Aaron Klug (1926–2018)

Aaron Klug was one of the scientific giants of the twentieth century and a pioneer in the field of structural biology. He was awarded the 1982 Nobel Prize in Chemistry for his development of 'crystallographic electron microscopy' and his structural elucidation of biologically important nucleic acid–protein complexes. Aaron was the Director of the Medical Research Council (MRC) Laboratory of Molecular Biology (LMB) from 1986 to 1996, and the President of the Royal Society from 1995 to 2000. He was knighted in 1988 and appointed to the Order of Merit in 1995 for his services to science. Aaron passed away on 20 November 2018, at the age of 92, in Cambridge, UK, where he had worked for over half a century.

Aaron's path to science is inspiring. He was born in 1926 in Lithuania to Jewish parents, but his family moved to South Africa when he was 2 years old. After a detour into premedical studies, he graduated with a Bachelor of Science degree from the University of Witwatersrand in Johannesburg and went on to receive a Master of Science degree from the University of Cape Town. Having been awarded an 1851 Research Fellowship from the UK's Royal Commission (awarded to young scientists or engineers with exceptional promise), he was able to travel to England to study, completing his PhD in solid-state physics at Trinity College Cambridge in 1953. As Aaron himself has stated, this PhD did not lead anywhere directly, but it prepared him for things to come and sparked his interest in understanding how structures are organized.

Credit: MRC LMB archive

After obtaining his PhD, Aaron moved to London to Birkbeck College, where he met Rosalind Franklin—a meeting that determined his future scientific career. With Franklin, the X-ray crystallographer who obtained the X-ray diffraction data that allowed Watson and Crick to propose the double-helical structure of DNA, he started working on the structure of helical viruses (the tobacco mosaic virus, which infects tobacco plants) by using X-ray diffraction. With that work, Aaron made the transition to biology, primarily to structural biology, in which he made multiple contributions, both in developing methods and in deciphering the structures of important protein–DNA complexes.

In 1962, Aaron returned to Cambridge to the newly built LMB, joining a stellar group of colleagues: LMB founder Max Perutz, Fred Sanger, Francis Crick, Sydney Brenner and John Kendrew, all of whom went on to be awarded Nobel Prizes. With them, he played a key role in the molecular and structural biology revolution that occurred in the 1950s through 1960s. With John Finch, a lifelong collaborator, Aaron started to image viruses through electron microscopy, and with Don Caspar, he proposed the general principles that underlie the structural organization of viruses[1]. But more importantly, this work led to the development of a novel method to determine the three-dimensional structure of large protein complexes that were not suitable for conventional X-ray crystallography, the structural method of choice at that time. The novel method was named crystallographic electron microscopy, a term that Aaron did not like; instead, he preferred 'Fourier electron microscopy'. With David DeRosier, Aaron figured out how to combine X-ray diffraction methods with the Fourier transform of electron micrographs to reconstruct three-dimensional structures from two-dimensional images, thus revolutionizing how complex structures are imaged and their images are interpreted[2]. This visionary early work is the basis upon which the more recent 'resolution revolution' in cryo-electron microscopy is built.

Aaron had a wide range of interests, and to him, structural information was a means to understanding biological function. In the late 1960s, he became interested in the structure of tRNA, the famous adaptor molecule originally proposed by Crick.

It was at this time that I encountered Aaron—he gave me my first job as a lowly technician, purifying and crystallizing tRNAs, and I was fortunate to work closely with him for the next two decades. The tRNA project was very challenging and competitive, and after a heroic effort to find derivatives required to obtain phase information, the structure of yeast phenylalanine tRNA—the first crystal structure of a nucleic acid—was determined to atomic resolution in 1974 (ref. [3]). This work later led him to determine the crystal structure of the hammerhead ribozyme found in some plant viruses.

Aaron also became interested in chromatin and the mechanism through which DNA is packaged into chromosomes. In the 1970s, work by his postdoctoral fellow Roger Kornberg (Nobel Prize in Chemistry in 2006) and other colleagues first led to the definition of the building block of chromosomes, the nucleosome[4], and later to the still-contested higher-order structure of chromatin[5]. The unraveling of the structure of chromatin is the result of Aaron's ingenuity, combining biochemistry with electron microscopy and X-ray diffraction to achieve an understanding of the nucleosome-core structure, consisting of two superhelical turns of DNA wound around an octamer of histones. The work is also a testament to his unparalleled ability to combine theory and mathematical physics to solve a practical problem. Because I had worked on crystallizing tRNA, Aaron brought me into the nucleosome-core project; the first crystals were obtained in 1976, and a medium-resolution structure was obtained in 1984 (ref. [6]). For that work and the development of crystallographic electron microscopy, Aaron was the single recipient of the Nobel Prize in Chemistry in 1982.

An interest in understanding the differences between active and inactive chromatin led Aaron to transcriptional regulation and the discovery of the zinc-finger DNA-binding module. Aaron's proposal of the zinc finger is another example of his intuition and knowledge. The idea arose overnight after he had studied the amino acid sequence of the *Xenopus* transcription factor TFIIIA and observed by eye a regular pattern of pairs of cysteines and histidines approximately every 30 amino acids. Remembering that zinc is tetrahedrally coordinated to cysteines and histidines, he came up with the idea of the zinc-finger module, a stretch of 30 amino acids folded around a zinc atom[7]. The discovery of this family of abundant proteins (2–3% of the genes in the human genome encode zinc fingers), in which each zinc finger reads 3 bp of DNA, as well as information from the structures of zinc-finger–DNA complexes, led to the engineering of a phage-display zinc-finger library by Aaron's graduate student Yen Choo[8]. By selection, one could then identify 'fingers' able to bind to a number of DNA triplets and, by stringing together a set of zinc-finger modules, achieve the recognition of any DNA sequence. This technology has been exploited to produce zinc-finger nucleases that facilitate the targeted editing of the genome by introducing double-strand breaks at predetermined DNA locations, thus opening the door to therapeutic possibilities.

Aaron transformed the lives of the people who worked with or knew him. He liked interacting with young people, because he believed that "they keep you on your toes," and he continued to be a tutor at his University of Cambridge college, Peterhouse, after being awarded the Nobel Prize. From him, we learned how to think about science—how to ask bold questions, develop a hypothesis and design a clever experiment to test it, and to be extremely rigorous in interpreting results. Working with Aaron also meant learning to take criticism—he could be a fierce critic but a forgiving one—and understanding that all that matters in science is getting to the truth. He taught us that "human curiosity, the urge to know, is a powerful force and is perhaps the best secret weapon of all in the struggle to unravel the workings of the natural world." Aaron had a photographic memory and a fantastic power of deduction, being able to draw correlations among different facts and bits of information. It was awe inspiring to see how, while carrying out discussions in his office, he was able to locate a folder among a wall of hundreds of brown folders, pull out a reprint, open it to a specific page and then proceed to read out some information pertinent to the discussion. He would often start a sentence with "Not many people know this, but…" and follow it with some insightful scientific fact or story, which was often a meandering detour into history or another subject but was always enlightening because Aaron was a polymath. He has left us with many wonderful memories of how science should be done, and he will be greatly missed. His legacy is his science and a generation of researchers whose science he shaped. ❐

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