Development of a Kidney Cancer ex vivo Tumor Model and Image-Based Artificial Intelligence Tool for Precision Immunotherapy and Combination Therapy Testing

1 Introduction

Precision medicine has the potential to revolutionize cancer treatment and drastically improve outcomes. While genomic screening has become the gold standard for personalized cancer therapy, its predictive power is confined to select cancers and drug modalities, and it is yet to show promise as a standalone drug selection tool for improving patient outcomes.

Pear Bio has developed an ex vivo IO model and multivariate analysis to predict clinical drug efficacy by combining patient tumor samples, clinical assays, artificial intelligence and omics. This model recapitulates each patient’s unique tumor-immune microenvironment (TIME) and allows time-course bulk and single-cell resolution analyses of functional metrics in 3D. Initial development was performed on retrospective biobanks samples across 9 solid tumor types. Ongoing observational clinical trials are aimed at establishing the tool’s sensitivity and specificity in triple-negative breast cancer (TNBC) in the neoadjuvant and metastatic settings, as well as validating the technology in renal, pancreatic, liver, and brain cancers.

2 Measuring ex vivo response biomarkers

Human renal tumor sections and matched blood (NHS) are processed for spatial transcriptomics and isolation of single tumor cells and PBMCs. Tumor-associated cells (stroma, immune, etc.) cells and PBMC subsets are characterized by flow cytometry (FCM). Target cells (tumor and effector cells (PBMCs) and subsets thereof, CD8+) are stained with different fluorochrome dyes including viability probes (Caspase 3/7, SYTOX) and encapsulated in hydrogels that recapitulate human TIME physiology. Figure 2. The Immuno-oncology (IO) cultures are treated with cytokines mimicking key immune checkpoint (IL-15, pembrolizumab) and receptor-tyrosine kinase (TKI) (cibalizumab, lenalidomide, axitinib) inhibitors. Cells are tracked up to 3 days using 3D-time course confocal microscopy. Computer vision analysis detects and quantifies cell behaviors such as immune infiltration, immune/tumor cell migration, T cell-mediated tumor killing and tumor viability in response to treatments.

Our preliminary data shows that treatment with pembrolizumab resulted in a 21% increase in the infiltration of CD8+ PBMC fraction into the microtumor core and a 14% increase in infiltration of the CD8+ subset. Tumor cell death was 15% higher in pembrolizumab-treated samples compared to tumor cultures with CD3-activated PBMCs and no treatment, and 30% higher compared to tumor cultures alone (no PBMCs). Migration speed of immune cells was found to be as cells invaded and slowed during engagement/killing, peaking at day 1 (Figure 2A) and slowing to 2 and 3 days. PFC was selected to characterize tumor cell subpopulations (cancer, endothelial, immune) and the expression of druggable targets in each patient. Treatment with TKI led to reduced phosphorylation of VEGF/VEGFR2 (Figure 3).

3 Immuno-oncology ex vivo 3D metrics

Our platform allows time-course analyses of functional cell response metrics. The model tests treatment combinations across multiple modes of action and quantifies cell response including viability, death, migration, immune infiltration and immune-surveillance. The technology has also been validated across 9 solid tumor types, where dissociated tumor cells show high viability in their physiologically-relevant 3D TIMEs. Future work aims to further develop the platform to predict patient responses in triple-negative breast cancer (NCT00433352), kidney, liver, pancreatic and brain tumors. Early R&D is progressing to include the testing of additional therapeutic modalities including immunotherapeutics, cell therapies, antibody-drug conjugates, small molecules, chemotherapies and combination therapies.

4 Cell therapy testing in Pear I/O model

Our data suggests that tumor-infiltrating lymphocytes (TILs) can be successfully expanded and transferred to patient tumors and demonstrated superior antitumor efficacy compared to Keytruda monotherapy. Additional studies are in progress to evaluate co-treatment with immune checkpoint inhibitors (ICIs) and standard-of-care chemotherapeutic agents. A multi-center clinical trial is currently recruiting patients with metastatic TNBC to test our proprietary computer vision pipeline on paired tumor resection samples. Early data suggests that a 3-fold increase in tumor cell death was observed after treatment with pembrolizumab and axitinib compared to Keytruda monotherapy. Further studies will be needed to confirm these results in a clinical setting.

5 Conclusions

Our platform allows time-course analyses of functional cell response metrics. The model tests treatment combinations across multiple modes of action and quantifies cell response including viability, death, migration, immune infiltration and immune-surveillance. The technology has also been validated across 9 solid tumor types, where dissociated tumor cells show high viability in their physiologically-relevant 3D TMEs. Future work aims to further develop the platform to predict patient responses in triple-negative breast cancer (NCT00433352), kidney, liver, pancreatic and brain tumors. Early R&D is progressing to include the testing of additional therapeutic modalities including immunotherapeutics, cell therapies, antibody-drug conjugates, small molecules, chemotherapies and combination therapies.

6 Get in touch

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