Cellular Therapies

442-A OPTIMIZATION AND VALIDATION OF NOVEL CHIMERIC ANTIGEN RECEPTOR (CARS) ARCHITECTURES FOR THE TREATMENT OF LEUKEMIA AND BEYOND

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Background One avenue of recent research has focused on harnessing the patient's immune system to eradicate tumors called immunotherapies. To do so, T cells from a cancer patient are harvested and genetically modified to express a chimeric antigen receptor (CAR), capable of recognizing tumor cells, then reinfused into the patient. CARs are synthetic transmembrane proteins composed of a tumor-targeting domain, a membrane anchoring domain and a complex signaling domain to activate T cells promoting tumor cell killing. These therapies have shown exceptional results in the treatment of young patients with leukemia and lymphoma. We hypothesize that CAR-based immunotherapy complications arise from faulty CAR architecture resulting in an aberrant immune response.

Methods To mitigate this, we have developed a new CAR architecture through functional screening, which mimics natural immune receptor assembly and surface expression. These new modular CARs (mCARs) show better efficacy in signaling and killing tumor cells compared to the standard of care (SOC-CAR). More so, mCARs are compatible for hematopoietic stem cell-based treatment avenue as mCAR-HSC are able to differentiate into a myriad of immune cells enable the deployment of an effector cell armada against target cells.

Results We are currently optimizing the signaling cues provided by mCARs by introducing new signaling motifs and benchmarking them to SOC-CAR in clinically relevant mouse tumor models. Additionally, we are screening novel signaling domains to improve tumor cell killing, functionality and longevity. Finally, these results will allow us to pick the best combination of signaling motif provided by the mCAR that result in an increase treatment outcomes and decrease in complications.

Conclusions Together, the findings made here will help determine the efficacy of the newly optimized mCARs in maintaining cell survival and functionality and set the framework for their clinical implementation.

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