Programming Cell Therapies with Targeted Protein Degradation

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The Jan Laboratory seeks to build clinically suitable synthetic biology technologies by reprogramming elegant and powerful cellular protein degradation machinery. With bespoke tools, we then design and test smart, next-generation cellular immunotherapies targeting unmet clinical needs.

Gene-modified cellular immunotherapies are transformative advances in the care of people with B cell cancers. However, toxicity, high rates of intensive care, and cost limit both patient outcomes and the accessibility of these autonomous, living therapies. While synthetic biology platforms to predictably tune and regulate cellular behaviors have enormous potential to refine cell-based therapies, toolkits of molecular parts, modules, and circuits designed for clinical use are in short supply.

Using lenalidomide, an FDA-approved anti-cancer drug that acts as a molecular glue to recruit select target proteins to an E3 ligase for ubiquitination and subsequent proteasomal degradation, we engineered lenalidomide-inducible dimerization and degradation systems. With these tools, we have developed drug ON- and OFF-switch chimeric antigen receptor (CAR) and cytokine systems to enable user control over anti-tumor and proliferative functions of cellular immunotherapies with small molecule pharmacokinetics. Current work in the lab aims to develop additional technologies at the interface of targeted protein degradation drug development and cell engineering, as well as to define the catalog of attractive space- and time-limited genetic perturbations to immune cells. Clinical development goals include using degrader synthetic biology to 1) alleviate risks associated with higher potency cellular immunotherapies and 2) safely deploy cell therapies as routine outpatient modalities.

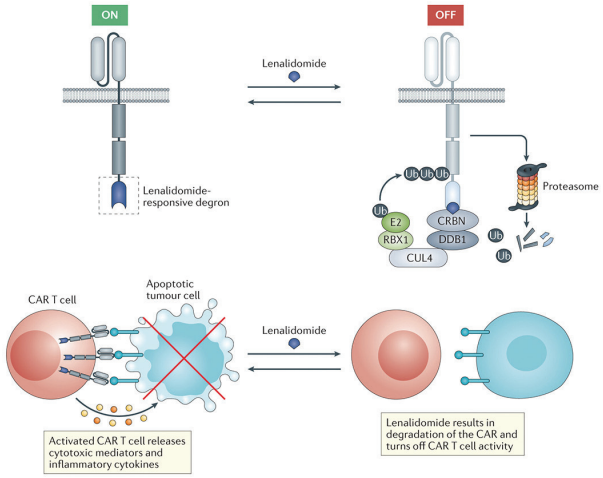

Figure 1. Molecular switch control of genetically engineered cell therapies. Incorporation of a lenalidomide-responsive degron tag into a chimeric antigen receptor (CAR) enables drug-dependent degradation mediated by the ubiquitin-proteasome system. Pharmacologic control can be used to mitigate CAR T cell hyperactivation toxicities or to tune CAR signaling. Image credit: Nature Reviews Clinical Oncology.