



[Home](#) > [Institute for Basic Biomedical Sciences](#) > [News & Events](#) > articles > technology

Building a better drug

Through prodrug design, Caren Meyers is making good drugs even better.



Prodrug design has yielded a host of new improved medications, including the anti-cholesterol drug lovastatin shown here.

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Author SubDural12

January 2012-- Chemist [Caren Meyers](#) has a calm and even-keeled demeanor. But when she starts to describe her research, this unassuming scientist begins to sound like a commander plotting an invasion. "We focus on getting compounds into cells that normally don't penetrate soft tissues," says Meyers, an assistant professor of [pharmacology and molecular sciences](#).

Her aggressive tone serves a noble goal, however. The compounds she focuses on have the potential to destroy cancer or infectious bacteria or parasites—if only they could cross the cell membrane. To breach that obstacle, Meyers has designed something called a prodrug.

In prodrug design, scientists start with a drug that is therapeutically effective but has a downside (for example, the compound is not well absorbed) and alter the drug to diminish the undesirable feature, making the good drug even better—less toxic, more soluble, more stable, less yucky-tasting. In the past 40 years, prodrug design has yielded a host of new improved medications, including the anti-cholesterol drug lovastatin and the anti-herpes drug acyclovir.

Meyers has several prodrug research projects under way, and recently, one of those yielded striking results. She began with a class of drug called bisphosphonates, substances that can normally barely penetrate soft tissue. She then generated prodrug versions of these compounds that no longer have this limitation. Lung cancer cells, Meyers found, readily take up the new drugs; furthermore, the prodrugs stop these cells from growing.

Bisphosphonates are widely prescribed for patients with osteoporosis and have also proven effective in the treatment of bone cancer. Encouraged by those results, scientists had hoped the drugs would prove useful in treating other types of cancer. But they've had limited success. While bone absorbs bisphosphonate like a dry sponge, soft tissues simply do not absorb the compounds.

The reason, explains Meyers, has to do with basic chemistry.

Bisphosphonates are negatively charged compounds. Bone contains an abundance of calcium—positively charged ions. Opposites attract. So bone has a natural affinity for bisphosphonate. The body's soft tissues (such as skin and

muscle), on the other hand, do not. Such cell membranes do not efficiently absorb negatively charged compounds.

To bypass this problem, Meyers employed a sort of chemical subterfuge. She attached special chemically reactive groups to hide, or “mask,” the bisphosphonate’s negative charges. She also attached two biodegradable “delivery groups” to help ease the drug’s entry into the cells and enable its reactivation once inside. The masking and delivery groups would enable the drug to slip covertly into the cells. Once inside, it would shed these chemical appendages and reassume its original, negatively charged state (which accords the drug its potency).

These efforts yielded two bisphosphonate prodrugs that appear to satisfy these requirements. The prodrugs pass readily through cell membranes and undergo rapid activation once inside the cell.

Marie Webster, once a graduate student in Meyers’ lab and now a postdoc at the Wistar Institute in Philadelphia, collaborated with professor of oncology Christine Hahn while at Hopkins on a series of experiments to determine the prodrugs’ ability to inhibit the growth of lung cancer cells. The researchers chose a lung cancer model in part because of the limited effectiveness of current drug treatment for the disease. In these experiments, Webster added a prodrug to lung cancer cells and measured the cells’ growth over time. As a comparison, she also added standard bisphosphonate to lung cancer cells and measured cell growth.

The results were dramatic, says Meyers. Whereas even large doses of bisphosphonate had virtually no effect on the proliferation or viability of the lung cancer cells, the team found that relatively small amounts of the prodrug quickly stopped the lung cancer cells from growing. Overall, the prodrugs were at least 250 times more potent than the standard bisphosphonates, reports Meyers, who published her results in a recent issue of the *Journal of Medicinal Chemistry*.

The recently published study, notes Meyers, is a proof of principle. Bisphosphonates belong to a broad category of drugs called poly-phosphorylated compounds, which have been notoriously difficult to deliver into cells. Previous attempts have been far less efficient at getting the drugs into the cells. Her recent experiments, says Meyers, “set the stage for the efficient, targeted delivery of poly-phosphorylated molecules as a potential therapeutic strategy.”

Many years of work remain before the bisphosphonate prodrugs can be given to a patient. For one thing, says Meyers, a safe and effective anticancer prodrug will need to distinguish between healthy and cancerous cells. So in the next phase of her research, Meyers plans to examine whether her prodrugs make this distinction. If they do not, she will chemically tune the prodrug delivery groups to make sure the drugs target cancer cells.

Then, somewhere down the road comes FDA testing. Even though bisphosphonates are FDA approved, the agency views prodrugs as novel molecules and requires that they go through its lengthy approval process. Says Meyers: “We’re early in the discovery stage.”

—Melissa Hendricks

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