CHAPTER 4

PHARMACOGNOSY IN ACTION. U. S. ACADEMIA

Arizona State University Cancer Research Institute

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In 1965, following eight years at the University of Maine where he had established an intensive program directed at the discovery and/or development of new plant and animal anticancer constituents, combined with total syntheses and structural modifications, Professor George R. (Bob) Pettit transferred with his research group to the Department of Chemistry at Arizona State University. This launched an extremely productive natural products drug discovery program which continues to this day. Research directed at the synthesis of antineoplastic peptide alkaloids, nucleopeptides, and steroidal bufadienolide toad venom constituents were continued and resulted in the syntheses of emetine peptides and total synthesis of a range of bufadienolides, including resibufogenin, sold in Asia to increase the force of heart contraction (cardiotonic), and marinobufagenin, of high interest in the etiology of preeclampsia in pregnancy.[1]

In 1973, the Pettit research group was officially recognized as the ASU-Cancer Research Laboratory, and by 1975 as the ASU Cancer Research Institute (ASU-CRI). Meanwhile, research focused on discovery of plant anticancer constituents became increasingly productive, and agents discovered include the amoorastatins, aphanastatin, bauhinia-statins, combretastatins (of which CA-4 and CA-1 are in clinical trials), the lychno-statins, the meliastatins, multigilin, multistatin, narcistatin, the nootkastatins, palstatin, pancratistatin[2] (in advanced preclinical development), pedilstatin, the phyllanthostatins (1 and 2 completed phase I clinical trials), radiatin, rolliniastatins, the sansevistatins, and the schleicherastatins. Highlights of parallel studies of microorganism anticancer constituents include the isolation and structural elucidations of carminomycin (in clinical use), kitastatin 1,[3] the labradorins, montanastatin, and the Streptomyces antitumor antibiotic 593A (clinical trials by the NCI), as well as convenient syntheses of the Streptomyces anticancer drugs, DON and azotomycin.

By 1965-1966, owing to increased resources, especially support from the U.S. National Cancer Institute (NCI), pioneering programs were initiated exploring the potential for discovery of new anticancer drugs from terrestrial arthropods, such as insects, and marine organisms, both promising areas of interest to the author from about 1955. The class Insecta was soon found to offer promise, and subsequently, the first insect antineoplastic constituents were isolated from Asian butterflies, an Asian beetle, *Allomyrina dichotomus*, the yellow jacket *Vespula pennsylvanica*, and more recently a Texas grasshopper that yielded a new source of the plant-derived pancratistatin.[4]

By 1968, the CRI group was able to show that marine invertebrates and vertebrates obtained from locations worldwide held the potential for eventual discovery of completely new types of anticancer drugs, and the intervening period has witnessed the accelerating discovery of potentially important anticancer drugs and other types of drugs based on marine animal and microorganism constituents.[5] Beginning in 1968-1973, these include: aplysistatin, the axinostatins, the bryostatins (in extensive human cancer clinical trials), the cephalostatins, cribrostatins, dolastatins[6] (analogs in human cancer clinical trials), geodiastatins, halistatin, the halichondrin series, the hemibastadins, hymenistatin 1, the hystatins, irciniastatins, lytechnistatin,

the palystatins, sesterstatins, spongistatins, sphyrnastatins, stichostatin 1, the strongylostatins, and turbostatins. Some of these series comprise twenty or more related anticancer active molecules.

Nine of the agents mentioned above are currently undergoing human cancer clinical trials, and three (bryostatins, combretastatins, dolastatins) are discussed further in the "Major Milestones" section of the text. Another twenty are at various stages of development that may justify preclinical development, and a large number of other leads have been uncovered, and are awaiting further research. In parallel, many of the naturally occurring small-molecule drugs discovered have the potential for being developed for other serious medical problems as illustrated by combretastatin A-4 phosphate (in phase 2 trials for macular degeneration), narcistatin (in preclinical development for arthritis), and pancratistatin (antiviral).

Very little of the preceding advances would have occurred without the extraordinary contributions of my colleagues (some 200 postdoctoral, faculty research associate, and research professors), doctoral candidates (over 70), a large number of undergraduate assistants. Key CRI professional staff included Drs. Zbigniew Cichacz, Cherry Herald, Delbert Herald, Jr., Fiona Hogan, Yoshiaki Kamano, John Knight, Noeleen Melody, Robin Pettit, Jean M. Schmidt, Thomas Smith, Rui Tan, and Jun-Ping Xu, while key administrative and technical staff included Marie Baughman, Drs. Jean-Charles Chapuis and Dennis Doubek, Christine Duplissa, Helen Farmin, Dr. Michael Hoard, Georgia Reimus, Denise and Larry Tackett, Theresa Thornburgh, Dr. Bruce Tucker, and Lee Williams. All, including expert colleagues at the NCI, and other universities and institutes, receive my warmest thanks and appreciation.

For the past 50 years, this research has been completely supported by funding from Federal and State research grant awards, augmented by personal philanthropic (foundation and individual) and invention licensing initiatives. The new ASU-CRI Research building incorporating extensive laboratories for chemistry, cancer biology, and microbiology was constructed (1995-2001) employing the same funding sources and with enthusiastic support of the ASU administration prior to 2002. Sadly, the new (as of 2002) ASU administration elected to terminate the ASU-CRI in July, 2005, and currently the program is proceeding with five (10%) of the original ASU-CRI group in the ASU Department of Chemistry and Biochemistry.

For leading references, consult: the "Major Milestones" section and the following:[1-7]

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The Ohio State University: Pharmacognosy and Natural Products Research in a Nutshell

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The Early Years (1870-1952) The Ohio State University (OSU) was founded in Columbus, Ohio in 1870. Sidney A. Norton, M.D., Ph.D. of Chemistry, in 1883 promoted a voluntary class in Materia Medica. On September 17, 1885, the new School of Pharmacy opened, offering a two-year non-degree course to students. A series of Deans of the School, including George B. Kauffman (1896-1915), Claire A. Dye (1915-1939), and Bernard V. Christensen (1939-1955), along with several faculty members, taught Materia Medica-Pharmacology and Pharmacognosy. During the time of Dean Christensen, Ph.D. research studies were instituted in 1941, and independent faculty research on medicinal plants was encouraged.[1] For example, John W. Nelson of Pharmacology and his graduate student, Carl A. Schlagel confirmed the long-lasting hypotensive action of an extract of *Rauvolfia serpentina* in the anesthetized dog.[2] In 1943, Arthur E. Schwarting became the first Ph.D. graduate of the OSU College of Pharmacy under the direction of his major professor, L. David Hiner. In addition to later establishing an excellent academic and research career at the University of Connecticut, Dr. Schwarting also served for 17 years as Editor of *Lloydia*.[3]

The Beal Era (1952-1986) In 1950, Jack L. Beal, M.S., an enthusiastic graduate student from the University of Kansas arrived at the then College of Pharmacy to conduct Ph.D. research under Dean Christensen. In 1952, he was appointed to the faculty to teach and conduct research on pharmacognosy and natural products under rather primitive and inadequate support conditions. Lloyd M. Parks, who had exceptional research training in plant chemistry along with outstanding leadership, was selected as Dean (1956-1977), and this led to the creation of additional facilities for research and teaching. Jack obtained his first funding from NIH in 1958. Then, in the early 1960s, he launched a lifelong search of alkaloids in many different species, but in particular of *Thalictrum* species (over 20, including varieties).[4] A biochemist and natural products chemist, Raymond W. Doskotch, Ph.D., from the University of Wisconsin, joined the group in 1963, and thus began what might be regarded as a golden age that led to a series of articles on various types of alkaloids from *Thalictrum* species, resulting from the research work of some excellent graduate, underdergraduate, and postdoctoral students.[5] Many of these younger colleagues went on to prominence in the field in their own right.

From 1977-1983, Dr. Beal served as Editor of *Lloydia*, and facilitated a formal change in the name of this scientific publication to the *Journal of Natural Products* in 1979. Also in 1979, the newly named Division of Medicinal Chemistry and Pharmacognosy was formed at the College of Pharmacy from the former Divisions of Medicinal Chemistry and of Pharmacognosy and Natural Products.

Dr. Doskotch also worked independently, particularly on the constituents of local North American flora, with cytotoxic (antitumor) activity and insect stimulants (for the elm bark beetle) and insect antifeedants (for gypsy moth larvae).[6] During the period 1968-1975, Professor Lester A. Mitscher was on the faculty of the College of Pharmacy at OSU, and he continued his interest in antibiotics from an earlier industrial position,[7] and also instituted a new program on antimicrobial agents from higher plants.[8] In 1975, Larry W. Robertson was hired from the

University of Mississippi to take over from Dr. Mitscher, and he developed a program on biostransformation of bioactive plant-derived natural products. The biocatalytic approach was employed both for model mammalian metabolism and to produce new and potentially active transformation products of such varied substrates as cannabinoids,[9] cardiac glycosides,[10] retinoids,[11] and flavonoids.[12] In addition, Dr. Robertson continued a program of antimicrobial screening, with several graduate students completing dissertations and theses on the bioactivity-derived isolation of plant and fungal products.

The program on natural products at the College of Pharmacy at OSU was enriched by an interest in evaluating these substances in the Division of Pharmacology. By 1986 when Professor Beal retired, the pharmacognosy group had characterized the structures of well over 50 different alkaloids. R. A. Hahn, J. Banning, N. Uretsky, K. Salman, A. M. Burkman, and P. N. Patil evaluated the pharmacological profile of alkaloids including (-)-canadine methochloride, obamegine, thalicarpine, thalistyline, thalrugosine, (+)-tembetarine chloride, and veronamine.[4]

The post-Beal Years (1986-present) In the years since the retirement of Professor Beal and his untimely death in 1998, to the present, there has remained a considerable presence in natural products research in the College of Pharmacy at OSU. During this period, the serving Deans were all from the Division of Medicinal Chemistry and Pharmacognosy, namely, Albert H. Soloway (1977-1988), John M. Cassady (1988-2003), and Robert W. Brueggemeier (2003-present). While Dean, Dr. Cassady maintained a research program on anticancer and chemopreventive agents from plants.[13] Emeritus Professors Doskotch[5] and Robertson[12] have retained their former research interests. Dr. Karl Werbovetz, although primarily a medicinal chemist, has worked on plant-derived antiprotozoal agents.[14] In May, 2004, A. Douglas Kinghorn, previously at the University of Illinois at Chicago, was appointed as the inaugural Jack L. Beal Professor and Chair of Natural Products Chemistry and Pharmacognosy, and has begun new collaborative research programs.[15-17] Dr. Kinghorn is also Editor of the *Journal of Natural Products* (1994-present). Dr. Esperanza J. Carcache-Blanco was appointed as Assistant Professor in 2005, and is interested in the screening of natural products using new target-based assays.[17] Additional pharmacological testing of natural products has also taken place.[16,18] Up to the present, over 50 excellent Ph.D. and M.S. students have graduated in pharmacognosy and natural products from the College of Pharmacy at OSU.

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Pharmacognosy at Oregon State University

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The Early Years (1959 – 1984): The earliest record that this author could locate for pharmacognosy research at Oregon State University (OSU; actually, Oregon State College at the time) was in 1959 (the birth year of the ASP!). This was a report by Gordon Smith and Leo Sciuchetti in American Pharmaceutical Association on the effects of gibberellic acid on the growth and alkaloid biogenesis in *Datura stramonium* and in *Atropa belladonna*. Sciuchetti's publication record began in 1944 with McMurray on the alkaloids of *Solanum triflorum*, and along the way he published a paper on the effects of atropine on leaf alkaloid accumulation in members of the Solanaceae with H.W. Youngken, Jr (ASP president 1969-70). Thus, it appears that Sciuchetti was the origin of the rich tradition in natural products chemistry that has evolved at OSU. Next on the scene was Philip Catalfomo, and he and Sciuchetti published in 1963 in PharmIndex "a discussion dealing with the semi-synthetic penicillins". Momentum built around this nucleus of investigators, and a new graduate student, George H. Constantine Jr. went on to publish several papers with both Sciuchetti and Catalfomo. Another key person came on the scene shortly afterwards, Eugene Lee, and a publication involving Lee, Sciuchetti and Catalfomo appeared in 1966 on "Preliminary investigations of *Heracleum mantegazzianum*", again in *J. Pharm. Sci.* While Sciuchetti subsequently moved on to another institution, Constantine and Catalfomo anchored natural products at OSU for the next several years, joined fairly early in this era by John Block, a physical chemistry student of S. Morris Kupchan (another legendary figure in our natural products discipline). Constantine, Block and Catalfomo teamed up several times through the 1970s to publish in Phytochemistry on Oregon plants. In 1973, this team explored a novel and quite "ahead of their time" dimension of natural products, the chemistry of cultured marine fungi. In fact, their study may well have been the first to explore marine fungi as a source of novel bioactive compounds, and led to three manuscripts in *Marine Chemistry*, *Food and Drugs from the Sea*, and *J. Pharmaceutical Sci.* that stand out as the earliest work at OSU in the marine natural products arena.

These investigations in the Pharmacy School stimulated efforts at OSU, and during this period, a connection was formed with synthetic organic chemist James D. White in the department of chemistry. White had arrived from Harvard and helped to develop the organic chemistry division with his research focus on the total synthesis of natural products. One such project derived from efforts by Catalfomo and Constantine on a new metabolite from a marine fungus, *Leptosphaeria oraemaris*, and chemical synthesis was indeed powerful in clarifying the relative placement of nitrogen and oxygen atoms. Later, White would team up with the author's laboratory to similarly clarify the structures and stereochemistry of several marine cyanobacterial natural products.

In part due to their active role in the ASP, Constantine and colleagues were eager to bring their fellow pharmacognosists from around the US, and from international locations as well, to visit the beautiful OSU campus and observe the rich environment that had been created there in the

natural products sciences. Accordingly, the OSU campus was the site for the 1969 annual meeting of the ASP, a conference which included such ASP notables as Norman Farnsworth, John Cassady, Heinz Floss, Bill Kelleher and Bob Krueger, and George Constantine and John Block.The 1969 ASP conference in Corvallis was one of the first national conferences to feature a marine symposium, a "tradition" we continued at the 2005 ASP conference in Corvallis. With their passion for and research activities in natural products chemistry, the early pioneers of this discipline at OSU became very active in the leadership of the ASP, with Phil Catalfomo and George Constantine serving as presidents in 1975 and 1976, respectively. Thus, by the end of the 1970s, a tradition was established on the OSU campus, begun in the School of Pharmacy in the late 1950s, spanning between Pharmacy to Chemistry to Botany and Oceanography, in the multi-disciplinary field of natural products research.

The Next Generation(s): As those who have visited know, the OSU School of Pharmacy, founded in 1898, is of relatively small size and located in a quaint historical brick building which houses the basic pharmaceutical sciences on the main campus. Dean Richard Ohvall, serving from 1979-1999, was thus faced with a strategic decision of whether to recruit new faculty to fully represent the very broad discipline of Pharmacy, or rather, to cluster hire in focused research disciplines; he took a gamble on natural products chemistry and hired three such scientists over his tenure. In 1984, he hired the author as an Assistant Professor and generously provided start-up equipment and excellent laboratory space (especially compared to then current standards!). Coupled with much sage advice from George Constantine and John Block, the OSU facilities, plus my momentum from a 2-year position at the U. Puerto Rico, Rio Piedras, and a reduction in other university responsibilities for the first few years, allowed me to develop a marine natural products program focused on marine algae and subsequently, on marine cyano-bacteria. As for all of us, some hard work on my part, a lot of luck, a number of really talented undergraduate and graduate students, great colleagues, and some advocates in different sectors (thanks Matt Suffness!), allowed my program to flourish with a combined focus on new compound discovery and the pathways of their biosynthesis. Hence, with strong support from the faculty and administration, this area was expanded through the sequential hires of Mark Zabriskie (graduate of Chris Ireland's program in Utah) and Phil Proteau (graduate of mine in 1993) as new faculty members in medicinal chemistry. Even with the departure of the author to his former Ph.D. institution at Scripps in 2005, the new dean, Wayne Kradjan has continued this vision in making additional faculty hires in natural products sciences, first Taifo Mahmud, and then Fred Stevens and Kerry McPhail, while further natural products principal investigators include Research Asst. Professors Patricia Flatt and Xihou Yin. Thus, seven full-time natural products research active faculty continue to flourish in the nourishing OSU environment, and OSU (west!) stands out as one of the leading institutions for the natural products sciences.

A tradition in the natural products sciences at OSU, begun many years earlier by Drs. Phil Catalfomo, George Constantine, John Block, has been carried on through the 1990s to 2005 by myself, Mark Zabriskie, Phil Proteau, Taifo Mahmud, Fred Stevens, Kerry McPhail, Patricia Flatt and Xihou Yin. With this rich history, a wonderful environment for collaborative scholarship, and a talented faculty, OSU promises to continue this tradition well into the future. Having hosted a second highly successful ASP meeting in 2005, the question is when will we be back in Corvallis for the third?

Pharmacognosy at Purdue University

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The School of Pharmacy at Purdue University was established in 1884. Its founder was John N. Hurty, an Indianapolis pharmacist, who also served as its first professor of pharmacy. The records show that A. W. Brayton, an M. D. from Indianapolis, taught the first course in *Materia Medica*, a broad subject which eventually evolved into pharmacognosy and pharmacology. Following the University of Michigan and the University of Wisconsin, Purdue was the third school to pioneer a scientifically-oriented pharmacy curriculum; earlier schools had focused on supervised practical experiences.

J. K. Lilly, President of Eli Lilly and Company, presented lectures for a number of years at the turn of the century and also served as a university trustee and benefactor. By 1908, pharmacy Professor Benjamin Hoak had published a 229 page textbook on *Materia Medica*. Several of Purdue's early professors were recognized for publishing such texts in their respective specialty areas, but graduate programs and research in the pharmaceutical sciences did not flourish at Purdue until the latter part of the reign of Dean Charles B. Jordan (1910 – 1941). Jordan's successor was Dean Glenn L. Jenkins (1941 – 1966) who is credited with the establishment of Purdue as a leader in research and graduate programs in all the pharmaceutical sciences.

By 1923, Chalmers J. Zufall was on board as the first full-time professor of pharmacognosy; his undergraduate courses were remembered as being "classic", and he is often remembered for having only one arm. In 1949, Egil Ramstad, a Norwegian with his Ph.D. from Liege University in Belgium, was hired as a new professor of pharmacognosy. Ramstad devoted 22 productive years of teaching and research to Purdue. His textbook, *Modern Pharmacognosy*, departed from the classical taxonomic approach and focused, instead, on the biogenesis of the bioactive constituents of natural medicinal compounds. He and his numerous M.S. and Ph.D. students published extensively and are best noted for their work on the biogenesis of the clavine alkaloids of ergot. Professor Ramstad left Purdue in 1971 for positions in Nigeria and South Africa.

In 1966, Varro E. ("Tip") Tyler followed Jenkins as Dean and also as professor of pharmacognosy. Tyler obtained his Ph.D. under Arthur Schwarting at the University of Connecticut and had previously held professorial positions at Nebraska and the University of Washington. Tyler was one of the founding fathers and the first President of the ASP and was internationally well-known as an expert in herbal supplements. Several editions of his textbook, *Pharmacognosy*, were used worldwide, and his books, *Herbs of Choice*, *The Honest Herbal*, and *Hoosier Home Remedies*, are still popular today. Tyler continued to expand the teaching and research faculty at Purdue and soon formed a Department of Medicinal Chemistry and Pharmacognosy. In 1968, he hired Heinz G. Floss, a bright, young, natural product chemist from Germany, who pioneered research in molecular mechanisms of microbial metabolite biosynthesis at the cell-free level, to head the new department. A new building, now named the R. E. Heine Pharmacy Building, was occupied in 1970, and this permitted the consolidation of the school into one location. For twenty years as dean and another five years as academic vice president, Tyler nurtured the research and education of pharmacognosy and natural products at Purdue.

By the mid 1970s, Floss has assembled a critical mass of professors, all of whose research interests focused on natural products: James E. Robbers (higher fungi, fermentation), John M. Cassady (synthesis, anticancer and cancer chemopreventive natural products), Ulfert Hornemann (biosynthesis and genetics of microbial metabolites), Peter Heinstein (plant tissue culture and enzymology of natural product biosynthesis), Jerry L. McLaughlin (cactus alkaloids, optimization of simple bioassays, antitumor compounds, commercial development of acetogenins), Steven R. Byrn (crystallography, solid state chemistry), Ching-jer Chang (bioorganic and natural product chemistry), David Smith (mass spectrometry), and John Schwab (bioorganic chemistry of natural products). Many of these professors have provided valuable contributions to the ASP in various ways for many years. Floss, Robbers, McLaughlin and Cassady served as Presidents of the ASP. Cassady is currently the Chair of the ASP Foundation Board of Directors. Robbers was the Editor of the *Journal of Natural Products* for ten years. Floss was a recipient of the ASP Research Achievement Award. McLaughlin was a recipient of the ASP Tyler Prize for Research in Botanicals. More importantly, this group mentored numerous young scientists, who have held influential positions at a host of academic and industrial institutions.

In the 1970s and 1980s, the collaborative efforts of the Purdue natural products and pharmacognosy researchers bore abundant fruit in the forms of a rapidly expanded graduate program and federal and industrial funding to support the research and establish a solid research infrastructure. In the early 1970s, this group was instrumental in the establishment of the Purdue Cancer Research Center – one of the few such federally supported centers in a university that lacks a medical school. This Center provided critical support of anticancer natural product research, and the university became one of the prominent institutions for natural products research from 1970 to 1990.

However, by the mid 1990s, new leadership had moved into the school and the department. As attrition occurred, the faculty positions in natural products were soon converted to the area of pharmacology so that today the programs and curricula at Purdue have been completely purged of the term "pharmacognosy". The huge collection of plants in storage, obtained from around the world, most through interagency agreement between the NCI and USDA, (greater than 6,000 accessions) was scheduled for the landfill, fortunately to be rescued by Tom McCloud and added to the NCI collection in Frederick, MD, and only one professor (C.- j. Chang) with interests in natural products, remains. A reprieve occurred with the hiring of John Pezzuto as dean but his time at Purdue failed to secure university support and cooperation and was only brief. Unfortunately, pharmacognosy and natural product research at the Purdue School of Pharmacy remain today as an item of the past.

Pharmacognosy at the University of Arizona

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The College of Pharmacy at UA was established in 1947. Originally, it occupied temporary buildings (Quonset huts) until an addition to the Chemistry-Physics building was completed for Pharmacy. In 1966 it shared a new building with Microbiology on the Main Campus until it moved in 1982 to a brand-new Pharmacy only building in the Arizona Health Sciences Center in proximity to the Colleges of Medicine and Nursing. Classical pharmacognosy research was

originally carried out by Dean Willis Brewer, and Mary Caldwell who investigated medicinal plants from the US Southwest. The classical Pharmacognosy course was taught by Brewer and Vartkes Simonian from 1948 to 1975 when it was permanently removed as a separate course from the professional pharmacy curriculum, and incorporated into the Medicinal Chemistry course. In 1957, Jack Cole joined the College as an assistant professor after graduation from the University of Minnesota where he studied under the direction of Ole Gisvold. He was the recipient of NIH grants and a federal contract from the NCI in collaboration with the USDA to investigate plants with anticancer activity throughout the decades of the 1960s, 70s and 80s. These projects allowed the random screening of hundreds of plant extracts in diverse tumor models and afforded compounds with novel anticancer mechanisms of action such as bouvardin. Among the numerous students and scientists who participated in this program and later became independent researchers were Joseph Hoffmann, Shivanand Jolad, Ayhan Ulubelen (University of Istanbul). Jack moved on to become Senior Vice President and Provost of UA (1990). Since the early 1960s, the Department of Chemistry had also contributed in a significant manner to the development of phytochemistry at the UA. Cornelius Steeling and Robert Bates were important collaborators in diverse projects involving NMR studies of anti-tumor compounds and mentors of numerous graduate students including Michael Tempesta who is an active member of the ASP and the International Organization for Chemistry in Developing Countries (IOCD).

After graduating in 1980, Joseph Hoffmann became the Director of the Bioenergy Research Facility, a unit of the Office of Arid Lands Studies at the College of Agriculture. In response to price hikes for crude oil, the original mission was to develop liquid fuels from desert plants such as those containing latex or non-polar materials amenable to catalytic cracking. In the early stages of the project, Melvin Calvin (1961 Nobel Prize in Chemistry) provided advice for the identification of plant biomass for liquid fuel production. Steven P. McLaughlin, an economic botanist and taxonomist on the project, developed a sustainable crop adapted to arid regions of the US Southwest. Barbara Timmermann joined the chemistry group in early 1981 after graduation from the University of Texas at Austin under the mentorship of Tom Mabry. Research on biofuels was funded by the petrochemical industry (Diamond Shamrock Corporation) until 1983 when crude oil became cheaper and interests shifted from renewable sources of bioenergy back to fossil fuels. It is interesting to note that after a hiatus of 25 years there is today a worldwide interest in developing renewable sources of energy following strategies similar to those developed by the Arizona group in the early 1980s.

In order to expand to other areas of research, this facility was, in 1985, re-named the Bioresources Research Facility, and later became the Arizona Board of Regents approved Southwest Center for Natural Products Research and Commercialization (SCNPRC). Since 1985, research has focused on arid-adapted plants as sources of resins for the naval stores industry (grindelia and rabbit brush), liquid waxes (jojoba), rubber (guayule), fibers (hesperaloe) as well as sources of bioactive compounds from medicinal plants and soil microbes. Dr. Hoffmann acted as its Director until his untimely death in 2002 when Dr. Leslie Gunatilaka assumed the Director's position. Dr. Gunatilaka completed his graduate studies at Imperial College, London, under the mentorship of Sir Derek Barton (1969 Nobel Prize in Chemistry). Before joining UA in 1997, Dr. Gunatilaka was Professor of Organic Chemistry and Head of Department of Chemistry, University of Peradeniya, Sri Lanka, and spent several years in the laboratories of Drs. Carl Djerassi (Stanford) and David Kingston (Virginia Tech). Current interests of his group include investigation of bioactive natural products from Sonoran desert plants, and plant- and

lichen-associated microorganisms, and their utilization for agricultural and medicinal applications. He was recently joined by the microbial geneticist, Dr. Istvan Molnar.

In 1983, Dr. Timmermann began conducting collaborative research in the College of Pharmacy and transferred her appointment to the College as part of the professorial track in 1990, rising through the ranks to become a Regents Professor in the year 2000. During her tenure in the College of Pharmacy, she established international and interdisciplinary teams in the field of biodiversity prospecting for drug discovery and other areas of biomedical research. The NIH-funded International Cooperative Biodiversity Groups (ICBG) Program was established in 1993 as an endeavor to integrate the process of drug discovery leads from natural products, biodiversity conservation, and sustainable economic growth in Latin America in a unique model that incorporated academic science, traditional knowledge, commercial research and novel intellectual property mechanisms. In 2000, she also established the Arizona Center for Phytomedicine Research, a Botanical Center funded by the NIH/NCCAM/ODS, to conduct studies on the safety and efficacy of botanical dietary supplements with anti-inflammatory activity. The Center was designated a Center of Excellence by the Arizona Board of Regents in 2002. These projects facilitated the training of numerous students and scientists and capacity building. Technology transfer to collaborating countries and the opportunity for natural product chemists to collaborate with botanists, ecologists, social scientists as well as pharmacologists and physicians were also important focuses of the Center. She re-introduced the field of Pharmacognosy to the professional pharmacy curriculum by teaching the course "Phytomedicine" to 4th year students. This course familiarized pharmacy students with medicinal plants, their chemistry, uses, pharmacology, plant/drug interactions and other aspects of concern for botanical dietary supplements.

In August 2005, after almost 25 years at UA, Dr. Timmermann joined the University of Kansas (KU) where she was recruited as University Distinguished Professor and Chair of the Department of Medicinal Chemistry (see chapter on KU).

University of California, Santa Cruz

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The University of California Santa Cruz (UCSC) has played a robust role in the history of pharmacognosy and natural products research, primarily due to one highly collaborative and energetic individual. In 1974, a young professor of chemistry, Phil Crews, decided to explore the chemistry of sponges. Perusing a book entitled *Poisonous and Venomous Marine Animals of the World*, he learned that extracts from sponges had shown antibiotic and antiparasitic properties and, even more interesting, the chemistry of sponges was largely unknown. Thus, he decided to embark on an adventurous and productive research path at UCSC that continues more than thirty years later.

Fast-forward to 2008 – the UCSC Department of Chemistry and Biochemistry is now the home of a Chemical Screening

Center created and directed by Assoc. Professor R. Scott Lokey. A promising, young marine natural products chemist, Asst. Professor Roger Linington, recently joined the department. The California Institute for Quantitative Biosciences (QB3), a collaborative effort between UC San Francisco, UC Berkeley, and UC Santa Cruz, is opening new avenues for natural products research with a focus on global health and neglected diseases. Notably, two marine sponge-derived compound classes discovered in the Crews lab, the bengamides and the psammaplins, provided the basis for synthetic derivatives (NVP-LAF389, LAQ-824, and LBH-589) for evaluation in past and current anticancer clinical trials. Several additional marine-derived compounds are undergoing preclinical evaluation, mainly at the Ford Cancer Center and the National Cancer Institute.

Dr. Phil Crews has been the principal investigator of a National Cooperative Drug Discovery Group (NCDDG) since 1990. The current co-principal investigators in this NCDDG include Professor William Fenical and Dr. Paul Jensen (UCSD-SIO), Professor William H. Gerwick (UCSD-SIO), and Dr. Amy Wright (HBOI-FAU). Originally, the pharmaceutical partner was Syntex (Dr. Tom Matthews), it transitioned to Sandoz (Dr. Ken Bair) and currently is Novartis Institutes for Biomedical Research (Dr. Alec Wood). The focus is on the targeted discovery of anticancer drugs from marine sources.

Another major and productive collaboration was forged in 1989 by Professor Crews with Dr. Fred Valeriote of the Ford Cancer in Detroit, Michigan and is currently funded until 2012. Thousands of crude extracts from marine sponges and marine-derived fungal cultures have been evaluated over the years in a soft agar colony-based disk diffusion assay using a panel of murine and human cancer and normal cell lines. Some of the major solid tumor selective compound discoveries include the milnamides, fijianolides, mycothiazole, and psymberin.

Beginning in 1980, the Crews lab has collectively conducted more than 80 field expeditions to oceanic study sites around the world including Papua New Guinea, Vanuatu, Fiji, Tonga, Solomon Islands, Indonesia, Malaysia, the Red Sea, Venezuela, U.S. Virgin Islands, Puerto Rico, Hawaii, Cayman Islands, Gulf of Mexico, and Monterey Bay. Evolving field strategies for the

collection of marine sponges and deep-water sediments are an integral aspect of the marine natural products research program at UCSC. This work has significantly deepened the understanding of chemical ecology and marine natural products biosynthesis, as well as the relationship between secondary metabolite chemistry and taxonomy. The field program has resulted in several international collaborations with scientists, students, research institutions and universities in the host countries.

A cadre of marine natural products researchers received training at UCSC and proceeded to establish productive careers in their own right. Professor David Sherman, Director of the Chemical Genomic Center at the University of Michigan, was an undergraduate researcher in the Crews lab. Professor Marcel Jaspers, now at the University of Aberdeen in Scotland, was a post-doctoral research fellow at UCSC. Other post-doctoral researchers include Professor Ivette C. Pina (Universidad Central de Venezuela), Asst. Professor Robert Cichewicz (Oklahoma University), Dr. Taro Amagata (San Francisco State University), Asst. Professor Chad Stessman (California State University Stanislaus), Asst. Professor Jennifer Carroll (California Polytechnic State University), Dr. Madeline Adamczeski (San Jose City College), and Asst. Professor Omar Christian (University of the Virgin Islands).

Vast arrays of unique compounds from marine sponges and marine-derived fungi have been discovered at UC Santa Cruz, nearly 1,000 compounds to date. Marine natural products research at UCSC continues to thrive and evolve as new molecular targets are revealed as well as new technologies for the rapid assessment of chemical complexity and structure elucidation.

Pharmacognosy Research and Teaching at U. Connecticut

Cedric Pearce[a], John P. N. Rosazza[b] and Robert J. Krueger[c]

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1.0 General description

The modern era for pharmacognosy at UConn was started by Arthur Schwarting who pioneered the use of chemistry and biochemistry for understanding medicinal plants and their components rather than the more traditional botanical approach. Schwarting was also instrumental in establishing the ASP and was editor of the *Journal* for seventeen years, an activity shared with his colleague Bill Kelleher who also spent his entire career in the pharmacognosy section at UConn's school of pharmacy. There was a very active research and teaching community within the pharmacognosy faculty, which included Professors Schwarting, Kelleher, Mike Edwards, Ana Rother, and Dick Hutchinson/Steve Gould/Chris Ireland overlapping in one of the major centers for natural products research in the US. Areas of research included medicinal plants and their active principles, fungal and bacterial metabolites, marine products, structure elucidation and biosynthesis. Many of the students who were trained during this period went on to have a major influence on the American Society of Pharmacognosy, in natural products research and development throughout the US and in other parts of the world, both at universities and in the private sector. These included a number of Presidents of the Society; Tip Tyler (Washington, Purdue), Dave Carew (Iowa), E. John Staba (Nebraska, Minnesota), Ralph (Swede) Blomster (Maryland), Jack Rosazza (Iowa), and Ara Paul Dean at Michigan, Lee Schramm (Georgia) who was a society treasurer, and Robert (Bob) Krueger who has held numerous ASP/ASPF positions. The annual ASP meeting was held in Storrs in 1975.

2.0 Pharmacognosy Faculty

Frederick S. Eaton (1925-1928)
Leslie Barrett ((1932-1950)
Josephine Izzo (1934-1951)
Arthur E. Schwarting (1949-1980; d1996)
William Kelleher (1960-1988; d2007)
Ana Rother (1964-1997)
J. Michael Edwards (1970-1997)
C. Richard (Dick) Hutchinson (1970-1974)
Steven J. Gould (1974-1982)
Christopher M. Ireland (1979-1983)
Cedric Pearce (1983-1988)
Zibigniew J. Witczak (1991-1998)

3.0 Natural Product Research at UConn

Arthur E. Schwarting joined the School of Pharmacy in 1949, and was promoted to Dean in 1970. His approach to teaching Pharmacognosy was radical in that he treated the field first from a chemistry perspective, classifying drug plants by their active components rather than traditional taxonomic and morphological groupings, and believed in the importance of considering the biosynthesis and biochemistry of the active principles. It is because of this that he is credited with setting the stage for modern pharmacognosy, with its emphasis on bioactive natural products and drug discovery. He was instrumental in the formation of the ASP, and in 1960, he took on the editorship of *Lloydia* (which did not became officially affiliated with the ASP until 1961), and served as the first editor for seventeen years, during which time the journal underwent many changes, including being renamed *Journal of Natural Products*.

William Kelleher was a professor of Pharmacognosy for 28 years and for part of that time he served as Assistant Dean for Graduate Education & Research. He had many collaborations within the College, including work with Dr. Arthur Schwarting and also was known to spend many long hours helping him with editing *Lloydia*, and then the *Journal of Natural Products*. His main research interests were in microbial biochemistry, fermentation, and applied microbiology. Much of his work focused on the secondary products of *Claviceps paspali* which produced lysergic acid, *Amanita muscaria*, and berberine. Among his students were Jack Rosazza, Leon Pacifici, Robert Dobberstein (with AES), Robert (Bob) Krueger and Christopher Beecher. President of ASP 1973-1974.

J. Michael Edwards was a professor of Pharmacognosy for 27 years and for part of that time he served as Assistant Dean. His major research interests centered on medicinal plants and biosynthesis of secondary metabolites and he co-authored *The Biosynthesis of Aromatic Compounds* with Ulrich Weiss (Wiley) in 1980. Projects included cell culture for the pigments of *Wachendorfia thyrsifolia* with Robert Dobberstein. President of the ASP in 1984-1985.

Ana Rother studied plant tissue culture and alkaloid biosynthesis including the alkaloids of *Heimia salicifolia* with AES.

Dick Hutchinson's major interest was the biosynthesis of antibiotics and during his tenure at UConn he worked with Sir Alan Battersby's lab in Cambridge UK. Dick was the recipient of the Research Achievement Award in 2000.

Steven J. Gould's major research interest was in the biosynthesis of antibiotics.

Chris Ireland's interests lie in marine derived bioactive compounds and their structure determination and bioactivity. President of ASP 1991-1992.
Cedric Pearce worked on microbial products and was PI together with co-project directors Bill Kelleher and Ralph Collins on National Cancer Institute-funded *Fungal Fermentation* during 1985-1988.
James M. Bobbitt (Chemistry) and Ralph Porter Collins (Botany) joined with Art Schwarting and Bill Kelleher in winning the first NIH Natural Products Training Grant involving students from Pharmacognosy, Chemistry and Botany. The program brought visiting faculty including Burchard Franck, Kiel Univ. (morphine synthesis), Anders Kjaer, Netherlands (glucosinolates), David Perlman (Squibb, later Dean at Wisconsin); outstanding natural products conferences, and interdisciplinary work by students in each of the three laboratories.

University of Georgia, Athens

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The University of Georgia has had a long history of natural products research. This began with S. William Pelletier with his studies on plant alkaloids from 1962 – 2000 and continues with the recent appointment of Lyndon West in the Department of Pharmaceutical and Biomedical Sciences in the College of Pharmacy at the University of Georgia in 2005.

S. William Pelletier received a B.S. degree in chemical engineering from the University of Illinois in 1947, and received a Ph.D. from Cornell University in 1950. In 1951, Pelletier took a staff position in the organic chemistry department at the Rockefeller Institute in New York with the distinguished alkaloid chemist Walter A Jacobs where he worked on aconite and veratrum alkaloids. He was appointed as the head of the chemistry department at the University of Georgia in 1962. His research at UGA was primarily focused on the isolation and structural elucidation of C_{19} and C_{20}-diterpene alkaloids of *Aconitum*, *Consolida*, *Delphinium*, and *Garrya* species. Pelletier stepped down as department head in 1969 to serve as the provost of the University of Georgia for seven years before becoming director of the Institute of Natural Products Research, a position he held until retiring in 2000. The Institute for Natural Products Research carried out a program of fundamental studies in the interdisciplinary areas of analysis, chemistry, and pharmacognosy of natural products of biological interest from plants. Projects involved research on plant alkaloids, terpenes, insect pheromones, phytoalexins, antitumor agents, plant pigments, the synthesis of biologically-active natural products, and the application of modern spectroscopic methods for the elucidation of the molecular architecture of natural products. The Institute served as a valuable training center for many graduate students, visiting faculty and postdoctoral associates with interests in advanced training in separation techniques and methods for structure elucidation of complex natural products.

Pelletier edited the widely used series of books, *Alkaloids: Chemical & Biological Perspectives*, and published more than 360 manuscripts. He was a fellow of the American Association for the Advancement of Science and of the Royal Society of Chemistry. In 1991, he received a top research award from ASP for his lifetime work on alkaloids. He also won the 1971 Hefty Award from the Georgia Section of ACS and the 1972 Southern Chemist Award for distinguished achievements in chemistry from the ACS Memphis Section. He helped form the Northeast

Georgia Section of ACS and served as its first chairman in 1968. He served as president of the American Society of Pharmacognosy in 2001-2002. He died on Feb. 21, 2004 at the age of 79.

Lyndon West obtained his Ph.D. in Organic Chemistry in 2001 from Victoria University of Wellington, New Zealand, working on the isolation and structural elucidation of secondary metabolites from marine invertebrates. West then worked for two years as a postdoctoral research chemist with the late D. John Faulkner at Scripps Institution of Oceanography in San Diego, California. He was appointed Assistant Professor in the Department of Pharmaceutical and Biomedical Sciences in the College of Pharmacy at the University of Georgia in 2005 and is an associate member of the UGA Center for Drug Discovery.

West's research at UGA focuses on the isolation and structural elucidation of biologically active natural products from marine organisms, in addition to the development of new methodology for natural products chemistry to accelerate the discovery of drug leads. In particular the West group is addressing the incompatibility of natural products chemistry and high-throughput screening (HTS) by developing natural products isolation approaches compatible with HTS for the rapid isolation and the identification of bioactive compounds. The longer-term impact of his research will be the development of more streamlined and practical approaches to circumvent the current restrictions and incompatibilities, and could result in renewed interest in natural products research and be a powerful resource for both the drug discovery and academic communities. West has also developed methodology for the efficient fractionation of crude marine extracts.[1] This method addresses the difficulty of working with and loading crude extracts on chromatographic supports for fractionation. This method is becoming the method of choice for the initial stages of purification in academic laboratories throughout the world and it shows great promise as a useful technique for analytical and industrial scale natural products isolation in the future.

In 2005 Dr. West received an ASP research starter grant for his proposal entitled, "A novel approach to the identification of biologically active marine natural products." His approach to the discovery of biologically active natural products was recently awarded a NIH grant in the new NIH Roadmap for Medical Research in the Pathways to Discovery Initiative. The objective of this research is to generate a library of marine natural products that can be used by a nationwide consortium of small molecule screening centers called the Molecular Libraries Screening Network (MLSCN) to identify small molecules that can be optimized as chemical probes to study the functions of genes, cells, and biochemical pathways. This could potentially lead to new ways to explore the functions of genes and signaling pathways in health and disease.

In addition to search for biologically active compounds with biomedical potential the West group is also very interested in learning about the ecological function and the source of the complex natural products found in marine organisms.

Natural products research at UGA has a made a considerable impact on the field natural products chemistry and is expected to continue to do so in the future.

(1) Houssen, W. E.; Jaspars, M. In Natural Products Isolation, 2nd Edition, Methods in Biotechnology; Sarker, S. D., Latif, Z., Gray, A. I., Eds.; Humana Press Inc.: Totowa, NJ, 2006; Vol. 20, pp 353–391.

Marine Natural Products at the University of Hawaii

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Paul J, Scheuer (1915 – 2003) arrived at the University of Hawaii, Manoa (UH) in 1950. He had been recruited to join the faculty of the Department of Chemistry by Leonora Bilger, who had traveled to Cambridge, MA in search of new talent. At the time, he was finishing his Ph.D. work at Harvard with Professor R. B. Woodward (Nobel Prize 1965) on the structure of strychnine. Although he had never been to Hawaii, he accepted the position, and with his new bride Alice, began an odyssey across the country by train, then ship, taking the SS Lurline from San Francisco to Honolulu. They arrived at the Aloha Tower, the main port of entry at the time to the US Territory of Hawaii.

At the time, the UH (founded in 1907 as a land grant university), was not involved in research to a significant extent. The Department of Chemistry was especially lacking, but "Ma" Bilger's recruitment trip was aimed at attracting bright new faculty to invigorate research in her department. With the young Scheuer, she struck gold! He quickly began a research program on the natural products of endemic plants, which he found to be a rich resource of novel natural products since chemists had not yet discovered the unique flora of the islands.

Although chemistry was not a particularly active field at UH, biological research in the marine field was very active, and involved many notable scientists. Among these were ichthyologist Hank Banner, who was studying cases of human toxicity caused by eating tropical reef fish. Known as "ciguatera," the toxicity was known from the times of Spanish Conquistadors, and was a serious public health hazard in Hawaii and other locations in the Pacific, as well as the Caribbean. Banner and Scheuer began a long collaboration to determine the identity of the causative agent of ciguatera. The toxin, called Ciguatoxin (CTX), was found to be lipid soluble and not a protein. The structure of CTX was later determined by Takeshi Yasumoto (Tohoku University), a former postdoc in the Scheuer lab, who determined that the producing organism of the toxin was the dinoflagellate *Gambierdiscus toxicus* that grew on algae upon which reef fish grazed.

Another significant project which was initiated in the Scheuer group dealt with a legendary toxin from the soft coral *Palythoa toxica*. Known by natives as "Limu-Make- o'Hana" ("deadly seaweed of Hana"), legend described that in preparation for battles during the days of the Hawaiian kingdom, spear tips were dipped in an extract of this "limu" (seaweed), which rendered them deadly to any unfortunate recipient. Learning of this legend, Scheuer spent a great deal of effort to find the source organism. Eventually, he found someone who directed him to the location: which was one tiny hidden tidepool on Maui. The organism turned out not to be an alga, but a soft coral, but the presence of an extremely potent toxin was confirmed. Among the early workers on Palytoxin was a young postdoctoral researcher, Richard E. Moore (1933 – 2007), who had just joined the Scheuer group after completing his Ph.D. at UC Berkeley with Henry Rappoport. Early work on the structure of the toxin was difficult due to the large molecular weight and limited spectroscopic techniques (for the time) and small sample size.

Richard Moore was appointed to the UH Chemistry faculty in 1966. Work on Palytoxin continued as a joint project in both groups for a time, but Moore eventually continued work on the challenging structure, using a combination of classical chemical techniques and improving NMR methods to arrive at the final structure in 1981 (along with the Hirata group). Palytoxin and Ciguatoxin are among the most significant structural discoveries in marine natural products, since for their respective times, they were deduced after surmounting substantial challenges in terms of chemistry and biology.

In his other work, Scheuer usually focused on natural products with biological relevance, such as defensive secretions of nudibranchs. The earliest work involved *Phyllidia varicosa*, a nudibranch with an unusual odor which was toxic to other marine animals. The structure was determined to be an unprecedented rearranged isocyanate sesquiterpene, 9-isocyano-pupukeanane. Manoalide was isolated from the Palauan sponge *Luffariella variabilis*; and it was later shown to have a novel mechanism of anti-inflammatory action on phospholipase A2. From the sacoglossan mollusk *Elysia rufescens* and it's algal food (*Bryopsis* sp.), the Scheuer group discovered an array of cyclic peptides. Among these, Kahalalide F has been found to have promising anticancer activity and is currently in human clinical trials in Europe.[1]

In addition to Palytoxin, Moore's work has focused primarily on algal and cyanobacterial natural products. His initial work involved volatile compounds from marine algae which had pheromone-like activity. Later, he worked on bioactive natural products from many Hawaiian macroalgae. From the 1990s onward, he worked almost exclusively on cyanobacteria, and for a time harbored a world-class collection of cyanobacteria at UH, from which his group identified many dozens of novel bioactive natural products. Among the many compounds he worked on was a family of cyclic peptides known as the Cryptophycins (originally found by Merck). In their work, Moore, *et al*. found them to have exceptionally strong antitumor activity, and a synthetic analog was advanced into clinical trials by Lilly Research Laboratories.[2]

The Hawaii program pioneered by Scheuer, then complemented by Moore, is recognized as where modern marine natural products chemistry was initiated and popularized as an area of productive research. Both were recognized for their accomplishments by ASP Research Achievement Awards (Scheuer, 1994; Moore 2002), and they trained many scientists who today populate academic, industrial and government labs worldwide. Among these is Moore's son, Bradley Moore, who is on the faculty of the University of California, San Diego, and works on the biosynthesis of marine microbes. Others have followed in the footsteps of Scheuer and Moore at UH, including Thomas Hemscheidt and Philip Williams (the last Ph.D. student of Moore).

(1) Newman, D. J., Milestones Section.
(2) Gerwick, W. H., Milestones Section.

University of Illinois at Chicago, 1959-2008

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1.0 Introduction

The University of Illinois at Chicago (UIC), College of Pharmacy has played a unique and central role in the history of the American Society of Pharmacognosy (ASP) from its founding to the present. As indicated elsewhere in this book, the ASP was founded at the 1959 Teachers of Plant Sciences Seminar held at UIC. Among the founders of the Society were four incumbent (Ralph Voigt, Frank Crane, Ed Mika and Stan Smolenski) and two future (Norman Farnsworth and Elmore Taylor) UIC faculty members. A Charter member (Harry Fong) also joined this faculty a decade later. From the outset, UIC ASP members served the Society in a variety of ways, from memberships and chairs on standing and ad hoc committees to treasurers, vice-presidents, presidents, *Journal of Natural Products* editors, and organizers/hosts of annual meetings (1974, 1991). Additionally, UIC members also contributed to pharmacognosy and to the ASP through their educational, research and scholarly efforts.

1.1 Faculty members and their ASP services In all, some 26 ASP members have served on the faculty (21 teaching and 5 research) in the College of Pharmacy, UIC. The roster of faculty members by chronological order are: 1960's: Ralph Voigt, Frank Crane, Ed Mika, Stan Smolenski, Audrey Bingel; 1970's: Norman Farnsworth, Harry Fong, Elmore Taylor, M. Tin Wa, Geoffrey Cordell, Robert Dobberstein, Douglas Kinghorn, Doel Soejarto; 1980's: John Pezzuto, Charles Phoebe; 1990's: Cindy Angerhofer, Chris Beecher, Darrick Kim, Gail Mahady; 2000's: Guido Pauli, Jimmy Orjala. Research faculty members: Wm Loub, C-t Che, Hongjie Zhang, Shaonong Chen, Birgit Jaki. Most have served the Society in one capacity or another. F. Crane was the first ASP treasurer. N. Farnsworth served as the first Vice President and the second ASP President (while at the University of Pittsburgh). Four other faculty members (E. Taylor, H. Fong, G. Cordell, and A.D. Kinghorn) and one former graduate student (Robert Borris) also served as ASP presidents. A.D. Kinghorn and H. Fong also served, respectively, as editor and associate editor of the Society's *Journal of Natural Products*. G. Pauli is presently serving as ASP Assistant Treasurer. In turn, the ASP has honored N. Farnsworth, H. Fong and G. Cordell as Honorary Members; and awarded Farnsworth the Research Achievement Award (since named after him). Although of little notice, the Society's official gavel was crafted by R. Voigt from the wood of *Rhamnus purshiana* L. (Rhamnaceae) (Cascara sagrada). Replicas of this gavel (made from the same wood) have been presented by Farnsworth to the outgoing ASP presidents as a highlight event at the annual ASP meeting.

1.2 Graduate and post-doctoral training at UIC

One of the enduring traditions at the ASP annual meetings has been the large contingent of participants, including faculty members, students, post-doctoral fellows and visiting scientists/scholars, from UIC. Since 1970, UIC has trained >105 Ph.D. and 10 M.S. graduates, and mentored >250 post-doctoral fellows/visiting scientists in pharmacognosy. Of the former Ph.D. students, >40 have become faculty members in pharmacy, other health or science colleges, and 10 have became Deans of pharmacy or related health profession faculties. Others found positions in industry and government. Our former post-doctoral fellows and visiting

scientists/scholars have been similarly positioned and, in turn, have contributed to the advancement of pharmacognosy in many ways.

1.3 Research and scholarly contributions

In the first decade of the ASP history, UIC members conducted independent research primarily in the area of plant physiology. With the appointment of N. R. Farnsworth as Head of the Department of Pharmacognosy and Pharmacology in 1970, chemical, biochemical and biological based drug discovery research begun, initially focusing on the search for anti-cancer agents (Farnsworth; Fong; Cordell) and natural sweeteners (Kinghorn). Shortly, the philosophy of a multidisciplinary, collaborative research approach took root. The first major multidisciplinary collaborative drug discovery research project concerned the search for fertility regulating agents from plants sponsored by the World Health Organization (WHO) (1977-1988) with the team composed primarily of ASP members (Fong [coordination]; Soejarto [botany], Cordell [phytochemistry], Bingel [reproductive pharmacology]) and a non-ASP member (D. Waller [reproductive toxicology]). A series of other collaborative projects followed: NIH/NCI NCDDG project (1990-2004; Cordell, Kinghorn, Farnsworth, Soejarto, Pezzuto); NIH/NCI PO1 cancer chemoprevention (1991-2004; Pezzuto, Farnsworth, Fong, Kinghorn, et al); NIH ICBG drug discovery/bio-conservation (1998-2008; Soejarto, Fong, Pezzuto, Zhang); NIH/UIC (NCCAM/ODS) Center for Botanical Dietary Supplements Research (1999-2010; Farnsworth, Fong, G. Pauli, *et al*.). Further, research collaboration with other institutions, including the Univ. Maryland (Fong, Zhang); Purdue/Univ. Hawaii Hilo (Fong); and the Ohio State Univ. (Orjala, Farnsworth, Soejarto) are ongoing. The research expenditures from these and other grants exceeded $75 million, and generated more than 1,200 research papers, 28 patents, >140 reviews, and >210 book chapters. In other scholarly activities, UIC ASP members edited >85 reference books, and served as editor or associate editors of major journals and references: *Journal of Natural Products* (Kinghorn, Fong); *Phytomedicine* (Farnsworth); *Pharmaceutical Biology* (formerly, *International Journal of Crude Drug Research*) (Pezzuto); *Journal of Ethnopharmacology* (Soejarto); *The Alkaloids, Chemistry and Biology* (Cordell); and *Phytochemistry* (Cordell). The WHO Collaborating Center for Traditional Medicine (1981-) and the NAPRALERT database www.napralert.org (1973-) were also established at UIC to promote research and scholarly activities.

Pharmacognosy at Iowa

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1.0 General description

Pharmacognosy and Natural Products research has a long and robust history at the University of Iowa (UI), with ASP faculty members from the divisions of Pharmacognosy and Medicinal and Natural Products Chemistry (MNPC) in the College of Pharmacy, and the Departments of Chemistry and Biological Sciences in the College of Liberal Arts and Sciences. Over 100 students have received Ph.D. degrees in pharmacognosy-related research, and over 75 postdocs and other visiting scholars have pursued research in faculty laboratories. Iowans have been very active in the ASP as long standing members of Executive and numerous other committees, and the editorial advisory board of the *Journal of Natural Products*. Dave Carew, Jack Rosazza, and

Jim Gloer were the 6th, 22nd, and 40th ASP Presidents, respectively, and Dave is a Charter Member, and Honorary Member.

After combining with Medicinal Chemistry in 1978 to form the new division of MNPC with Jack Rosazza as Head, pharmacognosy was replaced as a teaching course by MNPC courses. Relevant graduate courses offered at UI included Antibiotics, Separation Methods in MNPC, Biocatalysis in MNPC, Biogenesis of Natural Products, and Spectroscopic Methods in Organic Chemistry. Rosazza co-founded and was first Director of the world renowned UI Center for Biocatalysis and Bioprocessing, which provides fermentation and bioprocessing facilities, education, and training support (more than 300 graduate student-years), and fosters interactions among 55 faculty from eight departments, including Profs. Gloer, Poulton, and Wiemer.

2.0 Pharmacognosy/Chemistry/Biological Sciences Faculty

2.1 Dave Carew (1957-1993): Prof. emeritus Pharmacognosy, MNPC; Assistant Dean Pharmacy 1975-1991; Massachusetts College of Pharmacy, U.Connecticut, Ph.D. 1957; 7 Ph.D., 9 M.Sc. students, 1 postdoc; 28 publications.

2.2 Jack Rosazza (1969–2004) Prof. emeritus MNPC, U. Connecticut Ph.D., 1968; MNPC Head (1978-85; 1990-2001); 30 Ph.D., 7 M.Sc. students, 32 postdocs and visiting scientists, more than 50 lab techs; ~220 publications including patents.

2.3 Jonathan Poulton (1977-present), Prof. Biological Sciences, Ph.D. Oxford University, 1974; President Phytochemical Society of North America, 1989; PSNA Treasurer 1983-88; 7 Ph.D., 7 M.Sc. students, 6 postdocs; 48 publications

2,4 David Wiemer (1978-present) Prof. and Chair, Chemistry, Ph.D. U. Illinois, Champaign-Urbana 1976; 37 Ph.D., 15 M.Sc. students, 14 postdocs, ~150 publications.

2.5 Jim Gloer (1984-present), Shriner-Carver Prof. of Chemistry, Ph.D. U. Illinois, Champaign-Urbana 1983, 24 Ph.D., 11 M.Sc. students, 20 postdocs and visiting scientists, ~125 publications.

2.6 Thomas Prisinzano (2003 – 2007) Assoc Prof. MNPC, Ph.D. Virginia Commonwealth U., 2000, ASP Jack L Beal Prize, 2006; John D. Faulkner Award, ASP, 2005; 6 Ph.D. students, 3 Postdocs, ~50 publications. Moved to U. Kansas in 2007.

3.0 Natural Product Research at Iowa

3.1 Carew was one of the first to investigate medicinal plant tissue cultures for their ability to produce secondary metabolites. Dave's ground-breaking research with *Catharanthus roseus* cell cultures was supported by the first NIH grant to be awarded to a UI Pharmacy faculty member.

3.2 Rosazza's group developed: 1) microbial and enzymatic transformations of natural and synthetic compounds (natural antitumor agents, alkaloids, antibiotics, steroids and other terpenes, antioxidants, pesticides); 2) Microbial Models of Mammalian Metabolism (M^4); and 3) biocatalysts as reagents in organic synthesis including biorenewables. Bioorganic/mechanistic enzymology revealed mechanisms of oxidation, reduction, C-C bond fission, O-, N-dealkylation, and SAM-dependent methylation. Key discoveries include characterization of the first bacterial NOS system; and cloning, mechanism and applications of carboxylic acid reductase.

3.3 Poulton's lab combined biochemical, molecular, and immunocytochemical approaches to learn more about the biological roles played by various groups of hydrolases in plants. These included glycoside hydrolases, glucosidases and galactosidases in *Arabidopsis*, and expressing target hydrolases in *Pichia pastoris*. Evaluations of plant glucosidase aglycone specificity were evaluated by cloning cDNAs from *Prunus serotina* encoding amygdalin hydrolase and prunasin

hydrolase, and use of site-directed mutagenesis. Biochemical enzymology and genetic studies were used to evaluate the role of glucosidase in *Melilotus alba*.

3.4 Wiemer's group developed new strategies for organic synthesis based on organophosphorus compounds, designed and synthesized various "unnatural" compounds as metabolic probes or antimetabolites, and synthesized biologically active natural products. Targets included (+)-jatrophone, a potential anticancer agent, and the sesquiterpenoids arenarol and avarol, potential anti-HIV agents. Other research involved cylindrol A and related inhibitors of farnesyl:protein transferase, prenylated benzoic acids that his group isolated from tropical plants as leafcutter ant repellents and potential antiinsect and antifungal agents, and the schweinfurthins. Wiemer, *et al*. designed several families of terpenoid phosphonates as analogs of farnesyl pyrophosphate (FPP), a key metabolic intermediate in steroid biosynthesis, and as a metabolic reagent for addition of lipophilic terpenoid units to a variety of proteins.

3.5 Gloer's pioneering work on the isolation and structure determination of novel fungal natural products with pharmacological, agricultural, and/or ecological significance made use of observations in fungal ecology in order to target certain groups of fungi as logical sources of valuable new metabolites. Projects included studies of fungal metabolites that may be involved in inter-species competition or parasitism within natural ecosystems, and investigation of the possibility that some fungal metabolites may serve as chemical defenses against fungivorous predators. Compounds were evaluated using antiinsectan, antibacterial, antifungal, and anti-tumor screens. Discovery of many new bioactive natural products in this work reflects the value of this kind of targeted approach, and in some instances, contributed to a better understanding of the roles of secondary metabolites in the life cycles of the fungi that produce them.

3.6 Prisinzano's research combined natural product isolation and medicinal chemistry with a specific focus on structural modifications of the neoclerodane diterpene, salvinorin A, the ultimate goal being the production of novel non-morphinan opioid receptor ligands (agonists and antagonists) having fewer of the undesirable side effects found with opium alkaloids.

Pharmacognosy at the University of Kansas

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A disagreement between the state's pharmacists and physicians led to the establishment of The School of Pharmacy at KU in 1885 which occupied two rooms in the chemistry building. The program of study consisted of two years of academic work, and at the time, for entrance the school controversially required graduation from a four year high school. Dr. Lucius E. Sayre came from the Philadelphia College of Pharmacy to be the first dean. He was a well known pharmacognosist who had written 180 articles and several books, the most influential being *A Manual of Organic Materia Medica and Pharmacognosy* that went into four editions, the last being published in 1917.He was a progressive educator who lengthened the program of study to three years, and received numerous honors. He served as director of drug analysis for the State Board of Health, as a member of the botanical staff for the State Board of Agriculture, and on the USP revision committee from 1890 until his death in 1925, and was elected as president of the American Pharmaceutical Association (APhA) in 1919. The most lasting of his scientific

researches is his establishment of the utility and wholesomeness of corn oil, a by-product of cereal making, in cooking. The Corn Products Company in North Kansas City, MO, was established to exploit his findings.

Dean Sayre was succeeded as dean by faculty member L. D. Havenhill whose work blended both chemistry and pharmacognosy. After taking a leave of absence in 1907 and qualifying to become Federal Food and Drug Administration inspector, he tested the identity and quality of foreign drugs entering the port of New York, and returned to the faculty becoming chief of the drug laboratory for the State Board of Health. His research legacy is in pharmacognosy, drug analysis and pharmaceutical chemistry, and in 1932 he increased the academic program to four years of study. Dean Havenhill was president of the American Association of Colleges of Pharmacy (AACP; 1913), vice president of the APhA (1914) and vice president then president of the Kansas Academy of Science (1917-8), and retired as dean in 1940, and from teaching in 1945.

The tradition of pharmacognosists as deans continued with the appointment of Dean J. Allen Reece from the Medical College of Virginia. Dean Reece, who was the only faculty member at the time with a Ph.D., worked to establish a graduate program at KU. Under him the faculty grew to seven members, with graduate students making up 1/3 of the students in the school, and in 1958 he increased the B.S. graduation requirements to five years. He was a member of the Revision Committee of the USP for 10 years and was president of the AACP. Perhaps the most prominent of Dean Reece's graduate students was Jack L. Beal who had a spectacular career at The Ohio State University. Dean Reece died in 1963 and was replaced by Howard Mossberg, the first non-pharmacognosist to hold the deanship.

Just prior to this, Edward Smissman was attracted to KU from the University of Wisconsin where he was professor of medicinal chemistry. Best remembered today for his outstanding synthetic contributions to the molecular mode of action of drugs through molecular rigidification, Smissman also made important pharmacognostic contributions in the areas of insect feeding attractants and in the synthesis of shikimic acid. This started the tradition that henceforth pharmacognosy would be blended with medicinal chemistry at KU. He was instrumental in building the department to international prominence and was named University Distinguished Professor.

Following Smissman's untimely death in 1974, Lester A. Mitscher joined the medicinal chemistry department as University Distinguished Professor and chairman in 1975, leaving behind his post as professor of natural product's chemistry at The Ohio State University. Mitscher continued the tradition of blending pharmacognosy and medicinal chemistry research. Mitscher's natural product work concentrated on antiinfective agents, antimutagenesis and anticancer agents. He was elected President of the ASP in 1992 and chairman of the ACS Division of Medicinal Chemistry in 1973. Starting in 1975, Professor James D. McChesney held joint appointments in the Botany and Medicinal Chemistry Departments and made many contributions to pharmacognosy. He subsequently went to the University of Mississippi as chairman, and later became CSO of NaPro and ChromaDex corporations. Among his many important contributions is the implementation of the National Center for Natural Products Research at Ole Miss. In 1979, Dale L. Boger began his spectacular academic career in the department, later holding professorships at Purdue University and at the Scripps Research Institute. He has won many honors and distinctions for his work on the total synthesis of

biologically active natural products. In January 1985, Gunda Georg joined the faculty of medicinal chemistry and rapidly gained an international reputation for the synthesis of complex natural products, with an emphasis on anticancer and anti-Alzheimer's agents, including carbapenems, epothilone, cryptophycin and taxol analogs. She assumed the chair of Medicinal Chemistry at the University of Minnesota in 2006.

In 2005, Professor Barbara Timmermann moved from a Regents Professorship at the University of Arizona to take over the chairmanship of the department and assume the rank of University Distinguished Professor. Her research interests include biodiversity prospecting for drug leads from plants and microbes; chemical and biological standardization and preclinical evaluation of botanical dietary supplements for inflammation; molecular plant phylogeny and systematics and chemical ecology. Widely published in pharmacognosy and a member of the ASP Executive Committee, her appointment strengthens the departmental natural products program. A new course on modern pharmacognosy (Phytomedicinal Agents) was introduced in 2006 for 4th year students in the Doctor of Pharmacy Program, and in August 2007, Professor Thomas Prisinzano was recruited from the University of Iowa to further expand the area of natural products chemistry, with an emphasis on compounds affecting the central nervous system. He has a strong publication record on the action of salvinorin A and related neoclerodane diterpenes at opioid receptors, including the discovery of the first neoclerodane diterpene activity at opiod receptors; in 2006. He received the Jack L. Beal Award in recognition of the outstanding quality of his papers published by the *Journal of Natural Products*.

The University of Mississippi Natural Products Program

Charles D. Hufford,[†] Alice M. Clark,[†] Larry A. Walker,[†] James D. McChesney[‡]

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The natural products era at Ole Miss was truly born when Dr. Charles Hartman, Dean of the School of Pharmacy, convinced the State legislature in 1964 to create and fund the Research Institute of Pharmaceutical Sciences (RIPS), with the mission of establishing a program for the discovery and dissemination of knowledge concerning natural drug products. He served as the first director until 1970, and hired Dr. Norman Doorenbos in 1965 and Dr. Coy Waller in 1968; both were key individuals in the development of the natural products program. Doorenbos became Chair of the new Pharmacognosy department in 1968 and Waller became Director of RIPS in 1970. Detailed accounts of these early projects are published.[1,2] From about 1970, the Pharmacognosy and RIPS programs have developed along separate, but highly complementary paths.

From 1970-1995, the Pharmacognosy department initially consisted of Drs. Doorenbos, M. W. Quimby, L. W. Robertson and M. Corbett. Dr. Charles Hufford replaced the retiring Dr. Quimby and Dr. Farouk El-Feraly replaced Dr. Robertson. During these years, the fundamental foundation in pharmacognosy research was laid in the areas of plant, microbial and synthetic natural product chemistry. With the departure of Doorenbos as Chair in 1977 and the hiring of Dr. James D. McChesney as Chair, the department took on an even more energetic program in these areas with a special interest in tropical diseases. Dr. Alice Clark was hired in 1981 and during the next few years, vigorous research programs in the tropical disease and antifungal drug discovery areas were developed. When McChesney was appointed as RIPS Director in 1987, Hufford was named as Chair of Pharmacognosy. He continued to foster the excellent research

environment and stressed the importance of the undergraduate teaching mission of the School of Pharmacy. He recruited Drs. David Rotella, John Peterson and later Dr. Jordan Zjawiony, and in 1993, the program took on a new direction with the hiring of Dr. Mark Hamann, who has established a well-funded marine natural products program. Dr. Marc Slattery, who was hired two years later, has also been a significant contributor to the marine program. During these years the Pharmacognosy faculty were extremely productive in natural products research and teaching as both McChesney and Clark were named as F.A.P. Barnard Distinguished Professors of Pharmacognosy in 1993. In 1995, Hufford was appointed as Associate Dean for Research and Graduate Programs, but he continued to serve as Interim Chair of Pharmacognosy and hired Dr. Dale Nagle as a new faculty member who has developed a well-funded program in cancer research. Dr. Nikolaus Fischer was appointed as Chair in 1997 and served until 2001 when Dr. Daneel Ferreira became Chair. The current Pharmacognosy faculty consists of Drs. Ferreira, Hamann, Zjawiony, Slattery, Nagle, Yu-Dong Zhou, Hufford, Clark and Joint RIPS faculty Drs. David Pasco, Ikhlas X Khan, and Samir Ross; the department has contributed significantly to the natural products research and graduate education program.

Between 1970-1995, the RIPS program was also being established. A full time staff of natural products scientists was created in the early 1970s and the Marihuana Project was the most significant program to evolve. Started by Doorenbos and Waller, and later significantly expanded by Drs. Carlton Turner and Mahmoud ElSohly, this project evolved to a major project and remains so even today. Turner was appointed Director in 1980 and served until 1984, when he left to serve President Reagan on drug abuse policy. Dr. Tom Sharpe served as Interim Director until 1987, when McChesney was appointed Director. Under McChesney's leadership the RIPS Drug Discovery program evolved into a well organized program and the concept was developed for the establishment of a National Center for the Development of Natural Products (NCDNP). In 1991 the RIPS programs occupied a new research facility (later named the Coy Waller Research Complex) constructed on the grounds of the M. W. Quimby Medicinal Plant Garden, and expanded to include the marihuana growing facility.

Planning of the NCDNP was authorized in 1989, and it was implemented with $1 million from the State Legislature, first occupying the Thad Cochran Research Center in 1995.[1] Clark was named Interim Director, becoming Director in 1996, with Dr. Larry Walker who had become a significant contributor to the natural products program, as Associate Director. The program was renamed in 1999 as the National Center for Natural Products Research (NCNPR). In 2001 Walker was appointed Director when Clark became Vice Chancellor for Research and Sponsored Programs. The research program has focused on the discovery of anti-infectives, anticancer agents, and agents that are useful as anti-inflammatory agents or immune modulators. Studies are also conducted on the botanical, agronomic, chemical, and pharmacological aspects of medicinal plants, and recently the Center developed a program studying botanical products used as dietary supplements in the US, established through a Specific Cooperative Research Agreement with the Center for Food Safety and Applied Nutrition of the FDA. Walker has looked to Khan and Pasco to assume expanded roles as Assistant Directors.

In 1996, the USDA-ARS Natural Products Utilization Research Unit (NPURU) was formalized and Dr. Steve Duke was named research leader. Currently having about 20 faculty and staff members, efforts are focused on the development of pest management agents based on natural products with new fungicidal and insecticidal applications.

In summary, the natural products programs at Ole Miss have contributed significantly to the research and education environment of the School of Pharmacy, the State of Mississippi, the ASP, and the at-large scientific community as well. Three faculty members have served as Presidents of ASP (McChesney 1986-1987; Clark 1994-1995; Hufford 1996-1997), two annual ASP meetings were hosted (Oxford; 1982, 1995), as well as two interim meetings (Tunica, 1999; Oxford, 2008). Clark and Ferreira have made significant contributions as Associate Editors of the Journal of Natural Products. Nagle and Hamann were awarded ASP Matt Suffness Awards in 1995 and 2005, respectively. There have been many contributions to ASP committees and other student and faculty awards as well. The Pharmacognosy department still makes significant contributions to the undergraduate teaching mission on natural product information.

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University of North Carolina, Chapel Hill

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Natural Products Research Laboratories, School of Pharmacy, University of North Carolina, Chapel Hill, North Carolina

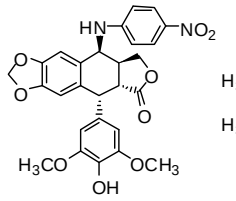
Natural products research at the School of Pharmacy, University of North Carolina at Chapel Hill (UNC-CH) was initiated by Dr. Jack K. Wier, a past President of the American Society of Pharmacognosy from 1980-1981. Dr. Wier was a devoted educator, and also involved in biosynthetic studies of the antitumor alkaloid camptothecin. His extensive collection of authentic herbal drug samples was displayed in a teaching laboratory that later became part of the Natural Products Research Laboratories (NPRL).

Dr. K.H. Lee has been the Director of the NPRL since 1983 and a member of the UNC faculty since 1970. His research on bioactive natural products and synthetic medicinal chemistry has been continuously funded from NIH and other research grants since 1971. Initially, Dr. Lee pursued structure-activity relationship and mechanism of action studies of the sesquiterpene lactone helenalin, leading to the discovery of several potent antitumor agents, some of which were also potent anti-inflammatory and anti-arthritis agents, better than indomethacin and phenylbutazone.[1] Subsequent research on antitumor quassinoids led to several potent antitumor, as well as antimalarial, agents.[2] A potent multipurpose antifungal agent, 1,4-bis-(1,3-epoxypropylamino)-9,10-anthraquinone, was also discovered and licensed to Rohm and Haas (Philadelphia, PA) for commercial use.[3] The NPRL also synthesized analogs of the Chinese antimalarial agent qinghaosu, and discovered compounds as potent as artemisinin *in vitro*.[4]

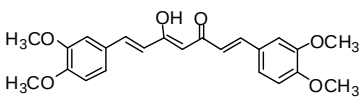
The NPRL's efforts in discovering antitumor agents are based on bioactivity-directed fractionation and isolation (BDFI) of medicinal plants, especially those used in traditional Chinese medicine, followed by rational drug design-based methods to produce the most promising lead for development. The synthetic etoposide analog, GL-331, derived from podophyllotoxin,[5] was designed successfully to combat solubility, drug resistance, and other detrimental issues of the anticancer drug etoposide. GL-331 was developed to Phase II clinical trials first by M.D. Anderson Cancer Research Center and later in Taiwan. In addition JC-9, discovered based on the curcumin model,[6] has been licensed and developed by Androscience (San Diego, CA). After successful Phase I clinical trials against acne, Phase II clinical trials should be completed in spring 2008. Androscience expects to conduct future clinical trials with

JC-9 against prostate cancer. Continuing BDFI as well as synthetic modification has also led to two additional promising anticancer leads: neo-tanshinlactone,[7] which is more active and selective than tamoxifen, and tylophorine-based analogs.[8] Neo-tanshinlactone and its analogs will be licensed and developed as clinical trials candidates with Calvert Research Institute (Cary, NC).

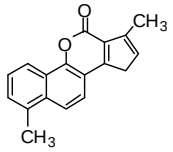
The NPRL's anti-AIDS studies were begun as part of the NCDDG research program. AIDS



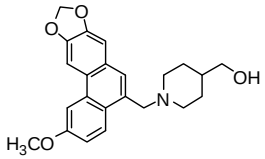
GL-331



JC-9

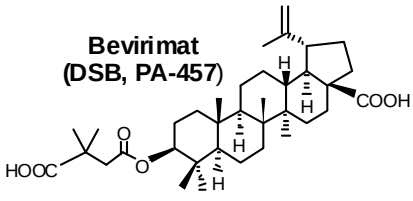


Neo-tanshinlactone

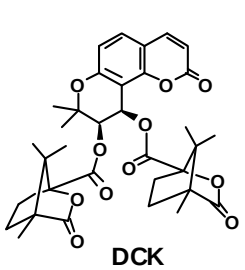


Tylophorine Analog

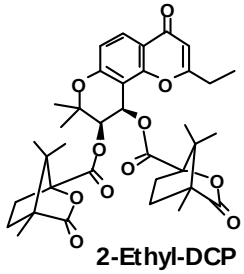
research in the NPRL has had continual NIH funding for 17 years, and has led to the discovery of many potent anti-HIV agents, which inhibit viral replication in H9 lymphocytes. Two lead compounds showed remarkable activities in this assay: DSB, a synthetic analog of the natural triterpenoid betulinic acid, and DCK, a coumarin-based analog of the natural product suksdorfin.[9] Both classes of compounds were patented and licensed to Panacos Pharmaceuticals (Gaithersburg, MD) for development into clinical trials candidates. DSB was renamed PA-457 and then Bevirimat and is in fast-track drug development status. It succeeded in Phase IIa clinical trials in September 2005. Phase IIb clinical trials should be completed soon, and Phase III trials are scheduled to begin in 2008. Bevirimat is the first in a new class of HIV drugs called maturation inhibitors, and its novel mechanism of action makes it promising for use alone or together with current anti-AID agents.[10] DCK has been modified to DCP,[11] which overcomes drug resistance problems encountered by DCK. Currently, many new analogs of DCP have been produced, and hopefully, one will be brought to clinical trials soon.



Bevirimat
(DSB, PA-457)



DCK



2-Ethyl-DCP

Since 1971, the NPRL has discovered over 3,000 bioactive natural products, their synthetic derivatives and analogs, which serve as new templates for drug design and development. Most recently, the NPRL is involved in the NIH Roadmap Initiative to supply natural products and analogs for novel and diverse chemical libraries to be screened against novel biological targets. This new program coupled with the research described above reflect the truth that natural products are a great resource for discovery of promising leads and the most effective way for new drug discovery and development.

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University of Pittsburgh

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1. Introduction

In 1955, the Department of Pharmacognosy at the Univ. Pittsburgh (Pitt) was a one-man operation, run by Edward P. Claus, whose major research interest was the study of allergenic plants, and there was only a Master's Program in Pharmacognosy. Claus left to become dean of the school of pharmacy at Ferris State College in Michigan in 1957. After receiving his M.S. Degree from the Massachusetts College of Pharmacy in 1955, Norman Farnsworth joined the Pharmacognosy Department at Pitt as instructor in biological sciences from 1955-1959, and during this time he was working toward his Ph.D. at Pitt. On receiving his Ph.D. in 1959 he became Assistant Prof. of pharmacognosy and acting chair of the Department. Ralph Blomster received his M.S. at Pitt in 1958, leaving to obtain a Ph.D. at the Univ. Connecticut, returning to Pitt as Assistant Prof. of Pharmacognosy in 1963, becoming Associate Prof. from 1966-1968, and leaving to become Chairman, Department of Pharmacognosy, Univ. Maryland at Baltimore. Harry Fong received his B.S. at Pitt in 1959 and his M.S. in 1961, leaving to obtain his Ph.D. in 1965 at Ohio State University under Jack Beal. After receiving his Ph.D. he returned to Pitt as Assistant Prof. in 1965. Paul Schiff (Chair) and Joe Knapp arrived in the autumn of 1970, after Norman Farnsworth and Harry Fong had moved to the Department of Pharmacognosy and Pharmacology, College of Pharmacy, Univ. Illinois (Chicago) (UIC). David Slatkin was recruited shortly thereafter and joined the faculty at Pitt in 1973.

2. August, 1955- August, 1970 (The Farnsworth, Blomster and Fong Years)

Research began developing in 1959-1960 with a grant from the Health Research Services Foundation of Pittsburgh to investigate the phytochemistry of *Vinca major* ($3558). This was followed by grants (1961-1964) from NIH, the National Heart Institute, to study the chemistry and hypotensive activity of Apocynaceous plants (ca $50,000 total!). From 1965-1970 the Department was a research contract lab for the NCI to study the isolation of antineoplastic

alkaloids from plants (ca. $220,000). In addition, from 1955-1970 small grants to support various natural products studies were obtained from Riker laboratories, the Eli Lilly Company, Schering AG, and the Amazon Natural Drug Company. During this time we initiated a collection program of native Pennsylvania plants which were extracted and evaluated by Eli Lilly for a variety of biological activities as well as conducting phytochemical screening. Major emphasis in phytochemistry during this period was in studying the anticancer alkaloids of *Catharanthus* species. Napralert (NAturalPRoductALERT), a major database on all natural products, was initiated and eventually was made available on the Web (http://www.napralert.org) at UIC.

From 1955-1970, 13 students received the M.S. in Pharmacognosy. In 1967 a Ph.D. program was approved, with 6 students receiving Ph.Ds through 1970. During this period, based on research conducted primarily at Pitt, Farnsworth *et al*. published some 60 research papers, 25 major review articles, 14 articles in professional journals emphasizing pharmacognosy and natural products research, as well as 6 books edited or co-edited.

3. August, 1970 onward (The Schiff, Knapp, Slatkin years)

All of these individuals had a research background that focused on the isolation and identification of plant metabolites, with Joe Knapp having additional training in study of microbial metabolites. In the years these scientists spent together, it was their privilege to have many wonderful collaborators, some of whom were also good friends or students.

3.1 Plant Metabolite Research

3.1.1 *West African Medicinal Plants.* A significant proportion of this research with Albert Tackie and colleagues (Ghana) focused on the isolation and identification of benzyl-isoquinoline-derived alkaloids from several species of the genera *Tiliacora* and *Triclisia*. Of note were funiferine (*Tilicaora funifera*) as only the second biphenyl bisbenzy-lisoquinoline alkaloid in nature, 8 other novel bisbenzylisoquinolines, several from *Tiliacora* and *Triclisia* species, the novel morphinan tridictyophylline, and novel nitriles griffonin and griffonilide (*Griffonia simplicifolia*). In all, 72 constituents (18 novel) representing 14 different classes of compounds were isolated from 17 medicinal plants.

3.1.2 *Cryptolepis sanguinolenta* indoloquinoline alkaloids. Collaboration with Gary Martin (Burroughs Wellcome) and application of his exceptional expertise in NMR contributed to the assignment of structure of 9 novel indoloquinoline alkaloids isolated by grad student Maged Sharaf from the West African antimalarial plant *Cryptolepis sanguinolenta* (Albert Tackie, Ghana), including the unique dimer cryptospirolepine, a spiro-nonacyclic compound with interesting bioactivity.

3.1.3 *Thalictrum* alkaloids. Continued study of the alkaloids of medicinal plants of the genus *Thalictrum* through collaboration with varying colleagues, including Anil Ray and Sunil Chattopadhyay (India), C,-Y. Gao and Z.-C. Lou (China), Jose Lopez (Costa Rica), Suleiman Al-Khalil (Jordan) and Raymond Doskotch (The Ohio State University), led to 35 different benzylisoquinoline-derived alkaloids from 11 species, the most notable being thalibealine (*T. wangii*), the first aporphine-tetrahydroprotoberberine found in nature, and named in honor of the memory of prominent ASP founding member, Jack Beal, (mentor of Knapp and Schiff), a great pharmacognosist and human being.

3.2 Microbial Research

3.2.1 *Microbial metabolites*. Work began with isolation and structure elucidation studies of the secondary metabolites of fungi belonging to the *Aspergillus cervinus* group within the genus *Aspergillus. A. parvulus* yielded the new quinols aparvenone and O-methyl-asparvenone, related derivatives, and the corresponding naphthoquinones, while other members yielded several known compounds. The focus was later changed to the metabolism of xenobiotics by fungi and microbial models of mammalian metabolism.

3.2.2 *Chlorine dioxide as a chemosterilant*. Successful feasibility studies on the use of gaseous chlorine dioxide (ClO_2) as a sterilizing agent for biomedical applications were followed by development of practical applications resulting in the award of 6 US patents. These were acquired by Johnson and Johnson and development work continued as a joint project to fully develop the technology. The technology was recently licensed to Chlor-DiSys Solutions, Inc. for use in the decontamination of microbiological isolators, clean rooms, animal care facilities and others.

3.2.3 *Genetic engineering*. This technology is being used to develop a mouse model to study aspects of the control of the expression of human cytochrome P450 (CYP) genes *in vivo,* providing a convenient method to study details of *in vivo* CYP induction and map the specific nucleotide sequences involved.

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The pharmacognosy program at the University of Rhode Island (URI) started in 1957, when Heber W. Youngken, Jr. (ASP President 1969-1970) arrived from the University of Washington as the dean of the newly opened College of Pharmacy. He quickly established the medicinal plant garden and the Ph.D. program, which was one of the first on the campus. Early faculty members included such prominent names as Daniel Tsao and Leonard R. Worthen (ASP President 1974-1975). Much of the early research involved the study of the higher plants and fungi. More recently, the departmental focus has shifted toward the study of marine organisms in accordance with the common theme of URI.

'Marine Pharmacognosy' and URI

The marine pharmacognosy program at URI owes much to the vision and vigor of Heber Youngken, Jr. In 1966, the National Sea Grant College and Program Act was enacted under the sponsorship of Senator Claiborne Pell of Rhode Island and Congressman Paul G. Rogers of Florida. URI, Oregon State University, University of Washington, and Texas A&M were designated as the first sea grant universities. Youngken, who was an avowed sailor, saw it as a great opportunity to start a new field of 'marine pharmacognosy'. He and John Knauss, Dean of the URI Graduate School of Oceanography (later the director of NOAA) and a strong proponent of the Sea Grant legislation, agreed to incorporate the program, 'Drugs from the Sea', as a major component in the new Sea Grant. The chair of the department of pharmacognosy at the time, Leonard Worthen, was instrumental in the implementation of the program. As a promotional move, URI hosted the first 'Drugs from the Sea Conference' in 1967, chaired by Hugo

Freudenthal.[1] This was followed by the second and third conference in 1969 and 1972 at URI. At the 1969 meeting, Al Weinheimer's group from the University of Oklahoma, startled the world by reporting the discovery of large amounts of prostaglandins in a soft coral.[2] At that time, prostaglandins were the hottest compounds as potential drugs, but their scarcity was considered to be one of the major problems. The discovery of this abundant marine source was an historic event and aroused enormous general interest in the oceans as a potential drug source.

The Drugs from the Sea program at URI officially started in 1968. This author (ASP President 1987-1988), along with a pharmacologist, Gary Carlson, were hired in 1969 as the first Sea Grant faculty. Initially the author's group focused on water-soluble compounds in marine algae and invertebrates, with the first paper reporting on the antiviral glycosides in starfish.[3] However, our research encountered an unexpected twist in 1972, when the New England coastline was hit by a wide-spread toxic red tide, causing human intoxication and large economic losses. The nature of the toxin appeared to be similar to paralytic shellfish poisoning (PSP), which was known in the US west coast. What was conceived as a brief public service turned out to be the life-long association with the dinoflaglellates and other microalgae associated with red tides. The algae were cultured and new toxins were identified, including such benchmark toxins as gonyautoxins and neosaxitoxin. In 1974, we reported the isolation of brevetoxin A and B toxins (initially named, GB-1 and GB-2 toxins) from the Florida red tide organisms.[4] They were later found to have an unprecedented polyether structure, and became the first of many polyether compounds found in dinoflagellates. For the next 15 years, most of the research at URI concentrated on the dinoflagellates and other algal toxins – biosynthetic studies, the toxin pharmacology, toxigenesis, etc. The program gained recognition for its marine toxin research which also made important contributions to biomedical research including drug development, but questions were often raised with regard to the lack of progress in the 'drugs from the sea', although the antitumor marine biopolymer work was continuing. Thus, around 1980, the decision was made to return the emphasis to the drug search, mostly in dinoflagellates and other microalgae, taking advantage of the tremendous expertise built in the toxin research. Since then, the program has been productive although it is still many steps away from a commercial drug product. The cancer screening research was initially supported by NCI RO1 grants, but after 1989, it received continued support from NCDDG until the time of author's retirement in 2006.

Another very important contribution of URI to marine natural products research was the establishment of the Gordon Research Conference on Marine Natural Products. Paul Scheuer of the University of Hawaii first came up with the idea of starting a conference on marine natural products modeled after the GRC on Natural Product Chemistry, of which he was a regular participant. The author, being at URI where the GRC headquarter was located, was asked to serve as the liaison. At that time, the GRC Board was very particular about starting new conferences, but fortunately, the director of GRC, Dr. Alex Cruickshank, who was also the chairman of the URI chemistry department and a close friend of Heber Youngken, had a good understanding of marine natural products. After a couple years of preparation, the first GRC on Marine Natural Products was held in 1975 at Santa Barbara with Paul Scheuer as chair and Yuzuru Shimizu as vice chair. As everybody knows now, the conference has become a very important site not only for the researchers in marine natural product chemistry, but also those in many other related fields. The Drugs from the Sea Conference was terminated after the 4th meeting in 1974.

The tradition of marine pharmaconosy is continuing at URI. David Rowley, who joined URI in 2000 from William Fenical's group, is leading the research on marine microbes. He has been recently joined by Daniel Udwary, also from Scripps Inst. Oceanography. The tradition at URI of research on higher plants will also continue with a new addition of faculty, Navindra Seeram. The H. W. Youngken Medicinal Plant Garden and Greenhouse is a very popular public site, which is tended by senior gardener, J. Peter Morgan.

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University of Utah

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Natural products research has a very rich history at the University of Utah spanning more than seven decades, centered in three Departments in two different Colleges. Natural Products/ Pharmacognosy research in the College of Pharmacy dates back to the origins of the College in 1947. The inaugural Dean, L. David Hiner (Ph.D. University of Florida) was a classically trained pharmacognosist and published extensively on cultivation of *Atropa* species and quantitization of alkaloid content in belladona plants from Utah. The emphasis shifted from plant to microbial natural products discovery and biosynthesis with the addition of H. Richard Shough in 1968 and Milton Zmijewski in 1978. Shough (Ph.D. University of Tennessee) worked on the biosynthesis of ergot alkaloids before moving to the University of Oklahoma in 1982, where he is currently head of the Department of Pharmaceutical Sciences. Zmijewski (Ph.D. University of Kentucky) studied DNA intercalation and biosynthesis of the naphthyridinomycin class of antibiotics before moving to Eli Lilly in 1983 to work on the human insulin project.

The marine era was ushered in with the recruitment of Chris M. Ireland (Ph.D. Scripps Institution of Oceanography-ASP President, 1991-1992), from the University of Connecticut School of Pharmacy in 1983 and Louis R. Barrows (Ph.D. UC, Irvine) from George Washington University in 1987. Over the years, the Ireland and Barrows labs developed an interdisciplinary program in marine natural products research that has been recognized internationally for their studies of the chemistry and pharmacology of marine natural product antitumor agents. In 1995, Ireland along with Raymond Andersen at UBC (ASP Executive Committee 2002-2005) and Jon Clardy at Harvard Medical School (ASP President 2003-2004, ASP Research Achievement Award 2004, ASP Fellow 2006) were awarded an NCDDG grant to discover "Anticancer Agents from Unique Natural Products Sources". The NCDDG grant supports a number of collaborative research programs worldwide including work with Dr. Veranja Karunaratne, Peradinya University, Sri Lanka; Dr. Teatulohi Matainaho, University of Papua New Guinea; Dr. Roberto Gomes de Souza Berlinck, Universidade de Sao Paulo at San Carlos, Brazil; Dr.Giselle Tamayo, National Biodiversity Institute (INBio), Costa Rica; Drs. Edgardo Gomez and Gisela

Concepcion, University of the Philippines and Dr. William Aalbersberg, University of the South Pacific in the Fiji Islands. In 2003 Barrows and Ireland were awarded an International Cooperative Biodiversity Group (ICBG) grant in collaboration with Dr. Matainaho to explore "Conservation and Sustainable Use of Biodiversity in Papua New Guinea".

The Ireland-Barrows collaboration also served as fertile training ground for future College of Pharmacy faculty as well as prominent members of the ASP - Joseph E. Biskupiak (University of Utah), T. Mark Zabriskie (Oregon State University, ASP Executive Committee 2005-2008), Tadeusz Molinski (UC, San Diego, Matt Suffness Award 1992, ASP Executive Committee 2001-2004), Tawyna McKee (NCI, Matt Suffness Award 1996, ASP Executive Committee 2007-2010, Chair, Organizing Committee, 47th Annual ASP meeting, 2006), Bradley Davidson (Utah State University, Matt Suffness Award 1996), Diana Swaffar (University of Southern Nevada), Deniz Tasdemir (University of London), Timothy Bugni (University of Utah), and Raquel Jadulco (University of the Philippines, Manila).

Utah solidified its leadership role in the marine natural products research field with the addition of Eric W. Schmidt in 2001 and Grzegorz Bulaj in 2006. Schmidt (Ph.D. Scripps Institution of Oceanography) studies the biosynthesis of marine natural products at the genetics level by characterizing the gene sequences that code for biosynthesis in the parent organism and subsequently expressing those pathways in a different host. He was the first person to show heterologous expression of a biosynthetic pathway from a marine obligate symbiont. Bulaj (Ph.D. University of Wroclaw) is studying the chemistry and neuropharmacology of cone snail toxins and is developing methodology for oral delivery of these peptides for treating epilepsy and chronic neurological pain. The University of Utah has also served as a host or co-host of two ASP national meetings. The 29th annual meeting in Park City, Utah in 1988 was an international symposium co-hosted with the Japanese Society of Pharmacognosy. The 34th annual meeting in San Diego in 1993 was co-hosted with UCSD.

Although somewhat peripheral to the ASP, natural products based research has also thrived in the Chemistry and Biology Departments in the College of Arts and Sciences. The effort in the Chemistry Department began in 1963 with the recruitment of William W. Epstein (Ph.D. UC, Berkeley). Epstein's seminal paper in *J. Biol. Chem*. in 1970 reporting the isolation of presqualene pyrophosphate provided important insights into how two farnesyl units condense to generate squalene the precursor for triterpenes and steroids. C. Dale Poulter (Ph.D. UC, Berkeley) joined the faculty in 1969. Over the years Poulter has gained international recognition for his elegant studies of the mechanistic enzymology of isoprenoid biosynthesis. Baldomero (Toto) Olivera (Ph.D. Cal Tech) joined the faculty in the Biology Department in 1968 and is now recognized as the world authority on the toxic venoms of *Conus* snails. One of the toxins discovered in Olivera's lab, MVIIa, is an FDA approved agent (Prialt®) for treating chronic neurological pain. The husband and wife team of Professors Phyllis Coley (Ph.D. University of Chicago) and Thomas Kursar (Ph.D. University of Chicago) who came to Utah in 1982 have developed a successful natural products drug discovery program in Panama based on ecological keys that suggest young foliage which is more vulnerable to predation is more chemically rich than mature leaves. They have participated as members of ICBG grant teams in Panama since 1998.

University of Virginia

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Natural Products research at the University of Virginia was established as part of a broader initiative in medicinal chemistry, which was nurtured by the early efforts of Alfred Burger and Robert Lutz. In parallel with the development of natural products isolation chemistry, the syntheses of pharmacologically active agents have been pursued productively at UVa in the laboratories of Richard Sundberg, Glenn McGarvey, Timothy Macdonald, T. Y. Shen, Robert Ireland, James Marshall, Milton Brown and Mario Geysen.

Natural Products isolation chemistry was initiated at UVa with the recruitment of Morris Kupchan from the University of Wisconsin. Early studies at Virginia included the identification of jatrophone with the assistance of Robert Bryan. Papers published in the early 1970s included some with Matthew Suffness (later of the National Cancer Institute) involving the isolation of stephavanine and stephisoferuline (hasubanan ester alkaloids). Also reported were the isolation of the bufadienolides bersenogenin, berscillogenin and 3-epiberscillogenin, and a number of sesquiterpene lactones including eupacunin and liatrin. Contributions to the era of chemically reactive antitumor agents included the isolation of vernolepin as well as the structurally unique epoxides triptolide and tripdiolide. The novel antileukemic ansa macrolide maytansine was reported in 1972, as were maytanprine and maytanbutine. Publications in the following year included a report of the isolation of bruceantin, eriolangin and eriolanin. The isolation of the antileukemic iridoid lactone allamadin was described jointly with Robert Bryan in 1974. Antileukemic principles reported shortly thereafter included mezerein, dehydroailanthinone, bruceantinol and podolide, as well as gnidimacrin, quassimarin, baccharin, maytoline, maytine, maytolidine and gnididione. Important papers published by the Kupchan laboratory in 1977 included a description of potent new antileukemic trichothecenes (with Bruce Jarvis, University of Maryland), phyllanthocin (with Edmond LaVoie, Rutgers University) and the cardiac glycoside elaeodendroside A (with Albert Sneden, Virginia Commonwealth University).

While the Kupchan laboratory is no doubt best remembered for its work on the isolation of an extraordinary variety of natural products, several of quite remarkable structure, there were also numerous reports from the laboratory dealing with synthesis and mechanism of action. These include papers dealing with the reactivity of α-methylene lactone tumor inhibitors with model biological nucleophiles, the total synthesis of tumor inhibitory alkaloids thalicarpine and hernandaline, the biomimetic synthesis of dibenzazonine, the photochemical synthesis of aporphines, and the oxidative coupling of monophenolic benzylisoquinolines, as well as nonphenol oxidative couplings and biomimetic alkylation of triptolides. The laboratory also collaborated in the pharmacological evaluation of extracts of Helicostylis (with Joseph Buckley and Robert Theobald, U. Pittsburgh), characterization of the antimitotic activity of maytansine and steganacin (with Lionel Rebhun, University of Virginia) and studies of the mechanism of action of vernolepin (with Joseph Larner, University of Virginia).

The Hecht laboratory moved to the University of Virginia from Massachusetts Institute of Technology in 1978 to initiate a broader program of work in the area of Natural Products. Ongoing efforts in the synthetic chemistry of bleomycin were transferred to UVa and led to a total synthesis of the natural product in 1982. Parallel efforts on mechanism of action began around 1980 and have led thus far to a description of the sequence selectivity of DNA cleavage,

a description of the chemical products resulting from DNA degradation and the finding that bleomycin also mediates the highly selective oxidative degradation of RNA, using chemistry not unlike that employed for DNA degradation. The identification of RNA species particularly susceptible to degradation by bleomycin has led to the recent suggestion that $tRNA_3^{Lys}$ may constitute a therapeutically relevant target for bleomycin. Participants in studies on bleomycin at UVa have included Hiroshi Sugiyama (Kyoto University), Li He Zhang (Beijing Medical University), Guy Miller (Edison Pharmaceuticals), Eric Long (Indiana University-Purdue University), Barry Gold (U. Pittsburgh), Chris Holmes (U. Vermont), Richard Manderville (University of Guelph), Steven Sucheck (U. Toledo) and Craig Thomas (NIH).

Natural Products isolation work was initiated at UVa in the late 1970s, aided by John Pezzuto (U. Hawaii, Hilo) who had moved with the Hecht laboratory from MIT. After a few years, the work developed a distinct mechanistic focus; one of the early screens employed a highly sensitive assay in which novel natural products capable of mediating metal ion-dependent relaxation of supercoiled DNA (i.e. analogous to bleomycin) were sought. The findings that alkylresorcinols and myristinins have these activities resulted from this initiative. Following the joint discovery between the Hecht laboratory (at Smith Kline & French Laboratories) and Leroy Liu (Johns Hopkins Univ.) that camptothecin acted as a topoisomerase I poison, the UVa isolations program was expanded to seek agents that function in the same fashion as camptothecin. Successes to date include the camptothecin poisons fagaronine, nitidine, luotonin A, coralyne, and dicentrinone (jointly discovered with David Kingston and Randall Johnson as part of a Natural Products Drug Discovery Group, funded by NCI). A recent synthesis of all four naturally occurring topopyrones by Mark Elban in the Hecht laboratory has provided access to yet another type of topoisomerase I poison for detailed biochemical characterization. Work carried out at UVa under the NPDDG program included a major effort to identify natural products that inhibit the function of DNA polymerase β. This enzyme is responsible for repairing the damage to DNA mediated by many DNA-directed antitumor agents (such as cisplatin and bleomycin); its inhibition by a suitable agent may well represent a viable strategy for adjuvant antitumor therapy. Polymerase β has two catalytic activities, namely lyase and polymerase activities, which are mediated by separate active sites. Numerous naturally occurring inhibitors of these activities have been identified, and some of these are of ongoing interest for mechanistic studies and structure modification efforts. One agent, which also potently cleaves DNA (myristinin), has been synthesized by David Maloney (NIH) and is of special interest.

One further effort is underway at UVa in collaboration with the laboratory of Deborah Lannigan. It has involved the identification of SL0101, a flavone glycoside which potently and selectively inhibits p90RSK, a kinase strongly implicated in the etiology of breast cancer. David Maloney has contributed importantly to the chemistry of SL0101.

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Natural Products research at the University of Washington (UW) took place during two distinct phases. The first, the Tyler era, lasted from 1957 to 1966 and dealt primarily with ergot alkaloids and other fungal/mushroom metabolites. The second phase involving the Floss group lasted from 1988 to 2006 and dealt with the biosynthesis of various antibiotics as well as the antitumor agent taxol.

The discipline of pharmacognosy at the UW School of Pharmacy was established by Heber Youngken (ASP President 1969-1970), who joined the faculty in 1942. Until 1956, when he became dean of the Rhode Island College of Pharmacy, Youngken with his studies on plant alkaloids and glycosides built a solid reputation for pharmacognosy at the UW. He was replaced as Professor and Chairman of Pharmacognosy and Director of the Drug Plant Gardens in 1957 by Varro E. Tyler from the University of Nebraska, a student of Art Schwarting at the University of Connecticut. One of his students, Lynn Brady, came with him to Seattle and, upon obtaining his Ph. D., joined the UW faculty in 1959. Both Tyler and Brady were founding members of the ASP, held leadership positions in the Society, Tyler as the first president in 1959-1961 and Brady as president in 1970-1971, and were recognized with honorary membership.

The therapeutically valuable alkaloids produced by the ergot fungus, *Claviceps purpurea*, had been Tyler's main research interest since his Ph.D. work. This work was continued and expanded at the UW, using saprophytic cultures of various grass ergot strains. An important breakthrough in ergot research was the production of lysergic acid derivatives in submerged cultures of *Claviceps paspali* reported first by Arcamone *et al*.[1] and subsequently, using a different process, by Tyler's group[2]. The Pacific Northwest, with its abundance of mushrooms, brought the opportunity for an important expansion of his research. The study of toxic or hallucinogenic mushroom constituents became another major research interest of the Tyler/Brady group, aided by close collaboration with the eminent mycologist and UW faculty member, Daniel E. Stuntz. By attracting the largest amount of grant support in the School of Pharmacy until then, an additional Research Professor, Robert G. Benedict, a microbiologist was hired who brought useful industrial experience to the group. Tyler published a classification of mushroom toxins[3] and he and his colleagues and students described members of most of the major categories.

During his time at the UW, Tyler, joined later by Brady, assumed responsibility for Claus' texbook of *Pharmacognosy*, which he thoroughly modernized and shepherded through several more editions, until it was taken over by James Robbers. This textbook, translated into Spanish and republished in several other countries, has had a major impact on the teaching of pharmacognosy worldwide. Another legacy of this period at the UW is the large number of Ph.D. students trained under the aegis of Tyler and Brady who have become prominent academicians and active members of the ASP. These include Jack Wier (U. North Carolina, ASP president 1980-1981), Charles Abou-Chaar (American U. Beirut, Lebanon), Phil Catalfomo (Oregon State U., U. Montana, ASP President 1975-1976), James Robbers (Purdue U., ASP President 1979-1980, Editor of JNP, Honorary ASP Member) and Byong Kim (Seoul National U.), among others.

In 1966, Tyler moved to Purdue U. as dean of the Pharmacy School and Jerry McLaughlin (ASP President 1982-1983, ASP Varro Tyler Prize 2007) joined the UW faculty in 1967. He initiated a research program on the chemical constituents of cacti, and one of his students, Bill Keller (Nature's Sunshine Products, Inc.) is the ASP secretary. The research tradition in pharmacognosy at the UW continued until ~1971, when McLaughlin moved to Purdue U. and Brady assumed administrative duties.

A second active period of natural products research began with the move of Heinz Floss (ASP President 1977-1978, ASP Research Achievement Award 1988) and his group from Ohio State U to the UW Department of Chemistry in 1988 and ended with his retirement in 2006. Incorporating the evolving tools of molecular genetics into natural products research, they cloned, sequenced and analyzed the biosynthetic gene clusters for the antitubercular antibiotic, rifamycin[4], and the potent anticancer agent, ansamitocin.[5] These studies elucidated the biosynthetic pathways to these two important compounds and paved the way for their manipulation by genetic engineering to generate modified structures. Additional work dealt with the biochemistry and molecular biology of formation of the antidiabetic drug, acarbose, and the crop protectant validamycin. With NCI's decision to develop taxol, some studies were also directed towards its biosynthesis. A second area of research dealt with the stereochemical analysis of biosynthetic reactions; in this work they pioneered the use of tritium NMR spectroscopy to determine the cryptic stereochemistry of enzymatic reaction products, as exemplified by a study (with M. H. Zenk) on berberine biosynthesis.[6]

The Floss group at the UW was also an important training ground for young natural products researchers from this country and abroad. From the US, notably Bradley Moore (UC San Diego, ASP Suffness Award 2001) and Taifo Mahmud (Oregon State U., ASP Suffness Award 2006) studied at the UW as Ph.D. students and/or postdocs and started their independent careers as Research Assistant Professors at the UW. From Germany, a generation of natural products researchers who were postdocs or on sabbatical at the UW now occupy prominent academic positions there. These include Lutz Heide (U. Tübingen), Andreas Kirschning (U. Hannover), Andreas Bechthold (U. Freiburg), Rolf Müller (U. Saarland), Michael Müller (U. Freiburg), Joern Piel (U. Bonn, ASP Suffness Award 2004), Christian Hertweck (HKI Jena) and, more recently, Stephanie Grond (U. Göttingen) and Peter Spiteller (TU Munich). The UW thus has had, and continues to have, a lasting impact on pharmacognosy and natural products research worldwide.

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University of Wisconsin-Madison

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The School of Pharmacy at the University of Wisconsin-Madison was established in 1883, and Frederick B. Power served as the first director (1883-1892). Edward Kremers, the second

director of the school (1892-1935), established the first four-year curriculum leading to the B.S. degree in pharmacy in America. The first Master of Science (M.S.) degree in pharmacy was awarded to John L. Mead in 1893, the first 4-year B.S. degree in pharmacy was awarded in 1895, and graduate education at the School culminated with the establishment of the first program in the U.S. leading to the Ph.D. in the pharmaceutical specialties. The first Ph.D. was awarded to Oswald Schreiner in 1902. Since the 1880s, pharmacognosy and natural products research have played major roles in defining the program at UW-Madison, and in 2008 the School is celebrating 125 years of excellence in research, education and service.

Research at the School of Pharmacy started when the School opened in 1883. Power and his students began to investigate the medicinal components of plants in Wisconsin and the preparation of extracts with therapeutic properties; the Pharmacy Department published the first periodical, *Contributions*, containing research results of students and faculty in 1885. Kremers was the dominant force behind formalizing the study of medicinal components of plant origin into a rigorous scientific discipline, and was considered to be the pioneer who started pharmacognosy in the US. Recognizing the lack of quality control of plant-based medicines at the time, Kremers established a pharmaceutical experiment station in 1913 as a way to produce high-quality medicinal plants through a scientifically controlled process. He also reasoned that a pharmaceutical station could revolutionize drug production. The station was an instant success in investigating the commercial aspects of growing medicinal plants in Wisconsin, as well as searching for new medicines from plants. Its impact was felt far beyond the borders of Wisconsin. When World War I broke out a few years later, America discovered a need to develop a domestic drug industry in a hurry. Kremers' station became a model of conducting research in this field, and the USDA's Bureau of Plant Industry recommended that every state in the nation set up a facility like the UW's. At the height of its influence, the station was lauded in *Science* and envied by scientists on both sides of the Atlantic. However, the emergence of the sulfonamides and penicillin shifted the pharmaceutical industry to specific chemical drugs at the time. The Great Depression led to the tightening of the state budget, ultimately cutting funding to the station in 1933. The station ceased operation shortly after Kremers' retirement in 1935.

The post-Kremer era began with the arrival of S. Morris Kupchan in 1957. Kupchan was trained in organic chemistry at Columbia (Ph.D. 1945) and joined the Department of Chemistry at UW-Madison in 1955. He developed an interest in the discovery of biologically active plant products and joined the Pharmaceutical Chemistry Department of the School of Pharmacy in 1957. Through contract and grant support from NCI, he rapidly built a large research group that isolated and characterized many still well-known of natural products. Notable are the maytansines, one of the most potent cytotoxins ever isolated from a plant, and α-methylene lactone terpenoids, potent cytotoxins that underwent alkylation by biological nucleophiles. Kupchan moved to the Department of Chemistry at the University of Virginia in 1969.

Charlie Sih arrived in 1960, following his training in biochemistry and microbiology at Wisconsin (Ph.D. 1958) and a brief stint at the Squibb Institute of Medical Research, to teach pharmacognosy and to develop the biological sciences for the School. Pharmaceutical biochemistry became increasingly significant during the 1960s after Sih joined the faculty. He initially developed an interest in the microbiological transformation of drugs and natural products, which often created new functional groups enabling further chemical transformation or endowed new pharmacological properties, notably with steroid hormones. By the early 1970s, Sih had begun to extend his interests into the pioneering use of enzymes and microbial

transformation in the total synthesis of natural products. This was the main focus of his research through the remainder of his career, resulting in seminal work on lovastatin, FK506, daunorubicin and the prostaglandins. Sih retired from the University in 2001.

David Perlman was recruited to the University in 1967, joining the Pharmaceutical Biochemistry faculty in the School of Pharmacy. Perlman received all his training in chemistry and biochemistry at Wisconsin (Ph.D. 1945) and worked for 22 years as a microbial biochemist in the fermentation phase of the pharmaceutical industry at Hoffman-LaRoche, Merck and the Squibb Institute for Medical Research (where he had known Charlie Sih) before returning to Wisconsin. These were exciting years for microbial technology at Wisconsin, and Perlman quickly established a research group in the School focused on microbial and biological studies of β-lactam antibiotics, then later vitamins, especially vitamin B12. In 1968 he became Dean of the School of Pharmacy and oversaw a rapid expansion in the medicinal chemistry, organic synthesis and natural products research areas. Dexter B. Northrup (retired in 2006), Daniel H. Rich (retired in 2006), Robert A. Ellison (1969-1975) and Robert Morin (1971-1973) joined the faculty during the early 1970s to carry on the tradition of organic chemistry and biochemistry. Sadly, Perlman died in 1980 after a heroic struggle with cancer.

C. Richard (Dick) Hutchinson (ASP Research Achievement Award, 2000), trained in organic chemistry at Minnesota (Ph.D. 1970), arrived in 1974 after a three-year stint at the U. Connecticut. He initially focused on the biosynthesis of plant products such as camptothecin and iridoids but, with the help of Bob Ellison, extended his work into microbial products, beginning with brefeldin A. In the early 1980s, attracted to microbial genetics, he shifted the focus of his biosynthetic work towards a genetic and biochemical approach. For the following 20 years, he studied the biosynthesis of polyketide natural products such as erythromycin, tetracenomycin, doxorubicin and lovastatin, heavily pioneering the field of combinatorial biosynthesis and drug discovery. Hutchinson retired from the faculty in 2000 but returned part-time in 2004 to help establish a National Cooperative Drug Discovery Group (NCDDG) funded by NCI.

Natural products research continues to be strong into the new millennium, with the recruitment of Jon Thorson and Ben Shen to the Division of Pharmaceutical Sciences in 2001, after a near 20-year hiatus of faculty hiring in natural products research areas in the School. Thorson, trained as an organic chemist at Minnesota (Ph.D. 1993), came to Wisconsin after a five-year stay at the Memorial Sloan-Kettering Cancer Center, while Shen, also an organic chemist by training at Oregon State University (Ph.D. 1991), served on the chemistry faculty at University of California, Davis for six years before arriving in Wisconsin. Thorson is most known for the invention of the glycorandomization platform and its application to natural product drug discovery. Shen has developed a multifaceted research program pursuing natural product isolation, production in heterologous hosts, and metabolic pathway engineering for structural diversity. They are committed to innovation and excellence in natural products research and drug discovery; the NCDDG exemplifies the kind of collaborative efforts they strive to continue and to expand as they carry on the Wisconsin tradition.

1. Buckner, C. et al.. in *The University of Wisconsin School of Pharmacy: Its First Century*, Office of University Publications, Madison, Wisconsin, **1997**.
2. Office of the Dean, School of Pharmacy, in *A Place in History: 125 Years of Excellence Celebrate!* University of Wisconsin-Madison, **2007**.

Natural Products Research at Virginia Polytechnic Institute and State University (Virginia Tech): Personal Reflections

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My interest in natural products research began as a undergraduate student at Cambridge University, where as an undergraduate student I attended a course of lectures on the subject from Professor Sir Alexander Todd (later to become Lord Todd). The beauty of Nature's molecules and their biological relevance fascinated me, and I resolved to devote myself to the study of their chemistry. After obtaining my Ph. D. under Lord Todd in 1963, and completing postdoctoral work at MIT and Cambridge, I moved to a position at SUNY Albany in 1966, and thence to Virginia Polytechnic Institute and State University (Virginia Tech) in 1971.

Although Virginia Tech is Virginia's Land Grant University, and thus has strong agriculture and engineering programs, it had not developed any particular focus on natural products research. Natural products research thus effectively began with my arrival in 1971. Thanks to previous work done at SUNY Albany, I was able to hit the ground running, since Jonathan Hartwell at the National Cancer Institute had been kind enough to send me some plant material with confirmed activity in the NCI assays, and I was funded on an R01 grant from NIH soon after arriving in Blacksburg. The equipment available at the time was primitive by today's standards; the only NMR instrument available was a 100 MHz JEOL PS-100, and the mass spectrometer was a low resolution Hitachi Perkin-Elmer RMU-7. Progress was thus relatively slow, but my students and I were able to isolate several bioactive compounds, including some novel bisindole alkaloids,[1] and develop the beginnings of a natural products research program.

One strong feature of the ethos in the Chemistry Department at Virginia Tech was its encouragement of collaborative work. Our work thus expanded in the mid 1970s in an enjoyable collaboration with John Vercellotti of the Biochemistry Department, and together we investigated new metabolites of *Aspergillus versicolor*. This work was done under a contract from the FDA, which was interested in the bioactivity of compounds such as versicolorin A, and some interesting chemistry of sterigmatocystin was discovered in the process.[2] My involvement with the ASP also began at this time; the first meeting I attended was the 1974 Chicago meeting, and I was instantly attracted by the friendliness of the members and by the fact that everyone was interested in natural products research! My first publication in what was then called *Lloydia* followed soon after.[3]

Three new research projects were started in the late 1970's. The first involved a throwback to my time as a NATO Research Fellow at Cambridge University, where I had worked on the structure of the antibiotic ostreogrycin A, also known as virginiamycin M, an intriguing compound with an unknown mixed biosynthetic origin. It turned out fortuitously that SmithKline Animal Health Products, which used it as an animal feed supplement, was interested in knowing where it was labeled by ^{14}C acetate, and they kindly provided some modest funding. This was later augmented by a grant from NSF, and we were able to make a detailed study of the biosynthesis of this interesting antibiotic.[4]

The second project involved a collaboration with Tracy Wilkins, a colleague then at the unique Laboratory for Anaerobic Microbiology at Virginia Tech. He had detected a potent mutagen in

human feces, and so we collaborated on the isolation and structure elucidation of this compound. I am glad to say that the sample collection and isolation was all carried out by Tracy's group! With the help of a gifted postdoctoral associate, Dr. Nobuhiro Hirai, we were able to determine the structure and stereochemistry of this unstable and elusive compound as a glycerol pentaene that was later named fecapentaene.[5] This collaboration continued for several years, and included the synthesis of fecapentaene-12, and studies of the anaerobic metabolism of various food mutagens.

The third new project also involved a collaboration, but this time with my then colleague Robert (Bob) Holton. Bob was an outstanding synthetic organic chemist, and he had undertaken the ambitious project of the total synthesis of taxol, which at that time was to most organic chemists simply a challenging synthetic target. One day in 1978 we discussed collaborating on this project, with the idea that I would investigate the chemistry of taxol, about which little was then known, while he continued on his synthetic approach. The basic idea was that I would determine which structural features of taxol were necessary for activity, so that we could together design a simplified and synthetically accessible taxol analog. We duly submitted an NIH grant proposal, but this did not get funded, in part because few people were really interested in taxol at that time. Nothing daunted, I began work on a shoestring budget. I was later able to obtain some funding from the American Cancer Society, and this really helped me continue the work at a higher level. Once taxol demonstrated clinical activity funding became more available, and my work has continued to the present. My initial emphasis on developing the SAR of taxol,[6] has evolved into studies of the nature of the binding of taxol to microtubules.[7,8]

Work in the natural products area has continued on two fronts. I collaborated with Sid Hecht at the University of Virginia and Randall Johnson at SmithKline Beecham in a successful National Cooperative Drug Discovery Group focused on DNA-damaging agents.[9] This project lasted from 1989 until 2005, with the project ending in part because Glaxo-SmithKline, as SmithKline Beecham became, withdrew its participation. In 1993 I began a very fruitful collaboration with a varied group of collaborators as part of an International Cooperative Biodiversity Group in Suriname,[10] that later metamorphosed into a Madagascar-based group. This work has been challenging and highly rewarding, as the fruits of the upfront funds contributed by our pharmaceutical and agrochemical partners Eisai Research Institute and Dow AgroSciences, are translated into tangible benefits for the people of Suriname and Madagascar, and as we continue to find potent cytotoxic agents.[11,12]

As the forgoing brief account has indicated, much of my work has been done in collaboration with other scientists, both within and outside Virginia Tech. It seems to me that this is the way of the future in natural products research; it is difficult if not impossible for one scientist to be expert in all the varied disciplines and methods needed for productive research in natural products. I have been blessed to have been able to work with a talented group of colleagues both at Virginia Tech and at other institutions. At Virginia Tech I collaborated briefly with Norman Lewis on a lignan biosynthetic project before he moved to Washington State University, as well as with Tracy Wilkins, John Vercellotti, and Bob Holton. I have also had many excellent postdoctoral associates and graduate students, as well as five outstanding senior scientist colleagues in Leslie Gunatilaka, Bing-Nan Zhou, Thota Ganesh, Shugeng Cao, and Qiao-Hong Chen. I owe my success in large measure to my colleagues, research associates, and students, as

well as to continued support from the NCI and support and encouragement from the staff of the Natural Products Branch, including the late Matt Suffness, Gordon Cragg, and Dave Newman.

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