

Tools of the trade

Even though the pace of drug discovery is hotting up, many candidate drugs fail late in development. **Caitlin Smith** looks at some of the tools used early in drug discovery that could help improve the situation.

The failure of hitherto promising drug candidates when they go into animal tests and clinical trials occurs far too often for the pharmaceutical industry's comfort. It represents costly failures for the companies involved and pushes up the overall cost of drug development.

Improving pipeline productivity is "clearly the biggest challenge", according to Kevin Hrusovsky, president and chief executive of microfluidics specialists Caliper Life Sciences in Hopkinton, Massachusetts.

Others agree. "The attrition rate of candidate drugs in later clinical development is still way too high," says Gary Franklin, industrial sector specialist in marketing communications at molecular-interactions company Biacore, based in Uppsala, Sweden, and recently acquired by GE Healthcare.

As well as interacting with its molecular target, a successful drug must also behave properly in the human body. It must be easily absorbed, not be broken down too quickly, and have no side effects that make it too toxic to use. Known as ADMET or ADMETox (for absorption, distribution, metabolism, excretion and toxicity), these tests are key to efficient drug discovery. ADMETox testing is initially carried out in



Kevin Hrusovsky: getting more drugs through the late stages of development is the big challenge.

cell-based and *in vitro* assays to determine properties such as a compound's solubility, its ability to cross cell membranes, and its cellular toxicity. But these tests are still far from perfect predictors, and improving them is a priority area in drug research. Undesirable ADMETox properties account for some 50–60% of drugs that fail at the preclinical stage.

Franklin believes that the biggest challenge is to obtain more comprehensive data much earlier in the drug-development process. He points to the Critical Path Initiative, published

in 2005 by the US Food and Drug Administration, which aims to stimulate a national effort to develop improved evaluation methods that provide better information and maximize the chances of clinical success.

To address this pressing need, researchers will need faster and more precise instruments that make measurements with greater information content than ever before. This is a big demand, but there are some new tools of the trade that may make a difference.

Automating ADMETox

Equipment companies have their sights set on improving ADMETox testing, including the tests that all new drugs must undergo for their possible adverse effects on the cardiac potassium channel (see 'Ion channels get automated').

Another routine ADMETox test predicts cellular uptake and efflux of a compound. The absorption of a compound across the epithelial lining of the human gut is conventionally predicted by assaying its transport into and out of Caco-2 cells. Caco-2 is a human colonic adenocarcinoma cell line that will differentiate in culture to express characteristic

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ION CHANNELS GET AUTOMATED

Ion channels currently represent a less well charted territory of druggable targets than cell-surface receptors and enzymes, but this is changing. The electrophysiological techniques traditionally used to study ion-channel activity (one-cell, one-pipette patch clamping) are too slow for screening drug candidates, but some companies are finding ways to adapt and automate these techniques. One factor driving this development is the requirement by the regulatory authorities that all drugs must be tested for possible effects on a cardiac potassium channel (the hERG channel), which can cause cardiac arrhythmia. Compounds with adverse effects need to be weeded out as early as possible in the drug-discovery process.

The Dynaflo Pro II system from Collectricon in Göteborg, Sweden, is based on a combination of patch clamping and microfluidics. "Dynaflo enables sequential

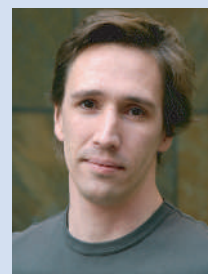
rather than parallel testing of compounds on ion channels by high-speed translational scanning of a single patch-clamped cell across a laminar stream of solution environments," says Mattias Karlsson, vice-president of research and development at Collectricon.

Use of patch clamping retains the high quality of data characteristic of the technique, which is crucial in regulatory testing for the hERG channel, but the microfluidics component increases throughput compared with traditional lab methods.

For the highest-throughput automated patch-clamping, turn to Sophion Bioscience in Ballerup, Denmark. Sophion's QPatch HT is a 48-channel gigaseal patch-clamp system that can be used to study both voltage-gated and ligand-gated ion channels. Each channel, which patches one cell, is controlled individually, so the

system consists of 48 individual low-noise patch-clamp amplifiers and pressure controllers (for individual gigaseal formation). The liquid-handling robot controls eight pipettes. The recording chambers are contained within Sophion's QPlates, which house 48 glass-coated microfluidic channels that hold about 5 µl. With the small recording volumes and a liquid-exchange time of about 100 milliseconds, it is possible to screen multiple compounds on the same cell, or perform cumulative dose-response experiments.

Npi Electronic in Tamm, Germany, has incorporated a Tecan liquid-handling system into its ScreeningTool instrument for automated, fast and precise



Mattias Karlsson: applying microfluidics to patch-clamping.

screening of ion-channel activity using two-electrode voltage clamping of *Xenopus* oocytes. Drugs are delivered by a rapid (millisecond resolution) automated system into the 15-ml bath of a miniature recording chamber. Npi plans to extend ScreeningTool to other cell types.

The ICR range of spectrometers from Aurora Biomed of Vancouver, British Columbia, provides a non-electrophysiological screen for ion-channel activity. The machines use atomic absorption spectroscopy and flux assays to detect activity and can be used to study both ligand- and voltage-gated channels. The new ICR 12000 is designed for ultra-high-throughput screening of compound libraries against ion-channel targets. C.S.

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