BIOGRAPHICAL SKETCH

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NAME: Aimin Liu

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POSITION TITLE: Professor of Chemistry & Lutcher Brown Distinguished Chair in Biochemistry

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Univ. Science & Tech. of China, Hefei, China	B.S.	06/1986	Chemistry
Stockholm University, Stockholm, Sweden	Ph.D.	06/1999	Biophysics
University of Minnesota, Minneapolis, MN	Postdoctoral	10/2002	Biochemistry

A. Personal Statement

My research career has provided an outstanding opportunity to understand metalloprotein structure-function relationships and protein-based free radicals involved in oxygen activation and electron/radical transfers in biology. I have a general chemistry, biochemistry, and biophysics background and expertise in protein chemistry, enzymology, spectroscopy, and molecular and structural biology. The long-term goal of my study is to determine the chemical basis for the biological roles and physiological effects of metal ions and protein-based free radicals. Since the inception of my independent metalloprotein research laboratory, the mixture of bioinorganic chemistry, bioinformatics, molecular biology, spectroscopic (EPR, ENDOR, and resonance Raman), stopped-flow and rapid freeze-quench-based transient kinetics, and structural biology (X-ray macromolecular crystallography) studies has created an interdisciplinary research environment for in-depth mechanistic enzymology and structure-function relationship studies. The research has also provided an outstanding training environment for students and aspiring professors (see the “student success” page on our lab website). Indeed, several of my Ph.D. student trainees took on academic careers and started independent laboratories in research-intensive universities or headed a large industrial lab. These include one who graduated in 2013 and is now a well-funded and tenured Associate Professor of Biochemistry and Biophysics at UPenn. A 2021 Ph.D. graduate became a tenure-track Assistant Professor of Bioinorganic Chemistry on 9/15/2021 at UGA and quickly became an “established investigator” by receiving a major NIH grant within the first independent year. Another previous Ph.D. student who graduated in 2021 was appointed as Chief of Operations, Applied Diagnostics, Diagnostic Systems Division, Medical Research Institute for Infectious Diseases, The U.S. Army (USAMRIID).

Our research revolves around the chemistry of amino acids—molecules that are fundamental to life. Our ongoing research includes the study of mechanistic enzymology, metalloprotein structure-function relationships, and protein-derived free radicals involved in amino acid primary and secondary metabolism (the latter of which is for biosynthesis of novel antitumor products and antibiotics), cofactor biogenesis via amino acid residue crosslink and/or further protein posttranslational modifications. Over the years, my laboratory has contributed to mechanistic enzymology and protein chemistry, especially in the iron-dependent oxygen (O_2 and derivatives such as H_2O_2) activating enzymes. Some led to significant findings, such as biological charge-resonance (CR) stabilization, a novel iron protein-dependent redox sensing (human Pirin), transition metal-catalyzed nonoxidative decarboxylation reactions, a large new subfamily of proteins in the amidohydrolase superfamily, and very recently, a new heme-dependent aromatic oxygenase (HDAO) superfamily. Other significant contributions include discovering a novel heme center in one HDAO enzyme (SfmD), an unprecedented *bis*-Fe(IV) intermediate (now other labs demonstrate many of which are present in other

systems), etc. We are the first group studying amino acid side chain crosslinked cofactors using non-canonical amino acid (ncAA) genetic code expansion (*i.e*., bringing the ncAA technology to a new field of protein-derived cofactor). Thus, I qualify to continue to lead the research on expanding the discoveries of the emerging members of the HDAO superfamily with novel cofactors or unique catalytic functions.

Currently funded ongoing research projects:

NIH 1R01GM152982-01 09/2024 – 08/2028
Liu, Aimin (PI)
Protein-Derived Cofactor in Bifunctional Enzyme KatG from *Mycobacterium tuberculosis*
The major goal of this project is to characterize the protein-derivced MYW crosslinked cofactor.

NIH 5R01GM108988-12 08/2022 – 08/2026
Liu, Aimin (PI)
Heme-Dependent Chemistry in Aromatic Oxidation
The major goal of this project is to characterize the structure and function of the representative members of a newly defined heme-dependent aromatic oxygenase (HDAO) superfamily.

NIH 1R21AG078775-01
Liu, Aimin (MPI and sub-PI; Lead PI: Altman, R.A.) 09/2022 – 06/2025
Identification of CNS-Penetrant Tryptophan 2,3-Dioxygenase Degrading Ligands
This project aims to design CNS-penetrant lead compounds targeting the kynurenine pathway.

NIH 5 R01CA247379-04
Liu, Aimin (Co-I and sub-PI, PI: Sun, L.) 07/2020 – 06/2025
Role of STEAP2 protein in hepatocarcinogenesis
This project aims to characterize human Steap2 protein and its role in cancer.

NSF CHE-2204225
Liu, Aimin (PI) 10/2022 – 09/2025
Project Title: Cys-Tyr Cofactor in Iron and Copper Proteins
This project aims to characterize the cysteine-tyrosine cofactor in galactose oxidase and thiol dioxygenases.

Welch Foundation AX-2110-20250403
Liu (PI) 06/2025 – 05/2028
Project Title: Fe-Dependent Peptide Cyclization: Mechanistic Divergence in C-C/C-O Bond Forming Reactions
This project aims to characterize peptide-cyclizing metalloenzymes, such as P450 enzyme CYP121

B. Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

01/2016 - present	Professor of Chemistry and Biochemistry with tenure, and Lutcher Brown Distinguished Chair in Biochemistry (“Chair” is an academic title, but not an administrative role), UTSA
02/2015-01/2016	Distinguished University Professor, Georgia State University, Atlanta, GA (voluntarily relinquished in 01/2016 due to relocation)
08/2012-01/2015	Full Professor with tenure, Department of Chemistry and the Center for Diagnostics And Therapeutics, Georgia State University, Atlanta, GA
08/2008-07/2012	Associate Professor, Department of Chemistry, Georgia State University, Atlanta, GA
07/2008-08/2008	Associate Professor of Biochemistry (tenured), Department of Biochemistry, School of Medicine, University of Mississippi Medical Center, Jackson, MS
10/2002-06/2008	Assistant Professor of Biochemistry (tenure track), Department of Biochemistry, School of Medicine, University of Mississippi Medical Center, Jackson, MS
01/2002-09/2002	Research Associate under Dr. John D. Lipscomb, Department of Biochemistry, Molecular Biology and Biophysics, University of Minnesota, Minneapolis, MN
06/1999-12/2001	Postdoctoral Research Associate under Drs. John D. Lipscomb and Lawrence Que, Jr.

	Center for Metals in Biocatalysis, University of Minnesota, Minneapolis, MN
1997-1999	Research Fellow under Dr. Astrid Gräslund, Department of Biochemistry & Biophysics Arrhenius Laboratories for Natural Sciences, Stockholm University, Sweden
1996-1997	Royal Society KC Wong Fellow (under Dr. Geoff Sykes, FRS), Department of Chemistry, University of Newcastle, Newcastle upon Tyne, UK
1992-1996	Faculty Member, State Key Laboratory of Physical Chemistry of Solid Surfaces and Department of Chemistry, Xiamen University, PR China

Other Professional Experience

2024 – 2029	Editorial Board Member, Journal of Biological Chemistry (JBC)
2024	Panelist, Special Emphasis Panel, National Center for Advancing Translational Sciences, Center for Scientific Review, NIH
2023 – 2028	Panelist (quarterly panel reviews), NRC Research Associateship Programs Fellowships, Fellowships Office of the National Academies of Sciences, Engineering, and Medicine
2021	Ad hoc grant reviewer, Le financement sur projet au service de la Recherche (ANR)
2021	Ad hoc grant reviewer, Einstein Stiftung Berlin (Einstein Foundation Berlin) of Germany
2021	Panelist, National Science Foundation (NSF) review panel for Chemistry of Life
2020	Grant Reviewer for ConTex Collaborative Research Grants Competition
2019 – 2023	Appointed Regular Member, MSFA Study Section, Center for Scientific Review, NIH
2019	Session Chair, The 26th Enzyme Mechanisms Conference, New Orleans, LA
2017	Discussion Leader, Gordon Research Conference–Enzymes, Coenzymes, and Metabolic Pathways, Waterville Valley, NH
2017-present	Editorial Board Member, Frontiers in Bioscience
2017-present	Editorial Advisory Board Member, Open Journal of Biochemistry
2016-present	Editorial Board Member, Reactive Oxygen Species (ROS)
2016	Discussion Leader, Gordon Research Conference - Metals in Biology, Ventura, CA
2015-2017	Alternate Councilor, American Chemical Society (ACS) Division of Biological Chemistry
2014-2015	Elected Member, Triennial Evaluation Committee of the College of Arts & Sciences Dean
2014, 2016, 2017	Panelist, Special Emphasis Panel for Members Conflict, CSR, NIH
2014-2016	University Faculty Senator, Georgia State University, Atlanta, GA
2014-2015	Program Committee Member, Enzymes in Drug Discovery Conference, GTC
2014-2017	Editorial Advisory Board Member, *J. Biol. Inorg. Chem.*, Springer
2013-2021	Ad hoc reviewer for national lab proposals of NHMFL and SSRL/SLAC
2013-2016	College Promotion and Tenure Area Committee (at-large seat), Georgia State University
2013-2018	Editorial Board Member, BBA Proteins and Proteomics, Elsevier
2013, 2014, 2017	Ad hoc reviewer, BBSRC and MRC grant proposal, U.K.
2012, 2017, 2018	Panelist, CAREER panels for Chemistry of Life Processes (CLP), NSF
2012	Discussion Leader, GRC - Protein Cofactors, Radicals & Quinones, South Hadley, MA
2011	Chair, The 40th Southeastern Magnetic Resonance Conference (SEMRC), Atlanta, GA
2010-2012	Elected member, the EMR User Committee, the National High Magnetic Field Laboratory (MagLab), Florida State University, Tallahassee, FL
2009, 2014	Panelist, Grant review panels for CLP and MCB, NSF
2008	Visiting Professor (two months), Kansai University, Japan
2006	Panelist, MSFA Study Section, NIH
2005-2008	Steering Committee Member, Neuroscience Graduate Curriculum, University of Mississippi Medical Center, Jackson, MS
2004-2008	Director, Biomedical EPR Facility, University of Mississippi Medical Center, Jackson, MS

Honors

2022	Accomplishment-Based Renewal (ABR) from NSF CHE
2021	Elected Fellow, American Association for the Advancement of Science (AAAS)
2021	Elected Fellow, Royal Society of Chemistry (FRSC)
2021	Elected to the Academy of Distinguished Researchers, UTSA
2015	Distinguished University Professor, Georgia State University
2014	Outstanding Senior Faculty Award, College of Sciences, Georgia State University
2009	Georgia Cancer Coalition Distinguished Cancer Scholar Award
2002	Paul D. Boyer Award for Research Excellence, Department of Biochemistry, Molecular Biology and Biophysics, University of Minnesota, Minneapolis, MN

2002	Cyrus P. and Anne R. Barnum Travel Award, the Minnesota Medical Foundation
2002	Young Investigator Award, 7th International Symposium on Spin Trapping, Chapel Hill, NC
2002	Ralph E. Powe Junior Faculty Enhancement Award in Life Sciences, The Oak Ridge Associated Universities (ORAU)
1995	National Prize for Promotion of Science and Technology from the National Education Commission (shared with five colleagues), Beijing, China
1991	Presidential Graduate Research Award, Chinese Academy of Science

C. Contributions to Science

1. My laboratory has been studying the **biogenesis of protein-derived cofactors** for over 20 years. We contributed to the discovery of a long-range remote enzyme catalytic mechanism for the biosynthesis of the tryptophan tryptophylquinone (TTQ) cofactor in methylamine dehydrogenase. Specifically, my lab has made the following breakthrough findings: the discovery of a high-valence ***bis*-Fe(IV) intermediate** of the di-heme enzyme MauG, which uncovered a novel natural strategy for storing two oxidizing equivalents; **a Trp-based diradical intermediate on the substrate protein** generated by the *bis*-Fe(IV) species through long-range remote oxidation by the diheme enzyme, and, most recently, an **innovative, long-distance, biological charge-resonance (CR) phenomenon** with a characteristic near-infrared spectral signature.

- A catalytic di-heme *bis*-Fe(IV) intermediate, an alternative to an Fe(IV)=O porphyrin radical (2008) Li X, Fu R, Lee S, Krebs C, Davidson VL*, and **Liu A***, ***PNAS*** (direct submission), 105, 8597-8600 [PMCID: PMC2438432]
- Diradical intermediate within the context of tryptophan tryptophylquinone biosynthesis (2013) Yukl ET, Liu F, Krzystek J, Shin S, Jensen LM, Davidson VL, Wilmot CM*, and **Liu A***, ***PNAS*** (direct submission), 110, 4569-4573 [PMCID: PMC3607037]
- Tryptophan-mediated charge-resonance stabilization in the *bis*-Fe(IV) redox state of MauG (2013) Geng J, Dornevil K, Davidson VL, and **Liu A***, ***PNAS*** (direct submission), 110, 9639-9644 [PMCID: PMC3683780]
- Probing *bis*-Fe(IV) MauG: Experimental evidence for the long-range charge-resonance model (2015) Geng J, Davis I, and **Liu A***, ***Angew. Chem. Int. Ed.***, 54, 3692-3696 [PMCID: PMC4363735]

2. My laboratory has contributed to the understanding of the tryptophan-kynurenine catabolic pathway, including tryptophan 2,3-dioxygenase (TDO). My lab **discovered the missing dehydrogenase** of the kynurenine pathway. This human dehydrogenase was misassigned by others to a retinal dehydrogenase. We trapped the **long-sought tetrahedral thiohemiacetal intermediate** from the dehydrogenase, which is a substantial contribution to the dehydrogenase chemistry. In the studies of the extradiol dioxygenase of the pathway, we structurally **characterized seven catalytic intermediates, making it one of the best-understood oxygen activation enzymes**. My lab has helped a clinician define the rationale for the illness in a female patient by investigating her TDO enzyme mutation. We found that TDO has a second, non-catalytic, yet more potent L-Trp binding site than the catalytic heme site. If L-Trp is depleted, this stronger L-Trp binding site will be empty, and the enzyme will be degraded. The proband has a mutation that destroys the integrality of this previously unknown site. This is why the individual presents with hypertryptophanemia and why she has had miscarriages. This case study not only **discovered a new genetic disorder** but also demonstrated that a subtle distortion at the newly discovered non-catalytic site substantially shortens the half-life of TDO in humans (which became a **novel immunotherapy target against TDO which overexpressed by cancers for immune escape)**. We have also **solved an 80-year-old mystery** of how the resting inactive TDO with a ferric heme becomes reduced and active by incubating with a low level of an oxidant, hydrogen peroxide (not a reductant). This seemingly impossible mission is accomplished in the enzyme by first going uphill (i.e., oxidizing the heme Fe to a high-valence state, and the substrate of the enzyme [L-Trp] functions as a reducing agent to bring the iron back to the ferrous state).

- Crystallographic and spectroscopic snapshots reveal a dehydrogenase in action (2015) Huo L, Davis I, Liu F, Andi B, Esaki S, Hiroaki I, Li T, Hasegawa Y, Orville AM, **Liu A***, ***Nat. Commun.***, 6:5935 [PMCID: PMC4286809]
- Observing 3-hydroxyanthranilate-3,4-dioxygenase in action through a crystalline lens (2020) Wang Y, Liu KF, Yang Y, Davis I, **Liu A***, ***PNAS*** (direct submission), 117(33) 19720-19730 [PMCID: PMC7443976]
- Reassignment of the human aldehyde dehydrogenase ALDH8A1 (ALDH12) to the kynurenine pathway in tryptophan catabolism (2018) Davis I, Yang Y, Wherritt D, and **Liu A***, ***J. Biol. Chem.***, 293(25), 9594-9603 [PMCID: PMC6016481]

- *O*-Atom transfer in heme-based tryptophan dioxygenase: The role of substrate ammonium in the epoxide ring opening (2018) Shin I, Ambler, BA, Wherritt B, Griffith WP, Maldonado A, Altman RA, and **Liu A***, ***J. Am. Chem. Soc.***, 140(12), 4372-4379 [PMCID: PMC5874177]

3. We discovered a transition metal cofactor in the decarboxylase of the tryptophan metabolic pathway; an enzyme that had long been thought to be cofactor-free before our work. We subsequently discovered that this decarboxylase belongs to the amidohydrolase superfamily and determined its first crystal structure from a bacterial source and later the human enzyme. Our work has **defined a new protein subfamily** within the amidohydrolase superfamily, which **helped to annotate correctly over 700 genes previously misannotated**. The subfamily enzymes (now over 3,500) are decarboxylases and hydrolases distinct from the rest of hydrolase enzymes. We found that the transition metal-catalyzed O_2-independent nonoxidative reaction is a novel decarboxylation that had never been described.

- Kinetic and spectroscopic characterization of ACMSD from *Pseudomonas fluorescens* reveals a pentacoordinate mononuclear metallocofactor (2005) Li T, Walker AL, Iwaki H, Hasegawa Y, **Liu A***, ***J. Am. Chem. Soc.***, 127, 12282–12290 [PMID: 16131206]
- Detection of transient intermediates in the metal-dependent nonoxidative decarboxylation catalyzed by α-amino-β-carboxymuconate-ε-semialdehyde decarboxylase (2007) Li T, Ma JK, Hosler JP, and **Liu A***, ***J. Am. Chem. Soc.***, 129, 9278-9279 [PMID: 17625866]
- The power of two: arginine 51 and arginine 239* from a neighboring subunit are essential for catalysis in α-amino-β-carboxymuconate-ε-semialdehyde decarboxylase (2013) Huo L, Davis I, Chen L, and **Liu A***, ***J. Biol. Chem.***, 288, 30862-30871 [PMCID: PMC3829401]
- Quaternary structure of α-amino-β-carboxymuconate-ε-semialdehyde decarboxylase (ACMSD) controls its activity (2019) Yang Y, Davis I, Matsui T, Rubalcava I, and **Liu A*** ***J. Biol. Chem.***, 294, 11609-11621 [PMCID: PMC6663868]

4. My laboratory has discovered **a novel C-F bond cleavage mechanism** mediated by iron enzymes. Along this line, we **introduced unnatural amino acids to protein cofactor studies** and found a novel heme center.

- Cleavage of a C–F bond by an engineered cysteine dioxygenase (2018) Li J, Griffith WP, Davis I, Shin I, Wang J, Li F, Wang Y, Wherritt D, and **Liu A***, ***Nat. Chem. Biol***., 14(9), 853-860 [PMCID: PMC6103799]
- Molecular rationale for partitioning between C-H and C-F bond activation in heme-dependent tyrosine hydroxylase (2021) Wang Y, Davis I, Shin I, Xu H, and **Liu A***, ***J. Am. Chem. Soc***. 143(12), 4680-4693 [PMCID: PMC8283942]
- Formation of monofluorinated radical cofactor in galactose oxidase through copper-mediated C−F bond scission (2020) Li J, Griffith WP, and **Liu A***, ***J. Am. Chem. Soc***. 142(44), 18753-18757 [PMCID: PMC7737484]
- A novel catalytic heme cofactor in SfmD with a single thioether bond and a *bis*-His ligand set revealed by *de novo* crystal structural and spectroscopic study (2021) Shin I, Davis I, Nieves-Merced K, Wang Y, McHardy S, and **Liu A***, ***Chem. Sci.***, 12(11), 3984-3998 [PMCID: PMC8179489]

5. We have described a **groundbreaking redox-sensing mechanism** that initiates the human immune system. We identified the biological function of a human iron-containing protein Pirin in the cell nucleus. We found that Pirin utilizes an **iron redox state-linked structural switch** to detect redox level shifts in the cell nucleus. Specifically, the ferric, not ferrous, form of Pirin substantially facilitates the binding of NF-κB proteins to target κB genes, suggesting that Pirin performs a redox-sensing role in NF-κB regulation. This finding sets a new stage for unveiling novel metalloprotein-dependent redox sensing in gene transcription regulation, establishes novel metalloprotein-induced redox stress responses via NF-κB, and provides improved comprehension of redox control in cells.

- Pirin is an iron-dependent redox regulator of NF-κB (2013) Liu F, Rehmani I, Esaki S, Fu R, Chen L, de Serroano V, and **Liu A***, ***PNAS*** (direct submission), 110, 9722-9727 [PMCID: PMC3683729].

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