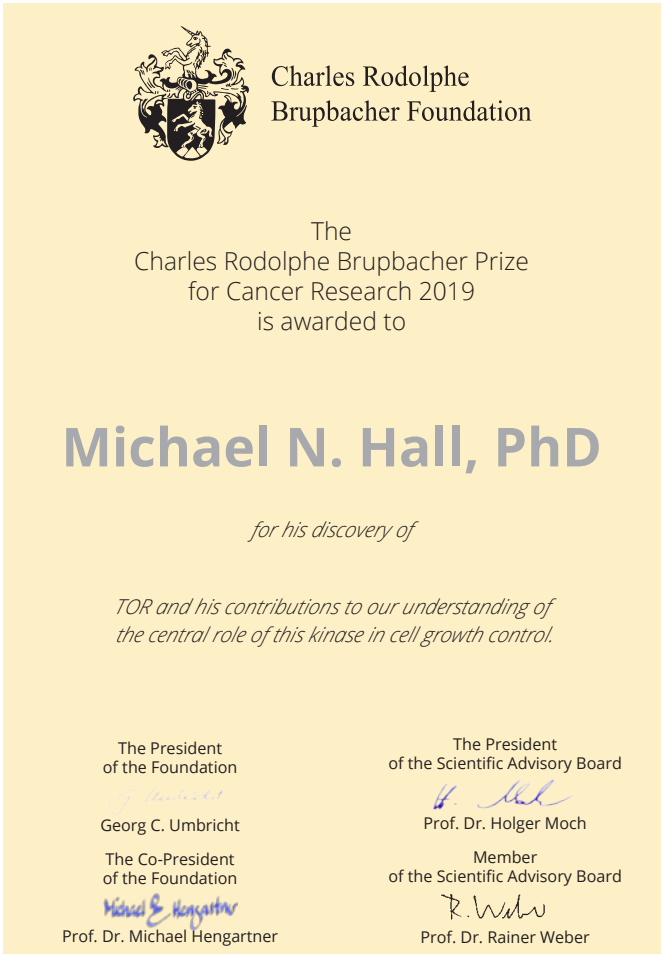
Laudatio

Nancy E. Hynes



On behalf of the Charles Brupbacher Foundation, I am pleased to write the laudatio for Professor Michael N. Hall, the winner of the 2019 Charles Rodolphe Brupbacher Prize for cancer research. Michael N. Hall is being given the award for his discovery of TOR (target of rapamycin) and his contributions to our understanding of the central role of this conserved kinase in cell growth control. His scientific achievements since the discovery of TOR more than 25 years ago have been essential for the development of TOR inhibitors, which are now used for cancer treatment.

Mike Hall joined the Biocenter at the University of Basel in the late 1980s after obtaining his PhD from Harvard and doing postdoctoral training at UCSF in California. During this period, the major focus of his work was to learn how proteins localize to particular cellular regions, using bacteria and yeast as model systems. At the Biocenter, Mike was hosting an MD/PhD student in his lab who was interested in how drugs work in humans. At the same time, Sandoz was working on cyclosporin A (CyA) and FK506, both of which have immunosuppressive activity and were used for treatment of rheumatoid arthritis and other diseases. Rapamycin had similar activity, although it was not in clinical usage at that time. Little was known about the mechanism of action of these drugs, however, it was known that they blocked the nuclear import of a signal downstream of the T-cell receptor. Considering Mike's interest in nuclear protein import, he thought that perhaps by studying these drugs, he could unravel a signaling pathway that connected the cytoplasm of the cell to the nucleus.

Mike's lab showed that one of these drugs, rapamycin, blocked proliferation of yeast cells. Working with yeast has many advantages when it comes to doing genetics. Following on this discovery, it was relatively straightforward to identify rapamycin-resistant mutants and to map the genes responsible for the phenotype, which were dubbed TOR1 and TOR2 for "target of rapamycin." The paper describing these findings was published in 1991 and has been cited more than 1000 times since then. Next, performing a clever genetic screen using the rapamycin-resistant cells, they isolated the TOR genes based on the functional regain of rapamycin sensitivity. Mechanistically, the immunosuppressive macrolide antibiotics rapamycin and FK506 form complexes with FKBP and it is this complex that binds and inhibits TOR resulting in blockade of cellular division. A paradigm shifting discovery was made a few years later by the Hall lab, when they found that the anti-proliferative effects of TOR inhibition were not due to direct effects on cell cycle regulators. Experimentally, this was based on the finding that TOR inhibition did not cause yeast cells to increase in cell size, which is what inhibitors of cell cycle proteins

were known to cause. Accordingly, they proposed that there must be a distinction between cell growth and cell division, and importantly cell growth must be a regulated process. This was a completely novel concept at that time and was not immediately accepted. However, over the past 20 years what was initially met with skepticism has become textbook dogma. Indeed, we now know that TOR, and its mammalian homolog mTOR, are evolutionarily conserved phosphatidylinositol 3-kinase (PI3K)-like serine/threonine protein kinases and that TOR is the central regulator of cell growth via its ability to respond to nutrients and growth factors.

I will next comment on what I think contributes to making Mike Hall`s scientific work special and deserving of this year's Brupbacher prize. Today the concept of using a model organism like yeast to unravel the mechanisms of action of human drugs is well accepted, but this was not the case 30 years ago when Mike began his work on rapamycin. Science functions best by allowing researchers to take seemingly wild approaches to uncover mechanisms underlying the phenomena they observe and that drive their scientific curiosity. This is certainly true of Mike's work on TOR, which started with an interesting observation of yeast mutants that failed to stop growing in response to treatment with a drug that had immunsuppressive activity in humans.

It is also essential to discuss the importance of Mike`s findings for medicine, particularly cancer. TOR is a central kinase on the PI3 kinase/AKT kinase pathway. In this short laudatio, it is impossible to describe all the beautiful work from the Hall lab, as well as many others working on TOR, that has led to our current understanding of this essential signaling pathway. We know that the PI3K/AKT/TOR pathway is constitutively activated by different mechanisms in most solid tumors and much effort has gone into developing inhibitors for each kinase. I will concentrate on how TOR inhibitors have significantly changed the management of patients with the diseases tuberous sclerosis (TS) and cancer. TS is a multiorgan genetic disease that causes benign tumors in brain, kidney and other organs. Although benign, tumor growth in vital organs can have drastic effects. Mutations in genes encoding TOR inhibitory proteins underly this disease and positive results in clinical trials resulted in the 2010 approval of the TOR inhibitor everolimus for distinct manifestations of TS. Considering solid cancers, in 2009 everolimus was approved for treatment of patients with advanced kidney cancer, in 2011 for advanced pancreatic neuroendocrine tumor treatment, and in 2012 for women with estrogen receptor positive advanced breast cancer. These approvals were based on the clinical findings that blocking TOR significantly prolonged disease-free patient survival.

In conclusion, I would like to go back to Mike's first goal in the 1980s, which was to uncover a cytoplasmic signaling pathway that converged on the nucleus. This goal has clearly been achieved. When TOR was first described as a target of rapamycin it could not be linked to any other proteins. Since then work from Mike's and other labs has revealed that TOR activates anabolic processes like ribosome biogenesis and protein synthesis, and inhibits catabolic processes including autophagy, to control cell growth. Since the major upstream activators of TOR, PI3K and AKT are often constitutively active in cancer, TOR inhibition is being actively pursued and has already had clinical success. Considering the high conservation of the PI3K/AKT/TOR pathway, I am convinced that we will be hearing about other indications for TOR inhibitors in the future.

Michael N. Hall

Summary Curriculum vitae

Appointment Professor, University of Basel

Address Biozentrum, University of Basel
Klingelbergstrasse 70
CH-4056 Basel, Switzerland

Date of Birth June 12, 1953.

Education

1981-1984	Postdoctoral Fellow, University of California, San Francisco, California
1981	Ph.D., Harvard University, Boston, Massachusetts
1976	B.S. with Honors, University of North Carolina, Chapel Hill, North Carolina

Academic Appointments/Affiliations

1992-present	Professor, University of Basel, Switzerland
2013-2016	Vice Director, Biozentrum, University of Basel
2002-2009	Vice Director, Biozentrum, University of Basel
2002-2008	Chairman, Division of Biochemistry, University of Basel
1995-1998	Chairman, Division of Biochemistry, University of Basel
1984-1987	Assistant Research Biochemist/Principal Investigator, Department of Biochemistry & Biophysics, University of California, San Francisco
1981-1984	Helen Hay Whitney Fellow, Department of Biochemistry & Biophysics, University of California, San Francisco
1981	Association pour le Développement de l'Institut Pasteur (ADIP) Fellow, Unité de Génétique Moléculaire, Institut Pasteur, France
1979-1981	Harvard University Traveling Scholar, NCI, Cancer Biology Program, Frederick Cancer Research Center, Frederick, Maryland
1976-1979	NIH Training Grant Fellow, National Research Service Award, Department of Microbiology &Molecular Genetics, Harvard Medical School, Boston, Massachusetts
1975-1976	Research Assistant with Marshall Edgell and Clyde Hutchison, Department of Bacteriology & Immunology, University of North Carolina, Chapel Hill, North Carolina

Awards & Honors

1981	Association pour le Développement de l'Institut Pasteur (ADIP) Fellowship
1981-1984	Helen Hay Whitney Fellowship
1982	Litton Advanced Technology Achievement Award
1987	Cuban Academy of Science Invited Lecturer, Havana, Cuba
1995	Member of the European Molecular Biology Organization (EMBO), elected
2003	Cloëtta Prize for Biomedical Research, Prof. Dr. Max Cloëtta Foundation
2004	Susan Swerling Lecture, Harvard Medical School
2008-2016	Swiss National Science Foundation Research Council
2009	Louis-Jeantet Prize for Medicine, Fondation Louis-Jeantet
2009	Runnström Lecture, University of Stockholm
2009	Fellow of the American Association for the Advancement of Science (AAAS), elected
2010	Mendel Lecture, Czech Academy of Arts and Sciences, Brno, Czech Republic
2011	Allan C. Wilson Lectures, University of California, Berkeley
2012	EMBO Lecture, Oslo, Norway
2012	Marcel Benoist Prize for Sciences or Humanities, Marcel-Benoist-Stiftung
2013	Swiss Academy of Medical Sciences, elected
2013	Jesus Montoliu Lecture, The Biomedical Research Institute of Lleida, Spain
2013	Christian de Duve Lecture (Inaugural), Université Catholique de Louvain, Brussels

2014	University Visiting Professorship, The Hebrew University, Jerusalem
2014	Sir Hans Krebs Medal, Federation of European Biochemical Societies (FEBS)
2014	Breakthrough Prize in Life Sciences
2014	Member of the National Academy of Sciences USA, elected
2015	UCSF Alumni Excellence Award
2015	Canada Gairdner International Award for Biomedical Research, Gairdner Foundation
2016	Benning Lecture, University of Utah, USA
2016	Thomson Reuters Citation Laureate
2016	Doctor *honoris causa*, University of Geneva
2016	Debrecen Award for Molecular Medicine, University of Debrecen, Hungary
2016	Distinguished Investigator, Instituto de Biomedicina de Sevilla (IBiS), Spain
2017	Szent-Györgyi Prize for Progress in Cancer Research, NFCR
2017	Albert Lasker Basic Medical Research Award, Albert and Mary Lasker Foundation
2018	Genome Valley Excellence Award, BioAsia, Hyderabad, India
2018	King Lecture, Clare Hall, University of Cambridge, UK

Professional Memberships & Activities

2008-2013	Editorial Board, FEBS Journal
2008-2012	Review Panel, National Center of Research (NCCR) in Structural Biology, Switzerland
2008	SNSF Ambizione Grants evaluation panel
2010	External Scientific Advisory Board, Faculty of Medicine, University of Geneva
2011	Scientific Committee, Louis-Jeantet Foundation, Geneva
2011	Editorial Board, The EMBO Journal
2011-2015	Review Panel, National Center of Research (NCCR) in Chemical Biology, Switzerland
2011	Scientific Advisory Board, Centre for Biological Signalling Studies (BIOSS), Germany
2012-2015	EMBO Young Investigator Programme (YIP) Selection Committee, Heidelberg
2012	Chair, Cell Metabolism and Cell Homeostasis Symposium, Dresden, Germany
2012-2017	Scientific Advisory Board, Max-Planck Institute for Biochemistry, Martinsried, Germany
2012	Co-organizer, Les Treilles Conference: Growth Regulation by the TOR Pathway, France
2012	Co-organizer, 2012 Louis-Jeantet Symposium, Geneva, Switzerland
2012	Scientific Advisory Board, PIQUR Therapeutics
2013	Instructor, FEBS-EACR advanced course on Signal Transduction, Spetses, Greece
2014	Selection Committee, Breakthrough Prize in Life Sciences Foundation
2014-2018	Scientific Council, de Duve Institute, Brussels, Belgium
2014	Board of Trustees, Louis-Jeantet Foundation, Geneva
2014	External Review Committee, Okinawa Institute of Science and Technology, Japan
2014	Roche Commissions, research as architecture, architecture as research, with J. Herzog
2014	External Review Committee, Okinawa Institute of Science and Technology, Japan
2015	Co-organizer, International Abcam Conference: PI3K-like Protein Kinases, Milan, Italy
2015	Instructor, FEBS advanced course on Signal Transduction & Cancer, Spetses, Greece
2015-2019	Scientific Advisory Board, Navitor Pharmaceuticals, Inc.
2015	Editorial Board, ScienceMatters
2015	American Association for Cancer Research (AACR)
2016	European Research Council (ERC) Advanced Grants evaluation panel
2016	Executive Board, Personalized Health Basel
2016	International Scientific Advisory Board, Cambridge Institute for Medical Research
2016	European Association for Life Sciences (EALS) Board
2016	Keynote Lecture, 9th International Symposium on AMPK, Xiamen, China
2017-2019	Advisory Board, Marcel Benoist Foundation, Bern
2017	Scientific Advisory Board, Swiss Institute for Basic Cancer Research (ISREC)
2017-2020	European Molecular Biology Organization (EMBO) Council
2017-2020	Editorial Board, Current Opinion in Cell Biology
2018	Co-organizer, EMBO at Basel Life Conference: Molecules in Biology and Medicine
2018	Selection Committee (Chair), Szent-Györgyi Prize, NFCR National Foundation for Cancer
2018	International Advisory Board, Melbourne bid for joint IUBMB/ComBio meeting

Keynote Lectures

2012	Keynote Lecture, Symposium of the Zürich Center for Integrative Human Physiology
2012	Inaugural Lecture, Instituto de Biología Funcional y Genómica, Salamanca, Spain
2014	Keynote Lecture, FASEB Research Conference, Steamboat Springs, USA
2014	Keynote Lecture, Israeli Society for Cancer Research, Haifa, Israel
2014	Sir Hans Krebs Lecture, FEBS-EMBO Congress, Paris, France
2014	Keynote Lecture, EMBO/EMBL Symposium, Heidelberg, Germany
2015	Honors Program Lecture, New York University School of Medicine, NYC
2015	Keynote Lecture, International TSC Research Conference, Windsor, England
2015	Keynote Lecture, 40th European Symposium on Hormones and Cell Regulation, France
2017	Lola and John Grace Distinguished Lecture in Cancer Research, Lausanne (EPFL
2017	Karl Wilhelm von Kupffer Lecture, The International Liver Congress, Amsterdam
2017	Keynote Lecture, Gordon Research Conference, Integrative Biology of Aging
2017	Plenary Lecture, ASCB-EMBO Congress, Philadelphia, USA
2018	EMBL Distinguished Visitor Lecture, Heidelberg, Germany
2018	Keynote Address, BioAsia 2018, Hyderabad, India
2018	Keynote Lecture, TOR de France, Nice, France
2018	Keynote Lecture, TOR de France, Nice, France
2018	Keynote Lecture, Roche Continents, Salzburg, Austria
2018	Keynote Address, Toyama Symposium, Japan

Publications

http://www.biozentrum.unibas.ch/research/groups-platforms/publications/unit/hall

mTOR signaling in growth and metabolism

Michael N.Hall

Cell division, growth and death are the most basic, fundamental features of biology. Research on cell growth started in earnest after mechanisms controlling cell division and cell death were already well elucidated. The turning point in our understanding of cell growth came in 1991 with the discovery of TOR (Target of Rapamycin), the key component of the cell growth control system. TOR is a highly conserved serine/threonine kinase that controls cell growth and metabolism in response to nutrients, growth factors, and cellular energy. TOR was originally discovered in yeast but is conserved in all eukaryotes including plants, worms, flies, and mammals. In mammals, TOR is known as mTOR. The discovery of TOR led to a fundamental change in how one thinks of cell growth. It is not a spontaneous process that just happens when building blocks (nutrients) are available, but rather a highly regulated, plastic process controlled by TOR-dependent signaling pathways. TOR controls cell growth by activating anabolic processes such as ribosome biogenesis, and protein, nucleotide and lipid synthesis, and by inhibiting catabolic processes such as autophagy. TOR is found in two structurally and functionally distinct multiprotein complexes, TORC1 and TORC2. The two TOR complexes, like TOR itself, are highly conserved. Thus, the two TOR complexes constitute an ancestral signaling network conserved throughout eukaryotic evolution to control the fundamental process of cell growth. As a central controller of cell growth, TOR plays a key role in development and aging, and is implicated in disorders such as cancer, cardiovascular disease, allograft rejection, obesity, and diabetes. While the role of TOR in controlling growth of single cells is relatively well understood, the challenge now is to understand the role of TOR signaling in disease and in coordinating and integrating overall body growth and metabolism in multicellular organisms.