Natural Products in Drug Discovery - Organizing for Success

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When I accepted the invitation to speak to you, my letter of invitation suggested that I address the opportunities Natural Products hold for Drug Discovery, particularly natural products from higher plants and teresterial organisms. Others will talk about the marine environment and the promise natural products from that source hold. This lecture will be topical rather than a specific technical talk.

I will review quickly my experience at the University of Mississippi, initially with the Research Institute of Pharmaceutical Sciences. The Institute was established there in the 1960's, and has a parallel organizational structure to that proposed for the Tropical Research Institute proposed to be established here. I will then describe how I was able to leverage the experience and expertise of the Research Institute of Pharmaceutical Sciences at Ole Miss into the Center for the Development of Natural Products. I will finish with some ideas for your consideration in that area.

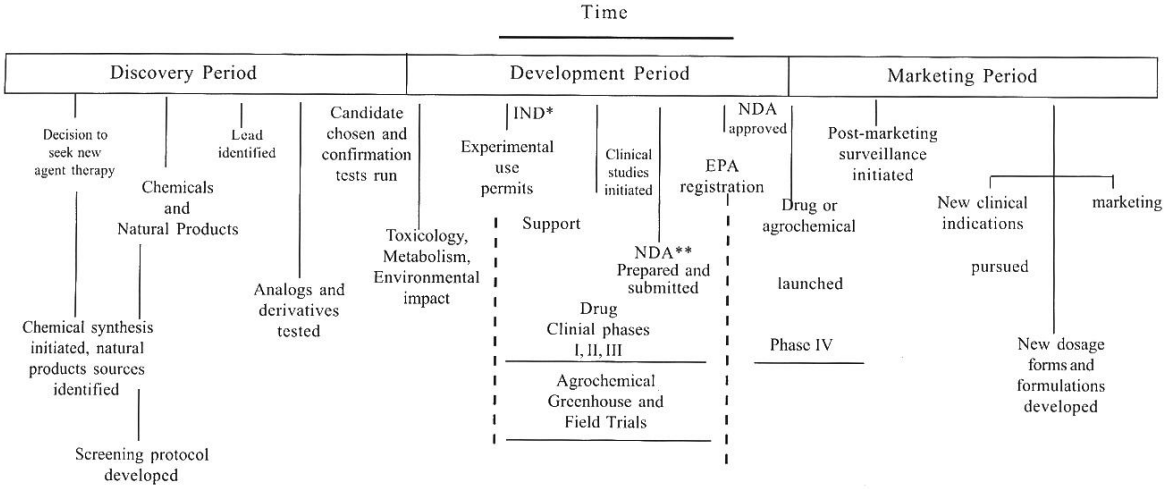
Discovery and Development from Natural Products. Some of the opportunities in natural products for discovery and development are:

- Pharmaceuticals
- Agrochemicals
- Cosmetics
- Fine Chemicals

We are all familiar with what it takes to discover, develop, and commercialize pharmaceuticals. In Figure 1, I have outlined the timeline for that activity. It is interesting that as one puts together information for a presentation on natural products for development, one does not find discussion of the most important issues relative to natural products. No where on this timeline is there any consideration given to supplying the quantities of drug needed for development, nor developing supply for commercial marketing. That in and of itself can be a very challenging issue and is often the primary constraint for development of natural products. Gordon Cragg discusses the necessary activities to address that issue.

Time for development of pharmaceuticals ranges anywhere from a few years up to as much as 20 years. I

Figure 1. Development Timeline for Pharmaceuticals and Agrochemicals.



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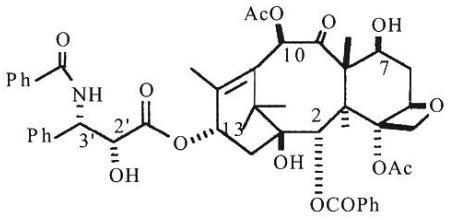
think paclitaxel or Taxol® (Figure 2), is still the champion. Its chemical structure was reported in 1971, as the cytotoxic active principal of extracts of *Taxus brevifolia*. Taxol was approved for marketing only at the end of 1992, so fully 20 years had elapsed. On average new pharmaceuticals require something on the order of a decade for development and commercialization.

Figure 2. Structure of Paclitaxel



For agrochemicals, a similar time frame is necessary. The time frame for agrochemical development is increasing because of concerns about release of these agents into the environment, and the consequences of those deliberate releases. Agrochemicals are designed for use as biocides in the environment, so we have to understand their impact over time. That is adding substantially to the time frames for agrochemical development and approval.

Figure 3 relates the costs of the development process for pharmaceuticals and agrochemicals. The costs detailed, $30-50 million for pharmaceuticals and $10 million or so for an agrochemical, are about an order of magnitude lower than what you see reported. I emphasize these are costs directly accountable for those products which actually go through the process successfully. If you actually account only the dollars spent on the specific compound at each stage, it comes to these numbers. What about the more than 10,000 other compounds that fall out of the process during discovery, and the 100 to 1000 compounds that fall out during development, etc? The success rate goes down very dramatically as one moves through the process. The costs associated with failed compounds all have to be paid and accounted, and so that is the difference between 30-50 million dollars for the successful one, and 300-500 million for the total process per new drug. So in effect, one spends more than 300 million dollars to bring a new pharmaceutical to the marketplace, and more than $75 million for a new agrochemical.

Biodiversity and Natural Products. Natural Products grow out of the phenomenon we recognize as biological diversity or biodiversity; all the kinds of organisms we find in the ecosphere here on earth. Chemical diversity grows out of that biological diversity. Not only are the interesting agents that we identify as natural products,

Figure 3. Direct Costs at Various Stages of Development

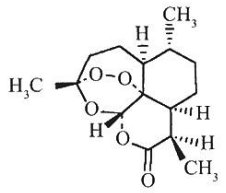
Pharmaceutical Drug		**Agrichemical**	
Stage	Cost ($10^6)	Stage	Cost ($10^6)
Pre-IND	2.4	Pre-Experimental Use	2.4
Phase I	2.6	Greenhouse/Fild Trials	6.0
Phase II	9.0	Registration Wait	1.1
Phase III	14.8	Total	9.5
NDA Wait	2.2		
Total	31.0		

the result of chemical diversity, but the food, clothing and the shelter that we all depend upon is similarly the product of chemical activity, chemical diversity on the part of organisms.

Natural products derive from biological diversity. They result from organisms interacting in their environment with one another. These interactions are very specific. In fact specificity is what we are looking for in the development of these natural products as pharmaceuticals.

Artemisinin (Figure 4) is an example of an interesting natural product, is the prototype of the next generation anti-malarial agents. We all know that malaria is an increasing world health problem. Artemisinin with its endoperoxide is very effective against drug resistant malaria.

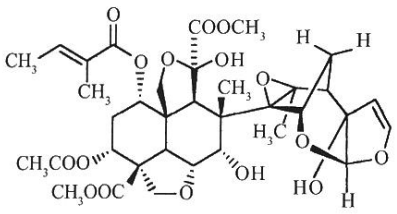
Figure 4. Structure of Artemisinin



There are millions of organisms interacting in the biosphere, and because there are millions of interacting organisms, then there are millions of chemical compounds (natural products) out there. When we discuss pharmaceutical discovery, we talk about the numbers game, thousands of chemicals evaluated to find a hit. We, as natural products researchers, have not yet capitalized to promote natural product preparations as a numbers game in terms of Nature's combinational chemistry. The interesting thing to realize is that Nature has been doing combinational chemistry for eons, not just a decade, and more importantly, has been selecting among that combinational library products for interesting biological activities. We need to realize that, and to take advantage of that.

Another example is azadirachtin (Figure 5). This is a product of the neem tree. Neem is a tropical or subtropical plant which has very potent activity as a bioinsecticide. Azadirachtin has significant potential agrochemical application among other activities.

Figure 5. Structure of Azadirachtin



Historically, we have utilized these natural products extensively, and until the last 100 years or so, natural products represented the primary or only source of pharmaceuticals for treatment of disease, prevention of disease etc.

To realize the potential natural products hold, there must be developed a systems approach to discovery and development. No longer will individuals working independently, the lone ranger working by himself, be successful. Rather, advantage must be taken of the capabilities from various scientific disciplines that can contribute to this multidisciplinary activity; chemists, biologists, pharmacologists - a true multidiciplinary team approach.

The Role of Higher Plants. For the sake of illustration let's focus on one class of organisms as the source of natural products. What about higher plants, why pay attention to those. There is a significant diversity of higher plants to evaluate. It is estimated that there are on the order of 300,000 recognized species. Even within recognized species we see recognized chemotypes, where a range of different concentrations of various chemical substances are present. Plants are found in every habitat. Also, plants have a large number of genes creating the chemical diversity we wish to exploit. The interesting thing to me about plants is that they cannot flee from attack. They can't run away as we do; they have to stand and take it. That means that plants have developed an alternative defense mechanism, that of chemical defense. Those chemical defense substances are what we can take advantage of. And importantly, less than 1% of plants have been evaluated in any systematic way. In effect, we could almost count on one hand those that have been evaluated in depth. Even well known plants such as the opium poppy are still incompletely evaluated for their chemistry; new alkaloids are being reported from *P. somniferum* all the time it seems.

We rely on plants for food. It is interesting that only about 20 or so feed the world's people. That is a different lecture, but non- the-less an important take home message: That it is a pretty narrow foundation from which to feed more than 6 billion people.

A substantially greater number of higher plants have some historical use as medicinal plants; some mention of use of about 10,000 species has been recorded. Probably 3%, and maybe as many as 5%, of all higher plants have been systematized into traditional systems of medicine. Traditional Chinese Medicine reports use of as many as 6000 to 8000 species, Ayuvedic another 1000 to 2000, etc. Interestingly about 150 species are utilized to produce substances that you can buy in the local pharmacy, substances used in important current western pharmaceuticals.

The Research Institute of Pharmaceutical Sciences. I became Director of the Research Institute of Pharmaceutical Sciences at the University of Mississippi in 1987. That organization was established in the early 1960's. It is a separate line item in the state budget, so each spring I had the opportunity to present to legislators arguments as to why they should give us money. If you have ever had that experience, I guarantee that it is an educational one not only for them but for yourself. How do you explain natural products and other kinds of sophisticated esoteric ivory tower kind of stuff to Mississippi cotton farmers. Even more difficult yet was to explain those topics to Mississippi lawyers. It was somewhat of a challenge. An important advantage of the Institute derives from its enabling legislation. It was given an economic development mandate; make jobs, make opportunity for the State of Mississippi through research. The Institute had been in existence since 1963. Under my direction, the Institute behaved pretty independently and pretty entrepreneurally. That independent behavior became an issue over time in the University environment. That is something I would caution you about at the University of Puerto Rico; academic environments do not mix well with entrepreneural behavior. Think about that carefully.

We had a full time research faculty within the Research Institute. They were not tenured faculty so they were accountable for productivity. I could leverage my faculty salaries by recapturing those salaries through grant and contract activities, and then reinvest the recaptured salaries myself back into the research enterprise. I did not have to go hat in hand begging of the University, "Please don't take my money and put it in the English Department" or "Please don't put my money into a computer purchase". I was able to decide where to reinvest my money. Because of the mission orientation of the Institute, we were successful. We could focus on contract research and be accountable for deliverables in a particular time frame. We were successful, and we became one of the examples that the legislature liked to quote in terms of the right way to invest their money. They would invest in us $1, 2, 3 million, and we would transform that through leveraging of activity

into 5, 6, 7 million dollars. Those extra dollars provided jobs and purchased services, etc. to bolster the economy of the State. That leveraging took place through federal contracts and through collaboration with industry. We were also successful in licensing intellectual properties, and again because of our independence as a separate agency, we were able to invest that income into the research enterprise. It didn't just go into the general university account.

Based upon the experience and success of the Research Institute, I developed the concept for the Center for the Development of Natural Products.

The Center for the Development of Natural Products. The Center for the Development of Natural Products was to discover, develop, and commercialize new pharmaceuticals and agrochemicals with the emphasis on commercialization. The major frustration I have felt as a natural products researcher relates to the outcome from our efforts. We do a very good job at discovering interesting natural products. We show that they have significant biological activity of an interesting sort, but it stops there. We are very anxious to protect our discovery in the academic environment, so we publish it. Suddenly it belongs to everybody, but in reality it belongs to nobody. It stops and goes nowhere once it is published. No company wishes to make a major investment to develop the natural product, if they cannot have a proprietary interest in the material. Those interests are forfeited once the information is published. Commercialization is the important outcome. Without commercialization our supporting constituents receive no benefits, they do not have the advantage of new pharmaceuticals to treat medical needs, etc.

We identified the Department of Agriculture as a major funding organization for the Natural Products Center. We believed that if we focused on higher plants, we could bring that around a full circle, and deal with the issues of supply by developing high value cash crops to produce the substances that we had discovered and were commercializing.

To implement the establishment of the Center, researchers of all types were needed. For the Center to be successful it must be multi-disciplinary. It must have the inputs of biologists, chemists, information scientists, etc., etc.

The efforts of all these researchers must be integrated into a systems approach to natural products development. Think about the various stages or steps of the development process. The capability, either through collaboration or directly by capturing, to deal with all aspects of development must be present. Don't get to the end and discover "oh my goodness, I can't find that interesting plant again which produces that important natural product.". Great biological activities from a novel compound that really looks exciting but can't ever be found again. Why?, because we didn't pay attention where it was collected, when it was collected, who collected it etc, etc. Perhaps it got mis-identified. All issues need to be addressed. This can only be accomplished effectively in an integrated, multi-discipline environment.

Focus on Commercialization. To accomplish effective commercialization, we must bring together the various partners necessary to development and commercialization in a true collaborative partnership arrangement. At the University, many capabilities were present, and we could tap into them. Government agencies would not only bring funding, but also contribute a great deal of expertise, particularly the US Department of Agriculture. And certainly industry, both the pharmaceutical and agrochemical industries, among others, bring expertise, commercialization experience and can provide development activity guidance. Emphasis must always be on commercialization.

One of the things I learned, talking to legislators, is that they want to know what they get for their dollar. It is the University's responsibility to produce teachers or students who become teachers, doctors, lawyers, etc. From a research organization, they want to see a tangible outcome. Papers don't count folks, papers go on the shelves of the library and your colleagues read them but nobody else does. Legislators generate lots more paper than we do and they know how to value it - not very much. So it carries no weight with those guys. They want to know, "What do the tax payers of the State get from this activity?" If they don't get a tangible result, your budget starts shrinking. Those are things you have to learn to communicate to legislators. Emphasis must always be on commercialization. It is all well and good for there to be discovery, but if the material does not get in the bottle so that the consumer can benefit with a new medication, it just doesn't count in the eyes of politician, the funding agency.

Were we successful to establish the Center for the Development of Natural Products? Yes. We gained, through the collaboration of the Department of Agriculture, resources to build the state-of-the-art facility. Some of you were at the 1995 ASP meeting at the University of Mississippi to see that facility. We put in place a program to provide operational funds from state, federal and corporate sources. That is a difficult and never ending effort, continuing today.

The research program of the Center was established around three themes; improved human health, increased agricultural productivity, and high value cash crops for

small farmers. In the area of improved human health we chose certain areas where we could make an impact; Anti-infectives, Drugs to modulate the immune system, Cancer chemotherapeutics.

The second theme was increased agricultural productivity. As you can all appreciate, the Department of Agriculture is very concerned about ways to enhance productivity, not only in terms of bushels of corn per acre, but in terms of real income for farmers. That is what they are after, increased quality of life in rural America. Efforts were initiated to discover less environmentally impacting pesticides and animal and plant growth regulators. Improved insect control agents derived from natural products could have very substantial impact on productivity in agriculture.

Finally, the third theme was high value cash crops which could represent potential production of these other agents.

Creating the Partnership. Collaborative agreements must be established between the organization and the sponsoring organizations, the federal government and various industrial company representations. In order for the organization to work, it takes resources. Part of the collaborative agreement must be the willingness to pay an operational fee. The advantage for the partners is that they do not individually pay the entire cost. That is, not every collaborator had to buy high cost instrumentation; NMRs, Mass Specs, etc; not every collaborator had to pay for numerous HPLC's. All together they paid for those kinds of equipment and those were available then to support the entire program. Similarly for state-of-the-art research space; something that is very expensive to build. They didn't have to pay $300 - $400 a square foot unless they wanted to use it 100% of the time, then they would build it in house. But if they wanted to do exploratory work and could use it part time, it was available at a fraction of the full cost. Set-up a committee representative of all the partners to deal with how to apportion these resources, how to emphasize the research program. Actually develop an R&D strategic plan. When the R&D effort was successful then licensing agreements could be developed. And finally, commercialization would follow naturally.

Benefits to Partners. Corporate organizations are always looking for rights, and particularly "first" rights. They want to look at new technology first and decide if they want it. So in the partnership they have rights to particular kinds of products. In addition, they are able to influence the direction of research. They have experience to say "Go forward or no that's not going to go anywhere so go ahead and publish. It's not going to have a future as a commercial product in our judgement".

Once products are identified for development, industry has a better feel for the development process, the things that need to be done and how to get them done. They can provide that kind of input very effectively.

Another important benefit to the corporate partners is that they get to look at the products from the whole program. They had first rights to specific areas but then additional rights as a consortium member to outcomes from all areas of the program of research.

The most important benefit to all members of the partnership has to do with leveraging. The State recognized the importance of this activity in terms of bringing prestige, in terms of bringing jobs, etc. to the economy. The corporate partners recognized that by entering into a collaborative relationship, they could spend a dollar and get more than a dollar's benefit. That is always of interest to all of us. The University gained visability, prestige and efficient development of new technology discovered in the program.

Finally let me close with the structure of podophyllotoxin, a material utilized by native American Indian populations and now modified to give an important cancer chemotherapeutic agent. Clearly natural products hold tremendous potential for discovery and development of pharmaceuticals, agrochemicals and other products. A potential that can best be realized by collaboration between academic institutions, government and industry.

Figure 6. Structure of Podophyllotoxin