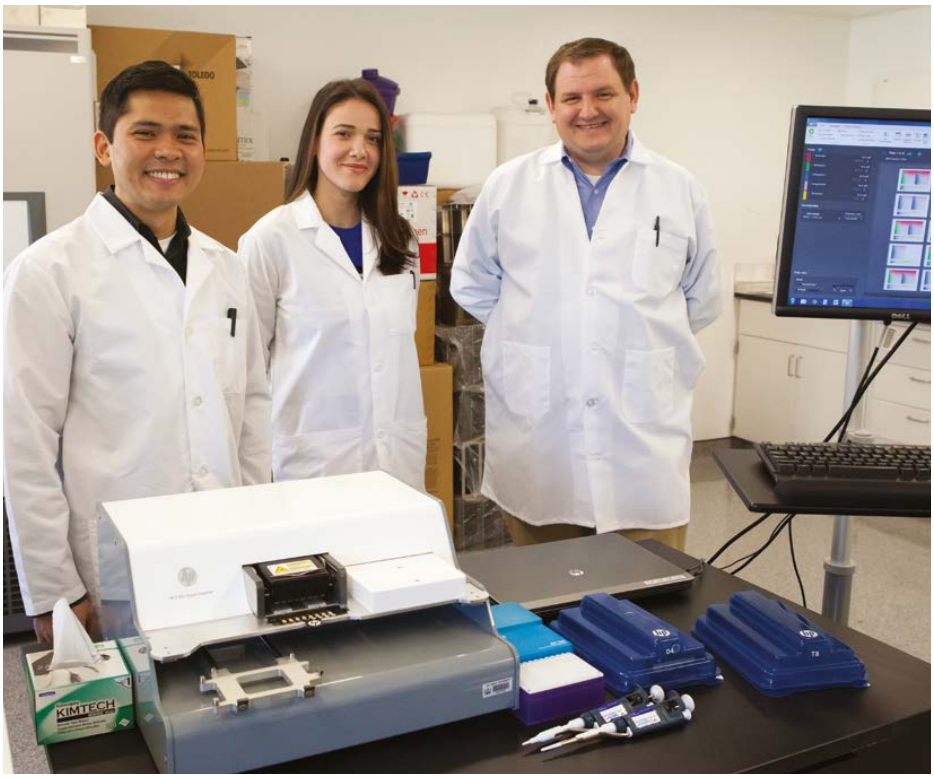
Rapid generation of dose-response curves for high throughput screening

The HP D300 Digital Dispenser is enabling researchers at the Columbia Genome Center's High-Throughput Screening Facility to quickly and simply create dose-response curves for combinations of up to nine compounds, allowing rapid generation of EC_{50} data for faster experimental progress.

The High-Throughput Screening Facility at the JP Sulzberger Columbia Genome Center, part of the Department of Systems Biology at Columbia University Medical Center in New York City, USA, provides molecular screening services to researchers within the University and in external laboratories. The Center is also the core screening facility for NYSTEM – the New York State Stem Cell Foundation – which supports stem cell researchers across the state, and has particular expertise in developing stem cell screening assays. Dr Charles Karan, Scientific Director of the High-Throughput Screening Facility, explained: "We work with scientists engaged in long-term research projects – mainly traditional high throughput screening (HTS) and discovery processes – to design, develop and execute their assays, and to understand the complex follow-up procedures and the implications of their experimental results. We also have a next generation sequencing (NGS) facility, and are currently working to bring these tools together."

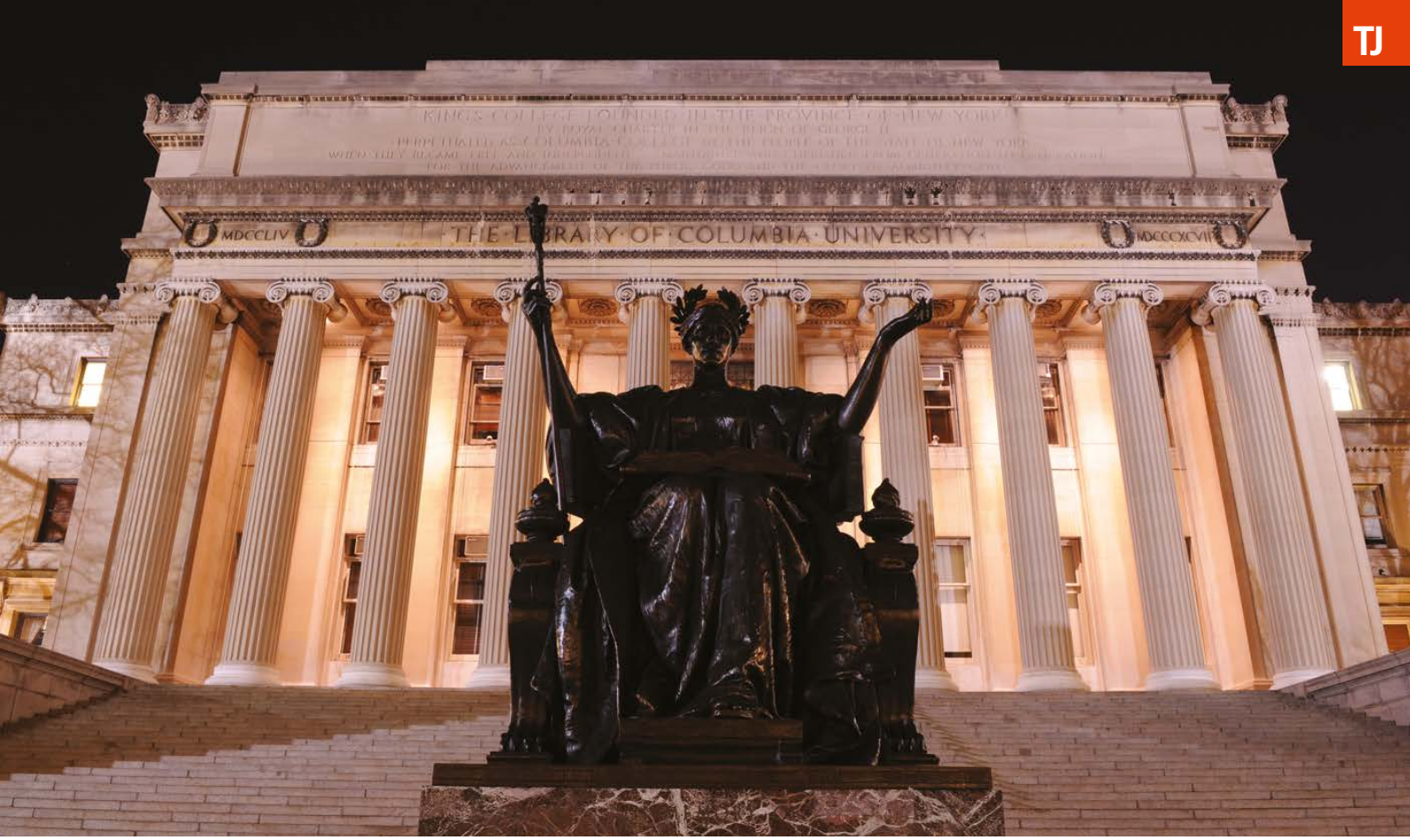
"Over the years, our collection of automated systems has evolved in response to specific needs. We run most of our ultra-high throughput assays on a large, automated system, purchasing other instruments – such as the HP D300 Digital Dispenser – to address specific needs as they arise. We do a lot of drug synergy experiments, simultaneously studying the effect of two compounds on cells, and the traditional HTS method of creating master plates and then running a dilution series is extremely laborious and material intensive. There is also an element of risk in using plastics with small molecules. We needed a rapid, flexible platform for more cost-effective drug synergy experiments, and chose the HP D300 rather than the alternative acoustic technology because it allows us to generate highly reproducible dose-response curves economically."



Left to right: Ronald Realubit, Xhensila Hyka and Charles Karan with the HP D300

Charles continued: "The HP D300 fills a particular niche in our department, allowing us to react rapidly, set up and run an experiment. Another big advantage for drug synergy studies is the excellent reproducibility of individual EC_{50} curves. With this level of confidence in our results, we can run our chosen experiments knowing that the results are consistent from one run to the next. The robust liquid handling capabilities of the HP D300 let us focus on the drug concentrations we are really interested in and, as we don't need to look at the initial curves and then create a different dilution series, assay series progress faster; we can generally hone in quite rapidly on an observed result for in-depth investigation. The HP D300 is invaluable in this respect."

"In the beginning, we carried out small-scale experiments with a single combination of compounds. Today, using the latest HP D300 software, we run larger, 30-plate assays, looking at replicate combinations of eight or nine drugs across different time points. We prepare stem cell plates on our large automation system, then simply transfer the



plates to the HP D300 to dispense screening compounds into the plate wells, using the instrument's plate randomization function to ensure robust data that is free from edge effects. For small molecule screening in DMSO – a solvent that can affect subsequent NGS assays – best practice is to normalize DMSO concentrations, and the large D4 cassette is perfect for this, allowing us to use far fewer cassettes per plate."

"The system is highly intuitive, and has proved very popular. We are increasingly finding that people from outside the facility are coming in to use the HP D300 for their own projects. It provides a simple method of generating dose-response curves that eliminates serial dilution, and is ideal for our drug combination studies. The instrument does exactly what we want it to do, fulfilling our need for an instrument that staff can just walk up to and use straight away for small molecule studies, with very little set-up time required. I am really happy with the HP D300," concluded Charles.

To find out more about the HP D300 Digital Dispenser, visit **www.tecan.com/digitaltitration**

To find out more about the High-Throughput Screening Facility, visit **systemsbiology.columbia.edu/genome-center/high-throughput-screening-automation**

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Charles Karan setting up an experiment on the HP D300