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Society for Immunotherapy of Cancer

# Harnessing Potent Immune Agonist Pathways through Kinetic and Molecular Engineering

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# Presenter Disclosure Information

*Deborah Charych, Ph.D.*

The following relationships exist related to this presentation:

*Consultant and former employee to Nektar Therapeutics, Inc.*
*Consultant to Third Rock Ventures*

# Cytokines are medically relevant endogenous small (~15kDa) proteins

Cytokine-based therapies in human disease

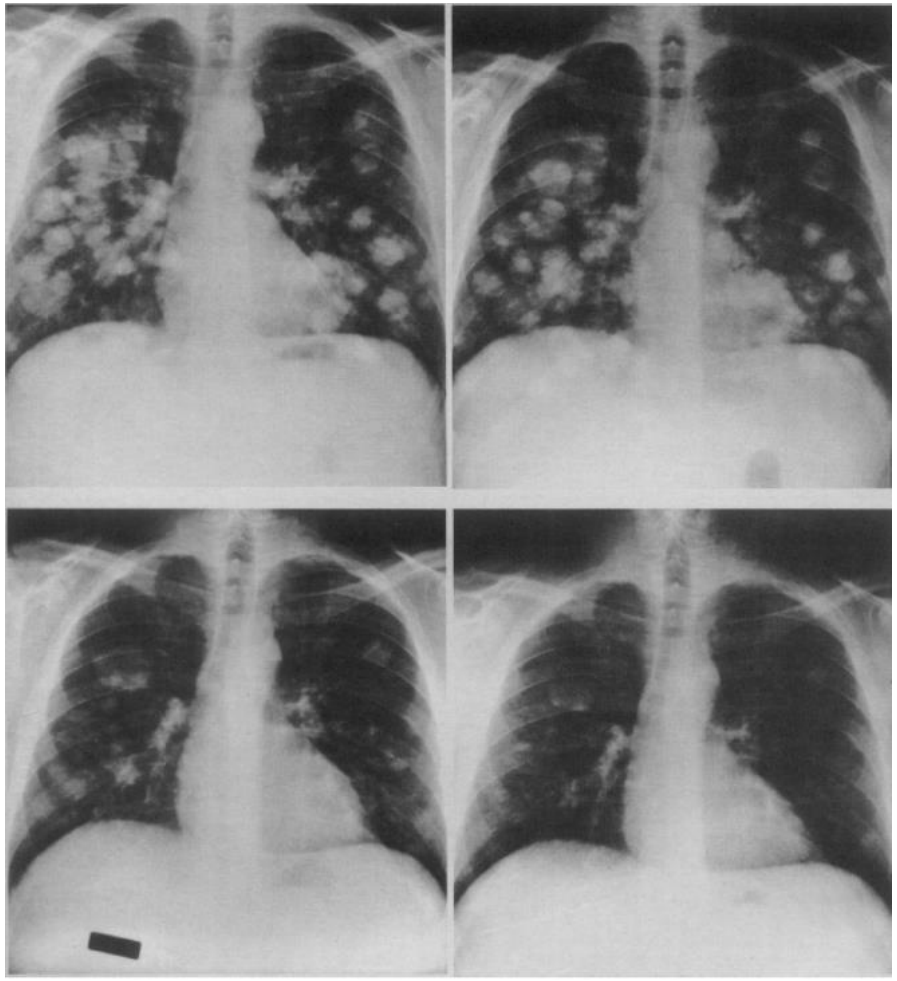
| Cytokine | Brand name | Status | Indication | Year of 1st FDA Approval |
|---|---|---|---|---|
| IL-2 | Proleukin | Approved | Cancer | 1992 |
| IL-11 | Neumega | Approved | Thrombocytopenia | 1994 |
| EPO | Epogen | Approved | Anemia | 1989 |
| GCSF | Neupogen | Approved | Myelosuppression from chemo | 1991 |
| GM-CSF | Leukine | Approved | Myelosuppression from chemo | 1991 |
| IFN-α | Intron-A | Approved | Hepatitis, Cancer | 1991 |
| IFN-β | Betaseron | Approved | Multiple sclerosis | 1993 |
| IFN-γ | Actimmune | Approved | Granulomatosis | 1990 |
| IL-7 | | Clin dev | Cancer, anti-viral | |
| IL-10 | | Clin Dev | Cancer, anti-inflammatory | |
| IL-12 | | Clin dev | Cancer, anti-viral | |
| IL-15 | | Clin dev | Cancer | |
| IL-21 | | Clin dev | Cancer | |



Baldo, 2018 Drug Safety

# High Dose IL-2: The first FDA-approved cancer immunotherapy

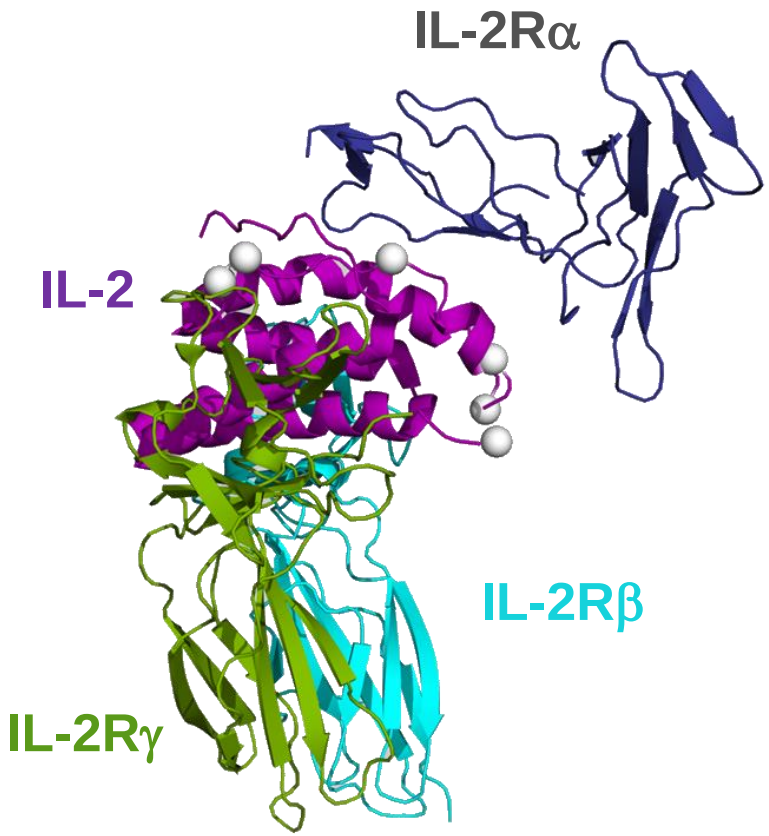
- IL-2 is a natural T cell growth factor
- First IL-2 response achieved in 1984
- Durable ‘curative’ responses in ~10%
- Approved 1992 for mRCC
- Approved 1998 for metastatic melanoma
- Challenges of high dose IL-2:
  - Toxic – hard to complete full course of therapy
  - Requires hospitalization
  - Frequent q8h dosing regimen
    - High $C_{max}$ spike, cleared, repeat….



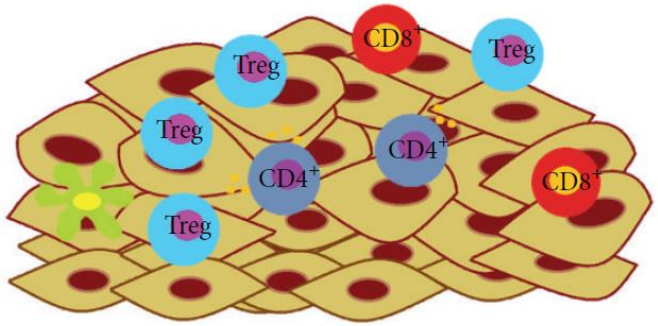
*Slide adapted from Dr. Heather McArthur, ASCO 2018*

Buchbinder et al, 2016, JITC
Donskov et al, ASCO, 2010
Lotze et al, JAMA, 1986
Atkins et al, JCO, 1999
Klapper et al, Cancer, 2008

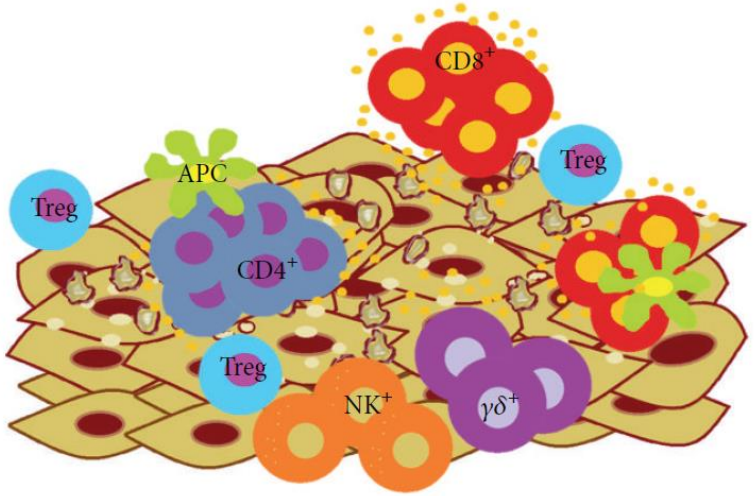
# Conundrum: IL-2 effects are pleiotropic, supporting both Teff and Tregs




Low concentrations of IL-2 activate Tregs




High concentrations of IL-2 sustain T effectors




High affinity receptor IL-2Rαβγ:

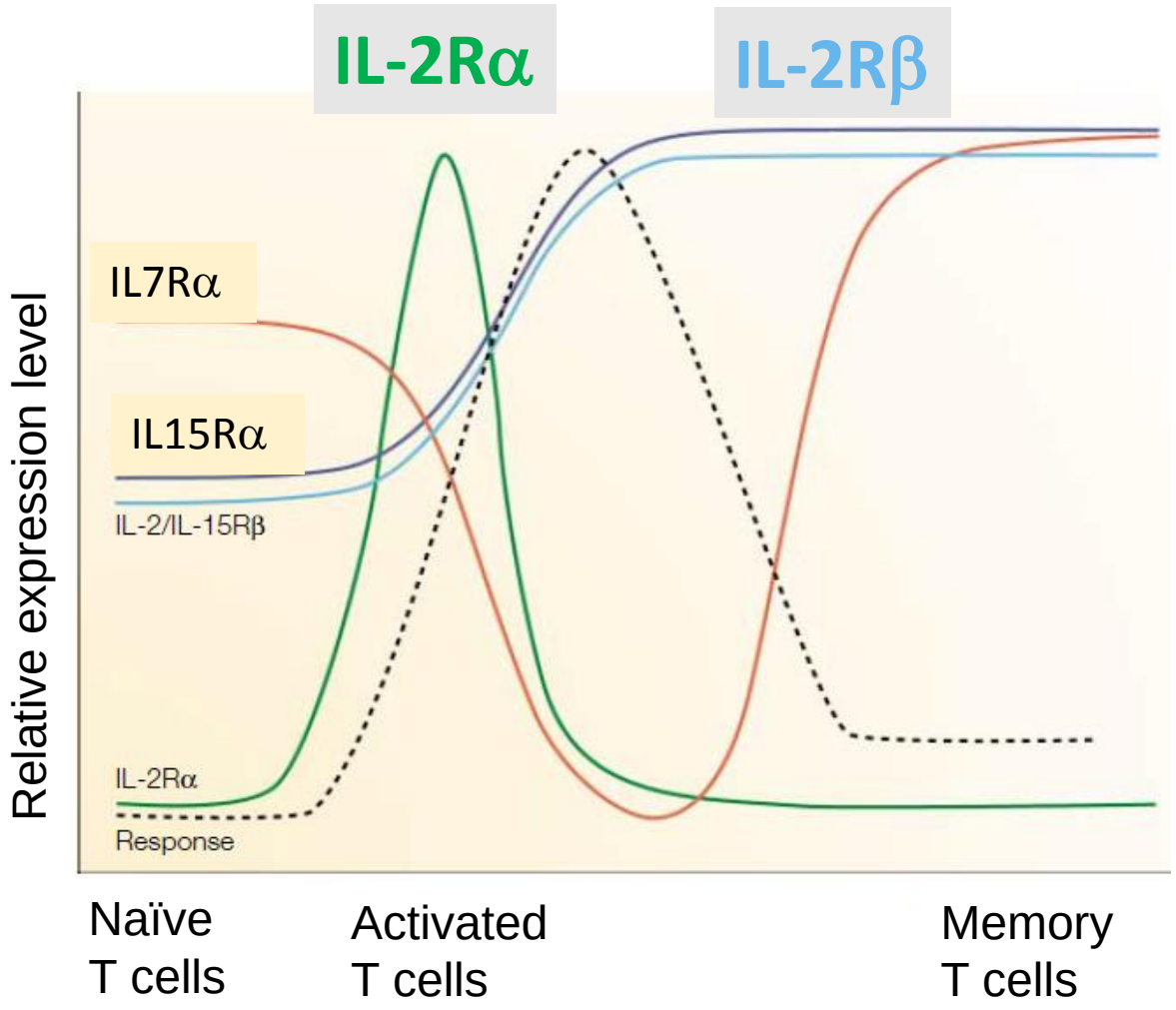
- constitutive on Tregs;
- **transient on activated CD8s**

Low affinity receptor IL-2Rβγ to activate:

- CD8, CD4 T
- γδ T
- NK cells

Mendiola et al, 2016, Mediators of Inflammation

# Natural effects of IL-2 are temporal with actions over time, and not all at once




Schluns et al, Nature Reviews Immunology

*Immune response is by nature's design, kinetically controlled….by cells*

- IL-2Rα is transiently up-regulated with delayed-onset on antigen-specific CD8 T[1]
- IL-2Rβ is persistent on memory T cells[2]
- But..IL-2Rα is constitutive on Tregs, for protective peripheral tolerance[3]

[1]Wong et al, J. Imm. 2004
[2]Beltra et al, PNAS 2016
[3]Malek et al, Ann. Rev. Immunol., 2008

# Knowing what we know now of high-dose IL-2 therapy and immunology….how can we make IL-2 better?

*Attributes of an ideal IL-2 cytokine therapy*

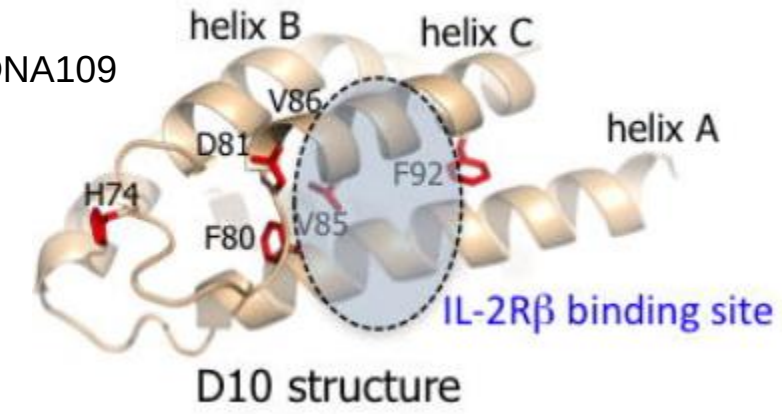
| **Cytokine score-card** |
| --- |
| Kinetic / temporal control of immune response |
| Minimize frequent dosing and toxicities |
| Increase and sustain TILs |
| Minimize Tregs in tumor |
| Allow protective Tregs in periphery |
| Not limited by tumor target expression |
| Be readily manufactured |
| In current clinical development |

# Molecular engineering of IL-2 often seek to abolish Tregs

*These are immediately active after in vivo administration*

## IL-2 mutein 'superkine' with 4 mutated residues

MDNA109

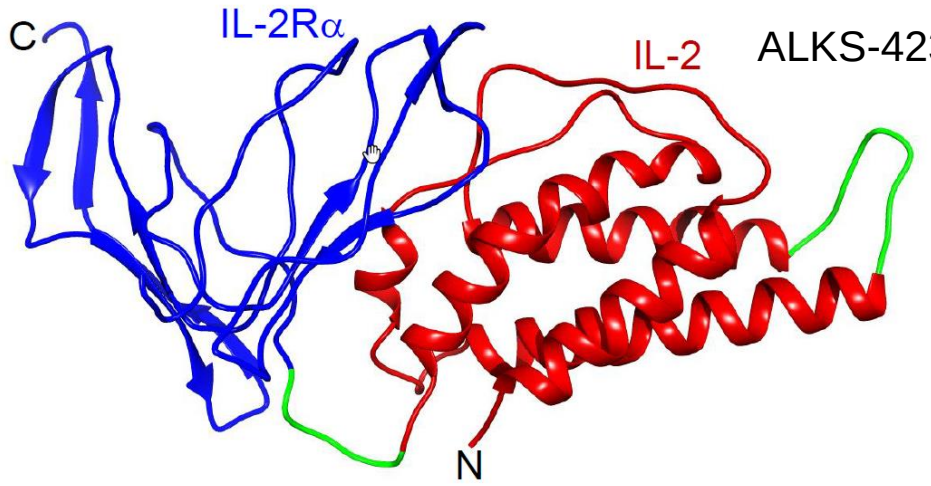



- Obliterates IL-2Rα binding
- Binds IL-2Rβ with 280-fold greater affinity compared to wt IL-2
- Anti-tumor response in small (just palpable) B16F10 mouse melanoma tumors
- Dosed daily for 5 days in mice
- Peripheral expansion of CD8s, not peripheral Tregs
- TILs..?

Levin et al, Nature 2012

## IL-2 fused to the IL-2Rα extracellular domain

ALKS-4230

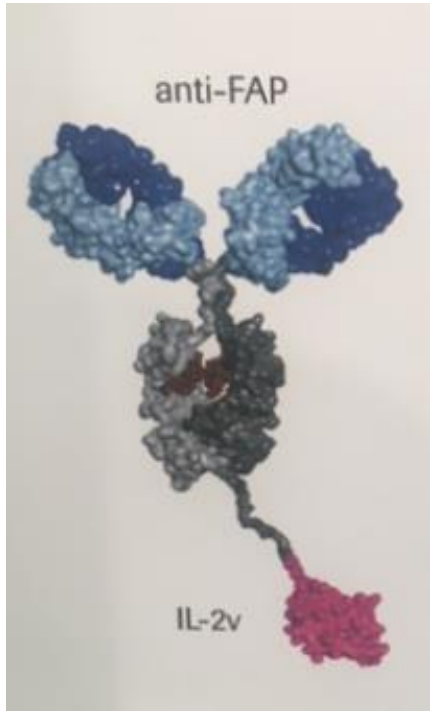



- Obliterates IL-2Rα binding
- 'Pre-formed' binding of IL-2 to IL-2Rα soluble domain
- Mouse melanoma lung metastasis model vs sc model
- Dosed i.v. daily x 5 in clinic
- Peripheral expansion of CD8 and NK, not peripheral Tregs
- TILs…?

Losey et al, Abstract 591, 2017, Cancer Research

# Molecular engineering of IL-2 may seek to decrease dosing frequency using antibody components

## Antibody-IL-2 covalent fusion

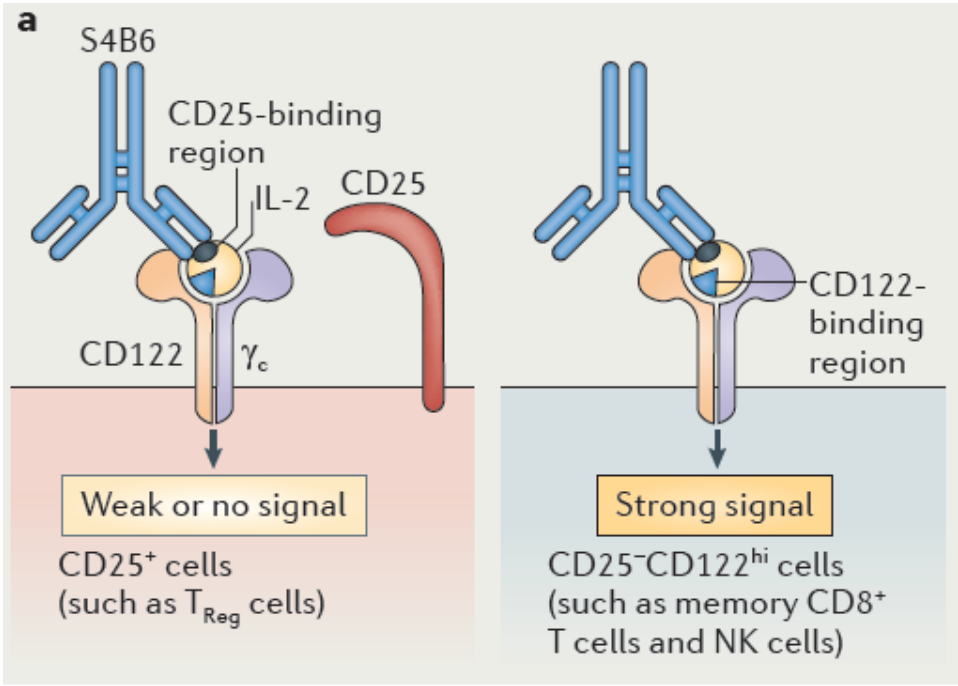



RO6874281

- IL-2 mutein with abolished binding to IL-2Rα
- Fusion to anti-FAP antibody
- Dosed weekly in clinic
- Peripheral expansion of CD8 and NK, no Tregs
- TILs..?

Klein et al, Blood 2013

## IL-2 / mAb non-covalent complex

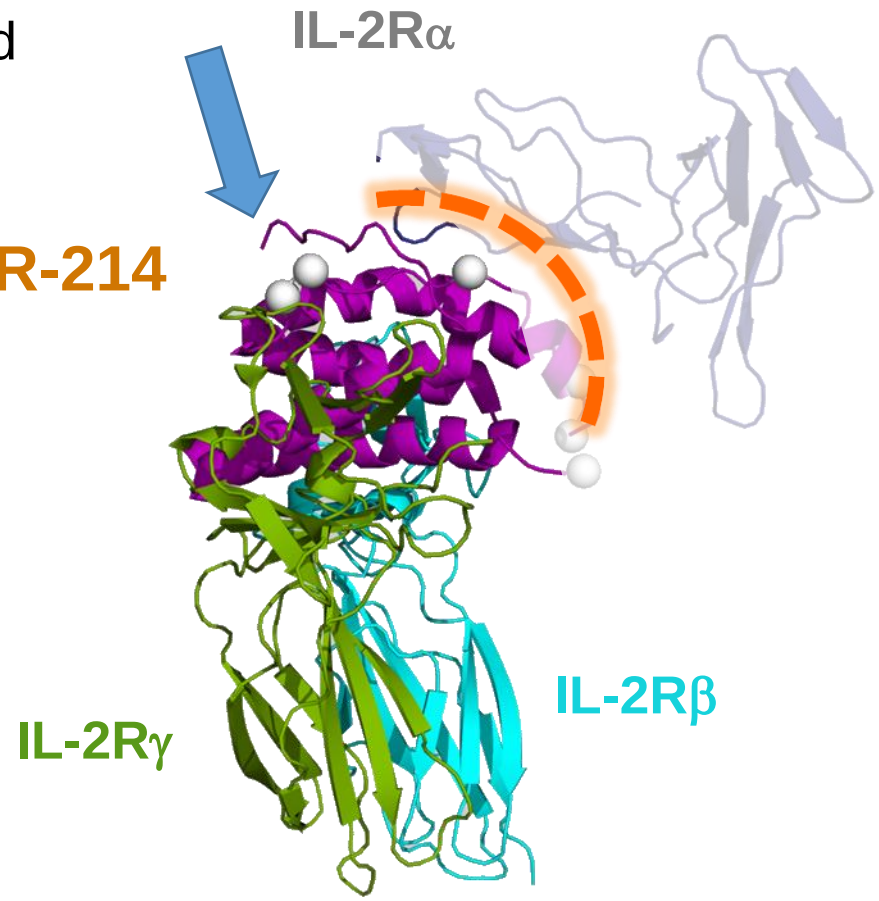


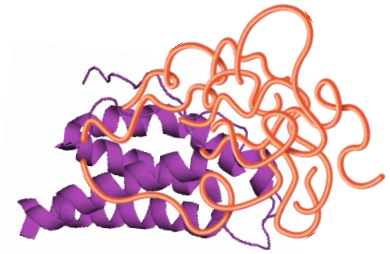

- mAb 'masks' region of IL-2 that binds IL-2Rα
- Some IL-2Rα may be conserved
- Stability of non-covalent complex..?
- Immediately active after in vivo administration
- Requires manufacture of two GMP proteins and mix

Boyman and Sprent, Nature Reviews 2012

# *Tip the balance* towards IL-2Rβγ and CD8 T in the tumor with an IL-2 prodrug polymer conjugate design

IL-2 (aldesleukin) sequence = FDA approved



NKTR-214

βγ

CD8+

Directly stimulates Teff in tumor to kill tumor cells

αβγ

CD4+ Regulatory T-Cells

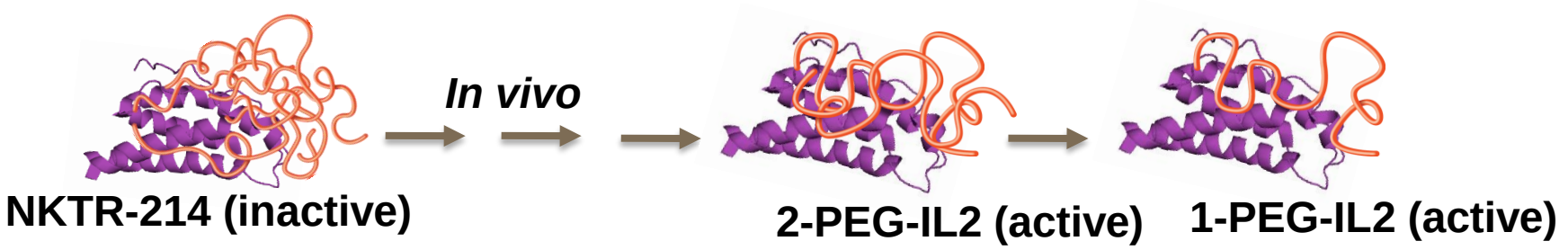
Down-Regulates Proliferation of CD8+ T-cells and Suppresses Immune Response in Tumor

Allow for some IL-2Rα binding to support peripheral Tregs and activated Teff TILs

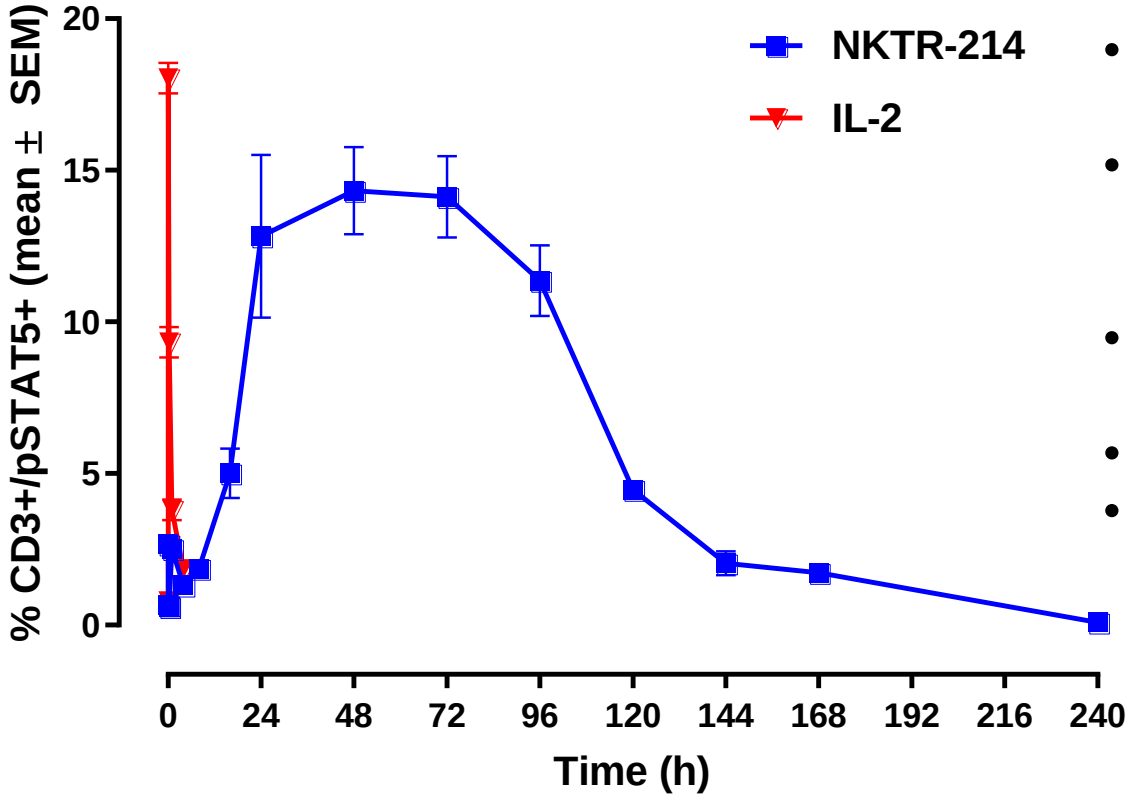

Charych et al, 2017, PlosOne

Charych et al, 2016, Clinical Cancer Research

# Kinetic control of IL-2 pathway signaling with NKTR-214




*In vivo mouse pSTAT5 signaling in lymphocytes*




- IL-2 produces rapid signal burst that declines by 4 hours
- NKTR-214 builds and sustains signal through 7 days after one single dose
- Kinetics mimic cellular secretion of IL-2
- Free-IL-2 undetectable
- Allows once every 3 week dosing of NKTR-214, out-patient

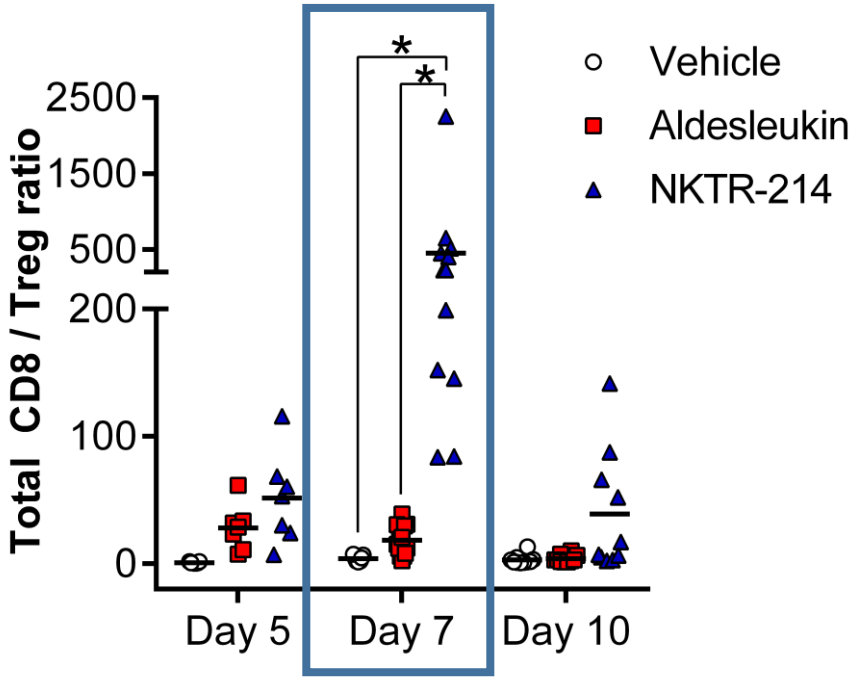
Charych et al, 2017, PlosOne

Charych et al, 2016, Clinical Cancer Research

Healthy mice were dosed with a single dose of either IL-2 or NKTR-214, 0.8 mg/kg, detailed methods are in Charych et al, 2017, PlosOne

# Receptor occupancy bias for NKTR-214 leads to significantly enhanced CD8 / Treg in scB16F10 murine tumor

CD8/Treg ratio > 400 in tumor




- CD8 T / Treg is > 400 in the tumor microenvironment, single agent
- CD8 T / Treg is ~10 in peripheral tissue

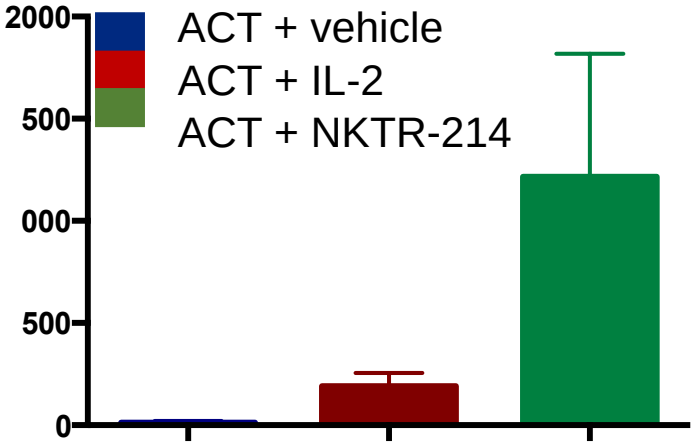


Charych et al, Clin. Cancer Res. 2016

# CD8/Treg ratio high in tumor but more balanced in peripheral tissues with NKTR-214 combinations

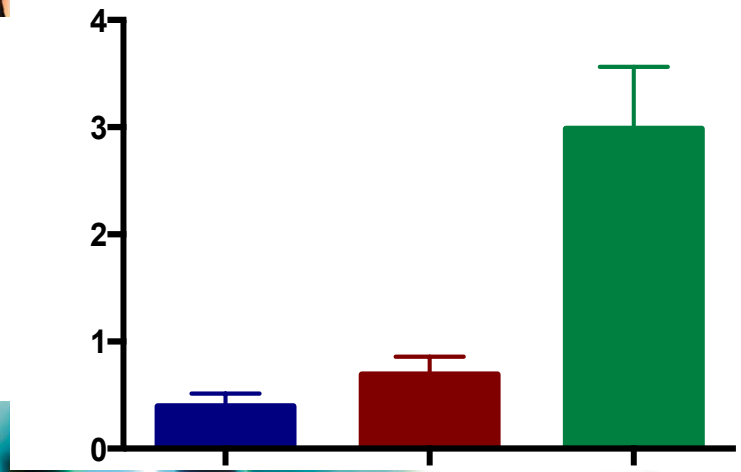
## Ribas Lab

**CD8/Treg ~ 1200 in tumor**

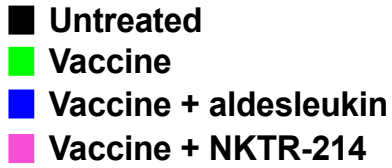



Parisi, Ribas et al, AACR 2018, AACR 2017

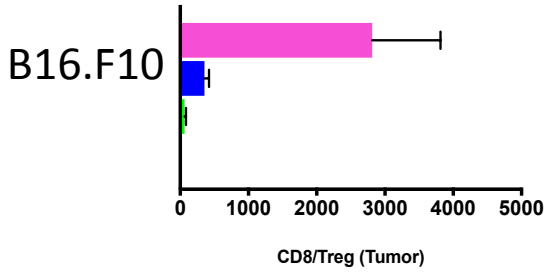
**CD8/Treg ~ 3 in spleen**




## Overwijk Lab

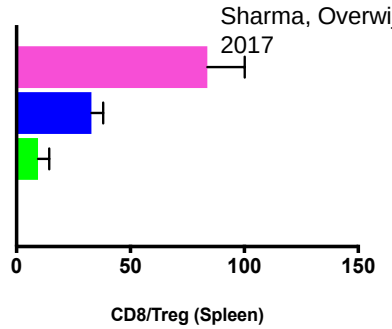



**Pmel CD8/Treg ~ 2800 tumor**



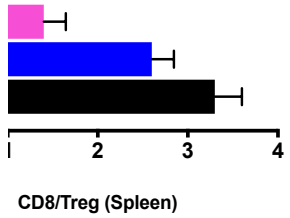

**CD8/Treg ~ 80 spleen**

Sharma, Overwijk et al, SITC 2017




**CD8/Treg ~ 200 tumor**

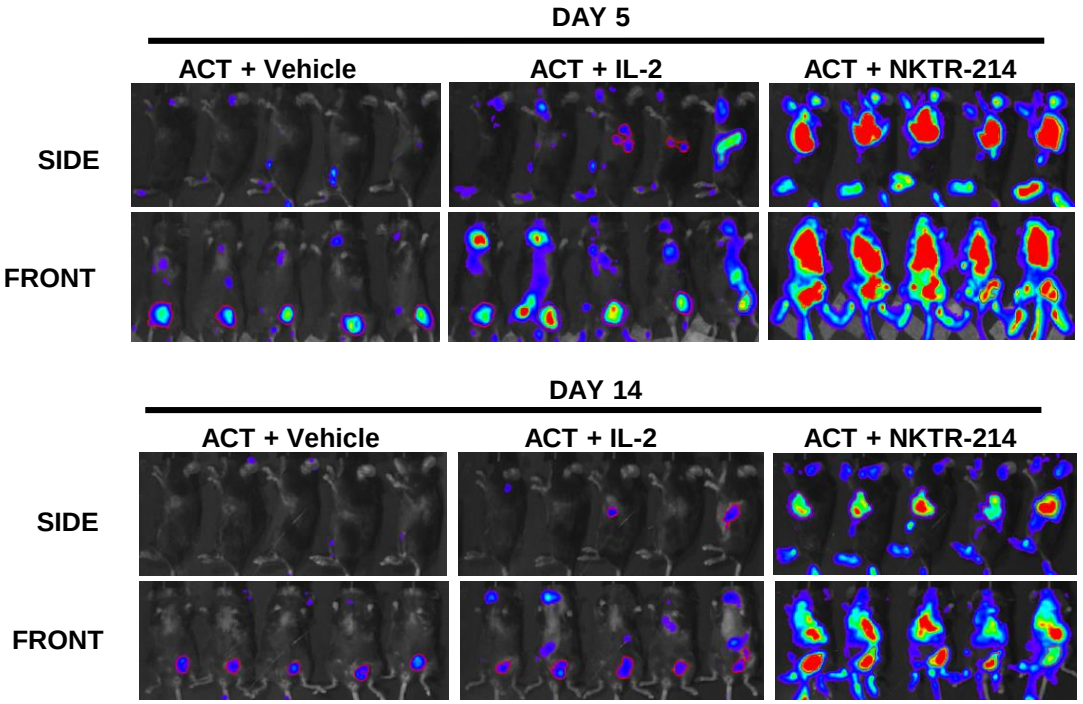
**CD8/Treg ~ 1.5 spleen**

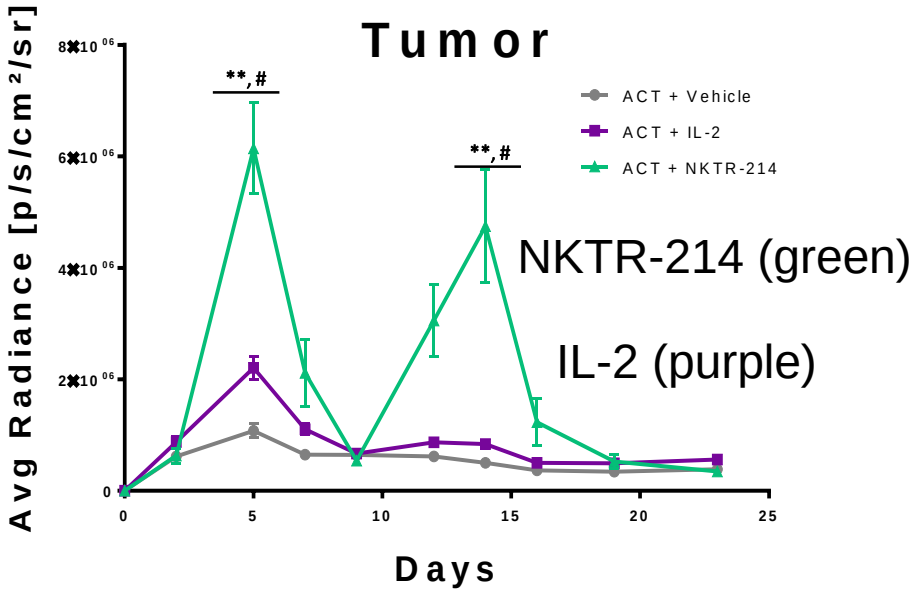



**Abstract #P424:** *"NKTR-214, an engineered IL-2, selectively depletes intratumoral Tregs and expands immunotherapy-induced effector T cell responses"*, Sharma, M., et al.

# Induced CD8 T cells home to tumor, are persistent in tumor and can be repeatedly stimulated (in tumor) after NKTR-214

Ribas Lab

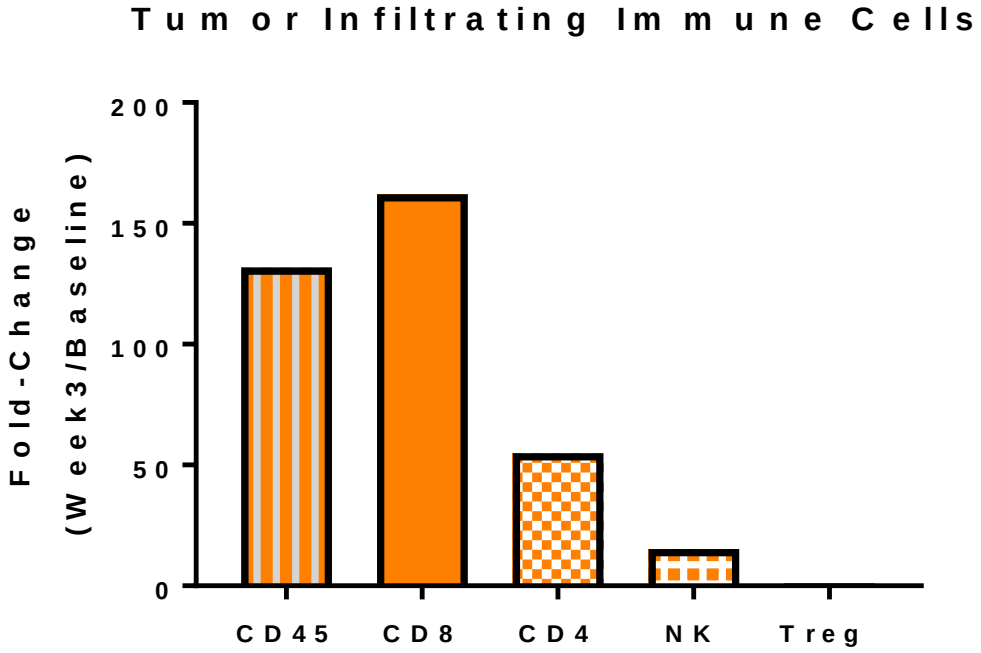



**Abstract #P557:***"Overcoming genetically-based resistance mechanisms to PD-1 blockade"*, Torrejon, D., et al.

# The ‘dichotomy’ between tumor and blood translates to human tumors

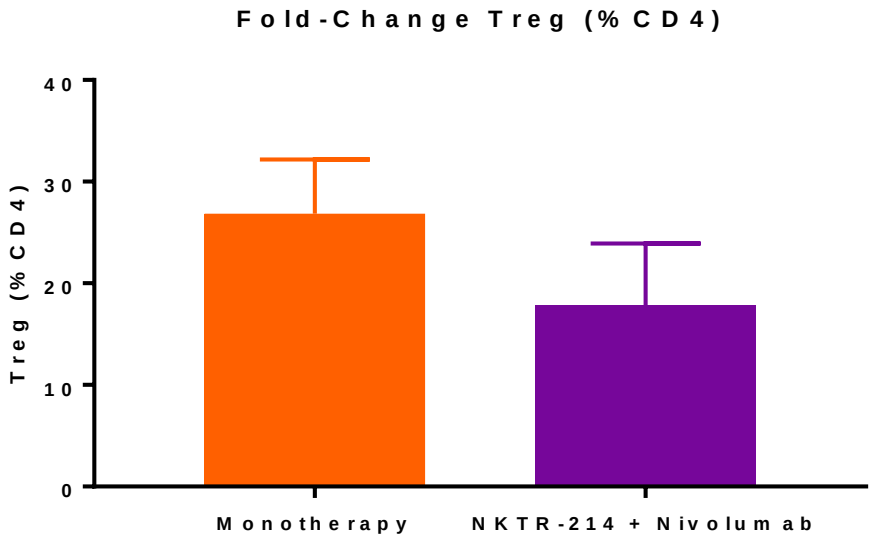
PIVOT-02 clinical trial




Data shown here for NKTR-214+Nivolumab; comparable results obtained for NKTR-214 monotherapy

PIVOT-02 clinical trial

**Blood**




NKTR-214 Monotherapy (N=21)
NKTR-214 + Nivolumab (N=4)

Method: Fresh tumor biopsy was disaggregated to single cell suspension and processed using flow cytometry. Total intratumoral immune cells were identified using CD45 staining and expressed as % of live cells for CD45, or as %CD45 for CD3+CD8+ (CD8 T Cells), CD3+CD4+ (CD4 T Cells, and CD3-CD56+ (NK Cells). Only patients with identifiable tumor by IHC at Baseline & Week 3, and on Q3WK NKTR-214 regimen were included.
Fold-Change: Week 3 value divided by Baseline, results shown are mean of N=4 patients.

# How do these molecular and kinetic engineering strategies address the problems of high dose IL-2?

| Cytokine score-card | IL-2 mutein superkine | IL-2 / IL-2Rα fusion | Immuno-cytokine to FAP | IL-2 / mAb complex | NKTR-214 |
|---|---|---|---|---|---|
| Kinetic/temporal control of immune response | | | | | |
| Minimize frequent dosing and toxicities | | | | | |
| Increase and sustain TILs | | | | | |
| Minimize Tregs in tumor | | | | | |
| Allow protective Tregs in periphery | | | | | |
| Not limited by tumor target expression | | | | | |
| Readily manufactured (based on structure) | | | | | |
| In current clinical development | | | | | |

Green = good
Red = not-so-good or unlikely
Yellow = possible or unknown

# Stacking up Cytokines in the I / O landscape

| Differentiation | Native cytokines | Checkpoint inhibitors | T cell co-stimulators | Vaccines | CAR-T therapies |
|---|---|---|---|---|---|
| Solid tumors | | | | | |
| Liquid tumors | | | | | |
| Growth factor for T cells | | | | | |
| Growth factor for NK cells | | | | | |
| Increase TILs | | | | | |
| Activate TILs | | | | | |
| Sustain TILs | | | | | |
| Potential autoimmune | | | | | |
| Increase sensitivity to checkpoint inhibition | | | | | |
| Scalable manufacture | | | | | |
| Convenient dosing regimen for patients | | | | | |
| Not limited by antigen or target expression | | | | | |
| Safety and tolerability | | | | | |

Green = good
Red = not-so-good or unlikely
Yellow = possible or unknown

# More examples of kinetic engineering in action…..

*Please check out these posters…..*

## Kinetically-engineered TLR agonist

- **Abstract #P364**: *"Systemic anti-tumor immunity and immune memory formation by a novel TLR7/8 targeting agent NKTR-262 combined with CD122-biased immunostimulatory cytokine NKTR-214",* Kivimae, S., et al.

## Kinetically-engineered IL-15 pathway agonist

- **Abstract #P418:***"Pre-clinical investigation of NKTR-255, a polymer-conjugated IL-15 with a potent NK cell dependent anti-tumor efficacy",* Miyazaki, T., et al.

## Novel combinations: Kinetically-engineered IL-2 agonist+PARPi

- **Abstract #P348:***"Survival and immune modulation in homologous recombination deficient murine ovarian tumors using the PARP inhibitor, rucaparib and immune agonist, NKTR-214",* Charych, D., et al.

# *Thank you!*

People and their families enrolled in the PIVOT clinical trials

Nektar Therapeutics colleagues and friends

Ribas Lab

Overwijk Lab

Redmond Lab

Recht Lab

Sondel Lab

Dr. Mario Sznol

IL-2 Collaborators and Enthusiasts