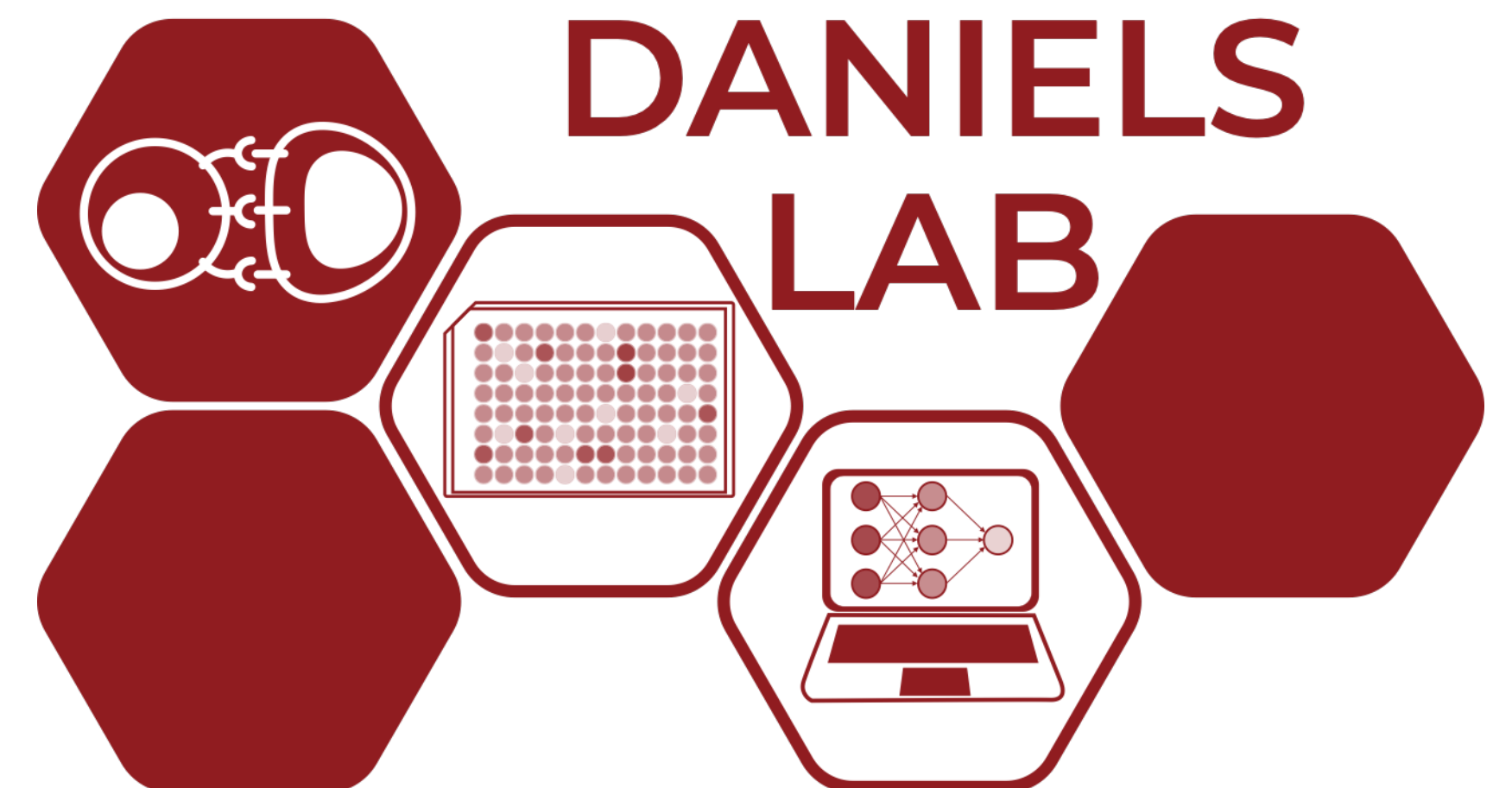


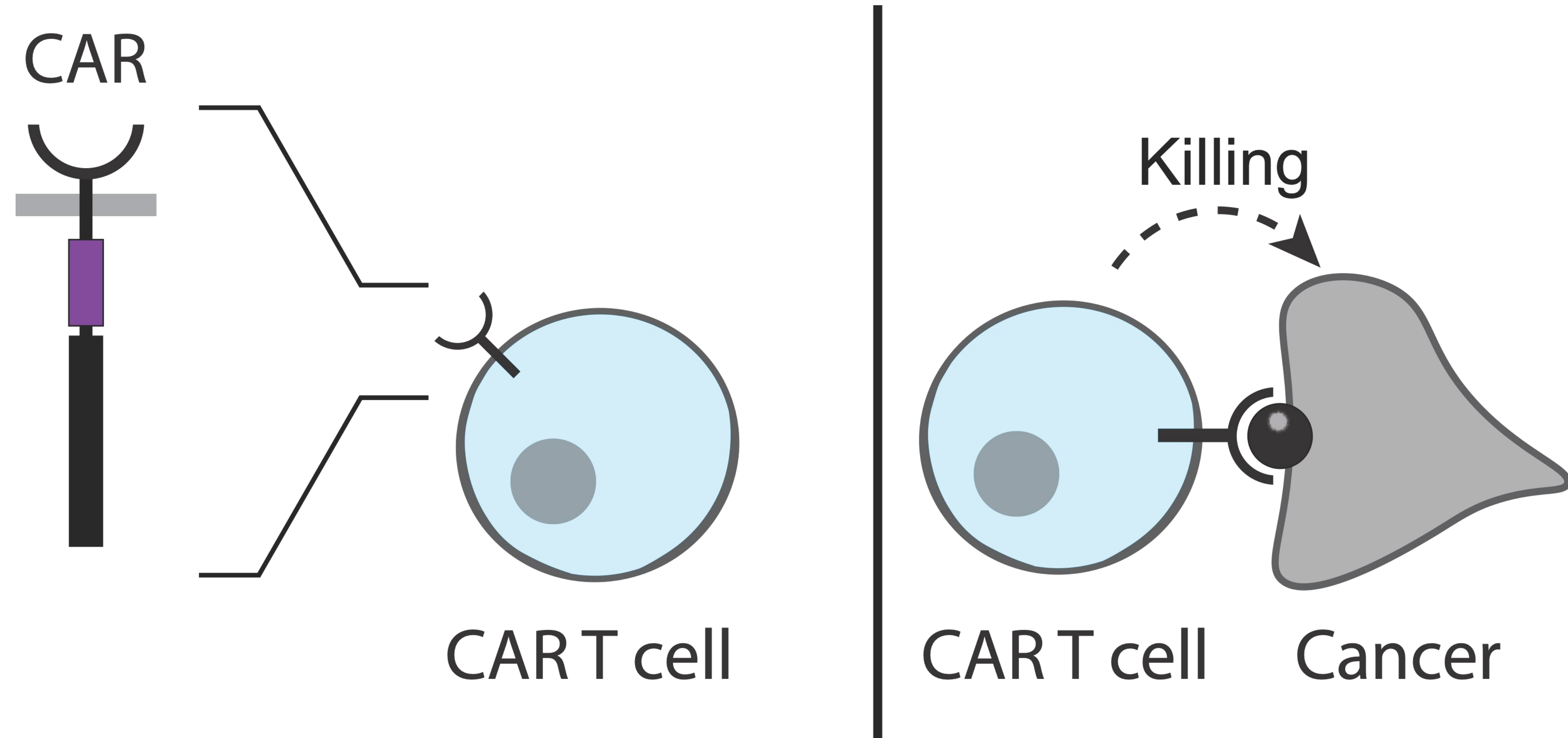
Programmable cell therapies

Using AI in the development of new technologies to control cells

Kyle G. Daniels, PhD
NASEM Regen. Medicine Forum
11/2025

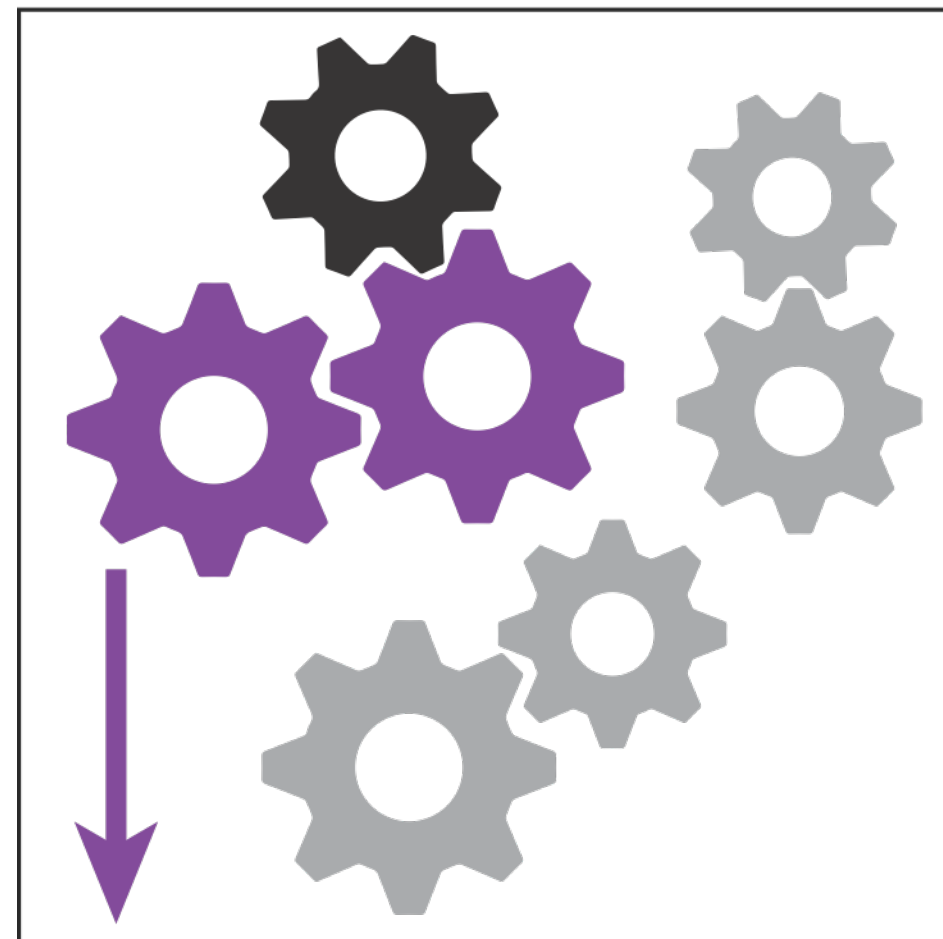
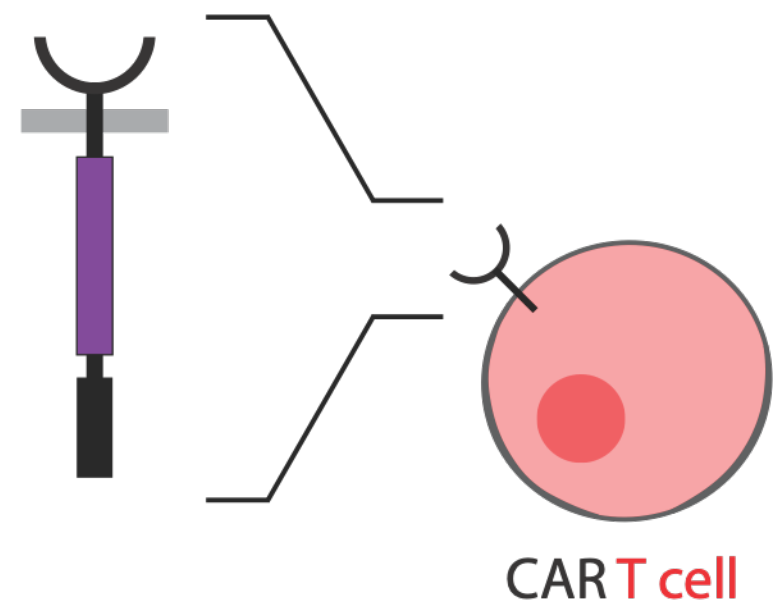


CAR T cell therapy



Brudno JN, Maus MV, Hinrichs CS. JAMA. 2024 PMID: 39495525
Patel KK, Tariveranmoshabad M, Kadu S, Shobaki N, June C. Mol Ther. 2025 PMID: 40070120

CAR T cells have limited efficacy against many cancers



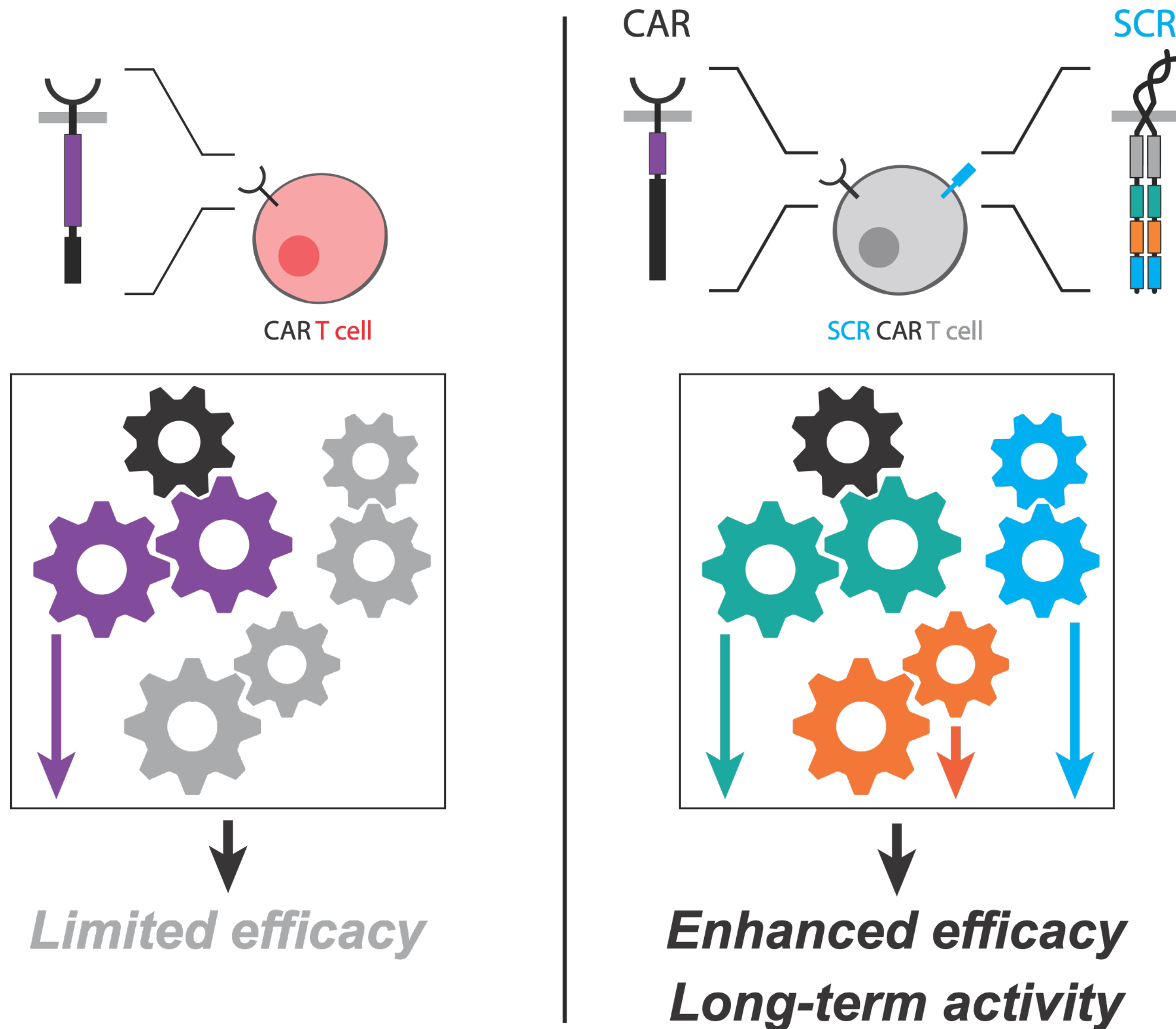
Limited efficacy

Poor T cell survival

Low proliferation

Insufficient tumor killing

Synthetic cytokine receptors (SCRs) can improve CAR T cell function

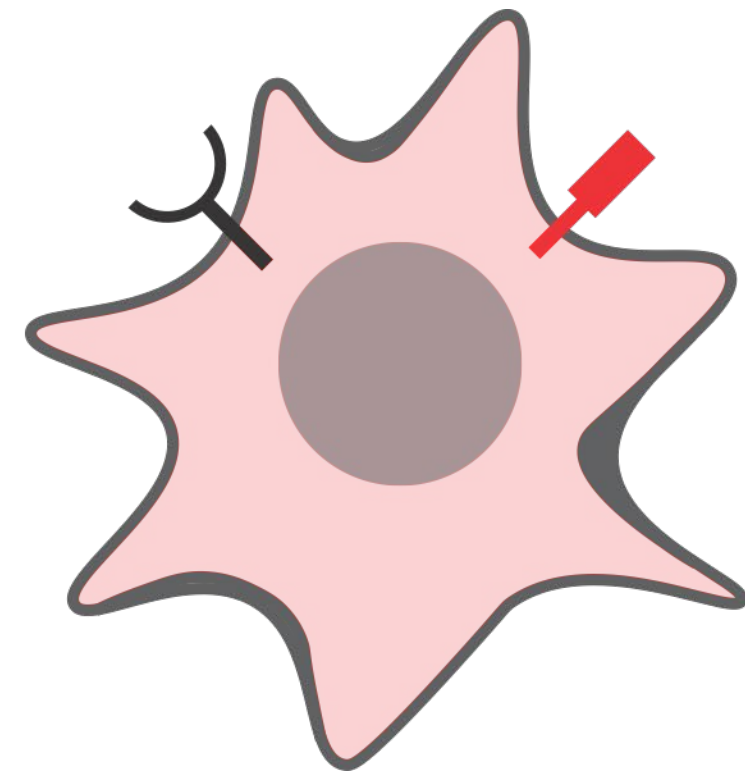
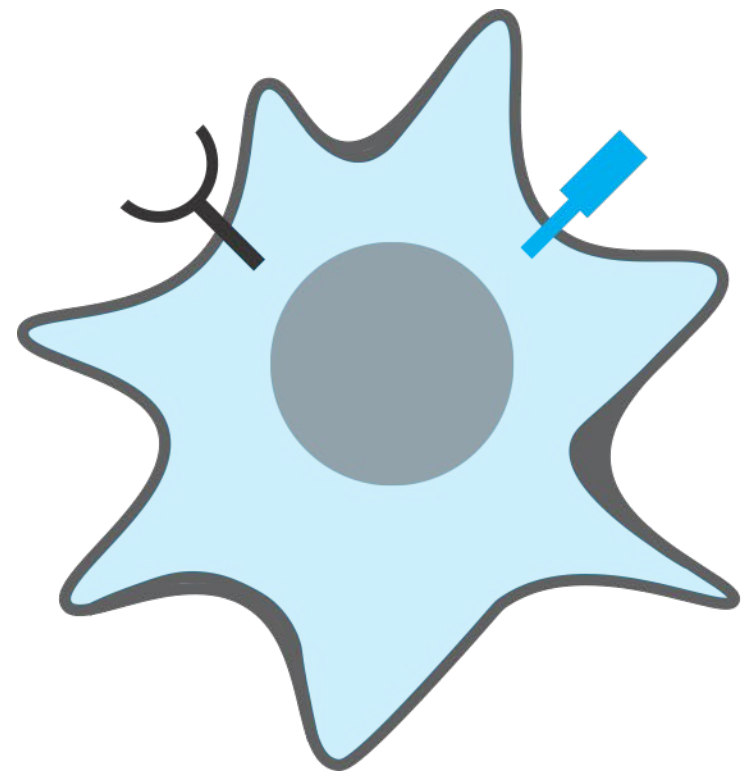


Prolong T cell survival

Increase proliferation

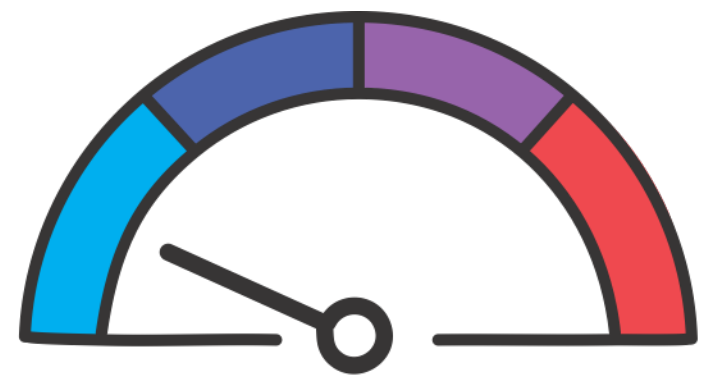
Enhance tumor killing

Challenges in CAR macrophage therapies

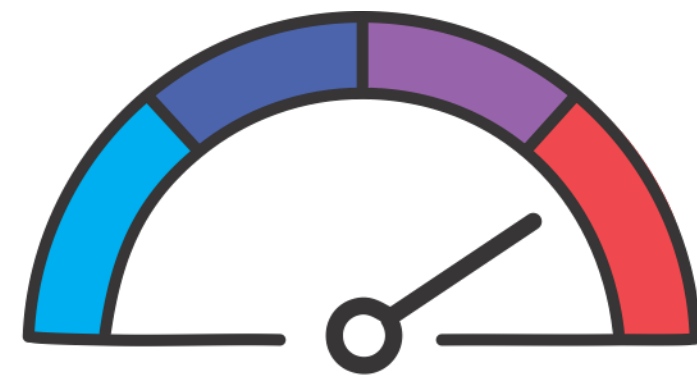


Polarization is temporary

Can be repolarized by tumors



***Anti-inflammatory
macrophage***



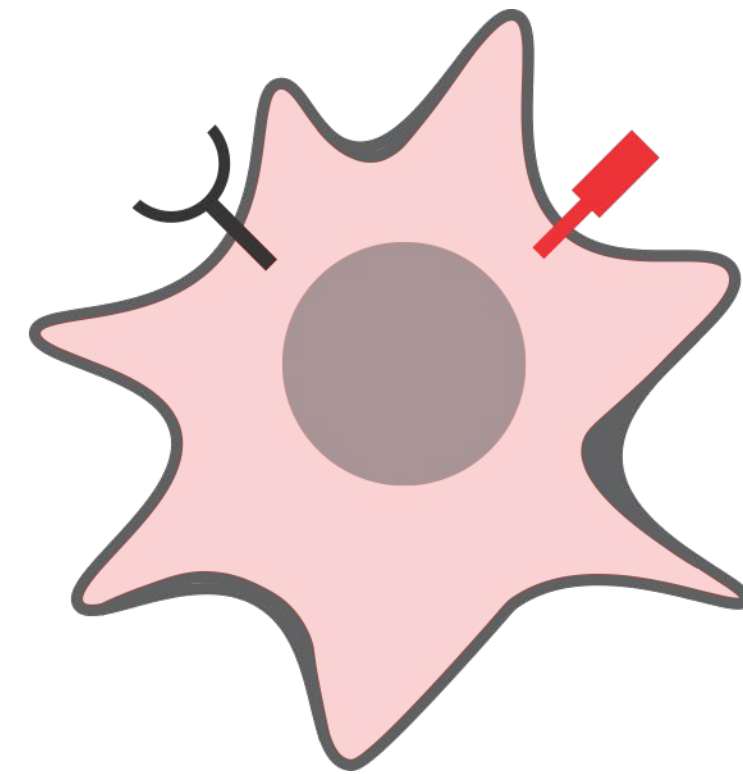
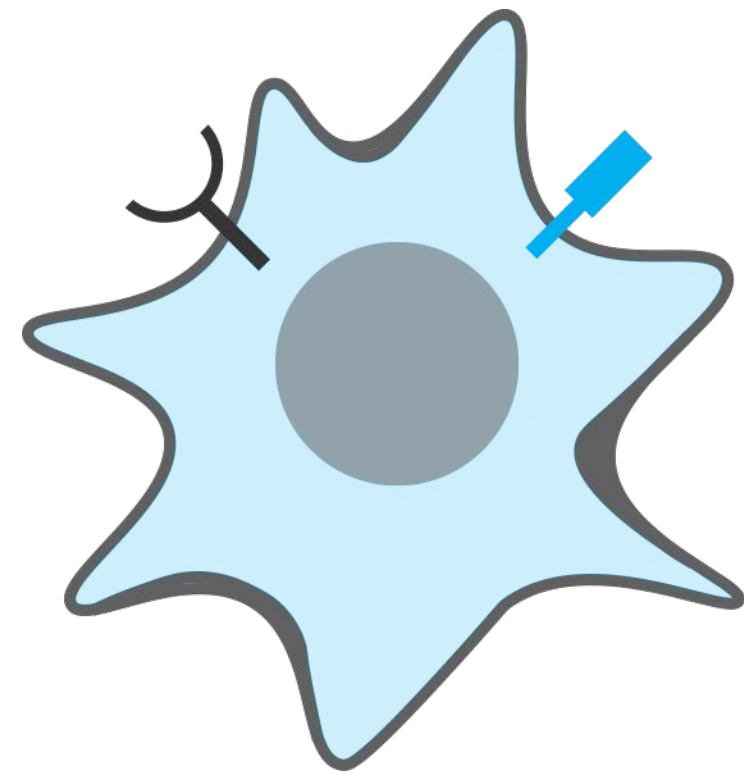
***Pro-inflammatory
macrophage***

Don't eat enough cancer

Wei D, Wang L, Liu Y, Zuo X, Shen X, Bresalier RS. Clin Cancer Res. 2025 PMID: 40757874

Na YR, Kim SW, Seok SH. Exp Mol Med. 2023 PMID: 37653035

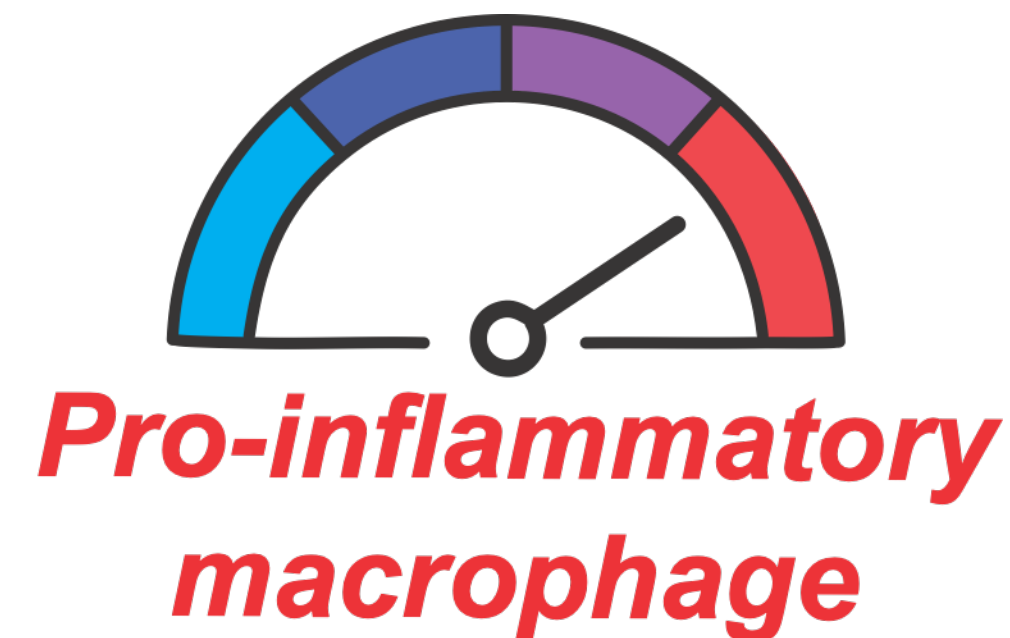
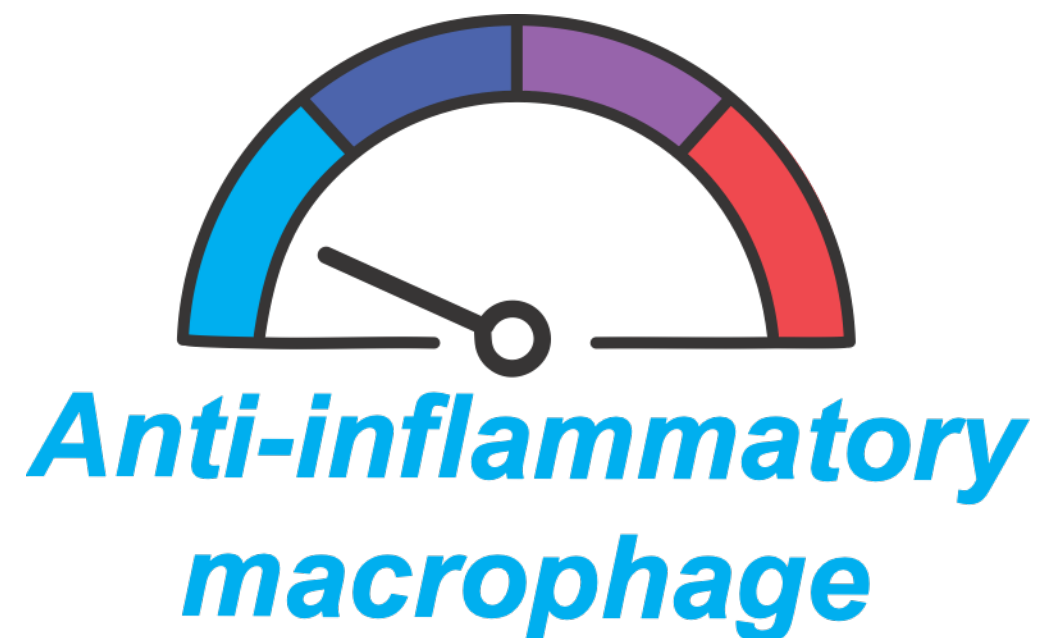
Synthetic cytokine receptors (SCRs) can improve CAR M function



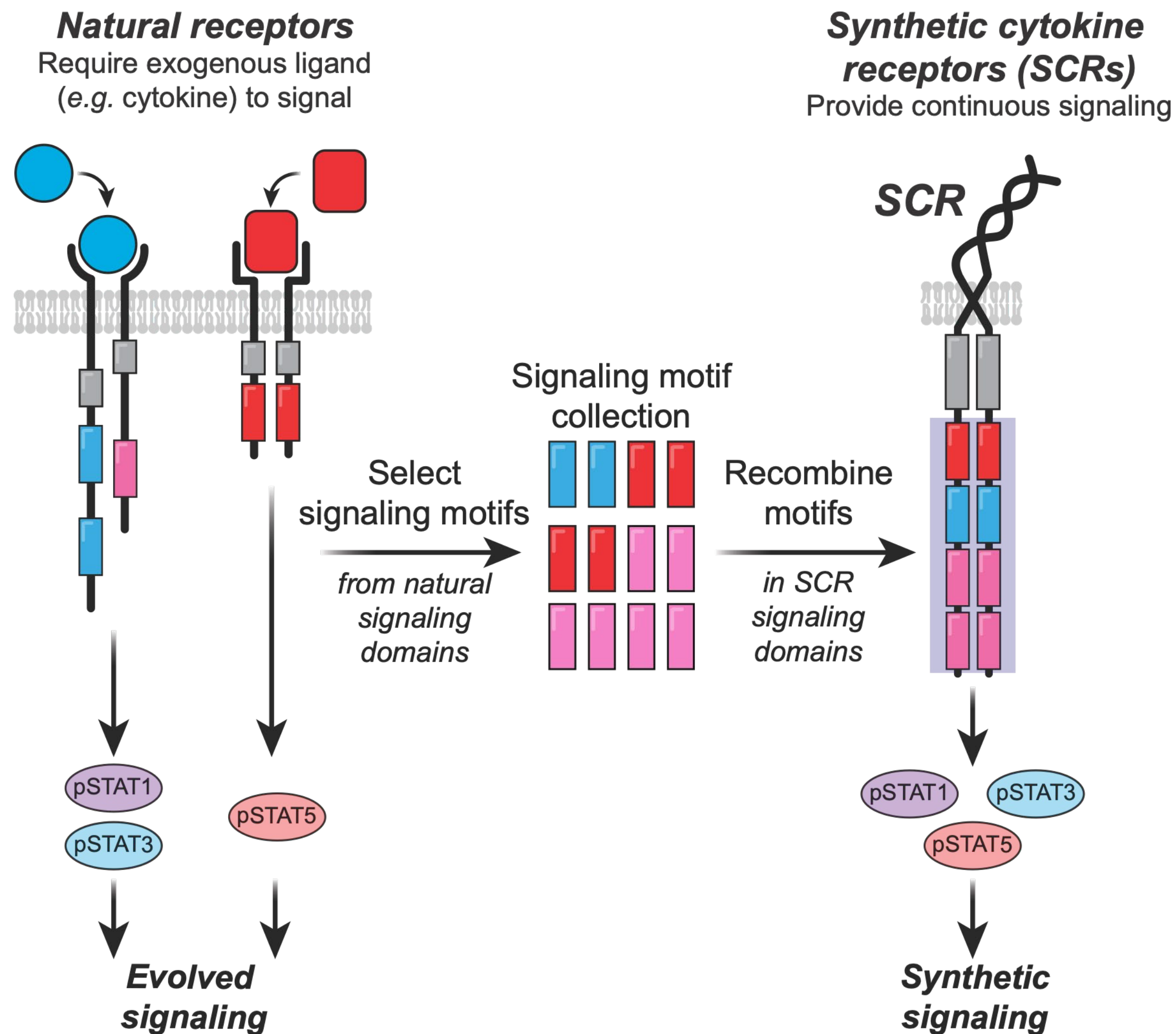
Set polarization state

Increase phagocytosis

Prolong survival



Synthetic cytokine receptors (SCRs) alter immune cell function

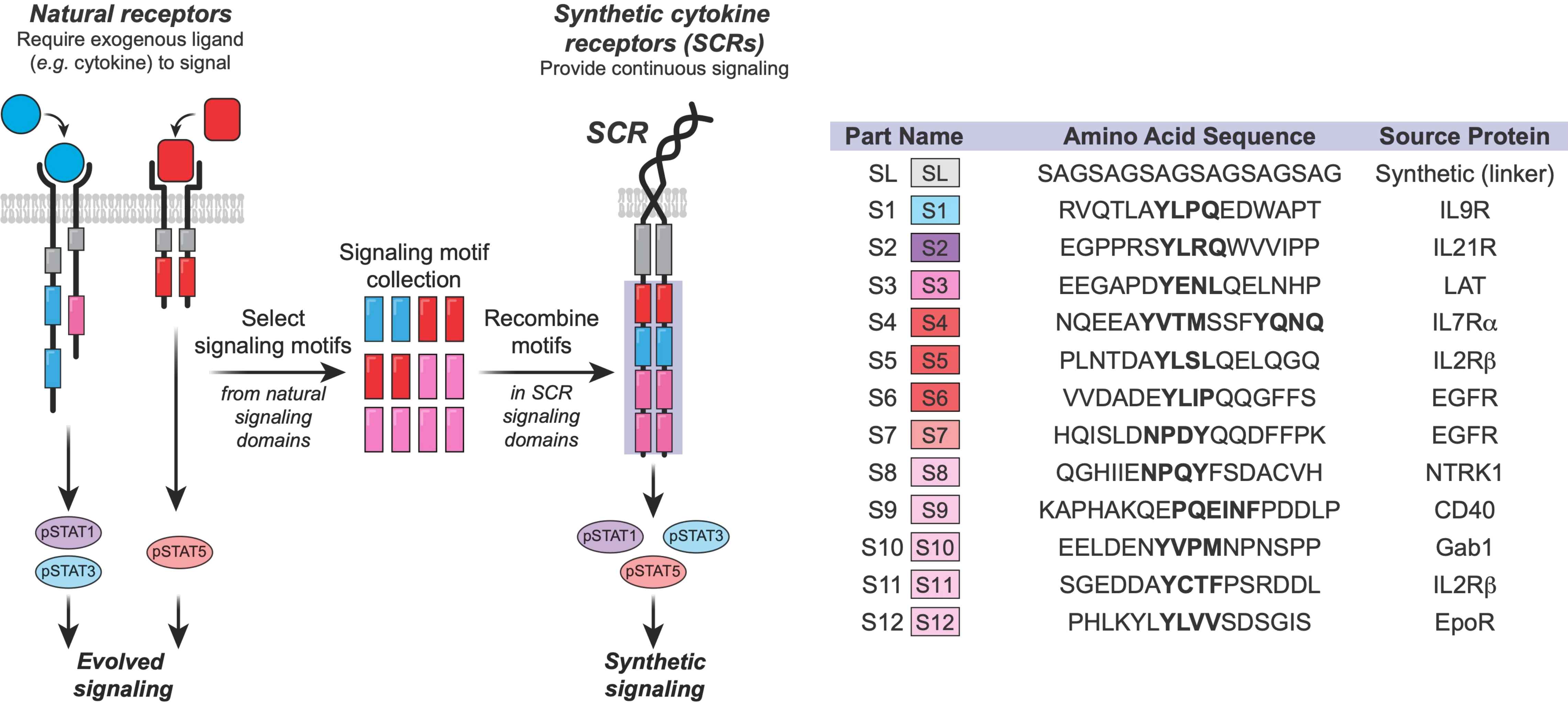


Continuous signaling

Programmable

Identify optimal signals that improve immune cell function

Synthetic cytokine receptors (SCRs) alter immune cell function

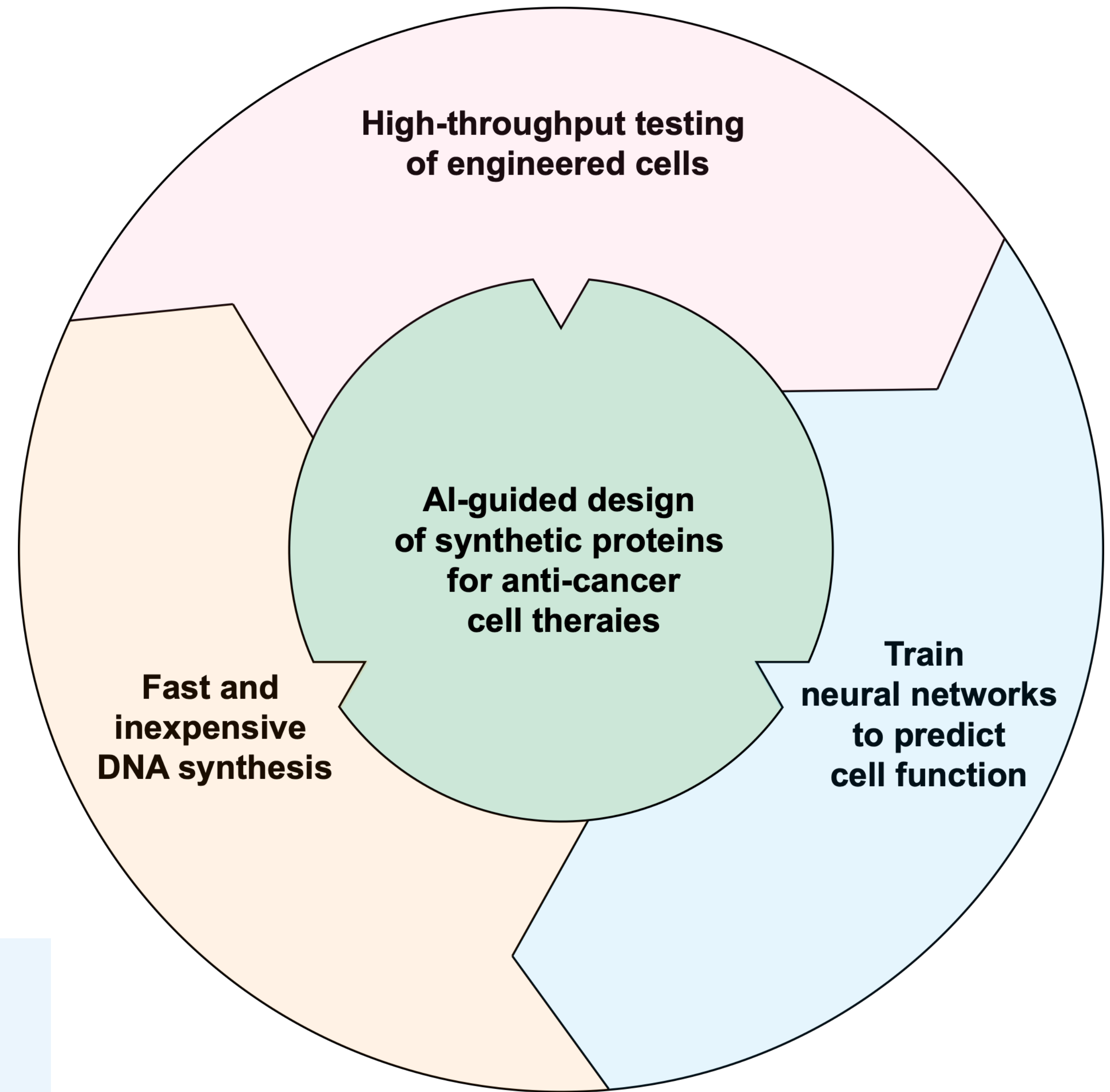


AI-augmented cell engineering

Design and build
libraries of SCRs

Test SCRs in human
T cells and macrophages

Train models to understand
protein structure-to-cell function

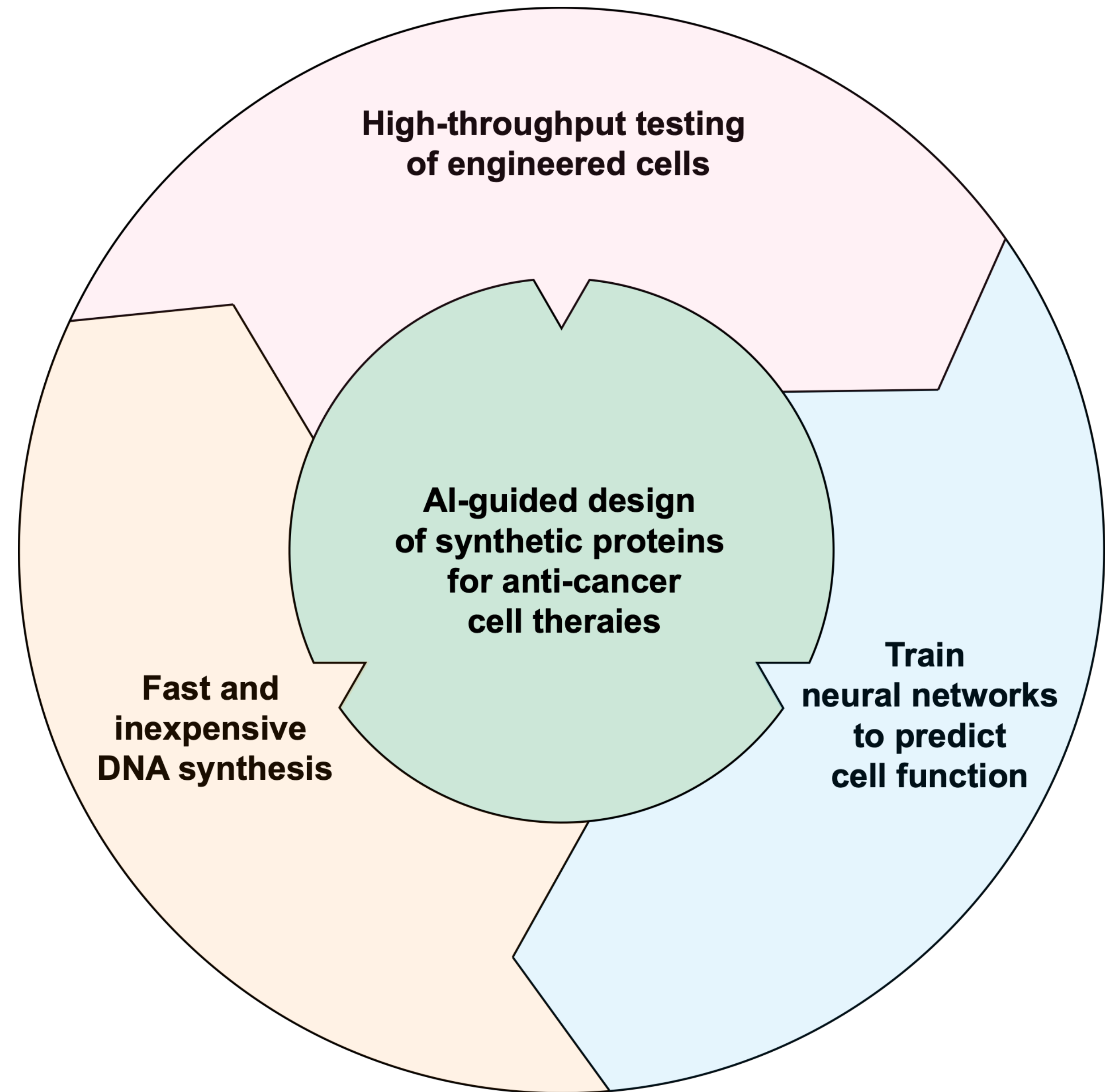


AI-augmented cell engineering

Protein composition-to- 3D structure (ex. AlphaFold)

Protein composition-to-binding (ex. BindCraft)

Protein composition-to-cell function



AI-augmented cell engineering

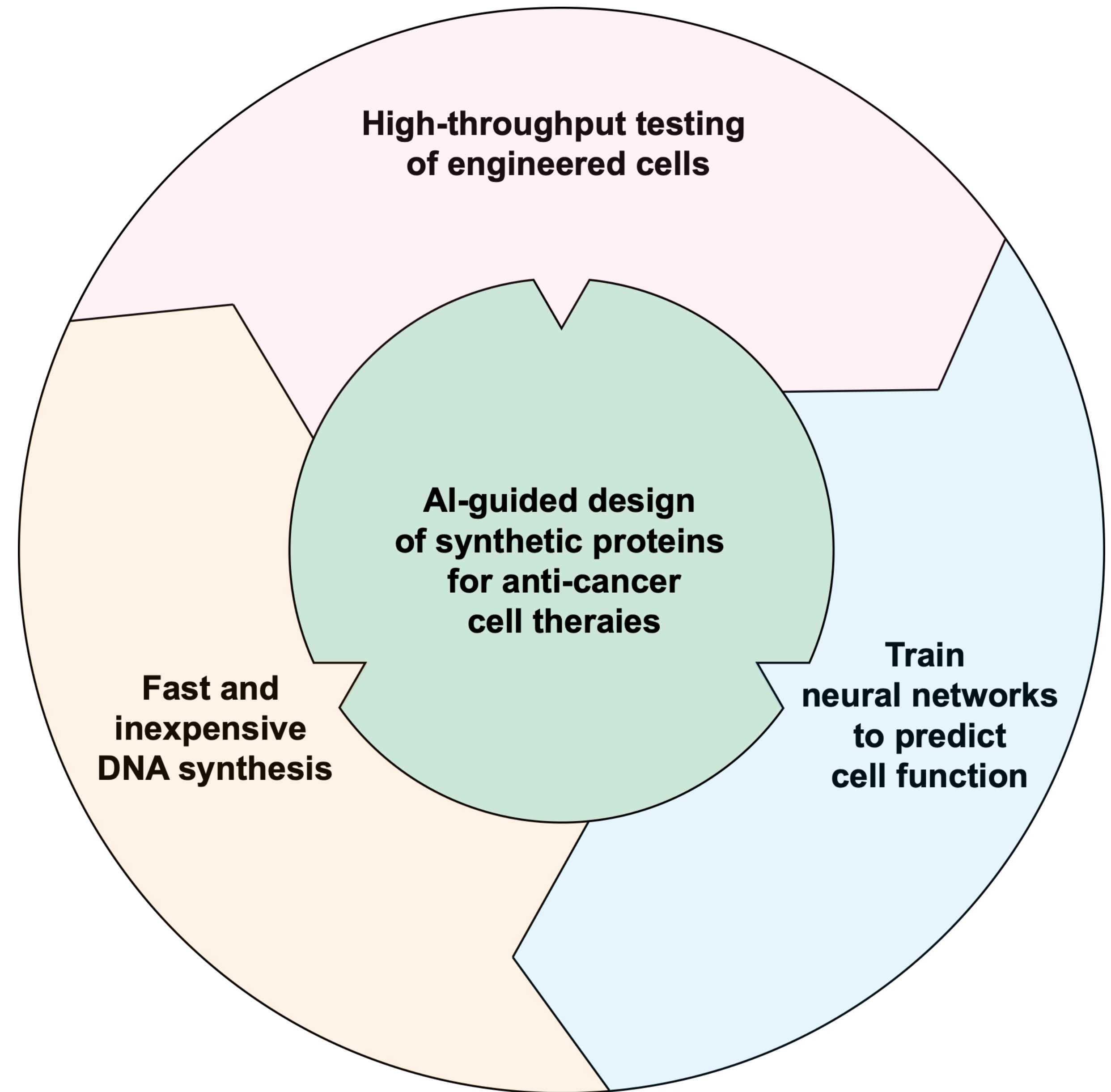
Cell functions:

Differentiation

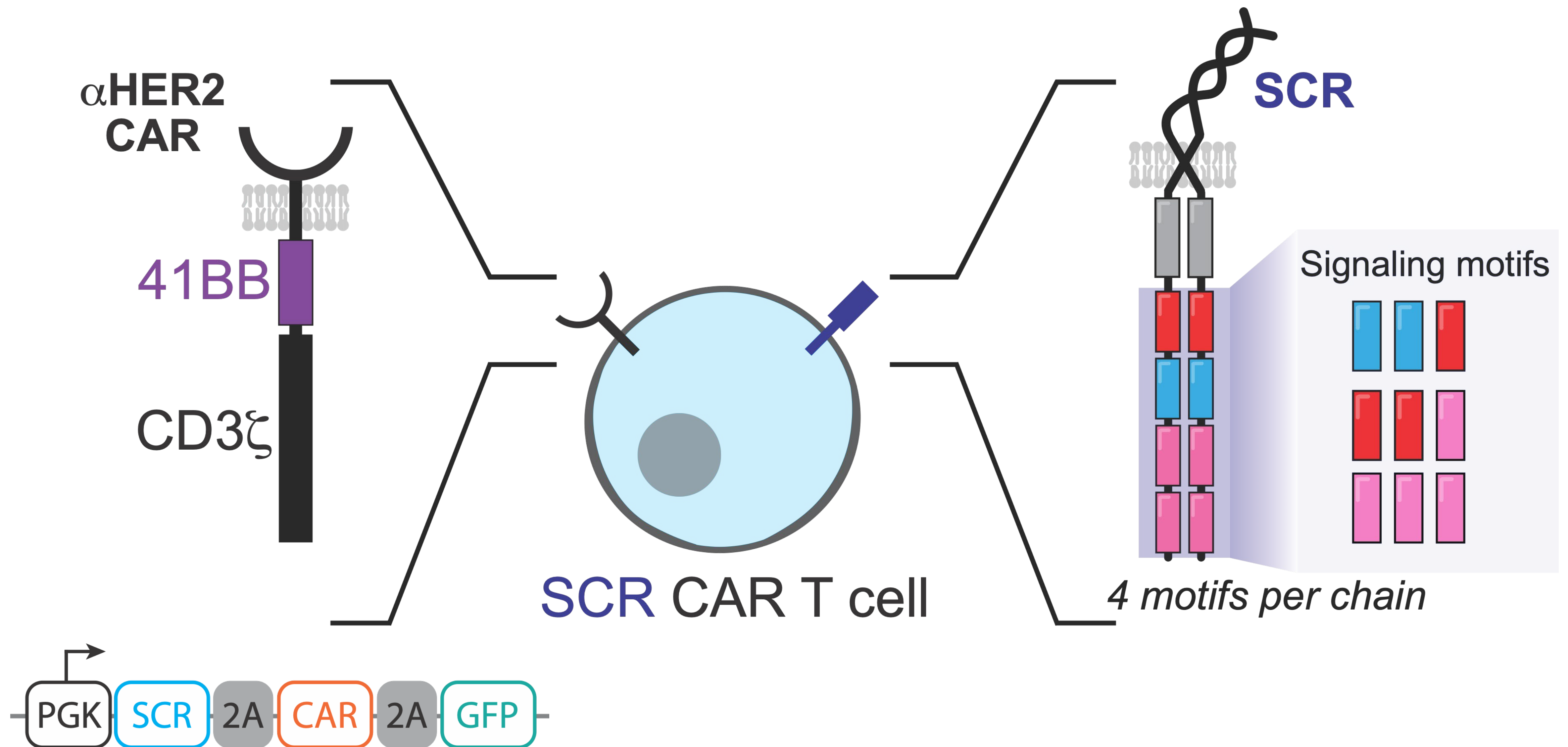
Survival

Proliferation

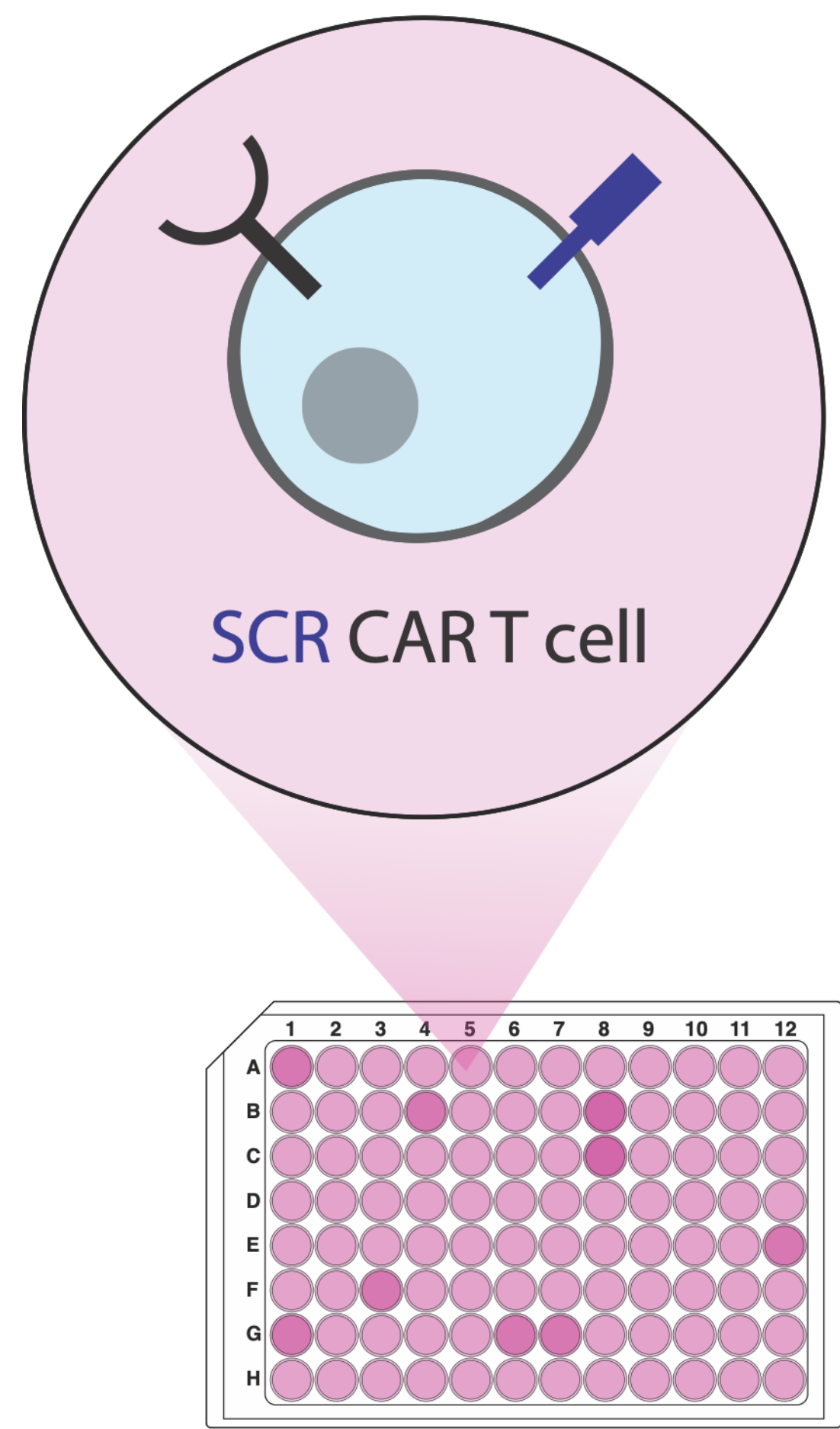
Tumor killing



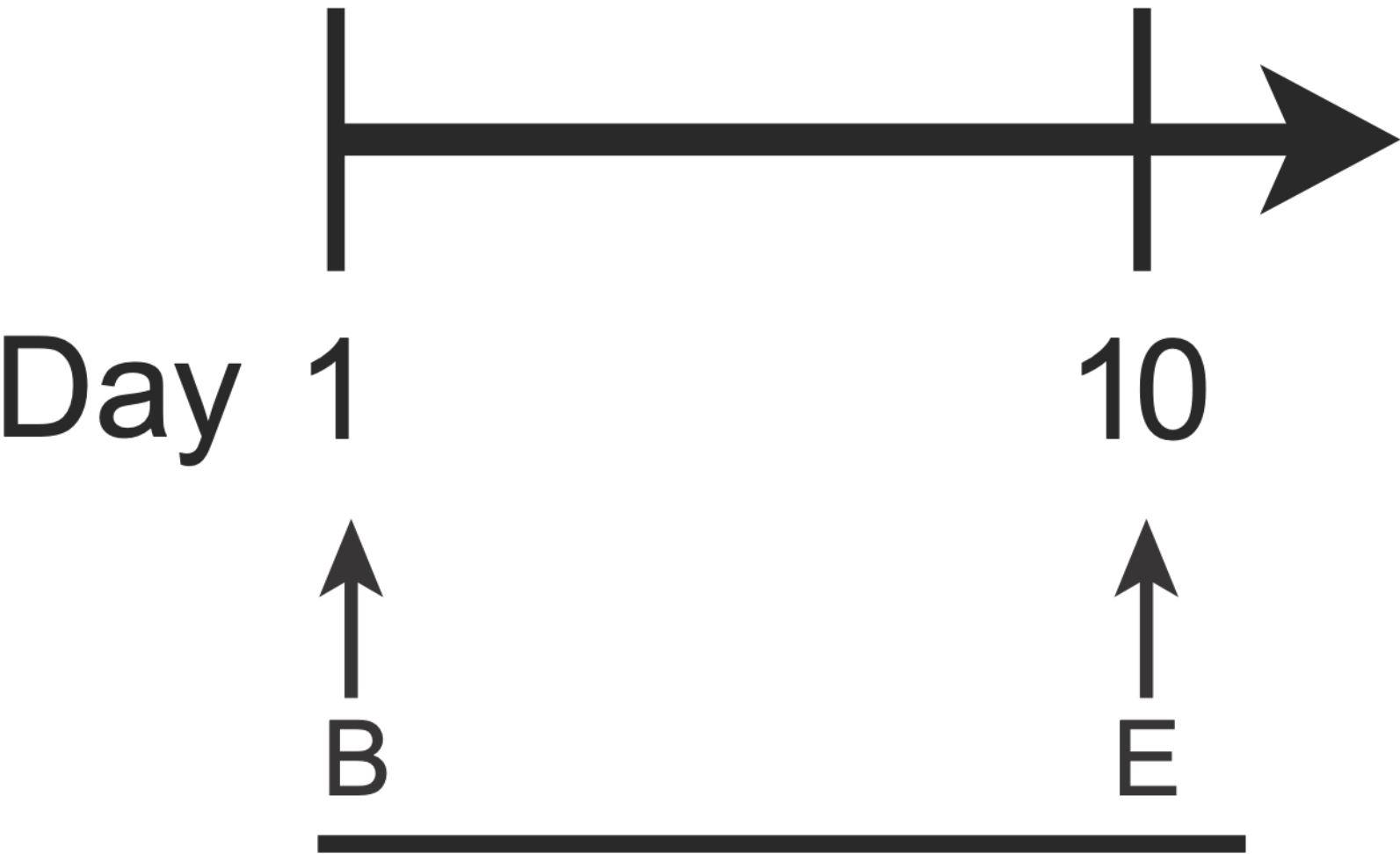
A combinatorial library of SCRs with synthetic signaling domains



SCR signaling programs encode survival in the absence of cytokine

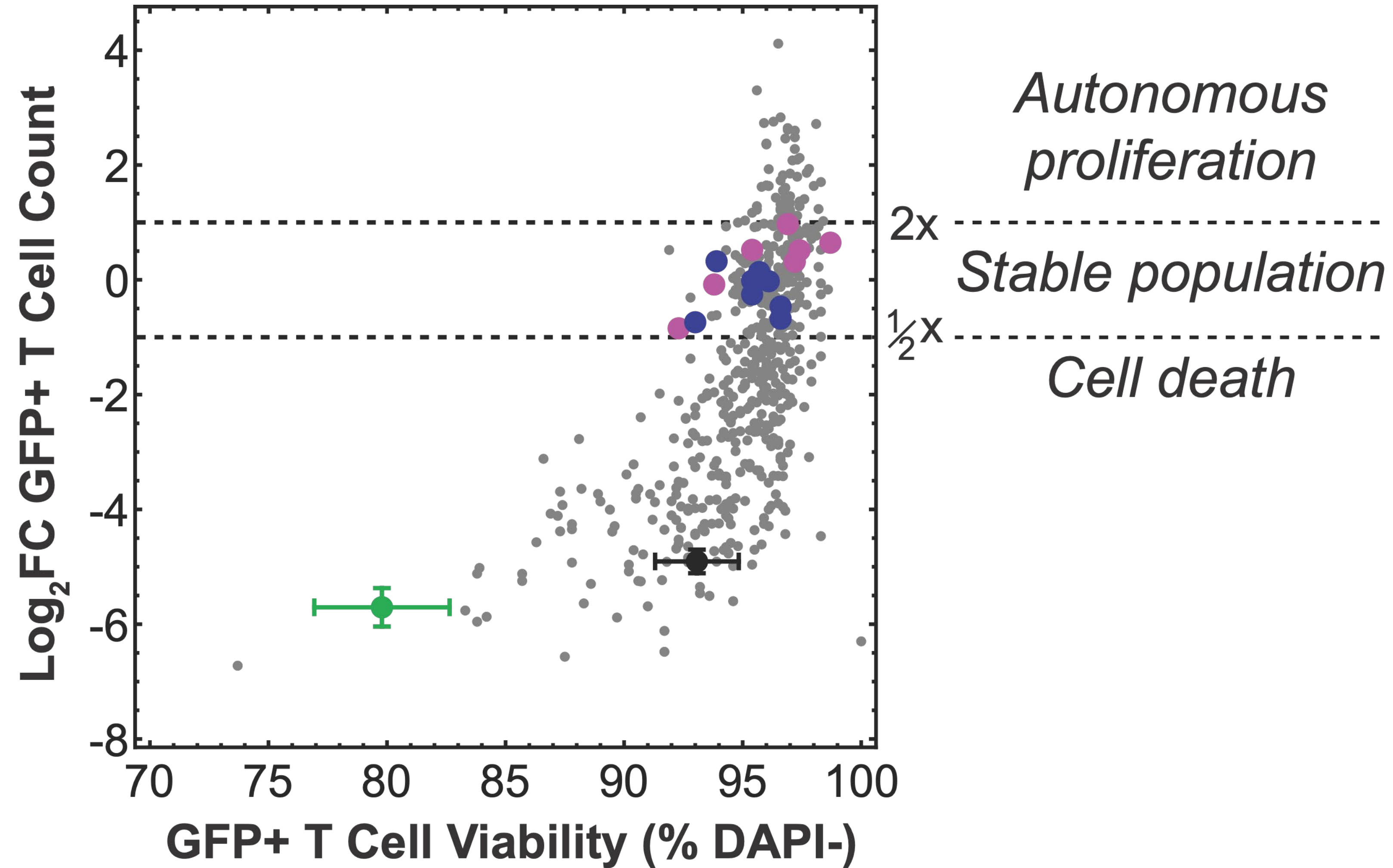


10 days, no cytokine



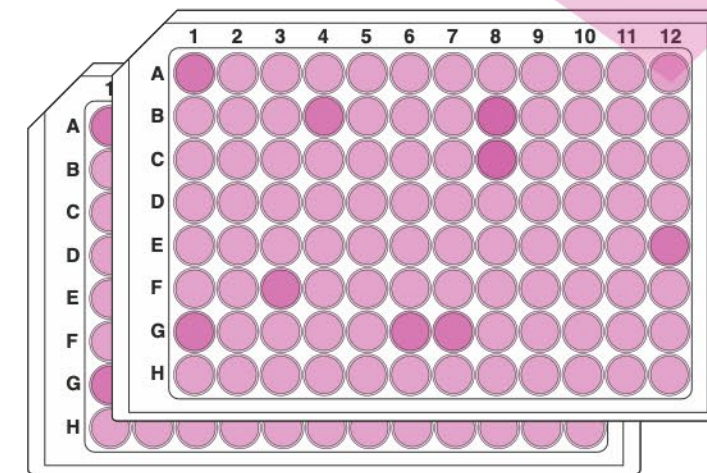
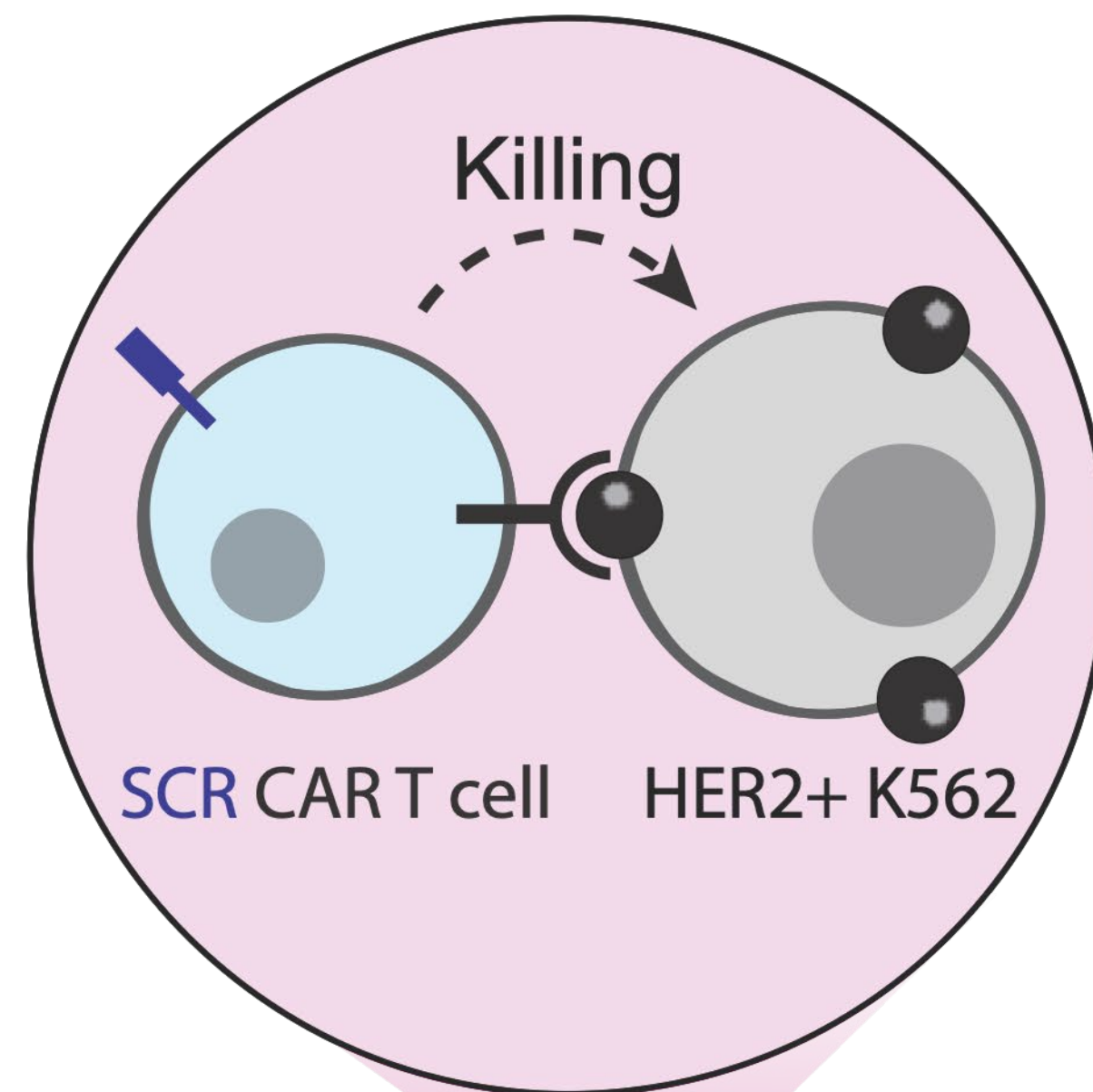
Flow cytometry
(*B, baseline; E, Endpoint*)

SCR signaling programs encode survival in the absence of cytokine



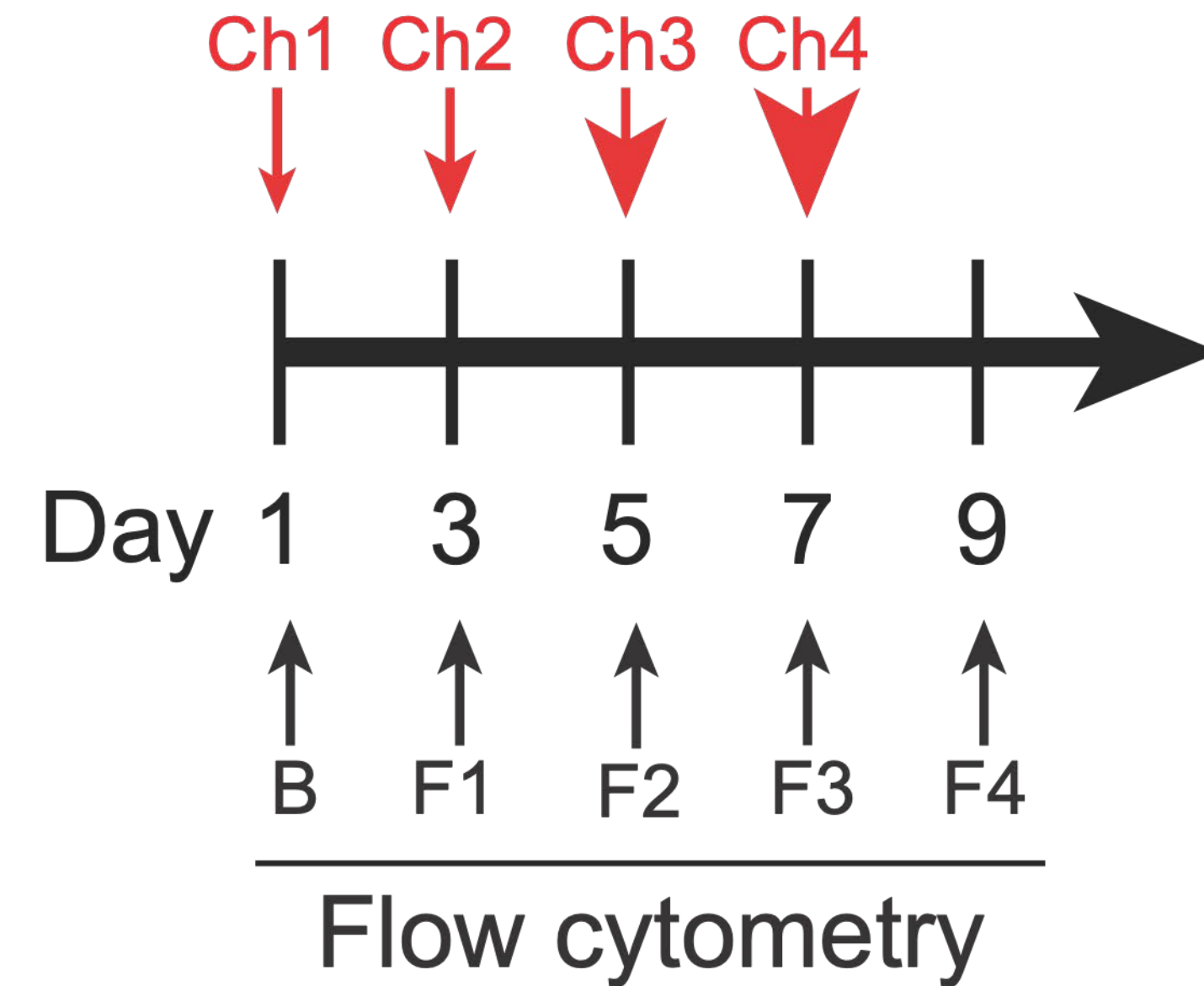
A combinatorial library of SCRs with synthetic signaling domains

CAR + 539 SCR Samples (457 Unique SCRs)



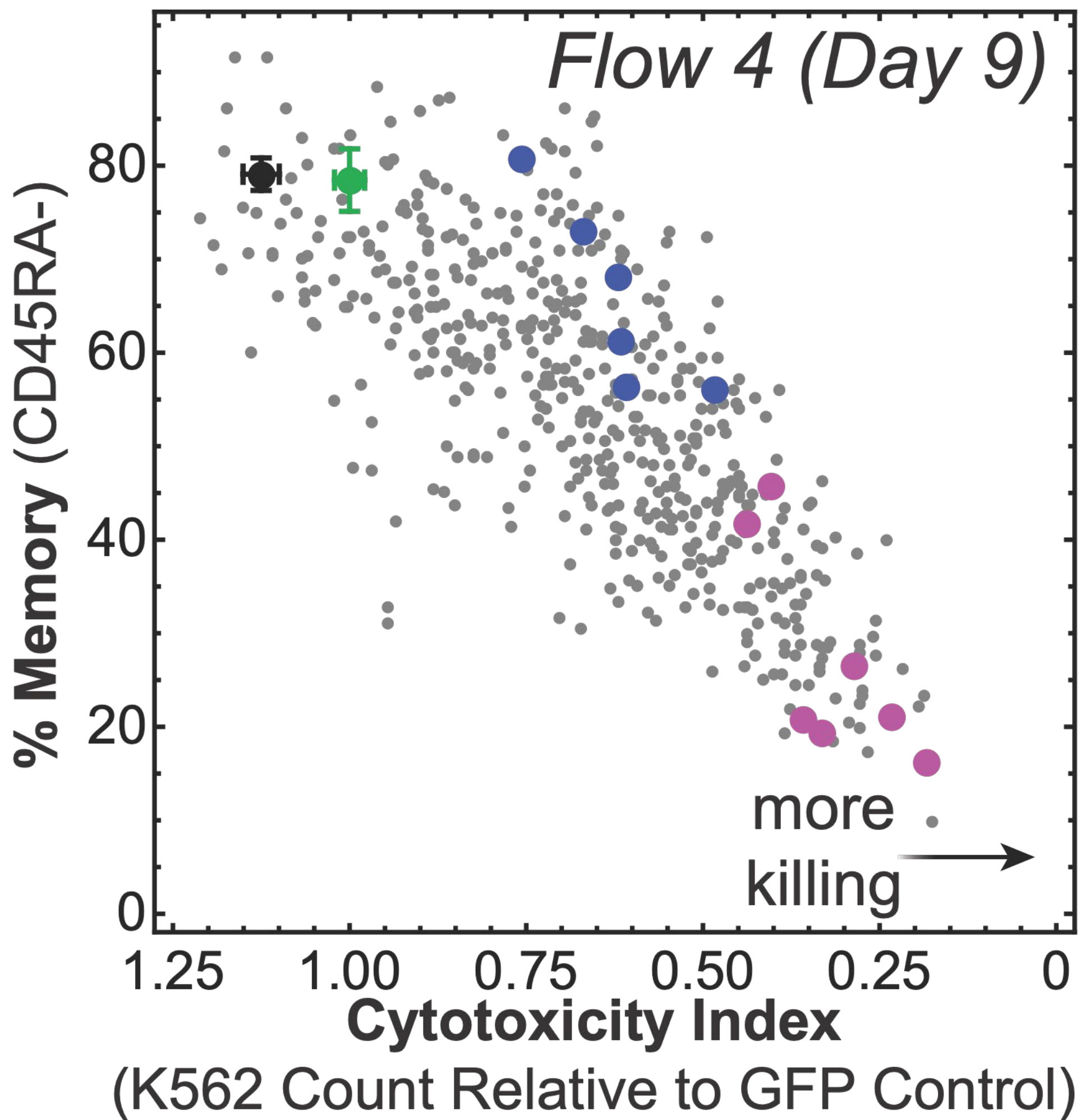
Arrayed screen >450 SCRs

+HER2⁺ K562 target cells

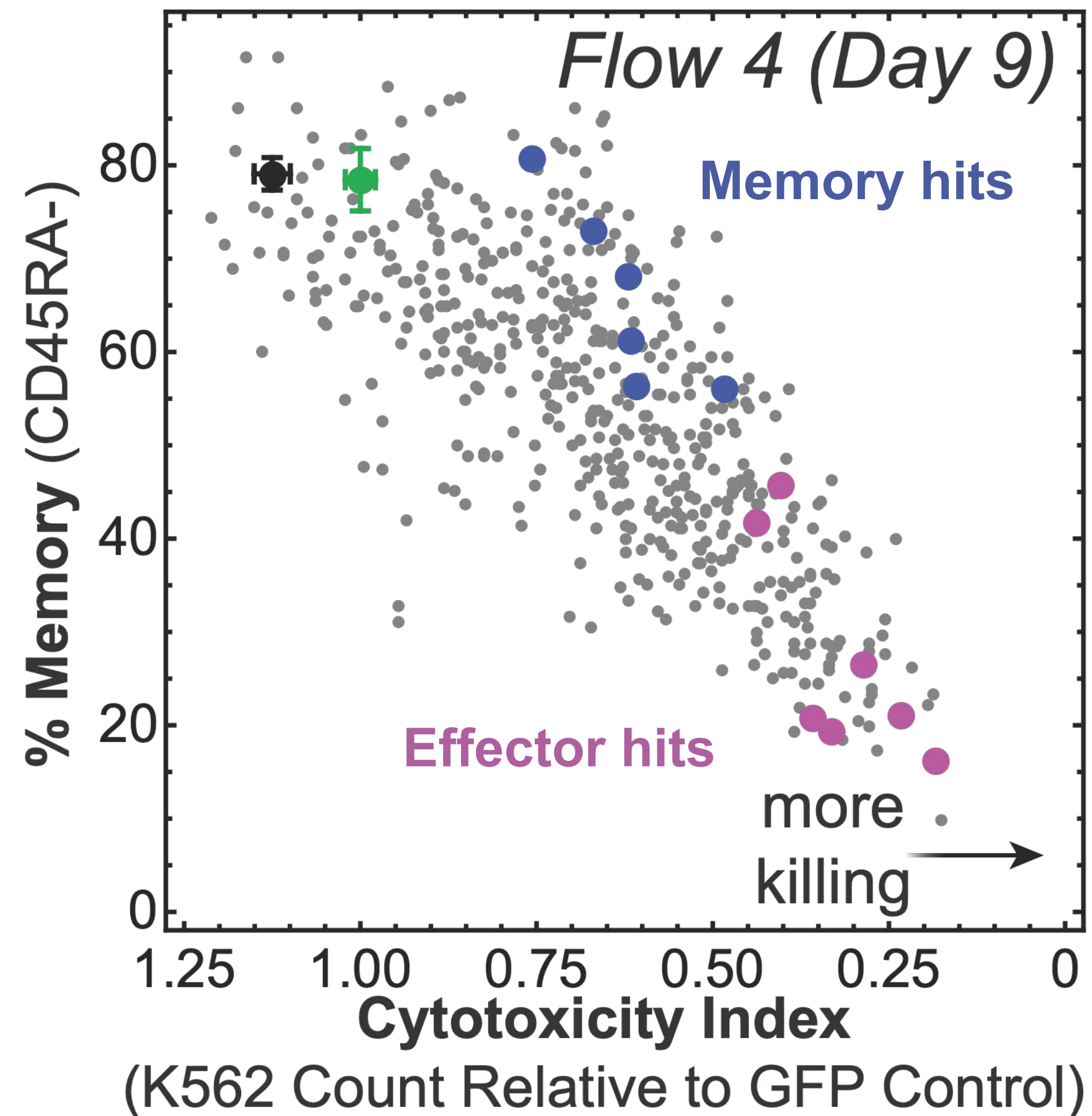


(B, baseline; Ch, challenge; F, flow)

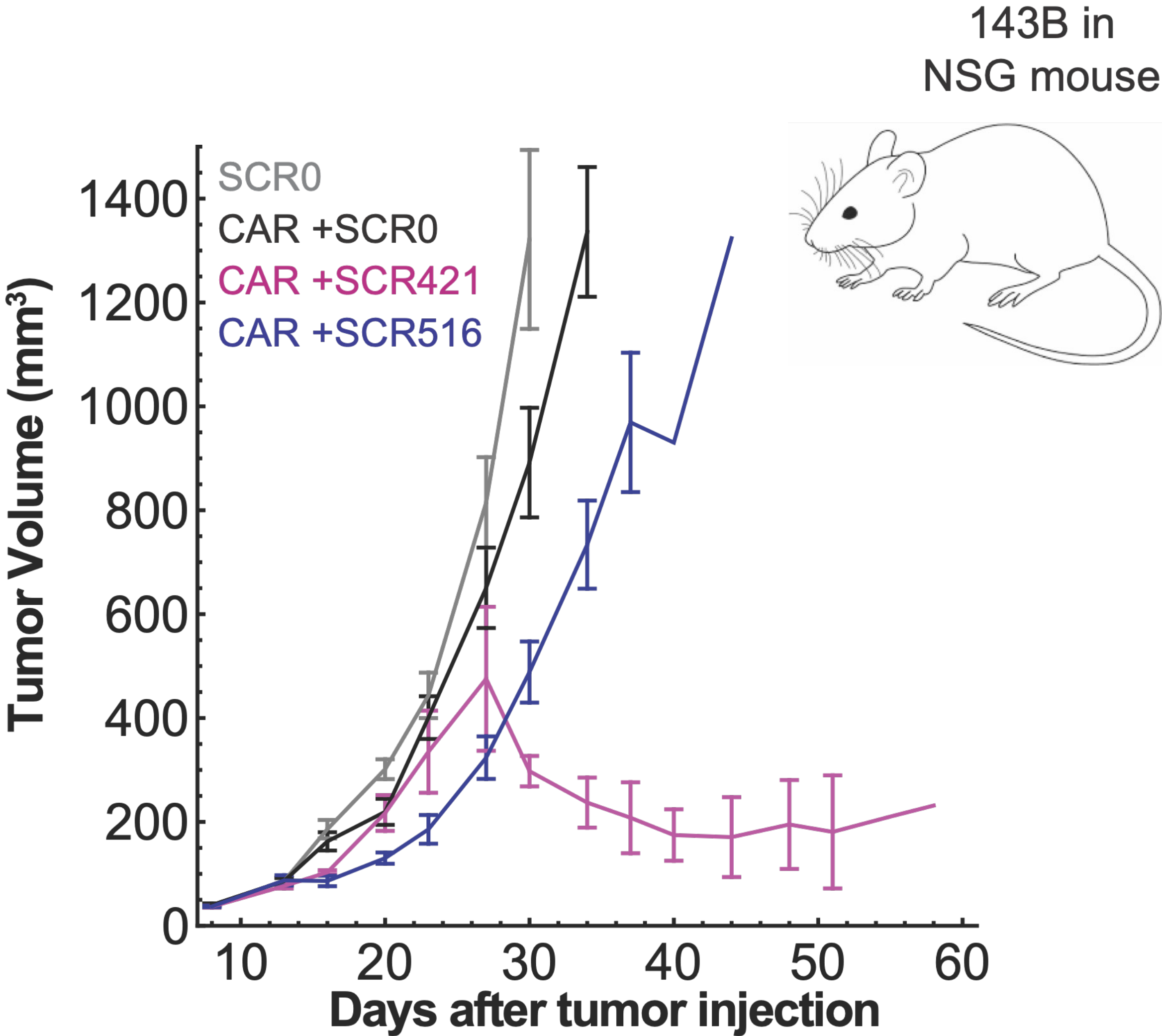
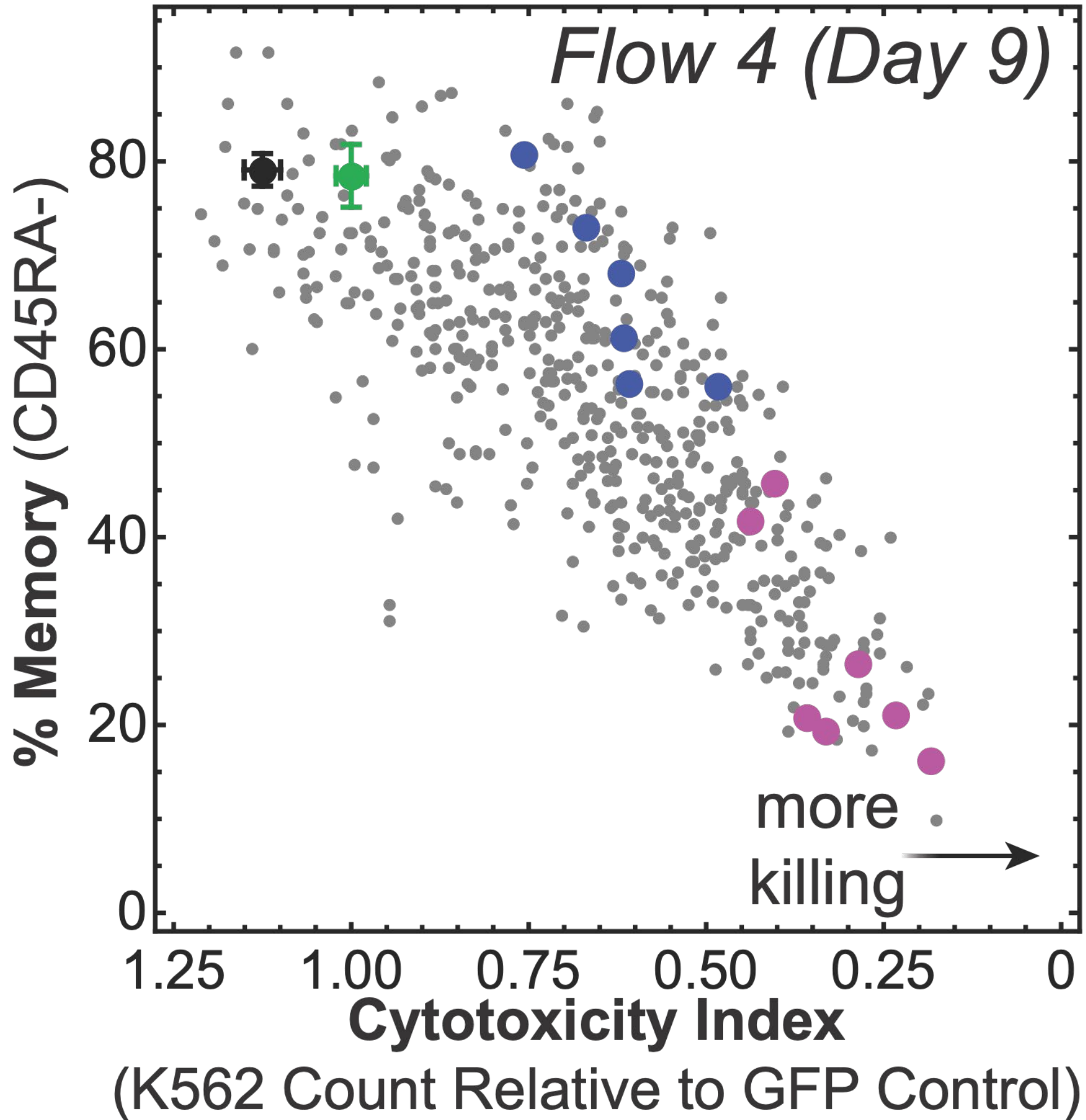
SCRs increase CAR T cell anti-tumor activity



SCRs increase CAR T cell anti-tumor activity

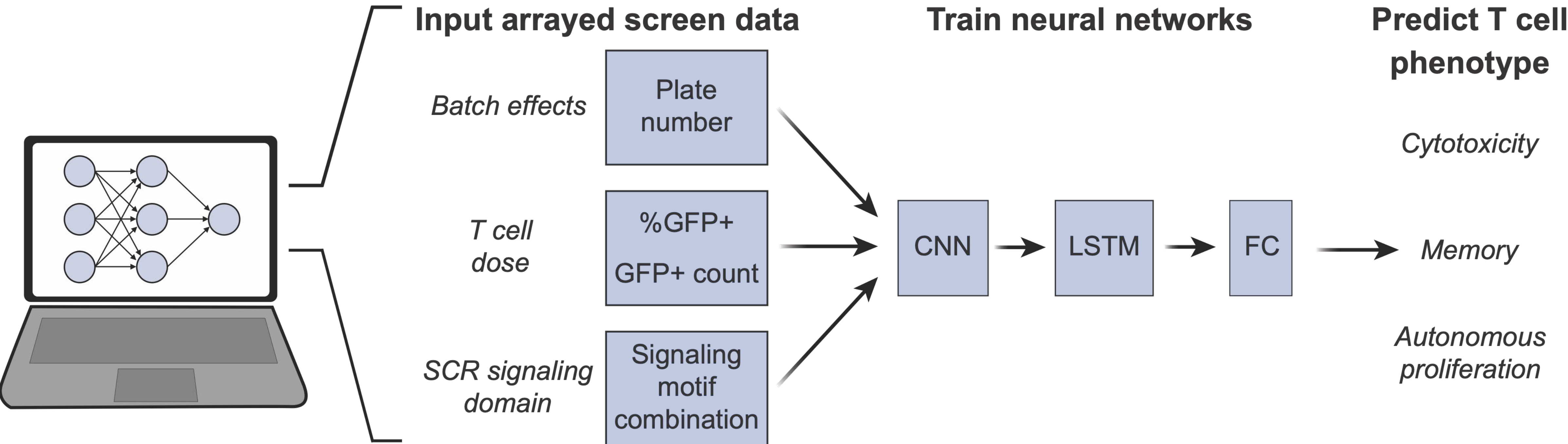


SCRs increase CAR T cell anti-tumor activity

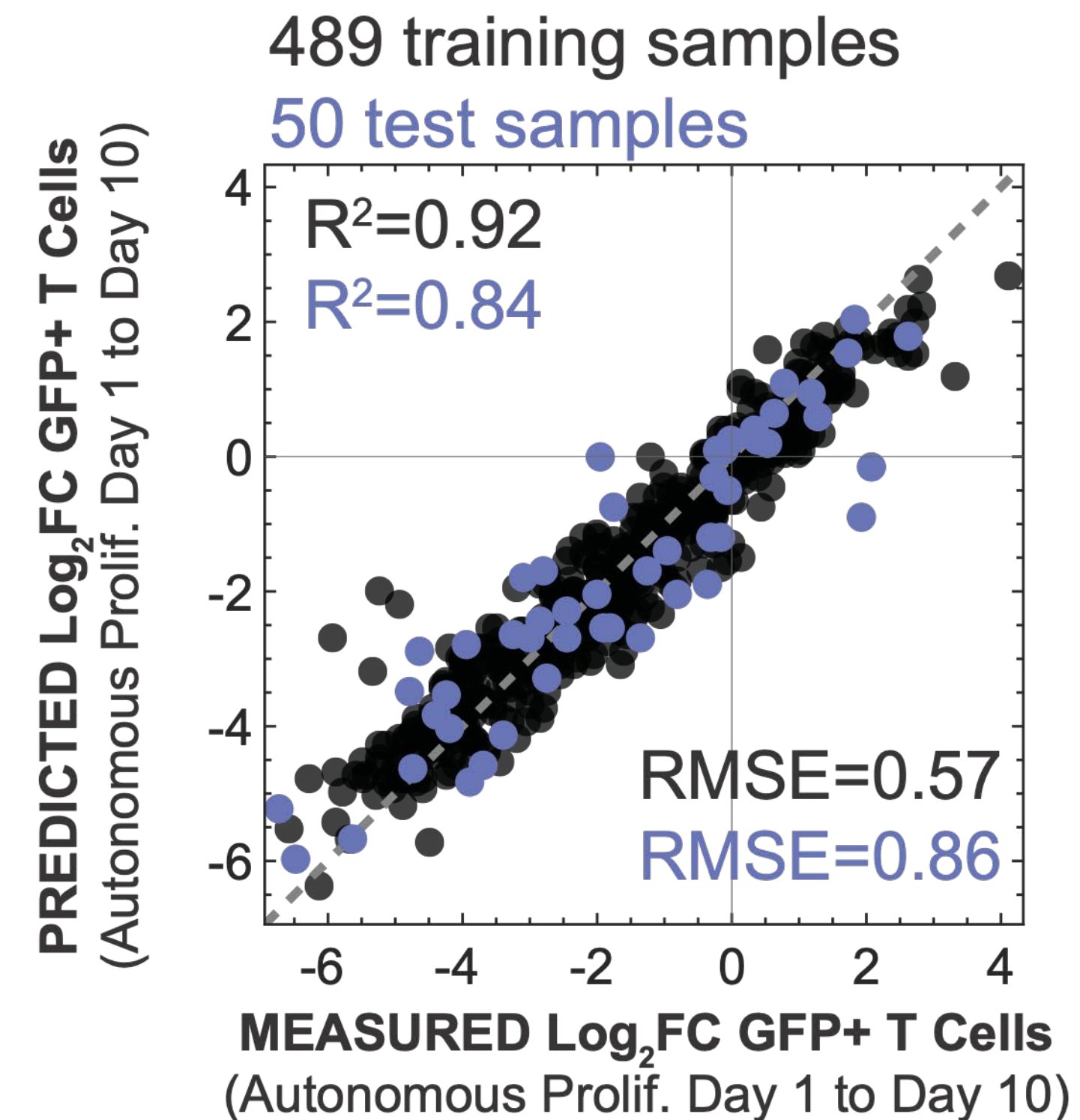
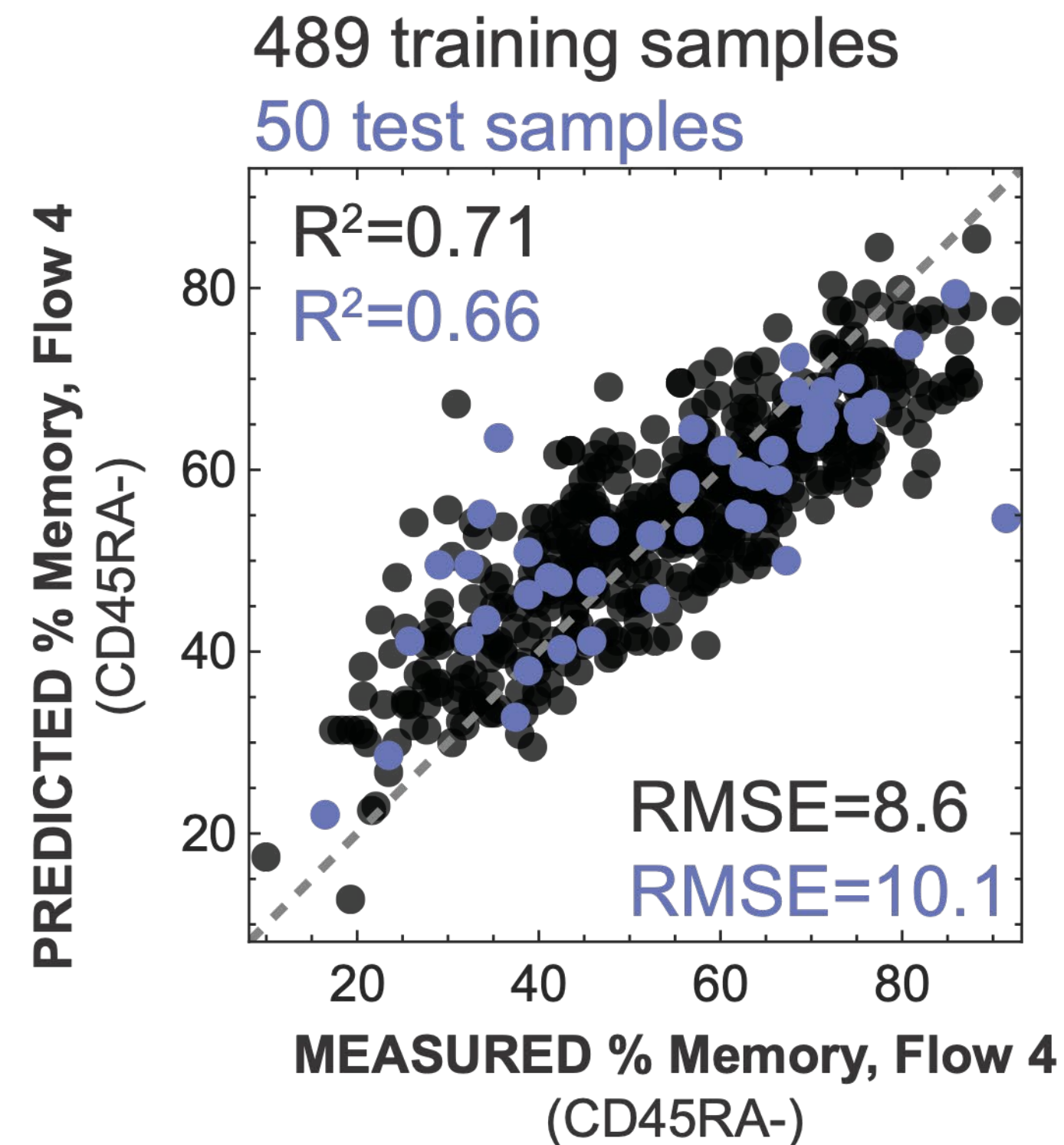
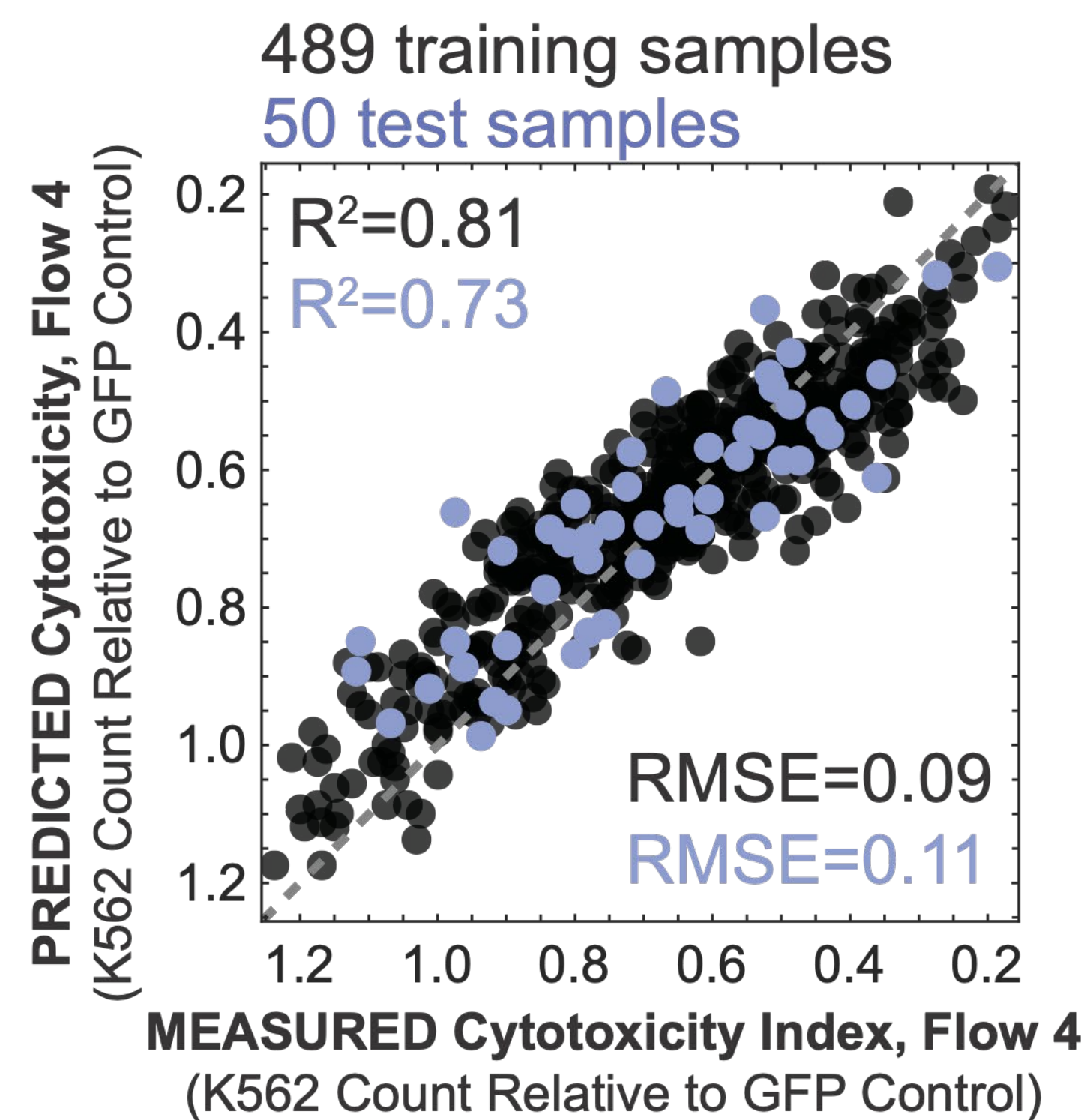


Peng Xu and Elena Sotillo (Mackall Lab)

Neural networks can predict SCR CAR T cell function

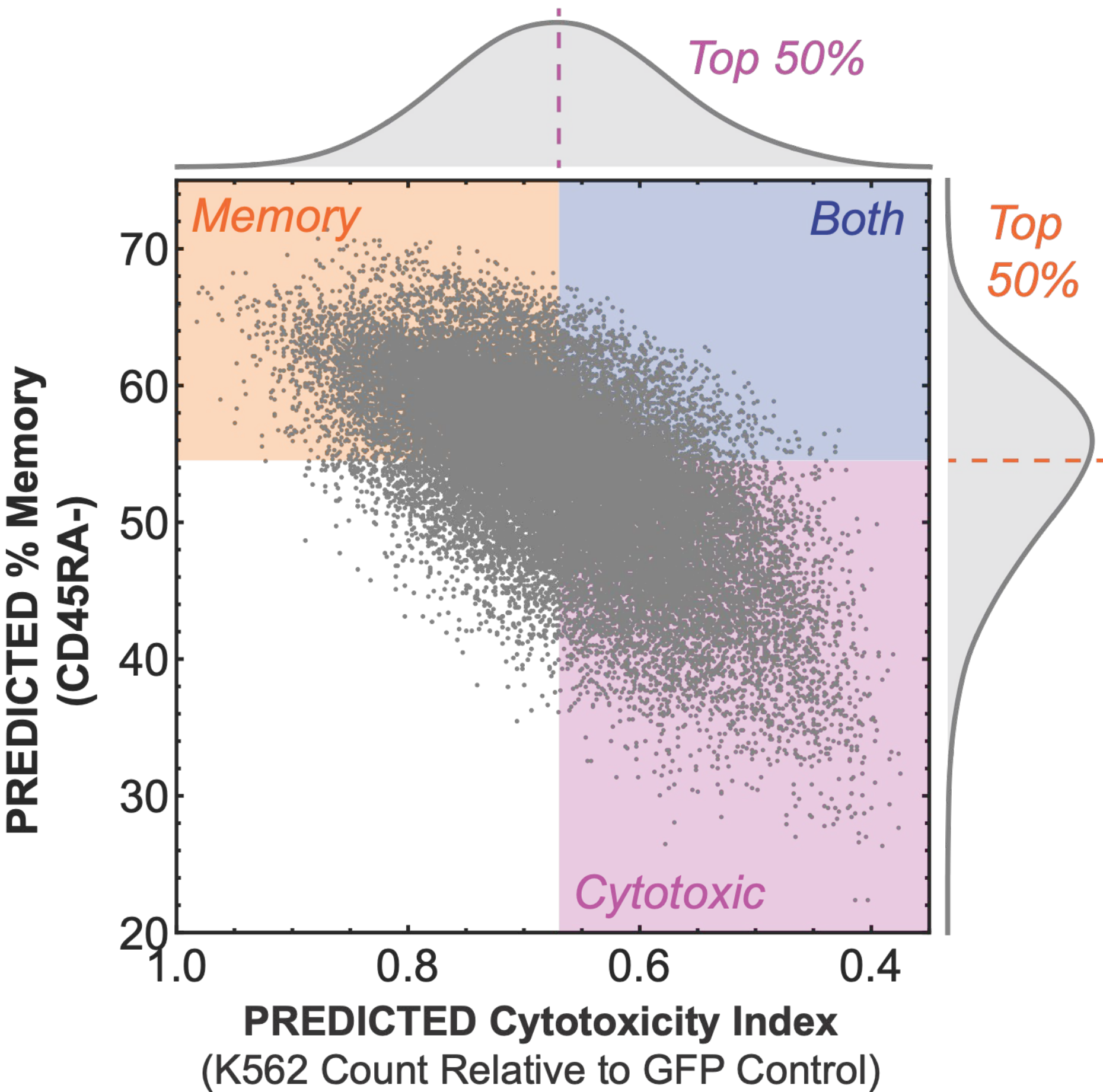


Neural networks can predict SCR CAR T cell function

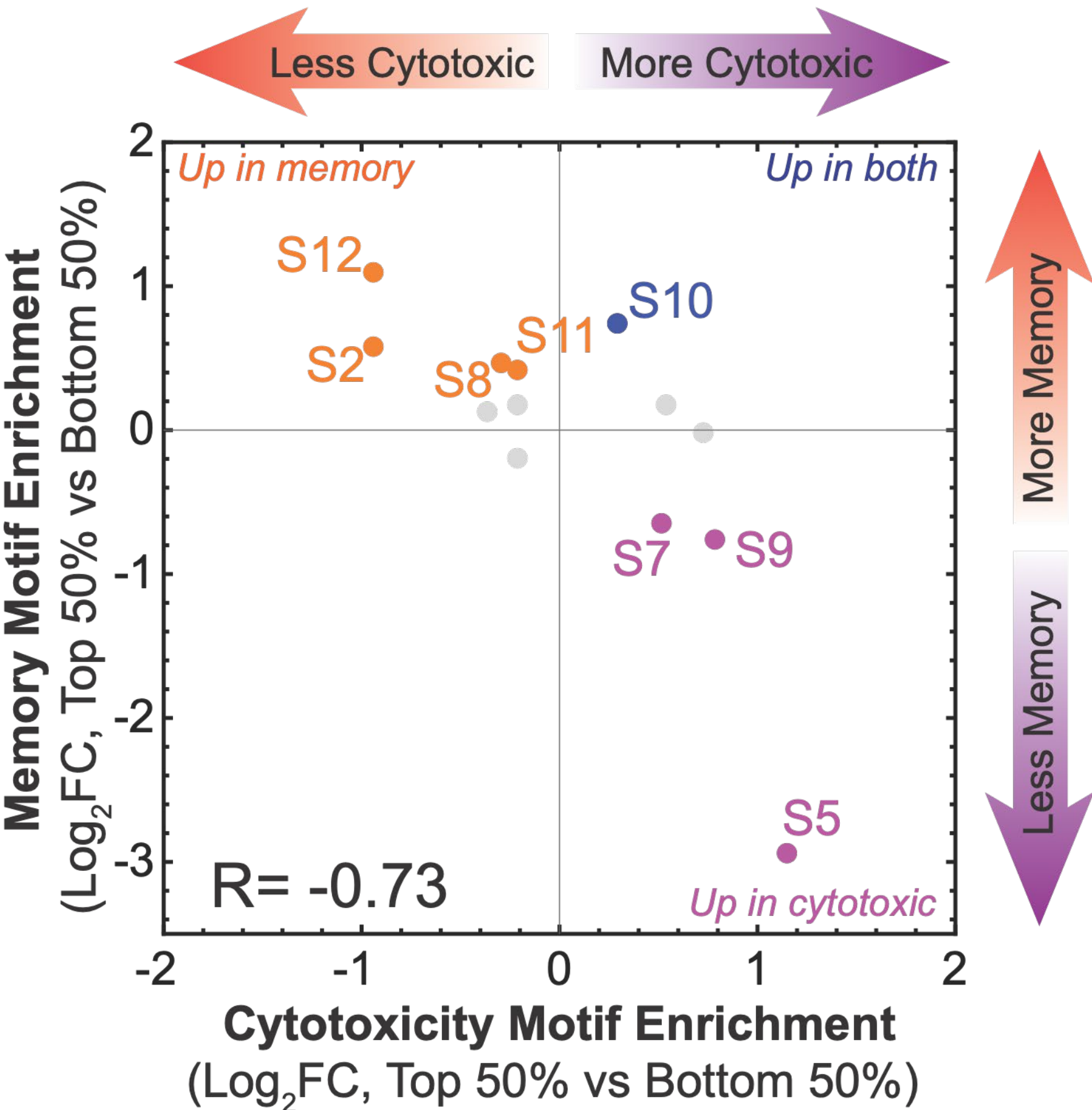


Use neural networks to understand how SCR components influence CAR T cell function

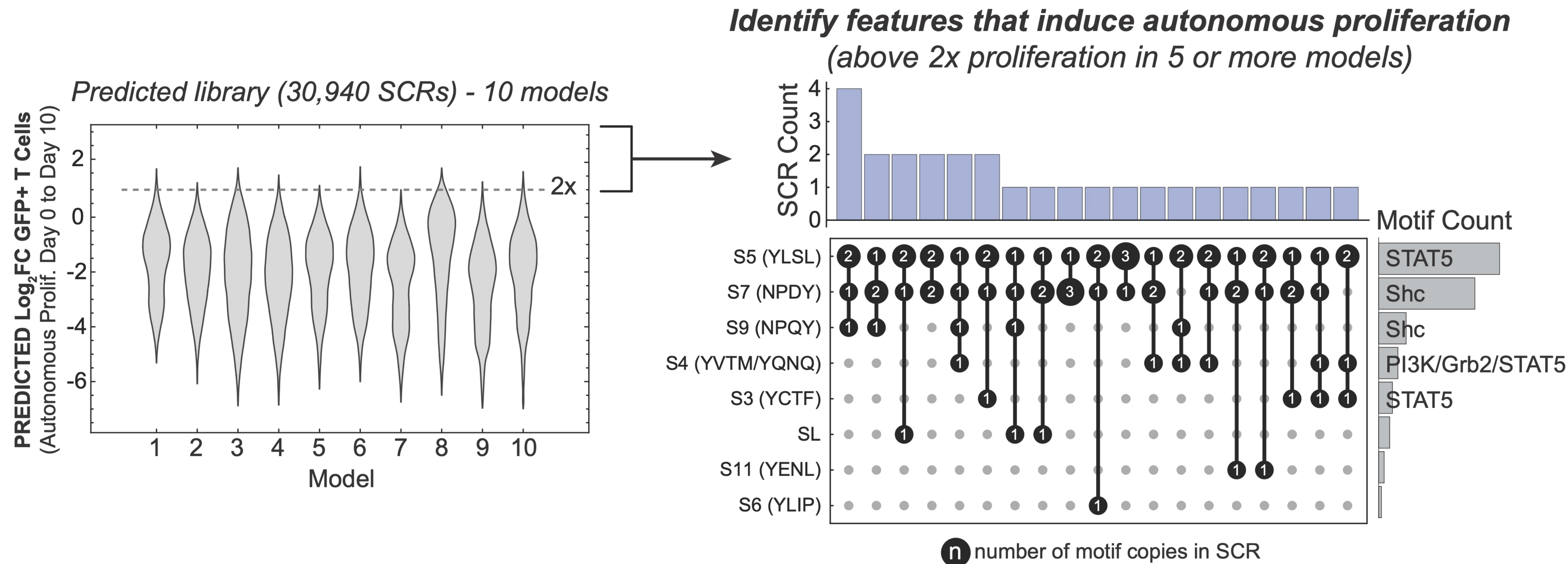
Predicted library (30,940 SCRs)



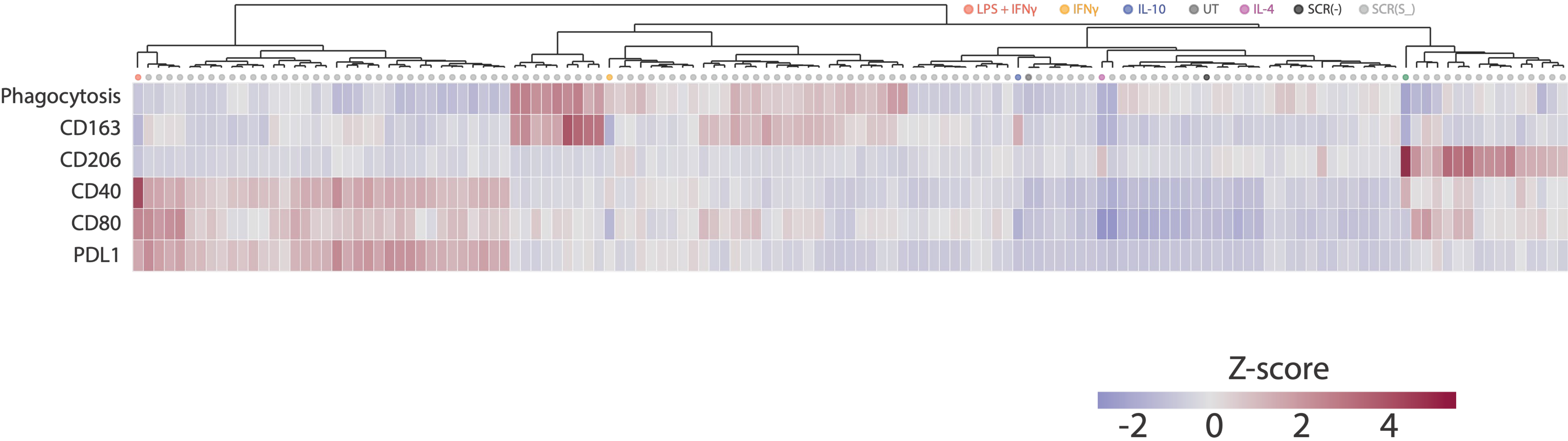
Motif enrichment
Top 50% vs. Bottom 50%



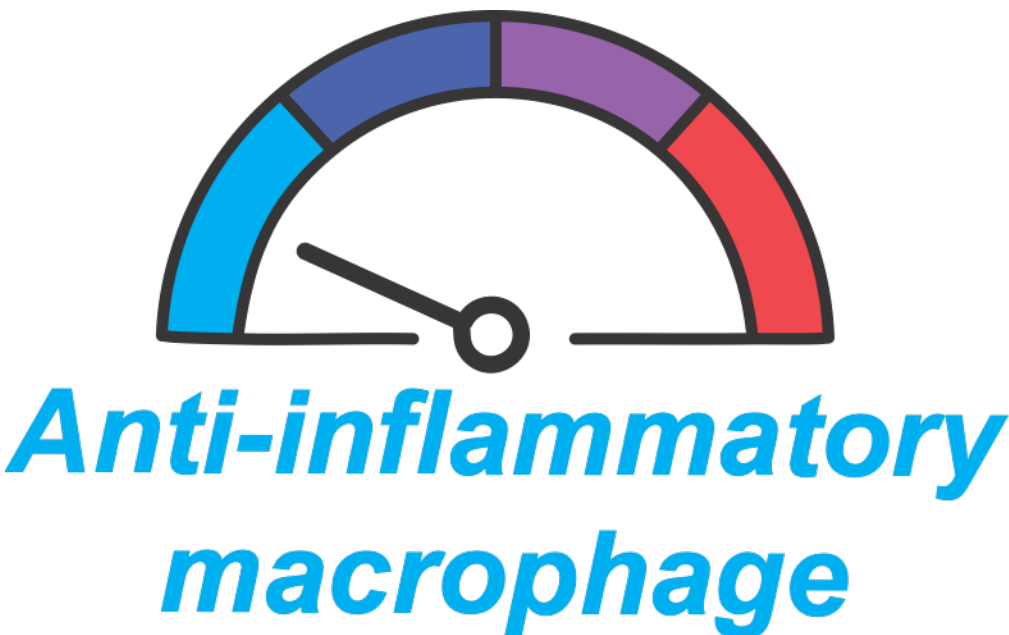
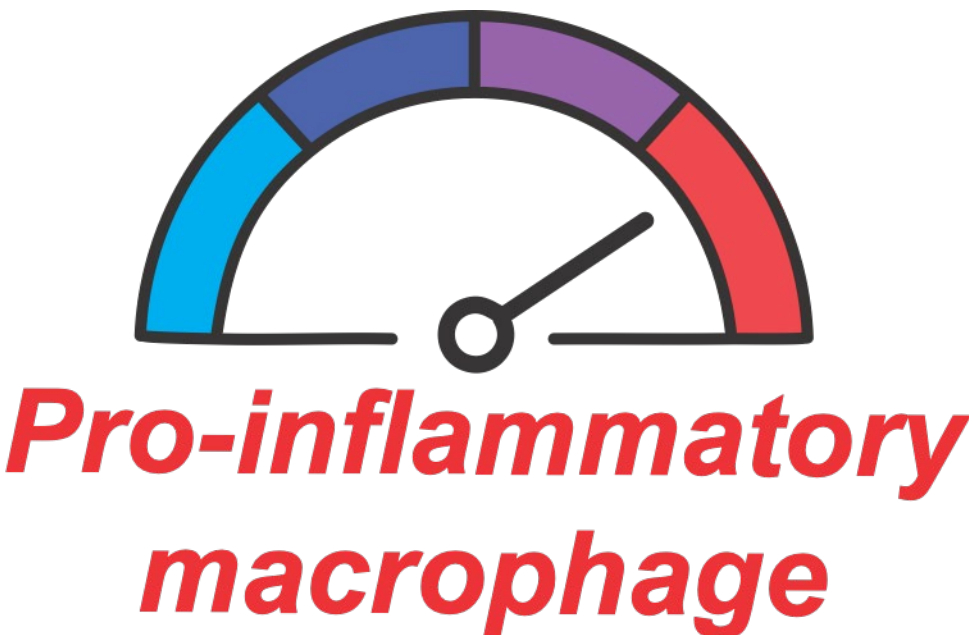
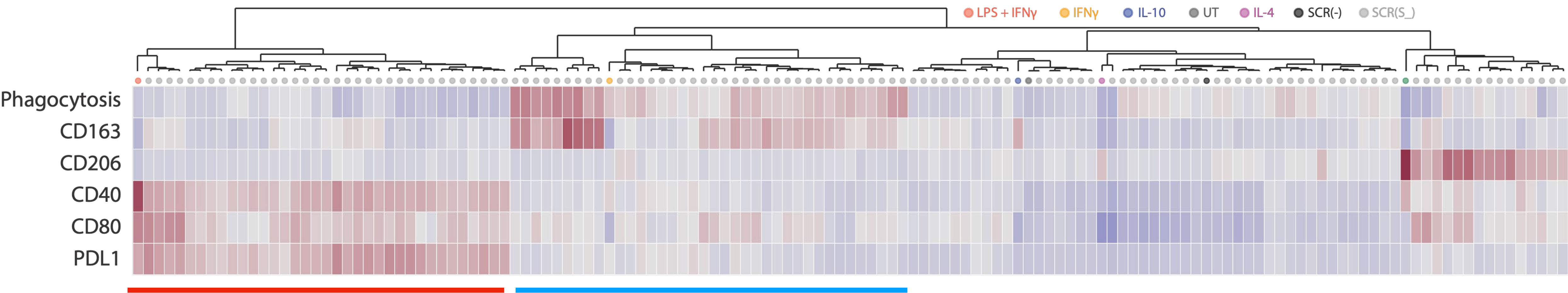
Use neural networks to identify dangerous SCR designs



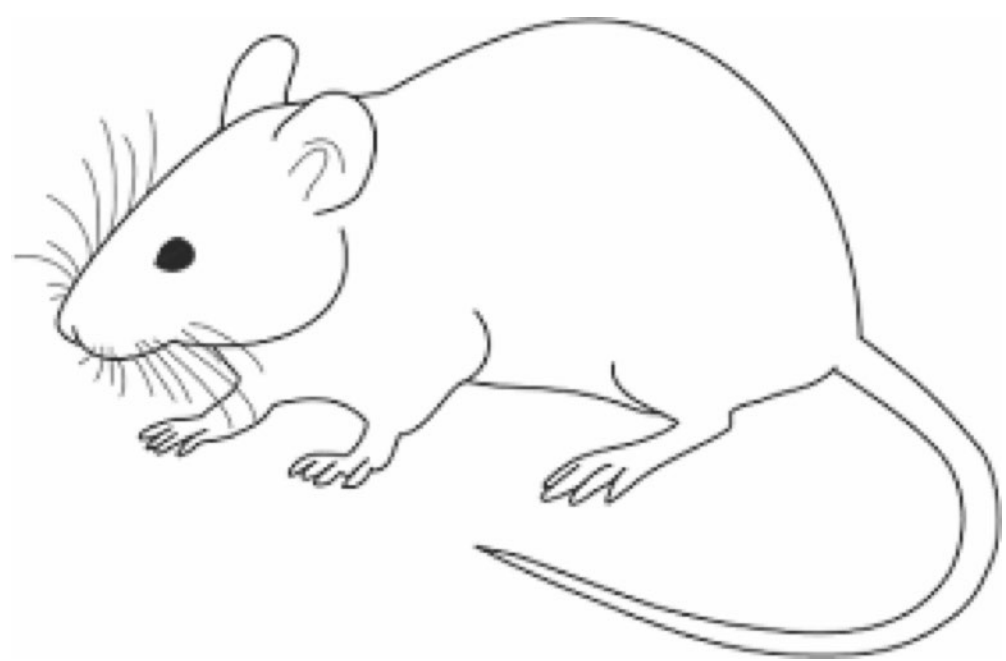
SCRs polarize macrophages to varied cell states



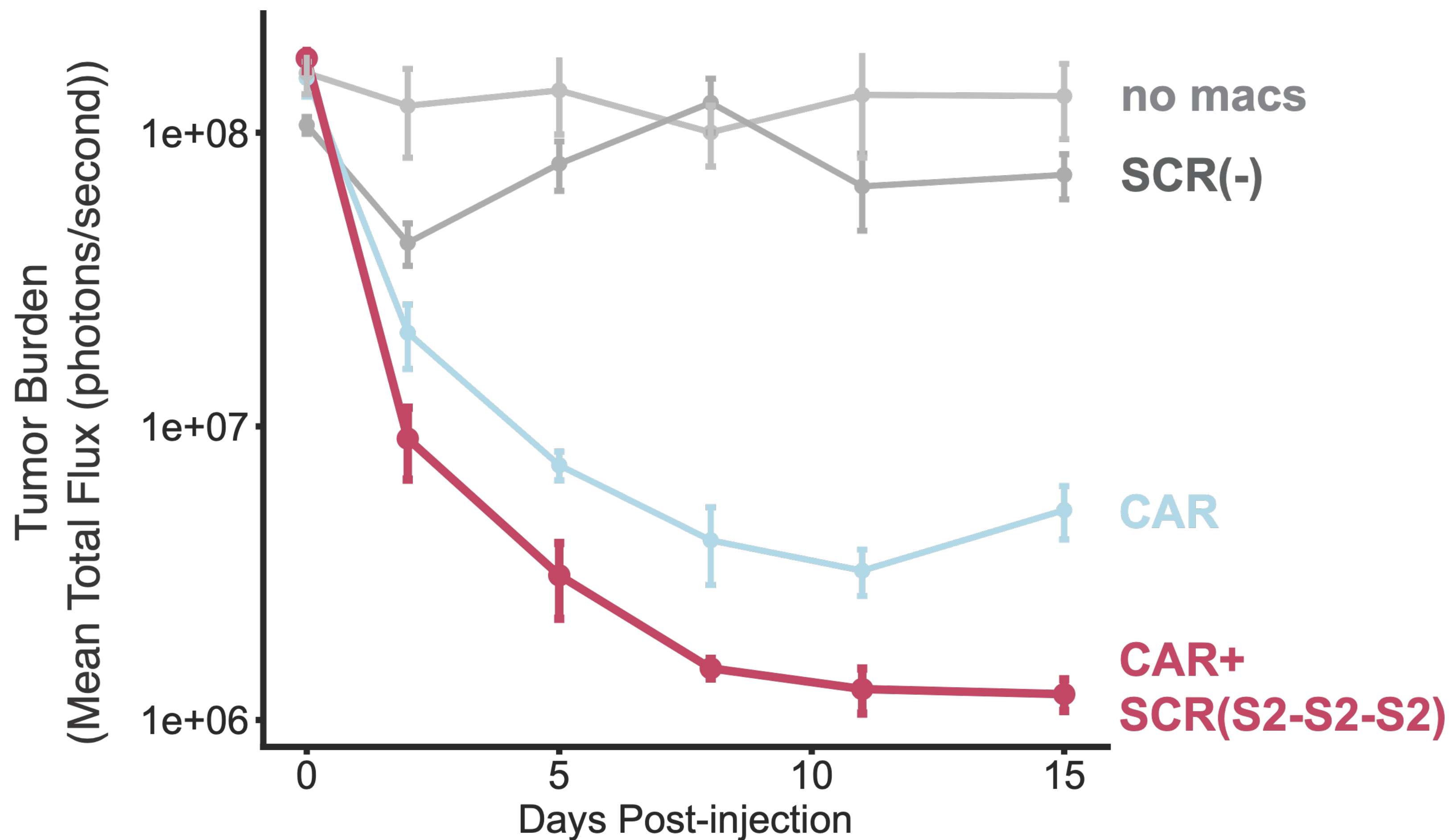
SCRs polarize macrophages to varied cell states



SCRs increase CAR macrophage anti-tumor activity

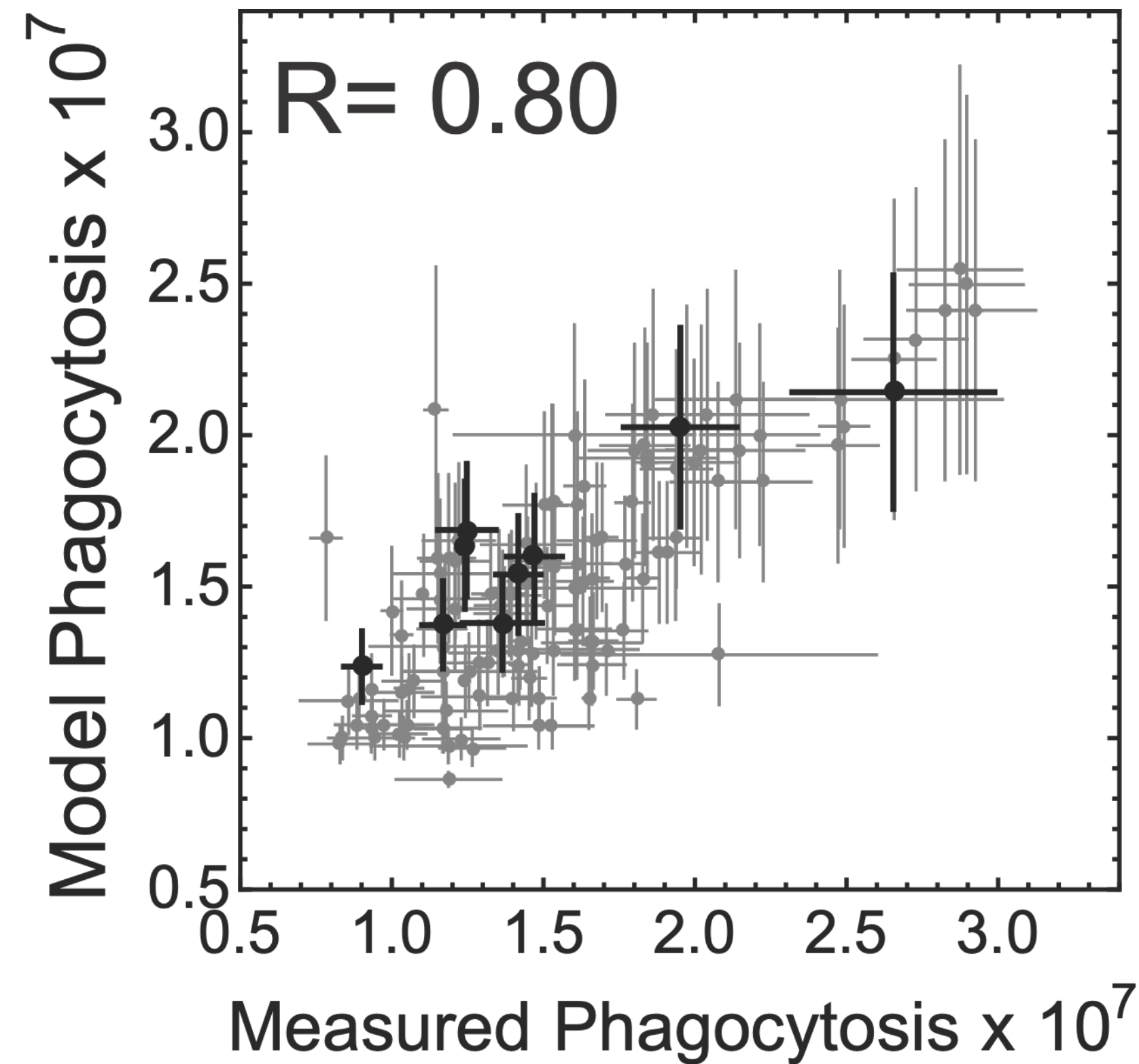


Mice with SKOV3 ovarian cancer

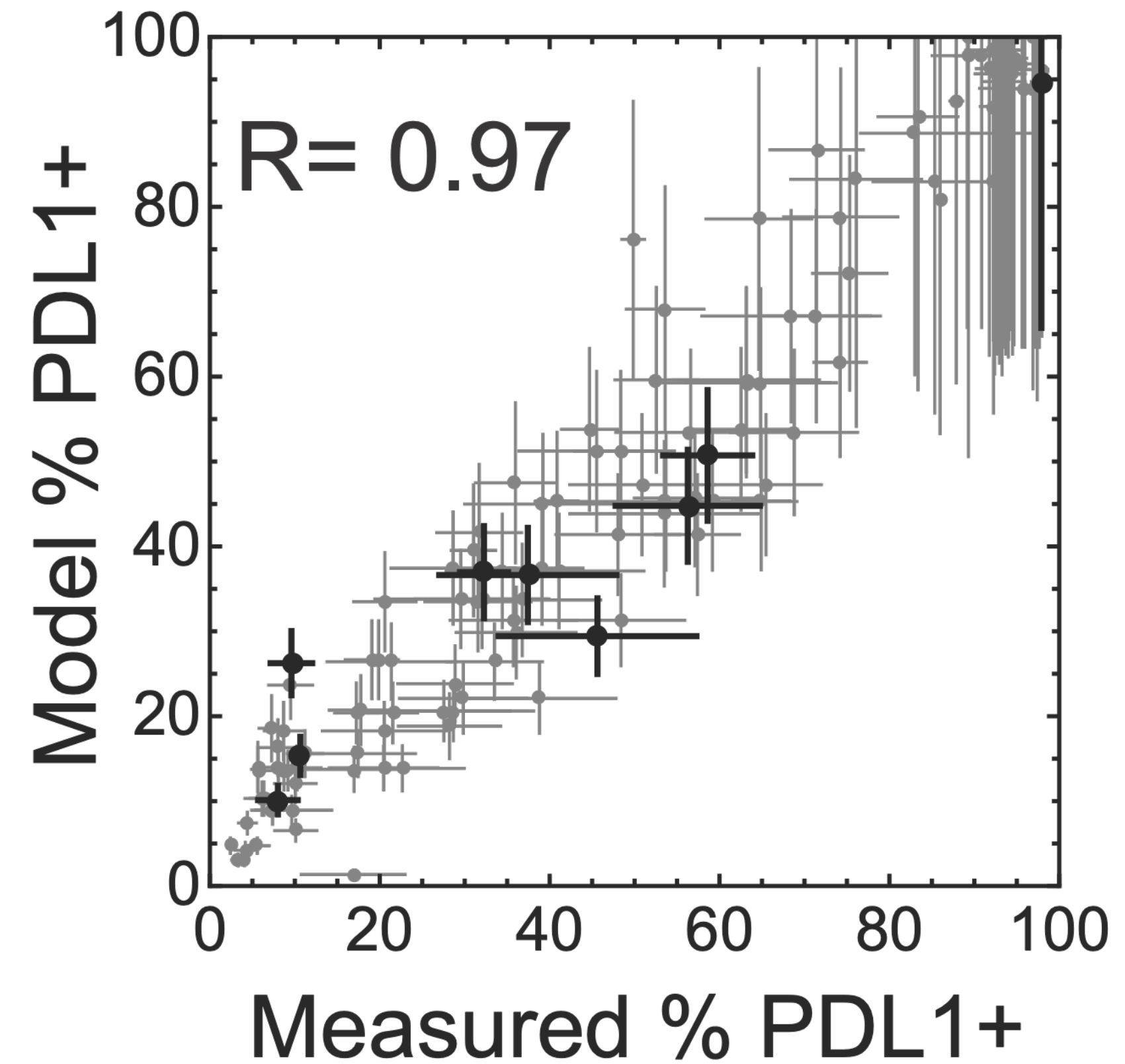


Quantitative models predict SCR macrophage function

Phagocytosis



PDL1



Conclusions

- SCRs enable us to program T cell and macrophage functions
- SCRs provide survival signals that keep CAR T cells alive without cytokines
- CAR T cells and CAR macrophages with SCRs have increased tumor killing abilities
- SCRs generate a broad spectrum of macrophage polarization states
- Neural networks trained on screening data can predict how changes to the SCR will affect immune cell function

Meet the Team



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Jenny Liu



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Jodie Lunger



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Sant'Anna



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Mingxin Gu

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Hernandez-Lopez Lab

Eyquem Lab

Blish Lab

Mackall Lab

Peng Xu

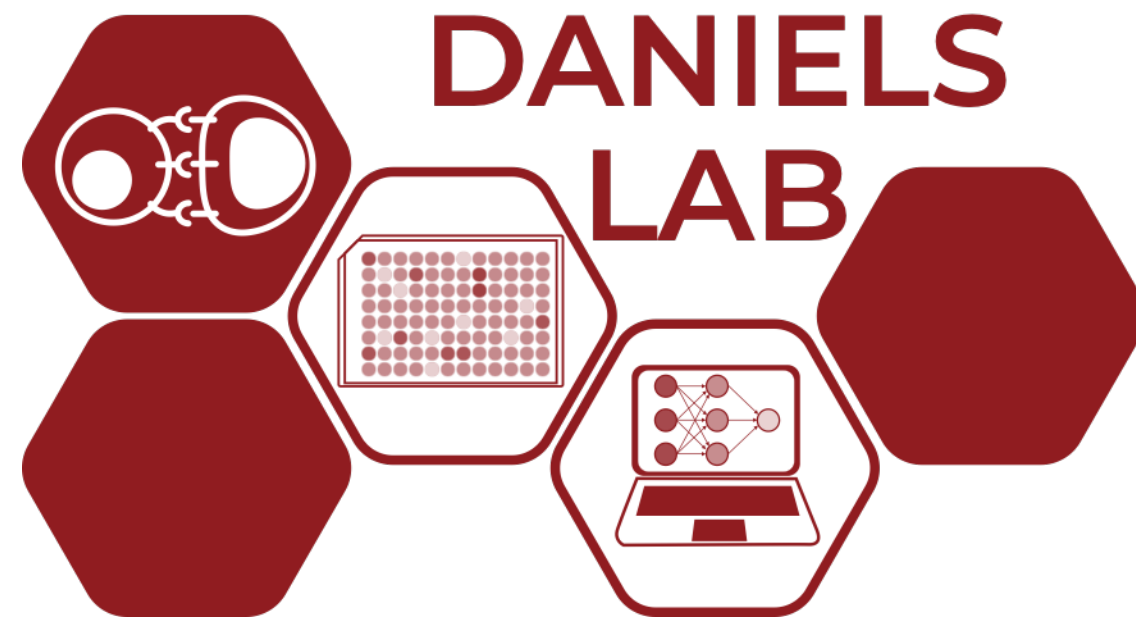
Elena Sotillo

Tibshirani Group

Erin Craig

Min Woo Sun

Thank You



Jenny Liu
Kamal Obbad
Ethan Chen
Kelcey Allen
Sophie Ong

Wansang Cho
Jodie Lungert
Tony Salcido-Alcantar
Lucas Sant'Anna
Vicky Chen

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Tibshirani Lab
Huttenhain Lab

Blish Lab
Satpathy Lab
Michael Lim Lab
Mayalu Lab

