DEXTER™ MICROFLUIDIC PLATFORM COUPLING SINGLE-CELL RESOLUTION OF DYNAMIC TUMOR-IMMUNE INTERACTION WITH AI FOR ELUCIDATING MECHANISTIC MODULATION IN CANCER IMMUNOTHERAPY

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Background Immunotherapies in recent years emerged as effective treatment modalities for primary and metastatic tumors. However, a durable response besides a high objective response rate (ORR) is still elusive. Limitations of predictive functional platforms in providing spatial and temporal mechanistic insights into tumors and their dynamic immune proximity at the single-cell level critically highlight the challenges of modeling successful therapy outcomes. Here we describe the development of a novel microfluidic platform integrated with AI that incorporates single-cell sorting and functional interactions between different immune cells and tumors.

Methods The Dexter™ microfluidic platform involves the generation of a large number of nanoliter droplets (> 10,000) and mechanical dispensing of sorted droplets in a spatially defined array of nano-wells and achieves high throughput (> 1,000) independent nano bioreactors. Its open design concept illustrates simple workflow, easy perfusion through a gas permeable oil, sufficient nutrient availability, and offers a protective cushion around the cell for minimizing any impending stress during the downstream process. Indeed, the droplets in the array are spatially segregated to avoid any cross-talk. The platform is integrated with a multicolor fluorescence and bright field imager equipped with a culture stage and precise motion robotic arm in proximity to the droplet of interest for its efficient aspiration and release into mapped well.

Results To demonstrate the applications of this platform for functional modulation, we used differentially labeled immune cells like CD45, CD4, CD8 and detected cytokines like IFN γ and granzyme B at single-cell level; antigen uptake by dextran-FITC endocytosis. We further quantified the functionalities critical for immune-immune interactions, tumor-immune synapse formation, and killing of target tumor cells in a dynamic PBMC and tumor (breast, colon, and head and neck cancer cells) coculture setting. Longitudinal imaging showed the ability of the platform to capture the dynamic state of the antigen uptake and presentation, functional activation of driver phenotypes like CD8+cytotoxic T cells, and subsequent directed killing of tumor cells upon reinvigoration of effector phenotypes. Further coupling of AI-guided matrix with features from polyfunctional modulation accurately demonstrated the mechanistic shift choreographed upon immune activation.

Conclusions Together, these findings illustrate the preclinical relevancy of a therapy agonist multimodality correlative platform integrating a controllable microfluid system and AI for real-time tracking of dynamic tumor-immune interplay at the level of single-cell resolution. Further validation of this system will offer opportunities for identifying driver modulation linked to predicted therapy response and modeling next-generation cell-based immunotherapies.

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