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Journal of Organoid & Bioscience

Editorial

Perspective on Tumor Organoids in Drug Screening and Cancer Precision Medicine

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The landscape of cancer research is swiftly evolving, presenting fresh optimism through innovative tactics that customize treatment for each patient. In 2016, Clevers unveiled a groundbreaking study in Cell, introducing organoids that emulate essential structural and functional traits of organs like the kidney, lung, gut, brain, and retina. This technology enables the replication of human organ development and various pathologies within a controlled laboratory environment. Mounting evidence underscores the potential of patient-derived organoids (PDOs) to reshape cancer treatment and revolutionize drug discovery in oncology. This commentary explores these pioneering research avenues and their profound implications for clinical oncology and pharmaceutical development.

The integration of tumor organoids into drug screening and cancer precision medicine marks a pivotal advancement in oncology research. Driehuis *et al*. have meticulously delineated protocols for establishing patient-derived cancer organoids from diverse epithelial tissues and cancers, streamlining in vitro testing of therapy sensitivity. These protocols, especially tailored for generating head and neck squamous cell carcinoma organoids, enable semi-automated therapy screens. Typically, organoid establishment and subsequent screenings can be completed within three months, with variations depending on factors like the starting material and the number of therapies examined. These protocols serve as invaluable references for developing organoids from other cancer types, enhancing the drug screening process.

Grossman *et al*. showcased the transformative capacity of PDOs in personalized oncology through the HOPE trial and subsequent investigations. By generating PDOs from patients with pancreatic ductal adenocarcinoma (PDAC) and evaluating their drug sensitivity, researchers were able to anticipate

clinical responses. This methodology tackles the intrinsic heterogeneity of human cancers, offering a functional precision medicine approach beyond static genomic features. PDOs provide a dynamic platform for evaluating diverse therapeutic agents and identifying effective combinations tailored to individual patients. The capability to categorize PDOs as sensitive or resistant to specific chemotherapy regimens and correlate these findings with patient outcomes underscores their utility as predictive models. This approach has been successfully extrapolated to other cancer types, such as head and neck squamous cell carcinoma and rectal cancer, illustrating its broad applicability in predicting treatment responses and guiding clinical decisions.

In a significant advancement, Dekkers *et al*. explored the interplay between engineered T cells and cancer organoids to enhance treatment outcomes. The BEHAV3D system enables the study of dynamic interactions between immune cells and patient-derived cancer organoids. Through live-tracking over 150,000 engineered T cells cultured with solid-tumor organoids, BEHAV3D identified a "super engager" cluster of T cells with potent serial killing capacity. This innovative system also unveiled behavior-specific gene signatures, including previously uncharacterized genes expressed by super engager T cells, offering fresh insights into effective T cell responses. Notably, type I interferon was found to prime resistant organoids for T cell-mediated killing, suggesting potential combination strategies to boost the efficacy of cellular immunotherapies. BEHAV3D stands out as a promising tool for characterizing the behavioral and phenotypic heterogeneity of cellular immunotherapies, paving the way for optimized, personalized treatments for solid tumors.

Letai *et al*. furthered the field by probing tumor vulnerabilities through functional precision oncology, directly examining live tumor cells with various drugs to uncover weaknesses. This strategy supplements genomic profiling by furnishing real-time, actionable insights into the most effective treatments. Emerging technologies enable the assessment of drug responses in a context mirroring the tumor microenvironment, overcoming the limitations of conventional static approaches. The utilization of pre-clinical models like patient-derived xenografts (PDXs) and PDOs, representing tumors from affected individuals, hones drug discovery and enhances the success of new therapies in clinical settings. The enhanced feasibility of developing models derived from affected individuals on a large scale for research has democratized these models for personalized therapy. For example, the realization that engraftment of breast and other tumors as PDXs predicted metastatic relapse sparked the notion that these models could customize therapy upon recurrence, resulting in the Functional Precision Oncology for Metastatic Breast Cancer study. Through the integration of functional assays with genomic and transcriptomic data,

researchers can construct a comprehensive understanding of tumor biology and resistance mechanisms. This holistic approach holds the promise of unearthing novel therapeutic targets and refining treatment regimens, ultimately augmenting patient outcomes. The dynamic nature of PDOs permits real-time testing and adjustments, furnishing a robust platform for precision medicine.

In conclusion, the incorporation of tumor organoids into drug screening and precision medicine represents a significant advancement in oncology. The ability to model patient-specific responses, test a variety of therapeutic agents, and identify effective treatment combinations offers a promising path toward more personalized and effective cancer treatments. As research continues to evolve, these innovative approaches will likely become integral to clinical decision-making, leading to better patient outcomes and advancing the field of oncology.

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