Laudatory speech for Christopher Walsh

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[Address]

Today, we honour Christopher Walsh, one of the forefathers of chemical biology, with the Robert Koch Medal in Gold. However, it is certainly far too simplistic to reduce his contributions to just one area. His interests include bio-organic chemistry, biochemistry, medical chemistry and molecular toxicology. However, his therapeutic focus was not restricted to antibiotics, they also encompassed interactions between hosts and pathogens, such as virulence factors and chemotherapeutics for treating cancer. His scientific approach was to investigate enzymes, the macromolecular proteins responsible for catalysis in living organisms. Chemical reactions of specific molecules are catalysed, with only a very low number of chemical reaction types observed. This knowledge gives an understanding of the logic of metabolic processes and transformations, such as biosynthesis of natural antibiotics, their effects and development of resistances in bacteria.

The following three areas are often used to describe the life's work of Chris Walsh, with a special focus on antibiotics research: Suicide substrates, vancomycin resistance and conveyor belt enzymology of natural products. Let us look at these areas individually.

After studying Chemistry of Natural Products at Harvard University in Boston, he moved on to the Rockefeller University in New York to complete a doctorate on mechanistic studies of an enzyme, the "Citrate Cleavage Enzyme". After his postdoctoral fellowship at Brandeis University in Waltham, he came to MIT in Boston until 1972.

There, he studied the mechanism of suicide substrates, compounds that irreversibly inhibit enzymes via covalent bonds to the active centre, rendering themselves non-functional in the process. According to Walsh himself, this research was initiated by a discussion of the impact of D-fluoralanine while attending a seminar at Merck in 1974. Walsh succeeded in proving that D-fluoralanine inhibits alanine-racemase in bacteria. This is the first step of biosynthesis of peptidoglycan, the essential component of the cell wall in many bacteria. These studies led to the identification of further enzymes in cell wall biosynthesis, like MurA, MurB and MurF. Key

inhibitors of the MurA and MurB enzymes, whose mechanisms can be explained based on this work, are the approved antibiotics fosfomycin and cylcoserine.

After 15 years at MIT, he became head of the Biochemistry and Molecular Pharmacology Department at Harvard Medical School in 1987, and was appointed President of the Dana-Farber Cancer Institute, a clinic with a staff of over 2000, in 1992. In early 1990, he noted with great concern the increasing resistance of enterococci to vancomycin, an essential glycopeptide antibiotic for treating potentially fatal infections that can occur during chemotherapy.

After his time as clinic president, he redoubled his research efforts. His goal was to understand the chemistry and biology of enzymatic production of smaller, complex natural products.

One focus was on understanding vancomycin resistance, in cooperation with Patrice Courvalin in Paris, who had identified five essential genes in enterococci. The enzymatic research at Harvard showed that this resistance is fundamentally caused by a changed intermediate in the biosynthesis of the peptidoglycan cell wall. The replacement of alanine with lactate is catalysed by the changed enzyme VanA, a D-Ala-D-Lac ligase. That reduces the affinity of vancomycin, which generally interacts with alanine, by a factor of 1000, so that there is no longer an antibiotic effect. This understanding allowed other groups and companies to search for new glycopeptides, with three new representatives of this class approved in recent years: dalbavancin, oritavancin and telavancin.

Another area of interest to the group was the biosynthesis of the enterobactin virulence factor in *E. coli*, an essential siderophore for iron absorption. The group also studied the biosynthesis of vancomycin to generate new analogues that could breach the resistance.
With this research on enzymes, Walsh found a gateway to understanding how these peptide antibiotics are assembled, similar to the conveyor belts used in modern factories. He aimed to understand the chemistry and molecular mechanisms in order to reprogram them and create new, improved antibiotics. He succeeded in decoding many of the main rules of NRPS, Non-Ribosomal Peptide Synthesis, as well as PKS, PolyKetide Synthesis, and comprehend the initiation, elongation, termination and post-translational modification. Without this work, modern chemistry of natural products, new concepts like combinatorial biology, or genomic analysis of potential sources of active ingredients would be inconceivable. He ended his active career in Harvard after 26 years. However, he recently became a member of the Chemical Faculty in Stanford.

Walsh mentored over 260 doctoral and post-doctoral candidates, published over 800 scientific papers and 5 books, received over 25 honours and awards and was on the executive or advisory boards of, or served as a consultant to 40 organisations. His work as scientific advisor to KOSAN Biosciences, Caliper Technologies and Millennium Pharmaceuticals and Versicor, Kosan Biosciences and Transform Pharmaceuticals are particularly worthy of mention. He is one of the scientific founders of Immunogen, a company that began investigating therapeutic antibody conjugates as early as 1981 – an idea that was not picked up by other companies until much later. He was also part of a group of MIT consultants to young innovative biotech startups, with the most successful support resulting in Genzyme.

As a researcher, he strives to understand fundamental contexts, to generate solutions that can be applied in practice. He not only combines diverse knowledge from a wide range of disciplines, but also builds bridges between academic basic research and industrial applications. His approach is always characterised by a great curiosity to gain new experiences. This is entirely in line with Robert Koch's thinking.

Dear Dr. Walsh,

On behalf of everyone here, it is my great honour and pleasure to congratulate you on winning the Robert Koch Medal in Gold 2017.