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Legacy

The legacy of Rosalind E. Franklin: Landmark contributions to two Nobel Prizes

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Rosalind Franklin's short scientific carrier produced brilliant contributions to the structure of carbon, DNA, and helical and spherical viruses. At 30, she was a recognized authority who switched from carbon to DNA research and, a few years later, to nucleic-acid-protein complexes known as viruses. She made landmark contributions that led to two Nobel Prizes. She did not receive or witness either of them. 100 years after her birthday, Franklin's scientific contributions are even more important now than during her lifetime.

On May 6, 1952, Rosalind Franklin and her PhD student Raymond G. Gosling recorded at the King's College London Medical Research Council (MRC) Biophysical Unit, led by Sir John Randall, the landmark photograph 51 (photo 51) that has been called by J.D. Bernal "among the most beautiful X-ray photographs of any substance ever taken." At that time, Rosalind Franklin was 31 years old and a recognized authority in the crystallography of coal and graphite. Photo 51 was taken from an oriented fiber of DNA at high humidity. Rosalind called it the B form of DNA, or B-DNA, whereas low-humidity DNA was named A-DNA.

Watson suggested that Franklin would have ideally been awarded the Nobel Prize in Chemistry along with Wilkins, but although there was not yet a rule against posthumous awards, the Nobel Committee generally did not give them.

Without her knowledge, in January 1953 her colleague Maurice H.F. Wilkins showed photo 51 to Francis H.C. Crick and James D. Watson from the Cavendish Laboratory of Cambridge University; they used it to build, between the end of February and March 7, 1953, the classic model of the double helix of DNA. On April 25, 1953, three papers[1–3] that changed our view of the world were published. "The structure of the DNA double helix, with its complementary base-pairing, is one of the greatest discoveries in biology in the 20th Century. It was also most dramatic, since, quite unexpectedly, the structure itself pointed to the way in which a DNA molecule might replicate itself, and hence revealed the 'secret of life.' The structure was solved in the Cavendish Laboratory, Cambridge by Francis Crick and James Watson, using X-ray diffraction data from [fibers] of DNA obtained by Rosalind Franklin at King's College, London."[3–5] In 1962, Francis Crick, James Watson, and Maurice Wilkins were awarded the Nobel Prize for Physiology or Medicine for "their discoveries concerning the molecular structure of nucleic acids and its significance for information transfer in living material." Watson suggested that Franklin would have ideally been awarded the Nobel Prize in Chemistry along with Wilkins, but although there was not yet a rule against posthumous awards, the Nobel Committee generally did not give them.

Above image: Rosalind Franklin. Credit: Elliott & Fry and the National Portrait Gallery.

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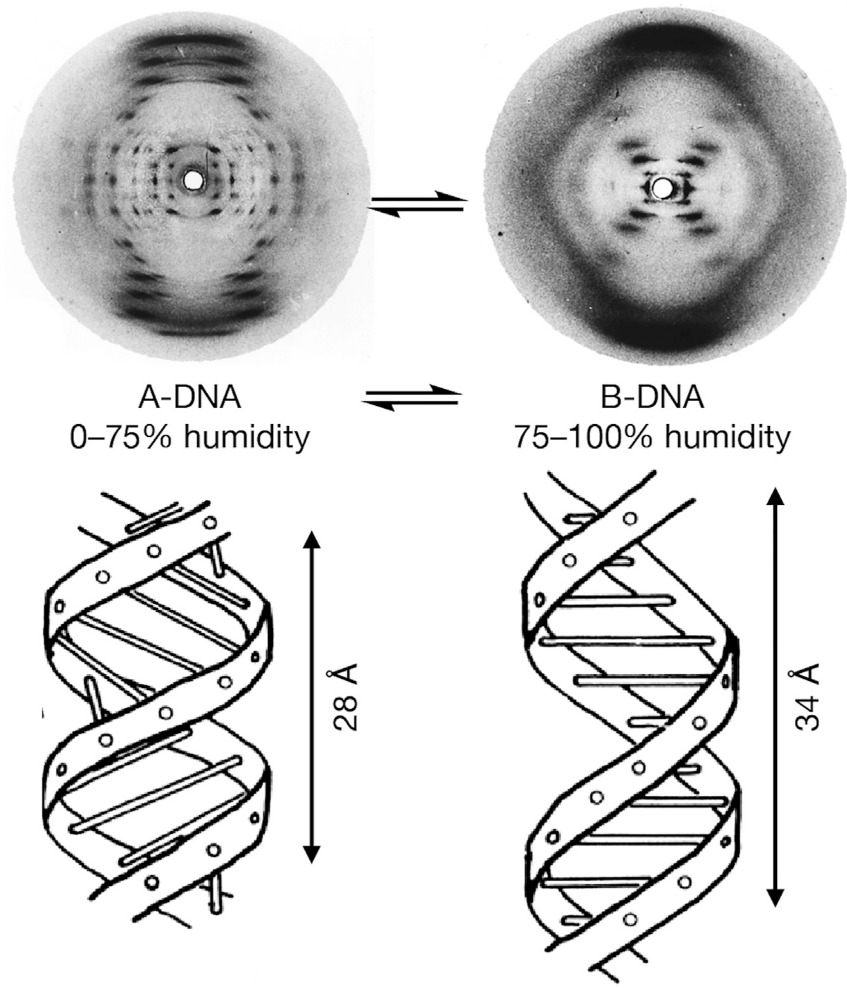

X-ray diffraction patterns of two forms of DNA: A-DNA and B-DNA. Originally published by Franklin and Gosling[13] and reproduced from Klug.[5] Copyright 2015 Elsevier.

At King's College, Randall did not communicate Rosalind Franklin's role to Maurice Wilkins, who was expected to become her boss, when she joined his lab on a Turner-Newal fellowship. This led to an unfriendly relationship between both. On March 14, 1953, at the invitation of J.D. Bernal, Rosalind Franklin joined the Physics Department of Birkbeck College, University of London, where she was offered an independent research group. At Birkbeck College, Rosalind Franklin switched from studying DNA to tobacco mosaic virus (TMV). She made an immediate impact on the structure of TMV.[6–11] She also demonstrated great organizing talent by attracting an excellent group of young scientists to Birkbeck College, including Aaron Klug, who later received the Nobel Prize in Chemistry in 1982 "for his development of crystallographic electron microscopy and his structural elucidation of biologically important nucleic acid-protein complexes." One of us (V.P.) attended his lecture and had dinner with him after the lecture, the evening before his Nobel Prize was announced. In his Nobel lecture, Aaron Klug stated, "In seeking to

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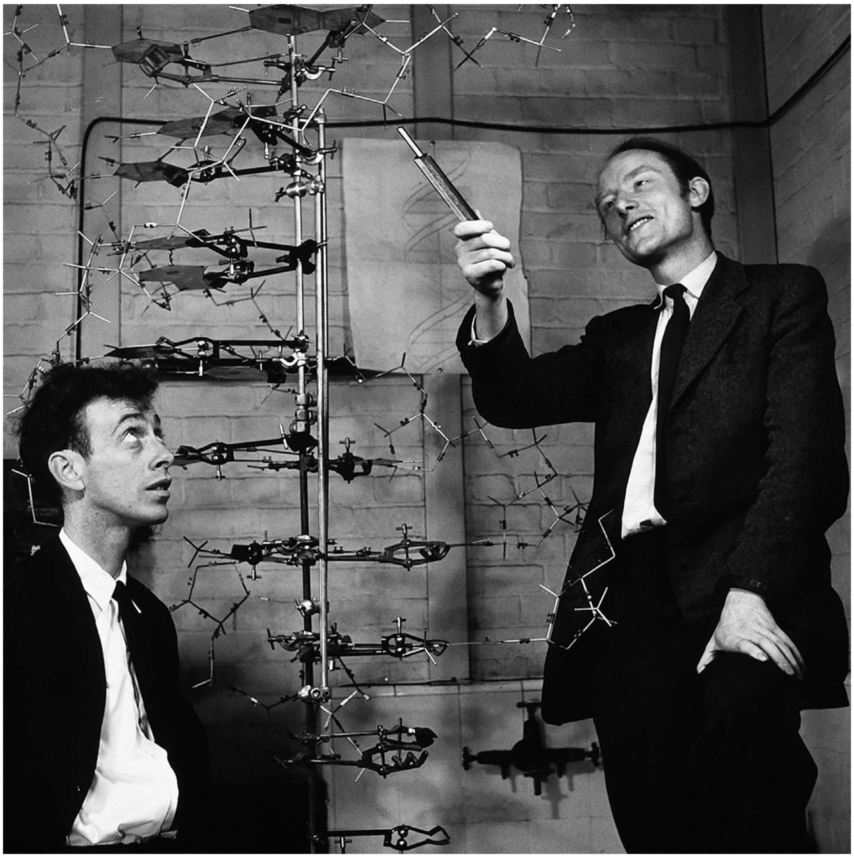
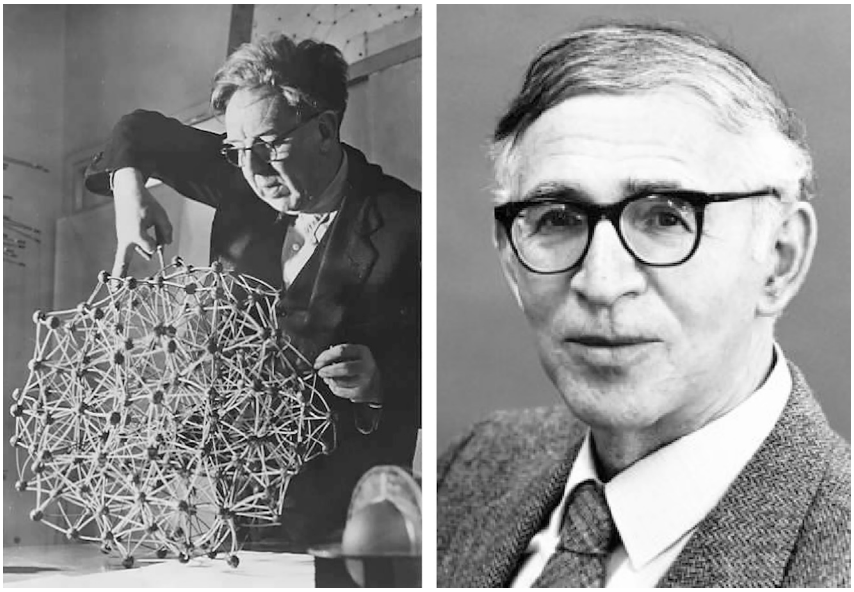

Watson and Crick with the DNA double-helix model. Credit: Antony Barrington Brown.

understand how proteins and nucleic acids interact, one has to begin with a particular problem, and I can claim no credit for the choice of my first subject, tobacco mosaic virus (TMV). It was the late Rosalind Franklin who introduced me to the study of viruses and whom I was lucky to meet when I joined J.D. Bernal's department in London in 1954. She had just switched from studying DNA to TMV, X-ray studies of which had been begun by Bernal in 1936. It was Rosalind Franklin who set me the example of tackling large and difficult problems. Had her life not been cut tragically short, she might well have stood in this place on an earlier occasion."[12] Thus, Rosalind Franklin had made landmark contributions to two Nobel Prizes but did not receive or even witness either of them.

Rosalind Elsie Franklin was born in London, England, UK, on July 25, 1920, and died of cancer in London on April 16, 1958. She was educated at elite private schools, where she demonstrated great intelligence and an unusual gift for science, as she indicated in a letter to her father from the summer of 1940. "Science and everyday life cannot and should not be separated. Science, for me, gives a partial explanation of life. In so far as it goes, it is based on fact, experience and experiment." She obtained her undergraduate degree in science from Newnham College, Cambridge University, in 1941 and a PhD in physical chemistry from Cambridge University in 1945.

In the absence of this race, Rosalind Franklin would have solved the structure of DNA on her own, as shown in a draft to *Nature* dated March 17, 1953, one day before she saw the manuscript of Watson and Crick.



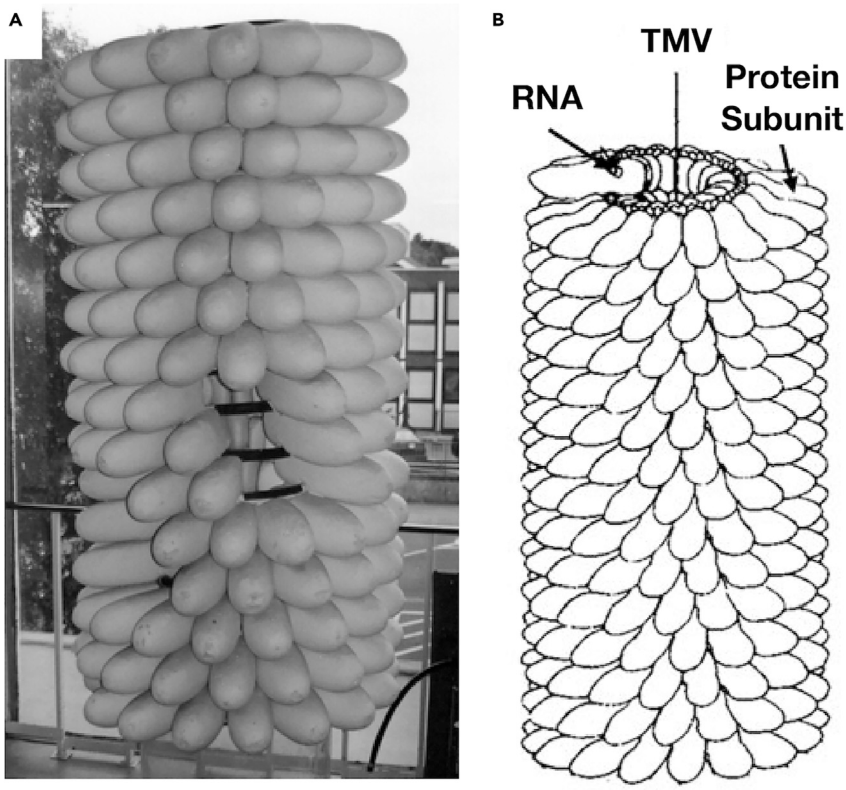
Portraits of J.D. Bernal (left; reproduced from Finney,[19] copyright 2007 IOP Publishing Ltd) and Aaron Klug (right; copyright 1982 the Nobel Foundation).

On February 14, 1947, she started a postdoc with Jacques Mering at the Centre National de la Recherche Scientifique in Paris, where she became an accomplished crystallographer. In January 1951, she was appointed on a Turner and Newall Fellowship in the MRC Biophysical Unit of King's College London. Her letter of appointment, written by Sir John Randall on December 4, 1950, underscores Rosalind's sole responsibility of this project: "On the experimental X-ray effort there would be at the moment only yourself and Gosling, together with a temporary assistance of a graduate from Syracuse, Mrs. Heller."[5] Wilkins, a senior research associate in the same laboratory, was on vacation at that time and was never informed by Randall about the independent appointment of Rosalind Franklin or her precise role. Wilkins handed the DNA material he received from Professor Signer from Bern to Rosalind. Together with Gosling, he obtained oriented fibers exhibiting remarkably good diffractograms, which Rosalind would later call A-DNA.

In a very rapid and crucial advance, Rosalind controlled the humidity of the X-ray camera chamber and discovered the A-DNA at below 75% humidity and the B-DNA at higher humidity, as well as the humidity-mediated reversibility between these two DNA forms.[13,14] The B-DNA recorded on May 6, 1952 (with preliminary data obtained by September 1951) is the spectacular photo 51 that received iconic status and that Watson and Crick used to solve the double helix of DNA.[4,5,13,14] Rosalind discussed part of this work in her colloquium given at King's College in November 1951. In this lecture, attended by Watson, Rosalind explained several potential helical DNA structures all with the sugar-phosphate backbone toward the exterior.[5] Watson returned to Cavendish Laboratory and built together with Wilkins a triple-helix DNA model with the phosphate toward the interior. Rosalind was asked to visit and see their model. In front of Bragg, she asked where the water was and received the reply that there was none. After this debacle, Bragg vetoed any further work on DNA in Cambridge. The Cavendish Laboratory was at that time under the influence of the lost race of Bragg, Kendrew, and Perutz[15] to Pauling's α-helix[16] of proteins. Sir

Part of the Rosalind Franklin group at the International Union of Crystallography Symposium on "Structures on a Scale between the Atomic and Microscopic Dimensions" in Madrid in April 1956. From left to right: Anne Cullis, Francis Crick, Donald Caspar, Aaron Klug, Rosalind Franklin, Odile Crick, and John Kendrew. Credit: Donald Casper.

Lawrence Bragg, the youngest scientist to receive a Nobel Prize at the age of 25, called this lost race "the greatest fiasco of my scientific life." Linus Pauling received the Nobel Prize in Chemistry in 1954 "for his research on the nature of the chemical bond and its applications to the elucidation of the structure of complex substances." Kendrew and Perutz received the Nobel Prize in Chemistry in 1962 "for their studies on the structures of globular proteins." Rosalind, aware of this disappointment of the Cavendish Laboratory, was very careful in supporting her hypothesis with strong experimental evidence. Early in 1953, Rosalind and the Cavendish Laboratory knew about a triple-helix model with a central phosphate-sugar backbone as suggested by Pauling for DNA,[17] just like the incorrect one proposed in the first model by Watson and Crick, and that it was incorrect. The Cavendish Laboratory knew Pauling would eventually correct his chemically impossible DNA model and did not want to lose a second race to him. At that point, this race for the DNA structure was still open. Crick stated to Bragg: "I doubt this Pauling was a man with great insight, but not a magician, who could manage without data."[5] In January 1953, Wilkins showed photo 51 from Rosalind Franklin to Crick and Watson, and within 1 week they built their famous model by using the helical diffraction theory,[18] which Crick developed to solve the Pauling debate on the α-helix of proteins. When referring to the helical diffraction theory, Crick and Kendrew stated: "Armed with the appropriate theory it is often possible to recognize the helical nature of a fiber structure at a glance, and sometimes to specify the main parameters of the helix and its subunits with very little trouble indeed." And when referring to the double-helix DNA model based on photo 51, Crick stated: "It did mean that I had the expertise at my fingertips."[18] In



(A) TMV model constructed for the International Exhibit in Brussels in 1958; it now sits in a stairwell in the Cambridge Laboratory of Molecular Biology (copyright Gregory J. Morgan). (B) TMV model by Rosalind Franklin and Aaron Klug[12] (copyright 1982 the Nobel Foundation and John Wiley & Sons).

the absence of this race, Rosalind Franklin would have solved the structure of DNA on her own, as shown in a draft to *Nature* dated March 17, 1953, one day before she saw the manuscript of Watson and Crick.[4]

After moving to Birkbeck College, Rosalind got involved in the race for the understanding of the structure of nucleic-acid-protein complexes, known as viruses. She obtained high-resolution X-ray photographs and demonstrated the helical structure of the rod-like TMV, the location of the RNA, the helical conformation of RNA in the helical TMV, and the disassembly and reassembly of TMV.[6–9] She also initiated research on the structure of spherical viruses.[10] Some of this work on poliomyelitis virus was continued, finished, and dedicated to her after her death.[11] She continued to work and publish to the last minute of her life.

In the summer of 1956, Sir Lawrence Bragg invited a group of molecular biologists, including Crick, Watson, Kendrew, and Franklin, to contribute to the upcoming 1958 World's Fair in Brussels. He was very specific that he was impressed by the work done by Franklin on the helical and spherical viruses and wanted a proper place for these results in this exhibition. On April 16, 1958, just as the exhibition in Brussels opened to international acclaim (where an over 5-ft-tall TMV helix model, built by Rosalind, would be on display), Rosalind Franklin passed away from cancer. The inscription on her tombstone from the London cemetery reads: "In Memory of Rosalind Elsie Franklin. Dearly loved elder daughter of Ellis and Mauriel Franklin, 25th July 1920 –

16th April 1958, Scientist. Her research and discoveries on the viruses remain of lasting benefit to mankind." Her DNA work is not mentioned on the tombstone. Rosalind Franklin's work on helical and spherical viruses is more important now than when it was actually done; it has even had an impact on the design of current vaccines for coronavirus disease 2019 (COVID-19). Franklin's science remains fundamental to the structure of biological macromolecules and their complexes and therefore to the most basic principles of supramolecular science. She will always remain a role model for many generations of scientists.

ACKNOWLEDGMENTS

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