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THE Current

March 22, 2006
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New Lipid Molecule Holds Promise For Gene Therapy

Scientists at the University of California, Santa Barbara have created a new molecule that holds promise in fighting disease via gene therapy. Inherited diseases, as well as many cancers and cardiovascular diseases, may eventually be helped by this approach, which delivers therapeutic genes directly to cells. These genes can correct genetic defects, for example, or help the body's immune system fight cancer cells.

For more than two decades, gene delivery has been accomplished by using engineered viruses as a vehicle to get into diseased cells and 70 percent of clinical trials worldwide continue to use this method. But, the viruses used for gene delivery occasionally evoke severe immune responses, so scientists continue to search for non-viral delivery vehicles.

Reporting in an article to appear in the March 29 print edition of the *Journal of the American Chemical Society* (published on-line on March 8), the authors describe the synthesis of the new lipid molecule.

Lipid DNA complexes are attracting increasing attention as non-viral DNA delivery vehicles. They have been described as one of the "hottest new technologies" for gene therapy, accounting for nearly 10 percent of ongoing clinical trials.

Lipids are molecules with two parts, a water-liking "headgroup" and oily tails that assemble together to avoid water. Lipids, along with carbohydrates and proteins, constitute the main structural material of living cells.

The novel lipid molecule created at UC Santa Barbara has a tree-shaped, nanoscale headgroup and displays unexpectedly superior DNA-delivery properties. "It generates a honeycomb phase of lipid DNA complexes," said Cyrus R. Safinya, a professor of materials; of molecular, cellular and developmental biology; and of physics at UCSB. The new molecule was synthesized in Safinya's laboratory by first author Kai K. Ewert, a synthetic chemist who is a project scientist in the research group.

"We've been trying to get a lipid-based honeycomb lattice for a long time," said Ewert. The structure of lipid DNA complexes strongly affects their ability to deliver DNA.

"Complexes containing sheets or tubes of lipids have been known since Safinya's group found these structures in 1997 and 1998, but no one had ever seen nanoscale cylinders such as the ones in our honeycomb lattice," Ewart said. The scientists proved the formation of this novel structure with X-ray scattering experiments.

Ewert designed and synthesized the new lipid by manipulating the size, shape and charge of a series of molecules. He explained that the new lipid molecule has 16 positive charges in its tree-shaped headgroup, the largest number by far in the field of gene delivery.

The process of delivering a gene of interest into the cell is known as "transfection." In the paper, the authors describe transfection efficiency studies carried out in four cancer cell lines using the new molecule. Two of these are mouse cell lines and two are human cell lines. The honeycomb structure turned out to be highly effective.

"Our new gene carrier shows superior transfection efficiency compared to commercially available carriers," said Ewert. "However, the most surprising result was obtained with the mouse embryonic fibroblast cells known as MEFs. These are empirically known to be extremely hard to transfect."

Safinya added: "Our data confirm that MEFs are generally hard to transfect. And the new molecule is far superior for transfection of these cells as compared to commercial lipids."

The other co-authors are Safinya's graduate students Alexandra Zidovska, Nate Bouxsein, Ayesha Ahmad (now a postdoctoral fellow at the Genetic Therapies Center at Imperial College in London) and Heather Evans (now a postdoctoral fellow at the Max Planck Institute for Dynamics and Self-Organization in Goettingen, Germany).

The research was supported by the National Institute of General Medical Sciences of the National Institutes of Health. The synchrotron X-ray scattering experiments were performed at the Stanford Synchrotron Radiation Laboratory, a facility supported by the Department of Energy.

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