



# 2008 LASKER AWARDS for MEDICAL RESEARCH

**Key Words:**

Lasker Awards – Lasker Foundation – small RNA – microRNA – gene silencing – statins – cholesterol – bacteria – microbes – microbiology – pathogenesis – infectious disease – Ambros – Ruvkun – Baulcombe – Endo – Falkow

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## **DISCOVERERS OF SMALL REGULATORY RNAS AND CHOLESTEROL-LOWERING DRUGS TO RECEIVE LASKER AWARDS FOR MEDICAL RESEARCH**

***PIONEER IN UNDERSTANDING HARMFUL BACTERIA***

***HONORED WITH SPECIAL ACHIEVEMENT AWARD***

*NEW YORK, Saturday, September 13, 2008* – The **2008 Albert Lasker Medical Research Awards** were announced today. First presented in 1946, the Lasker Awards are the nation's most distinguished honor for outstanding basic and clinical medical research discoveries and for lifetime contributions to medical science.

The **Lasker Award for Basic Medical Research** honors **Victor R. Ambros**, 54, of the University of Massachusetts Medical School, Worcester, **David C. Baulcombe**, 56, of the University of Cambridge, and **Gary B. Ruvkun**, 56, of Massachusetts General Hospital, Boston and Harvard University, who **discovered tiny RNAs that regulate gene function**. These RNAs, some of which are known as microRNAs, govern a multitude of activities in animals and plants, and they have been implicated in a wide range of diseases.

The **Lasker-DeBakey Award for Clinical Medical Research** honors **Akira Endo**, 74, of Biopharm Research Laboratories, Inc., Tokyo, who **discovered the first statin**. Statins significantly lower LDL-cholesterol quantities in the blood, thus dramatically reducing the risk of coronary heart disease, a leading cause of death worldwide and the number one killer in the U.S. Statins are now the most widely prescribed medications in the United States, and benefit an estimated 30 million people worldwide.

The **Lasker-Koshland Award for Special Achievement in Medical Science**, awarded biennially, honors **Stanley Falkow**, 74, of the Stanford University School of Medicine, for his **many contributions to our knowledge of disease-causing microbes**. Falkow's discoveries have shed light on how bacteria transmit antibiotic resistance and other traits to one another and revealed the means by which they infect animal hosts and elicit illness. He pioneered the field of molecular pathogenesis of infectious disease and trained an impressive number of leading investigators in this discipline.



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The Awards will be presented at a luncheon ceremony on **Friday, September 26<sup>th</sup>** at the Pierre Hotel in New York City. The Honorable **Michael Bloomberg**, Mayor of the City of New York, will be the keynote speaker.

**Dr. Joseph L. Goldstein**, recipient of the 1985 Lasker Award for Basic Medical Research and the Nobel Prize in Medicine in 1985, chairs the 24-member international scientific jury that selects recipients of the Lasker Awards. He said that “the 2008 Lasker Awards honor investigators whose open-minded thinking and experimentation challenged conventional wisdom. Their work launched new fields of scientific research that have fostered significant advances in the medical arena.”

The discovery of small regulatory ribonucleic acids (RNAs) by Victor Ambros, David Baulcombe, and Gary Ruvkun broke open an entire new field. Until that time, proteins, not RNAs, were thought to govern gene activity in animal cells. “No one imagined that such tiny RNAs could perform useful tasks. In fact, the notion that small RNAs could control gene expression was unheard of,” Goldstein said. “Now, laboratories all over the world study hundreds of these RNAs.” The tiny molecules control a vast number of genes in plants as well as animals, and play roles in human health and disease, including cancer, viral infections, and congestive heart failure.

Until Akira Endo, treatment for high LDL-cholesterol levels—the bad cholesterol—left much to be desired, a situation that resulted in an unacceptably high incidence of coronary heart disease and premature death. Dietary interventions and the few available drugs worked poorly and the medications came with unwanted side effects. Many scientists also worried that reducing cholesterol might be dangerous because the molecule carries out essential jobs in the cell. “Endo believed in the potential benefits of cholesterol-lowering drugs and toiled day and night for two years to find a compound, the first statin, with that effect,” Goldstein said. “Statins have prolonged countless lives and revolutionized the prevention and treatment of coronary heart disease.” Today, millions of people worldwide take statins to lower their LDL-cholesterol levels safely and markedly reduce their risk of heart attacks.

Early in his career, Falkow discerned that bacteria pass antibiotic resistance among one another on circular pieces of DNA—a finding that paved the way toward recombinant DNA technology. He then pioneered that new method to probe the molecular mechanisms by which bacteria invade their hosts, elude the immune system, and trigger disease. “Stanley Falkow has spent the last five decades delving into the workings of disease-causing microbes,” Goldstein said. “A legend in his own time, Falkow is regarded as one of the greatest microbe hunters ever and has trained more than 100 students, many of whom are making their own extraordinary contributions to the field of bacterial pathogenesis.”

This year marks the first presentation of the newly renamed **Lasker-DeBaakey** and **Lasker-Koshland** Awards, honoring the late **Michael DeBaakey** and **Daniel Koshland, Jr.** “We are proud to link the Lasker name with the names of these outstanding scientists and humanitarians, who dedicated their lives to medical science and human health and were lifelong supporters of the Lasker Foundation and the Lasker Awards,” said **Dr. Maria C. Freire**, President of the Albert and Mary Lasker Foundation.



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The Lasker Awards are given by the Albert & Mary Lasker Foundation. Dr. Freire said that she and the Board of Directors are delighted at the recommendations of the Lasker Jury, and congratulates the winners of this year's Awards. "They follow the tradition of prior laureates in their innovative scientific and medical research for the betterment of people worldwide."

### **The Albert and Mary Lasker Foundation**

The Lasker Foundation fosters the prevention and treatment of disease and disabilities by honoring excellence in basic and clinical science, educating the public, and advocating for support of medical research. This year the Lasker Awards carry an honorarium of \$300,000 for each Award category. The laureates will receive a citation highlighting their achievements and an inscribed statuette of the Winged Victory of Samothrace, the Lasker Foundation's traditional symbol representing humanity's victory over disease, disability, and death.

Lasker Awards often presage future recognition by the Nobel committee, so they have become popularly known as "America's Nobels." Seventy-five Lasker laureates have received the Nobel Prize, including 27 in the last two decades.

The list of the 2008 Lasker Award recipients with their current professional and institutional affiliations follows. Additional materials will be posted on Saturday, September 13<sup>th</sup> at [www.laskerfoundation.org](http://www.laskerfoundation.org) and will include:

- The full citations for each Award category;
- Photos of the Awardees;
- Video of the Awardees;
- Information about past Awardees; and,
- Links to Web sites for additional information about the Awardees.



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**2008 Albert Lasker Award for Basic Medical Research**

*For discoveries that revealed an unanticipated world of tiny RNAs  
that regulate gene function in plants and animals*

**Victor R. Ambros, Ph.D.**  
Professor,  
Department of Molecular Medicine  
University of Massachusetts Medical School



**David C. Baulcombe, Ph.D.**  
Professor of Botany  
Department of Plant Sciences  
University of Cambridge



**Gary B. Ruvkun, Ph.D.**  
Professor of Genetics  
Department of Molecular Biology  
Harvard Medical School  
Massachusetts General Hospital





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**2008 Lasker~DeBakey Award for Clinical Medical Research Award**  
*For the discovery of the statins – drugs with remarkable LDL-cholesterol-lowering properties that have revolutionized the prevention and treatment of coronary heart disease*

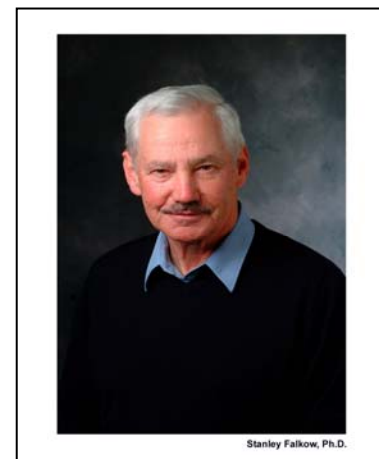
**Akira Endo, Ph.D.**  
Director  
Biopharm Research Laboratories  
Tokyo, Japan



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**Lasker~Koshland Award for Special Achievement in Medical Science**  
*For a 51-year career as one of the great microbe hunters of all time – he discovered the molecular nature of antibiotic resistance, revolutionized the way we think about how pathogens cause disease, and mentored more than 100 students, many of whom are now distinguished leaders in the fields of microbiology and infectious diseases*

**Stanley Falkow, Ph.D.**  
Robert W. and Vivian K. Cahill Professor of  
Microbiology and Immunology  
and of Medicine  
Department of Microbiology and Immunology  
Stanford University School of Medicine





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**2008 Lasker Award for Basic Medical Research**

Presented to  
**Victor R. Ambros**  
**David C. Baulcombe**  
**Gary B. Ruvkun**

*For discoveries that revealed an unanticipated world of tiny RNAs  
that regulate gene function in plants and animals*

The 2008 Albert Lasker Award for Basic Medical Research honors three scientists who discovered an unanticipated world of tiny RNAs that regulate gene activity in plants and animals. **Victor R. Ambros** (University of Massachusetts Medical School, Worcester) and **Gary B. Ruvkun** (Massachusetts General Hospital, Boston) unearthed the first example of this type of molecule in animals and demonstrated how they turn off genes whose activities are crucial for development. **David C. Baulcombe** (University of Cambridge) established that small RNAs silence genes in plants as well, thus catalyzing discoveries of many such RNAs in a wide range of living things. His findings led to the identification of the biochemical machinery that unifies numerous processes by which small RNAs govern gene activity.

Ambros, Baulcombe, and Ruvkun did not set out to unveil small regulatory RNAs. Ambros and Ruvkun were studying how the worm *Caenorhabditis elegans* develops from a newly hatched larvae into an adult. Baulcombe, in a seemingly unrelated line of inquiry, was probing how plants defend themselves against viruses. All three investigators possessed the open mindedness, wisdom, and experimental finesse to entertain the possibility—and then verify—that tiny RNAs could perform momentous feats. Their work has led to the realization that these molecules are pivotal regulators of normal physiology as well as disease.

**RNA—the little molecule that could**

In the early 1980s, Ambros joined the laboratory of Robert Horvitz at the Massachusetts Institute of Technology as a postdoctoral fellow. He wanted to outline the means by which genes choreograph the construction of fully formed adults from single cells. Analyses of flies had revealed that certain genes instruct embryos where to place body parts—for example, wings belong on each side and legs belong on the bottom. But Ambros was intrigued by the notion that other genes might specify the timing—rather than the location—of developmental events; alterations in such genes might cause cells and tissues to adopt fates that are normally associated with earlier or later stages of development.

He directed his attention toward one of the first-known genes of this type, called *lin-4*, which Sydney Brenner (Lasker Special Achievement Award, 2000) and colleagues discovered years earlier. During worms' trek toward adulthood, those with inactive *lin-4* get stuck repeating early larval stages. Consequently, they lack cell types and structures typical of fully formed animals and instead contain extra copies of cells ordinarily produced only at early stages. These observations suggested that normal *lin-4* allows immature worms to advance past a particular developmental stage; animals with the defective version can't overcome that hurdle. Ambros discovered that worms lacking a different gene—*lin-14*—were the antithesis of those with inactive *lin-4*. The animals skip early steps in development and



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prematurely acquire characteristics that normally appear later. These and other results suggested that *lin-4* and *lin-14* exert opposite effects in worm cells.

To dig further into *lin-14*'s function and its possible relationship with *lin-4*, Ambros—with Ruvkun, who by this time (1982) had joined Horvitz's laboratory as a postdoctoral fellow— isolated the *lin-14* gene. After the investigators set up independent laboratories in the mid 1980s, Ruvkun, at Massachusetts General Hospital in Boston, established that the protein product of *lin-14* is abundant during early larval stages and then its quantities plummet. Under conditions in which it unnaturally remains plentiful, early steps repeat, suggesting that the normal drop in the *lin-14* protein allows worms to proceed to later stages. Ambros, at Harvard University, found that *lin-4* dampens *lin-14* activity and thus a picture emerged about how the genes collaborate. At the appropriate time, *lin-4* blocks *lin-14* activity and thus allows worms to continue their developmental trajectory.

Ruvkun sought to identify the portion(s) of *lin-14* that *lin-4* targets, so he tracked down certain genetic anomalies in *lin-14*'s sequence that underlie excess production of the *lin-14* protein. He found that these alterations reside in the area of the gene that follows the protein blueprint, a span called the 3' untranslated region (3'UTR). The perturbations do not influence amounts of the protein's messenger RNA (mRNA), the molecule that carries genetic information from DNA to the cell's protein-making factory, Ruvkun showed. Rather, they alter protein quantities. Therefore, molecules that turn off *lin-14* after early stages of development presumably exert their effects through the 3' UTR region of the *lin-14* mRNA and prevent the cell from translating its code into protein.

In the meantime, Ambros's laboratory was isolating the *lin-4* gene, which they assumed encoded a protein; although a few RNAs were known to control gene activity in bacteria, conventional wisdom held that, in animal cells, proteins alone enjoy such powers. The team homed in on smaller and smaller pieces of DNA from normal animals that restore typical developmental behavior to a worm that lacks *lin-4*. Stretches of DNA worked that were far shorter than standard genes. Eventually, the researchers began considering the possibility that its product was an RNA, but they still assumed that the regulatory molecule they sought would be a respectable size. The smallest RNAs known to do anything important in cells contained about 75 nucleotide (nt) building blocks. Eventually, however, their experiments led them to a tiny RNA, composed of about 22 nucleotides. A somewhat larger—61 nt—molecule that contained the smaller one appeared as well and Ambros noticed that it could fold into a double-stranded "hairpin"—a structure whose significance would become clear years later.

In an exciting exchange of data, Ambros and Ruvkun realized that the 22-nt *lin-4* RNA matched sections within the 3'UTR of the *lin-14* mRNA: These sequences could bind one another by the same base-pairing rules that hold together the Watson and Crick DNA strands. In this view, the tiny *lin-4* RNA settles on the target *lin-14* mRNA—in its 3'UTR—and the resulting double-stranded structure somehow interferes with translation of the *lin-14* mRNA's genetic information into protein.

Despite verification that *lin-4* was a tiny RNA with huge regulatory powers, these 1993 findings constituted a mere blip on most biologists' radar screens: *lin-4* resided only in worms, so the phenomenon seemed like an oddity that most organisms did not exploit. Worms were exotic in many ways, experts reasoned, and the observation only fueled that attitude.



### Branching out to plants and beyond

Across the Atlantic, David Baulcombe, then of the Sainsbury Laboratory in Norwich, UK, was studying how plants resist viruses. When he and others added to viral-infected plants unusual versions of viral genes, the mRNA copies of the normal genes as well as the newly introduced ones disappeared. Similarly, experimentally added non-viral genes suppressed activity of plant genes that contained similar sequences. Baulcombe proposed that such gene silencing occurs when RNAs embrace target mRNA—through typical Watson-Crick base-pairing—and promote destruction of the mRNA or interfere with its translation into protein. However, no one could find such RNAs.

Baulcombe reasoned that the predicted RNAs might have eluded researchers because the molecules were shorter than anyone imagined and thus, experiments had not been designed to detect them. In 1999, he and a postdoctoral fellow in his laboratory, Andrew Hamilton, devised a hunt specifically for small RNAs. They added test genes to plants and found 25-nt long RNAs that matched them; furthermore, these small RNAs appeared only under conditions in which target mRNA activity was shut off. The stunning similarity in size between the plant and worm RNAs suggested that small regulatory RNAs existed in many organisms. Furthermore, it hinted at the presence of cellular machinery that dedicated itself to creating these precisely sized molecules and then used them to quash gene activity.

In 2000, Ruvkun's laboratory discovered a second tiny regulatory RNA in worms of exactly the same size as the *lin-4* RNA and in the same genetic pathway. Similar to the *lin-4* RNA, this *let-7* RNA dampens activity of its target gene through its 3' UTR. Furthermore, its sequence too resides within a larger molecule that folds up on itself to form a double-stranded hairpin structure. Later that year, Ruvkun found that many other creatures, including humans, fruit flies, chickens, frogs, zebrafish, mollusks and sea urchins, carried their own versions of *let-7*, which could also fold into hairpins. The apparent binding site for *let-7* RNA in its target was conserved in some of these organisms as well. Furthermore, *let-7* RNA appeared and disappeared at similar points during development in many of the animals.

The small RNAs, now called microRNAs (miRNAs), had broken through their designation as "worm curiosities." Researchers realized that the miRNAs likely execute vital functions during growth and development of other creatures as well. Multiple teams raced to expose regulatory RNAs of approximately 22 nucleotides in length. In 2001, Ambros's group, now at Dartmouth Medical School, in Hanover, as well as those of David Bartel (Massachusetts Institute of Technology) and Thomas Tuschl (Max Planck Institute for Biophysical Chemistry, Göttingen) discovered almost 100 of these small regulatory RNAs in flies, humans, and worms.

In addition to revealing that small regulatory RNAs dwell in organisms other than worms, Baulcombe's finding caught many researchers' attention because it seemed related to a process called RNA interference (RNAi), which had recently exploded onto the biological scene. In RNAi, long RNAs injected into cells hamper gene activity from similar sequences. No one knew why organisms possessed this ability, but presumably it played some role in normal physiology. In 1998, Andrew Fire (Carnegie Institution of Washington, Baltimore) and Craig Mello (University of Massachusetts Medical School, Worcester), published a watershed paper that defined the fundamental features of RNAi (which garnered them the Nobel Prize in 2006). That work yielded the surprising insight that the process depends on double-stranded RNA. However, the means by which double-stranded RNA triggered silencing remained mysterious.



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Experiments from Baulcombe's laboratory provided the crucial clues. Production of the silencing RNA strand depended on the presence of the other strand, he had noticed. This observation suggested that, at some point during manufacture of the small regulatory RNA, it exists as part of a double-stranded molecule. Suddenly it seemed possible that Baulcombe's tiny RNAs arose by trimming longer molecules of the type that Fire and Mello had discovered. Furthermore, this notion suggested that the hairpin-like *lin-4* and *let-7* RNAs similarly gave rise to the mature, 22-nt entities.

Scientists wondered whether the cell deployed the same biochemical machinery to create and use RNA molecules that subdued gene activity in all of these gene-silencing systems. However, the mechanisms of the worm miRNAs seemed to differ from those of the plant molecules as well as RNAi. Unlike the system that Ambros and Ruvkun had been untangling, which allowed mRNA to accumulate but thwarted cells' abilities to translate the information it contained into protein, the plant system and RNAi destroyed mRNA. For that reason and others, many people doubted that the processes were connected. Still the possibility that they shared a common mechanism and machinery tantalized researchers.

In 2001, the Mello, Ruvkun, and Fire groups collaborated to show that efficient liberation of the *lin-4* and *let-7* RNAs from the hairpin molecules relies on the *C. elegans* version of Dicer, an enzyme that Gregory Hannon (Cold Spring Harbor Laboratory) discovered and named for its ability to chop dsRNA into uniformly sized, small RNAs that direct mRNA destruction during RNAi. These results and others, including similar ones generated by Philip Zamore (University of Massachusetts Medical School, Worcester), cemented the connection between miRNAs and RNAi, thus providing one biological "reason" for the RNAi machinery. Moreover, they identified the apparatus by which cells generate miRNAs and harness them for key pursuits.

Studies in the past several years have indicated that the human genome contains more than 500 and perhaps as many as 1000 miRNAs that could collectively control a third of all of our protein-producing genes. These regulatory molecules have been implicated in a wide range of normal and pathological activities. They play roles not only in embryonic development, but in blood-cell specialization, cancer, muscle function, heart disease, viral infections, and possibly neurological signaling and stem-cell behavior. Researchers are exploring the possibility of using miRNAs "signatures" for diagnosis and prognosis and are considering manipulating their quantities for therapeutic purposes.

Looking where no one had looked before, Ambros, Baulcombe, and Ruvkun spied an unforeseen universe of potent molecules. Their work has elevated these hitherto unrecognized agents into the spotlight of biology and medicine.



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**2008 Lasker~DeBakey Clinical Medical Research Award**

Presented to

**Akira Endo**

*For the discovery of the statins – drugs with remarkable LDL-cholesterol-lowering properties that have revolutionized the prevention and treatment of coronary heart disease*

The 2008 Lasker~DeBakey Award for Clinical Medical Research honors a scientist who discovered statins—drugs with remarkable LDL-cholesterol-lowering properties that have revolutionized the prevention and treatment of coronary heart disease (CHD). **Akira Endo** (Biopharm Research Laboratories, Inc., Tokyo) sifted through thousands of organisms, hunting for natural substances that block a key enzyme in the biochemical pathway that produces cholesterol, a major contributor to CHD. Remarkably, the compound that Endo found lowers concentrations of LDL (the bad cholesterol) but not HDL (the good cholesterol) in the bloodstream of animals and humans. His work stimulated Merck, Sharp & Dohme Research Laboratories to launch a drug-development program that led to the first statin approved for medical use 20 years ago. This advance paved a path for other pharmaceutical companies to follow.

LDL in the bloodstream can form fatty deposits that narrow blood vessels. When this process occurs in arteries that deliver blood to the heart, it can lead to CHD, the major cause of chest pain and heart attack and the top killer in the industrialized world. In the US, more than 450,000 people died from CHD in 2004. In 2005, the American Heart Association estimated that 16 million Americans had CHD and 1.2 million would have a new or recurrent heart attack that year. Statin use is increasing—30 million people worldwide are taking them—and has begun to make a dent in those numbers. The drugs dramatically reduce the risk of CHD and its associated life-threatening events. Furthermore, studies with statins have erased long-standing doubt about the possibility of safely reducing cholesterol quantities with pharmaceutical agents.

**Promising Early Results**

In the 1950s and 1960s, epidemiological studies suggested a link between LDL cholesterol in the blood and CHD. Reducing LDL would shrink the incidence of this illness, some experts reasoned. However, many scientists and clinicians questioned whether doing so would stir trouble. Cholesterol is a crucial component of the membranes that encase our cells, and it serves as a raw material for other essential molecules, including some hormones and the sheath that insulates nerves. Further exacerbating uncertainty, most early agents that reduced cholesterol quantities in the blood cut concentrations only modestly and triggered unwelcome side effects. Therefore, skepticism simmered about the wisdom of lowering cholesterol concentrations.



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Despite the concerns, efforts pushed forward. Humans acquire cholesterol from food and we also make it in our bodies, mostly in the liver. Dietary interventions to limit cholesterol intake had met with poor success and the idea of short-circuiting our abilities to produce the compound seemed attractive. An enzyme called HMG-CoA reductase plays a central role in the manufacture of cholesterol. In the biochemical pathway that generates cholesterol, it converts a precursor molecule, HMG-CoA, into the next compound, mevalonate.

By 1971, when Endo began his work (at Sankyo Company in Tokyo), thwarting the reductase seemed like a possible way to keep the body's cholesterol production in check. Endo had a novel idea about how to find substances that block the reductase. Aware that organisms can secrete compounds with powerful biological activities—presumably to kill their competitors—Endo proposed that some creatures might spit out chemicals that foil the reductase and thus impede a vital activity of their neighbors.

Over the next two years, Endo and colleagues grew more than 6000 fungi, harvested the broth in which each had grown, and tested whether the material could interfere with an early step of cholesterol synthesis in a test tube. They then separated its components from one another, keeping track of the active material. By this and additional methods, he purified a substance from the fungus *Penicillium citrinum*, called mevastatin or compactin, that blocks the reductase.

Additional analysis revealed that compactin resembles HMG-CoA and competes strongly with it for the site on the enzyme that catalyzes HMG-CoA's conversion to mevalonate. This capacity to bind specifically to the spot normally reserved for the enzyme's substrate suggested that the potential drug would not randomly clasp molecules in cells and disrupt other important activities.

Endo wondered whether compactin would reduce enzyme activity in animals, as it does in test tubes. In 1979, he showed that the compound dramatically lowers blood cholesterol in dogs and monkeys with no obvious toxic effects.

While these results were coming in, Endo and physician Akira Yamamoto (National Cardiovascular Center in Osaka) gave compactin to patients with extremely high LDL-cholesterol levels. In 1980, they reported that it cut LDL in the blood by an average of 27%. The next year, Hiroshi Mabuchi of Kanazawa School of Medicine published similarly positive findings. Furthermore, he established that the compound did not perturb quantities of a molecule that is involved in the cell's energy-production system whose concentrations experts thought might drop when HMG-CoA activity was stymied. These observations fed hope that compactin could reduce cholesterol without causing harm.

At the same time, different researchers were demonstrating the mechanism by which the drug acted, which provided a rationale for how it could operate safely. In 1974, Michael Brown and Joseph Goldstein (Lasker Basic Medical Research Award and Nobel Prize, 1985) at the University of Texas Southwestern Medical School discovered that cell-surface molecules known as LDL receptors on liver cells grab LDL in the blood. In 1981, they showed that, when statins lower reductase activity and cholesterol production wanes, cells place additional LDL receptors on their surfaces. Statins thus harness a normal mechanism by which cells drain cholesterol from the blood, yet ensure a steady supply of the molecule internally for vital activities.



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### Statins in the Clinic

In 1978, Endo left Sankyo and joined the faculty of Tokyo Noko University. There, he isolated additional HMG-CoA reductase inhibitors, including one called monacolin K, from another fungus. Merck scientists, led by Alfred W. Alberts, independently identified—from a different organism—the same compound, which they called mevinoxin (and subsequently renamed lovastatin). The company had been pursuing statin-related research since soon after Endo published his first papers in 1976. At that time, P. Roy Vagelos, then President of Merck Research Laboratories, had signed an agreement with Sankyo and obtained samples of compactin from Endo, with which Merck confirmed Endo's results and launched its own program.

In April 1980, Merck began clinical studies of lovastatin. Several months later, rumors emerged from Sankyo that the drug caused tumors in dogs. Merck halted its studies. However, experts in the field urged the company forward. The dogs were receiving exceptionally high doses and Sankyo provided no data for others to assess. Investigators were witnessing dramatic benefits with compactin, particularly to individuals who have a genetic alteration in one of their two copies of the gene for the LDL receptor and thus carry colossal quantities of circulating cholesterol; these patients are extremely difficult to treat.

Several years later, Merck picked up its clinical trials on lovastatin. In 1987, the FDA approved the drug (Mevacor®).

The success of compactin and lovastatin inspired efforts to improve the statins by chemically modifying the natural compounds or crafting synthetic ones. Because the statins curb LDL so much more than any of the existing treatments, it became possible to demonstrate unequivocally that the drugs decrease CHD events without serious side effects. For example, in 1994, the Scandinavian Simvastatin Survival Study (4S study) showed that treatment with simvastatin (the second Merck statin) —for as short a period as five years—lowered LDL levels by 35%; this reduction was associated with a drop of 40% in CHD deaths. A 2005 analysis of more than 90,000 people in multiple 5-year randomized studies obtained similar results. Furthermore, this work established that people reap these benefits without an increase in cancer, other diseases, or deaths from any cause.

Statins are now routinely used to prevent and treat CHD throughout the world. Although CHD is aggravated by multiple risk factors in addition to high LDL—cigarette smoking, high blood pressure, obesity, and diabetes —reducing LDL levels alone makes a significant impact.

By discovering statins, Endo ushered in a new era in preventing and treating CHD, the leading cause of death in the US and a major source of human suffering. His work has touched millions of people and promises to prolong and improve the lives of many millions more.



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**2008 Lasker~Koshland Award  
for Special Achievement in Medical Science**

Presented to

**Stanley Falkow**

*For a 51-year career as one of the great microbe hunters of all time – he discovered the molecular nature of antibiotic resistance, revolutionized the way we think about how pathogens cause disease, and mentored more than 100 students, many of whom are now distinguished leaders in the fields of microbiology and infectious diseases*

The **2008 Lasker~Koshland Award for Special Achievement in Medical Science** honors one of the great microbe hunters of all time. In his 51-year career, **Stanley Falkow** (Stanford University) discovered the molecular nature of antibiotic resistance and revolutionized the way we think about how pathogens cause disease. He mentored more than 100 students, many of whom are now distinguished leaders in the fields of microbiology and infectious diseases. Falkow invented and exploited new techniques to study how bacteria pass traits to one another and pioneered the use of recombinant DNA technology and other molecular methods to untangle the details by which bacteria survive and spread. He made seminal breakthroughs in understanding causative agents of numerous maladies (including diarrhea, plague, ulcers, tuberculosis, typhoid fever, food poisoning, whooping cough, urinary tract infections, and sexually transmitted diseases) and influenced important advances in public health and in medical and agricultural practices.

**Passing resistance**

At age 11, Falkow stumbled across a copy of *The Microbe Hunters*, Paul de Kruif's book that describes the first microbiologists' explorations. Entranced by the world in which tiny creatures from pond water and bodily fluids wriggle under microscopes and provoke devastating epidemics, Falkow decided that he wanted to emulate those pioneers.

As an undergraduate, Falkow trained in a hospital microbiology laboratory. There, he learned how to discriminate between bacteria that live peacefully in our bodies and those that cause illness. Biochemical tests pinpointed features that distinguish the microbes from one another, but Falkow's instincts told him that additional traits dictated whether an organism would stir trouble. This hunch sparked questions that have captivated him ever since: Why do some bacteria, but not their close relatives, live harmlessly within us? What makes a pathogen a pathogen? This early immersion in medical microbiology forever tethered Falkow to the clinical world and led him into his first major research finding.



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In 1959, researchers isolated from a patient with typhoid fever a version of its causative agent—*Salmonella typhi*—that could use the sugar lactose as food. This characteristic violated one of the conventional properties of *S. typhi*. Falkow was intrigued. It was as if he had seen a lion with zebra's stripes. This *S. typhi* could transfer to other bacteria its ability to derive energy from lactose (lac<sup>+</sup>). The *S. typhi* observation grabbed Falkow because the germ had picked up its lac<sup>+</sup> attribute in nature.

At the time, researchers had detailed some mechanisms by which bacteria pass characteristics to one another, but the lac<sup>+</sup> transfer represented a different method from those that had been studied. Therefore, no one had established the molecular nature of the lac<sup>+</sup> element.

By exploiting the fact that bacterial species contain DNA of characteristic densities and the ability of the *S. typhi* strain to transfer its lac<sup>+</sup> element to distantly related bacteria, Falkow and the late Julius Marmur (Brandeis University) established in 1961 that the lac<sup>+</sup> element was made of DNA and, crucially, that it remains distinct from the chromosome. Such elements are now called plasmids. In addition to establishing that plasmids exist, Falkow's method broke open the ability to separate them from chromosomes, an advance that would have a dramatic impact on the entire future of molecular biology.

In this same set of experiments, Falkow showed that another ill-defined genetic element—R factor—was also a piece of DNA that resided outside the chromosome. This finding held extraordinary medical importance.

In the 1950s, clinicians had begun to notice that germs could acquire resistance to multiple antibiotics during transit through a patient's intestinal tract, and by 1962, this phenomenon had become a global health problem. Falkow's discovery that R factors are plasmids, like the lac<sup>+</sup> element, provided an explanation for the observations: Each R factor carried genes that encode resistance to one or more antibiotics, and destructive microbes can pick them up from harmless bacteria that dwell in the body. Falkow subsequently found that the antibiotic resistance genes reside on genetic elements that can hop from one piece of DNA to another. Several other laboratories simultaneously detected these so-called transposable elements—or transposons. Not only could bacteria pass R factors to one another, but the antibiotic genes on these R factors could jump from plasmid to plasmid or from plasmid to chromosome.

In addition to its implications for public health and understanding the basic biology by which bacteria transmit traits to one another, Falkow's work on lac<sup>+</sup> and R factors helped lay the groundwork for one of the first recombinant DNA experiments, in which Herbert Boyer (University of California, San Francisco) and Stanley Cohen (Stanford University) created a hybrid molecule composed of two completely unrelated parent DNAs, one of which Falkow provided. The resulting plasmid duplicated inside a bacterial cell and its descendants. Suddenly it was possible to isolate a gene of interest from any organism, manipulate it, and re-introduce it into living cells.

### **Opening the bacterial toolbox**

The ability to insert single genes into a bacterium of choice presented a new experimental playground for Falkow. This method provided a way to discern the function of any particular gene and thus, he could tease apart individual threads of pathogenesis.



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In 1976, Falkow and his student Magdalene So used the new recombinant DNA technology to isolate the heat-stable toxin gene from a type of *E. coli* that causes diarrhea, thus "cloning" the first gene involved in bacterial virulence. He subsequently pinned down genes that encode many functions—other toxins, molecules that deflect or undermine immune attack, proteins that attach bacteria to their target host cells, and regulators that govern the activity of other virulence genes. He began increasingly to think about virulence factors not as elements that define disease-causing bacteria in the laboratory, but as elements that help bacteria in their fundamental mission to duplicate.

One cloning experiment in particular changed the course of Falkow's work and the field. He and his postdoctoral fellow Ralph Isberg tracked down a molecule that could confer upon a normally non-invasive type of *E. coli* the ability to enter mammalian cells in culture dishes. When Falkow looked under the microscope at this event, he noticed that the host cells pucker at the point of bacterial contact and slurp up the *E. coli* carrying the invasion protein. The molecule seemed to be triggering a normal host process by which the cells usually ingest a useful particle from their surroundings.

Falkow knew then that the next frontier in studying disease-causing bacteria would involve probing interactions between host cells and bacteria rather than bacteria alone in petri dishes. His work in this arena with postdoctoral fellow B. Brett Finlay spurred a profound new approach in the field, a discipline that is now called cellular microbiology. Researchers have since found that bacteria harness multiple host talents to perform tasks that are crucial for the microbes' duplication and spread. This ability to co-opt host cells allows the germs to gain entry, escape from compartments that would otherwise kill them, hijack molecules and direct them to propel the bacteria into adjacent cells, trigger cell-suicide mechanisms that allow the bacteria to enter their preferred areas of the body, and so on.

Since the beginning of his career, Falkow has forged new tools with which to study infectious disease. In addition to introducing the use of recombinant DNA technology in the field, he initiated the discipline of molecular epidemiology and developed a method for identifying disease-causing bacteria that cannot be grown (and thus scrutinized by conventional means) in the laboratory; he was one of the first investigators to use DNA microarrays, deploying these devices to probe pathogen and host genes that play a role in infection; and he pioneered fluorescent imaging as a means to track microbes inside host cells.

Falkow has applied his knowledge and foresight to benefit the public. For example, he predicted the spread of clinical antibiotic resistance and, in the late 1970s, urged the Food and Drug Administration to remove antibiotics from animal feed. At the advent of the recombinant DNA era, Falkow's views on the risks of placing new genes into bacteria were widely sought and proved highly influential in developing the guidelines that govern such experiments.

Falkow's contributions to bacterial pathogenesis extend far beyond the walls of his own laboratory. An enormous number of researchers in the field, including many of its most illustrious members, have worked with him and he has influenced and inspired numerous other eminent investigators. Falkow is known for his wit and irreverence as well as an unmatched intuition about his miniscule study subjects. He possesses an unusual ability to "get inside" a bacterium and think about the world from the microbial point of view, a perspective that he instills in all audiences. Universally considered the father of modern molecular pathogenesis, he has earned from his trainees and colleagues an equal mix of overflowing respect and affection.