Obituary

Ira Herskowitz (1946–2003)

Ira Herskowitz died on 28 April 2003 of pancreatic cancer. He was a scientist of style and influence. Genetics was his path to truth, and he used that approach to make a string of important discoveries in cell and molecular biology.

Herskowitz made an impression early on, as a graduate student with Ethan Signer at the Massachusetts Institute of Technology (MIT) in Cambridge, Massachusetts. He took on the problem of how a protein can activate — increase the transcription of — a gene. Transcriptional activators (as opposed to repressors) were not much in vogue in the late 1960s, and there were no good ideas as to how they might work. Herskowitz studied a protein called Q, which is encoded by the bacterium-infecting virus (bacteriophage) λ and is required for the transcription of a group of other λ genes. He showed that a single DNA site in the λ genome is required for Q to activate all of these target genes. The result revealed that the so-called λ late genes must be transcribed into a single, long messenger RNA, and it set the stage for a full understanding of the molecular workings of Q that is only now coming to fruition.

Thus began a lifelong love affair with bacteriophage λ . Although his lab formally stopped working on the virus in the 1980s, Herskowitz remained engrossed by the subject. In the years before his death he spoke of writing a small book to tell the story of the λ *cII* and *cIII* gene products. Synthesized when λ first enters a host cell, these proteins sense the health of the cell and decide whether the virus should replicate itself and destroy the cell, releasing its progeny in the process, or whether it should silence its genes and integrate into the host genome. The book would have expanded on his influential review on the subject written thirty years ago.

Herskowitz left MIT in 1972 for the University of Oregon, Eugene, where he initiated a series of classic studies on the single-celled yeast *Saccharomyces cerevisiae*. He realized early on (and was instrumental in teaching the rest of us) the power of using yeast as a model organism to study fundamental biological problems. Like humans, other mammals, plants and insects (but unlike bacteria), yeast is a eukaryote — an organism whose cells have defined nuclei. Not only that, but genetic analyses with yeast are about as easy to do as they are with bacteria. This was the opening that fired Herskowitz's

Scientist who brought yeast genetics to the forefront of molecular and cell biology

imagination, and it was here that he made his greatest impact.

Herskowitz's studies on yeast 'mating-type switching' had a celebrated outcome. *S. cerevisiae* has two mating types, or sexes, and the cells, as they divide, switch back and forth between them. A set of simple experiments confirmed a most unlikely-seeming scenario: programmed DNA rearrangement was responsible for the switching. Few steeped in the world of bacteriophage λ , where proteins bind to DNA to turn genes on and off, would have been prepared to make Herskowitz's leap to a world in which gene control was effected by gene rearrangement.

In 1981, Herskowitz moved to the University of California, San Francisco, where he remained for the rest of his career. There, he initiated a series of studies that revealed fundamental features of eukaryotic cell growth and division. For example, cells often divide asymmetrically, one progeny cell differing

in important ways from the other. Herskowitz showed how this occurred in yeast: a key molecular determinant (in this case, a particular mRNA) is distributed to only one of the two progeny cells. The protein produced by this mRNA then initiates a developmental programme that distinguishes one cell from the other. To take another example, every time a yeast cell divides, a molecular mark is left on its surface, thereby recording the history of its cell divisions. Herskowitz showed how the cell then uses these marks to tell which end is which and to establish its subsequent patterns of growth and division.

Herskowitz also explored other aspects of cell biology, including signal transduction, cell-cycle progression, polarized cell growth, chromatin structure, meiosis, gene expression and RNA localization. Virtually all of these studies exploited properties of the yeast mating machinery that he was instrumental in characterizing. Thus, from modest and seemingly specialized questions about the mating behaviour of a single-celled organism, Herskowitz created a body of work with implications for many different branches of molecular and cell biology.

Herskowitz's science was always simply described, yet rich in metaphor and analogy. He trained more than 70 graduate students and postdoctoral fellows. He also helped many more scientists to clarify their ideas, design their experiments and write their papers. A discussion with Ira could entice a biologist, even one who had never studied with him, to delve into new experimental realms. Ira's style of presentation — the simple story, the coloured chalk and the hand-drawn diagrams (where simple arrows inevitably stood in for detailed mechanisms) — became a standard to be emulated. A biological polyglot, he chose his yeast projects with an eye to solving problems under study elsewhere with more complex organisms. He was the master of the simple, telling experiment. He was a gentle man and a gentle scientist. He will remain an unforgettable figure.

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