ACCELERATING DRUG DISCOVERY USING THE TRANSCRIPTIC ROBOTIC CLOUD LABORATORY

James C. Culver¹, Vanessa M. Biggers¹, Rhys A. Ormond¹, Yang Choo¹, Benjamin N. Miles¹, Yin He¹

INTRODUCTION
As the pace of drug discovery has quickened, the need for effective high-throughput screening pipelines has become more important than ever. However, establishing new pipelines while limiting fixed costs remains a significant problem. Here, we show how the Transcriptic Robotic Cloud Laboratory can be used to overcome these obstacles for three types of screening paradigms: Biomarker Quantitation, Biochemical Assays, and Cell-Based Assays. These data show that the Transcriptic platform can be used to quickly and effectively automate high-throughput biology to collect important experimental results. By integrating these validated tools into a drug-discovery pipeline, Transcriptic’s high-throughput platform provides new opportunities for using high-throughput screening to accelerate the discovery process.

MATERIALS AND METHODS

High-Throughput Automation
Transcriptic’s web platform was used to design and execute experiments using Transcriptic’s robotic Workcells (see Figure 1).

Biomarker Quantitation
Protein was extracted from mouse liver tissues, and cytokine levels were compared to commercial standards using an electrochemiluminescent immunoassay (Meso Scale Discovery’s V-PLEX proinflammatory panel 1 mouse kit). Quantitative analysis was performed in duplicate on each sample across the following biomarkers: IFN-α, IL-1α, IL-2, IL-4, IL-5, IL-6, KC/GRO, IL-10, IL-12p70, and TNF-α.

Biochemical Assays
Protein stability was measured using the Protein Thermal Shift Starter Kit (Thermo Fisher Scientific). Kit controls were used to prepare reactions by combining thermal shift dye with varying concentrations of control protein and control ligand. Melt curves were then generated using a CFX96 Real-Time PCR Detection System (Bio-Rad).

Cell-Based Assays
Cultured cells were plated onto 384-well plates and dosed with various drug combinations at nanoliter-scale volumes. Dosed cells were subsequently assayed for cell death using the CellTiter-Glo luminescent viability kit (Promega) on an Infinite M200 Pro plate reader (Tecan).

RESULTS

Biomarker Quantitation
Transcriptic’s platform was used to successfully extract protein from mouse liver biopsies and to quantify the levels of proinflammatory cytokines present in each sample. Ten targets were assayed per 25 µL sample replicate. The broad dynamic range of the assay allowed for accurate quantitation of target concentrations across 3-4 orders of magnitude (see Figure 2).

Biochemical Assays
Transcriptic’s platform was used to successfully screen for small molecules that affect protein thermal stability. Using a fluorimetric assay to measure protein melting temperatures, a small molecule was identified that stabilized the protein of interest (see Figure 3).

Cell-Based Assays
Transcriptic’s platform was used to successfully identify drug combinations that effectively target patient-derived tumor cells. Drugs were screened in high-throughput at nanoliter-scale volumes. Drugs with a cytotoxic effect were identified for further validation (see Figure 4).

CONCLUSIONS
Using the Transcriptic Cloud Laboratory to automate high-throughput screening proved to be fast, cheap, and effective for every assay we tested. These advantages represent new opportunities for leveraging high-throughput automation to accelerate traditional drug discovery pipelines.

ACKNOWLEDGEMENTS
We are grateful to the California Pacific Medical Center Research Institute (CPMCRI) for sharing cell viability data.

Figure 1. Transcriptic’s robotic Workcells were used to automate high-throughput assays.

Figure 2. Protein concentrations were quantified across a broad dynamic range using an electrochemiluminescent detection assay.

Figure 3. Melt curves were generated for the protein with or without ligand, and for buffer only (4 replicates each).

Figure 4. A luminescent viability kit was used to measure cell death following incubation with various drug combinations. Low luminescence indicates low viability (columns 1-2 and 23-24 are blank) [courtesy of CPMCRI].