An automated answer for molecular pharmacology

The Leibniz-Institut für Molekulare Pharmakologie is using Tecan's Freedom EVO® workstations for systematic high throughput screening of bioactive small molecule libraries for potential research tools and targets for drug development. These systems form the hub of ChemBioNet's Screening Unit, providing an interdisciplinary open access platform in support of academic research projects exploring biological function.

The team at the Screening Unit (front row, l to r): Dr Martin Neuenschwander and Dr Simone Graeber; (back row, l to r): Dr Silke Redetzky, Andreas Oder, Christoph Erdmann, Carola Seyffarth, Dr Jens Peter von Kries and Chris Eckert.

The Leibniz-Institut für Molekulare Pharmakologie (FMP) in Berlin, Germany, is a major international contributor to the field of molecular pharmacology. The FMP's research focuses on the structure, function and pharmacological interaction of proteins, compounds and small biomolecules to identify structures and molecular scaffolds of interest to both fundamental biology research and drug development. The Institute's broad interdisciplinary expertise and state-of-the-art technology place it at the forefront of drug development, as well as maintaining close ties with many academic organizations conducting fundamental research.

The FMP also plays host to the Screening Unit of ChemBioNet, an initiative by biologists and chemists in academia to provide an interdisciplinary open access platform in support of research projects exploring systematic usage of small molecules in biological systems. This initiative aims to provide access to high throughput technologies, allowing identification of compounds useful for dosage dependent, temporal or localized interference with biological function. The unique combination of technology available at the FMP includes the open screening platform, a state-of-art NMR facility and a mass spectrometry laboratory, providing an ideal environment for research projects aiming to discover biologically active substances.

The FMP's Screening Unit also manages a variety of technology platforms for other ChemBioNet members, working closely with the Max Delbrück Center for Molecular Medicine (MDC), the Helmholz Institute for Infection Research, the University of Oslo and the Berlin Institute for Medical Systems Biology (BIMSB). The FMP's advanced technology and unique position within the European research environment offer unprecedented opportunities for the study of chemical biology, providing a research hub to enable close collaboration between academic institutions. In addition, the Institute's structure allows a very broad range of projects to be investigated, using the same technologies available to the pharmaceutical industry but without the limitations associated with drug development, as Dr Jens Peter von Kries, Head of the Screening Unit, explained: "The research projects conducted at the FMP cover a wide variety of pharmacologically and biologically relevant pathways, and it is not essential that these are associated with a known disease state. Not being restricted in this way is very important to the way the Institute works, and this broad approach often leads to a surprising level of insight into the mechanisms of disease, even if the relevance of the research is not immediately and obviously relevant. It is

important for us not to try and compete with the pharmaceutical industry, which can easily lead to duplication of research, and the major focus of the FMP is on protein-protein interactions, which have not historically been of interest to pharmaceutical companies."

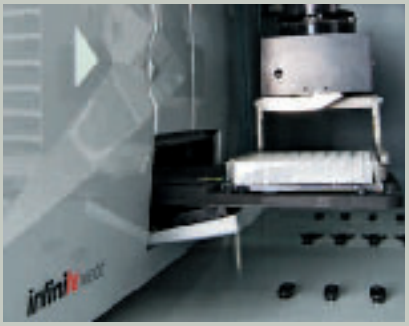
"The Screening Unit has a small team of staff performing compound library screens, and we work very closely with colleagues from other departments and institutions for both analysis of the data we generate, and to search global databases such as the World Drug Index for fragments of molecular scaffolds and sub-structures of interest. Our platform has a very high throughput, allowing us to screen an average of 20,000 compounds a day, and this capacity is partly thanks to the flexibility of our Freedom EVO workstations. Many of our projects use either high content screening with automated microscopes or genome-wide RNA interference (RNAi) studies, and we have a Freedom EVO system configured for each of these methods, and an additional platform for management of the ChemBioNet screening library. Each workstation has been collaboratively designed with the Tecan Integration Group (TIG) to create a robust system that is capable of very high throughput analysis, giving consistent results even with continuous use."

A Freedom EVO workstation at FMP, Berlin.

High content screening

"Our high content screening platform uses an automated microscope system, designed specifically for live cell imaging. This is integrated into the Freedom EVO workstation, and the whole system operates within a sterile environment. This system also has two automated nitrogen incubators at the back of the worktable for storage of cell culture flasks, compound libraries and 384-well test plates. The system is equipped with both 384-channel TeMO™ and 8-channel LiHa pipetting arms, allowing complete automation of the screening process, including harvesting of cells from culture flasks and parallel pipetting of candidate compounds and controls for fluorescent imaging.

The microscope software documents images and identifies objects, converting fluorescence intensities to multi-parameter tables for effective analysis of screening data. This enables measurement and documentation of cellular kinetics and events in 384-well format in just a few hours, with reaction volumes of just 20-40 µl."



Genome-wide RNAi

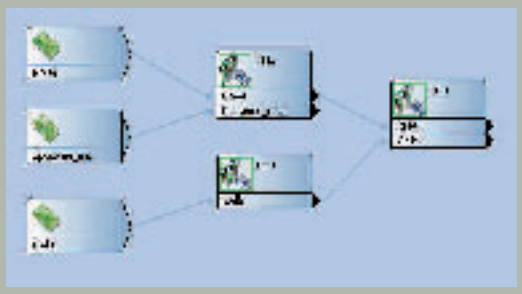
"The RNAi workstation has a very similar specification to the high content platform, without the automated microscope of course, and is used predominantly for studies of human and *C. elegans* cell lines in association with the MDC and BIMSB.

The human genome RNAi library encompasses approximately 20,000 genes, and our close association with the MDC means that many of the RNAi projects are relevant to various cancers, particularly control of metastasis.

By contrast, a majority of the work done with *C. elegans* cell lines is for systems biology studies, and we have a library of over 16,500 strains, covering around 87 % of C. elegans genes. For analysis of RNAi studies we are using a variety of optical methods, including both fluorescence and chemiluminescence techniques, and the Freedom EVO platform allows us to integrate several different reader technologies into the workstation."

Compound management

"The ChemBioNet screening collection is shared with many academic institutions in Germany and across Europe, and a Freedom EVO workstation with a REMP Small-Size Store™ (SSS) is used for both management and screening of this collection, with newly synthesized or purified compounds being added all the time. This workstation uses both an MCA™ 96 multi-channel arm and a LiHa arm for liquid handling, as well as a range of REMP sample storage modules, including the SSS. This is a very flexible system, bringing the powerful technology of larger REMP cold stores, which have become the industry standard in many sectors, to research laboratories. Our system was used to alpha test integration of the SSS into the Freedom EVO platform, and the resulting Freedom EVO / REMP SSS Factory represents the ideal combination for screening applications, improving throughput, maximizing walkaway time and allowing full sample traceability, while protecting precious library samples from denaturation, contamination and decomposition."



Screenshot of siRNA screening.

"As well as being able to integrate numerous robotics and detection modules, it is essential to have a straightforward and flexible software configuration. Tecan's Freedom EVOware® delivers this, allowing management of the entire screening process by directly interacting with control software for storage devices, incubators and readers, and has many innovative and unique features to provide robust control of screening assays with full documentation of every step. Tecan's software engineers have always provided us with excellent support for integration of new devices, and have also modified drivers as software configurations have been updated. This means that we are now able to use one software solution for complete control of screening, where previously two or three different packages would have been required. This simplifies sample tracking and documentation, making the system faster and easier to use."

"Each of our systems was carefully designed to meet our requirements, and the team at TIG have worked hard to make sure that the final configuration represents the best possible solution available. The approval procedure is central to this process, with both factory and site acceptance tests to guarantee that the platform exactly matches our needs. Validation of the system is then very simple, and Tecan staff are very willing to support us with further development of the platforms as new technologies become available. The core expertise of our staff at the Screening Unit is predominantly in biology or chemistry, and so we are dependent on our hardware suppliers' experience in biological process automation. Tecan takes a keen interest in its customers' projects, and our staff are trained by Tecan to a high standard to ensure we are able to maximize the potential of both our platforms and software. We enjoy a very good working relationship with Tecan's automation engineers, receiving immediate expert support for all our projects. Tecan has an exceptional culture of customer service, and our work here at the FMP undoubtedly benefits from this close partnership."

To find out more on Tecan's Freedom EVO workstations, visit **www.tecan.com/freedomevo**

To find out more on Tecan Integration Group, visit **www.tecan.com/tig**

Scientific instrumentation. Not for use in human clinical or *in vitro* diagnostic procedures.

Tecan Integration Group.