BBVA Foundation Frontiers of Knowledge Award in Biomedicine

The BBVA Foundation award goes to James Allison, creator of the first immunotherapy to prove highly effective against cancer

- His seminal research has "stimulated the development of a new class of drugs employing the immune system to fight cancer," an approach that has "provided clinical benefits" to thousands of patients, in the words of the jury's citation
- In experiments in mice conducted in the late 1990s, Allison showed that blockage of a molecule called CTLA-4 unleashed an immune response capable of destroying tumor cells in animals
- Allison's labors found practical expression in 2011 with the Federal Drug Administration's approval of the first anti-cancer drug based on mobilizing the immune system – ipilimumab – indicated for metastatic melanoma
- His research has paved the way for the development of other antitumor therapies that have shown effectiveness in patients with kidney, head and neck, bladder, lung and other cancers

Madrid, January 30, 2018.- The BBVA Foundation Frontiers of Knowledge Award in the Biomedicine category goes, in this tenth edition, to American immunologist James P. Allison, whose research, says the jury, "had led to harnessing the immune system to combat cancer in patients and the development of new therapies." Allison was the first to demonstrate that immunotherapy can treat cancer effectively, initiating an approach that "has provided clinical benefit to many cancer patients" and "stimulated the development of a new class of drugs employing the immune system to fight cancer."

In 2011, Allison's efforts led to the approval by the U.S. medicines agency (the FDA) of the first anti-cancer drug that works by activating the immune system, for the metastatic melanoma indication. The treatment would exceed all expectations, with around 20% of patients still living ten years later. The drug in question – ipilimumab – has produced a "complete paradigm shift" in the way medicine approaches cancer therapy, explains jury member Lélia Delamarre, Group Leader in the Cancer Immunology Department at biotech company Genentech.

Several drugs based on Allison's principle have since been approved, seeking to boost the percentage of melanoma patients who can benefit from immunotherapy. Effectiveness has also been found for this line of treatment in lung, kidney, bladder and head and neck cancers.

Immunotherapy works by mobilizing the system's natural defenses to combat and eliminate specific cancer cells. Over the years, various runs had been made at the strategy, but without success until Allison stepped in. The insight which would transform the therapeutic landscape was his discovery, in the mid-1990s, of a key mechanism in the functioning of the immune system T cells responsible for fighting tumor cells.

Allison and his group had determined that mobilizing these cells required the activation of two specific cell "switches"; yet this was not enough in itself to defeat the cancer cells. It was then that Allison proposed that a third signal must exist, with the ability either to boost the activity of these T cells or, conversely, block their function – the immune system is tightly regulated by positive and negative signals to stop it turning against the host body. Allison eventually "characterized a molecule called CTLA-4, which is displayed on the surface of T cells, and showed that it normally acts as a brake on this function," in the words of the citation.

The next step was to block this third signal, doing what jury member Robin Lovell-Badge of the Francis Crick Institute describes as "taking a foot off the brake" of the immune system. The T cells can then act unhindered against the cancer cells that are their target. Mouse trials of this strategy produced promising results, but the scientific community was not immediately convinced.

Allison recalled this period in a phone conversation yesterday after hearing of the award: "This skepticism was a reaction to the excess optimism of the early days of immunotherapy. At the start of the 1960s, people started talking about a new system destroying cancer, but the fact is that it only worked in mice. What happened I think is that people rushed in to do things without really understanding the underlying mechanism. They didn't realize that there are these negative signals built into the immune system, which are there to protect us. There were a lot of failures and people just gave up, insisting it was all hype."

The good results of clinical trials in humans, initiated in 2001, not only proved Allison right, but also inspired many other researchers to start searching for new immune system brakes or checkpoints. Immunotherapy is now one of the most active areas in oncology.

Among its advantages is that the response is lasting and may even lead, in some patients, to remission of the tumor, because the immune system will recognize the cancer cells if they reappear. Also, as Allison points out, "we don't tackle the cancer directly, we get the immune system to attack it," meaning immunotherapy can be effective against multiple tumors. A third advantage is that treatments generally have fewer side effects.

Allison, however, is the first to warn that immunotherapy is no one-stop solution: "We're not going to be able to cure all cancers," he admits. "But I think that in future immunotherapy will be a part of all cancer treatments, in combination with chemotherapy or radiation. I am optimistic that we will learn the right things to put together to cure a majority of patients, maybe even reaching from 60% or 90% of cases in some kinds of cancers."

Despite the good news, above all in cancers like melanoma that have so far proved largely intractable, immunotherapy still only works in a given percentage of patients. Some tumors manage to block the immune system or even slip by it unnoticed, and patients' treatment responses are at times unpredictable. That's why Allison insists on the need for more basic research: "The bottom line is we don't really know why the treatment doesn't work in all patients. A lot of people are looking for some sort of marker or sign so we can predict who is going to respond or not. But we just don't know. All the more reason to keep on doing the basic work."

Allison defines himself as a basic researcher, or at least that is how he started out: "I had a personal interest in cancer, because I lost my mother when I was a small child, and later my brother and two of my uncles. But I first wanted to figure out how T cells worked, so I could maybe apply the lessons of this basic research to come up with a cancer therapy. I think you first have to know basic science. Without that fundamental biology you do not have a rational basis for treating cancer. I always had possible cancer applications in the back of my head, but the priority has to be to do the best science you can, not necessarily with a specific goal in mind. That's what I always tell my students."

Despite this, Allison has had the rare privilege of meeting people who have benefited directly from his work: "One of the greatest moments of my life was seeing a woman who had been told she was going to be dead in a few months, and over 15 years later she is still alive and has two children. That motivates me to do all I can to get these therapies to work better. It's pretty rare for a basic scientist to get to see the application of their findings. I was lucky enough to have that experience."

Allison is now working with his wife and colleague at MD Anderson, Padmanee Sharma, on what they call the "Immunotherapy Platform": "We are currently involved in about a hundred clinical trials to analyze the effectiveness of these treatments. We are studying patients' tissues pre- and post-treatment to find situations where it works and where it doesn't, trying to probe the molecular details to understand where treatments may be falling down." All in all, the new laureate sees reasons to be hopeful: "we are not going to wipe out cancer, but we'll get a lot better at fighting many kinds."

Bio notes

James P. Allison (Texas, United States, 1948) earned a BS in Microbiology at the University of Texas, Austin, where he went on to complete a PhD in Biological Science in 1973. He later spent twelve years at the University of California, Berkeley, where he was Professor of Immunology and Director of the Cancer Research Laboratory.

After stints at the Memorial Sloan-Kettering Cancer Center and Cornell University, and as an investigator with the Howard Hughes Medical Institute, in 2012 he joined the team at Texas University's MD Anderson Cancer Center, where he is currently Chair of the Department of Immunology, Vivian L. Smith Distinguished Chair in Immunology, Executive Director of the Immunotherapy Platform, Deputy Director of the David H. Koch Center for Applied Research of Genitourinary Cancers and Co-Director of the Parker Institute for Cancer Immunotherapy.

He has also kept up a thirty-year association with the National Institutes of Health, where he chaired the Experimental Immunology Study Section and has served on expert panels on gene therapy, as well as organizing a think tank on cancer biology.

He sits on the editorial board of *Developmental Immunology* and *Journal of Clinical Investigation* and is a former reviewing editor of *Science*. The holder of six patents, he is also the co-founder, with his wife and scientific colleague Padmanee Sharma, of clinical stage immunotherapy company Jounce Therapeutics.

Biomedicine jury and technical committee

The rigor, quality and independence of the judging process has earned these awards the attention of the international scientific community and a firm place among the world's foremost prize families.

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 Centre for Neurodevelopmental Disorders and the Centre for Developmental Neurobiology 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 of Dundee University (United Kingdom); **Hagan Bayley**, Professor of Chemical Biology at the University of Oxford; **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 Department of Physiology in the Carl Gustav Carus Medical School at the Technical University of Dresden (TUD), and the Institute of Experimental Cardiovascular Medicine at the University Heart Center of the University of Freiburg. Institute of Experimental Cardiovascular Medicine at

the University Heart Center in the Medical Faculty of the University of Freiburg (Germany); **Ali Shilatifard**, Robert Francis Furchgott Professor, Chair of the Department of Biochemistry and Molecular Genetics and Director of the Simpson Querrey Center for Epigenetics at Northwestern University (United States); and **Bruce Whitelaw,** Deputy Director (Partnerships) at The Roslin Institute, University of Edinburgh (United Kingdom) and Genus Chair of Animal Biotechnology in the same institution's Royal (Dick) School of Veterinary Studies (RDSVS).

The **CSIC Technical Committee** was coordinated by **María Victoria Moreno**, the Council's Deputy Vice President for Scientific and Technical Areas, and formed by: **Susana Alemany**, Coordinator of the Biology and Biomedicine Area and Scientific Researcher in the Biomedical Research Institute "Alberto Sols"; **Dolores González**, Research Professor at the Institute of Parasitology and Biomedicine "López Neyra" (IPBLN); **Jesús Ávila**, Research Professor in the Molecular Biology Center "Severo Ochoa"; **Ana Aranda**, Research Professor in the Biomedical Research Institute "Alberto Sols"; and **María Isabel Medina**, Coordinator of the Food Science and Technology Area, and Research Professor at the Institute of Marine Research (IIM).

Previous awardees in this category

The **Biomedicine** award in last year's edition was shared by **Emmanuelle Charpentier, Jennifer Doudna and Francisco Martínez Mojica** whose pioneering work ignited "the revolution in biology permitted by CRISPR/Cas 9 techniques," facilitating genome modification with an unprecedented degree of precision.

Five of the 83 winners in earlier editions of the BBVA Foundation Frontiers of Knowledge Awards have gone on to win the Nobel Prize. Shinya Yamanaka, the 2010 Biomedicine laureate, won the Nobel Prize in Medicine in 2012; **Robert J. Lefkowitz**, awardee in the same Frontiers category in 2009, won the Chemistry Nobel in 2012. In Economics, Finance and Management, three Frontiers laureates were later honored with the Nobel: **Lars Peter Hansen**, winner of the Frontiers Award in 2010 and the Nobel Prize in 2013; **Jean Tirole**, Frontiers laureate in 2008 and Nobel laureate in 2014; and **Angus Deaton**, 2011 Frontiers laureate and Nobel laureate in 2015.

About the BBVA Foundation Frontiers of Knowledge Awards

The promotion of knowledge based on research and artistic and cultural creation, and the interaction of these domains, forms a core strand of **the BBVA Foundation**'s action program, along with the recognition of talent and excellence across a broad spectrum of disciplines, from science to the arts and humanities.

In line with these objectives, the **BBVA Foundation Frontiers of Knowledge Awards** were established in 2008 to recognize outstanding contributions in a range of scientific, technological and artistic areas, together with knowledge-based

responses to the central challenges of our times. The areas covered by the Frontiers Awards are congruent with the knowledge map of the 21st century, in terms of the disciplines they address and their assertion of the value of cross-disciplinary interaction.

Their **eight categories** span classical areas like Basic Sciences (Physics, Chemistry and Mathematics), Biomedicine and other areas characteristic of our time, like Biomedicine, Information and Communication Technologies, Ecology and Conservation Biology, Climate Change, Economics, Finance and Management and Development Cooperation, and the particularly innovative realm that is Contemporary Music.

The BBVA Foundation is aided in the evaluation process by the **Spanish National Research Council (CSIC)**, the country's premier public research organization. As well as designating each jury chair, the CSIC is responsible for appointing the technical evaluation committees that undertake an initial assessment of candidates put forward by numerous institutions across the world and draw up a reasoned shortlist for the consideration of the juries.

CALENDAR OF UPCOMING AWARD ANNOUNCEMENTS

Ecology and Conservation Biology	Tuesday, February 6, 2018
Contemporary Music	Tuesday, February 13, 2018
Economics, Finance and Management	Tuesday, February 20, 2018
Development Cooperation	Tuesday, February 27, 2018

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 name of the video is:

"PREMIO BIOMEDICINA"

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

Mobile: +34 619 30 87 74

E-mail: mgil@mediaset.es

Fundación BBVA

For more information, contact the BBVA Foundation Department of Communication and Institutional Relations (+34 91 374 5210; 91 374 3139; 91 374 8173/ comunicacion@fbbva.es) or visit www.fbbva.es