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Traditional Chinese Medicine Gets Down to Drug Discovery Roots



By Trista Morrison Editor

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Decades of improvement in drug discovery technology have failed to improve productivity, and with the patent cliff now at hand, some pharma firms are adopting a back-to-basics approach.

When it comes to getting back to basics, Traditional Chinese Medicine (TCM) is "about as low-tech as it comes," said David Kolb, founder and CEO of Insero Health Inc. "We're talking about old manuscripts written hundreds of years ago," he told *BioWorld Insight*.

Yet Kolb and others see an opportunity to apply modern drug discovery technologies to TCMs and other natural products, potentially resulting in better leads that may be less prone to failure because they've already demonstrated a clinical effect. And so, even as Western drugmakers look east for contract research, manufacturing and future markets, the Eastern tradition of TCM is moving west – although more as a resource for drug discovery than as ready-to-market products.

Lost in Translation

Conceptually, traditional Chinese medicinal approaches seek to restore balance to the body through the application of herbal-, animal- or mineral-based products. While Western medicine focuses on diagnosing and treating a condition in a specific body part, Eastern medicine views the patient more holistically.

In China, TCMs are big business: They boasted \$46 billion in sales in 2010 and were expected to hit \$56 billion in 2011, according to a research report written last year by Elemer Piros, analyst with Rodman & Renshaw. And those are not home-brewed remedies dispensed in local markets; many are tablets or injectibles administered in hospitals. The Chinese government has invested significantly in the modernization of TCMs, requiring that they conform to good manufacturing practices and other SFDA standards.

Even so, Curtis Tyree, vice president of operations at Huya Bioscience International LLC, is skeptical that TCMs will ever get much traction in the west. "There isn't the tradition of using uncharacterized extracts here," he said, noting that many TCMs are complex mixtures with batch-to-batch variability. He added that while a company can sell Echinacea extract at a drug store, it can't make claims about the ability to treat or prevent disease without going through the FDA approval process.

Insero's Kolb noted that while the FDA does have a guidance document covering the development and approval of botanical drugs, to his knowledge only one such drug has gained FDA approval: Veregen (sinecatechins, MediGene AG), a topical ointment for genital warts made from an extract of green tea leaves.

"It's great that the FDA did that, but from a practical standpoint, I'd be surprised to see big pharma utilizing the botanical guidance," Kolb said.

Yet Kolb noted that even though many TCMs are mixtures, a little research will often reveal the active compound. That compound can then be manufactured synthetically for "a fraction of the cost to pull it out of a plant," Kolb said.

It's an approach that is certainly not unfamiliar to Western drug development. Kolb noted that roughly one-third of FDA-approved new molecular entities over the past 25 years were derived from natural products, including Taxol (paclitaxel) and aspirin, which are synthetic versions of compounds originally derived from the yew tree and the willow tree, respectively. Gilenya (fingolimod, Novartis AG) came from TCM – it was derived from a fungus that lives on a silk worm.

But the interest in natural product chemistry that was so heavy in the late 1980s and early 1990s has waned in recent decades. "I think what happened is we all got caught up in the excitement and the technology available in terms of drug discovery tools" like high-throughput screening, Kolb said.

But, if recent movements by big pharma and start-up biotechs are any indication, that may be about to change.

Back to Basics

As a drug discovery tool, "TCM has two things going for it," Tyree said. "First, the extracts have been used for hundreds of years so they tend to have a good safety profile, and second, they are not manmade so they have novel chemistry."

Kolb agreed. "In drug discovery, what we are all about is finding good leads," he said. With high-throughput screening, drug companies might evaluate a library of thousands of compounds in search of one that hits a certain receptor, but that library itself has already been pre-screened, to some extent, for compounds that are easy to manufacture and have other desirable characteristics. "Maybe you're not giving yourself the full view," Kolb explained.

With TCM, however, Kolb said, "it's like a maze – you start at the cheese and work backwards." You know you have clinical activity, and only later do you narrow the field by what you think you can manufacture. "When you ask the questions in a different order, you may find yourself with different answers," he said.

That's the approach Kolb's company, Insero, has taken with lead product huperzine, a TCM used to treat memory loss. Insero licensed patents for the use of huperzine in epilepsy and other indications from Harvard University, but the start-up also licensed patents from Yale University that cover a manufacturing process for synthetic huperzine. Insero raised \$1.1 million last month and expects to launch a Phase I/II trial in epilepsy later this year. (See *BioWorld Today*, Feb. 27, 2012.)

For Insero, creating a synthetic version of huperzine was critical because the yield on extraction from the natural source was 0.01 percent. Additionally, the patented manufacturing process gives the biotech more intellectual property protection.

Huya also went the synthetic route with HBI-3000, its anti-arrythmic drug that was designed based on a TCM. The drug is finishing Phase II trials in China for ventricular arrhythmia and is completing preclinical work in the U.S. to support a Phase II trial in atrial fibrillation.

"Synthesis is always preferable," Tyree said. "It makes your analytical methods and interactions with the FDA much more straightforward. But some drugs cannot be synthesized."

That's the situation Huya found itself in with HBI-3802, a preclinical cardiovascular drug derived from TCM. Tyree said HBI-3802 is a "very complex molecule so it would be challenging to synthesize." Fortunately, however, the plant it is derived from is prevalent. Huya refined the molecule until it was 99 percent pure, and has patents covering both the composition of matter and the purification process.

"It is an extract modernized to a single component," Tyree explained. "That's where modernization really works to your advantage."

Kolb, too, sees plenty of opportunity to apply modern drug discovery techniques to TCM. Whether a molecule is created through purification or synthetic manufacturing, that molecule can benefit from characterization, structure-activity work, and other high-tech approaches. Once a molecule is identified, the subsequent tweaking is what's really exciting, Kolb said.

Big and Small Players

Insero and Huya are not the only companies pursuing TCM.

Last month, the UK's *Telegraph* reported that GlaxoSmithKline plc created a Discovery Performance Unit in China dedicated to researching how TCMs could be converted into synthetic drugs.

And Hutchison MediPharma Ltd., of London, a subsidiary of China-based Chi-Med, researches and develops TCM-derived botanicals, semi-synthetic drugs and synthetic single chemical entity drugs for the global market.

Even outside of TCMs, there seems to be a resurgence of interest in natural product drug discovery. Earlier this year, Third Rock Ventures and Sanofi SA teamed up to launch Warp Drive Bio, seeding the firm with up to \$125 million to support its genomic search engine that

enables hidden natural products to be revealed on the basis of genomic signatures. Warp Drive plans to tap natural products hidden in microbes as a way to attack currently undruggable targets.

Gregory Verdine, Warp Drive founder and Harvard professor, said that previously "no one had created a comprehensive discovery engine that selectively mines from nature those products with transformative pharmaceutical potential." Warp Drive is hoping to fill that void.

Altogether, Kolb pointed to a "renaissance" in drug discovery based on natural products. "The industry is coming back to its roots a little bit," he said, and Insero is "excited to be a part of it."

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