Project abstract

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Group homepage: Please visit our website for further information on our research and recent publications.	*https://www.dkfz.de/en/personalized-immunotherapy* *https://www.dkfz.de/en/dermal-oncoimmunology* *https://hi-tron.dkfz.de/research-divisions/divisions/tuereci-lab-personalized-immunotherapies-division.html* *https://hi-tron.dkfz.de/research-divisions/divisions/munir-lab-dermal-oncoimmunology.html*

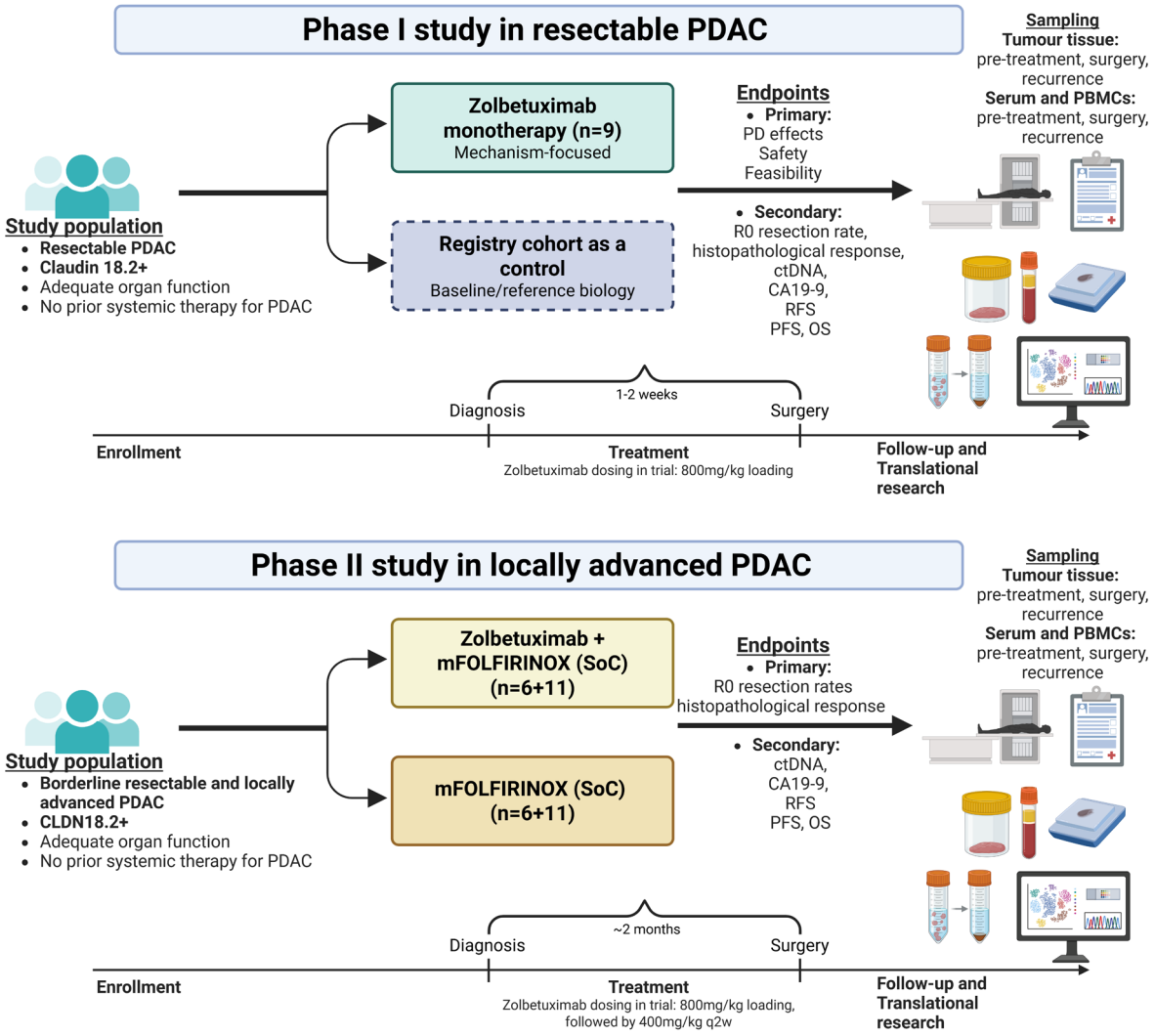
PROJECT PROPOSAL

PDAC is among the most lethal human malignancies, characterized by profound therapy resistance, early relapse, and a largely immunosuppressive tumor microenvironment. Despite advances in perioperative chemotherapy, complete (R0) resection rates and long-term survival remain unsatisfactory, and targeted or immunotherapy-based approaches are virtually absent outside rare molecular subgroups.

CLDN18.2 defines a biologically distinct subset of PDAC and represents a validated therapeutic target in gastric and gastroesophageal adenocarcinoma. Zolbetuximab, a first-in-class monoclonal antibody targeting CLDN18.2, mediates tumor cell killing via Fc-dependent immune mechanisms and has demonstrated clinical efficacy and acceptable safety in advanced gastrointestinal cancers. However, its safety, biological activity, and clinical utility in PDAC have never been systematically investigated.

This project establishes a biomarker-driven phase I/II clinical trial of Zolbetuximab in resectable and locally advanced CLDN18.2-positive PDAC, integrated with a deep translational research program. The overarching aim is to determine whether CLDN18.2-targeted therapy is safe, biologically active, and capable of improving surgically relevant outcomes, while

simultaneously elucidating the immune, stromal, and tumor-intrinsic mechanisms that govern response and resistance.



The clinical research fellow, in close collaboration with basic researchers, will play a central role in integrating clinical data with translational analyses, with responsibilities including:

- Coordination of longitudinal biospecimen collection, including pre-treatment biopsies, on-treatment samples, surgical resections, and peripheral blood
- Processing of patient-derived tumor samples for in-depth analysis of the tumor microenvironment, including immune and stromal compartments
- Identifying biomarkers of response and resistance to CLDN18.2-targeted therapy
- Defining immune effector pathways associated with clinical benefit
- Uncover microenvironmental and evolutionary adaptations that drive or constrain therapeutic efficacy