Edmond H. Fischer

1920-2021

BIOGRAPHICAL *Memoirs*

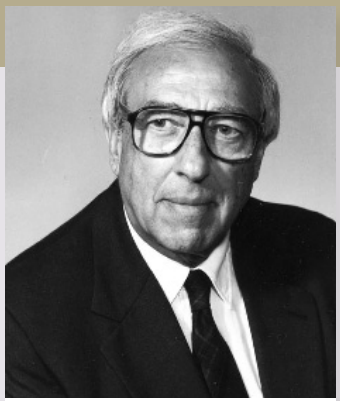
A Biographical Memoir by
Philip Cohen

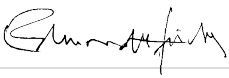
NATIONAL ACADEMY OF SCIENCES

EDMOND HENRI **FISCHER**

April 6, 1920 – August 27, 2021

Elected to the NAS, 1973





By Philip Cohen

Edmond Fischer, who discovered the first example of enzyme regulation by reversible protein phosphorylation, died on August 27, 2021, aged 101. This fundamental discovery, which led to the realization that this process controls most aspects of cell life, earned Fischer and his colleague, friend, and collaborator Edwin Krebs, the 1992 Nobel Prize for Physiology or Medicine. Subsequently, other researchers developed drugs that switch off protein kinases, the enzymes that catalyse the covalent attachment of phosphate to proteins. More than 75 kinase-inhibiting drugs have been approved so far during the twenty-first century, which have transformed the clinical care and treatment of many cancers.

Early Life

Edmond Henri Fischer, known as Eddy to all those who knew him personally, was born in the French Concession of Shanghai, China, in 1920, where his maternal grandfather had founded *Courrier de Chine,* the first French newspaper published in China, and helped to establish l'Ecole Municipale Française, where Eddy first went to school. His mother, Renee Tapernoux, was French, and his father Oscar Fischer came from Austria, where he had obtained doctorates in law and business. Oscar Fischer had taken Italian citizenship for business reasons (he was in the import-export trade), and so Eddy was born a citizen of Italy. Oscar's business was successful. The family lived in a large and beautiful house in Shanghai, employing a gardener, a cook, the main butler in charge of all the house help, and a dressmaker who made all the family's clothes. During their annual vacation in Japan, the family rented a large Rolls Royce with a chauffeur to take the family to Kobe, to the huge Kegon Falls, or to the ancient city of Nara.

In 1927, the family left China for Europe by train, traveling by the Trans-Siberian Railway. They settled in the French-speaking part of Switzerland, where Eddy and his two brothers were educated in the primary grades at La Châtaigneraie, an international

Figure 1: The Fischer family in 1926. The family are pictured in the grounds of the luxurious Fujiya Hôtel at Miyanoshita in the Lake Hakone State Park region of Japan, where they vacationed every year to escape the heat and humidity of Shanghai. Edmond Fischer (second from left) with his parents and to his right his elder brothers Georges and Raoul, who were six and seven years older than him).

school twenty miles to the east of Geneva overlooking Lake Geneva and the Alps. It was here that he became fascinated with science and the emerging field of biological chemistry. After his father's death from tuberculosis, the bacteriologist Louis Pasteur became a childhood hero, and Eddy's first scientific experiments were conducted with a research-grade microscope that he received as a gift.

At the age of 14, while attending the Collège Calvin (formerly the Collège de Genève, the oldest public secondary school there), he attended a performance of Beethoven's *Emperor Concerto* in which Johnny Aubert, a piano professor at the prestigious Conservatoire de Musique de Genève, was the soloist. The following day, Eddy asked the director of the conservatory if he could become Aubert's student. In the ensuing audition, Eddy impressed Aubert by playing Chopin's *Polonaise* in A major and Mendelssohn's *Rondo Capriccioso*. This resulted in Eddy studying with Aubert for seven years, and at one time he thought about becoming a professional musician.

When Italian leader Benito Mussolini made a pact with Adolf Hitler in 1939, Eddy Fischer burned his Italian passport on the steps of the Italian consulate in Geneva and took Swiss nationality. After graduating from high school in 1939, the year in which war was declared, Eddy stayed in neutral Switzerland throughout the Second World War and studied chemistry and biology at the University of Geneva, receiving a Bachelor of Science degree in organic chemistry. He then became a graduate student in the laboratory of Kurt Meyer, who had left Germany in 1931 to accept an appointment in Geneva. In 1947, at age twenty-seven, Eddy received a Ph.D. for research on the structure of polysaccharides and alpha-amylases, the enzymes that hydrolyse starch and glycogen to sugars.

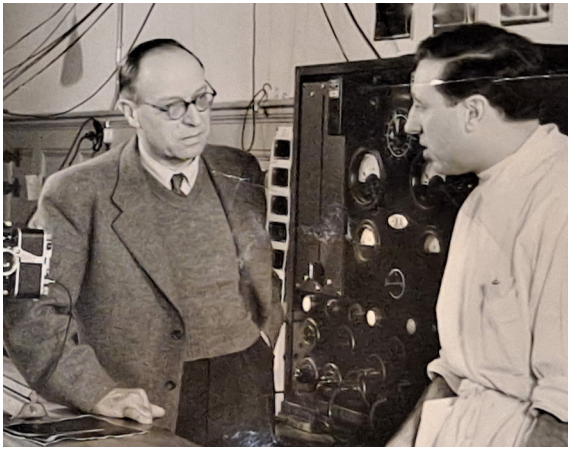


Figure 2: Eddy as a graduate student (right) with Kurt Meyer, his PhD supervisor, in Geneva in the late 1940s.

Meyer had a strong disagreement with Norman Haworth, the chair of the Chemistry Department at the University of Birmingham in the United Kingdom, about the structure of amylopectin and glycogen, and both groups needed pure starch and glycogen degrading enzymes, such as amylases, phosphorylase, and debranching enzyme, to study the structures of these polysaccharides. Meyer therefore sent Eddy to report on the crystallization of α-amylase at the First International Congress of Biochemistry held in Cambridge, United Kingdom, in 1948. It was here that he first met William "Bill" Whelan, who had been working for his Ph.D. on the structure of starch with Stanley Peat in Haworth's department. They found that they had much in common to discuss and became lifelong friends.

Following the death of Meyer from an asthma attack in 1952, Eddy moved to the United States in 1953 to begin postdoctoral research at the California Institute of Technology. On arrival, however, he unexpectedly received an offer for a position as an assistant professor in biochemistry at the University of Washington, Seattle, from Hans Neurath, then chair of the Department of Biochemistry. Seattle reminded him and his wife, Nelly, of Switzerland, and so he accepted, taking dual U.S. and Swiss citizenship and spending the next sixty-eight years there.

Discovery of Reversible Protein Phosphorylation as a Cellular Control Mechanism

In work performed in the 1930s and 1940s**,** the husband-and-wife team of Carl and Gerty Cori had discovered the enzyme glycogen phosphorylase and its role in the conversion of glycogen to lactate in muscle and to glucose in the liver. They also discovered that glycogen phosphorylase existed in two forms, which they termed *a* and *b.* Phosphorylase *b* was only active in the presence of adenylic acid (5′-AMP), whereas phosphorylase *a* was active in the absence of this molecule. They reasoned (incorrectly) that phosphorylase *a* probably contained tightly bound 5′-AMP and that another

enzyme activity they had detected in 1943, probably converted phosphorylase *a* to phosphorylase *b* by catalysing the removal of 5′-AMP. The effect of 5′-AMP on phosphorylase *b* was the first example of the allosteric activation of an enzyme**;** but the term *allostery* would not be coined until twenty years later by Jacques Monod. In those days, molecules that were required for enzyme catalysis, but did not participate directly in the catalytic process, were called "prosthetic groups." They therefore called the *a*-to-*b* converting enzyme the "prosthetic-group-removing" (or PR) enzyme.

Carl and Gerty Cori received the Nobel Prize in Physiology or Medicine in 1947 for "discovering the course of the catalytic conversion of glycogen," Gerty becoming the first woman to receive the Nobel Prize in that category. But they never managed to elucidate the molecular difference between phosphorylase *a* and phosphorylase *b* and dropped the problem.

When Eddy arrived in Seattle, he found that he shared common interests with fellow faculty member Edwin (Ed) G. Krebs. Ed had joined the department five years earlier, after completing a postdoctoral fellowship with Carl and Gerty Cori at Washington University in St Louis, where he had worked on the interaction of protamine with rabbit muscle glycogen phosphorylase. Eddy had also worked on glycogen phosphorylase in potatoes and its role in starch breakdown during his doctoral studies with Kurt Meyer. Together Eddy and Ed discussed why glycogen phosphorylase from potato did not require 5'-AMP and what the difference between phosphorylase *a* and *b* might be. They decided to take a crack at the problem, the two of them working side by side on the same bench, and thus started a lifelong collaboration.

The story of how Eddy and Ed solved the problem within eighteen months was documented by Eddy in his biographical memoir of Edwin Krebs in 2009. Briefly, when Eddy and Ed removed the structural muscle proteins from muscle homogenates by centrifugation, they found glycogen phosphorylase to be entirely in the *b* form, whereas Carl and Gerty Cori, who had removed the structural muscle proteins by passing homogenates through filter paper (preparative centrifuges had not yet been invented)**,** had found that phosphorylase was entirely in the *a* form. Fischer and Krebs then found that the *b* form could be converted to the *a* form if they passed their muscle extracts through filter paper and found that the key ingredients required for the conversion were Mg-ATP and calcium ions. The calcium ions leached from the filter paper itself during the filtration process. The requirement for Mg-ATP was suggestive of a phosphorylation reaction, which they confirmed by showing that ^{32}P- phosphate was incorporated into glycogen

phosphorylase from [γ-^{32}P]ATP during the b to a conversion, leading them to propose that the b to a converting enzyme was a phosphorylase kinase.

Fischer and Krebs showed subsequently that phosphorylase kinase transferred the phosphate from ATP on to a specific serine residue on glycogen phosphorylase b. This meant that the a-to-b converting enzyme had to be a phosphatase, although for many years it continued to be called PR enzyme (now standing for phosphate-releasing enzyme!).

Identifying the molecular mechanism by which calcium ions activated phosphorylase kinase turned out to be surprisingly difficult, and the solution to the problem emerged only after the relatively specific calcium chelator EGTA became available in the 1960s. It then became clear that calcium ions were activating phosphorylase kinase in two quite different ways. The first was through an indirect mechanism catalysed by a calcium-dependent proteolytic enzyme, which Fischer and Krebs termed kinase-activating-factor (KAF), now known to be the proteinase calpain. Activation by KAF required millimolar concentrations of calcium ions, was irreversible, and may not have any physiological relevance. The second way was by the direct and reversible binding of calcium ions to phosphorylase kinase at micromolar concentrations, a mechanism that explained how glycogen breakdown is synchronised with the onset of muscle contraction. Later, the author of this memoir found that calcium ions activate phosphorylase kinase by interaction with the calcium-binding protein calmodulin, which is an integral component of the phosphorylase kinase complex (its δ subunit), and closely related in structure to troponin C, the protein that confers calcium sensitivity to the muscle contractile apparatus.

In the early 1950s, Earl Sutherland, who had also trained with Carl Cori, found that the hormone epinephrine (adrenaline) stimulated the conversion of phosphorylase b to a and initiated glycogenolysis by generating 3′, 5′-cyclic adenosine monophosphate (cyclic AMP), the first “second messenger” to be identified and a discovery for which Sutherland was awarded the Nobel Prize in Physiology or Medicine in 1970. Krebs and Fischer found that partially purified preparations of phosphorylase kinase were activated by incubation with Mg-ATP and that this reaction was accelerated by the addition of cyclic AMP. Later, Donal Walsh, while working in Ed Krebs laboratory, discovered that the effect of cyclic AMP was mediated by a separate cyclic AMP-dependent protein kinase, traces of which contaminated the partially purified preparations of phosphorylase kinase that were being used at this time. The activation of phosphorylase kinase by cyclic AMP-dependent protein kinase was the first protein kinase “cascade” to be discovered in which one protein kinase activates another.

For many years it was thought that phosphorylation was a specialised form of enzyme control mechanism confined to the regulation of glycogen metabolism. But other examples of protein phosphorylation as a regulatory device gradually emerged during the 1970s and more rapidly during the 1980s. The protein products of cancer-causing oncogenes, such as *src* and *abl*, and the receptors for epidermal growth factor and insulin were also identified as protein kinases. Moreover, the overproduction or mutation of growth factor receptors to deregulated forms was found to cause cancers. It also became clear that progression through the cell division cycle is driven by the action of protein kinases. Then in 1990**,** cyclosporin, the immunosuppressant drug that permitted the widespread use of organ transplantation, was found to exert its effects by inhibiting a calcium/calmodulin-regulated protein phosphatase, highlighting the potential importance of both phosphatases and kinases as drug targets.

The Identification of Protein Tyrosine Phosphatases

Soon after their seminal discovery**,** Eddy and Ed agreed that one of them should focus on phosphorylase kinase (Ed Krebs) and the other on phosphorylase phosphatase (Eddy Fischer). Eddy published several papers on phosphorylase phosphatase in the 1960s and 1970s describing the partial purification and characterisation of the skeletal muscle enzyme, but the decisive breakthroughs in this area were made later by others. After oncogenes and growth factor receptors had been identified as protein kinases that attach phosphate to the hydroxyl group of the side chain of the amino acid tyrosine in proteins, Eddy became fascinated by protein tyrosine phosphatases and how they might be regulated. In the late 1980s he started to tackle this problem after Nick Tonks joined his laboratory as a postdoctoral researcher. Tonks and Fischer purified and characterised the first protein tyrosine phosphatases, revealing a new gene family that comprises about 100 members and includes both cytoplasmic and transmembrane receptor tyrosine phosphatases. Tonks and Fischer found that the leukocyte common antigen CD45 is a tyrosine phosphatase and laid the groundwork that led to the discovery of the key role of CD45 in T cell activation. They also identified the enzyme protein tyrosine phosphatase 1B (PTP-1B) and provided the first evidence that it might have an important role in insulin action, which was later established by the generation and characterisation of a PTP-1B knock-out mouse. Eddy forged a new collaboration with Ed Krebs at the start of the 1990s that resulted in the cloning and expression of the first cDNA encoding a protein tyrosine phosphatase (T cell protein phosphatase, or TC-PTP, also called PTP-N2).

Figure 3: Eddy Fischer and Ed Krebs at a joint research retreat of their labs, in late October 1992. Eddy (right) and Ed (left) in matching T-shirts at their joint lab meeting at Pack Forest, a Field Research Station and Conference Center for faculty and students from the University of Washington.

Eddy's last major paper on this topic, published in 1995, defined the alternatively spliced variants of TC-PTP. The field of protein tyrosine phosphatases remains a very active one to this day, in which Nick Tonks continues to play a prominent role. The first inhibitors of protein tyrosine phosphatases are only now beginning to enter clinical trials.

The Nobel Prize

By the early 1990s it had become clear that protein phosphorylation regulates most aspects of cell life and that the dysregulation of processes controlled by phosphorylation caused cancer and other diseases. It did not therefore come as much of a surprise when Eddy and Ed were jointly awarded the Nobel Prize in Physiology or Medicine in 1992 for their discoveries concerning "reversible protein phosphorylation as a biological regulatory mechanism," thirty-seven years after their seminal finding.

When a field of research is awarded a Nobel Prize, that frequently signifies the field is about to blossom, not that it has already flowered, and such a forecast has most certainly proven true for protein phosphorylation. Indeed, it is remarkable how much more has been discovered about this process over the last thirty years. More recent discoveries have included the identification of the multi-tiered mitogen-activated protein kinase cascades and the protein kinase cascade activated by second messenger phosphatidylinositol-3,4,5-phosphate, which mediates the intracellular actions of insulin. The protein phosphorylation and dephosphorylation events that regulate innate and adaptive immunity have also been elucidated. The first

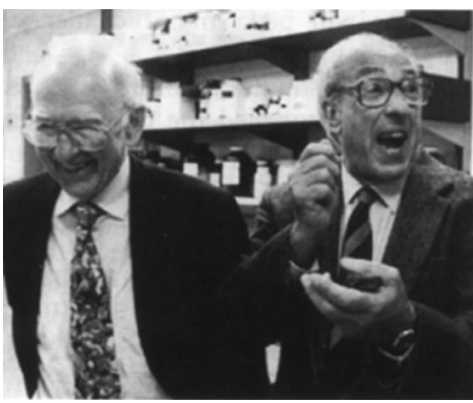


Figure 4: A joyous occasion. Eddy (right) and Ed (left) on first hearing that they have been awarded the Nobel Prize in Physiology or Medicine in 1992.

really potent and specific inhibitors of protein kinases were described between 1993 and 1995 and more than seventy-five drugs that target protein kinases have subsequently been approved for clinical use and transformed the clinical treatment of many cancers. For example, Imatinib, the first protein kinase inhibitor to be approved for clinical use in 2001, transformed chronic myelogenous leukaemia from a rapidly fatal disease to a manageable condition.

The Role of Pyridoxal Phosphate in Glycogen Phosphorylase

When I joined Eddy Fischer's laboratory as a postdoctoral fellow in 1971, I was surprised to find that about half of the laboratory was not working on the control of glycogen phosphorylase by phosphorylation, but on the role of the vitamin B6 derivative pyridoxal phosphate (PLP) in phosphorylase and in other PLP-dependent enzymes, such as bacterial amino acid decarboxylases. Phosphorylase isolated from all eukaryotes and higher plants contains stoichiometric amounts of PLP, which is essential for catalysis and, owing to its high abundance in skeletal muscle and liver, as much as 80 percent of the vitamin B6 in the body is tied up in this one enzyme. As observed for other PLP-dependent enzymes, PLP forms a Schiff base with the ε-amino group of a specific lysine residue in phosphorylase. Fischer made the remarkable and important discovery that phosphorylase retains its full catalytic activity when the Schiff base is reduced by treatment with borohydride, which fixes PLP irreversibly to the enzyme. This result was in contrast to all other PLP-dependent enzymes, which are inactivated by this treatment. The role of PLP in phosphorylase therefore had to be a unique one. The Fischer lab synthesized many PLP derivatives and developed methods for removing PLP from phosphorylase and then reinserting it or a derivative into the enzyme. These studies revealed that pyridoxal phosphate was essential for catalysis, but pyridoxal was not, pointing to the importance of the phosphate group of PLP in catalysis. The problem was eventually solved when the three-dimensional structure of phosphorylase was elucidated by Dame Louise Johnson and her Ph.D. student David Barford. It then became clear that the 5'-phosphate group of pyridoxal phosphate functions as an acid-base to promote attack by the substrate phosphate on glycogen.

Some Personal Reminiscences

As I found out when I joined Eddy's lab, he treated his research team as if they were his own family, meeting them personally at the airport on arrival and insisting that they stay at his house until they found a suitable apartment to rent. Soon after my arrival, he even took me to watch my first football game (the University of Washington Huskies against

the Stanford University Cardinal). An accomplished skier, he would take the lab skiing in the Cascade Mountains in the winter and to his vacation home on Lopez Island in the San Juan Islands in the summer. He bought an airplane and learned to fly at the age of sixty, so that he could get to Lopez faster on weekends, and he continued to fly until he was eighty. My one and only flying lesson was on "Air Fischer" when he flew me from Ed Krebs sixty-fifth birthday symposium on Orcas Island in the San Juans to Seattle in his four-seater Cessna, insisting that I sit in the cockpit and help him to fly the plane and land it on Boeing Airfield.

Eddy had a 1958 Cadillac of which he was very fond and affectionately referred to it as "the Bathtub" because of the shape of its trunk. When my car broke down six weeks before leaving Seattle to return to the United Kingdom, Eddy insisted that I use the Bathtub for the remainder of my time in Seattle and said that Bev (his second wife Beverly) would drive him to and from work over this period. Fortunately, I managed to return the Bathtub intact to Eddy at the airport prior to departure!

Eddy had a great knowledge and love of history and art, kindled during the many summers he had spent in Venice during his youth. At a meeting in Venice in 2004 to celebrate the fiftieth anniversary of the discovery of the first protein kinase, he gave me a personal walking tour of the city, amazing me with his encyclopedic knowledge of the history of many buildings that we passed, even in obscure backstreets not usually frequented by tourists. He also enjoyed painting, signing his works in the maiden name of his mother (Tapernoux). I am proud to have an original hanging in the study of my house.

Eddy spent a sabbatical leave at the Weizmann Institute of Science in Israel in 1963 and was later a member of its board of governors and its Scientific and Academic Advisory Committee and**,** from 2010**,** a life member of its International Board. During his sabbatical, he became a good friend of Ephraim Katzir, then known as Ephraim Katchalski, a well-known biophysicist who was later elected by the Knesset to serve as the fourth president of Israel. When President Katzir heard that his friend was attending a conference near the Dead Sea in 1978, he invited everyone at the conference to a reception at the President's House in Jerusalem, which included me! Unfortunately, not having been forewarned and knowing it would be rather hot, I had failed to bring any clothes with me that would be suitable for this grand occasion, but Eddy came straight to my rescue and lent me one of his jackets and a tie (Figure 5).

Figure 5: The President's Palace in Jerusalem 1978. Eddy Fischer (second from left) introducing the author (right) to President Efraim Katzir of Israel (left). The bearded chap (second from the right) is Ludwig Heilmeyer Jr, who was, like the author, a postdoctoral fellow in Eddy Fischer's lab at the time.

Although Eddy did not become a professional pianist, he gave recitals at many scientific meetings I attended, including one I organised in 2005 to celebrate the fiftieth anniversary of his great discovery and his eighty-fifth birthday held at Glamis Castle, an imposing fourteenth-century edifice about twenty kilometers north of Dundee, where Shakespeare's play *Macbeth* is set. Eddy continued to play the piano daily until a few weeks before his death. In June 2021, he sat at his piano and played the opening lines of Beethoven's "Ode to Joy" from memory as part of the Lindau organization's virtual orchestra and on July 31, 2021, he played the piano at the wedding of Leo, one of his grandsons.

Speaking about science Eddy once said: "As to what has always attracted me toward scientific research,...I believe it's the systematic way one has to proceed in science, the kind of logic one has to apply to solve a given problem. Science builds on science, where every result obtained suggests a number of questions, and every question asked suggests the next experiment. One must follow those leads just like a detective follows different leads to solve a murder mystery, never knowing whether it will lead you to a dead end or to the next big breakthrough. Because in science, one cannot order at will a great discovery, or buy it at any cost because there is no way of predicting when and from where it will come."

Eddy received many honors throughout his life, including honorary doctorates from the University of Montpellier, France (1985); the University of Basel, Switzerland (1988); the Medical College of Ohio (1993); Indiana University (1993); Ruhr-Universität, Bochum, Germany (1994); Gustavus Adolphus, Minnesota (2004); the University of Genova, Italy (2004); and the University of Dundee, Scotland (2008).

Family

Eddy had two sons and four grandchildren, and his granddaughter Elyse has become a scientist in her own right. Having valued his diverse education, Eddy was pleased when Elyse decided to become an undergraduate in Scotland and attended her gradu-

ation in biochemistry from the University of St. Andrews in 2017. Elyse then spent four years as a graduate student in David Barford's laboratory at the Medical Research Council's Laboratory of Molecular Biology, in Cambridge, England, receiving her Ph.D. in 2021 and becoming Dr. Elyse Fischer at the age of twenty-seven, exactly like her grandpa in 1947. Eddy lived long enough to witness the publication of Elyse's second research paper, which solved an important aspect of the regulation of the cell division cycle by phosphorylation!

Eddy Fischer was married to Nelly Gagnaux from 1948 until her death in 1961 and then to Beverly Bullock from 1963 until her death in 2006. He is survived by two sons from his first marriage, François and Henri, and by his four grandchildren.

Figure 6: Sharing his love of music. Eddy Fischer and his granddaughter Elyse, then age 5, playing the piano together in 2000.

SELECTED AWARDS AND DISTINCTIONS

1952 Werner Prize, Swiss Chemical Society

1956 - 1959 Lederle Medical Faculty Award, University of Geneva

1963- 1964 John Simon Guggenheim Memorial Foundation Fellow

1968 Prix Jaubert, University of Geneva

1972 Elected to the American Academy of Arts and Sciences

1973 Elected to the National Academy of Sciences U.S.A.

1988 Passano Laureate, Passano Foundation

1991 Steven C. Beering Award, Indiana University School of Medicine

1992 Nobel Prize in Physiology or Medicine

1993 Elected a Foreign Associate, Spanish Royal Academy of Sciences

1994 Elected to the Venice Academy of Sciences, Arts, and Letters

1998	Elected to the Royal Academy of Medicine and Surgery, Spain
	Named Bert and Kugie Vallee Visiting Professor, Harvard University
2000	Elected to the Korean Academy of Science and Technology, Korea
2004	Named Honorary Director of the Edmond H. Fischer Signal Transduction Laboratory, Jilin University, Changchun, China
2005	Lifetime Achievement Award, Miami Nature Biotechnology Winter Symposium
2007	Named an Honorary Citizen, City of New Orleans
2009	Medal of the International Union of Biochemistry and Molecular Biology
2010	Elected a Foreign Member of the Royal Society, United Kingdom

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