

## Profile of an Early-Career Researcher

**Matthias Stephan, MD, PhD**



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Current T-cell therapies often involve engineering a patient's own cells, by removing them, reprogramming them, and re-introducing them. The laboratory of Dr. Matthias Stephan is developing nanomedicines to reprogram T-cells inside the patient.

Dr. Stephan is a Laboratory Head and Associate Member at Fred Hutchinson Cancer Research Center and an Associate Professor at the University of Washington. He began specializing in this area as a graduate student at Memorial Sloan-Kettering Cancer Center, where he pioneered auto-costimulation and trans-costimulation as molecular strategies to augment the function of lymphocytes in the microenvironment created by tumors. During his postdoctoral training at the Massachusetts Institute of Technology, Dr. Stephan developed a nanoparticle-based strategy to provide autocrine sources of adjuvant growth factor that support adoptively transferred, tumor antigen-specific T lymphocytes. Much of this work became the intellectual and technical foundation for a Cambridge-based startup company (*Torque Therapeutics, Inc.*).

The long-term goal of Dr. Stephan's research at Fred Hutch is to make immunotherapy more practical and widespread by creating unconventional treatments at the interface between materials science and immunology. Sometimes dubbed "Immunobioengineering," his is an emerging but rapidly growing field originally centered on the creation of synthetic pathogen-mimicking vaccine particles. The field soon introduced a host of innovative materials and new concepts that serve as the basis of novel therapies.

Stephan's research group recently reported a strategy to program circulating T-cells with tumor-recognizing activities, which avoids the complex laboratory protocols usually used to achieve this transformation for use in patients (*Nature Nanotechnology* 12 (2017) 813-820). The lab developed DNA-carrying nanoparticles can efficiently introduce leukemia-targeting CAR genes into T-cell nuclei. Stephan's team developed biodegradable poly( $\beta$ -amino ester)-based nanoparticles targeted to T-cells via f(ab')<sub>2</sub> fragments and to the nucleus via nuclear-localization sequences. The particles were loaded with plasmid DNA encoding the leukaemia-specific 194-1BBz CAR. These particles programmed T-cells in quantities sufficient to bring about long-term disease remission with efficacies similar to adoptive T-cell therapy, demonstrated in mice. With industry partners, his group is currently developing this platform for clinical use.