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Editorial

Special Issue in Honor of Professor George Robert Pettit

It is an honor and a pleasure for us to serve as Guest Editors of this issue of the *Journal of Natural Products* dedicated to Professor George Robert (Bob) Pettit. We wish to express our sincere thanks to Bob's former students, postdoctoral fellows, visiting scientists, and his many colleagues from the former Cancer Research Institute at Arizona State University and institutions worldwide, for submitting such a diverse set of excellent manuscripts for this issue. Their generosity in terms of time and effort is greatly appreciated and provides well-deserved recognition of the many outstanding contributions that Bob has made to the field of natural products science and anticancer drug discovery over the past five decades.

Bob Pettit was born on June 8, 1929, in Long Branch, New Jersey. He gained his B.S. in chemistry at Washington State University in 1952 and proceeded to Wayne State University, where he completed his M.S. in heterocyclic chemistry in 1954 and his Ph.D. in steroid chemistry in 1956, both under the direction of Professor Carl Djerassi. Bob remembers the Djerassi group of the mid-1950s as an exciting and diverse group of talented young scientists from many parts of the world, including Australia, India, Israel, New Zealand, and the United Kingdom, who proceeded to prominent positions in academia, government, and industry. These included Albert Bowers and John Zderic, who later became CEO and Vice President of Syntex, respectively. In 1956, Bob moved to Norwich Eaton Pharmaceuticals (now Proctor and Gamble) as Senior Research Chemist, and in 1957 he transferred to the University of Maine as Assistant Professor, rising through the ranks to become Full Professor in 1965. After a period as Visiting Professor at Stanford University, he accepted a full Professorship in the Chemistry Department at Arizona State University in late 1965. From 1974 to 1975 he served as Director of the Cancer Research Laboratory, and in 1975 he became the Director of the newly established Cancer Research Institute. Since 1986 he has also occupied the position of Dalton Professor of Cancer Research and Medicinal Chemistry.

Bob Pettit's career has been devoted to the discovery and development of novel and more effective anticancer agents from natural sources, and those of us who have collaborated with Bob know him as an outstanding and resourceful scientist totally committed to improving the treatment and quality of life of cancer patients worldwide. During his distinguished and productive career of over 50 years, he has authored or coauthored 14 books, 10 book chapters, and over 700 scientific papers, and he is inventor and coinventor on 58 U.S. patents. His books include a series of six volumes on synthetic peptides published between 1970 and 1982, as well as a series of six volumes on *Biosynthetic Products for Cancer Chemotherapy* published between 1977 and 1989,[1] culminating in a volume on *Anticancer Drugs from Animals, Plants and Microorganisms*, published in 1993.[2] He has continued to update these useful volumes with chapters in books, the latest being titled

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"Evolutionary Biosynthesis of Anticancer Drugs" in *Anticancer Agents: Frontiers in Cancer Chemotherapy*.[3]

Bob's research has focused on all aspects of natural products chemistry, including isolation, structure elucidation, biological evaluation, biosynthesis, and chemical synthesis. He can truly be regarded as one of the great pioneers in natural products drug discovery. He was among the first to explore the realm of marine organisms as a source of potential antitumor agents,[4] but this was preceded by the isolation of antitumor agents from arthropods.[5] Both these marine and arthropod studies were reported in papers published in collaboration with his close colleagues from the U.S. National Cancer Institute (NCI), Drs. Jonathan Hartwell and Harry Wood, and they reflect a longstanding collaboration with the NCI that started in the early 1960s and has continued to the present time. His earliest research from the mid-1950s to the late 1960s focused on synthetic modifications of potential anticancer agents, with an emphasis on steroidal compounds, particularly bufadienolides; much of the research on the bufadienolides was conducted in close collaboration with Dr.Yoshiako Kamano (now at Kanagawa University, Japan), and their interest in this class of steroids continues to this day.[6,7]

His early research in the exploration of marine organisms as a source of potential antitumor agents blossomed into a marine natural products drug discovery program of exceptional productivity and achievement. Space does not permit the listing of the numerous active molecules discovered through this program, but several stand out as agents of considerable promise in the area of cancer chemotherapy. The bryostatins, originally isolated in minute yields from the bryozoan *Bugula neritina*, possess 20-membered macrocyclic lactone rings, and the isolation of bryostatin 1, the major member of the 20 structures isolated thus far, was reported in 1982.[8] Bryostatin 1 has been in more that 80 clinical trials to date, and while there have been some responses when used as a single agent, this is probably not the optimal application, and administration in combination with other cytotoxins, such as the *Catharanthus* alkaloids or nucleosides, is demonstrating improved efficacy.[9] The dolastatins are a family of peptides originally isolated from the mollusk *Dolabella auricularia*.[10,11] Of the more than 20 dolastatins reported, dolastatins 10 and 15 showed the most promising activity, and dolastatin 10 advanced to clinical trials, which have now been terminated. Several synthetic dolastatin analogues, however, are currently in clinical development; these include TZT-1027 (auristatin PE or soblidotin), cemadotin (LU-103793), and ILX651 (synthadotin or tasidotin), which is an orally active third-generation dolastatin 15 analogue.[12] Other agents that have shown potent activity and are now in preclinical development are cephalostatin 1 from *Cephalodiscus gilchristi*[13] and spongiastatin from a *Spongia* species.[14]

While Bob's research has been focused on the discovery of marine-derived anticancer agents, his group has also performed extensive studies of plants and has had considerable success in the identification of some promising agents. Most notable of these are the combretastatins isolated from *Combretum caffrum*.[15,16] (The cover illustration of *J. Nat. Prod.* for the months of January to June 2008 shows a photograph of this tree.) The combretastatins are a family of stilbenes, which act as antiangiogenic agents, and a water-soluble analogue, combretastatin A-4 phosphate, has shown promise against thyroid cancer in early clinical trials. This chemical class has served as a model for the synthesis of a host of analogues, three of which are in clinical trials, while 11 are in preclinical development.[17] Another plant-derived agent, pancratistatin, is also of interest as a potential candidate for preclinical development.[18]

The research of Bob Pettit has received strong support over the years from the National Cancer Institute, and from 1989 to 2001 his significant contributions to anticancer drug discovery were recognized through NCI funding as an Outstanding Investigator. He has also received considerable support from private foundations and individuals who have been inspired by his unbounded enthusiasm and commitment to improving the lives of cancer patients and his outstanding record in achieving this all important goal. His discoveries have spawned extensive research in the area of total synthesis aimed at the efficient production of further quantities of promising agents for preclinical and clinical development, as well as combinatorial approaches to the synthesis of more effective candidates for development, as is clearly demonstrated by the prolific exercise in the synthesis of combretastatin analogues. Likewise, many productive collaborations have been developed in the study of the mechanisms of action of the numerous promising agents discovered through his programs. It is indeed gratifying to see recognition of his outstanding contributions through the submission of papers to this issue by many of his collaborators.

Bob's contributions have also been recognized through the award of many honors, and invitations to deliver lectures at U.S. and international conferences. In addition to those already mentioned, awards include Distinguished Research (1978–1979) and Regents (1990−present) Professorships by Arizona State University, the Alumni Achievement Award by Washington State University (1983–1984), the Chemical Pioneer Award by the American Institute of Chemists (1988), the State of Arizona Governor's Excellence Award (1993), the Research Achievement Award by the American Society of Pharmacognosy (1995), the Mathias P. Mertes Memorial Lecture Award by the University of Kansas (1997), the Ernest Guenther Award in the Chemistry of Natural Products by the American Chemical Society (1998), and the Nolan and Gloria Sommer Award by the University of Nebraska in 2000. In addition, he is an Honorary Member of the ARCS Foundation (Achievement Rewards for College Scientists), the PAMM Group of the European Organization for Research and Treatment of Cancer (EORTC), and the International Foundation for Anticancer Drug Discovery, and he serves on the Editorial Advisory Boards of the *Journal of Natural Products*, *Synthetic Communications*, *Anticancer Drug Design*, and *Current Organic Chemistry*. Other services include as a member of the Advisory Boards of the NCI Division of Cancer Treatment (1971–1974) and the Walter Reed Medical Research Institute (1985−present), as well as the American Chemical Society Awards Committee (most recently 1998–2002), and the American Institute of Chemists Chemical Pioneer Award Selection Committee (1989–1997). During his tenure at the University of Maine and Arizona State University, Bob trained 70 graduate students, while 200 postdoctoral fellows and visiting scientists, including professors on sabbatical leave, many of whom were from overseas, have carried out research in his program. Also included in his program have been 60 staff, research assistants, and undergraduate research students, as well as over 100 undergraduates, who have gained technical experience in the processing laboratories as "work-study" students. Most of his graduate students and colleagues have progressed to positions of influence in academia, government, and industry and have continued to promote the cause of natural products drug discovery that he has so strongly advocated.

In closing, we would like to acknowledge the tremendous support given to Bob by his wife of over 50 years, Jean, who has been a constant companion and source of inspiration to him through times of good and travail, and to his wonderful family, Bill, Peggy, Robin, Lynn, and Bob Jr., who have all followed in their parents' footsteps of dedicated service to the community.

One of us (R.G.P.) first became associated with Bob in the late 1960s while attending various meetings of groups involved in the fractionation of confirmed antitumor active extracts that were hosted by NCI and the Cancer Chemotherapy National Service Center. Thus began a friendship, and exchange of information and ideas, that has continued over the years. Wherever he went Bob always seemed to have a camera at hand, and his presentations usually were fully documented and illustrated with photographs of the specimens as they were being collected, whether they were found under the sea or on the mountain. Two of us (G.M.C. and S.B.S.) were associated with Bob for several years during the late 1970s and 1980s and benefited from his guidance and enthusiastic

commitment to advancing the cause of improved cancer chemotherapy, as well as sharing in his other passion, wilderness hiking adventures, during which research was a constant topic for discussion, but this opened our eyes to the rugged beauty of the American Southwest.

References and Notes

(1) Pettit, G. R.; Herald, C. L.; Smith, C. R. *Biosynthetic Products for Cancer Chemotherapy*; Elsevier Scientific: Amsterdam, 1989; Vol. 6.
(2) Pettit, G. R.; Hogan-Pierson, F.; Herald, C. L. *Anticancer Drugs from Animals, Plants, and Microorganisms*; John Wiley-Interscience: New York, 1993.
(3) Pettit, G. R. In *Anticancer Agents: Frontiers in Cancer Chemotherapy*; Ojima, I., Vite, G. D., Altmann, K.-H., Eds.; American Chemical Society: Washington, DC, 2001; pp 16–42..
(4) Pettit, G. R.; Day, J. F.; Hartwell, J. L.; Wood, H. B. *Nature* **1970**, *227*, 962–963.
(5) Pettit, G. R.; Hartwell, J. L.; Wood, H. B. *Cancer Res.* **1968**, *28*, 2168–2169.
(6) Ode, R.; Pettit, G. R.; Kamano, Y. In *International Review of Science. Organic Chemistry Series Two*; Johns, W. F., Ed.; Butterworths: London, 1975; Vol. 8, Chapter 6, pp 145–171..
(7) Kamano, Y.; Yamashita, A.; Nogawa, T.; Morita, H.; Takeya, K.; Itokawa, H.; Segawa, T.; Yukita, A.; Saito, K.; Katsuyama, M.; Pettit, G. R. *J. Med. Chem.* **2002**, *45*, 5440–5447.
(8) Pettit, G. R.; Herald, C. L.; Doubek, D. L.; Herald, D. L.; Arnold, E.; Clardy, J. *J. Am. Chem. Soc.* **1982**, *104*, 6846–6848.
(9) Newman D. J. In *Anticancer Agents from Natural Products*; Cragg, G. M., Kingston, D. G. I., Newman, D. J., Eds.; Taylor & Francis: Boca Raton, FL, 2005; pp 137–150..
(10) Flahive, E.; Srirangam, J. In *Anticancer Agents from Natural Products*; Cragg, G. M., Kingston, D. G. I., Newman, D. J., Eds.; Taylor & Francis: Boca Raton, FL, 2005; pp 191–214..
(11) Pettit, G. R.; Herald, C. L.; Ode, R. H.; Brown, P.; Gust, D.; Michel, C. *J. Nat. Prod.* **1980**, *43*, 752–755.
(12) Rasila, K. K.; Verschraegen, C. *Curr. Opin. Investig. Drugs* **2005**, *6*, 631–638.
(13) Pettit, G. R.; Inoue, M.; Kamano, Y.; Herald, D. L.; Arm, C.; Dufresne, C.; Christie, N. D.; Schmidt, J. M.; Doubek, D. L.; Krupa, T. S. *J. Am. Chem. Soc.* **1988**, *110*, 2006–2007.
(14) Pettit, G. R.; Cichacz, Z. A.; Gao, F.; Herald, C. L.; Boyd, M. R.; Schmidt, J. M.; Hooper, J. N. A. *J. Org. Chem.* **1993**, *58*, 1302–1304.
(15) Pinney, K. G.; Jelinek, C.; Edvardsen, K.; Chaplin, D. J.; Pettit, G. R. In *Anticancer Agents from Natural Products*; Cragg, G. M., Kingston, D. G. I., Newman, D. J., Eds.; Taylor and Francis: Boca Raton, FL, 2005; pp 23–46..
(16) Pettit, G. R.; Cragg, G. M.; Herald, D. L.; Schmidt, J. M.; Lohavanijaya, P. *Can. J. Chem.* **1982**, *60*, 1374–1376.
(17) Li, Q.; Sham, H. L. *Expert Opin. Ther. Pat.* **2002**, *12*, 1663–1702.
(18) Pettit, G. R.; Gaddamidi, V.; Cragg, G. M.; Herald, D. L.; Sagawa, Y. *J. Chem. Soc., Chem. Commun.* **1984**, 1693–1694.

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