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Press release
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In the Biology and Biomedicine category

The Frontiers of Knowledge Award goes to Carl June and Michel Sadelain for revolutionizing cancer treatment using immunotherapy based on the patient's own genetically modified cells

- **Their groundbreaking work on the basic research and clinical application of CAR-T cells** has driven the development of "therapeutics for the treatment of patients with blood cancers like leukemia," which have already benefitted "tens of thousands of individuals, including many children," said the committee in its citation

- **The two researchers pioneered the technique that allows T cells to be isolated from the patient's own immune system,** grown in the laboratory and genetically engineered so they can recognize and selectively destroy cancer cells on being infused back into the patient's body, leading to remission of the disease

- **The approach they devised "is now being developed for the treatment of solid tumors,"** like breast, prostate, colon and pancreatic cancers, and to treat autoimmune conditions like lupus or even infectious diseases, "revolutionizing cell therapeutics through genetic engineering"

The BBVA Foundation Frontiers of Knowledge Award in Biology and Biomedicine has gone in this eighteenth edition to Carl June (University of Pennsylvania) and Michel Sadelain (Columbia University) for revolutionizing the treatment of cancer by means of CAR-T cell immunotherapy. The two laureates pioneered this innovative therapeutic strategy whereby T cells are extracted from the patient's own immune system, grown in the lab and genetically engineered so they recognize and selectively destroy cancer cells on being infused back into the body, leading to remission of the disease.

February 11, 2026

June and Sadelain's "complementary studies" on CAR-T cells on the path from basic research to clinical application have driven the development of "therapeutics for the treatment of patients with blood cancers like leukemia," which have already benefitted "tens of thousands of individuals, including many children," said the committee in its citation.

Their approach "is now being developed for the treatment of solid tumors," like breast, prostate, colon and pancreatic cancers, as well as "infectious and autoimmune diseases," the citation continues, catalyzing a vast and richly promising field of biomedical research that is "revolutionizing cell therapeutics through genetic engineering."

"With this technique, what genetic engineering gives us is the power to transform the patient's own T cells into soldiers trained to recognize and kill cancer cells," explains committee chair Ali Shilatifard, Robert Francis Furchgott Professor of Biochemistry and Pediatrics at Northwestern University (Chicago, United States). "Thousands of patients have already been treated using this method, and I have no doubt that many more will benefit in future."

"What June and Sadelain have achieved can be defined as a paradigm shift, which, like almost every great idea, is astounding in its simplicity," adds committee secretary Óscar Marín, Professor of Neuroscience and Director of the Centre for Developmental Neurobiology and MRC Centre for Neurodevelopmental Disorders at King's College London (United Kingdom). "We all have the idea that our immune system, our T cells, are designed to fight pathogens, but these scientists have shown that it is possible to reprogram our own T cells to directly attack cancer cells. They have in effect changed the paradigm with a new cell therapy where these cells are reprogrammed by genetic engineering to select the precise target they wish to act on. What is novel is not just their proven ability to transform the prognosis of certain types of cancer, but the myriad possibilities the technique opens up for new treatments for many other diseases."

Genetic engineering that equips our immune system to fight cancer

"We are fortunate to have an immune system that protects us from invaders like viruses, parasites or bacteria. But when it comes to cancer, even this wonderful system is not always up to the challenge," Michel Sadelain explains. In the early 1990s, while at the Memorial Sloan Kettering Cancer Center in New York, it was precisely this challenge that got the French-Canadian researcher thinking of ways to "help this immune system of ours by means of genetic engineering, teaching the all-important T cells to recognize cancer cells and then eliminate them."

February 11, 2026

Building on the findings of Israeli researcher Zelig Eshhar (d. 2025), who first proposed the chimeric antigen receptors (CAR) concept in 1993, Sadelain set out to establish the feasibility of the technique. Eshhar had developed a first generation of CARs – synthetic proteins designed in the lab that are added to T cells using genetic modification – but they proved unable to survive in any organism.

In 2002, after ten years of research, Sadelain and his team managed to engineer what were known as second-generation CAR-T cells, capable of surviving, proliferating, and killing cancer cells *in vitro* in the lab, thereby proving the viability of producing genetically instructed, targeted immune responses. "When we introduce a CAR into a T cell," says Sadelain, "it acquires the ability to recognize tumor cells and will then proceed to destroy them."

One year later, in 2003, he and his colleagues published a research paper in *Nature Medicine* showing that human CAR T cells targeting a protein known as CD19 – expressed in leukemias and lymphomas – could eradicate these malignant cells in mice.

From bench to clinic: a technique that worked better in humans than in mice

Carl June was researching potential treatments for AIDS patients at the University of Pennsylvania when he achieved an important milestone in the clinical development of CAR-T cells. He had developed an interest in immunology while studying medicine in the 1970s, spurred by the fact that his own mother had an autoimmune condition, common among members of her family. After the advances made by Sadelain on the experimental plane, it was time to establish whether cell therapy could also work in human patients, with some researchers concerned that their immune systems would attack and kill the CAR-T cells. In the mid 1990s, June showed that T cells modified to stave off infection with HIV could not only survive in the human body, but could do so long enough to trigger immune responses. This quality of persistence, critical for attacking cancer over time, opened the door to the first clinical trials with CAR-T cells in leukemia patients.

Around that time, June's first wife fell ill with ovarian cancer aged just 41 and sadly died seven years later. Getting the new therapeutic strategy into trials in human oncological patients accordingly became "the number one thing" in the researcher's life. It was finally in 2010 that the first two patients, with very late stage leukemia, signed up for what was then a highly experimental trial of June's own design, with each receiving an infusion of CAR-T cells. This would be the first application in a clinical setting of the findings developed in Sadelain's lab and tried with success in animal models.

February 11, 2026

June recalls his amazement at seeing that the treatment achieved better results in humans than it did in experiments run on rodents: "We cured a lot of mice, but the major surprise was that the therapy worked even better in humans. Remarkably, our first patient was cured with a single infusion and for ten years still had CAR-T cells in his body, although he later died of COVID-19. The second patient is still alive and continues to have CAR-T cells in his body. We never thought it would work so effectively."

Sadelain too led a series of clinical trials trying the same strategy with blood cancer patients: "The trials started in patients with relapsed refractory leukemias, meaning they had already undergone the standard of care and their cancer was nonetheless progressing. Very soon, the first results reported by my team, Carl June, and other researchers confirmed that CAR-T cells could be efficacious in these blood-borne cancers."

Authorized therapies that have already benefitted over 50,000 patients

In light of this clinical success, the first CAR-T cell therapy was granted FDA approval in 2017 for use in children and young adults with refractory acute leukemias and certain refractory lymphomas. And one year later, the European Medicines Agency approved its use throughout the EU. To date, more than 50,000 blood cancer patients have been treated and it is now widely accepted, as Sadelain affirms, "that engineered immunity exemplified by CAR-T cells can succeed where no other treatment, chemotherapy or bone marrow transplantation has succeeded before."

Carl June reveals a Spanish connection in his work. "The first Spanish scientist to get in touch with me about CAR-T therapies was Manel Juan from Hospital Clínic de Barcelona, who asked if he could visit me in Philadelphia and learn the technique. He spent six months in my laboratory and has since introduced the therapy in Spain." Juan, now leader of the hospital's Immunogenetics and Immunotherapy Group, looks back on the experience: "He encouraged me to start CAR-T therapy at our center. We have done so as part of an academic development covering the entire process from the preclinical stage through production to clinical application, which has allowed us to make it more affordable. In 2017 we began working with patients and in 2020 got our first drug approved, followed by a second drug in 2024, which has been used to treat around 600 patients."

February 11, 2026

Luis Álvarez-Vallina, Head of the Cancer Immunotherapy Clinical Research Unit at the Spanish National Cancer Research Center (CNIO) and a nominator of June and Sadelain, provided an update on the status of CAR-T therapies in Spain: "We are among the countries furthest ahead in this regard, because there has been a remarkable flourishing of academic CARs (attached to public institutions), especially around Hospital Clínic de Barcelona, which has made it possible to treat hundreds of patients at a considerably lower cost."

For Álvarez-Vallina, one of the challenges of CAR-T therapy is how to reduce its costs so it is more affordable for a greater number of patients. He points to three strategies being deployed to this end: the *in vivo* option, where instead of extracting, isolating and genetically modifying immune cells, the genetic information is added via a nanoparticle bearing an RNA or virus; the Fast CARs option designed to shorten the waiting time for patients; and off-the-shelf therapies, where rather than using cells from patient themselves, frozen CAR-T cells are collected and stored for administering to patients as soon as they are admitted.

"June and Sadelain have brought about a paradigm shift in modern medicine with the development of CAR-T cell immunotherapy. Their work has profoundly transformed the fields of oncology and immunology, to the extent that they are considered the fathers of the first 'living drug' in medical history. Unlike traditional drugs, which are metabolized over time and require repeat doses, CAR-T cells comprise the patient's own cells, which, after being genetically modified to selectively recognize and destroy tumor cells, can persist and function in the body for years, such that a single dose can provide lasting protection. Genetic engineering provides a level of precision that chemotherapy cannot achieve. While the latter acts in a non-selective manner, CAR-T cells attack only the target cells and leave healthy tissue untouched," explains Antonio Pérez-Martínez, Head of the Pediatric Hemato-Oncology Department at Hospital Universitario La Paz and another nominator of the winning entry.

Luis Paz-Ares, Head of Medical Oncology at Hospital Doce de Octubre in Madrid, also a nominator, sees the award as particularly well deserved, "because the laureates have had an immediate impact, offering new possibilities to our patients. But CAR-T therapies also open up new horizons in the field of cellular immunotherapy and T-cell redirection. Although they have yet to make major inroads in solid tumors, I believe they will do so in the near future, and Spain is well placed for that future thanks to the strength of its cancer research, both basic and translational and clinical."

The challenge of achieving the same success in solid tumors as in blood cancers

February 11, 2026

CAR-T cells have not so far shown the same effectiveness in solid tumors like breast, colon, pancreatic or lung cancers as they have in cancers of the blood, making this the next big hurdle for the genetically engineered immunotherapy led by the co-awardees.

"If you apply the same recipe to treat solid tumors, the CAR-T cells don't work as well as they do in leukemias and lymphomas," Sadelain admits. "But we are now starting to understand the barriers that need to be overcome in the context of solid tumors. Chief among them are the selection of therapeutic targets and the composition of the cancers themselves, which are different from leukemias and lymphomas."

June too is clear that "clinical trials with solid tumors have been basically disappointing," due to the greater complexity of these kinds of cancers. "In the case of blood cancer, we've been able to target just one molecule, CD19, but solid tumors are genetically more complex so we can't apply the same strategy."

That said, both researchers are confident that reaching this goal is just a matter of time: "Thousands of laboratories around the world, including mine, are striving to make CAR-T cells work in solid cancers, and I think we'll eventually see major progress," says June.

Sadelain concurs: "I believe there's every reason to be optimistic that in the next few years, certainly the next decade, we will have effective CAR-T cell therapies for lung cancer, brain tumors and others. Today, the scientific, medical and pharmaceutical establishments are convinced of the value of engineered immunity. And now it is our job to make it work for many other cancers."

The promise of CAR-T cell therapy for autoimmune and infectious diseases

As the committee notes in its citation, the potential of CAR-T cells is not confined to cancers, but may also extend to the treatment of autoimmune and infectious diseases.

Sadelain explains that when the CD19 molecule was identified as a target for CAR-T therapy in blood cancers, "we knew that a side effect would be to eliminate not only leukemias or lymphomas, but also normal B cells, the cells that produce antibodies." As a rule, antibodies play a vital role in protecting us against infections and other diseases, but in some circumstances they can also turn against us, attacking our own tissues. This is precisely what happens in patients suffering autoimmune disorders like lupus, and it has recently been found that CAR-T cells designed to act against the CD19 molecule that is a target for leukemia can also serve for this kind of condition.

February 11, 2026

"Remarkably, marvelously," Sadelain enthuses, "they immediately achieved complete responses in lupus patients." And this success has set in motion "a wave of new clinical studies in the worlds of rheumatology and neurology," to see whether CAR-T cells might be effective in controlling autoimmune diseases like arthritis and multiple sclerosis.

Other recent research has shown that the same strategy may be of benefit in refractory infectious diseases like AIDS. "The first patients I began using this approach with were HIV positive," June recalls. "And what happened around then was that protease inhibitors were invented, the antiretroviral drugs that turned AIDS from a lethal into a chronic disease, but with patients obliged to keep taking medicines every day of their lives without ever being cured. Research is now going on to see whether CAR-T cells can be used as a one-time treatment for HIV, so you can eliminate all reservoirs of the virus and achieve a complete cure, without the need to continue taking medication."

The objective here is to genetically modify T cells taken from a seropositive patient so they can identify specific proteins on the surface of the HIV infected cells and go on to destroy them.

"The same strategy has been tried for other infections like COVID, and there have been some very interesting papers recently about its possible use in diseases affecting the heart or lungs. In sum, CAR-T cells had their first successes with cancer, but I believe they are going to prove effective in many conditions."

Laureate bio notes

Carl H. June (Denver, United States, 1956) graduated with a BS in Biology from the United States Naval Academy in 1975, and received his medical degree from Baylor College of Medicine in 1979. He specialized in Internal Medicine at the National Naval Medical Center in Bethesda (1980-1983) and in Oncology at the Fred Hutchinson Cancer Center-University of Washington (1983-1985). He then returned to Bethesda, where he founded the Immune Cell Biology Program at the Naval Medical Research Center and headed the Department of Immunology from 1990 to 1995. During this time, he was also a Professor of Medicine and of Cell and Molecular Biology at the Uniformed Services University of the Health Sciences (1995-1999). In 1999, he joined the Perelman School of Medicine at the University of Pennsylvania, where he is currently the Richard W. Vague Professor in Immunotherapy, Director of the Center for Cellular Immunotherapies, and Director of the Parker Institute for Cancer Immunotherapy. Author of over 350 publications, among his many distinctions he is an elected member of the American Academy of Arts and Sciences.

February 11, 2026

Michel Sadelain (Paris, France, 1960), of French and Canadian nationality, earned his medical degree at the University of Paris (1984), before going on to complete a PhD in Immunology at the University of Alberta (Canada) in 1989, followed by a postdoctoral fellowship at the Whitehead Institute for Biomedical Research of Massachusetts Institute of Technology. In 1994 he joined the Memorial Sloan Kettering Cancer Center in New York, where he was the Stephen and Barbara Friedman Chair, founding director of the Center for Cell Engineering and head of the Gene Transfer and Gene Expression Laboratory. In 2024 he moved to Columbia University, also in New York, where he is currently Herbert and Florence Professor of Medicine, Director of the Columbia Initiative in Cell Engineering and Therapy and Director of the Cancer Cell Therapy Initiative at the Herbert Irving Comprehensive Cancer Center. A past president of the American Society of Gene and Cell Therapy, he has also served on the Recombinant DNA Advisory Committee of the National Institutes of Health. Sadelain has authored over 280 published papers and his research has resulted in more than 60 patents.

Nominators

A total of 111 nominations comprising 133 candidates were received in this edition. The awardee researchers were nominated by **Luis Álvarez-Vallina**, Head of the HMarBCN-CNIO Cancer Immunotherapy Clinical Research Unit at the Spanish National Cancer Research Center (Spain); **Rikardo Bueno Zabalo**, CEO of the Basque Research and Technology Alliance (Spain); **Joaquín Martínez-López**, Head of the H12O-CNIO Hematological Malignancies Research Unit at the Spanish National Cancer Research Center (Spain); **José Muñiz**, Rector of Nebrija University (Spain); **Luis Paz-Ares**, Head of the Medical Oncology Department at Hospital Universitario 12 de Octubre (Spain); **Fernando Peláez**, Acting Scientific Director and Biotechnology Program Director at the Spanish National Cancer Research Center (Spain); and **Antonio Pérez-Martínez**, Head of the Pediatric Hemato-Oncology Department at Hospital Universitario La Paz (Spain).

Biology and Biomedicine committee and evaluation support panel

The committee in this category was chaired by **Ali Shilatifard**, Robert Francis Furchgott Professor of Biochemistry and Pediatrics at Northwestern University (Chicago, United States). The secretary was **Óscar Marín**, Professor of Neuroscience and Director of the Centre for Developmental Neurobiology and MRC Centre for Neurodevelopmental Disorders at King's College London (United Kingdom).

February 11, 2026

Remaining members were **Dario Alessi**, Director of the MRC Protein Phosphorylation and Ubiquitylation Unit at the University of Dundee (United Kingdom); **Lélia Delamarre**, Director and Distinguished Scientist in the Department of Cancer Immunology at Genentech (United States); **Robin Lovell-Badge**, Principal Group Leader and Head of the Laboratory of Stem Cell Biology and Developmental Genetics at the Francis Crick Institute (London, United Kingdom); **Ursula Ravens**, Professor Emerita in the Carl Gustav Carus Faculty of Medicine at the Technical University of Dresden and Guest Scientist in the Institute of Experimental Cardiovascular Medicine at the University of Freiburg (Germany); **Angelika Schnieke**, TUM Emerita of Excellence of the School of Life Sciences at the Technical University of Munich (Germany); and **Bruce Whitelaw**, Professor of Animal Biotechnology in the Royal (Dick) School of Veterinary Studies (RDSVS) at the University of Edinburgh (United Kingdom).

The **evaluation support panel** was coordinated by **Elena Cartea**, Deputy Vice-President for Scientific-Technical Areas at the Spanish National Research Council (CSIC), and **José M. Mato**, General Director of CIC bioGUNE and CIC biomaGUNE, and formed by: **Edurne Berra**, CIC BioGUNE Associate Principal Investigator in the Hypoxia Lab; **Arkaitz Carracedo**, CIC bioGUNE Principal Investigator in the Cancer Lab; **Dolores González Pacanowska**, Research Professor at the Lopez Neyra Institute of Parasitology and Biomedicine (IPBLN, CSIC); **Óscar Millet**, CIC bioGUNE Principal Investigator in the Precision Medicine and Metabolism Lab; **Raúl Pérez-Jiménez**, Ikerbasque Research Professor in the CIC bioGUNE Synthetic Biology Lab; **Jordi Pérez-Tur**, Scientific Researcher at the Institute of Biomedicine of Valencia (IBV, CSIC); **James D. Sutherland**, CIC BioGUNE Associate Principal Investigator in the Developmental Biology Lab; **Isabel Varela Nieto**, Research Professor at the Sols-Morreale Biomedical Research Institute (IIBM, CSIC-UAM); and **Nuria Verdaguer Massana**, Deputy Coordinator of the Life Global Area and Research Professor at the Institute of Molecular Biology of Barcelona (IBMB, CSIC).

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 recognition 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 basic sciences, biomedicine, environmental sciences and climate change, social sciences, economics, the humanities and music. The goal of the awards, established in 2008, is to celebrate and promote the value of knowledge as a global public good, the best tool at our command to confront the

February 11, 2026

defining challenges of our time and expand individual worldviews. Their eight categories are congruent with the knowledge map of the 21st century.

The BBVA Foundation is partnered in these awards 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 candidates and drawing up a reasoned shortlist for the consideration of the award committees. CSIC is also responsible for designating each committee's chair across the eight prize categories and participates in the selection of remaining members, helping to ensure objectivity in the recognition of innovation and scientific excellence. The presidency of CSIC also has a prominent role in the awards ceremony held each year in Bilbao, the permanent home of the BBVA Foundation Frontiers of Knowledge Awards.

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