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Modular Synthetic JAK/STAT Signaling Domains to Program Macrophage Function

Researchers at Stanford have developed constitutively active, programmable synthetic cytokine receptors capable of polarizing human macrophages to a variety of user-defined cell states which may be useful for therapeutic applications.

Macrophages exist in virtually all tissues and critically contribute to maintaining homeostasis throughout life. Macrophage polarization status can have an outstanding impact on the immune microenvironment. For example, macrophage polarization into pro-inflammatory states can aid in overcoming immunosuppressive solid tumors, whereas polarization into anti-inflammatory states can wound healing. Thus, control over macrophage behavior would be advantageous for treating disease. Existing approaches to polarize macrophages use cytokines or ligand-dependent receptors (such as switch receptors). These approaches rely on exogenous signals and yield a limited set of polarization states largely dictated by natural signaling domains.

To address these challenges, the lab of Dr. Kyle Daniels has developed synthetic cytokine receptors (SCRs), which are engineered chimeric receptors with short signaling motifs capable of precisely modulating macrophage function. SCRs can be programmed by varying the combination of signaling motifs to induce diversity of macrophage polarization states including those with a pro-inflammatory profile, an anti-inflammatory profile, and those with an increased capacity for phagocytosis of diverse targets. These receptors function independently of extracellular cytokines, enabling sustained control over macrophage activity even in environments containing opposing signals. When co-expressed with chimeric antigen receptors (CARs), SCRs dramatically enhance phagocytosis of cancer cells that express the CAR antigen. SCR expression can decouple myeloid cell polarization from exogenous

signals, resulting in more durable and effective therapeutic responses.

Stage of Development
In-vitro, in NSG mice, quantitative predictive SCR-to-phenotype models available, proof-of-principle

Applications

- Cancer immunotherapy using engineered macrophages
- Enhancement of CAR-macrophage efficacy and persistence
- Cell therapies for neurological and immune-mediated diseases
- A kit that contains the SCRs or cells expressing the SCRs

Advantages

- Customizable macrophage/myeloid cell functions (inflammatory profile and phagocytosis) driven by specific motifs in the SCR signaling domain
- Cell autonomous. Eliminates reliance on external cytokines
- Compatible with existing CAR platforms
- A cost-effective tool for studying cell signaling in macrophages

Publications

- Judith C Lunger, Lucas E Sant'Anna, Antonio Salcido-Alcántar, Rebeca Arroyo Hornero, Wansang Cho, Alun Vaughan-Jackson, Mingxin Gu, Jenny Y Liu, Alex N Beckett, Joaquin Parrilla-Garcia, Sneha Ramakrishna, Michael C Bassik, Kyle G Daniels (2026). Programmable synthetic cytokine receptors polarize macrophages to user-defined functional states." *bioRxiv* 2026.05.12.724672.

Innovators

- Kyle Daniels
- Judith Lunger

Licensing Contact

Minxing Li

Licensing and Strategic Alliances Manager

Email