BIOGRAPHICAL SKETCH

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NAME: Fernandez, Elias

eRA COMMONS USER NAME: ejfernandez

POSITION TITLE: Associate Professor

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE (if applicable)	Completion Date MM/YYYY	FIELD OF STUDY
St. Joseph's College, Bangalore University, Bangalore	BS	06/1988	Physics with Chemistry and Mathematics
Loyola University Chicago, Chicago, Illinois	PHD	12/1995	Biophysical Chemistry
Yale University, New Haven, Connecticut	Postdoctoral Fellow	07/2001	Structural Biology

A. Personal Statement

I trained as a physical biochemist. My current research interests are directed at determining the role of allostery in nuclear hormone receptor signaling. We are specifically focused on the role of hormonal ligand combinations – the crosstalk between ligands independently bound to each subunit within the nuclear receptor heterodimer. This is the focus of the studies being proposed in this application. For several years my laboratory has investigated the heterodimeric complex of the constitutive androstane (CAR) and retinoid X receptors (RXR) and had generated substantial data utilizing state-of-the-art experimental and computational approaches to elucidate the effects of ligand binding on nuclear hormone receptor actions. The first structures of the inverse-agonist-bound constitutive androstane receptor (CAR)-retinoid X receptor (RXR) (CAR:RXR) complex and the heterodimeric thyroid and RXR (TR:RXR) ligand-binding domain complexes were determined in my laboratory at the University of Tennessee, Knoxville (UTK). My laboratory has also pioneered the use of isothermal titration calorimetry (ITC) for measuring nuclear hormone receptor (NR) multi-domain protein:protein and protein:DNA interactions with multi-molecular assemblies. Our ITC studies on the 7-component, DNA/TR:RXR/coactivator complex is a *tour de force* accomplishment in macromolecular calorimetric studies. We propose to use this same ITC methodology in some investigations that are being proposed in our application.

The studies being proposed in the application specifically directed at the structure determination of the RXRα(dioxin) molecular complex. I am excited about this proposed work because it links our detailed biophysical and molecular studies with outcomes identified in mouse models and cell culture.

B. Positions and Honors

Positions and Employment

2001 - 2007 Assistant Professor, Department of Biochemistry, Cellular and Molecular Biology, University of Tennessee, Knoxville, TN

2007 - Associate Professor, Department of Biochemistry, Cellular and Molecular Biology, University of Tennessee, Knoxville, TN

Other Experience and Professional Memberships

2007 - Member, American Society for Biochemistry and Molecular Biology

Honors

1989 Junior Research Fellowship, Council of Scientific and Industrial Research, India

C. Contribution to Science

1. Using the thyroid receptor (TR) and with a combination of biophysical and cell biology techniques we identified allosteric pathways that link the DNA-binding and coactivator-binding sites. We also showed that the direct interactions between DNA- and ligand-binding domains (LBD) of TR are regulated by DNA binding.

a. Putcha BD, Fernandez EJ. Direct interdomain interactions can mediate allosterism in the thyroid receptor. J Biol Chem. 2009 Aug 21;284(34):22517-24. PubMed PMID: 19561066; PubMed Central PMCID: PMC2755658.

2. We are the first to determine the structure of the thyroid and retinoid X receptors (TR:RXR) LBD heterodimer by crystallography. This much-sought-after structure has been the focus of several laboratories. From this structure we developed a molecular mechanism for the ligand-mediated negative cooperativity that is observed in TR:RXR transactivation. This cooperativity could not be explained by the traditional '*induced fit*' and '*lock-and-key*' allosteric mechanisms, we developed the novel '*frustrated fit*' mechanism for TR:RXR allostery.

a. Johnson QR, Lindsay RJ, Nellas RB, Fernandez EJ, Shen T. Mapping allostery through computational glycine scanning and correlation analysis of residue-residue contacts. Biochemistry. 2015 Feb 24;54(7):1534-41. PubMed PMID: 25658131.

b. Putcha BD, Wright E, Brunzelle JS, Fernandez EJ. Structural basis for negative cooperativity within agonist-bound TR:RXR heterodimers. Proc Natl Acad Sci U S A. 2012 Apr 17;109(16):6084-7. PubMed PMID: 22474364; PubMed Central PMCID: PMC3341017.

3. We were the also first to determine the structure of a constitutively active, ligand repressible nuclear receptor bound to inverse agonist. This constitutive androstane receptor (CAR):androstenol complex structured showed a novel structural mechanism of transcriptional repression by ligands. Increased CAR activity can be deleterious and is associated with paracetamol-induced liver toxicity and with liver tumors; the molecular mechanism of CAR repression is critical for therapeutic drug design.

a. Clark AK, Wilder JH, Grayson AW, Johnson QR, Lindsay RJ, Nellas RB, Fernandez EJ, Shen T. The Promiscuity of Allosteric Regulation of Nuclear Receptors by Retinoid X Receptor. J Phys Chem B. 2016 Apr 25;PubMed PMID: 27110634.

b. Wright E, Busby SA, Wisecarver S, Vincent J, Griffin PR, Fernandez EJ. Helix 11 dynamics is critical for constitutive androstane receptor activity. Structure. 2011 Jan 12;19(1):37-44. PubMed PMID: 21220114; PubMed Central PMCID: PMC3032979.

c. Shan L, Vincent J, Brunzelle JS, Dussault I, Lin M, Ianculescu I, Sherman MA, Forman BM, Fernandez EJ. Structure of the murine constitutive androstane receptor complexed to androstenol: a molecular basis for inverse agonism. Mol Cell. 2004 Dec 22;16(6):907-17. PubMed PMID: 15610734; PubMed Central PMCID: PMC2727924.

4. In 2014 we discovered a novel 1:2 (CAR-RXR):coactivator stoichiometry that departs from the paradigmatic 1:1 NR:coactivator stoichiometric association. The presence of endogenous ligands for nuclear receptors increases the likelihood of two agonists binding the heterodimers at once with important implications of this NR:coactivator assembly in pharmacology.

a. Pavlin MR, Brunzelle JS, Fernandez EJ. Agonist ligands mediate the transcriptional response of nuclear receptor heterodimers through distinct stoichiometric assemblies with coactivators. J Biol Chem. 2014 Sep 5;289(36):24771-8. PubMed PMID: 25053412; PubMed Central PMCID: PMC4155646.

Complete List of Published Work in MyBibliography:

https://www.ncbi.nlm.nih.gov/myncbi/elias.fernandez.2/bibliography/public/

BIOGRAPHICAL SKETCH

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NAME: Walden, Lauren

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

POSITION TITLE: Graduate Teaching Assistant

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)	END DATE MM/YYYY	FIELD OF STUDY
Middle Tennessee State University, Murfreesboro, TN	BS	05/2021	Biochemistry

A. Personal Statement

My research interests are in the structure, function, and dynamic interactions of proteins. I use both experimental and computational methods to explore interdisciplinary studies. Currently, my research focuses on determining the structure of a ligand-activated transcription factor when bound to a toxin, the allosteric effect it enacts in response, and ultimately the downstream effects in genetics. I plan on determining the structure through crystallographic means. I will assess allostery through molecular dynamics. Genome-wide impacts of this allosteric interaction will be elucidated using in vitro chromatin immunoprecipitation and next-generation sequencing.

B. Positions, Scientific Appointments and Honors

Positions and Scientific Appointments

2021 - Graduate Teaching Assistant, University of Tennessee - Knoxville, Koxville, TN
2020 - 2021 Sequencing Intern, GenHunter Corporation, Nashville, TN

Honors

2021 Graduate Fellowship, University of Tennessee - Knoxville

C. Contribution to Science