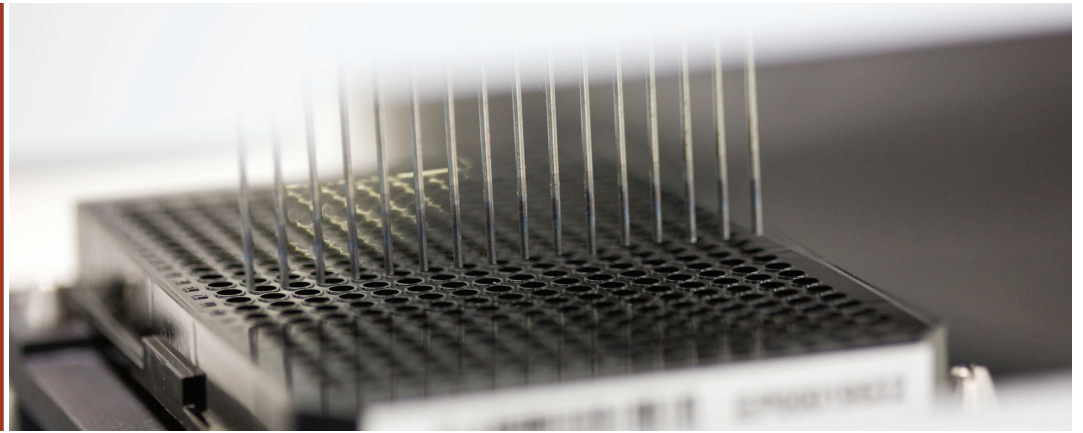


High Throughput Screening

Innovation in Novartis R&D



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–Ulrich Schopfer
Director, Center for
Proteomic Chemistry

“Add stuff to stuff and see the results. Scientists have been doing that for a hundred years,” says Vic Myer, Director, Developmental and Molecular Pathways, “but now it’s not ten experiments a week but a million.” That’s because High Throughput Screening (HTS), a technology introduced in the late eighties, permits scientists to generate vast amounts of data in a very short time. “HTS allows you to think of the complexity and scope of an experiment in a whole new way,” says Ulrich Schopfer, Director, Center for Proteomic Chemistry (CPC), in Basel. Indeed, in the last 20 years, HTS has transformed drug discovery.

In the past, researchers would test whether a particular substance worked against a disease by putting it into a sick animal and observing the results, a process that often took weeks. Today, scientists test hundreds of thousands of compounds against a disease target to discover “hits,” or “leads”: compounds that affect the target. At a first screening, thousands of compounds may offer evidence of biological activity. These hits are further tested to determine the best few molecules to develop into drugs. Today, of the lead compounds in the Novartis drug pipeline that are being pursued as drugs, about 60% can be traced to HTS.

“The drug is the key,” explains Schopfer, “and the target is the lock that it opens.” Before HTS can take place, a disease target is

identified at a molecular level. The target, determined through academic research or by internal discovery is often a receptor or enzyme that plays a role in a certain disease. For example, in working toward a drug to treat or prevent Alzheimer’s Disease (AD), one target would be the enzyme that leads to unwanted proteins in the brain. If we could inhibit this enzyme, we might well inhibit the disease. What are the keys that will fit the lock? What molecules might prevent this enzymatic action? To answer this question, scientists could put a small amount of the enzyme into a test tube with a pipette, add another substance, shake it up, and wait for a reaction to take place. Or through HTS, they could do the equivalent with a million test substances.

Test tubes aren’t used in HTS: the liquids are combined in tiny “wells,” or depressions, on a plastic disposable microplate a little larger than a cell phone. Miniaturization is key to HTS. The whole biochemical process has been designed to work with ultra small volumes: minute amounts of liquid combined in minuscule wells. Various microplates contain 96, 384, or 1536 wells, arranged in a rectangular matrix; about a billion of these microplates are used each year by the pharmaceutical industry.

Huge amounts of information are produced every hour. “Throughput” is the amount of data created in a period of time. HTS is “high”

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throughput (sometimes called “ultra high throughput”) because hundreds of thousands of data points are generated per day, thanks to sophisticated developments in software, robotics, instrumentation, and miniaturization.

Damien MacDougall and his colleagues at CPC in Cambridge, are taking miniaturization to a whole new level. They are dispensing samples onto the test (or “assay” plates) in volumes of 2.5 nanoliters. There are 100,000 nanoliters in a single medicine-dropper drop, so MacDougall is working with amounts so tiny they must be manipulated by sound waves. This acoustic dispensing employs a technology first developed for ink jet printers. A special machine uses a transducer to focus a sound wave onto the top of the well on the source plate. This beam of energy creates and moves a controllable micro-droplet to the pinprick well of the test plate. High Throughput Assay Ready Plates (HARP) save time and money by using minuscule volumes.

Scientists and engineers at the Genomics Institute of the Novartis Research Foundation (GNF) have designed and manufactured an HTS system, the Automated Cell Profile, that

is helping to expedite the drug discovery process. At the center of the machine, three 10-foot yellow arms move microplates up and down and from station to station. This machine is very robust, working in Cambridge 24/7 some 300 days a year. “We have found it to be tremendously reliable,” says Myer. “Now we’re using it for other applications than finding hits. Through pharmacological profiling across large panels of cell lines and ‘reverse genetics,’ we’re also using it to stratify patients and find novel targets.”

HTS is not the only approach to early drug discovery. Investigators at every pharmaceutical company look at recent discoveries to see if they can be improved, and researchers use computers to analyze molecules and experiment *in silico*, which offers great insight into drug discovery and design. But, as Scott Bowes, Scientist II in the Lead Finding Platform in Cambridge, remarks, “Even your *in silico* computer model is not as good as generating data and seeing what happens. HTS allows us to generate large high quality data sets for the very early drug discovery process. At the end of the day, there is nothing to replace the wet work.”