

described in which IL-2 inhibits its own production (Malek TR, *Annual review of immunology* 26, 453-479 (2008)).

[0005] The receptor for IL-2 (IL-2 R) consists of three chains, IL-2 R α (also known as CD25), IL-2 R β (also known as CD122), and the common gamma chain, γ_c (also known as CD132). The three receptor chains are expressed separately and differently on various cell types. IL-2 signals through interactions between IL-2 R β and γ_c that activate cellular pathways such as the Jak/Stat, PI3K-AKT, and MAPK pathways.

SUMMARY

[0006] The present disclosure provides methods and compositions for the treatment of disease or disorders associated with IL-2 signaling or where modulation of IL-2 signaling can lead to improved clinical (or immune) response. The disclosure provides antibodies that bind human IL-2. It is provided that the antibodies described herein can have differential effects on IL-2 binding to any or all of the IL-2 R chains (IL-2 R α , IL-2 R β , and γ_c). In particular, the present disclosure provides methods of use of such antibodies in the treatment of cancer.

[0007] In one aspect, the present disclosure refers to a human or humanized antibody that binds human interleukin-2 (IL-2) with an affinity K_D of 1×10^{-10} M or less and inhibits binding of IL-2 with an IL-2 receptor alpha (IL-2 R α) subunit, wherein the antibody inhibits IL-2 signaling through IL-2 R $\alpha\beta\gamma$ and through IL-2 R $\beta\gamma$, and wherein the antibody inhibits IL-2 signaling through IL-2 R $\alpha\beta\gamma$ to a greater extent than through IL-2 R $\beta\gamma$. In various examples, the disclosure provides an antibody specific for IL-2 with an affinity K_D of 2×10^{-9} M or less. In one aspect, the disclosure provides an antibody specific for IL-2 with an affinity K_D of 1×10^{-10} M or less. In some examples, an anti-IL-2 antibody described herein binds at least with an affinity of 10^{-10} M, 10^{-11} M, 10^{-12} M, 10^{-13} M or less. In certain examples, the affinity is measured by surface plasmon resonance or KinExA assay.

[0008] In another aspect, the antibody inhibits IL-2 signaling through IL-2 R $\alpha\beta\gamma$ and through IL-2 R $\beta\gamma$, and the antibody inhibits IL-2 signaling through IL-2 R $\alpha\beta\gamma$ to a greater extent than through IL-2 R $\beta\gamma$.

[0009] In a related aspect, the antibody binds IL-2 and inhibits binding of IL-2 with an IL-2 receptor alpha (IL-2 R α) subunit. In another aspect, the antibody inhibits IL-2 signaling through IL-2 R $\alpha\beta\gamma$ to a greater extent than through IL-2 R $\beta\gamma$.

[0010] In another example, the antibody does not completely block binding of human IL-2 to cells expressing human or mouse IL-2 R β or IL-2 R $\beta\gamma$ complex. In a related aspect, the antibody binds at a site allosteric to binding of IL-2 to IL-2 R α or IL-2 R β and γ c chains.

[0011] In some examples, the antibody is a negative modulator antibody, optionally wherein the antibody is capable of weakening the binding affinity between IL-2 and IL-2 receptor α (IL-2 R α) by at least about 2-fold, optionally up to 1000-fold. In other examples, an antibody described herein is capable of weakening the binding affinity between IL-2 and IL-2 R α by at least 2-1000 fold, 10-100 fold, 2-fold, 5-fold, 10-fold, 25-fold, 50-fold, 100-fold, 200-fold, 300-fold, 400-fold, 500-fold, 600-fold, 700-fold, 800-fold, 900-fold or 1000-fold. In various examples, the antibody complexed with IL-2 binds to cells expressing IL-2 R β and γ c with an EC₅₀ of about 5 nM or less. In various examples, the antibody binds to cells expressing IL-2 R β (but not γ c) with an EC₅₀ of about 200 nM or less. In some examples, the antibody complexed with IL-2 binds to cells expressing IL-2 R β and γ c with an EC₅₀ in a range of 0.1-100 nM, 0.1-10 nM, 1-5 nM. In various examples, the antibody complexed with IL-2 binds to cells expressing IL-2 R β and γ c with an EC₅₀ of 1, 2, 3, 4 or 5 nM. In some examples, the antibody complexed with IL-2 binds to cells expressing IL-2 R β (but not γ c) with an EC₅₀ in a range of 10-500 nM, 10-300 nM, 10-200 nM. In various examples, the antibody complexed with IL-2 binds to cells expressing IL-2 R β and γ c with an EC₅₀ of 10, 50, 100, 150 or 200 nM. In related examples, the antibody complexed with IL-2 binds to cells expressing IL-2 R β and γ c 9- to 40-fold more than cells expressing IL-2 R β (but not γ c).

[0012] In various examples, the antibody binds to human IL-2 and one or more of mouse, rat or rabbit IL-2.

[0013] In various examples, the antibody inhibits IL-2 stimulation of STAT5 activation in cells expressing IL-2 R α , IL-2 R β , and γ c to a greater extent than cells expressing IL-2 R β and γ c, but not IL-2 R α . For example, in cells expressing mouse IL-2 R α , R β and γ c (e.g., CTLL-2), EC₅₀ shifts can range from 293- to 793-fold compared to 13- to 16-fold for cells expressing mouse IL-2 R β and γ c (e.g., mouse primary NK cells). For cells expressing human IL-2 R α , R β and γ c (e.g., NK92 cell line), EC₅₀ shifts can range from 495- to 1855-fold compared to 45- to 104-fold for cells expressing human IL-2 R β and γ c (human CD25+ depleted primary NK cells) or 5- to 9-fold for CHO-K1 cells engineered to express human R β and γ c. The ratios of EC₅₀

shifts were 18- to 60-fold greater for mouse R α , R β , and γ c compared to mouse R β and γ c (76-fold for control antibody MAB602, also known as clone 5355) and 9- to 19-fold for human R α , R β , and γ c compared to human R β and γ c (50-fold for MAB602). In a related example, the antibody inhibits IL-2 stimulation of STAT5 activation in cells that express mouse IL-2 R α , IL-2 R β , and γ c by 200-fold or more for cells that express human IL-2 R α , IL-2 R β , and γ c by 400-fold or more. In a related examples, the antibody inhibits IL-2 stimulation of STAT5 activation in cells that express human IL-2 R β and γ c, but not IL-2 R α by less than 10-fold (CHO-R β γ) or 150-fold (e.g., in Human CD25+ depleted primary NK cells), or cells expressing mouse IL-2 R β and γ c (e.g., mouse NK cells) by less than 20-fold.

[0014] In various examples, the antibody inhibits IL-2 stimulation of proliferation in cells expressing IL-2 R α , IL-2 R β , and γ c to a greater extent than in cells expressing IL-2 R β and γ c, but not IL-2 R α . In various examples, the antibody inhibits IL-2 stimulation of proliferation of NK cells that express IL-2 R α , IL-2 R β , and γ c, by greater than 20-fold. In various examples, the antibody inhibits IL-2 stimulation of proliferation of BaF3 cells that express IL-2 R β and γ c, but not IL-2 R α , by less than 12-fold.

[0015] In one example, the IL-2 antibody is a monoclonal antibody.

[0016] In various examples, the IL-2 antibody is a human or humanized antibody.

[0017] In various examples, the antibody is selected from the group consisting of XPA.92.019, XPA.92.041, XPA.92.042 or XPA.92.099.

[0018] In another aspect, the current disclosure provides an antibody that binds human interleukin-2 (IL-2) comprising i) (a) a heavy chain CDR1 amino acid sequence set forth in SEQ ID NOs: 17, 20, 23, or 26; (b) a heavy chain CDR2 amino acid sequence set forth in SEQ ID NOs: 18, 21, 24, or 27 that is from the same heavy chain variable region as (a); and (c) a heavy chain CDR3 amino acid sequence set forth in SEQ ID NOs: 19, 22, 25, or 28 that is from the same heavy chain variable region as (a); and ii) (a) a light chain CDR1 amino acid sequence set forth in SEQ ID NOs: 29, 32, 35, or 38; (b) a light chain CDR2 amino acid sequence set forth in SEQ ID NOs: 30, 33, 36, or 39 that is from the same light chain variable region as (a); and (c) a light chain CDR3 amino acid sequence set forth in SEQ ID NOs: 31, 34, 37, or 40 that is from the same light chain variable region as (a). In one example, the disclosure provides an antibody that binds human interleukin-2 (IL-2) comprising (a) a heavy chain CDR1 amino acid sequence set

forth in SEQ ID NOs: 17, 20, 23, or 26, or a variant thereof in which one or two amino acids have been changed; (b) a heavy chain CDR2 amino acid sequence set forth in SEQ ID NOs: 18, 21, 24, or 27 that is from the same heavy chain variable region as (a), or a variant thereof in which one or two amino acids have been changed; and (c) a heavy chain CDR3 amino acid sequence set forth in SEQ ID NOs: 19, 22, 25, or 28 that is from the same heavy chain variable region as (a), or a variant thereof in which one or two amino acids have been changed.

[0019] In a related example, the disclosure provides an antibody that binds human interleukin-2 (IL-2) comprising: (a) a heavy chain CDR1 amino acid sequence set forth in SEQ ID NOs: 17, 20, 23, or 26, or a variant thereof having at least 70% identity thereto; (b) a heavy chain CDR2 amino acid sequence set forth in SEQ ID NOs: 18, 21, 24, or 27 that is from the same heavy chain variable region as (a), or a variant thereof having at least 70% identity thereto; and (c) a heavy chain CDR3 amino acid sequence set forth in SEQ ID NOs: 19, 22, 25, or 28 that is from the same heavy chain variable region as (a), or a variant thereof having at least 70% identity thereto.

[0020] In a further example, the disclosure provides an antibody that binds human interleukin-2 (IL-2) comprising: (a) a heavy chain CDR1 amino acid sequence set forth in SEQ ID NOs: 17, 20, 23, or 26, or a variant thereof having at least 70% identity thereto; (b) an independently selected heavy chain CDR2 amino acid sequence set forth in SEQ ID NOs: 18, 21, 24, or 27, or a variant thereof having at least 70% identity thereto; and (c) an independently selected heavy chain CDR3 amino acid sequence set forth in SEQ ID NOs: 19, 22, 25, or 28 or a variant thereof having at least 70% identity thereto.

[0021] In certain examples, at least two of the heavy chain CDR1, CDR2 or CDR3 amino acid sequences are set forth in any one of SEQ ID NOs: 17-28. In a related example, three of the heavy chain CDR1, CDR2 and CDR3 amino acid sequences are set forth in any one of SEQ ID NOs: 17-28.

[0022] In some examples, an antibody contemplated herein comprises an amino acid sequence at least 85% identical to a heavy chain variable region amino acid sequence set forth in SEQ ID NOs: 1, 3, 5, or 7. In some examples, provided herein is an antibody that comprises an amino acid sequence at least 95% identical to a heavy chain variable region amino acid sequence set forth in SEQ ID NOs: 1, 3, 5, or 7.

[0023] It is further exemplified that an antibody described herein comprises a polypeptide sequence having an amino acid sequence at least 70% identical over all three HCDRs in a heavy chain variable region, the amino acid sequences of HCDR1, HCDR2 and HCDR3 set forth in any one of SEQ ID NOs: 17-28.

[0024] In certain examples, an antibody contemplated herein comprises one or more heavy chain framework amino acids have been replaced with corresponding amino acid(s) from another human antibody amino acid sequence.

[0025] In one example, an antibody contemplated herein further comprises any one of the light chain CDR amino acid sequences set forth in any one of SEQ ID NOs: 29-40. In other examples, an antibody contemplated herein comprises at least two of the light chain CDR amino acid sequences set forth in any one of SEQ ID NOs: 29-40. In other examples, an antibody contemplated herein comprises at least three of the light chain CDR amino acid sequences set forth in any one of SEQ ID NOs: 29-40.

[0026] In another example, an antibody described herein comprises (a) a light chain CDR1 amino acid sequence set forth in SEQ ID NOs: 29, 32, 35, or 38, or a variant thereof in which one or two amino acids have been changed; (b) a light chain CDR2 amino acid sequence set forth in SEQ ID NOs: 30, 33, 36, or 39 that is from the same light chain variable region as (a), or a variant thereof in which one or two amino acids have been changed; and (c) a light chain CDR3 amino acid sequence set forth in SEQ ID NOs: 31, 34, 37, or 40 that is from the same light chain variable region as (a), or a variant thereof in which one or two amino acids have been changed.

[0027] In alternative examples, an antibody contemplated herein comprises: (a) a light chain CDR1 amino acid sequence set forth in SEQ ID NOs: 29, 32, 35, or 38, or a variant thereof in which one or two amino acids have been changed; (b) an independently selected light chain CDR2 amino acid sequence set forth in SEQ ID NOs: 30, 33, 36, or 39, or a variant thereof in which one or two amino acids have been changed; and (c) an independently selected light chain CDR3 amino acid sequence set forth in SEQ ID NOs: 31, 34, 37, or 40, or a variant thereof in which one or two amino acids have been changed.

[0028] In certain examples, at least two of the light chain CDR1, CDR2 or CDR3 amino acid sequences are set forth in any one of SEQ ID NOs: 29-40.

[0029] It is further disclosed that an antibody described herein comprises an amino acid sequence at least 70% identical to a light chain variable region amino acid sequence set forth in any one of SEQ ID NOs: 9, 11, 13, or 15. In a related example, the antibody comprises an amino acid sequence at least 85% identical to a light chain variable region amino acid sequence set forth in any one of SEQ ID NOs: 9, 11, 13, or 15. In a further example, the antibody comprises an amino acid sequence at least 95% identical to a light chain variable region amino acid sequence set forth in any one of SEQ ID NOs: 9, 11, 13, or 15. In still another example, the antibody comprises a light chain variable region amino acid sequence set forth in any one of SEQ ID NOs: 9, 11, 13, or 15.

[0030] In a further example, an antibody described herein comprises a polypeptide sequence having an amino acid sequence at least 70% identical over all three LCDRs of a light chain variable region, the amino acid sequences of LCDR1, LCDR2 and LCDR3 set forth in any one of SEQ ID NOs: 29-40.

[0031] In certain examples, an antibody described herein comprises (i) an amino acid sequence at least 70% identical over all three LCDRs, of a light chain variable region, the amino acid sequences of LCDR1, LCDR2 and LCDR3 set forth in any one of SEQ ID NOs: 29-40 and (ii) an amino acid sequence at least 70% identical over all three HCDRs of a heavy chain variable region, the amino acid sequences of HCDR1, HCDR2 and HCDR3 set forth in any one of SEQ ID NOs: 17-28.

[0032] In various examples, the disclosure provides an antibody that binds interleukin-2 (IL-2) comprising a light chain variable region and/or a heavy chain variable region, wherein (a) the light chain variable region comprises at least a CDR1 selected from SEQ ID NOs: 29, 32, 35, or 38, or sequences at least 80% identical thereto, a CDR2 selected from SEQ ID NOs: 30, 33, 36, or 39, or sequences at least 80% identical thereto, and/or a CDR3 selected from SEQ ID NOs: 31, 34, 37, or 40, or sequences at least 80% identical thereto; and/or wherein (b) the heavy chain variable region comprises at least a CDR1 selected from SEQ ID NOs: 17, 20, 23, or 26, or sequences at least 80% identical thereto, a CDR2 selected from SEQ ID NOs: 18, 21, 24, or 27, or sequences at least 80% identical thereto, and/or a CDR3 selected from SEQ ID NOs: 19, 22, 25, or 28, or sequences at least 80% identical thereto.

[0033] In various examples, the disclosure provides an antibody that binds IL-2 comprising a light chain variable region and/or a heavy chain variable region, wherein (a) the light chain variable region comprises at least a CDR1 selected from SEQ ID NOs: 29, 32, 35, or 38, or sequences at least 90% identical thereto, a CDR2 selected from SEQ ID NOs: 30, 33, 36, or 39, or sequences at least 90% identical thereto, and/or a CDR3 selected from SEQ ID NOs: 31, 34, 37, or 40, or sequences at least 90% identical thereto; and/or wherein (b) the heavy chain variable region comprises at least a CDR1 selected from SEQ ID NOs: 17, 20, 23, or 26, or sequences at least 90% identical thereto, a CDR2 selected from SEQ ID NOs: 18, 21, 24, or 27, or sequences at least 90% identical thereto, and/or a CDR3 selected from SEQ ID NOs: 19, 22, 25, or 28, or sequences at least 90% identical thereto

[0034] In certain examples, an antibody described herein inhibits binding of IL-2 with an IL-2 receptor alpha (IL-2 R- α) subunit. In a related example, an antibody described herein does not completely block binding of IL-2 to an IL-2 R $\beta\gamma$ complex.

[0035] In certain examples, an antibody described herein binds at a site allosteric to binding of IL-2 to IL-2 R α , IL-2R β , IL-2R γ and/or IL-2 R $\beta\gamma$. In certain examples, an antibody described herein binds to IL-2 and induces a conformational change that impacts binding preference to IL-2R α , IL-2R β , and/or γ c.

[0036] In certain examples, an antibody described herein does not shift the EC50 of binding of IL-2 to IL-2 R $\beta\gamma$ complex by more than 3-fold.

[0037] In certain examples, an antibody described herein inhibits STAT5 activation in a cell in response to stimulation of the IL-2 R with IL-2.

[0038] In some examples, an antibody of the disclosure further comprises a heavy chain constant region, wherein the heavy chain constant region is a modified or unmodified IgG, IgM, IgA, IgD, IgE, a fragment thereof, or combinations thereof.

[0039] In certain examples, an antibody is provided in which one or more light chain framework amino acids have been replaced with corresponding amino acid(s) from another human antibody amino acid sequence, optionally wherein the framework comprises one or more of the changes set out in Figure 12.

[0040] In one example, the antibody of the disclosure is selected from the group consisting of XPA.92.019, XPA.92.041, XPA.92.042 or XPA.92.099.

[0041] In one example, an antibody described herein further comprises a human light chain constant region attached to said light chain variable region. In some examples, the light chain constant region is a modified or unmodified lambda light chain constant region, a kappa light chain constant region, a fragment thereof, or combinations thereof.

[0042] In another example, the disclosure provides an isolated nucleic acid molecule comprising a nucleotide sequence that encodes the heavy chain or light chain as described herein. In various examples the nucleotide sequences are set out in SEQ ID NOs: 2, 4, 6, 8, 10, 12, 14, or 16.

[0043] In a further example, the disclosure provides an expression vector comprising a nucleic acid molecule contemplated herein operably linked to an expression control sequence. Also contemplated is a host cell comprising an expression vector or a nucleic acid molecule of the disclosure. In certain examples, the disclosure provides a host cell comprising a nucleic acid molecule encoding a heavy chain and a light chain variable region, wherein the heavy chain and light chain nucleic acids are expressed by different nucleic acids or on the same nucleic acid.

[0044] In a related example, the disclosure provides a method of using the host cell as described herein to produce an antibody, the method comprising culturing the host cell under suitable conditions and recovering said antibody. Also provided is an antibody produced by the method disclosed herein.

[0045] The disclosure further provides another aspect of a sterile pharmaceutical composition comprising the antibody as disclosed herein and a pharmaceutically acceptable carrier.

[0046] In another example, the disclosure provides a method for suppressing IL-2 activity in a patient in need thereof comprising the step of administering to a subject in need thereof a therapeutically effective amount of an antibody or a pharmaceutical composition contemplated herein. It is contemplated, in various examples, that the method suppresses IL-2 activity in cell populations such as regulatory T cells/CD25^{hi}, T effector/CD 25^{lo}, and/or cells with high affinity trimeric IL-2 receptor (IL-2 R $\alpha\beta\gamma$) or IL-2R α .

[0047] In another example, the disclosure provides a method for treating a disease, condition or disorder associated with increased interleukin-2 (IL-2) or interleukin-2 receptor (IL-2 R) expression or activity comprising the step of administering to a subject in need thereof a therapeutically effective amount of an antibody or a pharmaceutical composition contemplated herein.

[0048] In various examples, the disclosure provides a method for treating a disease, condition or disorder in which modulation of interleukin-2 (IL-2) signaling is beneficial to improve immune response in a subject comprising the step of administering to a subject in need thereof a therapeutically effective amount of an antibody or a pharmaceutical composition contemplated herein.

[0049] In another example, the disclosure provides a method for treating a disease, condition or disorder selected from the group consisting of cancer, microbial infection, asthma and autoimmune disease.

[0050] In various examples, the cancer is selected from the group consisting of melanoma, renal cell carcinoma, lymphoma, sarcoma, breast cancer, lung cancer, bladder cancer, colon cancer, gastric cancer, non-small cell lung carcinoma (NSCLC), bladder cancer, head and neck cancer, skin cancer, and squamous cell carcinoma (SCC).

[0051] In various examples, the microbial infection is a viral, bacterial or fungal infection.

[0052] In various examples, administering to a subject in need thereof a therapeutically effective amount of an antibody or a pharmaceutical composition contemplated herein reduces tumor volume in the subject.

[0053] In various examples, administering to a subject in need thereof a therapeutically effective amount of an antibody or a pharmaceutical composition contemplated herein increases the ratio of CD8⁺ T cells to CD4⁺ T cells in the subject. In various examples, the antibody increases the ratio of CD8⁺ to CD4⁺ T cells by at least about 1-fold, optionally up to 100-fold. In other examples, an antibody described herein is capable of increasing the ratio of CD8⁺ to CD4⁺ T cells by at least 1-100 fold, 10-100 fold, 1-fold, 2-fold, 3-fold, 4-fold, 5-fold, 6-fold, 7-fold, 8-fold, 9 fold, 10-fold, 25-fold, 50-fold, or 100-fold.

[0054] In various examples, the antibody disclosed herein is administered intravenously, intraarterially, intraperitoneally, intratumorally, intramuscularly, intradermally or subcutaneously.

[0055] In various examples, the antibody disclosed herein is administered in combination with a second agent. In related examples, the second agent is IL-2, an IL-2 variant, or an agent that can increase IL-2 levels, a checkpoint inhibitor, a CART/TIL agent, an antibody to a tumor antigen or a vaccine. In related examples, the checkpoint inhibitor is selected from the group consisting of an anti-PD-1 antibody, an anti-PDL-1 antibody, an anti-CTLA-4 antibody, a PD-1 inhibitor, a PDL-1 inhibitor or a CTLA-4 inhibitor.

[0056] In various examples, when the antibody is administered in combination with IL-2, the IL-2 or IL-2 variant and the IL-2 antibody are administered in a 1:1 molar ratio. In various examples, administering the IL-2 antibody in combination with IL-2 or an IL-2 variant increases the therapeutic index (TI) of IL-2 by at least 2, 3, 4, 5, 6, 7, 8, 9, or 10-fold or more.

[0057] In various examples, it is contemplated that the antibody can be administered in combination with IL-2 and a second agent such as a checkpoint inhibitor, a CART/TIL agent, an antibody to a tumor antigen or a vaccine.

[0058] In various examples, provided herein is a method of treating a disease, e.g., cancer, comprising administering an IL-2 antibody in combination with IL-2, optionally also in combination with a checkpoint inhibitor or other adjunctive oncology therapy, whereby efficacy against a non-IL-2 responsive tumor type is now made sensitive to growth and/or metastasis inhibition.

[0059] In various examples, IL-2 can be complexed to the antibody prior to administration, with or without administration of another second agent described herein.

[0060] In various examples, the antibody disclosed herein is administered once per week, once every 2 weeks, twice per month, once monthly, once every two months, or once every three months or less.

[0061] In various examples, when the IL-2 and IL-2 antibody are pre-mixed, the agents could be administered together twice weekly. In various examples, the IL-2 is administered at a dose of 0.1 to 10 mg/kg. In various examples, the IL-2 antibody is administered intravenously.

[0062] If adding IL-2 dosing relevant to IL-2 antibody, it is contemplated that the IL-2 is administered sequentially, for example on the same day, and in certain examples, the IL-2 antibody is administered prior to administration of the IL-2. In various examples, the IL-2 antibody is administered weekly with weekly or multi-times per week administration of IL-2 following administration of the antibody.

[0063] In various examples, the IL-2 antibody is administered 1 time per week and IL-2 therapy (e.g., Proleukin) is administered on the known prescribing schedule, but at a lower IL-2 dose.

[0064] In various examples, the disclosure provides a method for administering a composition comprising an antibody or a pharmaceutical composition disclosed herein in the treatment a condition or disorder associated with increased or decreased IL-2 or IL-2R expression or activity.

[0065] In one example, the disclosure provides a method for modulating IL-2 activity in a cell comprising the step of contacting the cell with an amount of an antibody or a pharmaceutical composition disclosed herein effective to modulate IL-2 activity in the cell.

[0066] Also disclosed herein is a composition comprising any of the foregoing antibodies or compositions of the disclosure that bind IL-2, or use thereof in preparation of a medicament, for treatment of any of the disorders described herein associated with IL-2 or IL-2R expression or activity. Syringes, e.g., single use or pre-filled syringes, sterile sealed containers, e.g. vials, bottle, vessel, and/or kits or packages comprising any of the foregoing antibodies or compositions, optionally with suitable instructions for use, are also disclosed.

[0067] It is understood that each feature or example, or combination, described herein is a non-limiting, illustrative example of any of the aspects of the disclosure and, as such, is meant to be combinable with any other feature or example, or combination, described herein. For example, where features are described with language such as “one example”, “some examples”, “certain examples”, “further example”, and/or “another example”, each of these types of examples is a non-limiting example of a feature that is intended to be combined with any other feature, or combination of features, described herein without having to list every possible combination. Such features or combinations of features apply to any of the aspects of the disclosure. Where examples of values falling within ranges are disclosed, any of these examples are contemplated as possible endpoints of a range, any and all numeric values between such endpoints are contemplated, and any and all combinations of upper and lower endpoints are envisioned.

[0068] The headings herein are for the convenience of the reader and not intended to be limiting. Additional aspects, examples, and variations of the disclosure will be apparent from the Detailed Description and/or Drawing and/or claims.

BRIEF DESCRIPTION OF THE DRAWINGS

[0069] **Figures 1A and Figure 1B** show multiple sequence alignments of the heavy and light chains of selected clones against the sequence of XPA.92.099.

[0070] **Figures 2A-2D** show the measurement of XPA.92.019 (Figure 2A), XPA.92.041 (Figure 2B), XPA.92.042 (Figure 2C), XPA.92.099 (Figure 2D) binding to cells expressing IL-2 R β or IL-2 R $\beta\gamma$ in the presence of variable IL-2 concentrations.

WHAT IS CLAIMED:

1. A human or humanized antibody that binds human interleukin-2 (IL-2) with an affinity K_D of 1×10^{-10} M or less and inhibits binding of IL-2 with an IL-2 receptor alpha (IL-2 R α) subunit,

wherein the antibody inhibits IL-2 signaling through IL-2 R $\alpha\beta\gamma$ and through IL-2 R $\beta\gamma$,
and

wherein the antibody inhibits IL-2 signaling through IL-2 R $\alpha\beta\gamma$ to a greater extent than through IL-2 R $\beta\gamma$.

2. The antibody of claim 1 wherein the antibody does not completely block binding of human IL-2 to cells expressing human or mouse IL-2 R β or IL-2 R $\beta\gamma$ complex.

3. The antibody of claim 1, wherein the antibody binds at a site allosteric to binding of IL-2 to IL-2 R α , IL-2 R $\beta\gamma$ or IL-2 R $\alpha\beta\gamma$.

4. The antibody of claim 1, wherein the antibody is a negative modulator antibody, optionally wherein the antibody is capable of weakening the binding affinity between IL-2 with IL-2 receptor α (IL-2 R α) by at least about 2-fold, optionally up to 1000-fold.

5. The antibody of claim 1 wherein IL-2 complexed to the antibody binds to CHO cells expressing IL-2 R β and γ_c with an EC₅₀ of 5 nM or less or wherein IL-2 complexed to the antibody binds to CHO cells expressing IL-2 R β (but not γ_c) with an EC₅₀ of 100 nM or less.

6. The antibody of claim 1 wherein the antibody binds to human IL-2 and one or more of mouse, rat or rabbit IL-2.

7. The antibody of claim 1, wherein the antibody inhibits IL-2 stimulation of STAT5 activation in cells expressing IL-2 R α , IL-2 R β , and γ_c to a greater extent than cells expressing IL-2 R β and γ_c , but not IL-2 R α .

8. The antibody of claim 1, wherein the antibody inhibits IL-2 stimulation of STAT5 activation in cells that express IL-2 R α , IL-2 R β , and γ_c by 200-fold or greater.

9. The antibody of claim 1, wherein the antibody inhibits IL-2 stimulation of STAT5 activation in cells that express IL-2 R β and γ_c , but not IL-2 R α by 10-fold or less.

10. The antibody of claim 1, wherein the antibody inhibits IL-2 stimulation of proliferation in cells expressing IL-2 R α , IL-2 R β , and γ_c to a greater extent than cells expressing IL-2 R β and γ_c , but not IL-2 R α .

11. The antibody of claim 1, wherein the antibody inhibits IL-2 stimulation of proliferation of NK cells that express IL-2 R α , IL-2 R β , and γ_c , by greater than 15-fold.

12. The antibody of claim 1, wherein the antibody inhibits IL-2 stimulation of proliferation of BaF3 cells that express IL-2 R β and γ_c , but not IL-2 R α , by less than 10-fold.

13. The antibody of claim 1, further comprising a heavy chain constant region, wherein the heavy chain constant region is a modified or unmodified IgG, IgM, IgA, IgD, IgE, a fragment thereof, or combinations thereof.

14. The antibody of claim 1, further comprising a human light chain constant region attached to said light chain variable region.

15. A sterile pharmaceutical composition comprising the antibody of claim 1 and a pharmaceutically acceptable carrier.

16. An antibody that binds human interleukin-2 (IL-2) comprising i)(a) a heavy chain CDR1 amino acid sequence set forth in SEQ ID NOs: 17, 20, 23, or 26;

(b) a heavy chain CDR2 amino acid sequence set forth in SEQ ID NOs: 18, 21, 24, or 27 that is from the same heavy chain variable region as (a); and

(c) a heavy chain CDR3 amino acid sequence set forth in SEQ ID NOs: 19, 22, 25, or 28 that is from the same heavy chain variable region as (a);

and ii)

(a) a light chain CDR1 amino acid sequence set forth in SEQ ID NOs: 29, 32, 35, or 38;

(b) a light chain CDR2 amino acid sequence set forth in SEQ ID NOs: 30, 33, 36, or 39 that is from the same light chain variable region as (a); and

(c) a light chain CDR3 amino acid sequence set forth in SEQ ID NOs: 31, 34, 37, or 40 that is from the same light chain variable region as (a).

17. The antibody of claim 16, that comprises an amino acid sequence at least 90% identical to a heavy chain variable region amino acid sequence set forth in SEQ ID NOs: 1, 3, 5, or 7.

18. An antibody of claim 16, in which one or more heavy chain framework amino acids have been replaced with corresponding amino acid(s) from another human antibody amino acid sequence.

19. An antibody of claim 16, comprising an amino acid sequence at least 90% identical to a light chain variable region amino acid sequence set forth in any one of SEQ ID NOs: 9, 11, 13, or 15.

20. An antibody of claim 16 wherein the antibody

i) inhibits binding of IL-2 to an IL-2 receptor alpha (IL-2 R- α) subunit; and/or

ii) partially inhibits binding of IL-2 to an IL-2 R $\beta\gamma$ complex; and/or

iii) binds at a site allosteric to binding of IL-2 to IL-2 R α , IL-2 R $\beta\gamma$ or IL-2 R $\alpha\beta\gamma$.

21. An antibody of claim 16, wherein the antibody is a negative modulator antibody, optionally wherein the antibody is capable of weakening the binding affinity between IL-2 with IL-2 receptor α (IL-2 R α) by at least about 2-fold, optionally up to 1000-fold.

22. An antibody of claim 16, wherein the antibody does not shift the EC₅₀ of binding of IL-2 to IL-2 R $\beta\gamma$ complex by more than 3-fold.

23. An antibody of claim 16 wherein the antibody binds to human IL-2 and one or more of mouse, rat or rabbit IL-2.

24. An antibody of claim 16, wherein the antibody inhibits STAT5 activation in a cell in response to stimulation of the IL-2 R with IL-2.

25. The antibody of claim 16 that is a human antibody or a humanized antibody.

26. An antibody of claim 16, in which one or more light chain framework amino acids have been replaced with corresponding amino acid(s) from another human antibody amino acid sequence.

27. An antibody of claim 16 that binds human interleukin-2 (IL-2) with an affinity K_D of 10^{-10} M or less.

28. An antibody of claim 16 comprising (a) heavy chain HCDR1-HCDR3 amino acid sequences set forth in SEQ ID NOs: 17-19; and (b) light chain LCDR1-LCDR3 amino acid sequences set forth in SEQ ID NOs: 29-31.

29. An antibody of claim 28 comprising a heavy chain variable region amino acid sequence set forth in SEQ ID NO: 1 and a light chain variable region amino acid sequence set forth in SEQ ID NO: 9.

30. An antibody of claim 16 comprising (a) heavy chain HCDR1-HCDR3 amino acid sequences set forth in SEQ ID NOs: 26-28; and (b) light chain LCDR1-LCDR3 amino acid sequences set forth in SEQ ID NOs: 38-40.

31. An antibody of claim 30 comprising a heavy chain variable region amino acid sequence set forth in SEQ ID NO: 7 and a light chain variable region amino acid sequence set forth in SEQ ID NO: 15.