BIOGRAPHICAL SKETCH

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NAME: Volkman, Brian F.

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

POSITION TITLE: Professor of 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
Butler University, Indianapolis, IN	B.S.	1985-1989	Chemistry, Physics
University of New South Wales, Sydney, Australia		1989	Chemistry
University of California at Berkeley, Berkeley, CA	Ph.D.	1989-1994	Biophysical Chemistry
University of Wisconsin–Madison, Madison, WI	(Post-doc)	1995-1997	Biochemistry

A. Personal Statement

I am a co-founder and chief scientific officer of XLock Biosciences, LLC (XL), and I am also employed as a professor of biochemistry at the Medical College of Wisconsin (MCW). My role as co-PI of this SBIR application reflects my interest in commercialization of a lead compound that was discovered in my academic laboratory for psoriasis, psoriatic arthritis and other inflammatory diseases. Since 1999, the NIH has funded my research at MCW to resolve the molecular details of protein complexes in order to understand how chemokines, chemokine receptors and other signaling proteins function in normal biology and in human disease. I have coauthored over 50 structural entries in the Protein Data Bank and over 200 peer-reviewed original research articles on structure-function relationships for a broad range of clinically relevant proteins. My academic laboratory solved the NMR structure of the first complex between a chemokine (CXCL12) and the extracellular domain of its G protein-coupled receptor (CXCR4). This work enabled the development of novel small molecule chemokine inhibitors and prompted the discovery of an engineered dimeric chemokine (CXCL12-α locked dimer) which has been patented by MCW as a potent inhibitor of metastatic tumor formation (1). Engineered chemokines and chemokine-targeted small molecule ligands thus represent *two novel classes of inhibitors pioneered by the Volkman lab*. XL's SBIR proposal builds on my close association with Dr. William Clarke, a clinician-scientist with deep leadership experience in big pharma and biopharma startup companies as well as an > 10-year scientific relationship with Dr. Sam Hwang, an internationally-recognized clinician and immunology researcher with deep expertise in melanoma, psoriasis and other dermatological indications. My collaboration with Dr. Hwang to study the chemokine CCL20 and its receptor CCR6 in psoriatic dermatitis led to the invention of an engineered form of human CCL20 that prevents psoriatic disease in mouse models of human psoriasis (2) and psoriatic arthritis (3).

On the basis of our detailed structure-function analysis and promising preclinical results, MCW (as assignee of IP developed by its employees) has filed patent applications in the US, Europe and other jurisdictions on this novel composition of matter, and XL has obtained an exclusive license for its commercial development. In this SBIR application we seek to validate and optimize this biologic inhibitor as a lead compound and clinical candidate for inflammatory diseases, with a focus on psoriatic arthritis. This project takes advantage of the unique and highly complementary expertise of the small business concern (XLock Biosciences, LLC: chemokine structure, protein engineering and manufacturing, GPCR pharmacology) and our academic partners (Sam Hwang, MD, PhD, UC Davis: pathophysiology and immunological origins of psoriasis and other skin disease; Michael Dwinell, PhD and Anna Huppler, MD, MCW: immunology and chemokine biology

in cancer, inflammation and infectious disease). As co-PI and XL CSO, I will assist the contact PI (XL CEO William Clarke, MD), Dr. Hwang (XL CMO) and Dr. Dwinell (XL CTSO) in supervising and coordinating all work by XL scientists and the academic collaborators to achieve the aims of the research strategy, and work with the executive team to build potential investor and pharmaceutical company partnerships.

1. Takekoshi T, Ziarek JJ, **Volkman BF** and Hwang ST, A locked, dimeric CXCL12 variant effectively inhibits pulmonary metastasis of CXCR4-expressing melanoma cells due to enhanced serum stability (2012) *Mol Cancer Ther,* **11** 2516-25. PMC3496366

2. Getschman AE, Imai Y, Larsen O, Peterson FC, Wu X, Rosenkilde MM, Hwang ST and **Volkman BF**, Protein engineering of the chemokine CCL20 prevents psoriasiform dermatitis in an IL-23-dependent murine model (2017) *Proc Nat Acad Sci USA* **114** 12460-12465.

3. Shi Z, Garcia-Melchor E, Wu X, Getschman AE, Nguyen M, Rowland DJ, Wilson M, Sunzini F, Akbar M, Huynh M, Law L, Raychaudhuri S, **Volkman BF**, Millar NL, and Hwang ST, Targeting the CCR6/CCL20 axis in entheseal and cutaneous inflammation (2021) *Arthritis & Rheumatology* **73** 2271-2281.PMID 34081845.

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

Source: NIH R37 AI058072
PI: Volkman
Title: Structural basis for chemokine function
Dates: 12/01/03–6/30/2025

Source: NIH R01 GM097381
PI: Volkman
Title: Sulfotyrosine-guided discovery of small molecule chemokine inhibitors
Dates: 3/01/2011–2/28/2022

Source: NIH/NIAMS R44 AR074363-01
PI: Koplinski (Volkman co-PI)
Title: Development of an engineered CCL20 protein as a lead therapeutic molecule for psoriasis
Dates: 8/1/2020-7/31/2022

B. Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

2021	NIH ZRG1 BCMB-N (50) special study section
2020-	Chief Scientific Officer and co-founder, XLock Biosciences, LLC, Milwaukee, WI
2020-	Director, Structural Genomics Unit, Genomic Science and Precision Medicine Center, MCW
2020	NIH ZRG1 F04B-T (20) special study section
2020-2021	Co-leader, Cancer Biology program, Medical College of Wisconsin Cancer Center
2017-	Director, Program in Chemical Biology, Medical College of Wisconsin
2016	Reviewer, Science Foundation Ireland
2016	NIH ZRG1 AARR-K(92) special study section
2015	Chair, NIH ZRG1 BCMB-S (40) P41 site visit review panel
2014-	President and co-founder, Protein Foundry, LLC, Milwaukee, WI
2013-2018	NIH MSF-C study section (full member)
2013	Reviewer, US-Israel Binational Science Foundation
2013	NIH ZRG1 BCMB-H special study section
2011	NIH ZRG1 BCMB-R special study section
2011	NIH ZRG1 IMM-N special study section
2010-	Professor, Department of Biochemistry, Medical College of Wisconsin
2010	NIH ZRG1 BCMB-B special study section
2010	NIH ZRG1 BDA-P special study section
2009	Reviewer, NIH Challenge Grants
2006-2008	NIH MSF-B study section (temporary member)
2005-2010	NIH AMCB study section (temporary member)
2005-2010	Associate Professor (tenured), Department of Biochemistry, Medical College of Wisconsin

2005	NIH NCF special study section
2004-2008	NIH CMI-A study section (temporary member)
2001	NIH MBC-2 study section (temporary member)
2000-2005	Assistant Professor, Department of Biochemistry, Medical College of Wisconsin
2000	Associate Scientist, National Magnetic Resonance Facility at Madison, Department of Biochemistry, University of Wisconsin–Madison
1997-2000	Assistant Scientist, National Magnetic Resonance Facility at Madison, Department of Biochemistry, University of Wisconsin–Madison
1995-1997	Postdoctoral Research Associate, National Magnetic Resonance Facility at Madison, Department of Biochemistry, University of Wisconsin–Madison
1989-1994	Research Assistant, Department of Chemistry, University of California at Berkeley
1989-1991	Graduate Student Instructor, Department of Chemistry, University of California at Berkeley
1989	Undergraduate Research Assistant, University of New South Wales
1988	Undergraduate Research Assistant, University of Iowa
1986-1987	Undergraduate Research Assistant, Butler University

Honors

2022	MCW Society for Research Excellence
2020	NIAID MERIT Award
2019	Director's Award for Promising R01 Pilot Funding, MCW Cancer Center
2015	MCW Community of Innovators Award
2014	Advancing a Healthier Wisconsin (AHW) Excellence Award
1989-1992	U.S. Department of Education Graduate Research Fellowship
1989	Sigma Xi, Butler University Chapter
1986, 1987	Butler Student Academic Grant, Holcomb Research Institute
1986	Butler University Outstanding Student in Freshman Chemistry
1985-1989	Butler University Cislak Fellow
1985-1989	Butler University Presidential Scholar
1985	National Merit Scholarship Winner

C. Contribution to Science

1. **Conformational dynamics in protein allostery and functional evolution.** Early in my career, I used NMR structure determination and ^{15}N relaxation measurements to demonstrate a dynamic population shift between two preexisting conformations as the underlying mechanism of allosteric activation of a bacterial signaling protein. This seminal work, published in *Science*, has been cited more 700 times. Subsequently, I discovered an unprecedented type of dynamics in the protein lymphotactin/XCL1, now recognized in leading biochemistry textbooks as the prototypical 'metamorphic' protein. Most recently, we used ancestral sequence reconstruction to reveal the role of conformational dynamics in the creation of a new protein interaction domain from an ancient guanylate kinase enzyme, and track the evolution of metamorphic XCL1. Collectively, my contributions have enhanced our understanding of how conformational dynamics on many time scales can enhance, regulate or create entirely new functions or categories of proteins.
    1. **Volkman BF,** Kustu S, Wemmer DE, and Kern D, Two-state allosteric behavior in a single-domain signaling protein, (2001) *Science* **291** 2429-2433.
    2. Tuinstra, RL, Peterson, FC, Kutlesa, S, Elgin, ES, Kron, MA and **Volkman, BF**, Interconversion between two unrelated protein folds in the lymphotactin native states, (2008) *Proc Natl Acad Sci USA* **105** 5057-62.
    3. Whitney DS, **Volkman BF** and Prehoda KE, Protein dynamics underlies the evolution of a metabolic enzyme to a protein interaction domain (2016) *J Am Chem Soc* **138** 15150-15156.
    4. Dishman AF, Tyler RC, Fox JC, Kleist AB, Prehoda KE, Babu MM, Peterson FC and **Volkman BF**, Evolution of Fold-Switching in a Metamorphic Protein (2021) *Science* **371** 86-90.

2. **Structural basis of chemokine function.** Chemokines are small, secreted proteins that orchestrate immune function by guiding the migration of leukocytes. For over 20 years, I have solved chemokine structures and characterized their functional interactions including self-association, glycosaminoglycan binding, and GPCR activation. Notable achievements include the NMR structure of the first complex between a chemokine and a post-translationally modified (sulfotyrosine-containing) receptor fragment and

the discovery that the dendritic cell chemokine CCL21 is autoinhibited by its disordered C-terminal domain. Most recently, we assembled and validated the first complete model of an active chemokine-GPCR complex from separate NMR and crystal structures and published a new method for homology modeling of chemokine-receptor complexes.

1. Veldkamp, CT, Seibert, C, Peterson, FC, De la Cruz, NB, Haugner, JC, Basnet, H, Sakmar, TP, and **Volkman, BF**, Structural basis of CXCR4 sulfotyrosine recognition by the chemokine SDF1/CXCL12 (2008) *Science Signaling* **1** *ra4.* PMC2692298
2. Kiermaier E, Moussion C, Veldkamp CT, Mühlenhoff M, Williams LG, Chaffee GR, Phillips AJ, Freiberger F, Imre R, Payne R, Mechtler K, Gerardy-Schahn R, **Volkman BF** and Sixt M, Polysialylation of CCR7 enables ligand discrimination and control of dendritic cell trafficking (2016) *Science,* **351** 186-90. PMC5583642
3. Fox JC, Thomas MA, Larson O, Nakayama T, Dishman AF, Yoshie O, Rosenkilde MM and **Volkman BF**, Structure-Function Guided Modeling of Chemokine-GPCR Specificity for the Chemokine XCL1 and its Receptor XCR1 (2019) *Science Signaling* **12** eaat4128. PMC6733756
4. Kleist AB, Jenjak S, Sente A, Laskowski LJ, Anderson EI, McNally LM, Heukers R, Bobkov V, Peterson FC, Thomas MA, Chevigne A, Smit MJ, McCorvy JD, Babu MM and **Volkman BF**, Conformational selection guides β-arrestin recruitment at an intrinsically biased G protein-coupled receptor (2022) *Science* **377** 222-228.

3. **Structure-based inhibition of chemokines in cancer and other human diseases.** Chemokines contribute directly to many inflammatory diseases, and many types of cancer exploit the chemokine system to guide the spread of metastatic tumors. We use our detailed structural knowledge to target various chemokines for therapeutic intervention. Our primary focus has been anti-cancer drug development against the CXCL12-CXCR4 axis, and we have employed three parallel strategies. First, we developed a hybrid in silico/NMR screening strategy to identify small molecules that bind and inhibit the chemokine ligand CXCL12. Second, we used in silico screening against the CXCR4 structure (in collaboration with Brian Shoichet, UCSF) to identify small molecule ligands function as receptor antagonists that block chemotaxis. Most significantly, we discovered that an engineered dimeric version of CXCL12 acts as a biased or partial agonist of CXCR4 that potently inhibits cell migration. We patented this molecule and showed that it blocks metastatic tumor formation in mouse models for colon cancer and melanoma. Most recently, we implemented an NMR-based chemical fragment screening pipeline for discovery of small molecule ligands.
    1. Veldkamp CT, Ziarek JJ, Peterson FC, Chen Y and **Volkman BF**, Targeting SDF-1/CXCL12 with a ligand that prevents activation of CXCR4 through structure based drug design, (2010) *J Am Chem Soc* **132** 7242-3*.* PMC2941798
    2. Drury LJ, Ziarek JJ, Gravel S, Veldkamp CT, Takekoshi T, Hwang ST, Heveker N, **Volkman BF** and Dwinell MB, CXCL12 treatment inhibits metastasis: regulation by agonist-biased CXCR4 signaling (2011) *Proc Nat Acad Sci USA* **108** 17655-60. PMC3203819
    3. Mysinger MM, Weiss DR, Ziarek JJ, Gravel S, Doak AK, Karpiak J, Heveker N, Shoichet BK, **Volkman BF**, Structure-based Ligand Discovery for Chemokine Receptor CXCR4, (2012) *Proc Nat Acad Sci USA* **109** 5517-22*.* PMC3325704
    4. Egner JM, Jensen DR, Olp MD, Kennedy NW, **Volkman BF**, Peterson FC, Smith BC, Hill RB, Development and Validation of a 2D Difference Intensity Analysis for Chemical Library Screening by Protein-Detected NMR (2018) *ChemBioChem* **19** 448-458.

4. **Regulation of abiotic stress by the plant hormone abscisic acid.** In collaboration with Sean Cutler (UC Riverside), we provided direct NMR evidence that the PYR/PYL family of protein functions as receptors for the plant stress hormone abscisic acid (ABA). This article has been cited over 1500 times and was honored as *Science* 2009 'Breakthrough of the Year'. My laboratory solved a succession of X-ray crystal structures of ABA receptor complexes that revealed the mechanism of selective activation by synthetic ABA agonists and guided the development of engineered receptors with potential utility in drought-resistant crop plants.
    1. Park SY, Fung P, Nishimura N, Jensen DR, Fujii H, Zhao Y, Lumba S, Santiago J, Rodrigues A, Chow TF, Alfred SE, Bonetta D, Finkelstein R, Provart NJ, Desveaux D, Rodriguez PL, McCourt P, Zhu JK, Schroeder JI, **Volkman BF** and Cutler SR, Abscisic Acid Inhibits Type 2C Protein Phosphatases via the PYR/PYL Family of START Proteins (2009) *Science*, **324** 1068-71.

2. Peterson FC, Burgie ES, Park S-Y, Jensen DR, Weiner JJ, Bingman CA, Chang CA, Cutler SR, Phillips GN, and **Volkman BF**, Structural basis for selective activation of ABA receptors (2010) *Nature Structural and Molecular Biology* **17** 1109-13. PMC2933299
3. Park S-Y, Peterson FC, Mosquna A, Yao J, **Volkman BF** and Cutler RS Agrichemical Control of Drought Tolerance using Engineered Receptors, (2015) *Nature* Feb 4. doi:10.1038/nature14123
4. Vaidya AS, Helander JDM, Peterson FC, Elzinga D, Dejonghe W, Kaundal A, Park S-Y, Xing Z, Mega R, Khanderahoo B, Bishay S, **Volkman BF**, Okamoto M, Cutler SR, Broad-spectrum control of crop water use using designed ABA receptor hyperagonists (2019) *Science* **366** 6464.

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https://www.ncbi.nlm.nih.gov/myncbi/brian.volkman.1/bibliography/public/