Phyllis D. Coley

on turning green into gold

Anthropogenic effects on the climate and biodiversity of our planet are among the most troubling and perhaps irreversible threats facing scientists, policymakers, and citizens. Yet many scientists are reluctant or unsure of how to apply their expertise in basic science to these pressing real-world problems. A dozen years ago I would certainly have counted myself as one of these. I had spent twenty-five years studying how rainforest trees defend their leaves against hungry, diverse, and abundant leaf-feeding insects. With my husband and collaborator Thomas Kursar, I found that mature leaves are well defended by high fiber, making the leaves tough and low in nutrients. As a consequence, most herbivores consume tender, young leaves. Although leaves are young and expanding for only two to three weeks of their two- to three-year lifespan, 85 percent of damage in a leaf's lifetime occurs during this small window.

Thus natural selection strongly favors age-specific defenses. Our work showed that for survival, young leaves depend heavily on toxic compounds, which are recycled once the leaf stops growing and lays down tough, fibrous cell walls. The specialization of leaf-feeding insects on young leaves also means that insects must have evolved complex adaptations for finding this ephemeral resource and for detoxifying or circumventing the chemical arsenal within.

But as we studied these fascinating interactions, the rainforests of the world were disappearing at an alarming rate. Frequently, we would not only read about the accelerating pace of deforestation (and hence loss of species and ecosystem services), but also be confronted by the destruction of beautiful sites where we had once worked. We felt unprepared to do anything, but we thought that perhaps we could use our ecological knowledge about plant defenses to design a better drug discovery program – often called bioprospecting. Humans have long used plant toxins as medicines, and even today, 50 percent of prescription drugs were discovered in or modified from natural products. Plant compounds have been particularly effective for cancer treatments and remain a promising source of potential pharmaceuticals.

We hoped that bioprospecting might be an ecologically gentle but financially productive use of forests that could encourage their protection. But conventional bioprospecting projects faced two

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formidable problems. One was the difficulty of finding active compounds, and the second was returning meaningful benefits to the source country. To address the first issue, we proposed collecting young leaves, as we hypothesized that they would have more promising lead compounds than mature leaves. Bioprospecting endeavors typically gather mature leaves because they are more common; however, our work showed that mature leaves rely primarily on toughness and tannins, two defenses with little therapeutic use. The collection of young leaves did in fact improve our results by an order of magnitude.

Providing immediate and meaningful benefits to the host country was the second major hurdle. In return for the export of raw leaves to the United States or Europe, countries receive, on average, royalties of 1 to 3 percent if a drug makes it to the market. But the chance of producing a marketable drug is much less than 1 in 100,000 samples tested. And even if a country were to hit the jackpot, it would take seven to twelve years for the revenue flow to appear. As a result, alternatives that provide immediate economic benefits, such as logging and cattle ranching, appear more attractive.

Because of the uncertainty of royalties, we had to explore other ways to create benefits that would provide the host countries an incentive to protect their forests. We proposed moving as much of the drug discovery process to the source country as possible. Over 45 billion dollars are spent annually on the drug discovery process, yet essentially all of this occurs in the developed world. While only a few dozen drugs emerge annually from this enormous pyramid of drug discovery research, a large number of research programs at universities and small biotechnology firms are supported directly or indirectly by funds from pharmaceutical companies and governments. An estimated one-third of these funds support the type of research that could currently be accomplished in developing countries.

Moving this research to the source countries would not only create jobs dependent on intact rainforests, but would also provide valuable opportunities for enhancing scientific infrastructure and education. This move would assure immediate and lasting benefits whether or not a drug ever made it to market. The measure of success would not be whether one discovers a drug, but whether one is a player in the process of drug discovery. Until now, developing nations had not even been players.

We spent several frustrating years trying to convince funding agencies that despite the fact that we had no experience in drug discovery, we had a novel approach to bioprospecting that would aid conservation and economic development within biodiverse nations. Finally, with the help of a novel program at the National Institutes of Health – The Fogerty International Center's International Cooperative Biodiversity Groups – our large group of Panamanian and U.S. scientists was able to make the dream a reality. We chose Panama because we had focused our research there for decades. It is also politically stable and at the center of the world's most diverse hotspot for vascular plants.

In the nine years since the project's inception and with a modest funding rate of approximately $500,000 a year, we have established an effective program in Panama primarily carried out by Panamanians (www.icbgpanama.org). As the majority of the research activities had not been underway in Panama prior to the project, considerable funds were invested in equipment and training. For example, project funds played a major role in establishing a chemistry laboratory at the University of Panama that has successfully purified active compounds, the majority of which are only found in the young leaves. The infrastructure improvements required the purchase of simple items such as chairs and air conditioners, as well as more sophisticated equipment such as high-pressure liquid chromatographs and the country's first nuclear magnetic resonance instrument. These improvements have been key, as it is only when scientists have local access to such resources that research and training become truly effective. Moreover, both students and principal investigators have been able to travel abroad to learn new techniques.

For the first time, Panamanian scientists established bioassays for a number of tropical diseases (malaria, American sleeping sickness, and leishmaniasis), and used three cancer cell lines and assays with the aphid and the whitefly. These tropical disease assays had to be modified so that they could be accomplished in a developing nation. Typically, these bioassays use radioactive materials, which are expensive and difficult to obtain and dispose of in many countries. This novel technology has already been freely shared with scientists from Bolivia, Madagascar, Colombia, Switzerland, and Peru. A novel assay for dengue is currently under development. New sources in nature, such as marine organisms and endophytic fungi, are also being explored. Additional funds would allow the establishment of vertebrate models in Panama, a key advance allowing testing for toxicity and efficacy of several promising leads active in the tropical disease screens.

How has this program helped Panama? Most apparently, it has provided economic benefit to Panama by creating jobs, perhaps more than would have resulted from alternative, destructive uses such as logging and cattle ranching. Furthermore, these bioprospecting research opportunities have increased the ability of Panamanian scientists to publish regularly in high-quality international journals, making them more competitive in attracting additional international funding for their research, even though such funding is not widely available.

With this rise in publishing has also come an increase in educational opportunities in Panama. In the nine years of the project, almost one hundred student assistants have participated in research published in international journals. This experience has allowed them to compete successfully for admission to foreign graduate institutions. To date, seven students are abroad in doctorate programs and seventeen in master's programs. Of course, our hope is that they will return to contribute to science and conservation in Panama. In our experience, international agencies provide little support for the training and repatriation of scientists. Unless young scientists can obtain good training and also be enticed to return to their countries, developing countries will be slow at best to establish the capacity to solve their problems.

Less tangibly but equally important, the project has instilled in Panamanians greater knowledge of and pride in their country's exceptional biodiversity and their scientists, who are making important discoveries to cure national health problems. As a primarily Panamanian endeavor, the project is viewed by the public, the press, and the government as a boon to Panama, rather than as biopiracy. To maintain transparency and to spread the word about the value of biodiversity, the Panamanian students and principal investigators give dozens of talks annually to schools, farmers and fishermen, government officials and foreign visitors. The demographic that the bioprospecting project engages is also broader than those targeted by most conservation efforts – typically rural and forest communities. Little international attention has focused on engaging the urban community, despite the fact that it could be a powerful voice for policies favoring conservation. Our bioprospecting project has broad appeal to the urban audience.

The greater national interest in biodiversity has allowed us to share our inventories of plant species in protected areas, and our experience with database design, with Panama's Interior Department, advice which they solicited to assist with their mandate of managing protected areas. The visibility of the project was also instrumental in helping the government of Panama apply for and receive World Heritage Status for one of its national parks, a jewel with an uncertain future. Naturally, the Panamanians now have a greater voice at the table regarding decisions about conservation. And in contrast to developers, extractive companies, and farmers, bioprospectors will argue for preserving forest and marine habitats.

By providing direct financial benefits in terms of jobs, enhancing educational and research experiences, creating a local voice for conservation, and raising national interest and pride in the remarkable biodiversity that exists in this small country, we are hoping to help promote the long-term conservation of these valuable resources. Their future is primarily in the hands of Panamanians, and it is therefore critical that the Panamanians receive and recognize the benefits that accrue from sustainable use of their wildlands.

Our learning curve in this project has been nearly vertical. Despite our naiveté, we established a research and training program to promote human health, conservation, and economic development. We view these efforts as the beginning, as the program in Panama clearly works and can be an example for other countries. Regardless of the area of one's professional training, there are undoubtedly aspects that could be usefully applied to managing our planet. Although curiosity-driven research is extraordinarily appealing and may be the reason most of my generation gravitated toward our professions, now is the time to raise our noses from the microscope and stick them into world affairs. It is not only rewarding and challenging but critical.