

Accelerating results from bench to bedside

The direct digital dispensing capabilities of the HP D300 are helping to identify potential new treatments for acute lymphoblastic leukemia at University Children's Hospital Zurich. By enabling picoliter drug volumes to be dispensed straight into cell-based assay plates, the system is helping researchers to rapidly test novel drug combinations directly in patient-derived leukemia cells.



The Division of Pediatric Oncology at University Children's Hospital Zurich (Kinderspital Zürich), Switzerland, has an active translational research program, working in close collaboration with the University of Zurich and other institutes to identify potential new treatments for a number of childhood cancers. As the most frequent form of childhood leukemia, acute lymphoblastic leukemia (ALL) is a key area of research, and the hospital has a special interest in drug-resistant ALL, using a combination of cell-based assays and mouse models to identify novel therapeutic strategies. Dr Jean-Pierre Bourquin, Associate Medical Director of Oncology at the hospital, explained: "We have built a model system that allows us to test material from selected clinically-relevant patients against new drugs and drug combinations. We use a mouse xenograft technique – implanting patient-derived leukemia cells into a tolerant mouse system – to both generate cells for microplate-based co-culture assays and to provide an *in vivo* model. This approach ensures we have enough material to do large-scale investigations which are directly relevant to our patients."

"Due to the drug-resistant nature of the ALL samples we use, we do a lot of drug combination studies, and perform all our cell-based assays in 384-well plates.

Designing and pipetting these studies in such high density formats manually can be very time consuming and, like any manual activity, can be prone to errors and inter-operator variability, and so we were looking for ways to improve and streamline our workflow. Automation was an obvious option but, because we are only a small satellite laboratory without the resources and support of a major university facility, a large liquid handling workstation was not a viable option. We discussed our needs with our local Tecan representative, who suggested the HP D300 Digital Dispenser. This instrument is ideal for us; it doesn't take up much space, it's cost effective, and it's very easy to use."

"The D300 is also very convenient for our drug combination studies, allowing us to rapidly design and plan experiments simply by entering the relevant parameters into a matrix. The system then randomizes the plate layout and dispenses the correct volumes of each compound directly into the microplate wells. It's incredibly fast and so simple; what would take half an hour by hand is done in just a few minutes. This is a huge advantage when handling human-derived cells, as they spend as little time as possible outside of the incubator."

"The speed of the instrument is also of potential clinical importance, as we

are currently exploring using it for drug activity profiling as part of a clinical trial for pediatric patients whose leukemias do not respond to the standard treatments. These patients are offered highly accelerated whole genome investigations and, at the same time, we profile the activity of a selection of compounds for compassionate use 'salvage' treatments. In this situation, the speed and reproducibility offered by the D300 is obviously a real benefit."

"For example, in a recently published study¹, we used this approach to help us investigate the drug susceptibility of a very rare TCF3-HLF-positive ALL characterized by a chromosomal translocation. Using the D300, we were able to investigate the sensitivity of this ALL to venetoclax – a drug more commonly used in chronic leukemias – in combination with a range of other therapeutics. The data from this study was very promising, and we are now investigating these combinations using the *in vivo* mouse model, with outstanding results."



Viktoras Frismantas and Dr Scott McComb with the hospital's D300 instrument

“The introduction of the D300 has been a big improvement for our workflow, proving the ideal complement to the equipment we already had in the lab. It has enabled us to substantially accelerate many experiments, exploring more complex drug combinations and asking more focused questions. We mostly work with small molecules in DMSO, but the recent upgrades to the D300 mean that we now also have the ability to dispense aqueous solutions, allowing us to investigate biological agents, such as antibodies and antibody-derived therapeutics. Ultimately, the system is helping us to take a more personalized approach to the management of this rare population of patients with highly resistant disease.”

To find out more about Tecan’s D300e, visit www.tecan.com/d300e

To learn more about University Children’s Hospital Zurich, go to www.kispi.uzh.ch

1) Fischer, U *et al.* Genomics and drug profiling of fatal TCF3-HLF-positive acute lymphoblastic leukemia identifies recurrent mutation patterns and therapeutic options. *Nature Genetics*, 2015, **47**, 1020-1029.

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