Edmond Fischer
(1920–2021)

Nobel-winning biochemist who discovered a ubiquitous cell-regulatory mechanism.

Edmond Fischer discovered the first example of reversible protein phosphorylation, a process that regulates most aspects of cell life. Two classes of enzymes, protein kinases and protein phosphatases, attach and remove phosphate to and from proteins. This simple modification alters their functions in many ways, switching their activities on or off, inducing them to interact with other proteins, or triggering their migration from one subcellular compartment to another. This fundamental discovery earned Fischer and his collaborator Edwin Krebs the Nobel Prize in Physiology or Medicine in 1992.

In the course of his long life, Fischer, who has died aged 101, witnessed his discovery being applied in ways that have saved millions of lives. Human cells contain more than 500 protein kinases and nearly 200 protein phosphatases, which act on thousands of proteins. The mutation or overproduction of kinases and phosphatases causes cancer and other diseases. Imatinib, the first drug developed by targeting a specific protein kinase, transformed chronic myeloid leukaemia from a rapidly fatal disease to a manageable condition soon after it entered clinical trials in 1998. Protein kinases have since become the pharmaceutical industry's most popular class of drug target. More than 70 kinase-inhibiting drugs have already been approved this century, transforming the clinical treatment of many cancers.

Fischer was born in Shanghai, China, in 1920. His French mother and Austrian father had taken Italian nationality for the family to help his father's business. At seven he was sent to be educated in Switzerland, where he and a school friend later resolved that one would become a doctor and the other a scientist, so that they "could cure all the ills of the world". Furious at the Italian leader Benito Mussolini's 1939 pact with Adolf Hitler, Fischer burnt his passport on the steps of the Italian consulate in Geneva and became a Swiss citizen. He studied chemistry and biology at the University of Geneva during the Second World War, receiving a PhD in 1947 for research on α-amylases, digestive enzymes that degrade glucose polymers such as starch and glycogen.

Moving to the United States in 1953 to begin postdoctoral research at the California Institute of Technology in Pasadena, he was unexpectedly offered an assistant professorship in biochemistry at the University

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of Washington, Seattle. The city reminded him of Switzerland, so he accepted, spending the rest of his life there. Within months of arriving, Fischer began to collaborate with Krebs, another young faculty member. Krebs had worked with Carl and Gerty Cori at Washington University in St. Louis, Missouri. The Coris had won the 1947 Nobel Prize in Physiology or Medicine for their discovery of the glycogen-metabolizing enzyme phosphorylase, which liberates glucose from stores in muscle and liver cells to fuel the body. They found that muscle phosphorylase existed in two forms, which they termed b and a. The b-form required the metabolite adenylic acid for activity, whereas the a-form, which could be converted to the b-form by enzyme activity present in cell extracts, did not. The source of this difference remained mysterious.

> **"A talented pianist, he thought about becoming a professional musician."**

Fischer and Krebs decided to track it down and within 18 months had succeeded. They found that a previously unknown enzyme, phosphorylase kinase, converted phosphorylase b to a by transferring phosphate from the metabolite adenosine triphosphate (ATP) to phosphorylase. The cell-extract enzyme that converted phosphorylase a to b reversed this process, they found, by releasing phosphate, so they named it phosphate-releasing enzyme. Fischer and Krebs went on to discover that phosphorylase kinase was switched on by calcium ions, which also initiate muscle contraction. This explains how glycogen is mobilized to provide glucose for energy when muscles are active.

It later emerged that cancers are frequently caused by mutations in protein kinases that attach phosphate to the amino acid tyrosine. Fischer studied enzymes that counter this process by releasing phosphate from tyrosine. During the mid- to late 1980s, his laboratory defined the first few members of an entirely new family of phosphatases. One is PTEN, encoded by a gene that others later discovered is often silenced in cancer cells. Alpelisib, a drug that switches off a kinase that opposes the action of PTEN, was approved for breast cancer in 2019.

Fischer was gifted in other ways. A talented pianist, as a schoolboy he began six years of training at the Geneva Conservatory of Music, and thought about becoming a professional musician. He continued to play the piano daily, and shortly before his death he played at the wedding of one of his grandsons. He had a great knowledge and love of history and art, and enjoyed painting, signing his works 'Tapernoux', his mother's unmarried name.

Eddy was informal and kind. It was important to him that science should always be fun. He treated his researchers as if they were his family, meeting new arrivals at the airport, and insisting that they stay at his house until they had found an apartment. In the winter, he'd take the entire lab skiing in the Cascade mountains, and in the summer they'd all go to his holiday home on Lopez Island in the San Juan Islands, off Washington State. He bought an aeroplane and learnt to fly at the age of 60, so that he could get to Lopez faster at weekends, and continued to fly until he was 80.

Engaged to the end, he held the distinction of being the oldest living Nobel prizewinner, and greatly enjoyed the virtual symposium that was held in October 2020 to celebrate his 100th birthday.

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