BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors. Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: **Janet Rubin MD**

eRA COMMONS USER NAME (credential, e.g., agency login): jrubi02

POSITION TITLE: Professor of Medicine

Joint appointments as Professor in Depts of Pharmacology, Pediatrics and Bioengineering

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Bryn Mawr College, Bryn Mawr, PA	BA	1976	Biology
Brown University School of Medicine, RI	MD	1980	Medicine
Northwestern Univ. School of Medicine, Ill	resident	1983	Internal Medicine
University California, San Diego, CA	fellow	1985	Endo/Metabolism

A. Personal Statement

My cell and molecular biological investigations over the last 20 years have been aimed at understanding the control of bone remodeling. In the last several years, we have studied how mechanical forces, including strain, shear and vibration, alter the lineage decisions which are made by mesenchymal stem cell (MSC) precursors of bone, fat and other musculoskeletal elements. Our fundamental studies have characterized signaling pathways by which loading prevents adipogenesis and promotes osteogenesis. The MSC cytoskeleton undergoes reorganization upon stimulus of the same mechanical signal pathways, both affecting βcatenin delivery to the nucleus as well as other signals. Recently we have found that intranuclear actin induces osteogenesis in MSC, and enhances other osteogenic programs.

B. Positions and Honors

Professional Experience

Associate Investigator of the Veterans Administration	2/85-6/96
Clinical Instructor, Medicine, UCSD Medical Center	2/85-6/96
Assistant Professor of Medicine, Emory School of Medicine, Atlanta	7/86-9/94
Research Associate of the Veterans Administration, VAMC, Atlanta	7/87-6/91
Staff Physician, Medical Service VAMC, Atlanta	7/87-2/06
Associate Professor *with tenure*, Department of Medicine	9/94- 8/00
Endocrinology and Metabolism Division Emory University School of Medicine, Atlanta	
Professor, Emory University School of Medicine, Atlanta	9/00-2/06
Professor, *with tenure*, Department of Medicine	3/06-current
Endocrinology Division, University of North Carolina @ Chapel Hill	
Joint Appointment: Professor, Department of Pharmacology	5/07-current

University of North Carolina @ Chapel Hill

Joint Appointment: Professor, Department of Pediatrics, UNC	9/08 -current
Adjunct Professor, Department of Bioengineering, UNC/NCSU	6/10- current
Vice Chair, Research, Department of Medicine, UNC	6/15 -current

Other relevant experience

NIH SBSR Study Section Permanent Member 2009-2013, Chair July 2011-July 2012
NIH OBM-2 Study Section Permanent Member 1997-2001
ASBMR Council member 2005-2008
Chairman, ASBMR Advocacy Committee, 2004-2005
VA Research Enhancement Award Program: Director 1999-2004

Honors and Awards

Norwich-Eaton Young Investigator Award of ASBMR, 1985
Robert I. Goodman Award, Society for Physical Regulation in Biology and Medicine, 1994
Associate Investigator, VAMC 85-86
Research Associate VAMC 87-90
Best Doctors in America 2007-current
Academy of Educators, 2011 - current

C. Contribution to Science (>100 publication)

1. **Mechanical control of MSC lineage allocation**. MSC lineage is dependent on chemical and physical factors present in the microenvironment. To understand how mechanical factors control MSC lineage decisions, we undertook to define the signaling pathways necessary for MSC to recognize the mechanical signal, and to generate a cellular response. We found that mechanical stimulation decreased MSC adipogenesis, and that this derived from a stimulation of FAK-mTORC2-AktGSK3β-βcatenin. Most recently we have become interested in out intranuclear actin control gene expression, with a rapid, robust induction of osteogenesis both in vitro and in vivo.

1. Sen B, Xie Z, Case N, Ma, M, Rubin CT, Rubin J 2008 Mechanical strain prevents adipogenesis in mesenchymal stem cells by stimulating a durable β-catenin signal. Endocrinology 149:6065-75. PMC2613068
2. Case N, Ma, M, Sen B, Xie Z, Gross TS, Rubin J 2008 Mechanical loading of bone cells activates β-catenin through GSK3β inactivation. J Biol Chem 283:29196-205. PMC2570859
3. Sen B, Styner M, Xie Z, Case N, Rubin CT, Rubin J 2009 Mechanical loading regulates NFATc1 and β-catenin signaling through a GSK3β control node, J Biol Chem, 284:34607-34617. PMC2787323
4. Case N, Thomas J, Styner M, B Sen, Xie Z, and Rubin J 2011 Mechanical activation of Akt via serine 473 phosphorylation requires mTORc2 in MSC. J Biol Chem. 2011 Nov 11;286(45):39450-6. PMC3046385
5. Sen B, Xie Z, Thomas J, Uzer G, Styner M, Rubin J 2015 Intranuclear actin regulates osteogenesis, *in press* Stem Cells.

2. **Physical force interaction with the cytoskeleton.** In an effort to understand the types of physical signals responsible, we have studied not only high intensity substrate strain, but also the very small vibrational signals that are osteoactive/anti-adipogenic. This led to our understanding that the cell responds to physical force by rearrangement of the cytoskeleton, which allows signal amplification.

6. Sen B, Styner M, Xie Z, Case N, Rubin CT, Rubin J 2011 Mechanical inhibition of adipogenesis achieved via a regenerated β-catenin signal is amplified by incorporating a refractory period, Journal Biomechanics 44(4):593-9. PMC3042527
7. Sen B, Guilluy C, Xie Z, Case N, Styner M, Thomas J, Oguz I, Rubin C, Burridge K, Rubin J, 2011 Mechanically induced focal adhesion assembly amplifies anti-adipogenic pathways in mesenchymal stem cells. Stem Cells 29:1829–1836. PMID:21898699

8. Thompson WR, Guilluy C, Case N, Styner M, Sen B, Xie Z, Burridge K, Rubin J 2013 Mechanically activated Fyn induces activation of RhoA through mTORC2 in mesenchymal stem cells, Stem Cells, 31:2528-2537. PMID:23836527
9. Sen B, Xie Z, Thomas W, Case N, Uzer G, Styner M, Rubin J 2014 mTORC2 regulates mechanically induced cytoskeletal reorganization and lineage selection in marrow derived mesenchymal stem cells, Journal of Bone and Mineral Res 29: 78-89. PMID:23821483
10. Uzer G, Thompson WR, Case N, Xie Z, Sen B, Yen S, Styner M, Rubin C, Judex S, Burridge K, Rubin J 2015 Cell mechanosensitivity to extremely low magnitude signals is enabled by a LINCed nucleus, Stem Cells 33(6):2063-76. PMID: 25787126

3. **Exercise stimulates bone formation in vivo, and decreases marrow adipogenesis**. In longstanding associations with collaborators, we have shown that physical force stimulates osteogenesis. Recently we have been able to demonstrate that running exercise not only stimulates osteogenesis, but also decreases marrow fat.

11. Ozcivici E, Luu YK, Adler B, Qin Y, Rubin J, Judex S, Rubin CT 2010 Mechanical signals as anabolic agents in bone, Nature Reviews in Rheumatology, 6:50-59. PMID:20046206
12. Duan J, Lee Y, Corey J, Gong J, Rojas M, Burk L, Willis M, Homeister J, Tilley S, Rubin J and Deb A 2013 Rib fractures and death due to deletion of osteoblast βcatenin in adult mice is rescued by corticosteroids, PLoS One, 8(2):355757. PMC356485
13. Styner M, Kadari S, Galior K, Uzer G, Thompson W, Case N, Xie Z, Sen B, Romaine A, Styner MA, Pagnotti GM, Rubin CT, Horowitz MC, Rubin J 2014 Bone marrow fat accumulation accelerated by high fat diet is suppressed by exercise, Bone 64:39-46. PMC4041820
14. Styner M, Wu X, Uzer G, Thompson WR, Sen B, Xie Z, Styner MA, Rubin J, 2015 Exercise regulation of marrow fat in the setting of PPAR-γ agonist treatment, Endocrinology, 156(8):2753-61. PMID:26052898

4. **Physical force controls other bone cell lineages in vivo and in vitro**. We were the first to show (2000) that osteoblast respond to mechanical input with a reduction in RANKL, which then leads to decreased osteoclast recruitment. We currently have a manuscript under review that shows osteocytes are sensitive to vibration, with decrease generation of sclerostin. As well, we have co-authored clinical studies that speak to mechanical force (obesity) in humans.

15. Rubin J, Murphy T, Nanes M, Fan X 2000 Mechanical strain inhibits expression of osteoclast differentiation factor (ODF/TRANCE) by murine stromal cells. American Journal Physiology: Cell Physiology, 278:1126-1132. PMID:10837340
16. Gourlay ML, Specker BL, Li C, Hammett-Stabler CA, Renner JB, Rubin JE 2012 Follicle stimulating hormone is independently associated with lean mass and fat mass but not BMD in younger postmenopausal women, Bone 50(1):311-6. PMC3246561
17. Thompson WR, Yen S, Rubin J 2014 Vibration Therapy: Clinical Applications in Bone Current Opinion in Endocrinology and Diabetes, 21(6):447-53 PMID:25354044
18. Thompson WR, Uzer G, Yen S, Styner M, Sen B, Xie Z, Rubin J 2015 Osteocyte specific responses to soluble and mechanical stimuli in a stem cell derived culture model Sci Rep. 5:11049. PMID: 26140478