

## KNOWLEDGE

## v2n2 - Pinpointing progress

BY DIANA STEELE

Finding a new anti-cancer drug is a little like looking for a needle in a haystack. Scientists have to look through a lot of hay before they find something that looks anything like a needle.

But if you do have to look for that needle, it helps if you can look at thousands of pieces of hay at once, rather than sifting through one-by-one.

In drug discovery these days, robotic machinery helps to do the sifting in a technique called “high-throughput screening.” This can be used not only to find potential drug candidates, but also to look for genes important in cancer.

Until the 1990s, most drugs were found by isolating natural products — organic molecules produced by plants and animals that were discovered to have some desirable biological activity in humans. Unfortunately, the molecules are often large, complex and difficult to synthesize in a laboratory, which is a problem if the drug comes from a rare natural source. Taxol, for example, later patented as an anti-cancer drug, was isolated in the 1960s from the bark of the Pacific yew tree. Demand for the drug led to concerns about environmental effects of harvesting the endangered trees — until scientists developed a semi-synthetic method for making the drug in 1993.

Instead of continuing to run into problems trying to copy nature’s handiwork, “someone came up with the idea that you could bypass all those difficulties if you just made a whole lot of simple compounds that are easy for an organic chemist to make,” says biochemist Michael Roth, PhD, “and then screen through these very large arrays of compounds to find one that has biological activity.”

For high-throughput screening, chemists make “libraries” of thousands, hundreds of thousands or even millions of compounds. Roth, who directs the high-throughput screening lab at the University of Texas Southwestern Medical Center at Dallas, says he assembled a library of 200,000 compounds purchased from various pharmaceutical companies; first looking through their catalogs of compounds using software tools to see which ones were most likely to have drug-like activity.

Then biologists develop an assay, a screening tool to look through the library for a particular type of biological activity. Because the experiment has to be performed a hundred thousand to a million times, it has to work on a very small scale — about the size of one drop from an eyedropper.

Unfortunately it’s a little like looking through the haystack and finding a few things that might eventually be able to be used as a needle: a lump of metal, a

stick with an eye, or something with a sharp point.

“Natural products are produced by millions of years of evolution so that they are really designed to do exactly what they do,” Roth says. “And these random compounds are not.”

But because the synthetic compounds are easy to make, they’re also easy to modify. A typical assay might come up with tens of would-be needles. Chemists alter the compounds and screen them again to see whether the changes have made them more active.

A case in point is the drug Nexavar, approved in 2005 for treating kidney cancer, and in 2007 the first drug approved to treat advanced liver cancer.

Chemists from the pharmaceutical companies Bayer and Onyx screened 200,000 compounds starting in 1994, looking for any compound that could inhibit the activity of an enzyme called Raf kinase, which is important in cancer. They found several, says Hanno Wild, PhD, of Bayer HealthCare AG, based in Wuppertal, Germany. “There was one particular one which we thought was a good starting point for an optimization program,” Wild says.

The company ended up making about 6,000 variations until the one that eventually became Nexavar was developed. It was a thousand times more potent at inhibiting Raf kinase than the original.

High-throughput screening can also be used to hunt for disease-related genes, checking each of the 25,000 or more genes in the human genome.

In a study published in *Nature* last year, Roth and his collaborators found 80 genes that, when turned off, made a Taxol-resistant strain of cancer sensitive to the drug again. The hope is to eventually develop a drug that counters Taxol resistance, or devise combination therapies that prevent it from developing in the first place.

*Diana Steele is a freelance science writer based in Oberlin, Ohio.*