Acceptance speech

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F. Ulrich Hartl, awardee in the Biology and Biomedicine category (16th edition)

Receiving the BBVA Foundation Frontiers of Knowledge Award is truly a fantastic honor. I am very grateful to the selection committee for choosing our work for this important recognition, which I am pleased to share with my early collaborator Art Horwich, and with our colleagues Kazu Mori and Peter Walter. I see this award foremost as a recognition of the many talented students and postdocs who I had the privilege of working with over the years. Most important are the invaluable contributions made by Manajit Hayer-Hartl, my wife and closest colleague.

Proteins are the molecules in our cells that control practically all life processes. Each cell contains thousands of different proteins. Encoded by our genes, they are made as long chains of amino acid building blocks, like a string of pearls, by specialized machineries called ribosomes. But in order to fulfill their various biological functions, the newly made protein chains must first fold into a defined three-dimensional structure – an origami at the nano-scale. How this works is one of the most fascinating problems in biology. It was my mentor, the late Walter Neupert, who introduced me to Art Horwich. Together we were lucky to make an exciting discovery. We found that in order to fold, proteins require help from so-called molecular chaperones, themselves proteins – a conclusion summarized in two 1989 *Nature* papers. This finding was unexpected and contradicted the prevailing dogma that protein folding is a spontaneous process, independent of cellular machinery.

In 1991, I moved from Munich to New York to join the new department of James Rothman at Sloan-Kettering Cancer Center. There I continued to investigate how different chaperone machineries cooperate in the pathway of protein folding. At the same time, Art Horwich at Yale University devoted himself to a structural and functional analysis of the chaperonin GroEL, in collaboration with Paul Sigler. The basic mechanisms of cellular protein folding that emerged are impressively simple and beautiful. We both showed that GroEL, a barrel-shaped protein complex, captures a newly made protein in the center of the barrel. Another protein, called GroES, then closes the barrel like a lid. The protein is now encapsulated and folds while shielded from the rest of the cellular environment. Because only a single protein chain is inside the barrel, it cannot clump together with other chains. Indeed, molecular chaperones prevent proteins from misfolding and clumping together to aggregates, which

can be toxic to cells - and therein lies the analogy to the role of the human chaperone in preventing undesired interactions between its protégés. Such a chaperone is beautifully portrayed in *Las Meninas*, the famous painting by the Spanish master Velazquez.

Over the last 25 years, the molecular chaperone field has experienced a truly brilliant development, with connections to almost every other aspect of biology. The medical relevance of molecular chaperones has become abundantly clear, especially in understanding neurodegenerative conditions such as Alzheimer's and Parkinson's disease, which are linked with the formation of protein aggregates. Many eminent researchers have contributed, and I would like to mention here in particular the important work of the late Susan Lindquist. The elucidation of cellular protein folding and protein quality control now informs on new ways of treatment. It has become clear that limitations of chaperone function with age play an important role in many diseases, and even in the aging process itself. However, none of this was foreseeable at the beginning – after all, we just wanted to find out how protein folding works.

The chaperone story exemplifies the importance of basic, curiosity-driven research in generating insights of far-reaching significance, and I am grateful to my past and present employers, the Howard Hughes Medical Institute and the Max Planck Society, for their unwavering support.

Let me once again thank my teachers and my colleagues, and especially my wife Manajit, who always keeps me grounded when thoughts about molecular chaperones carry me away.

Thank you.