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Synthetic Circuits for Engineering T cells that Overcome Heterogeneity in Neuroendocrine Tumors

Stanford scientists have discovered a novel method for treating neuroendocrine tumors by engineering T cells with Synthetic Notch (SynNotch) circuits that enable precise and durable tumor targeting while overcoming antigen heterogeneity.

Heterogeneity in tumor antigen expression is a major challenge in the development of effective cell-based immunotherapies, often resulting in incomplete tumor clearance and poor clinical outcomes. Small-cell neuroendocrine tumors (SCNTs), including small-cell lung cancer (SCLC), have particularly limited therapeutic options due to their pronounced antigenic heterogeneity. Researchers at Stanford have engineered synthetic T cell circuits that leverage a SynNotch receptor responsive to the cancer-specific antigen DLL3, a marker expressed on the surface of SCNTs but absent on healthy cells. Upon DLL3 binding, the SynNotch induces the expression of chimeric antigen receptors (CARs) that target a broad spectrum of tumor-associated antigens. This novel design ensures that CAR expression is spatially restricted to DLL3-positive tumor sites, enhancing tumor specificity while expanding coverage against heterogeneous cancer cell populations. Importantly, SynNotch anti-DLL3 CARs outperform traditional CAR therapy in vitro as a result of the expanded antigenic coverage. By coupling precise antigen recognition with controlled and inducible CAR expression, this approach offers a powerful strategy to improve the efficacy and safety of T cell therapies for SCNTs.

Stage of Development: *In vivo* mouse flank xenograft model

Applications

- Cell therapy for SCLC

- Other SCNT cancers

Advantages

- Enhanced specificity
- Improved safety
- Overcomes antigen heterogeneity
- Modular design

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