Leopoldina
Nationale Akademie
der Wissenschaften

Leopoldina Symposium

# Molecular Biology of Aging – Sino-German Perspectives

**12 – 13 October 2017**
Berlin

## Impressum



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# Content

Leopoldina Symposium

# Molecular Biology of Aging – Sino-German Perspectives 2017

In Europe as well as Asia, population aging has a tremendous societal impact. At the same time, life science research in advanced countries like China and in Europe has the potential to establish a solid understanding of cellular aging and, in the future, to offer remedies for some of the flip sides of aging. Matching Chinese and German top-level academics in a discussion on aging research should generate new ideas and fuel new research.

Maintaining and extending the healthy lifespan is one of the central concerns and goals of aging research. While healthy aging has offered people and societies many new opportunities, it is undisputed that aging is a key risk factor for late-onset diseases. At the level of cells, aging brings about multiple interconnected defects. Pathological and 'normal' aging overlap. Several pathways or mechanisms are currently discussed (e.g., genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, deregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, and altered intercellular communication). The conference aims to bring together experts from China and Germany to discuss such issues.

**Leopoldina:**
Ursula M. Staudinger
(Chair Standing Committee on Demographic Change,
National Academy of Sciences Leopoldina)

**Scientific Conference Chairs:**
Ulrich Hartl, Michael Hengartner

# Program

## Thursday, 12 October 2017

### 13:00 – 13:30 | Welcome Address

Jörg Hacker ML
*President, German National Academy of Sciences Leopoldina*

Depei Liu
*Chinese Academy of Engineering*

### Opening

Ursula M. Staudinger ML
*Standing Committee Chair, German National Academy of Sciences Leopoldina*

Ulrich Hartl ML
*Scientific Conference Chair*

**Topic I: Epigenetic Regulation of Aging**
(Chair: Thomas Lengauer ML, Max Planck Institute for Informatics)

### 13:30 – 14:10

**Genome Architecture Mapping:**
**Discovering Chromatin Contacts in Rare Cell Types**
Ana Pombo
*Max Delbrueck Center for Molecular Medicine*

### 14:10 – 14:50

**Integrative Data Analysis for Aging Research**
Jing-Dong Jackie Han
*CAS-MPG Institute for Computational Biology, Chinese Academy of Sciences*

### 14:50 – 15:30

**The Four Layers of Aging and Epigenetic Regulation**
Depei Liu
*Chinese Academy of Engineering*

### 15:30 – 16:00 | Discussants

Helmut Sies ML
*University of Dusseldorf*

Thomas Lengauer ML
*Max Planck Institute for Informatics*

### 16:00 – 16:30 | Coffee Break

**Topic II: Aberrant Protein Folding**
(Chair: Christian Haass ML, German Center for Neurodegenerative Diseases)

**16:30 – 17:10**

**Cellular Chaperone Machinery and Neurodegenerative Diseases**
Ulrich Hartl ML
*Max Planck Institute for Biochemistry*

**17:10 – 17:50**

**The Surprising Biology of Mammalian Prions**
Adriano Aguzzi ML
*University of Zurich*

**17:50 – 18:30**

**Genetic Mechanisms Underlying Natural Variation in Aging**
Shi-Qing Cai
*Institute of Neuroscience, Chinese Academy of Sciences*

**18:30 – 19:00 | Discussant**

Christian Haass ML
*German Center for Neurodegenerative Diseases*

**19:30 | Dinner**

## Friday, 13 October 2017

**Topic III: Programed Cell Death (Apoptosis)**
(Chair: Michael Hengartner ML, University of Zurich)

**09:00 – 09:40**

**Molecular Mechanisms of Alzheimer's Disease**
Christian Haass ML
*German Center for Neurodegenerative Diseases*

**09:40 – 10:20**

**Structural and Functional Investigations of Human Secretase**
Linfeng Sun
*University of Science & Technology of China*

**10:20 – 10:45 | Discussant**

Michael Hengartner ML
*University of Zurich*

**10:45 – 11:15 | Coffee Break**

## Topic IV: Genome Instability/Oxidative Stress as Accelerators of Aging
(Chair: Ulrich Hartl ML, Max Planck Institute for Biochemistry)

**11:15 – 11:55**

**The Role of the Mitochondrial Genome in Aging**
José Antonio Enríquez Domínguez
*Spanish National Center for Cardiovascular Research*

**11:55 – 12:30**

**Genome Variations Are Associated with Aging and Aging-Related Diseases**
Huanming Yang ML
*Beijing Genomics Institute*

**12:30 – 13:00 | Discussant**

Ulrich Hartl ML
*Max Planck Institute for Biochemistry*

## Summary and Closing Remarks

**13:00 – 13:15**

**Sino-German Perspectives on the Molecular Biology of Aging – What Have We Learnt?**
Ulrich Hartl ML, Michael Hengartner ML
*Scientific Conference Chairs*

**13:15 – 13:30 | Closing Remarks**

Ursula M. Staudinger ML
*German National Academy of Sciences Leopoldina and Columbia University*

**13:30 | Lunch**

**14:30 – 16:00 | Social Program: Boat Trip**

ML = Member of the Leopoldina

## Symposium Venue

Tagungs-und Kongresszentrum Reinhardtstraßenhöfe
Reinhardtstraße 14
10117 Berlin



# Ana Pombo

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## Genome Architecture Mapping: Discovering Chromatin Contacts in Rare Cell Types

The folding of chromosomes and the structural organization of the genome impacts human health and disease. Gene expression is controlled by long-range chromatin contacts between non-coding regulatory regions and their target genes. Recent development in novel methodologies to map chromatin contacts have shown that disruption of chromatin contacts due to disease-associated structural changes in the linear genome can result in altered patterns of gene expression. However, the analyses of specific cells types, such as neurons in specific areas of the brain remain a challenge.

To study the relationship between 3D genome folding and gene expression in specific cell types, we have developed Genome Architecture Mapping (GAM), a novel ligation-free technique, which overcomes limitations of current 3C-based approaches. GAM extracts spatial information by sequencing DNA from a large collection of thin nuclear sections, before quantifying the frequency of locus co-segregation across the collection of sections. By applying GAM to mouse embryonic stem cells, we have identified specific chromatin contacts enriched for interactions between active genes and enhancers spanning large genomic distances. We currently apply GAM in neuronal subtypes directly microdissected from mouse brain. Our work shows that genome architecture is highly dependent on cell-type specific gene expression patterns at both short and long genomic distances.

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# Integrative Data Analysis for Aging Research

New high-throughput technologies have provided unprecedented opportunities for mapping mutations, transcripts, transcription factor binding and histone modifications at high resolution and at genome-wide level. This has revolutionized the way regulations of diseases and other biological processes are studied and generated a large amount of heterogeneous data, which is begging to be unbiasedly and efficiently integrated. How to integrate these data still remains a big challenge. We have explored to *ab initio* predict or reconstruct regulatory networks based on heterogeneous data on gene expression, histone modification and genomic changes. We find that innovative integrations of these data can lead to not only global pictures of the complex biological processes, but also key regulatory events of these processes. As an example, we integrated various mRNA expression and ChIP-seq data to reverse engineer a Dietary restriction (DR) induced longevity regulatory network. We uncover three network modules of regulators by target specificity. By genetic manipulations of nodes representing discrete modules, we induce transcriptomes that progressively resemble DR as multiple nodes are perturbed. Targeting all three nodes simultaneously results in extremely long-lived animals that are refractory to DR. These results and dynamic simulations demonstrate that extensive feedback controls among regulators may be leveraged to drive the regulatory circuitry to a younger steady state, recapitulating the full effect of DR.


# Depei Liu

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## The Four Layers of Aging and Epigenetic Regulation

With an aging population, age-related diseases, such as cardiovascular diseases and cancers, are becoming the leading causes of death worldwide. To analyze how aging lays the foundation for diseases, we dissect the manifestations of aging into four layers, each at a biological scale. From the overall phenotype to the molecular mechanism, the four layers of aging are (1) decline in physical function and increased susceptibility to diseases; (2) systemic immune, metabolic and endocrine dysfunction; (3) cellular malfunction; and (4) failure of biomolecule maintenance. The interlayer connections are extensive. Both positive and negative feedback mechanisms determine the progression or the temporary arrest of the aging cascade. Importantly, from the perspective of this four-layer view of aging, we may delay aging and prevent chronic diseases with minimal side effects by effectively harnessing the inherent adaptive responsive mechanisms at the appropriate intensity and time.

Calorie restriction is an efficient method to delay aging. Sirtuin gene family is thought to partly mediate effects of calorie restriction. We studied effects of several members of this family in cardiovascular diseases, the very prevalent aging-associated diseases nowadays. We found that SIRT1 prevents atherosclerotic development and inhibits neointima formation. Calorie restriction increases SIRT1 expression and ameliorates abdominal aortic aneurysm, while aging decreases SIRT1 expression and accelerates abdominal aortic aneurysm. In addition, we found that SIRT4 plays crucial roles in mediating Ang II-induced cardiac hypertrophy. Thus, the sirtuin gene family is of potential significance for treating aging-related cardiovascular diseases.

Ulrich Hartl

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# Cellular Chaperone Machinery and Neurodegenerative Diseases

Proteins are the most versatile macromolecules in our cells. They are responsible for almost all biological functions. Proteins are synthesized as chain-like polymers of amino acids. In order to become biologically active, most protein chains must collapse into a well-defined three-dimensional structure in a process called protein folding. The past two decades have witnessed a paradigm shift in our understanding of this process. While the three-dimensional structures of functional proteins are determined by their amino acid sequences, it is now firmly established that in the cell many proteins depend on specialized helper proteins, 'molecular chaperones', to reach their folded states efficiently and on a biologically relevant time scale. Assistance of protein folding is provided by different types of chaperone which act to prevent misfolding and aggregation, often in an energy (ATP)-dependent mechanism.

When proteins fail to fold correctly or when they unfold under conditions of cell stress, they may clump together to form aggregates. Such aggregates are dangerous, especially to the cells in the brain. Aggregate deposition inside or around neuronal cells is known to cause several age-dependent neurodegenerative diseases, including Alzheimer's, Parkinson's and Huntington's disease. Molecular chaperones normally prevent the formation of aggregates and cooperate with degradation machinery to mediate the removal of misfolded proteins. However, a decline of cellular chaperone capacity during aging facilitates neurodegenerative aggregate deposition in the elderly. Finding ways to maintain the activity of the chaperone system may provide a useful strategy to delay the age-dependent onset of neurodegeneration and dementia.



# Adriano Aguzzi

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## The Surprising Biology of Mammalian Prions

Transmissible spongiform encephalopathies (TSEs) are neurodegenerative diseases of humans and many animal species caused by prions. The main constituent of prions is PrPSc, an aggregated moiety of the host-derived membrane glycolipoprotein PrPC. Prions were found to encipher many phenotypic, genetically stable TSE variants. The latter is very surprising, since PrPC is encoded by the host genome and all prion strains share the same amino acid sequence. Here I will review what is known about the infectivity, the neurotoxicity, and the neuroinvasiveness of prions. Also, I will explain why I regard the prion strain question as a fascinating challenge – with implications that go well beyond prion science. Finally, I will report some recent results obtained in my laboratory, which is attempting to address the strain question and some other basic issues of prion biology with a "systems" approach that utilizes organic chemistry, photophysics, proteomics, and mouse transgenesis.

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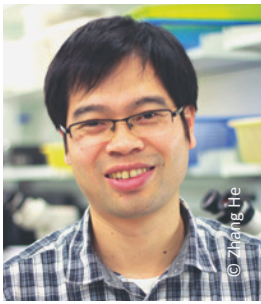
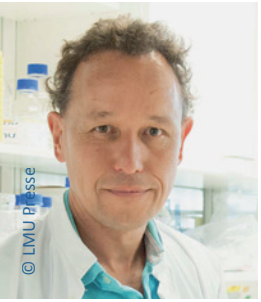



# Genetic Mechanisms Underlying Natural Variation in Ageing

The rate and severity of behavioural and cognitive decline in ageing population are remarkably different among individuals. Despite great interest in studying individual variation in ageing rate to identify factors that control healthy ageing, so far no such factor has been found. Here we discover a genetic basis for natural variation in ageing rate in Caenorhabditis elegans. We found that natural C. elegans isolates showed diverse lifespan and age-related decline in mating virility, pharyngeal pumping, and locomotion. Polymorphisms in a novel peptide-coding gene, named regulatory-gene-for-behavioural-ageing-1 (rgba-1), and a neuropeptide receptor gene npr-28 regulated age-related deterioration of mating virility and pharyngeal pumping, but not the lifespan. Selective deletion of rgba-1 in glia, but not neurons or intestinal cells, prevented deterioration of mating virility. RGBA-1 activated NPR-28 signaling and loss-of-function npr-28 mutations prevented mating virility deterioration. The latter effect was not additive to that induced by rgba-1 mutation, and was abolished by expressing NPR-28 in serotonergic or dopaminergic neurons. The ageing rate reduction by down-regulating RGBA-1/NPR-28 signaling required SIR-2.1-dependent activation of mitochondrial unfolded protein response, a pathway modulating ageing. Population genetic analysis showed that rgba-1 and npr-28 might be subjected to recent selective sweep. Furthermore, rgba-1 is a novel gene because no RGBA-1 homologue was found in other nematode species. Thus, evolution in the ageing rate may have been affect by multiple factors, such as the emergence of new genes, natural selection, and the interaction among genetic loci. Together, our work suggests that natural variation in neuropeptide-mediated glia-neuron signaling modulates ageing rate.





# Christian Haass

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## TREM2 – From Microglial Dysfunction to Alzheimer Patients

Sequence variations in the triggering receptor expressed on myeloid cells 2 (TREM2) have been linked to an increased risk for Alzheimer's disease and frontotemporal dementia (FTD). Missense mutations associated with FTD and FTD-like syndrome reduce TREM2 maturation, abolish shedding by ADAM proteases, and impair the phagocytic activity of TREM2-expressing cells. As a consequence of reduced shedding, TREM2 is virtually absent in the cerebrospinal fluid (CSF) and plasma of a patient with FTD-like syndrome. TREM2 loss-of-function has profound effects on the microglia transcriptome. Among the differentially expressed messenger RNAs in wild-type and Trem2-/- microglia gene clusters were identified, which represent gene functions in chemotaxis, migration and mobility. Using CRISPR/Cas9 genome editing, we generated a knock-in mouse model for the FTD-like syndrome associated Trem2 p.T66M mutation. Consistent with a loss-of-function mutation we find impaired maturation of mutant Trem2 resulting in an almost complete reduction of soluble Trem2. Immunohistochemistry together with in vivo TSPO small animal positron emission tomography (µPET) demonstrated an age-dependent reduction of microglial activity. Unexpectedly, perfusion magnetic resonance imaging and FDG-µPET imaging revealed a significant reduction in cerebral blood flow and brain glucose metabolism. Using mass spectrometry we determined the cleavage site of TREM2. TREM2 matures within the secretory pathway and its ectodomain is shed on the plasma membrane. TREM2 is shed by proteases of the ADAM family C-terminal to histidine 157, a position where an AD-associated coding variant has been discovered (p.H157Y) in the Han Chinese population. The p.H157Y variant leads to enhanced shedding of TREM2. Elevated ectodomain shedding reduces cell-surface full-length TREM2 and lowers TREM2-dependent phagocytosis.

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# Structural and Functional Investigations of Human γ-Secretase

Alzheimer's disease is one of the most devastating age-related, neurodegenerative diseases worldwide. The four-component intramembrane protease γ-secretase is intricately linked to the development of Alzheimer's disease. By single-particle, cryo-electron microscopy (cryo-EM), we solved the three-dimensional structure of human γ-secretase at atomic resolution. Molecular mechanism for substrate recognition and cleavage was proposed based on the atomic resolution structure of γ-secretase complex. We explored the molecular mechanism of its enzymatic function, especially for the Familial Alzheimer's Disease related mutants, and analyzed 138 reported mutations in PS1 by individually reconstituting the mutant PS1 proteins into γ-secretases and examining their abilities to produce Aβ42 and Aβ40. Structural and functional studies of γ-secretase provide an important framework for the understanding of AD pathogenesis, and molecular basis for drug design targeting human γ-secretase.

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# The Role of the Mitochondrial Genome in Aging

Animal models with identical nuclear genomes but with different mtDNA haplotypes (conplastic mice) generate functionally different OXPHOS systems that shape the organismal metabolism and determine heathy ageing1, supporting the conclusion that different mtDNA wild type haplotypes are phenotypically relevant. We will discuss the molecular basis of this influence and at what extension is the interaction mtDNA/nDNA or just the mtDNA variant what matters.

Mitochondrial DNA (mtDNA) is present in multiple copies in each nucleated cell of our body, all derived from the clonal expansions of those in the oocyte. Therefore, all mtDNAs of a given cell are essentially identical, a situation named homoplasmy. Heteroplasmy refers to the presence of more than one variant of mtDNA co-existing in the same cytoplasm. Heteroplasmy is actively combated by several mechanisms, including degradation of the paternal mtDNA upon fertilization, and the existence of a genetic mtDNA bottleneck in oocyte development. Heteroplasmy may be naturally generated by mutagenesis during mtDNA replication, but also can be caused by novel medical technologies.

We will explore the unsolved controversy regarding the possible functional consequences of the impact of heteroplasmy in OXPHOS performance.

1 Latorre-Pellicer, A. et al. Mitochondrial and nuclear DNA matching shapes metabolism and healthy ageing. Nature 535, 561–565 (2016).

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# Genome Variations Are Associated With Ageing and Ageing-Related Diseases

Genomic variations, both germline and somatic, are known to be related to human aging processes and longevity. Sequencing can provide information about interaction between genomic variations, environmental factors including life styles, and aging. Sequencing of mitochondrial DNA (mtDNA) of ultranonagenarians with controls of younger individuals has demonstrated that mutations of mtDNA are associated with longevity. Sequencing of cfDNA, cell-free DNA in blood originating from various organs, showed that somatic mutations increase with age and are closely related with cancers. Our sequencing results also showed that longevity-associated SNPs, Single Nucleotide Polymorphisms, have significant gender differences. Smaller numbers and shorter length of CNVs, Copy Number Variations, are associated with longevity. Influences of life style with different genetic backgrounds are different as indicated by our previous results that associations between tea drinking and reduced cognitive disability are much more significant for old individuals with specific SNPs in FOXO genes. We are now launching a multi-omics project, sequencing mtDNA, exosomal contents, cfDNA, microRNA, and the immune repertoire in blood, skin, brain, heart and other organs, as well as the gut metagenome.

**Co-contributors:** Huanming Yang, Lars Bolund, Yonglun Luo, Chao Nie, Rui Li, and Hefu Zhen

## Adriano AGUZZI

Adriano Aguzzi studied Medicine at the University of Freiburg and received his MD in 1986. At the University Hospital of Zurich he trained in neuropathology (1986 – 89) and developed models of glioma induction by gene transfer to telencephalic grafts. In 1989, he joined Erwin Wagner at the Institute of Molecular Pathology (Vienna) as postdoc and continued his studies of neurooncogenesis and neurovirology. In 1992, he was recruited as PI to the Institute of Neuropathology at the University Hospital of Zurich, where he worked with Charles Weissmann, then Director of the Institute of Molecular Biology at the University of Zurich.

He became the Founding Director of the Swiss National Reference Center for Prion Diseases in 1995. In 1997, he received full tenure professorship for Neuropathology and started to serve as Director of the Institute of Neuropathology, University of Zurich. A year later, Aguzzi became joint Professor of the Medical Faculty and Faculty of Natural Sciences, University of Zurich. Since 2004, he has been Chairman of the Department of Pathology, University Hospital of Zurich.

From analyzing gene expression in prion replication Aguzzi went on to explain the mechanism by which prions reach the brain. He also developed diagnostic procedures and established molecular mechanisms of therapeutic effect of inhibited prion replication. Among other things, he also found that neutralizing antibodies can protect against prions. His interest now focuses onto what happens after prions reach the brain. His laboratory has therefore developed a conditional microglial paralysis model.

Among other honors, Prof. Aguzzi has won the Ernst-Jung, Marcel-Benoist, Baillet-Latour, and Robert-Koch Prizes as well as the Gold Medal of the European Molecular Biology Organization (EMBO). He was awarded three Doctorates honoris causa from the Universities of Bologna, Teramo, and Liège.

## Shi-Qing CAI

Shi-Qing Cai studied at the China Agricultural University in Beijing and obtained his PhD at the Shanghai Institute of Plant Physiology & Ecology, Chinese Academy of Sciences, in 2002. From 2004 – 2009, he received

postdoctoral training at the Robert Wood Johnson Medical School, Rutgers University. Following that, he became Principal Investigator and head of the Laboratory of ion channel regulation, Institute of Neuroscience, Chinese Academy of Sciences, Shanghai.

The lab focuses on the role of potassium channels in physiological processes. Potassium channels are found in virtually any living cell from bacteria to humans where they play multiple functions. Even though it is well known that the potassium channels are critical for life, the big challenge is to determine how these channels participate in biological processes, such as development, ageing, learning and memory. By combining biochemistry, biophysics, genetics, behavioral analysis and electrophysiology, the Cai lab studies the following questions: 1. Interaction of potassium channel α subunit and β subunit; 2. Mechanism of potassium channel expression and trafficking; 3. Physiological role of potassium channels in muscle aging.

## José Antonio ENRÍQUEZ DOMÍNGUEZ

José Antonio Enríquez graduated in Biochemistry and Molecular Biology at the Universidad Autónoma de Madrid and obtained his PhD from the Universidad de Zaragoza in 1992. His thesis examined various aspects of mitochondrial DNA biogenesis.

From 1993 to 1997 he worked with Giuseppe Attardi at the California Institute of Technology, where he studied the pathogenic action of mutant mitochondrial tRNAs. His work in this period contributed to define the molecular mechanism underlying this phenomenon, and helped to establish the general methodologies for studying mitochondrial tRNAs. These methodologies have found application in studies of mitochondrial biogenesis and in the analysis of mtDNA-linked diseases. José Antonio established his own laboratory on his return to the Universidad de Zaragoza, where he became a Full Professor in 2007. His group has made important contributions to the understanding of mitochondrial biogenesis and bioenergetics, the role of mitochondria in apoptosis, the structure, formation and regulation of the respiratory chain, and the pathological consequences of altered mitochondrial function in human disease. He recently established a possible explanation for the phenotypes associated with common mouse mtDNA variants affecting ROS production. He joined the CNIC in 2009, where his work focus-

es on the molecular processes underlying the involvement of mitochondrial dysfunction in cardiovascular diseases and ischemic processes.

## Christian HAASS

Christian Haass obtained his Ph.D. in 1989 and was trained as postdoctoral fellow at the Harvard Medical School from 1990 to 1992. From 1993 to 1995, he was Assistant Professor of Neurology at Harvard Medical School and became Professor (C3) of Molecular Biology at the Central Institute of Mental Health, Mannheim in 1995. Since 1999, he has been Professor of Biochemistry (W3) and serves as coordinator of the German Center for Neurodegenerative Disorders (DZNE) in Munich since 2009. From 2000 to 2006, he was coordinator of the DFG- Priority Program "Cellular Mechanisms of Alzheimer's Disease". Since 2000, Haass has been speaker of the Sonderforschungsbereich 596 (Collaborative Research Center) "Molecular Mechanisms of Neurodegeneration". Since 2012, he is speaker of the Munich Cluster of Systems Neurology.

Christian Haass has served as member of various editorial / reviewer boards, such as J. Biol. Chem., EMBO Reports, EMBO Mol. Medicine, Science, J. Neuroscience. He has received many awards and honors, among them the Gottfried Wilhelm Leibniz Award of the DFG, the Family Hansen Award, and the Ernst Jung Award for Medicine in 2002, the MetLife Foundation Promising Award for Medical Research and the Sheik Hamdan Award for Medical Sciences (in the category Biology of Aging) in 2006, the MetLife Foundation Award for Medical Research in 2015, and the AFTD Biomarkers Award in 2017. He received an Honorary Doctorate of the University of Zurich in 2010 and was elected EMBO and Leopoldina member in 2003 as well as of the Bavarian Academy of Sciences and Humanities in 2016. In 2013, he won an ERC Advanced Grant.

## Jörg HACKER

Jörg Hacker was born in 1952. From 1970 to 1974, he studied biology at Martin Luther University Halle, where he also obtained his PhD in 1979. From 1980 to 1988, he worked at the Department of Microbiology at the University of Würzburg, where he was promoted to Professor in 1986. His

research focussed on the molecular analysis of pathogenic bacteria and host-microbe interaction. Since 1988, Jörg Hacker worked as Professor at the University of Würzburg and since 1993, also led the Würzburg Institute for Molecular Infection Biology. In 2000 and 2005, Jörg Hacker did his research at the Pasteur Institute in Paris as a visiting researcher. Furthermore, he taught at Tel Aviv University as guest professor in 2006. From 2003 until 2009, Jörg Hacker was Vice President of the German Research Foundation (DFG), and from 2008 until 2010, he was President of the Robert Koch Institute. Since March 2010, Jörg Hacker has been President of the German National Academy of Sciences Leopoldina. He received numerous awards and honors and is honorary citizen of his home town Grevesmühlen. Jörg Hacker is member in national and international academies, scientific societies and committees. 2014 – 2016 he was member of the Scientific Advisory Board set up by the UN Secretary-General Ban-Ki Moon.

## Jing-Dong Jackie HAN

Jing-Dong Jackie Han obtained a Ph.D. degree from the Albert Einstein College of Medicine. She received her postdoctoral training at the Rockefeller University and Dana-Farber Cancer Institute. In 2004, she became an investigator/professor at the Institute of Genetics and Developmental Biology, Chinese Academy of Sciences. She is currently a director of the CAS-Max Planck Partner Institute for Computational Biology. Her research focuses on the structure and dynamic inference of molecular networks, using a combination of large-scale experiments and computational analysis to probe the networks and to integrate functional interaction data in order to explore the design principles of the networks and to find how the complex phenotypes, such as aging, cancer and stem cell development are regulated through molecular networks. She was awarded the Chinese Academy Sciences Hundred Talent Plan and NSFC Outstanding Young Scientist Award in 2006, and the Hundred Talent Plan Outstanding Achievement Award in 2009, selected as a Max Planck Fellow in 2011 and a MaxNetAging Fellow in 2014.

## Ulrich HARTL

Ulrich Hartl studied medicine at the University of Heidelberg and received his MD degree in 1985, with a study on the regulation of rat liver peroxi-

somal metabolism by thyroid hormones. He then became a Postdoctoral Fellow in the laboratory of Prof. W. Neupert at the Institute of Physiological Chemistry, University of Munich and subsequently continued his training in the laboratory of Prof. W. Wickner, University of California at Los Angeles as a Fellow of the Deutsche Forschungsgemeinschaft (German Research Council). He received his medical Habilitation in Munich with a work on mitochondrial protein sorting and assembly mechanisms in 1990.

Following appointments in Munich, Ulrich Hartl was recruited to the Sloan-Kettering Institute as well as to Cornell University, Graduate School of Medical Sciences, New York where he was appointed tenured Professor in 1993. In 1994, he also became an Associate Investigator of the Howard Hughes Medical Institute. In 1997, he left the United States to become a Director at the Max Planck Institute for Biochemistry in Martinsried. He is currently Managing Director of the institute.

Ulrich Hartl won numerous prestigious prizes including the Leibniz Prize of the German Research Council, the Koerber European Science Award, the Wiley Prize, the Heineken Prize, the Lasker Award, the Shaw Prize, the Albany Medical Center Prize and the Ernst Schering Prizes. He holds a honorary doctorate of La Trobe University, Melbourne. He is member of the German National Academy of Sciences Leopoldina, of Academy of Science of Nordrhein-Westfalen, the Bavarian Academy of Sciences, the American Academy of Arts and Sciences, and the American National Academy.

## Michael HENGARTNER

Michael Hengartner studied biochemistry at the Université de Laval in Canada. He received his PhD from the Massachusetts Institute of Technology in the laboratory of Nobel Prize Winner H. Robert Horvitz in 1994.

He then led a research group at the Cold Spring Harbor Laboratory until 2001, when he was recruited to the new Ernst Hadorn Endowed Chair at the Institute for Molecular Biology of the University of Zurich. He served as Dean of the School of Mathematics and Sciences from 2009 to 2014. He was elected Rector of the University of Zurich for 2014 – 2018 and President of the Swiss Rectors' Conference.

Michael Hengartner's work on the molecular basis of apoptosis has been acknowledged by several prizes such as the National Latsis Prize of Switzerland. He became member of the German Academy of Sciences Leopoldina in 2009.

## Thomas LENGAUER

Thomas Lengauer is Director at the Max Planck Institute for Informatics, Saarbrücken, Germany and honorary professor at Saarland University and the University of Bonn, Germany. In the 1970s, he performed research in theoretical computer science, in the 80s on design methods for integrated circuits. Since the 90s, he has been in computational biology with focuses on protein bioinformatics, drug screening, computational epigenetics and design and bioinformatics for understanding and curing diseases. He has been full professor at the University of Paderborn, Germany (1984 – 1992) and Director of the Institute for Algorithms and Scientific Computing at the German National Research Center for Computer Science in Sankt Augustin, Germany (1992 – 2001). Dr. Lengauer is a founding member, a Fellow and the President-elect of the International Society for Computational Biology (ISCB). Also, he has been a founding member of the steering board of the international conference series RECOMB and the steering board of the European bioinformatics conference series ECCB. In 2001, he co-founded the BioSolveIT GmbH, Sankt Augustin, Germany, which develops and distributes Cheminformatics software. Lengauer received the Konrad Zuse Medal of the German Informatics Society (2003), the Karl Heinz Beckurts Award (2003), the AIDS Research Award of the Heinz-Ansmann Foundation (2010), and the Hector Science Award (2015). He is a member of the German National Academy of Sciences Leopoldina and of its Presidium. He also is a member of acatech – German National Academy of Science and Engineering and of Academia Europaea.

## Depei LIU

Dr. Liu is a medical molecular biologist. He graduated from Peking Union Medical College with a Ph.D. degree in biochemistry and molecular biology in 1986. During 1987 – 1990, he worked as a postdoctoral research fellow at the University of California, San Francisco. Since 1992, he has been a professor and doctoral supervisor.

He served as the President of Chinese Academy of Medical Sciences (CAMS) and Peking Union Medical College (PUMC) during the year of 2001 – 2011, and as the Vice President of Chinese Academy of Engineering (CAE) during the years of 2002 – 2010. He was elected as member of the Chinese Academy of Engineering (CAE) in 1996, and as member of the U.S. National Academy of Medicine (NAM) and member of Third World Academy of Sciences (TWAS) in 2008. He has been the director of the State Key Laboratory of Medical Molecular Biology of China since 2004, Vice President of the Chinese Medical Association since 2010, and the chairman of Division of Medical Biochemistry and Molecular Biology, CSBMB (Chinese Society of Biochemistry and Molecular Biology) since 2011. He also has been member of the eleventh and twelfth session of the Standing Committee of the National People's Congress of China.

Dr. Liu's research expertise is gene regulation, gene therapy and molecular mechanisms of cardiovascular diseases. He studies the cis-elements, trans-factors, higher-order chromatin conformation and nuclear matrix-associated proteins in regulation of globin gene transcription. He investigates the methods to increase the gene expression of globin in anemic status and methods to increase efficiency of gene repair of mutated globin genes. He investigates the roles of calorie restriction and sirtuin gene family in metabolism and cardiovascular diseases. He has published more than 200 original research articles and invited reviews, which have been cited more than 4000 times.

## Ana POMBO

Ana Pombo investigates how the 3D folding of chromosomes influences gene expression in mammalian development and disease, and mechanisms of RNA polymerase II poising which prime genes for future activation. She received her DPhil from University of Oxford (1998, UK) where she pioneered high resolution imaging of transcription sites in mammalian nuclei. She was awarded the Royal Society Dorothy Hodgkin Fellowship (UK; 1998 – 2002), and started leading her research group in 2000 at the MRC Clinical Sciences Centre, Imperial College London (UK). Her laboratory showed that Polycomb repression is associated with RNA polymerase II poising, and developed high-resolution cryoFISH approaches to study spatial relationships between genomic regions and nuclear

landmarks. She was awarded the Robert Feulgen Prize 2007 for her contributions to imaging nuclear architecture. Her laboratory moved to the Berlin Institute for Medical Systems Biology, at the Max Delbrueck Center (Berlin, Germany) in 2013, and she was appointed Professor (W3) at Humboldt University of Berlin. Her laboratory developed Genome Architecture Mapping, an orthogonal ligation-free approach to map chromatin contacts genome-wide.

## Helmut SIES

Helmut Sies studied medicine in Tübingen, Paris and Munich (M.D. from the LMU Munich in 1967). He received his habilitation at LMU Munich for Physiological Chemistry and Physical Biochemistry in 1972. He was appointed professor and chairman at the University of Dusseldorf in 1979. Since 2008, he is emeritus research professor at University of Dusseldorf. He is also senior scientist at the Leibniz Research Institute for Environmental Medicine. He is Adjunct Professor at the University of Southern California, Los Angeles. Sies held visiting professorships at Universities of California, Texas, Sydney, Beijing and Siena.

Helmut Sies is the founder of the concept of oxidative stress. He discovered that hydrogen peroxide (H2O2) is a normal metabolite in aerobic metabolism. He investigated the molecular basis of action of oxidants and antioxidants. In nutritional biochemistry, carotenoids (singlet oxygen), selenium (ebselen) and polyphenols (flavanols) were research topics. He was named “Redox Pioneer”.

As for professional functions, Sies served as President of the North Rhine-Westfalian Academy of Sciences, and as Vice President of the Lindau Nobel Winners Meetings. Sies won numerous prizes, such as Ernst Jung Prize, Claudius Galenus Medal, Werner Heisenberg Medal, the Linus Pauling Institute Prize and the Trevor Slater Award. He holds honorary doctorates from Universities of Buenos Aires, Argentina, and of Montevideo, Uruguay. He was elected member to the German National Academy of Sciences Leopoldina, the North Rhine-Westfalian Academy of Sciences, the Heidelberg Academy of Sciences and Humanities and the Academy of Medicine at Buenos Aires.

## Ursula M. STAUDINGER

Ursula M. Staudinger is a lifespan psychologist. She is known for her work on the positive plasticity of aging as well as her research on resilience and wisdom. Recently she has conducted groundbreaking studies on the effects of work on aging. Dr. Staudinger is the Robert N. Butler Professor of Sociomedical Sciences and Professor of Psychology at Columbia University. She is the Founding Director of the Columbia Aging Center. She started her career as a Group Leader at the Max Planck Institute for Human Development. She is Vice President and Foreign Secretary of the German National Academy of Sciences and Chair of the Board of the Federal Institute of Population Research. She received the Braunschweig Research Prize, the Seneca Medal, and is a Fellow of GSA, APA and APS.

## Linfeng SUN

Linfeng Sun studied at the Department of Biological Sciences and Biotechnology, Tsinghua University, China. In 2014, he received his PhD from the School of Life Sciences, Tsinghua University, where he also was trained as postdoctoral fellow with Dr. Yigong Shi until 2017 when he was recruited as professor by the same school. He was honored as Advanced Innovation Fellow of the Advanced Innovation Center for Structural Biology, Tsinghua University, in 2016.

His research is on mechanistic studies of important membrane proteins using structural biology techniques such as Cryo-EM 3D reconstruction and X-ray crystallography.

## Huanming YANG

Dr. Yang is the co-founder and Chairman of BGI-China. He and his partners have made a significant contribution to the international HGP, HapMap, and G1K projects, as well as many other animals, plants, and microorganisms, with many publications in Science, Nature, and other internationally prestigious journals.

Dr. Yang obtained his Ph.D. from University of Copenhagen (Denmark) and postdoctoral trainings in France and USA. He was elected as an associate

member of the European Molecular Biology Organization (EMBO) in 2006, an academician of Chinese Academy of Sciences in 2007, a fellow of TWAS in 2008, a foreign associate of National Academies of India in 2009, of Germany in 2012, of the USA in 2014 and of the Royal Danish Academy of Sciences and Letters in 2016.

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