Acceptance Speech by Christopher Walsh

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[Address]

I thank the Koch gold medal selection committee and offer my strongest congratulations to Profs Rafi Ahmed and Antonio Lanzavecchia for their much deserved recognition as they receive the 2017 Robert Koch Award for their accomplishments at the intersection of immunology and microbiology.

My own road to microbiology research and discovery has been more winding than most, but once on that path I have found it a sustaining one for four decades. After undergraduate research at Harvard with both E.O. Wilson in Biology and in the group of John Law, adjacent to the group of Konrad Bloch in Chemistry, I went to The Rockefeller Institute for Medical Research, then newly reorganized as The Rockefeller university, for doctoral studies.

Rockefeller, many of you will know, has a famous history in infectious disease research. Two prominent examples were the work of Peyton Rous and his studies on what became the Rous Sarcoma virus, and the discovery of Avery, McCarty and Macleod, from streptococcal microbiology and genetics, that DNA was the molecular basis of genes and inheritance in the 1940s

I became embedded in the interface between chemistry and biology, taking up faculty appointments in both Biology and Chemistry Departments at MIT. In my second year on faculty I visited the Merck Research laboratories in New Jersey to give a seminar and converse with research groups. My serious intersection with microbiology began that day from a two hour discussion with a Merck group working on how fluoroalanine killed bacterial cells by inhibition of alanine racemase and so blocks bacterial cell wall biosynthesis.

My interpretation of their results differed mechanistically. Even though the Merck the team had some 25 person years of experience on this and related projects, my insights turned out to be correct. I was offered a consultancy at Merck that very day, which endured for 7 years.

I took up fundamental research on alanine racemase mechanism and ultimately the mechanism of the other enzymes in the construction of the pentapeptide moiety of bacterial peptidoglycan. That interest merged with a long term examination of mechanism-based enzyme inhibitors, aka “suicide substrates” that were instructive for antibiotic design.

Later, at my second academic institution Harvard Medical School where I also took on the role of CEO of Harvard’s cancer hospital, The Dana Farber Cancer Institute, we turned our attention to deciphering the molecular basis of vancomycin resistance. Vancomycin was then, and often still now, is an antibiotic of last resort, treating life-threatening gram positive bacterial infections in patients undergoing cycles of chemotherapy.

Together with Patrice Courvalin’s group at The Pasteur Institute we determined that in the resistant bacterial entercocci a molecular switch from D-Ala-D-Ala dipeptide to D-Ala-D-lactate depsipeptide (amide to ester) in the cell wall peptidoglycan meant the difference between life and death for bacteria exposed to vancomycin. And also life or death for the immunocompromised cancer patients. Only one hydrogen bond difference between wild type and mutant resistant peptidoglycan: devilishly clever bacterial pathogens.

Vancomycin is a natural glycopeptide antibiotic, made and secreted by a strain of bacteria. *Amylocaptosis orientalis*, was originally isolated from the island of Borneo and called vancomycin because it could ***vanquish*** infectious bacterial pathogens.

We then became intrigued by the thought that one might be able to reprogram the producing microbes to make engineered variants of vancomycin: engineered variants that might overcome the resistance mechanisms . My group became expert in natural product biosynthesis, including the underlying molecular logic that guides how molecules such as vanocycin are assembled.

Despite a couple of hundred research papers on the chemical logic and protein strategy for assembly of many kinds of natural products over a 15 year period, neither we nor others have coerced bacteria into making clinically usefully resistant vancomcyins *de novo*. That has now been achieved by Dale Boger’s group synthetically at The Scripps Institute in CA.

We did learn a lot of principles about other natural molecules of therapeutic relevance as thousands of bacterial and fungal genomes have been deciphered over the past two decades.

Over the years I wrote a book on Antibiotics, in 2003, and then did a total rewrite with a coauthor in 2016. We also wrote a recent monograph on natural product biosynthesis that has been published in 2017.

I have been involved in three startup companies that have focused on new antibiotics, in efforts to translate basic microbiology and medicinal chemistry into new drugs. One of them has brought a third generation vancomcyin derivative, *dalbavancin*, through FDA clinical approval. Another of the companines has brought a neo-aminoglycoside *plazomicin* through phase III clinical trials for treating carbapenem-resistant bacterial infections.

These days I am at my third institution, Stanford University in an institute lodged between Chemistry, Engineering, and Medicine where I teach, listen, and sometimes give advice. In that happy intellectual and physical climate I have written the Antibiotics book, version II, and the Biosynthesis of Natural Products over the past three years.

When I was a young faculty member at MIT and even later at Harvard Medical School where Koch's postulates are taught as the foundational principles of infectious disease, I could never have imagined I would receive a Gold Medal named after this true biomedical giant who introduced the world to the infectious theory of human diseases. It is indeed a unique honor.