Comment

Ira

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Like one of the Brazilian soccer stars, Pele or Ronaldo, he was often referred to by one name only. When he died, on April 28 this year from pancreatic cancer - one of the cancers you don't want to get - at the tragically young age of 56, it left a hole in the fields of genetics and genomics the size of the Grand Canyon. Many other fine scientists have the same first name, but for a quarter of a century in genetics if you said Ira the chances were you meant Ira Herskowitz.

I think the genuine sense of loss that accompanied his untimely death - his obituaries literally spanned the country, from the *San Francisco Chronicle* and *Los Angeles Times* to the *New York Times* and *Boston Globe* - was a reflection on more than the quality of his work, outstanding though that was. He was the geneticists' geneticist, a man whose work on the simple single-celled fungus *Saccharomyces cerevisiae*, budding yeast (also known as brewer's or baker's yeast), had important implications for understanding the behavior of all eukaryotic cells. He himself was living testimony to the power of genes: his father, Irwin Herskowitz, was a famous fly geneticist at Indiana University. He was also living testimony to the limitations of that power: he had an identical twin, Joel Herskowitz, who went not into genetics but into pediatric neurology and is free of the disease that killed his brother.

Ira started off fast: his graduate work on 'phage lambda, a virus that infects bacteria, was classic. But like most of the 'phage people who shaped the early days of molecular biology, he moved on to the study of a free-living organism. As a young faculty member at the University of Oregon he switched to yeast genetics because he felt, as did several others at that time, that the cell biology of 'higher' eukaryotes such as *Homo sapiens* could best be illuminated through an understanding of this model organism. Yet he never felt that was its only value: he genuinely loved the organism he studied, and he celebrated its beauty and surprising complexity in every conversation he had, every seminar he gave, and every paper he wrote.

His best-known work concerned yeast mating. Yeast cells come in two sexes, denoted **a** and α. Interestingly, like some types of frog, yeast cells are able to change sex under certain conditions: type **a** can switch to α or *vice versa*. Ira showed how the yeast cells could flip from one mating type to another by reshuffling their DNA, a process involving the endonucleolytic excision of segments he termed 'cassettes', which could then recombine elsewhere. This finding was one of the earliest demonstrations of how differentiation could occur, and it had important consequences for developmental biology as well as for the field of gene regulation. Yeast mating-type switching is a complicated business, and the story could easily have been relegated to the archives of obscure behavior by atypical organisms. But one of Ira's great gifts was to see - and to be able to explain - complex things in straightforward language. He was what Aristotle admired most in a creative person: a master of metaphor. His friend and colleague Gerry Fink, of Massachusetts Institute of Technology, said that he could "look at a large set of confusing and contradictory data and come up with a metaphor that put it all together in a magnificent way." This talent allowed Ira's findings to have an influence beyond the confines of yeast genetics.

In the 1980s he and a colleague developed a method for producing foreign proteins in yeast. This patented expression system is used to produce human insulin for diabetics, among other things. Over the years Ira donated half his patent income for fellowships for students in his laboratory. In recent years he became interested in pharmacogenomics, including the question of why different cancer patients respond differently to antitumor drugs such as cisplatin. His last two papers, on the distribution of transporter genes in people from different ethnic groups, were published in the *Proceedings of the National Academy of Sciences of the USA* on the day he died.

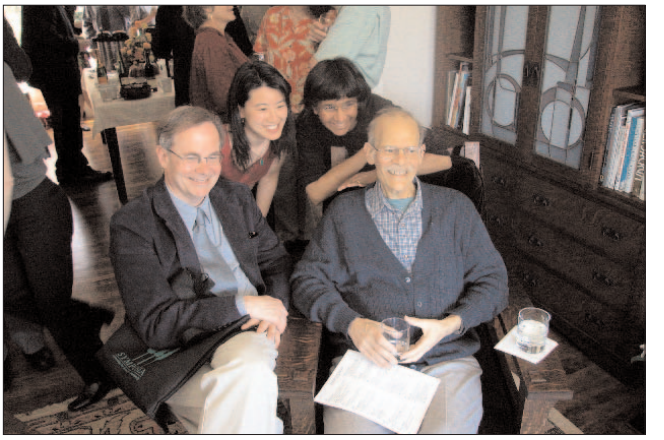
So Ira's was clearly a magnificent career, and worthy of note. But as I said, I don't think that's the real reason for the huge

sense of loss that those of us who knew and liked and admired this man feel. What made Ira Herskowitz special was his style. Harold Varmus, Nobel Laureate and former Director of the US National Institutes of Health, called him a romantic. Jim Watson, of double helix fame, referred to him as an idealist. I spent a wonderful sabbatical year in Ira's lab, from 1995 to 1996, and I agree with them. The great thing about Ira was that he was always just as enthusiastic about other people's ideas and results as about his own. Talking with him was a tonic. The last time I saw him, about a week before he died, he was obviously in pain and very tired, yet the first thing he said to me was, "After we catch up on some things I want you to tell me all about your latest results."

In addition, he was one of the least stuffy people in science. It is said that Ira was responsible for the Cold Spring Harbor meetings becoming jacketless and tieless, and I believe it. He loved playing his guitar at meetings, and in addition to singing folk and blues songs, he also wrote scientific song parodies, such as the immortal "I've Been Working on the Genome". He was especially fond of performing a song written by his twin Joel called "Double Talking Helix Blues". He never gave the impression that he cared about being Ira Herskowitz, famous geneticist. One of my friends met him for the first time when she was a young bacterial geneticist. She sat next to him at lunch at a meeting and when he asked her what she worked on, she proceeded to give one of the world's great geneticists a 20 minute explanation of bacterial genetics. He never interrupted her, except to ask questions or to share her excitement with her ideas. It was only later at the meeting that someone else told her who he was.

Yeast genetics has the reputation of being open and welcoming to newcomers, of being characterized by sharing of ideas and data, of being just plain fun. That reputation owes everything to the great scientists who founded the field, Ira among them. Do giants emerge because they work in fast-moving and important areas, or do areas become fast-moving and important because they are lucky enough to have giants working in them? I don't know the answer, but I am fairly sure that the atmosphere, the character - the *gestalt*, if you will - of a field comes from the top down. Some fields are stiff, insular and mean-spirited, hyper-competitive and ill-using of their young people, while others are relaxed, friendly, and nurturing. Genomics is too new to have fully developed its culture yet, although what I see so far is encouraging. I think part of the great sadness of Ira Herskowitz's death is that he would have brought to genomics - a field he was only beginning to work in - that same attitude that he brought to yeast genetics.

What kind of field will genomics become? Will it welcome new blood from other subjects and will it rejoice in, and foster, the success of its young people? Will the big names in it share data and reagents and behave with generosity instead of suspicion and selfishness? Will those who practice it poke fun at themselves and not take things too seriously? Will people in the field write and sing silly songs and take their ties off and not put on airs? Ira's life reminds us that the kind of field we get is the one we make for ourselves.



Greg Petsko presenting the 2003 Lewis S Rosenstiel Award for Distinguished Work in Basic Medical Research to Ira Herskowitz, April 2003.