BIOGRAPHICAL SKETCH

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NAME: Creamer, Trevor Paul

eRA COMMONS USER NAME (credential, e.g., agency login): Trevor.Creamer

POSITION TITLE: Professor of Molecular and Cellular 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
University of Western Australia, Perth, Australia	B.Sc. (Hons)	1985	Chemistry
University of Western Australia, Perth, Australia	Ph.D.	1989	Physical chemistry
The Pennsylvania State University, Hershey, PA	Postdoctoral	1989-1991	Biochemistry/biophysics
University of North Carolina, Chapel Hill, NC		1991-1992	Biochemistry/biophysics
Washington University in St. Louis, MO		1992-1994	Biophysics
The Johns Hopkins University, Baltimore, MD		1994-1997	Biophysics

A. Personal Statement

My research is centered on the function and regulation of calcium regulated proteins such as calmodulin and the essential Ser/Thr phosphatase calcineurin. Disruption of calcium homeostasis in Alzheimer's disease will interfere with the regulation of these proteins and subsequently of downstream processes. We are beginning to probe the role of calmodulin in regulating microtubule formation through its interactions with the microtubule-binding protein tau.

My laboratory has a significant amount of experience with a variety of biophysical approaches to studying interactions between proteins and their ligands and/or effectors. This includes the use of various biophysical approaches including fluorescence techniques, as well as enzymatic assays. My position as Associate Director of the Center for Structural Biology at the University of Kentucky ensures that I have ready access to the facilities required for such studies.

i. E.C. Cook and T.P. Creamer (2016) Calcineurin in a crowded world. *Biochemistry* **55**, 3092-3101.

ii. T.B. Dunlap, H.-f. Guo, E.C. Cook, E. Holbrook, J. Rumi-Masante, T.E. Lester, C.L. Colbert, C.W. Vander Kooi and **T.P. Creamer** (2014) Stoichiometry of the calcineurin regulatory domain-calmodulin complex. *Biochemistry* **53**, 5779-5790.

iii. T.B. Dunlap, E.C. Cook, J. Rumi-Masante, H.G. Arvin, T.E. Lester and **T.P. Creamer** (2013) The distal helix in the regulatory domain of calcineurin is important for domain stability and enzyme function. *Biochemistry* **52**, 8643-8651.

iv. J. Rumi-Masante, F. Rusinga, T.E. Lester, T.B. Dunlap, T.D. Williams, A.K. Dunker, D.D. Weis and **T.P. Creamer** (2012) Structural basis for the activation of calcineurin by calmodulin. *J. Mol. Biol.* **415**, 307-317.

B. Positions and Honors

Positions and Employment

1997-2002 Assistant Professor, Department of Molecular and Cellular Biochemistry, University of Kentucky, Lexington, KY
1997-present Member of the University of Kentucky Center for Structural Biology, Lexington, KY
2003-2013 Associate Professor, Department of Molecular and Cellular Biochemistry, University of Kentucky, Lexington, KY
2011-present Associate Director, Center for Structural Biology, University of Kentucky, Lexington, KY
2013-present Professor, Department of Molecular and Cellular Biochemistry, University of Kentucky, Lexington, KY

Other Experience and Professional Memberships

1992-present Member of the American Chemical Society
1997-present Member of the AAAS
1998-present Member of Editorial Board of *Proteins: Structure, Function and Bioinformatics*
2002-present *Ad hoc* grant reviewer for the National Science Foundation
2002-present Member of the Biophysical Society
2008-present Review panel member for American Heart Association
2008-present *Ad hoc* grant reviewer for the Oak Ridge Associated Universities
2008-present *Ad hoc* grant reviewer for the Agence Nationale de la Recherche, France
2002-2006 Member of the University of Kentucky College of Medicine Postdoctoral Advisory Committee
2003-2005 Chair of the University of Kentucky College of Medicine Postdoctoral Advisory Committee
2007-2010 Secretary/Treasurer of Intrinsically Disordered Proteins Subgroup of the Biophysical Society
2006-2012 Member of the Biophysical Society Education Committee
2007-2011 Editorial Board Member of the *Open Proteomics Journal*
2007-2013 Editorial Board Member of *Biochemistry Research International*
2003-2004 Member of NSF review panel
2009-2010 Member of NSF review panel
2015-2018 Member of NSF review panel

C. Contributions to Science

1. *α-Helix Formation*

My first significant contribution to biomolecular science came from a study of the determinants of α-helix formation. Working with Professor George Rose I was able to demonstrate that the propensity for a non-Gly/Pro residue to be a part of an α-helix is determined in part by the amount of conformational entropy lost by the side chain when folding from an unfolded state into the helix. I was able to show that there is a strong correlation between ΔS_{conf} and experimentally determined helix propensity scales. I was also able to estimate the strength of interactions between hydrophobic chains within an α-helix. Coupled, these findings have contributed to our understanding of α-helix formation.

i. **Trevor P. Creamer** and George D. Rose (1992) Side chain entropy opposes α-helix formation but rationalizes experimentally-determined helix-forming propensities. *Proc. Natl. Acad. Sci., USA* **89**, 5937-5941.

ii. **Trevor P. Creamer** and George D. Rose (1994) α-Helix-forming propensities in peptides and proteins. *Proteins* **19**, 85-97.

iii. **Trevor P. Creamer** and George D. Rose (1995) Interactions between hydrophobic side chains within α-helices. *Protein Science* **4**, 1305-1314.

iv. Rajeev Aurora, **Trevor P. Creamer**, Rajgopal Srinivasan and George D. Rose (1997) Local interactions in protein folding: Lessons from the α-helix. *J. Biol. Chem.* **272**, 1413-1416.

2. *Conformational Properties of Polyproline II (PII) Helices*

When I established my own laboratory, we began work on another type of helix, the polyproline II (PII) helix. This structure is predominantly, but not solely, formed by proline-rich sequences. Many proline-rich sequences act as mediators of protein-protein interactions (e.g. binding targets of SH3 domain). We applied a variety of

experimental and computational approaches to study the formation of this structure. Polymers of proline appear to adopt the PII fold primarily as a result of steric interactions between a prolyl ring, backbone atoms and adjacent prolyl rings. My laboratory went on to publish the first scale of PII propensities using a proline-rich peptide as the host system.

i. Benjamin J. Stapley and **Trevor P. Creamer** (1999) A survey of left-handed polyproline II helices. *Protein Science* 8, 587-595.

ii. Melissa A. Kelly, Brian W. Chellgren, Adam L. Rucker, Jerry M. Troutman, Michael G. Fried, Anne-Frances Miller and **Trevor P. Creamer** (2001) Host-guest study of left-handed polyproline II helix formation. *Biochemistry* 40, 14376-14383.

iii. Adam L. Rucker, Cara T. Pager, Margaret N. Campbell, Joseph Qualls and **Trevor P. Creamer** (2003) Host-guest scale of left-handed polyproline II helix formation. *Proteins* 53, 68-75.

iv. Brian W. Chellgren and **Trevor P. Creamer** (2004) Short sequences of non-proline residues can adopt the polyproline II helical conformation. *Biochemistry* **43**, 5864-5869.

3. *Models of Protein Disordered/Unfolded States*

The conformational properties of unfolded protein ensembles have been a long time interest. My work in this area started while a postdoc, and continued once I established my own laboratory. This work has evolved from using computational approaches to estimate the conformational entropy of side chains in models for unfolded proteins, to the use of experimental approaches to studying short peptides as models. Over time this has evolved into a strong interest in intrinsically disordered regions within proteins.

i. **Trevor P. Creamer** (2000) Side chain conformational entropy in protein unfolded states. *Proteins* **40**, 443-450.

ii. Adam L. Rucker and **Trevor P. Creamer** (2002) Polyproline II helical structure in protein unfolded states: Lysine peptides revisited. *Protein Science* **11**, 980-985.

iii. Shelly J. Whittington, Brian W. Chellgren, Veronique M. Hermann and **Trevor P. Creamer** (2005) Urea promotes polyproline II helix formation: implications for protein denatured states. *Biochemistry* **44**, 6269-6275.

iv. Angela M. Firestine, Veronique M. Chellgren, Shelly J. Rucker, Terrence E. Lester, and **Trevor P. Creamer** (2008) Conformational properties of a peptide model for unfolded α-helices. *Biochemistry* **47**, 3216-3224.

4. *Conformational Properties of Polyglutamine*

My interest in proline-rich sequences broadened to investigations of sequences highly enriched in other amino acids – simple sequences. Our bioinformatic studies revealed that glutamine-rich sequences are the most common simple sequences in eukaryote, but not prokaryote, proteomes. Around the same time, experimental work in my laboratory revealed that short polyglutamine sequences have a high propensity to adopt the polyproline II helical conformation. This led to a productive collaboration with Professor Ron Wetzel looking at the conformational properties and aggregation of polyglutamine sequences and Huntington's disease.

i. Kim Lan Sim and **Trevor P. Creamer** (2002) Abundance and distributions of eukaryote protein simple sequences. *Molecular and Cellular Proteomics* **1**, 983-995.

ii. Brian W. Chellgren, Anne-Frances Miller and **Trevor P. Creamer** (2006) Evidence for polyproline II helical structure in short polyglutamine tracts. *J. Mol. Biol.* **361**, 362-371.

iii. Anusri Bhattacharyya, Ashwani K. Thakur, Veronique M. Hermann, Geetha Thiagarajan, Angela D. Williams, Brian W. Chellgren, **Trevor P. Creamer** and Ronald Wetzel (2006) Oligoproline effects on polyglutamine conformation and aggregation. *J. Mol. Biol.* **355**, 524-535.

iv. Ashwani Thakur, Murali Jayaraman, Rakesh Mishra, Monika Thakur, Veronique M. Chellgren, In-Ja Byeon, Dalaver H. Anjum, **Trevor P. Creamer**, Angela M. Gronenborn and Ronald Wetzel (2009) Competing kinetic pathways in the aggregation of Huntingtin exon 1 related peptides. *Nat. Struct. Mol. Biol.* **16**, 380-389.

5. *Function and Regulation of the Essential Phosphatase Calcineurin*

My interest in protein unfolded and disordered states has led to my laboratory's work on the essential protein phosphatase calcineurin (CaN). CaN possesses an intrinsically disordered regulatory domain and interacts with disordered substrates/modulators. CaN plays central roles in numerous calcium-mediated signaling processes including neuron growth and signaling, activation of T-cells within the immune system, heart growth and function, and apoptosis. It is also essential for the lifecycle of pathogens such as *Aspergillus fumigatus*. Despite its importance, we know little about the molecular details of CaN regulation and interactions with substrates and endogenous inhibitors. Our initial work on CaN has focused on its activation by calcium and calmodulin (CaM). As calcium concentrations rise, both CaN and CaM will bind the metal ion, leading to CaM binding to the disordered CaN regulatory domain. This domain folds, causing an autoinhibitory domain to be removed from the phosphatase active site, thus activating the enzyme. This folding upon binding is the largest observed for a CaM:binding partner interaction. One component of this folded regulatory domain, is a marginally stable (T_m of 37°C *in vitro*) distal helix that appears to interact with the surface of CaM. Folding of this distal helix is essential for activation of CaN and thus represents a potential new target for drugs designed to inhibit the phosphatase. Our studies of the activation of CaN are ongoing and will enable a better understanding of its regulation. We are also working on the determinants of CaN:substrate interactions.

i. J. Rumi-Masante, F. Rusinga, T.E. Lester, T.B. Dunlap, T.D. Williams, A.K. Dunker, D.D. Weis and **T.P. Creamer** (2012) Structural basis for the activation of calcineurin by calmodulin. *J. Mol. Biol.* **415**, 307-317.

ii. T.B. Dunlap, E.C. Cook, J. Rumi-Masante, H.G. Arvin, T.E. Lester and **T.P. Creamer** (2013) The distal helix in the regulatory domain of calcineurin is important for domain stability and enzyme function. *Biochemistry* **52**, 8643-8651.

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iv. E.C. Cook and T.P. Creamer (2016) Calcineurin in a crowded world. *Biochemistry* **55**, 3092-3101.

Complete List of Published Work:

http://www.ncbi.nlm.nih.gov/sites/myncbi/trevor.creamer.1/bibliography/44815189/public/?sort=date&direction=ascending