Modular Microscope-Based Screening Station

Drug Discovery has driven our understanding of scientific principles as well as advanced the equipment and processes used to research them. One overriding principle applied to this industry, is the drive for more data, in less time with fewer overheads. The scan^R Screening Station for Life Science is an instrument with the potential to meet all of these requirements and provide users with advantages over other products on the market.

Many protocols have been developed to show the effects of compounds at both the biochemical and cellular level. For example, some drugs are targeted at changing gene expression levels and this parameter needs to be assessed accurately via a range of standardised assays. The undesirable effects of potential pharmaceutical compounds is also an important factor to be quantified and therefore toxicology screens measuring apoptosis, micronuclei or DNA fragmentation (comet assays) are often used. With these screening protocols, plus many others (some listed below) in mind the Olympus scan^R Screening Station for life science was designed to provide a single, highly adaptable platform for all live cell-based screening assays.

Example Cellular Screening Assays

- Cell counting
- Gene expression
- Intracellular transport
- Translocation
- Cell proliferation
- Promyelocytic leukemia (PML) body assay
- Bacterial infection assay
- Cell cycle analysis
- Protein localisation and co-localisation
- Live cell assays
- Multi-colour assays
- Rare event analysis
- Automated FISH analysis
- Fluorescence analysis in tissue sections
- Cell array screens
- Micronuclei and comet Assays

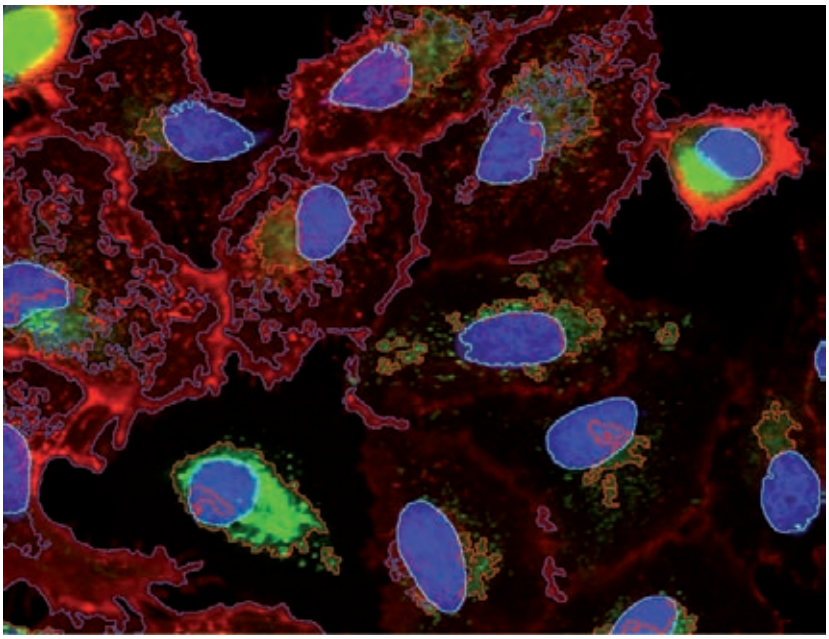

Fig. 1: Image screen shots following data acquisition using scan^R, demonstrating the detection and separation of labels. The blue DAPI-stained nuclei are circled in cyan; the detected CFP tagged VSVG in the Golgi are circled in red and the detected Cy-5 VSVG antibodies at the cell surface are circled in blue.

Acquire more

Each cell-based experiment produces a plethora of information, most of which is not fully collected since many assays endpoint studies. As a result, many key dynamic cellular and sub-cellular events are missed. The scan^R can track the changes over time in tens of thousands of living cells enabling dynamic time-lapse assays, with high data content. To achieve this, the scan^R incorporates advanced software and hardware modules controlled via an easy to use interface that provides access to all acquisition and analysis parameters. The system produces multi-dimensional (X, Y, Z, τ, λ & location) images with great ease, which once acquired can be automatically analysed by the powerful software. The multi-dimensional data sets are handled in a cytometry-oriented way, providing the best use of the data for immediate or downstream processes. Furthermore, the software allows for full image processing (e.g. background correction), object and sub-object detection, parameter calculation as well as sophisticated gating and classification schemes.

Flexible Format and Design

The list of assays is forever growing, therefore any system used in this arena must have the flexibility to be adapted quickly to new protocols, formats and output requirements. scan^R handles all standard assay formats with ease and can also be configured to accept any custom designs, such as spotted arrays and biochips. To extend the functionality further, a series of components can be added: The Olympus cell^cubator environmental chamber enables sensitive live cell imaging and a plate-loading robot greatly enhances throughput. Other features, such as an IR laser-based autofocus, terabyte data storage systems and a professional workbench add even more flexibility. scan^R is also available in a special development version that provides LabView source code interfaces for the ultimate experimental screening development platform. LabView is a powerful

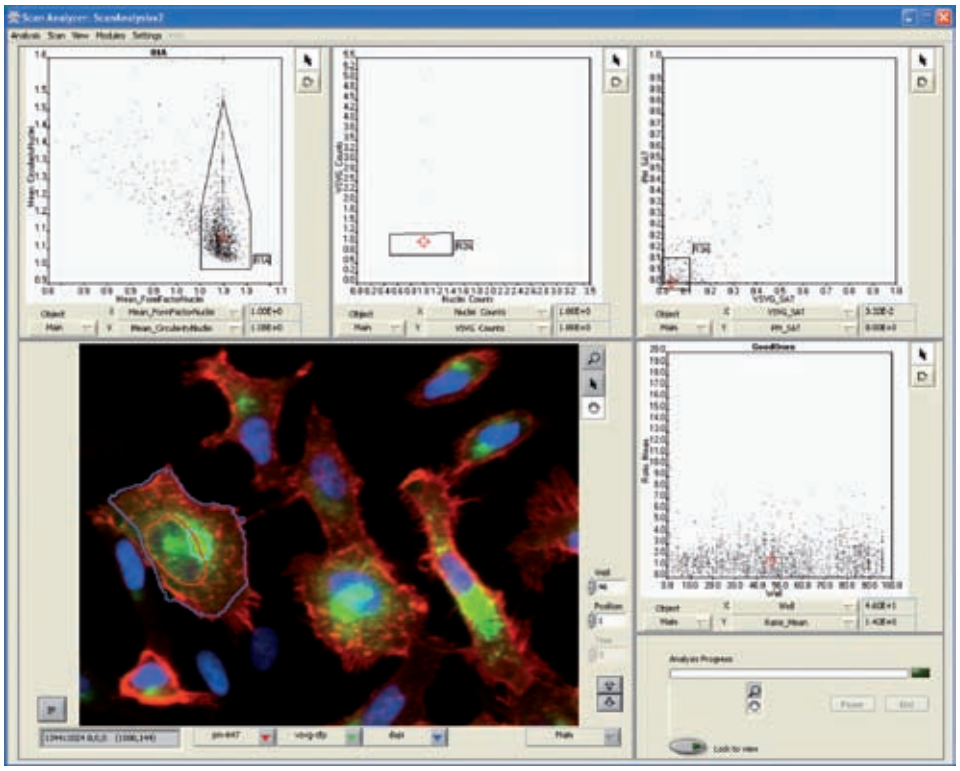

Fig. 2: Gating, classification and data evaluation by multiple selection of data sub-populations according to specific criteria.

graphical development environment for automation from National Instruments.

Precise Control

Capturing data for all events requires instruments with very fine and often high speed control of components such as illumination, filters and shutters as well as stage movement and focus. To achieve this, the scan^R Screening Station is fully integrated with a hyper-precise hardware Real Time Controller. This enables parallel operation of all components at sub-millisecond rates due to the independent CPU board, which ensures interrupt-free data exchange. Furthermore, scan^R can acquire images using both transmitted and fluorescent light in parallel and can also use contrast enhancing methods, such as differential interference contrast (DIC) or phase contrast.

scan^R provides a number of different auto-focus algorithms. The "cell-based" auto-focus uses specific features to identify the relevant objects and cells, thereby avoiding damaged or altered cells, cell fragments, dirt or dust. For highly variable samples an "image-based" auto-focus is used on information from the entire field of view. Image acquisition can be performed with a z-offset, with respect to the auto-focus plane, so that structures that are located in different focal planes can be imaged in focus.

Advanced Analysis

With the huge amount of data that is collected from these assays, there is a need for coherent and careful quantitative automated analysis. Also, depending on the type of protocols used, analyses may be needed immediately or at a later time. scan^R can complete both on- and off-line image processing and analysis, giving the choice to the user. Another advantage of collecting more assay data is that there are more analytic techniques that can be applied to the data. These can be as simple as counting all the cells on display or as complex as ratiometric feature-based analysis of multi-colour labelled objects and sub-objects in different cell-types. Image analysis is carried out as a logical multi-step procedure consisting of: Image processing, object detection, feature extraction and data analysis by gating and classification.

The scan^R analysis module not only provides powerful image processing but also excels in the subsequent data analysis and evaluation. For this purpose the powerful data analysis concepts that are successfully applied in cytometry are adapted to the specific demands of the analysis of large image data sets. The multi-dimensional image data generated are displayed in 2-dimensional scatter plots or 1-dimensional histograms. From these, clustered data populations of interest can be selected via graphical tools. Selected data sets can be repeatedly gated for further investigation. Gates form different plots can be combined with Boolean operators to create complex derived gates.

Conclusions

Designed for fully automated image acquisition and data analysis of biological samples, scan^R Screening Station for Life Science can handle many different formats e.g. multi-well plates, slides or custom-built arrays. This unmatched flexibility and open design make it equally adept at routine and advanced applications. With its powerful analysis module for functional assays, it is the perfect tool for assay development as well as high content screening. scan^R is an excellent analytical tool too, providing complex image analysis and advanced data evaluation, which enable it to complete a whole range of standard and bespoke assays.

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