



FROM: The Albert and Mary Lasker Foundation
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2014 LASKER AWARDS HONOR SCIENTISTS WHO ADDRESSED KEY QUESTIONS IN BIOLOGY AND MEDICINE

Kazutoshi Mori and Peter Walter for discoveries concerning the unfolded protein response—an intracellular quality-control system that detects harmful misfolded proteins in the endoplasmic reticulum and signals the nucleus to carry out corrective measures.

Alim Louis Benabid and Mahlon R. DeLong for the development of deep brain stimulation of the subthalamic nucleus, a surgical technique that reduces tremors and restores motor function in patients with advanced Parkinson's disease.

Mary-Claire King for bold, imaginative, and diverse contributions to medical science and human rights—she discovered the BRCA1 gene locus that causes hereditary breast cancer and deployed DNA strategies that reunite missing persons or their remains with their families.

New York, September 8, 2014—The Albert and Mary Lasker Foundation today announced the winners of the 2014 Lasker Awards: Kazutoshi Mori and Peter Walter for basic medical research; Alim Louis Benabid and Mahlon R. DeLong for clinical research; and Mary-Claire King for special achievement.

“For nearly 70 years the Lasker Awards have honored extraordinary individuals who have made fundamental biological discoveries, developed therapies to dramatically improve patient care, and provided mentorship and leadership to pave the way for the next generation of scientists,” said Claire Pomeroy, President of the Lasker Foundation. “This year’s laureates join that tradition and illustrate to the public why science is so worthy of our support.”

Walter (University of California, San Francisco) and Mori (Kyoto University, Japan) will receive the 2014 Albert Lasker Basic Medical Research Award for discoveries that elucidate a key quality-control system in the cell, the unfolded protein response. DeLong (Emory University School of Medicine, Atlanta) and Benabid (Joseph Fourier University, Grenoble, France) will receive the 2014 Lasker-DeBakey Clinical Medical Research Award for developing a surgical technique that reduces tremors and restores motor function in patients who have advanced Parkinson’s disease. Mary-Claire King (University of

Washington, Seattle) will receive the 2014 Lasker~Koshland Special Achievement Award for her contributions to medical science and human rights.

Joseph L. Goldstein, Chair of the Lasker Medical Research Awards Jury, observed that the award-winning research was spurred by scientists who anticipated key questions. “This year’s Lasker winners have the uncanny ability to spot the next big thing in their field,” he said. “Walter and Mori zeroed in on the molecular machinery that senses excessive unfolded proteins, and they exposed the process by which cells correct that problem; DeLong pinpointed a region of the brain that plays a central role in Parkinson’s disease, and Benabid applied a novel technique to that region and alleviated symptoms; and King demonstrated that certain women with early-onset breast cancer owe their disease to a harmful version of a particular gene, *BRCA1*.”

Kazutoshi Mori and Peter Walter for Discoveries Concerning the Unfolded Protein Response

The 2014 Albert Lasker Basic Medical Research Award honors Peter Walter, 59, and Kazutoshi Mori, 56, for research that illuminated the unfolded protein response, a biological quality-control system by which cells detect the presence of excess unfolded proteins and then alleviate the problem.

Proper protein folding has long been recognized as a process that is essential to all organisms. In the 1950s, Frederick Sanger demonstrated that every cellular protein has a unique amino acid sequence. Later research established that as a protein is formed, it folds into a precise structure based upon the bonding capabilities of its amino acid building blocks and the interactions among them. A properly folded protein assumes a specific three-dimensional shape that can perform particular tasks. An unfolded protein is a jumble of amino acids, which can be harmful to the cell.

Proteins that are destined for the cell’s surface or export to the surrounding environment fold in an organelle called the endoplasmic reticulum (ER). Walter and Mori began their award-winning work in the late 1980s and early 1990s, after scientists had begun to explore how cells recognize a dangerous accumulation of unfolded proteins in the ER and reverse the problem. Intrigued by the phenomenon, Mori and Walter independently embarked upon research to discover the complex choreography through which cells send a signal to the nucleus that activates transcription of genes whose products help correct the situation.

Mori and Walter’s work has led to a better understanding of inherited diseases such as cystic fibrosis, retinitis pigmentosa, and certain elevated cholesterol conditions in which unfolded proteins overwhelm the unfolded protein response. So important is protein folding to biology that a previous Lasker Award (Basic, 2011) recognized Ulrich Hartl and Arthur Horwich for their discovery of a molecular chaperone that helps proteins fold in the cellular cytoplasm. This year’s award is given for showing how problems with a different class of proteins—membrane-bound and secretory—are dealt with. Together, the awards demonstrate the elegant and complex mechanisms that cells have evolved to cope with proteins that do not fold correctly.

Alim Louis Benabid and Mahlon R. DeLong for Development of Deep Brain Stimulation of the Subthalamic Nucleus

The 2014 Lasker-DeBakey Clinical Medical Research Award honors Mahlon R. DeLong, 76, and Alim Louis Benabid, 72, for the development of high-frequency deep brain stimulation of the subthalamic nucleus, a surgical technique that provides relief from the tremors and other motor problems that afflict individuals with advanced Parkinson's disease.

Parkinson's disease is the second most frequently diagnosed neurodegenerative disorder after Alzheimer's disease. The tremors of Parkinson's are caused by the loss of dopamine-producing cells in the brain's basal ganglia region. For decades, the only viable treatment was the oral administration of L-dopa, which is converted into dopamine by metabolic processes in the brain (the Lasker Foundation recognized George Cotzias in 1969 for his development of effective L-dopa treatment). However, people can develop troubling side effects after prolonged use of L-dopa.

In 1990, Mahlon DeLong reported a crucial experiment that showed, in an animal model of Parkinson's disease, that creating a lesion in a region of the basal ganglia called the subthalamic nucleus could improve the animal's motor symptoms. This experiment provided the key for Alim Louis Benabid, who in the late 1980s had developed an approach to treating patients with essential tremor. Benabid had discovered that applying high-frequency electrical stimulation to a patient's thalamus could diminish tremors. When he read about DeLong's work, Benabid decided to target the subthalamic nucleus with high-frequency stimulation in Parkinson's disease patients. In 2002, the FDA approved this method as a treatment for advanced Parkinson's.

The work of DeLong and Benabid has enhanced the lives of more than 100,000 patients worldwide who have undergone the procedure, and it has spurred further investigations into the use of electrical stimulation that is already helping others with neurological and psychiatric diseases.

Mary-Claire King for Contributions to Medical Science and Human Rights

The 2014 Lasker-Koshland Special Achievement Award in Medical Science honors Mary-Claire King, 68, for contributions to medical research and human rights.

King's demonstration of the existence of familial susceptibility to breast cancer and her discovery of the *BRCA1* gene locus took place in the era before high-speed sequencing technology and at a time when few scientists believed that susceptibility to a complex disease such as breast cancer could be linked to a single mutated gene.

King began her search for the putative gene in 1974. The hunt took her through meticulous analysis and mathematical modeling of more than 1500 families of women with breast cancer, from which she concluded that a single gene was indeed responsible for breast cancers in some families. She then analyzed the DNA of 329 participating relatives with 146 cases of invasive breast cancer. In 1990, King reported that a section of chromosome 17 was responsible for early-onset breast and/or ovarian cancer in some of the families she

analyzed. She named the gene locus *BRCA1*. King's approach has since become a model for the identification of genes that cause complex diseases.

King also developed DNA-based analysis to help families prove genetic relationships and find the "lost children" of Argentina who had been kidnapped as infants or born while their mothers were in prison during the military regime of the late 1970s and early 1980s. This and related approaches have been used to identify soldiers who went missing in action, including the remains of an American serviceman who was buried beneath the Tomb of the Unknowns in Arlington National Cemetery, as well as victims of natural disasters and man-made tragedies such as the 9/11 attacks, providing solace to untold people throughout the world.

Additional Information

About the Foundation: Founded in 1942, the Albert and Mary Lasker Foundation envisions a healthier world through medical research. It seeks to improve health by accelerating support for medical research through recognition of research excellence, public education, and advocacy. For much of the 20th Century, the Foundation was led by Mary Lasker, who was America's most prominent citizen-activist for public investment in medical research. She is widely credited with motivating the White House and Congress to greatly expand federal funding for medical research, particularly through the National Institutes of Health.

About the Awards: The Lasker Awards recognize the contributions of scientists, clinicians, and public servants who have made major advances in the understanding, diagnosis, treatment, cure, or prevention of human disease. Recipients of the Lasker Medical Research Awards are selected by a distinguished international jury chaired by Joseph L. Goldstein, recipient of the 1985 Lasker Award for Basic Medical Research and the Nobel Prize in Physiology or Medicine. Eighty-six Lasker laureates have received the Nobel Prize, including 47 in the last three decades. More details on the Lasker Award recipients, the full citations for each award category, video interviews and photos of the awardees, and additional information on the foundation are available at www.laskerfoundation.org.

Awards Presentation: The Lasker Awards, which carry an honorarium of \$250,000 for each category, will be presented on Friday, September 19, in New York City.