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**Abstract:** Chemist David Liu and colleagues from Harvard University in Cambridge, Massachusetts have prepared a diverse set of small organic compounds to understand the manufacturing of organic molecules from the mutations in DNA. By linking organic reactants to a series of DNA molecules preprogrammed to bind to one another, organic molecules can be coaxed to react together in multiple steps to form desired compounds. The researchers have created a collection of 65 related compounds in chemical jargon. "This is something other chemists will want to know about," says Craig Townsend, an organic chemist at Johns Hopkins University in Baltimore, Maryland. INSET: Snapshots From the Meeting.

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### **Synthetic Chemists Cast DNA As Molecular Dance Master**

Over the past century, organic chemists have devised hundreds of reactions to tweak molecules into just the right shape. But they've never mastered biology's way of sculpting molecules: evolution. New molecules evolve when natural mutations in DNA alter proteins that help synthesize needed small organic molecules. If the change helps an organism survive, natural selection makes it standard issue for the organism's descendants. Now, Harvard University chemist David Liu and colleagues have adapted this strategy to evolve a diverse set of small organic compounds as well.

At the meeting, Liu reported that by linking organic reactants to a series of DNA molecules preprogrammed to bind to one another, his team coaxed the organic molecules to react together in multiple steps to form desired compounds. The molecules can then be exposed to another reactant to alter their shape and function. By starting with an assortment of DNA molecules, the researchers can choreograph reactants to assemble themselves into a wide variety of products in the same beaker. Liu's team used the technique to create a collection of 65 cyclic compounds closely related to known protease inhibitors, drugs used to fight AIDS and other diseases.

"This is something other chemists will want to know about," says Craig Townsend, an organic chemist at Johns Hopkins University in Baltimore, Maryland. "It's potentially quite useful." But Townsend notes that for now the technique relies on reactions that take place in water, whereas most organic reactions are designed to work in organic solvents.

Liu's team began working on using DNA to control organic reactions 3 years ago. The researchers started with organics that react with one another only at high concentrations. By harnessing the ability of precise sequences of single-stranded DNA to bind to one another, Liu hoped to bring the reactants close enough together to increase their effective concentration. The scheme worked, and Liu's team has since used the approach to forge more than a dozen different types of organic reactions.

Last year, the team took another key step by making an organic compound undergo a series of preprogrammed chemical reactions, a prerequisite for making complex synthetic molecules. The researchers started by attaching an initial organic compound to a long "template" strand of single-stranded DNA. Then, one after another, they introduced three different organic complexes, each attached to a short length of single-stranded DNA programmed to bind to a different region on the template strand. Liu's team found that the scheme created three sequential modifications to the initial compound (see figure).

In their most recent work, the researchers extended their multistep scheme to create a collection of 65 related compounds — a "library," in chemical jargon. The researchers followed standard combinatorial chemistry techniques to link a series of building blocks together in all their possible combinations. But they added their own twist: They used 65 different template DNAs to direct the organic groups to their appropriate reaction partners. To prove that the technique had worked, they pulled a single member of the library out of solution and verified that it was the compound they desired.

Right now, a library of 65 compounds pales beside the legions of chemicals created by other combinatorial techniques. But unlike other approaches, Liu notes, in this case molecules found to be reactive can easily be identified, selected, and put to work, just by borrowing tools nature has used for billions of years.

NEW ORLEANS, LOUISIANA — Approximately 11,000 chemists, materials scientists, and physicists swung into the Big Easy from 23 to 27 March for the 225th National Meeting of the American Chemical Society.

PHOTO (COLOR): Find your partner. Short DNA tags (colored) bind to complementary sequences on a long DNA "template," causing linked organic molecules (shapes) to react.

#### Snapshots From the Meeting

**Preferred Painkiller.** Morphine can be powerful medicine, but it's addictive and carries intestinal side effects. At the meeting, Robin Polt, a chemist at the University of Arizona in Tucson, reported devising a novel peptide that in animal studies appears even more potent than morphine and is less addictive. Polt's team found that linking a small sugar molecule to the peptide helped it find its way into the brain. You can expect to see similar sugars decorate other peptide-based brain drugs in the future.

**Heads Up.** Sure, a massive meteor impact killed off the dinosaurs 65 million years ago. But new calculations by John Birks of the University of Colorado, Boulder, suggest that

smaller, more frequent meteor impacts may wipe out global ozone as often as once every 40,000 years. Look for future ice core measurements to see if paleoclimatologists can spot the expected chemical signature.

**DNA Computing Twist.** Conventional DNA computers are prized for their ability to solve complex tasks, such as the classic traveling salesrep problem. But they don't use conventional computer-based logic based on 1's and 0's. At the meeting, Reza Ghadiri of the Scripps Research Institute in La Jolla, California, reported creating a scheme to coax DNA molecules to work as a standard logic circuit. So far, the circuits carry out only three operations, but efforts are under way to boost their complexity.

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