

briefing

Nature 392, 535 - 540 (1998) © Macmillan Publishers Ltd.

When rhetoric hits reality in debate on bioprospecting

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ST LOUIS, MISSOURI

By a twist of fate, the world's biological resources are distributed in approximately inverse proportion to its material wealth. The United Kingdom — typically for its size and latitude — has around 1,800 plant species. Peru probably has 18,000.

At the start of this decade, the economically poor nations of the tropics began to anticipate some payback from their biological riches. In 1991 the drug manufacturer Merck struck a pioneering, \$1 million deal with the Costa Rican government to exploit the biodiversity of the tiny central American nation's national parks.

Other drug companies, aware in particular of the success of the anti-cancer drug Taxol, derived from the Pacific yew tree, seemed poised to follow suit. At the 1992 Earth Summit in Rio de Janeiro, 140 nations signed up to a Convention on Biological Diversity, endorsing the concept of nations holding property rights to their indigenous species (see [page 537](#)).

The developing countries began to prepare for a gold rush of prospecting scientists from the United States and Europe. Their environmental ministers addressed the issue and made uncompromising public declarations of their readiness to strike a hard bargain — did everything, in fact, short of opening bars and brothels for the anticipated flood of bioprospectors.

But so far at least, the rush has not materialized. After all the hype, according to two dozen experts interviewed for this article, there is not much more bioprospecting activity going on now than there was

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ten years ago, although many in industry predict that interest is likely to accelerate, particularly in the search for new genes.

One reason for the current slow-down is the growing reliance of pharmaceutical companies on combinatorial chemistry, as opposed to natural products, as their favoured source for biologically active molecules that they can test as drugs.

Although most of what sits on the shelves of today's pharmacy was derived from natural products, the research arms of most drug companies now see the systematic testing of synthetic molecules as the most promising route to tomorrow's therapies.

A commercial case for biodiversity conservation can be made on the basis of uses for natural products other than drug design. Better food supplements, and the genetic engineering of crops using genes from exotic species, are only two examples of multi-billion dollar businesses which could yet be built on the back of a fuller understanding of the world's plants, animals and microorganisms.

Where past bioprospecting activity has concentrated on the collection and identification of natural chemicals which organisms may use to protect themselves against predators or disease, the emphasis in future will be on the collection of genetic information from exotic species, for possible application in both genetic medicine and genetic engineering of crops. But both fields of activity are currently at an early stage of development, and no-one wants to make major investments in gathering and sequencing wild genes that they don't yet know how to use.

Great expectations

So action on these fronts will take decades, rather than years, to unfold — leaving developing countries well short of the expectations they held a few years ago. "There is this tremendous expectation on the part of the developing countries," says Stephen Blackmore of the Museum of Natural History in London, who argues that the alleged value of biodiversity for drug development was "hyped up" by conservationists. "It was a poorly developed argument for biodiversity conservation."

Western scientists involved in the collection and screening of biological samples say that their work is harder to do — and far harder to find funding for — than many people realize. "From our point of view, it is developing a lot more slowly than we expected," says Robert Magill, head of research at the Missouri Botanical Garden, a major centre for botanical research. "It is not the windfall that we thought it might be."

It is already possible to sequence genetic material from wild microbes and plants, with a view, for example, to the genetic engineering of crops. But the core of today's bioprospecting activities is comparable to what it has always been. Plants and other organisms are collected, ground down, dissolved, concentrated and tested against a target.

Thirty years ago, the US National Cancer Institute (NCI) would inject the resultant extract into cancer-

ridden mice, and watch for the result — an immensely costly and time-consuming process. More recently, the concentrate has been tested in vitro against healthy and cancerous human cell lines.

David Newman is a senior chemist working at the natural products branch of the NCI's pharmaceutical development programme, which has collected about 70,000 samples of plants and microbes over the past 12 years. According to Newman, it is the extremely small odds against finding anything useful that keeps private drug companies from engaging in bioprospecting on their own. "Industry is not doing that much, compared with what it used to do," he says.

Newman finds this unsurprising. Roughly speaking, one sample in ten thousand will show promising activity in the area that is of interest to researchers, he says. One in ten of these promising samples might go to clinical trial, and one in ten of those to market. Giving bioprospecting the benefit of the doubt, Newman estimates that only one sample in 250,000 will directly yield a commercial drug, although many more samples may serve as useful leads for modification through combinatorial chemistry.

The NCI has learned from bitter experience to collect enough material — about a kilogram is needed — to allow a given sample to be thoroughly investigated without a return into the field, and each sample costs about \$500 to collect, transport and store. History shows that the process from sampling to market can take anything from 8 to 15 years. Drug companies found this arithmetic unappealing even before developing countries started making aggressive demands of would-be bioprospectors.

The NCI requires anyone who exploits its repository to involve the country of origin in the development of any derivative products, and to pay royalties that increase with the scale of exploitation. But in some places, Newman says, this is no longer enough. "We've stopped collecting in some countries because they wanted things that we just couldn't give," he says (see [page 538](#)).

In a bid to satisfy these new demands, three US bodies — the National Institutes of Health (NIH), the National Science Foundation and the US Agency for International Development (USAID) — established a programme in 1992 to build four-way partnerships between industry and science in both the United States and in the donor country.

Five of these International Co-operative Biodiversity Groups (ICBGs) have been established (although the USAID has withdrawn from the programme), each costing the US government about \$500,000 a year to run. "They have been very challenging to set up," says Josh Rosenthal, who runs the programme from NIH's Fogarty International Center (see [page 539](#)). "It is very novel terrain."

"The idea is that the groups should serve as models for how drug discovery could be done, while serving broader conservation goals," says Rosenthal. He adds that industrial corporations are ready to share costs with host countries and to pay royalties to them — but are not ready to make major, up-front investments to meet these conservation goals. "We'd like to see the private sector do it, but my sense is that that is not going to happen. Industry isn't interested in raising its budgets for natural products research."

Synthetic alternatives

Instead, industry is pursuing increasingly powerful techniques for developing drugs based on molecules that scientists can create for themselves in the laboratory, using new combinatorial chemistry techniques.

Until a few years ago, the *in vitro* screening of a given compound against a target was a time-consuming process that constrained the number of samples that the drug companies needed or wanted to test. The task was to select the most promising compounds for test. These were usually natural products.

Today, however, assays can be done 5,000 at a time in automated machines, and the sources of properly documented natural products can't keep up. Combinatorial chemists can use modern techniques to create arrays of thousands of slightly different molecules, ready to go into screening and, perhaps, feed the drug firms' insatiable appetite for a 'hit'.

At present, all these synthetic molecules are polymers. The understanding of structural biology doesn't allow for the creation of anything with such a novel structure as, say, Taxol, which consists of four intricately entwined carbon rings. But even simple polymers have their uses, and combinatorial chemistry gives the developers complete knowledge and control over what they are working with.

Some supporters of combinatorial chemistry question the value of biodiversity as a source of new drugs. "I think it leaves [biodiversity] completely high and dry," says David Galas, formerly head of the Department of Energy's human genome sequencing efforts, and now president of Darwin Molecular, a biotechnology company based in Seattle.

"As we learn more about three-dimensional structures, it appears there is nothing special about natural products," he asserts. For Galas, the study of biodiversity is useful primarily because it provides insight into what evolution has produced. "The idea of exploiting the rain forests to find wonderful drugs is, quite frankly, not credible," he says.

Galas further claims that romantic sentiment is blinding plant scientists to this reality. "Plant scientists have come to have such reverence for plants that you'll find a lot of reverence for natural products — but I think it is misplaced."

Most other observers, however, expect that a combination of natural and synthesised products will lead to future drugs. "Both paths have a very rich future," says Robert Horsch, manager of Monsanto's Agracetus Campus at Madison, Wisconsin. The ability to synthesize proteins is growing exponentially, he says, "but we can't even dream of making all possible combinations. Nature has been trying this experiment for two billion years".

Eric Fischer, head of the science, technology and medicine division of the Congressional Research Service in Washington, DC, and former director of the biology board at the United States' National Research Council, concurs. Fischer says our current understanding of structural biology is far too shallow to allow for the synthesis of the kinds of molecules that nature can produce. "Natural prospecting can get

you whole new classes of materials that you couldn't even have imagined," he says.

The biological approach

At present, however, that fact isn't sufficient to push major drug companies to invest seriously in bioprospecting. To give that impetus, scientists advocate a more selective approach, based on a better understanding of systematic biology — allowing more suitable plants and microbes to be chosen for sampling — and on the study of the use of natural products by indigenous peoples.

Peter Raven, director of the Missouri Botanical Garden and one of the most prominent plant scientists in the United States supports both approaches. "Most useful drugs come from molecules that people were already using," says Raven, who returned last month from visiting India. "Thousands of materials have been catalogued in India and China. It is true that the large drug companies aren't spending much time looking at them now — but they will."

Although "one could imagine a partnership between systematic biology and the drug companies" to increase the efficiency of bioprospecting, he says that isn't happening because "it is just not promising enough".

Another area of significant potential is the prospecting of less-studied forms of life on earth, including insects and microbes. "People are becoming aware of vast categories of organisms that have never been looked at," says Tom Eisner of Cornell University, New York.

This area is also proving controversial. Last year, for example, the US Park Service reached an agreement with Diversa of San Diego, California, to allow it to search for heat-resistant micro-organisms in the hot springs of the Yellowstone National Park. But this pioneering deal is causing trouble within the United States: environmental groups have charged that it is unlawful (see [Nature 392, 117; 1998](#)).

Perhaps most significant, however, is the vast potential that prospecting for genetic information is opening up. Where past emphasis has been on finding organic molecules that will perform some biochemical function, future bioprospectors will seek gene-sequence information for use in medicine and in agricultural biotechnology.

But for now, such applications are underdeveloped. According to Raven, we don't yet know enough about the relationship between different genomes to use sequence information from exotic species. "Right now, it's a question of finding genes to do what?" he says.

The organization most likely to answer that question is probably Monsanto, the former chemicals manufacturer based in St Louis, which has converted itself into a multi-billion dollar life sciences corporation with major interests in pharmaceuticals, agricultural products and food additives.

The view from industry

Bob Shapiro, Monsanto's chairman since 1995, has sold Wall Street a new image for his corporation,

based around such unfamiliar concepts as biodiversity and sustainable development, and watched its stock market value balloon from \$7 billion to \$31 billion since 1995. During that time, Monsanto has brought the first genetically modified crop strains into mainstream use, culminating ten years of research at its vast research village at Chesterfield, outside St Louis.

"We've had projects that involve getting genetic material from exotic locations," says Shapiro. "But now there is so much out there on Internet databases that you can do a lot without leaving home. To really take advantage of the materials out there is a 50-year task. But it definitely will happen."

Shapiro says he is "uncomfortable" with the concept of biodiversity as a resource for his corporation to exploit. Instead, he says, Monsanto is interested because "diversity gives you the best chance of being robust". "It's easy to get romantic about biodiversity conservation," he says. "But no-one knows what the uses of the genes will be. It would be idiotic to say that they'll be of no value."

With the recent introduction of crops that resist pests because their genome incorporates genes from *Bacillus thuringiensis* (*Bt*) — a naturally occurring organism — and others genetically engineered to tolerate Monsanto's Roundup weedkiller, the St Louis corporation has led a sometimes-sceptical world into a new age of genetically modified crops.

David Fischhoff, Monsanto's director of advanced genomics, expects systematic bioprospecting to play a larger role in future. "When we started developing resistant crops, the world had at its disposal a few hundred genes," he says. "For agricultural purposes, we had a handful of them — and out of that, Monsanto has started some very successful projects.

"We're now about to have some understanding of literally tens of thousands of genes," he adds. "Bioprospecting for genes will become more important than bioprospecting for proteins and organisms has been in the past."

Need for dialogue

An equally broad array of opportunities could exist in the use of genes from natural products to modify foodstuffs to enhance human health, says Ganesh Kishore, co-president of Monsanto's nutrition branch. Kishore envisages the discovery of natural genes that can be added to foods such as cooking oil, and so reinstated in the food chain.

But the Indian-born scientist has a warning for his former compatriots: "When I harness a gene, the fruits of the work are for everybody — but the person who developed it was me," he asserts. Like others involved, Kishore is deeply concerned about the state of relations between the rich and poor nations on this topic. He says the parties haven't struck up the right conversation because "there has been a polarization, and we've ended up arguing over who is in the wrong."

Kishore says that Monsanto will "put its best foot forward" to make arrangements with countries such as India. But the Missouri life sciences corporation knows that it can expect to encounter a great deal of

suspicion as it seeks to extend its leadership position in agricultural biotechnology (see [Nature 388, 817](#) & [389, 534; 1997](#)), and Kishore's stance on property rights is unlikely to go down well in developing countries.

The gap between what the developed world wants from biodiversity, and what the developing world thinks it should retain for itself, seems to be widening. Tensions between the two sides seem unlikely to relax in the near future.

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