Dankesrede

von

Prof. Dr. Arthur L. Horwich

anlässlich der Verleihung

des Paul Ehrlich- und Ludwig Darmstaedter- Preises

2019

in der Paulskirche Frankfurt am Main

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Es gilt das gesprochene Wort

Honorable guests

I am greatly honored and humbled to be receiving the 2019 Paul Ehrlich and Ludwig Darmstaedter Prize together with my collaborator Professor Ulrich Hartl. I have known about the work of Professor Ehrlich from the time of medical school, when I learned in hematology class about his work while he was a student, developing staining techniques with acidic, basic, and particularly neutral dyes to recognize specific white cell maturation stages as well as distinguishing mast cells and bacteria. Of course, in pharmacology, I learned about Salvarsan, his compound number 606, an arsenical that cured syphilis, a "Zauberkugel", as he had termed it.

He had leapt from developing dyes as a way of selectively targeting and staining specific cell types, to conceiving that such targeting, either with dyes or with chemical compounds, might be used to ablate specific cell types, such as bacteria or even tumor cells. What an honor to celebrate today the birthday of this Giant of Science.

I think he might have been amused to think about the uncovering of "Zauberringe" as molecular machines inside cells that could mediate the folding of proteins to their active form. For my student Ming Cheng and me, it was also a search of sorts, through baker's yeast mutants, where our mutant #143 turned out to be a strain that could import proteins into its mitochondrial organelles but could not fold the imported proteins to their active forms. Here we had asked a question, whether the cell needs machines to assist proteins to reach the folded active native state, and to our surprise, found evidence that there might be such a thing. We were frightened to be facing a decades-old concept that proteins inside cells must fold spontaneously, as had been observed in test tube studies.

We were unbelievably lucky to receive a phone call from Ulrich Hartl and Walter Neupert, who wondered if they might be of help with analyzing some of our mitochondrial import mutants. They did not know at that moment how profoundly we needed their help to understand our mutant #143 yeast strain!! What a delight to have their collaborative involvement - the shared understanding of big questions and how to experimentally address them, their boundless understanding of mitochondria, and skills in mitochondrial biochemistry, and their companionship! Walter became a Father Figure, energizing but also gently advising and guiding his excited brood, Ulrich and Art, and their teams.

What an exciting moment when, early into the work, we rescued the folding-defective mutant cells with DNA clones, and Ulrich and I, standing together on a dock in front of our little house on Long Island Sound in Connecticut on a summer's afternoon in 1988 with Ming Cheng and other members of my lab, could look at a sequencing gel that had just that day matched the rescuing gene to one known to encode a double ring structure inside mitochondria! It supercharged a 3-year period of absolute electrical intensity as we progressed on dissecting the physiology of the ring machines in cells, in organello, and with isolated components, then moving more generally to understanding in vivo folding pathways as Ulrich did, and to beginning to describe the magic of the double ring machines in biochemical terms as we both did.

I am deeply grateful to so many people:

Ming Cheng, of course, one of my first students, who came to Yale as a young physician wanting to explore fundamental biology; Kerstin Braig, a student from Berlin originally scheduled to visit for one year, but who stayed four years, a major contributor to our structural collaboration with Paul Sigler's group in the lab next door to us. She crystallized the bacterial GroEL after Andrzej Joachimiak from Paul's group and I were able to massively overproduce and purify the ring assembly. It was a year of Kerstin's trial and error efforts with different versions of GroEL. There in one little drop in one well of one tray out of hundreds of trays of crystallization set-ups, lining a whole wall of the laboratory, was a beautiful crystal that diffracted to nearly 3 Angstrom resolution on the area detector next door!!

Paul Sigler was equally excited when he came into the room and saw that diffraction pattern, literally jumping up and down, and within an hour scheduling weekend synchrotron time for looking at Kerstin's new crystals.

Paul was just so much another Father figure, teaching us all facets of crystallography but sharing with me all manner of life: Chicago sports – I grew up there and he had been a long-time faculty member at University of Chicago before coming to Yale - there was the Bears football and Bulls basketball, Ohio Street Pizza; jazz music – the beboppers - and Medicine. Both of us had been clinically trained and could see a pretty broad biomedical landscape.

Zbyszek Otwinowski, a remarkable crystallographer in Paul's group and producer of the data reduction software used by most of the X-ray community, solved the structure of GroEL once we had a heavy atom derivative data set, in a single day, an amazing feat given the complexities. Jonathan Weissman who studied topology of the machine and its ligands, establishing in parallel with Ulrich's group that folding occurred in an encapsulated chamber. Hays Rye who watched polypeptide and cochaperonin come and go from GroEL in real-time with fluorescence studies. These are just a few of the wonderful trainees and collaborators with whom I've had the enormous pleasure to work side-by-side over the years. And mixed into all of the discoveries, supporting them, advancing them, on a steady basis, were my senior team members, Wayne Fenton, George Farr, and Krystyna Furtak, who have always been a well-spring of thought and action in all of the work – we have watched not only our understanding of folding machines grow but have watched each other's kids grow up!

I owe much to my original and more recent mentors and collaborators – Mike Czech who awakened at Brown my love for design, execution and analysis of experiments; Tony Hunter at the Salk Institute who, along with Walter Eckhart, taught me how to think about and carry out molecular biology studies – I watched Tony discover tyrosine phosphorylation and that was inspirational; Leon Rosenberg who taught me Human Genetics and how to organize ideas and express them; Helen Saibil, with whom I shared many years of thought on how ring machines are working, who carried out a myriad of breathtaking EM studies that enabled visualization of reaction intermediates; and Kurt Wüthrich who guided us through making chaperonin complexes that could display themselves in TROSY-NMR spectroscopy.

I'm most grateful to my family members – My parents who are past an age of easy travel but who were delighted to hear of this recognition, who were ever-supportive of my interest in Science as a kid, plying me with captivating reading materials and supporting my efforts as a "ham" radio operator. My kids who have tolerated my deep involvements in experiments, reading/writing, and travel, but who have taught me how to ski, how to fish for and release trout, and how to handle inevitable defeat on the tennis court. And finally, Martina, my wife, the love of my life. We have enjoyed together all of the vagaries of each other's lives in science and medicine along with the pleasures of family life. It has all been a lot of fun.

I want to thank you all for coming to celebrate today.