FASTFACTS

Identify and Select Optimal T Cell Phenotypes

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PERFORMING MULTIDIMENSIONAL, FUNCTIONAL ASSAYS ON SINGLE T CELLS CAN ADDRESS KEY CHALLENGES IN ADOPTIVE CELL THERAPY DEVELOPMENT

When developing an adoptive cell therapy (ACT), identifying and selecting optimal cell phenotypes is a critical step – but identifying which cell characteristics correlate to clinical efficacy is an ongoing challenge for the field. The Berkeley Lights Platform allows the characterization and selection of T-cell phenotypes at a single-cell level, in order to ensure the best chance of developing powerful and effective therapies.

KEY CHALLENGES FACING ACT DEVELOPMENT

While immune checkpoint blockade therapies have greatly improved the survival of cancer patients, many patients still see their disease progress. It is thought that ACTs could be an additional treatment option for patients whose cancers do not respond to checkpoint blockade. However, a lot is still unknown about ACT, and many research groups are working to identify which T-cell phenotypes correlate to clinical efficacy.

Using traditional approaches, different subpopulations of cells are used for cytokine secretion analysis, tumor killing assays, and transcriptional analysis to associate a gene expression pattern with cellular function. This approach does not provide a complete profile of any single cell. However, a study has shown that a single CAR T-cell, and the progeny of that one cell, was able to cure patients with chronic lymphocytic leukemia [1], highlighting that finding the right cell can be the key to a successful therapy.

IDENTIFYING THE BEST T CELLS FOR ADOPTIVE THERAPIES

Important characteristics of T-cells which are likely to be associated with patient response include cells with early, less differentiated memory phenotypes that maintain proliferative capacity in the presence of a tumor cell, providing durable anti-tumor immunity. Polyfunctional cytokine secretion to mediate a wide breadth of immune mechanisms is also important, as is serial killing behavior – i.e., cells which are able to kill multiple tumor cells quickly.

THE BERKELEY LIGHTS PLATFORM

The use of optofluidic chips is a key component of the Berkeley Lights Platform and there are two commercially available instruments: the Beacon® and Lightning™ optofluidic systems, which can perform various automated workflows for cell discovery and development.

MULTIDIMENSIONAL, FUNCTIONAL ASSAYS ON SINGLE T-CELLS

With the Opto™ Cell Therapy Development workflow, a variety of assays can be used to study T-cells and identify the most useful phenotypes:

- Polyfunctional cytokine secretion
- Cytotoxicity
- Antigen-specific proliferation

Layering these assays together makes it possible to identify T-cells with the ideal combination of functions.

FINDING THE RIGHT CELL MATTERS

Using the Opto Cell Therapy Development workflow on the Berkeley Lights Platform, a variety of assays can be performed to measure T-cell characteristics in thousands of individual cells, which can then be recovered for further analysis. This uniquely empowers the correlation of gene expression patterns to multidimensional phenotypes, in order to identify the most effective therapeutic cells.

REFERENCE

1. DOI: 10.1038/41591-018-0010-1

Figure 1. OptoSelect™ chips contain thousands of NanoPen™ chambers, each less than one nanoliter in volume. Using opto-electropositioning (OEP™), single cells are imported and stored. Once assaying and culturing is completed, cells can be dispensed into well plates for downstream expansion or genomic analysis.

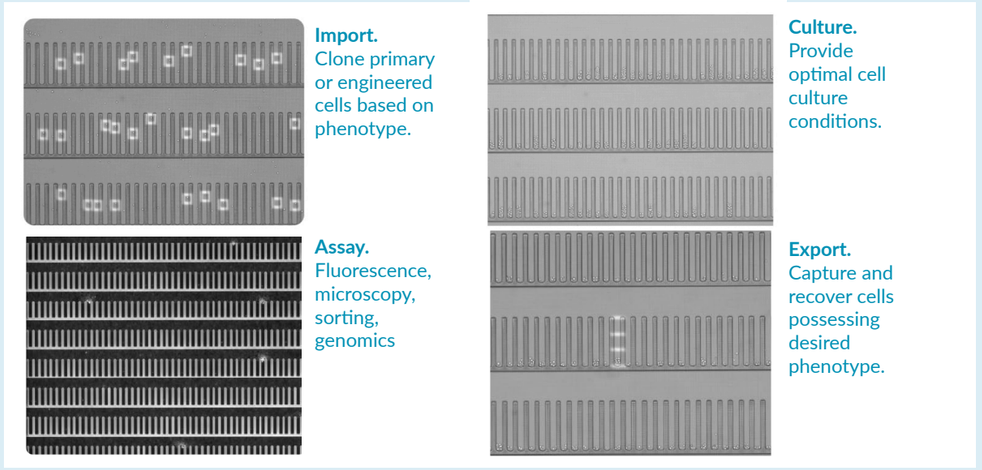


Figure 2. To identify T-cells which are prolific killers, cytotoxicity and proliferation assays were combined to find a subset of cells which were both capable of tumor killing and also proliferative.

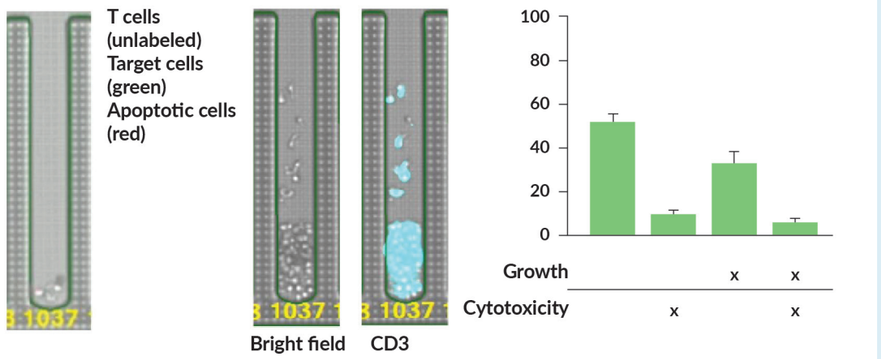
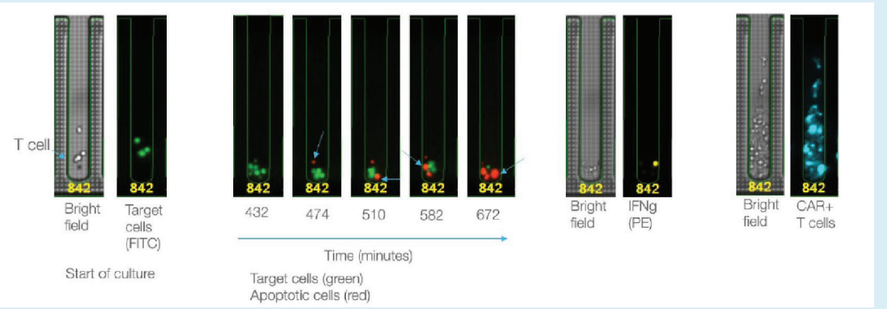


Figure 3. Every function can be studied collectively. A single T-cell with several tumor cells (green) was studied, and 4 separate killing events (blue arrows) were identified. IFNγ secretion from the cell was then measured. After the chip was left to culture for 5 days, a colony of proliferating T-cells was observed. This single T-cell was shown to kill multiple tumor cells, secrete cytokines, and proliferate. The T-cell colony can easily be recovered for downstream analysis.



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