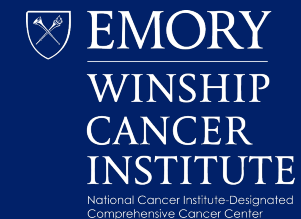


ROLE OF INTERLEUKINS TO IMPROVE EFFICACY OF IMMUNOTHERAPY

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nature

Defining CD8⁺ T cells that provide the proliferative burst after PD-1 therapy

Se Jin Im¹, Masao Hashimoto¹, Michael Y. Gerner^{2,3}, Junghwa Lee¹, Haydn T. Kissick^{1,4}, Matheus C. Burger⁵, Qiang Shan⁶, J. Scott Hale¹, Judong Lee¹, Tahseen H. Nasti¹, Arlene H. Sharpe^{7,8}, Gordon J. Freeman⁹, Ronald N. Germain², Helder I. Nakaya⁵, Hai-Hui Xue^{6,10} & Rafi Ahmed¹

15 SEPTEMBER 2016 | VOL 537 | NATURE | 417

Immunity

Proliferating Transitory T Cells with an Effector-like Transcriptional Signature Emerge from PD-1⁺ Stem-like CD8⁺ T Cells during Chronic Infection

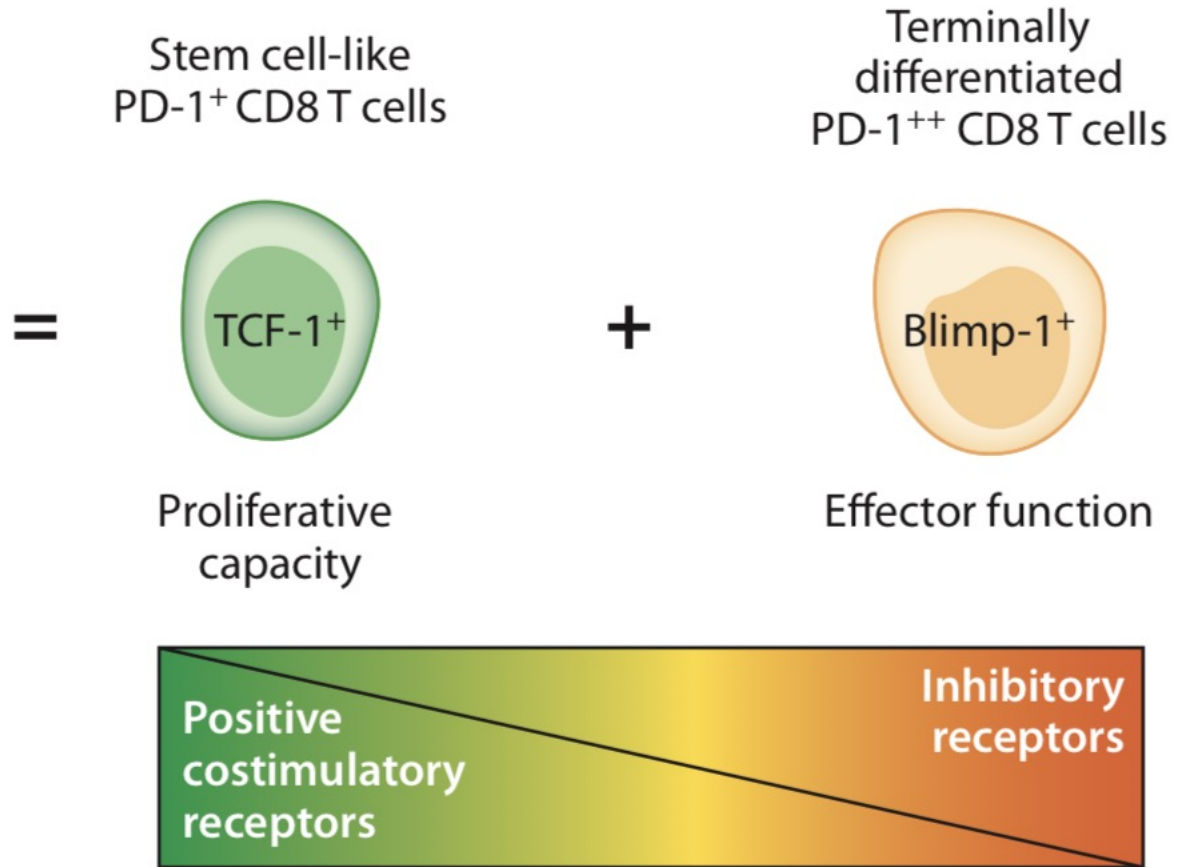
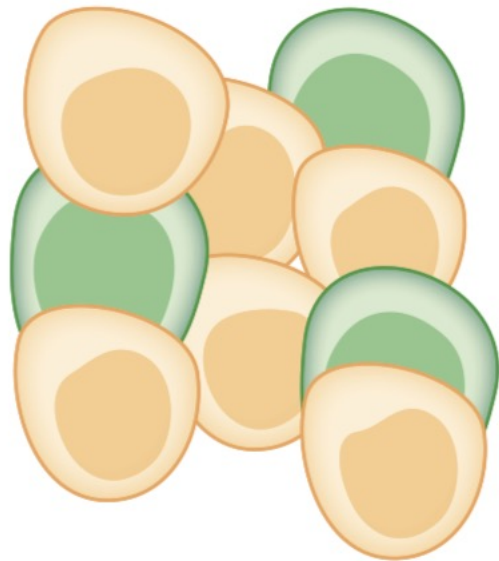
William H. Hudson,¹ Julia Gensheimer,¹ Masao Hashimoto,¹ Andreas Wieland,¹ Rajesh M. Valanparambil,¹ Peng Li,² Jian-Xin Lin,² Bogumila T. Konieczny,¹ Se Jin Im,¹ Gordon J. Freeman,⁴ Warren J. Leonard,² Haydn T. Kissick,³ and Rafi Ahmed^{1,5,*}

Immunity 51, 1043–1058

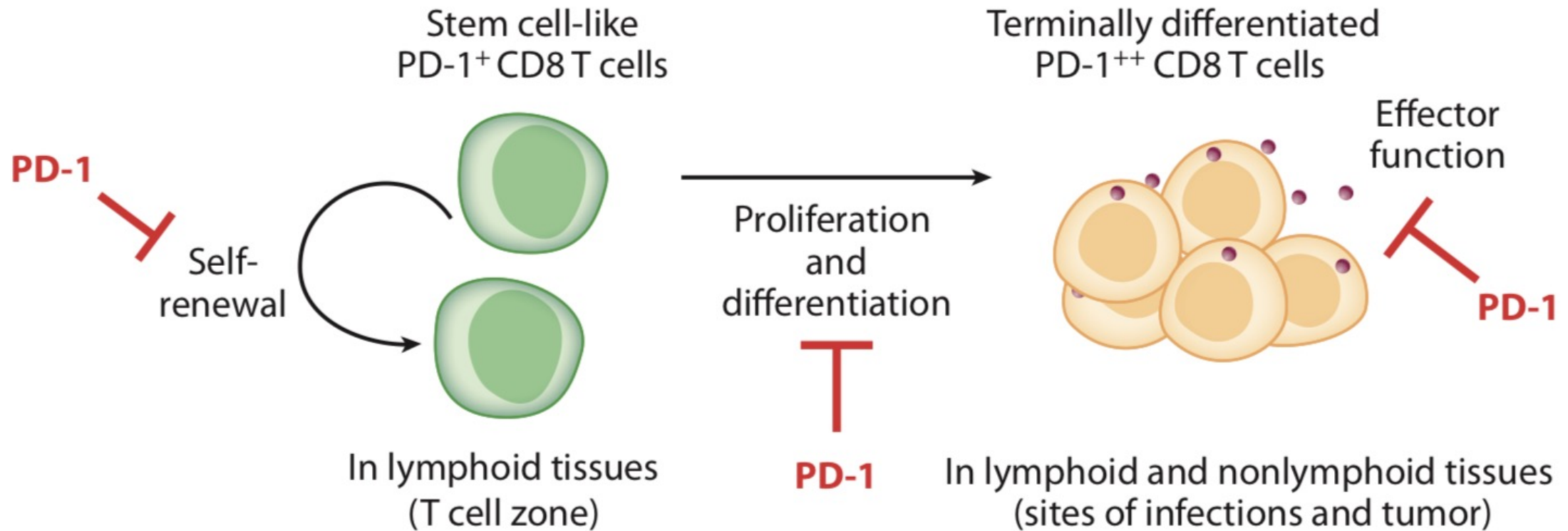
Zajac et al. J Exp Med 1998
Barber et al. Nature 2006
Wherry et al. Immunity 2007

REGULATION AND MAINTENANCE OF CD8 T CELL EXHAUSTION

CD8 T cell exhaustion



CD8 T CELL EXHAUSTION REGULATION BY PD-1

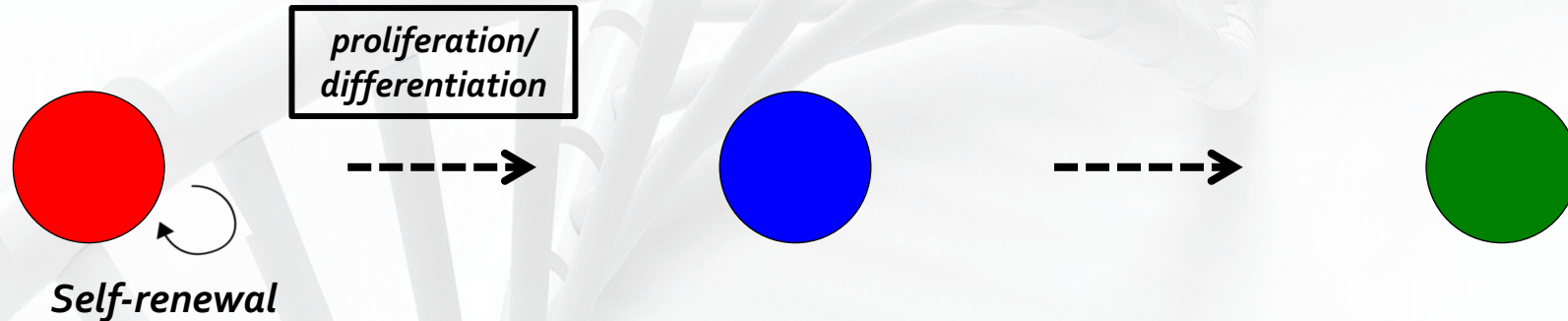


Rational design of immunotherapy

**PD-1⁺TCF-1⁺
Stem-like
CD8 T cells**

**Transitory
Effector
CD8 T cells**

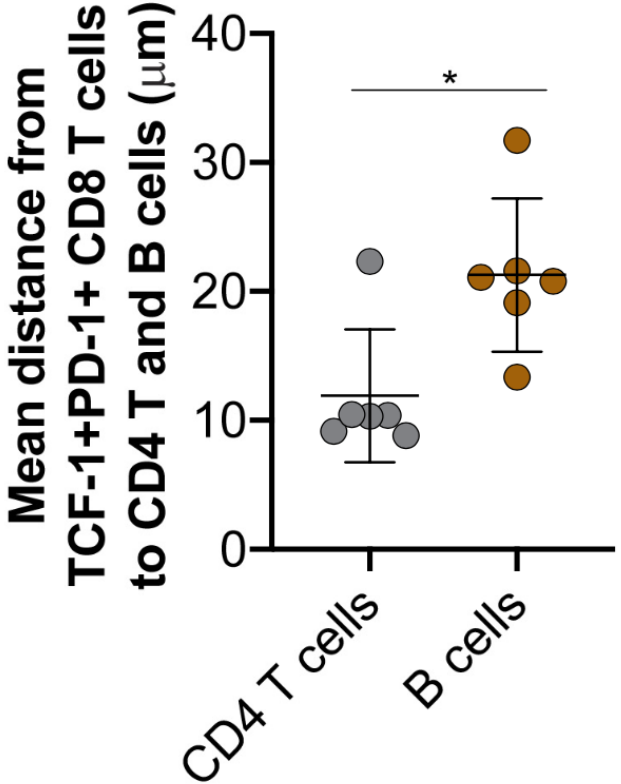
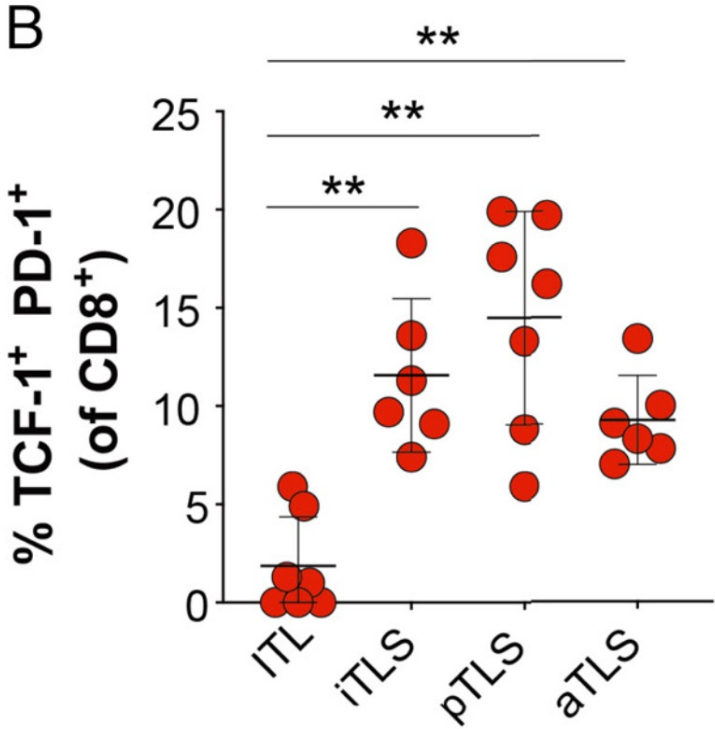
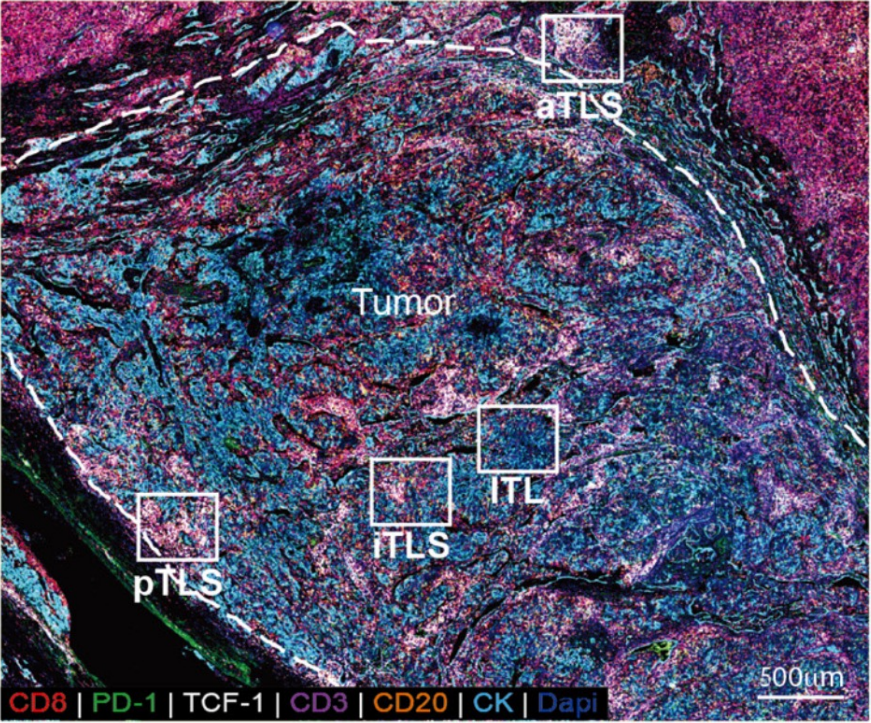
**Terminally
Differentiated
CD8 T cells**



- Increasing the number of stem-like CD8 T cells?
- Improving the quality of effector CD8 T cells?

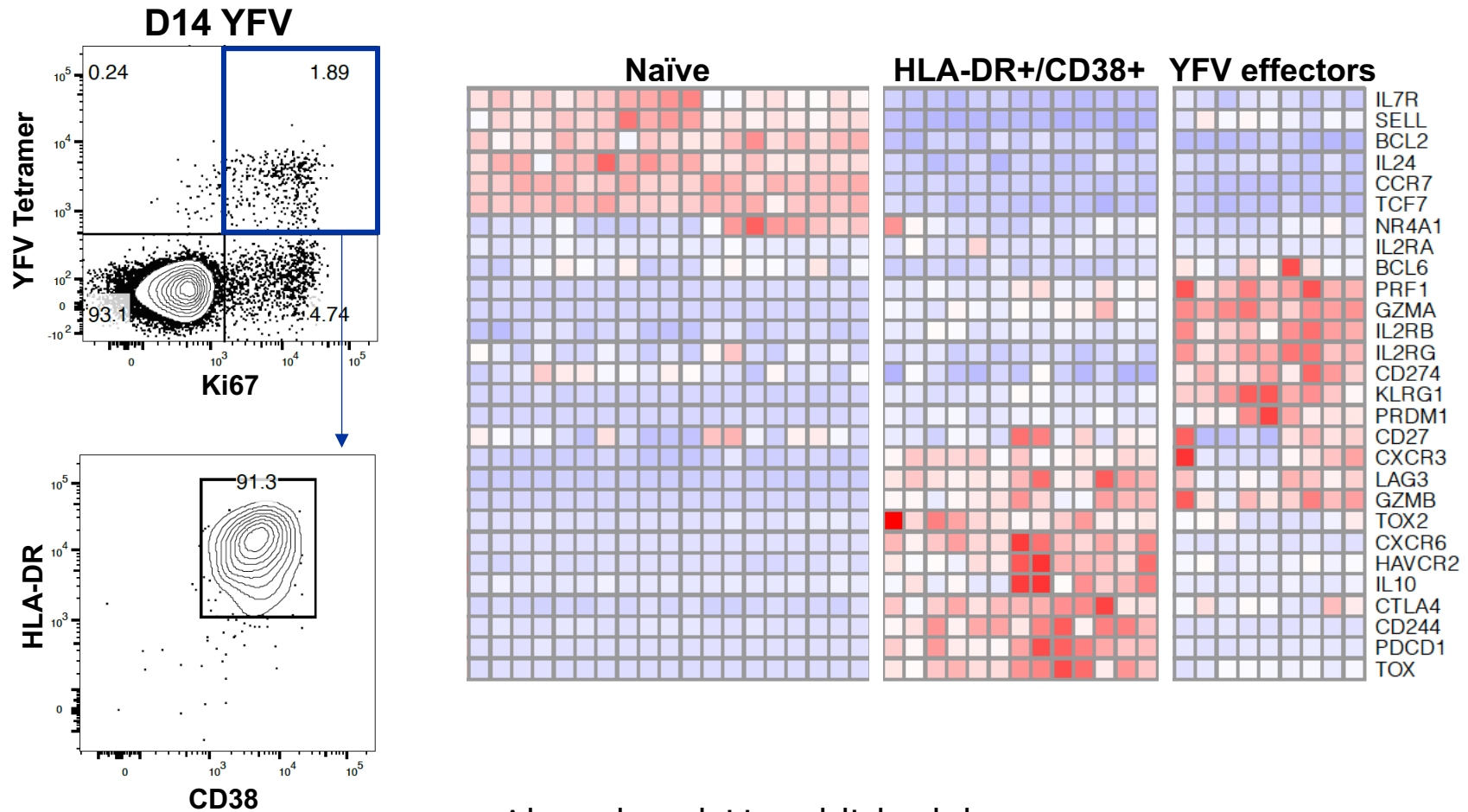
PD-1/IL-2 combination therapy (West et al. JCI 2013)

LOCATION OF STEM-LIKE CD8 T CELLS



Im S et al, PNAS, 2023.

THE GENE SIGNATURE (RNASEQ) OF PROLIFERATING PD-1+ HLA-DR+/CD38+ CELLS FROM CANCER PATIENTS DIFFERS FROM EFFECTOR CELLS GENERATED FROM AN ACUTE VIRAL INFECTION



Ahmed et al, Unpublished data

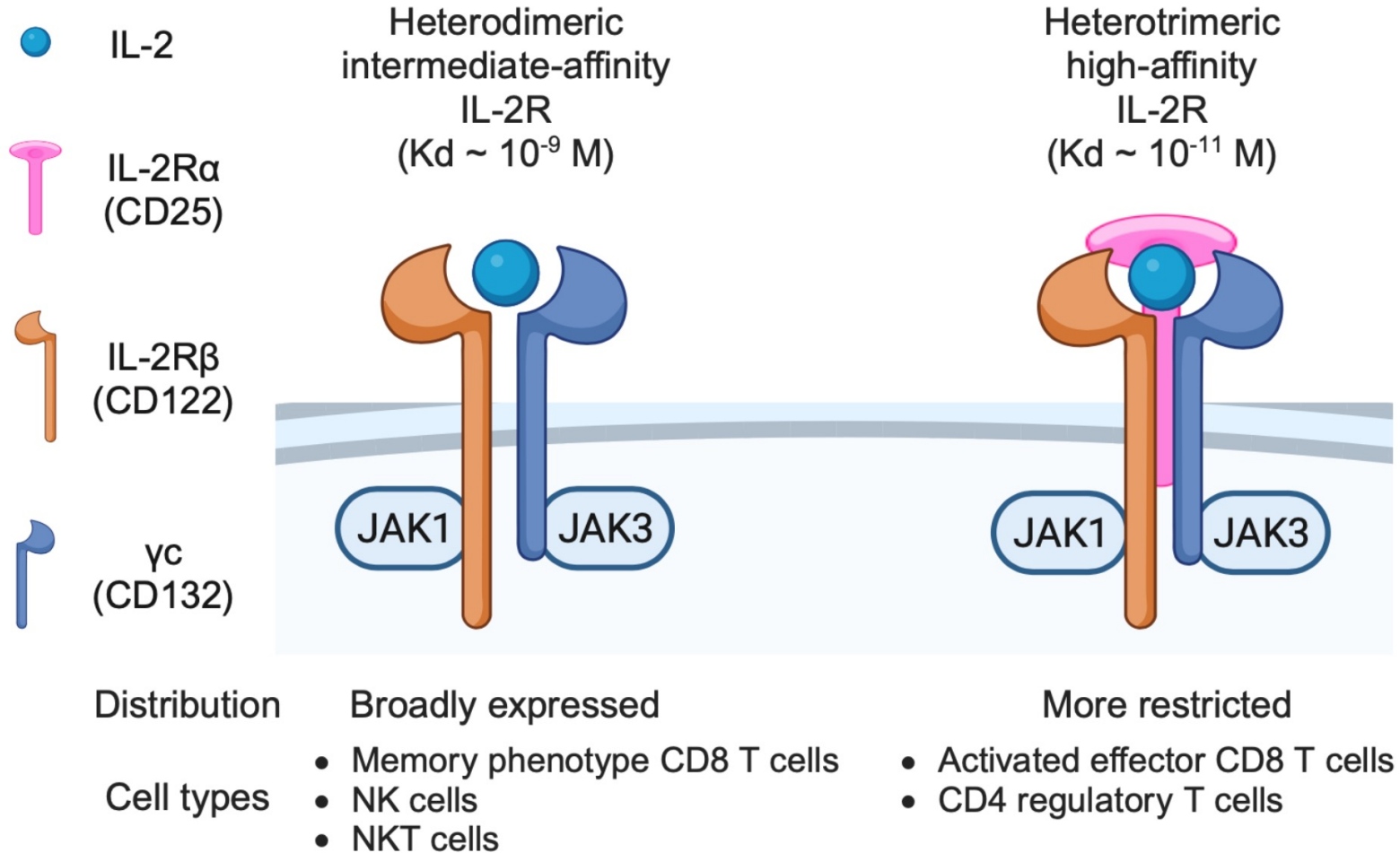


Article

Understanding how IL-2 cytokine synergizes with PD-1 directed immunotherapy during chronic viral infection

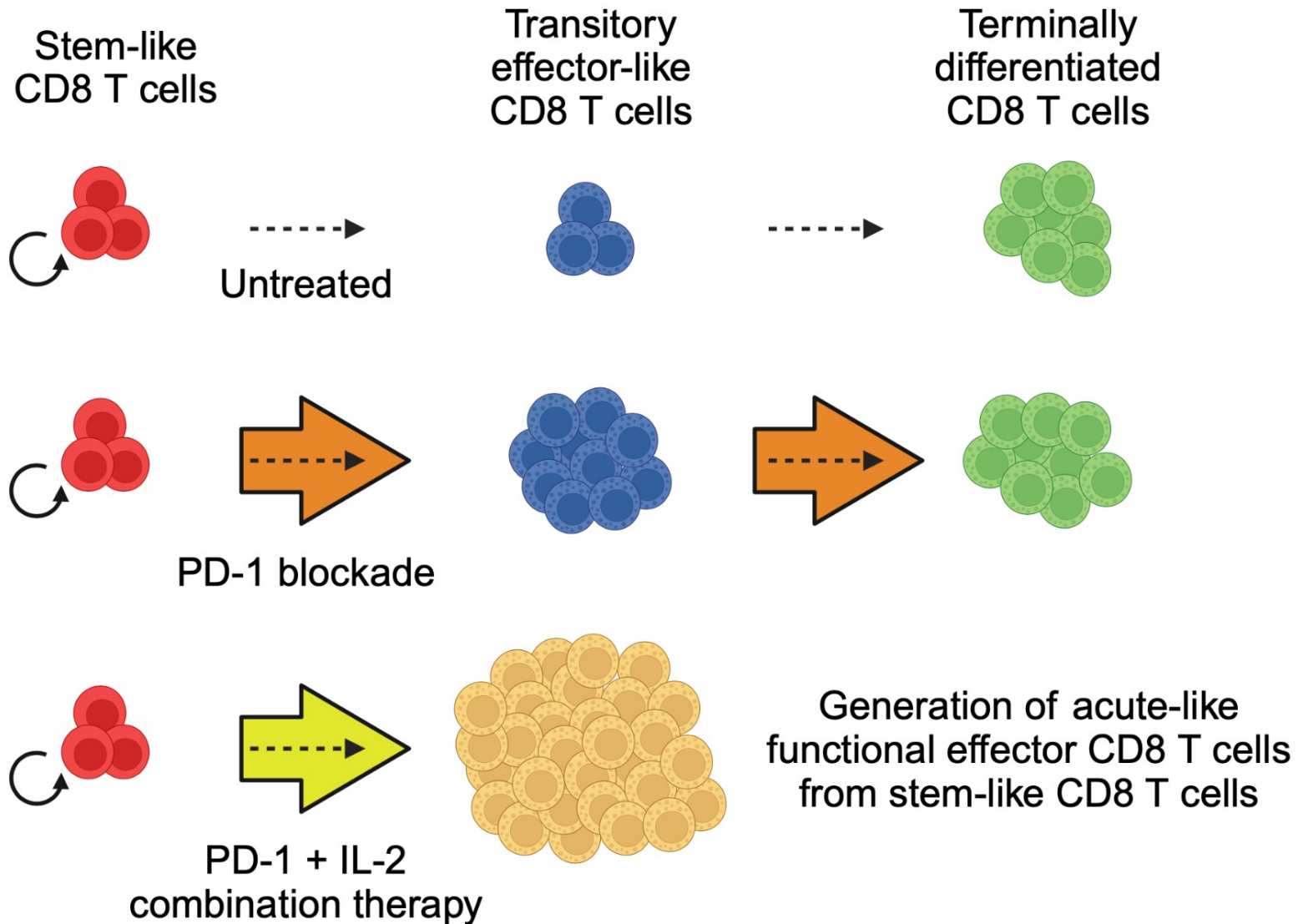
Hashimoto M et al, Nature, 2022.

IL-2/IL-2R SYSTEM



Hashimoto M et al, Trends in Cancer, 2023.

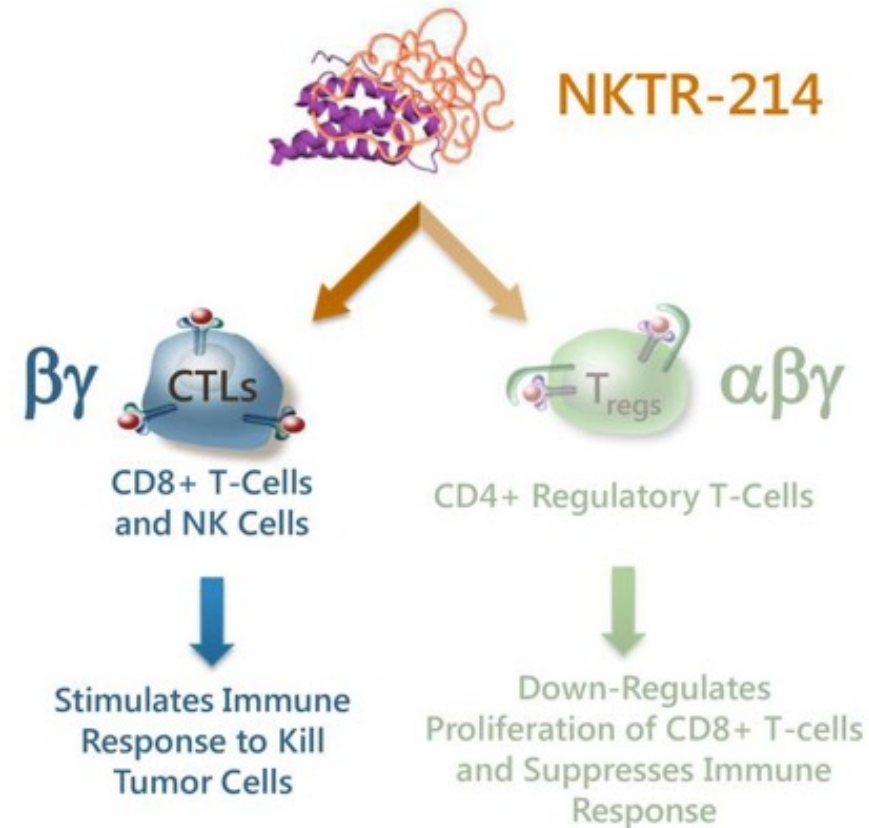
PD-1 BLOCKADE + IL-2 PROMOTE SUPERIOR QUALITY T CELLS



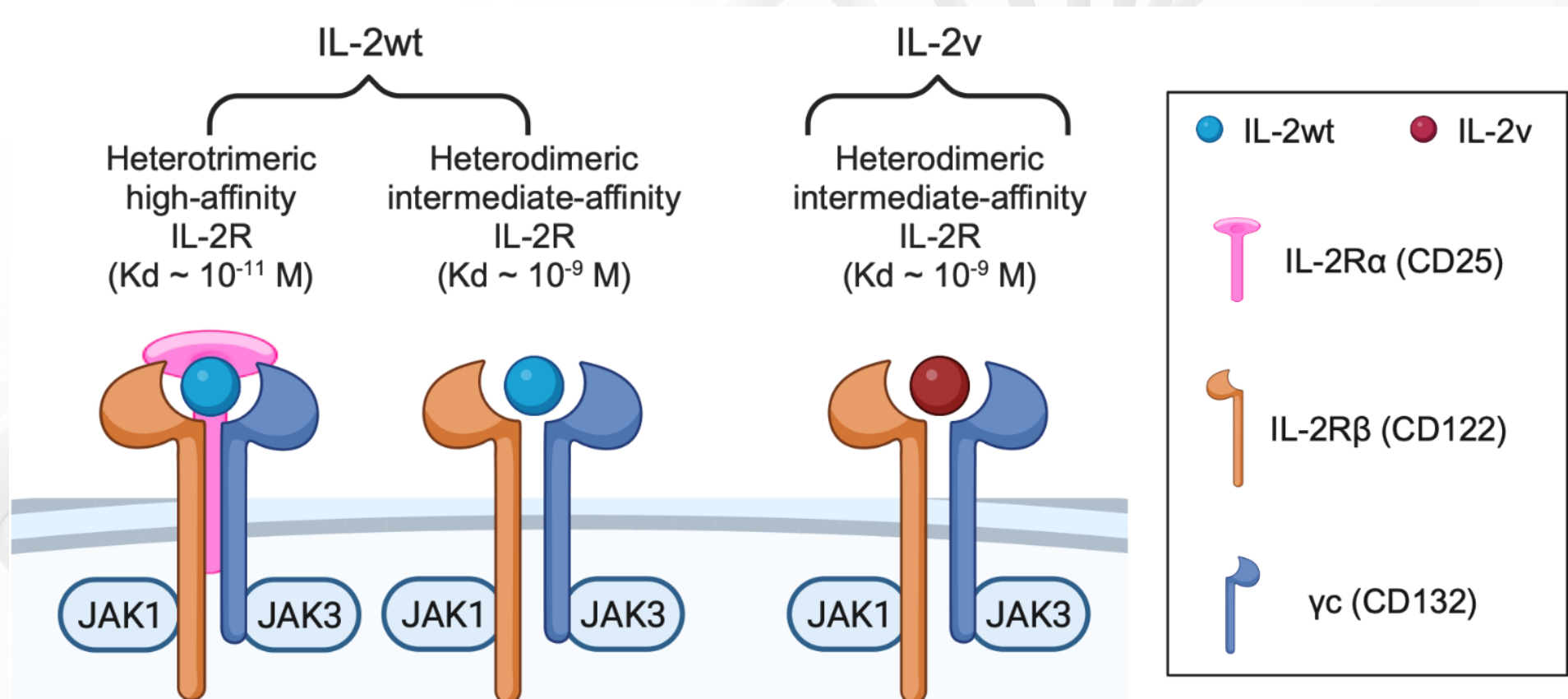
Hashimoto M et al, Trends in Cancer, 2023.

NKTR-214: Biasing Action to CD 122, or IL-2R Beta, to Stimulate T-Cell Production

- ▶ Biases signaling to favor the CD122 Receptor (IL-2R $\beta\gamma$ complex)
- ▶ Eliminates over-activation of IL-2 pathway that results in serious safety issues
- ▶ Achieves antibody-like dosing schedule in outpatient setting

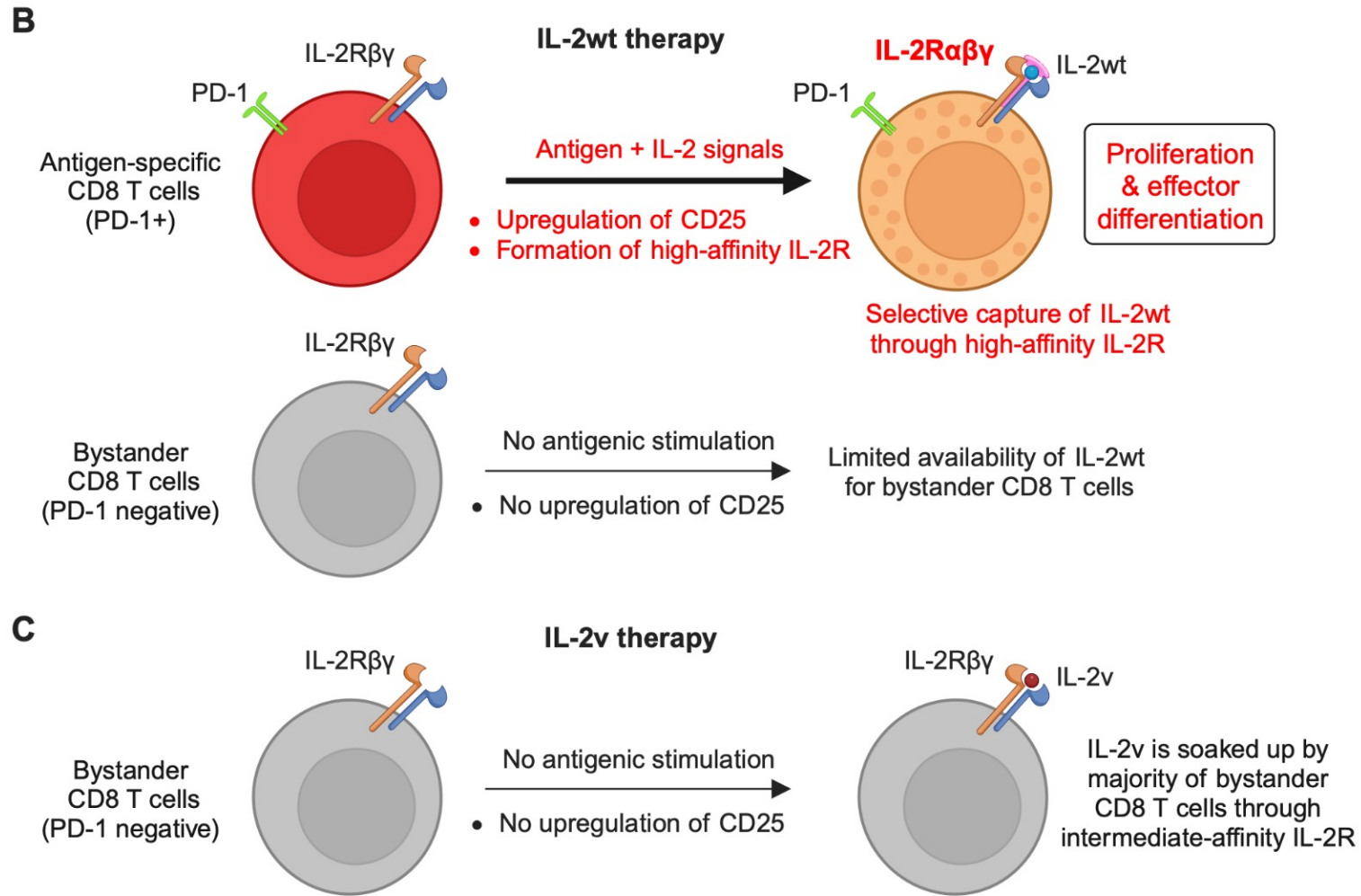


IL-2 WILD TYPE VERSUS IL-2 VARIANT: FUNCTIONAL CONSEQUENCES



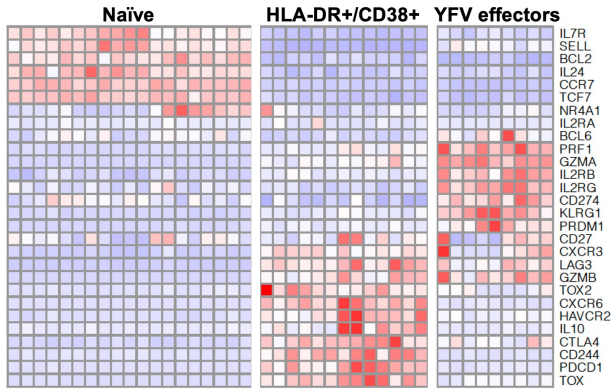
Hashimoto M et al, Trends in Cancer, 2023.

ANTIGEN-SPECIFIC VERSUS BYSTANDER CD8 T CELLS



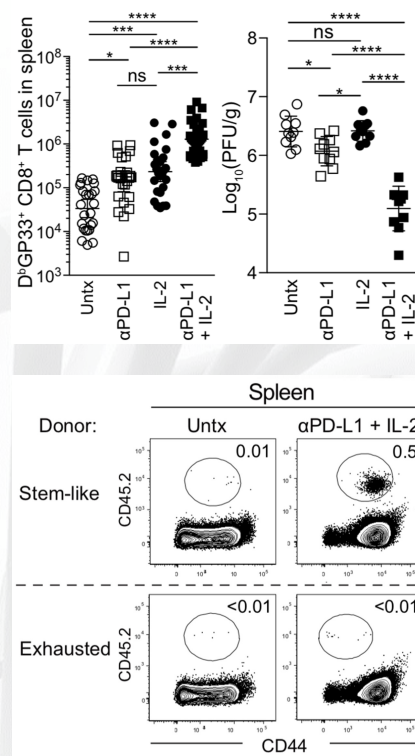
Hashimoto M et al, Trends in Cancer, 2023.

IMPROVING EFFICACY OF IMMUNOTHERAPY FOR LUNG CANCER: BEDSIDE TO BENCH TO BEDSIDE

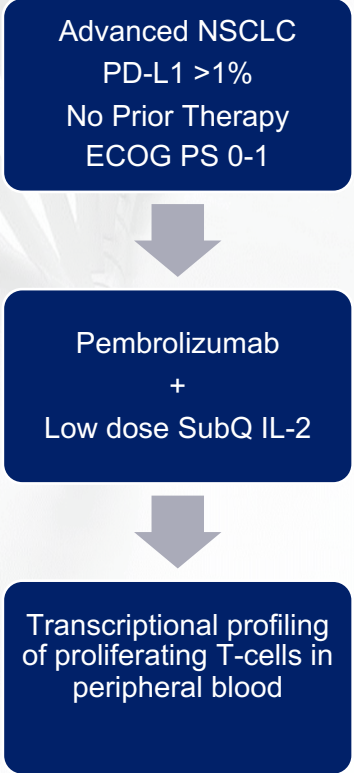


Proliferating T-cells with PD-1 blockade in advanced NSCLC

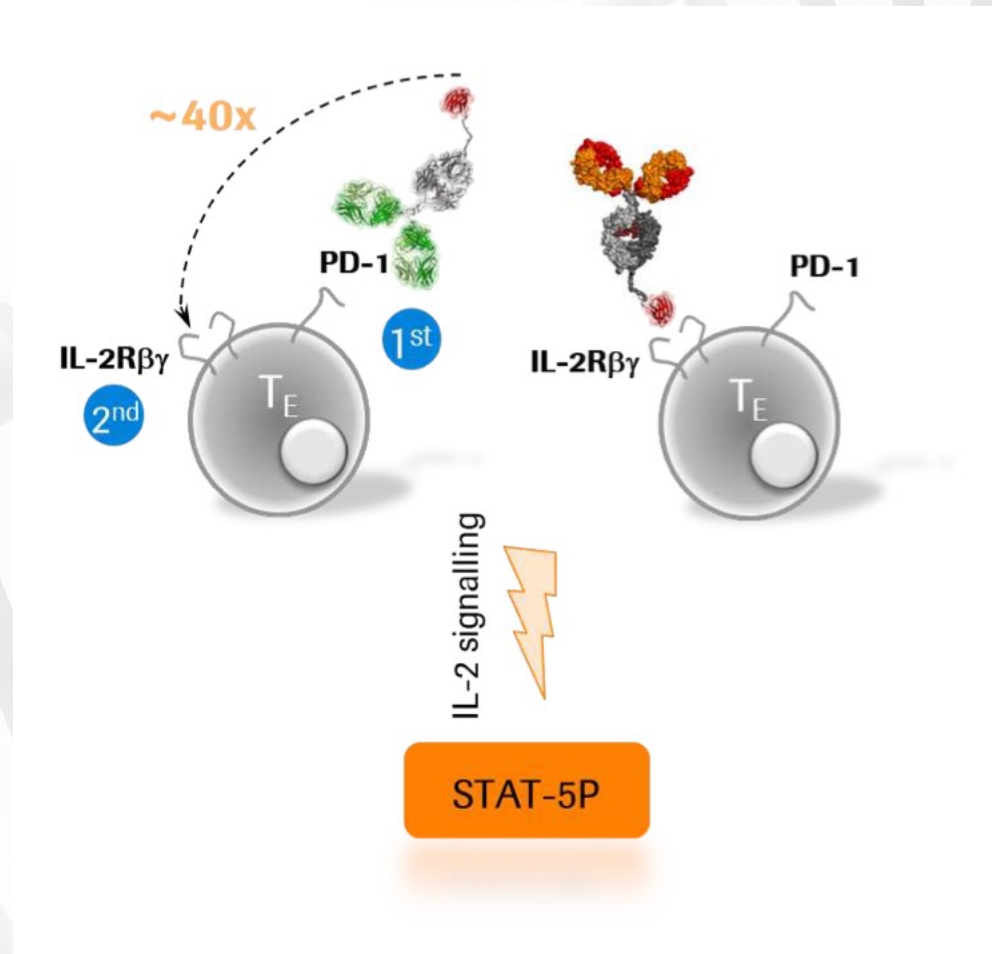
Obeng R et al, SITC 2021, Manuscript under review.



Hashimoto et al, Nature, 2022 (in press)



ENGINEERED IL₂ TARGETED TO PD-1



Umana et al, Pre-publication; Source: Research Square

CONCLUSIONS

- PD-1 blockade promotes reversal of T cell exhaustion
- The proliferating T cells are lacking in quality
- Combination of PD-1 blockade with IL-2 produces effective qualitative and quantitative T cell response
- CD25 engagement appears critical for IL-2 efficacy
- Clinical trials are ongoing