James A. Fee 1941–2012

ARTICLE *in* JOURNAL OF INORGANIC BIOCHEMISTRY · NOVEMBER 2012

Impact Factor: 3.44 · DOI: 10.1016/j.jinorgbio.2012.08.016

Journal of Inorganic Biochemistry 116 (2012) 229–230

Contents lists available at SciVerse ScienceDirect

Journal of Inorganic Biochemistry

journal homepage: www.elsevier.com/locate/jinorgbio

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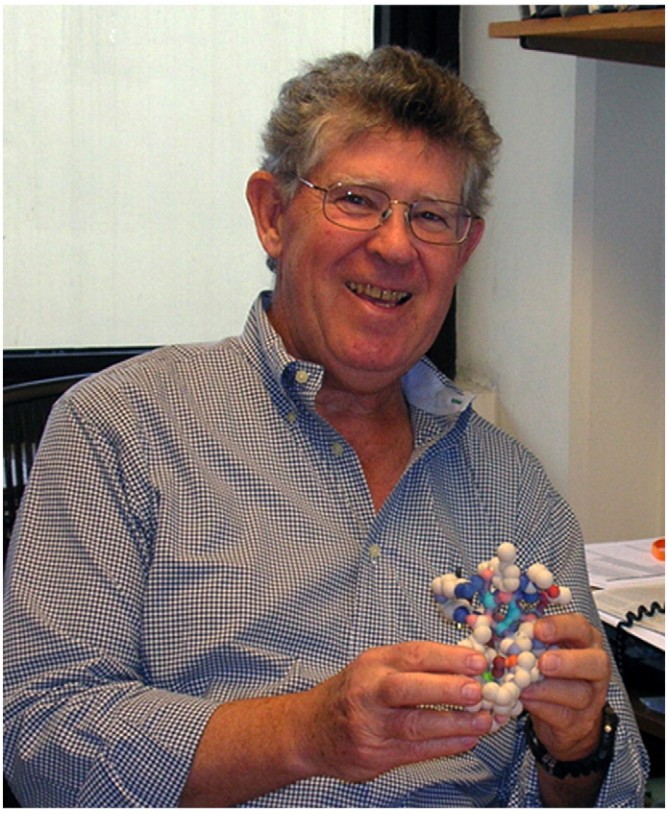

James Fee passed away last April 17 in San Diego at the age of 72 after a battle with prostate cancer. Jim's scientific work on superoxide dismutases and the respiratory oxidases from thermophilic bacteria constitutes seminal contributions that have provided important insights into the structure and function of these enzymes. Jim was best known for his pioneering work in bioenergetics, an area that was the focus of his research interests during most of his career. We feel privileged to have known him.

Jim's scientific education began in 1961 with a double major in Chemistry and History at Pasadena College in California, followed by a Ph.D. in Biochemistry at the University of Southern California in 1967. He was a Postdoctoral Fellow at the University of Göteborg with Bo Malmström and Tore Vänngård between 1967 and 1969, during which time he worked on the mechanism of O_2 reduction by the fungal laccase. Jim began his independent academic career in 1970 as an Assistant Professor in the Department of Chemistry at the Rensselaer Polytechnic Institute. In 1974, he moved to the University of Michigan as an Associate Professor, and a few years later became a Full Professor in the Department of Biological Chemistry, School of Medicine, University of Michigan. Never one to be easily categorized, Jim left the University in 1985, to become the Director of the NIH Stable Isotope Resource at the Los Alamos National Laboratory, and a Section Leader in Biological Chemistry. Jim was a glider pilot, and the appeal of the wide-open air space and updrafts of the Southwest surely influenced his decision to move to New Mexico. He also maintained an appointment as an Adjunct Professor of Biochemistry at the University of New Mexico Medical School, 1989–1993. In 1993 Jim moved to the University of California, San Diego, as a Research Scientist, where he remained until 2001, at which point he moved to the Scripps Research Institute as a Professor of Research. The move to California allowed Jim to develop another passion, sailing.

During the course of his career, Jim made fundamental contributions to our understanding of redox metalloproteins, and his scientific achievements are reflected in more than 150 publications. Jim was well funded, attesting to the vitality of his research program and the high esteem of his peers. He also provided service to the science community by serving on NIH study sections and the editorial boards of journals. Jim gave many research talks at conferences and universities, both within the US and abroad and was a regular participant in the Metals in Biology Gordon Conference, serving as a Vice-Chair (1976–78) and Chair (1979–1980). Jim's honors include the Harry J. Duell Award from the University of Southern California and a National Science Foundation Fellowship at the University of Göteborg, Sweden. He was a member of the American Association for the Advancement of Science, American Chemical Society, and American Society for Biochemistry and Molecular Biology.

Jim's early work focused on biophysical studies of the newly discovered copper–zinc and then the manganese, and iron superoxide dismutases (SOD), key enzymes in defense against oxidative stress. His studies of enzymatic mechanisms and of structure–function relationships created the foundation for our current understanding of the biophysical and functional properties of these important enzymes. He also played an important role in the development of our understanding of biological oxidative stress, challenging investigators to discover the exact identities of toxic reactive oxygen species and the chemical nature of their toxic reactions. In the 1980s, Jim jumped into the study of large, membrane-bound metalloproteins, and more specifically, the respiratory proteins of thermophilic bacteria, in particular, *Thermus thermophilus*. For Jim, it was the beautiful colors of the metalloproteins and their consequent optical spectra, which held the promise to reveal their inner workings. Above all, Jim was absorbed in understanding the cytochrome ba_3 oxidase from *T. thermophilus*, which represented to him the ultimate problem in bioenergetics. Jim recognized that since *T. thermophilus* grows optimally at 75 °C, the *Thermus* ba_3 oxidase

http://dx.doi.org/10.1016/j.jinorgbio.2012.08.016

would likely be very stable and well behaved. He understood that in the long run, this stability would likely facilitate more precise measurements and higher resolution structural data. This intuition about the virtues of working on this protein proved to be accurate.

Overcoming all challenges by a combination of creativity and persistence, studies on *Thermus* ba_3 occupied the remainder of Jim's career. Apart from the thermal stability of the membrane enzymes isolated from *T. thermophilus*, the choice to work with this organism provided many unexpected benefits. It is now known that each of the two respiratory oxygen reductases, cytochromes ba_3 and caa_3, represents major and distinct classes with significant differences from the standard cytochrome oxidases studied by others. This fit well with Jim's personality: he thoroughly enjoyed both the pursuit of truth as well as being an iconoclast. His work on *T. thermophilus* cytochrome oxidases required both mastering and developing a variety of biochemical and molecular genetics tools to work with these large membrane proteins. At Los Alamos, Fee and his collaborators, in a series of elegant time-resolved infrared and optical experiments, provided important insights into the dynamics of ligands, such as carbon monoxide, as they equilibrate with the metals in the enzyme active site. More recently, the advantages of *T. thermophilus* for the expression of recombinant proteins and genetic manipulation were exploited by Jim and his collaborators, including his long-time, close, and very talented assistant, Ying Chen. They succeeded in expressing recombinant ba_3 in *T. thermophilus*, leading to the production of large quantities of highly purified mutants of ba_3, contributing to a period of exhilarating progress in the last few years. As a result of Jim's collaboration with the structural biologists at Scripps, David Stout and Vadim Cherezov, we now have very high quality X-ray structures of cytochrome ba_3 as well as a number of mutants. The channels for delivering protons and oxygen are well defined structurally, providing the basis for cutting edge studies of the mechanism of how the oxygen chemistry is coupled to proton pumping. To assist in this effort, Jim learned computational methods and worked with David Case and Lou Noodleman at Scripps to define the free energies of different intermediate states of the enzyme during its catalytic cycle. Jim would take his sailboat off the coast from San Diego in order to contemplate the oxidase mechanism, and would come back with new insights and a resolve to carry out each and every one of the very demanding computations.

Jim's approach to understanding ba_3 was total. He wanted to understand electron transfer, oxygen diffusion, proton translocation, and most critically, the chemical basis of the proton pump. Jim was always very focused on the project at hand, and exemplified scientific discipline in pursuing all aspects of a problem in depth. He knew how to ask the critical scientific questions, and then find the right experimental approach to obtain the answers. This often required close collaboration with others, and Jim had a knack for attracting the right people to help him solve each problem as it arose.

Jim enjoyed discussing day-to-day research problems, and throughout his career, he maintained high standards and expected the same of others. He was passionate and unafraid to express contrarian positions. However, Jim always maintained a sense of proportion and a sense of humor. His career illustrates a scientific paradigm combining passion with a deep commitment to solving problems and a sharp focus on finding ways to solve those problems. Although Jim is no longer with us, he leaves a legacy of his research accomplishments and the inspiration of his intellectual strengths. Happily, Jim's research momentum will continue through the efforts of his colleagues and collaborators. We are saddened by his passing, and were truly fortunate to have had Jim Fee as a colleague and friend.

Ólöf Einarsdottir
Robert Gennis
David Stout
Joan Valentine
Shelagh Ferguson-Miller
Woody Woodruff