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: Jeffry S. Nyman

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

POSITION TITLE: Associate Professor of Orthopaedic Surgery and Rehabilitation

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
The University of Memphis	Memphis, TN	B.S.	1996	Mechanical Engineering
The University of Memphis	Memphis, TN	M.S.	1998	Mechanical Engineering
University of California, Davis	Davis, CA	Ph.D.	2003	Biomedical Engineering
University of Texas at San Antonio	San Antonio, TX	Post-doc	2003-2006	Bone Mechanics

A. Personal Statement

The ultimate goal of my research is to lower the number of bone fractures associated with diabetes, aging, osteoporosis, cancer, and genetic diseases. Building from my post-doctoral research on identifying determinants of bone toughness, my research program involves the assessment of structural, architectural, compositional, and biomechanical properties of bone from genetic and pre-clinical models of disease as well as from cadavers. I have 10+ years of experience training students, post-doctoral fellows, and surgical residents in the use of both dynamic material testing systems and micro-computed tomography (μCT) scanners. Assessing the fracture resistance of bone in my lab includes flexural tests (three-point bending), fatigue (axial and flexural), cyclic reference point indentation and impact micro-indentation (RPI), ^{1}H nuclear magnetic resonance (NMR), Raman spectroscopy (RS), high performance liquid chromatography, and finite element analysis. Being an active investigator on several federal grants, I direct the work of research assistants, undergraduate and graduate students, and engineers to attain the research goals of each project.

B. Positions and Honors

Professional Experience

1995-1996	Intern, Orthopaedic Research, Wright Medical Technology.
1997-1998	Research Assistant, Department of Mechanical Engineering, The University of Memphis.
1998-2001	Teaching Assistant, Materials Science, University of California, Davis.
1999-2003	Research Assistant, Orthopaedic Research Laboratory, University of California, Davis.
2003-2006	Post-doctoral Fellow, Department of Mechanical Engineering and Biomechanics, The University of Texas at San Antonio.
2006-2007	Research Instructor, Center for Bone Biology, Vanderbilt University Medical Center.
2007-2011	Research Assistant Professor, Department of Orthopaedics & Rehabilitation, Vanderbilt University Medical Center.
2008-present	Research Assistant Professor, Department of Biomedical Engineering, Vanderbilt University.
2009-2016	Research Health Scientist, Department of Veterans Affairs, Tennessee Valley Healthcare System
2011-present	Associate Professor of Orthopaedic Surgery and Rehabilitation

Honors and Award

1996	Participant in the Research Experience for Undergraduates Program, sponsored by the National Science Foundation, at Worcester Polytechnic Institute

1996	Magna Cum Laude at The University of Memphis
1997-1998	Regents Scholar and Herff Fellow at The University of Memphis
2001	Recipient of a Floyd and Mary Schwall Dissertation Year Fellowship
2002	Recipient of the Achievement Reward for College Scientists given by the ARCS Foundation
2006	Recipient of Alice L. Jee Memorial Young Investigator Award at the 2006 Sun Valley Workshop on Skeletal Tissue Biology
2009-2011	A Top Reviewer for *Bone*

Other Experience and Professional Memberships

2004-present	Member, Orthopaedic Research Society
2006-present	Member, American Society for Bone and Mineral Research
2006-present	Member, Vanderbilt Center for Bone Biology
2011-2015	Chair, Vanderbilt Orthopaedic Institute Pilot Project Review Committee
2012-2015	Member, International Bone & Mineral Society
2013-2016	Member, ASBMR Ethics Advisory Committee
2014-2016	Member, Advisory Committee for the ORS Sun Valley Workshop: Musculoskeletal Biology
2014	Co-section Editor for Bone Quality in Osteoporosis in *Current Osteoporosis Reports*
2014-present	Member, Skeletal Biology Structure & Regeneration Study Section
2017-present	Member, Society for Applied Spectroscopy
2017-present	Member, The International Society for Clinical Densitometry

Editorial Appointments

Bone, Clinical Reviews in Bone and Mineral Metabolism

C. Contribution to Science

1. *Effect of diabetes on bone* – Those with diabetes are at a greater risk of fracture than those without diabetes, and that risk is even greater for individuals with type 1 diabetes. The reason for this elevated fracture risk is not entirely clear, but my research in collaboration with Dr. Fowlkes (Director of Barnstable Brown Diabetes and Obesity Center, University of Kentucky) and Dr. Kathryn Thrailkill strongly suggests that a decrease in insulin signaling has two dominant effects on bone: loss of bone accrual and increase in bone brittleness. There is also a decrease in the structural strength of long bones when we injected mice with streptozotocin, a toxin that kills beta cells of the pancreas, to induce diabetes. In addition to the structural difference between normal and diabetic mice, our first publication reported that the bones become brittle as the duration of diabetes progresses. In follow-up work in which I measured the biomechanical properties of bone, we reported that insulin therapy partially rescued the deleterious effects of type 1 diabetes on bone. More recently, my lab published how fracture resistance decreases as type 2 diabetes progresses in the ZDSD rat model. The ITED supported graduate student also recently published that the fracture resistance of bone does not progressively worsen as TallyHO mice (juvenile mode of type 2 diabetes) age. Our work strongly indicates that the prevention of diabetic bone disease will require multifactorial approach addressing anabolic nature of insulin and the contribution of poor glycemic control to bone brittleness.

a. Nyman, J.S., Even, J.L., Jo, C-H, Herbert, E.G., Murry, M.R., Cockrell, G.E., Wahl, E.C., Bunn, R.C., Lumpkin, Jr., C.K., Fowlkes, J.L., and K.M. Thrailkill. Increasing duration of type 1 diabetes perturbs the strength-structure relationship and increases brittleness of bone. *Bone*. 48:733-40, 2011. PMCID: PMC3062641
b. Nyman J.S., Kalaitzoglou E., Bunn R.C., Uppuganti S., Thrailkill K.M., and J.L. Fowlkes. Preserving and restoring bone with continuous insulin infusion therapy in a mouse model of type 1 diabetes. *Bone Reports*. 7:1-8, 2017. PMCID:PMC5508511
c. Creecy A., Uppuganti S., Merkel A.R., O'Neal D., Makowski A.J., Granke M., Voziyan P., and J.S. Nyman. Changes in the fracture resistance of bone with the progression of type 2 diabetes in the ZDSD rat. *Calcified Tissue International*. 99:289-301, 2016. PMCID: PMC4961536
d. Creecy A., Uppuganti S., Unal M., Bunn R.C., Voziyan P., and J.S. Nyman. Low bone toughness in the TallyHO model of juvenile type 2 diabetes does not worsen with age. *Bone*. 110:204-14, 2018. PMCID:PMC5878744.

2. *The application of Raman spectroscopy to bone* – Because Raman spectroscopy (RS) is non-destructive, requires minimal sample preparation, and is sensitive to collagen, it has been used to analyze bone in numerous studies. While RS has given insight into how various proteins, signaling pathways, and diseases affect the matrix of bone, the best way to analyze the Raman spectrum of bone has not been established when the goal is to predict fracture resistance. Since my arrival at Vanderbilt University Medical Center, my research program has included developing Raman approaches that help differentiate high bone quality from low bone quality. After initially reporting that nu1 Phosphate peak per Proline peak (v_1PO_4/Proline) was more effective than the traditional nu1 phosphate peak per Amide I peak (v_1PO_4/AmI) in differentiating osteonal tissue from the more mineralized interstitial tissue, my former graduate student and I, along with Professor Mahadevan-Jansen, performed a comprehensive assessment of polarization bias within a standard Raman microscope and established that the out-of-phase v_1PO_4/AmI is sensitive to organization and composition of bone tissue while the nearly in-phase v_1PO_4/Proline was primarily sensitive to composition of bone tissue. We subsequently demonstrated the usefulness of analyzing the entire spectra from bone to classify genotypes and predict fracture toughness of cortical bone. There is a growing recognition that multiple peaks should be analyzed when assessing compositional properties of bone with RS, partly due to our publications.

a. Nyman, J.S., Makowski, A.J., Patil, C.A., Masui, T.P., O'Quinn, E.C., Bi, X., Guelcher, S.A., Nicollela, D.P. and A. Mahadevan-Jansen. Measuring differences in compositional properties of bone tissue by confocal Raman Spectroscopy. *Calcified Tissue International*. 89:111-22, 2011.
b. Makowski, A.J., Patil, C.A., Mahadevan-Jansen, A., and J.S. Nyman. Polarization control of Raman spectroscopy optimizes the assessment of bone tissue. *Journal of Biomedical Optics*. 18: 055005, 2013. PMCID: PMC3662990
c. Makowski A.J., Pence I., Uppuganti S., Zein-Sabbato A., Huzagh M.C., Mahadevan-Jansen A., and J.S. Nyman. Polarization in Raman spectroscopy helps explain bone brittleness in genetic mouse models. *Journal of Biomedical Optics*. 19:117008, 2014. PMCID: PMC4240742
d. Makowski A.J., Granke M., Ayala O., Uppuganti S., Mahadevan-Jansen A. and J.S. Nyman. Applying full spectrum analysis in the Raman spectroscopic assessment of fracture toughness of human cortical bone. *Applied Spectroscopy*. 71:2385-94, 2017. PMCID: PMC5561524

3. *Regulators of bone material properties* – While there are numerous studies reporting factors that affect bone mass or volume, little is known about regulators of material properties. Initially supported by a Career Development Award from the VA, I characterized the bone phenotype of several genetic mouse models. These studies included Raman spectroscopy. In one of my first publications as an independent investigator, I reported that the loss of MMP-2 and the loss of MMP-9, two similar matrix-associated genes, caused a loss in material strength and a loss in toughness of bone, respectively. More recently, my research team and I found that a transcription factor (ATF4) important to osteoblast differentiation is also important to bone toughness. In collaboration with my colleagues at the Vanderbilt Center for Bone Biology, I've been fortunate to be involved in several important studies. Bringing my expertise to biomechanics, I helped my colleagues show that inhibiting transforming growth factor beta (TGF-β) improves the material properties and tissue-level properties of cortical bone and that the loss of neurofibromatosis type 1 affects structural and material strength of bone through its regulation of mineralization. All these findings indicate that material properties, not just bone mass, can be a target for preventing fractures.

a) Edwards, J.R., Nyman, J.S., Lwin, S.T., Moore, M.M, Esparza, J., O'Quinn, E.C.; Hart, A.J., Biswas, S.; Patil, C.; Lonning, S.; Mahadevan-Jansen, A., and G.R. Mundy. Inhibition of TGF-β signaling by 1D11 antibody treatment increases bone mass and quality in vivo. *Journal of Bone and Mineral Research*. 25:2419-26, 2010.
b) Nyman, J.S., Lynch, C.C., Perrien, D.S., Thiolloy, S., O'Quinn, E.C., Patil, C.A., Bi, X., Pharr, G.M., Mahadevan-Jansen, A., and G.R. Mundy. Differential effects between the loss of MMP-2 and MMP-9 on structural and tissue-level properties of bone. *Journal of Bone and Mineral Research*. 26: 1252-60, 2011. PMCID: PMC3312757
c) Makowski A.J., Uppuganti S., Waader S.A., Whitehead J.M., Rowland B.J., Granke M., and Mahadevan-Jansen A., Yang X., and J.S. Nyman. The loss of activating transcription factor 4 (ATF4) reduces bone toughness and fracture toughness. *Bone*. 62: 1-9, 2014. PMCID: PMC3992706
d) de la Croix Ndong J., Makowski A.J., Uppuganti S., Vignaux G., Ono K., Perrien D.S. Joubert S., Baglio S.R., Granchi D., Stevenson D.A., Rios J.J. Nyman J.S., and F. Elefteriou. Asfotase-α improves bone

growth, mineralization and strength in mouse models of neurofibromatosis type-1. *Nature Medicine*. 20:904-10, 2014. PMCID: PMC4126855

4. *Age-related changes in the fracture resistance of bone* – While the toughness and strength of bone has been known to decrease with age for some time, **clinically viable methods for assessing these material properties are lacking**. During my post-doctoral training, I learned to quantify non-enzymatic collagen crosslinks, namely pentosidine, in bone, and published a paper with my mentor reporting the relative contribution of pentosidine to the age-related decrease in post-yield toughness. Then, when I became an independent investigator, I set out to find collaborators with the goal of developing novel ways to assess the effect of aging on fracture resistance (beyond strength). One example is the use of ^{1}H nuclear magnetic resonance (NMR) to quantify bound water and pore water in bone. My collaborator Professor Mark Does and I have ten papers on the role of water in bone mechanics, and recently, we reported that the combination of bound water and pore water helped explain the age-related variance in fracture toughness of human cortical bone. In addition, we found that i) the resistance of human bone tissue to micro-indentation using reference point indentation (RPI) is anisotropic, ii) age combined with bound water are potential predictors of fracture toughness, and iii) bound water in rat cortical bone decreases while pentosidine increases with advanced aging. The clinical assessment of bound water and pore water using ultra-short echo-time MRI is now an active area of research, partly due to our research as well as others.

a. Nyman, J.S., Roy, A., Tyler, J.H., Acuna, R.L., Gayle, H.J., and X. Wang. Age-related factors affecting the post-yield energy dissipation of human cortical bone. *Journal of Orthopaedic Researc*h. 25:646-655, 2007. PMCID: PMC1994146
b. Granke M., Coulmier A., Uppuganti S., Gaddy J.A., Does M.D, and J.S. Nyman. Insights into Reference Point Indentation involving human cortical bone: sensitivity to tissue anisotropy and mechanical behavior. *Journal of the Mechanical Behavior of Biomedical Materials*. 37: 174-185, 2014. PMCID: PMC4112765
c. Granke M., Makowski A.J., Uppuganti S., Does M.D., and J.S. Nyman. Identifying novel clinical surrogates to assess human bone fracture toughness. *Journal of Bone and Mineral Research*. 30:1290-300, 2015. PMCID: PMC4478129
d. Uppuganti S., Granke M., Makowski A.J., Does M.D., and J.S. Nyman. Age-related changes in the fracture resistance of male Fischer F344 Rat Bone. *Bone*. 83:220-32, 2016. PMCID: PMC4724327

URL to a list of published work (85+ peer-reviewed papers):
https://www.ncbi.nlm.nih.gov/myncbi/browse/collection/41322667/?sort=date&direction=ascending

D. Research Support

Ongoing Research Support

NIH/NIAMS 1R01 AR063157-01 Nyman 09/01/2012 – 08/31/2017 (NCE)
Roles of Collagen and Water in the Fracture Resistance of Bone
The overarching goal of this proposal is to determine whether the functional state of water in bone explains the disproportionate increase in fracture risk relative to age- and diabetes-related changes in bone mineral density (BMD).
Role: PI

NIH/NIAMS 1R21 AR067871 Nyman 07/01/2016 – 06/30/2018
The Role of Tissue Matrix in the Fracture Resistance of Diabetic Bone
The objective of this project is to identify pathogenic changes in the bone tissue matrix that contribute to bone fragility as diabetes progresses and determine how well clinically translatable diagnostic tools (sensitive to the matrix and the mineral of the bone) reflect the diabetes-related changes in fracture resistance.
Role: PI

NIH/NIAMS 1R21 AR070620-01 Thraillkill/Nyman 07/01/2016 – 06/30/2018
Effects of Sodium-dependent Glucose Co-transporter 2 Inhibition on Bone

The objective of this project is to utilize several relevant rodent models (slc5a2-functional mutants, STZ-induced diabetes, TallyHo) to investigate potential mechanisms contributing to the adverse effects of SGLT2-inhibitor therapy on the skeleton.
Role: Site PI

DOD/CDMRP NF140017 Elefteriou 09/30/2015 – 09/29/2018
Targeting RAF1 with C-type Natriuretic Peptide to Promote Bone Union in NF1
The objective of this project is to determine whether a CNP analog promotes fracture healing in mice lacking neurofibromatosis type 1.
Role: Site PI

NIH/NIBIB 2R01 EB014308 Does 09/01/2017 – 10/31/2021
Bone Fracture Risk Assessment Through Bound- and Pore-Water MRI
The objective of this project is to develop, optimize, and quantitatively evaluate magnetic resonance imaging (MRI) methods for assessing bone fracture risk.
Role: Site PI

NIH/NIAMS 1R21 AR072483-01A1 Nyman/Elefteriou 03/01/2018 – 02/29/2020
Matrix-Sensitive Tools for Detecting NF1-Related Changes in Bone Quality
The objective of this project is to compare matrix-sensitive methods for their ability to predict NF1-related deficits in bone quality and assess the response of bone to NF1-specific treatments.

Completed Research Support
NIH/NIDDK 1R01 DK084045 Fowlkes 7/1/2012 – 06/30/2017 (NCE)
The Insulin/GF-I Axis in Diabetic Osteopathy
This proposed project aims to elucidate the mechanism of how diabetes affects bone using conditional knock-out mouse models.
Role: Site PI

VA BLR&D Merit Award 1I01 BX001018-04 Nyman 7/1/2011 – 6/30/2015
Aging and Diabetes-Related Factors Compromising Bone Fracture Resistance
The goal of this study is to establish the role of AGEs in age- and diabetes-related changes in the fracture resistance of bone.
Role: PI

NSF7074068 Nyman 07/1/2011 – 6/30/2014
Dynamic Mechanical Behavior of Bone Tissue as Characterized by Nanoindentation
The objectives are to develop a dynamic nanoindentation test for bone tissue and then identify whether there are differences in the viscoelastic properties of 1) human bone tissue between young and old donors and 2) rodent bone tissue between normal and diseased animals.
Role: Co-PI