Bench-to-Bedside: Decoding the PDAC Ecosystem to Drive AI Diagnostics and Precision Therapeutics

Abstract

Pancreatic ductal adenocarcinoma (PDAC) is a highly lethal malignancy hindered by delayed diagnosis and an immunosuppressive, fibrotic tumor microenvironment (TME). This presentation outlines a comprehensive "bench-to-bedside" roadmap that intercepts PDAC at both its initiation and advanced metastatic stages.

First, we elucidate the origins of PDAC, demonstrating that high glucose metabolism induces KRAS mutagenesis via RRM1 O-GlcNAcylation. Cooperating with Muc4, these mutated cells secrete Activin A to recruit fibroblasts, driving early PanIN formation. Translating these mechanistic insights, we developed PanMETAI, a pioneering AI-driven diagnostic platform. By integrating 600 MHz ^{1}H NMR serum metabolic profiles, Activin A, and clinical parameters (CA19-9, age) via a Tabular Foundation Model (TabPFN), PanMETAI achieves unprecedented accuracy (AUC > 0.90) in identifying early-stage (Stage I/II) PDAC across both Taiwanese and Lithuanian cohorts, delivering a robust, non-invasive screening solution.

To combat advanced PDAC, we mapped the cellular interactions at the tumor's invasive front, identifying the ATP1A1/Activin A and ATP1A1/SEMA7A/IL-17RB signaling axes as fundamental drivers of fibroblast activation, EMT, and invasion. To dismantle this ecosystem, we advanced a dual-pronged therapeutic pipeline. First, utilizing ACK900—a first-in-class complex N-glycan remodeling agent developed by our GRC colleague—we successfully disrupted tumor-fibroblast crosstalk, selectively inhibited cancer-associated fibroblasts, and enhanced chemosensitivity. Second, we developed potent protein-protein interaction (PPI) disruptors targeting the oncogenic IL-17RB/MLK4 axis. This encompasses rationally engineered cyclic peptides based on structural homology, and the discovery of Hydroxyzine Pamoate (HP), an FDA-approved compound identified via high-throughput screening. Preclinical in vivo models confirmed that HP synergizes with standard-of-care gemcitabine to severely impair metastasis and substantially extend overall survival.

Ultimately, by seamlessly uniting fundamental mechanism discovery, AI diagnostics, and precision drug innovation, this independent translational portfolio provides highly actionable strategies to overcome critical clinical bottlenecks in PDAC.