# BIOGRAPHICAL SKETCH

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NAME: Ellsworth, Buffy

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

POSITION TITLE: Associate Professor

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 |
|---|---|---|---|
| South Dakota State University, Brookings, SD | BS | 09/1995 | Biological Science |
| South Dakota State University, Brookings, SD | BS | 12/1996 | General Chemistry |
| South Dakota State University, Brookings, SD | MS | 08/1997 | Biology |
| Colorado State University, Ft. Collins, CO | PHD | 09/2002 | Cell and Molecular Biology |
| University of Michigan, Ann Arbor, MI | Postdoctoral Fellow | 09/2007 | Human Genetics |

## A. Personal Statement

My role in this project is that of PI. I have a broad background in molecular biology and genetics, with specific training in research areas that are essential to the success of the proposed project. For example, during my doctoral training with Dr. Colin Clay at Colorado State University, I used cell culture studies to identify regulatory mechanisms of pituitary genes. I used a yeast hybrid approach to identify the forkhead transcription factor, FOXL2, as part of a transcriptional complex that binds the gonadotropin-releasing hormone receptor gene, which is expressed in gonadotrope cells. Using transient transfection studies, I found that FOXL2 could stimulate the GRAS element, which contributes to activity of the gonadotropin-releasing hormone receptor promoter. As a postdoctoral fellow with Dr. Sally Camper at the University of Michigan Medical School, I designed and executed developmental mouse studies using mouse models of gene mutations such as spontaneous mutations, targeted mutations, transgenics and cre/loxp strategies to determine the role of transcription factors in pituitary gland development and function. Using these approaches, I demonstrated that FOXL2 protein is present in the prospective anterior lobe of the developing pituitary gland beginning at e11.5 and continuing through adulthood in gonadotrope and thyrotrope cells. I found that FOXL2 stimulates expression of the glycoprotein hormone α-subunit gene in cell culture studies and by over-expression of Foxl2 in transgenic mice.

In my current position as associate professor at Southern Illinois University, I organized a research team that demonstrated that the forkhead factor, FOXP3, is required for normal gonadotrope function and that Foxp3 mutant mice exhibit hypothyroidism. We have also shown that loss of FOXD1 causes reduced Lhb expression and increased pituitary cell proliferation. As PI on two previous NIH-funded grants, I laid the foundation for this application by identifying FOXO1 as a candidate gene for somatotrope-based diseases, particularly growth hormone deficiency. My graduate student, Caitlin Stallings, is a contributing author on the paper describing these studies (Part C), and generated much of the preliminary data for this application. Ms. Stallings has extensive experience in cell culture and analyzing mouse models. My expertise in both forkhead transcription factor function and pituitary gland development, together with those of Ms. Stallings, places us in a position to successfully address the roles of FOXO1 in somatotrope differentiation and function.

1. Stallings CE, Ellsworth BS. Premature Expression of FOXO1 in Developing Mouse Pituitary Results in Anterior Lobe Hypoplasia. Endocrinology. 2018 Aug 1;159(8):2891-2904. PubMed PMID: 29796621.
2. Kapali J, Kabat BE, Schmidt KL, Stallings CE, Tippy M, Jung DO, Edwards BS, Nantie LB, Raeztman LT, Navratil AM, Ellsworth BS. Foxo1 Is Required for Normal Somatotrope Differentiation. Endocrinology. 2016 Nov;157(11):4351-4363. PubMed PMID: 27631552; PubMed Central PMCID: PMC5086538.
3. Calderon MJ, Ploegman AG, Bailey B, Jung DO, Navratil AM, Ellsworth BS. Loss of Foxm1 Results in Reduced Somatotrope Cell Number during Mouse Embryogenesis. PLoS One. 2015;10(6):e0128942. PubMed PMID: 26075743; PubMed Central PMCID: PMC4468165.
4. Gumbel JH, Patterson EM, Owusu SA, Kabat BE, Jung DO, Simmons J, Hopkins T, Ellsworth BS. The forkhead transcription factor, Foxd1, is necessary for pituitary luteinizing hormone expression in mice. PLoS One. 2012;7(12):e52156. PubMed PMID: 23284914; PubMed Central PMCID: PMC3526578.

## B. Positions and Honors

### Positions and Employment

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|---|---|
| 1993 - 1995 | Undergraduate Researcher, South Dakota State University, Brookings, SD |
| 1995 - 1997 | Graduate Research Assistant, South Dakota State University, Brookings, SD |
| 1997 - 2002 | Graduate Research Assistant, Colorado State University, Ft. Collins, CO |
| 2002 - 2007 | Postdoctoral Fellow, University of Michigan, Ann Arbor, MI |
| 2007 - 2013 | Assistant Professor, Southern Illinois University, Carbondale, IL |
| 2013 - | Associate Professor, Southern Illinois University, Carbondale, IL |

### Other Experience and Professional Memberships

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|---|---|
| 1999 - 2017 | Member, The Endocrine Society |
| 2000 - 2017 | Member, Women in Endocrinology |
| 2002 - 2002 | Embryonic Stem (ES) Cell Training, The University of Michigan |
| 2003 - 2003 | Attendee, Developmental Biology Gordon Conference |
| 2004 - 2004 | Mouse Embryo Microinjection Training, University of Michigan |
| 2004 - 2013 | Member, Society for the Study of Reproduction |
| 2005 - 2005 | Postdoctoral Fellows' Career Workshop, NIH/NICHD |
| 2010 - 2011 | Communications Committee, Member, Women in Endocrinology |
| 2011 - 2011 | Chair of Symposium, "New Aspects of Signaling & Secretion in the Gonadotrope", The Endocrine Society |
| 2011 - 2013 | Editorial Board, Biology of Reproduction |
| 2012 - 2012 | Program Committee, Module Session co-chair: Reproductive Endocrinology, Society for the Study of Reproduction |
| 2012 - 2014 | Communications Committee, Chair, Women in Endocrinology |
| 2013 - 2013 | Chair of Symposium, "Neuroendocrinology and Pituitary - Basic", The Endocrine Society |

### Honors

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|---|---|
| 1997 - 2000 | Biotechnology Training Grant, United States Department of Agriculture |
| 2000 | Travel Award, Women in Endocrinology |
| 2000 | Travel Award, Neuroendocrinology Satellite Meeting of the International Congress of Endocrinology, Coffs Harbour, Australia |
| 2001 | Travel Grant Award, The Endocrine Society |
| 2003 | University of Michigan Reproductive Sciences Program Postdoctoral Fellowship, T32 Training Grant, NIH |

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| 2004 - 2006 | Ruth L. Kirschstein National Research Service Award, NIH: National Institute of Child Heath & Human Development |
| 2008 | Faculty Seed Grant, SIUC Office of Research Development and Administration |
| 2008 | Outstanding Mentor Award, McNair Scholar Program |
| 2009 | Starter Grant, SIU Central Research Committee |
| 2012 | Excellence in Academic Medicine Award, SIU School of Medicine |
| 2012 | Invited talk: The forkhead Transcription Factor, Foxp3, is Required for Normal Pituitary Function. Session: The Foxy Pituitary: Emerging Roles for Forkhead Transcription Factors in Gonadotrope Development and Function., The Society for the Study of Reproduction |
| 2013 | Near Miss Award, SIU School of Medicine |
| 2013 | Invited talk: Forkhead Transcription Factors in Pituitary Development. Session: The Secret Lives of Gonadotropes., The Endocrine Society Ann. Mtg. San Francisco, CA |
| 2017 | Invited talk: The Role of FOXO Transcription Factors in Somatotrope Differentiation and Function, Life Science Seminar Series. South Dakota State University, Brookings, SD |

## C. Contribution to Science

1. Identification of FOXO1 as an Important Factor in Somatotrope Differentiation. In my current position as an associate professor at Southern Illinois University, I organized a research team to investigate the role of FOXO1 in pituitary gland development. We determined that FOXO1 is present in the nuclei of pituitary cells at e14.5, immediately prior to the onset of somatotrope differentiation. We found that FOXO1 is present in somatotrope cells of the developing pituitary and mature gland. To determine the role of FOXO1 in pituitary differentiation and function, we studied mice in which Foxo1 is deleted from the pituitary gland. Mice lacking FOXO1 in the pituitary gland exhibit delayed somatotrope differentiation suggesting that FOXO1 is necessary for normal somatotrope differentiation. While pituitary progenitor cells are able to commit to the POU1F1 lineage, terminal differentiation of somatotropes is delayed, suggesting that the requirement for FOXO1 occurs after commitment of progenitor cells. This impairment in somatotrope differentiation appears to involve the transcription factor, NEUROD4. Other pituitary cell types are present in normal numbers suggesting that FOXO1 is not required for differentiation of other pituitary cell types. Interestingly, premature expression of FOXO1 reduces the ability of cells to adapt a pituitary fate. This work is novel because FOXO1 had not previously been identified as an important factor in somatotrope differentiation. This work is of importance because it identifies a candidate gene that could be targeted to develop novel and much-needed approaches to improved therapeutics for somatotrope-based diseases.

    a. Stallings CE, Ellsworth BS. Premature Expression of FOXO1 in Developing Mouse Pituitary Results in Anterior Lobe Hypoplasia. Endocrinology. 2018 Aug 1;159(8):2891-2904. PubMed PMID: 29796621.
    b. Kapali J, Kabat BE, Schmidt KL, Stallings CE, Tippy M, Jung DO, Edwards BS, Nantie LB, Raeztman LT, Navratil AM, Ellsworth BS. Foxo1 Is Required for Normal Somatotrope Differentiation. Endocrinology. 2016 Nov;157(11):4351-4363. PubMed PMID: 27631552; PubMed Central PMCID: PMC5086538.
    c. Majumdar S, Farris CL, Kabat BE, Jung DO, Ellsworth BS. Forkhead Box O1 is present in quiescent pituitary cells during development and is increased in the absence of p27 Kip1. PLoS One. 2012;7(12):e52136. PubMed PMID: 23251696; PubMed Central PMCID: PMC3522653.

2. Identification of FOXP3 as a Necessary Factor for Gonadotrope Function. In my current position as an associate professor at Southern Illinois University, I organized a research team that demonstrated the forkhead transcription factor, FOXP3, is required for normal gonadotrope function. We determined that expression of the gonadotropin genes, Lhb, Fshb and Cga, is significantly reduced in mice lacking functional Foxp3 (Foxp3sf/Y), demonstrating that the hypogonadism in these mice is hypogonadotropic in nature. Gonadotropin replacement rescued gonadal function in Foxp3sf/Y mice.

Foxp3 is not expressed in the pituitary gland or the hypothalamus suggesting that the effect on pituitary function is indirect. This work is novel because FOXP3 was not previously known to affect pituitary function. This work is important because it identifies a potential cause of hypogonadotropic hypogonadism providing an additional molecular diagnosis for this disease.

a. Jasurda JS, Jung DO, Froeter ED, Schwartz DB, Hopkins TD, Farris CL, McGee S, Narayan P, Ellsworth BS. The forkhead transcription factor, FOXP3: a critical role in male fertility in mice. Biol Reprod. 2014 Jan;90(1):4. PubMed PMID: 24258212; PubMed Central PMCID: PMC4076402.
b. Jung DO, Jasurda JS, Egashira N, Ellsworth BS. The forkhead transcription factor, FOXP3, is required for normal pituitary gonadotropin expression in mice. Biol Reprod. 2012 May;86(5):144, 1-9. PubMed PMID: 22357547; PubMed Central PMCID: PMC3364925.

3. Genetic, Molecular and Developmental Characterization of FOXL2 in the Pituitary Gland. During my doctoral training with Dr. Colin Clay at Colorado State University I showed that the forkhead transcription factor, FOXL2, is part of a transcriptional complex that binds the gonadotropin-releasing hormone receptor gene. As a postdoctoral fellow in the laboratory of Dr. Sally Camper at the University of Michigan Medical School, I performed developmental mouse studies to demonstrate that FOXL2 protein is present in the prospective anterior lobe of the developing pituitary gland beginning at e11.5 and continuing through adulthood in gonadotrope and thyrotrope cells. I found that FOXL2 stimulates expression of the gene encoding the glycoprotein hormone-subunit in cell culture studies and by over-expression of Foxl2 in mice. This work was novel because the function of FOXL2 in pituitary had not previously been addressed. This work is important because it identifies a factor that is important in gonadotrope function.

a. Ellsworth BS, Egashira N, Haller JL, Butts DL, Cocquet J, Clay CM, Osamura RY, Camper SA. FOXL2 in the pituitary: molecular, genetic, and developmental analysis. Mol Endocrinol. 2006 Nov;20(11):2796-805. PubMed PMID: 16840539.
b. Ellsworth BS, Burns AT, Escudero KW, Duval DL, Nelson SE, Clay CM. The gonadotropin releasing hormone (GnRH) receptor activating sequence (GRAS) is a composite regulatory element that interacts with multiple classes of transcription factors including Smads, AP-1 and a forkhead DNA binding protein. Mol Cell Endocrinol. 2003 Aug 29;206(1-2):93-111. PubMed PMID: 12943993.

Complete List of Published Work in My Bibliography:
https://www.ncbi.nlm.nih.gov/myncbi/buffy.ellsworth.1/bibliography/48496630/public/

## D. Additional Information: Research Support and/or Scholastic Performance

### Completed Research Support

R15 HD078885-01 Ellsworth, Buffy Sue (PI) 09/20/14-06/30/17
Mechanism by Which FOXO1 Regulates Somatotrope Differentiation and/or Function
The goals of this project are to 1) investigate FOXO1 regulation of Gh1 and its upstream regulators, 2) determine when FOXO1 is required for somatotrope cell specification/function.
Role: PI

Discovery Science Grant, SIU School of Medicine Ellsworth, Buffy (PI) 01/01/17-05/31/18
Identification of Somatotrope Proteins within the FOXO1 Transcriptional Complex
The objective of this grant is to identify FOXO1 binding partners by rapid immunoprecipitation mass spectrometry of endogenous proteins (RIME).
Role: PI