BIOGRAPHICAL SKETCH

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NAME: Tanner, John, J.

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POSITION TITLE: Professor of Biochemistry and Chemistry

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
University of Missouri, Columbia	BS	05/1983	Chemistry
Brown University	PHD	05/1988	Physical Chemistry
University of Houston (with J. Andrew McCammon)	Postdoctoral	1991	Computational Biology
University of Houston (with Kurt L. Krause)	Postdoctoral	1997	Protein Crystallography

A. Personal Statement

I am a structural biologist with a background in theoretical physical chemistry and computational biology. My research group studies enzyme structure and function using X-ray crystallography, small-angle X-ray scattering (SAXS), electron microscopy, site-directed mutagenesis, enzyme kinetics, chemical probes, and other biophysical tools. My research has produced 166 peer-reviewed publications (> 50 in the last 5 years) and 186 depositions to the Protein Data Bank. I have trained 16 Ph.D. students, 5 M.S. students, and 1 PREP postbaccalaureate student. My current group consists of a postdoctoral associate, a research technician, three graduate students and two undergraduates.

I am well-suited to leading cryo-EM studies of proline catabolic enzymes [1]. My group has done foundational research in on these enzymes, including determining the first structures of proline dehydrogenase, bifunctional proline utilization A (PutA) [2], and the PutA ribbon-helix-helix domain complexed with DNA [3]. We have also been leading the way in discovering chemical probes against proline metabolic enzymes for use in cancer biology research and drug discovery [4]. The proposed cryo-EM studies represent a new chapter in the structural biology of proline catabolism by providing the first structures of trifunctional PutA and elucidating long-distance allosteric conformational changes in PutAs.

Ongoing and recently completed projects that I would like to highlight include:

R01 GM065546-12
Tanner (PI)
05/05/2002 – 04/30/2022 (A1 renewal application in preparation)
Coordination of Functions by Proline Metabolic Enzymes

R01 GM132640
Tanner (PI)
09/15/2020 – 08/31/2022
Investigating the Proline Cycle as a Potential Cancer Therapy Target

NSF CHE 2003986
Tanner (PI)

07/01/2020 – 06/30/2023
Collaborative Research: Structure and function of flavin-dependent N-monooxygenases

R01 GM093123
Cheng (PI), Role: co-investigator
06/01/2020 – 05/31/2024
Distance-based ab initio protein structure prediction

Citations:

1. Tanner, J.J., *Structural Biology of Proline Catabolic Enzymes.* Antioxid Redox Signal, **2019**, 30(4), 650-673.
2. Liu, L.K., D.F. Becker, and J.J. Tanner, *Structure, function, and mechanism of proline utilization A (PutA).* Arch Biochem Biophys, **2017**, 632, 142-157.
3. Zhou, Y., J.D. Larson, C.A. Bottoms, E.C. Arturo, M.T. Henzl, J.L. Jenkins, J.C. Nix, D.F. Becker, and J.J. Tanner, *Structural basis of the transcriptional regulation of the proline utilization regulon by multifunctional PutA.* J Mol Biol, **2008**, 381(1), 174-88.
4. Tanner, J.J., S.M. Fendt, and D.F. Becker, *The Proline Cycle As a Potential Cancer Therapy Target.* Biochemistry, **2018**, 57(25), 3433-3444.

B. Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

2021	NIH SEP 2021/05 ZRG1 F04B Fellowships panel
2020	NIH R35 MIRA for ESIs review panel
2019 – Present	Associate Chair, Department of Biochemistry, University of Missouri
2019	NIH SEP ZRG1 BCMB-G (02) review panel
2018	Interim Chair, Department of Biochemistry, University of Missouri
2018	NSF Chemistry of Life Processes Enzyme Chemistry Panel
2018	NIH R35 MIRA review panel
2016 – Present	Editorial Board, Journal of Biological Chemistry
2016 – 2017	Chair-Elect & Chair, American Crystallographic Association BioMac SIG
2016	NIAID SEP on Structural Genomics for Infectious Diseases
2013 – Present	Professor, Department of Biochemistry, University of Missouri
2012 – 2016	NIH MSFA Study Section (regular member)
2012	NIH P41 Site Visit Review Team, MacCHESS, Cornell University
2011 – Present	Editorial Board, Archives of Biochemistry and Biophysics
2011	NIH MSFB Study Section (temporary member)
2010	NIH MSFE Study Section (temporary member)
2010	NCI Site Visit Review Team (Frederick, MD)
2009	NIH MSFC Study Section (temporary member)
2008	Chair, NIH Biophysical and Chemical Sciences IRG Postdoctoral Fellowships Panel
2006 – 2013	Professor, Department of Chemistry, University of Missouri
2006 – 2008	Secretary-Treasurer, American Crystallographic Association BioMac SIG
2006	Chair, NIH Biophysical and Chemical Sciences IRG Postdoctoral Fellowships Panel
2005	NIH Special Emphasis Panel on Macromolecular Structure and Function
2005	NIH Study Section on National Centers for Biomedical Computing
2004 – 2009	NIH Biophysical and Chemical Sciences IRG Postdoctoral Fellowships Panel
2004	NIH BBCB Study Section (temporary member)
2002 – 2006	Associate Professor, Department of Chemistry, University of Missouri
1997 – 2002	Assistant Professor, Department of Chemistry, University of Missouri

Honors

2017	William Evans Fellowship, University of Otago, Dunedin, NZ

2017 MU Biochemistry Faculty Fellowship
2011 MU Gold Chalk Award for excellence in graduate teaching

C. Contributions to Science

1. First structure of the proline catabolic enzyme, proline dehydrogenase (PRODH). Proline metabolism has been a major focus of the Tanner lab since the early 2000s. Proline metabolism refers to the five enzyme-catalyzed reactions that interconvert L-proline and L-glutamate. The enzymes and intermediates of proline metabolism have been implicated in many aspects of human health and disease, including cancer, inherited metabolic disorders, neurological disorders, life-span extension, and pathogen virulence and survival. We initially focused on the catabolic arm of proline metabolism and determined the first structure of proline dehydrogenase (PRODH), the flavoenzyme that catalyzes the oxidation of proline to Δ^1-pyrroline-5-carboxylate (P5C) [5]. This structure revealed the fold of the enzyme and insight into the catalytic mechanism. Subsequent studies revealed conformational changes induced by reduction of the FAD [6], variations in the enzyme fold [7], and evidence for gating of the active site [8].

5. Lee, Y.H., S. Nadaraia, D. Gu, D.F. Becker, and J.J. Tanner, *Structure of the proline dehydrogenase domain of the multifunctional PutA flavoprotein.* Nat Struct Biol, **2003**, 10(2), 109-114.
6. Zhang, W., M. Zhang, W. Zhu, Y. Zhou, S. Wanduragala, D. Rewinkel, J.J. Tanner, and D.F. Becker, *Redox-induced changes in flavin structure and roles of flavin N(5) and the ribityl 2'-OH group in regulating PutA-membrane binding.* Biochemistry, **2007**, 46(2), 483-91.
7. White, T.A., N. Krishnan, D.F. Becker, and J.J. Tanner, *Structure and kinetics of monofunctional proline dehydrogenase from Thermus thermophilus.* J Biol Chem, **2007**, 282(19), 14316-27.
8. Luo, M., B.W. Arentson, D. Srivastava, D.F. Becker, and J.J. Tanner, *Crystal structures and kinetics of monofunctional proline dehydrogenase provide insight into substrate recognition and conformational changes associated with flavin reduction and product release.* Biochemistry, **2012**, 51(50), 10099-108.

2. Structural biology of the bifunctional proline catabolic enzyme, proline utilization A (PutA). In some organisms, the two proline catabolic enzymes are combined into a bifunctional enzyme known as PutA. PutAs are large (>1000 residues) bifunctional enzymes that catalyze the 4-electron oxidation of proline to glutamate using proline dehydrogenase (PRODH) and L-glutamate-γ-semialdehyde dehydrogenase (GSALDH) active sties. In the late 2000s, we defined five distinct classes of PutA proteins based on domain architecture and sequence identity. We then embarked on a homolog screening campaign to find PutAs that were amenable to high resolution crystallography. This effort produced crystal structures of PutAs from four of the five classes [9-12]. These structures revealed a complex multidomain fold, spatially-separated active sites connected by a narrow tunnel, and unique and unexpected modes of oligomerization.

9. Srivastava, D., J.P. Schuermann, T.A. White, N. Krishnan, N. Sanyal, G.L. Hura, A. Tan, M.T. Henzl, D.F. Becker, and J.J. Tanner, *Crystal structure of the bifunctional proline utilization A flavoenzyme from Bradyrhizobium japonicum.* Proc Natl Acad Sci USA, **2010**, 107(7), 2878-83.
10. Singh, H., B.W. Arentson, D.F. Becker, and J.J. Tanner, *Structures of the PutA peripheral membrane flavoenzyme reveal a dynamic substrate-channeling tunnel and the quinone-binding site.* Proc Nat Acad Sci USA, **2014**, 111(9), 3389-94.
11. Luo, M., T.T. Gamage, B.W. Arentson, K.N. Schlasner, D.F. Becker, and J.J. Tanner, *Structures of Proline Utilization A (PutA) Reveal the Fold and Functions of the Aldehyde Dehydrogenase Superfamily Domain of Unknown Function.* J Biol Chem, **2016**, 291(46), 24065-24075.
12. Korasick, D.A., T.T. Gamage, S. Christgen, K.M. Stiers, L.J. Beamer, M.T. Henzl, D.F. Becker, and J.J. Tanner, *Structure and characterization of a class 3B proline utilization A: Ligand-induced dimerization and importance of the C-terminal domain for catalysis.* J Biol Chem, **2017**, 292(23), 9652-9665.

3. Substrate channeling in proline catabolism
PutA structures revealed active sites separated by 42 Å and connected by a long tunnel. The tunnel immediately suggested that the intermediate of the PutA reaction is channeled from the PRODH site to the GSALDH site. As part of this project, we have developed sophisticated kinetics approaches for studying channeling, and used them to show that substrate channeling is a conserved feature of PutA [13-15]. We further demonstrated that monofunctional PRODH and GSALDH interact and channel the intermediate, analogous to PutA [16].

13. Arentson, B.W., M. Luo, T.A. Pemberton, J.J. Tanner, and D.F. Becker, *Kinetic and Structural Characterization of Tunnel-Perturbing Mutants in Bradyrhizobium japonicum Proline Utilization A.* Biochemistry, **2014**, 53(31), 5150-61.
14. Moxley, M.A., N. Sanyal, N. Krishnan, J.J. Tanner, and D.F. Becker, *Evidence for Hysteretic Substrate Channeling in the Proline Dehydrogenase and Delta1-Pyrroline-5-carboxylate Dehydrogenase Coupled Reaction of Proline Utilization A (PutA).* J Biol Chem, **2014**, 289(6), 3639-51.
15. Luo, M., S. Christgen, N. Sanyal, B.W. Arentson, D.F. Becker, and J.J. Tanner, *Evidence that the c-terminal domain of a type b puta protein contributes to aldehyde dehydrogenase activity and substrate channeling.* Biochemistry, **2014**, 53(35), 5661-73.
16. Sanyal, N., B.W. Arentson, M. Luo, J.J. Tanner, and D.F. Becker, *First Evidence for Substrate Channeling Between Proline Catabolic Enzymes: A Validation of Domain Fusion Analysis for Predicting Protein-Protein Interactions.* J Biol Chem, **2015**, 290(4), 2225-2234.

4. Discovery of chemical probes targeting proline metabolic enzymes. The proline metabolic enzymes proline dehydrogenase (PRODH) and Δ^1-pyrroline-5-carboxylate reductase (PYCR) are recognized as *bona fide* cancer targets, and the Tanner lab is a leader in the development of chemical probes directed at these enzymes. We discovered the noncovalent PRODH inhibitor (S)-(-)-tetrahydro-2-furoic acid and determined several structures of PRODHs complexed with this compound [8, 10, 11]. This probe remains the most potent noncovalent PRODH inhibitor known and has been a useful probe in cellular studies of cancer metabolism. We also discovered three different classes of mechanism-based inactivators, which covalently and irreversibly modify the N5 atom of the FAD of PRODH [17-19]. For PYCR, we employed a focused target-specific (a.k.a. "knowledge-based") screening approach to identify *N*-formyl-L-proline as an inhibitor of PYCR1 [20]. Currently, *N*-formyl-L-proline is the only inhibitor of PYCR1 that has been thoroughly validated by demonstrating the kinetic mechanism of action against the purified enzyme, the mode of binding to the enzyme by X-ray crystallography, and activity in cancer cells.

17. White, T.A., W.H. Johnson, Jr., C.P. Whitman, and J.J. Tanner, *Structural basis for the inactivation of Thermus thermophilus proline dehydrogenase by N-propargylglycine.* Biochemistry, **2008**, 47(20), 5573-80.
18. Campbell, A.C., D.F. Becker, K.S. Gates, and J.J. Tanner, *Covalent Modification of the Flavin in Proline Dehydrogenase by Thiazolidine-2-Carboxylate.* ACS Chem Biol, **2020**, 15(4), 936-944.
19. Campbell, A.C., A.R. Prater, A.N. Bogner, T.P. Quinn, K.S. Gates, D.F. Becker, and J.J. Tanner, *Photoinduced Covalent Irreversible Inactivation of Proline Dehydrogenase by S-Heterocycles.* ACS Chem Biol, **2021**.
20. Christensen, E.M., A.N. Bogner, A. Vandekeere, G.S. Tam, S.M. Patel, D.F. Becker, S.M. Fendt, and J.J. Tanner, *In crystallo screening for proline analog inhibitors of the proline cycle enzyme PYCR1.* J Biol Chem, **2020**, 295(52), 18316-18327.

5. The role of oligomeric structure in enzyme function and dysfunction

Collectively, our structural studies of proline metabolic enzymes and aldehyde dehydrogenases have caused us to think deeply about how oligomeric structure underlies enzyme function. This theme grew out of the diversity of oligomeric forms and shapes that we discovered in these enzyme families. As part of this effort, my group has developed expertise and negative electron microscopy [21-23] and SAXS [24] to study the relationship between oligomeric structure and enzyme function and to understand how disruption of oligomeric structure can underly enzyme dysfunction in metabolic diseases.

21. Korasick, D.A., A.C. Campbell, S.L. Christgen, S. Chakravarthy, T.A. White, D.F. Becker, and J.J. Tanner, *Redox Modulation of Oligomeric State in Proline Utilization A.* Biophys J, **2018**, 114(12), 2833-2843.
22. Korasick, D.A., T.A. White, S. Chakravarthy, and J.J. Tanner, *NAD(+) promotes assembly of the active tetramer of aldehyde dehydrogenase 7A1.* FEBS Lett, **2018**, 592(19), 3229-3238.
23. Wyatt, J.W., D.A. Korasick, I.A. Qureshi, A.C. Campbell, K.S. Gates, and J.J. Tanner, *Inhibition, crystal structures, and in-solution oligomeric structure of aldehyde dehydrogenase 9A1.* Arch Biochem Biophys, **2020**, 691, 108477.
24. Korasick, D.A. and J.J. Tanner, *Determination of protein oligomeric structure from small-angle X-ray scattering.* Protein Sci, **2018**, 27(4), 814-824.

Complete List of Published Work in MyBibliography:

https://www.ncbi.nlm.nih.gov/myncbi/john.tanner.1/bibliography/public/