Synthekine

STK-012: An Engineered Selective IL-2 Mutein That Promotes Anti-Tumor Responses Without Related Toxicities

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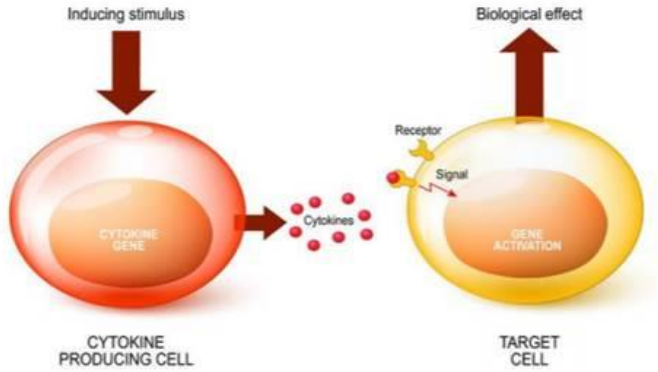
VP, Head of Protein Sciences
PEGS Boston May 2023

The Opportunity and the Challenge of Cytokine Therapeutics

Cytokines: Small proteins that facilitate immune system signaling to maintain immune homeostasis and respond to infections and tumors



Challenges of Developing Cytokine Therapeutics:

Wild type cytokines are highly pleiotropic

- Drive divergent activity on multiple cell types, and when used therapeutically frequently result in:
  - Dose limiting toxicities
  - Limited efficacy, and
  - Narrow therapeutic window
- Half-life extended versions of wild-type cytokines (PEG or Fc) have the similar challenges

Harnessing the Power of Cytokines Requires:

- Deep understanding of cytokine structure, function, and downstream immunological signaling
- Extensive insights into cytokine receptor expression on immune cells at various activation states
- Creative protein engineering to introduce selectivity and improve drug like properties
- Innovative development strategies to rapidly evaluate clinical significance

Synthekine Was Founded By Licensing World-Class Cytokine Receptor-Ligand Interaction Insights From Garcia Lab

Stanford University

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RESEARCH

RESEARCH ARTICLE SUMMARY

IMMUNOLOGY

Structure-based decoupling of the pro- and anti-inflammatory functions of interleukin-10

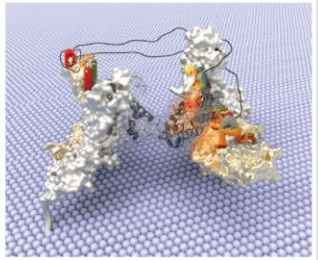
Robert A. Saxton, Naotaka Tsutsumi, Leon L. Su, Gita C. Abhiraman, Kritika Mohan, Lukas T. Henneberg, Nanda G. Aduri, Cornelius Gati, K. Christopher Garcia*

INTRODUCTION: Interleukin-10 (IL-10) is an important immunoregulatory cytokine that acts to suppress and terminate inflammatory immune responses, largely through the inhibition of monocyte and macrophage activation. Polymorphisms in genes encoding IL-10 and IL-10 receptor (IL-10R) subunits are associated with autoimmune diseases, most notably inflammatory bowel disease (IBD). IL-10 has consequently garnered substantial clinical interest for use as an anti-inflammatory immune modulating agent. However, IL-10 has shown limited therapeutic efficacy, due in part to its pleiotropic nature and its capacity to also elicit proinflammatory effects, including the stimulation of interferon-γ (IFN-γ) and granzyme B production by $CD8^+$ T cells.

RATIONALE: We hypothesized that obtaining structural information for the complete IL-10 receptor complex would enable the rational design of IL-10 analogs with enhanced functional specificity and improved therapeutic utility. Mechanistically, IL-10 functions as a secreted homodimer that engages two copies of a heterodimeric receptor complex comprising the private receptor subunit, IL-10Rα, and the shared subunit, IL-10Rβ. The IL-10–dependent dimerization of IL-10Rα and IL-10Rβ in turn initiates activation of the transcription factor STAT3, which mediates the diverse biological effects of IL-10. However, structural information for the complete IL-10 receptor signaling complex is lacking, due in part to the extremely low affinity of IL-10 for IL-10Rβ.

RESULTS: To overcome this limitation, we first used yeast display–based directed evolution to engineer a "super-10" variant with greatly enhanced affinity for IL-10Rβ, enabling assembly of the hexameric IL-10–IL-10Rα–IL-10Rβ complex. Using this stabilized complex, we then determined the structure of the complete IL-10 receptor complex at 3.5 Å resolution by cryo-electron microscopy (cryo-EM). The structure revealed how IL-10 engages IL-10Rβ to initiate signal transduction, and also uncovered the molecular basis for a mutation in IL-10Rβ associated with early-onset IBD. In addition, the structure provided an engineering blueprint for the design of IL-10 variants with which we could pharmacologically probe the nature of IL-10's functional pleiotropy.

Characterization of these IL-10 variants revealed that the plasticity of IL-10 signaling varies extensively across immune cell types, inversely correlating with the level of IL-10Rβ expression. In particular, we found that myeloid cells exhibit robust STAT3 activation in response to IL-10 variants across a wide range of IL-10Rβ–binding affinities, whereas IL-10 signaling in lymphocytes was highly tunable. Several engineered IL-10 variants exploited these differences to elicit myeloid-biased signaling in both cell lines and human peripheral blood mononuclear cells (PBMCs). Functionally, these variants effectively inhibited inflammatory monocyte and macrophage activation in vivo and promoted survival in a mouse model of sepsis, thus retaining the major anti-inflammatory effects of IL-10. However, they showed significantly reduced capacity to stimulate proinflammatory gene expression in $CD8^+$ T cells and failed to potentiate IFN-γ or granzyme B production, thereby uncoupling



Engineering IL-10. The structure of the IL-10 receptor complex is shown on a cell surface with "engineers" depicted as welders making alterations to IL-10 at the receptor-binding interface that was the focus of Saxton et al.

Saxton et al., Science 371, 1223 (2001) 19 March 2021

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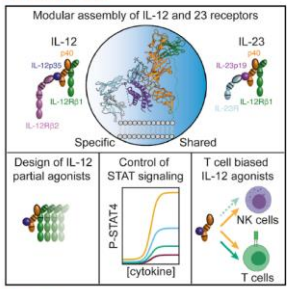
Cell

Structural basis for IL-12 and IL-23 receptor sharing reveals a gateway for shaping actions on T versus NK cells

Graphical abstract



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In Brief

Structures of the IL-12 and IL-23 recepto complexes guide design of T-cell-biase IL-12 agonists with reduced cytokine pleiotropy to support anti-tumor immunity without inducing toxicity.

Highlights

- Crystal structure of the complete IL-23 receptor complex
- Cryo-EM maps of the complete IL-12 and IL-23 receptor complexes
- The p40 subunit of IL-12 and IL-23 is a common gateway for induction of STAT signaling
- T-cell-biased IL-12 agonists elicit anti-tumor response without inducing toxicity

Glassman et al., 2021, Cell 184, 983–999 February 18, 2021 © 2021 Elsevier Inc. https://doi.org/10.1016/j.cell.2021.01.018

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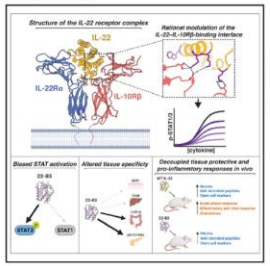
Immunity

Article

The tissue protective functions of interleukin-22 can be decoupled from pro-inflammatory actions through structure-based design

Graphical abstract



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In brief

Saxton et al. engineer a high-affinity interleukin-22 (IL-22) super-agonist that enables structure determination of the IL-22-IL-22Rα-IL-10Rβ ternary complex. IL-22 receptor agonists designed based on these structural insights elicit activation of STAT3 but not STAT1 and promote epithelial protection without inducing loc inflammation.

Highlights

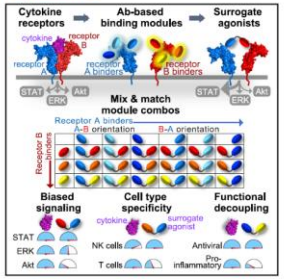
- 2.6-A-resolution structure of a stabilized IL-22 receptor ternary complex
- Structure-based design of STAT3-biased IL-22 receptor agonists
- Biased IL-22 variant 22-B3 elicits tissue-selective STAT3 activation *in vivo*
- 22-B3 uncouples the tissue-protective and pro-inflammatory functions of IL-22

Saxton et al., 2021, Immunity 54, 660–672 April 13, 2021 © 2021 Elsevier Inc. https://doi.org/10.1016/j.immuni.2021.03.006

Cell

Facile discovery of surrogate cytokine agonists

Graphical abstract



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In brief

A discovery platform for functio diverse cytokine surrogates.

Highlights

- A platform to expand and diversify cytokine biology with modular surrogate agonists
- IL-2 surrogates reveal signaling plasticity and biased activities on T and NK cells
- Type-I IFN surrogates are potent antiviral agents with reduced cytotoxic properties
- IL-2/10 surrogates drive non-natural receptor hetero-dimerization on T and NK cells

Yen et al., 2022, Cell 185, 1414–1430 April 14, 2022 © 2022 Elsevier Inc. https://doi.org/10.1016/j.cell.2022.02.025

CellPress

RESEARCH

IMMUNE ENGINEERING

Selective targeting of engineered T cells using orthogonal IL-2 cytokine-receptor complexes

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Interleukin-2 (IL-2) is a cytokine required for effector T cell expansion, survival, and function, especially for engineered T cells in adoptive cell immunotherapy, but its pleiotropy leads to simultaneous stimulation and suppression of immune responses as well as systemic toxicity, limiting its therapeutic use. We engineered IL-2 cytokine-receptor orthogonal (*ortho*) pairs that interact with one another, transmitting native IL-2 signals, but do not interact with their natural cytokine and receptor counterparts. Introduction of *ortho*IL-2Rβ into T cells enabled the selective cellular targeting of *ortho*IL-2 to engineered $CD4^+$ and $CD8^+$ T cells in vitro and in vivo, with limited off-target effects and negligible toxicity. *Ortho*IL-2 pairs were efficacious in a preclinical mouse cancer model of adoptive cell therapy and may therefore represent a synthetic approach to achieving selective potentiation of engineered cells.

Adoptive transfer of tumor-reactive T cells has evolved into a clinically useful therapy capable of inducing antitumor immunity in patients (*1*, *2*). However, the broad application of adoptive T cell transfer (ACT) therapies to treat cancer has several limitations, including the production of sufficient quantities of cells for infusion and the failure of transferred T cells to persist and remain functional in vivo. In the clinic, the concomitant administration of the T cell growth factor interleukin-2 (IL-2) improves the survival, function, and antitumor activity of transplanted T cells (*3*, *4*). However, the use of IL-2 to potentiate ACT is complicated by the pleiotropic nature of IL-2, which induces both immune stimulatory and suppressive T cell responses as well as potentially severe toxicities (*5*). This is governed by the interaction between IL-2 and the IL-2 receptor (IL-2R), which consists of α, β, and γ subunits (*6*). IL-2Rβ and the common γ-chain (IL-2Rγ) together form the signaling dimer and bind IL-2 with moderate affinity, whereas IL-2Rα (CD25) does not signal but increases the affinity of IL-2 for the binary (βγ) IL-2 receptor to sensitize T cells to low concentrations of IL-2.

The activity of IL-2 as an adjuvant to ACT is dependent on the balance between activation of transplanted and endogenous T cell subsets bearing natural IL-2 receptors, as well as host responses that cause dose-limiting toxicities. Strategies to overcome these limitations could improve T cell immunotherapy (*7*, *8*). Recognizing the need for new approaches that afford precise targeting of IL-2–dependent functions to a specific cell type of interest, we devised a strategy to redirect the specificity of IL-2 toward adoptively transferred T cells. This method, based on receptor-ligand orthogonalization, uses a mutant IL-2 cytokine and mutant IL-2 receptor that bind specifically to one another but not to their wild-type counterparts (Fig. 1A).

We focused on the murine IL-2/IL-2Rβ interaction to enable in vivo characterization in syngeneic mouse models. The IL-2Rβ chain was chosen as the mutant receptor because the β chain is required for signal transduction and can bind IL-2 independently. We devised a two-step approach to engineer orthogonal IL-2/IL-2Rβ pairs informed by the crystal structure of the IL-2 high-affinity receptor complex (*6*) (Fig. 1B). First, point mutations of the IL-2Rβ chain were identified from inspection of the interface between IL-2 and IL-2Rβ that abrogated binding to wild-type IL-2 (Fig. 1, C to E). The IL-2Rβ hotspot residues His^{134} and Tyr^{135} make numerous contacts with IL-2 that contribute a majority of the binding free energy between IL-2 and IL-2Rβ (*6*) (Fig. 1E). A double mutant IL-2Rβ (His^{134} → Asp (H134D) and Tyr^{135} → Phe (Y135F)), referred to herein as *ortho*IL-2Rβ, lacked detectable binding to IL-2 (Fig. 1D), even in the presence of CD25 (fig. S1) (*7*, *9*).

Next, we used yeast display–based evolution to mutate, and thus remodel, the wild-type IL-2 interface region that was opposing (or facing the site of) the IL-2Rβ mutations in the crystal structure, in order to create a molecule that bound to *ortho*IL-2Rβ but not to wild-type IL-2Rβ. IL-2 residues in proximity to the *ortho*IL-2Rβ binding interface were randomly mutated and were chosen on the basis of a homology model of the mouse IL-2/IL-2Rβ complex (Fig. 1E) derived from the crystal structure of the human IL-2 receptor complex (*6*). A library of ~10^9 unique IL-2 mutants was displayed on the surface of yeast (fig. S2) and subjected to multiple rounds of both positive (against *ortho*IL-2Rβ) and negative (against IL-2Rβ) selection (figs. S2 and S3). This collection of yeast-displayed IL-2 mutants bound the *ortho*IL-2Rβ, but not wild-type IL-2Rβ, and retained CD25 binding (Fig. 1D). Sequencing of yeast clones from the evolved IL-2 libraries revealed a consensus set of mutations at IL-2 positions in close structural proximity to the *ortho*IL-2Rβ mutations (fig. S4). Interestingly, a Gln^{70} → Asn (Q70N) mutation was highly conserved across three independent mutant IL-2 yeast libraries, whereas all other IL-2 positions used a restricted but not specific mutational signature. We found that IL-2 mutations Q70N, Met^{23} → Val (M23V), and Asp^{20} → Leu or Met (D34L/M) appear to form a small nonpolar pocket to compensate for the IL-2Rβ Y135F mutation, whereas Gln^{126} → Thr, Ser, Lys, or Gln (Q126T/S/K/Q) and Glu^{17} → Tyr or His (E17Y/H) mutations present a polar or charged surface to compensate for the IL-2Rβ H134D mutation (Fig. 1F).

Because of the affinity-enhancing effects of CD25 expression on the interaction of IL-2 with the binary (βγ) IL-2 receptor (*10*), IL-2 mutants with negligible binding to IL-2Rβ alone may still form a functional signaling complex on cells that also express CD25 (*8*). Therefore, we used a yeast-based functional screen to further triage IL-2 mutants that bound specifically to the *ortho*IL-2Rβ and signaled selectively on T cells that express the *ortho*IL-2Rβ (Fig. 1G and fig. S5), and produced recombinant forms of select IL-2 mutants (*ortho*IL-2) for characterization (figs. S6 to S8).

We focused our efforts on two *ortho*IL-2 mutants, IG12 and 3A10. *Ortho*IL-2 IG12 and 3A10 share the consensus Q70N, M23V, and D34L mutations but differ at positions Glu^{20}, Gln^{126}, Glu^{17}, and Arg^{81} (Fig. 1I). *Ortho*IL-2 IG12 and 3A10 bound the *ortho*IL-2Rβ with an affinity comparable to that of the wild-type IL-2/IL-2Rβ interaction and displayed little to no detectable binding to wild-type IL-2Rβ (Fig. 1H and figs. S7 and S8) but differed in their ability to activate IL-2Rβ signaling in CD25-positive wild-type

Sockolosky et al., Science 359, 1037–1042 (2018) 2 March 2018

1 of 6

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Synthekine

Foundational Research and Platforms From the Garcia Lab

Developing potentially paradigm-changing programs using three distinct protein engineering platforms

Cytokine Partial Agonists Platform

- Engineered from cytokine structural insights
- Published in Science, Cell, and Immunity
- ***Ph1 dose escalation ongoing for lead program***

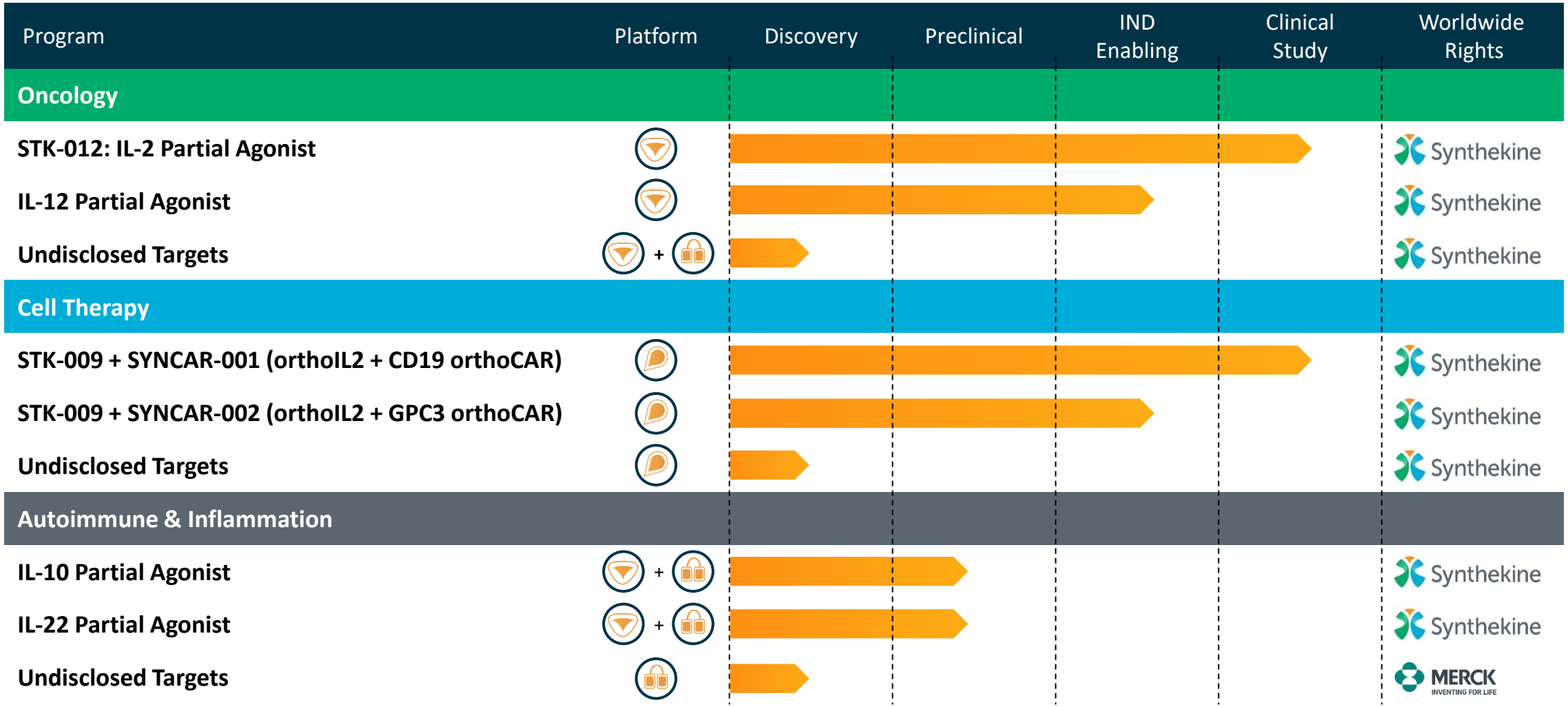
Orthogonal Cytokine Cell Therapy Platform

- Engineered cytokine receptor expressed on CAR-T and other ACTs
- ***Ph1 enrolling for lead program***

Surrogate Cytokine Agonist Platform

- Novel cytokine engineering approach using surrogate binders
- ***Collaboration with Merck and robust internal pipeline***

These Platforms Have Fueled a Deep, Differentiated, and Multi-Modality Pipeline



STK-012

An α/β-biased IL-2 partial agonist

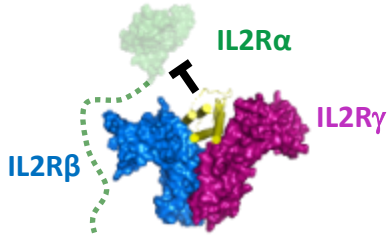
Synthekine's Goal: Delivering on the Promise of IL-2 Therapy

The Promise:

- IL-2 is a potent activator of T cells, which are critical for anti-tumor immunotherapy
- Proleukin® (aldesleukin) is approved as monotherapy in several tumor types

The Limitations:

- Proleukin is toxic and difficult to dose for more than several days
- Many engineered IL-2 molecules have failed to deliver enhanced anti-tumor activity in the clinic

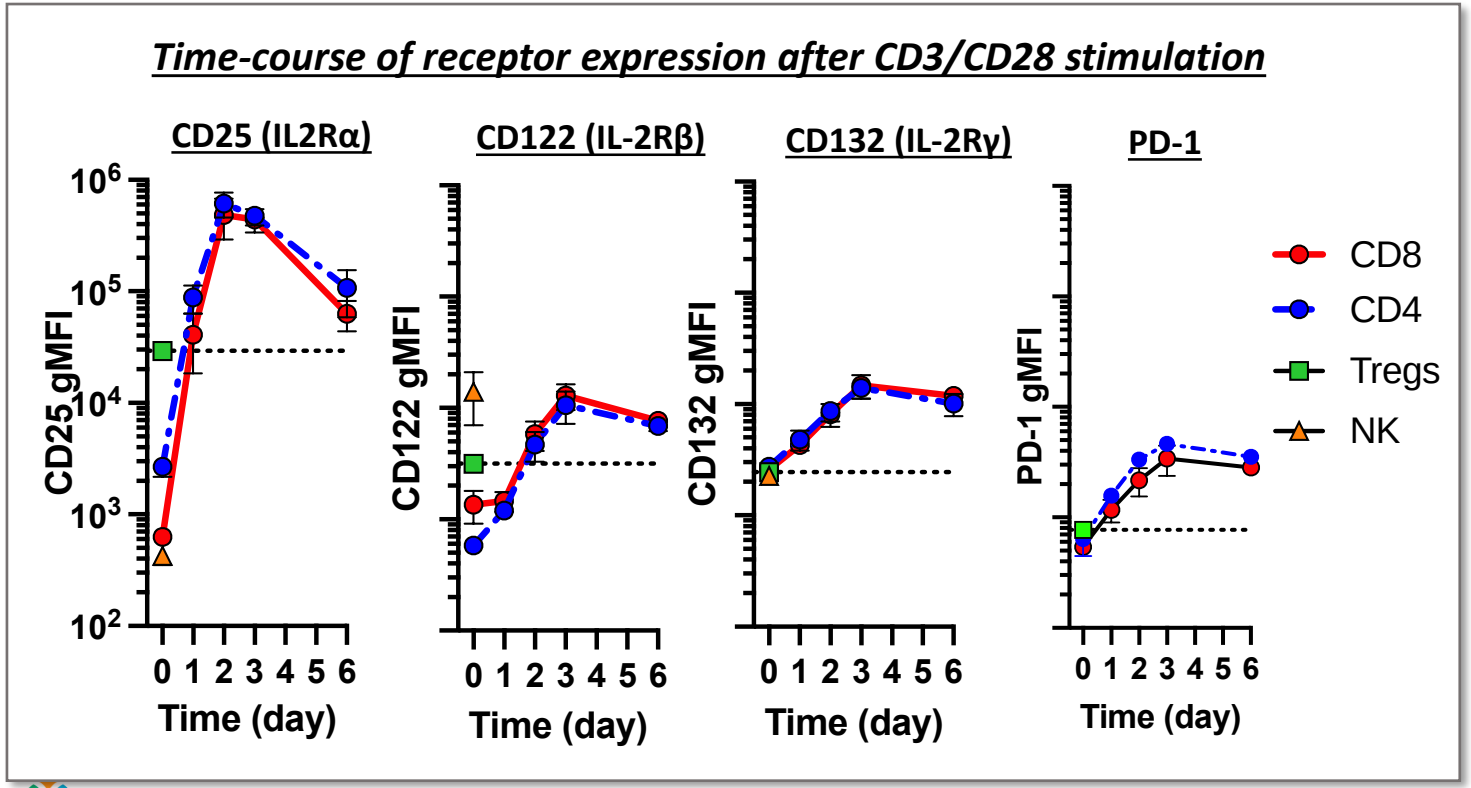


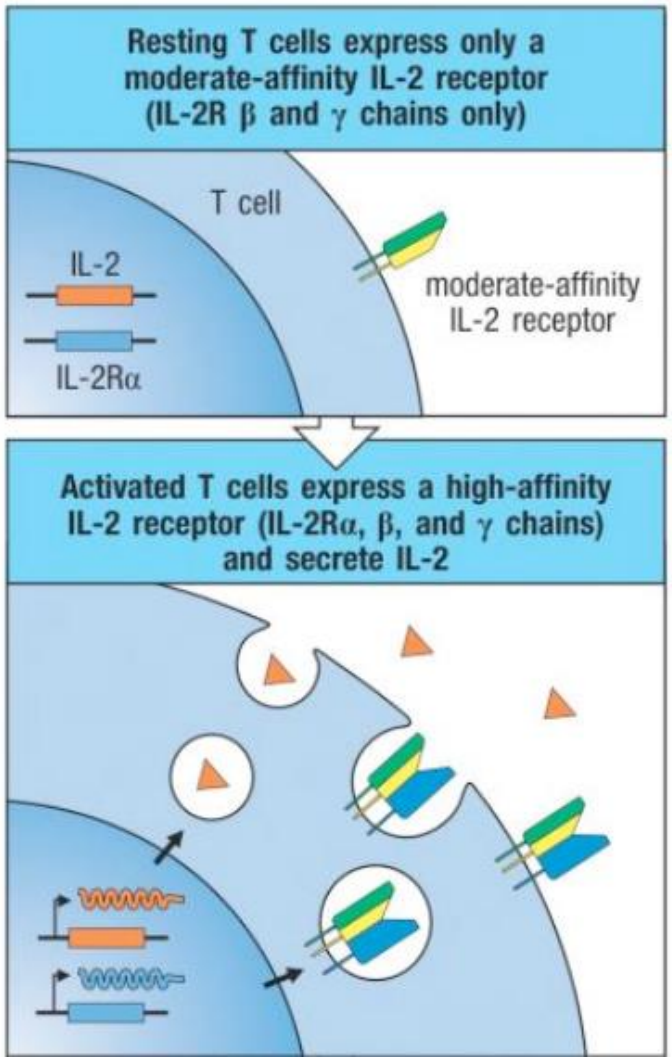
	1st Generation IL-2: (Proleukin®)	2nd Generation Engineered IL-2: (NKTR-214, THOR-707, NL-201, etc.)
Design	High Dose IL-2	"Non-α" IL-2
IL-2R Bias	Binds to both trimeric high & dimeric intermediate affinity IL-2R	Binds only to dimeric intermediate affinity IL-2R

Best-In-Class Engineered IL-2

The Rationale for Targeting the High Affinity IL-2 Receptor on Antigen Activated T-cells in Cancer

- Antigen-induced activation of T cells induces expression of immune checkpoint receptors and the IL-2 receptor subunits IL2Rα and IL2Rβ





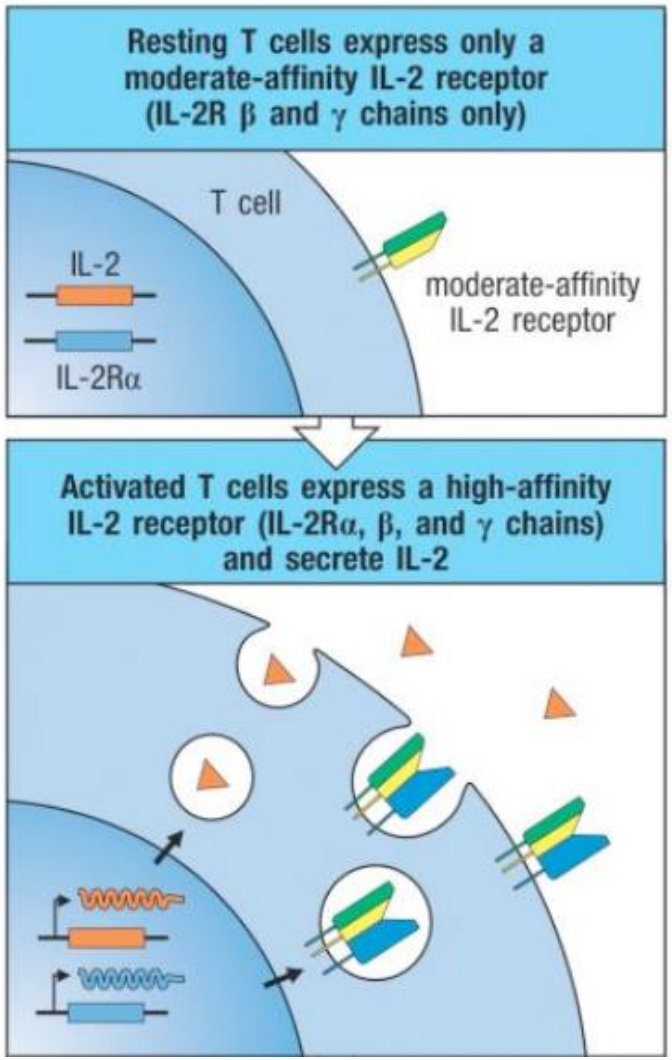
Dimeric β/γ IL-2 Receptor

Trimeric α/β/γ IL-2 Receptor

Janeway's Immunobiology

The Rationale for Targeting the High Affinity IL-2 Receptor on Antigen Activated T-cells in Cancer

- Antigen-induced activation of T cells induces expression of immune checkpoint receptors and the IL-2 receptor subunits IL2Rα and IL2Rβ
- Checkpoint inhibitors (e.g., α-PD1) block upregulated immune checkpoint receptors to activate TILs
- **An engineered IL-2 that targets the upregulated IL-2 receptor subunits may:**
  - ***Further stimulate antigen-activated TILs***
  - ***Spare non-specific NK and T cell activation***



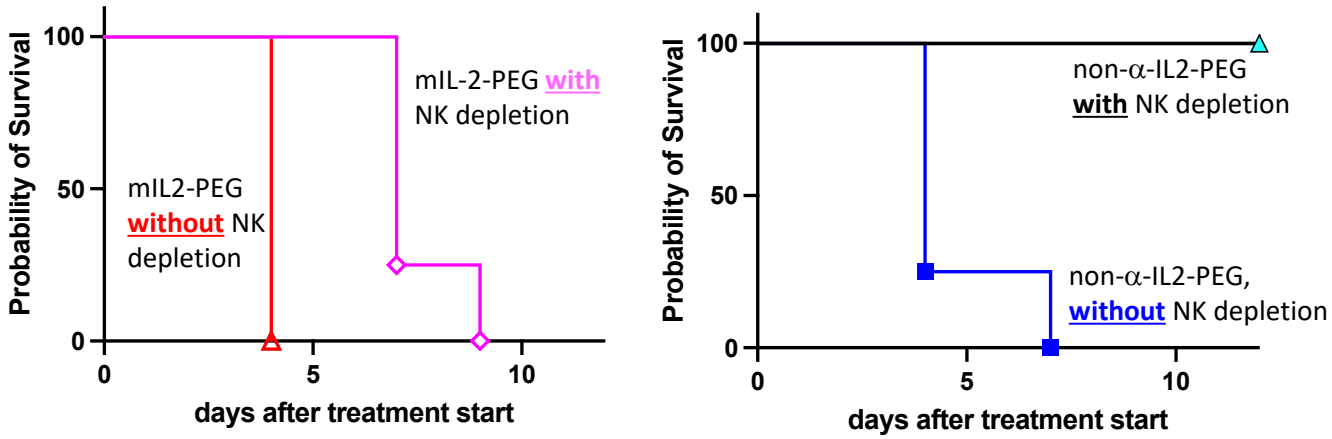
Janeway's Immunobiology

Dimeric β/γ IL-2 Receptor

Trimeric α/β/γ IL-2 Receptor

NK Cells Mediate Capillary Leak Syndrome (CLS) in Mice

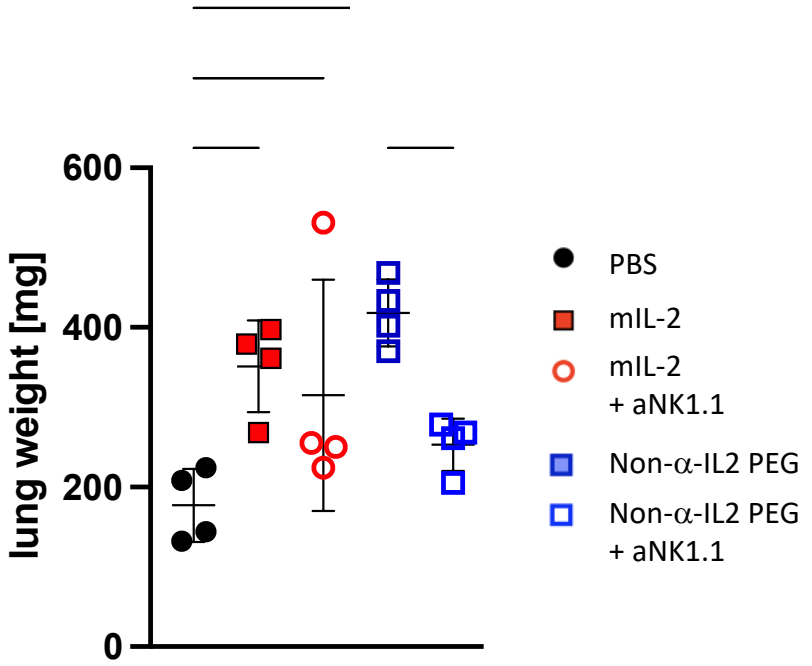
Depletion of NK cells using NK1.1 antibody abrogates IL-2 mediated lethality for WT and non-α-IL2 in C57BL/6 mice



Toxicity of IL-2 is mediated by NK cells, where:

- CD25 expression is low
- IL-2 signaling is primarily mediated by IL2Rβ/IL2Rγ

Lung weight increase with WT and non-α-IL2 abrogated after NK cell depletion



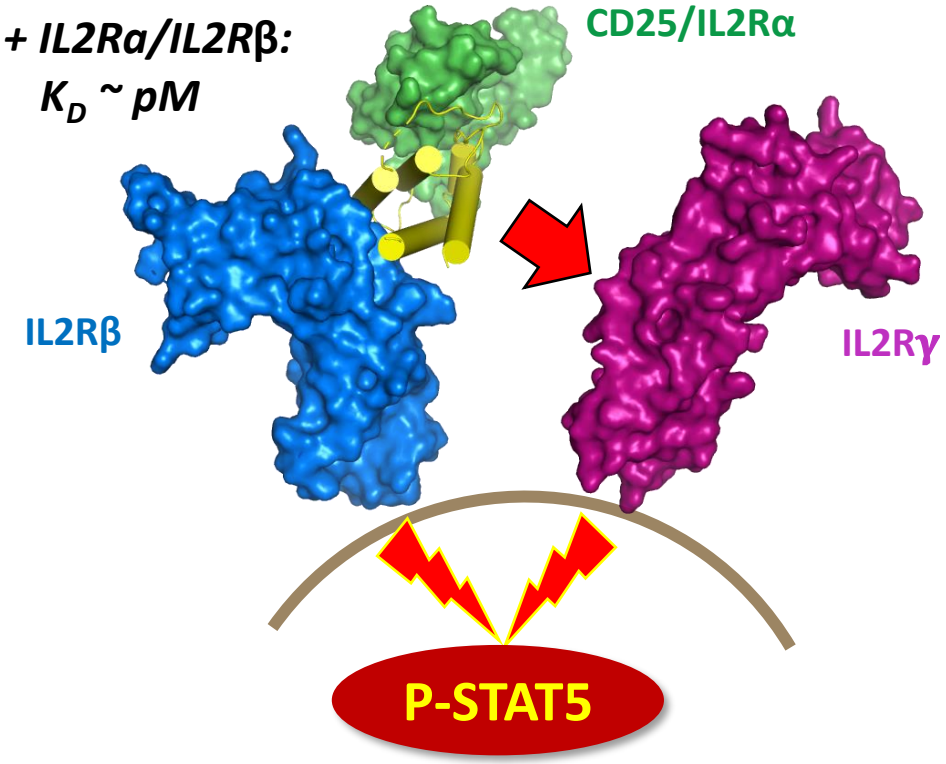
Dosing: acute IL-2 toxicity was analyzed in mice treated every second day with α/β-mIL-2-PEG (10µg), mIL-2-PEG (10µg), or non-α-IL-2-PEG (3µg).

Targeting the High Affinity IL-2 Receptor by Disrupting the IL-2Rγ Binding Site on IL-2

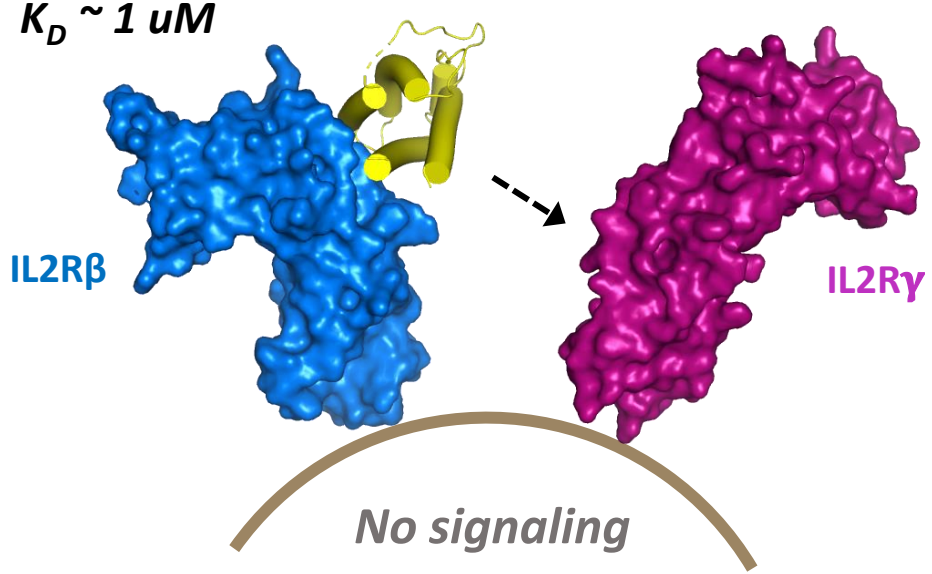
Antigen activated T cells: CD25 high

Naïve T-cells and NK cells: CD25 low

IL2 + IL2Rα/IL2Rβ:
K_D ~ pM



IL2 + IL2Rβ alone:
K_D ~ 1 uM



High CD25 expression increases IL-2 potency on ***activated T cells***

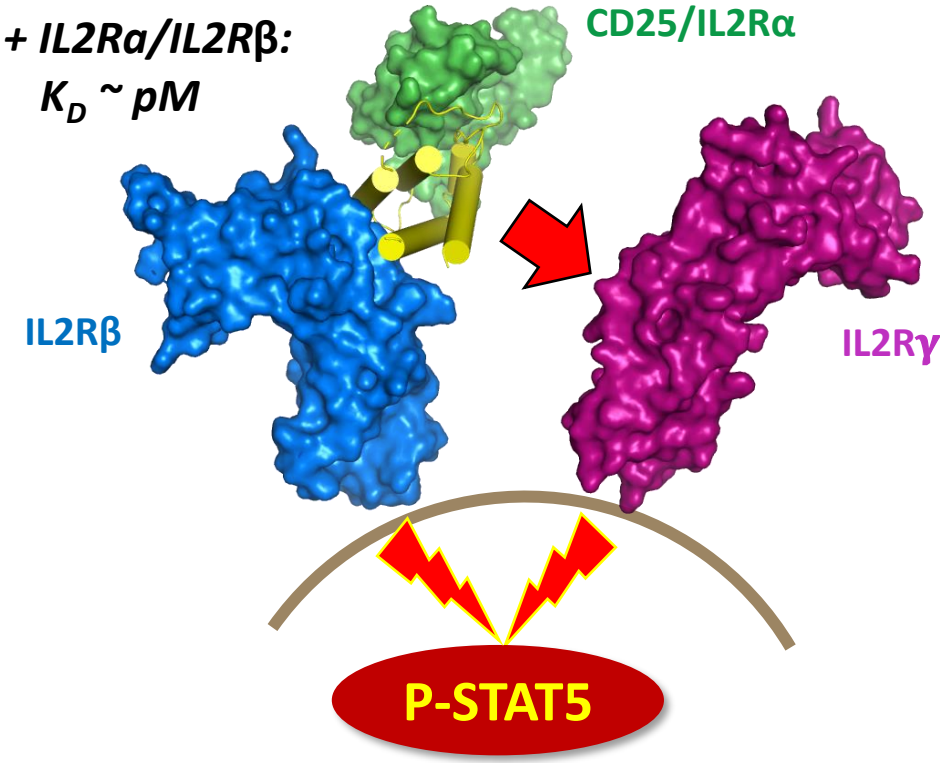
Low CD25 expression reduces IL-2 potency on ***naïve T cells and NK cells***

Targeting the High Affinity IL-2 Receptor by Disrupting the IL-2Rγ Binding Site on IL-2

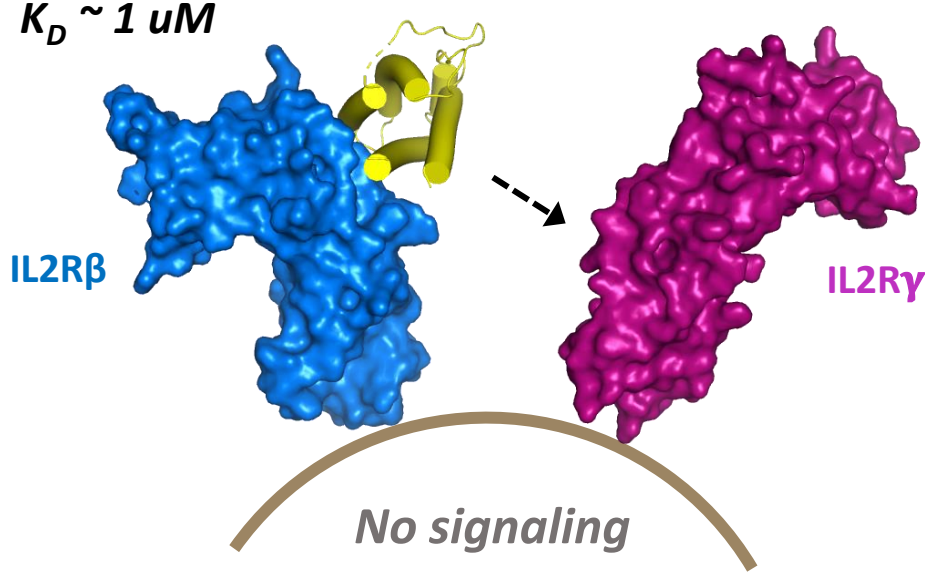
Antigen activated T cells: CD25 high

Naïve T-cells and NK cells: CD25 low

IL2 + IL2Rα/IL2Rβ:
K_D ~ pM



IL2 + IL2Rβ alone:
K_D ~ 1 uM



Hypothesis: ***weakening the IL2Rγ interaction will widen the IL-2 activity window between activated T cells and naïve T cells + NK cells***

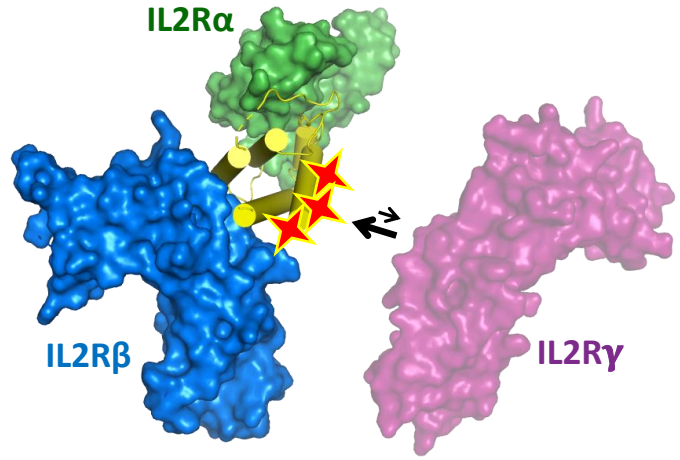
Synthekine

Structure/Function-Based Discovery of an α/β-Biased IL-2

<u>Design goal:</u> Engineer an IL-2 mutein with:

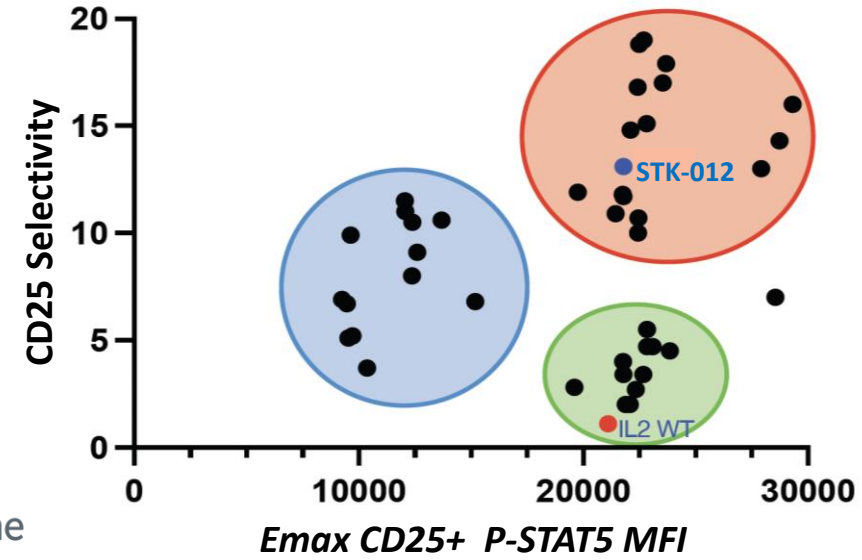
1) Strong selectivity for CD25+ cells
2) P-STAT5 "signal strength" (EC50 and Emax) equivalent to wild type IL-2

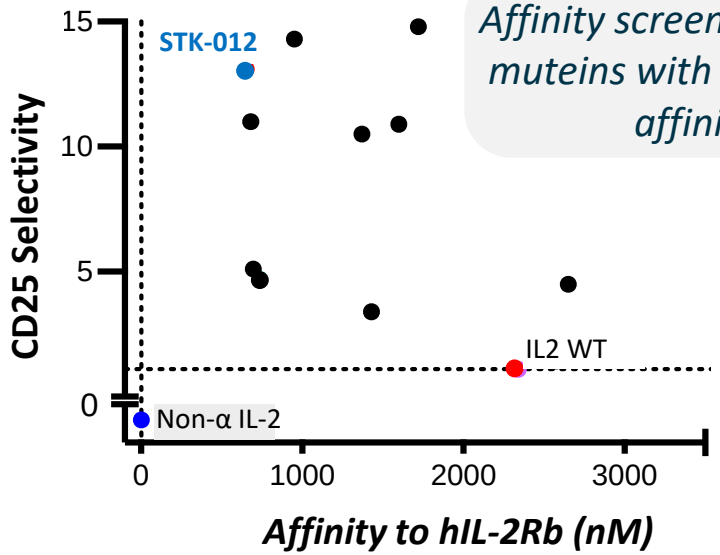
Mutagenesis of the IL-2/IL2R©interface



Cell based screen to identify muteins with:
– P-STAT5 selectivity for CD25+ cells
– Emax maintained at similar level to wt IL-2

<u>EC50 CD25+</u>
EC50 CD25-



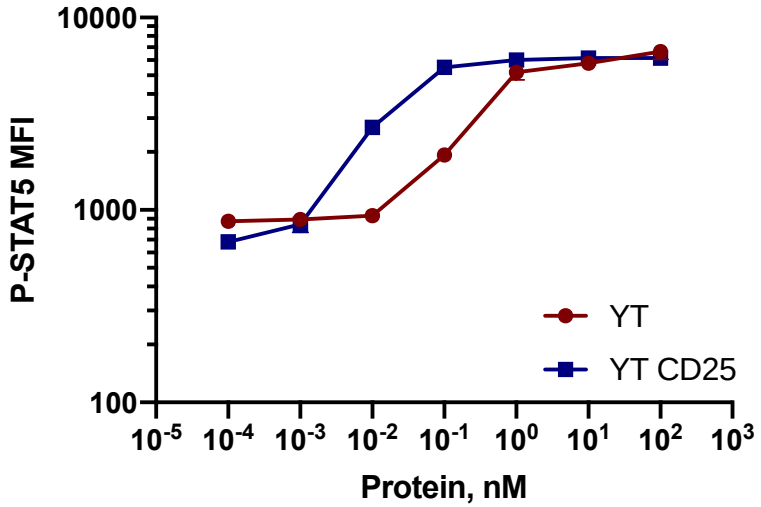


Affinity screen to identify muteins with high IL2Rb affinity

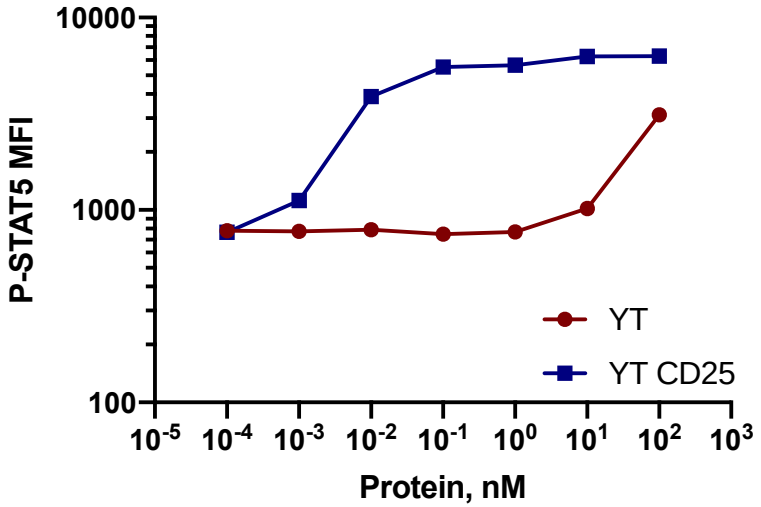
Synthekine

α/β-Biased STK-012 is Highly Selective for CD25+ Cells

wild type IL-2



STK-012: pegylated α/β IL-2



	EC50 (nM)		
	YT	YT (CD25+)	selectivity
wild type IL-2	0.33	0.02	**21x**
STK-012	17.97	0.01	**2522x**

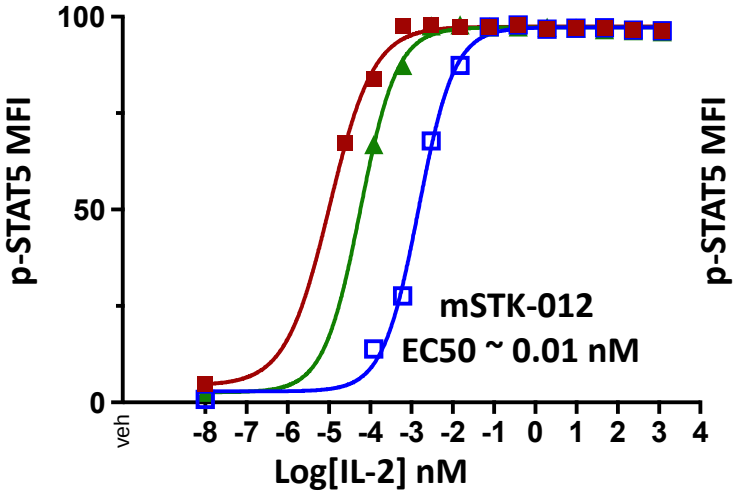
YT: human NK cell line that expresses IL2Rb/Rg

YT (CD25+): engineered to overexpress CD25

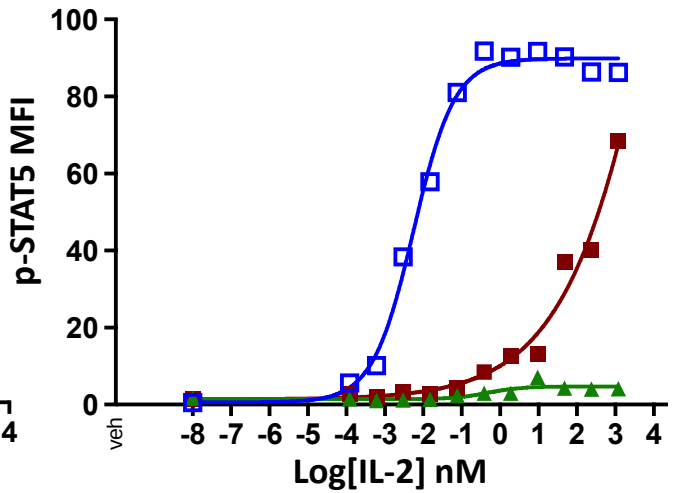
Synthekine

mSTK-012 is Highly Selective for CD25+ CD8+ T Cells

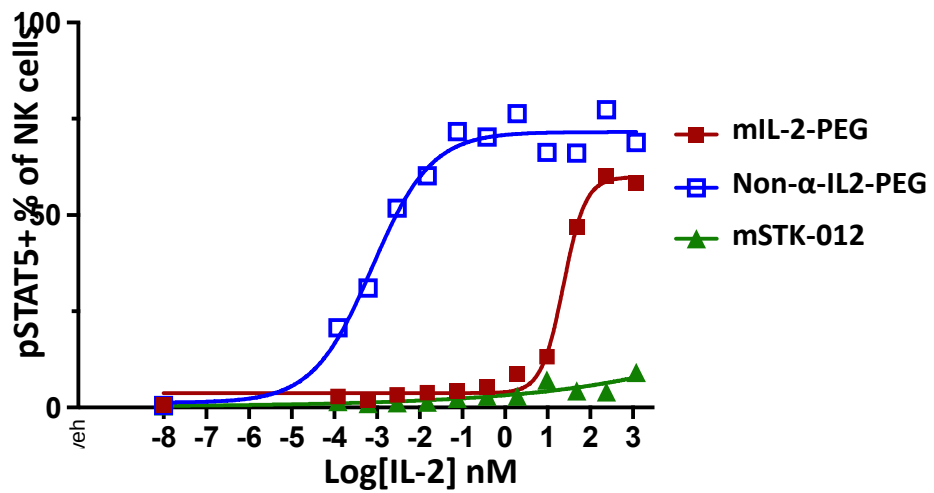
CD25+ CD8+ T cells



CD25- CD8+ T cells



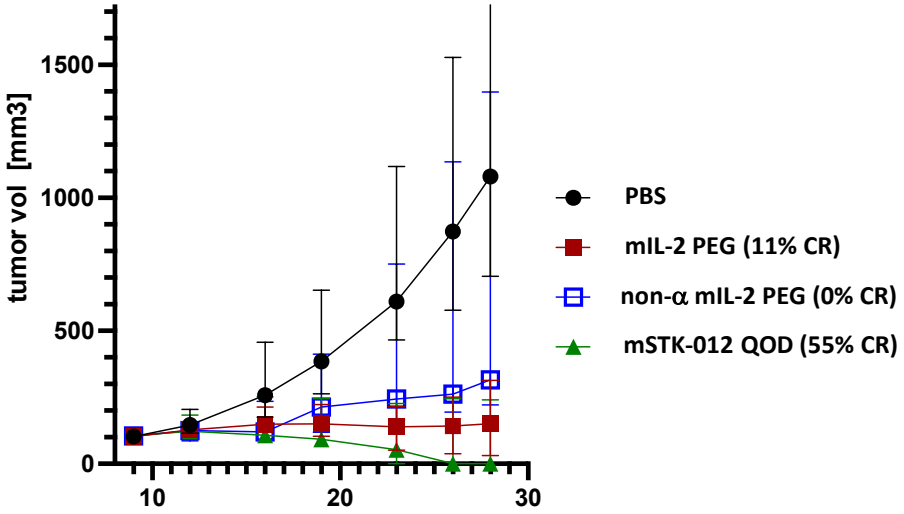
NK cells (CD25-)



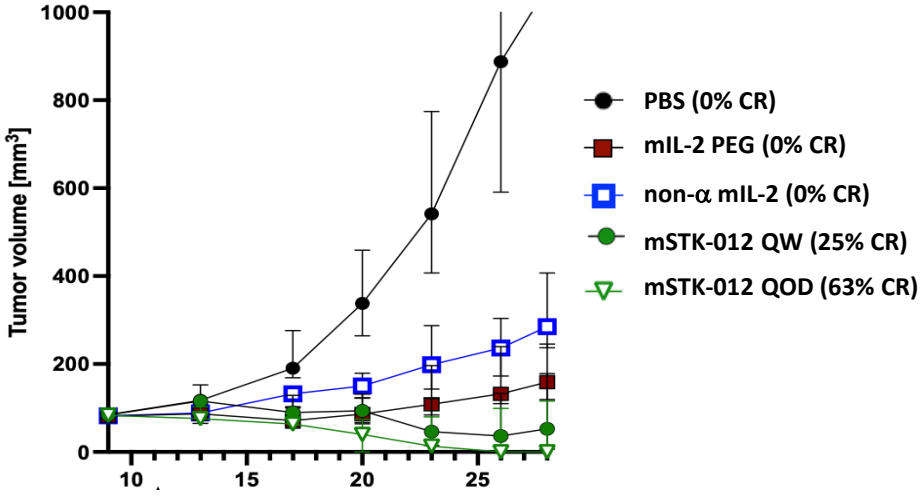
- Pegylated mouse surrogate of STK-012 (mSTK-012) is highly selective for CD25+ CD8+ T cells (similar for CD4+)
- Little to no activity seen on CD25- CD8+ T cells or NK cells
- Mirrors the activity of STK-012 on human PBMCs

mSTK-012 Induces Complete Responses in Syngeneic Mouse Models

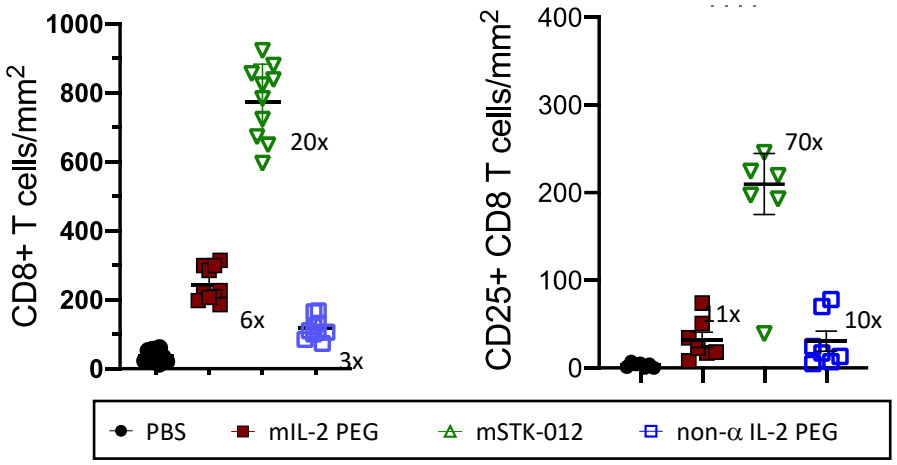
CT-26 Tumor Model



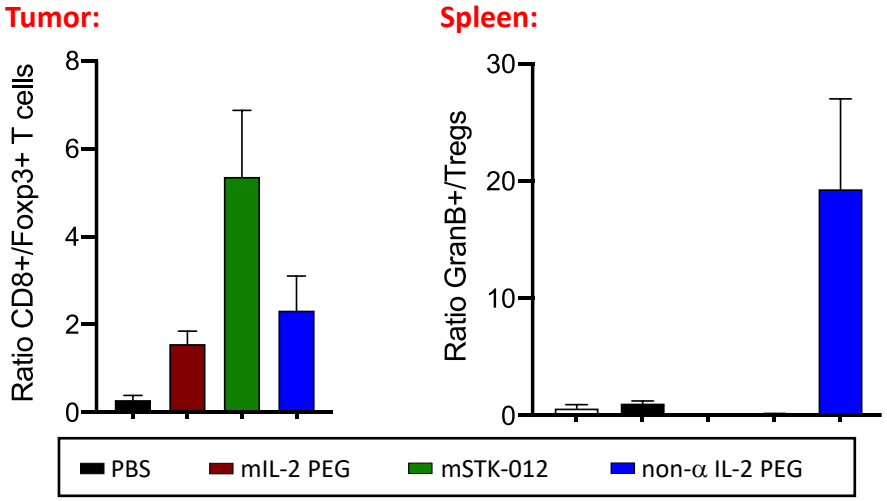
MC-38 Tumor Model



Intratumoral CD8 T cells



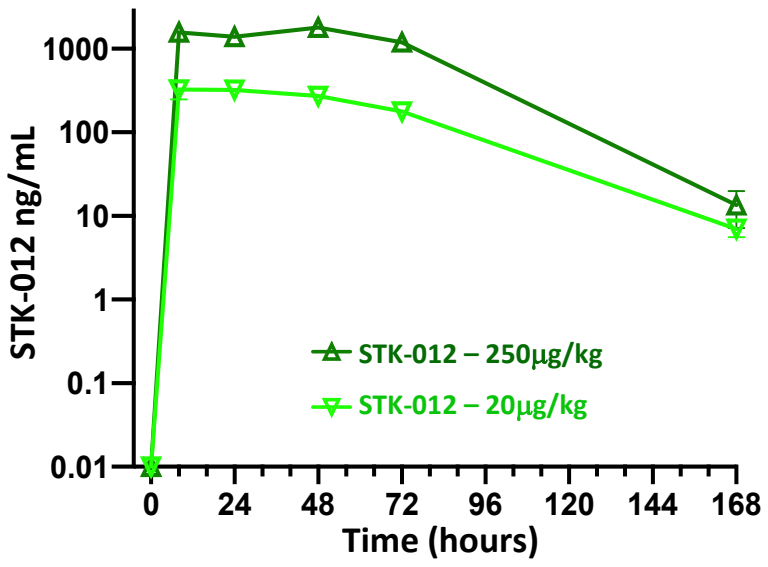
Treg Ratios in Tumor vs. Spleen



Dosing: mIL-2-PEG (2.5µg every other day) or non-α-IL-2-PEG (3µg, weekly) were dosed at their maximum tolerated dose while mSTK-012 was dosed at 10µg weekly or every other day.

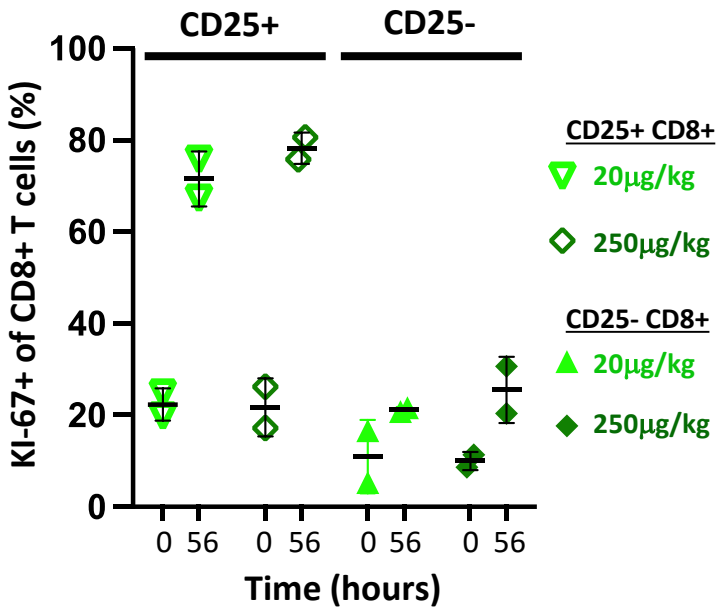
STK-012 Specifically Activates CD25+ T cells in Non-Human Primates (NHP)

STK-012 pharmacokinetics

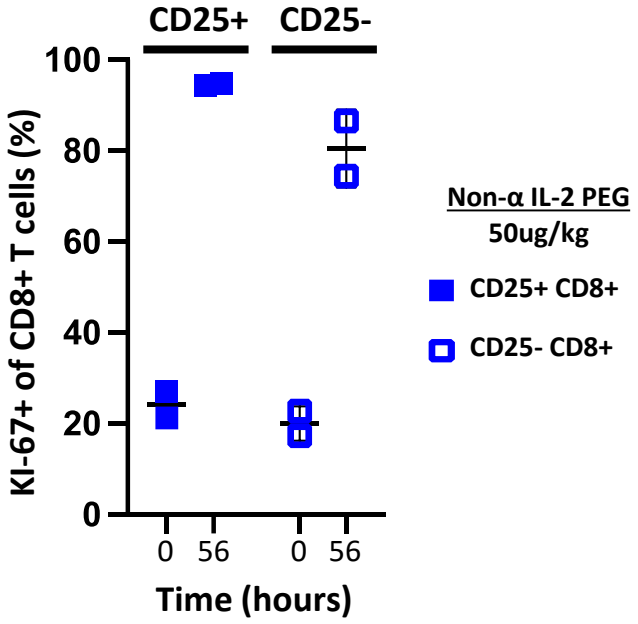


STK-012 demonstrates multi-day PK in cynomolgus monkeys

STK-012 activates CD25+ CD8+ T cells



Non-α IL-2 activates all CD8+ T cells

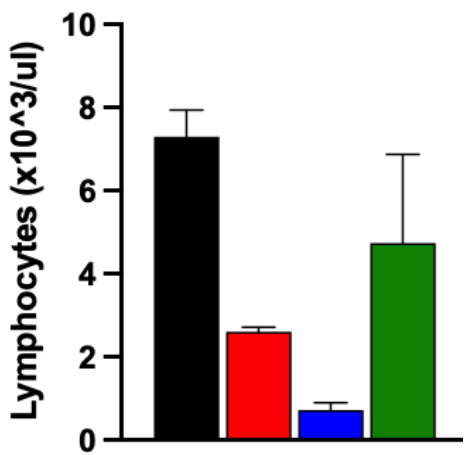


STK-012 demonstrates potent and selective activation of CD25+ CD8 T cells vs a non-alpha IL-2 competitor

STK-012 Does Not Induce CLS in Non-Human Primates

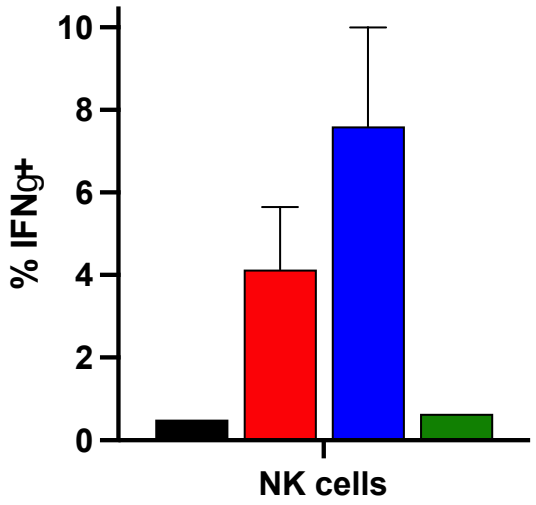
STK-012 does not induce lymphopenia in NHPs

Absolute lymphocyte count



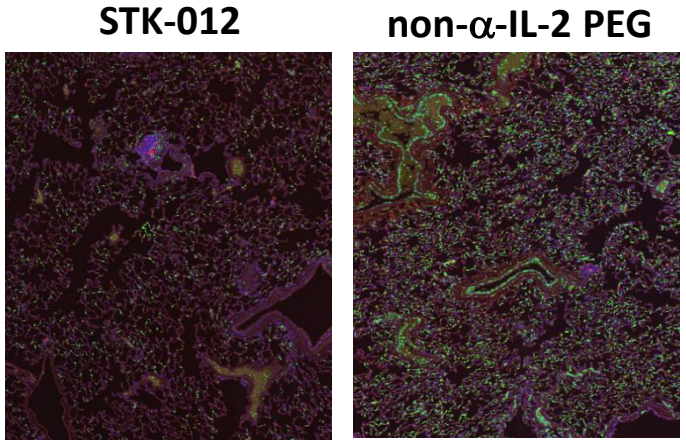
STK-012 does not activate NK cells in the lung in NHPs

Lung-infiltrating NK cell FACS



STK-012 does not induce infiltration of immune cells into the lung in NHPs

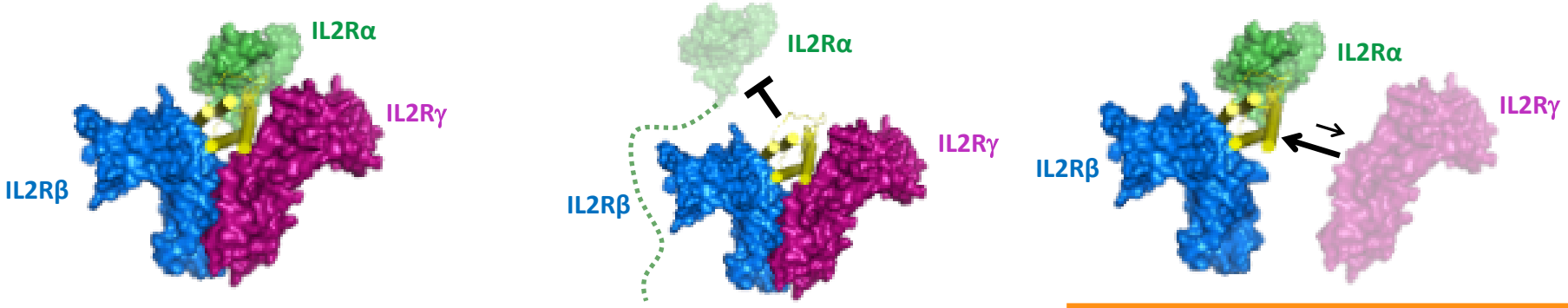
Lung tissue CD11b immunohistochemistry



CD11b in GREEN

Dosing: aldesleukin (37µg/kg every 8 hours, x8), non-α-IL-2-PEG (50µg/kg, x2) or STK-012 (250 µg/kg followed by 150µg/kg) (both every 36 hours)

STK-012: Next Generation Pegylated α/β-Biased IL-2



	1st Generation IL-2: (Aldesleukin)	2nd Generation Engineered IL-2: (NKTR-214, THOR-707, NL-201, etc.)	Best-In-Class Engineered IL-2: STK-012
Design	High Dose IL-2	"Non-α" IL-2	**α/β-biased IL-2**
IL-2R Bias	Binds to both trimeric high & dimeric intermediate affinity IL-2R	Binds only to dimeric intermediate affinity IL-2R	Binds to trimeric high affinity IL-2R
IL-2R Subunit Sparing	None	Reduced binding IL-2Rα	Reduced binding to IL-2Rγ
Cell Selectivity	No selectivity	NK cells and naïve T cells	Antigen-activated T cells

STK-012: Synthekine's α/β-biased IL-2

- **Designed to improve efficacy**
  - Selectively proliferate and activate-antigen activated T-cells, the driver of anti-tumor efficacy
  - Single agent efficacy including complete responses demonstrated by murine surrogate of STK-012
  - Superior to WT IL-2 and non-α-IL-2 in multiple syngeneic models
- **Designed to reduce toxicity**
  - Avoids proliferation and activation of NK cells, the driver of IL-2 toxicity
  - Improved safety demonstrated in mice and NHPs versus WT IL-2 and non-α-IL-2
- **IND cleared in Q4 2021; First patient dosed in Q1 2022**

Synthekine

Harnessing the power of cytokines

with a **world class team** and using **multiple engineering platforms** to build novel, selective cytokine therapeutics for cancer and inflammatory diseases as part of a **rapidly maturing pipeline** with **emerging partnerships**