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BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.

NAME: HARTL, Franz-Ulrich

eRA COMMONS USER NAME (credential, e.g., agency login):

POSITION TITLE: Prof. of Biochemistry; Chair of the Dept of Cellular Biochemistry, Max Planck Institute of Biochemistry

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	Completion Date	FIELD OF STUDY
University of Heidelberg, Germany	M.D.	1982	Medicine
University of Heidelberg, Germany	Dr. Med.	1985	Biochemistry
Postdoc, University of Munich with Walter Neupert		1985-1987	Biochemistry
Postdoc, UCLA with William Wickner		1990-1991	Biochemistry

A. Personal Statement

Research in my laboratory focuses on the mechanisms of protein folding and quality control in the cell. Our goal is to reach a comprehensive understanding, at the structural and functional level, of how the machinery of molecular chaperones assists folding through the cooperation of co- and post-translational mechanisms. A long-standing interest is to understand how the cylindrical chaperonins of the GroEL type promote and modulate the folding process. Our second major research focus concerns the molecular mechanisms of proteotoxicity in diseases associated with protein misfolding and aggregation, including Parkinson's, Alzheimer's and Huntington's diseases. Here we wish to understand how the cellular machinery of protein homeostasis (proteostasis) normally provides protection and why these defense mechanisms increasingly fail during aging, facilitating the manifestation of neurodegeneration. We are using a wide range of methods from cellular biochemistry, biophysics and structural biology. In understanding the proteostasis network we are increasingly using systems-based approaches, including quantitative proteomics and genetic screens.

B. Positions, Scientific Appointments, and Honors

Positions and Employment

1997 -- Director at Max Planck Institute of Biochemistry, Department of Cellular Biochemistry
1994-1997 Associate Investigator, Howard Hughes Medical Institute
1991-1997 Associate Member and Member with tenure, Sloan-Kettering Institute, New York
Professor of Cell Biology, Cornell University, New York
1987-1990 Group leader, Institute of Physiological Chemistry, University of Munich

Other experience and professional memberships

2017 -- Member Board of Reviewing Editors, eLife
2012 -- Member Editorial Board, PNAS
2006 -- Member Editorial Board, Molecular Cell
2005-2007 Chairman of the Biomedical Section of the Max Planck Society
2004 -- Member Editorial Committee, The Annual Review of Biochemistry
2003-2005 President, German Society for Biochemistry and Molecular Biology
1999 -- Member Editorial Board, The EMBO Journal
1996 -- Member Editorial Board, The Journal of Cell Biology

Honors and Awards (selection):

2022 Nakasone Award for Frontier Research of the Human Frontier Science Program
2022 ERC Advanced Grant
2021 Bavarian Maximilian Order for Science and Art
2020 Breakthrough Prize in Life Sciences
2019 Paul Janssen Award for Biomedical Research
2019 Paul Ehrlich and- Ludwig Darmstaedter-Prize (University of Frankfurt)
2018 Induction to 'Hall of Fame of German Research'
2017 E.B. Wilson Medal, American Society of Cell Biology
2017 Debrecen Award for Molecular Medicine
2016 Award of Vallee Visiting Professorship (Vallee Foundation, Boston)
2013 Biochemical Analytic Prize, German Society for Clinical Chemistry and Laboratory Medicine
2013 Herbert Tabor Award of ASBMB, USA
2012 Shaw Prize in Life Science and Medicine, Hong Kong
2011 Heinrich Wieland-Prize of the Boehringer Ingelheim Foundation
2011 Massry Prize, Los Angeles, USA
2011 Lasker Award for Basic Medical Research, New York, USA
2011 Foreign Associate of the National Academy of Sciences, USA
2010 The Dr H.P. Heineken Prize for Biochemistry and Biophysics, Netherlands
2010 Van Gysel Prize for Biomedical Research in Europe- 2009, Belgium
2009 Otto Warburg Medal of the German Society for Biochemistry and Molecular Biology (GBM)
2008 Louisa Gross Horwitz Prize, Columbia University, USA
2008 Lewis S. Rosenstiel Award, Brandeis University, USA
2007 Wiley Prize in Biomedical Sciences, Rockefeller University, USA
2006 Koerber European Science Award
2006 Stein and Moore Award of the Protein Society, USA
2005 Ernst Jung-Prize for Medicine
2004 Gairdner Foundation International Award, Canada
2003 Feldberg Prize, UK
2002 Member Leopoldina, German Academy of Sciences
2002 Gottfried Wilhelm Leibniz-Prize of the Deutsche Forschungsgemeinschaft
2000 Foreign Honorary Member of the American Academy of Arts and Sciences
1998 EMBO Member
1997 Lipmann Award of ASBMB, USA

C. Contributions to Science

Chaperone-assisted protein folding

Demonstration (collaboratively with A. Horwich) that the process of *in vivo* protein folding depends on assistance by molecular chaperones, in contrast to the earlier view that folding is generally a spontaneous reaction. This discovery was made for the Hsp60 chaperonin in mitochondria (Cheng et al., Nature 1989; Ostermann et al., Nature 1989; Martin et al., Nature 1991). Through the use of a monomeric substrate protein (DHFR), Ostermann et al. specifically demonstrated the role of chaperones in protein folding rather than oligomeric subunit assembly. Martin et al. reported the *in vitro* reconstitution of chaperonin-assisted folding for monomeric proteins (DHFR and rhodanese).

Chaperonin mechanism

Elucidation of the basic mechanism of chaperonins in allowing protein chains to avoid aggregation by folding each protein molecule individually within an enclosed cage (Martin et al., Nature 1991; Langer et al., EMBO 1992; Martin et al., Nature 1993; Mayhew et al., Nature 1996). This work was extended in more recent years by the demonstration that the chaperonins can also substantially accelerate folding by sterically confining the encapsulated protein, thereby modulating the folding energy landscape (Brinker et al., Cell 2001; Tang et al., Cell 2006; Sharma et al., Cell 2008; Chakraborty et al., Cell 2010; Georgescauld et al., Cell 2014). In a recent study (Balchin et al., Cell 2018) we analysed the role of the eukaryotic chaperonin TRiC/CCT in the folding of actin. We showed that actin does not fold spontaneously, even in the absence of aggregation (at single molecule concentration). Instead, the actin folding pathway needs instruction from TRiC through subunit-

specific chaperonin binding, followed by encapsulation. This work demonstrates the limitation of the Anfinsen dogma, according to which the information provided by the amino acid sequence is sufficient for folding.

Cellular chaperone pathway

Development of the concept of a functional cooperation between the Hsp70 and chaperonin systems in the process of protein folding in both prokaryotic and eukaryotic cells. Hsp70 stabilizes nascent polypeptides attached to ribosomes, while the cage-containing chaperonins act immediately downstream. This model was first proposed based on in vitro reconstitution experiments (Langer et al., Nature 1992) using the bacterial chaperones and then shown to be conserved in the eukaryotic system (Frydman et al., Nature 1994). The model was then extended to incorporate the function of the Hsp70 system in assisting protein folding independently of chaperonin for a subset of proteins (Szabo et al., PNAS 1994; Hartl, Nature 1996). Proteins that cannot utilize Hsp70 to reach native state are transferred into the central cavity of the chaperonin for folding. Sequential chaperone pathways have since been demonstrated in numerous studies.
Determination of the spectrum of polypeptides that bind to the GroEL chaperonin inside the *E.coli* cell, and identification of some of the relevant features of GroEL substrates (Houry et al., Nature 1999; Kerner et al., Cell 2005). This work was subsequently extended to a comprehensive analysis of the *E. coli* chaperone network by analysing the interactome of Hsp70 (DnaK) under various conditions (Calloni et al., Cell Reports, 2012; Zhao et al., Mol Cell 2021).

Co-translational protein folding

Demonstration of sequential domain folding during translation, and involvement of chaperones in this process, as a basic mechanism of avoiding misfolding due to unwanted interactions between concomitantly folding domains (Frydman et al, Nature 1994; Netzer and Hartl, Nature 1997; Frydman et al., NSMB 1999). Proposal that the evolution of proteins was constrained by the properties of the translation and folding machineries, based on results showing that the efficiency of co-translational folding of eukaryotic multi-domain proteins is higher in the eukaryotic translation system than in the bacterial translation system (Netzer and Hartl, 1997; Chang et al., JMB 2005). These differences could be attributed to differences in translation speed (5-10-times faster in prokaryotes) and chaperone composition (Agashe et al., Cell 2004; Kaiser et al., Nature 2006)

Protein assembly

Discovery (in collaboration with M. Hayer-Hartl) of a new class of assembly chaperones for oligomeric protein complexes such as the photosynthetic enzyme Rubisco. These factors act downstream of the GroEL chaperonin and mediate specific contacts between folded subunits (Saschenbrecker et al., Cell 2007; Bracher et al., NSMB 2011). The Rubisco enzyme of plants requires multiple such factors that function along an assembly line. Co-expression of these factors in *E. coli* allowed the recombinant expression of plant Rubisco (Aigner et al., Science 2007), which now enables screening for Rubisco variants with improved enzymatic performance. This advance is of particular interest in agricultural biotechnology.

Proteostasis and disease

Demonstration that the Hsp70/Hsp40 chaperone system is able to specifically suppress the formation of amyloid fibrils associated with neurodegenerative syndromes such as Huntington's and Parkinson's disease and proof-of-principle demonstration that chaperones can be upregulated by small molecule compounds to achieve inhibition of aggregation (Muchowski et al., PNAS 2000; Sittler et al., Hum Mol Genet 2001; Schaffar et al., Mol Cell 2004). The chaperones act in preventing amyloid fibril nucleation. Upregulation of cellular chaperones by small molecule drugs is currently being explored as a strategy for the treatment of neurodegenerative syndromes.

Demonstration that pathological protein aggregates are toxic owing to their aberrant interactions with multiple cellular factors, including critical components of the chaperone network, and characterization of the structural features that mediate these aberrant interactions (Olzscha et al., Cell 2011; Park et al., Cell 2013). Of significance in this context are recent findings that the toxicity of aggregates depends on their cellular location, with aggregates in the cytosol often interfering with nucleo-cytoplasmic transport of proteins and RNA (Woerner et al., Science 2016). Inhibition of nucleo-cytoplasmic transport has since been confirmed by others to contribute to the cytopathology of several neurodegenerative diseases, including ALS and tauopathies.

Discovery of a new mechanism by which faulty translation products (so-called non-stop proteins) cause the formation of toxic aggregates when the machinery for their timely removal fails (Choe et al., Nature 2016, Izawa et al., Cell 2017). Interestingly, this mechanism is mediated by a specific C-terminal peptide tag (discovered by J. Weissman, A. Frost and O. Brandman) that is added to faulty proteins on the ribosome and results in aggregation properties similar to those of the polyglutamine protein aggregates that cause Huntington's disease. For non-stop proteins destined to subcellular compartments such as the mitochondria, aggregation occurs within the organelles and results in severe cellular dysfunction (Izawa et al., 2017). This is consistent with findings that the accumulation of non-stop proteins causes neurodegeneration in a mouse model.

Analysis of aggregates of Huntingtin *in situ* in intact cells using cryoelectron tomography (collaboration with W. Baumeister and R. Fernandez-Busnadiego) (Bäuerelein et al., Cell 2017). This study demonstrated the ability of amyloid-like fibrillar aggregates to displace endomembrane structures, particularly of the endoplasmic reticulum, and to disrupt such membranes, suggesting that the fibrillar deposits found in many neurodegenerative diseases are not inert but participate in driving cellular pathology.

Publications (as of 6/2021: 317 publications, ~74,000 citations, h-index = 133; source Google Scholar)