In specific embodiments, the fusion protein has an improved activity over the native or recombinant IL-2. For example, the effect of the IL-2/IL-2Rα fusion protein can increase tolerogenic Tregs at about 2 fold, 5 fold, 10 fold, 20 fold, 30 fold, 40 fold, 50 fold, 60 fold, 70 fold, 80 fold, 90 fold, 100 fold 150 fold, 200 fold or lower level IL-2 activity in comparison to native or recombinant IL-2. In other embodiments, the IL-2/IL-2Rα fusion protein is more effective than native or recombinant IL-2 in inducing persistent augmentation of Tregs and related properties.

Various IL-2 and IL-2Rα fragments and variants from a variety of organism can be used to generate the IL-2/IL-2Rα extracellular domain fusion proteins provided herein. Such components are discussed in further detailed elsewhere herein. Examples of non-limiting unprocessed IL-2/IL-2Rα extracellular domain fusion proteins are set forth in SEQ ID N0: 17, 19, 21, 23, 25, 27, 36, 38, 44, 46, 54, 55, 56, 57, 58, 59, 60, and 61, while non-limiting examples of mature forms of the IL-2/IL-Ra extracellular domain fusion proteins are set forth in SEQ ID NOS: 16, 18, 20, 22, 24, 26, 37, 39, 43, 45, 62 and 64. Non-limiting examples of polynucleotides encoding such fusion proteins are set forth in SEQ ID NO: 29, 30, 31, 32, 33, 34, 42, 47, 48, 49, 63, and 65.

The term "secretory signal sequence" denotes a polynucleotide sequence that encodes a polypeptide (a "secretory peptide") that, as a component of a larger polypeptide, directs the larger polypeptide through a secretory pathway of the cell in which it is synthesized. The larger polypeptide is commonly cleaved to remove the secretory peptide during the transit through the secretory pathway. As used herein, a "mature" form of a fusion protein or polypeptide comprises the processed form of the polypeptide that has had the secretory peptide removed. As used herein, the "unprocessed" form of the fusion protein retains the secretory peptide sequence.

Biologically active fragments and variants of the mature and unprocessed form of the IL-2/TL-Rα extracellular domain fusion proteins, and the polynucleotide encoding the same, are also provided. Such a functional polypeptide fragment can comprise at least 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 30, 40, 50, 75, 100, 150, 200, 250, 300, 350, 400, 450, 500 or more continuous amino acids of any one of SEQ ID NO: 16, 17, 18, 19, 20,

Table 1. Summary of Sequences

SEQ ID NO	AA/ NT	Source	Description	
1	AA	human	IL-2- unprocessed	GenBank Acc. No. AAB46883 IL-2 myrmqllsci alslalvtns aptssstkkt qlqlehllld lqmilnginn yknpkltrmltfkfympkka telkhlqcle eelkpleevl nlaqsknfhl rprdlisnin vivlelkgsettfmceyade tativeflnr witfcqsiis tlt
2	AA	Human	IL-2 – mature form	GenBank AAB46883 with first 20 aa removed aptssstkkt qlqlehllld lqmilnginn yknpkltrmltfkfympkka telkhlqcle eelkpleevl nlaqsknfhl rprdlisnin vivlelkgse ttfmceyade tativeflnr witfcqsiis tlt
3	AA	Mouse	IL-2 unprocessed	Acc No. P04351 MYSMQLASCV TLTLVLLVNS APTSSSTSSS TAEAQQQQQQ QQQQQQHLEQ LLMDLQELLS RMENYRNLKL PRMLTFKFYL PKQATELKDL QCLEDELGPL RHVLDLTQSK SFQLEDAENF ISNIRVTVVK LKGSDNTFEC QFDDESATVV DFLRRWIAFC QSIISTSPQ
4	AA	Mouse	IL-2 mature form	Mature form of Acc No. P04351 APTSSSTSSS TAEAQQQQQQ QQQQQQHLEQ LLMDLQELLS RMENYRNLKL PRMLTFKFYL PKQATELKDL QCLEDELGPL RHVLDLTQSK SFQLEDAENF ISNIRVTVVK LKGSDNTFEC QFDDESATVV DFLRRWIAFC QSIISTSPQ
5	AA	Human	IL-2Rα unprocessed form	Genebank Acc No. NP_000408.1 mdsyllmwgl ltfimvpgcq aelcdddppe iphatfkama ykegtmlnce ckrgfrriksgslymlctgn sshsswdnqc qctssatrnt tkqvtpqpee qkerkttemq spmqpvdqaslpghcreppp weneateriy hfvvgqmvyy qcvqgyralh rgpaesvckm thgktrwtqpqlictgemet sqfpgeekpq aspegrpese tsclvtttdf qiqtemaatm etsiftteyqvavagcvfll isvlllsglt wqrrqrksrr ti
6	AA	Human	IL-2Rα mature form	First 1-21 AA removed from NP_000408.1 elcdddppe iphatfkama ykegtmlnce ckrgfrriksgslymlctgn sshsswdnqc qctssatrnt tkqvtpqpee qkerkttemq spmqpvdqas lpghcreppp weneateriy hfvvgqmvyy qcvqgyralh rgpaesvckm thgktrwtqpqlictgemet sqfpgeekpq aspegrpese tsclvtttdf qiqtemaatm etsiftteyqvavagcvfll isvlllsglt wqrrqrksrr ti
7	AA	Human	Mature form of IL-2Rα extracellular domain	ELCDDDPPEIPHATFKAMAYKEGTMLNCECKRGFRRIKSGSLYMLCTGN SSHSSWDNQCQCTSSATRNTTKQVTPQPEEQKERKTTEMQSPMQPVD QASLPGHCREPPPWENEATERIYHFVVGQMVYYQCVQGYRALHRGPA ESVCKMTHGKTRWTQPQLICTGEMETSQFPGEEKPQASPEGRPESETS CLVTTTDFQIQTEMAATMETSIFTTEYQ
8	AA	Mouse	IL-2Rα unprocessed form	Acc No. NP_032393.3 meprllmlgf lsltivpscr aelclydppe vpnatfkals ykngtilnce ckrgfrrlkelvymrclgns wssncqctsn shdksrkqvt aqlehqkeqq tttdmqkptq smhqenltghcrepppwkhe dskriyhfve gqsvhyecip gykalqrgpa isickmkcgk tgwtqpqltcvderehhrfl aseesqgsrn sspesetscp itttdfpqpt ettamtetfv ltmeykvavasclfllisilllsgltwqhr wrksrrti
9	AA	Mouse	IL-2Rα mature form	aa 1-21 removed from Acc No. NP_032393.3 elclydppe vpnatfkals ykngtilnce ckrgfrrlke lvymrclgns wssncqctsn shdksrkqvt aqlehqkeqq tttdmqkptq smhqenltgh crepppwkhe dskriyhfve gqsvhyecip gykalqrgpa isickmkcgk tgwtqpqltc vderehhrfl aseesqgsrn sspesetscp itttdfpqpt ettamtetfv ltmeykvava sclfllisil llsgltwqhr wrksrrti

				CTGTGACGATGACCCGCCAGAGATCCCACACGCCACATTCAAAGCCA TGGCCTACAAGGAAGGAACCATGTTGAACTGTGAATGCAAGAGAGG TTTCCGCAGAATAAAAAGCGGGTCACTCTATATGCTCTGTACAGGAA ACTCTAGCCACTCGTCCTGGGACAACCAATGTCAATGCACAAGCTCTG CCACTCGGAACACAACGAAACAAGTGACACCTCAACCTGAAGAACAG AAAGAAAGGAAAACCACAGAAATGCAAAGTCCAATGCAGCCAGTGG ACCAAGCGAGCCTTCCAGGTCACTGCAGGGAACCTCCACCATGGGAA AATGAAGCCACAGAGAGAATTTATCATTTCGTGGTGGGGCAGATGGT TTATTATCAGTGCGTCCAGGGATACAGGGCTCTACACAGAGGTCCTG CTGAGAGCGTCTGCAAAATGACCCACGGGAAGACAAGGTGGACCCA GCCCCAGCTCATATGCACAGGTGAAATGGAGACCAGTCAGTTTCCAG GTGAAGAGAAGCCTCAGGCAAGCCCCGAAGGCCGTCCTGAGAGTGA GACTTCCTGCCTCGTCACAACAACAGATTTTCAAATACAGACAGAAAT GGCTGCAACCATGGAGACGTCCATATTTACAACAGAGTACCAGGGTG GACATCACCATCACCATCACTAATAA
50	AA		(G1y4Ser)3 linker	GGGGSGGGGSGGGGS
51	AA		(G1y4Ser)2 linker	GGGGSGGGGS
52	AA		(G1y4Ser)1 linker	GGGGS
53	NT		Kozak sequence	gccaccATGG
54	AA	Mouse	Unprocessed form of IL-2 (G1y4Ser)4-extracellular domain of IL-2 Rα + glycine spacer and poly-histidine region	MDSMQLASCVTLTLVLLVNSAPTSSSTSSSTAEAQQQQQQQQQQQQH LEQLLMDLQELLSRMENYRNLKLPRMLTFKFYLPKQATELKDLQCLEDEL GPLRHVLDLTQSKSFQLEDAENFISNIRVTVVKLKGSDNTFECQFDDESA TVVDFLRRWIAFCQSIISTSPQGGGGSGGGGSGGGGSGGGGSELCLYDP PEVPNATFKALSYKNGTILNCECKRGFRRLKELVYMRCLGNSWSSNCQC TSNSHDKSRKQVTAQLEHQKEQQTTTDMQKPTQSMHQENLTGHCRE PPPWKHEDSKRIYHFVEGQSVHYECIPGYKALQRGPAISICKMKCGKTG WTQPQLTCVDEREHHRFLASEESQGSRNSSPESETSCPITTTDFPQPTET TAMTETFVLTMEYKGGHHHHHH
55	AA	Mouse	Unprocessed form of IL-2 (G1y4Ser)5-extracellular domain of IL-2 Rα + glycine spacer and poly-histidine region	MDSMQLASCVTLTLVLLVNSAPTSSSTSSSTAEAQQQQQQQQQQQQH LEQLLMDLQELLSRMENYRNLKLPRMLTFKFYLPKQATELKDLQCLEDEL GPLRHVLDLTQSKSFQLEDAENFISNIRVTVVKLICGSDNTFECQFDDESA TVVDFLRRWIAFCQSIISTSPQGGGGSGGGGSGGGGSGGGGSGGGGSE LCLYDPPEVPNATFKALSYKNGTILNCECKRGFRRLKELVYMRCLGNSWS SNCQCTSNSHDKSRKQVTAQLEHQKEQQTTTDMQKPTQSMHQENLT GHCREPPPWKHEDSKRIYHFVEGQSVHYECIPGYKALQRGPAISICKMKC GKTGWTQPQLTCVDEREHHRFLASEESQGSRNSSPESETSCPITTTDFPQ PTETTAMTETFVLTMEYKGGHHHHHH
56	AA	Mouse	Unprocessed form of IL-2 (Gly3Ser)4-extracellular domain of IL-2 Rα + glycine spacer and poly-histidine region	MDSMQLASCVTLTLVLLVNSAPTSSSTSSSTAEAQQQQQQQQQQQQH LEQLLMDLQELLSRMENYRNLKLPRMLTFKFYLPKQATELKDLQCLEDEL GPLRHVLDLTQSKSFQLEDAENFISNIRVTVVKLKGSDNTFECQFDDESA TVVDFLRRWIAFCQSIISTSPQGGGSGGGSGGGSGGGSELCLYDPPEVP NATFKALSYKNGTILNCECKRGFRRLKELVYMRCLGNSWSSNCQCTSNS HDKSRKQVTAQLEHQKEQQTTTDMQKPTQSMHQENLTGHCREPPPW KHEDSKRIYHFVEGQSVHYECIPGYKALQRGPAISICKMKCGKTGWTQP QLTCVDEREHHRFLASEESQGSRNSSPESETSCPITTTDFPQPTETTAMTE TFVLTMEYKGGHHHHHH
57	AA	Mouse	Unprocessed form of IL-2 (G1y3Ser)3-extracellular domain of IL-2 Rα + glycine spacer and poly-histidine region	MDSMQLASCVTLTLVLLVNSAPTSSSTSSSTAEAQQQQQQQQQQQQH LEQLLMDLQELLSRMENYRNLKLPRMLTFKFYLPKQATELKDLQCLEDEL GPLRHVLDLTQSKSFQLEDAENFISNIRVTVVKLKGSDNTFECQFDDESA TVVDFLRRWIAFCQSIISTSPQGGGSGGGSGGGSELCLYDPPEVPNATFK ALSYKNGTILNCECKRGFRRLKELVYMRCLGNSWSSNCQCTSNSHDKSR KQVTAQLEHQKEQQTTTDMQKPTQSMHQENLTGHCREPPPWKHEDS KRIYHFVEGQSVHYECIPGYKALQRGPAISICKMKCGKTGWTQPQLTCV DEREHHRFLASEESQGSRNSSPESETSCPITTTDFPQPTETTAMTETFVLT MEYKGGHHHHHH

THAT WHICH IS CLAIMED

1. A fusion protein comprising:

(a) a first polypeptide comprising Interleukin-2 (IL-2); and

(b) a second polypeptide, fused in frame to the first polypeptide by a linker, wherein the linker is the sequence set forth in SEQ ID NO: 13, and wherein the second polypeptide comprises an extracellular domain of Interleukin-2 Receptor alpha (IL-2Rα), which is capable of binding to IL-2;

wherein the fusion protein has IL-2 activity.

2. The fusion protein of claim 1, wherein the fusion protein has an increased IL-2 activity when compared to native IL-2.

3. The fusion protein of any one of claims 1 or 2, wherein the fusion protein has an increased persistent IL-2 stimulation of IL-2R bearing lymphocytes *in vivo* when compared to native IL-2.

4. The fusion protein of any one of claims 1-3, wherein the first polypeptide comprising IL-2 has at least 70% sequence identity to SEQ ID NO: 2.

5. The fusion protein of any one of claims 1-4, wherein the second polypeptide comprising the extracellular domain of IL-2Rα has at least 70% sequence identity to SEQ ID NO: 7.

6. The fusion protein of any one of claims 1-5, wherein the first polypeptide comprising IL-2 has at least 75%,80%, 85%, 90%, 95%, or 99% sequence identity to SEQ ID NO: 2.

7. The fusion protein of any one of claims 1-6, wherein the second polypeptide comprising the extracellular domain of IL-2Rα has at least 75%, 80%, 85%, 90%, 95%, or 99% sequence identity to SEQ ID NO: 7.

8. The fusion protein of any one of claims 1-7, comprising

(a) the amino acid sequence of any one of SEQ ID NO: 26, 27, 36, 37, 57, or 59; or,

(b) a sequence having at least 70%, 75%, 80%, 85%, 90%, or 95% sequence identity to any one of SEQ ID NO: 26, 27, 36, 37, 57, or 59.

9. The fusion protein of claim 8, comprising the amino acid sequence of any one of SEQ ID NO: 26, 27, 36, 37, 57, or 59.

10. The fusion protein of claim 9, comprising the amino acid sequence of SEQ ID NO: 26.

11. The fusion protein of any one of claims 1-10, wherein the fusion protein comprises one or more substitutions, deletions, truncations, or insertions in the extracellular domain of IL-2Rα.

12. The fusion protein of claim 9, wherein the fusion protein comprises:

(a) the amino acid sequence of SEQ ID NO: 62; or

(b) a sequence having at least 70%, 75%, 80%, 85%, 90%, or 95% sequence identity to SEQ ID NO: 62.

13. The fusion protein of claim 12, comprising the amino acid sequence of SEQ ID NO: 62.

14. A polynucleotide comprising a nucleotide sequence encoding the fusion protein of any one of claims 1-13.

15. A host cell comprising the polynucleotide of claim 14.

16. The host cell of claim 15, wherein the host cell comprises a CHO cell or a COS cell.

17. A method for producing a fusion protein of any one of claims 1-13, the method comprising (i) introducing into a host cell a polynucleotide encoding the fusion protein of any one of claims 1-13 and (ii) expressing the fusion protein in the host cell.

18. The method of claim 17, wherein the polynucleotide encoding the fusion protein is operably linked to a promoter active in the host cell.

19. Use of the fusion protein of any one of claims 1-13 in the manufacture of a medicament in decreasing an immune response in a subject in need thereof.

20. The use of claim 19, wherein the subject has an autoimmune disease.

21. The use of claim 20, wherein the autoimmune disease comprises type l diabetes, multiple sclerosis, rheumatoid arthritis, celiac disease, systemic lupus erythematous, juvenile idiopathic arthritis, Crohn's disease, ulcerative colitis or systemic sclerosis, graft versus host disease, psoriasis, alopecia areata, or HCV-induced vasculitis.

22. The use of any one of claims 19-21, wherein a therapeutically effective amount of the fusion protein comprises 10^3 to 10^6 IU of IL-2 activity per subject or $10^4 \pm 100$ fold of IL-2 activity per subject.

23. Use of the fusion protein of any one of claims 1-13 for the manufacture of a medicament in enhancing the immunogenicity of a vaccine in a subject in need thereof.

24. Use of the fusion protein of any one of claims 1-13 for the manufacture of a medicament in overcoming a suppressed immune response to a vaccine in a subject in need thereof.

25. The use of claim 23 or 24, wherein the fusion protein and the vaccine are to be administered sequentially, in any order.

26. The use of claim 23 or 24, wherein the fusion protein and the vaccine are to be administered simultaneously.

27. The use of any one of claims 23-26, wherein the vaccine is a cancer vaccine.

28. The use of any one of claims 23-27, wherein a therapeutically effective amount of the fusion protein comprises at least 10^4 to 10^7 IU of IL-2 activity per subject or at least 10^5+100 of IL-2 activity per subject.

29. The use of any one of claims 19-28, wherein the subject is a human.