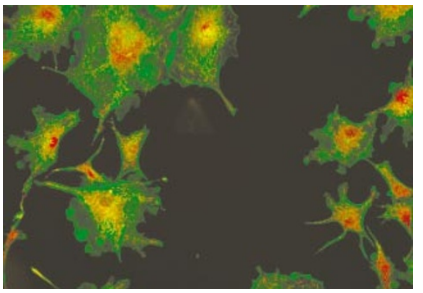
The UltraView system is based on confocal microscopy, an optical sectioning technique that uses a scanning laser to produce high-resolution images from the fluorescence emitted by the sample. Traditional confocal microscopes can be too slow to study the most rapid cell processes, and the intensity of laser light can damage living cells.

Rather than using a single pinpoint laser beam, UltraView uses a broad beam imaged through two rapidly rotating discs: one, called a Nipkow disc, contains several thousand pinpoint holes; the other is an aligned disc featuring an equal number of microlenses to focus light onto the former. "You end up with 1,000 laser beams which shower the sample with light," says McCann. "Instead of one point being imaged, you have 1,000 points being imaged. You can see the whole field of view more quickly, and you also use very much less light."

High-throughput scanning

Live-cell imaging is also being taken into the high-throughput environment of industrial drug screening. The combination of high-throughput screening and high-content imaging of cells was pioneered by Pittsburgh-based Cellomics (see 'High throughput goes 3D'), and the major producers of automated lab equipment are now moving into the field.

The IN Cell Analyzer 3000 produced by Amersham Biosciences of Buckinghamshire, UK, is a confocal imaging system designed to perform high-resolution cellular assays at the rates demanded by today's automated drug-discovery labs.



Y. SOEN, A. MORI, T. PALMER, P. BROWN/STANFORD MEDICAL CENTER

ImageXpress: neural stem cells.

"There's an increasing need to understand what's going on within the cell, and to do that in the environment of high-throughput screening is extremely valuable," says John Anson, vice-president for bioassay development at Amersham. "The objectives and a lot of the resolution come from existing technology, but what we've been able to do is build in the robustness and speed to take this through to the high-throughput environment."

Although the system uses laser-based autofocusing and other technologies to ensure rapid imaging of its well plates, the key to high throughput is in the software. "What we've been able to do is develop a software regime with the capability and speed not only to capture the data but to analyse it in a very short space of time," Anson says. "In the time it takes to mechanically move from one cell to the next, the software is doing all the work to generate knowledge from the image it's just taken." Integrated software also allows data to be combined with data from other Amersham systems such as its Typhoon and Storm series of gel scanners. "This technology isn't necessarily stand-alone," notes Anson. "Everyone would be interested in comparing data from cellular assays with *in vitro* assays such as gene expression in gel."

Integrated software is also at the heart of the high-throughput capabilities of the ImageXpress system produced by Axon Instruments of Union City, California. Like Amersham's IN Cell, ImageXpress is a rapid, robust automated system for imaging and analysing live cells, with applications in target evaluation, compound optimization and toxicology tests. The system incorporates a general-purpose analysis engine that can be applied to many different assays through a toolbox of dedicated software. Axon has recently developed sophisticated neuronal image-analysis software in association with the Australian research body CSIRO, which is now included in ImageXpress's toolbox.

Automated operation and image processing are based on the common VB scripting protocol, allowing ImageXpress to be integrated with plate-loading robots and other automated systems. Axon's Acuity image-analysis software, meanwhile, allows the import of data from other systems for multiparametric data mining.

"I think this technology is reaching a consolidation phase where the capabilities of the

HIGH THROUGHPUT GOES 3D

High-throughput analysis of cellular processes is now entering the mainstream for drug discovery, but Pittsburgh-based Cellomics has been working in this area for some time. Founded in 1996 to focus on the automated analysis of cell arrays, Cellomics offers an integrated package of imaging platforms with full environmental control, bioassays and bioinformatics and analysis software.

The firm produces two core platforms: KineticScan analyses cellular and intracellular interactions over time, and can deal with either live or fixed cells, whereas ArrayScan generates information-rich data on the effects of drug candidates on cells and is aimed at target validation and lead optimization applications.

The modular architecture of ArrayScan VTI, the fifth and latest generation of the system, allows users to increase optical capabilities by adding filters and objectives, and software to handle and visualize data better. The system also addresses the two conflicting aims of array screening — the need for high throughput, and the need for information-rich, high-resolution data including three-dimensional imaging.

"It takes time to acquire various *z*-positions and use higher magnification, so throughput is at odds with 3D resolution," says Martin Pietila, high-content screening instrumentation product manager at Cellomics. "For the first time we've been able to offer both operating modes."

The latest ArrayScan includes the ApoTome optical-sectioning device developed by Carl Zeiss Microscopy of Jena, Germany, which can be deployed as required. ApoTome allows confocal-style three-dimensional imaging with a conventional fluorescence microscope, by projecting the image of a grid structure into the focal plane of the specimen. Combining images with the grid in three positions within this plane produces an optical section with improved contrast and resolution in the *z*-axis.

"This affords scientists precise control of sampling applications," Pietila says. "It allows them to take multiple measurements of different *z*-positions to look for structures with variable distribution in three dimensions." The ArrayScan VTI can analyse up to 150 96-well plates a day using ApoTome, or 260 a day without. **T.C.**

CELLOMICS

ArrayScan VTI: high-throughput screening goes confocal.