

LINDA COLUMBUS

University of Virginia
Department of Chemistry

McCormick Road P.O. Box 400319
Charlottesville, VA22904-4319

Phone: (434) 243-2123

Fax: (434) 924-3710

Email: columbus@virginia.edu

EDUCATION, RESEARCH EXPERIENCE & EMPLOYMENT

University of Virginia, Charlottesville, VA

Assistant Professor of Chemistry, August 2007

The Scripps Research Institute, La Jolla, CA

Postdoctoral Fellow with Scott Lesley, June 2006-July 2007

Postdoctoral Fellow with Kurt Wüthrich, Aug. 2002-June 2006

University of California, Los Angeles, Los Angeles, CA

Postdoctoral Fellow with Wayne Hubbell, June 2001-Aug. 2002

University of California, Los Angeles, Los Angeles, CA

Graduate research with Wayne Hubbell, Sept. 1996-June 2001

Ph.D. in Biochemistry and Molecular Biology, May 2001

Thesis: "Investigating backbone and side chain dynamics of α -helices in the nanosecond regime with site-directed spin labeling"

Smith College, Northampton, MA

Undergraduate study with David Bickar, June 1993-May 1996

B.A. in Chemistry (*High Honors*), May 1996

Honors Thesis: "Investigation of MPP⁺ binding to neuroreceptors"

PUBLICATIONS

1. Gross A, **Columbus L**, Hideg K, Altenbach C, Hubbell WL. Structure of the KcsA potassium channel from *Streptomyces lividans*: A site-directed spin labeling study of the second transmembrane segment. *Biochemistry* 38: 10324-10335 (1999)
2. Gaponenko V, Howarth JW, **Columbus L**, Gasmi-Seabrook G, Yuan J, Hubbell WL, Rosevear PR. Protein global fold determination using site-directed spin and isotope labeling. *Protein Science* 9: 302-309 (2000)
3. **Columbus L**, Kalai T, Jeko J, Hideg K, Hubbell WL. Molecular motion of spin labeled side chains in α -helices: Analysis by variation of side chain structure. *Biochemistry* 40: 3828-3846 (2001)
4. **Columbus L**, Hubbell WL. A new spin on protein dynamics. *Trends in Biochemical Sciences*, 27: 288-295 (2002)
5. **Columbus L**, Hubbell WL. Mapping backbone dynamics in solution with site-directed spin labeling: GCN4-58 bZip free and bound to DNA. *Biochemistry* 43: 7273-7287 (2004)
6. Liang ZC, Lou Y, Freed JH, **Columbus L**, Hubbell WL. A multifrequency electron spin resonance study of T4 lysozyme dynamics using the slowly relaxing local structure model. *Journal of Physical Chemistry B* 108: 17649-17659 (2004)
7. **Columbus L**, Peti W, Herrmann T, Etezady T, Wüthrich K. NMR structure determination of the conserved hypothetical protein TM1816 from *Thermotoga maritima*. *Proteins: Structure, Function and Bioinformatics* 60: 552-557 (2005)
8. **Columbus L**, Lipfert J, Klock H, Millet I, Doniach S, Lesley SA. Expression, purification, and characterization of *Thermotoga maritima* membrane proteins for structure determination. *Protein Science* 15: 961-975 (2006)
9. Lipfert J, **Columbus L**, Chu V, Doniach S. Analysis of small-angle X-ray scattering data of protein-detergent complexes with singular value decomposition. *Journal of Applied Crystallography* 40: (2007)
10. Lipfert J, **Columbus L**, Chu V, Lesley SA, Doniach S. Size and shape of detergent micelles determined by small-angle X-ray scattering. *Journal of Physical Chemistry B* 111: 12427-12438 (2007).

11. McCleverty C*, **Columbus L***, Kreusch A, Lesley SA. Structure and ligand binding of the soluble domain of a *Thermotoga maritima* membrane protein of unknown function TM1634. *Protein Science* 17: 869-877 (2008)
12. **Columbus L**, Nakamoto, R.K., Cafiso, D.S. Properties of Membrane Proteins in Wiley Encyclopedia of Chemical Biology (2008)
13. **Columbus L**, Lipfert J, Jambunathan K, Fox DA, Sim AYL, Doniach S, Lesley SA. Mixing and matching detergents for membrane protein NMR structure determination. *Journal of the American Chemical Society* 131: 7320–7326 (2009)
14. Beuck C, Szymczyna BR, Kerkow DE, Carmel AB, **Columbus L**, Stanfield RL, and Williamson JR. Structure of the GLD-1 homodimerization domain: Insight into STAR protein-mediated translational regulation. *Structure* (submitted)

HONORS, AWARDS, & FELLOWSHIPS

2008	UVA Mead Honored Faculty
2003-2006	NIH Ruth L. Kirschstein National Research Service Award Postdoctoral Fellowship
2000	Eli Lilly & Company Best Poster Award at the 14th Protein Society Symposium
1999 - 2001	NRSA Institutional Training Grant
1997 - 1999	Chemistry-Biology Interface Training Grant
1996 - 1997	Alumnae Association Fellowship Award
1996	American Chemical Society Student Award
1996	Smith College Chemistry Award

RECENT INVITED TALKS

- 2009 Department of Chemistry, Northeastern University
- 2009 Southeast Magnetic Resonance Conference
- 2009 Physical Chemistry Division of the Southeast Regional Meeting of the American Chemical Association
- 2009 Department of Structural Biology, University of Pittsburgh
- 2009 Department of Chemistry, University of Florida
- 2009 Institute for Structural Biology and Drug Discovery, Virginia Commonwealth University
- 2009 53rd Annual Biophysical Society Meeting
- 2009 Department of Chemistry, Mount Holyoke
- 2009 Department of Chemistry, Smith College
- 2008 NIH Protein Structure Initiative Bottlenecks Workshop
- 2007 UCLA Chemistry-Biology Interface Day: Membrane proteins at the interface.
- 2007 *Thermotoga* 2007 Workshop: Structure and function at the *Thermotoga maritima* membranes
- 2007 JCSG 6th Annual Meeting: Biophysical characterization of membrane proteins
- 2007 American Chemical Society 233rd National Meeting & Exposition: Membrane proteins at the interface.

CURRENT FUNDING

RO1GM087828-02 Columbus (PI) 07/01/2009-06/30/2014

NIH/NIGMS

Award amount: \$207,000/yr (direct)

Structure and dynamics of bacterial membrane protein - receptor interactions

Role: Principal Investigator

MCB 0845668 Columbus (PI) 07/1/2009 – 06/30/2014

NSF

*These authors contributed equally

Award Amount: \$136,000/yr (total)

CAREER: An innovative study of membrane protein – detergent interactions

Role: Principal Investigator

J-885 Jeffress Memorial Trust Columbus (PI)

07/1/2009-06/30/2010

Award Amount: \$10,000.00 (direct)

Determining the structure and molecular determinants of membrane protein interactions involved in bacterial pathogenesis using NMR and EPR spectroscopy

Role: Principal Investigator

PENDING FUNDING

1 U01 GM094775-01

Robert Nakamoto (PI)

2010 – 2015

NIH/NIGMS

Award Amount: \$112,441/yr (direct)

Structural Biology of Bacterial Surfaces and Host-Pathogen Recognition

Role: Co-investigator

PAR-07-412

Eduardo Perozo (PI)

2010 – 2015

NIH/NIGMS

Award Amount: \$548,523/5 yr (direct)

Membrane Protein Structural Dynamics Consortium

Role: Co-investigator

COMPLETED FUNDING

J-885 Jeffress Memorial Trust Columbus (PI)

01/2008-12/2008

Award Amount: \$20,000.00

Determining the structure and molecular determinants of membrane protein interactions involved in bacterial pathogenesis using NMR and EPR spectroscopy

Role: Principal Investigator

5 F32 GM068286-03 NIH/NIGMS Columbus (PI)

06/16/03 – 06/15/06

This study targets helical membrane proteins with two, three, and four predicted transmembrane segments for NMR structure determination in order to significantly diversify the different types of membrane protein structures known.

Role: Principal Investigator

CURRENT RESEARCH

Structure and dynamics of bacterial membrane protein - receptor interactions. Many obligate bacterial membrane proteins hijack human cellular pathways by mimicking or manipulating host machinery. Of specific interest to this proposal are the outer membrane opacity-associated proteins (Opa) from *Neisseriae*, which induce engulfment of the bacterium in non-phagocytic host cells by binding to receptors on those cells. We aim to determine the specific interactions that occur between Opa proteins and the human host receptors that facilitate *Neisseriae* invasion. Nuclear magnetic resonance (NMR), in conjunction with site-directed spin labeling (SDSL), are the primary structural tool for determining the high-resolution structures of several Opa proteins with heparin (a competitive inhibitor of HSPG binding) and the N-domains of CEACAM receptors. The proposed research to determine the molecular determinants of the interactions between Opa and host receptors will provide insight into the pathogenesis of *Neisseriae* and, therefore, the potential for the rational design of novel antibiotics. In addition, the reconstituted Opa proteins may be useful for vaccine development. However, the most novel application of this research lies in the ability of Opa proteins to target host receptors specifically via three different mechanisms to induce endocytosis in non-phagocytic cells. This ability may be useful for liposome pharmaceutical carriers. The potential ability of liposome encapsulated therapeutics (e.g. enzymes, inhibitors, and peptides) to enter the cytoplasm of living cells and possibly tissue selectively is of crucial importance to the treatment of many diseases. Understanding the molecular determinants of the three Opa-mediated entry mechanisms may facilitate the development of liposome delivery mechanisms.

Investigating protein – detergent interactions. One major obstacle to membrane protein structure determination is the selection of a detergent micelle that mimics the native lipid bilayer. Currently, detergents are selected by exhaustive screening because the effects of protein-detergent interactions on protein structure are poorly understood. We are studying how detergent – protein interactions modulate structure and dynamics and, therefore, structure determination of membrane proteins. Specifically, we use small angle X-ray scattering, NMR, and SDSL to investigate the properties, structure and dynamics of both the protein and detergent in protein – detergent complexes to determine the requirements of membrane mimics in stabilizing the membrane protein structure and function.

Development of new strategies for the study of membrane protein structure and dynamics with SDSL and NMR. Currently membrane protein investigations rely on a qualitative understanding of the nitroxide side chain dynamics. Quantifying dynamic modes requires an understanding of the dynamics of the nitroxide in the lipid environment. Using x-ray crystallography, EPR spectral simulations, and nitroxide side chain derivatives we are investigating the molecular determinants of the dynamics of lipid exposed α -helical sites. In addition to advancing SDSL, these studies will advance NMR structure determination as well.

COURSES TAUGHT

CHEM441 Biological Chemistry I

Focuses on the structure and function of biomolecules.

Fall 2007 and 2008

Enrollment: 150 undergraduates

CHEM451 Biological Chemistry Lab I

Revised curriculum for the biochemistry undergraduate laboratory.

Fall 2008 and 2009

Enrollment: 80 undergraduates

CHEM452 Biological Chemistry Lab II

Research based biochemistry laboratory that has students apply knowledge from the fall semester to design experiments to investigate protein function based on structure.

Spring 2009

Enrollment: 78 undergraduates

SERVICE

University

2009 – present Postdoc Programs Faculty Advisory Board

2009 – present College Science Scholars Advisor

2009 – present Echols Scholars Program Advisor

Department

2007 – 2009 Department Seminar Committee

2009 – present Department Awards & Development Committee

Granting Agencies

Mail-in reviewer for NSF

Reviewer for Jeffress Memorial Trust