Fred Sherman

In Memoriam
Fred Sherman —The First Yeast Molecular Biologist

FRED Sherman died September 16, 2013 at the age of 81 years after a long illness. A renowned molecular biologist, Fred obtained his Ph.D. with Robert Mortimer at the University of California, Berkeley, followed by postdoctoral training with Boris Ephrussi in France and Herschel Roman in Seattle. He spent his entire career as a Professor at the University of Rochester School of Medicine. Fred received many awards, including election to the National Academy of Sciences.

The emergence of yeast as a premier organism for molecular biology has often been ascribed to Jim Watson's casual comment in the 1970 edition of *The Molecular Biology of the Gene:* "There are many reasons to intensify work on organisms such as yeast". Watson saw yeast as the eukaryotic analog of *Escherichia coli*—a microorganism with which one could quickly answer fundamental questions about eukaryotic molecular biology, such as whether the genetic code and the Central Dogma were universal. At the time, yeast was not a popular experimental organism, although many luminaries of that era (*e.g.*, Joshua Lederberg, Francois Jacob, and Sol Spiegelman) had dallied with it. But their flirtation was fleeting, and they focused instead on *E. coli* or bacteriophage, where answers to these questions seemed more accessible.

It was Fred Sherman who rose to Watson's challenge. He developed the only eukaryotic experimental system that could answer the critical questions of the time. Long before DNA sequencing was possible or the term "genomics" had been coined, the Central Dogma was being probed by focusing on single genes and inferring the sequence of the corresponding DNA from the sequences of genetically altered proteins. This tack was taken with *E. coli* by Charles Yanofsky and with phage by George Streissinger. The strategy required a system for facile genetic analysis and a corresponding protein that could be easily purified and sequenced. Only Fred's *CYC1/*Iso1-cytochrome c yeast system had these features in eukaryotes.

In the late 1960s and early 1970s Fred devised an ingenious method for identifying *cyc1* mutants and their revertants, along with a remarkably simple, almost one-step, purification of the Iso-1-cytochrome c protein. Even by today's standards his achievement is astonishing: he isolated over 500 *cyc1* mutants and determined the amino acid sequences of more than 100 different Iso-1-cytochromes c. Together with his colleague, John Stewart, they ultimately analyzed over 3000 variants of the protein. The insights obtained from the *CYC1* system were stunning and brought yeast to the attention of world science.

These studies enabled Fred to deduce that the genetic code in eukaryotes is the same as that in bacteria, as were the chain-terminating codons UAA, UAG, and UGA. But only the first AUG codon in the *CYC1* message could serve to initiate translation, suggesting that polycistronic messages, and hence operons, are typical of bacteria but not of eukaryotes. Fred's decoding of the first 44 nucleotides of the *CYC1* DNA sequence by sequencing the protein of a frameshift revertant was a masterpiece. This led to Fred's determination of the sequence of the *CYC1* gene and then the *CYC1* mRNA itself, in collaboration with Jack Szostak and Ray Wu. For more than a decade *CYC1*was the archetype of the eukaryotic genome.

Although this was the golden age of *CYC1*, the glitter should not blind us to Fred's ingenious use of this system to answer questions still at the forefront of research. Using the *CYC1* gene as the fulcrum, Fred subsequently made important discoveries about post-translational protein modifications (acetylation and methylation), ubiquitin-mediated protein degradation, and the relationship between termination and initiation in mRNA synthesis. A particularly fine example of Fred's prescience was his insight that gene duplication played an important role in yeast evolution, a finding that foreshadowed the genomic analysis that solidified this conclusion more than 10 years later.

Many scientists trace their subsequent success to Fred's dedication to teaching yeast technology and his joy at regaling them with the lore necessary to master the technology. I had the opportunity to observe Fred in this role each summer for 17 years when he and I taught the Cold Spring Harbor Yeast Course, a 3-week boot camp of nonstop

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immersion in yeast molecular biology. The intense scientific and social climate of that course has been recounted in several essays, which contrast Fred's formal demeanor in his scientific presentations with his zany sense of humor outside the lecture hall (Fink 1993).

During the Cold Spring Harbor Course Fred worked tirelessly to organize experiments. His presence in the laboratory from early in the morning until late at night set the standard for the students. The exception to this dogged dedication was his conspicuous absence from the Cold Spring Harbor grounds for an hour or two each day. Curious about his mysterious disappearance, I asked him where he had been. His reply, "I take ballet lessons at a studio in Huntington." Fred loved to dance and had decided to refine his social dancing by learning the *arabesque* and *plié*. But his ballet poses did not end in the dance studio. While conversing, he often moved from one balletic position to another, some with an unanticipated abrupt extension of his leg. These ever-changing balletic poses coupled with a stream of amusing quips became his standard form of communication. This performance was doubtlessly the source of the smiles on the faces of the students, their difficulty in concentrating on Fred's narrative, and comic relief from the relentless laboratory work.

Fred's science paved the way for the blossoming of yeast molecular biology. His humor entertained and delighted many. He is survived by his wife Elena Rustchenko-Bulgac, his children Mark and Rhea, and six grandchildren.

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