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Our research activities are directed towards investigating the underlying mechanisms of tumor reliance on oncogenic drivers and comprehending how genomic or functional modifiers impact such dependencies, particularly in colorectal cancer. Our experimental approach encompasses multidimensional data analysis, followed by preclinical validation in patient-derived xenografts (PDXs) and detailed mechanistic studies in PDX-matched tumoroids.

Significant accomplishments include the identification of novel targets with direct clinical relevance. For example, our preclinical discovery linking HER2 oncogene amplification to resistance against EGFR blockade paved the way for the HERACLES clinical trial. This study exhibited promising outcomes in heavily pre-treated patients with HER2-positive tumors, showcasing objective response and disease control rates that surpass other therapies used in similar treatment regimens.

We explored adaptive drug tolerance to EGFR inhibition in metastatic colorectal cancer, pinpointing pharmacological strategies to enhance the efficacy of anti-EGFR therapy. These investigations also brought attention to lineage-based adaptive reprogramming as a mechanism for cancer cells to evade pathway dependence and resist eradication by therapy.

Our contribution to the global reconsideration of colorectal cancer molecular taxonomy involved the development of new transcriptional classifiers. These classifiers have helped refine our understanding of colorectal cancer biology, offering both prognostic and predictive insights.

Finally, as part of an international collaboration, including the EurOPDX Consortium and the US National Cancer Institute (NCI) PDX Development and Trial Centers Research Network (PDXNet) Consortium, we systematically examined DNA copy number changes during PDX engraftment and passaging. The collected data demonstrated high retention of copy number profiles in hundreds of publicly available PDXs, providing researchers with the means to evaluate the suitability of individual models for personalized treatment studies.

Overall, our studies provide a systematic functional framework for assessing anticancer therapy response in human cancer, uncover novel mechanisms influencing responsiveness to anti-EGFR therapies, and introduce a new molecular language for the clinical management of colorectal cancer, with immediate translational and clinical implications.