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Screening cancer therapeutic agents in ex vivo controlled microenvironment for solid patient tumors

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Personalized cancer medicine is currently focused on knowledge of the cancer mutation repertoire and the tailored application of drugs that target altered genes or pathways in individual patients. Thus, a critical need exists for more sophisticated ex vivo diagnostic methods that recapitulate human tumor biology and predict response to targeted and immune-based therapies in real-time. We have developed a 3D Microfluidic controlled microenvironment device that consists of two media channels running parallel to and located on either side of an extended, central region containing tumor cell spheroids embedded within an extracellular matrix1. Here, we demonstrated the ability to interrogate ex vivo from a Her2 mutant derived from PDX model. The results showed that how two Her2-EGRFR inhibitors (Neratinib and Afatinib) can kill the tumor cells compare to the gefitinib resistance, then, we tried to use the benefit of combination therapy of Neratinib with Herceptin and we have confirmed the tumor killing effect by immune fluorescent (IF). Finally, we have evaluated patient-derived organotypic tumor spheroids (PDOTS), isolated from non-small lung cancer cells, colorectal, pancreatic, melanoma and thyroid patients. The data showed that how the tumor cells were killed vs immune cells and how the combination therapy works better than the single agent alone. Taken together, these data provide the first demonstration that ex vivo functional tumor killing using PDOTS is feasible and recapitulates key futures of in vivo response and resistance. In summary, we provide here the first evidence that short-term organotypic tumor spheroid culture can model response to the target therapy and much needed advance given the challenges of testing the massive number of potential combination therapies in vivo. We recently demonstrated the capacity of this system to culture primary human tumor as patient derived organotypic tumor spheroids. Importantly, these spheroids not only contain tumor cells, but also bring with them their unique repertoire of infiltrating immune cells, enabling the capacity to study the phenotypes and function of these immune cell populations cytokine and other responses ex vivo2.

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