Research profile for applicants

Name of DKFZ research division/group:	*Division of Translational Cancer Research (Saur Lab)* *DKTK Munich | Cost center: MU05-SOB-TransTF-SAR*
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Group homepage: *Visit this website for further information on current research and recent publications.*	dktk.dkfz.de/en/research/dktk-researchers/saur-group

RESEARCH PROFILE AND PROJECT TOPICS

Research focus. The Saur laboratory investigates how oncogenic signalling, cellular plasticity and reciprocal interactions between cancer cells and the tumour microenvironment drive gastrointestinal cancer progression, metastasis, immune escape and therapy resistance, with a major focus on pancreatic ductal adenocarcinoma (PDAC). We combine genetically engineered mouse models, patient-derived and murine organoids, syngeneic orthotopic transplantation, inducible genetic systems, CRISPR screening, lineage tracing and barcoding, single-cell and spatial multi-omics, and functional immune profiling. Our goal is to identify context-specific dependencies and translate them into rational combination therapies.

Potential project - Immune-enabled cotargeting of RAS-driven pancreatic cancer. RAS-directed therapy can induce profound tumour regression in KRAS-mutant PDAC, but responses are heterogeneous and commonly followed by adaptive resistance. The postdoctoral project will determine how acute pharmacological RAS inhibition and orthogonal genetic extinction of oncogenic KRAS remodel malignant cell states and tumour-immune interactions, and will exploit these changes to develop immune-enabled cotargeting strategies. Using a panel of molecularly defined human and murine PDAC models, the candidate will compare clinically relevant pan-RAS(ON) and mutant-selective inhibitors with inducible KRAS knockout or deletion. Time-resolved single-cell RNA sequencing, spatial transcriptomics, lineage tracing and multiplex immune profiling will resolve drug-sensitive, persisting and relapse-seeding tumour states and define associated changes in antigen presentation, interferon signalling, innate immune sensing and myeloid and T-cell composition.

Focused pooled CRISPR-Cas9 screens will then perturb adaptive signalling nodes, tumour-cell-intrinsic immune-evasion genes and candidate secreted mediators in the presence or absence of RAS inhibition. Top genetic interactions will be validated by individual and combinatorial knockouts, pharmacological inhibitors, organoid-immune co-cultures and orthotopic immunocompetent models. Comparisons with immunodeficient hosts and selective depletion or blockade of immune-cell populations will establish which combinations depend on CD8 T cells, natural killer cells, macrophages or neutrophils. The final aim is to nominate biomarker-guided combinations that convert transient RAS-inhibitor responses into durable immune-mediated tumour control, including rational combinations with checkpoint blockade, myeloid reprogramming or activation of innate immune pathways. The project offers substantial freedom to develop an independent mechanistic focus while