

# WILL COMBINATORIAL CHEMISTRY KEEP ITS PROMISE?

**T**hrough the 1990s, combinatorial chemistry was a hot technology in drug research — seen as a shortcut to important new therapies.

Vast libraries of diverse compounds were created using combinatorial techniques, then screened for biological activity using automated systems. Yet, with declines in big pharma's pipelines, combi-chem has drawn considerable criticism. Where is the next generation of

**Although this technology has come under fire, it isn't being abandoned. Biotechs that use combi-chem are developing new strategies — replacing diverse compound libraries with smaller, targeted libraries.**

**BY JOHN CARROLL, Senior Contributing Editor**

new drugs? Where are the cost savings in research and development?

“The promise of combinatorial chemistry has not developed as expected,” says Peter Crooks, PhD,

chair of drug design and discovery at the American Association of Pharmaceutical Scientists. “We haven't seen the enormous increase of new drugs in development.”



PHOTOGRAPH BY JIM STRATFORD

**The field of** combinatorial chemistry has moved beyond serendipity, says Bill Caldwell, PhD, vice president for drug discovery and development at Targacept. “I've seen a movement toward a more rational approach, where tools like computer-aided drug design are used to refine the process before you make the library — so-called 'targeted libraries.'”

Yet the field isn't being abandoned. A number of biotechs that use combichem have new strategies. Diverse compound libraries are being replaced by smaller, targeted libraries; researchers rely on software to do the virtual modeling that, it is hoped, will improve the probability of finding the right molecules to develop. Others are taking the random approach of molecular chemistry to a new level; to find that one special structure that could become the next blockbuster drug, greater numbers are being processed.

### SERENDIPITY VS. RATIONAL

The purpose of combichem is simple: create a new molecular structure that can be patented, proven in trials, and developed into a marketable therapy. It emerged in the 1950s, when Nobel prize winner R. Bruce Merrifield developed a resin for synthesizing peptides, making it possible to create chemical reactions on an immobilized resin.

"The pharmaceutical industry began to recognize that this kind of technology also could be used in a different way for a large array of drug molecules," explains Crooks, professor of pharmaceutical sciences at the University of Kentucky. "That started in the late '80s, when people began to look at the synthesis of drugs using solid-phase techniques."

From those advances came a wide array of synthetic structures that now comprise a number of marketed drug products.

These days, chemists commonly start off with anything from a 96- to 1,000-well plate. A chemical is added to each well, which binds to the resin and is immobilized. Then, up to a thousand unique chemicals

are added in each well, and the chemical reaction creates new compounds. All that is done robotically.

"So, you get 1,000 compounds made in minutes, which — again in a matter of minutes — is analyzed for purity. Those that make the grade are passed on to the high throughput screening unit (HTS)." HTS is used to determine if the new compounds can produce a "hit" against a disease target, signifying its potential as a new therapy.

At that first step of drug discovery, research chemists must choose which strategy to use to hunt down the structure they're after. If a chemist is working in a relatively new disease field, such as obesity, he can start by purchasing random compound libraries, delivered in well plates, that can be screened for biological activity.

"That's called serendipity," says Crooks. "You just don't know what is going to hit."

If you have a well-defined biological target, good structural information, and data on what compounds you want to focus on, there's more rationality in the method. In that case, molecular modeling will give you a good idea of the kind of structures that are most promising.

For example, researchers looking for a new and better painkiller know they are aiming for the body's opiate receptor. If they can find or develop a molecule that will influence that receptor, then they're onto a potential new therapy.

For Crooks, it's the rational, more targeted approach that seems to be winning out. Serendipity and big numbers just haven't generated enough promising drugs to justify the high-stakes gamble that lies in each run of the wells.

"There are lots of great targets out there that translate into enormous markets worldwide, where there really aren't any great drugs in the pipeline," notes Crooks. "It's kind of surprising, but I believe it's beginning to make the big pharmaceutical companies rethink how they do their combinatorial chemistry design. There's probably greater interest now in a more rational approach, which takes into account a much better focus on synthetic structures."

And that's precisely how a host of biotechs are building a reputation.

### VIRTUAL COMBICHEM

"There's a sense that combinatorial chemistry has not delivered on the promise of the '90s," agrees Bill Caldwell, PhD, vice president for drug discovery and development at Targacept. In some respects, though, that's attributable to the fact that while the biology of drug research is benefiting greatly from the genomics revolution, "the chemistry is only now catching up."

At Targacept, a biotech spun off from R.J. Reynolds and based in Winston-Salem, N.C., the focus on rational drug design work has taken the company well down the road to improved methods of computer-design work.

"The thinking was that just as the aerospace and auto industries needed to start failing in simulation — as opposed to failing in prototype — our approach has been to do as much discovery as possible in the virtual world, so we fail there," said Caldwell. "We do combinatorial chemistry in a virtual world, not a real one."

For Boeing, that would mean if a plane cannot get off the ground in a

virtual simulation flight, it's grounded. At Targacept, if a new molecular structure cannot affect the target, it's scrapped.

When Targacept researchers synthesize a new compound, it has been prescreened by the company's Pentad simulation technology. Thus, screening 1,000 compounds may yield a hundred that are made and run through a screen.

"It's a system we've used for over 10 years that has delivered a robust clinical and pre-clinical pipeline," says Caldwell. "In the '90s, it was common to make extremely large libraries. Yet, what I've experienced, is that if you take a random approach, you have a high likelihood of creating compounds that can never be drugs. They may be insoluble or have other properties that render the compound unexceptional. Then you have the expense of making and screening, and the realization that you are going to get a very low hit rate.

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### QUALITY OVER QUANTITY

"Everything has come back to improved quality to provide for better decision making," says Kevin Koch, PhD, president and chief scientific officer of Array BioPharma.

"To the extent that you can have high throughput with high quality, that's great. But people are asking more complex questions."

And they're doing it earlier in the discovery process. At the beginning stages of lead identification, re-



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searchers are optimizing a drug's ADMET (absorption, distribution, metabolism, excretion, and toxicity) properties, surveying patent literature to identify "new chemical space" and creating small sets of 100 to 500 compounds for careful study.

Rather than taking a shotgun approach to huge numbers of compounds in HTS, says Koch, the emphasis is on synthesizing the right compounds, then purifying them up to 90 to 95 percent, and designing them for a family of targets. Leads are optimized by making small changes in the chemical structure that affect physiochemistry, toxicology, potency, and binding interaction — all key elements in finding a compound with the best chance of surviving clinical trials.

Combinatorial chemistry may help to identify a compound that works against the target — say, by killing cancer cells — but doesn't work in actual practice, possibly because it's metabolized too quickly or not absorbed in a way that is needed to make it work.

At that point, "you can go back ... and make changes that can improve the original molecule," says Crooks.

Drug researchers then can ex-

periment with other formulations — delivering them intranasally rather than in the bloodstream, for instance — or transforming them into nanoparticles to change absorption rates.

### A BETTER WAY

"Was the whole combichem craze a total loss?" asks Bryan Koontz, who cofounded Optive Research and joined Tripos as vice president of corporate development when the University of Texas-Austin spin-off was snapped up last year. "Not necessarily," he answers. Advances in purification and quality control were clearly identified, and many clever new synthesis techniques were developed.

Also, with labs at drug giants like Pfizer operating under clear marching orders to accelerate leads into pipelines more efficiently — and considering the substantial capital investments large pharma has made in combichem — the practice won't go away soon. But the shift to synthesize smaller, focused compound libraries has been evident in the past three to four years, Koontz adds.

A chance to improve lab efficiency, in his view, is to move certain software tools from the hands of computational scientists to those of lab chemists, who can use their knowledge of synthesis to design the compound libraries.

Koontz has seen small groups of chemists using such software to design small, 30- to 60-compound libraries, sending the library back to computational scientists to see which can bind — dock — to a protein, or ligand, which is the target. They then can make plates by hand and actually synthesize compounds they know have a higher potential.

Tripos has a big stake in that trend as it develops software specifically designed for use by chemists. In March, the National Institutes of Health gave Tripos an \$860,000 grant to develop a library design system for use by research chemists; the goal is to create a proprietary system that can search a million times more structures, opening a much broader universe of synthetic structures to a narrower focus.

If Koontz is right, Caldwell and the rest of the virtual combinatorial crowd are that much closer to achieving combichem's original goal: shaving 18 months to two years off the time it takes to bring a drug to market. That's two years sooner to a potential market of hundreds of millions, if not billions,

## One promising approach is to combine already-approved drugs and study the effect on disease. One company doing this got 7 compounds to clinical trials — in just 7 years.

of dollars. It's also extra time for a company to own an approved drug under patent and a less expensive way to push along an experimental drug — to the point where a big drug company licenses it in multi-million-dollar pacts.

Yet, even if discovery is not shortened, Koch sees important gains from the new emphasis on smaller numbers. If new technologies and strategies allow a biotech just to keep to the same development pace, he says, that can be a big advantage.

"The diseases the pharma industry are tackling are more difficult," says Koch, who currently has an experimental cancer drug in a phase 1 trial. "New technologies have allowed the industry to keep pace with new hurdles posed by these diseases, where the medical aspects are becoming more complex."

### APPROVED DRUGS

Few biotechs have achieved the same kind of buzz as CombinatoRx, a Boston-based drug discovery company with seven compounds in trials. They got that far in seven years by developing a unique approach to combinatorial chemistry; pairing approved drugs and seeing how they act against a model of a target disease. Researchers found that pairing drugs allowed them to demonstrate efficacy against new targets, sometimes pointing to a wholly unexpected disease pathway. Pairing also created synergies, making a pair of compounds more effective than the original drug approved for a particular disease.

By using a combination of treatments, they were able to create the kind of novel structures that could be patented as new therapies. And they used a proprietary combinatorial high throughput screening system to test the effects of millions of dose-specific combinations.

Their success had an almost viral effect on investors. Last year, the company raised \$90 million in three rounds of venture capital.

CombinatoRx is in a mandated Securities and Exchange Commission quiet phase leading up to an

initial public offering, but the company's S1 registration statement is not bashful about touting its likely success in bringing these new combined compounds to market. By relying on a relatively small library of approved drugs, the company takes the view that it can get a leap on the approval process by relying on compounds that have undergone extensive safety testing already.

There's lots of outside-the-box thinking in research. Crooks and Stu Kauffman, a noted thinker in the realm of complexity theory, have helped to found a new company with Jeff Schmitt, who also works with Caldwell at Targacept.

Schmitt says he's developed a new way to rapidly develop "huge and diverse" new libraries of compounds. "We have done a pilot experiment showing that a chemist, practiced in the art, should be able to produce 100,000 compounds a month." Recognizing that even big drug companies have libraries of up to 2 million compounds, he clearly is talking revolution.

"It's serendipitous," says Schmitt. "We start this proprietary process with information that allows chemistry to be guided into uncharted areas of chemical space."

The key words here are *proprietary* and *uncharted*. Schmitt says he is keeping the process under wraps as he gets the angel-stage upstart off the ground. He's well aware that skeptics will wait to see how this process delivers in human trials before feeling the contagion of another bright trend emerging from combinatorial chemistry. **BH**

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