A HIGH THROUGHPUT SCREENING SYSTEM TO IDENTIFY ACTIONABLE TREATMENTS FOR CANCER PATIENTS

Notable Labs is a startup biotechnology company in San Francisco focusing on the repurposing of FDA-approved drugs to improve personalized chemotherapy. Using their Biosero WorkCell, Notable Labs identifies actionable treatments for cancer patients by screening a patients cancer cells against a vast number of drug and drug combinations (drug/drug combinations) which can then be prescribed by their physician without clinical trials. They are currently concentrating on two types of cancers, acute myeloid leukemia and glioblastoma multiforme. Prior to purchasing their WorkCell, Notable Labs needed a way to make their patient cell screening process robust, scalable and cost effective.   In addition, to maximize the number of drug/drug combinations tested with the limited number of patient cells they receive, they needed to miniaturize their assays. Notable Labs collaborated with Biosero, Inc. to develop an automated cellular screening WorkCell capable of screening up to 30,000 drug/drug combinations with multiple assays against a cancer patients cells.

Automated WorkCell to Screen Drug and Drug Combinations

To achieve Notable Labs objectives, a WorkCell with automated sample handling, compound management, and comprehensive results management was developed. By adopting acoustic liquid handing technology, Notable Labs miniaturized their assays using an EDC Biosystems™ Gen 4 Acoustic Transfer System (Gen 4 ATS). To create their drug/drug combination plates for screening, the Gen 4 ATS dispenses from 1 nL to 2 µL of drug to the wells of a 384 well microplate. Dispensing compounds via acoustic energy eliminates costly pipette tips from their assay and any opportunity for carryover between dispenses. The other elements of the Workcell are a Tecan Infinite® M200 Pro Series Multimode Microplate Reader, PAA microplate storage solution, Precise Automation PreciseFlex Sample Handler, Thermo Fisher Scientific Multidrop™ Combi Reagent Dispenser and Cytomat™ 24C Automated Incubator, and IntelliCyt iQue® Screener Plus System (Figure 1). System control is provided by Green Button

Go (GBG) automation and scheduling software that schedules the assays, provides real-time monitoring of instrument status, plate location, assay details, and data management. Titan, Notable Labs proprietary LIMS system, manages the process at a high level and analyzes the data.

Figure 1. Notable Labs high throughput WorkCell driven by Biosero's Green Button Go software.

High Throughput Screening of Cancer Patient Cells

Notable Labs workflow to screen patient cells is shown in Figure 2. Patients with poor "Standard of Care" treatment options are referred to Notables Labs. Tumor resections or blood/bone marrow samples from the patient are sent overnight to San Francisco for screening. Samples are manually assessed immediately using an internal assay and strategically classified for further screening analysis. Cancer and healthy white blood cells are harvested/enriched from the delivered sample and seeded into 384 well microplates. Prior to a screen, Titan uses both patient history and sample information to generate a list of drug/drug combinations from Notable Labs 1000 drug library, randomizes their location on the compound plate and passes the information and triggers GBG to carry

Your doctor sends	Based on your tumor	We test	We provide	Your doctor uses
a sample of your tumor to Notable Labs.	we choose a panel of FDA-approved drugs that have published anti-cancer effects.	thousands of combinations of these drugs against your tumor.	a report of the results to your doctor within several days.	our report to make treatment recommendations for you.

Figure 2. Notable Labs workflow to screen patient cells

out patient specific protocols (Figure 3). After incubation with the drug/drug combinations, cells are assayed for viability and apoptosis. For viability, cells are assayed using Promega's Cell-Titer Glo luminescence assay and read on the Infinite M200 Pro Microplate Reader. For apoptosis, multiple assays are multiplexed within the same well and analyzed by the Intellicyte iQue Screener Plus System to enable comparison of the effect of drug/drug combinations on normal versus cancer cells with single cell resolution. After the screen is complete, information flows back from GBG to Titan for consolidation, automated data analysis and a comprehensive report is generated for the physician. By using their Biosero WorkCell to miniaturize and automate their assays, Notable Labs can screen up to 30K drug/drug combinations against a cancer patient's cells, which would have been impossible to do with a manual assay.

Identification of Alternative Treatment Options for Cancer Patients

By repurposing FDA-approved drugs, Notable Labs helps physicians identify alternative treatment strategies that cancer patients can use immediately. Their custom WorkCell provides a scalable and affordable approach to screening a vast number of drug/drug combinations against a cancer patient cells and completely automates sample handling, compound management, screening and results management. The automation enables the generation of large datasets that can be viewed as clustermaps (figure 4) to show how groups of patients respond to different drug/drug combinations to identify specific compounds or combinations that perform optimally in vitro on individual patients cells. By using a Gen 4 ATS they've miniaturized their assay to maximize the number of drug/drug combinations tested while minimizing their usage of valuable patient cells.

The flexibility of Gen 4 ATS to dispense compounds from any source plate well into any destination well provides the possibility for Notable Labs to customize a patient screening protocol to screen the entire combinatorial space of drug/drug combinations of their compound library or focus on a specific subset of drugs/drug combinations. GBG software oversees the entire operation and scheduling of the WorkCell. GBG was selected because of it's broad instrument driver set, ease of developing a custom driver for the Intellicyt iQue Screener Plus System, and ease of programming for non expert users. This makes the WorkCell extensible to many types of assays and simplifies the integration of new instrumentation. Using the system, Notable Labs routinely screens 5K to 10K drug/drug combinations per run with the possibility of screening up to 30K drug/drug combinations. In addition to providing cancer patients with actionable treatment options, the large data sets are being used to build models for a structured approach to identify drug/drug combinations for cancer treatment.
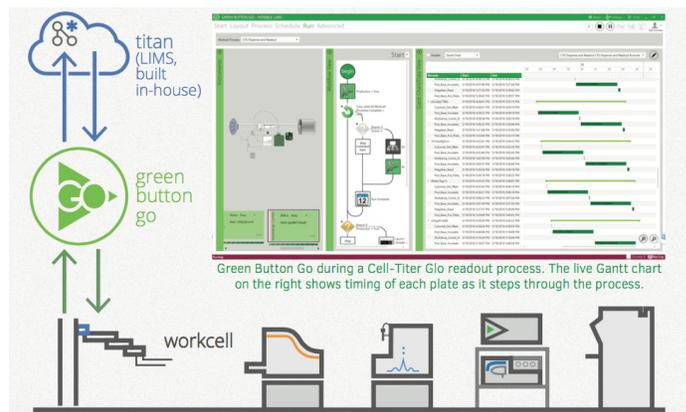

Figure 3. Diagram of the information flow to perform a screen. Notable Labs proprietary LIMS system, Titan, generates a list of test conditions. This information is passed to GBG which overseas scheduling and general WorkCell control. At the completion of a screen, data flows back from the WorkCell instruments to GBG and is uploaded to the LIMS system for data consolidation and automated analysis.
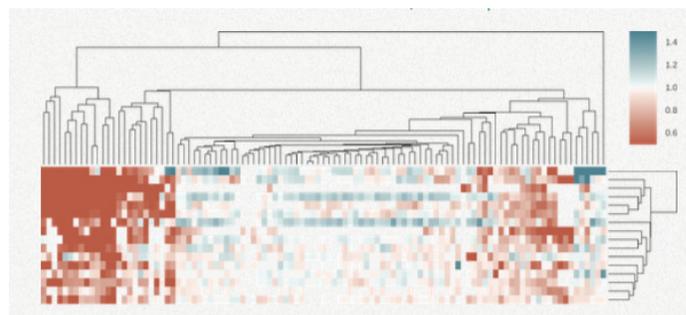

Figure 4. Clustermaps are generated from the data. Each column is a drug/drug combination and each row is a different primary cell sample from a patient. From this we can identify that certain groups of patients are responsive to different drug/drug combinations. Red colors signify inhibition, while blue colors signify differentiation.