Oliver Smithies

(1925–2017)

Nobel-winning inventor of ways to modify genes.

Oliver Smithies had a habit of inventing ways to do the experiments he wanted to do, and crafted tools that are now used widely in biology. He won the Nobel Prize in Physiology or Medicine in 2007 for developing methods to genetically modify individual mammalian genes.

His work provided the means to modify any gene in mouse embryonic stem cells. This approach, known as gene targeting, has been used to create thousands of lines of mice carrying desired genetic mutations. It transformed our knowledge about the roles that many genes have in human health and disease. Few areas of mammalian physiology were not touched by these methods.

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Smithies died on 10 January, aged 91. He and his twin brother were born in Halifax in Yorkshire, UK, on 23 June 1925. His mother introduced him to literature, his father to mathematics. His grandfather taught him how to make useful things from junk, a talent that served him throughout his career. Smithies attended the University of Oxford. He worked with chemist A. G. 'Sandy' Ogston and received his undergraduate degree in animal physiology in 1946, and his PhD in biochemistry in 1951. Smithies came to the University of Wisconsin–Madison, for a postdoc and later worked at the Connaught laboratories, part of the University of Toronto in Canada. He moved back to Madison in 1960 and stayed there until he moved to the University of North Carolina at Chapel Hill in 1988, where he remained for the rest of his career.

Smithies' first major contribution came when he was working in Toronto trying to find the precursor to insulin. The separation of proteins at that time depended on how quickly they moved through a matrix of filter paper. Frustrated with the shortcomings of this method, Smithies developed an alternative. He used common starch to make a gel that could replace the filter paper, which made the job easier and more precise. This first application of gel electrophoresis found widespread use in separating proteins and other biomolecules of different sizes. Smithies used it to reveal variation in a group of blood proteins called haptoglobins.

When DNA-cloning technologies became available, Smithies studied some of the human genes for haptoglobin and haemoglobin. Some are present in two copies, near one another, on the same chromosome. Smithies discovered that genetic material was exchanged between duplicated genes. That sparked his interest in a naturally occurring process called homologous recombination, in which genetic material is swapped between paired chromosomes during the production of gametes.

Smithies' Nobel-prizewinning work came from his desire to replace the gene responsible for sickle-cell disease with a normal gene. Through a series of experiments in the early 1980s, he harnessed homologous recombination to insert a gene into a specific location in the mammalian genome. He went on to use this technique to modify a gene in a mouse embryonic stem cell and produce mice carrying that mutation. For this pioneering work Smithies shared the prize with Mario Capecchi and Martin Evans.

The ability to target and modify individual genes has proved powerful in deciphering gene function, including in human health and disease. Smithies contributed to these efforts by creating the first animal model for cystic fibrosis.

Smithies was a problem solver. His lab bench was his office. He loved physically doing science: designing his experiments, mixing his own reagents and building new equipment when what he wanted was not commercially available. He was working in the lab until a few days before the end of his life.

Besides his passion for science, Oliver loved flying single-engine aeroplanes and gliders. In 1980, he was a co-pilot on a record-breaking crossing of the Atlantic Ocean in a single-engine plane. The speed record held for 20 years. I flew with him in a small plane in 1984 from Chicago, Illinois, to Cold Spring Harbor, New York, where we missed the runway at the small local airport on our first approach, because of low cloud, and had to circle around. On the second approach, we were thrilled to see the runway and land safely. Oliver referred to this frequently in his later lectures. The thrill of discovery was like finding the runway.

Oliver never sought fame and lived a simple life. He was always in the lab or — when the weather was fine — in the air. Throughout his career he made significant contributions to the many aspects of science that fascinated him. He used to boast that he was over 60 years old when he did his Nobel-prizewinning work. His career demonstrates that one is never too old to advance — or enjoy — science. ■

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