

Bioprospects less than golden

The search for potentially valuable natural products is flagging. Could new rules on ownership of these resources give it a boost? Rex Dalton investigates.

In the balmy atmosphere of the 1992 Earth Summit in Rio de Janeiro, a convention to conserve global biodiversity seemed like an idea whose time had come.

The Convention on Biological Diversity was agreed at Rio, in principle, as a framework that would help the world's biological resources to be utilized in a controlled and prudent way. Scientists, governments and commercial companies would work together in harmony, the convention's authors hoped.

But progress towards these goals has been painfully slow. Searching for genetic resources among plants and animals has never been easy: the richest biodiversity is found in exotic but sometimes lawless locales. Its study requires not just scientific perseverance but the construction of an intricate web of relationships with local people, landowners and government officials.

And the convention has done little to ease tensions that exist between scientists searching for potentially valuable compounds and officials in the developing countries where most bioprospecting takes place. If anything, this tension is growing as nations become more aware of their rights under the Rio convention.

Bioprospecting still takes place in "an environment of suspicion", explains Rohan Pethiyagoda, a biomedical engineer and conservationist who founded the Wildlife Heritage Trust of Sri Lanka. He adds that suspicion usually falls equally on corporate bioprospectors and academics — to the disadvantage of researchers such as taxonomists, whose main aims are non-commercial.

The mistrust is based on decades of "academic scientists bringing home suitcases full of leaves, mushrooms or whatever", says Daniel Janzen, an entomologist at the



Hide and seek: finding useful medicinal compounds in the Costa Rican rainforest has proven more difficult than anticipated.

University of Pennsylvania who conducts fieldwork in Costa Rica. The samples would sometimes be sold for cash, Janzen says.

The treaty has reined back such excesses. Most major corporations in the United States and in Europe officially adhere to its principles, even though the United States is not a party to the convention. But it has done little to quell poor nations' fears of exploitation. Nor has it yielded the anticipated bioprospecting bonanza. On the contrary, many pharmaceutical companies have withdrawn from the field for a variety of reasons, including doubts about its commercial benefits.

Getting it right

This has left the backers of the convention seeking new instruments to shore up its effectiveness. Developing nations, many scientists and even some companies that want to exploit biodiversity would welcome more specific rules on how the origins of valuable samples should be recorded and their benefits shared between the nation of origin, the discoverer and the commercial sponsor.

But such rules have powerful opponents, including government and pharmaceutical company officials in the United States, who claim that proposed rules would run counter to the existing US patent system. Their implementation — which was discussed earlier this year in Kuala Lumpur, Malaysia, at the seventh conference of the parties to the convention — is set to be a long, hard slog¹.

On the ground there are some successes, however. Just as the Rio convention was taking shape in 1992, Phyllis Coley, a plant ecologist at the University of Utah in Salt Lake City, launched a bioprospecting project in Panama to look for potential drugs against the parasites that cause malaria, leishmaniasis and Chagas' disease. Today, the project has evolved into a network of six laboratories, employing ten senior scientists, nearly 60 technicians and training dozens of local students.

Coley's team looks specifically at young plant leaves, which they have found to contain higher levels of compounds such as alkaloids². These bioactive compounds protect the plant against insect predators and can be potential drug candidates.

Support for the network comes primarily from the Fogarty International Center, a branch of the US National Institutes of Health that specializes in work overseas. From the start, Coley ensured that the project was deeply rooted in Panama. All its research is done there. Laboratories have been created, staff trained and more affordable assays developed to test plant samples for activity. Project managers are meticulous about transparency: each time a sample is to be transported out of the country, approval is sought from the Panama National Authority on the Environment.

Coley is proud of the project's track record. A fluorescence assay for antimalarial agents has been developed and patented, and



Take your pick: Panamanian biologists collect leaves in a project backed by the US National Institutes of Health.

is now being used by research groups in Africa³. The patent for the assay has been filed in the United States, with rights assigned to researchers and institutions in Panama. And the project team helped Panama to apply for World Heritage Site status to protect Coiba National Park, a region of islands and coral reefs on the Pacific Coast.

The training of young scientists has been the project's greatest achievement, says Luis Cubilla, a project scientist from the University of Panama. "That is very important for my

country," he says. "We are developing a core group that have the skills needed to build a research enterprise."

But in drug discovery — the project's central objective — results have been less stellar. After 12 years and US\$6.55 million investment, the project has yet to deliver a compound ready even for safety trials in humans. This lack of commercial prospects is fairly typical of otherwise successful projects worldwide.

A handful of promising agents have been identified, Coley says. A patent is being sought on a plant compound that shows activity against leishmaniasis⁴. Toxicity studies in mice are under way in Panama, and additional work will be conducted this summer at the London School of Hygiene and Tropical Medicine.

Coley remains optimistic that useful drug leads will eventually be found. In the meantime, the project is building up capacity on the ground. "Waiting for royalties is not going to help countries like Panama, because the timescale is too long," she says. "You have to train people, create jobs, and develop local awareness of biodiversity."

Protecting interests

The transparency of the Panama project and its depth of local involvement make it a useful model for others. In the Philippines, for example, bioprospecting has often been problematic. In 2000, for instance, three French scientists masquerading as ecotourists were caught trying to smuggle out medicinal plants.

This context presents a challenge for a collaboration of Philippine and American scientists, who have a planning grant from the Fogarty centre to start bioprospecting in the Bataan National Park, which covers some 23,700 hectares of highlands 150 kilometres west of Manila. Research at the Bataan park is further complicated by concern that it might unfairly exploit the traditional knowledge of the indigenous Ayta people who live nearby.

Past experience in places such as the Philippines has made bioprospecting difficult for taxonomists, who are seeking to catalogue the world's plants and animals. Usually, their work is purely academic. But as nations learn to defend their genetic resources, local officials sometimes suspect them of biopiracy, and prohibit the export of specimens for analysis.

But Lourdes Cruz, a member of the Bataan project and a biochemist at the University of the Philippines, says considerable headway has been made. "We are the first to get prior informed consent from the Ayta people to work in the park," says Cruz.

A Bataan Technology Park has been established to house research and development facilities, and scientists from the

university's medical school and Marine Science Institute are engaged in project planning.

Nevertheless, says physician Michael Kron of Michigan State University in East Lansing, the principal US investigator on the project, it is likely to take all of the two-year period of the planning grant just to negotiate a collaborative research agreement with the Philippine Ministry of Health. "If we get an agreement, I will consider it a major accomplishment," says Kron, a specialist in infectious diseases.

All this preparation is necessary, bioprospectors believe, to avoid the pitfalls that await them in countries that are only now learning to assert their rights under the biodiversity convention (see "Bermuda gets tough over resource collecting", overleaf).

One reason for the regulations that may be added to the convention is to secure the conservation of biodiversity. But another is to create a more robust framework that will entice major drug manufacturers back into bioprospecting.

Few large pharmaceutical companies now have serious investment in the search for natural products. Coley, for example, had spent years negotiating with Monsanto, of St Louis, Missouri, on a legal agreement for any products discovered in Panama, only to see the deal collapse when the company's natural products section closed. "Suddenly, we were

frantically looking for a corporate partner," she recalls. Swiss-based pharmaceutical company Novartis eventually stepped in, agreeing to contribute \$50,000 for laboratory equipment. She says she is unsure why companies are reluctant to participate. "It's strange," she shrugs. "It's almost a free lunch for them."

In 1991, amid much fanfare, pharmaceutical giant Merck, based in Whitehouse Station, New Jersey, made a deal with Costa Rica to provide about \$1.2 million over ten years for bioprospecting and conservation. But no comparable arrangements have been announced since. And most companies have taken a more tentative approach. Some, including Monsanto and New York-based Bristol Myers Squibb have shut down their natural products divisions entirely.

Merck itself has now halted investment in the Costa Rica project, providing its last grant of \$130,000 in 2001. A company spokeswoman said that no products had come out of the project. Officials at Merck and the other two firms refused to discuss in detail why they have folded their bioprospecting tents.

But Lila Feisee, director of intellectual property at the Biotechnology Industry Organization in Washington DC, says that she suspects the push for benefit-sharing by developing nations has given drug companies "a negative image of bioprospecting".

"Companies need incentives," says Feisee.

"Waiting for royalties is not going to help. The timescale is too long. You have to train people, create jobs, and develop local awareness of biodiversity."

— Phyllis Coley

"But those incentives are being undermined. When risks outweigh the benefits, companies will do something else."

Natural remedy

This choice frustrates scientists who believe that natural products remain the most promising source of new drug treatments in the long term. David Newman, a chemist and leading authority on natural products who runs the marine and microbe collections of the National Cancer Institute in Bethesda, Maryland, blames the drug company pull-outs on corporate inertia. "There is a fear of gambling, then failing," he says.

In a study⁵ published last year, Newman and his co-authors wrote: "The decision on the part of several pharma companies to get out of the natural products business is gross foolishness. The utility of natural products as sources of novel structures, but not necessarily the final drug entity, is still alive and well."

Reviewing drug discovery over the 22 years up to 2002, Newman's study found that almost two-thirds of anticancer agents being investigated as drug candidates were derived from natural products.

One reason for the low level of interest of large companies, bioprospecting advocates believe, is the lack of a firm framework for benefit-sharing between host nations, scientists and commercial companies.

At this year's Kuala Lumpur conference,



Local involvement: Lourdes Cruz (right) explains the Bataan project to Aya tribespeople in the Philippines.

representatives of 188 nations agreed to try to build such a framework, to be considered at the next meeting in Brazil in 2006. Matthew Jebb, acting director of Ireland's National Botanic Garden in Dublin, who led the European Union delegation in the negotiations, says that "a vital underpinning can be created to dispel that air of suspicion" through such a benefit-sharing agreement.

A clear title document for each compound discovered would be an important element of such an agreement. Advocates envision a

document that would follow compounds around like a passport, stating where they came from and who holds rights on them.

Bioprospectors say that this arrangement could help entice drug companies back into the game. At the Kuala Lumpur meeting, the United States resisted the concept of a new, benefit-sharing agreement under the convention. But Leonard Hirsch, a Smithsonian Institution economist who is vice-chair of the US delegation, says he remains open to the idea. The United States is "seriously engaged in an analysis of the most efficient and cost-effective mechanism for a certificate of origin", he says. At upcoming meetings in Thailand next February and in 2006 in Spain, Hirsch says, the United States "looks forward to honing proposals and developing a user-friendly certificate system".

But despite such reassuring words, concern remains about the future of the convention's goal. "My biggest fear is that no new access and benefit-sharing agreement will be reached," says Jebb. "There is a great urgency — a finite biological resource is disappearing. It is going to cost all of us if no regime is enacted."

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1. Dalton, R. *Nature* 427, 769 (2004).
2. Coley, P. et al. *Front. Ecol. Environ.* 1, 421–428 (2003).
3. Corbett, Y. et al. *Am. J. Trop. Med. Hyg.* 70, 19–124 (2004).
4. Montenegro, H. et al. *Planta Med.* 69, 677–679 (2003).
5. Newman, D. J., Cragg, G. M. & Snader, K. M. *J. Nat. Prod.* 66, 1022–1037 (2003).
6. Venter, J. C. et al. *Science* 304, 66 (2004).

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Bermuda gets tough over resource collecting

When Craig Venter steered the *Sorcerer II* into Bermudian waters early last year, he was searching for ocean microbes. And he found plenty: in a paper published in March, he recorded 1,800 microbial species, including 148 previously unknown bacteria⁶.

But his voyage into the Sargasso Sea also took the genomics pioneer into uncharted waters. The rules on bioprospecting in this small British protectorate are still a

work in progress. And experience with expeditions such as Venter's has prompted Bermuda to temporarily shut down some research projects until it strengthens its regulations.

Bermuda is now rewriting its scientific collection rules completely, in preparation for joining the Convention on Biological Diversity as a protectorate of the United Kingdom, which has already adopted the convention. And lessons learned from Venter's scientific expedition and from a separate commercial project started in 1999 by Diversa, a San Diego firm seeking drugs from microbes, technology tools and industrial chemicals, will influence the



Craig Venter (left) and Anthony Knap aboard *Sorcerer II*.

formation of these rules.

Both Venter's group and Diversa gathered marine samples under the umbrella of a long-standing collection permit held by the Bermuda Biological Station for Research in St. George. Nearly 100 years old, the station gets most of its funding from NASA and the US National Science Foundation.

In 1999, Diversa struck a deal with the station to bioprospect in the waters off Bermuda.

But Jack Ward, the official at the Bermuda Ministry of the Environment responsible for developing bioprospecting policy, says that the government only learned of Diversa's project from a newspaper article published at the time. After enquiries, Ward says, station officials explained that Diversa was only studying organisms that could be found in many locations in the Atlantic Ocean, not looking for new ones. Subsequently, Bermuda didn't require Diversa to secure a government permit.

But in May this year, Ward learned that Diversa was marketing a biotechnology tool called DiscoveryPoint Fluorescent Proteins, which was based on a protein collected from

a coral in Bermuda, and for which the firm is seeking a patent. The research station is to get a 1% royalty, but the government and people of Bermuda will get nothing.

Meanwhile, Venter sailed into the Sargasso Sea in February 2003. The organisms collected were shipped to Maryland, where a US Department of Energy grant paid to have them sequenced at the Venter Science Foundation Joint Technology Center.

"We do this as part of discovery to enhance science," says Venter. "We are trying to benefit every country we work in." Bermudian officials don't fault Venter, who says that the Bermuda Biological Station's director, oceanographer Anthony Knap, assured him that no government permits were required — advice that Knap confirms. The microbial DNA sequences are being placed in the publicly accessible GenBank for scientific use.

But Ward says that the ministry is unhappy about the outcomes of both projects, and that Bermuda is revoking the station's collection permit. A new permit, with stricter controls, will be in place within the next month.

Bermudian officials regret what they regard as a lost opportunity. "There is a value issue here," says Ward. "Something that held value has been put in the public domain and made valueless for the people of Bermuda."

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