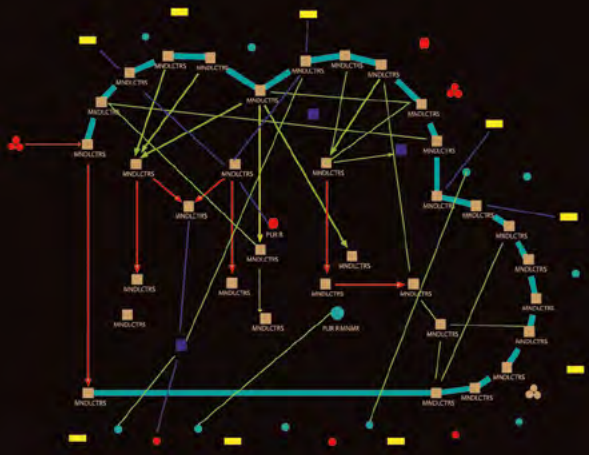
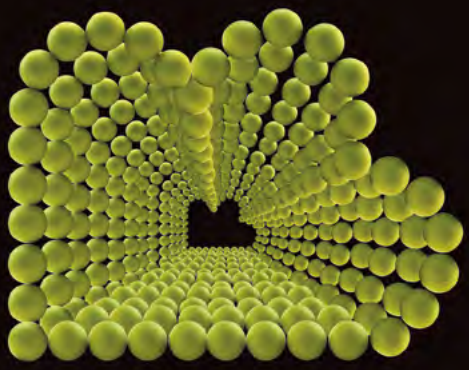
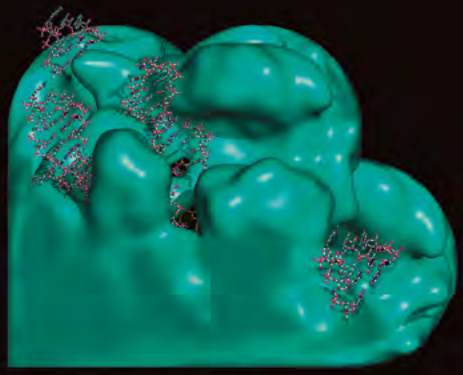
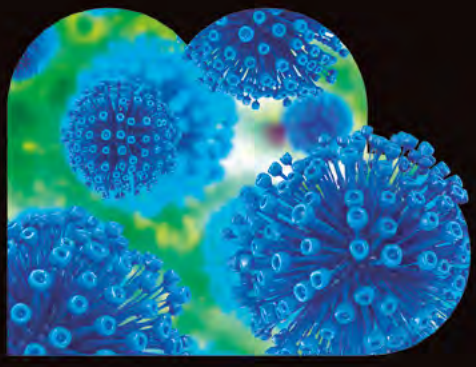
Mendel Lectures
2015—2016

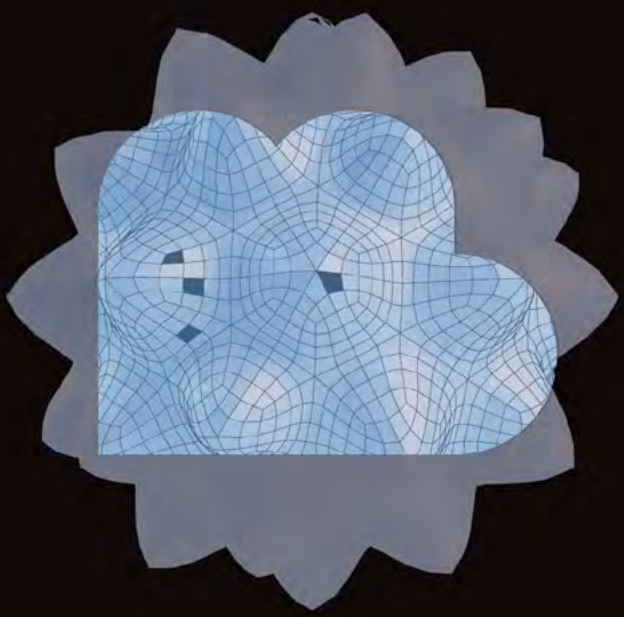








2015 — 2016



Masaru Okabe

*1948

Research Institute for Microbial Diseases, Osaka University, Japan

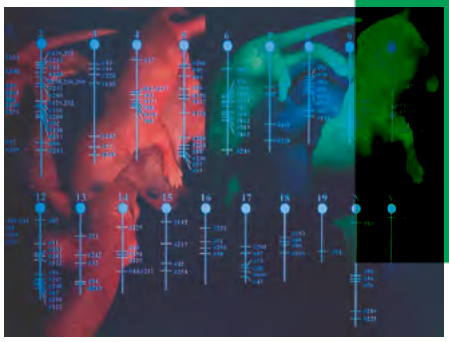
October 1, 2015

Dr. Masaru Okabe received his PhD from Osaka University and has spent the entirety of his career at this institution, with the exception of one and a half years at the National Institute of Environmental Health Sciences in Research Triangle Park, North Carolina, USA.

He served as a professor in the Genome Information Research Center of the Research Institute for Microbial Diseases and became Director of the Animal Resource Center for Infectious Diseases at the Research Institute for Microbial Diseases, Osaka University, in 2002.

His general research area is reproduction, with a specific research interest in the mechanism of sperm-egg interaction. He published the first fusion factor on mouse sperm (IZUMO1) and was involved in the finding of fusion-related factor CD9 on eggs. He believes in the power of gene-manipulated animals and utilizes many transgenic and knockout mouse lines in his research. He is also known as the scientist who demonstrated that GFP is usable in mice by producing the first "green mice" in the world.

The First "Green Mice" and the Mechanism of Mammalian Fertilization Revised by Gene-manipulated Animals



It was a memorable honour for me to be invited to participate in the Mendel Lectures and savour the rare opportunity to speak in the historical building Mendel himself once used.

Aaron Ciechanover

*1947

The Rappaport Faculty of Medicine and Research Institute, Technion-Israel Institute of Technology, Haifa, Israel

October 22, 2015

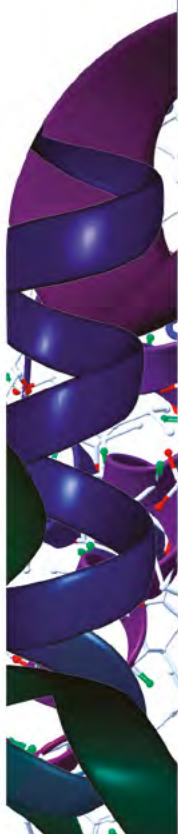
Aaron Ciechanover is an Israeli biochemist well known for characterizing the cellular pathway to degrade and recycle protein via ubiquitin.

He received his MSc (1971) and MD (1973) from the Hebrew University in Jerusalem. He then completed his national service (1973–1976) as a military physician, and continued his studies to obtain a doctorate in biological sciences in the Faculty of Medicine in the Technion (DSc, 1982). There, as a graduate student with Dr. Avram Hershko and in collaboration with Dr. Irwin A. Rose from the Fox Chase Cancer Center in Philadelphia, USA, they discovered that covalent attachment of ubiquitin to a target protein signals it for degradation. They deciphered the mechanism of conjugation, described the general proteolytic functions of the system, and proposed a model according to which this modification serves as a recognition signal for a specific downstream protease. As a postdoctoral fellow with Dr. Harvey Lodish at MIT, he continued his studies on the ubiquitin system and made additional important discoveries. Over the years it has become clear that ubiquitin-mediated proteolysis plays major roles in numerous cellular processes, and aberrations in the system underlie the pathogenetic mechanisms of many diseases, among them certain malignancies and neurodegenerative disorders. Consequently, the system has become an important platform for drug development.

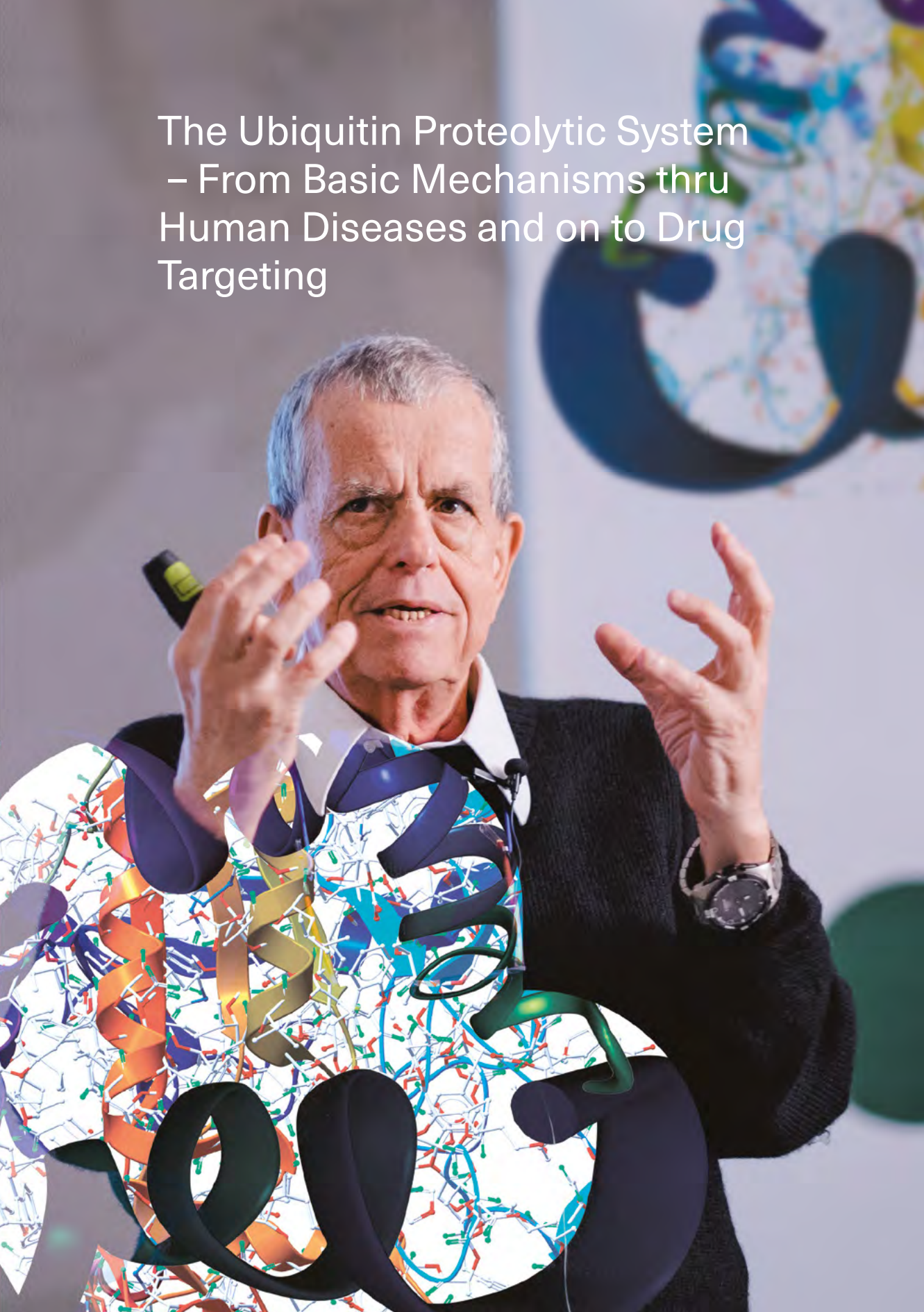
Among the numerous prizes Ciechanover received are the 2000 Albert Lasker Award, the 2002 EMET Prize, the 2003 Israel Prize, and the 2004 Nobel Prize (Chemistry, shared with Drs. Hershko and Rose).

Ciechanover's membership in many academies includes the Israeli National Academy of Sciences and Humanities, the European Molecular Biology Organization (EMBO), the American Academy of Arts and Sciences (Foreign Fellow), the American Philosophical Society, the National Academies of Sciences (NAS) and Medicine (NAM) of the USA (Foreign Associate), the Pontifical Academy of Sciences at the Vatican, the Chinese Academy of Sciences (Foreign Member), the Russian Academy of Sciences (Foreign Member), and the German Academy of Sciences (Leopoldina).

He is currently a Distinguished Research Professor in the Faculty of Medicine at the Technion-Israel Institute of Technology in Haifa.



The Ubiquitin Proteolytic System – From Basic Mechanisms thru Human Diseases and on to Drug Targeting



Michael G. Rosenfeld

*1944

School of Medicine, University of California, San Diego, USA /
HHMI, University of Rochester, USA

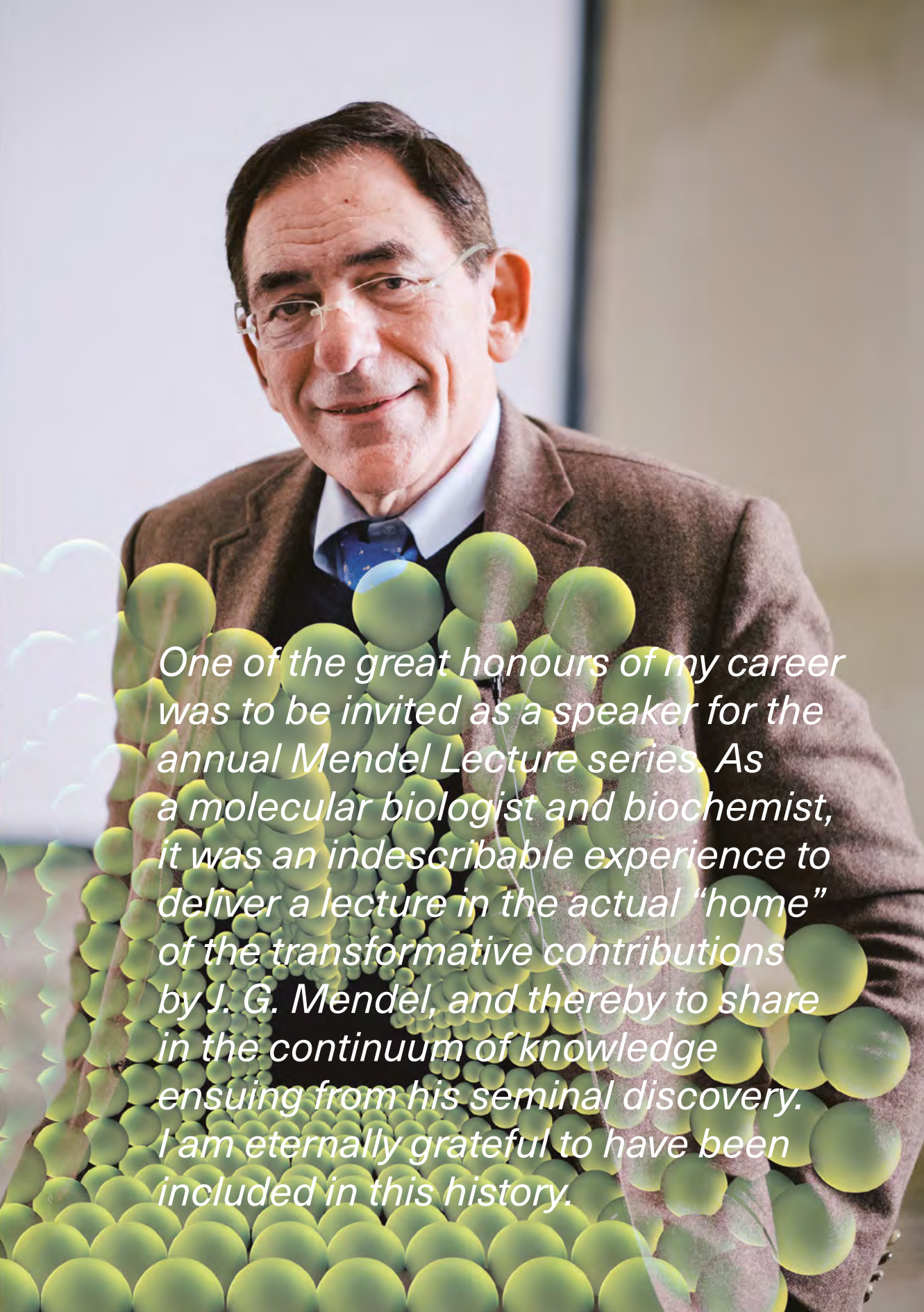
November 12, 2015

Michael Geoffrey Rosenfeld earned a bachelor's degree from Johns Hopkins University and an MD from the University of Rochester. He worked as an assistant doctor at Washington University in St. Louis and as a research assistant at the National Institutes of Health (NIH). He was briefly a doctor at Barnes Hospital before working as a postdoctoral fellow at the University of California San Diego (UCSD). Rosenfeld holds a professorship at UCSD and is adjunct professor at Scripps Research Institute and at the Salk Institute. Since 1985 Rosenfeld has also been affiliated with the Howard Hughes Medical Institute.

Using genetic, biochemical, and biological approaches, Michael G. Rosenfeld's work focuses on deciphering on a genome-wide scale how cells control gene expression through the integration of the output to these diverse signals, which is crucial to the body's development and cell differentiation. His studies have revealed surprising new gene-specific strategies that precisely link regulated gene responses to other cellular response programmes including DNA damage and repair. These studies have elucidated novel families of tissue-specific transcription factors, allosteric control of transcription factor function roles of polarity in positive and negative gene transcription control, the role of nuclear receptors, and linkage of transcription to growth. This knowledge provides the basis for developing new treatments for diseases that occur when gene expression goes awry, such as diabetes, atherosclerosis, cancer, and growth defects in children.

Michael G. Rosenfeld became a Member of the American Academy of Arts and Sciences in 1991 and a Member of the National Academy of Sciences in 1994. In 1999 he received (together with Ronald M. Evans) the Fred Conrad Koch Award, and in 2012 (together with David M. Livingston and Joan Massagué) the Pasarow Award for cancer research.

Mendel's Messengers: Enhancers and Transcriptional Programmes



One of the great honours of my career was to be invited as a speaker for the annual Mendel Lecture series. As a molecular biologist and biochemist, it was an indescribable experience to deliver a lecture in the actual "home" of the transformative contributions by J. G. Mendel, and thereby to share in the continuum of knowledge ensuing from his seminal discovery. I am eternally grateful to have been included in this history.

Michael G. Rossmann

*1930

Purdue University, West Lafayette, USA

March 3, 2016

Michael G. Rossmann was a German-American physicist and microbiologist who helped to establish and define the very basis of structural biology as it is known today.

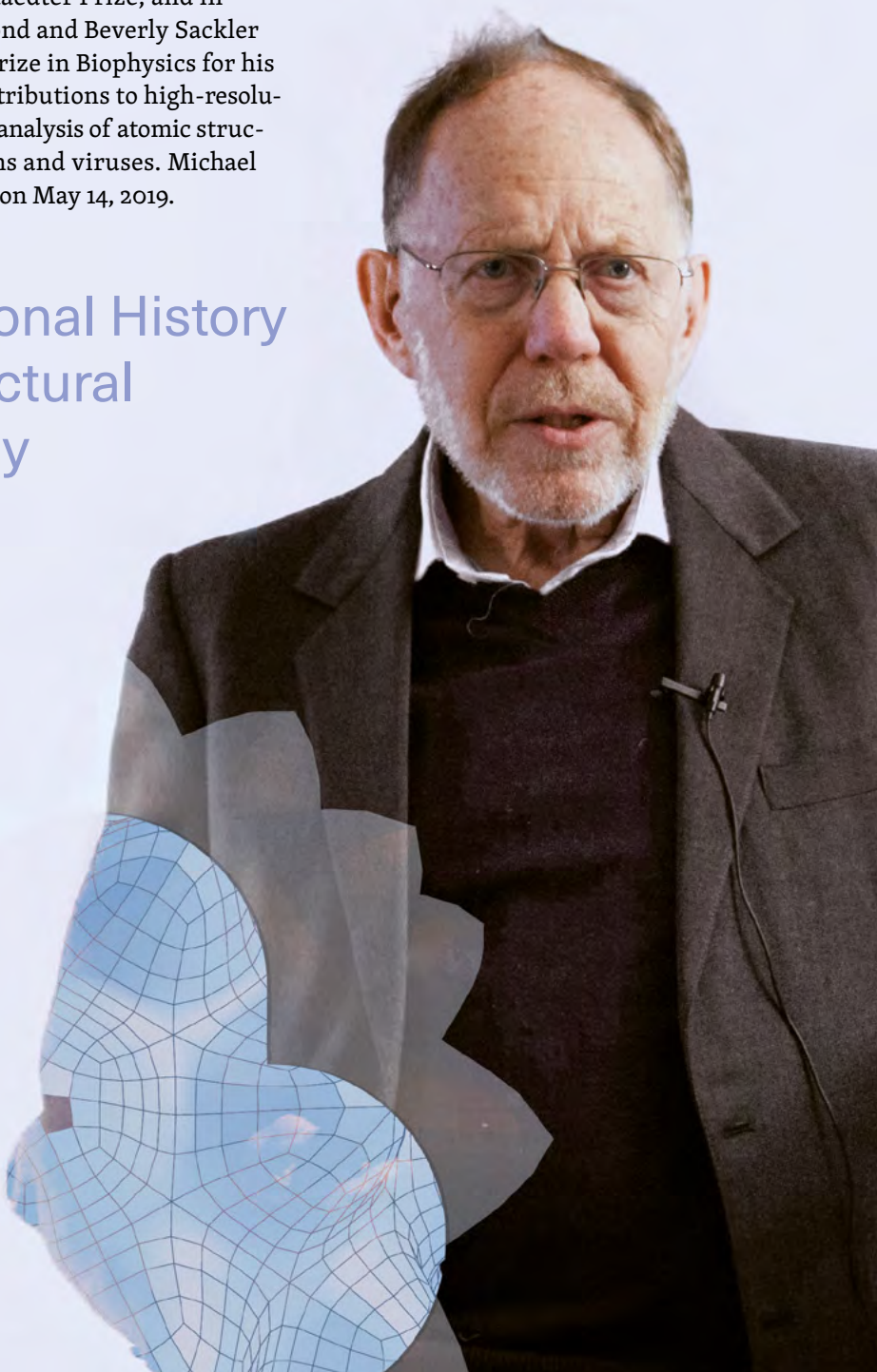
Michael Rossmann studied physics and mathematics at the University of London, where he received BSc and MSc degrees. He moved to the University of Glasgow in 1953 where he taught physics in the technical college and received his PhD in chemical crystallography. Rossmann then spent two years at the University of Minnesota as a postdoctoral fellow. Returning to the UK, to the University of Cambridge in 1958, he worked with Max Perutz as a research associate at the MRC Laboratory of Molecular Biology. There he led the computational effort for the structure determination of haemoglobin, a result that was recognized with the Nobel Prize in Chemistry awarded to Max Perutz and John Kendrew in 1962. In 1964 Rossmann joined the Department of Biological Sciences at Purdue University. He became full professor in 1967 and from 1978 he was Hanley Distinguished Professor of Biological Sciences at the university.

Rossmann and his team determined the structures of lactate dehydrogenase and glyceraldehyde 3-phosphate dehydrogenase. Rossmann recognized that the two enzymes share a common structural motif that enables them to bind nucleotides. Further studies identified this structural motif in numerous other protein enzymes and it became known as the Rossmann fold. Rossmann made major contributions to the methodology of macromolecular crystallography, namely to the development of molecular replacement, multi-wavelength anomalous dispersion phasing of diffraction data, phase improvement by utilizing non-crystallography symmetry averaging, phase extension, and to the processing and indexing of protein diffraction images. In 1985, Rossmann published the structure of a human common cold virus, determined using x-ray crystallography. This work laid the foundation for a molecular understanding of cell entry of enteroviruses and for the development of capsid-binding inhibitors against a broad range of enteroviruses. In 2016, using cryo-electron microscopy, his lab reported the first structure of the Zika virus, responsible for a severe epidemic at the time.

Among other honours, Rossmann was elected Fellow of the American Academy of Arts and Sciences in 1978, Member of the National Academy of Sciences in 1984, Foreign Member of the Royal Society of London in 1996, and Fellow of the American Association for the Advancement of Science in 1999. He was awarded the 1990 Louisa Gross Horwitz Prize, the Gregori

Aminoff Prize in 1994, the 1995 Purdue University Medal of Honor, the 1996 Ewald Prize, the 2001 Paul Ehrlich and Ludwig Darmstaedter Prize, and in 2016 the Raymond and Beverly Sackler International Prize in Biophysics for his pioneering contributions to high-resolution diffraction analysis of atomic structures of proteins and viruses. Michael Rossmann died on May 14, 2019.

A Personal History of Structural Virology



Steve Jackson

*1962

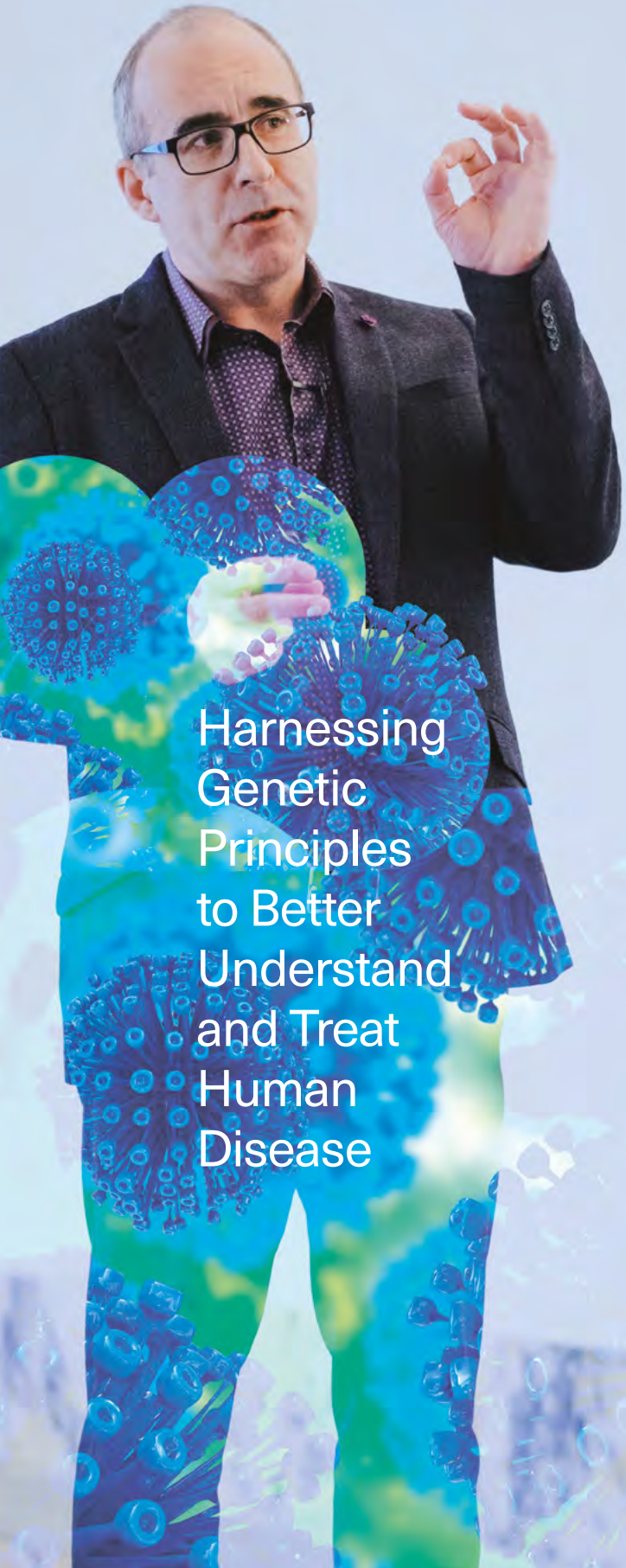
Gurdon Institute, University of Cambridge, UK

April 7, 2016

Stephen Philip Jackson received a BSc degree in biochemistry in 1983 from the University of Leeds. He then carried out his PhD research at the Imperial College London and Edinburgh University, earning his PhD in 1987. Jackson then spent four years as a postdoctoral fellow at the University of California, Berkeley, where he developed an interest in the regulation of transcription. He returned to the UK in 1991 as a junior group leader at the Wellcome-CRC Institute in Cambridge, now the Gurdon Institute, where he became head of the Cancer Research UK Laboratories.

Here, he continued his research on transcription by eukaryotic RNA polymerases and expanded this work to include the transcriptional apparatus of *Archaea*. In the process of identifying and characterizing the functions of the human DNA-dependent protein kinase (DNA-PK) protein, he was led into the field of DNA repair and DNA-damage signalling, which is now the major focus of his academic group. Jackson's work provided key insights into the cellular processes that respond to DNA damage. The discovery of DNA-PK and its activation by DNA double-strand breaks (DSBs) led him to identify and characterize various components of the non-homologous end joining pathway for DSB repair. His work helped to establish how DNA-damage signalling coordinates DNA repair, how this repair is controlled during the cell cycle at telomeres and within chromatin. In 1997, Jackson founded the company KuDOS Pharmaceuticals with the aim of translating knowledge of DNA damage response pathways into new treatments for cancer. KuDOS evolved into a fully integrated drug-discovery and drug-development company that developed the blockbuster drug Olaparib (Lynparza), which is now used to treat ovarian, breast and other cancers worldwide (marketed by AstraZeneca, which acquired KuDOS in 2005/2006, and Merck). In 2011, Jackson founded MISSION Therapeutics, a firm to develop drugs to improve the management of life-threatening diseases, particularly cancer. In 2017, he founded Adrestia Therapeutics Ltd and currently serves part-time as its chief executive and chief scientific officer.

Jackson has received various prizes, including the Inaugural Eppendorf-Nature European Young Investigator Award (1995), the Biochemical Society GlaxoSmithKline Award (2008), the BBSRC Innovator of the Year Award (2009), the Royal Society Buchanan Medal (2011) in recognition of his "outstanding contributions to understanding DNA repair and DNA damage response signalling pathways", the King Faisal International Prize for Science (2016), the Royal Netherlands Academy of Arts and Sciences



Harnessing Genetic Principles to Better Understand and Treat Human Disease

Dr. A. H. Heineken Prize for Medicine (2016) for "fundamental contributions to our understanding of the repair of DNA in human cells and for turning this knowledge into the development of new cancer drugs", the Genome Stability Network medal (2017), the Fondation ARC's Leopold Griffuel Prize in Translational and Clinical Research (2019), and the Royal Society Mullard Award (2020). He was elected a member of the European Molecular Biology Organization (EMBO) in 1997, a fellow of the Academy of Medical Sciences in 2001, and a fellow of the Royal Society in 2008.

It was a great honour and privilege to deliver a lecture in the Mendel Lecture series, to meet the various leading Czech scientists and to sightsee the wonderful city of Brno.

Joan Steitz

*1941

Howard Hughes Medical Institute / Yale University, New Haven, USA

May 5, 2016

Joan Elaine Argetsinger Steitz is known for her discoveries involving RNA, including ground-breaking insights into how ribosomes interact with messenger RNA by complementary base pairing, and that introns are spliced by small nuclear ribonucleic proteins (snRNPs).

Steitz received her BSc degree in chemistry from Antioch College in 1963. After completing her undergraduate degree, Steitz applied to Harvard's new programme in biochemistry and molecular biology. There, she was the first female graduate student to join the laboratory of Nobel Laureate James Watson, with whom she first worked on bacteriophage RNA. Steitz completed postdoctoral research at the Medical Research Council (MRC) Laboratory of Molecular Biology (LMB) at the University of Cambridge, UK, where she was guided by Francis Crick, Sydney Brenner, and Mark Bretscher. In 1970, Steitz joined the faculty at Yale. She is now Sterling Professor of Molecular Biophysics and Biochemistry at Yale University and continues her work with the HHMI and advocates for gender equity in the sciences.

Dr. Steitz is one of the pioneers of the field of RNA biology and is world-renowned for her many seminal contributions. She showed how ribosomal RNA uses base-pairing to initiate translation at the start sites of bacterial mRNA. She discovered snRNPs, the cellular particles that assemble to form spliceosomes, which carry out the splicing of pre-messenger RNA into the final mature mRNA, and elucidated many of their roles. She discovered that introns, which were thought to be inert, code for RNA that target the modification of other cellular RNAs during their maturation. More recently she has found new roles for microRNAs in gene regulation.

In addition to being one of the first two women scientists to receive the Albany Medical Center Prize (2008), America's largest prize in medicine, Dr. Joan Steitz has been honoured by many awards including the Eli Lilly Award (1976), the US Steel Foundation Award (1982), membership in the National Academy of Sciences (1983), the National Medal of Science (1986), the Novartis-Drew Award (1999), the FASEB Excellence in Science Award (2003), the RNA Society Lifetime Achievement Award (2004), the ASCB's highest scientific honour – the EB Wilson Medal (2005), the Rosalind E. Franklin Award for Women in Science (2006), and the Gairdner International Prize (2006). In 2011, Dr. Steitz was awarded the Robert J. and Claire Pasarow Foundation 23rd Annual Medical Research Award for Extraordinary Achievement in Cancer Research, and in 2012 the Pearl Meister Greengard Prize and the Vanderbilt Prize in Biomedical Science. In 2015, she received the Herbert Tabor Award. In 2018 Dr. Steitz won the Lasker-Koshland Award for Special Achievement in Medical Science.

Viral and Cellular Noncoding RNAs: Insight into Evolution

Stephen J. Benkovic

*1938

Department of Chemistry, The Pennsylvania State University, USA

May 19, 2016

Stephen James Benkovic is an American chemist studying mechanistic enzymology and the discovery of enzyme inhibitors.

Benkovic received his BS degree in chemistry and AB degree in English literature from Lehigh University, and his PhD in organic chemistry from Cornell University. After a stay as a postdoctoral research associate at the University of California, Santa Barbara, he joined the Chemistry Department at Penn State University in 1965 and was appointed a full Professor of Chemistry in 1970, became the Evan Pugh Professor of Chemistry, and in 1988 the holder of the Eberly Chair in Chemistry.

He is known for his major contributions that have initiated or shaped our understanding of biological processes. He was the first to hypothesize that conformational changes outside the enzyme's active site were necessary for achieving maximal catalysis. This is illustrated by his studies on dihydrofolate reductase (DHFR). In addition, he showed how multi-enzyme complexes are assembled to achieve specificity and function, and, where several activities are present, how they are mediated. This was demonstrated in studies on DNA replication that featured the assembly, disassembly and function of the T4 replisome that coordinated DNA replication. Benkovic discovered the first example of a reversible metabolon, the purinosome, which only assembles in response to cellular demands, and has demonstrated that it acts temporarily and spatially to form and deliver needed metabolites to cellular constituents.

Benkovic's work has been recognized by numerous awards and fellowships, including the Pfizer Enzyme Award (1977), the Gowland Hopkins Award (1986), the Alfred Bader Award of the American Chemical Society (1994), the Chemical Pioneer Award (1998), the Christian B. Anfinsen Award (2000), the Nakanishi Prize (2005), the Benjamin Franklin Medal in Life Science (2009), and the President's National Medal of Science (2010). He was elected a member of the American Academy of Arts and Sciences (1984), the National Academy of Sciences (1985), the National Academy of Medicine (1995), the American Philosophical Society (2002), and to the Royal Society (2021).

Benkovic holds 28 US and seven foreign patents and co-founded Anacor Pharmaceuticals (acquired by Pfizer in 2016) and Boragen.

On *De Novo* Purine Biosynthesis: The Purinosome