nature biotechnology
VOLUME 14 AUGUST 1996

Biodiamonds and paying back debts

The recent Monroe Wall Symposium at Rutgers University (New Brunswick, NJ), honoring the discoverer of taxol, and a new book, *Medicinal Resources of the Tropical Forest* (1996, Columbia University Press, NY), highlight a growing, renewed interest in the largely unexplored and vast pools of chemical and genetic resources that lie in the forests of the developing world. The screening of microbial and plant-derived products has always had a prominent role in the pharmaceutical industries—25% of all prescription drugs are from botanical sources. Now, however, the advent of powerful, automated selections and screens in concert with combinatorial chemistries, the development of a robust agricultural biotechnology and, perhaps most importantly, an increasing sophistication on the part of the owners of the biodiversity "diamond mines," have created an unprecedented opportunity for biotechnology to have a profound impact on how the world's economic and environmental balance sheets will look in the next century.

Although companies like Abbott (Abbott Park, IL), Bristol-Myers Squibb (Princeton, NJ) and Eli Lilly (Indianapolis, IN) have been active in botanical bioprospecting since the 1950s, other pharmaceutical giants such as GlaxoWellcome (Beckenham, UK), Bayer (Leverkusen-Bayerwerk, Germany), SmithKline Beecham (King of Prussia, PA) and, most notably, Merck (Whitehouse Station, NJ) have only recently begun to invest. Even so, there is not yet, nor is there likely to be, a major commitment on the part of big pharmaceutical companies to these approaches. For example, the agreement between Merck and INBio of Costa Rica, which has received considerable attention as a model for ethical and mutually beneficial drug discovery programs between developed and developing countries, represents only a small fraction of what Merck has invested in drug discovery programs based on genomics. But that said, it is also true that these companies will continue to seek partners for biodiversity prospecting. This presents attractive opportunities for universities and research institutes, which possess the necessary wide range of disciplines—Rutgers University and the Scripps Research Institute (La Jolla, CA), for example, have recently made serious investments—to act as intermediaries between biodiversity sources and the pharmaceutical industry through collaborative research agreements.

In addition (and this was the subject of much discussion at the Monroe Wall Symposium), science-based natural product and "nutraceutical" companies are now evolving alongside traditional pharmaceutical concerns. Start-up companies, such as Shaman (South San Francisco, CA), Pharmagenesis (Palo Alto, CA), and XeChem (New Brunswick, NJ), have already emerged. And in an echo of the early, halcyon days of biotechnology, Julian Davies at the University of British Columbia (Vancouver, Canada), who has developed a series of molecular techniques to directly clone novel enzymatic activities from environments expected to be especially rich in such genes, now sits on the advisory board of Recombinant BioCatalysis, one of the newest of these ventures.

This merging of lead-compound discovery—through developments that are transforming traditional disciplines like pharmacognosy and ethnobotany into "ethnopharmacology"—with molecular and structural biology lends a new vitality to "rational drug design."

But as lucrative as natural product and gene discovery may be in the pharmaceutical and industrial realms, perhaps even greater benefits are to be found in agricultural applications. The ability to harness biodiversity via molecular genetics has already been demonstrated by transferring numerous, heterologous, single-gene, traits. For example, in this issue, Ishizaki-Nishizawa and colleagues (p. 1003) have expressed a cyanobacterium Δ9 desaturase gene in tobacco to increase resistance to cold stress, and Smith and colleagues (p. 995) have overexpressed a phytochrome gene in tobacco to enhance agricultural productivity. But this represents only the beginning of what can be accomplished as plant biotechnology continues to mature. As one example, consider the consequences of efforts to understand, and subsequently manipulate, the molecular basis of apomixis, the process by which many plant species set unreduced seed parthenogenetically. The controlled introduction of an apomictic gene cassette into crop species would not only enable the immediate fixation of complex heterologous genotypes uncovered by the new bioprospectors, but would simultaneously effect a major change in the way farmers propagate hybrid seed.

The scope of the prospects outlined here clearly require the creation of new economic models and strategies for the world's agricultural and pharmaceutical industries. But such strategies must do more than "simply" redress the obscene underpayment the national sources of biodiversity have so far received. Although lending agencies, such as the International Monetary Fund and the World Bank, could (and should) pursue significant "debt for research" and "debt for conservation" exchanges, it is finally less a task for these, and the plethora of national and international oversight bodies, than it is for scientists and biotechnology entrepreneurs themselves to organize the necessary restructuring. Scientists and entrepreneurs can, and must, ensure that source countries participate as equal partners in all phases of the new biodiversity-centered programs. The mechanisms for achieving this include establishing in situ facilities for collecting, extracting, and screening, inclusion of local scientists and local inputs in the numerous genome projects already underway, and the creation of truly first-rate international laboratories dedicated to the production of economic and social well-being through the best applications of biotechnology.

Finally, by placing emphasis on the inherent ecological soundness of these approaches, biodiversity prospecting offers a chance to reverse much of the misinformation that has led to the negative public perception of gene manipulation technologies. Those technologies have not even delivered an effective malaria vaccine, let alone other promised benefits to the Third World. Perhaps the economic incentives of enlightened bioprospecting will reactivate these noble intentions in ways that replace the specter of paternalism with the spectrum of equalities. ///