Finding Reactions in a Haystack: Try ’em All, See What Works

For synthetic chemists, improving on nature is, well, second nature. For over 150 years they have used new types of chemical reactions to craft molecules never seen before. “That strategy is very effective, particularly when you know what you’re trying to make,” says David Liu, a synthetic chemist at Harvard University in Cambridge, Massachusetts.

But is this goal-oriented approach the best way to find all the different types of possible chemical reactions under the sun? Liu suspected not. So he and his team set out to find new types of reactions by harnessing biology’s prowess for synthesizing a diverse set of compounds. In Philadelphia, Liu unveiled an approach that shepherds molecules together with strands of DNA. The group has already spotted one new reaction with the technique and is casting its net wider to see what other reactions may be lying in wait.

Liu’s talk was “pretty cool,” says Kenneth Suslick, a chemist at the University of Illinois, Urbana-Champaign. “I was really taken with it.” A chief goal of the new work is to discover novel reactions that chemists can then use in DNA-directed synthesis or with their traditional methods. But Suslick notes that not all reactions discovered by the new technique will make the jump: The DNA approach might prevent side reactions that would spoil the recipe in a conventional synthesis. So far, the technique has been used only to search for reactions that take place in water, but Liu says his team is expanding its search to include reactions in organic solvents.

Over eons of evolution, biological organisms generate a diversity of compounds and simply select those that work best. Liu and colleagues brought that kaleidoscopic approach to bear on the small organic molecules that synthetic chemists favor. They started with two flasks of small organic molecules, each tethered to a unique DNA snippet. Each DNA strand in flask A was designed to identify its own small-molecule cargo (A1, A2, and so on) and to attract a complementary DNA identity tag attached to one of the small molecules in flask B (B1, B2, etc.). Each B molecule also sported a molecular “hook” called biotin.

When the researchers poured the contents of the two flasks together, the complementary DNAs paired up, bringing their small molecules into close contact with one another in every possible combination of A’s and B’s. In the few cases in which conditions were right, the small molecules reacted to form larger molecules. To find which compounds had combined, the researchers weeded them out in several steps. First, they dropped in iron beads studded with streptavidin, a molecule that binds to biotin. The researchers then pulled the beads out again, dragging with them B molecules snagged by their biotin hooks, as well as other molecules entangled by their DNA, and washed the compounds in a solution that unzipped the intertwined DNA strands. Lone A molecules that had not reacted fell off and were washed away, leaving unreacted B molecules and the newborn AB compounds attached to the beads (see figure).

The researchers then used the polymerase chain reaction (PCR) to amplify trailing DNA strands containing a certain nucleic acid sequence—a sequence found only in the A strands. Because all the unattached A molecules had been left behind in a previous step, only the A strands that had formed new molecules survived to be amplified by PCR. The researchers read the amplified DNAs with a standard gene chip, which identified their full sequences and thus revealed which A and B molecules had paired off.

Liu reported that in one experiment, with 168 possible small-molecule products, his group found a new reaction that uses a palladium catalyst under mild conditions to link simple hydrocarbon molecules called alkenes and alkynes into a more complex group called a trans-enone. Using the setup, Liu says, a single researcher can scan thousands of possible combinations of small molecules and reaction conditions for new reactions in just days.

Enzyme Deactivates Heart-Friendly HDL

Not all “good” cholesterol in your bloodstream keeps good company. In patients with coronary artery–clogging plaques, as much as half of the high density lipoprotein (HDL), which carries the “good” cholesterol, is chemically altered, blocking its normal ability to combat the buildup of cholesterol deposits, researchers reported at the meeting. The new work, led by chemist and physician Stanley Hazen and graduate student Lemin Zheng of the Cleveland Clinic Foundation in Ohio, is expected to lead to novel drugs that help prevent atherosclerosis by blocking the damage to HDL. It may also spur better diagnostics for heart disease: At the meeting, another group reported preliminary progress on one such test.

“This is pretty exciting,” says Ian Blair, a disease biomarker expert at the University of Pennsylvania in Philadelphia. “[They] seem to have a biomarker that is far better than existing biomarkers for cardiovascular disease.” For the first time, he adds, the new work lays out a clear molecular mechanism that explains how HDL can become “dysfunctional” and why high HDL cholesterol levels may not always ward off heart disease.

The research grew out of efforts to find...