Research profile for applicants

Name of DKFZ research division/group:	***Division of Personalized Immunotherapies (D193)***
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Group homepage: *Visit this website for further information on current research and recent publications.*	***https://hi-tron.dkfz.de/research-divisions/personalized-immunotherapies.html***
Eligibility:	• ***DKFZ Postdoctoral Fellowships***

RESEARCH PROFILE AND PROJECT TOPICS

Prof. Dr. Özlem Türeci heads the Personalized Immunotherapies division, while Dr. Ibrahim Murathan Sektioglu serves as the senior scientist, leading the Türeci Laboratory at the Helmholtz-Institute for Translational Oncology Mainz (HI-TRON Mainz). Our laboratory focuses on pioneering immunotherapies and identifying novel biomarkers for personalized cancer treatment strategies.

Project 1:

The exhausted CD8+ T cell population in human tumors is highly heterogeneous, with multiple subsets defined by surface phenotype, function, and differentiation and proliferation potential. Precursor/progenitor cells exhibit both exhausted and stem-like qualities. These subsets express TCF-1, have enhanced proliferative capacity and polyfunctionality, and give rise to intermediate, then terminally exhausted cells. The intermediate and terminally exhausted subsets have higher killing capacity but also higher expression of inhibitory receptors.

Anti-PD-1 treatment has shown remarkable clinical success in treating certain cancer types, including melanoma and non-small cell lung carcinoma. However, many patients remain refractory to this therapy, primarily due to the lack of an existing T cell response. Interestingly, some patients still do not respond to anti-PD-1 treatment despite having CD8+ T cells in their tumors. The reasons for this lack of response are not fully understood, but one contributing factor could be the heterogeneity within the exhausted CD8+ T cell population. Indeed, recent pre-clinical and clinical data have demonstrated that precursor/progenitor exhausted CD8+ T cells are essential for the response to immune checkpoint blockade. Therefore, strategies to expand the population of precursor/progenitor exhausted CD8+ T cells could significantly enhance the response to checkpoint blockade. To achieve this, we propose enforcing expression of particular transcription factors in T cells through targeted mRNA delivery. This

approach could potentially lead to the expansion of precursor/progenitor cells and improve response to immune checkpoint blockade.

Project 2:

ADCs represent a promising avenue for cancer treatment, allowing targeted delivery of potent toxins to tumors. However, maximizing their efficacy requires a deeper understanding of factors influencing response to ADC therapy, including overcoming drug resistance and managing treatment-related side effects.

The advent of CRISPR-based genetic screening enables comprehensive analyses of gene-drug interactions in cancer cells, offering an unbiased approach to assessing cellular responses to drugs. Recent studies have demonstrated the effectiveness of such screens in uncovering new DNA repair mechanisms, shedding light on the workings of genotoxic drugs, and revealing connections between genotoxic stress and patient genetics.

Utilizing unbiased in vitro and in vivo genome-wide CRISPR screening, our goal is to elucidate the mechanisms underlying ADC toxicity and the interplay between ADCs and host's immune system, offering crucial insights for ADC development and identifying potential targets for combination therapies.