doi:10.2533/chimia.2023.609 Chimia 77 (2023) 609–610 © L. Meier

Jonathan L. Vennerstrom: I Was Standing on the Shoulders of Giants

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Abstract: Jonathan L. Vennerstrom grew up in Ethiopia, where he was witness to the effects of leprosy and other infectious diseases of poverty on the local population. After his studies in organic chemistry, he began to research antiprotozoal agents, which resulted in the discovery of the synthetic ozonides. Fruitful collaborations with the Swiss Tropical and Public Health Institute (Swiss TPH) and the Medicines for Malaria Venture (MMV) have paved the way for antimalarial and antischistosomal drugs. In recognition of his many achievements, Vennerstrom received the 2019 ACS Award for Creative Invention.

Keywords: Antimalarial drugs · Antischistosomal agents · Synthetic ozonides

The OZ team in Uganda (2007). From left to right: Jonathan L. Vennerstrom, Sarah Arbe-Barnes, Susan A. Charman, William N. Charman, Jacques Chollet, Sergio Wittlin, Hugues Matile.

Medicinal chemist ***Jonathan L. Vennerstrom*** spent his childhood in Ethiopia, where his parents taught at a missionary school. Just a few child's steps away was a leprosarium, where the patients were cared for by a friend of his parents. Apart from leprosy, there was no shortage of other infectious diseases that are intimately connected with poverty. Indeed, people also suffered from schistosomiasis, a neglected parasitic helminth infection, and malaria. Back in the United States of America, Jonathan attended Bethel University in Arden Hills, Minnesota, and immersed himself in the world of organic chemistry. "My chemistry teacher, Dale Stephens, drew my attention to organic chemistry, a fascination that has never left me", he recalls. With a PhD from the University of Minnesota in his pocket, Vennerstrom pursued postdoctoral research at the Walter Reed Army Institute (WRAIR) from 1985 to 1987. The research institute had a long tradition of malaria research, driven in no small part by the war in Vietnam, during which more soldiers died from the bite of the *Anopheles* mosquito than from bullets.

At the University of Nebraska Medical Center, Vennerstrom embarked on a successful research programme to identify new antiprotozoal agents. In 1992, he reported on a new class of symmetrical dispiro-1,2,4,5-tetraoxanes as a new class of antimalarial peroxides. A key advance during this time was the synthesis of unsymmetrical 1,2,4-trioxolanes (ozonides) using a newly developed co-ozonolysis by chemist Karl Griesbaum working at the University of Karlsruhe in Germany. "Standing on the shoulders of Charles Jefford, Gary Posner and others who had been interested in the chemical structure of artemisinin, we used Karl Griesbaum's new chemistry to try to come up with something better and less expensive", Jonathan humbly recalls.

New Forms of Collaborations in R&D

In 1994, Robert Ridley invited Vennerstrom to come to Basel to give a talk at the pharmaceutical company Roche. Importantly, Roche had long been a leader in R&D of new antimalarial drugs. However, the environment in the 1990s was difficult, and the high investments and low profits of R&D against malaria and other poverty-related diseases led Roche to abandon its malaria research programme in 1997. Seasoned Roche malaria researchers Robert Ridley, Hugues Matile and Jacques Chollet moved on, the former to the World Health Organization (WHO), the latter two to the Swiss Tropical and Public Health Institute (Swiss TPH). Despite the great loss, the departure of the big pharmaceutical companies in R&D for infectious diseases of poverty was not the end for neglected populations, but meant a new beginning. In the late 1990s, Medicines for Malaria Venture (MMV) was formed, a product development partnership that redefined collaboration between industry and academia (see interview with Lutz Hegemann and Marcel Tanner in this issue[1]) and paved the way for new antimalarial drugs.

A Scientific Breakthrough: The Synthetic Ozonide Programme

Jonathan Vennerstrom's synthetic ozonide project was one of the first programmes funded by MMV and ran from 2000 to 2010. It led to the advanced clinical candidate OZ277 (arterolane), which was subsequently developed and marketed as a combination therapy with piperaquine by Indian Ranbaxy Laboratories. "I was blessed with many outstanding collaborators on this project – it

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was a real team effort – we became the ozonide (OZ) family", summarises Vennerstrom.

New Compounds against Schistosomiasis

In his research programme, Vennerstrom and his team also focused on human schistosomiasis, a parasitic worm infection caused by blood flukes that still affects an estimated 200 million people mainly in Africa. In collaboration with Jacques Chollet and later Jennifer Keiser at Swiss TPH, the team discovered the antischistosomal properties of synthetic ozonides against various *Schistosoma* species and other trematodes. "Jonathan Vennerstrom is an outstanding medicinal chemist and yet, he has both feet on the ground and is one of the most humble persons I ever met. You can toss ideas with Jonathan and he turns them into palpable chemical structures that – I am confident – will one day make the breakthrough in novel drugs against schistosomiasis and other infectious diseases", says Jennifer Keiser, the Head of the Helminth Drug Development unit at Swiss TPH and Professor of Neglected Tropical Diseases at the University of Basel.

In recognition of his many achievements, Jonathan Vennerstrom received the 2019 ACS Award for Creative Invention, which strengthened his confidence of having chosen the right track: "Although we will not be able to keep up with big pharma and their multimillion compound screens, we will continue to focus on our chemical strengths and seek out data which have been forgotten or ignored", he says.

Received: August 8, 2023

[1] L. Meier, *CHIMIA* ***2023,*** *77,* 613, https://doi.org/10.2533/chimia.2023.613.

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The definitive version of this article is the electronic one that can be found at https://doi.org/10.2533/chimia.2023.609