

# This Week's Citation Classic®

Harris H & Watkins J F. Hybrid cells derived from mouse and man: artificial heterokaryons of mammalian cells from different species. *Nature* 205:640-6. 1965.  
[Sir William Dunn School of Pathology, University of Oxford, England]

A parainfluenza virus inactivated by ultraviolet light was used to fuse together cells derived from mouse and man. The resulting heterokaryons were viable, and some went on to form hybrid mitoses and single composite nuclei containing both human and mouse chromosomes. [The SCI® indicates that this paper has been cited in more than 510 publications.]

## Four Accidents and an Idea

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The first accident was that, after seven years' work on animal cells in the Dunn School at Oxford, I was offered a job at a botanical institute, the John Innes at Bayfordbury. This brought me into contact for the first time with the green world, and more particularly with John Fincham, who was working with *Neurospora* in an adjoining laboratory. The parasexual genetic exchanges achieved in *Neurospora* by fusion of hyphae suggested to me that great things might be expected if we could bring about such exchanges in animal cells by some analogous process. That was the idea, but I couldn't see how it could be done.

The second accident was the arrival of an issue of *Experimental Cell Research* that contained three papers by Okada and his colleagues. They showed that cells could be rapidly fused together by HVJ (Sendai) virus and

that the ability of the virus to fuse the cells was not impaired by inactivation with ultraviolet light. That showed me how my idea might be put into practice; but for a number of humdrum reasons I did nothing about it. The third accident was that I was appointed to succeed Howard Florey at Oxford in 1963 and returned to the Dunn School. The fourth was that the staff there now included a virologist, John Watkins, who was familiar with all the virological techniques that would be required.

I wanted to fuse cells from different species because interspecific crosses would provide a plenitude of stable genetic markers, which were in short supply in animal cells. I was convinced that cells from different species would accept each other if amalgamated into a single unit. John got the ingredients together, and when we tried the experiment it worked the first time. Within a few months we knew we could fuse any cell with any other, across species and across differentiation.<sup>1</sup> We had imposed on the cells of the body a form of artificial sexuality that was completely promiscuous. For somatic cells, the consequences of this discovery were much like those produced in microbiology by the discovery of bacterial sexuality. There are far too many to enumerate; within a decade it was possible to devote a large textbook to the subject.<sup>2</sup> If I had to choose no more than four developments, one to commemorate each of the four fortunate accidents, my choices would be (1) the mapping of human genes, (2) the analysis of differentiation, (3) monoclonal antibodies, and (4) the discovery of tumour suppressor genes.<sup>3,4</sup>

Anyone interested in reading a fuller account of this unlikely story might find a source of amusement in *The Balance of Improbabilities*.<sup>5</sup>

1. Harris H, Watkins J F, Ford C E & Schoeffl G I. Artificial heterokaryons of animal cells from different species. *J. Cell Sci.* 1:1-20. 1966. (Cited 340 times.)
2. Ringertz N R & Savage R E. *Cell hybrids*. New York: Academic Press. 1976. (Cited 340 times.)
3. Harris H, Miller O J, Klein G, Worst P & Tachibana T. Suppression of malignancy by cell fusion. *Nature* 223:363-8. 1969. (Cited 330 times.)
4. Harris H. The analysis of malignancy by cell fusion: the position in 1988. *Cancer Res.* 48:3302-6. 1988. (Cited 30 times.)
5. ----- . *The balance of improbabilities*. Oxford, England: Oxford University Press. 1987.

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