Max Jan, MD, PhD

The Jan laboratory primarily focuses on the development of clinically suitable synthetic biology platforms in order to advance next-generation cellular immunotherapies. Harnessing elegant protein degradation cellular machinery that has evolved to control fast biologic transitions related to information flow and signal processing, we have developed molecular switch technologies regulated by the FDA-approved drug lenalidomide as generalizable chemical biology tools and cell therapy controllers. We use genomics, synthetic biology, and biochemistry to build new technologies, explore design principles for adaptive, user-controllable immune cells, and investigate clinical settings to deploy smart cell therapies.

Jan Laboratory

Max Jan, MD PhD
Gabriele Kembuan, MD
Joanna Kim
William Lin
Noor Radde*
Ditsa Sarkar, PhD
Emily Schneider*#
Manuella Talla

* Graduate students

Co-mentored with Marcela Maus lab

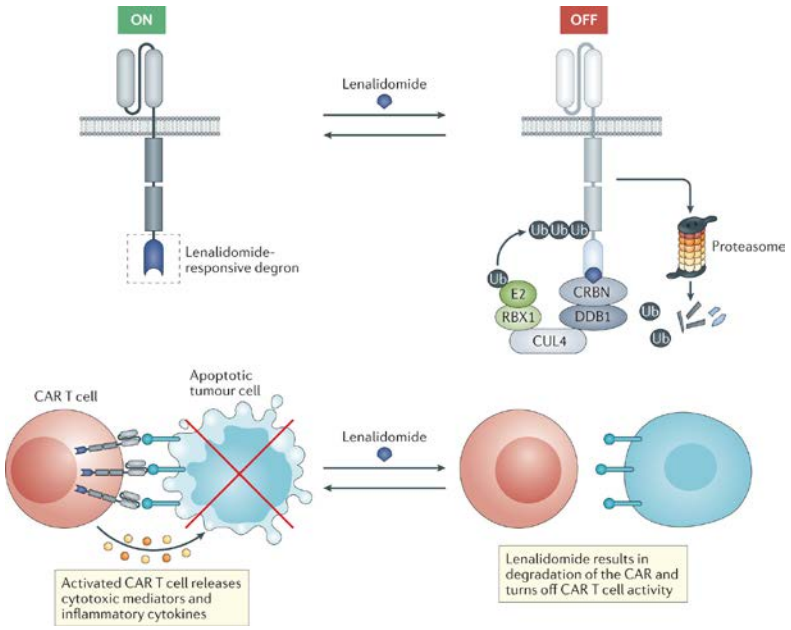
Programming cellular immunotherapies using targeted protein degradation

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 Drs. Marcela Maus and Benjamin 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 drug ON- and OFF-switch CAR T cells (see Figure). We are now exploring specific scenarios where control over the dynamics of CAR signaling can mitigate T cell hyperactivation toxicities and allow for higher potency designs. These inducible degradation systems have also been further leveraged to encode additional functions in investigational cellular immunotherapies. To tune up the anti-tumor potency of CAR T cells, we have developed chemical genetic cytokine delivery systems, enabling spatiotemporally controlled release of potent T cell proliferative and anti-tumor cytokine signals that have a poor therapeutic window when delivered systemically. For highly potent and/or novel investigational cell therapies with unproven safety profiles, together with the Manguso lab, we are developing cell therapy suicide switches induced by lenalidomide that may act as safeguards in early-stage clinical testing.

We have also developed a new technology to genetically reprogram E3 ubiquitin ligases to bind and degrade customizable sets of endogenous proteins. This system for targeted endogenous protein degradation in engineered cells can act constitutively, in response to a small molecule controller drug, or in integrated sense-and-response synthetic circuits. Using this protein-protein interaction-based molecular logic for post-translational endogenous protein regulation, we are exploring diverse applications to engineer new and therapeutically useful functions not only in T cells but also in NK cells and hematopoietic stem cells.

Design and evaluation of cellular immunotherapies targeting novel antigens

CAR T cells can be highly effective and well-tolerated therapeutics when they are targeting antigens that are homogenously expressed on tumor cells and are also



Molecular switch control of genetically engineered cell therapies. Incorporation of a lenalidomide-responsive degron tag 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. *Image credit: Nature Reviews Clinical Oncology.*

absent from essential normal tissues. In collaboration with the Villani lab, we are leveraging single cell genomics and large-scale tumor and normal tissue gene expression datasets to nominate novel target antigens in select solid tumors. In collaboration with the Manguso lab and others, we are leveraging innovative approaches to engineer affinity reagents for tumor sensing by CAR T cells, here applied to target a founding, clone-specific surface neoantigen in a subtype of myeloproliferative neoplasm. In the long term, we seek to integrate novel tumor antigen discovery and fit-for-purpose molecular logic systems into investigational cellular immunotherapies targeting malignancies with limited treatment options.

Understanding anti-tumor T cell fate and plasticity using dynamic perturbations

Having developed a suite of tools, including small molecule-controllable genome editing proteins, that can be used in primary human T cells for fast and reversible perturbations of target genes and proteins, we seek to understand how dynamic perturbations can shape and even reprogram T cell fate and function. Transient and traceable perturbations may enable the study of stage-specific molecular mechanisms governing T cell lineage and differentiation trajectories, as well as nascent therapeutic opportunities leveraging rapid development of targeted in vivo delivery modalities.

Selected Publications:

Sreekanth V, **Jan M**, Zhao KT, Lim D, Davis JR, McConkey M, ... & Choudhary A. A molecular glue approach to control the half-life of CRISPR-based technologies. *bioRxiv*. 2023 Mar 20:2023.03.

Bouzid H, Belk JA, **Jan M**, Qi Y, Sarnowski C, Wirth S, ... & Jaiswal S. Clonal hematopoiesis is associated with protection from Alzheimer's disease. *Nature Medicine*. 2023 Jul;29(7):1662-1670.

Lane IC, & **Jan M**. SEAKER cells coordinate cellular immunotherapy with localized chemotherapy. *Trends in Pharmacological Sciences*. 2022 Oct;43(10):804-805.

Jan M*, Sperling AS*, & Ebert BL. Cancer therapies based on targeted protein degradation—lessons learned with lenalidomide. *Nature Reviews Clinical Oncology*. 2021 Jul;18(7):401-417.

Jan M, Scarfò I, Larson RC, Walker A, Schmidts A, Guirguis AA, ... Maus MV, & Ebert BL. Reversible ON-and OFF-switch chimeric antigen receptors controlled by lenalidomide. *Science Translational Medicine*, 2021 Jan 6;13(575):eabb6295.

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*., 2019 Jul 11;134(2): 160-170.

*Equal contribution