PRESS RELEASE
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2023 LOUIS-JEANTET PRIZES

The 2023 Louis-Jeantet Prizes are awarded to DARIO ALESSI, Director of the MRC Protein Phosphorylation Unit at the University of Dundee, UK, and, jointly, to IVAN ĐIKIĆ, Director of the Institute of Biochemistry II at Goethe University Frankfurt, and BRENDA SCHULMAN, Director at the Max Planck Institute of Biochemistry in Martinsried, Germany.

2023 Jeantet-Collen Prize for Translational Medicine

DARIO ALESSI, of British nationality, is awarded the 2023 Jeantet-Collen Prize for Translational Medicine for elucidating molecular bases of neurodegenerative disorders and developing novel approaches to therapeutic intervention in Parkinson's disease.

Dario Alessi has discovered components which regulate protein phosphorylation or ubiquitination pathways that are linked to human disease, in particular neurodegenerative diseases and cancer. His research efforts have led to fundamental breakthroughs in unravelling the role of LRRK2 kinase in Parkinson's disease. This has enabled clinical development of LRRK2 inhibitors which are currently being tested in late phase clinical trials promising therapeutic strategies to slow the progression of Parkinson's disease in patients.

2023 Louis-Jeantet Prize for Medicine

IVAN ĐIKIĆ, of Croatian nationality, and **BRENDA SCHULMAN**, of American nationality, will share the 2023 Louis-Jeantet Prize for Medicine for their contributions to our understanding of the functions of ubiquitin and the mechanisms of ubiquitination.

Ubiquitination is one of the most important post-translational modifications regulating the stability and functional activity of proteins, thereby playing a pivotal role in protein homeostasis. Failure of the ubiquitin system causes various diseases such as cancer, neurodegenerative diseases, cardiovascular diseases, and hypertension. Using complementary approaches, Ivan Đikić and Brenda Schulman have been key contributors to our understanding of the ubiquitin field. Brenda Schulman discovered secrets of ubiquitin conjugation cascades and Ivan Đikić discovered how conjugated ubiquitin alters cellular functions in innumerable ways.

The LOUIS-JEANTET FOUNDATION endows each of the two prizes with CHF 500,000, of which CHF 450,000 is intended to finance the continuation of the of the prize-winners' research and CHF 50,000 is for their personal use.

THE AWARD CEREMONY WILL BE HELD IN GENEVA (SWITZERLAND) ON **WEDNESDAY, APRIL 26th, 2023.**

DARIO ALESSI

Dario Alessi was born in Strasbourg in 1967. He earned his Bachelor's and PhD degrees from the University of Birmingham and carried out postdoctoral work at the MRC Protein Phosphorylation Unit at the University of Dundee. He has been a group leader in this Unit since 1997 and was appointed its director in 2012.

Dario Alessi was elected as a member of the European Molecular Biology Organization (EMBO) in 2005 and as Fellow of the Royal Society of Edinburgh in 2002, of the Royal Society in 2008 and of the Academy of Medical Sciences in 2012. Throughout his career, he has been honoured with awards and recognitions, including the EMBO Gold Medal (2005) and the Francis Crick Prize of the Royal Society (2006). He currently serves as President elect of the International Union of Biochemistry and Molecular Biology.

Deciphering Parkinson's disease: disruption on the highways of cell communication

Dario Alessi's research focuses on unravelling the roles of biological pathways controlling cellular communication that become disrupted in disease. He has contributed to understanding pathways involved in diabetes, cancer and blood pressure. In 2004, Alessi concentrated his research to understand how mutations that disrupt a communication network termed the "LRRK2 pathway" cause Parkinson's disease. His research was motivated by the lack of treatments that slow the progression of Parkinson's, a long-term degenerative disorder of the central nervous system estimated to impact around 10 million people worldwide.

In painstaking work that took over 12 years, Alessi revealed that genetic mutations linked to Parkinson's hyper-activate the LRRK2 pathway and impact on cell biology via another class of enzymes, termed Rabs. This research contributed to understanding how LRRK2 might be linked to causing disease and the notion that drugs targeting LRRK2 could have utility in preventing and/or slowing down progression of Parkinson's. Pharmaceutical companies have exploited this knowledge to develop compounds that target LRRK2, and these have entered late-phase clinical trials. Alessi identified and characterized several other components of the LRRK2 pathway, including the PPM1H protein phosphatase that counteracts LRRK2 by dephosphorylating Rab proteins. Alessi is exploring whether it is possible to develop enhancers of PPM1H for the treatment of Parkinson's.

Alessi is passionate about open science, sharing, working with industry and clinicians, as well as fostering a collaborative culture. He has established platforms to enable proactive dissemination of reagents/technologies developed at his institute (the MRC-PPU) to researchers worldwide. These platforms are now being extended so that all MRC Units/Institutes can more easily share their resources. He is motivated to improve awareness of issues relating to equality, diversity, inclusion, gender, and mental health and acknowledges that these issues have not been adequately considered previously.

IVAN ĐIKIĆ and BRENDA SCHULMAN

Born in 1966**, Ivan Đikić** was trained as a medical doctor in Zagreb and pursued his PhD at New York University. He established his first independent group at the Ludwig Institute for Cancer Research in Uppsala, before moving to the Goethe University Frankfurt, where he was recruited as Professor of Biochemistry. Since 2009, Đikić has led the Institute of Biochemistry II at Goethe University as Director. He was also a founding Director of the Buchmann Institute for Molecular Life Sciences from 2009 to 2013. In 2018, Đikić was appointed as a Fellow of the Max Planck Institute of Biophysics in Frankfurt.

Born in 1967, **Brenda Schulman** obtained her Bachelor's degree from the Johns Hopkins University and her PhD from MIT. She carried out her postdoctoral work at Massachusetts General Hospital and Memorial Sloan-Kettering before starting her independent career at St. Jude Children's Research Hospital. From 2005 to 2017, she was a Howard Hughes Medical Institute Investigator. In 2016, she was recruited as a Director at the Max Planck Institute of Biochemistry in Martinsried, Germany, where she heads the Department of Molecular Machines and Signaling. She is also an Honorary Professor at Technical University of Munich.

Both **Ivan Đikić** and **Brenda Schulman** are elected members of the German National Academy of Sciences Leopoldina, the European Molecular Biology Organization (EMBO) and the American Academy of Arts and Sciences. They have received numerous prizes, including, by Đikić, the Sir Hans Krebs Prize, the German Cancer Award, and the William C. Rose Award, and by Schulman, the US Presidential Early Career Award for Scientists and Engineers, and election to the National Academy of Sciences (USA). They both received the Gottfried Wilhelm Leibniz Prize and the Ernst Jung Prize for Medicine.

Ubiquitin: a protein with many faces and functions

To function properly, cells rely on thousands of different proteins to perform their jobs, which must be degraded and recycled after completing their task. Proteins are labelled for degradation by the attachment of ubiquitin in a process known as ubiquitination, which is performed by a family of proteins called E3 ligases. There are hundreds of different E3 ligases, allowing for tremendous diversity and substrate specificity. The deregulation of this process is frequently associated with the development and progression of human pathologies and diseases, in particular neurodegenerative diseases. In recent years, we have witnessed a great deal of interest around ubiquitin, opening many new avenues for the development of novel therapies.

The complementary research of Brenda Schulman and Ivan Đikić highlights the importance of scientific co-operation to better understand complex biological processes. Schulman investigates how E3 ligases are structured, operated, and controlled. She seeks to understand how ubiquitination is performed, and how this process is regulated to ensure that recycling is confined exclusively to proteins that are toxic or unnecessary for ongoing cellular tasks. One challenge is that ubiquitination occurs rapidly, in only milliseconds. Schulman and her team devised methods to obtain 3D structure imaging of E3 ligases essentially "frozen" along the different steps of the ubiquitination process. Connecting the suite of structures, much like frames in a movie, allowed the visualization of the kinetic process of ubiquitination. Schulman's team has also visualized how E3 ligases are kept off until needed, and how they are switched on by tweaking the structures of proteins destined for recycling and by signals to E3 ligases that such proteins should be ubiquitinated.

Ivan Đikić spearheaded the concept that ubiquitination affects proteins in many ways, not just marking them for degradation. Although specific types of ubiquitin chains were known to bind to the proteasome, the cellular shredding machine, Đikić uncovered that alternative types of chain linkages exert regulation of other processes, revealing ubiquitin as one of the most versatile cellular signals regulating virtually all cellular functions. He has contributed critically to discovering the spectrum of ubiquitin "readers", enabling diverse ubiquitin functions. One of those functions is the regulation of a central quality control process in our cells: autophagy. Ubiquitin signals determine which cellular components (e.g. mitochondria, bacteria, protein aggregates) must be sent for destruction via autophagy. With these studies, he broke new ground in understanding the functions of both the ubiquitin and autophagy systems, and uncovered their relations to pathophysiological processes driving cancer, neurodegeneration, and infection.

Through their combined work, we have gained insights into diseases such as neurodegeneration and cancer. Recently, using complementary approaches, both groups were involved in revealing how bacteria and viruses evolved new types of ubiquitin signals and developed the capability to hijack the host ubiquitin system to drive the proliferation of pathogens and the spread of infections within the organism. Many compounds affecting ubiquitination and presenting high pharmacological activity have been identified at the basic research level and offer great clinical potential.

THE LOUIS-JEANTET PRIZES

Every year, the Louis-Jeantet Prizes distinguish leading-edge researchers who are active in the member states of the Council of Europe.

As one of the best-endowed awards in Europe, the Louis-Jeantet Prizes foster scientific excellence. They are not intended solely as the recognition of work that has been completed, but also to encourage the continuation of innovative research projects. When the research being recognised is close to practical applications for combating illnesses affecting humankind, one of the Louis-Jeantet Prizes converts into a Jeantet-Collen Prize for Translational Medicine, supported by generous donations from the Désiré Collen Stichting.

Established in 1986, the Louis-Jeantet Prizes have thus far been awarded to 103 researchers: 29 in the United Kingdom; 21 in Germany; 17 in Switzerland; 15 in France; 4 each in Sweden, Italy and the Netherlands; 2 each in Austria, Belgium, Finland and Norway; and 1 in Hungary. Among the 103 prize-winning researchers, 15 have subsequently won the Nobel Prize in Physiology or Medicine, or the Nobel Prize in Chemistry.

Since 1986, a total sum of more than CHF 60 million has been awarded by the Foundation to the 103 prize-winners for the continuation of their work.

THE LOUIS-JEANTET FOUNDATION

Founded in 1983, the Louis-Jeantet Foundation is the legacy of Louis Jeantet, a French businessman and a citizen of Geneva by adoption. The Foundation's aim is to move medicine forward and to defend the role and identity of European biomedical research vs. international competition. Established in Geneva, the Foundation is part of an open Europe and devotes its efforts to recognizing and fostering medical progress for the common good.

The Louis-Jeantet Foundation allocates some CHF 2.5 million each year to promoting biomedical research. It invests this sum for European and for local research projects. At the local level, the Foundation encourages teaching and the development of research at the Faculty of Medicine of the University of Geneva.

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