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Mutant IL-9 Receptor Platform for Enhanced Adoptive T Cell Therapy

Stanford researchers have developed a novel mutant IL-9 receptor (IL9R) that significantly enhances the *in vivo* engraftment, expansion, and anti-tumor activity of adoptively transferred T cells. By increasing the number of engineered T cells within tumors and maintaining a greater proportion of these cells in a stem-like state, the IL9R mutant improves tissue infiltration and sustained anti-tumor efficacy without compromising effector function.

Existing adoptive T cell therapies often require large cell doses and cumbersome conditioning regimens due to the limited *in vivo* expansion and persistence of transferred cells. The IL9R mutant engineered by the inventors addresses these challenges, offering improved expansion from smaller initial T cell numbers and potential for active *in vivo* engineering. By preserving critical downstream signaling *via* STAT3 and STAT5 while selectively attenuating STAT1 activation, which acts as a rheostat between proliferative stem-like and terminally differentiated effector T cell states, the mutant dramatically improves both T cell proliferation and anti-tumor effector activity. Additionally, the IL9R intracellular domain harboring the mutation can be deployed modularly within other receptor constructs to promote expansion, stemness, and tumor infiltration across diverse cellular therapies. This approach has immediate translational relevance to TCR-engineered T cells and CAR T cell products aimed at treating hematologic and solid tumors, leveraging optimized signaling to reduce the toxicity and markedly enhance the efficacy of adoptive cell therapies.

Stage of Development
Proof of concept — *in vivo* data

Applications

- Enhanced adoptive T cell therapies for solid tumors, hematologic malignancies and other cancers, including TCR-T and CAR-T cells
- Cell therapies requiring improved T cell expansion, infiltration, and persistence
- *In vivo* T cell engineering approaches with limited starting cell numbers
- Modular intracellular domain engineering for synthetic receptor design

Advantages

- Improved *in vivo* T cell expansion, persistence, and tumor infiltration from low initial cell doses, resulting in superior anti-tumor activity
- Selective STAT pathway modulation optimizes T cell proliferation and differentiation to maintain anti-tumor effector function while preserving stem-like T cell states
- Reduced dependence on dosage-related conditioning requirements such as lymphodepletion and systemic cytokine administration
- Enhanced safety profile and therapeutic window relative to existing therapies
- Modular design enables integration into diverse cellular engineering platforms

Publications

- Jiang et al. (2025). IL-9 as a naturally orthogonal cytokine with optimal JAK/STAT signaling for engineered T cell therapy. *Immunity* (2025).

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