Cashing in on nature's pharmacy

Bioprospecting and protection of biodiversity could go hand in hand. But for a successful collaboration, the rewards still have to show

The human genome is largely sequenced now and available for analysis of its gene content. And none of the contenders, private or public, grow tired of stressing the importance of this undertaking for the development of new drugs and therapies against pretty much everything that ails humankind. Indeed, by knowing the structure and function of proteins and their interplay, biochemists

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and pharmacologists can more effectively seek ways to block or enhance the function of a protein. This approach has already given rise to promising compounds, such as a number of angiogenesis inhibitors for the treatment of cancer, angiotensin converting enzyme (ACE) inhibitors that lower blood pressure or HIV protease inhibitors.

But as bright as this vision of future healthcare looks, there is a drawback. The large number of possible new drug targets has already outgrown the number of existing compounds that could potentially serve as drug candidates, and classical and combinatorial chemistry have their limits when it comes to synthesising new structures. Also, rational drug design—although successfully used to develop HIV protease inhibitors—is still in its infancy. 'If you asked me what I lay awake at night worrying about today: It's not genomics. It's not genetics. I lay awake worrying about chemistry,' commented Peter N. Goodfellow, Senior Vice-President of Discovery at SmithKline Beecham on this dilemma last year, at the 'Developing a New Dialogue' conference in Heidelberg, Germany.

But what chemists are desperately seeking, Mother Nature often already has in stock. 'The molecular diversity found in nature has, of course, evolved to interact with biological structures—both the biological targets of the natural products, and the enzymes that synthesise and degrade the natural products,' Lynn Caporale, a consultant to biotechnology companies and former Senior Director at Merck, said. Consequently, pharmaceutical companies have been looking to the wild in search of new compounds. Biologists have roamed the rainforests in South America and islands in the Pacific, as well as the depths of the sea to find new compounds, while anthropologists interviewed native medicine men about their uses of medicinal herbs. In fact, many effective drugs are based on compounds found in Mother Nature's pharmacy. Be they from rainforest plants, invertebrates dwelling in deep seas or underground

greater biodiversity increases the chance of discovering potentially useful compounds. Still, when the bulk of biodiversity seems to do nothing more than photosynthesise and take up space where a cattle ranch could stand, 'the more' does not seem economically the 'better'. Most ecosystems with extensive biodiversity, such as the rainforests of South America, Africa and Southeast Asia, are in Third World countries that seek a quick profit from these natural resources rather than preserving them. The pristine rainforests in Indonesia, Thailand and Madagascar disappeared due to unsustainable logging. The Amazon rainforest in Brazil is still being cut down at an alarming rate despite all national and international efforts to preserve it. With the loss of these ecosystems, plant and animal species that could have produced hitherto unknown drug candidates against a number of diseases become extinct.

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micro-organisms, naturally-occurring compounds account for about a third of the products that comprise the US\$ 200 billion plus prescription drug industry. Prospecting in the wild has yielded substances such as antibiotics from terrestrial actinomycetes and the tumour-reducing agent, taxol, from the Pacific yew tree. Two therapeutic agents for cancer, vinblastine and vincristine, owe their economic success to shamans, spiritual herbalists, who led Eli Lilly researchers to the rosy periwinkle plant in Madagascar in 1958.

For bioprospecting to yield new drug candidates, the old economic wisdom 'the more the better' appears true when

Meanwhile, 'blockbuster drugs' based on natural compounds generate more than US\$ 100 million each year for the pharmaceutical industry, without returning profits to the countries in which the original compounds were found. 'Bioprospecting can be economically viable, but not conservation biology viable,' reflected Daniel H. Janzen, an entomologist at the University of Pennsylvania. 'The whole business structure is aimed at making human beings richer, not making forests conserved.' However, the growing understanding that destroying rain forests means depleting Mother Nature's medicine cabinet has raised the expectation

among conservationists that some of these profits could, and should, be used to finance measures to preserve biodiversity, particularly in species-rich developing countries.

One of the earliest examples of such mutual benefit-sharing was initiated in 1991 between Merck & Co. in Rahway, NJ, and Costa Rica's National Biodiversity Institute (INBio). Thomas Eisner, a chemical ecologist at Cornell University who recognised a 'win-win' situation, brought the two groups together. Merck advanced INBio US\$ 1 million in addition to training, technology and infrastructure support for a National Park Fund. By 1999, Merck had invested over US\$ 3.5 million for a number of natural extracts, and INBio intends to allocate half of an undisclosed percentage of future royalties to the Costa Rican Ministry of Environment and Energy, for conservation purposes.

Also, in 1991, the National Institutes of Health, the National Science Foundation and the US Agency for International Development planned funding of International Cooperative Biodiversity Group (ICBG) grants for research on natural products and drug discovery. These grants acknowledged the problems of responsible economics and sustainable resources in developing nations, and integrated

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efforts to promote training, infrastructure, conservation, preservation of traditional medicinal practices and catalogue biodiversity. Also sympathetic to biodiversity preservation, the US National Cancer Institute devised a 'Letter of Collection' for researchers and host nations in recognition of the need to compensate countries if a drug originating from a particular region becomes a commercial success.

In 1992, participants of the Rio de Janeiro Earth Summit discussed the topic of bioprospecting and signed the UN Convention on Biological Diversity (CBD), which recognises that the impact of specimen collection on the state of wildlands could be carried out in a responsible way if carefully regulated within frameworks promoting the conservation of biodiversity, sustainable devel-

opment of genetic resources and fair and equitable benefits sharing. In compliance with these guidelines—ratified by 179 countries and the European Union—companies could no longer harvest bioresources without acknowledgement of indigenous ownership. The US Senate, however, has not yet ratified former President Clinton's 1993 signature of the CBD, based on concerns over intellectual property rights and technology transfer.

But despite all these attempts, the double-edged cure for afflictions of both the earth and humans has yet to come. So far, neither the Merck-INBio agreement, nor CBD, has produced any major revenue-producing drug that benefits both the pharmaceutical industry and the environment. Scale remains a major obstacle. The chance of a successful hit is one in 10 000 for synthetic compounds, while

laboratories, are the more stringent criteria for selecting compounds for product development imposed by the US Food & Drug Administration. Consequently, it has become clear that the illusion of easy gains is gone. 'The field is more mature than it was ten years ago and, I think fortunately, a lot of the players from ten years ago who did not have realistic expectations are now gone,' Borris said. INBio already had a high level understanding of its biological resources and a stable country infrastructure when Merck began to set up its scientific programme in Costa Rica. 'It is, unfortunately, a situation that doesn't exist in most countries,' Borris commented. Indeed, the Merck-INBio agreement raised the expectations of immediate benefits in many developing countries unrealistically, suggested Gordon Cragg, chief of the Natural Products Branch at the NCI.

But to say that the deals between big pharmaceutical companies and poor countries have not worked is unfair, Eisner protested, because the total number of natural samples that have been tested so far is less than the calculated sample volume needed to get a 'hit'. As a pragmatic way to use biodiversity, prospecting for natural products no doubt continues to appeal to researchers. 'I see the information embodied in the genes of nature as being the most valuable resource that we've got,' Eisner emphasised. 'Accessing that information has got to be the prime endeavour of the next century.' The hard part is not finding support for the scientific reasoning, Janzen argues, but rather is the lack of imagination and boldness in current economics and politics. Even Eisner agrees, reluctantly. 'We're not going to find the pharmaceutical industry helping

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the rate for natural products is as low as one in 30 000 or 40 000. In addition, difficulties in purifying extracts and the low number of non-microbial specimens pose major obstacles, and drugs can take ten, even 20 years to pass clinical trials.

A further cause of delay, according to Robert P. Borris, Senior Research Fellow at Merck's Natural Products Discovery

out in a big way,' he said. 'It sounds so great because it's so simple a scheme, but the players are not committed. Pharmaceuticals are not interested; governments could not care less; biologists are interested but don't have the political leverage.' Without alternative ways to bring funds back to conservation, biodiversity and associated natural products, research might

face a world in which sophisticated laboratory equipment collects dust from a lack of use—and extinction of useful specimens.

INBio has since begun to collaborate on more agreements that make near-future returns for conservation. Giselle C. Tamayo, Technical Coordinator of INBio's Biodiversity Prospecting Division, remarked, 'These kinds of agreements and relationships in the medium and long term would increase society's awareness towards conservation. In the end, bioprospecting must be considered as an alternative for biodiversity conservation, but not the only one.'

Other groups such as Bioresources and Development & Conservation Programme (BDCP) organise partnerships focused on building strategic alliances between industry and conservation organisations in African countries such as Nigeria and Cameroon. Rather than plant commodities, the gains from experience and access to technology are the coveted pieces in these deals, which benefit the local economies. With the help of the National Agency for Science and Engineering Infrastructure, BDCP has

established a Biodiversity Development Institute in Nigeria and applied for an ICBG grant with the Walter Reed Army Institute of Research. 'Technology transfer is far more important than any cash,' Maurice Iwu, Executive Director of BDCP, said, 'for deliberate efforts to design effective partnerships can truly make short-term benefits tangible.'

Although the waiting time for a 'hit' to reach the market is too long for conservationists and the international development community, the ease of molecular structure determination from modernised instruments and techniques has actually made natural products research considerably more efficient in the last ten years. The reduced speed of laboratory-based synthetic discoveries has influenced bioprospecting demands. As companies push natural product discovery programmes to be more cost-effective, 'the new trend is to drop the bioassay guided fractionation that is very expensive, and adopt an efficient natural products library programme,' Tamayo explained. 'While building such libraries would be rather expensive at the

very beginning, the costs associated in the overall R&D program would be less.'

Even as combinatorial chemistry and rational drug design are becoming more important, natural products will stay valuable for pharmaceutical companies due to their wide structural diversity and their excellent adaptation to biologically active structures, Cragg thinks. 'The chemists at the bench, no matter how good they are, just cannot produce the wonderful chemicals nature has,' he said.

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The same, only different

Postdoctoral experience in Japan: an alternative worth considering

Postdoctoral funding often comes with mobility as a precondition, so that a lot of new postdoctoral fellows get a ticket abroad with their stipend. For most Europeans, 'abroad' means the USA, with its highly competitive scientific environment. Japan offers a significant alternative,

various allowances. Their application procedure is relatively straightforward. I had a productive and enjoyable time there, so I would like to give some impressions of working as a foreign postdoctoral fellow in Japan and some advice for those who might consider doing scientific research there.

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allowing one to try to combine science with a sort of tourism, although the country is not renowned for its short, stress-free working days. In addition, the Japan Society for the Promotion of Science (<http://www.jsps.go.jp>) offers generous support—current stipends are ¥270 000 (2535 Euro) tax-free per month, with

The 'normal' laboratory has many students, a few technicians or postdoctoral fellows, a sprinkling of assistant professors and one all-powerful professor. Of these more senior positions, very few are filled by women. This imbalance is evident even at postgraduate and postdoctoral levels, although the government

is trying to redress it. Each laboratory has a great deal of autonomy in terms of resources and of ideas—external review is not a particular feature of Japanese research. Since this can translate into isolation, anyone interested in Japanese laboratories should pick the host carefully to ensure that the furrow you plan to plough will not become a rut. The lab I chose was a little unusual by Japanese standards. The chair was partly funded by industry and was only for a limited period, in contrast to the usually tenured chairs. As a consequence, there were only a few students, although the laboratory did have technical support—a rarity due to the lifelong contracts that are usual for university staff in Japan. The government is reluctant to fund new permanent positions, and because of that financial support for technicians is difficult to