Press release

27 January, 2021

The BBVA Foundation recognizes David Julius and Ardem Patapoutian for identifying the sensors that enable us to feel pain, temperature and pressure

- **The two researchers distinguished** with the Frontiers of Knowledge Award in Biology and Biomedicine discovered the receptors that mediate the touch sensations of temperature and pressure
- **David Julius** identified and characterized a receptor that responds to both the burning sensation we get from spicy food and the feeling of heat on the skin, then discovered another that governs both the cool sensation evoked by mint and our body's perception of cold
- **Ardem Patapoutian** discovered the receptors for the mechanical forces that sense pressure on the skin and in blood vessels, thus advancing "mechanobiology," a new field of science that intersects biology, engineering and physics
- **Their groundbreaking work** has opened up new therapeutic avenues "to reduce acute and chronic pain" associated with trauma and a range of diseases, said the committee in its citation

The BBVA Foundation Frontiers of Knowledge Award in Biology and Biomedicine has gone in this thirteenth edition to David Julius, from the University of California, San Francisco, and Ardem Patapoutian, from the Scripps Institute, La Jolla (United States), "for identifying the receptors that enable us to sense temperature, pain and pressure."

"Temperature, pain and pressure are part of our sense of touch, perhaps the least understood of the five main senses of humans," read the opening words of the citation. "Julius and Patapoutian provided a molecular and neural basis for thermosensation and mechanosensation."

This line of research holds out exciting medical possibilities, because "it sheds light on how to

reduce chronic and acute pain associated with a range of diseases, trauma and their treatments." In fact, several pharmaceutical laboratories are working to identify molecules that act on these receptors with the aim of treating different forms of chronic pain, for example, those associated with inflammatory processes like arthritis.

But the committee also highlighted "the immense value that comes with understanding from a fundamental standpoint how we perceive the world," in the words of Óscar Marín, committee secretary and Director of the MRC Centre for Neurodevelopmental Disorders at King's College London (United Kingdom). "Although we have yet to see practical applications from these discoveries, their potential is so great as to mark a transformative milestone. Understanding how our bodies sense changes in temperature or pressure is so conceptually important that it is surprising how little we knew until recently, or rather, how we knew which part of the nervous system processes the information, but not the molecular sensors it uses. This is the kind of finding where it is hard to grasp the full scope of its potential applications, although work is already underway on some, such as chronic pain management and blood pressure control."

For Marín, the award is also a timely reminder of the importance of basic science: "Think back 20 years to the researchers working on RNA biology. Not even they could imagine that they had found the key to a new generation of vaccines likes those now being deployed against Covid 19."

The two laureates' findings have opened an area of research with the power to transform how we understand the physiological processes that govern our bodies' functioning, with important medical implications.

This new field, mechanobiology, is taking a first look at the role of pressure receptors inside the body. In the excretory system, for instance, to indicate a full urinary bladder, or the circulatory system, to control blood pressure.

Taste and touch sensors

The first surprise came when David Julius found that the receptor that triggers a burning sensation in the mouth on ingesting capsaicin – the pungent ingredient in chili peppers – is also responsible for sensing heat. Julius, says the committee, "identified the gene encoding the first temperature sensor, the ion channel TRPV1, using capsaicin, and discovered that TRPV1 is also activated by high temperatures." The signal emitted by this receptor reaches the brain, which determines whether the heat is strong enough to burn tissue and, if so, produces the sensation

of pain.

Julius explained after hearing of the award that though the link between the burning sensation of spicy food and high temperature was "obvious with hindsight," it was not so at the time. It was his basic curiosity about how we use natural products that attracted him to this area of research, eventually leading him to investigate the molecular basis of pain.

"Plants defend themselves by generating substances that cause predators pain, and we thought we could use these tools to try and understand the sense of pain on a molecular scale," says Julius. His research group started by studying the molecular bases for the perception of capsaicin, which they knew from research done elsewhere could be linked to pain sensation. They were successful in identifying the gene of the receptor for the hot ingredient of chili, but the real surprise came when they began looking at the same protein's function in humans. "There was no way," says Julius, "that we would have it just to enjoy spicy food."

They discovered in cultured cells that heat too would activate the capsaicin receptor. "We realized that heating the cells produced an intense activation of the receptor," the new laureate recalls. "It was a truly thrilling moment."

They decided to pursue this line of research and search for the cold receptor. Armed with their knowledge of the link between temperature and certain taste reactions, they turned to menthol, an ingredient of mint associated with a cool or icy sensation. In effect, they found that the receptor for menthol and low temperature was one and the same. And, to Julius's astonishment, it resembled that of capsaicin.

"What was really fascinating about this discovery was that that molecule is very close genetically to the receptor activated by the capsaicin of chili peppers and by heat. So together these findings told us that nature uses a common strategy that enables our nervous system to detect changes in temperature through a family of similar molecules."

Wasabi and inflammatory pain

Julius then went on to identify the receptor for wasabi, the pungent compound belonging to the mustard family. Again the clues were found in nature: "Extracts from mustard have been used for many years in pain tests: a physician would rub a tincture of mustard oil on a patient's skin to generate a sense of irritancy that tests acute pain response, but also generates inflammation which makes the area more sensitive to temperature and touch. So this was used as a model to

understand the mechanisms associated with inflammatory pain, such as you would feel with an arthritic joint. We asked how this process worked and identified a receptor in the nerve cells that is the mechanism through which wasabi and other mustard plants produce a pungent sensation."

It has since been found that the wasabi receptor is implicated in the stinging of the eyes experienced when chopping an onion, and is also activated by the toxins of certain animals, among them the scorpion. But "the crucial point" about this mechanism, Julius explains, is that "it is important for understanding the pain of an inflammatory injury" and may serve "to understand how tissue injury generates not only acute but persistent pain, leading on to chronic pain syndromes."

Pressure in skin and blood vessels

The discovery of the capsaicin receptor gene was published in 1997. At that time Ardem Patapoutian – an Armenian immigrant fleeing the war in Lebanon who had come to the USA to become a doctor but quickly "fell in love with research" – had also begun to study the molecular bases of sensory perception.

The two laureates, who coincided at the University of California, San Francisco, during Patapoutian's postdoctoral stay, described their relationship as moving from "competitive" to "complementary" as they began specializing in different receptors. Patapoutian, the citation says, "identified the genes encoding a family of stretch-activated ion channels." Known as Piezos, these proteins "are responsible for pressure sensing in the skin and blood vessels, so their importance in health and disease extend beyond the sense of touch."

"These findings," it continues, "opened the door to understanding mechanobiology, an emerging field of science that intersects biology, engineering and physics."

Touch and neuropathic pain

The starting point for Patapoutian's research was the observation that touch is the only sense based on the translation of a physical signal, like pressure, into the chemical language that the body understands. "When studying the peripheral nerves that help us feel touch and pain, we realized something very special, which is that they do something that the rest of the body doesn't. They sense physical forces like temperature and touch. There is really very little known about

how the body translates these physical forces into a chemical language."

Patapoutian and his group looked for cells that reacted electrically in a lab culture to the physical stimulus of pressure. Once found, they systematically suppressed the expression of candidate genes via RNA interference until they had isolated the receptor. At this stage, they still had no inkling of how this finding might relate to other physiological processes: "We knew there were proteins involved in the perception of pain, touch, heating or blood pressure, but no one had any idea that a single family, the Piezo 1 and Piezo 2 receptors discovered by our group, could explain all these processes," said Patapoutian yesterday.

This breakthrough was the first in a chain of discoveries in this research field. Patapoutian's group has since revealed the three-dimensional structure of the Piezo receptors, helping to elucidate their mechanical functioning. They are, it turns out, large proteins that move repeatedly in and out of cell membranes, like an elastic band fastened to the membrane that alternately stretches and contracts. Last October, an article in *Nature* described how Piezo 2 indicates when the urinary bladder is full. It is also Piezo 2 that detects when the skin is brushed lightly or caressed. Or warns that the skin is inflamed by sunburn.

Patapoutian elaborates further: "Piezo 2 is required for a very specific subset of pain. The pain of being hit with a hammer has little to do with this receptor, but if you get sunburn, for example, and just touching your shoulder hurts, that form of pain seems to be Piezo 2 dependent. This could be important for the treatment of neuropathic pain [when pain lasts for a long time after the original injury has gone away]. I believe it will be interesting to see what the next five or ten years bring in terms of the medical repercussions of these findings."

The Scripps Institute investigator has also shown that these sensors play an essential role in "proprioception," our ability to feel the relative position of the parts of our body. This is a sense, he points out, that we largely ignore "because we cannot turn it off," but that we rely on completely to do such simple things as stand up or walk.

He is confident that mechanobiology will uncover additional means of inter-cell communication, with potentially enormous implications for biomedical research: "Until now we have treated life mainly as a bag of chemicals that talk to each other by chemical synthesis, but more and more we are realizing that mechanobiology, mechanical forces, play important roles in everything from cell division all the way up to hearing, touch and pain. What we have discovered so far is very

exciting, but it's just the tip of the iceberg of this new science."

Laureate bio notes

David Julius (New York, 1955) completed an undergraduate degree in Life Sciences at Massachusetts Institute of Technology in 1977. He then entered the Department of Biochemistry at the University of California, Berkeley, earning his PhD there in 1984. After six years postdoctoral research at Colombia University, in 1990 he began teaching and research at the University of California, San Francisco, first in the Department of Cellular and Molecular Pharmacology then in the Department of Physiology, where he is currently a full professor. Author of over one hundred published papers in scientific journals, Julius has served as chair of the Physiology and Pharmacology Section of the U.S. National Academy of Sciences and on the National Advisory Neurological Disorders and Stroke Council of the National Institutes of Health, among other service roles. He belongs to the Scientific Advisory Board of the Howards Hughes Medical Institute, and is a former editor of *Annual Review of Physiology* and member of the editorial board of *Proceedings of the National Academies of Science*.

Ardem Patapoutian (Lebanon, 1967) earned his BS from the University of California, Los Angeles (UCLA) in 1990, then went on to complete a PhD in Biology at California Institute of Technology (Caltech) in 1996, followed by a postdoctoral fellowship at the University of California, San Francisco. In the year 2000, he joined the faculty of the Scripps Research Institute, where he now combines a professorship in the Department of Neuroscience at the Dorris Neuroscience Center with his work as a Howard Hughes Medical Institute (HHMI) Investigator. He also held a series of posts at the Genomics Institute of the Novartis Research Foundation between 2000 and 2014. Author of more than a hundred published papers in scientific journals, he belongs to the American Association for the Advancement of Science (2016), the U.S. National Academy of Sciences (2017), and the Society for Neuroscience.

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

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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**, Robert Francis Furchgott Professor of Biochemistry and Pediatrics at Northwestern University Feinberg School of Medicine (United States); and **Bruce Whitelaw**, Professor of Animal Biotechnology and Interim Director of the Roslin Institute at the 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: **José Félix de Celis Ibeas**, research professor at the Severo Ochoa Molecular Biology Center (CBMSO); **Dolores González Pacanowska**, Coordinator of the Global Life Area and research professor at the López-Neyra Institute of Parasitology and Biomedicine (IPBLN); **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, funded with 400,000 euros in each of their eight categories, recognize and reward contributions of singular impact in science, technology, social sciences and the humanities, privileging those that significantly expand the frontiers of the known world, open up new fields, or emerge from the interaction of various disciplinary areas. The goal of the awards, established in 2008, is to celebrate and promote the value of knowledge as a public good without frontiers, the best instrument at our command to take on the great global challenges of our time for the benefit of all humanity. Their eight categories are congruent with the knowledge map of the 21st century, ranging from basic science to key challenges for the natural environment by way of domains characterized by the overlap of disciplines – Biology and Medicine; Economics, Finance and Management – or the supremely creative realms of music and the opera.

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With the collaboration of CSIC

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The BBVA Foundation has been aided in the evaluation of the 98 nominees for the Frontiers Award in Biology and Biomedicine by the Spanish National Research Council (CSIC), the country's premier public research organization. CSIC appoints evaluation support panels made up of leading experts in the corresponding knowledge area, who are 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 each committee's chair and participates in the selection of its members, thus helping to ensure objectivity in the recognition of innovation and scientific excellence.

WINNER INTERVIEWS AND PHOTOGRAPHS CAN BE DOWNLOADED FROM
THIS DROPBOX LINK

Calendar of forthcoming announcement events

Ecology and Conservation Biology	Wednesday, 3 February, 2021
Information and Communication Technologies (ITC)	Wednesday, 10 February, 2021
Basic Sciences	Wednesday, 24 February, 2021
Economics, Finance and Management	Thursday, 4 March, 2021
Music and Opera	Wednesday, 10 March, 2021
Humanities and Social Sciences	Wednesday, 17 March, 2021

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

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