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Single Cell Droplet Sequencing to Accelerate Functional Genomic Studies

As more and more genomic sequencing data is gathered, further light is being shed on all the somatic mutations in cancer. These mutations include unique combinations of driver and passenger mutations; there could be hundreds of such mutations of which only a small number contribute to cancer progression. Figuring out the relevant combinations of mutations is key for understanding the development of cancer and creating personalized and targeted therapeutics. Thus, there is increasing demand for better functional genomics screens.

In most genome-wide functional genomics screens, pooled libraries of perturbagens are used; however, only one perturbagen per cell can be tested at a time. This results in multiple rounds of stepwise clonal screening which is not only difficult to scale up but is also time and labor intensive. Additionally, some perturbagen combinations become functionally active only when all the components exist in a cell, thus, these are missed in conventional approaches. Further still, the stepwise approach suffers from low discovery rate as only some of the founding mutations can be selected and carried over to the next screening rounds.

Researchers at Arizona State University have developed a novel single-cell droplet sequencing-based screening approach which is designed to amplify and detect multiple perturbations at the single cell level for functional genomics screens. By allowing for the transduction and testing of multiple perturbagens in parallel, this platform will provide significant advantages over conventional screening methods. It can unveil novel mutational combinations that contribute to cancer progression as a group and it can accelerate target discovery by eliminating the time/labor intensive process of multiple screening rounds and clonal expansion needed with single perturbations. Additionally, this platform can be adapted for many other single-cell targeted omics applications such as targeted exome sequencing, RNA-Seq, metagenomics and metatranscriptomics.

This novel platform has the ability to greatly accelerate the discovery process of pathologically important mutational combinations for advancing cancer research, drug discovery and personalized therapy.

Potential Applications

- Functional genomics screens

o Target discovery & drug development in cell lines and patient-derived cells

o Single-cell targeted sequencing of DNA and RNA for integrated target discovery

o Metagenomics & Metatranscriptomics

- Building a metabolic flux model from host and microbial species-specific gene expression profiles & metabolomics

- Mapping pathways altered by mutations or gene expression to determine tumor heterogeneity in aggressiveness and drug resistance

- For protein multimers (T cell receptors, TKRs, other cell receptor) – determines which chains/subunits partner together in individual cells for tumor immunotherapy

Benefits and Advantages

- Provides information on co-occurrence of multiple genome-integrated perturbagens in a single cell

- Accelerates functional characterization of cancer somatic mutations & drug target discovery

- Can handle the complexity of combinatorial perturbagens by targeted sequencing of millions of cells with existing NGS technologies

- Can unveil previously unknown functional crosstalk between multiple genes and mutations for discovery of novel drug targets

For more information about the inventor(s) and their research, please see Dr. LaBaer's Biodesign webpage Dr. Park's Biodesign webpage