Using evolution, scientists create a template for many new therapeutic agents

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By guiding an enzyme down a new evolutionary pathway, a team of University of Wisconsin-Madison researchers has created a new form of an enzyme capable of producing a range of potential new therapeutic agents with anticancer and antibiotic properties.

Writing in the current issue (Sept. 9, 2007) of the journal *Nature Chemical Biology*, a team of researchers from the UW-Madison School of Pharmacy describes a novel enzyme capable of changing the chemical properties of a variety of existing drugs and small molecules to make new agents to treat cancer and fight infection.

"We're finding this enzyme glycosylates all sorts of molecules," says Jon Thorson, a UW-Madison professor of pharmaceutical sciences describing the process of adding natural sugar molecules to other chemical molecules to enhance their biological effects.

The newly evolved enzyme developed by Thorson and colleagues Gavin. J. Williams and Changsheng Zhang, according to Thorson, is akin to a "Swiss Army enzyme," a catalyst that can decorate many different chemical molecules with all sorts of sugars to alter their biological effects.

Enzymes are proteins that act as catalysts across biology, from single-celled organisms to humans. They promote chemical reactions in cells and are used widely in industry for everything from making beer and cheese to producing paper and biofuel.

They are also important for making so-called natural drugs, therapeutic agents based on the blueprints of chemicals produced in nature by plants and microorganisms. Such natural sugar-bearing chemicals are the basis for some of medicine's most potent antibiotics and anticancer drugs as exemplified by the antibiotic erythromycin and the anticancer drug doxorubicin.

Important chemical features of such drugs are natural sugars, molecules that often determine a chemical compound's biological effects. Although scientists can sometimes manipulate how sugars are added or subtracted to a chemical molecule to alter its therapeutic properties, it is difficult and not always possible to routinely modify them to enhance their beneficial effects.

The new enzyme was created by generating random mutations in genes that make a naturally occurring enzyme. The altered genes were then put into a bacterium, which fabricated a series of randomly mutated new enzymes. These enzyme variants were then tested in a high throughput screen where chemical molecules engineered to fluoresce stop glowing when a sugar is successfully attached.

"We're transferring the sugar to a beacon," Thorson explains. "When you attach a sugar, you shut off the fluorescence."

The development of the screen, according to Thorson, was critical, overcoming a key limitation in the glycosyltransferase field.

"We're assaying hundreds of very interesting drug-like molecules now with newly evolved glycosyltransferases. The ability to rapidly evolve these enzymes has opened a lot of doors."

The range of potential therapeutic agents that might be generated with the new technology includes important anti-inflammatory and anti-

cancer compounds, and antibiotics.

What's more, the work could lead to the creation of a "super bug," an engineered bacterium that can perform the entire process in a laboratory dish: "There's no doubt that this is going to work in vivo," says Thorson. "We can create a bug where you feed it sugars and the compounds you want to hang those sugars on" to arrive at new medicines.

Source: University of Wisconsin-Madison