Chapter 1
Bioprospecting: An Industrial Perspective

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Abstract The discovery of promising new biologically active molecules from natural products was a mainstay of the pharmaceutical industry for many years. While interest in this field has fluctuated over the years, it entered a boom period following the Earth Summit and Rio Convention in the early 1990s lasting into the twenty-first century. This boom period was followed by the industry's almost complete exit from this field of endeavor. This chapter presents a discussion of the changes in the capabilities of natural products research and factors contributing to the demise of natural products in the drug discovery programs in Big Pharma.

1.1 Introduction

When first approached about writing this chapter I had very mixed emotions. Over 20 years ago, I had the privilege of contributing a lecture entitled, "Natural Products Research: Perspectives from a Major Pharmaceutical Company," at a conference on *Intellectual Property Rights, Naturally-derived Bioactive Compounds and Resource Conservation* held in San Jose, Costa Rica (during October 1994). That paper was eventually published (Borris 1996), and has often been cited by later authors. Much has happened since that paper was written. Most, if not all, of the major American pharmaceutical corporations (including my former employer, Merck) have exited the field of natural products research, at least as in house ventures, not even maintaining a small core of scientists experienced in the field to resuscitate their programs at a later date. The technologies that enable this kind of research continue to evolve at an ever accelerating rate. It could be an exciting time to be a young natural products researcher! It should be an exciting time to be a young natural products researcher! Is it?

Of necessity, this chapter will not be a review of the role industry has played in biodiversity prospecting. Little information has been published on screening strategies, hit rates, successes and failures to make such a review meaningful. It is, as the

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R. Paterson, N. Lima (eds.), *Bioprospecting*, Topics in Biodiversity and Conservation 16, DOI 10.1007/978-3-319-47935-4_1

title suggests, one perspective of the industrial experience from a person who has spent an entire career in this field. Any opinions expressed are my own and do not necessarily express the opinion of past or present employers.

This chapter will compare the current state of natural products research with the state of the art at the height of the biodiversity boom in the mid-1990s. At that time, it was still relatively unusual for an academic laboratory to be involved in the patenting of inventions or other forms of protecting their intellectual property. This has changed dramatically. Some granting agencies now require a plan for the protection of intellectual property and many labs routinely apply for patents on their promising discoveries. Many faculty members and their institutions have formed startup companies to develop these inventions. In certain ways this trend is making academic labs take on a more industrial perspective. The advancement of science may still be the primary driving force of academic research, but the allure of an eventual (big) payday is also an incentive.

One often ignored fact must be mentioned. In the late twentieth century, and perhaps still today, industrial researchers were expected to contribute to the understanding of the basic science of their disciplines, not just the applied research leading to product discovery. Much energy went into the discovery of molecules that helped to elucidate the nature of biological targets under investigation, driving forward our understanding of the etiology of disease.

It is difficult to overstate the continuing importance of natural products in the drug discovery process. In the most recent of their reviews on the subject (Newman and Cragg 2012), David Newman and Gordon Cragg have shown that over the 30 year period from 1981 to 2010, 33.9 % of all small molecule new chemical entities (NCEs) approved by the U.S. Food and Drug Adninistration (FDA) were either natural products or compounds derived from natural products. In contrast to the 363 natural products or natural product derivatives, to the best of my knowledge only one approved compound, sorafenib (Nexavar), has been produced by *de novo* combinatorial chemistry since the advent of that technique (Wilhelm et al. 2008). The interested reader is referred to the excellent series of Newman and Cragg reviews on natural product drug discovery (Newman and Cragg 2007, 2012; Cragg et al. 1997; Newman et al. 2003), the detail of which is clearly beyond the scope of this chapter.

1.2 Pharmaceutical Research and Development

It is a given that the *raison d'etre* for research at a pharmaceutical company is to discover and develop new drugs that will address medical needs and make a profit for the shareholders. Even at their highest point, natural product research programs were only a small part of the drug discovery effort. As one of the earliest stages of the discovery process, natural product discovery was often the source of the original hit in a new bioassay or therapeutic area. Compounds discovered from natural sources had the potential to become actual products, as did lovastatin (Mevacor),

but more frequently served as leads for medicinal chemistry programs or tools for assay refinement. While a lead compound had to demonstrate reasonable potency and some specificity, it was expected that the medicinal chemist would modify the structure to build in better potency, selectivity, and appropriate ADME (*A*dsorption, *D*istribution, *M*etabolism and *E*xcretion) characteristics, while reducing any toxicities which may have been observed. This is an iterative process. Compounds were first optimized for the *in vitro* assay in which they were discovered. Oftentimes, compounds optimized for an *in vitro* system require further optimization when evaluated in animals and still more optimization before introduction into the clinic. It is not difficult to see why the native natural product is unlikely to become a marketed product.

1.3 Screening in the Boom Years

Finding a lead compound is the necessary second step in the drug discovery process. Preceding the evaluation of the first samples is the discovery of a biological target and development of an assay to measure the interaction of the drug/lead with that target. Assays have evolved significantly over the last 50–60 years. Phenotypic screening using animals was the prevalent methodology in the 1950s and into the 1970s. These assays were not terribly sensitive, often subjective and difficult to interpret. The interaction of a chemical with an intact macro-organism can be a complicated process. Numerous metabolic processes may be affected in both positive and negative ways. Administration of a crude plant extract containing hundreds, if not thousands, of compounds dramatically increases the complexity of the problem. That said, observation of a positive result in a phenotypic screen had much significance. A substance could only show activity in such an assay if it was biologically available via the route of administration employed and acted at one or more steps in a metabolic pathway that was relevant to the disease or metabolic process under investigation. On the down side, phenotypic screening assays were unable to elucidate exactly how a drug/lead elicited its activity, i.e., which steps in the metabolic pathway or pathways were being affected.

Humanity's understanding of biochemistry and metabolism has evolved dramatically over the last 60 years. The details of many metabolic pathways have been elucidated allowing us to understand, or at least hypothesize, how some derangement in a particular step may result in an observed disease. As this mechanistic knowledge of metabolism developed, so too did a dissatisfaction with the level of detail offered by the results of phenotypic screening. Science, and especially industry, was no longer satisfied by the knowledge that a sample could evoke a desired biological response. We needed to know why and how that happened. To answer these questions, science in general, and industry in particular, turned away from phenotypic screening in favor of the newly developed biochemical mechanism of action screens. Thus was born industry's "one drug – one target" paradigm for drug discovery.

Much can be said for mechanism of action screening. When an enzyme is isolated from an intact cell, its activity can be accurately measured using standard biochemical techniques. Inhibition of that activity can then be measured quantitatively. Similarly, the interaction of a receptor and its natural ligand can also be accurately measured, and inhibition of that interaction can also be quantitated. It was a straightforward task to miniaturize these biochemical tests so that they required less sample and less reagent (meaning less money). Format standardization using the now ubiquitous 96-well, 384-well and 1536-well microplates allowed a proliferation of laboratory equipment specifically for these assays, leading inevitably to automation. While any good technician can easily perform pipetting tasks in 96-well plates, I would challenge anyone with even the slightest hint of astigmatism to try pipetting to or from a 384-well plate. Miniaturization and automation effectively removed throughput as a barrier to discovery. While the miniaturization and automation of biochemical assays facilitated natural products research in the industrial environment, it must be recognized that these same technologies also enabled the development of combinatorial chemistry and chemical library screening as potentially viable areas of endeavor.

Of course, every silver lining has its gray cloud. Mechanism of action screening was fast, relatively inexpensive and quantitative, but there was a cost for this information. These screening techniques could no longer tell us whether an activity was actually biologically relevant, or whether a sample had any bioavailability or any observable toxicity. These parameters would all need to be addressed elsewhere in the discovery and development process.

Once an assay, biochemical or biological, has been developed it can be used to evaluate a range of samples, natural product extracts, synthetic libraries, combinatorial chemistry libraries, corporate compound collections, looking for one or more initial hits. These first hits must then be refined to pure compounds active in the assay which can be used to test the hypothesis that the target is truly relevant to the disease state being studied. If relevance is established, then broad screening for new leads spanning chemical space will commence. If not, the assay must be refined or discarded. In Pharma, there is a constant turnover of assays used in screening.

For natural products, it is possible to hypothesize a generic process for creating extract samples for screening. While the actual nature of each kind of sample, i.e., plants, microorganisms, insects, marine invertebrate, reptile/amphibian, etc., may be quite different, the initial goal is always to separate the interesting small molecules from the rest of the biomass. (NOTE, for the remainder of this chapter the terms lead and drug will be used to refer only to small molecules. This is a bias of the author.). Over the years, there have been many discussions touting the merits of various extraction schemes over all others, but in the final analysis the only real criteria for acceptability are that the extraction scheme produces samples that are reasonably representative of the chemical diversity of the material being extracted and compatible with the assays in which they will be tested. Large screening programs tend to establish an extraction protocol for plant samples, a separate protocol

for microbial fermentation broths, another separate protocol for solid-phase fermentations, and so on. Each protocol is optimized for the kind of sample on which it will be used. This level of standardization generates samples that can easily be compared to all other similar samples in the extract collection. Some organizations choose to retain bulk samples of all extracts in a library, ready to be re-evaluated as new assays come on line. Others do not. This choice is often based on the cost per sample and the perceived level of difficulty or uncertainty in obtaining a new supply if/when needed. Simply stated, there is no single "correct" way of processing samples or making extracts for screening.

1.4 Pharmaceutical Bioprospecting

Collecting samples legally and in a cost effective manner was and is, of course, of great importance. Multinational pharmaceutical corporations could not afford the fallout that could ensue from making collections without the necessary permits. The availability of permits, or lack of same, was often a criterion for selecting locations for collection activities. Countries having interesting floras but lacking a government framework for making permits were generally considered off limits, as were countries that actively discouraged or prohibited collections.

As research has progressed, it has become evident that terrestrial plants produce a fairly well proscribed suite of secondary metabolites, fungi produce a different (but overlapping) suite, marine invertebrates another different suite, prokaryotes a still different suite and so on. In order to capture the breadth of the chemical space occupied by secondary metabolites, it is necessary to sample all of these groups. Such a broad based approach is expensive and requires a long term commitment from corporate management. In practice, most pharma programs focused on one or two groups of organisms and perhaps dabbled in others.

The 1990s saw a near perfect storm for a resurgence in interest in natural products as a source of new drug leads. The 1992 Earth Summit and Rio Convention on Biological Diversity focused attention on the loss of habitat and loss of species that is still ongoing on the planet. The potential impact of these losses on drug discovery was not lost on the senior scientists running research at that time for the major pharmaceutical companies. Fueled by an earlier generation of billion dollar blockbuster products derived from natural products, e.g., Mevacor and the Avermectins, at Merck, decisions were made to broaden and accelerate the screening of natural products across the full range of disease targets. Using Merck as an example, ongoing collaborations with the New York Botanical Garden and its partners, and with INBio, the Costa Rican Institute for Biodiversity, were expanded to support screening at greater depth and breadth in line with the "now or never" theme of the time. The relatively high throughput of mechanism of action screens enabled these expansions.

1.5 Natural Products Chemistry in the Boom Years

By the mid 1990s, natural products chemistry was a mature discipline. HPLC had extended the chemists' ability to isolate active compounds in very small quantities, while countercurrent chromatography had evolved from the Craig apparatus through droplet countercurrent chromatography (DCC) and rotational locular countercurrent chromatography (RLCC) to centrifugal countercurrent chromatography (CCC) and centrifugal partition chromatography (CPC), facilitating isolation of labile molecules not amenable to the more traditional chromatographic techniques. High field NMR and mass spectrometry allowed identification of compounds in sub-milligram quantities. NMR spectrometers of 500 MHz had become routinely available in industrial labs while early 600 MHz instruments had more limited availability. Many 2D-NMR experiments were already in routine use enabling rapid structure determination. While mass spectrometry already had more than enough sensitivity for analyzing sub-milligram quantities of material, its utility was greatly expanded with the introduction of LC-MS in the early 1990s. With LC-MS came the ability to obtain reliable mass spectra from samples that were not homogeneous, opening the door to performing structure determinations on samples that were not completely purified, potentially saving days or weeks of isolation time.

With higher screening throughput came a greater need for dereplication of active extracts. Dereplication is the process by which a researcher determines whether he/she has encountered the same active constituent previously. For some groups of organisms, taxonomic relationships and chemotaxonomy could predict the probability of a known compound being present in a new organism. This approach was far from perfect as the knowledge of the distribution of secondary metabolite families was far from complete. While LC-MS is well suited to this kind of study, it too is an imperfect tool, especially for use in dereplicating crude extracts of complex organisms like higher plants. While the mass spectrometric detection of metabolites was certainly adequate for the purposes of dereplication, the ability to separate the full range of compounds represented in a typical plant extract in a single chromatographic experiment, even with HPLC, was still lacking. Some organizations chose to delay dereplication until after an initial isolation step in the hope of sufficiently simplifying the active fraction to allow LC-MS analysis. Other organizations chose to pre-fractionate every extract prior to screening. Analysis of the fractions by LC-MS or LC with photodiode array detection could then be used for dereplication. Of course, this latter approach greatly magnified the cost of the initial screening. Again, there was no single "correct" way of performing dereplication.

1.6 Production Issues

One area that received much attention during the Boom period was the topic of production of natural products on an industrial scale. While this was never an issue for microbial products, it was a major consideration for macro-organisms such as plants or marine invertebrates. If a real lead or a real potential product were found, how would a corporation make tons of it each year for the life of the product? Pharma has often been portrayed as being ready to over-exploit the environment by collecting vast amounts of plant material needed to support production from wild populations. While this may have been the opinion of potential collectors, it was and is the least likely scenario for industrial scale production of a new natural product. Such an extractive process would continuously diminish the available supply of the source of the product. Relying on natural populations, especially those under the control of someone other than the corporation, simply does not make business sense.

Agriculture was another possibility. While potentially applicable for fast growing herbaceous plants, it is, at best, a long term effort for slower growing organisms such as trees. Given the 17 year patent life for a new chemical entity, major investments in agricultural production of a slow growing organism seems unlikely unless there was no other way of making a real blockbuster product.

Perhaps a step closer to reality for complex products is production by plant cell or tissue culture of either the desired product or a related metabolite that could be readily transformed into the desired product. This was an approach I advocated in 1994. Once established and optimized, a cell culture process removes the need for collections or farms and eliminates the potential adverse environmental impact. This approach was successfully employed for the production of paclitaxel, for example (Onrubia et al. 2013).

Ultimately, for a variety of reasons, the most likely method that would be used for the production of all but the most complex of natural products is total synthesis. The scientific community has repeatedly shown that even complex natural products can be made by total synthesis, with paclitaxel (Wang et al. 2011) and tacrolimus (Ireland et al. 1996) as examples of marketed products successfully synthesized. Arguably, synthesis offers the best prospects for establishing and maintaining a patent position for the life of the product.

1.7 The Demise of Natural Products in Big Pharma

In the decade following the Earth Summit, it was easy to be excited and bullish about the future of natural products research in the pharmaceutical industry. Researchers had a seemingly endless array of potential targets, numerous collection projects were popping up and an incredible array of chemical and biochemical tools were available for pursuing new discoveries. By the end of the next decade,

however, most, if not all, of the in-house natural products programs in Big Pharma in the United States had ceased to exist. Merck, for example, shut down its entire natural products research effort in the USA and in Spain in the Spring of 2008 after a very productive history spanning over 50 years. What happened?

A confluence of several factors resulted in the demise of natural products research in Big Pharma in the United States. During the Biodiversity Boom, the value of natural products was grossly overhyped. Without naming any names, on the bioprospecting conference circuit in the 1990s, is was not unusual to hear someone banter about the opinion that there are X number of drugs on the market that were found after studying only a few thousand species of plants, and there are over 300,000 plant species, so there must be 1000 times X drugs in the remaining unstudied species. Any responsible scientist sees immediately the fallacy in this argument. Unfortunately, this argument had the dual effect of driving up the expectations of source countries regarding the potential financial returns for use of their natural resources (and price of using those resources) while simultaneously inflating the expectations of the business community, including Pharma's senior management. At the same time, despite an investment of many millions of dollars by Pharma and by the US National Cancer Institute, no new chemical entities in clinical development had come from recent bioprospecting activities. Other competing technologies, e.g. combinatorial chemistry and library screening, offered more compounds for less money. From the perspective of a businessperson, it is not hard to come to the conclusion that this relatively unproductive endeavour was too costly to continue. Indeed, costs were cited as the reason why Merck's program was closed.

On a more macroscopic scale, the decision to end in house natural products research could be viewed as one manifestation of a larger shift in the constantly evolving business model for the industry. Functions that were important enough to continue, but not perceived as valuable enough to require headcount in house, could be outsourced to other organizations with lower expenses. Frequently this meant relocating these functions to other parts of the world where labor was cheaper. It is a short jump from this point to eliminating the function altogether, in favor of monitoring the activities of academic groups and smaller companies still active in the field, for the discovery of any promising development candidates which could then be purchased or licensed for internal development. For a risk-averse industry, this is an attractive, lower-risk approach to research. The ultimate expression of this approach *will be* a company that is no longer involved in any basic research, relying only on licensing and acquisition for its new product pipeline.

1.8 The Evolution of Natural Products Chemistry in the Twenty-First Century

While corporate business plans have continued to evolve, science has not stood still. Many of the tools used in natural products research have experienced major enhancements in capabilities. HPLC has been a routine tool for many years in most chemistry labs. Using 5 and 10 micron particles, one could separate most kinds of mixtures in a reasonable length of time within the 400 bar pressure limits of most commercially available pumps. Driven by the desire for faster separations, greater resolution and better sensitivity, column manufacturers introduced newer particles with mean diameters extending below 2 microns, dramatically increasing speed, resolution and sensitivity but requiring UHPLC pump technology capable of delivering mobile phase at pressures of 600–900 bar or higher. The higher speed of separation required detectors and data systems with higher sampling rates, able to properly digitize the narrower peaks. Of course, to embrace all of these new capabilities requires a significant investment in new equipment. More recently, column manufacturers have re-introduced pellicular packings on small particles, offering separations comparable to UHPLC but at pressures accessible to the large base of users with traditional HPLCs.

Nuclear Magnetic Resonance spectrometry has also changed dramatically in the last 20 years. The gigahertz spectrometers and cryoprobes capable of achieving signal to noise ratios on 10,000:1, now commercially available, would have been considered science fiction at the Rio Conference. While these gigahertz instruments are not widely deployed (for obvious reasons of cost and upkeep), there is now a substantial user base of instruments in the 700–800 MHz range. These instruments have made it possible to obtain usable data on samples substantially less than 100 micrograms. The increases in hardware capabilities have been matched by a dizzying array of new experiments easily implemented on the modern spectrometers, further simplifying the task of structure determination.

Similarly, mass spectrometry has made major strides in this time period. While mass spectrometry has always been an extremely sensitive method, current generation ion trap, Orbitrap and quadrupole time of flight (qTOF) instruments now boast sensitivities down to femtogram level samples with high mass accuracy. Tandem MS methods add fragmentation information for each ion in the spectrum. When coupled to an HPLC or UHPLC, such an instrument makes it possible to collect mass spectra for every compound eluting from an HPLC column, truly enabling the fingerprinting of an extract. The application of these techniques to dereplication is obvious and becomes even more powerful with the addition of statistical (chemometric) methods such as principle component analysis (PCA). These statistical tools are already available in bundled software packages from the instrument manufacturers. One can easily envision developing a system that uses a standardized, gentle, initial fractionation step (preferably orthogonal to HPLC) such as countercurrent chromatography, followed by assay and LC-MS/MS analysis using PCA to elucidate

the peaks of interest. While perhaps not universally applicable, I would be hard pressed to produce an example where it was not.

1.9 The Evolution of Screening in the Twenty-First Century

In biology, what's old is new again. Over the last several years there has been a resurgence in interest in phenotypic screening. This is not to say that interest has resurfaced for using animals in the screening of samples in drug discovery, rather the advent of technologies for imaging cellular processes, coupled with cells engineered to overexpress metabolic pathways, has enabled the development of high content screening. Molecular biologists have studied cellular processes for years using imaging tools such as laser confocal microscopy, but these experiments were laborious and time consuming. High content imaging systems have taken these experiments, adapted them to microplate formats (96, 384 and perhaps 1536 well formats) and automated acquisition and processing of the data. As the development of microplate technology allowed the miniaturization and automation of biochemical assays, enabling high throughput target-based screening with high content imaging, now allows miniaturization and automation of screening at the biological level in intact cells. Phenotypic screening addresses some of the perceived problems involved with target based screens, namely target relevance and bioavailability among others. Observing change in the morphology or behavior of cells is a direct indication of the biological activity of an applied substance. Elicitation of that activity is predicated on the ability of the applied substance to penetrate the cell and access the underlying metabolic process. The ability to work at this level in a high throughput manner is a real game changer.

For decades, the mantra of drug discovery in Big Pharma has been, "one drug, one target". Compounds displaying more than one bioactivity (or interacting with more than one target) were considered inadequately selective for development as products. Recently, interest in polypharmacology has grown in the research community. Polypharmacology accepts that a compound may interact with more than one step in a metabolic pathway and that the net overall effect on the entire pathway is the relevant indicator of biological activity, not just the effect on a single step. Phenotypic assays allow the researcher to observe the net overall effect, positive or negative, of a compound's interaction with an intact metabolic pathway. While polypharmacology may not be the optimal way for finding the most potent HMG-CoA reductase inhibitor, it may well allow for the discovery of safe, effective and novel modulators of cholesterol metabolism.

While most of the world's population still relies on traditional medicines to meet their healthcare needs (World Health Organization 2013), relatively few "modern" medicines have been developed from traditional medicines. Clearly some traditional medicines have some level of efficacy. Why else would their use have persisted for hundreds or even thousands of years? Oftentimes, traditional medicines are comprised of multiple ingredients prepared in a formulaic manner that may be

difficult to reproduce accurately in the laboratory. In labs constrained by the "one drug, one target" philosophy of drug discovery, a reductionist approach has been taken, evaluating each component ingredient individually against an individual target. While this approach has yielded many biologically active compounds, few, if any, blockbusters have emerged. Why not? The complex nature of traditional medicines suggests that the observed effects may be the result of multiple biological activities. This is not to suggest that true synergism occurs at a single target, rather that inhibition of multiple steps in a pathway may lead to a net effect that is greater than the sum of the inhibition of each step. Modulation of multiple steps in a metabolic pathway is an example of polypharmacology in action.

1.10 New Frontiers

Over the years, I have heard many administrators suggest that natural products may be played out as a source of new leads or drugs and that some novel approach would surely increase the pace of new drug discovery. Thus were born *de novo* rational drug design, combinatorial chemistry and the all inclusive approach to compound library screening. Like natural products, each of these approaches has had its ups and downs. Natural products can be played out only in the mind of a person lacking imagination and curiosity. During the boom years, studies focused primarily on terrestrial plants, microorganisms and marine invertebrates, each taken out of the context of the environment in which they lived. Each of these groups was known to produce a wide range of secondary metabolites with little apparent overlap with the other groups. More recently, endophytic fungi such as *Taxomyces* (Stierle et al. 1993) have been found that are capable of producing some of the same metabolites produced by their host organisms. Similarly, some of the metabolites ascribed to marine invertebrates have been found to be produced also (or solely) by their microbial symbionts (Gerwick and Fenner 2013), and poison arrow frog toxins actually come from the ants the frogs eat (Daly 1998). Perhaps the ants are eating the true producing organisms. It is not surprising therefore, that marine microbes and terrestrial endophytes have become hotspots of interest.

One further area of interest pushes the boundaries of the definition of natural products. That is metagenomics. We have long been told that the vast majority of microorganisms cannot be cultured, and culturable microbes may represent less than 1 % of the species in the environment (Rappe and Giovannoni 2003). Metagenomics attempts to isolate DNA directly from the environment, without first isolating a producing organism. It then seeks to identify genes and gene clusters analogous to the genes in known biosynthetic pathways, isolates them, and then inserts them into the genome of a suitable heterologous host, hopefully thereby expressing the biosynthetic potential of the isolated genes ((Charlop-Powers et al. 2014); (Brady et al. 2009)). These methods hold great potential for tapping the biological and biochemical diversity of this largely unexplored resource. Perhaps a limiting factor is that the sequence based metagenomics approach relies on our

existing knowledge of the genetics of biosynthesis, and is thus more likely to provide variations on known groups of compounds rather than truly novel chemotypes. Nonetheless, as our understanding of biosynthesis is continuously expanding, so too are the opportunities that will be afforded by metagenomic small molecule discovery.

Looking back with the clarity of 20/20 hindsight, many of the advances of the last 20 years could be considered predictable. Certainly, improvements to the quality and capabilities of laboratory equipment happen continuously. Why else would researchers flock to the Pittsburgh Conference (Pittcon) every year? While some of the details may have been surprising, the general trend is not. The resurgent interest in phenotypic screening and polypharmacy are likely a response to years of dealing with the limitations and vagaries of target-based discovery that have led to the questioning of the validity of the "one drug, one target" paradigm. The real breakthroughs in sourcing are really only in their infancy. Aside from the dearth of new blockbusters based on natural products, the science is pretty much right where it would be expected.

1.11 Into the Future

The only thing certain about the road forward is that it will be a bumpy ride. Pharma's interest in natural products research has always been a cyclical phenomenon, but the recent wholesale abandonment of the field suggests that the current cycle may have a longer period than the last few. Pharma's business plan of outsourcing research and relying on acquisitions to fill the pipeline may be myopic, but it does open the door to an expanded emphasis on innovation and the entrepreneurial drive of academia and smaller business entities. It must be noted that American Pharma's business plan is not the *de facto* standard in other parts of the world. There is still substantial interest in natural products in places such as China and Japan where natural remedies had been a part of the culture and tradition long before Europeans laid claim to the New World, and still are in widespread use today. One major discovery, one blockbuster, may be all it takes to start the next cycle of interest in the United States.

There are a few confounding factors. Pharma's abandonment of natural products research has dramatically reduced the number of attractive (i.e. lucrative) jobs in the field. Predictably, this will act as a disincentive for attracting students to become the next generation of natural product researchers. Smaller companies may be able to generate a significant number of positions for these students, but it unlikely that they will be able to offer the compensation packages we have come to expect from multibillion dollar multinationals. Second is the lack of stable, significant, government funding for natural product research in academia. As anyone in Pharma R&D management will tell you, natural products research is expensive and is a long term endeavor. Without stable funding at a level sufficient to maintain this kind of

research, the pipeline of well trained and qualified young scientists will surely dwindle.

Will natural products research disappear completely from pharmaceutical R&D? I think not. There is still too much value, too much potential, for this resource to no longer be of relevance. It appears more likely that speciality discovery organizations will evolve to service the discovery needs of Big Pharma via its existing business model. Whether such organizations evolve as broad-based discovery groups or groups focusing on specific niches (sources, disease targets, etc.) or some combination of the two remains to be seen.

Will natural products ever regain the prominence it once enjoyed in Big Pharma? Probably not. It must be understood that Pharma's departure from natural products research was a business decision, not a scientific one, and is part of a much larger business plan. Pharma, as an industry, continues to evolve. Evolution is a prospective, progressive phenomenon. While it is important to learn from the past, it is equally important not to dwell on it. Pharma will eventually see again the wisdom of using natural products to modulate the inherently natural functions of metabolism to meet medical needs. When will this happen? To quote Niels Bohr, "Prediction is difficult, especially about the future."

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