Advances with Switchable CAR-T Cells

David T Rodgers[1], Eduardo Laborda[1], Elvira Khialeeva[1], Magdalena Mazagova[1], Eric N. Hampton[1], Sophie Viaud[1], Christopher Ackerman[1], Ashley K Woods[1], Peter G Schultz[1,2], Travis S Young[1]*

[1]Biology Department, California Institute for Biomedical Research, La Jolla, CA 92037
[2]Department of Chemistry and the Skaggs Institute for Chemical Biology, The Scripps Research Institute, La Jolla, CA 92037

To improve the control of CAR-T cells with the goal of overcoming associated toxicities and tumor resistance mechanisms, we have designed a switchable CAR-T cell platform using antibody-based molecular switches. This platform is differentiated from other antibody-based redirection strategies in that the interaction between the switch and CAR is bio-orthogonal, enabling highly specific and fully tunability control of the CAR-T cell towards any tumor associated target. The fully controllable platform is expected to reduce the risk of cytokine release syndrome and double as a safety switch to turn the therapy off in the case of an adverse event. This is expected the facilitate the translation of CAR-T cells to solid tumors by enabling titration of activity to an appropriate therapeutic index.

Here, we present new data that demonstrate the universal nature of the switchable platform can redirect a single CAR-T cell product to multiple antigen targets to prevent antigen loss relapse or treat heterogeneous disease in mouse models. We have extended the platform further to immunocompetent mouse models to show iterative stimulation of the switchable CAR-T cells affords repeated, cyclical depletion of B cells. This recall of the CAR-T cell response was enabled through via extensive hinge, transmembrane, and costimulatory domain engineering to achieve long-term persistence and activity. Further, we present new data on the humanization of the human switchable CAR and switch towards establishment of a clinical candidate for a planned first in human clinical trial.