thereof of any of claims 1-15 that comprises the modifications corresponding to R219Q/S262N/--→N1/--→A2/--→S3; R219Q/S262N/R20N/V22S; R219Q/S262N/K371N/D373S; R219Q/S262N/K372N/I374S; R219Q/S262N/T403N/H405S; or R219Q/S262N/G404N/P406S, with reference to amino acid positions set forth in SEQ ID NO:5.

19. The variant ADA2 protein or catalytically active portion thereof of any of claims 1-15 that comprises amino acid replacements corresponding to R219Q/S262N/R125N/P126A; R219Q/S262N/S127N/K129S; R219Q/S262N/P126N/E128T; R219Q/S262N/R112N/I114T; R219Q/S262N/I134N/L135C/L136T; R219Q/S262N/I134N/L135S/L136T; R219Q/S262N/R142N/Q144S; R219Q/S262N/E137N/Y139T; or R219Q/S262N/P111N/G113S, with reference to amino acid positions set forth in SEQ ID NO:5.

20. The variant ADA2 protein or catalytically active portion thereof of any of claims 1-19, further comprising a modification in the putative receptor binding (PRB) domain, corresponding to one or more of the modifications selected from among: R125N/P126A; S127N/K129S; P126N/E128T; R112N/I114T; I134N/L135C/L136T; I134N/L135S/L136T; R142N/Q144S; E137N/Y139T; and P111N/G113S, with reference to amino acid positions set forth in SEQ ID NO:5.

21. The variant ADA2 protein or catalytically active portion thereof of any of claims 1-15, comprising amino acid replacements selected from among replacements corresponding to R219Q/S262N/F119S; R219Q/S262N/F119K; R219Q/S262N/Y224R; R219Q/S262N/Y224N; R219Q/S262N/Y191S; R219Q/S262N/Y191D; R219Q/S262N/F183K; R219Q/S262N/Y191D/Y224R; R219Q/S262N/F109S; R219Q/S262N/F109A; R219Q/S262N/R118D; R219Q/S262N/R118A; R219Q/S262N/Y139T; R219Q/S262N/Y139A; R219Q/S262N/W133S; R219Q/S262N/W133T; R219Q/S262N/P124A; and R219Q/S262N/P124S, with reference to amino acid positions set forth in SEQ ID NO:5.

22. The variant ADA2 protein or catalytically active portion thereof of any of claims 1-15 that comprises amino acid modifications selected from among R219Q/S262N/C105-T147del→$(Gly)_{15}$; R219Q/S262N/C105-T147del→$(Gly)_{10}$; R219Q/S262N/C105-T147del→$(Gly)_7$; R219Q/S262N/C105-T147del→$(Gly)_5$; R219Q/S262N/C105-T147del→$(Gly)_3$; R219Q/S262N/V99-Q144del→$(GGGGS)_1$; R219Q/S262N/V99-Q144del→$(GGGGS)_2$; R219Q/S262N/V99-Q144del→$(GGGGS)_3$; R219Q/S262N/C105-T147del→$(GGGGS)_1$; R219Q/S262N/C105-T147del→$(GGGGS)_2$; R219Q/S262N/C105-T147del→$(GGGGS)_3$; R219Q/S262N/K371D/V99-Q144del→$(GGGGS)_1$; R219Q/S262N/K371D/V99-Q144del→$(GGGGS)_2$; R219Q/S262N/K371D/V99-Q144del→$(GGGGS)_3$; R219Q/S262N/K371D/C105-T147del→$(GGGGS)_1$; R219Q/S262N/K371D/C105-T147del→$(GGGGS)_2$; R219Q/S262N/K371D/C105-T147del→$(GGGGS)_3$; R219Q/S262N/C105-T147del→$(Gly)_n$, where n = 2 to 20; R219Q/S262N/V99-Q144del→$(GGGGS)_n$, where n = 1 to 5; R219Q/S262N/C105-T147del→$(GGGGS)_n$, where n = 1 to 5; R219Q/S262N/N98-N156del; R219Q/S262N/C105-E148del; R219Q/S262N/C105-T147del; R219Q/S262N/V99-Q144del; R219Q/S262N/K371D/C105-T147del→$(Gly)_n$, where n = 2 to 20; R219Q/S262N/K371D/C105-T147del→$(Gly)_{15}$; R219Q/S262N/K371D/C105-T147del→$(Gly)_{10}$; R219Q/S262N /K371D/C105-T147del→$(Gly)_7$; R219Q/S262N/K371D/C105-T147del→$(Gly)_5$; R219Q/S262N/K371D/C105-T147del→$(Gly)_3$; R219Q/S262N/K371D/V99-Q144del→$(GGGGS)_n$, where n = 1 to 5; R219Q/S262N/K371D/C105-T147del→$(GGGGS)_n$, where n = 1 to 5; R219Q/S262N/K371D/N98-N156del; R219Q/S262N/K371D/C105-E148del; R219Q/S262N/K371D/C105-T147del; and R219Q/S262N/K371D/V99-Q144del, with reference to amino acid positions set forth in SEQ ID NO:5.

23. The variant ADA2 protein or catalytically active portion thereof of claim 1, wherein the variant ADA2 protein comprises the sequence of amino acids set forth in any of SEQ ID NOS:38-40, 53, 54, 59-63, and 263-273 or a catalytically active portion thereof.

24. The variant ADA2 protein or catalytically active portion thereof of claim 1, wherein the variant ADA2 protein comprises the sequence of amino acids set forth in any of SEQ ID NOS: 596-645, 658-700, 702-710, 713-791, 807-822, and 838-931 or a catalytically active portion thereof.

25. The variant ADA2 protein or catalytically active portion thereof of any of claims 1-15, comprising amino acid replacements selected from among replacements corresponding to R219Q/S262N/K371D; R219Q/S262N/R20E; R219Q/S262N/K371E/R20E; R219Q/S262N/K371D/R20E; R219Q/S262N; R219Q/S262N/K11A; R219Q/S262N/K11D; R219Q/S262N/K11E; R219Q/S262N/K13A; R219Q/S262N/K13D; R219Q/S262N/K13E; R219Q/S262N/K371A; R219Q/S262N/K372A; R219Q/S262N/K372D; R219Q/S262N/K372E; R219Q/S262N/K452A; R219Q/S262N/K452D; R219Q/S262N/K452E; R219Q/S262N/R20A; R219Q/S262N/R20D; R219Q/S262N/R366A; R219Q/S262N/R366D; R219Q/S262N/R366E; R219Q/S262N/H264A; R219Q/S262N/H264Q; R219Q/S262N/H264N; R219Q/S262N/H264G; R219K/S262N; R219N/S262N; R219Q/S262N/L221A; R219Q/S262N/L221V; R219Q/S262N/L221G; R219Q/S262N/E179D; R219Q/S262N/E179A; R219Q/S262N/E179S; R219Q/S262N/E179T; R219Q/S262N/E179V; R219Q/S262N/E179G; R219Q/S262M; R219Q/S262N/K11A/R20A; R219Q/S262N/K11A/R20A/K371A; R219Q/S262N/R20A/K371A; R219Q/S262N/K11A/K371A; R219Q/S262N/K26A; R219Q/S262N/K26D; R219Q/S262N/K26E; R219Q/S262N/R217A; R219Q/S262N/R217D; R219Q/S262N/R217E; R219Q/S262N/K258A; R219Q/S262N/K258D; R219Q/S262N/K258E; R219Q/S262N/R277A; R219Q/S262N/R277D; R219Q/S262N/R277E; R219Q/S262N/R283A; R219Q/S262N/R283D; R219Q/S262N/R283E; R219Q/S262N/K309A; R219Q/S262N/K309D; R219Q/S262N/K309E; R219Q/S262N/K317A; R219Q/S262N/K317D; R219Q/S262N/K317E; R219Q/S262N/K321A; R219Q/S262N/K321D; R219Q/S262N/K321E; R219Q/S262N/R352A; R219Q/S262N/R352D; R219Q/S262N/R352E; R219Q/S262N/R441A; R219Q/S262N/R441D; R219Q/S262N/R441E; R219Q/S262N/K444A; R219Q/S262N/K444D; R219Q/S262N/K444E; R219Q/S262N/K461A; R219Q/S262N/K461D; R219Q/S262N/K461E; R219Q/S262N/K469A; R219Q/S262N/K469D; R219Q/S262N/K469E; R219Q/S262N/K470A; R219Q/S262N/K470D; R219Q/S262N/K470E; R219Q/S262N/D86A; R219Q/S262N/D86C; R219Q/S262N/D86E; R219Q/S262N/D86F; R219Q/S262N/D86G; R219Q/S262N/D86H; R219Q/S262N/D86I; R219Q/S262N/D86K; R219Q/S262N/D86L; R219Q/S262N/D86M; R219Q/S262N/D86N; R219Q/S262N/D86P; R219Q/S262N/D86Q; R219Q/S262N/D86R; R219Q/S262N/D86S; R219Q/S262N/D86T; R219Q/S262N/D86V; R219Q/S262N/D86W; R219Q/S262N/D86Y; R219Q/S262N/E179C; R219Q/S262N/E179F; R219Q/S262N/E179H; R219Q/S262N/E179I; R219Q/S262N/E179K; R219Q/S262N/E179L; R219Q/S262N/E179M; R219Q/S262N/E179N; R219Q/S262N/E179P; R219Q/S262N/E179Q; R219Q/S262N/E179R; R219Q/S262N/E179W; R219Q/S262N/E179Y; R219Q/S262N/L221C; R219Q/S262N/L221D; R219Q/S262N/L221E; R219Q/S262N/L221F; R219Q/S262N/L221H; R219Q/S262N/L221I; R219Q/S262N/L221K; R219Q/S262N/L221M; R219Q/S262N/L221N; R219Q/S262N/L221P; R219Q/S262N/L221Q; R219Q/S262N/L221R; R219Q/S262N/L221S; R219Q/S262N/L221T; R219Q/S262N/L221W; R219Q/S262N/L221Y; R219Q/S262N/H264C; R219Q/S262N/H264D; R219Q/S262N/H264E; R219Q/S262N/H264F; R219Q/S262N/H264I; R219Q/S262N/H264K; R219Q/S262N/H264L; R219Q/S262N/H264M; R219Q/S262N/H264P; R219Q/S262N/H264R; R219Q/S262N/H264S; R219Q/S262N/H264T; R219Q/S262N/H264V; R219Q/S262N/H264W; R219Q/S262N/H264Y; R219Q/S262N/S266A; R219Q/S262N/S266C; R219Q/S262N/S266D; R219Q/S262N/S266E; R219Q/S262N/S266F; R219Q/S262N/S266G; R219Q/S262N/S266H; R219Q/S262N/S266I; R219Q/S262N/S266K; R219Q/S262N/S266L; R219Q/S262N/S266M; R219Q/S262N/S266N; R219Q/S262N/S266P; R219Q/S262N/S266Q; R219Q/S262N/S266R;

R219Q/S262N/S266T; R219Q/S262N/S266V; R219Q/S262N/S266W; R219Q/S262N/S266Y; R219Q/S262N/K267A; R219Q/S262N/K267C; R219Q/S262N/K267D; R219Q/S262N/K267E; R219Q/S262N/K267F; R219Q/S262N/K267G; R219Q/S262N/K267H; R219Q/S262N/K267I; R219Q/S262N/K267L; R219Q/S262N/K267M; R219Q/S262N/K267N; R219Q/S262N/K267P; R219Q/S262N/K267Q; R219Q/S262N/K267R; R219Q/S262N/K267S; R219Q/S262N/K267T; R219Q/S262N/K267V; R219Q/S262N/K267W; R219Q/S262N/K267Y; R219Q/S262N/V296A; R219Q/S262N/V296C; R219Q/S262N/V296D; R219Q/S262N/V296E; R219Q/S262N/V296F; R219Q/S262N/V296G; R219Q/S262N/V296H; R219Q/S262N/V296I; R219Q/S262N/V296K; R219Q/S262N/V296L; R219Q/S262N/V296M; R219Q/S262N/V296N; R219Q/S262N/V296P; R219Q/S262N/V296Q; R219Q/S262N/V296R; R219Q/S262N/V296S; R219Q/S262N/V296T; R219Q/S262N/V296W; R219Q/S262N/V296Y; R219Q/K11A/R20A; R219Q/K11A/R20A/K371A; R219Q/R20A/K371A; R219Q/K11A/K371A; S262N/K11A/R20A; S262N/K11A/R20A/K371A; S262N/R20A/K371A; and S262N/K11A/K371A, with reference to SEQ ID NO:5.

26. The variant ADA2 protein or catalytically active portion thereof of any of claims 1-25, wherein the variant ADA2 protein is PEGylated.

27. The variant ADA2 protein or catalytically active portion thereof of claim 15, wherein the sequence of the variant ADA2 protein is set forth in SEQ ID NO:273.

28. The variant ADA2 protein or catalytically active portion thereof of claim 27, wherein the variant ADA2 protein is PEGylated.

29. The variant ADA2 protein or catalytically active portion thereof of any of claims 1-28 that lacks all or a portion of the PRB domain, wherein residues corresponding to residues 98-156 of SEQ ID NO:5 comprise the PRB domain.

30. The variant ADA2 protein or catalytically active portion thereof of any of claims 1-29, wherein the catalytically active portion comprises the ADA domain that corresponds to residues 77-473 of the sequence of amino acids set forth in SEQ ID NO:5.

31. A variant ADA2 multimer, comprising a plurality of variant ADA2 proteins or catalytically active portions thereof of any of claims 1-30, wherein the variant ADA2 proteins or catalytically active portions thereof are the same or different.

32. A variant ADA2 dimer, comprising a variant ADA2 protein or catalytically active portion thereof of any of claims 1-30.

33. A variant ADA2 dimer, comprising a variant ADA2 protein or catalytically active portion thereof of claim 15.

34. The variant ADA2 dimer of claim 33, wherein the variant ADA2 protein comprises the sequence of amino acids set forth in SEQ ID NO:273.

35. The variant ADA2 dimer or catalytically active portion thereof of any of claims 32-34 that is a homodimer comprising two variant ADA2 proteins or catalytically active portions thereof that are the same.

36. The variant ADA2 dimer or catalytically active portion thereof of any of claims 32-34 that is a heterodimer comprising two variant ADA2 proteins or catalytically active portions thereof that are different from each other.

37. A conjugate, comprising the variant ADA2 protein or catalytically active portion thereof of claim 15, linked directly or indirectly via a linker to a heterologous moiety, wherein the heterologous moiety is a half-life extending moiety.

38. A conjugate, comprising the variant ADA2 protein or catalytically active portion thereof, or the multimer, or the dimer, of any of claims 1-36, linked directly or indirectly via a linker to a heterologous moiety, wherein the heterologous moiety is a half-life extending moiety.

39. The conjugate of claim 37 or claim 38, wherein the half-life extending moiety is a PEG and the variant ADA2 protein or catalytically active portion thereof is PEGylated.

40. A nucleic acid molecule encoding the variant ADA2 protein or catalytically active portion thereof, or the multimer, or the dimer, of any of claims 1-36.

41. A vector, comprising the nucleic acid molecule of claim 40.

42. An isolated cell or a cell culture, comprising the vector of claim 41.

43. The cell or cell culture of claim 42, wherein the cell is selected from a tumor-infiltrating lymphocyte (TIL), a cytotoxic T lymphocyte (CTL), a natural killer (NK) cell or a lymphokine-activated killer (LAK) cell.

44. The cell or cell culture of claim 43, wherein the cell is a T cell that encodes and expresses chimeric antigen receptor (CAR) and the variant ADA2 protein or dimer, wherein the CAR is specific for a tumor cell antigen.

45. A method of producing a variant ADA2 protein or catalytically active portion thereof, comprising culturing the cell of any of claims 42-44, under conditions whereby the variant ADA2 protein is expressed.

46. The method of claim 45, wherein the resulting variant ADA2 protein is a dimer.

47. A method, comprising culturing or expanding the cell of any one of claims 42-44 to produce expanded cells.

48. The expanded cells produced by the method of claim 47.

49. Use of the expanded cells of claim 48 in the manufacture of a medicament for treating a tumor or cancer.

50. The expanded cells of claim 48 for use in the treatment of a tumor or cancer.

51. A pharmaceutical composition, comprising the variant ADA2 protein or a catalytically active portion thereof, or the dimer, or the multimer of the variant ADA2 protein or catalytically active portion thereof of any of claims 1-36, or the conjugate of any of claims 37-39.

52. The pharmaceutical composition of claim 51, wherein the variant ADA2 protein or catalytically active portion thereof is PEGylated.

53. The pharmaceutical composition of claim 51, wherein the variant ADA2 protein comprises the sequence of amino acid residues set forth in SEQ ID NO: 273 or a catalytically active portion thereof.

54. The pharmaceutical composition of claim 53, wherein the variant ADA2 protein or catalytically active portion thereof is PEGylated.

55. The variant ADA2 protein or catalytically active portion thereof, or the multimer, or the dimer thereof of any of claims 1-36, or the conjugate of any of claims 37-39, for use in the treatment of a tumor.

56. The variant ADA2 protein or catalytically active portion thereof, or the multimer, or the dimer, or the conjugate of claim 55, wherein the variant ADA2 protein comprises the sequence of amino acid residues set forth in SEQ ID NO: 273 or a catalytically active portion thereof.

57. The variant ADA2 protein or catalytically active portion thereof, or the multimer, or the dimer, or the conjugate of claim 56, wherein the variant ADA2 protein or a catalytically active portion thereof is PEGylated.

58. Use of the pharmaceutical composition of any of claims 51-54 in the manufacture of a medicament for treating a tumor.

59. The expanded cells of claim 50 or the use of claim 58, wherein the variant ADA2 protein comprises the sequence of amino acid residues set forth in SEQ ID NO: 273 or a catalytically active portion thereof.

60. The expanded cells or the use of claim 59, wherein the variant ADA2 protein or a catalytically active portion thereof is PEGylated.