Max Jan, MD, PhD

Jan Laboratory

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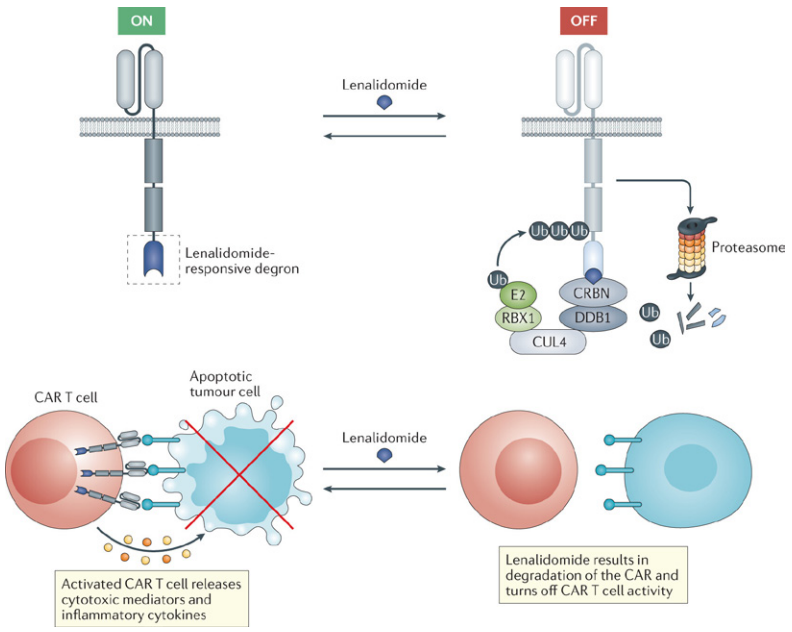
The current moment in cancer immunotherapy has been likened to the early days of the space race, and in this all-too-accurate analogy the patients are the astronauts sent on ballistic therapeutic arcs at the leading edge of human possibility. **The Jan laboratory** seeks to refine cell therapies as safe, effective, accessible, and ultimately routine modalities that ask less of people with cancer. We contribute to these goals by harnessing elegant protein degradation cellular machinery that has evolved to control fast biologic transitions related to information flow and signal processing. Our multidisciplinary translational research group investigates the following questions: How does protein degradation shape immune cell function? How can our protein degradation machinery be retargeted to tune and customize therapeutic cell programs? What are the design principles for adaptive, user-controllable cell therapies? What are the clinical settings to deploy smart next-generation cellular immunotherapies?

Targeted protein degradation for cell therapy

Genetically modified (CAR) T cells have emerged as transformative agents in the care of people with cancer. To reach their full potential, cellular immunotherapies must become safer, more effective, and more accessible. Mentored by Marcela Maus and Ben Ebert, we recently developed chemical genetic controls systems around the FDA-approved drug lenalidomide and its analogs, which act as molecular glue targeted protein degraders, recruiting neosubstrate proteins to E3 ubiquitin ligases for polyubiquitination and proteasomal degradation. We engineered clinically suitable lenalidomide-inducible dimerization and degradation systems, and with them lenalidomide ON- and OFF-switch CAR T cells (see: Figure). In collaboration with Amit Choudhary and David Liu, we have further demonstrated the generalizability of these tools by engineering a suite of lenalidomide switchable, sequence programmable Cas9-derivative genome editing proteins. Looking forward, we have established a multidisciplinary research program using functional genomics, biochemistry, and synthetic biology to explore the design principles of immune cell programming and advance next-generation cellular immunotherapies to treat cancers with limited treatment options.

Ubiquitin-dependent control of immune cell function

Our >600 E3 ubiquitin ligases encode diverse post-translational regulatory programs that are particularly well-suited to govern fast, activity-dependent transitions in signal transduction and gene expression. While important examples of E3 ligases that govern individual functional modules and lineage decisions are known, a systems-level understanding of ubiquitin-dependent control in the immune system remains elusive. As an entry point to engineering with the ubiquitin code, we leverage functional genomics and biochemistry to systematically identify mechanisms of control over immune cell state, fate, and function.



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.

Reprogramming protein degradation

Molecular glue degraders are frontline anti-cancer agents and herald extraordinary promise for degrader drug development. The target-drug-E3 ligase ternary complexes enforced by small molecule degraders are our starting point for synthetic biology development. We are learning to chemically and genetically retarget protein degradation machinery in order to control immune cell programming in new and therapeutically impactful ways. By advancing clinically suitable tools composed of human proteins and FDA-approved small molecules, we envision a platform for direct clinical translation.

Expanding the design space of cellular immunotherapy

Cellular states of dysfunction undermine CAR T effectiveness and are a prominent mechanism of treatment failure that could in theory be overcome by tuning therapeutic cell self-renewal and differentiation. Yet there are few static, irreversible genetic modifications that can safely manipulate these core cell fate dynamics. We are leveraging user-controlled, chemical biology approaches to hack the central cellular processes that determine therapeutic potential.

Design and evaluation of cellular immunotherapies targeting novel antigens

In the current CAR T cell paradigm, target antigens must be present on tumor cells and absent from essential normal tissues (e.g. CD19, BCMA). We and collaborators have identified novel antigens consistent with this pattern in select solid tumors. Integrating novel targeting and molecular switch systems, we seek to pre-clinically validate candidate next-generation cellular immunotherapies targeting malignancies with limited treatment options. The MGH Cellular Immunotherapy Program can advance promising designs via investigator-initiated clinical trials.

Selected Publications:

Jan M*, Sperling AS*, & Ebert BL (2021). Cancer therapies based on targeted protein degradation—lessons learned with lenalidomide. *Nature Reviews Clinical Oncology*, 1-17.

Jan M, Scarfò I, Larson RC, Walker A, Schmidts A, Guirguis AA,... Maus MV & Ebert BL (2021). Reversible ON-and OFF-switch chimeric antigen receptors controlled by lenalidomide. *Science Translational Medicine*, 13(575).

Miller PG, Sperling AS, Brea EJ, Leick MB, Fell GG, **Jan M**,... & Ebert BL (2021). Clonal hematopoiesis in patients receiving chimeric antigen receptor T-cell therapy. *Blood Advances*, 5(15), 2982-2986.

Sperling AS, Burgess M, Keshishian H, Gasser JA, Bhatt S, **Jan M**,... & Ebert BL (2019). Patterns of substrate affinity, competition, and degradation kinetics underlie biological activity of thalidomide analogs. Blood, *The Journal of the American Society of Hematology*, 134(2), 160-170.

Jan M, Leventhal MJ, Morgan EA, Wengrod JC, Nag A, Drinan SD,... & Ebert BL (2019). Recurrent genetic HLA loss in AML relapsed after matched unrelated allogeneic hematopoietic cell transplantation. *Blood Advances*, 3(14), 2199-2204.

Jan M*, Snyder TM*, Corces-Zimmerman MR*, Vyas P, Weissman IL, Quake SR, & Majeti R (2012). Clonal evolution of preleukemic hematopoietic stem cells precedes human acute myeloid leukemia. *Science Translational Medicine*, 4(149), 149ra118-149ra118.

*Equal contribution