NATIONAL ACADEMY OF SCIENCES

MARTHA L. LUDWIG
1931–2006

A Biographical Memoir by
ROWENA G. MATTHEWS

Any opinions expressed in this memoir are those of the author and do not necessarily reflect the views of the National Academy of Sciences.

Biographical Memoir

Photograph courtesy University of Michigan.

Martha L. Ludwig

MARTHA L. LUDWIG

August 16, 1931–November 27, 2006

BY ROWENA G. MATTHEWS

MARTHA L. LUDWIG WAS BORN IN Pittsburgh, Pennsylvania, on August 16, 1931, and died on November 27, 2006, in Ann Arbor, Michigan, after a distinguished academic career as scientist, mentor, teacher, and administrator. She is survived by her husband, Frederic Hoch, M.D., her companion in 44 years of happy marriage. Martha was a macromolecular crystallographer whose research focused on proteins involved in electron and group transfer reactions. She participated in the determination of the structure of carboxypeptidase in William Lipscomb's laboratory, the first protein structure to be determined in the United States, and as an assistant professor at the University of Michigan she solved the first flavoprotein structure, that of flavodoxin. Other memorable structures solved in her laboratory include those of iron-superoxide dismutase, p-hydroxybenzoate hydroxylase, and phthalate dioxygenase reductase. Her laboratory later solved the first structure of vitamin B_{12} bound to a protein, the cobalamin-binding domain of methionine synthase, revealing a totally unexpected change in the ligation of the cobalamin prosthetic group. Martha's scientific contributions were recognized by the Garvan Medal of the American Chemical Society in 1984, by the Distinguished Faculty Achievement Award from the University of Michigan

in 1986, by election as a fellow of the American Association for the Advancement of Science in 2001, and by election to membership in the National Academy of Sciences in 2003 and in the Institute of Medicine in 2006. Following her death her husband established the Martha L. Ludwig Professorship in Macromolecular Structure and Function at the University of Michigan, currently held by Janet Smith.

Martha's father, Leon Ludwig, a distinguished physicist, worked for the Westinghouse Company. Her mother, Agnes Sutermeister Ludwig, would later earn a degree in social services. The family moved to Buffalo when Leon became a director of the Westinghouse facility there. From a very early age Martha loved mathematical puzzles and desired a career as a scientist. She studied chemistry at Cornell University, graduating in 1952. She then earned a master's degree in biochemistry from the University of California, Berkeley, supported by a Helen Hay Whitney Fellowship. A highlight of her training there was taking a course in physical biochemistry taught by Howard Schachman. In Martha's own words, "It totally changed what I decided I wanted to do in research."[1]

Her Ph.D. thesis research was conducted at Cornell University Medical College in the Department of Biochemistry, headed by Nobel Laureate Vincent du Vigneaud. She studied the biosynthesis of ergothionine with D. B. Melville, and published several papers on this topic, graduating in 1956. From New York she moved to Harvard Medical School for postdoctoral studies with Lawrence Oncley in the Physical Chemistry Department headed by E. J. Cohn. It was there that she met her husband-to-be, Frederic Hoch. Fred was a young M.D. doing research on carboxypeptidase in the laboratory of Bert Vallee. Martha was sent over to the Vallee laboratory to collect some distilled water, because in Fred's words, "The

Vallee laboratory had the purest (lowest conductivity) water in the world at that time. We collected it in a quartz bucket." Fred continues, "I set my eyes on that woman." They married in 1961 and enjoyed a long and happy marriage. They shared a passion for red convertible sports cars, skiing, tennis, and hiking, bird-watching, and cooking. In Fred's words again, "We cooked some fancy grub together."

Martha continued her postdoctoral training at the Massachusetts Institute of Technology. Up to this point she had used classical techniques of biochemistry, such as protein purification and chromatography, to study interactions between proteins. In 1962 Ludwig became interested in the developing field of X-ray crystallography. "It was the realization that we could finally look at where the atoms were. I became an early convert of three-dimensional structures," she said. "I'm always delighted to look at a new structure. The visual part of it is personally satisfying, and many of the basic hypotheses about how enzymes work have come directly from observing structures."[1] She joined the laboratory of William Lipscomb, a distinguished chemist at Harvard University who was one of the earliest practitioners of the emerging field of macromolecular crystallography. While there she helped to solve the structure of carboxypeptidase, the first protein structure to be solved in the United States. The emerging story of carboxypeptidase attracted worldwide attention, leading to the first of many trips to present her research at scientific meetings.

A side benefit of attending these meetings for Martha (whose mother was Swiss), and her husband, Fred (who was born in Austria) was the opportunity to go hiking in the Alps. Tom and Joan Steitz (Tom was a graduate student in Lipscomb's laboratory and a coauthor on several of the carboxypeptidase papers) recall happy hikes together in the mountains.

In 1967 Martha and her husband moved to Michigan, where she joined the faculty as an assistant professor in the Department of Biological Chemistry and an assistant research biophysicist in the Biophysics Research Division, where her laboratory was located. At that time a distinguished group of faculty, including Vincent Massey and Graham Palmer, were studying flavoproteins, and she chose to study the smallest of these flavoproteins: flavodoxin. This electron transfer protein is induced in bacteria under conditions of iron limitation, and had been shown to substitute for the iron-dependent ferredoxin in several reactions, including the phosphoroclastic splitting of pyruvate, the fixation of nitrogen, and the photosynthetic reduction of pyridine nucleotides. At this early stage in the application of X-ray crystallography to protein structure, the ~15 kDa molecular mass of flavodoxins made them attractive candidates for structure determination.

Flavodoxins contain one equivalent of flavin mononucleotide (FMN) per mole, and typically exhibit highly stabilized one-electron-reduced forms, or semiquinones. In her first independent paper in 1969 the Ludwig laboratory collaborated with Palmer and Massey to show that the protein from *Clostridium pasteurianum* could be crystallized in both oxidized and semiquinone forms. The structure of the semiquinone form of the clostridial enzyme was reported in 1972, and could then be compared with the structure of oxidized flavodoxin from *Desulfovibrio vulgaris* reported by Watenpaugh et al. in the same year.[2] The two proteins were clearly structurally homologous, but significant questions about the orientation of the FMN and its interactions with the apoprotein remained, and could not be answered at the 3.25 Å resolution of the *Clostridium MP* flavodoxin structure. These issues were resolved with the determination of a structure of the clostridial enzyme in the oxidized form at 1.9 Å. By this time the chemical sequence of flavodoxin had been

determined, allowing assignment of the amino acids in the sequence.

One of the most interesting issues for flavodoxins is the molecular basis of the semiquinone stabilization seen in these electron transfer proteins. To quote from the 1974 paper, "Combination of FMN with the protein profoundly modifies the oxidation-reduction potentials of FMN, decreasing the potential of the semiquinone-reduced couple from –0.18 V to the range of values observed for ferredoxin, –0.4 to –0.5 V." The 1.9 Å structure of the oxidized clostridial flavodoxin could be compared with the 3.25 Å structure of the semiquinone form. Although two-electron reduction of free FMN leads to a bending of the flavin along the N5-N10 axis, the apoprotein constrains the semiquinone to a planar conformation, allowing Ludwig to suggest that this is partially responsible for the low reduction potential associated with the semiquinone-reduced flavin. The 1.9 Å structure greatly enhanced understanding of the mechanism for electron transfer between flavodoxin and other proteins. The occurrence of tyrosine near the chromophores of ferredoxin and flavodoxin had led to speculation that tyrosine radicals might be involved in electron transfer in these proteins. However, tyrosine was absent from the vicinity of the bound FMN. Rather, the solvent exposure of the dimethylbenzimidazole portion of FMN suggested direct electron transfer from the reduced FMN itself.

The subsequent determination of a 1.8 Å structure of clostridial flavodoxin in the semiquinone form shed further light on the mechanism of stabilization of the semiquinone. Because the crystals of the oxidized and semiquinone forms were not isomorphous, this structure required *de novo* phasing with heavy metal derivatives. It had previously been proposed that the semiquinone would be stabilized by a hydrogen bond from the apoprotein to N5 of FMN, which is protonated in

the neutral semiquinone but unprotonated in the oxidized flavin. No hydrogen bond donor and acceptor could be identified near N5 in the structure of the oxidized enzyme. In the 1.8 Å semiquinone structure, the carbonyl group of Gly57 was positioned pointing toward N5 of FMN, while in the oxidized structure it is pointed away from the flavin. In the semiquinone the O-H-N5 distance is appropriate for a hydrogen bond and the geometry is favorable. This new hydrogen bond was proposed to be the primary factor leading to the dramatic stabilization of the flavin semiquinone. This brief summary of her first major independent project reveals several of the characteristics that defined her: a passionate interest in mechanism as well as structure, with attention to structural details that illuminate mechanism.

Although at this point Martha began to tackle numerous other proteins involved in electron and group transfer, she remained fascinated by flavodoxin and continued to study it throughout her career. In 1990 Martha collaborated with Vincent Massey to show that the very low potential associated with the reduction of the semiquinone to the fully reduced flavodoxin is in part because reduction causes the development of negative charge at N1, which is buried in an acidic region of the protein that generates charge repulsion.

In a collaboration with Richard Swenson of Ohio State University the conformation of the peptide bond between Gly57 and Asp58 was examined as a function of the redox state of flavodoxin from *Clostridium beijerinckii*. In oxidized flavodoxin the carbonyl oxygen of Gly57 points away from the flavin and cannot serve as a hydrogen bond acceptor. Furthermore, the peptide bond isomerizes to the *cis* form, which is stabilized by hydrogen bonding interactions in the crystal. In the semiquinone and reduced forms the peptide bond adopts the *trans* conformation with O57 directed toward N5 of the flavin so as to serve as a hydrogen bond acceptor

to the protonated N5 in these states. Mutational analyses of residue 57 confirmed the importance of the changes in peptide conformation in the marked stabilization of the flavin semiquinone in flavodoxins. I am particularly fond of this paper, because it illustrates the analytical skills that Martha applied to the structural problems she investigated. She probes deeply and wants to understand precisely the structural and thermodynamic basis for experimental observations.

In the 1980s Martha initiated a long-term collaboration on superoxide dismutase with James Fee, a faculty colleague in the Biophysics Research Division at Michigan, where her laboratory was also located. There are three types of superoxide dismutases: a copper- and zinc-containing enzyme that predominates in eukaryotic cells, an iron-containing enzyme found in plants and some prokaryotes, and a manganese-containing enzyme found in the mitochondria of aerobic organisms. In 1983 the Ludwig laboratory reported the structure of the iron superoxide dismutase from *Escherichia coli*, and simultaneously a structure of the iron-containing enzyme from *Pseudomonas ovalis* was reported by the laboratory of Greg Petsko and Dagmar Ringe. These structures revealed that the iron-containing and copper-zinc-containing enzymes are completely unrelated, in accord with predictions from other laboratories based on partial sequences and circular dichroism data. Determination of the structure of the manganese superoxide dismutase from *Thermus thermophilus* revealed that the manganese- and iron-dependent enzymes are homologous, and in fact others showed that the apoenzyme of the iron-dependent superoxide dismutase could be reconstituted with manganese with restoration of activity.

Martha continued close collaborations with faculty studying redox biology at the University of Michigan, resulting in structure determinations of phthalate dioxygenase reductase in collaboration with the laboratory of David Ballou, p-hydroxy-

benzoate hydroxylase in collaboration with the laboratories of Ballou and Vincent Massey, thioredoxin reductase in collaboration with the laboratory of Charles Williams Jr., and cobalamin-dependent methionine synthase in collaboration with my laboratory. An emerging theme of these studies was the elucidation of the ways proteins undergo conformational changes to facilitate sequential steps in a complex catalytic cycle and the illumination of the role of protein cofactors in directing these conformational changes.

Phthalate dioxygenase reductase is a prototype for a large family of flavoenzymes that accept reducing equivalents from pyridine nucleotides and in turn reduce one-electron carriers. Because the one-electron carrier in phthalate dioxygenase reductase is a [2Fe-2S] domain that forms the C-terminus of the chain, the structure reveals directly the interactions that are important in orienting the flavin and [2Fe-2S] cofactors for electron transfer.

Pioneering investigations of the flavoprotein p-hydroxybenzoate hydroxylase revealed movements of the FAD cofactor that appeared to be required for substrate entry and release. In the initial structural studies the isoalloxazine ring was found at one or other of two positions, an "in" site that could support the hydroxylation of substrates or an "out" site that was presumably required for reduction of the flavin by NADPH. The out orientation was elicited by cocrystallization with the alternate substrate dihydroxybenzoate or by appropriate mutations. These seminal structures provided the foundation for a series of investigations in the Ludwig lab and by others that have firmly established the gating functions performed by flavin motion (also known locally as "the wavin' flavin"), examined the equilibria between in and out conformations, and suggested how NADPH is bound. The initial structural work stimulated similar studies of p-hydroxybenzoate hydroxylase in other laboratories, and the

principle of alternating flavin environments has subsequently been confirmed for other flavin hydroxylases.

Thioredoxin reductase is a flavoprotein that transfers reducing equivalents between NADPH and an internal disulfide, and thence to the external disulfide of thioredoxin. The initial structure of thioredoxin reductase determined in John Kuriyan's laboratory revealed the enzyme in a conformation where the flavin cofactor was poised to donate electrons to the internal disulfide but inappropriately positioned to receive electrons from NADPH. In a collaboration with Brett Lennon and Charles Williams, a complex of thioredoxin reductase with thioredoxin was stabilized by mutating out one of the cysteines of the internal disulfide, stabilizing a crosslinked mixed disulfide between the two proteins. This ingenious strategy allowed the structural characterization of the complex, and revealed the alternate domain arrangement that enables reaction of the flavin with NADPH, and reaction of the internal dithiol pair with the external disulfide of thioredoxin. Switching between these two conformations requires swiveling of the substrate-binding domain of thioredoxin reductase, and this swiveling was shown to occur in a catalytically competent fashion that partially limits the rate of catalysis.

The theme of molecular acrobatics was further developed in her investigations of cobalamin-dependent methionine synthase, an enzyme we jointly studied for many years. This enzyme consists of four modules, containing binding determinants for the substrates methyltetrahydrofolate, *S*-adenosylmethionine (AdoMet), homocysteine, and for the cobalamin cofactor. Since methyl groups must be transferred from methyltetrahydrofolate or AdoMet to the cobalamin cofactor and from methylcobalamin to homocysteine, these transfers require conformational changes that position the appropriate module vis-à-vis the cobalamin. Such flexible

modular enzymes are typically difficult to crystallize, and Martha adopted a divide-and-conquer strategy, crystallizing fragments of the enzyme. The structure of the cobalamin-binding module was determined in 1994, that of the AdoMet-binding module in 1996, and the structure of the first two modules, responsible for binding homocysteine and methyltetrahydrofolate in 2004. Martha chose the latter paper as her inaugural paper, following her election to the National Academy of Sciences in 2003. These structures predicted that the bound substrates would form an important part of the contacts between the cobalamin and the substrate-binding domains, and it was shown that binding of substrates and products does indeed alter the distribution of conformers. The effects of substrate binding are not propogated allosterically through the polypeptide chain but rather by alterations in the relative stability of the conformers, resulting in a thermodynamic redistribution of the conformational ensemble.

Again, using an ingenious strategy, Martha locked methionine synthase into a conformation suitable for methyl transfer from AdoMet to cobalamin, and an X-ray structure of the second half of the protein was determined in 2002. This structure revealed the important role of the cobalamin prosthetic group in controlling access of substrate-bearing modules to the cobalamin. Assumption of the activation conformation requires the cobalt of cobalamin to be pulled away from its histidine ligand: the cobalt moves 2.3 Å away from the α-carbon of this residue to assume the activation conformation. The strength of the association between the ε-nitrogen of the histidine ligand and cobalt determines the ease of entering a conformation in which AdoMet has access to cobalamin. This “simple” strategy controls the conformational equilibrium: when the cobalamin cofactor is methylated, the Co-N bond is too strong to allow the enzyme to

juxtapose AdoMet with cobalamin, but when the cobalamin cofactor is oxidized to cob(II)alamin, the bond weakens and the activation conformation becomes populated. The analysis of conformational redistribution in methionine synthase has implications that extend far beyond this enzyme. Many modular proteins are involved in signal transduction, and their output is modulated by binding of ligands to effector modules. The simple rules for conformational redistribution being elucidated for methionine synthase, where the colored prosthetic group can be used as an embedded reporter of conformational change, are expected to describe the conformational interconversions of these proteins, which lack such an embedded reporter.

The final chapter of the methionine synthase story came in work that was completed shortly after Martha's death in November 2006. A structure of the C-terminal half of methionine synthase locked in the activation conformation revealed that not only is the Co-N bond broken but the histidine ligand, now released, also forms a hydrogen bond with an aspartate residue that further stabilizes the activation conformation, preventing release of the cobalamin-binding domain until the cofactor has been remethylated by AdoMet.

Curiously, the studies of methionine synthase again led Martha back to her earlier work on flavodoxin. Subsequent to her initial studies on this electron transfer protein, studies in other laboratories demonstrated a role for flavodoxins in bacteria under iron-replete growth conditions: in *E. coli* the FldA flavodoxin protein is required for the activation of pyruvate-formate lyase, anaerobic ribonucleotide reductase, biotin synthase, cobalamin-dependent methionine synthase, and the 2-*C*-methyl-D-erythritol 4-phosphate pathway for isoprenoid biosynthesis, and is essential for bacterial viability. In the case of methionine synthase, flavodoxin serves not only to provide an electron in the activation of the oxidized enzyme

by AdoMet but also to stabilize the activation conformation of methionine synthase, as shown by her graduate student David Hoover. Flavodoxin binding results in the dissociation of the histidine ligand of cobalamin, which is associated with the transition to the activation conformation.

Martha's scientific contributions were recognized by the Garvan Medal of the American Chemical Society in 1984, the Distinguished Faculty Achievement Award from the University of Michigan in 1986, election as a fellow of the American Association for the Advancement of Science in 2001, and election to membership in the National Academy of Sciences in 2003 and the Institute of Medicine in 2006. Her induction into the Academy was a particularly celebratory occasion: she was joined for that occasion by many current and former colleagues, including Minor J. ("Jud") Coon, Cathy Drennan, Carl Correll, Vahe Bandarian, Rowena Matthews, and her long-term research associate Katherine Pattridge.

In addition to her elegant research, Martha made significant service contributions to her university and her field. She directed the Molecular Biophysics Training Grant at the University of Michigan, and served twice as chair of the Biophysics Research Division there. Her teaching was known for its rigor and depth, as well as for its ability to challenge the student. For many years she taught her version of Howard Schachman's physical biochemistry course—Biological Chemistry 807. The students remember it as one of the most difficult courses they took in graduate school; the problem sets were legendary for their challenge. But in retrospect they also remember it as teaching them to think.

Martha also served as a teacher and mentor to many young crystallographers. Cathy Drennan, who was a graduate student in Martha's laboratory and is now a professor of chemistry at MIT, recalls that Martha was a patient, caring mentor who demanded excellence and thoroughness every step of the

way. Using computers to calculate data, for example, was fine, she believed—once the theory and mechanism they utilized were fully understood. Says Drennan, "The fact that a computer program could spit out a data collection strategy in 60 seconds did not release us from this exercise: Martha insisted that we understand the underlying theory." Martha spent an enormous amount of time with her students. There were frequent five- to six-hour meetings during which they would write papers and solve problems together. "Martha was never motivated by a desire for fame or external recognition," says Cathy. "Her love for science was her only motivation. Instead of spending time networking and promoting her work at meetings, she spent her time with her students and in the laboratory. As a result, she is one of the most respected people in crystallography. Now those of us who benefited from her teaching and her science can do for her what she never did for herself: sing her praises."[3]

Marrtha Ludwig with Cathy Drennan at a luncheon for Dr. Ludwig in honor of her induction into the NAS in 2001.

NOTES

1. Excerpted from E. Hitt. Biography of Martha L. Ludwig. *Proc. Natl. Acad. Sci. U. S. A.* 101(2004):3727-3728.

2. K. D. Watenpaugh, L. C. Sieker, L. H. Jensen, J. LeGall, and M. Dubourdieu. *Proc. Natl. Acad. Sci. U. S. A.* 69(1972):3185-3188

3. I am indebted to Whitley Hill, a senior writer at the University of Michigan Medical School, who obtained this description of Martha's mentoring from Cathy Drennan in connection with the establishment of the Martha L. Ludwig Professorship in Protein Structure and Function in 2010.

SELECTED BIBLIOGRAPHY

1966

With W. N. Lipscomb, J. C. Coppola, J. A. Hartsuck, H. Muirhead, J. Searle, and T. A. Steitz. The structure of carboxypeptidase A. III. Molecular structure at 6 Å resolution. *J. Mol. Biol.* 19:423-441.

1967

With J. A. Hartsuck, T. A. Steitz, H. Muirhead, J. C. Coppola, G. N. Reeke, and W. N. Lipscomb. The structure of carboxypeptidase A. IV. Preliminary results at 2.8 Å resolution, and a substrate complex at 6 Å resolution. *Proc. Natl. Acad. Sci. U. S. A.* 57:511-514.

With T. A. Steitz, F. A. Quiocho, and W. N. Lipscomb. The structure of carboxypeptidase A. V. Studies of enzyme-substrate and enzyme-inhibitor complexes at 6 Å resolution. *J. Biol. Chem.* 242:4662-4668.

With G. N. Reeke, J. A. Hartsuck, F. A. Quiocho, T. A. Steitz, and W. N. Lipscomb. The structure of carboxypeptidase A. VI. Some results at 2.0 Å resolution and the complex with glycyl-tyrosine at 2.8 Å resolution. *Proc. Natl. Acad. Sci. U. S. A.* 58:2220-2226.

1969

With R. D. Anderson, S. G. Mayhew, and V. Massey. The structure of a clostridial flavodoxin. I. Crystallographic characterization of the oxidized and semiquinone forms. *J. Biol. Chem.* 244:6047-6048.

1972

With R. D. Anderson, P. A. Apgar, R. M. Burnett, G. D. Darling, M. E. Lequesne, and S. G. Mayhew. Structure of the radical form of clostridial flavodoxin: A new molecular model. *Proc. Natl. Acad. Sci. U. S. A.* 69:3189-3191.

1974

With R. M. Burnett, G. D. Darling, D. S. Kendall, M. E. Lequesne, S. G. Mayhew, and W. W. Smith. The structure of the oxidized form of clostridial flavodoxin at 1.9 Å resolution. Description of the flavin mononucleotide binding site. *J. Biol. Chem.* 249:4383-4392.

1977

With W. W. Smith, R. M. Burnett, and G. D. Darling. Structures of the semiquinone form of flavodoxin from *clostridium* MP. Extension to 1.8 Å resolution and some comparisons with the oxidized state. *J. Mol. Biol.* 117:195-225.

1983

With W. C. Stallings, T. B. Powers, K. A. Pattridge, and J. A. Fee. Iron superoxide dismutase from *E. coli* at 3.1 Å resolution. *Proc. Natl. Acad. Sci. U. S. A.* 80:3884-3888.

1985

With W. C. Stallings, K. A. Pattridge, and R. K. Strong. The structure of manganese superoxide dismutase from *Thermus thermophilus HB8* at 2.4 Å resolution. *J. Biol. Chem.* 260:16424-16432.

1990

With L. M. Schopfer, A. L. Metzger, K. A. Pattridge, and V. Massey. Structure and oxidation-reduction behavior of 1-Deaza-FMN flavodoxins: Modulations of redox potentials in flavins. *Biochemistry* 29:10364-10375.

1992

With C. C. Correll, C. Batie, and D. P. Ballou. Phthalate dioxygenase reductase: A modular structure for electron transfer from pyridine nucleotides to [2Fe-2S]. *Science* 258:1604-1610.

1994

With D. L. Gatti, B. A. Palfey, M. S. Lah, B. Entsch, V. Massey, and D. P. Ballou. The mobile flavin of 4-OH benzoate hydroxylase. *Science* 266:110-114.

With C. L. Drennan, S. Huang, J. T. Drummond, and R. G. Matthews. How a protein binds B_{12}. A 3.0 Å X-ray structure of the B_{12}-binding domains of methionine synthase. *Science* 266:1669-1674.

1996

With M. M. Dixon, S. Huang, and R. G. Matthews. The structure of the C-terminal domain of methionine synthase: Presenting adenosylmethionine for reductive methylation of B_{12}. *Structure* 4:1263-1275.

1997

With D. M. Hoover, J. T. Jarrett, R. H. Sands, W. R. Dunham, and R. G. Matthews. Interaction of *E. coli* cobalamin-dependent methionine synthase and its physiological partner flavodoxin: Binding of flavodoxin leads to axial ligand dissociation from the cobalamin cofactor. *Biochemistry* 36:1259-1280.

With K. A. Pattridge, A. L. Metzger, M. M. Dixon, M. Eren, Y. Fang, and R. P. Swenson. Control of oxidation-reduction potentials in flavodoxin from *Clostridium beijerinckii*: The role of conformation changes. *Biochemistry* 36:1259-1280.

2000

With B. W. Lennon and C. H. Williams Jr. Twists in catalysis: Alternating conformations of thioredoxin reductase from *Escherichia coli*. *Science* 289:1190-1194.

2002

With V. Bandarian, K. A. Pattridge, B. W. Lennon, D. P. Huddler, and R. G. Matthews. Domain alteration in B_{12}-dependent methionine synthase: Switching to the activation conformation. *Nat. Struct. Biol.* 9:53-56.

2003

With V. Bandarian and R. G. Matthews. Factors modulating conformational equilibria in large modular proteins: A case study with cobalamin-dependent methionine synthase. *Proc. Natl. Acad. Sci. U. S. A.* 100:8156-8163.

2004

With J. C. Evans, D. P. Huddler, M. T. Hilgers, G. Romanchuk, and R. G. Matthews. Structures of the N-terminal modules imply large domain motions during catalysis by methionine synthase. *Proc. Natl. Acad. Sci. U. S. A.* 101:3729-3736.

2008

With S. Datta, M. Koutmos, K. A. Pattridge, and R. G. Matthews. A disulfide-stabilized conformer of methionine synthase reveals an unexpected role for the histidine ligand of the cobalamin cofactor. *Proc. Natl. Acad. Sci. U. S. A.* 105:4115-4120.