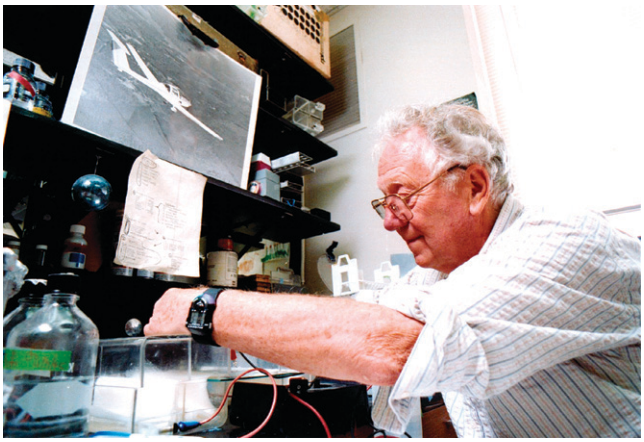
The 2007 GSA Honors and Awards

The Genetics Society of America annually honors members who have made outstanding contributions to genetics. The Thomas Hunt Morgan Medal recognizes a lifetime contribution to the science of genetics. The Genetics Society of America Medal recognizes particularly outstanding contributions to the science of genetics within the past 15 years. The George W. Beadle Medal recognizes distinguished service to the field of genetics and the community of geneticists. A new award, The Genetics Society of America Award for Excellence in Education, recognizes individuals or groups who have had a significant, sustained impact on genetics education at any level, from kindergarten through graduate school and beyond. We are pleased to announce the 2007 awards.



Oliver Smithies

The 2007 Thomas Hunt Morgan Medal

Oliver Smithies

IT is a great pleasure to recognize Oliver Smithies on his receipt of the 2007 Thomas Hunt Morgan Medal. To us, there is no person who is more deserving of this lifetime honor. Throughout his career, Oliver has made major contributions to the advancement of genetics and is a very distinguished and influential scientist. He is full of interesting ideas with broad contributions in the form of technical innovations and new tools, new hypotheses, and new knowledge. His work has completely changed the ways by which the majority of groups study mammalian genetics. It has had a substantial impact on the development of science. In a 1995 *New York Times* article, at the age of 70, Oliver was appropriately described as "a scientific phenomenon, a man whose intellectual pace has continued unabated for half a century . . . and who continues to break new scientific ground." Now, almost 12 years later, this remains true.

Oliver Smithies was born on June 23, 1925 in Halifax, Yorkshire, England. His father was an insurance salesman and his mother a teacher. Oliver recounts his father's kindness and his mother's keen intellect, two traits amply displayed by him to the great benefit of his students and trainees. Oliver provides the very best kind of example to students and colleagues through his creativity, daring, resolve, modesty, good humor, intelligence, compassion, and love of invention. For as long as he can remember, Oliver has been interested in science and since the age of seven or eight he wanted to be an inventor. Growing up in Yorkshire, he actively pursued these interests by conducting many experiments at home, building a telephone with a pig's bladder and constructing telescopes and radios.

Oliver's abilities shone through as a boy and he was among a select group of students admitted to the very distinguished Heath Grammar School. Due to his aptitude for physics and mathematics, he then won a scholarship to Balliol College, Oxford University where he read physiology (B.A. First Class Honors, 1946). After his B.A., Oliver completed the chemistry curriculum and then continued to earn his doctorate degree from Oxford in biochemistry (Ph.D., 1951). At Oxford, his tutor Sandy Ogston, who became a close friend, nurtured Oliver's broad interests and abilities and encouraged Oliver to pursue his next studies abroad to further broaden his perspective. Taking this advice to heart, Oliver conducted his postdoctoral training in physical chemistry at the University of Wisconsin. Subsequently, he joined the faculty of the Connaught Medical Research Laboratory at the University of Toronto in 1953, and his research from this point on is briefly summarized later in this citation. In 1960, he returned to the University of Wisconsin as Assistant Professor of Genetics and rapidly advanced to full professor (1963). Oliver remained at the University of Wisconsin until 1988 and became a distinguished member of the faculty. From 1988 to the present, Oliver has been Excellence Professor of Pathology and Laboratory Medicine at the University of North Carolina at Chapel Hill.

Oliver has a remarkable scientific memory and remembers almost everything he has learned. When coupled with his unusually broad interests and abilities, this makes Oliver an exceptional scientist, a versatile innovator, and a very valuable colleague and mentor. During discussions, he readily effuses the details of specific biochemical pathways, chemical structures, chemical reactions, or physical effects. His deep insight and knowledge of chemistry and physics enhance his ability to see the merits and pitfalls of a biological hypothesis and he quickly applies this insight to the subject under discussion. These interactions and insights are instrumental in making those who train with Oliver better scientists. Additionally, his unusually broad and deep insights are important characteristics that are key to his personal success. They have been major factors driving both his remarkable experimental and his conceptual innovations.

Over the years, Oliver's research interests have focused on diverse areas, including insulin, biochemistry and genetics of serum proteins, hemoglobinopathies, homologous recombination, evolution and gene families, hematopoetic stem cells and gene therapy, and recently essential hypertension and kidney function. In these areas, he has generated important ideas and tools and used them to arrive at solutions to important biological problems. Oliver's accomplishments are too numerous and too diverse to cover in any detail in this citation. Without his contributions, the fields of modern experimental genetics and molecular biology would be far behind their current state of development. From 1961 to 1975, he was one of the top 250 most cited authors, a list marked by continuous, usually quite prolific contributions over the entire period. We now briefly describe his research, focusing on a few key contributions and on how his experience led him to the idea of using homologous recombination to correct and otherwise modify genes in living cells.

During his postdoctoral training at the University of Wisconsin in the early 1950s, Oliver tested different methods for their ability to separate distinct proteins and evaluate their purity. With this experience, he next moved to the University of Toronto, where he started to search for a precursor for insulin (insulin was discovered at the University of Toronto in 1921). He was frustrated by his previous experience, including the large quantities of protein required for studies and the artifacts of accepted technologies. Therefore, he tested the newly published procedure of zone electrophoresis on filter paper. This required much less material and provided superior separation. No matter how he altered the conditions, however, the technique proved useless for his studies, since insulin absorbed tightly to the filter paper. Undaunted and in typical Smithies style, he next combined experimental observation with his great insight and a childhood memory to invent the tool required for his studies.

One Saturday in January 1954, he visited a laboratory using a new method of separating proteins using starch grains. Although it was laborious, he noted the true merit of the system in that "the starch grains were gloriously free from [protein] absorption problems." This observation initiated a train of thought about how starch could solve his problems. He remembered helping his mother with the laundry, as a child, and observing that her starch was a liquid when hot but turned to a jelly when cold. It immediately occurred to him that if he boiled the starch in a buffer and allowed it to cool, then the proteins could be separated as they migrate through the jelly and then be detected by staining. That same Saturday, he found that 15% (w/v) starch cooled to a usable consistency and promptly performed the first starch gel electrophoresis experiment. Oliver had invented the first high-resolution electrophoresis method, the first of his major technical advances. This first experiment was very promising and so he continued to refine the method. Soon after and out of pure curiosity, Oliver tested serum and the use of a single gel more than doubled the known number of separable proteins. Oliver remembers, "it was with neither qualms nor regrets that I forever left my search for the precursor of insulin and concentrated on serum." He soon had evidence suggesting the existence of inherited differences in the serum protein profile of healthy people, initiating the field of normal protein polymorphisms. (At that time, the only known molecular variation in a protein was the sickle-cell variant of β-globin. In 1949, this variant was shown to have altered chemical properties by Linus Pauling and colleagues.) Oliver's 1955 article, describing the starch gel method and his results, was one of the most cited for a number of years. For the period 1945–1988, it was overall the 107th most cited article in the Science Citation Index.

During the years following the invention of starch gel electrophoresis, Oliver returned to the University of Wisconsin as a molecular geneticist and continued to pursue his serum protein findings. He ultimately demonstrated that the hereditary variations were in the hemoglobin-binding protein haptoglobin. After much trouble understanding the nature of the haptoglobin variants, it occurred to him that one of the alleles (*Hp2*) may have arisen by a joining of two other alleles (*Hp1F* and *Hp1S*). With the example of the Drosophila Bar locus (a tandem duplication that can be seen in the polytene chromosomes), and its rich history of repeated mutations from unequal crossing over, it was hypothesized that the *Hp2* allele resulted from a unique nonhomologous recombination event that tandemly joined *Hp1F* to *Hp1S*. As a result of this event, *Hp2* would contain a small duplication, predicting that further, more common unequal homologous recombination would produce a triplicated allele. It was now 1962, and that prediction soon proved true. This knowledge of recombination and the predictability of homologous

recombination remained with Oliver, and it was to have an important influence on future directions.

Due to a growing interest in the evolution of multigene families and recombination, Oliver later transitioned his research from proteins to DNA. To do so, he did a sabbatical with Fred Blattner who also was at the University of Wisconsin and they soon made important new tools. At this time, there was significant concern about the safety of the emerging recombinant DNA methods. Collaboratively, they designed the Charon phage vectors for gene cloning. These new vectors contained crippling mutations and required complementary suppressors for growth. (Oliver and Fred consumed a "milk shake" of *Escherichia coli* to prove the safety of the new tools.) With the DNA technologies in hand, Oliver now set out to clone and analyze globin genes. His group successfully cloned the fetal globin genes *G*γ and *A*γ and determined the nucleotide sequence of their coding, intronic, and flanking sequences (one of the first human genes sequenced). Upon analyzing the fetal globin sequence data, Oliver was again confronted with the predictability of homologous recombination. An exchange of DNA sequences had occurred between the *G*γ and *A*γ genes by homologous recombination as a gene conversion event. These findings were published in 1980. Continuing the trend of tool making, Oliver's group also developed computer programs to effectively analyze and align nucleotide sequence data. To do so, they utilized the expertise and mainframe computers of the University of Wisconsin and the resulting package of programs became the community's first widely used sequence analysis bundle (the Wisconsin Genetics Computational Group programs, better known as GCG). Their 1984 article describing this comprehensive set of programs is another citation superstar, being the fifth most cited article from 1983 to 2003.

With the recurrent theme of recombination and his work on globins, the thought of correcting the sickle-cell β-globin gene by homologous recombination kept occurring to Oliver, but he had no means of identifying the event if it occurred or of estimating its frequency. This changed in April 1982 when he read an article authored by Goldfarb, Wigler, and colleagues that described an elegant technique that they used to isolate a mutated gene in a carcinoma genome. Oliver realized that he could adapt this technique to determine whether homologous recombination could be used to alter the β-globin gene. Simplistically, the strategy involved using β-globin locus homology to insert a *supF* gene into the locus and then randomly cloning genomic restriction fragments into a phage vector that required *supF* for plaque formation. The *supF* gene suppresses an amber mutation. Using cafeteria trays as petri dishes, a β-globin probe, and whole X-ray films for detection, the experiments began in earnest. It took 3 years of hard work, including changes in the cell type used and the design and construction of an electroporator (at that time not commercially available), to successfully isolate a phage that grew due to *supF* and that also hybridized to a β-globin probe. Over the next months, Oliver and co-workers were able to isolate DNA from a pure clone of cells and for the first time prove by Southern blot analysis that homologous recombination can be used to make planned modifications in living cells (on May 18, 1985).

The landmark article describing this homologous recombination in mammalian cells was reported in 1985. To Oliver, it is the favorite of his publications. A selectable neomycin marker was introduced into the exact position of the human β-globin gene as planned via homologous recombination. This site-directed mutagenesis occurred without the addition of DNA into other sites within the genome. Following this report, the groups of both Oliver Smithies and Mario Capecchi independently showed that this approach could work in mouse ES cell lines (previously developed by Martin Evans), heralding the common use of gene targeting to produce mutant mice by many investigators throughout the world. The availability of gene-targeted mice to the broader scientific community has revolutionized the study of mammalian development and human disease. In fact, an international effort is currently underway to mutate every gene in the mouse genome. A few of the new animal models made possible by the development of gene targeting include cystic fibrosis, Huntington's disease, sickle-cell anemia, fragile-X disease, Tay-Sach's disease, and various cancers.

Oliver quickly recognized the potential for applying the gene targeting technology to creating animal models of complex diseases in humans. He noted that the mouse system is particularly valuable because the effects of combinations of genetic changes can be studied and because environmental influences can be varied in a controlled fashion. Consequently his recent research has been focused on understanding the genetics of common diseases, such as hypertension and atherosclerosis, which have strong multigenic and environmental components. For example, Oliver and colleagues have shown unequivocally that quantitative genetic changes that affect the levels of expression of genes for angiotensinogen, the endothelial form of nitric oxide synthase, or the atrial natriuretic peptide are direct determinants of blood pressure in mice. (Even here, Oliver utilized his imagination and experience with recombination to mimic quantitative changes. He duplicated genes in their endogenous locus to modestly increase gene product without any obvious effect on gene regulation.) Surprisingly, changes in the gene coding for the angiotensin-converting enzyme (ACE) do not alter blood pressures, even though ACE inhibitors are effective blood pressure-lowering drugs. By the use of computer simulations, Oliver was able to uncover the theoretical basis for this unexpected result.

These findings are of considerable help in understanding how genetic factors influence vascular disease in humans. Thus, demonstration by Oliver of gene targeting and its application to the study of genetics of complex but common diseases has generated new approaches to basic questions in physiology and medicine.

To this day, Oliver retains his boyish enthusiasm for science and cherishes the joy of conducting experiments with his own hands. His office still houses a telescope and he remains active at the bench most days including weekends. Oliver is convinced that continued "hands-on" science is key both to his success and to the continued pleasure he derives from being a scientist. Anticipation of the results is instrumental in compelling him to rush to the laboratory each day. In addition to bench work, Oliver continues to make important conceptual advances. For example, he recently developed a model that overturns approximately 30 years of dogma on kidney function and how the glomerulus limits the loss of protein. The insight came to Oliver when listening to a presentation on glomerular function in Stockholm. The conventional model did not make sense to him because it placed the supposedly coarse filter (the glomerular basement membrane) before the fine filter (the podocyte slit diaphragms). Since there is no rapid blood flow at the slit-diaphragm fine filter, this configuration would result in clogging. Oliver realized that the basement membrane must be the fine filter and that it accomplishes separation by gel permeation and diffusion. He spent the next 6 months learning about kidney function and evaluating this hypothesis. The article was published in 2003 and is gathering interest and support as it explains phenomena that could not be previously understood. Oliver has since continued with this new line of study. Rewardingly for Oliver, Sandy Ogston his Oxford mentor had a hand in this realization and latest change in research direction. Prior to Stockholm, Oliver had recently written Ogston's memoirs. He had reread all of Ogston's papers and was completely familiar with his equations for gel permeation and diffusion, highlighting the importance of older literature and a prepared mind.

In addition to his remarkable success in the laboratory, Oliver has had a remarkable life. He believes that to be successful three components are needed: good science, a good hobby, and a good family life. Regarding hobbies, Oliver is fond of sailing and flying.

He is particularly passionate about flying, especially gliding. Even in this area he has excelled and held two world records. In the fall of 1980, he asked his friend and original flight instructor Field Murray (named as he was born at an airfield and whose father flew with Lindbergh) to attend his cousin's wedding in England. Murray agreed as long as they could fly. Thus, Oliver became copilot in their attempt to gain speed records for a single-engine Cessna across the Atlantic. For the first leg of the transatlantic flight, they started at Goose Bay, Labrador, and headed for Reykjavik, Iceland. They encountered unexpected headwinds that raised serious concern about fuel levels (they had added no extra fuel tanks to the plane and had no GPS to be certain of location). At 23,000 feet over Iceland, they had to glide to ration fuel. They arrived at Reykjavik 13 min ahead of the previous record. From Reykjavik, they continued to Prestwick, Scotland, setting a second speed record for that leg of the flight.

Oliver has won many scientific honors including the top accolades: the Albert Lasker Award for Basic Medical Research in 2001, the Gairdner Foundation International National Award in 1990 and 1993 (one of only three two-time winners), and the Wolf Prize in 2003. He was elected to the National Academy of Sciences in 1971 and the American Academy of Arts and Sciences in 1978, was a Foreign Member of the Royal Society in 1998 and a Fellow of the American Association for the Advancement of Science in 1998, and was elected to the Institute of Medicine in 2003. Other honors not yet mentioned include the William Allen Memorial Award from the American Society of Human Genetics in 1964, the Karl Landsteiner Memorial Award in 1984, the Alfred P. Sloan Award of the General Motors Foundation in 1994, the American Heart Association's Ciba Award in 1996, the Bristol-Myers Squibb Award in 1997, the International Okamoto Award from the Japan Vascular Disease Research Foundation in 2000, one of Japan's highest honors, the Massry Award in 2002, and the March of Dimes award in 2005. He has received Honorary Doctorate of Sciences degrees from both the University of Chicago and Duke University (Durham, NC).

Simon John and Terry Magnuson