
**Experimental and statistical analysis of synthetic signaling programs
to enhance CAR T cell function**

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Abstract:

Chimeric antigen receptor (CAR) T cell anti-tumor activity improves significantly with signaling provided by cytokine receptors. Thus far, signaling from these cytokine receptors has been limited to natural signaling programs defined by the evolved combinations of short peptide signaling motifs found in natural signaling domains. We hypothesized that recombination of signaling motifs from various receptors could generate synthetic signaling programs that tune CAR T cell phenotypes such as proliferation, cytotoxicity, differentiation, and safety. In this work, we created synthetic cytokine receptors (SCR) that continuously provide user-defined cell signaling through signaling pathways.

We experimentally tested 570 of these SCRs which induced a broad range of CAR T cell phenotypes including enhanced T cell survival and cancer killing.

To understand how the SCR signaling programs encode these CAR T cell phenotypes, we trained models (neural networks, lasso linear regression) that use signaling motif combinations to predict phenotype. These models also provide insights into motif combinations that drive dangerous unstimulated proliferation, enhance cytotoxicity, or promote survival. For example, SCRs with signaling motifs that bind STAT5 enhance cytotoxicity, while combinations of signaling motifs that bind STAT1, 3, and 5 steer cells to CD45RA⁻CD62L⁺ central memory state. These results demonstrate that combinatorial motif engineering of JAK/STAT receptors can be used to tune CAR T cell phenotypes, improve antitumor activity, and increase safety. Furthermore, machine learning-guided design of SCRs that encode desired cell states will enable predictable, precise engineering of immune cell therapies.

Reading List:

- Harnessing the power of artificial intelligence to advance cell therapy