Tackling leukemia relapse after allogeneic hematopoietic cell transplantation by hematopoiesis-specific TCR-engineered donor T cells

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Background and central scientific questions or problem:

Transplantation of hematopoietic cells from healthy donors into patients affected by onco-hematologic disorders such as leukemia, also referred to as allogeneic hematopoietic cell transplantation (alloHCT), is the clinically most consolidated form of cancer immunotherapy, and has served as hub for novel platforms of adoptive transfer of genetically modified immune cells for targeted treatments. In alloHCT, polymorphic human leukocyte antigen (HLA) molecules present in the patient but not in the donor, represent potent targets of graft-versus-leukemia (GvL) responses mediated by alloreactive donor T cells, but can mediate also harmful graft-versus-host disease (GvHD) in healthy patient tissues. Despite GvL, the most frequent lethal complication after alloHCT remains relapse of the underlying disease, which occurs in over 40% of patients and has a severe prognosis, due to a limited array of treatment options. Here we propose to develop a new approach to tackling post-alloHCT relapse, by identifying alloreactive T-cell receptors (TCR) specific for peptides presented by patient-specific HLA selectively on hematopoietic tissues including the patient's leukemia, but not on non-hematopoietic GvHD target tissues. These allohem-TCR will induce selective GvL after HLA-mismatched alloHCT, because the engrafted blood cells are of donor origin and hence not target of alloreactivity against patient-specific HLA.

Technical and conceptual approach to address the research question

We already established an experimental platform for the identification of allohem-TCR, using *in vitro* T-cell stimulation with relevant mismatched HLA on leukemia cells, followed by limiting dilution cloning, re-expression in primary T cells and screening for hematopoiesis-specificity on a large panel of target cells from different tissues. We will isolate an allohem-TCR against frequent HLA mismatches, re-express them in primary T cells and characterize them after both *in vitro* and in humanized mouse leukemia models *in vivo*. The long-term goal is the design of clinical trials using donor T cells equipped with the relevant allohem-TCR for leukemia relapse treatment after alloHCT.

Scientific expertise within the group: immunogenetics and immunobiology of alloHCT and cellular therapy, in vitro models of single HLA antigen expressing hematopoietic and non-hematopoietic cells, T-cell biology and in vitro characterization, TCR cloning and re-expression in primary immune cells.

Website:
https://zelltherapeutische-forschung.uk-essen.de/

Selected publications:

Arrieta-Bolanos et al, J Clin Oncol 2024
https://ascopubs.org/doi/10.1200/JCO.24.00582?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%200pubmed

Arrieta-Bolanos et al, Blood 2024
https://pubmed.ncbi.nlm.nih.gov/39102621/

Crivello et al, J Clin Oncol 2023
https://pmc.ncbi.nlm.nih.gov/articles/PMC10150892/