clinical trial of GEM91 in AIDS patients, he told participants in the antisense meeting. Agrawal also reported that patients getting the higher doses are showing signs of clinical improvement in that their viral counts drop a few days after the treatments, although it is far too soon to tell whether this translates into improved survival. To Agrawal, it doesn't matter how the drugs work, if they end up helping AIDS patients. "Despite all the other properties [in addition to actual gene targeting], we feel that if we find an antisense effect ... then we have a new drug," Agrawal says.

Looking to the future

Agrawal is not the only one who hasn't lost faith in the technology. Biotechnology representatives argue that the problems turning up with antisense oligonucleotides are common in drug development, especially when untested, new technologies are being explored. "Every new technology starts at the bottom, in essence, getting your foot in the door," says Gerald Zon, vice president of medicinal chemistry at Lynx Therapeutics Inc., a biotech company in Hayward, California. He notes that every new drug has negative effects that must be weighed against clinical benefits. The answer, he says, is to design better second- and third-generation drugs in order to boost drug efficacy while, at the same time, minimizing unwanted side effects.

Indeed, researchers at companies such as Hybridon, Isis, and Gilead say they are applying the lessons they are learning from the animal studies and early clinical trials to try to come up with better and less toxic compounds. The options they are exploring include modifying the structures of oligonucleotides so that they bind less readily to proteins or more readily to their target genes. All three companies are also generating fat-soluble delivery molecules called cationic liposomes. The researchers hope these lipid-loving shuttles will help antisense compounds break through cellular barriers that prevent entrance into the nucleus.

These new compounds and delivery systems carry no guarantees that they will be any better than the phosphorothioates used in the current clinical trials. But even some of the critics, such as Stein, agree the field still holds great promise, as long as the researchers recognize that antisense drugs don't always work the way they are supposed to. "My guess is that we will find that the current generation of phosphorothioates are extremely active biological molecules," Stein concludes, "and that they work by many mechanisms, of which antisense is one. The truth is that we'll have to wait and see. None of us really knows what is going to come out of it."

–Trisha Gura

Trisha Gura is a reporter on leave from the Chicago Tribune.

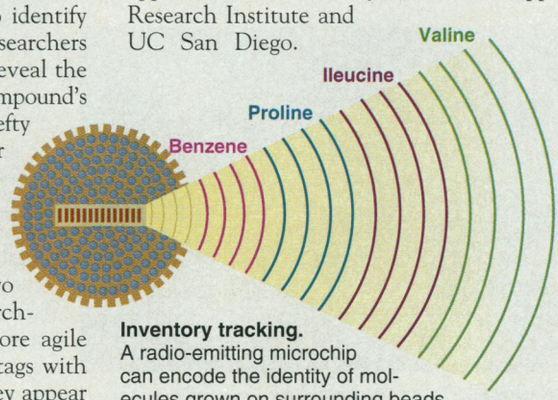
CHEMISTRY

Radio Tags Speed Compound Synthesis

Like aging computers, it doesn't take long for scientific techniques to seem slow and cumbersome. Take combinatorial chemistry. When it was introduced a few years ago, it was the supercomputer of chemical synthesis. The technique allows chemists to quickly paste together several different chemical building blocks into millions of combinations, in hopes that one will prove to be a new drug or a useful material. To identify each one of the new compounds, researchers typically affix chemical tags that reveal the unique arrangement of each compound's components. But these tags carry a hefty price: Their use doubles the number of chemical steps—and the time—involved in the assembly process, and their fragility prevents the synthesis of some compounds.

In the past 2 weeks, however, two separate groups of California researchers have unveiled a faster and more agile model. By replacing chemical ID tags with tiny radio-emitting microchips, they appear to have overcome both of the problems inherent in the old one. "The upshot is that it makes the whole process of drug discovery more efficient," says Rob Armstrong, a chemist at the University of California (UC), Los Angeles, who led one of the research groups, which includes scientists from Ontogen Corp. in Carlsbad, California. "This has the potential to be a significant advance in simplifying the encoding process," adds Michael Pavia, who heads combinatorial research at Sphinx Pharmaceuticals in Cambridge, Massachusetts. The technique not only saves time, says Pavia, "it gives you a wider range of chemical diversity to select from in building your new molecules."

Armstrong's group presented its findings at last week's meeting of the Western Biotech Conference in San Diego, as did the second team, led by Michael Nova at IRORI Quantum Microchemistry in La Jolla, California, and K. C. Nicolaou, who holds dual appointments at the La Jolla–based Scripps Research Institute and UC San Diego.



Inventory tracking. A radio-emitting microchip can encode the identity of molecules grown on surrounding beads.

The IRORI group was, however, the first in print, with a paper in the 15 October issue of *Angewandte Chemie*.

Both techniques add considerable power to combinatorial chemistry, which already made traditional synthetic chemistry look like an old IBM punch card. Traditionally, novel compounds are synthesized one at a time, but combinatorial chemists create huge numbers in a single process by assembling a few chemical building blocks—each of which has a corresponding ID tag, such as a short nucleotide sequence—in all possible combinations. Chemists need these tags to decipher the makeup of compounds that show promise in an assay, such as the ability to kill cancer cells (*Science*, 3 June 1994, p. 1399).

But because a tag has to be added with each building block, assembling a 10-component molecule actually involves at least 20 time-consuming chemical steps. And the technique runs into trouble when creating small organic molecules, which constitute most of today's drugs. Some of the synthetic reactions involve potent reagents, such as hydrofluoric acid, which can rip ID tags apart.

The new microchip tags appear to solve both these problems at once. A chip, which emits a binary code, is inserted into a mesh capsule loaded with polymer beads—the "seeds" to which combinatorial building blocks are added by dunking the capsule in a series of beakers. In the Ontogen approach, a nearby radio scanner registers both the identity of a capsule and the contents of each beaker it enters. These data are uploaded to a computer that keeps track of the order of building blocks in the growing molecule. In the IRORI approach, the information is stored on the microchip itself, using a transmitter that writes the information to the chip. The information is uploaded to the computer only when the assembly run is complete.

By eliminating the chemical tags, both approaches do away with half the synthetic steps involved, yet end up with an instantly available computer record of the precise structure of the compounds in each capsule. Moreover, says Nicolaou, "now you are free to use any chemistry you want to build your molecules." Speed and flexibility—for chemists, it's a winning combination.

–Robert F. Service