Cashing in on the rich coast

Costa Rica's flagship conservation institute needs help. Can a new deal with industry save it? Rex Dalton investigates.

F. HIDALGO/INBIO

INBio has a huge collection of Costa Rican insects, but exploiting their chemistry has proved tough.

Along Costa Rica's Pacific coast, scientific explorers are trying to turn over a new leaf for a storied institute — the National Biodiversity Institute, or INBio.

Near a crocodile-infested river in Guanacaste province, an international team searches for bacteria that one day may become a drug or industrial product. Taking advantage of the dry months, they are focusing on a microbe-rich forest zone — hoping to flip a leaf to find a fungus, either attacker or defender[1]. If they get lucky and isolate a fungus that produces a useful compound, any economic rewards will be shared with INBio, a once-model organization that is struggling to survive.

Created in 1989, INBio, based in a suburb of the capital San Jose, became an early symbol for how developing nations might participate sustainably in the biotechnology revolution. World-class researchers joined with Costa Rica's well-trained academics, hoping to save the nation's biodiversity — 4% of the world's total — by making money from it.

In the first years, more than US$4 million in grants flowed from the drug giant Merck[2]. Foundations and other nations added more, with total donations eventually topping $63 million. But no major products emerged.

There have been some modest successes, including a couple of industrial compounds and an over-the-counter hangover remedy. More significantly, INBio set itself up as a training ground for marrying traditional conservation values with modern high-tech methods. Today, other developing nations look to INBio as an example of how to achieve the goals of the 1992 Convention on Biological Diversity, which encourages sustainable development worldwide.

But INBio's scanty returns, and Costa Rica's limited ability to fund research, has raised doubts about the institute's survival. Its future may depend on an ambitious new bioprospecting plan, funded by the United States, in which scientists will canvas the country for new drug candidates. Others are holding out hope for a far-reaching goal for a $500 million endowment to preserve a quarter of Costa Rica's biodiversity (see 'A fund for the future').

"INBio is a high-quality machine with no gasoline," says Daniel Janzen, an entomologist at the University of Pennsylvania in Philadelphia who has worked in the country for decades and is trying to create the endowment. "The sooner we can get gas in the system, the sooner it can be cranked up."

Fuel source

Advocates hope the fuel for that engine will come from the Fogarty International Center at the US National Institutes of Health, which is giving the new bioprospecting team $3.5 million over four years. The effort is one of several International Cooperative Biodiversity Group (ICBG) projects, designed in part to put a value on preserving biodiversity[3].

Led by chemist Jon Clardy of Harvard Medical School, the five-year project includes researchers from the University of Michigan in Ann Arbor, the Broad Institute — a joint venture of Harvard and the Massachusetts Institute of Technology — and the Novartis Institutes for Biomedical Research in Cambridge, Massachusetts. Team members will be happy with whatever they find, but their assays and screens are designed to find compounds that can fight malignancies, infectious agents or neurodegenerative disease.

For five years ending in 1997, INBio was involved with a different ICBG, led by researchers from Cornell University in Ithaca, New York. But that programme produced no money-making products, and, in hindsight, some scientists believe its goals — such as trying to extract useful compounds from insects — were unrealistic.

The current project is designed to learn

A fund for the future

"Nibble by nibble," Costa Rica's fabulous biodoversity is disappearing, says entomologist Daniel Janzen.

The way to save precious habitats, he says, is to raise a US$500 million endowment. Annual earnings then would fund conservation efforts — hopefully saving 25% of the country's land. "Right now, it is death by a thousand cuts," says Janzen, of the University of Pennsylvania.

In recent months, he and colleagues have prepared the concept to present to Oscar Arias, recently reinstalled as the country's president. They call it Costa Rica Sostenible — sustainable Costa Rica.

On 26 May, the researchers were to brief ministry officials on the endowment concept. On 2 June, key government and environmental players will meet to begin planning the process to create it. "I've come to the conclusion that biodiversity won't survive if we don't do something like this," says Janzen.

He bases this on 40 years of studying some of the 9,600 species of butterflies, moths and caterpillars in the Pacific coastal province of Guanacaste — equal to the number in the United States and Canada combined.

Alvaro Ulgalde, a conservation biologist in San Jose who created Costa Rica's national park system 36 years ago, endorses the endowment idea. "It makes sense in every respect," he says. "But it needs to be complemented by clear government enforcement policies."

Under the plan, about $100 million would be used to buy pockets of private land within the country's national parks and other reserves. The remaining $400 million would be invested outside Costa Rica.

The estimated $20 million that would result annually would be shared equally by the nation's 11 conservation areas, with the National Biodiversity Institute (INBio) also receiving an equal portion for its conservation efforts.

Powerbrokers in San Jose are enthusiastic, particularly as the money will be outside the country and well accounted for, an aspect they hope will appeal to donors. **R.D.**

from the past. In particular, it is structured to be as open as possible about any potential new drug candidates. With the earlier grants, any compounds of interest left Costa Rica, disappearing behind the proprietary walls of corporate science. Clardy, who was part of the earlier ICBG when at Cornell, says he didn't want the new programme making the same mistakes. "I specifically formed it this way," he says.

To Rodrigo Gamez — a Costa Rican plant virologist who was key to forming INBio and remains president of its governing body — the experience was invaluable in securing the new pact. "We developed a capacity to negotiate," he says.

But some question how hard the companies may or may not have tried to develop products in those earlier deals. Merck, for instance, is believed to have found that about 200 substances tested positively in preliminary screens against disease. But Clardy's group thinks the firm did not go far beyond initial screening.

"I think they bought good public relations with the grants," says one informed scientist, privately. Merck declined to respond. Similarly, in a separate deal, Bristol-Myers Squibb is believed not to have pursued promising signals from compounds it may have found in insects. Neither company has said much publicly about results from the tested compounds.

Bugged out

In the earlier ICBG, scientists from Cornell and INBio set out to learn from the country's insects, which use an array of chemicals for digestion and protection. Insects were a natural choice, given INBio's extensive documentation of the country's butterflies, moths and caterpillars.

But the team found insect substances were present only in incredibly small quantities, making the material scarce for studies. And culturing them to produce enough material for lab experiments was onerous or worse.

Clardy eventually came to believe that working with insect material was too difficult. "We are only going to work on compounds that can be easily cultured and duplicated for studies" — from fungi, leaves, or other sources, he says.

In addition, the data will be publicly accessible, in a database containing information such as where the compounds were collected and under what conditions. Clardy foresees an eventual library with some 5,000 to 10,000 compounds collected during the project. The database could even contain details on how compounds respond in various screening tests against pathogens, information that is usually considered proprietary.

Clardy's group would get first shot at studying any promising disease-fighting compounds. But eventually the data would enter the publicly accessible ChemBank.

The work is possible because academic groups, such as those at the Broad Institute

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Hot property: the rivers of Palo Verde National Park, in northwest Costa Rica, could be a source of useful bacteria.

and Harvard's Institute for Chemistry and Cell Biology, are getting hold of the sophisticated and expensive testing equipment that in the early 1990s, when the first projects got under way, was the preserve of drug companies. In Novartis, the project has a partner willing to adapt to the new environment — and one that apparently still has faith in drug development from natural products, a faith that many pharmaceutical companies have lost.

As a team member, Novartis will get first opportunity to run its proprietary assays on promising compounds. But then the firm will have to negotiate agreements with INBio to advance any material to drug stage.

"I am very comfortable with this set up," says chemist Alexander Wood, a Novartis executive director for oncology research. "We want to have as many opportunities from new compounds as possible. When it comes to design, medicinal chemists can't match the natural process."

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Gut instinct: INBio staff inspect a termite mound. US collaborators are probing insects' enzymes and symbionts.

Revenue trickle

Such a deal might also address the lingering issue of a developing nation sharing in benefits from bioprospecting — which some activists call biopiracy.

Historically, countries housing microbes that led to blockbuster drugs got virtually nothing. The diabetes drug acarbose, for instance, was derived from a bacterium in a Kenya lake; proceeds from its sales, about $380 million in 2004, go entirely to the drug company Bayer, which developed it.

Under the diversity convention, a nation such as Costa Rica — which has adopted the pact — is to secure some reward from any pharmaceutical proceeds. In the past few years, Costa Rica has adopted and implemented laws specifically to address this access and benefit sharing.

Costa Rica — and in turn INBio — is among the few developing nations currently receiving license fees from natural products. Diversa, a San Diego-based biotech company, is currently paying Costa Rica nearly $6,000 a year for two products developed from the country's resources. One is DiscoveryPoint, a fluorescent protein used for tagging material in experiments that comes from a marine organism found in the Caribbean Sea. The second is Cottonase, an enzyme for processing raw textile material to reduce the use of harsh chemicals. It was discovered in warm mud in a volcanic area just west of INBio's suburban campus.

And INBio's knowledge of plants helped a Costa Rican firm, Lisanatura, develop a treatment for hangovers or indigestion — Hombre Grande — from a plant called amargo (*Quassia amara*).

Diversa is also persisting with the insect world. Along with the California Institute of Technology in Pasadena and the US Joint Genome Institute in Walnut Creek, California, the company has contracted with INBio staff to probe the guts of Costa Rican termites for useful compounds. The project involves analysing how termites use microorganisms or enzymes to dissolve cellulose. Some termites have 100 species living in their gut[4]. The team isolates organisms or enzymes, sequences key genetic material, and then studies it.

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INBio's annual operating budget is around US$6 million. About 70% of that comes from grants and contracts, such as those from the ICBG and Diversa. In addition to bioprospecting, INBio has two other divisions — a nature park, where schoolchildren and others learn about the importance of preserving biodiversity, and its inventory work, largely involving Janzen. With such revenue sources, when grants run out it can mean staff layoffs; late last year, about 15 workers were let go.

Those who remain are dedicated. In March, project leaders laid out an ambitious schedule for collecting, culturing and screening compounds. In Palo Verde National Park, they began searching river channels and an estuary on the Gulf of Nicoya. Scooping up bottom silt, they immediately found hair-thin, noodle-like filaments that are a type of cyanobacteria.

So far, no drug has come from cyanobacteria. Their history traces back more than two billion years, and today there are hundreds of types that thrive in salt, fresh and brackish waters. Such bacteria are known to host protective molecules, which chemists hope to isolate[5].

Organic chemist David Sherman of the University of Michigan has joined with Jorge Cortes, a University of Costa Rica marine biologist who is an authority on sea fans. Since 2000, Sherman has been diving in oceans from Papua New Guinea in the South Pacific to waters off the Central American isthmus in search of new compounds[6]. Together, he and Cortes explore the environments cyanobacteria thrive in.

Local knowledge

In December, as part of an ICBG workshop, the pair found cyanobacteria while diving on reefs in the Pacific Gulf of Santa Elena, just south of Nicaragua. "The diving is very challenging — low visibility, a pronounced surge, and high surf," says Sherman. "It was really great to have a local expert involved."

In the search for fungi on land, the process also involves unravelling the role of microbes. On a field trip this spring, INBio chemist Giselle Tamayo noted areas of interest in trees and shrubs. Two metres up from the ground, the vegetation is rich with fungi. Leaves will be collected and treated with antibiotics at INBio's labs. Then the fungi-bearing material will be cultured for weeks.

Periodically, fungi will be removed from the sample vials. "The last ones to grow are what we are interested in," says Tamayo. "These slower growing ones probably have not been described before."

Already, the team is seeing they will need luck. In the laboratory, technicians isolated DNA from water in a Costa Rican bromeliad plant. The DNA segments were then inserted into *Escherichia coli* bacteria, which produced a compound that has shown antibiotic activity in culture tests[7]. "We did get lucky with that," says Clardy. "But it could be nothing, and it could fall apart tomorrow."

The same, they hope, won't happen to INBio. ■

Rex Dalton is *Nature*'s West Coast correspondent.

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