Frederick Sanger

(1918–2013)

Double Nobel-prizewinning genomics pioneer.

Frederick Sanger, 'the father of genomics', was one of just four scientists to win two Nobel prizes and the only one to receive both in chemistry. Both were awarded for the invention of methods to determine the order of the biological building blocks of life.

Sanger will be remembered especially for developing techniques to read out the As, Cs, Gs and Ts in a strand of DNA. This work provided the means to decipher genetic material and led to his second prize, which he shared with Paul Berg and Walter Gilbert in 1980. In the 1990s, Sanger's eponymous method was used by laboratories around the world to work out the sequence of the human genome.

His first prize came in 1958 for his discovery of how amino acids are strung together in the protein insulin. In the 1950s, many thought that the amino acids within a protein were arranged randomly, but Sanger proved beyond doubt that they instead form a unique sequence. Although he made light of this conclusion, saying that those who knew about proteins expected this outcome, the knowledge that proteins had a precise sequence suggested that this information must be codified in DNA.

Sanger, who died in Cambridge, UK, on 19 November aged 95, was born in 1918 in Gloucestershire. Raised as a Quaker, he learned self-reliance and practical manual skills as a schoolboy. These aptitudes were used to great effect in his laboratory and in building sailing boats.

He developed an interest in science from his physician father and his older brother, with whom he enjoyed the outdoors. In 1939, he graduated in biochemistry from St John's College, Cambridge. A conscientious objector, he stayed on at the University of Cambridge during the Second World War to study the nutritional benefit of lysine in potatoes under biochemist Albert Neuberger. In 1940, Sanger married Margaret Joan Howe, an economics graduate. They had three children and remained married until her death in 2012. Sanger ascribed his wife and his fellow researchers key roles in his success.

After receiving his PhD in 1943, Sanger began the research that led to his first Nobel prize, working out how amino acids link up in the two polypeptide chains of insulin. He labelled the ends of the separate chains with a yellow dye, then hydrolysed them to amino acids and identified the tagged amino acid in each case. After using acid and enzymes to split each chain into defined fragments, he tagged purified fragments with the dye and repeated the process. From this, and from the amino-acid composition of the fragments, he deduced the order of

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amino acids in the intact protein, rather like building up a picture from the pieces of a jigsaw puzzle.

Sanger preferred to be in the background but was not afraid to use his clout. He supported a successful bid to the UK Medical Research Council (MRC) to build the Laboratory of Molecular Biology in Cambridge, which opened in 1962. Here, Sanger spent the rest of his active scientific life.

After first working out ways to sequence RNA molecules, by which sequence information in genes is transferred into the sequences of proteins, Sanger took up the challenge of sequencing genes themselves. He developed a method that used enzymes to copy fragments of DNA. Four reactions were set up side by side, each supplied with the four standard building blocks, or nucleotides, (As, Cs, Gs and Ts), one of which was labelled with radioactive atoms. Each reaction also contained a modified version of A, C, G or T. Unlike standard nucleotides, these 'chain terminators' did not allow the DNA strand to grow further after they had been incorporated. Interrupted copies were separated according to their size on gels by an electric current and exposed to photographic film, allowing the radioactivity to produce the now-iconic 'ladders' of dark bands. These bands revealed the length of the DNA copy and allowed the sequence to be read simply. By combining sequences of many DNA fragments, the sequence of the larger DNA molecule from which the fragments were derived could be deduced.

Sanger demonstrated the power of his method by sequencing genomes of ever-increasing size, starting with a simple bacterial virus (5,386 nucleotides) in 1977, then the DNA in the mitochondria of human cells (16,569 nucleotides) in 1981 and, finally, the genome of a complex bacterial virus, bacteriophage lambda (48,502 nucleotides), in 1982.

In 1993, nine years after Sanger retired, the Wellcome Trust and the MRC opened the Sanger Centre (now the Wellcome Trust Sanger Institute) near Cambridge, where a considerable part of the human genome was decoded with the technique he developed. In the 2000s, Sanger sequencing gradually gave way to faster, cheaper techniques that detect nucleotides as they attach to growing DNA strands. But Sanger sequencing remains the gold standard. The highly accurate technique is increasingly being applied to the genomes of individual humans and even individual cells within tumours. Sanger's impact on biology is as dramatic as that of Charles Darwin.

Sanger was happiest at the laboratory bench, where he worked tirelessly and single-mindedly. He performed elegant experiments with simple apparatus to solve extremely difficult problems. In so doing, he inspired younger scientists and attracted some of the best biologists in the world to Cambridge.

Sanger was famously understated, but he knew that he was an extraordinary scientist, and when the occasion demanded it he was prepared to say so. When colleagues assembled after the announcement of his second Nobel Prize, one praised his characteristic modesty. Sanger responded: "I want you all to know that I think that I am bloody good." He was showered with awards and quietly enjoyed the recognition. After retirement, he continued to build boats and developed a magnificent English garden. ■

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