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Special Feature

James P. Allison received the 2014 Szent-Györgi Prize for Progress in Cancer Research

Jie Zhao, Peter Scully and Sujuan Ba*

Abstract

The Szent-Györgyi Prize for Progress in Cancer Research is a prestigious scientific award established by the National Foundation for Cancer Research (NFCR)—a leading cancer research charitable organization in the United States that is committed to supporting innovative cancer research on the global scale that aims to cure cancer. Each year, the Szent-Györgyi Prize honors an outstanding researcher whose original discoveries have expanded our understanding of cancer and resulted in notable advances in cancer prevention, diagnosis, or treatment. The prize also promotes public awareness of the importance of basic cancer research and encourages the sustained investment needed to accelerate the translation of these research discoveries into new cancer treatments. This report highlights the history and mission of the Szent-Györgyi Prize, its role in promoting discovery-oriented cancer research, and the pioneering work led by the 2014 prize winner, Dr. James Allison. Dr. Allison's work in the area of cancer immunotherapy led to the successful development of immune checkpoint therapy, and the first drug approved by the United States Food and Drug Administration for the treatment of metastatic melanoma.

Key words The National Foundation for Cancer Research, the Szent-Györgyi Prize, James Allison, immune checkpoint therapy

On April 30, 2014, the National Press Club in Washington, DC, the United States (US), was filled with nearly 200 scientists and thought leaders from top-tier cancer research institutions, hospitals, and biopharmaceutical corporations around the globe, all of whom came to celebrate the new winner of the Szent-Györgyi Prize for Progress in Cancer Research.

The Szent-Györgyi Prize for Progress in Cancer Research is a prestigious scientific award established by the National Foundation for Cancer Research (NFCR)—a leading cancer research charitable organization in the US that has gained international recognition for its vision and unique approaches to accelerating cancer research toward a cure.

Each year, the prize honors an outstanding researcher whose scientific achievements have expanded our understanding of cancer and what causes it, whose vision has moved cancer research in new directions, and whose discoveries have resulted in notable advances in cancer prevention, diagnosis, or treatment. The prize also promotes public awareness of the importance of basic cancer research and encourages the sustained investment needed to accelerate the translation of these research discoveries into new cancer treatments.

NFCR established the prize in honor of its co-founder, Albert Szent-Györgyi (**Figure 1**), MD, PhD, recipient of the 1937 Nobel Prize for Physiology or Medicine. Dr. Szent-Györgyi was a pioneer who constantly challenged the conventional thinking of the day to pursue his novel and promising ideas. After winning the Nobel Prize for his research on vitamin C and cell respiration, Dr. Szent-Györgyi set his sights on finding a way to defeat cancer.

Beyond his laboratory, Dr. Szent-Györgyi was a leading advocate for developing resources to provide scientists with the financial support necessary to pursue novel cancer research ideas. In 1973, he changed the face of cancer research funding by co-founding NFCR with entrepreneur Franklin C. Salisbury. Since then, NFCR has provided more than $320 million in support of discovery-oriented cancer research and prevention education programs.

Committed to upholding Dr. Szent-Györgyi's vision of curing cancer through innovation and collaboration, NFCR established this prize to honor scientists who have made extraordinary progress in

Authors' Affiliation: National Foundation for Cancer Research, Bethesda, MD 20814, USA.

Corresponding Author: Sujuan Ba, 4600 East West Highway, Suite 525, Bethesda, MD 20814, USA. Tel: +1-301-654-1250; Fax: +1-301-654-5824; Email: sjb@NFCR.org.

*Dr. Sujuan Ba is the Chief Operating Officer of National Foundation for Cancer Research.

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cancer research and to focus attention on the essential role of basic research in unraveling the mysteries of cancer (**Figure 2**). The prize also serves to stimulate continued investment in the pioneering research that will produce scientific breakthroughs and lead to a deeper understanding of the genetic and molecular underpinnings of cancer.

Since its establishment in 2006, the prize has been awarded to 10 outstanding cancer researchers from around the world. Among the past awardees is Dr. Zhu Chen, chairman of the Chinese Medical Association and former Minister of Health of China, who won the 2012 prize together with his mentor, Dr. Zhen-Yi Wang.

The 2014 Szent-Györgyi Prize

In 2014, the Szent-Györgyi Prize for Progress in Cancer Research was awarded to James Allison, PhD, chairman of the Department of Immunology at The University of Texas MD Anderson Cancer Center (**Figure 3**). Dr. Allison's pioneering cancer research in the area of immunotherapy led to the successful development of immune checkpoint therapy and the first drug approved by the US Food and Drug Administration for the treatment of metastatic melanoma.

In bestowing the award, NFCR's selection committee recognized Allison's momentous achievement in the fight against cancer and his extraordinary leadership in the modern era of oncology. While mainstream cancer research and treatment focused for decades on radiation therapy and chemotherapy, Dr. Allison's trailblazing work in immunotherapy—using the body's own immune system to fight off cancer—never ceased.

"Dr. Allison has revolutionized the way science approaches cancer treatments," said Sujuan Ba, PhD, co-chair of the 2014 Szent-Györgyi Prize Selection Committee and chief operating officer of NFCR (**Figure 4**). "He is on the front line in the war against cancer and could not be more deserving of this award."

This year's Szent-Györgyi Prize celebrates "the world-renowned immunologist who opened the doors for an understanding of fundamental immune mechanisms and who used this newly found knowledge to advance cancer immunotherapy in a spectacular way," said Dr. Alex Matter, chief executive officer of the Experimental Therapeutics Centre & D3, A*STAR, Singapore, winner of the 2013 Szent-Györgyi Prize, and chair of this year's prize selection committee. "He has validated the immunotherapy approach and turned previously widely held beliefs on their heads with his discoveries. His work is extremely significant and constitutes a turning point in the history of progress in cancer treatments."

James P. Allison: A True Pioneer in Cancer Immunotherapy

Dr. Allison earned his Bachelor of Science in Microbiology in 1969 and his PhD in Biological Science from the University of Texas, Austin, the US, in 1973. He was appointed a professor of immunology and director of the Cancer Research Laboratory at the University of California, Berkeley in Berkeley, California, the US, in 1985. In 2004, he moved to the Memorial Sloan-Kettering Cancer Center in New York, New York, the US, where he was director of the Ludwig Center for Cancer Immunotherapy, chair of the immunology

Figure 1. **Albert Szent-Györgyi, MD, PhD, recipient of the 1937 Nobel Prize for Physiology or Medicine and co-founder of the National Foundation for Cancer Research.**

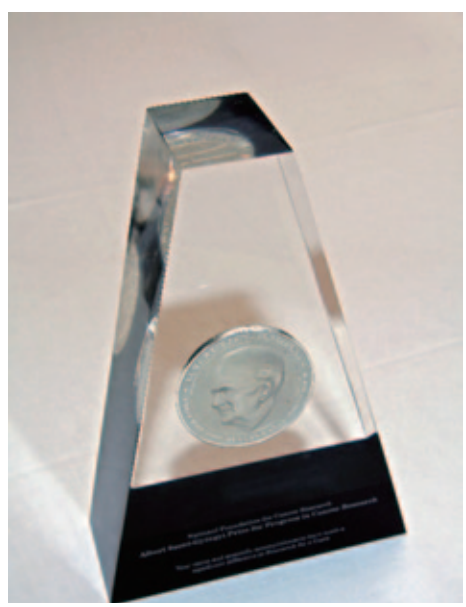

Figure 2. **The Szent-Györgyi Prize award**

program, David H. Koch Chair in Immunologic Studies, and attending immunologist. In 2012, he joined MD Anderson Cancer Center, where he currently holds the position of professor and chair of immunology and executive director of the center's Immunotherapy Platform.

Dr. Allison is a member of the National Academy of Sciences and the Institute of Medicine, a Howard Hughes Medical Institute (HHMI) alumnus, and a fellow of the American Academy of Microbiology and the American Association for the Advancement of Science. Previously, he served as president of the American Association of Immunologists. He has received numerous awards, including a recent AACR/SU2C/CRI cancer immunotherapy dream team grant, for which he will serve as the team leader. In December 2013, he was awarded the Breakthrough Prize in Life Sciences for his work.

The cancer research community has been brewing the idea of harnessing the immune system to fight cancer for decades, but early attempts all failed. "At least in part that was because we did not understand how complicated the immune system is. It's not just a system of recognizing a signal and starting to go. There are also a lot of signals that are required to stop an immune response," said Dr. Allison (**Figure 5**). "You have to stop an immune response or it will destroy you—you'll just get collateral damage. What people didn't realize is there were negative signals."

The recognition of the role played by these negative signals was Dr. Allison's major breakthrough. By the late 1980s, it was understood that recognition of antigens by the T-cell antigen receptor was not sufficient to activate an immune response; there had to be another co-stimulatory signal at the same time, and that kind of signal could only be provided by highly specialized cells. Making an analogy to driving a car, Dr. Allison said, "The T-cell antigen receptor is kind of like the ignition switch. Every T cell has a different one, and unless you activate that, nothing is going to happen. But unless you get the gas pedal pushed at the same time, it's going to be an ineffective immune response." The gas pedal in this analogy was a co-stimulatory molecule called CD28.

In the mid-1990s, Dr. Allison and Dr. Jeff Bluestone at the University of Chicago realized that another molecule—cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), which was known to compete with CD28—was not an analogous co-stimulatory molecule, but actually quite the opposite. If CD28 is the gas pedal, CTLA-4 is the brakes, and CTLA-4 was only induced after the T cells were activated.

"It immediately occurred to me and to others in my lab that this might be the reason that attempts to vaccinate therapeutically against cancer wouldn't work because every time you gave vaccination—gave the "go" signal—that resulted in inducing the off signal as well," said Dr. Allison. This led to a simple idea. "If we could just block that signal, take it out of the pathway by something as simple as an antibody… we could just let T-cell receptor and the gas pedal go to the floor and the T cells keep going, and hopefully eradicate the tumor cells."

This was the paradigm shift: "We're not treating the tumor cells, we're treating the immune system. We're treating the patient, we're treating his or her T cells," said Dr. Allison. Therefore, this has the possibility of becoming a treatment for all types of cancer. "This is a gross simplification, obviously, but the cancer cell's irrelevant. You're just making the immune system attack something that oughtn't to be there, whether it be melanoma, lymphoma, renal cancer, or colon cancer."

The reach of this approach is actually even greater. Anything that kills tumor cells under inflammatory conditions will present tumor antigens to T cells, priming them for response. So an anti-CTLA-4 approach could also increase the effect of certain chemotherapies, radiotherapy, hormone therapy, or even new targeted therapies that kill tumor cells. "It could give memory to other therapies that kill tumor cells and give you that long-lived response that lasts for the rest of your life."

The experiments started in mice, and the results were stunning. "In our early experiments we cured between 90% and 100% of the mice in most of these experiments, and the mice were permanently immuned when re-challenged with the tumor." said Dr. Allison. "All we were doing was covering up this one molecule—out of all the things that are going on when the host immune system is detecting the tumor—and turning tumor growth and inevitable death of the mice to a cure and long-lived immunity to re-challenge."

In the late 1990s, Dr. Allison's lab teamed up with Medarex to make completely human antibodies to CTLA-4. The resulting drug, ipilimumab, has been used to treat over 30,000 patients to date. "It's been incredibly successful, having at least anecdotal responses in many kinds of cancer, including melanoma, renal cancer, prostate cancer, glioblastoma, pancreatic cancer, ovarian cancer, and lung cancer… And the adverse effects are a lot milder than what you see with conventional chemotherapy."

During his acceptance speech at the award ceremony, Dr. Allison presented the story of a woman named Sharon, who developed metastatic melanoma in her late 40s and subsequently failed every therapy. "At the time," recalls Dr. Allison, "she just said she wanted to live long enough to see her sons graduate from high school." Sharon was placed on the phase I trial of ipilimumab and got a single dose at 3 mg/kg. Six months later, she was completely clear of tumor. "And she's still completely tumor free, with no need for subsequent therapy at all, and now she's 14 years out." There are similar anecdotes for patients with metastatic melanoma to the brain, completely cured, and patients with prostate cancer and bone metastases, completely gone after anti-CTLA-4 treatment.

The real proof was in an 800-patient, randomized, placebo-controlled trial of ipilimumab in metastatic melanoma. Median survival increased four months for patients in this trial, a result that had never been achieved with any therapy for metastatic melanoma. Even more remarkably, "The survival curve flattens out at about 23% at two and a half years and goes out to three years, three and a half, four years, four and a half, and is absolutely flat. Recently there was actually a 5,000 patient retrospective study [that] showed that people who make it three years after this single round of therapy do not die of melanoma; they die of something else."

CTLA-4 is not the only molecule involved in down-regulating the immune response, and not all patients respond to anti-CTLA-4 treatment. Work with another signaling molecule, programmed cell death 1 (PD-1; which competes with the ignition switch and not the

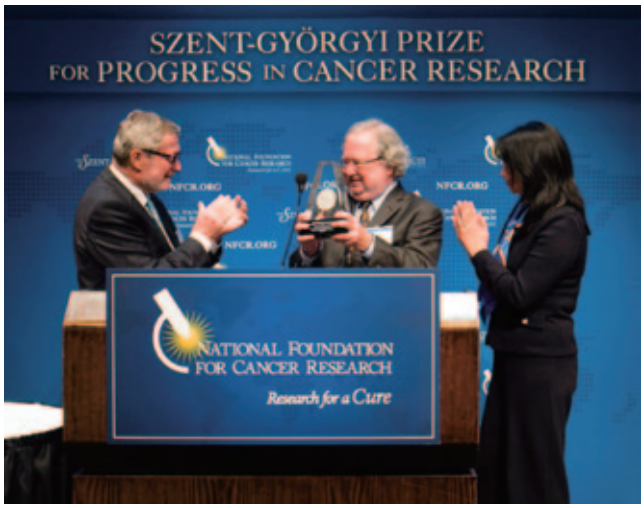

Figure 3. Dr. Alex Matter (left), winner of the 2013 Szent-Györgyi Prize and chair of the 2014 Prize Selection Committee, and Dr. Sujuan Ba (right), co-chair of the Prize Selection Committee and chief operating officer of the National Foundation for Cancer Research (NFCR), presented the award to the 2014 prize winner, Dr. James Allison.

Figure 4. From left to right: Dr. Sujuan Ba, co-chair of the Szent-Györgyi Prize Selection Committee and chief operating officer of NFCR; Dr. James Allison, winner of the 2014 Szent-Györgyi Prize; and Dr. Pam Sharma, Allison's colleague.

Figure 5. Dr. James Allison, winner of the 2014 Szent-Györgyi Prize, was giving an acceptance speech at the award ceremony held on April 30, 2014, in Washington, DC, the US.

gas pedal, as the CTLA-4 molecule does), demonstrated not just similar outcomes, but in fact, additive effects when combined with ipilimumab.

"We're at a point where we know that immunotherapy by checkpoint blockade works—it works regularly and in a significant fraction of patients," said Dr. Allison. But questions remain. "We need to figure out exactly how it works. Can we predict who's going to respond and who won't respond? How do we identify the best combinations to use, to try to raise the efficacy?" In addition, "The concentration of translational research was on moving the median survival a few months to the right [of the curve]…What ipilimumab showed is that you can do that, but you can also get a tail on the curve where you get durable survivals that last for years and decades even of those patients."

"Our goal now in this field is really to raise that tail—not to move the median, but to raise the tail of the response—to as high as we can get it in as many cancer types as we can get it," said Dr. Allison in his closing remarks. "And I'm really optimistic that we can do that pretty soon, with continuing support for the basic science from the [National Cancer Institute, National Institutes of Health], as well as from the National Foundation for Cancer Research. But also for support of the more translational aspects of this that you don't get from the [National Cancer Institute]—they don't provide [this support]; you can get [it] only from organizations like the National Foundation for Cancer Research—that enable us to make that jump from basic demonstration that CTLA-4 is an important regulatory molecule to letting us show that it works in preclinical and clinical models."

The 2014 Szent-Györgyi Prize Selection Committee was chaired by Alex Matter, MD, and co-chaired by Sujuan Ba, PhD. Other selection committee members included leaders in cancer research and drug development from academic institutes and biotech and pharmaceutical industries: Steven D. Averbuch, MD, Bristol-Myers Squibb Company; Webster K. Cavenee, PhD, Ludwig Institute for Cancer Research; Zhu Chen, MD, PhD, Shanghai Jiao Tong University; Sara Courtneidge, PhD, Sanford-Burnham Medical Research Institute; Carlo M. Croce, MD, The Ohio State University; Stan Kaye, MD, Royal Marsden NHS Foundation Trust; Marsha A. Moses, PhD, Boston Children's Hospital; Richard O'Reilly, MD, Memorial Sloan Kettering Cancer Center; Scott D. Patterson, PhD, Amgen, Inc.; Peter K. Vogt, PhD, The Scripps Research Institute; and Yi Michael Wang, MD, PhD, General Secretary of NFCR.

Previous Recipients of the Szent-Györgyi Prize for Progress in Cancer Research

2013 - Alex Matter, MD Chief Executive Officer, Experimental Therapeutics Centre, Agency for Science, Technology and Research (A*STAR), Singapore.

2012 - Zhu Chen, MD, PhD Professor, School of Medicine of the Shanghai Jiao Tong University; Chairman, Chinese Medical Association; former Minister of Health of China, Shanghai, P. R. China.

2012 - Zhen-Yi Wang, MD Professor, School of Medicine of Shanghai Jiao Tong University; Honorary Director, Shanghai Institute of Hematology, Shanghai, P. R. China.

2011 - Beatrice Mintz, PhD Professor and Jack Schultz Chair in Basic Science, Fox Chase Cancer Center, Philadelphia, Pennsylvania, US.

2010 - Peter K. Vogt, PhD Professor, Department of Molecular and Experimental Medicine, The Scripps Research Institute, La Jolla, California, US.

2009 - Ronald A. DePinho, MD President, MD Anderson Cancer Center, Houston, Texas, US.

2008 - Carlo M. Croce, MD Director, Human Cancer Genetics Program; Director, Institute of Genetics, The Ohio State University, Columbus, Ohio, US.

2007 - Webster K. Cavenee, PhD Director, Ludwig Institute for Cancer Research, San Diego Branch; Distinguished Professor, University of California, San Diego, California, US.

2006 - Harold F. Dvorak, MD Mallinckrodt Professor Emeritus of Pathology, Harvard Medical School; Chief, Department of Pathology, Beth Israel Deaconess Medical Center, Boston, Massachusetts, US.

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