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WARREN ALPERT FOUNDATION HONORS FIVE PIONEERS IN CYSTIC FIBROSIS

-Scientists recognized for identifying faulty gene behind devastating disease, development of precision-targeted therapies

The 2018 Warren Alpert Foundation Prize has been awarded to five scientists for transformative discoveries in the fields of genetics, physiology, pulmonology and pharmacology that have led to the development of life-altering precision-targeted treatments for the devastating multiorgan disease cystic fibrosis (CF).

The Warren Alpert Foundation, in association with Harvard Medical School, honors trailblazing scientists whose work has improved the understanding, prevention, treatment or cure of human disease.

This year's five honorees will be recognized at a symposium on Oct. 4 at Harvard Medical School.

CF affects some 75,000 people in the United States, Canada, Europe and Australia. Life expectancy has improved steadily over the past several decades. The median age of survival in the United States and other developed countries is now estimated to be in the early 40s, compared with a mere few months for children born with CF in the 1950s.

Thanks to the discoveries made by the five award recipients, this upward trend is likely to continue, with the advent of new therapies that repair the underlying disease-fueling protein malfunction and, in doing so, stave off organ damage and boost survival.

The 2018 Warren Alpert Foundation Prize recipients are:

- Francis Collins, Director, National Institutes of Health
- Paul Negulescu, Senior Vice President for Research, Vertex Pharmaceuticals
- Bonnie Ramsey, Vice Chair and Endowed Professor of Pediatrics, University of Washington School of Medicine; Director, Center for Clinical and Translational Research, Seattle Children's Research Institute
- Lap-Chee Tsui, Founding President, The Academy of Sciences of Hong Kong; University Professor Emeritus, University of Toronto
- Michael Welsh, Professor of Internal Medicine—Pulmonary, Critical Care and Occupational Medicine, University of Iowa

"Over the years, the Warren Alpert Foundation has honored some of the most elegant and transformative scientific achievements of our time, and the work of this year's recipients is the very embodiment of the spirit of the award," said George Q. Daley, dean of Harvard Medical School. "More importantly, the five scientists' collective work powerfully illustrates the promise of basic discoveries made in the lab to profoundly alter the lives of patients through collaboration among fundamental researchers, biochemists and frontline clinicians."

The Warren Alpert Foundation Prize is given internationally. To date, the foundation has awarded more than $4 million to 64 scientists. Since the award's inception in 1987, eight honorees have also received a Nobel Prize.

Negulescu, Ramsey, Tsui and Welsh will share $500,000 in prize money. Collins will decline the cash component of the award.

"The work of the five scientists we are honoring is a triumph of modern medicine," Joseph Martin, director and chairman of the board of the Warren Alpert Foundation and former dean of Harvard Medical School. "We are humbled by the passion, dedication and acumen of a truly remarkable group of individuals whose achievements have touched the lives of patients and families across the world."

A protein-to-person story

The elucidation of the genetic defect behind the disease, defining the molecular mechanisms that fuel CF development and the design of precision-targeted therapies are the collective work of multiple scientists over several decades. However, the five award recipients made the key discoveries that propelled this quest forward.

The hallmark of CF is a genetic mutation that impairs cells' ability to transport chloride, leading to the buildup of sticky mucus in the lungs and other organs and causing a constellation of symptoms, most notably recurrent lung infections and progressive scarring and loss of lung function, as well as a range of pancreatic, liver and other gastrointestinal problems.

Until 2012, treatment for CF remained purely symptomatic, focused on mitigating the effects of the disease.

In 2012, however, following decades of painstaking work in genetics, physiology and biochemistry, the FDA approved the first treatment that restores the cells' ability to transport chloride. That achievement was the cumulative result of work done by the five award recipients and their teams. Two dual-drug combination treatments followed, and triple-combination therapies are currently in development as a result of these initial discoveries.

The pivotal CF discoveries honored this year include:

- Identification of the gene responsible for CF and its cardinal sign—cells' inability to ferry chloride in and out.
- Discovery of how mutations in the CFTR gene and its product—CFTR protein—precipitate disease development, its key symptoms and related downstream complications.
- Development of precision-targeted small-molecule treatments that correct the activity of the mutated protein.
- The design, oversight and execution of clinical trials that led to the FDA approval of the first two precision-targeted treatments of CF.

The foundational work was conducted by Lap-Chee Tsui and Francis Collins and their teams, whose research led to the discovery of the cystic fibrosis gene, elucidated its molecular structure and function and pinpointed its location. In doing so, they provided an entry point to understanding the basic defect that fuels a complex disease affecting multiple organs and organ systems.

Michael Welsh led the team that made key discoveries toward elucidating the role of the product of this gene, the CFTR protein, as the chemical transporter that allows chloride to move in and out of cells, showing how mutations in the gene and its product cause cells to malfunction and fuel disease development. These insights provided the rationale for the subsequent quest toward targeted therapies to repair the function of the aberrant protein.

Building on these key discoveries, a team of scientists at Vertex, led by Paul Negulescu, initiated research in 1998 to identify compounds that modulate the

function of the CFTR protein. This work led to the discovery and development of the only CF medications available today that correct the underlying protein defect responsible for disease symptoms and restore cells' ability to transport chloride. These medicines have ushered in a new era of CF treatment, which continues to advance with more compounds in development.

Pediatric pulmonologist Bonnie Ramsey was the architect of the clinical trial network and seminal studies that led to the approval of the first, and subsequent, small-molecule treatments in current use and played a critical role in ensuring the translation of these therapies from lab to clinic.

Additionally, the Cystic Fibrosis Foundation, a research and advocacy group, provided catalytic support in the early-stage research that eventually led to the development of today's small-molecule therapies. In doing so, the foundation played a decidedly transformative role and propelled forward the work we honor today, according to members of the Warren Alpert committee.

"The successes we celebrate today are an instructive lesson in the power of collaboration—among basic scientists, translational researchers and frontline clinicians," Daley said. "Just as importantly, these achievements remind us how much we can do when academicians, industry scientists and nonprofit partners come together, sharing their acumen, talent and passion on a common mission to alleviate human suffering caused by disease."

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Discovery Highlights

In 1985, Lap-Chee Tsui and his team narrowed down the likely location of the CFTR gene to chromosome 7. In 1989, Tsui teamed up with Francis Collins and his collaborators to publish a seminal trio of papers that pinpointed the exact location of the CFTR gene on chromosome 7 and defined the precise array of genetic mutations that cause the cells' chloride-transporting protein to malfunction.

In the 1980s, Michael Welsh made the initial observations that cells lining the organs of patients with CF profoundly lack the ability to transport chloride. In 1990, Welsh and colleagues demonstrated that correcting the CFTR protein could restore defective chloride transport in cells—a proof-of-principle demonstration that linked the mutation of the CFTR gene to actual protein malfunction and then to the hallmark failure in cell physiology that fuels the disease and its symptoms. These pivotal findings set the stage for subsequent drug development.

The treatment of CF improved steadily over the past several decades, but well into the 2000s it remained focused on managing the symptoms and consequences of the disease. Such supportive care included preventing malnutrition stemming from digestive malabsorption, treatment and prevention of lung infections, administering insulin for CF-related diabetes and lung transplantation as an option of last resort to treat the most severe complication of the disease. Despite prolonging survival and improving quality of life, these approaches fell short of the ultimate goal—to remedy the underlying defect of the disease.

Even though CF is a genetic disease, these treatments are not genetic therapies. Instead, the drugs deliver small molecules inside cells to restore protein function and correct the cellular dysfunction fueled by the genetic defect and thus ensure that cells are capable of transporting chloride properly.

Paul Negulescu spearheaded a nearly 20-year CF research project at Vertex Pharmaceuticals that has resulted in the approval of three treatments that address the defect responsible for CF, including ivacaftor—the compound that eventually became the first CFTR modulator and gained FDA approval in 2012.

In clinical trials, ivacaftor not only restored CFTR function but—contrary to expectations—also markedly improved lung function even among people with already compromised pulmonary capacity. Although the medication redefined disease treatment, it was initially approved only for people with a rare CF mutation that accounts for fewer than 5 percent of all patients with the disease.

In 2017, the FDA expanded approval of ivacaftor for the treatment of additional mutations. The move was unprecedented because the decision was based not on clinical trials—impractical given the small number of patients with these rare mutations—but on lab studies that demonstrated improved chloride function in cell lines engineered to carry such mutations. The compound is currently approved in the United States for the treatment of 38 types of CF mutations in patients 2 years and older. This FDA decision, experts say, may transform testing and approval protocols for other rare genetic diseases, for which clinical trials are not feasible.

Pediatric pulmonologist Bonnie Ramsey, who graduated from Harvard Medical School, was pivotal in the translation of these compounds for clinical use. She, alongside scientists at Vertex, oversaw the conceptualization, design and oversight of the clinical trials that enabled their development and approval. As a clinician with rich and deep expertise in clinical trial design and drug development, Ramsey became the architect of the Cystic Fibrosis Foundation's Therapeutics Development Network, which has made possible nearly every new CF therapy developed since 1998. The CF Foundation was also a critical funder of the early-stage research into the compounds that would eventually become

of the first defect-correcting treatments. Ramsey was the principal investigator overseeing the definitive last step of the trial that led to the development and approval of ivacaftor, the first drug to repair the underlying defect in CF.

Negulescu's team also oversaw the discovery and development of the first dual-compound treatments for CF in people with the most common form of CF, found in half of all CF cases. This genetic mutation was particularly challenging to treat because it required therapies that restored the protein-folding and chloride-trafficking defects it caused. Two combination treatments—lumacaftor/ivacaftor and tezacaftor/ivacaftor—became the first such medications. They were approved in 2015 and in early 2018, respectively.

Despite these successes, about half of all CF patients have mutations that remain untreatable with either the single-drug or dual-compound therapy. To address this, Negulescu and colleagues identified and are currently developing next-generation triple- combination treatments for this group of patients. Although these next-gen therapies require further testing and remain experimental, they carry the promise to expand therapeutic benefits to 90 percent of all CF patients.

In their own words

"Shortly after the discovery of the CFTR gene, I wrote a song called "Dare to Dream." The lyrics expressed the hope that someday the gene discovery would lead to effective treatments for cystic fibrosis—that someday we would see "all our brothers and sisters breathing free." It is intensely gratifying to see that dream now coming true. And it is a profound honor to have the chance to share in this Warren Alpert recognition with other heroes who have made it possible. That includes my friend Lap-Chee Tsui, whose team worked with Mitch Drumm, Mike Iannuzzi, and others in my group in an unprecedented international collaboration that effectively merged our labs. And it includes Drs. Welsh, Ramsey and Negulescu, who are truly inspiring leaders in the work that led to the current therapeutic advances. They all dared to dream."

-Francis Collins

"This award recognizes the remarkable path from the discovery of the CF gene to the development of therapies that treat the cause of CF. It has been a privilege for me to be part of this journey and I am honored to receive the Alpert Award with such accomplished scientists and physicians as Drs. Collins, Tsui, Welsh and Ramsey. I am also humbled and grateful to represent the amazing team that discovered and brought these medicines to patients. This award is meaningful for all of us because it acknowledges that our work over the past 20 years has had a positive impact on people with CF and their families."

-**Paul Negulescu**

"*I was shocked and humbled that I would be considered for this prestigious award with four outstanding scientists, Francis Collins, Lap-Chee Tsui, Michael Welsh and Paul Negulescu. The Alpert Award is very meaningful to me, especially as an alumna of Harvard Medical School. Receiving the award recognizes the scientific and therapeutic revolution that has occurred over the past three decades in the field of cystic fibrosis. The award also acknowledges the importance of team science spanning from basic to clinical investigation that is required to translate our understanding of molecular biology into life-changing new therapies. I am honored to receive this award."*

-Bonnie Ramsey

"I am very much humbled by all the great scientists before us. Although our initial mapping of the CF gene to chromosome 7, followed by the gene identification work, was the first step in defining the basic defect of CF, difficult as it was, I am happy that the award also recognizes those people who have spent their lives improving the health of patients with this devastating disease, studying its pathophysiology and devising effective treatments. I would be remiss if I did not mention also the contributions of Jack Riordan, Johanna Rommens and Batsheva Kerem and the rest of my Toronto team in the CF gene cloning effort."

-Lap-Chee Tsui

"*I am deeply honored to be recognized with Lap-Chee Tsui, Francis Collins, Bonnie Ramsey, and Paul Negulescu. In accepting this award, I acknowledge so many other people who contributed: talented students and trainees, my tireless and innovative assistants, my cherished colleagues and my collaborator, Alan Smith and his team at Genzyme. I thank the University of Iowa, the Howard Hughes Medical Institute, the National Institutes of Health, and the Cystic Fibrosis Foundation for their support. Most of all, I thank my family, whose love and support made everything possible."*

-Michael Welsh

Past winners

The 2017 award went to five scientists for their work toward elucidating foundational mechanisms in cancer's ability to evade immune recognition. Collectively, their discoveries profoundly altered modern-day understanding of the disease and precipitated the development of a class of immune therapies for a range of cancers.

Other past recipients of the Warren Alpert award include:

- Radolphe Barrangou, Philippe Horvath, Jennifer Doudna, Emmanuelle Charpentier and Virginijus Siksnys for CRISPR-related discoveries.
- Tu Youyou of the China Academy of Chinese Medical Science, who went on to receive the 2015 Nobel Prize in Physiology or Medicine with two others, and Ruth and Victor Nussenzweig, of NYU Langone Medical Center, for their pioneering discoveries in chemistry and parasitology of malaria and the translation of their work into the development of drug therapies and an anti-malarial vaccine.
- Oleh Hornykiewicz of the Medical University of Vienna and the University of Toronto; Roger Nicoll of the University of California, San Francisco; and Solomon Snyder of the Johns Hopkins University School of Medicine for research into neurotransmission and neurodegeneration.
- Alain Carpentier of Hôpital Européen Georges-Pompidou in Paris and Robert Langer of MIT for innovations in bioengineering.
- Harald zur Hausen and Lutz Gissmann of the German Cancer Research Center in Heidelberg for work on the human papillomavirus (HPV) and cancer of the cervix. Zur Hausen and others were later honored with the Nobel Prize in Physiology or Medicine in 2008.

The Warren Alpert Foundation

*Each year the **Warren Alpert Foundation** receives between 30 and 50 nominations from scientific leaders worldwide. Prize recipients are selected by the foundation's scientific advisory board, which is composed of distinguished biomedical scientists and chaired by the dean of Harvard Medical School. Warren Alpert (1920-2007), a native of Chelsea, Mass., established the prize in 1987 after reading about the development of a vaccine for hepatitis B. The inaugural recipient of the award was Kenneth Murray of the University of Edinburgh, who designed the hepatitis B vaccine. To award subsequent prizes, Alpert asked Daniel Tosteson (1925-2009), then dean of Harvard Medical School, to convene a panel of experts to identify scientists from around the world whose research had a direct impact on the treatment of disease.*

Harvard Medical School

Harvard Medical School (http://hms.harvard.edu) has more than 11,000 faculty working in 10 academic departments located at the School's Boston campus or in hospital-based clinical departments at 15 Harvard-affiliated teaching hospitals and research institutes: Beth Israel Deaconess Medical Center, Boston Children's Hospital, Brigham and Women's Hospital, Cambridge Health Alliance, Dana-Farber Cancer Institute, Harvard Pilgrim Health Care Institute, Hebrew SeniorLife, Joslin Diabetes Center, Judge Baker Children's Center, Massachusetts Eye and Ear/ Schepens Eye Research Institute, Massachusetts General Hospital, McLean Hospital, Mount Auburn Hospital, Spaulding Rehabilitation Network and VA Boston Healthcare System.

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