

Sweet insight: New discovery could speed drug development

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The surface of cells and many biologically active molecules are studded with sugar structures that are not used to store energy, but rather are involved in communication, immunity and inflammation. In a similar manner, sugars attached to drugs can enhance, change or neutralize their effects, says Jon Thorson, a professor of pharmaceutical sciences at the University of Wisconsin-Madison School of Pharmacy.

Thorson, an expert in the attachment and function of these sugars, says that understanding and controlling them has major potential for improving drugs, but that researchers have been stymied because many novel sugars are difficult to create and manipulate. "The chemistry of these sugars is difficult, so we have been working on methods to make it more user friendly," he says.

Now, in a study published online in *Nature* [Chemical Biology](#) on Aug. 21, Thorson, graduate student Richard Gantt and postdoctoral fellow Pauline Peltier-Pain have described a simple process to separate the sugars from a carrier molecule, then attach them to a drug or other chemical. The process also causes a color change only among those [molecules](#) that have accepted the sugar. The change in color should support a [screening system](#) that would easily select out transformed molecules for further testing. "One can put 1,000 drug varieties on a plate and tell by color how many of them have received the added sugar," Thorson says.

Attached sugars play a key role in pharmacy, says Thorson. Not only can

they change the solubility of a compound, but "there are transporters in the body that specifically recognize certain sugars, and [pharmaceutical companies](#) have taken advantage of this to direct molecules toward specific tissue or cell types. If we can build a toolbox that allows us to make these molecules on demand, we can ask, 'What will sugar A do when it's attached to drug B?'"

And although the new study was focused more on an improved technique rather than the alteration of drugs, Thorson adds that it does describe the production of some "really interesting sugar-appended drugs: anti-virals, antibiotics, anti-cancer and anti-inflammatory drugs. Follow-up studies are currently under way to explore the potential of these analogs."

The new molecules included 11 variants of vancomycin, a powerful antibiotic, each distinguished by the nature and number of attached sugars.

The essence of the new process is its starting point: a molecule that changes the energy dynamics of the sugar-attachment reaction, Thorson says. "This is one of the first systematic studies of the equilibrium of the reaction, and it shows we can drive it forward or in reverse, depending on the molecule that we start with."

In a single test tube, the new technique is able to detach the sugar from its carrier and reattach it to the biological target molecule, Thorson says. "Sugars are involved a vast range of biology, but there are still many aspects that are not well understood about the impact of attaching and removing sugars, partly because of the difficulty of analyzing and accessing these species."

Making variants of potential and existing drugs is a standard practice for drug-makers, and a recently published study by Peltier-Pain and Thorson

revealed that attaching a certain sugar to the anti-coagulant Warfarin destroys its anti-clotting ability. The transformed molecule, however, "suddenly becomes quite cytotoxic — it kills cells," he says. "We don't know the mechanism, but there is some interest in using it to fight cancer because it seems to act specifically on certain cells."

Sugars are also attached to proteins, cell surfaces and many other locations in biology, Thorson says. "By simplifying the attachment, we are improving the pharmacologist's toolbox. This study provides access to new reagents and offers a very convenient screening for new catalysts and/or new drugs, and for other things we haven't yet thought of. We believe this is going to open up a lot of doors."

Provided by University of Wisconsin-Madison

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