

## Notebook

News and analysis from the life science community

### Antifungal fight

**K**ishor Wasan, a pharmacologist at the University of British Columbia, needed a negative control. It was 2000, and he was investigating a new way to deliver anti-fungal drugs in pill form, generally cheaper and easier to administer than intravenous injections. “I said, ‘Let’s take a drug I know doesn’t work,’” Wasan recalls. He turned to amphotericin B, an antifungal membrane disruptor that Wasan had studied a decade earlier for his PhD, and is not normally absorbed by the body when administered orally. He embedded amphotericin B and a batch of other drugs into his newly devised lipid-based delivery vehicle, and fed them to rats. This turned out to be perhaps one of the worst negative control experiments ever—but a lucky break for Wasan.

Compared to the other drug treatments, the rats on amphotericin B had the highest blood levels and lowest kidney levels of the drug, indicating that the body more readily absorbed amphotericin B than any other drug. What’s more, oral amphotericin B seemed to bypass the renal toxicity normally associated with intravenous forms of the drug (*Antimicrob Agents Chemother*, 47:3339–42, 2003).

Wasan was bewildered: “I thought, what the heck is going on?” Further experiments showed the drug was actually working: Amphotericin B fed to rats wiped out *Aspergillus fumigatus* infections (*Drug Dev Ind Pharm*, 33:703–7, 2007), and 90% of *Candida albicans* kidney infections, which is similar to the 95% success rate seen with intravenous

delivery. All with no renal toxicity. “The fact that we’ve got an oral formulation that’s mimicking IV—that’s a major finding,” Wasan says.

“Amp-B is basically the best antifungal agent we have; the problem with it is that it has to be given IV and it’s toxic,” says David Stevens, a clinical mycologist at the Santa Clara Valley Medical Center in San Jose, Calif. Eliminate the need for IV and “they’ve got half the battle solved,” he adds. “And if it’s less toxic, it’s a home run.”

Amphotericin B in poppable pill form could treat systemic fungal infections, particularly in patients with cancer or HIV/AIDS. This may make it highly profitable in the developed world, but it can also combat parasitic infections, such as trypanosomiasis and visceral leishmaniasis, that are more prevalent in developing nations. “We’ve got a first-world need where we can make money,” says Wasan, “and a third-world need where you can sell the drug at a subsidized cost.”

To commercialize his formulation, in 2007 Wasan teamed up with the UBC chapter of Universities Allied for Essential Medicines, an international organization that aims to improve access to medicines and research on neglected diseases at academic research institutions. In May 2008, Wasan licensed his oral amphotericin B formulation to iCo Therapeutics, a Vancouver-based biotech company, which agreed to make the drug available at a subsidized cost to combat leishmaniasis in developing nations. It’s a “win-win” situation, says John Clement, iCo’s chief business officer.

### Who will release the first oral fungicide?

Wasan’s amphotericin B formulation could prove to be the world’s first available oral fungicidal agent. (Pfizer’s oral antifungal Diflucan (fluconazole) stops fungal growth but does not kill the infectious agent.) But Raleigh, NC-based BioDelivery Sciences International (BDSI) has its own oral formulation of amphotericin B based on its patented Bioral delivery technology, which wraps the drug in a coiling structure of alternating lipid layers, currently in phase I trials. (Clearly, amphotericin B is more ‘oral-izable’ than originally believed.) Still, Wasan thinks his drug, in preclinical trials, should have an advantage. His formulation solubilizes the drug in a glyceride-based liquid, whereas Bioral relies on a liposomal suspension, which can be difficult to bring up to a commercial scale, he notes.

Raphael Mannino, BDSI’s chief scientific officer, disagrees. “This is a very simple manufacturing process,” he says. What’s more, BDSI’s formulation is effective, nontoxic, and “even in suspension, we have very long stability of our product,” he says.

The irony of Wasan’s drug discovery, he notes, is that he didn’t even want to study amphotericin B again after finishing his PhD; he only resorted to the drug because he expected it to fail. “Am I lucky as hell? Yes. Did I think it was going to work? No. Am I fully believing it? Well, human studies will be needed to play this out.”

—Elie Dolgin