## PUBLICATIONS

(15/15 Research Papers)


1. Seldeen KL, McDonald CB, **Deegan BJ** & Farooq A (2008). Coupling of Folding and DNA-Binding in the bZIP Domains of Jun-Fos Heterodimeric Transcription Factor. ARCH BIOCHEM BIOPHYS 473, 48-60 (PMID# 18316037).
2. McDonald CB, Seldeen KL, **Deegan BJ**, Lewis MS & Farooq A (2008). Grb2 Adaptor Undergoes Conformational Change Upon Dimerization. ARCH BIOCHEM BIOPHYS 475, 25-35 (PMID# 18442468).
3. Seldeen KL, McDonald CB, **Deegan BJ** & Farooq A (2008). Thermodynamic Analysis of the Heterodimerization of Leucine Zippers of Jun and Fos Transcription Factors. BIOCHEM BIOPHYS RES COMMUN 375, 534-538 (PMID# 18725194).
4. McDonald CB, Seldeen KL, **Deegan BJ** & Farooq A (2008). Structural Basis of the Differential Binding of the SH3 Domains of Grb2 Adaptor to the Guanine Nucleotide Exchange Factor Sos1. ARCH BIOCHEM BIOPHYS 479, 52-62 (PMID# 18778683).
5. Seldeen KL, McDonald CB, **Deegan BJ** & Farooq A (2008). Evidence that the bZIP Domains of the Jun Transcription Factor Bind to DNA as Monomers Prior to Folding and Homodimerization. ARCH BIOCHEM BIOPHYS 480, 75-84 (PMID# 18940179; PMCID# PMC2597728).
6. Seldeen KL, McDonald CB, **Deegan BJ** & Farooq A (2009). Single Nucleotide Variants of the TGACTCA Motif Modulate Energetics and Orientation of Binding of the Jun-Fos Heterodimeric Transcription Factor. BIOCHEMISTRY 48, 1975-1983 (PMID# 19215067; PMCID# PMC2693225).
7. McDonald CB, Seldeen KL, **Deegan BJ** & Farooq A (2009). SH3 Domains of Grb2 Adaptor Bind to PXΨPXR Motifs within the Sos1 Nucleotide Exchange Factor in a Discriminate Manner. BIOCHEMISTRY 48, 4074-4085 (PMID# 19323566; PMCID# PMC2710136).
8. Seldeen KL, McDonald CB, **Deegan BJ**, Bhat V & Farooq A (2009). DNA Plasticity Is a Key Determinant of the Energetics of Binding of Jun-Fos Heterodimeric Transcription Factor to Genetic Variants of TGACGTCA Motif. BIOCHEMISTRY 48, 12213-12222 (PMID# 19921846; PMCID# PMC2807364).
9. McDonald CB, Seldeen KL, **Deegan BJ**, Bhat V & Farooq A (2010). Assembly of the Sos1-Grb2-Gab1 Ternary Signaling Complex Is Under Allosteric Control. ARCH BIOCHEM BIOPHYS 494, 216-225 (PMID# 20005866; PMCID# PMC2819574).
10. Seldeen KL, McDonald CB, **Deegan BJ**, Bhat V & Farooq A (2010). Dissecting the Role of Leucine Zippers in the Binding of bZIP Domains of Jun Transcription Factor to DNA. BIOCHEM BIOPHYS RES COMMUN 394, 1030-1035 (PMID# 20331972; PMCID# PMC2860604).
11. **Deegan BJ**, Seldeen KL, McDonald CB, Bhat V & Farooq A (2010). Binding of the ERα Nuclear Receptor to DNA Is Coupled to Proton Uptake. BIOCHEMISTRY 49, 5978-5988 (PMID# 20593765; PMCID# PMC2912409).
12. **Deegan BJ**, Bhat V, Seldeen KL, McDonald CB & Farooq A (2011). Genetic Variations within the ERE Motif Modulate Plasticity and Energetics of Binding of DNA to the ERα Nuclear Receptor. ARCH BIOCHEM BIOPHYS 507, 262-270 (PMID# 21216218; PMCID# PMC3044919).
13. McDonald CB, Seldeen KL, **Deegan BJ**, Bhat V & Farooq A (2011). Binding of the cSH3 Domain of Grb2 Adaptor to Two Distinct RXXK Motifs within Gab1 Docker Employs Differential Mechanisms. J MOL RECOG 24, 585-596 (PMID# 21157774; PMCID# NIHMS226045).
14. Seldeen KL, **Deegan BJ**, Bhat V, Mikles DC, McDonald CB & Farooq A (2011). Energetic Coupling Along an Allosteric Communication Channel Drives the Binding of Jun-Fos Heterodimeric Transcription Factor to DNA. FEBS J 278, In Press (PMID# N/A; PMCID# NIHMS287456).
15. **Deegan BJ**, Bona AM, Bhat V, Mikles DC, McDonald CB, Seldeen KL & Farooq A (2011). Structural and Thermodynamic Consequences of the Replacement of Zinc with Environmental Metals on ERα-DNA Interactions. J MOL RECOG 24, In Press (PMID# N/A; PMCID# N/A).


The Sheila and David Fuente
Graduate Program in Cancer Biology
*proudly announces the*
*Final Oral Examination of*

# Brian Deegan, MD/PhD Candidate

FOR THE DEGREE OF
**DOCTOR OF PHILOSOPHY**

Thursday, May 26, 2011 at 2:00 p.m.
Thesis Seminar Gautier #118 Conference Room

Thursday, May 26, 2011 at 3:30 p.m.
Thesis Defense Gautier #127 Conference Room

SYLVESTER COMPREHENSIVE CANCER CENTER
UNIVERSITY OF MIAMI HEALTH SYSTEM

MILLER SCHOOL OF MEDICINE
UNIVERSITY OF MIAMI

## BIOGRAPHICAL SKETCH

## "Biophysical Studies of the Binding of ERα Nuclear Receptor to DNA"

**Brian Deegan, MD/PhD Candidate**

Brian was born and raised in the great state of Iowa. He attended Luther College in Decorah, Iowa where he studied chemistry and biology graduating *summa cum laude*. In the summer of 2003, Brian helped develop a thermal decomposition method for the synthesis of monodisperse iron oxide nanoparticles in Dr Stephen O'Brien's laboratory at Columbia University in New York City. In the following summer of 2004, Brian investigated the relationship between lipid composition and electrostatic surface potential in an artificial planar bilayer system in Dr. Jay T. Groves' lab at the University of California, Berkeley. These research experiences exposed him to the potential for physical chemistry to impact biology and cemented his desire to pursue a scientific career. However, it was not until a class in nuclear chemistry and physics that Brian became drawn towards cancer.

This course not only afforded him the opportunity to learn the principles of nuclear transformation reactions but exposed him to the basis of therapeutic applications in the context of radiation oncology. This powerful application of physicochemical science sparked his interest in the medical field. Collectively, the experiences of both coursework and wet-lab research solidified his desire to pursue training toward becoming a physician scientist.

Upon graduation, he enrolled in the University of Miami Miller School of Medicine MD/PhD program with the vision to seek training at the interface of physics, chemistry and biology addressing problems in cancer. The Sheila and David Fuente Program in Cancer Biology and the Farooq Laboratory provided the ideal opportunity to fulfill these training aspirations. Training with the Cancer Biology Graduate Program has given him an extensive background in not only the basic scientific principles and approaches to cancer biology but also its clinical implications. Brian's work, under the guidance of Dr. Amjad Farooq, has been instrumental in developing his physicochemical approach and understanding of biology, particularly in the areas of molecular biophysics and structural biology.

Outside of science, Brian is an avid homebrewer and has two maltese dogs named Barley and Hops. He is an enthusiast of college sports and a huge Miami Hurricanes fan. When he can find the time, he enjoys golfing, fishing and listening to classic rock. Most importantly, this past March Brian married his high school sweetheart, Jocelyn, who has been an unwavering source of support and inspiration to him throughout the years.


Estrogen receptor a (ERa) is a member of a family of ligand-modulated transcription factors that have come to be known as nuclear receptors. ERa mediates the action of estrogens and plays an integral role in a wide range of physiological processes. Malfunction of the estrogen system is associated with a host of pathological conditions such as osteoporosis, heart disease and most notably breast cancer. Essential to its functioning as a transcription factor are specific protein-DNA interactions which are mediated by the binding of the DNA-binding (DB) domain of ERα to particular DNA sequences located within target gene promoters called estrogen response elements (EREs). Here, using biophysical approaches, I provide new insights into the ERα-DNA interaction in thermodynamic and structural terms.

My data provide evidence that the binding of ERa to DNA is coupled to proton uptake by two ionizable residues, H196 and E203. Such protonation is requisite for high affinity binding. These residues are predominantly conserved across the nuclear receptor family, implying that protonation may be a hallmark of nuclear receptor function. Additionally, the effect of symmetric introduction of single nucleotide variations within each half-site of the estrogen response element (ERE) on the binding of ERa was analyzed. ERa tolerates all genetic variants, binding in the physiologically relevant nanomolar-micromolar range. I provide rationale for how these genetic variations may reduce its affinity for ERa by orders of magnitude at atomic level. Lastly, I probe structural consequences of the replacement of zinc within the DB domain of ERa with environmental metals and their effects on the thermodynamics of binding to DNA.

While the DB domain reconstituted with divalent ions of zinc, cadmium, mercury and cobalt binds to DNA with affinities in the nanomolar range, divalent ions of barium, copper, iron, lead, manganese, nickel and tin are unable to regenerate DB domain with DNA-binding potential though they can compete with zinc for coordinating the cysteine ligands. I also show that metal-coordination may only be essential for DNA-binding but not folding. Collectively, my findings provide novel mechanistic insights into the physicochemical basis of a key protein-DNA interaction central to human health and disease.


Brian Deegan's Dissertation Defense Committee

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