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Breathing New Life into Old Drugs

By Alissa Poh

Sept. 24, 2008 | Thinking outside the box is generally a good idea. And in drug development, it's not always out with the old and in with the new.

Some companies feel that drug repurposing – while mostly still easier said than done – remains a viable alternative to the oft-financially crippling process of getting a new drug from pipeline to market, and one worthy of more consideration.

Certainly, many biotech firms have made use of the FDA's electronic Orange Book, querying its "Disc (Discontinued Drug Products)" list, which contains thousands of drugs that made it through Phase I testing, only to be withdrawn for reasons other than safety – lack of efficacy; replacement with better drugs; commercial constraints, to name just a few. These firms are constantly looking to "purposefully repurpose" this warehouse of abandoned drugs, finding new targets among protein families like kinases and G-protein-coupled receptors. But so far, only ChanTest Corp., based in Cleveland, is solely focused on reincarnating drugs by matching them with ion channel targets.

Now a decade old, ChanTest grew out of consulting work its founder and CEO, Arthur M. "Buzz" Brown, did in the late 1980s for pharmaceutical companies, on drug risk assessment related to cardiac ion channels. Brown's focus then was to find the target for Seldane (terfenadine), the first non-sedating antihistamine and also the "poster child" for non-cardiac drugs that caused sudden cardiac death.

"Seldane was a big breakthrough because previous antihistamines crossed the blood brain barrier; people taking them often fell asleep at the wheel and died in car accidents," Brown remarks. But blockbuster properties aside, unexpected deaths from cardiac problems were noted among those on this new drug; as well, enough prescriptions were being written that the numbers started to get attention.

"We showed that Seldane was directly blocking a particular potassium channel, hERG," Brown says, "and our cardiac risk assessment assay, which we then introduced, became very popular. One thing led to another, and ChanTest was formed."

Nowadays, ion channel testing for drug safety is a standard component of regulatory submissions at the FDA, prior to any drug being approved in humans. And ChanTest has an ongoing $10 million program aimed at developing the world's largest ion channel library, overexpressing important ion channels from the human genome in cell lines and validating each for its function. This library, Brown says, can be divvied up into "channel panels" according to tissue (e.g., cardiac, respiratory, CNS), therapeutic area (e.g., pain, seizure, diabetes/obesity), or ion channel family. The panels allow for primary and secondary pharmacodynamic profiling, where the first determines whether a particular channel is a drug target, and the second examines other channels said drug might hit, which could produce unwanted, off-target effects. Currently, there are about 70 such panels within ChanTest's library, with 120 being the ultimate goal.

"Think of it as a type of Amazon.com – each panel is like having all the books on a particular topic in your shopping cart," Brown elaborates.

Where drug repurposing is concerned, ChanTest has made use of the Orange Book to come up with a collection of approximately 3,000 drugs left by the wayside, and the firm's scientists are running these against their extensive ion channel library, searching for channel targets.

"We got the idea after investigating a drug for a client that, based on our hERG assay, should've been killing people," Brown explains. "However, the drug had been in man without such dire results; it also didn't have any efficacy for its indication, so it ended up being discontinued." ChanTest scientists then produced a hypothesis explaining why this drug wasn't lethal as expected, supporting the notion with their cardiac channel panel. And because the drug's profile (in a panel screen) looked intriguing, they decided to see if it would successfully terminate atrial fibrillation (AF) in an animal model, which it did. Compound CT-1, as the drug is called, is currently undergoing a Phase 2a proof-of-concept clinical trial and looks "very promising," Brown says, with an AF termination rate of 60 percent, as opposed to 30 percent for present anti-arrhythmics.

Besides blending both their repurposed and ion channel libraries in search of potential drug candidates, ChanTest also offers fee-for-service drug repurposing to interested clients. For apart from the Orange Book, there are likely hundreds to thousands more abandoned drugs in the compound libraries of drug companies. "So a client says, 'I've got a hundred drugs I'm not using, but they're safe in man – think some might have an ion channel target?' and we go from there," Brown says.

ChanTest's foray into drug repurposing is still in the early days, Brown adds, so major success stories "are yet to come." But just because a drug fails against one target doesn't mean it can't be tried against another, he emphasizes, citing Viagra as a good example.

"Repurposing is not only a faster and cheaper way of getting drugs to the market; but thanks to genomics, we now have a lot more targets than we did before," Brown says.