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NATURAL PRODUCTS

Satoshi Ōmura

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This special issue of the Journal of Industrial Microbiology and Biotechnology, entitled "Natural Product Discovery and Development in the Genomic Era," is dedicated to Satoshi Ōmura in recognition of his outstanding contributions to the discovery of microbial natural products over a research career spanning 50 years. It is a pleasure to write this short appreciation of his achievements.

After receiving a Master's degree from Tokyo University of Science in 1963, Ōmura began his academic career as a Research Associate at Yamanashi University, in his home prefecture. Then, in 1965, he moved to the Kitasato Institute to begin a lifelong association with that prestigious institution, named for Shibasaburō Kitasato, best known for his first cultivation of the tetanus bacillus (the logo of the Institute, now University, incorporates two crossed clubs reflecting the shape of the sporulating bacilli). Working his way up through the ranks at Kitasato, meanwhile completing a Ph.D. in Pharmaceutical Sciences from Tokyo University in 1968 and another, in Chemistry, from Tokyo University of Sciences in 1970, he became President in 1990, President Emeritus in 2008 and is now Distinguished Emeritus Professor. He is also President of the Joshibi University of Art and Design.

Right from the start, the drug discovery group at Kitasato, under Ōmura's leadership, pursued a highly original approach to the isolation of potentially valuable microorganisms, aimed at maximizing the probability of discovering taxonomic novelty and hence the likelihood of finding natural products with as yet undiscovered chemical structures and modes of action. Perhaps Ōmura's skill in finding antibiotics owes something to his early training as a geologist. I once accompanied him on a trip to the Southern Alps, the range of mountains inland from Mount Fuji, and he told me that he loved the outdoors, not only for the beautiful scenery but also because he can "tell the structure of land where microorganisms are living." It was fascinating to see this small, dapper figure striding through the swirling mist in a quest for the microbes' secret homeland.

At last count, the group has discovered 43 new species of soil actinomycetes and fungi, including members of 13 novel genera, and identified 470 new compounds. This nicely illustrates the momentum of the group because the fourth and latest edition of the compilation "Splendid Gifts from Microorganisms" in 2008 listed "only" 380 compounds. As many as 26 of the compounds have found a use, in human or veterinary medicine, as agrochemicals, or as biochemical research tools; a remarkable statistic.

Undoubtedly, avermectin (see below) is the jewel in the crown of these discoveries from a practical point of view, but a couple of others should be mentioned in this short appreciation. One, cerulenin, became a major research tool because of its unique ability to inhibit a key step—the condensation reaction—in lipid biosynthesis by the eukaryotic Type I fatty acid synthases. Another antibiotic, staurosporine, inhibits protein kinase C, a key player in carcinogenesis, and so has become a research reagent of major importance, with over 600 papers annually over a 20-year period referring to the use of staurosporine. The compound also led to the development of Imatinib (Gleevec®), a widely used anti-cancer agent. Lactacystin, produced by *S. lactacystinicus* (the fundamental structure was actually named Ōmuralide by E. J. Corey), proved to be a proteasome inhibitor. It played a crucial role in pioneering

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research in this field, such as its use in elucidation of ubiquitin-mediated protein degradation by Nobel laureates Ciechanover, Hershko and Rose.

Fig. 1 Ōmura sampling the soil at the spot where *Streptomyces avermitilis* was found. Photo Andy Crump

In the late 1970s, the Kitasato Institute entered into a research agreement with Merck and Co. in the USA to carry out collaborative research with microbes isolated in Japan being screened for specific targets in the company's facilities. As a result of this research came avermectin, produced by *Streptomyces avermitilis* isolated from Ōmura's favorite golf course (Fig. 1), and found to clear mice of an experimental nematode infestation. Thus was born—as a chemical derivative of the natural compound, called Ivermectin—the animal health drug with the largest worldwide sales over a long period. More importantly, the compound was found to be highly effective against the parasitic worms responsible for Onchocerciasis (called River Blindness in Africa) and lymphatic filariasis, and these afflictions are well on the way to being eradicated in Latin America and Sub-Saharan Africa as a result of donations of the drug by Merck (Fig. 2).

These practical applications of Ōmura's work are complemented by a huge body of rigorous research on the biosynthesis and mode of action of natural products. Probably the most pervasive studies concern the macrolides, as evidenced by two 600-page volumes on their chemistry, biology, and practice edited by Ōmura in 1984 and 2002, which became the Bibles for researchers on this, one of the most important classes of natural products.

My own research converged with Ōmura's in 1984. At the John Innes Centre, Francisco Malpartida had cloned the complete set of genes for the blue-pigmented antibiotic

Fig. 2 Ōmura at WHO headquarters with the statue showing a boy leading a blind man with a stick, hopefully a thing of the past. Photo Andy Crump

actinorhodin produced by *Streptomyces coelicolor*, as evidenced by transfer of the ability to make the compound into a heterologous host. We were thus in a position to test the idea that novel, "hybrid" antibiotics might be made by combining genes from strains making-related compounds. Actinorhodin is a benzoisochromanequinone, and Ōmura had published on other members of this chemical class, so I requested strains making two of them from him. However, he also sent the producer of the brown-pigmented medermycin, of which I was not aware, predicting possible structures for recombinant molecules that might arise, and this turned out to be an inspired choice. The result was the purple-colored mederrhodin, the first "hybrid" antibiotic, heralding the dawn of the age of genetic engineering as applied to antibiotic discovery.

Later, in parallel, we led the genome sequencing projects for *S. coelicolor* and *S. avermitilis*, at the Sanger Centre and the Kitasato Institute, respectively, leading to the striking prediction that each organism had the innate capacity to synthesis 20–30 potentially interesting natural products, of which only a small minority were detectable under standard laboratory screening conditions. The concept of "sleeping" gene clusters waiting to be "awakened" has become a guiding light in the current resurgence of interest in natural product discovery in the genomic age.

No account of Ōmura's contributions would do justice to the man without some reference to his philanthropic programs made possible by the avermectin royalties. He has combined these with his passion for modern art, particularly the work of living Japanese artists. He funded construction of the district hospital, nursing college, and vaccine production plant in Saitama, just north of Tokyo. The wards, corridors, and foyer of the hospital display some of the huge collection of Japanese artists' work purchased by Ōmura, in keeping with the concept of Healing Art which he has promoted. In his native city of Nirasaki, he has donated both an *onsen* (a traditional Japanese bath house) and an art museum to the people, the latter containing many paintings from his own art collection. Nor is his philanthropy confined to Japan. For example, to help Ivermectin reach as many people as possible in Africa he has financed the donation of bicycles and mobile phones for community-based Ivermectin deliverers in the remotest areas.

Naturally, Ōmura has received awards from innumerable prestigious bodies in many countries, including the Nakanishi Prize (Japan Chemical Society and American Chemical Society); Ernest Guenther Award for Chemistry of Natural Products (American Chemical Society); Hamao Umezawa Memorial Award (International Society of Chemotherapy); Japan Academy Prize; Robert Koch Gold Medal (Germany); Prince Mahidol Award (Thailand); Gairdner Global Health Award (Canada); l'Ordre National de la Legion d'Honneur (Chevalier), France; and Person of Cultural Merit (Japan). He is an elected member of many august bodies, including Japan Academy; Deutsche Akademie der Wissenschaften, Leopoldina; European Academy of Sciences; U.S. National Academy of Sciences; and Institut de France Academie des Sciences.

To conclude, Satoshi Ōmura is a giant among natural product scientists whose legacy will continue to inspire researchers as we enter what we hope will be a new Golden Age of discovery of "Splendid Gifts from Microorganisms," the spirit of the meeting that occasioned the publication of this volume.