OBITUARY

Hidesaburo Hanafusa (1929–2009)

Inspiration and innovation in molecular cancer research.

THE ROCKEFELLER UNIV.

Much of the molecular basis of cancer was revealed by research done during the last 40 years of the twentieth century, radically changing both diagnosis and treatment. One of the most influential and prolific contributors to this era was Hidesaburo Hanafusa, who died on 15 March at the age of 79. In the 1960s and early 1970s, Hanafusa's investigations of RNA 'tumour viruses' established that the cancer-causing genes of these retroviruses, now called oncogenes, have counterparts in normal animal and human cells. Then, during the 1980s and 1990s, work from his group on retroviral oncogenes provided insights into how cellular genes that normally regulate intracellular signalling go awry in cancer cells.

Born and educated in Japan, Hanafusa came to the United States in 1961 to work in Harry Rubin's laboratory at the University of California, Berkeley. The ability to quantitatively study the viral transformation of normal cells into cancer cells using the 'focus assay' had just been developed there by Howard Temin. While in Rubin's lab, Hanafusa published papers that laid the foundation for the 'oncogene hypothesis' of cancer.

Rubin and another postdoctoral fellow in the lab, Peter Vogt, had discovered that preparations of Rous sarcoma virus — RSV, first discovered in a chicken sarcoma by Peyton Rous in 1911 — contained another virus, which they called Rous-associated virus (RAV). Rubin suggested that Hanafusa try to isolate pure RSV and, in doing so, Hanafusa discovered that RSV was 'defective' — meaning that it lacked the genetic components necessary to replicate itself, but was able to transform normal cells into cancer cells. Hanafusa and Rubin isolated transformed cells infected with RSV that did not produce infectious virus. RAV was a 'helper' virus that provided the viral genes needed for replication. In return, the cancer-causing RSV promoted host-cell proliferation, aiding RAV in the production of the components needed for virus replication. This explained why the two viruses propagated together. That the non-transforming RAV could replicate without RSV, and that RSV could transform cells without RAV, implied that RSV carried a gene (or genes) that was not required for viral replication but was responsible for cell transformation and tumour growth. This was the earliest clear indication of the existence of a transforming oncogene.

Hanafusa established his own lab with his wife Teruko — herself a noted virologist — at the Public Health Research Institute of the City of New York in 1966, and in 1973 moved uptown to The Rockefeller University. By this time, the region in RSV responsible for transformation had been mapped, and the gene located in this region had come to be known as *src* — for sarcoma. Hanafusa's and also Vogt's continuing research provided a foundation for the well-known 1977 report from the Hanafusa lab demonstrating that a transformation-defective RSV mutant was able to recover the ability to transform from a host cell. The reconstituted virus had regained the *src* gene. This work closely followed the classic 1976 report from the laboratories of Michael Bishop and Harold Varmus demonstrating that viral *src* sequences are similar to sequences in uninfected cells. The recovery of an active transforming *src* (later shown to be mutated) from a host cell by a transformation-defective virus confirmed that the sequences responsible for viral oncogenesis are captured and mutated cellular genes. Hanafusa shared the 1982 Lasker award with Bishop and Varmus for this work.

Subsequent research in many other laboratories identified other mutated cellular genes that had been captured by transforming retroviruses, including the well-known *ras* oncogene. All of these studies substantiated the hypothesis that cancer-causing genes carried by transforming retroviruses are mutated, usually overactive, versions of normal cellular genes. In 1982, it was discovered that DNA isolated from human cancer cells could by itself induce transformation in mouse fibroblast cells in culture. The gene in this human DNA was a mutant form of a gene originally characterized as a retroviral oncogene — namely, *ras*.

In the 1980s, Hanafusa's research shifted to the structure and function of proteins encoded by viral oncogenes. By this time it had been discovered that the *src* gene product was a protein kinase — an enzyme that phosphorylates and so regulates other proteins — and that it was specific for the tyrosine amino acid. In 1982, Hanafusa's group published the sequence of the Fujinami sarcoma virus and its oncogene *fps*, which, like *src*, also encodes a tyrosine kinase. Sequencing of *fps* revealed similarities between *fps* and *src*. This point did not escape the notice of Tony Pawson, who identified regions in *fps* that were homologous to regions in *src* — most significantly, the now-famous *src*-homology domain SH2. The significance of this discovery became evident when Hanafusa's group revealed that the *crk* oncogene, carried by the CT10 transforming retrovirus, encoded a small protein that consisted only of SH2 and another domain with homology to *src* — the SH3 domain.

In the early 1990s, Hanafusa's group, along with Pawson and Bruce Mayer, a Hanafusa lab graduate working in David Baltimore's lab, went on to demonstrate that SH2 domains bind proteins in a manner that depends on tyrosine phosphorylation. This observation provided a molecular explanation for the protein–protein interactions induced in response to the phosphorylation of proteins on tyrosine. For this and all his previous work, Hanafusa received the 1993 General Motors Sloan award.

With the untimely death of Teruko, his life-long collaborator, in 1996, Hanafusa left Rockefeller in 1998 to become the director of the Osaka Bioscience Institute in Japan, where he continued to contribute to our understanding of oncogenesis while inspiring a new group of Japanese scientists. He retired from the institute in 2008.

Apart from his enduring contributions to an unprecedented era of cancer research, Hanafusa trained a host of graduate students and postdoctoral fellows, many of whom have had notable scientific careers of their own. Hidesaburo Hanafusa had much to be proud of during his long scientific career. But perhaps his most enduring legacy will be his inspiration and nurturing of a generation of scientists who revered him for his sagacity, and for his warmth and quiet support.

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