BIOGRAPHICAL SKETCH

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NAME	POSITION TITLE
Sepideh Khorasanizadeh	Associate Professor
eRA COMMONS USER NAME KHORASANNIH	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
University of Massachusetts	B.S.	1990	Chemistry
University of Pennsylvania	Ph.D.	1995	Chemistry
University of Maryland Baltimore County	Post-doc	1999	NMR Spectroscopy

A. Personal Statement

My group investigates the structural and thermodynamic basis for the interaction of proteins with nucleic acids, peptides and small molecules associated with chromatin. In eukaryotes, genomic DNA and histones form a conserved unit particle known as the nucleosome. Methyllysines along the histone H3 and H4 tails have emerged as important epigenetic marks. These contribute to a histone code that extends the information in the genetic code, and dictates the transition between transcriptionally-active and transcriptionally-silent chromosomal domains. To understand epigenetic regulation by lysine methylation, we have been studying the SET-domain (lysine methyltransferase) and the chromodomain (methyllysine binding) polypeptides. By studying these factors across diverse species we have uncovered differences in the epigenetic potentials among different eukaryotes. We implement biophysical tools such as NMR spectroscopy, X-ray crystallography, fluorescence spectroscopy, circular Dichroism spectroscopy, analytical ultracentrifugation and mass spectrometry to extract quantitative information for delineating specific biological observations.

B. Positions and Honors

Positions and Employment

1990 Technician, Bio-Science Department, Westreco Inc. (Nestle), New Milford, CT
1991-1995 Graduate Student at Penn and Fox Chase Cancer Center; Mentor: Heinrich Roder
1995-1999 Postdoctoral Fellow, UMBC, Howard Hughes Medical Institute; Mentor: Michael F. Summers
1999-2004 Assistant Professor, Biochemistry & Molecular Genetics, University of Virginia
1999- Member, Cell and Molecular Biology and Biophysics Programs, University of Virginia
2002- Member, Molecular Medicine and Medical Scientist Training Programs, University of Virginia
2004- Associate Professor, Biochemistry & Molecular Genetics, University of Virginia
2004- Member, Pharmacological Sciences Training Program, University of Virginia
2005- Member, Cancer Center, University of Virginia
2010 Professor, Sanford-Burnham Medical Research Institute

Other Experience and Professional Memberships

1990- Member, American Chemical Society
1996- Member, Protein Society
2000- Member, Biophysical Society
2001 NIH/NCI Peer Review Committee: Molecular Targets Drug Discovery for Cancer
2003 NIDDK/DEA/RB Peer Review Committee: Androgen Receptor in Prostate Growth and Cancer
2003 NIH Special Emphasis 2003/10 Council Peer Review Committee: Shared NMR Instrumentation
2003 NIDDK Special Emphasis ZDK1 GRB-6 (J1) Program Projects Peer Review Committee
2004-2006 NSF, MCB – Biochemistry of Gene Expression, Ad hoc reviewer

2004 Alberta Heritage Foundation for Medical Research Peer Review Committee: Senior Scholar
2005 Association of International Cancer Research, Peer Review Committee:Research Grant Application
2005-2007 AHA National Center, Peer Review Committee: Basic Cell and Molecular Biology 1
2006 NIH Special Emphasis 2006/10 Council Peer Review Committee: Shared NMR Instrumentation
2007 NIH Macromolecular Structure and Function B (MSFB), Peer Review Committee
2007- Member, ASBMB Society
2008- Member, American Heart Association (AHA)
2008-2009 AHA National Center, Peer Review Committee Chair, Basic Cell and Molecular Biology 4
2008 NHLBI BSC Site Review, Peer Review Committee
2008 NIH Roadmap Epigenomics, Peer Review Committee
2010 NIH Macromolecular Structure and Function B (MSFB), Peer Review Committee

Honors

1990 The American Chemical Society Outstanding Senior Award
1995-1998 HHMI postdoctoral associate, University of Maryland
1998 Cancer Research Institute Postdoctoral Fellowship
1999-2001 Special Fellow of the Leukemia and Lymphoma Society
2007-2011 Established Investigator of the American Heart Association

C. Peer-Reviewed Publications

1. S. Khorasanizadeh, I.D. Peters, T.R. Butt & H. Roder (1993) Folding and stability of a tryptophan-containing mutant of ubiquitin. *Biochemistry* 32, 7054-7063.
2. P.B. Laub, S. Khorasanizadeh, & H. Roder (1995) Localized solution structure of an F45W variant of ubiquitin using stochastic boundary molecular dynamics and NMR distance restraints. *Protein Science* 4, 973-982.
3. S. Khorasanizadeh, I.D. Peters & H. Roder (1996) Evidence for a three-state model of protein folding from kinetic analysis of ubiquitin variants with altered core residues. *Nature Structural Biology* 3, 193-205.
4. Q. Zhao, S. Khorasanizadeh, Y. Miyoshi, M.A. Lazar & F. Rastinejad (1998) Structural elements of an orphan nuclear receptor-DNA complex. *Molecular Cell* 1, 849-861.
5. S. Khorasanizadeh, R. Campos-Olivas & M.F. Summers (1999) Solution structure of the capsid protein from the human T-cell leukemia virus type I. *Journal of Molecular Biology* 291, 491-505.
6. S. Khorasanizadeh, R. Campos-Olivas, C.A. Clark & M.F. Summers (1999) Sequence-specific ^{1}H, ^{15}N, ^{13}C assignment and secondary structure of the HTLV-I capsid protein. *Journal of Biomolecular NMR* 14, 199-200.
7. F. Rastinejad, T. Wagner, Q. Zhao & S. Khorasanizadeh (2000) Structure of the RXR-RAR DNA-binding complex on the retinoic acid response element DR1. *EMBO Journal* 19, 1045-1054.
8. S.A. Jacobs, S.D. Taverna, Y. Zhang, S.D. Briggs, J. Li, J.C. Eissenberg, C.D. Allis & S. Khorasanizadeh (2001) Specificity of the HP1 chromo domain for the methylated N-terminus of histone H3. *EMBO Journal* 20, 5232-5241.
9. S.A. Jacobs & S. Khorasanizadeh (2002) Structure of HP1 chromodomain bound to a lysine 9-methylated histone H3 tail. *Science* 295, 2080-2083.
10. S. A. Jacobs, J. M. Harp, S. Devarakonda, Y. Kim, F. Rastinejad & S. Khorasanizadeh (2002) The active site of the SET domain is constructed on a knot. *Nature Structural Biology* 9, 833-838.
11. L-z Mi, S. Devarakonda, J. M. Harp, Q. Han, R. Pellicciari, T. M. Wilson, S. Khorasanizadeh & F. Rastinejad (2003) Structural Basis for Bile Acid Binding and Activation of the Nuclear Receptor FXR. *Molecular Cell* 11, 1093-1100.
12. W. Fischle, Y. Wang, S. A. Jacobs, Y. Kim, C. D. Allis & S. Khorasanizadeh (2003) Molecular basis for the discrimination of repressive methyl-lysine marks in histone H3 by Polycomb and HP1 chromodomains. *Genes & Development* 17, 1870-1881.
13. M. Lindroth, D. Shultis, Z. Jasencakova, J. Fuchs, L. Johnson, D. Schubert, D. Patnaik, S. Pradhan, J. Goodrich, I. Schubert, T. Jenuwein, S. Khorasanizadeh & S. E. Jacobsen (2004) Dual histone H3 methylation marks at lysines 9 and 27 required for interaction with CHROMOMETHYLASE3. *EMBO Journal*, 23, 4146-55.

14. S. Khorasanizadeh (2004) The Nucleosome: From Genomic Organization to Genomic Regulation. *Cell* 116, 259-272. [article for 30th Anniversary Issue]
15. J. F. Flanagan, L-Z Mi, M. Chruszcz, M. Cymborowski, K. L. Clines, Y. Kim, W. Minor, F. Rastinejad & S. Khorasanizadeh (2005) Double Chromodomains cooperate to recognize the methylated Histone H3 Tail. *Nature* 438, 1181-1185.
16. J. F. Flanagan, B. J. Blus, D. Kim, K. L. Clines, F. Rastinejad & S. Khorasanizadeh (2007) Molecular Implications of Evolutionary Differences in CHD Double Chromodomains. *J. Mol. Biol.* 369, 334-342.
17. R. M. Hughes, K. R. Wiggins, S. Khorasanizadeh & M. L. Waters (2007) Recognition of Trimethyllysine by a Chromodomain is Not Driven by the Hydrophobic Effect. *Proc Natl Acad Sci U S A* 104, 11184-8.
18. X. Zhang, S. Germann, B. J. Blus, S. Khorasanizadeh, V. Gaudin & S. E. Jacobsen (2007) The *Arabidopsis* Chromodomain-containing Protein LIKE HETEROCHROMATIN PROTEIN 1 Colocalizes with Histone H3 Lysine27 Trimethylation. *Nature Structural & Molecular Biology* 14, 869-871.
19. S. Raghuram, K. R. Stayrook, P. Huang, P.M. Rogers, A.K. Nosie, D.B. McClure, L.L. Burris, S. Khorasanizadeh, T.P. Burris & F. Rastinejad (2007) Identification of heme as the ligand for the orphan nuclear receptors REV-ERBalpha and REV-ERBbeta. *Nature Structural & Molecular Biology* 14, 1207-13.
20. S.E. Rosasco-Nitcher, W. Lan, S. Khorasanizadeh & P.T. Stukenberg (2008) Centromeric Aurora-B activation requires TD-60, microtubules, and substrate priming phosphorylation. *Science* 319, 469-72.
21. W. Fischle, H. Franz, S.A. Jacobs, C.D. Allis, S. Khorasanizadeh (2008) Specificity of the CDY family of chromodomains for lysine-methylated ARKS/T motifs. *J. Biol. Chem.* 283, 19626-35.
22. D. Kim, B. J. Blus, V. Chandra, P. Huang, F. Rastinejad & S. Khorasanizadeh. Corecognition of DNA and a Methylated Histone Tail by MSL3 Chromodomain. *Nature Structural & Molecular Biology*. In press.

D. Research Support.

Ongoing Research Support

1R01 GM070558 Khorasanizadeh (PI) 8/1/2005-7/31/2010
"Structural determinants of chromodomain function"
The focus of this application is to delineate the physical interactions of *Drosophila* and human chromodomains with methylated histone tails and nucleic acids. The biological significance of these interactions for epigenetic pathways in Drosophila and human will be investigated in collaboration.
Role: PI,

0740058N American Heart Association Khorasanizadeh (PI) 1/1/2007-12/31/2011
"Structural determinants of PPAR alpha activation by CHD9 protein"
Physical interactions of a human nuclear receptor with a chromatin remodeling enzyme will be investigated to delineate the basis for gene activation.
Role: PI

Pending Research Support

1 R21 AI085339-01 Khorasanizadeh (PI)
"Discovery of Epigenetic Methyl-marks in *E. histolytica*"
E. histolytica is an anaerobic parasitic protozoan that infects human intestine. It is considered a biodefense category B pathogen by NIAID. In the active stage of *E. histolytica*, trophozoites have the potential to bore into the intestinal wall and reach the blood stream to infect many organs in the human body. A significant divergence in the sequences of the histone H3 and H4 tails prohibits the use of currently available antibodies to detect and study lysine methyl-marks in *E. histolytica*. Genome sequence for this organism has prompted our de novo identification of histone methyl-marks. We plan to delineate substrate specificity of *E. histolytica* lysine methyltransferases as well as to determine the selective recognition of the lysine-methylated histone tails by *E. histolytica* chromodomains. Appropriate biological assays will be performed in collaboration with Dr. William Petri.
Role: PI

1R01 CA152053-01 Mayo, Khorasanizadeh, Chruma
"RelA/p65: A novel cancer therapy target to initiate Bim-mediated apoptosis"
The ability of a cancer cell to overcome programmed death signals is one of the rate-limiting events in metastasis. A novel NF-κB interaction was identified: the binding of p65 component to a pro-death protein called Bim. We hypothesize that NF-κB facilitates metastasis by sequestering Bim, and propose to design and prepare small molecule inhibitors of p65-Bim interaction.
Role: Co-PI

Completed Research Support

Leukemia and Lymphoma Society Special Fellow Khorasanizadeh (PI) 7/1/98-6/30/01
"Structure of HTLV-I Capsid Protein"
The solution structure and backbone dynamics of HTLV-I capsid protein were investigated using state-of-the-art NMR techniques. This elongated two-domain polypeptide is at the size limit of atomic characterization by NMR spectroscopy.
Role: PI

AHA-BGIA Khorasanizadeh (PI) 7/1/01-6/30/03
"Ligand-induced control of LXR and FXR in cholesterol homeostasis"
The focus of this project was to obtain preliminary data using NMR spectroscopy, CD spectroscopy and calorimetry to investigate the structure and ligand and/or peptide binding for the human FXR and LXR ligand binding domains.
Role: PI

1 S10 RR023035-01 Bushweller (PI) 7/2006
"800 MHz NMR spectrometer for high-end NMR structural studies "
This award paid for the purchase and installation of the 800 MHz Bruker Ultrashield spectrometer equipped with a TXI cryoprobe that was installed at the UVA biomolecular NMR facility in April 2008.
Role: Major User

1R0 1GM064786 Khorasanizadeh (PI) 7/1/02-6/31/08
"Structural basis of histone tail recognition"
These studies focused on histone tail structure and their recognition by chromodomains of Heterochromatin protein 1 (HP1), Polycomb (Pc), essential histone acetyltransferase of yeast (Esa1) and chromodomain on Y chromosome (CDY) proteins. This award made it possible for us to apply a series of biophysical techniques including fluorescence, CD and NMR spectroscopy, X-ray crystallography and calorimetry to understand the molecular basis for a common histone code in diverse eukaryotes.
Role: PI