Perry Frey

A passion for novel chemistry and experimental surprises has led Perry Frey through 40 years of inspiring enzymology research.

When Perry Frey attended a lecture by Robert Abeles about cofactor-mediated enzyme catalysis, he reacted radically, switching from a focus in pure organic chemistry to one in biochemistry and joining Abeles' lab. Throughout his graduate work, a postdoctoral position with Frank Westheimer and faculty appointments at Ohio State and the University of Wisconsin, Frey has been dedicated to understanding the fundamental basis of enzyme catalysis, and indeed he suggests that "any biologist who follows their research interest to the finest level of detail will become an enzymologist." Within the field, he has particularly focused on elucidating the complex and unusual chemistry of cofactor-based reactions. His studies have spanned diverse enzymes and chemical transformations, with similarly transformative conclusions and new ways of thinking at each step.

Throughout his studies, Frey has placed an emphasis on using and developing new methodologies, adding mass spectrometric analysis of transient kinetics and undecagold labeling reagents to the enzymology toolbox. However, Frey's early yen for organic chemistry remained, and he argues that synthesizing likely reaction intermediates to determine the spectroscopic readouts of particular chemical properties is one of the best ways to interrogate enzyme mechanisms. For example, his group's synthesis of chiral, isotopically labeled nucleotide phosphorothioates resolved ambiguities about whether phosphotransfer reactions were proceeding via single displacement (inversion of configuration) or double displacement (retention of configuration) mechanisms, establishing that both reactions occur, but in different enzymes. Frey's enthusiasm for chemistry also led to the synthesis of the putative intermediate 2-acetylthiamin pyrophosphate, a compound that was generally thought to be too reactive to work with. Careful planning of an appropriate synthetic protocol allowed Frey and his colleagues to create and study this molecule, assigning it as a true intermediate in the reaction of pyruvate dehydrogenase.

Though the mechanism of phosphotransfer was an important question of the day, John Richard, a former graduate student and now professor at the University at Buffalo of the State University of New York, notes that Frey "is not reluctant to study an unfashionable problem that he finds interesting and challenging intellectually." This sentiment is particularly true when Frey feels he can uniquely contribute to a scientific topic, and led to the study of, as Richard calls it, "the seemingly obscure bacterial enzyme lysine 2,3-aminomutase." Frey was curious to know whether the cofactor of this enzyme, *S*-adenosylmethionine (SAM), might serve the same function as the more metabolically complex adenosylcobalamin, a coenzyme he had studied as a graduate student. These investigations led to the first identification of both the radical SAM mechanism and iron-sulfur clusters as participating in the reaction. The superfamily of enzymes that use the radical SAM mechanism has since grown to include nearly 3,000 enzymes.

Regarding his original motivation for the study, Frey was pleasantly surprised to discover that his early idea that SAM was merely an evolutionarily necessary predecessor of adenosylcobalamin was wrong. He argues that this type of experience is the most valuable and stimulating thing about running a research lab, saying: "If the research has been properly designed, the unexpected result almost inevitably means that there is something new to be learned." However, Richard is not surprised that Frey put these ideas together. He notes, "Problems in science sometimes appear difficult because of the failure to find a coherent context for earlier experimental observations. Perry is very good at defining what is known about a particular problem and what one should be trying to learn." Tadhg Begley, who works on two radical SAM enzymes involved in thiamin biosynthesis at Texas A&M University, agrees, saying Frey "has remarkable instincts for what is fundamentally significant."

In addition to his research contributions, Frey has also followed his instincts in engaging broadly with the scientific community. He served for 16 years as an associate editor of *Biochemistry* and is seen by Squire Booker, a former postdoc in his lab and currently an associate professor at Pennsylvania State University, as "one of the best communicators of science that I know." In 2007, Frey authored a textbook on enzyme reactions in an effort to clarify the current state of knowledge, identify open questions in the field, and help young students decide whether they were interested in biochemistry. He and his wife have also established the α-Helix Scholarship, supported by the Perry and Carolyn Frey Life Sciences Scholarship Fund, to help mitigate what they see as prohibitive costs for undergraduate education.

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Beyond providing this scientific context and financial support, Frey suggests that the onus is on young professors to "decide what is important and how to work on it." To complement this commitment to independence, he provides only this advice: "Be rigorous. Work hard. Be inventive." He apparently has taken his own counsel to heart, as Begley describes Frey as, exactly, "rigorous and innovative." Though Frey's advice doesn't touch on the idea of being a good colleague, Richard fondly remembers that "Perry was quick to point out the importance of my own contributions and made me feel like a partner in our research." Booker agrees, noting that "the environment in his lab was very warm." This welcoming environment was reflected in a reunion in 2007 where current and past colleagues convened at an American Chemical Society meeting to celebrate his career and commemorate his official retirement.

In looking back at Frey's career, Begley says, "Perry showed a high level of intellectual courage in tackling some of the most challenging problems in enzymology." Booker not only echoes this sentiment but perhaps poses a challenge for the next generation of scientists, saying: "How his retirement will impact the field will depend on the extent that those of us remaining in it will be willing to roll up our sleeves and tackle the difficult fundamental questions as he routinely did." It seems Frey's example will continue to catalyze new ideas for some time to come.

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