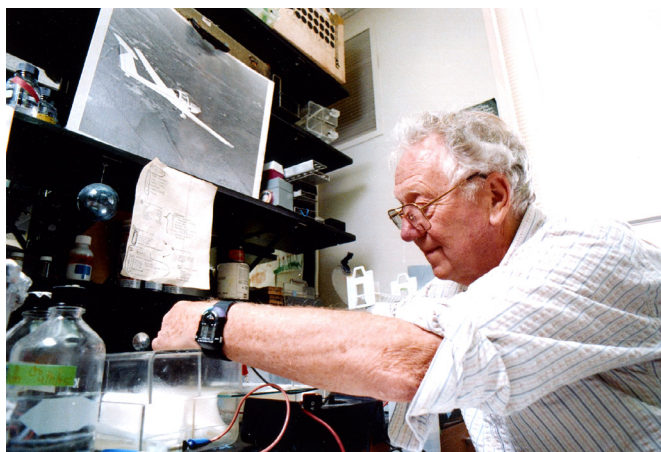


## Oliver Smithies, DPhil 1925–2017

Jeffrey Robbins

Dr Oliver Smithies, Weatherspoon Eminent Distinguished Professor of Pathology and Laboratory Medicine at the University of North Carolina, Chapel Hill, passed away on January 10 after a short illness at the age of 91. Dr Smithies made many contributions to biomedical science during his more than 60 years at the laboratory bench but is best known for his contribution to developing the concepts and operative techniques that



enabled thousands of laboratories to carry out targeted, homologous recombination in mammalian cells, enabling targeted genetic modifications in mice. The ability to rapidly effect directed changes at the genetic site of one's choice opened a golden age for establishing cause-and-effect relationships for normal and mutated genes. Indeed, the sequences that both control gene activity and modulate the protein complement of different cells were suddenly amenable to mechanistic dissection. The development of gene targeting via homologous recombination led to his sharing the Nobel Prize in Physiology or Medicine in 2007, with Mario Capecchi, Howard Hughes Medical Institute and University of Utah, and Sir Martin Evans, University of Cambridge, United Kingdom.

The Nobel was only one of many prestigious honors awarded to Dr Smithies during his long career. He was elected to the United States National Academy of Sciences in 1971 and inducted into the American Academy of Arts and Sciences in 1978. He won the Albert Lasker Award for Basic Medical Research in 2001; again along with Drs Capecchi and Evans, the Alfred P. Sloan, Jr Prize from the General Motors Foundation; jointly with Capecchi in 1994, the March of Dimes Prize in Developmental Biology; again jointly with Capecchi in 2005; and the Thomas Hunt Morgan Medal in 2007. A complete listing of all his awards and honors, regional, national, and international would fill this entire *In Memoriam*, but suffice it to say that if there is a prize for achieving the exceptional in biomedical sciences, a plaque, medal, or scroll for it probably resides in his library.

Oliver Smithies was one of the first scientists with whom I associated bench science. It was back in 1967, when I was a junior in high school and had come up with the idea that I could separate out some blood proteins for a science project. To my dismay, I discovered that I would need to set up a procedure called electrophoresis. Luckily, Oliver (once you met him, or even read about his exploits and joy in discovery science, Dr Smithies

becomes Oliver to you) had developed his first transformative tool, starch gel electrophoresis, which you could make from potatoes. A few sacks of potato starch, some high-voltage batteries, and a locked bedroom door—I was well on my way to my first experiment. It didn't work, of course. I told Oliver that story many years later when I actually met him. His obvious and infectious delight in inspiring a high school student to tinker and try an experiment was memorable.

I'm not sure that Oliver ever did a day's work in the laboratory; to him, it was never work, although he filled over 150 laboratory notebooks. It was clear from listening to his stories, talking science with him, and watching numerous videos of his talks online, that being at the bench was never really work: it was a calling, a pleasure and something that was truly joyful. To Oliver, the laboratory was always home.

Oliver Smithies was born in Britain and attended Balliol College at the University of Oxford. He initially focused on medicine and studied anatomy and animal physiology, where he won his first scholarships and prizes, obtaining his Bachelors in 1946. He switched out of medicine and obtained a second undergraduate degree in chemistry, publishing his first article with his undergraduate mentor, Alexander G. Ogston in 1948.<sup>1</sup> He retained tremendous respect for Ogston and sometimes finished his lectures with one of his mentor's quotes:

*For science is more than the search for truth, more than a challenging game, more than a profession. It is a life that a diversity of people lead together, in the*

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*closest proximity, a school for social living. We are members one of another (A.G. Ogston, Australian Biochem. Soc. Annual Lecture, 1970).*

He did his first postdoctoral fellowship at the University of Wisconsin-Madison, crystallizing and then studying  $\beta$ -lactoglobulin in a series of what he termed unimportant experiments. He then got a job at the University of Toronto, studying insulin, which led to his first important contribution: pioneering the technique of starch gel electrophoresis. This led to a transformative increase in our ability to facily resolve protein species by electrophoresis. While at Toronto, he was promoted to an Associate Research Faculty position, and he first became interested in genetics under the tutelage of Norma Walker Ford at the University's pediatric hospital. Returning as a faculty in the Department of Genetics at the University of Wisconsin-Madison in 1960, he rose through the academic ranks and was named the Leon J. Cole and Hilldale Professor of Genetics and Medical Genetics. It was during his time at Wisconsin in the early 1980s that he came up with the idea of targeted gene modification, outlining the process in his laboratory notebook on June 22, 1982 under the title "Assay for Gene Placement." Subsequently, he, his colleagues, students, and fellows performed a series of seminal experiments that resulted in the targeting of selected genes via homologous recombination in mammalian stem cells. These targeted cells were then implanted into mouse blastocysts, which, when implanted into surrogate dams, subsequently developed into gene-targeted, chimeric mice.<sup>2</sup>

As an illustration of Oliver's impact on cardiovascular science, I want to recall how this work changed my own. In 1985, I had moved my own laboratory to the University of Cincinnati College of Medicine and was busily isolating skeletal muscle genes. In reading Oliver's *Nature* article describing the Targeted Correction of a Mutant *HPRT* Gene in Mouse Embryonic Stem Cells,<sup>3</sup> I saw that a close friend of mine from graduate school, Tom Doetschman, a fellow in Oliver's laboratory, was lead author. When we spoke and he noted that he was looking for his first faculty position, I excitedly told him about Cincinnati and we were fortunate enough to recruit him to the Medical School's faculty. Tom's friendship, influence, and generosity transformed research across departments at Cincinnati and soon many laboratories, including my own, had newly embraced the mouse as the experimental system of choice. He also persuaded Oliver to visit and talk about his work. Convinced of the technique's power, we all quickly started our own series of experiments in gene targeting. As many laboratories in a number of the Medical School's departments were already fully invested in studying cardiac physiology, this quickly led to gene targeting being directed to the genes encoding proteins critical to normal and diseased cardiac function. Studies establishing structure-function relationships of phospholamban led by Litsa Kranias, and the myosins in our laboratory quickly followed.<sup>4,5</sup>

The ability to carry out, first, gene ablation and then directed gene mutations in a mammalian system revolutionized the cardiovascular community's ability to establish cause-and-effect relationships among genes, function, and disease. Oliver was always delighted with the fact that so many people used his tools to ask their own questions and devise their own experiments. He was completely open and eager to share his thoughts, his philosophy, his tools and reagents and always, his joy of life and science.

When Oliver's future wife, Nobuyo Maeda, who is currently Robert H. Wagner Distinguished Professor in the Department of Pathology and Laboratory Medicine, obtained a tenure track position at the University of North Carolina, Chapel Hill in 1988, he relocated his laboratory to that campus. Oliver then spent the last 25 odd years enriching the campus and world with his skills, philosophy, sense of wonder and joy. By the end of his career, he had published close to 350 articles, changing the scope of biomedical basic research and educating countless undergraduates, graduate students, fellows, and faculty in both science and life. I consider myself fortunate to have met and spent a bit of time with him at various seminars and meetings.

I remember speaking with him some time ago when he was in his mid-80s, still active, still doing experiments, still traveling, and talking about his work. I marveled at his vitality and ability to inspire. If getting old is when your hopes turn to regret, Oliver never really aged. He was always interested in the next experiment, the next, new hypothesis, and the next new tool that he could build out of discarded junk, materials that others had thrown away. We would do well to emulate his sense of larger community, continuing sense of wonder, his joy in laboratory work and generosity of spirit. We are fortunate to have lived in his time.

## Disclosures

None.

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