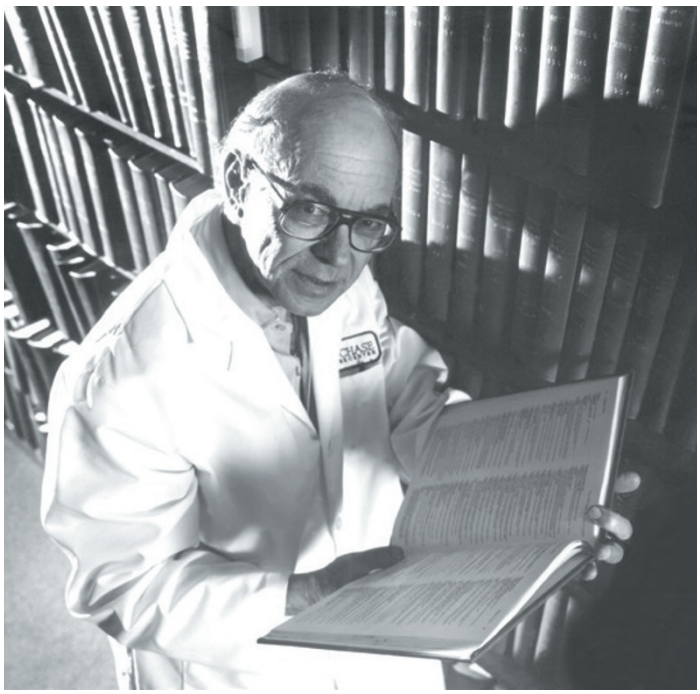
Irwin Allan Rose

(1926–2015)

Established role of ubiquitin in the destruction of cellular proteins.



FOX CHASE CANCER CENTRE ARCHIVES

Irwin Allan Rose (Ernie) helped to elucidate how cells identify damaged proteins and break them down into their constituent amino acids. His discoveries led to the development of 'proteasome inhibitors', drugs used to treat certain types of cancer.

Rose, who died on 2 June, was born in 1926 in Brooklyn, New York, where his father ran a flooring business. Rose attended Washington State College in Pullman and after a brief period in the US Navy during the Second World War, he completed a bachelor's degree at the University of Chicago in Illinois in 1948. In 1952, he obtained a doctorate in biochemistry from Chicago.

After two years of postdoctoral work, Rose became a faculty member of the Yale School of Medicine's biochemistry department in New Haven, Connecticut. While at Yale, he met and married Zelda Budenstein, a graduate student in his department. Then, in 1963, he moved to the Fox Chase Cancer Center in Philadelphia, Pennsylvania, where he spent most of his career.

By the mid-1970s, scientists had discovered that a certain protein — which came to be known as ubiquitin — occurred in numerous tissues and organisms, but its function was unknown. In the latter part of the decade, in collaboration with one of us (A.H.) and biologist Aaron Ciechanover, Rose began to investigate this protein. By studying ubiquitin in reticulocytes — immature red blood cells, which are simpler to use than other cells — we worked out that it was crucial to protein degradation. This was the first step to discovering that proteins bound to ubiquitin are broken down by protein complexes called proteasomes and the fragments recycled into new proteins.

The discovery of ubiquitin-based protein degradation has since shed light on various diseases, such as cancer, which can occur when the pathway is defective. The work has also led to the development of several drugs that are used to treat blood cancers. These act by disrupting the protein-disposal system; the cancer cells are killed when the damaged proteins pile up.

Although Rose is best known for his contribution to the ubiquitin field, he had established himself as a leader in the study of enzyme mechanisms long before. In the late 1950s, for instance, he had been among the first to attach radioactive compounds to track the fate of metabolites in cellular pathways. By radiolabelling precursors of DNA, he showed in his PhD studies that the nucleotide cytidine is directly incorporated into DNA, and that the reduction of cytidine to deoxycytidine is a necessary step in DNA synthesis.

Later on at Yale, he investigated how enzyme mechanisms depend, in part, on the spatial arrangement of the atoms that make up both the substrate and the enzyme molecule, focusing on processes involved in carbohydrate metabolism.

At Fox Chase, he became interested in the regulation of glycolysis, the breakdown of glucose, in red blood cells. Many cancer cells are more dependent on glycolysis than are normal cells — a phenomenon called the Warburg effect, after the biochemist Otto Heinrich Warburg. Working out why was of key interest to the cancer-research community at the time. Rose's work on the enzyme hexokinase showed that its phosphorylation of one of the carbon atoms in glucose is the main rate-limiting step in glycolysis. Rose described in detail the various mechanisms and steps involved in the pathway — by adding certain stimulants and toxins, such as inorganic phosphate and methylene blue.

In 1979, Rose was elected to the US National Academy of Sciences for his studies on enzyme mechanisms. In fact, in many ways, his three decades of experience had prepared him for the complexities of ubiquitin enzymology — a reminder of the value of pursuing basic science. In 2004, he shared the Nobel Prize in Chemistry with one of us (A.H.) and Ciechanover for the ubiquitin work.

Ernie was so brilliant that people did not always understand his ideas, and were a little afraid of him. People were also often apprehensive of interacting with him because he could be very critical, and did not hesitate to voice his judgements. But he was incredibly generous in collaborations, a rare phenomenon in science today.

He always downplayed his contributions to the ubiquitin field. He wrote an autobiographical article for *Protein Science* in 1995, in which the word 'ubiquitin' is not even mentioned; in conversations, he described his role in the ubiquitin story as being merely supportive. In fact, Ernie's input of ideas, inspiration and helpful criticism were essential for the discovery of the ubiquitin system and for the delineation of some of the main enzyme reactions in the pathway.

After Ernie retired, he kept coming up with bright ideas about problems such as the origin of life, and more recently, about how to solve global warming. He will be missed. ■

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