The Search for Natural Substances with Therapeutic Activity: Summary of a Tribute to ASP Member Pettit

By Dr. Charles Chapuis and Dr. Gordon M. Cragg

In 2014, the eminent French natural products chemist and pharmacologist, Dr. Laurent Meijer, together with two of his colleagues, dedicated a review in *Médecine Sciences* to ASP Fellow Dr. George R. Pettit.[1] The French journal has published a series of reviews covering the "life and work" of famous researchers who have discovered major chemotherapeutics from natural products.

Dr. Pettit was awarded the Norman R. Farnsworth Research Achievement Award by the ASP in 1995 and the Ernest Guenther Award in the Chemistry of Natural Products by the American Chemical Society in 1998. From 1989 to 2001, his significant contributions to anticancer drug discovery were recognized; the National Cancer Institute (NCI) designated him an Outstanding Investigator, and in March 2008, a special issue of the *Journal of Natural Products (J. Nat. Prod.)* was published in his honor. In addition, he has served as a member of the *J. Nat. Prod.* Editorial Board. As noted by Editor-In-Chief Dr. Douglas Kinghorn, "In my opinion, the work of Dr. Pettit and his colleagues in natural product drug discovery is unparalleled, and it would behoove ASP and *J. Nat. Prod.* to disseminate information on his many contributions as widely as possible."

The authors briefly note Dr. Pettit's early life studying marine invertebrates on the beaches near his home in New Jersey and the development of a passion for chemistry at the age of ten. His observation of the ravages of cancer while assisting a pathologist in postmortem examinations at the age of 15 led him to speculate that the chemical defenses used by marine invertebrates to deter attacks by predators may well be useful in the fight against cancer. This set the stage for a lifelong career devoted to the "worldwide exploration of natural products, especially of marine origin, in search of promising anticancer leads, the discovery and structural elucidation of very potent drug candidates, their synthesis, and the launch of some of them into the pharmaceutical market."

A timeline illustrating key events and discoveries in Dr. Pettit's life to date is given in Figure 2 of the review,[1] dating from his birth in 1929 and proceeding through the award of Bachelors, Masters and Doctorate (1956) degrees, to faculty appointments at the University of Maine, Orono, Maine (1957-65), and Arizona State University, Tempe, Arizona (ASU, 1965-present). A highlight was the establishment of the ASU Cancer Research Institute (ASU/CRI) in 1975, and the authors note that, "against all odds and common sense," the ASU authorities closed the ASU/CRI in 2005. However, Dr. Pettit continues to pursue cutting edge research with a reduced research team. Discussed further are some of the most important molecules emanating from Dr. Pettit's productive program, research which has resulted in "more than 800 publications and 67 patents, covering all aspects of the chemistry of natural products extraction, purification, structure determination, biosynthesis, total chemical synthesis, biological and clinical evaluations." A comprehensive list of novel antitumor compounds isolated from arthropods, plants, marine and microbial sources by the Pettit team is reported in Chapter 4 of the *The American Society of Pharmacognosy. 50 Years of Progress in Natural Products Research*.[2]

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Most prominent among the detailed discoveries are the dolastatins, originally isolated in minute yields from the marine mollusk, *Dolabella auricularia*, (Aplysiidae), collected off the coast of Mauritius in the early 1970s. The synthesis of the most promising lead, dolastatin 10 (D-10; Fig. 1), provided sufficient material for preclinical and clinical studies. While clinical trials of D-10 have not shown significant

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promise, a synthetic derivative, soblidotin (auristatin PE; TZT-1027; Fig. 1), is currently in Phase II clinical trials in Japan, the U.S., and Europe. Another derivative, monomethyl auristatin E, conjugated to a monoclonal antibody directed against the CD30 epitope (SGN- 35 or brentuximab vedotin; Fig.1) has completed clinical trials against refractory lymphomas and large cell lymphomas and has been marketed worldwide since the end of 2011 under the trade name Adcetris® . Combinations of the same derivative with other antibodies targeting broad cancer epitopes are in early clinical trials.[3]

Halichondrin B (HB; Fig. 5, ref. 1), first reported by Uemura and Hirata from the marine sponge *Halichondria okadai* in 1986, was also isolated in 1987 by Blunt and Munro and colleagues from two species of New Zealand sponges, *Raspalia agminata* and *Lissodendoryx* spp. and by Dr. Pettit and colleagues in 1991 from an *Axinella* spp. collected from the Republic of Palau. Obtaining sufficient supplies of HB for further development proved to be challenging, but completion of the total synthesis of HB by Kishi et al. in 1992 led to a collaboration between the Kishi group and scientists at the then Eisai Research Institute (currently Eisai Co., Ltd., Tokyo, Japan). They identified the ring-portion of the molecule as being mainly responsible for the biological activity, and close to 200 derivatives of the truncated natural product were prepared and evaluated, paving the way for the selection of E7389 (eribulin; Fig. 5, ref. 1) as the candidate for preclinical and clinical development. Following advanced preclinical development and extensive clinical studies, eribulin mesylate (proprietary name, Halaven®) was approved by the Food and Drug Administration (FDA) in 2010 for the treatment of metastatic breast cancer in patients who had already been subjected to two chemotherapy treatments. In 2011, it received European marketing authorization (AMM) for the same indication.

Another important marine-derived discovery was bryostatin 1 (Fig. 3, ref. 1). This compound was isolated from the bryozoan, *Bugula neritina*, first collected in the Gulf of Mexico and subsequently from the Gulf of California and the California coast. A large scale recollection yielded sufficient bryostatin 1 to initiate clinical trials, and while monotherapy does not appear to be efficacious, it has been shown to increase the effectiveness of vincristine in the treatment of large cell lymphomas. However, extensive studies aimed at the reduction of the main side effect, myalgia, will be needed before the therapeutic potential of bryostatin 1 can be fully exploited. Bryostatin 1 also has antidepressant effects and is currently in Phase II clinical trials for the treatment of Alzheimer disease; early results indicate that it blocks the progression of cognitive decline and reduces depression associated with this neurodegenerative disease. Simpler synthetic analogs, the so-called "bryologs," are currently being tested against HIV infections. They have been shown to flush out the latent virus, making it sensitive to highly active antiretroviral therapy (HAART), which would permanently eliminate the virus from the patients.

Other marine-derived compounds discovered by the Pettit group are the cephalostatins (isolated from *Cephalodiscus gilchristi* collected in 1972 off the east coast of South Africa) and the spongistatins (isolated from a sponge of the family Spongiidae, collected in the Maldives in 1988). Cephalostatin 1 and spongistatin 1 (Fig. 6, ref. 1) both showed potent *in vitro* activity against various cancer cell lines, as well as promising in vivo activity in xenograft models, but further development has been hampered by the very low yields obtained from their respective source organisms. The recent development of efficient total syntheses, however, could provide sufficient amounts to permit advanced preclinical studies and clinical development.

Finally, the discovery of two classes of plant-derived

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compounds is discussed. The most significant of these is the combretastatins isolated from the bark and wood of *Combretum caffrum*, collected in southern Africa in 1979. Being members of the stilbene family, these are more readily amenable to chemical synthesis. The most promising of these is combretastatin A4, which was converted to the water-soluble phosphate prodrug, combretastatin A4 phosphate (CA4P; Fosbretabulin; Zybrestat®; Fig.1). Following several clinical trials, it was granted orphan drug designation by the FDA in 2003 for the treatment of anaplastic thyroid cancer, medullary thyroid cancer, and stage IV papillary or follicular thyroid cancer. In 2006, it was granted orphan drug designation for the treatment of ovarian cancer. Another promising analog combretastatin A1, as its diphosphate prodrug CA1P (OXI4503; Fig.1), has shown promising efficacy in the treatment of patients with relapsed and refractory acute myelogenous leukemia and myelodysplastic syndromes. In 2012, orphan drug designation for this compound was assigned by the FDA for the treatment of acute myelogenous leukemia.

The second plant-derived compound is pancratistatin (Fig. 7, ref. 1), isolated from *Hymenocallis littoralis* (*Pancratium littorale*), which was collected in 1980 in Hawaii. Early testing demonstrated good in vivo activity in the P388 murine lymphocytic leukemia and M-5076 ovarian sarcoma models, and more recently it has been shown to completely inhibit tumor vascularization after only 2 hours of treatment. Several syntheses have been developed, holding out the prospect for further preclinical and possible clinical studies.

As the authors remark, it has been "an extraordinary scientific career which has led Dr. Pettit from exploration of nature to state-of-the-art organic and synthetic chemistry and from clinical trials to therapeutic successes."

In closing, they observe that "Dr. Pettit has combined research funding and optimization of results to allow the continuation of many promising projects in an academic setting sometimes not conducive to the development of candidate drugs. Tenacious and passionate, Dr. Pettit is only beginning his work at over 84 years old!" We might now add, at over 87 years old!

To sum up in the words of the late Dr. Carl Djerassi, "Pettit is one of the great heroes in the chemistry of marine natural products out of which he created a battery of anti-cancer agents not equaled anywhere."[4] ■

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