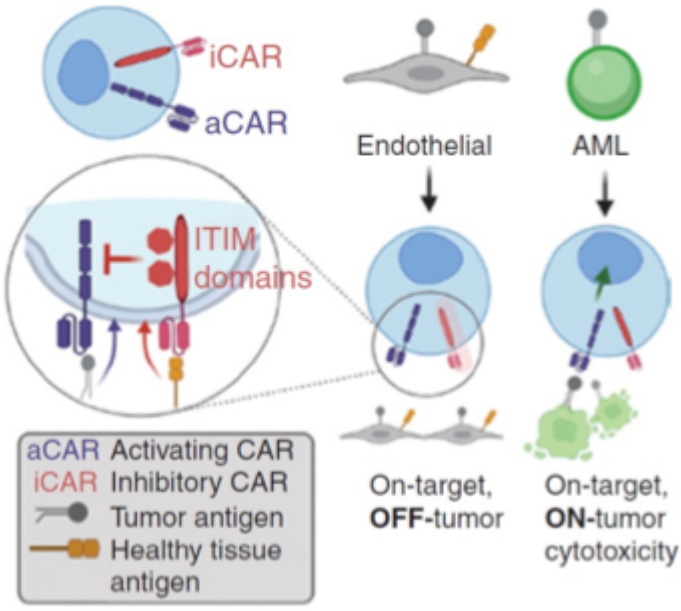
Docket #: S21-214

NOT-gated CAR T Cells to Ameliorate On-target, Off-tumor Toxicity of CAR T Therapy

Stanford scientists have developed novel, inhibitory chimeric antigen receptor T cells (iCARs) based on immunoreceptor tyrosine-based inhibitory motif (ITIM)-containing signaling domains that can inhibit standard activating CAR (aCARs) activity **(see figure* below)**.

Chimeric antigen receptor (CAR) T cells are a promising therapeutic option, especially for cancers like acute myeloid leukemia (AML) with high mortality and relapse rates. However, the phenomenon of "on-target, off-tumor" toxicity is a barrier to clinical translation of many CAR T cells, including CD123 CAR T cells targeting AML. Combinatorial CAR T cells based on logic gating, including NOT-gated CAR T cells, can address this problem. NOT-gated CAR T cells have a tissue or antigen-specific inhibitory mechanism that limits CAR T cell killing of healthy tissues that may share expression of the main CAR target antigen while maintaining their ability to kill on-target tumor cells. Stanford researchers have developed inhibitory CARs (iCARs) based NOT-gated CAR T cells to circumvent CAR–mediated endothelial cell toxicity. This approach could allow CAR T therapy to safely target new antigens and new cancers.

***Figure:**



Stage of Development
Research - in vitro

Applications

- NOT-gated CARs to ameliorate on-target, off-tumor toxicity of CAR T cells

Advantages

- Reduced toxicity to healthy cells, increasing the safety of CAR T therapies
- Maintains CAR T cell therapy efficacy against cancer cells
- Increased breadth of tumor antigens that can be targeted by CAR T cells

Publications

- Rebecca M. Richards, Feifei Zhao, et al. (2021). NOT-Gated CD93 CAR T Cells Effectively Target AML with Minimized Endothelial Cross-Reactivity. *Blood Cancer Discov, 2* (6): 648–665.

Patents

- Published Application: WO2023044350
- Published Application: 20240390497

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