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802.CHEMICAL BIOLOGY AND EXPERIMENTAL THERAPEUTICS

High Throughput Microfluidics Platform to Assess Synthetic Lethality and Novel Therapeutic Drug Combinations

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Molecularly targeted therapies have reshaped cancer treatment in recent decades; however, not all patient cancers are eligible for or effectively treated by such approaches. In addition, resistance mechanisms (both pre-existing and acquired) limit clinical benefit. To these ends, combination therapies involving targeted agents are increasingly being developed for their potential to induce potent synthetic lethalities, bypass drug resistance, promote durable responses, limit adverse side effects via reduced dosing, and expand treatment options. In the context of acute myeloid leukemia (AML) specifically, several efficacious combination therapies have been approved for specific patient subsets, such as all-trans retinoic acid (ATRA) plus arsenic trioxide in the *PML-RARA* fusion acute promyelocytic subtype and Midostaurin plus Cytarabine and Daunorubicin in *FLT3*-mutant AML. Despite the availability of these and other therapies, there remains an unmet need for treatments against AML subtypes lacking actionable driver alterations or for which current therapies are insufficient.

A major hurdle limiting novel combination therapy discovery is the sheer combinatorics associated with mixing two or more agents (e.g., screening all possible pairs of 100 drugs in a single cell line requires nearly 5,000 combination experiments). Thus, there is a practical need for methodologies that prioritize test compounds among broad candidate sets and high throughput technologies for rapid and efficient screening. We have developed a combination drug screening workflow that integrates machine learning-based predictions of potentially synergistic compound pairs with a droplet microfluidics-based screening platform. Our physical platform, termed the FlowMatrix, contains a series of nano wells arrayed in a 96 x 96 grid (for 9,216 total wells) in which cells are incubated and compounds delivered via emulsified droplets. To facilitate drug combination screening, the FlowMatrix is loaded column-wise with a 96-element library and subsequently loaded a second time along its rows with either the same or an independent drug library. In our current setup, one FlowMatrix can capture complete data for up to 100 unique drug pairs, which includes control, single-agent, and 4x4 dose combination measurements for each pair. Following multi-day incubation, viability for each well is assessed by the number of live cells imaged with fluorescence microscopy. Combinations with high scoring synergy based on Bliss independence criteria are then pushed to validation and further characterization pipelines.

We are currently focused on identifying novel combination therapies for AML. Using small molecule libraries of diverse compound classes and machine learning to prioritize initial screening candidates, we have to-date profiled >8,500 AML cell line-drug combinations in our system. This encompasses >2,900 unique drug combinations profiled in 7 distinct AML cell lines. Among ~270 hits that emerged from these screens are established clinical and preclinical AML combination therapies, in addition to candidates that, to the best of our knowledge, are novel in the context of AML. Strong established hits in our screen include ATR inhibition plus Gemcitabine treatment as well as several combinations involving the BCL-2 inhibitor Venetoclax with chemotherapies (Decitabine and Daunorubicin), Quizartinib, Idasanutlin, and mTOR inhibitors. Thus, we have developed an efficient and cost-effective high throughput drug combinations profiling system that has uncovered candidate therapies that may expand treatment options for patients afflicted by AML.

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