The American Society of Pharmacognosy

Discovering Nature's Molecular Potential

The ASP Newsletter: Winter 2018, Volume 54, Issue 4

January 2019

Working in China: Land of Opportunity for Pharmacognosy

Dr. Ben Naman at a conference in Zhejiang, China.

By Dr. C. Benjamin Naman

Americans are accustomed to hearing the phrase "the State of the Union is Strong" to describe current economic and geopolitical situations, but different words often emerge when colleagues are asked about the funding situation for pharmacognosy research. Never mind the vocabulary of postdoctoral scholars who describe the process of finding a tenure-track appointment in US academia. Opportunities and success stories in both areas do exist and remain worth the significant efforts required to obtain them. What follows, though, is a slightly different outcome to a mostly traditional US academic pedigree: employment in the People's Republic of China.

Chinese institutions are investing heavily in instrumentation and infrastructure to conduct world-class research and are actively recruiting strong scientists. Positions are more available for foreigners, funding is more accessible, and natural products research is thriving. It does not hurt that the food is diverse and delicious. Likewise, the biodiversity here is extensive and easily accessible for research in China.

The proverbial door to employment of foreign faculty in

continued on page 3

IN THIS ISSUE: WINTER 2018

EDITOR'S CORNER

This is the first *ASP Newsletter* with a major focus on employment in pharmacognosy. The

ASP employment website has traditionally been one of the Society's most visited pages (www.pharmacognosy.us/jobs/). Employment opportunities for people trained in pharmacognosy has changed considerably in recent years in many sectors, including government, education, and industry. The *Newsletter* has asked members with ties to each of these to help navigate this rapidly changing landscape. One of the most impressive changes has been the investment of the People's Republic of China in natural products research. ASP member Dr. Benjamin Naman landed a full-time position at Ningbo University. Dr. Naman paints a vivid picture of what it is like to work in China.

Two ASP Fellows, Drs. Guy Carter and Bill Fenical, explain what it is like to start a biotech company. Many ASP members have discovered new bioactive compounds, but the process of commercializing that discovery may seem daunting for many members, especially those in academia. I encourage all ASP members to read this helpful and educational article.

Regarding government work in pharmacognosy, ASP member Dr. Joseph Betz explains his career path, and how opportunities became available to him at the US Food and Drug Administration and later at the National Institutes of Health. His insights provide a helpful perspective on jobs that may not immediately come to mind but are in great need of pharmacognosy/natural products expertise. With the changing laws on marijuana legalization, for both medicinal and recreational uses, a number of members have found related jobs, and we plan to cover this specific topic in an upcoming *ASP Newsletter.*

Some terrific new resources for natural products researchers were announced at the ASP Annual Meeting in Lexington this past summer. Dr. Roger Linington announced his Atlas open access database of microbial natural products. Also, ASP Vice President, Dr. Barry O'Keefe, announced that the NCI would make available over one million partially-purified fractions that can be requested for high-throughput screening upon request.

I hope you will take some time to read our regular columns as well. The *Newsletter* continues to strive to cover our diverse membership in a fair and hopefully informative manner. The Society as well as the *Newsletter* have reflected in the past year and a half on the role of women in the ASP as invited speakers at meetings as well as how they are represented on the pages of this publication. We found that we often have fallen short, but we are actively trying to address this. "Field Notes," by ASP member Dr. Cassandra Quave, describes, in a very powerful way, the joy of fieldwork and the challenges it presents for all, but especially for women and those, like Dr. Quave, with physical challenges.

Finally, "From the Archives" is part two of our coverage of Dr. Anna Koffler Wannamaker, a major but rarely spoken-about figure from the founding of the ASP. Her many contributions to the ASP's founding are detailed beautifully by Ms. Devhra BennettJones. It made me realize that although the ASP prides itself on its many named awards, large and small, not one of these is named in honor of a female member of the Society.

I hope you have a wonderful 2019, and I hope you start making plans to attend the Annual Meeting in Madison, July 13-17.

Dr. Edward J. Kennelly

EMPLOYMENT SERVICE

The Society offers a placement service to aid our members in seeking positions or employees. This service is available only to ASP members and is free to both the applicant and the employer.

For more information see the services website.

www.pharmacognosy.us/jobs/

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The contribution deadlines are:
Spring Issue Feb. 15
Summer Issue May 15
Fall Issue Aug. 15
Winter Issue Nov. 15

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ISSN 2377-8520 (print)
ISSN 2377-8547 (online)

Working in China: Land of Opportunity for Pharmacognosy

continued from page 1

China is very open. In 2006, the Chinese government announced regulation for improving foreign involvement in academic development, which was then called "brain gain through Plan 111," or, put another way, a massive funding effort to bring foreign talent to China.[1] An expansion of this program was enacted from the end of 2008 by way of the "Thousand Talents Plan," which enables the recruitment of specific key individuals for part-time, or ideally full-time, professional engagement in China.[2]

Aside from 111 and the Thousand Talents Plan, foreign faculty spending sabbatical time in China is also on the rise, including ASP Fellow Prof. Bill Gerwick who, recently, after returning from sabbatical, co-hosted in La Jolla, CA the 2nd US-China Summit on Marine Natural Products Sciences. The host from the other side, Prof. Wen Zhang, was unfortunately unable to secure a visa to visit America in time. He was replaced by Prof. Renxiang Tan from Nanjing University, China, who will also co-host the next Summit in China along with Prof. Dale Nagle.

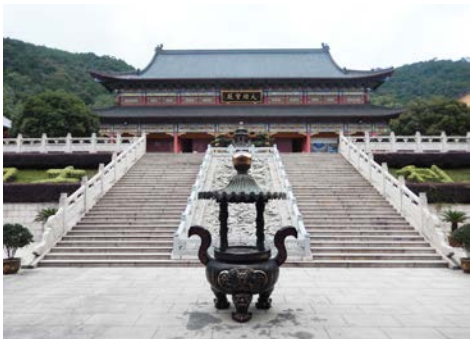
During his sabbatical, Dr. Gerwick recognized an opportunity for scientific diplomacy and international exchange that would be executed when I, then a postdoc in his lab, came off of fellowship funding in June 2017. Ningbo University, one recipient of a 111 project award specifically designated the "Foreign Experts Base for Marine Biopharmaceutics," provided travel and living expenses for a one month visit, which was designed as a mixture of an on-site visit for recruitment, research collaboration, curriculum consultation, an interpersonal and cultural exchange, and so on.

Tianjin University, for one leading example among several others now, has expanded international cooperation and English-based curriculum by building its School of Pharmaceutical Science and Technology around a group of foreign faculty, including ASP members Drs. Bob Borris and Ben Clark. Other interested scientists will very easily find connections to host institutions in China, with or without a 111 award or current foreign faculty. These interactions, or a direct communication about or application for employment in China, will almost certainly be met with excitement, enthusiasm, and a world of possibilities.

One perk (there are many) is that, with an appropriate pedigree and publication record, assistant professorships may be available to recent PhD graduates, and associate professorships with tenure to those having suitable postdoctoral experience. More senior faculty could be met with compelling package offers to transition fully to China, run a second lab, and/or receive a "summer salary" appointment here. Many positions in China are posted online at familiar websites (e.g. jobs.sciencecareers.org, nature.com/nature careers, chemistryjobs.acs.org), and even more will manifest once sincere interest is expressed by qualified candidates. For example, Ningbo University, where I am employed, is planning to hire many more foreign faculty at multiple levels in the next few years. Incidentally, an entirely new campus was constructed and completed in about two years' time, which is not atypical in China. Be aware that Ningbo is "a small town of only about 8.5 million people," and approximately one percent or less are foreigners. Small communities of expatriates tend to congregate together, though, and socialize in groups for occasions such as berry picking, happy hours, holidays, Sunday

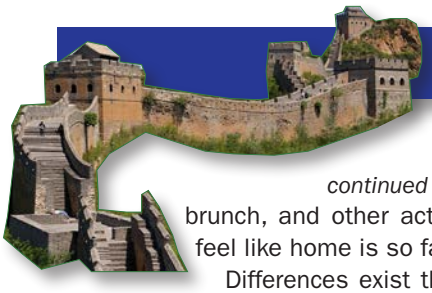
continued on page 4

Positions are more available for foreigners, funding is more accessible, and natural products research is thriving.



Above left to right: A tranquil setting built to resemble life in earlier China, at Hangzou West Lake (Xihu); one of the many temples located in officially designated "scenic areas" around Ningbo, China, at Jiufeng Mountain; the iconic Shanghai tower and nearby buildings, not even really "downtown," viewed at night from the Old Bund.

One perk (there are many) is that, with an appropriate pedigree and publication record, assistant professorships may be available to recent PhD graduates, and associate professorships with tenure to those having suitable postdoctoral experience.



Working in China: Land of Opportunity for Pharmacognosy

continued from page 3

brunch, and other activities. One need not always feel like home is so far away.

Differences exist that should be recognized. For example, hiring in China need not follow the academic cycle. In 2017, I received my offer in June after giving a department seminar and informal discussion of future research directions, which led to a negotiation of terms that I accepted in July. I was then asked to fill out an application for the position and later interviewed for it in October; and, while the outcome was positive, this compelled a mandatory external review that eventually approved the decision to hire me in November. This permitted the university to formally prepare my contract, which was only able to be executed in December after a work and residence permit was issued by the government. Those were some stressful months, both at the time and in retrospect, but all things ended quite well even with the timing and sequence of events being foreign and confusing for me. However, the fact that China's population is more than four times that of the US might explain the situation and suggest that by interviewing candidates who have effectively accepted offers, the university administration and department faculty can save an incredible amount of time and energy. Potential candidates can thus get pretty far through the application process informally in the current state of affairs, and then be "back-checked" by the procedural policy to ensure that everything happened appropriately. For Chinese natives, the process proceeds distinctly, due to less and different bureaucratic paperwork being required.

Another notable difference was in the application itself, because filling out a standardized form with a first-authored publication list that included the Science Citation Index (SCI) level and impact factor of each journal, along with a current citation count for each paper, was unfamiliar to me. How many publications to expect in what SCI level (top, 1st tier, 2nd, 3rd) of journal is relatively fixed for hiring at each level and also gets included in the contract. This understandably makes some people uncomfortable, and more so when trying to determine how many "top" journal articles in, for example, *Cell, Nature*, or *Science* equate to however many more "tier 1" papers, published in authoritative journals like *J. Nat. Prod., J. Agric. Food Chem.,* and *Org. Lett.* However, the transparent system for hiring, review, and promotion can also be quite welcome. The emphasis seems to be placed on research, most probably due to the currently available systematic metrics of university rankings. As a foreign faculty member, the teaching and laboratory management are expected to be conducted in English. One can negotiate to teach fewer classes per year with counterbalances such as having other professional obligations and responsibilities including a society leadership role, journal editorial position, or opening a startup company. A more comprehensive look at entrepreneurship can be found in Drs. Guy Carter and Bill Fenical's column in this issue, but, to augment that, the government of China has shown strong willingness to invest funding support and provide long-term rent-free incubator space in selected foreigner-run startups, making this in some ways a very attractive location in which to venture.

There is also an included contractual obligation to at least apply for a specific amount of grant funding, and many opportunities are available at municipal, provincial, and federal levels. During the last funding cycle, in March 2018, I submitted a research grant proposal in the National Natural Science Foundation of China (NSFC) International Young Scientists category. Not only was this application submitted exclusively in English, but I am excited to say that it was positively reviewed and awarded for January 2019

continued on page 5

Chinese language proficiency is not necessary while on campus, but it can be helpful. One taxi ride, DiDi (think Uber), or failed attempt to order a meal while off campus may be encouragement enough to at least download a phone app to learn Chinese or facilitate translation on the go.

Above left to right: English signs, signals, and recorded messages onboard the subway make for convenient travel; a few colleagues hike UNESCO World Heritage Site Yellow Mountain (Huangshan); plenty of food on sticks await you in China. This unfortunate squid was delicious.

Working in China: Land of Opportunity for Pharmacognosy

continued from page 4

through December 2020. Colleagues, including Dr. Ben Clark at Tianjin University, have also met the same success. These grants, available only to younger researchers, are very accessible but are associated with strict limits on their total value. In practice, being a Co-PI with a top researcher in China is a common way to access pieces of large grants that are reminiscent of program project (P01) awards in America. One such avenue for funding is through any typical call for NSFC or Ministry of Science and Technology (MOST) grant application. Since these are to be completed exclusively in written Chinese, good options include being a Co-PI with a native speaker or relying heavily on students, local colleagues, or a professional service for translation, and then hoping for the best.

Life in China is in many ways quite convenient for foreigners. The Chinese culture is very accommodating and polite to outsiders (guests). People from smaller towns may still be unfamiliar with foreigners, but the larger cities and regions along the more developed coastline grow increasingly more international in population, cuisine, and culture.

Chinese language proficiency is not necessary while on campus, but it can be helpful. One taxi ride, DiDi (think Uber), or failed attempt to order a meal while off campus may be encouragement enough to at least download a phone app to learn Chinese or facilitate translation on the go. Google Translate, with offline Chinese, and Youdao Translator, with an active internet connection, are fan favorites. It should be mentioned that the "Great Firewall" is alive and well, but international data plans on cellular networks seem to be exempt from any and all blocked internet access. Users of Google, Facebook, Dropbox, and many other filtered services can rejoice. On the topic of communication, go ahead and download the phone application "WeChat" if you ever plan to work in China, as here this has largely replaced phone calls, text messaging, and email alike, and furthermore offers a so-so in-app translation.

Life in China is in many ways quite convenient for foreigners. The Chinese culture is very accommodating and polite to outsiders (guests). People from smaller towns may still be unfamiliar with foreigners, but the larger cities and regions along the more developed coastline grow increasingly more international in population, cuisine, and culture. The airline, subway, and high speed rail systems appear to all have redundant Chinese and English in place, making travel easy in addition to affordable and comfortable. The cost of living here can be roughly equated with the exchange rate, although different living environments will have an obvious impact. Relocating to Ningbo, Zhejiang, China from San Diego, CA, USA felt like a 5-10x increase in spending power, while the Chinese yuan has fluctuated from 6-7 per US dollar in the last year or so. The salary available for foreign faculty in China is competitive with or exceeding what is typical at US institutions, so it goes quite a long way, but it is also paid in yuan and by default taxed in China before the country of citizenship. Many ex-pats pray that the more than 30 year-old US-China tax treaty outlives the current "trade war" and harsh political rhetoric of our time. This treaty mutually prevents double taxation of income by allowing, for example, Chinese citizens working in the USA to deduct employer-withheld taxes when paying China, and Americans working in China to deduct Chinese tax withholdings when paying USA federal income taxes. Aside, Chinese universities are known to partially or fully subsidize on-campus dining and housing for faculty members, and special arrangements are often made for foreigners regarding space, location, quality, and cost. Healthcare for all faculty members is free and at the top quality offered, and there is also a retirement plan that comes in yuan but will likely matter less than personal savings. Accommodations can often, but not always, be made for leave time and travel to attend family events and celebrate holidays that otherwise would not be observed in China. It never hurts to ask.

Foreigners may also find that their experiences from outside of China will be called upon by local leadership in the university, or government, for advising policy making. This form of consultation and scientific diplomacy should be considered carefully due to the vast potential for impact (positive or negative). At the forefront, China appears to be adaptive in all things, including policy. A local saying goes as such, "The only thing that is constant in China is change." Working here makes for quite the adventure, and, for a growing number of foreigners, a very desirable experience. The history, culture, landscape, exotic food, and life "outside of the lab" play a role in that as well. So for the open-minded and adventurous, consider that your next stop may be China. ■

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[1] Li, X. "China to Undergo Brain Gain Through Plan 111." Accessible from www.china.org.cn/english/China/181075.htm

[2] Anonymous. "The Thousand Talents Plan: History and Background." Accessible from www.1000plan.org/en/history.html

ASP Fellows: Challenges, Benefits, and Drawbacks in Forming a Natural Products Company

By Drs. William Fenical and Guy T. Carter

PREAMBLE

Guy Carter and I prepared the following article to offer our respective experiences in creating a new natural products-based company. The views expressed are mostly relevant to university researchers who are most likely to make discoveries in this area. However, an important part of this article provides advice on the criteria needed for development from a "big pharma" perspective.

What Exactly Is a Founder?

The founder of a biotech company can be an academic or an independent researcher who has a valuable discovery or discovery platform, and who is willing to offer this technology as the foundation of a new company. If the founder is an academic, his/her "know how" may be independent from their responsibilities to their university. However, if a discovery covering intellectual property is owned by the university, the technology will need to be licensed by the university to the new company. Obviously under this situation, the academic has no or limited control over who will be the licensee. The university may look favorably upon the new company, however, recognizing that the technology was discovered in house.

What is the role of a founder? A founder could be involved in numerous ways, but exactly how this is accomplished is a complex topic. It is a reasonable assumption that the founder has more background in the IP licenses or establishing an effective platform. Consequently the founder can be an essential component of a newly established company. However, if the founder is an academic, he/she is likely to be restricted in formal employment. Academic policies vary, but typical universities allow an academic one day per week to provide community service. Acting as a non-employed founder or consultant during that day is a component of community service. Typically, acting as a consultant without demands for formal employment allows the academic to avoid being in conflict of interest (COI). This latter term is of growing importance in technology-rich universities to protect academics and the university from illustrating the appearance of unprofessional transfer of technologies to third parties. Almost every university now has a COI committee composed of fellow academics tasked with the responsibility to determine if the academic-company relationship is honest and mutually beneficial.

How does a founder benefit? Assuming an academic researcher wants to retain his/her university affiliation, benefiting from being a founder is somewhat limited. Perhaps the best avenue to follow is to be a paid consultant and/or perhaps chair of the company's scientific advisory board (SAB). For this service a founder can expect to share in the company's stock and receive a generous consulting contract. One

continued on page 7

continued from page 6

recommendation is to receive a yearly retainer that is considered an essential component of the company. A discussion of the value of stock will be dealt with in a subsequent component of this article.

Of course, if an academic is strongly suggested to play an enlarged role in the company, i.e. as director of research or other employee roles, it is likely that either a leave of absence or a reduction in percent time of university employment will be required. Most university policies do not allow full-time faculty to gain additional employment.

Patenting versus Publishing —Sometimes a Difficult Decision?

A prerequisite for the successful creation of a new company is to have considerable intellectual property secured as patents or technologies. Most universities have aggressive technology transfer offices that assist investigators in securing patent protection. Often, however, it is necessary for the inventors to convince university officials that their discovery is of sufficient value to move forward. It is becoming more common that university officials may require that a licensee be identified prior to the costly process of securing a full patent. For an academic, the decision to file patent protection may be a difficult one, since having open publications of one's work is the foundation for academic advancement. In the beginning, filing a "provisional patent" is simple and low cost. Provisional patents are considered a one-year "place holder" for the discovery. However, the one-year anniversary date approaches very quickly and the next step is costly and complex. Without moving to a regular patent, the intellectual property becomes difficult to retain and of little value.

Rewards – Financial, Societal and Personal

There can be substantial rewards associated with the successful creation of a natural products-based company. However, there can also be downsides in terms of time invested versus achievement. This is particularly true for academic scientists who must weigh their time in developmental activities versus academic pursuits. Certainly, there can be significant financial rewards for service on advisory boards and as a paid consultant. A major role of the founder can be to chair the Scientific Advisory Board (SAB). This aspect of forming a company needs to be carefully negotiated since considerable effort will be required of the founder to see the new company be established. A component of potential rewards is the receipt of company common stock and stock options. These can be significant, but it needs to be realized that preferred stock will be valued well before common stock. Owning common stock may not be as valuable in the long run.

The societal and personal rewards for founding a company are usually substantial. Having founded a company is clear evidence of the value of your science. This can be a significant component of your overall rewards.

The Role of the CEO, Senior Personnel, and Board of Directors/Advisors

Once your new company has been established, it will rapidly evolve into a form that may not be familiar to an academic. Administrative staff will be hired, and their views and experiences will become dominant. Business is business, a concept that academics may not have experienced. Some of the new company culture will depend on how the company is financed. Is this a venture funded or privately funded activity? If venture funded, a Board of Directors composed of representatives of the financiers will take center stage. Your CEO, who is hopefully experienced in pharma and knows the "ropes" of venture funding, will be critical. The role of the CEO will be to produce the financial and scientific foundation for the company. It will be his or her responsibility to fundraise and to protect all aspects of the growth of the company.

As funding is achieved and components of the company are purchased by investors, it is quite likely that these investors will join the Board of Directors (BOD). The BOD can be a very productive group illustrating full support and assisting in further financing, or they may be impatient looking for rapid return of their investments. Accordingly, managing the BOD is one of the important jobs for the CEO.

As a new company matures and evolves, the role of the founder may diminish or even be eliminated. Perhaps this is natural since either your IP discoveries or platform should have been fully encapsulated by the new company staff. Your potential role as chair of the Scientific Advisory Board (SAB), however, may still be a critical contribution to the company, as your academic background, reputation and relationships with other SAB advisors is an important component of the stature of the company.

There can be downsides, however, as your company matures. Company researchers may see natural extensions of your work, and having greater resources to develop new IP that might well be developed by you. This needs to be tolerated since this was part of your goals in founding this company. However, in this researcher's opinion, it needs to be made clear that these are your ideas, and publications could not have been conceived or finalized without you. Consequently, you need to be positioned

continued on page 8

continued from page 7

in the company to share in academic rewards as they occur. This is critical!

An important question is whether your dedication and hard work will have a positive impact on your university advancement. This is not clear. Perhaps at some universities yes, but at others this activity may never be appropriately recognized. Different stages of drug discovery and development require massive outlays of time and effort, but these do not (necessarily) qualify as academic achievements. For this reason, it is critical that your academic research continue, with and without the participation of the company's researchers.

Forming a Lead Compound-Based Company

Are your discoveries of sufficient value for the foundation of a company?

Have you discovered a novel natural product that shows potent biological activity in an assay that targets a particular disease? Let us assume that the disease state is also one where there are insufficient effective drugs on the market, and the population of patients is substantial and growing. So there is no doubt that a new drug against this condition is highly desirable, and we won't debate whether there is sufficient demand for such a product – we take that as a given.

You have decided to launch a company based on your discovery in order to develop it as a pharmaceutical product. Of course this is an enormous undertaking that will require millions of dollars just to get through all of the pre-clinical development steps. Let us assume that your company's objective is to take a compound based on your original discovery up to the Investigational New Drug (IND) stage, at which point they plan to license the compound to a Pharma company to take the compound into the clinic.

Novel natural products that show significant biological activities are not rare. Your discovery is highly significant to you and your team, but its potential as a lead to a pharmaceutical product requires cautious assessment. In particular, you are asking potential investors to bet on the success of a compound to overcome the daunting challenges of pre-clinical development. So what are the critical characteristics that your compound(s) must possess, and what pivotal data do you need in order to convince investors to back your company? The following bullet points outline some typical questions that savvy investors will ask regarding the chemistry, biology and pharmaceutical properties of your lead series. In general these questions are focused on the "developability" of your leads.

Patent status: Are the compounds eligible for patent coverage? Have applications been filed? Under current US Patent Trademark Office guidelines, natural products are not eligible; however, even simple derivatives likely are. Most investors would be encouraged if some steps had been taken in this direction, such as filing provisional applications.

Mechanism of Action: What is the molecular mechanism? Is it unprecedented? A novel mechanism of action could forecast a "first-in-class" therapy that would be most highly valued. Lack of a well-defined MOA for your compounds presents a major obstacle. The MOA must be defined early on.

Efficacy: Does the compound work in living systems? Even with the most innovative and convincing MOA for a novel therapy, the compounds have to demonstrate functional activity in cells or, better yet, in animal models of disease. A substantial amount of effort will be devoted to optimizing the chemical properties of the compounds to enhance bioavailability.

Safety: What is known about the toxicity? Are off-target effects already known? With a novel class of NP, it is unlikely that the literature will have useful data, so some measures of safety need to be made. Inherent toxicity is hard to fix.

Progress: What has been done to optimize the compound? Is there more than just one path forward? What are the critical structural features for activity, etc.? Multiple paths forward argue more favorably for success.

Production: How will the compound be manufactured? This is often the most obvious problem limiting the progression of a natural product–based lead. It also is a criticism that experienced synthetic chemists are well schooled in. Hand-waving away the synthetic/production challenges is a non-starter position. A feasible, cost effective approach (or well thought out concept) is essential.

It is fair to say that the more positive answers you have for these questions, the better your chances for success. Often the key to generating meaningful discussions with pharmaceutical companies is hitting a specific disease of current interest, so timing is always a factor. Also, any compound that seems to have first-in-class potential will get greater attention.

Forming a Platform Technology-Based Company

Is your new technology sufficiently revolutionary and promising to attract investment?

As natural products scientists we are often so enamored of our field, so it is easy to lose objectivity. This is particularly true when it comes to evaluation of a technology platform in which we have a substantial personal stake. In moving forward to launching a business based on this new technology platform, it is essential to step back and address the factors that will make this attractive to savvy investors.

Natural products (NP) have a rich history as a source for novel chemicals that have had a major impact, particularly

continued on page 9

continued from page 8

Another common notion that stifles NP-based drug discovery is that NP are inherently toxic and that this will be a barrier to drug development.

on human medicine. The antibiotics that were discovered in the era from 1940-1960 provided the financial foundation for large segments of the pharmaceutical industry. These discoveries represent an explosion of productivity in new pharmaceutical products that has never been equaled. History tells us that this level of productivity was unsustainable, and Pharma abandoned antibiotics discovery and the associated microbial NP programs. One can argue how unwise or shortsighted this strategy was, but nevertheless the fact remains: Big Pharma abandoned natural products-based drug discovery – it was a business decision. So any new venture into NP-based discovery must justify how the new platform will overcome the perceived limitations.

The oft-cited limitations to businesses based upon the discovery and commercialization of NPs are quite well entrenched, particularly in the pharmaceutical industry. Some of the major concerns that are raised regarding natural products-based R &D are as follows:

Difficulty in accessing novel chemistry
(aka old compound Re-discovery Problem)
Compound supply, from gram-scale to commercial production
Overcoming the inherent poor properties of NPs
(toxicity, solubility, stability, etc.)
NP-based drug discovery is too random
(Fishing)

The above concerns make the case for the new technology platform. In crafting a pitch aimed at securing investment or SBIR funding, etc., it is critical to address at least some of these issues. How does the new platform overcome these hurdles? Why is the technology compelling, and how does it elevate the science behind natural products R & D? How does this new platform make NP-based drug discovery more rational? What practical evidence is there to support these claims? These are obvious and extremely critical questions. As clever and innovative as the new technology may be, investors will need to understand how they will profit from their support. This is an especially difficult challenge for a platform technology company at very early stages. In the following paragraphs we briefly examine the key issues and provide some thoughts about attracting investment in a new venture.

Pharma based its exit decision upon the notion that all the significant NP had been discovered and all that remained were "diminishing returns." This decision was in part data-driven: the rate of rediscovery, particularly of antibiotics, was problematic, resulting in too much time and effort for dereplication and very few new NPs. However, over the last decade genomics have shown that even our most exhaustively studied industrial microorganisms, such as various *Streptomyces* species, harbor biosynthetic clusters whose products have yet to be seen. Given our increasing appreciation for the fundamental role that microbes play in the production of NPs, this surprising finding is helpful in justifying the return to exploration of NP, particularly from microorganisms. Whether the new platform is an approach that enables expression of such cryptic gene clusters or another technique that generates novel products by other means, the next significant hurdle is compound supply.

At the discovery stage, only relatively small amounts of compound are needed to move into pre-clinical work (tens of grams), but a realistic path toward large-scale production must be feasible. Historically, his issue has derailed incipient technology companies because, as exciting as the new concept may be, investors will be reluctant to spend money without a path for commercialization. This makes sense. The question is likely to be how much evidence is needed to convince investors that your production methods are feasible.

Another common notion that stifles NP-based drug discovery is that NP are inherently toxic and that this will be a barrier to drug development. This notion is intriguing. Why are NP thought to be intrinsically more toxic than synthetic compounds? This belief may be derived from the success-

As clever and innovative as the new technology may be, investors will need to understand how they will profit from their support.

continued on page 10

continued from page 9

As scientists we are used to justifying our hypotheses and supporting conclusions with critical data – but this is different. This is marketing. Selling your concept to non-experts (or non-scientists) requires a separate skill set.

es in developing "cytotoxic" anticancer drugs. Also, possibly because NP are fully elaborated by nature and then must be modified to overcome some toxicity, while synthetic compounds are built stepwise with opportunities to eliminate toxic effects along the way. In any case, there is some bias regarding the toxicity of NP that may require attention in a pitch to investors.

Despite the fact that most synthetic drug discovery efforts begin with the random screening of millions of small molecules, which are then further elaborated into leads, NP-based drug discovery is negatively portrayed as "fishing" because we don't know what the target compounds look like. Because of this, it is desirable to be able to characterize a technology more in the vein of "hunting" for drugs, rather than fishing for them. An obvious example would be targeting a particular structural feature known to be important for biological activity, such as the enediyne chromophore or beta-lactams, etc.

Having addressed the aforementioned issues to whatever extent is possible at this early stage of launching a business, how well can you sell the concept? As scientists we are used to justifying our hypotheses and supporting conclusions with critical data – but this is different. This is marketing. Selling your concept to non-experts (or non-scientists) requires a separate skill set. Effectively communicating just how revolutionary your technology is requires thoughtful presentation in readily understandable terms that clearly shows the advantages. Consider giving your platform a cool (memorable) name that reinforces your message.

At the end of the day there is no better argument than having strong data in support of your novel concept. Of course this takes time to generate, so you have to target what you believe are the critical data sets needed. By carefully defining and achieving these deliverables you will be better prepared to pitch your concept to savvy investors.

What Happens Next?

Surviving the Development of a Biotech Company

As time passes, the goals and targets of your company may drastically change. Rather than continuing with a platform-based drug discovery effort, for example, the company may choose to abandon discovery and work toward the development of one or more new drugs. New medical staff will need to be hired and a new focus of preclinical drug development and moving toward a "New Drug Application" (NDA) for your compound(s) can occur. This is generally a very positive event, but also one that requires additional financial support and, typically, the reorganization of the company.

Support for development from the company's BOD is critical during this activity, as additional funding will likely be needed for early human clinical trials (Phase 1). At this point, the role of the founder is likely to be minimal, as discovery processes may no longer be a part of the company.

The Ultimate Fate of a Biotech Company

In its inception, the company will have had a long-term goal, which can vary depending on numerous factors. In some cases, company CEOs have the long-term goal of establishing a full-fledged small or medium-sized pharmaceutical company. While notable, this goal is only infrequently achieved. More typically, a successful company with promising drugs in development will be acquired by larger pharmaceutical companies that specialize in the company's therapeutic successes. This is likely to be a win-win for all involved but is especially lucrative for the CEO, other high level staff, and the investors. How the founder fares in this scenario is less clear. Presumably, the founder's university negotiated royalty and milestone payments that will be shared with inventors. Also, if the founder has been awarded significant stock or stock options, there can be significant financial rewards. However, there are other scenarios in which the founder is poorly rewarded, if rewarded at all. Business is business and founders need to enter into business relations being fully informed. Founders would be well advised to seek legal representation at the time the company is established. ■

At the end of the day there is no better argument than having strong data in support of your novel concept.

Contributing to the Nation's Wellness through a Career in Government

By Dr. Joseph Betz

I began my academic career with the intent of becoming a field biologist. My undergraduate degree in biology led to an MS in marine and environmental science. During the course of study for my Master's degree I became interested in the chemistry of marine toxins, which led me to a PhD program in pharmacognosy. As is usual for that degree, my coursework included chemistry, nutrition, pharmacology, toxicology, and botany. My doctoral research was to seek antimicrobial compounds from marine organisms. I worked on a jellyfish with modest activity but only managed to rediscover some nucleoside analogs. During a period of relative inactivity due to seasonal unavailability of the jellyfish, I worked on a side project to authenticate ginseng products. This project developed into a major ginseng quality initiative in which I developed methods for distinguishing between authentic *Panax* species as well as species falsely sold as ginseng. This work affected the US ginseng industry by decreasing fraud in the marketplace.

When I entered the doctoral program, I fully expected to take an academic or industrial position doing drug discovery work. That changed my last year in graduate school when a carload of graduate students took a road trip to Pittcon. There I ran into a chemist from the Division of Natural Products at FDA's Center for Food Safety and Applied Nutrition (CFSAN). He was at Pittcon to recruit a natural products person to fill a staff fellow (postdoc) position in cancer chemopreventive agents in *Brassica* vegetables. He provided a card, and I contacted him when I got back to the lab. Much to my surprise, I got a letter inviting me to apply for the job and to give a seminar on my ginseng work. They were not at all interested in the jellyfish work. The prospect of working in DC only a block from the Capitol was pretty exciting, so I accepted the position.

This project developed into a major ginseng quality initiative in which I developed methods for distinguishing between authentic *Panax* species as well as species falsely sold as ginseng.

I worked on broccoli chemistry for about two years but was diverted from that project when I became part of an emergency response team tasked with identifying the causal agent of an epidemic of L-tryptophan supplement associated eosinophilia-myalgia syndrome. By the time this work was completed, Dr. Paul Talalay had published his sulforaphane work, so my research focus changed to development of analytical methods for natural toxins. I was converted from staff fellow to full-time research chemist and worked on methods for agaritine in mushrooms, pyrrolizidine alkaloids in comfrey, ergot alkaloids in grain, and glycoalkaloids in potatoes.

During the lead up to the passage of the Dietary Supplement Health and Education Act (DSHEA), the FDA commissioner assigned to me the task of developing methods and analyzing for hazardous natural compounds in marketed supplement products. These included lobeline in *Lobelia* and yohimbine in yohimbe products. A few years later, I was part of a team that identified the source of the illness caused by a multi-herb supplement. The labeled ingredients were not consistent with symptoms, but the team did some chemical and physical detective work to discover that foxglove (*Digitalis* spp.) had been substituted for *Plantago* spp. in the product.

Following serious adverse events associated with *Ephedra* supplements, I became part of another team that developed analytical methods and performed analyses for enforcement actions on ephedrine containing products. If the reader is detecting a pattern, it is that we research chemists were responsible for mission relevant research projects that came with hard money, but were expected to drop the projects and work on public health emergencies when they arose. During the ephedra crisis I was a principal investigator on the National Cancer Institute's Designer Foods Program, where I directed good laboratory practice chemistry support for nutritionists investigating safety of target foods. I also directed FDA's Natural Toxicants in Food Plants Program. Once DSHEA was enacted, the plant toxins program expanded to include development of analytical methods for bioactive substances in dietary supplements.

In addition to laboratory work, I participated in rulemaking processes by responding to public comments on proposed dietary supplement regulations and by sitting on the first FDA committee developing dietary supplement GMP regulations. In response to a number of high-profile outbreaks of foodborne illness, FDA shifted agency priorities from hazardous natural chemicals in food (including dietary supplements) to microbial foodborne illness. De-emphasis on pharmacognosy

continued on page 12

continued from page 11

and emphasis on microbiology influenced my decision to seek another career path.

In 1999, I accepted a position as vice president for scientific affairs at a trade association, the American Herbal Products Association (AHPA). There I became familiar with the inner workings of the dietary supplement industry. While at AHPA, I led the industry in areas related to science and public health. I worked with industry to help FDA craft regulation of herbs such as *Ephedra* and *Aristolochia*. Following the anthrax attacks in 2001, I provided the scientific leadership that led AHPA and other trade associations to condemn opportunistic sales of "herbal anthrax cures." As the liaison to a number of AHPA technical committees, I educated the membership on interpretation of clinical and non-clinical research on herbs and also provided information regarding the nature of reliable analytical methods and the need for authentic reference materials.

FOXGLOVE

...the team did some chemical and physical detective work to discover that foxglove (*Digitalis* spp.) had been substituted for *Plantago* spp. in the product.

In 2001 I met the director of the NIH Office of Dietary Supplements (ODS) at a conference. He let me know that he was recruiting a director for a new ODS Analytical Methods and Reference Materials Program (AMRM). I told him that I was interested and shortly thereafter joined NIH. This change posed a challenge because it involved the creation and direction of a congressionally mandated program where none had previously existed and that was uniquely non-NIH like in its goals. From the outset, I was required to formulate and direct the strategic planning and tactical execution of the program.

The work of the AMRM involved the development and implementation of a number of initiatives. My duties were to foster research into development, validation, and dissemination of analytical methods and reference materials for dietary supplements by planning, organizing, developing, and providing oversight in these areas. I was also charged with developing and implementing strategies to publicize and disseminate the methods and materials via appropriate outlets. I maintain my scientific competence by participating in and lecturing at conferences and universities, remaining active in relevant scientific societies, writing and publishing in peer reviewed literature, and acting as an active liaison with national and international governmental and non-governmental organizations that make science-based public health and regulatory decisions.

I found my years as AMRM director stimulating and enjoyable. In June 2018, I agreed to serve as acting director of ODS. I soon realized that leading ODS could be a challenge similar to the one I accepted when I became AMRM director, but on a larger scale. I have come to appreciate the diversity of the work of ODS and the oversized impact on public health that this small office can make. I have designed curricula, taught, and worked as researcher and administrator in government, academia, and the private sector. After almost 30 years in the public sector, I believe that I made the right career choice and continue to make a positive contribution to the nation's wellness by assuring that the health effects of dietary supplements are evaluated rigorously, and the results widely disseminated to practitioners and the public. ■

After almost 30 years in the public sector, I believe that I made the right career choice and continue to make a positive contribution to the nation's wellness by assuring that the health effects of dietary supplements are evaluated rigorously, and the results widely disseminated to practitioners and the public.

ASP Can Help in Your Job Search

By Dr. Lou Barrows

The ASP Jobs Service maintains a page on the Society website (www.pharmacognosy.us/jobs/) that advertises employment and training opportunities in a wide range of fields related to natural product discovery, development and industry. From postdoc positions to government directorships, from medicinals to big pharma, from biosynthesis to mass spectrometry, you can find training and employment openings posted there.

The "Jobs" webpage is one of the most visited pages on the ASP website, and this year there has been a record number of opportunities posted reflecting the dynamic growth in this sector of the economy. To post a job, visit the ASP homepage and go to the "Resources" tab. Click the "Post a Job" link, fill in the form and submit it. ASP Jobs Service committee members track the site almost daily and will post your advert promptly.

To view employment opportunities, also included under the "Resources" tab of the ASP homepage, click the "Employment Opportunities" link and scroll through the (often) several pages of opportunities. The jobs are posted as they are received, the most recently submitted appearing at the top of the list.

If you are looking to advertise an open position in your lab, university or business, or if you are just curious about opportunities available, take advantage of this free service to connect with the ASP community. ■

The ASP International Relationships Committee

By Dr. Nam-Cheol Kim

The ASP International Relationships Committee was initiated in early 2018 to help facilitate collaboration with international societies, businesses, governments and other stakeholders. In recent years, ASP's activities involving members and natural products societies in other countries have increased. Therefore it became necessary to organize an ASP committee to assist these activities by individual members and other committees. The aim of this committee is to determine and help with issues involving ASP's relationship with members, international societies, and/or groups on natural products research/business. As global commerce and research collaboration increase, smooth collaboration with international bodies becomes an integral part.

The objectives proposed for the International Relationships Committee are as follows:

- To promote ASP's activities to international societies dedicated to biodiversity and natural products
- To promote membership internationally

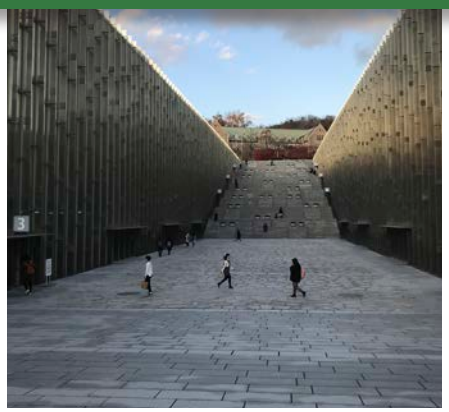
The committee is comprised of an international group of ASP members as they understand and interact better with particular regions around the world.

The committee discussed and suggested the following action items:

- Engage international members and non-members to be involved in ASP's activities
- Find the strengths and weaknesses of ASP's interactions with international colleagues and determine international opportunities
- Facilitate joint meetings with international societies
- Engage with international younger members

continued on page 14

Asian Pharmacognosy Societies Gather in Seoul


KSP President and ASP member Professor Eun-Kyoung (Yuny) Seo from Ewha Womans University (left). The conference was held at Ewha Womans University ultramodern Campus Complex (center). ASP member Dr. Dong-Chan Oh from Seoul National University presents (right).

By Dr. Edward Kennelly

The 49th Annual Meeting and Symposium of the Korean Society of Pharmacognosy in conjunction with the Korean Society of Pharmacognosy–Japanese Society of Pharmacognosy–Chinese Society of Pharmacognosy Joint Symposium took place at Ewha Womans University in Seoul, Korea on November 22-23, 2018. ASP member Dr. Yuny Seo, president of KSP, welcomed participants, along with representatives from JSP and CSP.

Speakers from South Korea, Japan, China, and the United States participated in this dynamic international conference. JSP President Professor Ikuro Abe from The University of Tokyo spoke about advances in synthetic biology. ASP former president Dr. Edward Kennelly was one of the keynote speakers and talked about metabolomics approaches to the study of medicinal plants. A number of other ASP members, mostly based in Korea, also gave presentations.

This is the 10th KSP-JSP-CSP Joint Symposium, which occurs every two years. KSP, meanwhile, will participate for the first time in the 12th ICNPR meeting. Representatives from ASP, KSP, and JSP met to discuss logistics for this meeting, which will be held in San Francisco July 25-30, 2020.

The ASP International Relationships Committee

continued from page 13

- Promote women in science, following UNESCO initiatives
- Establish regional focal points
- Encourage the incorporation of values of inclusiveness, collaboration, and social and intellectual diversity within ASP
- Pursue travel funding grants for ASP members in low- and middle-income countries
- Select the best annual paper in the *Journal of Natural Products* presented by an international author(s)
- Develop a functional international academic website with meaningful access to its members, to provide information on international work opportunities, exchange programs, participation in international rotations and fellowships, as well as courses and training

The committee will evaluate and prioritize tasks for short and long term goals and will discuss these goals with other committees, including the ASP's Executive Committee. As the IRC committee just initiated its tasks, any suggestions and feedback from EC and ASP members are welcome. ■

The Natural Products Atlas: A New Data Resource for the Natural Products Community

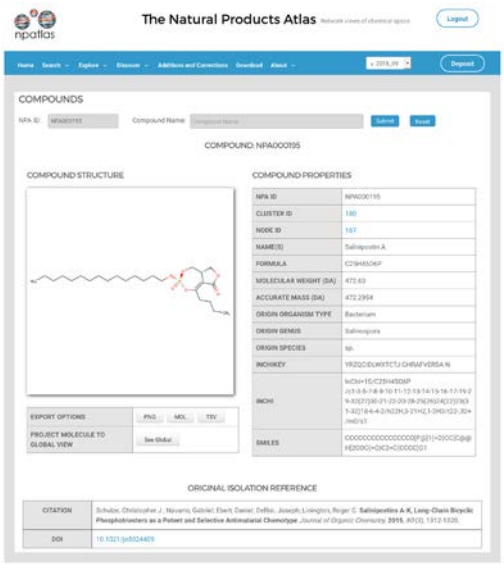
By Dr. Roger Linington

Natural products science is rapidly embracing new technologies for natural products discovery, from genomics to untargeted metabolomics. Yet surprisingly, there exists no public, comprehensive, open access database of microbial natural products. This is important for two reasons: firstly, absence of a central repository of chemical structures hampers efforts to relate results from different characterization platforms (e.g. biosynthetic gene clusters from MIBiG and MS spectra from GNPS); secondly, predictive tools in NMR, MS or genomics are restricted in their ability to identify known and unknown compounds without a clear picture of what has already been discovered.

At the ASP annual meeting in Kentucky this summer, the Linington group from Simon Fraser University in Canada presented a new collaborative effort to fill this gap through the development of a comprehensive, fully referenced database of microbial natural products, termed the Natural Products Atlas (www.npatlas.org). This effort has developed new computational tools to review the historical literature to identify papers describing novel natural products. A large group of volunteer curators has reviewed these manuscripts to ensure that the relevant data have been extracted, and the resulting entries have been inserted into a structured database format. The names of all curators can be found here: www.npatlas.org/joomla/index.php/about.

The NP Atlas contains three main sections: Search, Explore and Discover. The Search section provides tools to search the dataset by name, formula, structure, substructure or other parameters. These results are exportable and can be interrogated from a range of different perspectives using the Explore and Discover sections. The Explore section contains different viewpoints on natural products chemical diversity, from single natural products (compounds) to groups of closely related structures (clusters) to more distantly related groups of compounds (nodes) to a full view of the relationship between all nodes (global). These different viewpoints allow the user to examine how a given compound or group of compounds relates to previously discovered natural products in order to place new discoveries in the context of previous work. Finally, the Discover section provides a growing set of dashboards that present alternative viewpoints on natural products discovery. For example, the Author dashboard connects to the ORCID author database to retrieve all of the articles published by a given author and displays a set of graphs and graphics that summarize this chemical diversity in terms of publication venue, timeline of discovery, etc.

The NP Atlas contains three main sections: Search, Explore and Discover. The Search section provides tools to search the dataset by name, formula, structure, substructure or other parameters.



The NP Atlas is designed to encourage and facilitate community data deposition and curation. There are pages on the website to deposit articles that are not yet included or to notify us of corrections or omissions in the current dataset. Currently the Atlas contains 20,000 compounds, with a further 10,000 entries being curated. To be of highest value we need the participation of the natural products community to help find and insert the remaining missing compounds. ASP members can contribute to this effort by searching the Atlas for their own compounds and depositing any missing articles (www.npatlas.org/joomla/index.php/deposit). Members who support the principles of open data can also volunteer as curators (volunteer@npatlas.org).

Future extensions include incorporating compounds from the patent literature, extending the range of physicochemical data reported, and exploring options to extend the resource to source organisms beyond microorganisms. For now, we invite you to dive in and explore the wonderful and diverse world of microbial natural products chemistry. Happy searching! ■

Natural products science is rapidly embracing new technologies for natural products discovery, from genomics to untargeted metabolomics. Yet surprisingly, there exists no public, comprehensive, open access database of microbial natural products.

NCI Launches Program to Reinvigorate Natural Products-based Research

By Drs. Tanja Grkovic, Christopher C. Thornburg, John R. Britt and Barry R. O'Keefe

Natural products (NP) are an attractive starting point for drug discovery with a proven track record in use as anti-cancer and anti-infective agents. As of 2014 NP, NP pharmacophores, and NP mimics, such as modified nucleosides and peptides, represented more than 50% of small molecule-based anti-cancer and antimicrobial drugs.[1] Moreover, NP have been shown to be an unparalleled source of chemical diversity, novelty, and structural complexity that can be used to identify new chemical scaffolds with which to study the interactions between small molecules and their targets. However, accessing the potential of NPs in high-throughput screening (HTS) campaigns has been challenging due to the complexity of the crude NP extracts and the time necessary for follow-up isolation efforts. These challenges have been further exacerbated by the fact that many large pharmaceutical companies have reduced their research and development budgets in infectious disease due to perceived deficiencies in potential profitability. These unfortunate realities have resulted in NP-based libraries being significantly underrepresented in most recent large-scale HTS programs, despite their successful track record.[2]

The NCI Program for Natural Products Discovery (NPNPD) is a newly launched, priority NCI program that aims to reinvigorate NP-based research. The NCI has outstanding expertise and unique resources in NP, including the NCI Natural Product Extract Repository, a collection of more than 230,000 diverse crude NP extracts derived from plants, marine organisms and microbes. The repository is a unique, well-annotated, library of chemical diversity that can be used for the discovery of new bioactive compounds with the potential to be developed for clinical utility. One recent example is the antiviral lectin, griffithsin, which is currently being evaluated in first-in-human clinical trials as a microbicide for the prevention of HIV transmission.[3] Despite this and other success stories, in its original form, the NCI NP repository could only offer crude extracts that represent mixtures of up to hundreds of small molecules, are difficult to assess in HTS, and are challenging to isolate and characterize. To address the current impediments to research into bioactive NP, the NPNPD plans to chromatographically pre-fractionate over 140,000 crude extracts by polarity and, in an automated manner, generate a library of over one million partially-purified fractions suitable for modern HTS technologies. In addition, the NPNPD has developed integrated analytical resources for the rapid isolation and structure elucidation of biologically active NP. The NPNPD pre-fractionated library will be publicly accessible in 384-well plates, free of charge (recipients pay only the cost of shipping), and open to screening against any disease target starting in January 2019.

Figure 1: Tecan Freedom Evo 200 – customized to perform positive pressure SPE-based fractionation of the crude extracts. The methodology is fully automated and capable of processing 88 extracts in a single run to generate 616 fractions in under three hours. The fractions are dried, weighed and then plated on 384-well plates suitable for biological testing.

Part of the effort to re-establish integrated NP screening is the development of new technologies and methods for the facile production of fractionated NP libraries, the efficient isolation, dereplication and structure elucidation of active principles, and the user-friendly aggregation, visualization and interrogation of the resulting data sets that include geographic, taxonomic, biological, chemical and target annotation. Towards that end, the NPNPD is developing infrastructure, both hardware and software, to increase the utility of NP-based libraries in HTS as follows:

- Automated chromatographic prefractionation of crude NP extracts (Figure 1). The developed procedure uses a two-component positive pressure solid-phase extraction to separate the crude extract into seven fractions of decreasing polarity. The system was created by modifying current liquid-handling robotic technology to enable the pre-fractionation of 88 extracts simultaneously using parallel pro-

continued on page 17

NP have been shown to be an unparalleled source of chemical diversity, novelty, and structural complexity that can be used to identify new chemical scaffolds with which to study the interactions between small molecules and their targets.

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The NCI Program for Natural Products Discovery (NPNPD) is a newly launched, priority NCI program that aims to reinvigorate NP-based research.

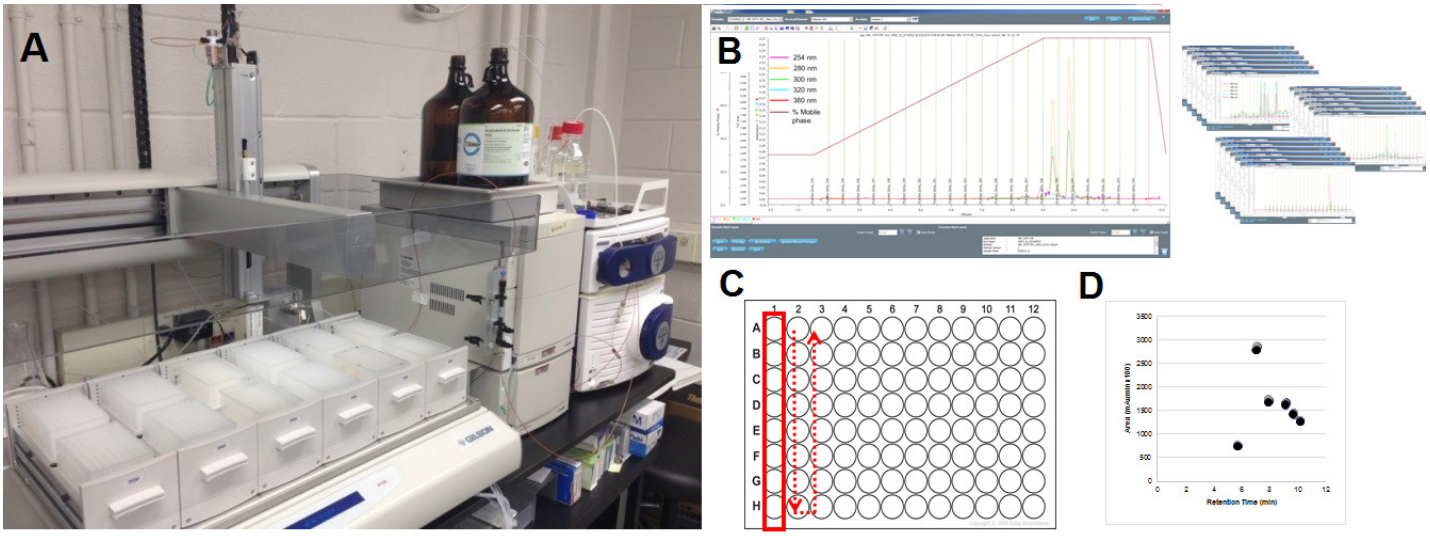


Figure 2: Second stage rapid compound isolation. A) Gilson LC-MS instrument equipped with a GX-281 liquid handler, 322 HPLC pumps, 172 diode array detector and a Verity 1900 mass spectrometer. B) Examples of HPLC spectra. C) 96-well plate fraction collection layout, where column 1 is kept empty for assay controls and 22 subfractions are collected for each HPLC run. In the developed workflow, a single instrument is capable of fractionating 44 samples to produce 968 fractions in a single run. D) Quality control spectra where chromatography standards are run every nine HPLC injections and monitored for changes in the retention time of the analytes.

cessing. The resulting library is the largest, most diverse, publicly available source of chemical diversity from natural sources. A recent publication by Thornburg et al. 2018 reports full details of the procedure and assesses the quality and chemical diversity of the resulting fractions.[4] All bulk fractions created will be stored in 10ml, 2D-barcoded tubes in a large automated repository that will allow for rapid access to active fractions for further study.

- In addition to the bulk fractions, the NPNPD has undertaken the automated plating of fractions in 384-well plate-based format to enable subsequent screening. Each fraction is plated at ten micrograms of material per well in five microliters of DMSO. Each "set" of two 384-well plates contains samples of 88 crude extracts and each of the seven purified fractions from that set of crude extracts. The fractions (and crude extracts) are plated in quadrants (crude extract and fractions 1-3 on plate #1 and fractions 4-7 on plate #2) with the first two columns left empty for use as controls.

- Secondary HPLC-based fractionation of active primary fractions to enable efficient project prioritization and dereplication. The automated system will produce 22 subfractions from each identified active fraction using a NPNPD-developed process that will enable secondary fractionation of up to 500 samples in two weeks. From 500 "hit" fractions, approximately 11,000 subfractions will be produced, dried and shipped back to the screening center for follow-up screening. Initial chemical evaluation of the sub-fractions indicates that most of the subfractions are made up of

continued on page 18

To address the current impediments to research into bioactive NP, the NPNPD plans to chromatographically pre-fractionate over 140,000 crude extracts by polarity and, in an automated manner, generate a library of over one million partially-purified fractions suitable for modern HTS technologies.

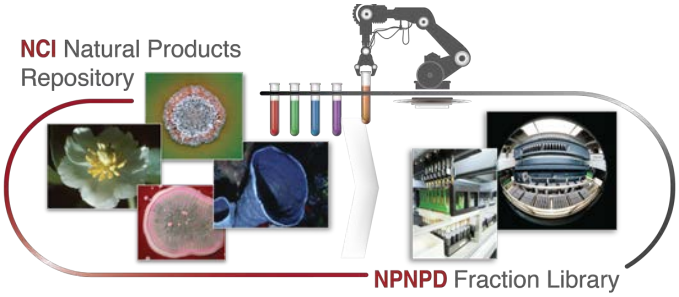
continued from page 17

predominantly a single chemical scaffold. This system will significantly reduce timelines for active compound isolation (Figure 2A-D) and subsequent structure elucidation studies.

- After subfractionation and receipt of an active subfraction "hit list," the NPNPD has integrated high resolution analytical chemistry capabilities including UV, IR, and NMR spectroscopy, as well as mass spectrometry that can quickly determine the chemical scaffold likely responsible for the discovered biological activity in approximately 70% of the subfractions. This chemical annotation of active samples will enable better informed decisions about which samples merit further chemical and biological evaluation and will increase overall knowledge of active NP-based pharmacophores.
- The NPNPD is also actively engaged in the creation of a bioinformatics platform capable of integrating collection location, source organism, biological activity, and chemical structure data into a single database enabling a multifaceted approach towards project prioritization. The NP extract samples are already annotated with taxonomic, photographic and geographic information including voucher specimen compilation at the Smithsonian Institution. Initial biological data aggregation and visualization strategies have centered on the use of self-organizing map technologies to enable pattern-matching of concentration-response data sets. Additional data handling techniques are being evaluated for the chemical annotation of fractions. The systems under development are aimed at capturing raw analytical data files (MS, NMR, etc.) and enabling the rapid evaluation of similarity of new data sets to those already housed in the database. This should empower more rapid project prioritization and compound identification. The quality of this database and bioinformatics tool kit will be dependent on the accurate annotation of assays performed using the fraction library to better inform continuing screening efforts by all users. The eventual goal is to make as much of the data as possible accessible to the public.

The overarching goal of the NPNPD is to implement these technologies and increase the scope and efficiency of NP drug discovery across all disease states throughout the world. The first 150,000 NP fractions will become available in January 2019, with additional fraction sets added to the screening set each consecutive year. The final expected total fractions to be produced is more than one million individual fractions.

The NCI considers the Natural Products Repository as a national treasure but also a working library. The samples housed in the NCI repository were obtained through agreement with "host countries" who allowed NCI-contracted collecting expeditions. Access to the NPNPD pre-fractionated library and parent crude extracts is subject to agreeing to and signing a Material Transfer Agreement protecting the rights of all parties, including the host countries in which source organisms were collected. For further information on how to receive a copy of the MTA to gain access to this resource contact Dr. Barry O'Keefe at the NCI Natural Products Branch [NCINatProdRep@mail.nih.gov]. ■



**This project has been funded in whole or in part with federal funds from the National Cancer Institute, National Institutes of Health, under contract HHSN261200800001E. The content of this publication does not necessarily reflect the views or policies of the Department of Health and Human Services, nor does mention of trade names, commercial products, or organizations imply endorsement by the U.S. Government.*

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Opinion: Appropriate Research Outcomes?

By Dr. James D. McChesney

There is a continuing discussion in the natural products research community regarding the quality of publications and impact factor of the journals. This debate is tending, in my judgment, to tip the balance unfairly against publication of investigations involving medicinal plant extracts/complex mixtures which do not include purification and characterization of "active" compounds or marker compounds. I feel this reflects an infatuation within the community with the tools of our trade – analytical methodology (HPLC and other separations technologies), various spectroscopic/spectrometric methods (high-field NMR technologies, various mass spectrometry technologies, etc.), coupled (or hyphenated) methodologies, etc., rather than recognition that these are *tools* useful to research and understanding of the role natural product compounds play in the grand scheme of nature. Currently there are thousands of new natural products compounds reported each year. They are usually identified as "active principals" by an arbitrarily selected *in vitro* assay which may have little or no real connection to how or why the selected plant, animal, or microorganism preparation is used traditionally.

Successful validation of the potential therapeutic activity of these traditionally used preparations can provide immense benefit to the health and well-being of the populace of these countries.

The exploratory work done in those programs examining natural product preparations used in traditional practices, especially those located in resource-poor countries (i.e., developing countries) which pursue validation of their biological activities, are certainly appropriate for publication. Successful validation of the potential therapeutic activity of these traditionally used preparations can provide immense benefit to the health and well-being of the populace of these countries. That the research is done with complex mixtures/crude extracts is also appropriate since that is usually the manner in which the materials are used traditionally. We need to pay close attention to the methodology of the experimentation. Is the biomass correctly authenticated? Is it collected at the appropriate time consistent with traditional practices and the correct plant part used? Are the methods of extract preparation consistent with traditional use or connected in some logical fashion to traditional use (not a chloroform extract when a decoction is the usual dosage form)? Is the preparation being evaluated for the appropriate indication? Is the biological assay consistent with the expected application and dosing appropriate (not the equivalent of grams per kg as is often the case in *in vitro* assays)? Are the statistics sufficient? Is the documentation of the work recorded in sufficient detail that subsequent work can build from it?

It is the quality of the science we need to maintain, not holding researchers to some arbitrary, largely analytical, chemistry-based requirements. I would point out the increasing evidence in support of the synergistic activities found in these complex mixtures and the increasing acceptance of the concept of botanical drugs/phytomedicines, even at the historically conservative FDA. Our usual single chemical entity approach being applied by the pharmaceutical industry is increasingly less productive as attested by the paucity of new drug approvals in recent years. Indeed the increasing prevalence of drug resistance to single chemical entity medications is more and more recognized, case in point antibiotic resistant infections. I think we all recognize that nature operates via complex signal transduction networks (the "new" systems biology), so why is it any surprise that the concept of a magic bullet (i.e., the "active principal" of natural product preparations) may be outmoded in the discovery of new leads for the development of pharmaceuticals, agrochemicals, and other useful materials?

The exploratory work being reported in these manuscripts on crude preparations holds great value, which may lead to new treatments for increasingly prevalent complex disorders for which current approaches are not yielding leads. Indeed, it is my expectation that complex mixtures derived from plants (botanical drugs) will be the next wave of new and effective therapeutics. Incidentally, that would represent a renaissance for our discipline of natural products research. We as researchers need only practice good science in the research methodology. Our supporters (the taxpaying public) have every right to expect a return for their continued support. ■

It is the quality of the science we need to maintain, not holding researchers to some arbitrary, largely analytical, chemistry-based requirements.

Slatkin Honorary Lecture: A Career That Bridged the Divide between Practice and Research

By Dr. Melany P. Puglisi

Chicago State University College of Pharmacy continued the tradition of honoring the memory of the late Emeritus Dean David Joseph Slatkin by hosting the 2018 Dr. David J. Slatkin Honorary Lecture on November 13, 2018 at the Gwendolyn Brooks Library. This event is held bi-annually to commemorate the many contributions of Dr. Slatkin to Chicago State University, the pharmacy profession and the American Society of Pharmacognosy. Dr. Slatkin, who served as treasurer of the ASP for 31 years and was a longtime honorary member of the ASP, passed away on November 16, 2015 after a long battle with Parkinson's disease.

Our speaker this year was Dr. Craig Hopp, deputy director of the Division of Extramural Research at the National Center for Complementary and Integrative Health (NCCIH) of NIH. Dr. Hopp received his BS in chemistry from James Madison University in 1993 and his PhD in pharmacognosy from Purdue University in 1997. He completed his postdoctoral fellowship at Shaman Pharmaceuticals. Subsequently, he worked for two years at an herbal company, Phyto-Technologies, where he was responsible for research and development on multiple herbal formulas used in traditional Chinese medicine.

Above from top: Dr. Craig Hopp; Interim Provost Dr. Leslie Roundtree provides opening remarks, along with ASP member Dr. Melany Puglisi.

Dr. Hopp delivered a lecture titled, "Herb-Drug Interactions: Separating Myth from Reality," to more than 125 faculty, students and staff from Chicago State University. In his talk, Dr. Hopp discussed critical issues in herb-drug interactions including the difference between pharmacodynamic and pharmacokinetic interactions between dietary supplements and prescription medication, the difference between statistical significance of an interaction and its clinical relevance, and the limitations of animal models in predicting herb-drug interactions. Attendees had the opportunity to speak with Dr. Hopp during lunch following the lecture.

As in previous years, the symposium brought together the college community, friends and colleagues of Dr. Slatkin to honor his memory. Interim Provost Dr. Leslie Roundtree provided opening remarks describing Dr. Slatkin as a mover and a shaker at Chicago State University with an extraordinary vision to bring a college of pharmacy to the university. Dr. Hopp shared stories of his interactions with Dr. Slatkin at the ASP early in his career. There continue to be very few academicians that have made as great an impact on their field of expertise as Dr. Slatkin has in pharmacy education. ■

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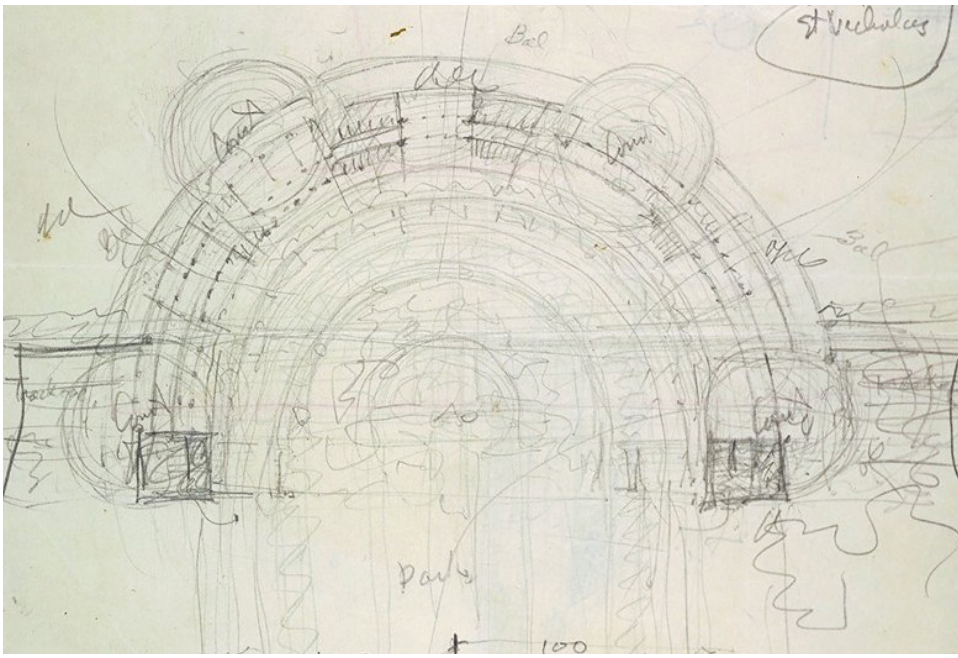
ASP 60th Anniversary: Innovations in Natural Products Chemistry

By Drs. Melany P. Puglisi and Tim Bugni

On behalf of the organizing committee we invite you to Madison, Wisconsin! 2019 marks the 60th Anniversary of the American Society of Pharmacognosy. Rooms have been reserved at the Madison Concourse Hotel located in the center of Madison within steps of the Wisconsin State Capitol and a short walk to the Monona Terrace on Lake Monona.

The Monona Terrace is an architectural icon located in the heart of Madison. From the website www.mononaterrace.com: "Frank Lloyd Wright originally proposed a design for a 'dream civic center' in 1938. His architectural vision for the City of Madison – a curvilinear gathering place that would link the shore of Lake Monona to the State Capitol – has now been realized. With interiors redesigned by Taliesin architect Tony Puttnam, Monona Terrace spans ninety feet out over shimmering waters, incorporating thoroughly modern technology and amenities with the architect´s signature organic design."



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Some highlights from the upcoming meeting in 2019 include special symposia. On Sunday, the American Chemical Society will sponsor a symposium for the "Heroes" of the *Journal of Natural Products* organized by Professor A. Douglas Kinghorn. The session will celebrate the careers of Drs. Gordon Cragg, David Kingston, Rachel Mata and David Newman and their contributions to the *Journal of Natural Products*. Professor Nadja Cech, winner of the Jack L. Beal Award in 2011, will moderate this session.

On Monday, the National Institutes of Health National Center for Complementary and Integrative Health will sponsor a session featuring the interactions between dietary natural products and the microbiome, a timely topic and new area for dietary supplement research. Speakers will include: Dr. Annadora Bruce-Keller, from the Louisiana State University Biomedical Research Center; Dr. Diana Roopchand, Rutgers University; Dr. Michael Snyder, Stanford University; Dr. Jan Stevens, Oregon State University; and Dr. Hang Xiao, University of Massachusetts at Amherst.

On Tuesday, the ASP Foundation will sponsor a young members' symposium in memory of ASP long-time treasurer Emeritus Dean David Slatkin. Participants in this session will be chosen from the abstracts submitted by graduate students and postdocs. Each speaker will receive an award of $200 to be applied to their registration. The session will be moderated by Dr. Skylar Carlson from the Smithsonian Marine Station at Fort Pierce.

POSTER COMPETITION

The 2019 Poster Competition is open to all students and postdocs presenting posters at the annual meeting. Interested attendees need to indicate that they will enter the competition by checking the correct box when submitting their abstracts. Posters in pdf format must be submitted via the link provided on the meeting website by midnight on **June 13, 2019** for preliminary judging. Fifteen (15) finalists will be contacted prior to the conference opening. Final judging by members of the editorial board of the *Journal of Natural Products* will be held at the posters during the poster sessions. Three prizes will be awarded for the best posters during the banquet. More information will be available on the website in the upcoming months.

TRAVEL INFORMATION

Two hotel venues have been reserved for attendees – the Madison Concourse Hotel located on the square in downtown Madison (www.concoursehotel.com) and the Hilton adjacent

continued on page 22

continued from page 21

to the Monona Terrace (www3.hilton.com/en/hotels/wisconsin/hilton-madison-monona-terrace-MSNMHHF/index.html). The hotels are located five miles from Dane County Regional Airport. Attendees can also fly into the General Mitchell International Airport in Milwaukee, WI or O'Hare Airport in Chicago, IL. Shuttle service to Madison can be arranged from both airports.

SPEAKER SPOTLIGHT

Laura Sanchez

Dr. Sanchez, assistant professor of medicinal chemistry and pharmacognosy at the University of Illinois at Chicago, will deliver an invited talk titled, "Imaging Mass Spectrometry Reveals Crosstalk between Microbes and Cells." Dr. Sanchez attended Whitman College in Walla Walla, WA where she obtained a Bachelor of Arts degree in chemistry (2007). She completed her PhD in chemistry at the University of California, Santa Cruz with Prof. Roger Linington as an NSF graduate research fellow. In the fall of 2012, she joined Prof. Pieter Dorrestein's lab at UC San Diego as an NIH IRACDA Fellow. Her postdoctoral research focused on establishing methods for probing and characterizing metabolic exchanges in polymicrobial communities, specifically those associated with cheese rinds. Since 2015, she has been at UIC and her NIH and NSF funded research program utilizes a variety of mass spectrometry techniques to probe how cells and microbes use chemistry to coordinate activities in a variety of biological systems.

Dr. Laura Sanchez

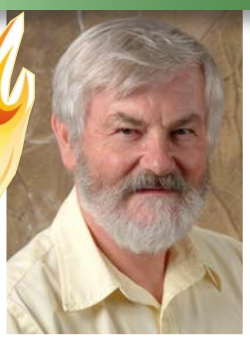
Helen Blackwell

Dr. Blackwell, professor of chemistry at the University of Wisconsin at Madison, will deliver a lecture titled, "Chemical Tools to Intercept and Interrogate Bacterial Communication Pathways." She is a native of Cleveland, OH and attended Oberlin College in Ohio for her undergraduate studies. Dr. Blackwell pursued her graduate studies in organic chemistry at the California Institute of Technology (PhD 1999 with Dr. Bob Grubbs, *Nobel Prize 2005*), and performed postdoctoral research in chemical biology at Harvard University (Jane Coffin Childs Postdoctoral Fellowship, 1999–2002, with Dr. Stuart Schreiber). She has been a faculty member at the University of Wisconsin–Madison since 2002, where she is currently full professor of chemistry. She leads a research program at the very interface of organic chemistry and bacteriology. Their broad goal is to understand the role of chemical signals in bacterial interactions and infectious disease. Over the past 15+ years, her research lab has developed a range of synthetic compounds that allow her to intercept a key cell-cell signaling pathway in bacteria called "quorum sensing." She is also a dedicated educator in the undergraduate chemistry mission of her department and leads both the Chemical Biology path to the PhD and the NIH Chemistry-Biology Interface training program on the UW-Madison campus.

Dr. Helen Blackwell

Dr. Blackwell and her research team have received numerous awards for their interdisciplinary research. She is the recipient of a Shaw Scientist Award (2004), a National Science Foundation CAREER Award (2005), a Research Corporation Cottrell Scholar Award (2005), a Burroughs Wellcome Fund Investigators in the Pathogenesis of Infectious Disease Award (2006), a DuPont Young Professor Award (2007), a Camille-Dreyfus Teacher-Scholar Award (2007), a 3M Non-Tenured Faculty Award (2007), and an American Chemical Society Arthur C. Cope Scholar Award (2010). She was also selected as an MIT Technology Review "Top 35 Innovator under the Age of 35 in the US" (2005), an Alfred P. Sloan Foundation Fellow (2006), one of Popular Science's "Brilliant 10" (2007), and a fellow of the American Association for the Advancement of Science (AAAS, 2010). Lastly, she held the Romnes Professorship at UW–Madison (2012–2018) and was awarded one of the first inaugural Wisconsin Alumni Research Foundation Innovation Awards (2013) for her patent on bioactive molecules that target quorum sensing in *S. aureus*. ■

Hot Topics in Pharmacognosy: Cannabinoid Receptor Drugs and Drug Candidates



By Dr. David Newman

Due to the massive amount of "information" (and I put this in quotes as the vast majority of it is not scientific studies with known compounds, but from "social and other media"), one would gain the impression that the various drug approval agencies in the West have been way behind in approving drugs based on cannabinoid receptor-directed drugs, and that one has to rely upon "grass growers" to help in this field.

As I will show below, there are a number of approved drug entities based upon the major components of *Cannabis sativa* that have either been approved by the FDA, the Canadian FDA or the EMA, plus a significant number of other variations, including some novel modifications of the basic pharmacophore, that are in clinical trials or advancing in preclinical studies. Yes, there are a number of others that are said to be in either phase I or preclinical trials, but other than code names, no information is available as to their "components" so I have not included them.

First some basic pharmacology. The endocannabinoid system is involved in many of the regulatory pathways in the body at the most basic levels. As quoted in the excellent recent review by Aizpurua-Olaizola et al.,[1] "The ECS includes two major G-protein-coupled receptors (GPCR): CB1, mainly expressed in brain structures, and CB2, whose expression is more limited to immune system cells. Recent studies revealed that the vanilloid type 1 receptor (TRPV1) and G-protein-coupled receptor 55 (GPR55) act as putative cannabinoid receptors (CRs) that are directly related to the ECS. The activation of CB1 and CB2 is mediated by two endogenous ligands, anandamide (AEA) and 2-arachidonoyl-glycerol (2-AG), which are considered to be the main endocannabinoids (ECs)."

The same authors also have a telling quote later in the paper which bears directly upon the choice of a particular "plant" as the drug of choice. "Another drawback to correlating a *Cannabis* variety with specific health effects is the lack of plant standardization. Even though some companies are dispensing standardized plants, most users of medical cannabis consume non-standardized plants. As an example, Elzinga et al.[2] observed that the cannabinoid and terpene content is highly variable for Californian medical strains, highlighting that the strain name cannot be used as indication of either potency or chemical composition."

COMPOUNDS THAT HAVE BEEN APPROVED AS DRUGS BASED UPON COMPONENTS OF CANNABIS

In 1985, the US FDA approved two compounds: in May, the Abbott drug Dronabinol (Marinol), which was totally synthetic THC (delta-9-tetrahydrocannabinol) (**1**); then, in December, the Lilly drug Nabilone **(2**), which can be thought of as the oxidized version of the current phase I compound (Dexanabinol, **10**) was also approved and was also totally synthetic.

In 2005, the UK company GW Pharmaceuticals had a defined mixture of *C. sativa* components approved in Canada. This defined mixture, named as Nabiximols (**4**), which is an NB in the lexicon of Newman and Cragg, is predominately THC and CBD cannabidiol (**3**). The latter compound, also from GW Pharmaceuticals, was approved as a single agent by the FDA in June 2018. In both cases, the source was the plant, but grown under highly controlled and reproducible conditions in the absence of any exogenous treatments. It is interesting that the correct structural identification

continued on page 24

...there are a number of approved drug entities based upon the major components of *Cannabis sativa* that have either been approved by the FDA, the Canadian FDA or the EMA, plus a significant number of other variations, including some novel modifications of the basic pharmacophore, that are in clinical trials or advancing in preclinical studies.

continued from page 23

was in a 1940 paper in *JACS* using Minnesota wild hemp by Adams et al.[3] though they reported that probably the earliest isolation and partial purification was in an 1896 paper in the *Journal of the Chemical Society*, that reported toxicity in that product.

Then in July 2016, the FDA approved a variation on dronabinol, a compound known as Syndros (**5**) where a hemi-succinate ester was attached in order to produce an orally effective variation on THC. The original idea came from the University of Mississippi where *Cannabis* plants have been grown under very strict conditions for the provision of cannabinoids to approved researchers in the USA for many years.

In June 2018, where the press lauded the "first cannabinoid to be approved by the FDA," though as one can see, the reporters obviously did not look back into the past, which implies a lot about the scientific knowledge/backgrounds of such reporters, when the GW Pharmaceuticals drug known as Epidiolex or Nabidiolex (**3**) which is CBD but isolated from *C. sativa*, was only 23 years behind dronabinol (THC).

CANNABINOIDS CURRENTLY IN CLINICAL OR ADVANCED PRECLINICAL TRIALS

As mentioned earlier, there are significant numbers of reports of such compounds but, except for the ones shown below, all are simply code names with no data available as to what they actually are.

At the Phase III level there is the following drug candidate, Lenabasum (**6**) or ajulemic acid, which is an orally available compound under Corbus Pharmaceuticals (originally JB Pharmaceuticals). In a recent paper, the ultrapure compound was found to have significantly reduced activity on the CB1 receptor versus CB2.[4] Thus it has significantly reduced adverse effects compared to earlier materials and is currently in trials for treatment of diffuse cutaneous systemic sclerosis. In addition, there is an investigator-initiated phase III trial at Yale, utilizing a fixed dose of dronabinol and palmitoylethanolamide for Tourette's syndrome under NCT03066193.

At the phase II level, the following compounds or defined mixtures of pure compounds are underway. GW Pharmaceuticals has cannabidivarin (**7**) for the treatment of epilepsy and in phase I development for the treatment of autism spectrum disorders. In addition, with no information as to levels available, MedChewRL (**8**) is a mixture of CBD and gabapentin currently in phase II for the treatment of restless legs syndrome as a medicated chewing gum by Axim Biotechnologies.

At the phase I level, there are a variety of fixed dose combinations of THC/CBD in clinical trials with one, TN-TC11G (**9**), being directed against glioblastoma in addition to temozolomide treatment under NCT03529448 in Spain. This study is entitled, "TN-TC11G (THC+CBD) Combination with Temozolomide and Radiotherapy in Patients with Newly-diagnosed Glioblastoma (GEINOCANN)."

The older drug, dexanabinol (**10**), which had been in a phase III trial in the US in the early 2000s having failed in patients with traumatic brain injury, is now in phase I trials in the EU against various cancers under the aegis of e-Therapeutics. Also at this level is an interesting variation on cannabigerol (**11**, VCE-004.8 aka EHP-101) that has a safety trial underway under NCT03745001, and, if not toxic, will then be scheduled of scleroderma trials.

In the preclinical arena there are more interesting variations on basic cannabinoid structures. The first is a prodrug of THC, NB-1111 (**12**) that is directed against nausea and potentially as an anti-glaucoma treatment. Evidently Albany Molecular is now providing the compound, but the original THC source may well have been from the University of Mississippi. The second, also a cannabigerol derivative[5], VCE-003.2 (**13**) is directed against Huntington's disease and has a recent Orphan Drug Designation from the FDA.

KLS-13019 (**14**) is a very interesting variation on CBD where medicinal chemists designed this molecule to increase hydrophilicity while optimizing neuroprotective potency against oxidative stress toxicity relevant to hepatic encephalopathy. Full details are given in two papers by Kinney et al.[6] and Brenneman et al.[7] which should be consulted for further details of this interesting molecule.

Finally, there are two variations by the company Medlab where they have filed INDs for NanaBis (**15**), a defined mixture of THC and CBD, and NanaBidal (**16**), a nanocelle delivery of CBD.

LEGAL AND OPERATIONAL AREAS

From a legal and operational viewpoint at the federal level, the two recent papers by Mead[8] and Thomas and Pollard[9] give the current details and make interesting reading.

IN CONCLUSION

Perhaps contrary to what "the lay press might think," there are both compounds from *C. sativa* and subtle modifications that have been approved for between 6 months and over 23 years, and currently there are significant numbers of variations upon the basic components of the cannabis plant in preclinical to phase III clinical trials. The comments alluded to earlier on the sheer numbers of compounds isolable from cannabis plants should make natural product chemists, pharmacognosists and pharmacologists sit back and think a little about the "unwanted effects" of such components upon human physiology. As far as can be determined, perhaps only two sources of cannabis plants and/or compounds (GW Pharmaceuticals and the University of Mississippi) are "controlled" from the aspect of herbicides/insecticides and taxonomic variation.

As far as I can tell, though people can challenge this comment, there are no published details of any effects of the plant's endogenous or exogenous microbial flora upon the "content," and it is now becoming evident that, in a number of medicinal plants, such flora can have an effect upon the chemical components of the plant itself. One is reminded of the instructions in TCM as to where, when and how one collects a medicinal plant! ■

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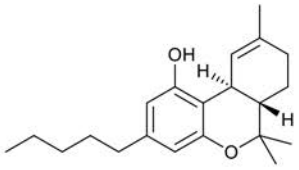
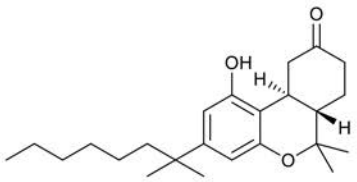
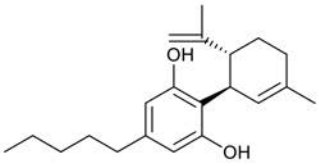
STRUCTURES



1, Dronabinol FDA 05/1985
Marinol; Abbott
delta-9-Tetrahydrocannabinol



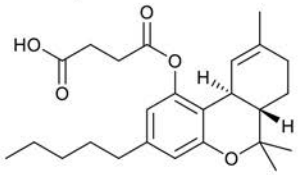
2. Nabilone, FDA 12/1985
Lilly



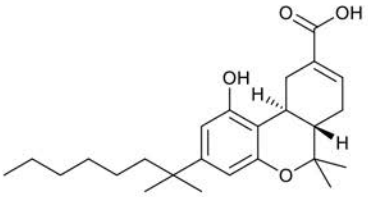
3. Cannabidiol FDA 2018
Epidiolex, Nabidiolex
GW Pharma

4. Nabiximols

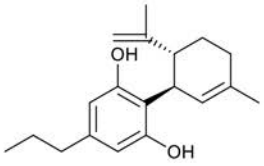
Defined extract of *C. sativa*
Mainly THC/CBD
GW Pharma, Canada 2005



5. Dronabinol Hemisuccinate FDA 2016
delta-9-Tetrahydrocannabinol ester
Syndros InCys Therapeutics



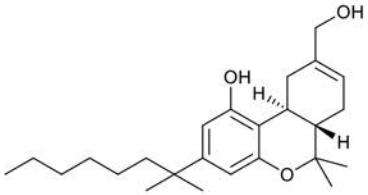
6. Lenabasum Phase III
Ajulemic acid
Corbus



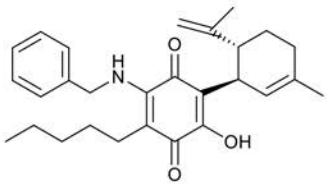
7. Cannabidivarin Phase II
GW Pharma

8. MedChew-RL; CBD/Gabapentin
Phase II

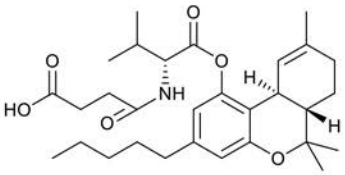
9. CBD/THC; TN-TC11G
Glioblastoma, Phase I



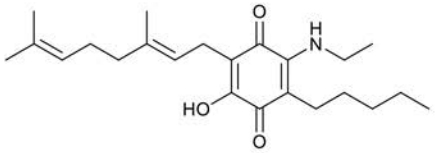
10. Dexanabinol
e-Therapeutics, Cancers
Phase I in EU



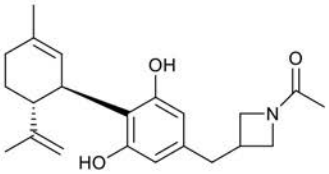
11. VCE-004.8 Phase I
Scleroderma



12. NB-1111 Preclinical
THC-valinate-hemisuccinate
Pro-drug of THC



13. VCE-003.2 Preclinical
Cannabigerol derivative
Huntington's Disease



14. KLS-13019
Liver/Bilary Tract. Preclinical

15. NanaBis
THC/CBD & Nanocelle Delivery
IND Filed

16. NanaBidal
CBD & nanocelle Delivery
IND Filed

continued on page 26

continued from page 25

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Behind the Scenes in Pharmacognosy: Computer-Assisted 3D Structure Elucidation of Natural Products

By Ms. Andrea Ague

In January 2018, the *Journal of Natural Products* published an article entitled, "Computer-Assisted 3D Structure Elucidation (CASE-3D) of Natural Products Combining Isotropic and Anisotropic NMR Parameters," authored by ASP member Dr. Armando Navarro-Vázquez and collaborators Drs. Roberto R. Gil and Kirill Blinov. Dr. Navarro-Vázquez is currently a professor of chemistry at the Universidade Federal de Pernambuco in Recife, Brazil. We thank Dr. Navarro-Vázquez for taking some of his time to share his work and insights with ASP members. Please read the full article in the *Journal of Natural Products,* **2018**, *81*, 203-210.

Dr. Navarro-Vazquez's group at the Universidade Federal de Pernambuco.

How did you become interested in developing new strategies to automate structure elucidation?

Nearly all my research in NMR-based structural elucidation has been oriented to the development of tools and methodologies to facilitate and make existing and new NMR experiments more accessible to synthetic and natural products chemists with structural elucidation problems. Particularly, while still working in the University of Santiago de Compostela, I became very interested in the application of NMR in aligned media (residual dipolar couplings) to structural elucidation. It has been fascinating that simultaneous development of new materials, pulse sequences, as well as computational methodologies and software, with contributions from different groups, has led the technique to a point that I began to think that automated 3D structural elucidation was indeed a reachable dream. It became possible with the help of these new techniques, either alone or combined with more conventional NMR analysis, such as J-couplings or NOEs. Luckily, I was not alone in the pursuit of this dream, which was also shared by Professor Roberto R. Gil at Carnegie Mellon University. He collaborated with me closely over the years, and the present CASE-3D work represents the distillation of many experimental and methodological contributions from our groups.

Could you provide a brief explanation of the work and results in your own words?

We provide here an automated methodology to solve relative configuration problems with a minimum of human intervention. Basically we select the simplest conformational model, in terms of number of conformations, which reproduces the observed NMR data, according to the estimated level of uncertainty. For configurational problems the selection is performed for all structural possibilities. The results, similar to the popular DP4 technique, can then be cast in terms of relative probabilities, a feature very much liked by organic and natural products chemists. Molecular modelling and NMR analysis steps are tightly integrated. Very importantly our methodology (CASE-3D) can make use of nearly all available spectral NMR information, both common observables, such as chemical shift or scalar couplings, and anisotropic parameters, such as the residual dipolar couplings. After successfully testing this CASE-3D method on molecules of known structure, such as artemisinin or homodimericin A, we applied it to the structural re-

continued on page 28

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continued from page 27

vision of the curcursones I and J. In some cases only a ^{13}C unassigned spectrum is needed to solve the structure!

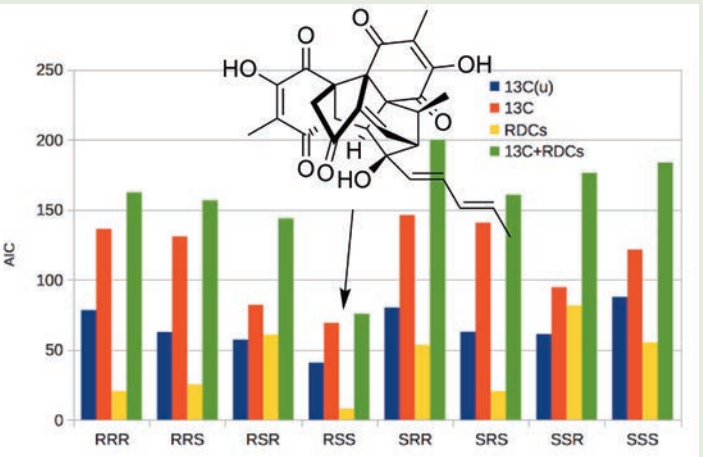
Who in your lab was involved with this research?
Initial work on the CASE-3D methodology, later published in *Angewandte Chemie*, was performed by my student Eduardo Troche-Pesqueira. However, the present work in *J. Nat. Prod.* is a direct collaboration between senior researchers. The experimental part was performed by Dr. Gil while I performed the computational analysis here in Pernambuco. Later, Dr. Blinov at Mestrelab Research Company helped us to combine our CASE-3D methodology with their "2D" CASE software.

Were there any new techniques or instrumentation that you learned to use specifically for this research?
This work was based on experimental technologies developed in the last few years by Dr. Gil's group, and the challenge was more on the side of the design of the algorithms.

What was the greatest challenge in developing this methodology?
Since for flexible molecules the presented methodology needs to evaluate a very large number of conformational models, perhaps the greatest problem was to develop a fast enough algorithm which could tackle complex problems. This was difficult since the analysis of residual dipolar couplings in conformationally flexible systems is a priori a non-linear problem. We were now able to find a solution enlarging very much the scope of the technique.

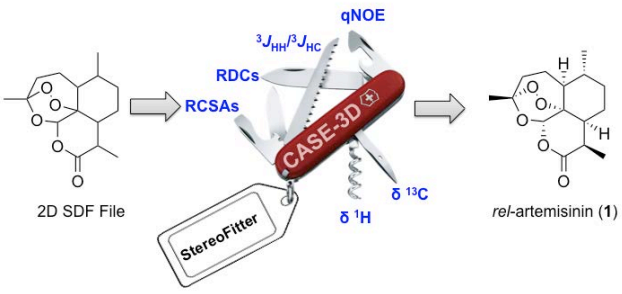
In this study CASE-3D was used to determine relative configurations of complex natural products based on isotropic/anisotropic NMR data. What relevance does this have to other fields of science?
Beyond the obvious application to synthetic chemistry, since the developed CASE-3D methodology is no more than a conformational model selector, it can be very well applied to the study of conformation in solution and therefore to aspects of drug design based on three-dimensional structures. We have been collaborating with pharmaceutical companies in this respect with very nice results that we hope will be published soon.

How do you see the role of the natural products chemist evolving as structure elucidation becomes a more automated process?
I think that elucidation of small or medium-size semi-rigid molecules, let us just imagine something like strychnine or α-santonin, will be soon completely automated. Chemists will focus on the difficult problems such as large, flexible molecules. Also, I think that these tools will make natural products chemists more aware of conformational and dynamic aspects. Noteworthy, the use of these tools will decrease the number of wrongly reported structures and facilitate the revision of already published data.



CASE-3D makes use of nearly all available spectral NMR information to elucidate the relative configuration and preferred conformation of complex natural products, such as artemisinin.

What advice would you give to scientists starting their careers in natural products?
In general, I always advise my students to be very suspicious and critical with their experiments and analysis. Always investigate data that seems to be in conflict with the proposed structure because errors can be present at any state of the research. Sometimes this effort rewards with beautiful discoveries on chemical structure. ■



AIC values for NMR data fitting in homodimericin A.

Meet a New ASP Member

Dr. Tamam M. El-Elimat is our featured new member in this issue of the Newsletter. *She is an assistant professor of Natural Products Chemistry in the Department of Medicinal Chemistry and Pharmacognosy at the College of Pharmacy, Jordan University of Science and Technology (JUST). She joined JUST in 2014 and was recently appointed as Chair of the department. Dr. El-Elimat had previously been involved with ASP as a student member. We are grateful for the opportunity to welcome her back to ASP as a full member.*

By Dr. James Fuchs

What is your scientific background?
I earned a Bachelor of Science degree in Pharmacy and a Master of Science degree in Medicinal Chemistry and Pharmacognosy, both from the College of Pharmacy, JUST, Jordan. Next I worked as a researcher at the Pharmaceutical Research Center at JUST. Then I earned a PhD degree in Natural Products Chemistry in 2014 from the University of North Carolina at Greensboro (UNCG) under the supervision of Dr. Nicholas Oberlies, after which I returned back to JUST as a faculty member.

Dr. Tamam M. El-Elimat

How did you hear about ASP?
I came to know about the ASP meeting in 2004, when my master research advisor, Dr. Feras Alali, participated in the ASP meeting to present my research. After joining UNCG as a PhD student, I had the chance to participate via student membership at three consecutive ASP meetings from 2011 through 2013.

Did your experience with ASP as a student play a direct role in your decision to join the Society now?
Yes. From the positive experience that I had as a graduate student during my participation in the ASP meetings, I have made the decision to join the ASP community and be a part of the ASP meetings.

What would you like to achieve through your membership?
Networking with researchers from the different natural products sectors and being up to date with the current trends in natural products research.

What are your own research interests in pharmacognosy?
My current research work includes the discovery of bioactive compounds from endemic medicinal plants of Jordan, evaluation of the health benefits of botanical products and nutraceuticals and their chemical analysis, and pharmacokinetic herb-drug interactions. I have supervised and co-supervised a number of students in the field of natural products chemistry and analysis.

Are you involved with teaching in this area too?
Yes. I am teaching Chemistry of Natural Products and Phytotherapy for PharmD undergraduate students. At the graduate level, I am teaching a course entitled, "Organic Structure Determination." This is the most joyful course for me since it enables me to teach new graduate students NMR skills that draw on my PhD study and research expertise.

What do you like doing in your spare time?
I am a big fan of reading news, all types of news from all over the world. I also like to participate in local community services to increase public awareness about health problems such as cancer, diabetes, and hypertension.

Other than the news, what are you currently reading?
Hadeeth al-Junud (The Story of the Soldiers), a novel written by Jordanian poet and novelist Ayman Otoom.

Do you have any favorite movies?
Gladiator, Braveheart, and *A Beautiful Mind*. ■

New Members of ASP 2018

ASP would like to welcome new members. The Society's main objectives are to provide the opportunity for association among the workers in pharmacognosy and related sciences, to provide opportunities for presentation of research achievements, and to promote the publication of meritorious research.
New members include 8 full members and 2 associate members.
We look forward to meeting you and learning more about you and your work

FULL MEMBERS

Dr. Paul Boudreau
Postdoctoral Researcher
Harvard University
Cambridge, Massachusetts

Mr. Marc Fluitt
President and CEO
Phlight Pharma, LLC
Ocean Springs, Mississippi

Dr. Scott Hemby
Professor and Chair of
Basic Pharmaceutical Sciences
High Point University
High Point, North Carolina

Dr. Shahan Khokhar
Teacher
University of Queensland
Brisbane, Queensland, Australia

Dr. Kenneth Kongstad
Assistant Professor
University of Copenhagen
Copenhagen, Denmark

Dr. Andrew Lowell
Assistant Professor
Virginia Tech
Blacksburg, Virginia

Dr. Ulyana Muñoz-Acuña
Pharmacist
Apoteket AB
Ronneby, Sweden

Mr. Georg Wikman
Research Director
Swedish Herbal Institute
Research and Development
Vallberga, Sweden

ASSOCIATE MEMBERS

Mr. Kirk Lawson
Graduate Student
University of Alabama
Gurley, Alabama

Ms. Olga Haygood
Student
Colorado School of Traditional
Chinese Medicine
Denver, Colorado

Fieldwork with Family... and a Fake Leg

By Dr. Cassandra L. Quave

My husband, Marco, and I welcomed our first of three children in the fall of 2005. I was a graduate student at Florida International University in Miami, FL at the time, and finished my qualifying exams for PhD candidacy just a few weeks shy of my due date. This was not an easy thing – like most of my peers, I had been hooked on some of the best alkaloids (caffeine and nicotine) and was denied that stimulant boost while prepping for my qualifying exams. Not a fun time for me, but Marco and I were overjoyed to greet Donato, our first addition to the family. Just five short months later, I would be on a plane solo with our new addition – Marco staying behind in Miami for his job – as I embarked on my doctoral fieldwork project that would keep Donato and me away from home and from Marco for the next seven months. Our destination was the rural center of southern Italy in the Basilicata province where Marco and I had met years before. I had the connections of both family to help with childcare and established field sites in a number of villages across the Vulture Alto Bradano region.

On my first field research expedition in the Peruvian Amazon, along the upper Napo River – 1999-2000. The combination of sweat, heat and friction led to a number of skin infections on my stump during the trip.

Today, as a medical ethnobotanist and pharmacognosist, I seek out medicinal plants in my drug discovery lab research program. I currently have over 600 species and 1800 extracts (plus hundreds of fractions) in my customized collection, the Quave Natural Products Library. An active collection program is key to the expansion of the library; I personally collect or direct field collections of all species that we work on in the lab. Over the past 18 years, my field research sites have included the flooded forests of the Peruvian Amazon, rural agricultural villages of central Italy, isolated island chains in the Mediterranean, rugged mountain peaks in Albania and Kosovo, gator-infested swamplands of south Florida, and the rattlesnake territory of the Georgia pinelands. Field research is many things for me. It is fun and exciting, but, at the same time, physically and mentally challenging. In addition to the physical rigors of collecting and processing kilos of plants in the sweltering heat or bitter cold, I also spend part of my days interviewing people about traditional uses of those plants – and often in a different language. By the end of the day, my head is a jumble of words in Italian, Spanish or even Albanian as well as Latin from keying out and recording all of the plant names.

Working in the field as an amputee with a below knee prosthesis has especially thrown some hurdles my way. Injury to my good leg would be disastrous. As for my stump, I have to remain vigilant in wiping the excess sweat from it on long walks to keep it clean and reduce the risk of heat rash and infection. My first field experience as an undergraduate student in the Peruvian Amazon taught me that lesson well. On the third day of long walks down jungle paths, I developed a large boil in the crease under my knee where my prosthetic had rubbed the skin raw in the heat. It left me immobilized for nearly a week because I couldn't wear the prosthetic and I didn't have crutches with me. Luckily, the boil cleared with standard wound care, and I didn't develop a more serious infection or need for IV antibiotics, which had happened before. From that day on, I traveled by canoe or motorboat whenever I could for longer distances.

Most days in the field my body is bruised and battered from just the process of getting to the plants I seek. Whenever possible, I try to incorporate alternative modes of transportation to get

continued on page 32

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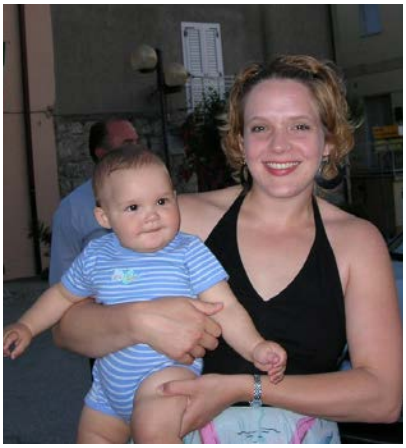
continued from page 31

me as close to my collection spots as possible, be it by canoe, truck, airboat or donkey. These days are long, meant to maximize the precious time I have to work at a site. Having students and trainees along certainly makes things easier too – now they can scramble up the hill to grab the species we seek.

When my children were infants and toddlers, I'd often bring them along in a stroller with me to interviews. The elderly people that I spent the most time interviewing loved to dote on them and give them cookies and sweets as we chatted. As they've grown older, my kids see these times as the idyllic days of summer, spent playing soccer and running free in the small villages we visit for work or joining the field team armed with clippers and collection bags. On the days spent near the village, I never have to worry about where they are throughout the day; the tightknit network of village grannies gives me an update on their location about every 30 minutes or so. It is just as effective as using a tracking device! Marco and I take turns watching our youngest child, who at five still requires more supervision than the 11 and 13 year olds.



ABOVE LEFT: **Doctoral field research in 2006 with my eldest son, Donato, in Ginestra, Italy.**

ABOVE RIGHT: In 2014, the roads into the Sharri mountain villages in Albania were rough and muddy, requiring a 4-wheel drive vehicle to reach them. From there, Dr. Andrea Pieroni and I took off on foot for interviews with local residents and plant collections.

Why include my family in fieldwork? In some ways, my answer is simple; in others, it is not. Family is incredibly important to me and, unfortunately, the life of a PI, or lab leader, requires that I already spend too much time away from my husband and kids, and that is when I am in town, living with them at home! Field research often requires weeks to months away, and to maximize this time I often plan my field seasons in the summer, while I am not teaching and the kids are not in school. One simple answer is that I cannot bear to be away from them for that long. Another answer is that I want this to be an opportunity to enrich their lives through exposure to different languages and culture. This does not come without extra expenses though. Family expenses are not considered a part of the research budget; we have had to put many of our personal financial and airline miles savings into making this possible. While my airline tickets are covered, those of my husband and three kids (who all pay full fare) are not and can amount to several thousand dollars each summer.

The major lesson that I have learned from my time in the field when it comes to family and accessibility is simple: anything is possible with a bit of creativity and perseverance, but there is no "one size fits all" solution for these logistics. Every scientist has different family dynamics and different personal physical

continued on page 33

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The excitement of uncovering the mystery of how a medicinal plant works in our lab models, or the thrill of discovering which compounds are responsible for the medical benefits of the traditional therapy, verge on addictive for me.

continued from page 32

abilities and disabilities. My advice is to plan your expeditions carefully, taking these factors into consideration as you work out logistics with team members and collaborators. Clear communication regarding expectations is crucial, and this spills over into the budget planning. Whether it is an off-road truck, an airboat or a team of donkeys you need to rent to access your collection sites, be sure to account for those additional expenses in your budget.

Fieldwork is one of the highlights of my career in science. I relish the opportunities to travel and experience nature through the lens of different cultures. The excitement of uncovering the mystery of how a medicinal plant works in our lab models, or the thrill of discovering which compounds are responsible for the medical benefits of the traditional therapy, verge on addictive for me. My goal moving forward is to see projects go from the field to the lab, and then someday, onto pharmacy shelves. ■

ABOVE LEFT: Working in south Florida, we used an airboat to access plants growing along the shores of the Peace River. Whenever it was exposed to water, I had to dry out my prosthetic foot shell with a hair dryer in the evenings to protect it from breaking down or molding.

LEFT: We used a team of donkeys to scale the rough trails up the central peak on the island of Marettimo, Italy in 2017. Isabella and Giacomo rode up the trail with Marco beside them.

ABOVE: Group photo on a 2018 expedition to a long leaf pine habitat in southern Georgia, at the Jones Ecological Research Station. From left to right: Giacomo, me, Donato, Isabella, Ella, Marco, Monique, Kat, James, Thara and Afam.

Conference Calendar

The *Newsletter* is pleased to announce the following upcoming conferences and meetings. The events portrayed here reflect what listings and notices the *Newsletter* has specifically received. For a more extensive calendar, please visit the ASP website at www.pharmacognosy.us. If you have a conference or event you would like mentioned, please send us relevant information, including any graphics or appropriate fliers, at asp.newsletter@lehman.cuny.edu.

4th Drug Discovery Re-Invented Conference

Emerging Role of Biotechs, Academics and Non-Profits

February 21 – 24, 2019

Nassau, Bahamas

www.fusion-conferences.com/conference80.php?utm_medium=email&utm_campaign=April%20update&utm_content=April%20update+CID_cc54f1b9c0767df70f1f6a29eeaa40a5&utm_source=Campaign%20Monitor&utm_term=4th%20Drug%20Discovery%20Re-Invented

19th Annual Oxford International Conference on the Science of Botanicals

April 8-11, 2019

Oxford, MS

www.oxfordicsb.org/

6th World Congress on Medicinal and Aromatic Plants for Human and Animal Welfare

May 1-5, 2019

Antalya, Turkey

wocmap2019.org/

19th International Congress of the International Society for Ethnopharmacology

June 12-14, 2019

Dresden, Germany

tu-dresden.de/mn/internationales/veranstaltungen/symposien-kolloquien/2019-international-ethnopharmacological-congress

3rd International Conference of Marine Fungal Natural Products (MafNap 2019)

June 26 - 28, 2019

Athens, Greece

docs.wixstatic.com/ugd/a5860a_f0f3102c38294d488621b056b236824e.pdf

60th Annual Meeting of the American Society of Pharmacognosy

July 13-17, 2019

Madison, Wisconsin

aspmeetings.pharmacognosy.us

Natural Products in Drug Discovery and Human Health

July 28-31, 2019

Lisbon, Portugal

www.ff.ul.pt/pselisbonmeeting2019/

12th International Congress on Natural Products Research

July 25-30, 2020

San Francisco, California

icnpr2020.org

Brief News from Washington

By Dr. Georgia Perdue

- **As of November, National Center for Complementary and Integrative Health (NCCIH) has a new Director: Dr. Helene M. Langevin, MD, CM. She was formerly Director at the Osher Center for Integrative Medicine at Brigham and Women's Hospital and professor-in-residence of medicine, Harvard Medical School, Boston.** In his announcement, NIH Director Dr. Francis Collins thanked Dr. David Shurtleff "…for his outstanding leadership as Acting Director for the past year…" **The good news for Dr. Langevin is that NCCIH received a 3.02% increase in its FY 2019 budget for a total of $146,473 million.**
- **The end of October the NIH announced it is "seeking exceptional candidates for the position of Director, Office of Dietary Supplements" within the NCCIH.** The position was formerly held by Dr. Paul Coates who retired. ASP member Dr. Joseph Betz is currently the Acting Director.
- **At the October 4 NCCIH Advisory Council Meeting,** one of the topics was cannabinoids. **Council member, ASP member Dr. Barbara Timmermann, recommended that focus be given to one class of compounds. She is starting a second term that lasts until 2021. Another ASP member on the Advisory Council is Dr. Alice Clark whose term expires in January.**
- In early October **National Cancer Institute (NCI) Director, Dr. Norman E. Sharpless, commented on the Annual Plan for NCI. "We are in the midst of an historic moment in cancer research.** Groundbreaking discoveries from multiple disciplines … [including] medicinal chemistry, structural biology, molecular biology … triggered unprecedented industry investment, philanthropic support and patient advocacy for cancer research." **Dr. Sharpless discussed reality: "… as we celebrate new successes, we face new and existing challenges…too many cancers for which we lack effective screening and prevention …. [or] a lack of effective therapies." "We are tackling these issues head on." The Annual Plan includes:**
  - Develop a workforce of cancer investigators
  - Reaffirm our commitment to basic science… novel approaches and technologies
  - Innovate the design, administration and analysis of clinical trials

  Dr. Sharpless closed his remarks saying, "These are times of great hope and challenges. [The plan] lays out a vision to achieve our goals at an even faster rate…."
- On August 14 NCI's National Cancer Advisory Board held a virtual meeting. **Dr. Sharpless noted in his NCI Director's Report that the Cancer Moonshot program within the 21st Century Cures Act has been fully funded. Among the recommendations of the Blue Ribbon Panel:**
  - Research Specialist Award (R50)
  - Stable careers for exceptional scientists who do not want to be independent investigators
  - They will receive salary support and sufficient independence

continued on page 36

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continued from page 35

- **Another award discussed by Dr. Sharpless was the Lasker Clinical Research Scholars Program at NIH.** In the first five years of this intramural program the scientist is provided with full salary and research support. From years 6-8 the salary and research support can be up to $500,000/year at an outside institution or continuation at the Intramural Research Program. "Early stage researchers become candidates within 10 years of completing core residency and ability to conduct independent research" (see nih.gov/science/laskerscholar).
- **FDA will issue "draft guidance" in 2019 to clarify its approach to plant biotech.** The agency guidance will be based on the knowledge it has gained over the last 25 years overseeing genetically modified plants.
- **In a statement the end of October, FDA Commissioner Dr. Scott Gottlieb noted that the agency is "beginning to see evidence that sesame allergies may be a growing concern in the U.S."** And, he noted that since sesame is not considered a "major allergen," it is not a requirement it be declared an allergen on food products. However, FDA will be seeking the advice of specialists to learn more about this possible allergen. **So remember when eating tahini spread or dip, you are eating sesame seed!!**
- **What many people consider a nemesis in their yards "companies and governments are spending heavily on it." What is this plant? Dandelion!!!!** An agronomist at Ohio State University is trying ways to grow MORE dandelions. Why? Well, **Dr. John Cardina and a team are working with Goodyear Tire and Rubber Co. and Cooper Tire and Rubber Co. to turn the humble rubber dandelion plant—a cousin of the common weed—into a commercial source of rubber.** During WWII latex was extracted from dandelion roots as a source of rubber!! Dr. Katrina Cornish, who leads the alternative rubber production program at Ohio State, sees "dandelion-rubber-soled running shoes as more likely than tires in the near term." A lot of the work is under wraps!!! (see *Wall Street Journal*, October 3, 2018)
- A tree which is an enormous pest hit the news on November 7. It competes in fame with the pesty kudzu vine. The "Tree of Heaven," *Ailanthus altissima*, was introduced in the US in the late 1700s as an ornament. Now a Virginia Tech doctoral student, Rachel Brooks, is inoculating the trees with a fungus, verticillium, which is killing the trees. The ultimate goal is to formulate a marketable product of the fungus. (source: *Washington Times*)
- President Trump announced on October 18 that he would like his Cabinet to cut 5% from their budgets. Where this will go is anybody's guess. However, forewarned is forearmed!!! ■

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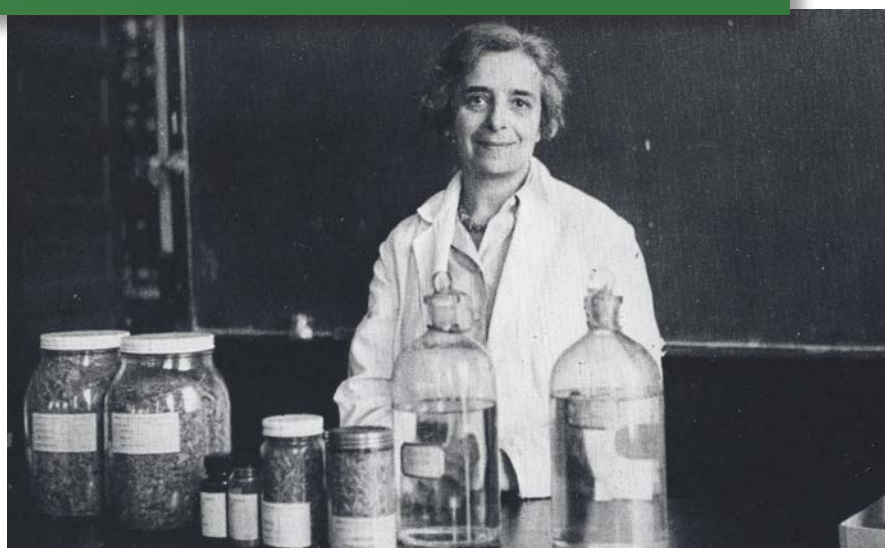
From the Archives: Anna Koffler Wannamaker, Pharmacognosy Pioneer, Part II

By Ms. Devhra BennettJones



Dr. Anna Koffler Wannamaker in 1957, Ohio Northern University.

Who was Anna Koffler Wannamaker (1902-1980s)? While her name may not be easily recognizable by current ASP members, Wannamaker's pharmacognosy legacy made a deep-rooted impression on her students, colleagues and those she sought to educate about the scientific and healthful value of plants. Dr. Anna Koffler Wannamaker spent her life in the service of pharmacognosy education for academicians and the public. She made a seminal contribution to pharmacognosy history in documenting the origins of the ASP through the manuscript *The History of the Plant Science Seminars* (1973). This article is part two in a series following the stages of her career and enduring impact on the field of pharmacognosy. Part one described Wannamaker's immigration to the United States and quest to find a pharmacognosy position in academia.

It took almost ten years for Wannamaker to secure a pharmacognosy tenure-track position. In July 1953 she was hired as an associate professor with Ohio Northern University's (ONU) College of Pharmacy. During her career path to ONU she was a research associate at Rutgers University, Hoffman Laboratories and E.R. Squibb. She gained teaching experience at the University of Kansas City.[1] In 1947 Wannamaker was honored by the American Association for the Advancement of Science awarding her an AAAS Fellow in Pharmacognosy.[2]

Upon arriving at ONU Wannamaker quickly established her reputation as an inspirational teacher and trendsetter among peers. In the mid-1950s, technology in the classroom was utilized on a limited scale, consisting primarily of microscopes, slide rulers, and audio headphones. Between 1950-1954 Wannamaker was appointed to the Plant Science Seminar committee to study the challenge of employing visual technology aids in teaching pharmacognosy.[3] Her conscientiousness about students' classroom experience extended to their social lives. Wannamaker was instrumental in establishing the ONU chapter of Kappa Epsilon, a professional pharmacy fraternity for women.[4] She served as the faculty sponsor of the fraternity, inspiring generations of women pharmacists.

Wannamaker's scientific research interests focused on grasses and mistletoe. At the 35th Plant Science Seminar in Big Rapids, Michigan, August 18 – 22, 1958 she presented *A Historical Sketch of the Uses of Mistletoe (Viscum Album)*.[5] In her presentations about mistletoe, Wannamaker described how scientists in Europe have investigated mistletoe's efficacy with certain types of cancer. She and ONU students studied the bacteria on unsterilized mistletoe. They found that bacteria on the European variety held anti-cancer properties that were absent in the American variety.[6] She received grant support to study the medicinal plant potential of mistletoe, grasses, and cereals.[7] In 1961 the Homeopathic Institute of America awarded $3,000, which is equivalent to nearly $25,000 in 2018.[8]

Wannamaker's achievements were covered in the local news on January 26, 1965. "Professor Wins Acclaim in Research" appeared in *The Lima News*:

> Dr. Anna Koffler, professor of pharmacognosy at Ohio Northern University, is receiving congratulatory letters from friends and fellow scientists around the world as a result of press reviews on a paper she presented before the American Association for the Advancement of Science meeting held in Montreal, Canada, recently. She is on a one-year leave of absence from the university.

continued on page 38

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From the Archives: Anna Koffler Wannamaker, Pharmacognosy Pioneer, Part II

Dr. Anna Koffler Wannamaker, 1963

continued from page 37

> The six-day conclave in Montreal was a joint meeting of The Geological Society of America and The Canadian Association of Geographers and brought together 8,000 scientists from the U.S., Canada, and 11 other countries. Her paper, "Trace Elements in Plants" was read during an interdisciplinary symposium and has been published in its entirety in scientific journals, and portions have appeared in leading newspapers here and abroad.[9]

In that same year the young ASP organization acknowledged her accomplishments and devotion to the development of the society by the appointment, Historian of the Plant Science Seminar.[10] Drs. Wannamaker and Rolf Westby advocated that the ASP fund a historical publication. The manifestation of their efforts culminated in the early 1970s with *The History of the Plant Science Seminar* by Dr. Anna Koffler Wannamaker. Her colleagues wrote:

> This document, compiled by Dr. Anna Koffler Wannamaker, represents a history of the Plant Science Seminar. It covers the existence of the Seminar from its beginning in 1923 until organization of the more formal American Society of Pharmacognosy in 1959. Dr. Wannamaker enjoyed longstanding participation in the Plant Science Seminars, and she was a charter member of the American Society of Pharmacognosy. She was charged with preparing the historical treatise by the Executive Committee of the American Society of Pharmacognosy, and duplication and distribution of the unedited manuscript was authorized at the 1972 annual meeting of the Society.
>
> The history is arranged in a chronological sequence and was compiled primarily from files and records transmitted to the American Society of Pharmacognosy as the successor organization to the Plant Science Seminar and from published reports of annual meetings. The format of the compilation has led understandably to a degree of repetition in parts of the manuscript. Occasional typographical errors were noted which do not detract significantly from the comprehension or historic value of the text.
>
> Special Committee on Evaluation of the History of the Plant Science Seminar, 1971-72. Harold E. Bailey, Jerry L. McLaughlin, Lynn R. Brady, Chairman.[11]

In 1973 the ASP Executive Committee approved the publication and made subscription bound copies available for $30-$35. Dr. Jack K. Wier of the School of Pharmacy at University of North Carolina, Chapel Hill coordinated the sales and distribution.[12]

Wannamaker's contributions to scientific botanical research, her impact on generations of college students, and efforts to educate the public about the medicinal and healthful value of plants cannot be understated. All known accounts about her life and career describe an exceptional individual transcending life's challenges. A newspaper article titled, *Dr. Anna Koffler Named to Honors*, vividly portrayed her character:

> Before coming to ONU in 1953, Dr. Koffler did research work in the woods close to Vienna, where leaf trees grow in profusion and the greenness of the grass and plants growing along the hills. Swimming, boating and just resting along the famed Danube River were ordinary weekend occurrences. She misses all of this.
>
> She was in the Austrian youth movement from the beginning and hiking, cooking, and eating in the open were combined with mountain climbing to give her a glow of vitality that she possesses to this day. She still enjoys walking and wouldn't think of riding in a car if her destination is within walking distance.
>
> She purposely lives in an apartment far enough away from the college so she will have to walk.
>
> She attributes her good health and buoyant spirit to the early part of her life in the Vienna countryside, where she says, "We sang at the top of our voices and laughing was oh so easy." Describing it her way, "It was easy to carry sunshine in our hearts."[13.] ■

Wannamaker's contributions to scientific botanical research, her impact on generations of college students, and efforts to educate the public about the medicinal and healthful value of plants cannot be understated.

continued from page 38

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