Heavy drugs draw heavy interest from pharma backers

It's an age-old problem in drug development: a compound that seems to exert its desired effects against cells in a Petri dish, but flops *in vivo*, either in animal models or, later, in humans. One common reason for such failures is how the body metabolizes drugs. Enzymes in the liver can break down molecules quickly, substantially limiting their potency. They might produce toxic metabolites in the process to boot.

If you could fortify the chemical bonds that hold those drugs together, thereby modulating the metabolism of the compound, would they be more efficacious? A trio of biotech companies has been banking on this prospect for the last decade, and their efforts are starting to trickle into the clinic.

Their strategy involves selectively replacing hydrogen atoms in oral small-molecule drugs with another isotope of the element: deuterium. Normally, a hydrogen atom consists of just one proton and one electron, but deuterium also has a neutron. This doubles the molecular weight of this 'heavy hydrogen', leading to stronger molecular bonds—and, researchers hope, more stable resulting drugs.

According to Roger Tung, president and chief executive of Concert Pharmaceuticals, based in Lexington, Massachusetts, "We have demonstrated repeatedly in human clinical trials that deuterium has the potential to change the properties of a compound, such as absorption, distribution and toxicology, while retaining its original potency and selectivity."

Last month, Concert announced a strategic collaboration with Celgene Corporation to advance deuterium-modified versions of the larger New Jersey–based company's therapeutics for inflammation. That agreement, Concert's third in just over a year, is part of an industry-wide growing interest in deuterated drugs from notable pharma players. In December, for example, Celgene also acquired Deuteria Pharmaceuticals, a 'virtual' biotechnology company based in Andover, Massachusetts; in 2010, Auspex Pharmaceuticals of La Jolla, California, struck a deal with Israel's Teva Pharmaceuticals over an undisclosed deuterated compound; and the New York–based drug giant Pfizer, for the past five or six years, has run a program investigating the possibility of using deuterium to enhance the properties of prospective drugs.

"There is no drug on the market that contains deuterium yet, but it won't be long before it happens," says Alfin Vaz, a drug metabolism scientist who leads Pfizer's deuterium activities from the company's research labs in Groton, Connecticut.

Time hangs heavy

The idea of using deuterium to improve the properties of drugs is not entirely new. More than 50 years ago, in one of the earliest descriptions of the isotope's effects on a drug's pharmacodynamic properties, chemists from the Canada's University of Ottawa, in collaboration with US scientists at what is now Bristol-Myers Squibb, reported that adding deuterium isotopes to a molecule that modulated the sympathetic nervous system limited its metabolism in cats (*Science*, **133**, 102–104, 1961). A handful of companies pursued the strategy in the following decades, including the New Jersey drug giant Merck, which tried to use the process to reduce the toxicity of an antibiotic, but nothing ever panned out.

So why the resurgence of interest now? "I asked myself that question a lot in the early period," says Pratik Shah, executive chairman of Auspex's board of directors and a partner in the venture capital firm Thomas, McNerney & Partners. "What am I missing? Why hasn't someone already done this?" One reason is that chemistry techniques have improved significantly, notes Sheila DeWitt, chief executive of DeuteRx, which was spun out of Deuteria after its acquisition late last year. "Analytical methods have caught up to what is needed," she says.

Between the various companies working in this space, a handful of deuterium-containing agents have gone into human trials. Auspex's SD-809, a deuterated version of a drug called tetrabenzine, which is used for treating abnormal movement disorders, is the most advanced: in June, the company launched a 100-person, phase 3 study testing the SD-809 in people with Huntington's disease. Meanwhile, Concert's lead candidate—CTP-499, a first-in-class agent that aims to treat diabetic kidney disease by inhibiting multiple isoforms of the phosphodiesterase enzyme—is now undergoing phase 2 testing. Company scientists published positive phase 1 safety data in February (*Clin. Pharmacol. Drug Dev.* **2**, 53–56, 2013). CTP-499's phase 2 trial is expected to wrap up late this year.

Despite the clinical momentum, Vaz cautions that designing deuterium-containing drugs is far from straightforward. "Just sticking deuterium on a molecule won't do it for you," he says. Vaz's team at Pfizer has begun systematically looking at how to determine whether using deuterium will benefit a compound. "The question is finding the right system that will translate to an *in vivo* effect," he says.

Plus, even if the science can be worked out, success for deuterated drugs will ultimately require navigating a dizzying patent landscape that, in recent years, has undergone "a land-grab for deuterium-containing chemical entities," notes Shah. Dozens of patent applications for deuterated compounds have been approved, but since most are for improvements to already-existing agents, questions are increasingly being raised about whether the use of deuterium is novel and non-obvious.

So far, companies have been able to argue that the isotope's effects are not predictable. But as the space gets crowded, that could change. "Someday," predicts Vaz, "it's probably going to go to court."

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Concerted effort: It's heavy going research for scientists at Concert Pharmaceuticals.