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AKADEMIE VAN WETENSCHAPPEN

Dr H.P. Heineken Prize for Biochemistry and Biophysics 2010 awarded to Professor Ulrich Hartl of the Max Planck Institute for Biochemistry in Martinsried, Germany

Your Royal Highness,

Members of the Board of the Dr H.P. Heineken Foundation

and the Alfred Heineken Fondsen Foundation,

in particular their chairwoman, Mrs. De Carvalho,

Esteemed laureates,

Ladies and gentlemen,

It is the opinion of the jury for the 2010 Dr H.P. Heineken Prize for Biochemistry and Biophysics that Professor Franz-Ulrich Hartl merits this award for his outstanding contribution to our understanding of protein folding. The discovery of the way in which proteins take on their three-dimensional structure, which is decisive for their actions and functioning, is one of the greatest challenges of the life sciences. Franz-Ulrich Hartl has shown that chaperone proteins are required for the process of protein folding and has clarified the mechanism of chaperone-assisted protein folding in detail.

Franz-Ulrich Hartl was born in Germany on 10 March 1957. He studied in Heidelberg, where he received his PhD. In 1990, he obtained his Dr. Med. Habil. After working as a postdoctoral fellow with Professor Walter Neupert's group at the University of Munich and Professor William Wickner's group at UCLA, he was awarded an appointment at Cornell University's Sloan-Kettering Institute in 1991. From 1994 to 1997, he also worked as an associate investigator at the prestigious Howard Hughes Medical Institute. He has been the managing director of the Max Planck Institute for Biochemistry in Martinsried, Germany, since 1997.

Hartl's pioneering research has been vital to our understanding of protein chaperones and he is without a doubt one of the most important researchers in this field. It had long been assumed, based on research involving small, relatively simple proteins, that protein folding was generally a spontaneous process. The discovery of the role of chaperones in this process led to a drastic overhaul of the basic principles of protein biogenesis. While researchers knew that HSPs – heat shock proteins – had a hand in assembling denatured proteins, they had not identified the precise mechanism. Hartl conducted a series of ingenious experiments that revealed the role played by the chaperone protein Hsp60 – or GroEL in bacteria – in folding a mitochondrial enzyme. He showed that the enzyme binds in the central cavity of the cage-like Hsp60 complex, and that this protected environment accelerates enzyme folding during a reaction triggered by ATP. The protein in fact goes through several rounds of partial folding and unfolding before finally achieving the correct conformation. Hartl's discovery led to a series of articles in *Nature* that launched a broad field of research.

Most of the relevant experiments were conducted *in vitro* at first, with use being made of purified or synthetic proteins assembled to form a functional system. It was once again Hartl

who conducted a number of effective experiments revealing the role of Hsp60 *in vivo*. This brilliant achievement was a huge impetus for the field. Hartl's pioneering research also clarified a system of cooperating chaperones, these being Hsp70 and Hsp60. He discovered that the folding process begins with chaperone Hsp70 and is continued by Hsp60. Chaperone Hsp70 prevents protein folding and aggregation of new proteins and keeps them from being rendered non-functional. The protein is then transferred to Hsp60, where final folding takes place in a protected environment. In addition, Hartl has clarified the effects of a series of other chaperone proteins, many of which play specific roles in protein biogenesis. He has also identified a large number of categories of proteins that rely on chaperones for folding.

Because most proteins depend on chaperones to acquire their three-dimensional shape, and consequently to perform their physiological activity, a proper understanding of protein folding has enormous implications for medicine and biotechnology. For example, a disruption in the folding mechanism leads to diseases such as Parkinson's and Huntington's. Hartl and his colleagues have shown that chaperones can prevent the formation and aggregation of fibrils into Huntingtin fragments – one of the causes of Huntington's Disease. This original and ground-breaking work by Hartl and his colleagues is not only helping to solve the mechanistic aspects of these neurodegenerative diseases, but is also playing a role in developing new therapeutic strategies. The importance of protein folding for molecular medicine has been underlined by the fact that numerous other diseases – for example Alzheimer's, Parkinson's and prion diseases – are the result of protein aggregation. Professor Hartl is an eminent scholar, and the jury believes that he will continue to make major contributions to a field in which many of his discoveries have already become textbook knowledge.