XII Edición
Premios Fundación BBVA Fronteras del Conocimiento
BBVA Foundation Frontiers of Knowledge Awards
12th Edition

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Press release
22 January, 2020

The BBVA Foundation recognizes Michael Hall and David Sabatini for discovering the mechanism that regulates cell growth, opening up new therapeutic approaches against cancer, diabetes and ageing

- The two laureates discovered that the mTOR molecular pathway is "the major regulator of growth in animal cells, and plays a central role in physiology, metabolism, ageing and cancer," in the words of the award committee
- **Hall's research in yeast**, and Sabatini's subsequent work with mammalian cells, brought to light the molecular mechanisms driving organismal growth in response to the availability of nutrients
- Their findings holds out exciting biomedical potential, since the mechanism they discovered is implicated in up to 60% of cancer cases, as well as in diabetes and ageing-related diseases like Alzheimer's and Parkinson's
- Their research has also revealed how controlled fasting or caloric restriction can promote longevity, a phenomenon observed in numerous species in the past century and more recently demonstrated in mice

The BBVA Foundation Frontiers of Knowledge Award in Biology and Biomedicine has gone in this twelfth edition to U.S. researchers Michael Hall and David Sabatini, for discovering the cellular mechanism that is "the major regulator of growth in animal cells, and plays a central role in physiology, metabolism, ageing and cancer," in the words of the committee.

Their discovery of mTOR (mammalian target of rapamycin) is of singular relevance in basic science. "The molecular mechanisms that regulate the growth of organisms and coordinate it with the availability of nutrients were unknown until two decades ago," the committee points out at the start of its citation. Yet a number of clinical implications are already with us: rapamycin, the drug acting on this molecular target, is administered for an array of conditions, including cancer, diabetes and ageing-related diseases in general.

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Not only that, the trailblazing work of Hall and Sabatini – nominated by David Page, Professor of Biology and Director of the Whitehead Institute at MIT – offers clues as to how controlled fasting or "caloric restriction" is able to prolong lifespan, a phenomenon observed in numerous studies since the past century, and demonstrated in mice in the last ten years.

"The function of the mTOR protein is to control cell growth," explained Michael Hall yesterday after hearing of the award. "In simple terms," adds Hall, a Professor of Biochemistry in the Biozentrum Center for Molecular Life Sciences at the University of Basel, Switzerland, "mTOR is what makes us grow when we eat."

"Cell growth is important not only after the fertilization of an egg, giving rise to a full organism, but also in other contexts, such as muscles getting bigger after exercise," he continues. "Any situation where there is cell growth is controlled by mTOR in response to the availability of nutrients, also in disease contexts like cancer, where cells that are not supposed to grow are growing."

Sabatini, Professor of Biology at the Massachusetts Institute of Technology, borrows a metaphor from electricity to explain how the mechanism operates: "mTOR is a switch that turns on in the presence of nutrients, so the body can build material [grow], and when there are no nutrients available it breaks the material down." The on/off of the mTOR switch controls a cascade of hundreds of molecular signals – some of them still unknown to science – and it is this we are referring to when we talk about the mTOR molecular pathway.

The work of the two scientists, who arrived at their findings independently, is the sum of several complementary parts. Hall discovered the target of rapamycin (TOR) protein in yeast cells in 1991 during his time as a senior investigator; Sabatini isolated it in mammals while still a doctoral student, in 1994, and gave it the name mTOR.

Sabatini said yesterday that he "could never have imagined" the implications of this first discovery, made when he was still thinking of devoting himself to clinical medicine. With his PhD thesis, he had set out to explore the therapeutic applications of rapamycin, a natural anti-fungal agent found in the 1970s during an expedition to Easter Island that had proved to have immunosuppressive properties and was used to prevent organ rejection in transplant patients.

After the molecule was isolated in yeast and mice, both researchers began the task of unraveling its multiple organismal functions. Hall would start by showing that TOR represented a paradigm shift in biology. Until then, the general understanding was that the growth of the cell was not an actively regulated physiological process, meaning it was possible to talk about cell division but not cell growth. His group demonstrated that in fact these are two separate, though related processes.

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A mechanism implicated in 60% of cancers

Subsequent research has largely focused on mTOR's role in a series of pathologies. As the committee points, "disruption of the mTOR signaling pathway is linked to numerous diseases, from cancer to neurodevelopmental disorders, and many clinical approaches have been designed to target mTOR or other molecules in the pathway."

In Hall's words, "mTOR has a central role in the cell, so central that when it doesn't work properly it can lead to many different diseases. Cancer is an obvious one, because it is a disease of inappropriate cell growth. And it was known early on that rapamycin had anti-cancer activity, so it has been developed as an anti-cancer drug and is used in the clinic. But what has also emerged in the last 10 or 15 years is that mTOR has a role in many other diseases including diabetes, as well as disorders like obesity."

Rapamycin is already employed as an immunosuppressant to prevent rejection of transplanted organs, as an anti-cancer agent and in cardiovascular diseases; for example, as a coating for coronary stents to stop new blockages forming in the bloodstream. "It is rare that a drug is used in three major therapeutic areas," Hall points out, "but that just underscores the central role of mTOR." Asked about its future potential, he replies that "the most important thing is that what we know about the pathway's basic biology is exploited to cure disease. I think that is what we're all shooting for."

Sabatini takes up the story: "people estimate that 60% of cancers have some mechanism for turning on the mTOR pathway." And interest is also growing around its role in neurological disorders like epilepsy and ageing-related diseases. "There is evidence that inhibition of the mTOR pathway could also ameliorate the symptoms of conditions like Alzheimer's or Parkinson's." In reality, he adds, "we are just scratching the surface" of possible mTOR applications.

Caloric restriction and longevity

The mTOR pathway and its link with ageing, or rather its prevention or mitigation, is currently among the most active areas of research in this field. And Hall and Sabatini's findings have provided key insights into how dietary or caloric restriction can promote longevity.

Says Hall, "the molecular basis of this phenomenon was not understood, it was a complete mystery. Then we discovered that mTOR is a nutrient sensor, and if you inhibit it with rapamycin – in animals – it is equivalent to eating less: you 'trick' the cells, so they respond as if there were fewer nutrients and prolong their lifespan. This has created a lot of excitement, because of its potential to delay ageing."

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In fact, healthy people are already dosing themselves with rapamycin having read that it extends lifespan in mice. Something both laureates advise against: "I wouldn't do that," Hall hastens to say. "I would want it to be studied more carefully before thinking about any kind of anti-ageing therapy on the strength of animal studies."

However both see promise in the use of mTOR inhibitors to prevent the diseases of age. For Sabatini, "we're not there yet and we need to do a lot more research, but I think there is a good chance we may be able to exploit this pathway to combat ageing-related diseases."

"I don't know if it will help us live to be 120, but I think it will have beneficial effects on different physiological systems," he concludes, "and I am practically sure that it will ameliorate aspects of ageing-related diseases."

Bio notes

Michael Hall (San Juan, Puerto Rico, United States, 1953) completed his PhD in the Department of Microbiology & Molecular Genetics of Harvard University in 1981, followed by postdoctoral fellowships at the Pasteur Institute in Paris and the University of California, San Francisco. In 1987, he joined Biozentrum at the University of Basel, where he has held the post of Professor of Biochemistry since 1992, as well as serving as the center's Vice-Director on two separate occasions.

He has authored almost 300 scientific papers and served on the editorial boards of publications such as *Current Opinion in Cell Biology, Journal of Molecular Cell Biology* and *Aging*, and of the *ScienceMatters* platform.

David Sabatini (New York, United States, 1968) graduated from Brown University with a degree in Biochemistry and from Johns Hopkins Medical School in 1997 with an MD/PhD.

That same year he joined the Whitehead Institute, a division of the Massachusetts Institute of Technology engaging in basic biomedical research. In 2002, he became a Member of the Whitehead, and was also appointed to the faculty at MIT, where he is now a Professor of Biology.

Sabatini, the author of some 200 scientific papers, became an Investigator of the Howard Hughes Medical Institute in 2008. Since 2004, he has also held appointments at the Broad Institute launched by MIT and Harvard to promote genome research for application in biomedical science, and at MIT's Koch Institute for Integrative Cancer Research.

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Biology and Biomedicine committee and evaluation support panel

The jury in this category was chaired by Angelika Schnieke, Chair of Livestock Biotechnology in the Department of Animal Sciences at the Technical University of Munich (TUM) (Germany). The secretary was Óscar Marín, Professor of Neuroscience and Director of the MRC Centre for Neurodevelopmental Disorders at King's College London (United Kingdom). Remaining members were Dario Alessi, Director of the Protein Phosphorylation and Ubiquitylation Unit in the School of Life Sciences at Dundee University (United Kingdom); Lélia Delamarre, Group Leader in the Department of Cancer Immunology at biotech company Genentech (United States); Robin Lovell-Badge, Senior Group Leader and Head of the Laboratory of Stem Cell Biology and Developmental Genetics at the Francis Crick Institute (United Kingdom); Ursula Ravens, Senior Professor in the Institute of Experimental Cardiovascular Medicine of the University of Freiburg (Germany); Ali Shilatifard, Chairman of the Department of Biochemistry and Molecular Genetics at Northwestern University Feinberg School of Medicine (United States); and Bruce Whitelaw, Deputy Director (Partnerships) at the Roslin Institute, University of Edinburgh (United Kingdom).

The evaluation support panel of the Spanish National Research Council (CSIC) was coordinated by M. Victoria Moreno, Deputy Vice President for Scientific and Technical Areas, and formed by: Dolores González Pacanowska, Coordinator of the Global Life Area and research professor at the López-Neyra Institute of Parasitology and Biomedicine (IPBLN); Santiago Lamas Peláez, research professor at the Severo Ochoa Molecular Biology Center (CBMSO); José Luis Martínez Menéndez, research professor at the National Center of Biotechnology (CNB); M. Isabel Medina Méndez, Deputy Coordinator of the Global Life Area and research professor at the Institute of Marine Research (IIM); and Isabel Varela Nieto, research professor at the Alberto Sols Biomedical Research Institute (IIBM).

About the BBVA Foundation Frontiers of Knowledge Awards

The BBVA Foundation centers its activity on the promotion of world-class scientific research and cultural creation, and the encouragement of talent.

The BBVA Foundation Frontiers of Knowledge Awards, established in 2008, recognize and reward contributions of singular impact in diverse fields of science, technology, social sciences and the humanities that have demonstrably expanded the frontiers of the known world, opening up new paradigms and knowledge fields. Their eight categories are reflective of the knowledge map of the 21st century, encompassing basic research in Physics, Chemistry and Mathematics,

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Biology and Biomedicine, Information and Communication Technologies, Humanities and Social Sciences, Economics, Finance and Management, Ecology and Conservation Biology, Climate Change, and, within the arts, the supremely creative realm of music.

The BBVA Foundation is aided in the evaluation process by the Spanish National Research Council (CSIC), the country's premier public research organization. The Foundation and CSIC jointly appoint the evaluation support panels charged with undertaking an initial assessment of the candidates proposed by numerous institutions across the world and drawing up a reasoned shortlist for the consideration of the award committees. CSIC is also responsible for designating the chair of each committee, formed by eminent authorities in the subject area.

LAUREATE'S FIRST DECLARATIONS AND IMAGES

A video recording of the new laureate's first interview on receiving news of the award is available from the Atlas FTP with the following coordinates:

Server: 5.40.40.61

Username: AgenciaAtlas4

Password: mediaset17

The video is in the folder labelled:

"PREMIO BIOLOGÍA Y BIOMEDICINA**"**

In the event of connection difficulties, please contact Miguel Gil at production company Atlas:

Mobile: 619 30 87 74

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Calendar of announcement events

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Ecology and Conservation Biology	Tuesday, 4 February, 2020
Information and Communication Technologies (ICT)	Wednesday, 19 February, 2020
Basic Sciences	Tuesday, 3 March, 2020
Economics, Finance and Management	Tuesday, 17 March, 2020
Music and Opera	Tuesday, 31 March, 2020
Humanities and Social Sciences	Wednesday, 15 April, 2020

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For more information on the BBVA Foundation, visit: www.fbbva.es