Lily Huschtschain

Robin Holliday 1932–2014

Penny Jeggo & Fotini Gounari

It takes an extraordinary talent to accurately describe a biological process from limited available data. It is more remarkable when charisma is combined with the ability to identify key fundamental questions that pave the path for entirely new research areas. Robin Holliday possessed these distinguishing traits and survived to see several of his proposed models withstand decades of experimental scrutiny and remain as the founding principles for various scientific fields. Robin died peacefully on 9 April 2014 in Sydney.

Robin, a British national, was born in the British Mandate of Palestine in 1932. He spent his childhood and adolescence in Sri Lanka, South Africa and Gibraltar before returning to Britain to complete his secondary education. He continued his studies at Cambridge University, where he graduated in 1955 with First Class Honours in Natural Sciences. After a successful career in the UK, Robin moved in 1988 to Sydney, where he continued his research until his retirement in 1997.

Robin started his research career at the John Innes Institute in 1958, only three years after the structure of DNA was revealed by Watson and Crick to be a double-stranded helix. During his PhD work and early research career, he established genetic experimental models using the parasitic dimorphic fungus *Ustilago maydis*. These included the isolation of the first eukaryotic mutants in DNA repair and recombination, which established the proof of principle that such mutants could be obtained from genetic screens. Robin's own research, as well as earlier studies on fine-structure genetic mapping, strongly suggested that DNA molecules must be capable of recombining with homologous partners.

Robin proposed a molecular model, based on the insight provided by these studies, to describe the process of homologous recombination. In this model, unraveling DNA strands anneal with complementary bases in opposite partners, thus accounting for the genetic phenomenon of crossing over. Robin went on to suggest that if the crossover occurred at a DNA site where the parental molecules differed, the mismatched region would be corrected, and this would lead to gene conversion, a form of inheritance that does not follow Mendel's laws. He proposed that the point at which the strands exchanged partners would be the site of DNA recombination. Robin predicted that the DNA structure at this exchange point would be a symmetrical four-way junction that could be resolved in either of two orientations, to yield DNA molecules with distal genetic markers in the recombinant or the parental configuration. Publication of this model stimulated discussion and experimentation worldwide, and the model became known as the Holliday model. Its major predictions, including the formation of the symmetrical four-way intermediate, now known as the Holliday junction, were confirmed experimentally in numerous laboratories. The Holliday model has been elaborated upon and amended over the past five decades to accommodate and explain new genetic data, but the four-way Holliday junction is universally recognized as the central intermediate structure underpinning genetic recombination in all domains of life.

Bernie Broughton

Robin's sculpture depicting the DNA crossover, on show at the Genome Damage and Stability Centre, University of Sussex.

In 1965, Robin moved to the National Institute for Medical Research in Mill Hill, London. Three years later, he was promoted to head the Genetics Division, which grew dramatically under his leadership and thrived as a highly successful research environment. Here, Robin expanded his research interests to encompass epigenetics and aging. In 1975, Robin and his student John Pugh proposed a model to explain how the pattern of gene expression between tissues or cell types differs, even though cells share the same DNA. They predicted that epigenetic mechanisms silence groups of genes and that the pattern of such silencing should be heritable. Their molecular model for the heritable switching of gene activities was based on the methylation of C residues in DNA. This model, based entirely on theoretical considerations, suggested that DNA methylation would control gene expression and establish tissue-specific expression profiles during development. Further, to account for the heritability of methylation, they predicted the existence of a maintenance DNA methyltransferase that would recognize hemimethylated DNA shortly after replication and copy the pattern on the newly synthesized strand. The proposal that methylation causes gene silencing proved to be correct, and the model is now supported by substantial evidence, some of which emerged from Robin's own studies on epigenetic regulation. Moreover, maintenance DNA methyltransferase enzymes have been identified and characterized, proving that heritable patterns of DNA methylation indeed provide a mechanism to regulate developmental processes.

As understanding of the importance of maintaining genome integrity grew, the close interface between cellular and organismal aging came to be appreciated. This represented a third area of research in which Robin made notable contributions. Through longstanding association with Leslie Orgel, Robin played a leading part in testing Orgel's hypothesis that cyclical feedback of errors in protein synthesis might have a fundamental role in aging. He used an array of biological models, from *Escherichia coli* to primary human cells in culture, to address the mechanisms of cellular senescence and aging. Robin's interest in the molecular causes of aging helped to spotlight this crucial problem in biology.

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At the National Institute for Medical Research, Robin led a team of researchers that made important contributions to all the areas mentioned above. He trained many scientists who have progressed to run their own laboratories or pursued other careers within science. During this time, he also hosted many visiting scientists from around the world. For many of us, the learning experience at the Genetics Division occurred at multiple levels, including philosophical discussions during coffee breaks on such diverse questions as the evolution of morals. Robin often led these discussions, which provided a profound perspective on everyday research and emerging scientific questions. For the younger students, there was constant intellectual stimulation, with Robin insisting that we should never stop thinking about the relevance of our findings to the fundamental principles of life. In this way, Robin endowed us with a passion for science.

Robin was a prolific writer, continuing to publish well after his retirement. In addition to research publications, he wrote a large number of reviews covering scientific as well as historical reflections. He was a Fellow of the Royal Society, a member of the European Molecular Biology Organization, a member of the Australian Academy of Science and a Foreign Fellow of the Indian National Science Academy. He received prestigious awards including the Royal Medal, one of the Royal Society's premier awards, highlighting excellence in science, and the Lord Cohen Medal for Gerontological Research. Finally, Robin was also an outstanding sculptor, with many of his sculptures inspired by his biological studies. Some of his sculptures are now on display in scientific institutions including the Royal Society, the Laboratory of Molecular Biology in Cambridge, UK and the Genome Damage and Stability Centre in the University of Sussex.

Robin mentored us to the end of his life. His last advice to Fotini, two weeks before his death was: "Do good science, and don't worry about the rest." How characteristic of Robin, and how priceless this advice will always be.