BIOGRAPHICAL SKETCH

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NAME: Mark B. Meyer

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

POSITION TITLE: Assistant Professor of Nutritional Sciences

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	BS	05/2002	Chemistry
University of Wisconsin-Madison, Madison, WI	PhD	08/2007	Biochemistry
University of Wisconsin-Madison, Madison, WI	Postdoc	09/2009	Biochemistry

A. Personal Statement

From my early interest in chemical design and compound structure, I became intrigued by the cascade of biological mechanisms these compounds, chemicals, hormones, and growth factors impose on the human body. My interest has been with the mechanism of nuclear receptors, most specifically the vitamin D receptor (VDR), and their transcriptional effects. Recently, we've deciphered the mechanism of endocrine activation of the *Cyp27b1* gene in mice, in vivo utilizing transcription factor binding and epigenetics. Furthermore, the chromatin environment is dominated by histone modifications that give transcriptional cues to these transcription factors and their affected genes. There are several layers of regulation in the cell that can be revealed by these studies, not only regulation of the genes themselves, but also regulation of the dynamic chromatin environment in which they reside. Of particular interest of mine, is the bioinformatic processing of these data sets. From assignment of raw sequencing reads to discovery of binding elements, I have constructed a computational cluster and applied sets of tools that can rapidly analyze high throughput ChIP-seq, RNA-seq (gene expression), GRO-seq (global nuclear run-on), DNAse-seq (DNAse hypersensitivity assay), and more on a genome-wide basis. To compliment these bioinformatic endeavors, I also attempt to adapt and apply the newest molecular biology and biochemical techniques for our investigations from these datasets. Whether it be bacterial or mammalian recombinogenic techniques, gene silencing through RNAi, or new methods of cloning (ie, Gibson Isothermal Assembly), no greater advance to genomic science in the past decade may be poised to have as much impact as the newly discovered CRISPR/Cas genome editing system. I have adapted the CRISPR/Cas techniques to our investigations through enhancer knock-outs, point mutations, as well as gene knockouts in cultured cells and in our mouse model system. With rapid and direct genome editing, we are learning a great amount of information about transcriptional mechanisms of essential genes in the osteoblast, kidney, thyroids, and other cell types that was not previously possible. My goal is to use these genomic findings to understand more about human disease.

My lab now studies the dynamic chromatin environment responsible for serum calcium and phosphate maintenance and the impacts of vitamin D metabolism in skeletal, renal, and intestinal biology. A triumvirate of endocrine hormones – parathyroid hormone (PTH), fibroblast growth factor 23 (FGF23), and calcitriol ($1,25(OH)_2D_3$) – maintain this delicate balance by influencing enzymes, transporters, and transcription factors to drive genomic change. When dysfunctional, these mechanisms allow chronic inflammation and disease progression to worsen in chronic kidney disease-metabolic bone disorder (CKD-MBD), atherosclerosis, inflammatory bowel disease (IBD), and many others. Cancer is a particular interest to my lab as low vitamin D status has a correlation with an increase in cancer risk in cancers such as colorectal, breast, and prostate. Higher vitamin D status has been linked to longer survival rates in cancer patients. Dietary and nutritional

supplementation of vitamin D rapidly corrects the body's mineral deficiencies, however its ability to ameliorate inflammatory disease progression or improve cancer outcomes remains controversial. We study the intricate genomic and molecular mechanisms that regulate the biological changes controlling the intersection of metabolism, inflammation, and disease progression using unique animal models, genomic editing techniques, and -omics bioinformatic approaches to generate unbiased interrogation of chromatin changes.

Ongoing projects that I would like to highlight include:

R01HL159645 07/1/2021 – 06/30/2025
NIH/NHLBI
Contribution of nonrenal calcitriol production in chronic inflammation
The goal of this project is to quantify the presence of calcitriol in nonrenal tissues in health and disease, investigate a mechanism for the inflammatory upregulation of the gene responsible for the enzymatic conversion to calcitriol, *Cyp27b1*, and define the biological benefits of local calcitriol production on atherosclerosis disease progression.
Role: PI

R01DK117475 (PI: Pike) 04/11/2018-03/31/2024
NIH/NIDDK
Regulatory Mechanisms of Renal Vitamin D Activation and Degradation
The major goals of this project are to characterize the endocrine module and its individual components in the mouse kidney that mediates *Cyp27b1* expression and regulation by PTH, $1,25(OH)_2D_3$ and FGF23 *in vivo*, to characterize the regulatory sub-modules that control *Cyp24a1* expression and regulation by PTH, $1,25(OH)_2D_3$ and FGF23 in the kidney *in vivo*, and to utilize dietary manipulation to test and confirm regulatory hypotheses developed in *Cyp27b1*-compromised mouse strains relevant to disease.
Role: Key Scientist

R01-CA260140 (PI: Elaine Alarid) 07/01/2021 – 06/30/2026
NIH/NCI
Mechanisms of Variant ER-alpha Function in Breast Cancer
The major goals of this project are to delineate the activity of phosphorylated ER in patients with treatment refractory metastatic breast cancer, define the molecular requirement for phosphorylated ER and GRHL2 in therapy resistance mediated by ER mutations, and to develop DNA-binding inhibitors of GRHL2: ER interactions.
Role: Co-Investigator

B. Positions, Scientific Appointments, and Honors

Positions

2023-present	Assistant Professor, Department of Nutritional Sciences, University of Wisconsin-Madison
2019-2023	Associate Lecturer, Department of Biochemistry, University of Wisconsin-Madison
2019-2023	Senior Scientist (Scientist III), Department of Biochemistry, University of Wisconsin-Madison
2012-2019	Associate Scientist, Department of Biochemistry, University of Wisconsin-Madison
2009-2012	Assistant Scientist, Department of Biochemistry, University of Wisconsin-Madison
2007-2009	Postdoctoral Researcher, Department of Biochemistry, University of Wisconsin-Madison

Honors

2019	Bortree Lecturer, Penn State University (University Park, PA) invited speaker
2019	22nd Vitamin D Workshop (New York, NY) invited speaker
2018	American Society for Bone and Mineral Research Webinar on CRISPR/Gene Editing
2018	American Society for Nutrition annual meeting (Boston, MA) invited speaker
2017	American Society for Bone and Mineral Research Meet-the-Professor presenter: Gene Editing
2017	Advances in Mineral Metabolism (AIMM, Snowmass, CO) invited speaker
2017	20th Vitamin D Workshop (Orlando, FL) invited speaker
2017	Endocrinology Grand Rounds University of Arkansas Medical School (Little Rock, AR) invited speaker

2015 18th Vitamin D Workshop (Delft, The Netherlands) invited speaker
2013 Seventh Bone Research Seminar (Tokyo, Japan) invited speaker
2012 American Society for Bone and Mineral Research Young Investigator Award recipient
2009 14th Vitamin D Workshop (Brugge, Belguim) travel award recipient
2008, 2009 BioPharmaceutical Technology Center Institute invited lecturer: "Computational Approaches to Analyzing Microarray Data"
2007 Biochemistry Scholar Departmental Fellowship
2004 Biochemistry Teaching Fellowship
2002 Butler University Excellence in Chemistry Senior Award

C. Contributions to Science

1. Despite our advanced knowledge of the vitamin D receptor (VDR) and its role in the regulation of mineral homeostasis, many transcriptional mechanisms that govern the systems biology remain poorly understood. These gene regulatory mechanisms with a genome-wide perspective, or over-arching principles, are what I've been working towards for the past decade in my research. These principles, made possible by the genomic advances of ChIP-seq, RNA-seq and others, have encompassed ideas such as long range distal regulatory actions of VDR with transcriptional start sites, interactions with other regulatory proteins such as RUNX2 in bone cells, co-activator or co-regulatory molecule interactions, histone modifications near the sites of VDR genomic binding, modified analog ligand interactions with the receptor, and finally, combinatorial enhancer interactions that drive transcription of vitamin D-responsive genes. These studies have allowed a more complete and contemporary view of vitamin D regulation that continues in our work today.
    a. Meyer MB, Zella LA, Nerenz RD, Pike JW. *Characterizing Early Events Associated with the Activation of Target Genes by 1,25-Dihydroxyvitamin D_3 in Mouse Kidney and Intestine In Vivo*. J Biol Chem. 2007; 282:22344-22352. PMID: 17556365.
    b. Meyer MB, Zella LA, Nerenz RD, Pike JW. *The Enhanced Hypercalcemic Response to 20-Epi-1,25-Dihydroxyvitamin D_3 Results From a Selective and Prolonged Induction of Intestinal Calcium-Regulating Genes*. Endocrinology. 2009; 150(8):3448-56. PMC2717886.
    c. Pike JW, Meyer MB. *The vitamin D receptor: new paradigms for the regulation of gene expression by 1,25-dihydroxyvitamin D_3*. Rheum Dis Clin North Am. 2012; 38(1):13-27. PMC4448919.
    d. Meyer MB, Pike JW. *Corepressors (NCoR and SMRT) as well as Coactivators are Recruited to Positively Regulated 1α,25-Dihydroxyvitamin D_3-Responsive Genes*. J Steroid Biochem Mol Biol. 2013; 136:120-4. PMC3548980.

2. One of the more fascinating discoveries in transcriptional regulation in the past 8 to 10 years has been the identification of distal-acting gene enhancers. As these observations were first made in a genome-wide fashion through ChIP-seq by groups focused on the estrogen receptor, I extended those observations to the VDR and its role in regulation. We found that the vast majority (>90%) of VDR binds to gene enhancers that are greater than 3-5 kb away from the transcriptional start site (TSS). These sites can be tens, if not hundreds, of kilobases away as I have shown with many vitamin D responsive genes. Identification of these sites can have significant impact if they are correlated with known disease SNPs, novel regulatory regions, or sites of chromatin organization. Our studies have shown that the investigations in the VDR field over the past 2 to 3 decades focused on gene control at the promoter (within 1kb of the TSS) were greatly incomplete, as distal enhancer regulation is frequently observed even at genes such as the "classic" promoter-proximal VDR driven gene, *Cyp24a1*.
    a. Meyer MB, Watanuki M, Kim S, Shevde NK, Pike JW. *The human transient receptor potential vanilloid type 6 distal promoter contains multiple vitamin D receptor binding sites that mediate activation by 1,25-dihydroxyvitamin D_3 in intestinal cells*. Mol Endocrinol. 2006; 20 (6):1447-61. PMID: 16574738.
    b. Meyer MB, Goetsch PD, Pike JW. *VDR/RXR and TCF4/β-Catenin Cistromes in Colonic Cells of Colorectal Tumor Origin: Impact on c-FOS and c-MYC Gene Expression*. Mol Endocrinol. 2012; 26(1):37-51. PMC3248320.
    c. Meyer MB, Goetsch PD, Pike JW. *Genome-wide analysis of the VDR/RXR cistrome in osteoblast cells provides new mechanistic insight into the actions of the vitamin D hormone*. J Steroid Biochem Mol Biol. 2010; 121(1-2):136-41. PMC2901394.

d. Meyer MB, Goetsch PD, Pike JW. *A downstream intergenic cluster of regulatory enhancers contributes to the induction of CYP24A1 expression by 1alpha,25-dihydroxyvitamin D_3*. J Biol Chem. 2010; 285(20):15599-610. PMC2865326.

3. After the identification of long-range interacting enhancers, their activities must be assessed and more importantly, the mechanism by which they control genes. I have studied genes with complex regulatory patterns (often 2 to 4 enhancers) to better understand the combinatorial approach that happens in vivo for gene regulation through the VDR. These enhancers are also co-occupied by other transcription factors that are known to interact with the VDR. In the bone cells, I have found a heavy reliance on interaction with RUNX2 which is an essential factor for the maturation and differentiation of osteoblast cells. Furthermore, we have found a great reliance on epigenetic plasticity for differentiation and trans-differentiation to occur from the mesenchymal stem cell (MSC) to a bone or fat cell. These relationships reveal the idea of the osteoblast enhancer complex and epigenetic signatures that can be used to predict the regulatory patterns of vital genes in bone cells.
    a. Meyer MB, Benkusky NA, Pike JW. *The RUNX2 Cistrome in Osteoblasts: Characterization, Downregulation Following Differentiation and Relationship to Gene Expression*. J Biol Chem. 2014. Jun 6;289(23):16016-31. PMC4047377.
    b. Meyer MB, Benkusky NA, Lee CH, Pike JW. *Genomic Determinants of Gene Regulation by 1,25-Dihydroxyvitamin D_3 During Osteoblast-Lineage Cell Differentiation*. J Biol Chem. 2014 Jun 11;289(28):19539-54. PMC4094065.
    c. Meyer MB, Benkusky NA, Sen B, Rubin J, Pike JW. *Epigenetic Plasticity Drives Adipogenic and Osteogenic Differentiation of Marrow-Derived Mesenchymal Stem Cells*. J Biol Chem. 2016 July 11. doi:10.1074/jbc.M116.736538. PMC5016174.

4. Our transcriptional studies have been greatly advanced through the discovery of genome editing techniques like the CRISPR/Cas9 system pioneered by Jennifer Doudna's group. I have brought those techniques to our research group and used them for fine dissection of the transcriptional mechanism of the gene *Mmp13*, which is important in osteoblast and chondrocyte biology. We also have delineated the roles for $1,25(OH)_2D_3$, PTH, and FGF23 activation in the kidney for the regulation of *Cyp27b1*. This study used enhancer deletion in the mouse to identify and eliminate the specific enhancers that recapitulated the full *Cyp27b1* knockout mouse phenotype.
    a. Meyer MB, Benkusky NA, Pike JW. *Selective Distal Enhancer Control of the Mmp13 Gene Identified through Clustered Regularly Interspaced Short Palindromic Repeat (CRISPR) Genomic Deletions*. J Biol Chem. 2015; 290(17):11093-107. PMC4409268.
    b. Meyer MB, Benkusky NA, Kaufmann M, Lee SM, Onal M, Jones G, Pike JW. *A kidney-specific genetic control module in mice governs endrocrine regulation of the cytochrome P450 gene Cyp27b1 essential for vitamin D_3 activation*. 2017 June 14. pii: jbc.M117.806901. doi: 10.1074/jbc.M117.806901. PMC5655528.
    c. Meyer MB, Benkusky NA, Kaufmann M, Lee SM, Redfield RR, Jones G, Pike JW. *Targeted genomic deletions identify diverse enhancer functions and generate a kidney-specific, endocrine-deficient Cyp27b1 pseudo-null mouse*. J Biol Chem. 2019 Jun 14;294(24):9518-9535. doi: 10.1074/jbc.RA119.008760. PMC6579472.
    d. Meyer MB, Lee SM, Carlson AH, Benkusky NA, Kaufmann M, Jones G, Pike JW. *A chromatin-based mechanism controls differential regulation of the cytochrome P450 gene Cyp24a1 in renal and non-renal tissues*. J Biol Chem. 2019 Aug 22; doi: 10.1074/jbc.RA119.010173. PMC6768633.

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