Innovations

Rainforest remedies

Shaman Pharmaceuticals, Inc.

Chemistry & Biology March 1998, 5:R63–R64

 ISSN 1074-5521

There is a bold sociological experiment being planned in South San Francisco, but its execution will have to wait on the fate of a single compound. Shaman Pharmaceuticals, Inc., is basing their development of natural product drugs on the knowledge of native healers. Provir™, a diarrhea treatment derived from the red latex of a plant with the familiar name sangre de drago (dragon's blood), is their shot at the big time. If it succeeds, the real experiment begins: distribution of a percentage of the profits to collaborators in 70 different language groups in 30 different countries.

New drugs from an old source

The idea behind Shaman is simple. "We want to utilize this information base that native people have, to recognize that they have had a long history of using these plants," says Wayne Inman, associate director of natural products chemistry at Shaman. Looking for drugs in plants is far from new: an estimated 120 drugs based on plant products are now on the market. Some of the more famous examples include quinine for malaria (from the bark of Peruvian cinchona trees), salicin (from white willow bark, converted to aspirin by Bayer in 1899), and opiates (from the opium poppy). But Shaman is the first company to devote itself to finding these chemicals by systematically consulting native peoples, using ethnobotanist–physician teams.

David Kingston of Virginia Polytechnic Institute and State University in Blacksburg, Virginia, is trying to find out whether native healers are worth the effort. As group leader of one of five US-government-sponsored International Cooperative Biodiversity Groups (ICBGs), he is coming to a mixed conclusion. "Probably for high throughput screening, a random botanical collection is just as good [as consulting native healers]," he says. "The particular screen has no relation to the shaman's information, so you wouldn't expect a correlation." These *in vitro* screens, typically performed in large numbers against proteins known to cause disease, are the favored tools of large pharmaceutical companies. But Shaman takes a very different approach, testing only a few, hand-picked plant extracts (~100 per year) in animal models of the disease. "Then I would expect to find quite a high correlation between the shaman's information and an increased hit rate," says Kingston, "because you are testing for something that is relevant to the disease indication."

With native people acting as a first-line screen for activity and bioavailability, Shaman scientists report that ~50% of their extracts show activity in initial *in vivo* tests. But the animal models are not perfect. The researchers track a variety of physiological markers, but they do not know the exact mechanism of action of the extract, so rational modification of the isolated compound is difficult. And the target may be involved in the symptoms not the cause of the disease, although the success of drugs like aspirin makes this caveat seem less than troubling.

Dragon's blood

The polyphenol from *Croton lechleri*, now called Provir, was initially identified as a potential treatment for respiratory synctial virus. It became an anti-diarrhea candidate when Shaman scientists witnessed use of *Croton lechleri* during a cholera outbreak in Peru in 1993. The switch in indications appears to have been a good decision. When separated from other compounds in the plant extract, the polyphenol has poor bioavailability. This is a plus for diarrhea treatment, as the compound can be administered orally and reach high concentrations in the gut without showing toxicity. It appears to act, at least in part, by blocking the excretion of chloride ions by the cystic fibrosis transmembrane conductance regulator (CFTR), a channel found in both the lungs and the gut. By reducing ion secretion, Provir slows the loss of water in secretory diarrhea and allows the body to rid itself of toxins and bacteria at a more gradual pace.

Shaman is marketing Provir as an alternative to antibiotics, which require diagnosis of the causative organism, and antimotility agents, which often result in rebound diarrhea once treatment is stopped. Phase II trials of Provir for mild diarrhea were not successful, but Shaman is pursuing Phase II trials for more serious traveler's diarrhea, and a single pivotal phase III trial for AIDS-related diarrhea starts March 1998.

Shaman's next move

Many biotech start-ups are glorified branch divisions of large pharmaceutical companies, with most of the research funds coming from, and most of the potential profits going to the partner. This is not the case for Shaman. After almost nine years and $104.5 million in accumulated deficits, Shaman is still blazing the trail with Provir. If it makes it to the finish line the rewards will keep the company going for a long time.

Shaman was also on its own with Virend™, a topical formulation of the polyphenol found in Provir. This drug died in Phase III trials for herpes. But in diabetes and anti-fungals the company is increasing the level of collaboration. An anti-fungal called Nikkomycin Z, licensed from Bayer after they discovered it would not work for the huge market of candidiasis, is now in Phase I trials for various fungal infections, including some that are particularly troublesome in AIDS patients.

Shaman's discovery efforts are now focussed solely on therapies for non-insulin-dependent (adult-onset) diabetes (NIDDM). This disease is a good fit for the *in vivo* approach. Current drugs, such as the sulfonylureas and metformin, have significant drawbacks, and further discovery using *in vitro* assays is hampered by the multiple causes of the disease.

NIDDM is not a new disease; it was described in China as early as 3000 B.C. But it does not dominate the thoughts of the developing world. Fortunately, its symptoms lend themselves to simple cross-cultural translation. The obvious symptoms — fatigue, chronic foot sores, and increased urination and thirst — can be supplemented with the less obvious: urine that attracts ants and leaves a white, sugary spot when dry. "In many cultures of the world," explains Tom Carlson, senior director of ethnobiomedical field research at Shaman, "the word for diabetes means sweet urine."

The company has at least 15 different compounds that lower blood glucose in an animal model, including triterpenoids, cryptolepine, and SP-134101, a compound now entering Phase I trials. Unfractionated plant extracts are first tested in a mouse deficient in the leptin receptor (*db/db*), and the most promising candidates advance to the more sophisticated rat model. The two treatments used to construct the rat model — a high lipid diet to build peripheral insulin resistance, followed by streptozocin, a drug that kills pancreatic cells — mimics the biphasic disease course in humans.

From plant to pill

Modern analytical methods, particularly two-dimensional nuclear magnetic resonance, have reduced the amount of raw material needed to determine the structure of a natural product. Synthetic chemistry then comes in as a source of material for biological trials, or even as the creator of modified drugs. "The original philosophy was that from the ethnobotanical source would come a compound that would go all the way to being a drug," says Donald Bierer, associate director of medicinal chemistry at Shaman. "The reality is that this won't always be the case." Bierer has modified various natural products to reduce toxicity, increase efficacy, and even remove extraneous chemical complexity. "If it's a complicated natural product that can't be isolated in a large quantity without depleting the plant species in nature, then we need to simplify its structure," he says. Bierer has not succeeded in simplifying or synthesizing Provir, but the abundance and fast growth of *Croton lechleri* and high yield of the compound (2%) mean that collection in the field is a viable option.

No more raping and pillaging

The Convention on Biological Diversity (CBD), arising from the Rio Earth Summit in 1992, included sharp admonitions that native people should be compensated for their medicinal knowledge. There are still few laws to make sure that this takes place, but Shaman has heavily promoted its own voluntary efforts to do so. "The countries and cultures are part of our R&D and they are pivotal in this process," says Carlson. "That's where it starts, with these people. They are and will be beneficiaries."

Eloy Rodriguez, an ethnobotanist at Cornell University (Ithaca, New York), admits he does not know the details of Shaman's efforts. But he is cautious of their claims. "After all," he says, "exploitation has been the history of the world." And the realities of the world mean that only those in the developed world, with diseases of the developed world, have the money to buy drugs and bankroll further research. "Pharmaceutical companies are concerned about CEOs who are running around golf courses about to have heart attacks," says Rodriguez. "The people in the rainforest are worried about malaria, dengue, [and] rotavirus."

Carlson admits that native peoples, even if they are interested in the diseases investigated by Shaman, will probably not be able to afford the final product. But that, he says, is not the point. "The whole notion that they would need a pure compound doesn't make sense, because they already have the whole plant traditional medicine." Shaman's role, says Carlson, is to confirm the biological activity of certain plants (assay results are returned to the native collaborators), and to fund efforts to preserve and extend native knowledge of plant-based treatments used for other diseases such as malaria. A percentage (yet to be determined) of drug revenues will be given to the Healing Forest Conservancy (HFC), a non-profit set up by Shaman. The HFC will then distribute the money equally to all government and community collaborators. A trial run, using a grant of $40,000 from the HFC, is underway in Nigeria.

But that's not all. "If the benefits they get are only on revenues, the time they have to wait is far too long," says Carlson. Shaman therefore sets aside 10–15% of the budget of each expedition for short-term projects to be selected by the hosts: school desks and a hospital in Tanzania, an extended airstrip in Ecuador, legal expertise for land demarcation in Peru, and a clean-water project in Indonesia. Scientists from six countries have also visited and worked at Shaman, and Shaman has organized workshops on collecting and categorizing native plant knowledge.

When and if the money starts to flow in greater amounts, the distribution politics will also intensify. "To do good well is not easy," says Carlson. "But we believe that, with our long-term working relationships in tropical countries, we're up to the challenge." If all works as planned, Carlson will be part of a new way, a future with mutual cultural respect.

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