Treatment for uncontrolled T Cell Receptor Activation

Immune Modulators Targeting TCR-LCK Protein-Protein interaction

Technology

Excessive or dysregulated T-cell activation is a central driver of many autoimmune and inflammatory diseases, graft-versus-host disease (GVHD), transplant rejection and severe toxicities of modern T-cell based immunotherapies such as CAR-T cells. Current LCK kinase inhibitors are poorly selective and broadly suppress Src-family kinases, which limits their clinical utility where precise immune modulation rather than global immunosuppression is required.

Prof. Minguet's team has discovered a unique, druggable interaction between the SH3 domain of the kinase LCK and the receptor kinase motif within the CD3ε subunit of the T-cell receptor (TCR). By high-throughput in silico screening and extensive *in vitro* validation, they identified small molecules that bind to the SH3 domain of LCK and selectively disrupt its interaction with CD3 without blocking LCK's catalytic activity. Lead compound C10 inhibits TCR-driven signaling, T-cell activation and proliferation, while sparing IL-2-driven T-cell responses, B-cell activation, myeloid cell activation and TCR-independent pathways, thus offering unprecedented selectivity for TCR-mediated signaling. The development is still ongoing and exciting new compounds were discovered since filing the patent application.

The main envisioned applications are targeted immunomodulation of pathological T-cell responses in autoimmune and inflammatory diseases, and prevention and control of harmful allogeneic T-cell activity in transplantation and graft-versus-host disease. In addition, the compounds enable pharmacological tuning of engineered T-cell therapies to improve safety, durability and clinical manageability.

For patients, this technology promises more precise control of pathogenic T-cell activity with a lower risk of systemic immunosuppression, potentially reducing flares, organ damage and life-threatening complications of cell therapies while preserving protective immunity. For physicians, it offers a novel mechanism-based tool to fine-tune T-cell responses across a broad spectrum of indications, including as an on-demand, reversible safety and performance switch for engineered T-cell products.

The target markets include large, growing segments such as autoimmune and inflammatory diseases, GVHD and transplantation, as well as the fast-expanding CAR-T and engineered T-cell therapy market. Because the compounds act on a newly validated, highly T-cell-specific protein-protein interaction, they have strong differentiation potential as first-in-class SH3LCK modulators for both systemic therapies and advanced immuno-oncology products.

The technology is open to licensing, as well as for co-development with the inventors.

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Innovation

- Selective, tunable down-modulation of TCR-mediated T-cell signaling via disruption of the LCK–TCR protein-protein interaction.
- First-in-class small molecules targeting the SH3 domain of LCK rather than its conserved kinase domain, enabling high pathway specificity.
- Lead compound C10 shows potent inhibition of TCR-driven activation and proliferation while sparing B cells, myeloid cells and TCR-independent T-cell pathways, supporting an improved safety profile.
- Pharmacological “fine-tuning” of CAR/TRuC T-cell activity and phenotype, allowing better control of efficacy, toxicity and exhaustion without permanent genetic changes.

Application

- Treatment of T-cell-driven autoimmune and chronic inflammatory diseases, including rheumatoid arthritis, multiple sclerosis, psoriasis, inflammatory bowel disease and type 1 diabetes, where selective TCR-pathway dampening is desired.
- Prevention or mitigation of graft-versus-host disease and solid-organ allograft rejection by suppressing alloreactive T-cell activation while preserving graft-versus-leukemia activity.
- On-demand control of CD3-containing CARs and TRuC T-cell products to reduce cytokine release syndrome, neurotoxicity and other toxicity associated with excessive activation.
- Use as a reversible “resting” agent during CAR-T manufacturing to promote central-memory-like CAR-T phenotypes and improve CAR T cell persistence without compromising cytotoxic function.

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Further Reading

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