BIOGRAPHICAL SKETCH

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NAME	POSITION TITLE
Stephen R Hammes	Professor Chief, Division of Endocrinology and Metabolism
eRA COMMONS USER NAME (credential, e.g., agency login) shammes	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	MM/YY	FIELD OF STUDY
Cornell University, Ithaca, NY	A.B.	06/85	Chemistry
Duke University, Durham, NC	M.D.	12/92	Medicine
Duke University, Durham, NC	Ph.D.	12/92	Microbiol & Immunol
University of California San Francisco	Residency	06/95	Medicine
University of California San Francisco	Fellowship	06/99	Endocrinology

A. Personal Statement

My primary research interest is in steroid signaling in reproductive systems, with an emphasis on the biological processes mediated by steroids. When my laboratory started, we had one distinct focus: to understand how steroids mediate extranuclear, transcription-independent, processes. We use(d) perhaps the only biologically relevant process unambiguously known to be mediated by steroids completely independent of transcription: steroid-triggered maturation, or meiotic progression, in *Xenopus laevis* oocytes. We showed *in-vitro* and *in-vivo* that, despite decades of using progesterone to promote maturation *in vitro*, in fact androgens were the true physiologic regulators of oocyte maturation in *Xenopus laevis*. By starting with the correct agonist, we were then able to show that classical androgen receptors outside the nucleus regulated androgen-triggered meiosis by altering G protein and kinase signaling. Notably, many of our findings on the mechanisms of nongenomic androgen signaling in oocytes are now considered commonplace in a myriad of mammalian systems and steroids.

We have now taken the concepts discovered in frog oocytes and applied them to somatic cell systems. We have found that both genomic and nongenomic androgen signaling are critical normal ovarian follicular development and eventual ovulation. We have discovered several androgen-mediated signaling pathways that regulate both follicular growth and follicular atresia, and we are involved in multiple clinical trials examining both the positive and negative effects of androgens on female fertility.

In the last few years, we have focused on a new steroid-dependent tumor: lymphangioleiomyomatosis (LAM). This estrogen-dependent tumor only affects women and tumors contain inactivating mutations in the Tsc complex. Pathologically, LAM looks like uterine leiomyomas in the lungs. In fact, we have created a mouse model whereby we delete Tsc2 specifically in the uterus and mice develop leiomyomas early on and lung LAM lesions later in life. Thus, we believe that LAM is a metastatic disease that originates in the uterus.

B. Positions

1999-2005	Assistant Professor, W. W. Caruth Scholar in Biomedical Research, Division of Endocrinology and Metabolism, Departments of Internal Medicine and Pharmacology, University of Texas, Southwestern Medical Center, Dallas, TX.
2005-2008	Associate Professor, Division of Endocrinology and Metabolism, Departments of Internal Medicine and Pharmacology, UT Southwestern Medical Center, Dallas, TX
2006-2008	Co-Director, Endocrinology and Metabolism Fellowship Training Program, UT Southwestern Medical Center, Dallas, TX
2009-present	Louis S. Wolk Distinguished Professor or Medicine and Chief, Division of Endocrinology and Metabolism, University of Rochester Medical Center, Rochester, NY

Honors

1984	Alpha Lambda Delta Honor Society
1985	Phi Beta Kappa, Cornell University
1984-85	Honors Program in Chemistry, Cornell University
1985	Merck Chemistry Award, Cornell University
1985	Summa Cum Laude in Chemistry, Cornell University
1985-1992	Medical Scientist Training Program (MSTP), Duke University
1987-1989	President, Duke University MSTP Program
1987-1989	Member, Duke University Medical Center Davison Council
1996-1997	American Heart Association California Affiliate Postdoctoral Fellowship
1997-1999	Howard Hughes Postdoctoral Research Fellowship
1998	1998 Endocrine Society Travel Award for ENDO'98
1996	Diplomate, American Board of Internal Medicine
1998	Diplomate, American Board of Endocrinology
1999	Endowed Scholars Award, UT Southwestern Medical Center
2003-present	Standing member, NIDDK-B study section
2005-2011	Editorial Board, Molecular Endocrinology
2006-2009	Editorial Board, Biology of Reproduction
2007	Elected into the American Society of Clinical Investigation
2008	Co-Organizer of 2008 FASEB Summer Research Conference on Steroid Signaling
2008	Outstanding reviewer of the year – Molecular Endocrinology
2009	Chair: Louis S. Wolk Distinguished Professor of Medicine
2009	Outstanding reviewer of the year – Molecular Endocrinology
2010-present	Editorial Board, Steroids
2010	Chief Organizer of 2010 FASEB Summer Research Conference on Steroid Signaling
2010-present	Chair, NIDDK-B Study Section
2012	Organizer of 2012 Annual LAM Meeting
2013-present	Editor in Chief, Molecular Endocrinology

C. Selected Publications:

Lutz, L.B., Kim, B.E., Jahani, D., and **Hammes, S.R.** (2000) G Protein βγ Subunits inhibit Nongenomic Progesterone-Induced Signaling and Maturation in Xenopus Laevis Oocytes: Evidence for a Release of Inhibition Mechanism for Cell Cycle Progression, Journal of Biological Chemistry **275**, 41512-41520.

Lutz, L.B., Cole, L.M., Gupta, M.K., Kwist, K.W., Auchus, R.J., **Hammes, S.R.** (2001) Evidence that Androgens are the Primary Steroids Produced by *Xenopus laevis* Ovaries and may Signal Through the Classical Androgen Receptor to Promote Oocyte Maturation, Proc. Natl.Acad.Sci. USA. **98**, 13728-33

Yang, W-H, **Hammes, S.R** (2003) *Xenopus laevis* Ovarian CYP17 is a Highly Potent Enzyme Expressed Exclusively in Oocytes: Evidence that Oocytes Play a Critical Role in *Xenopus* Ovarian Androgen Production, Journal of Biological Chemistry 278, 9552-9.

Gill A., Jamnongjit, M., and **Hammes, S. R.** (2004) Androgens Promote Maturation and Signaling in Mouse Oocytes Independent of Transcription: A Release of Inhibition Model for Mammalian Oocyte Meiosis, Molecular Endocrinology **18**, 97-104.

Haas, D., White, S.N., Lutz, L.L., Rasar, M., and **Hammes, S.R.** (2005) The Modulator of Nongenomic Actions of the Estrogen Receptor (MNAR) Regulates Transcription-Independent Androgen Receptor-Mediated Signaling: Evidence that MNAR Participates in G Protein-Regulated Meiosis of *Xenopus Laevis* Oocytes, Molecular Endocrinology **19**, 2035-2046.

Jamnongjit, M., Gill, A., and **Hammes, S.R.** (2005) Epidermal Growth Factor Signaling is Required for Normal Ovarian Steroidogenesis and Oocyte Maturation, Proc. Natl. Acad. Sci. USA **102**, 16257-16261.

Rasar, M. DeFranco, D.B., and **Hammes, S.R.** (2006) Paxillin Regulates Steroid-Triggered Meiotic Resumption in Oocytes by Enhancing an All-or-None Positive Feedback Kinase Loop, Journal of Biological Chemistry **281**, 39455-64.

Evaul, K., Jamnongjit, M., Bhagavath, B., and **Hammes, S.R.** (2007) Androgens Rapidly Attenuate Plasma Membrane Gβγ-Mediated Signaling in *Xenopus Laevis* Oocytes, Molecular Endocrinology **21**, 186-96.

Hammes, S.R. and Levin, E.R. (2007) Extra-Nuclear Steroid Receptors: Nature and Actions, Endocrine

Reviews **28**, 726-41.

Deng, J., Lang, S., Wylie, C., and **Hammes, S.R.** (2008) XGPR3 is a Constitutively Active Cell Surface G Protein-Coupled Receptor that Participates in Maintaining Meiotic Arrest in Xenopus Laevis Oocytes, Molecular Endocrinology **22**, 1853-65.

Evaul, L. and **Hammes, S.R**. (2008) Cross Talk Between G Protein-Coupled and Epidermal Growth Factor Receptors Regulates Gonadotropin-Mediated Steroidogenesis in Leydig Cells, Journal of Biological Chemistry **283**, 27575-33

Sen, A. and **Hammes, S.R**. (2010) Granulosa Cell-Specific Androgen Receptors are Critical Regulators of Ovarian Development and Function, Molecular Endocrinology, **24**, 1393-403 (featured on the cover).

Sen, A., O'Malley, K., Wang, Z., Raj, G.V., Defranco, D.B., **Hammes, S.R.** (2010) Paxillin Regulates Androgen- and Epidermal Growth Factor-Induced MAPK Signaling and Cell Proliferation in Prostate Cancer Cells, Journal of Biological Chemistry **285**, 28787-95.

Strauss, T.J., Castrillon, D.H., and **Hammes, S.R.** (2011) GATA-Like Factor 1 (GLP-1) is Required for Normal Germ Cell Development During Embyrogenic Oogenesis, Reproduction **141**, 173-81.

Carbajal, L., Biswas, A., Niswander, L.M., Prizant, H., **Hammes, S.R.** (2011) GPCR/EGFR Cross Talk is Conserved in Gonadal and Adrenal Steroidogenesis but is Uniquely Regulated by Matrix Metalloproteinases 2 and 9 in the Ovary, Molecular Endocrinology **25**, 1055-65.

Yang, L., Ravindranathan, P., Ramanan, M., Kapur, P., **Hammes, S.R**., Hsieh, J.T., Raj, G.V. (2012) Central Role for PELP1 in Non-Androgenic Activation of the Androgen Receptor in Prostate Cancer, in press, Molecular Endocrinology

Sen, A., De Castro, I., DeFranco, D.B., Deng, F-M, Melamed, J., Kapur, P., Raj, G.V., Rossi, R., **Hammes, S.R.** (2012) Paxillin regulates extranuclear and intranuclear signaling in prostate cancer proliferation, Journal of Clinical Investigation 122, 2469-81.

Prizant H., Sen, A., Light, A., Cho, S.N., DeMayo, F.J., Lydon, J.P., **Hammes, S.R.** (2013) Uterine-Specific loss of Tsc2 Leads to Myometrial Tumors in Both the Uterus and Lungs, Molecular Endocrinology 27, 1403-14.

Sen, A., Prizant, H., Light, A., Biswas, A., Hayes, E., Lee, H.J., Barad, D., Gleicher, N., **Hammes, S.R.** (2014) Androgens regulate ovarian follicular development by increasing follicle stimulating hormone receptor and microRNA-125b expression, PNSA 11, 3008-13.

D. Ongoing Research Support:

R01GM101709-01A1 Hammes (PI) 2013-2017 1.5 months effort
National Institutes of Health
"Paxillin as a Liaison between Extranuclear and Intranuclear Steroid Signaling"

This grant is aimed toward studying the role of paxillin in regulating steroid signaling, with a focus on paxillin's actions in the prostate.

TS110032 Hammes (PI) 2012-2014 0.5 months effort
Department of Defense
"Uterine-Specific Knockout of TSC-2: A Mouse Model for Lymphangioleiomyomatosis (LAM)"

This grant is investigating the origins of LAM tumor cells, focusing on the role that the uterus plays in LAM. We propose that TSC-2 mutations in the uterine myometrium lead to LAM disease in the lungs.

LAM12 Hammes (PI) 2013-2016 0.5 months effort
LAM Foundation
"TSC-2 Knockout in the Uterus: A Mouse Model for Lymphangioleiomyomatosis"

This grant uses a novel mouse model for LAM to study how LAM grows and metastasizes. This model will also be used to look for novel treatments for LAM

056131-002 Hammes (PI) 2012-2013 0.5 months effort
Foundation for Reproductive Medicine
"Role of Androgens in Female Fertility"

In this grant we focus on androgen effects in the ovary, with a focus on folliculogenesis.

Past Research Support

R01 DK059913 Hammes (PI) 2002-2011
NIH/NIDDK
"Nongenomic Signaling by Steroids at the Cell Membrane"
This project investigates nongenomic steroid-mediated signaling in *Xenopus laevis* oocytes. Funding from this project has led to seminal discoveries concerning the role of androgens and the androgen receptor in mediating *Xenopus* oocyte maturation. Further, these studies have allowed us to characterize the role of cAMP and G proteins in mediating frog oocyte maturation. Finally, these studies has allowed us to examine nongenomic androgen signaling in mammalian ovaries as well as in prostate cancer.

LAM Foundation Pilot Award Hammes(PI) 1/15/2010 – 1/14/2011
LAM Foundation
"Uterine-Specific Knockout of TSC-2"
This project is aimed toward finding a mouse model for lymphangioleiomeiomatosis (LAM) and involves creating a mouse with the TSC-2 gene specifically mutated in the uterus.
I-1506 Hammes (PI) 2001-2008

Welch Foundation
"The Role of Cytochrome b_5 in CYP17-Mediated Steroid Metabolism"
This project studies progesterone metabolism in isolated Xenopus oocytes. Specifically, we study the enzyme CYP17, which we is expressed in oocytes and converts progesterone to androstenedione. We study CYP17 expression, as well as its role in the maturation response to steroids. We also examine interactions between CYP17 and its cofactor cytochrome b5.

FY05-78 Hammes (PI) 2005-2008
March if Dimes
"Androgen Signaling in the Mammalian Oocytes"
The aims of this project are to study nongenomic androgen effects in the mammalian ovary. Specifically, we will examine steroid-mediated oocyte maturation in mouse oocytes to determine the signals that are regulating this process. In addition, we will investigate the role of steroidogenesis in regulating steroid-triggered signaling.

R13DK082023-01 Hammes (PI) 2008
National Institutes of Health
"Extranuclear Steroid Receptors: Integration with Multiple Signaling Pathways"
This grant helped fund a FASEB Summer Research Conference on steroid signaling. The funds were used to bring in young investigators to the meeting. In fact, we were able to use this support to assist in travel for every trainee who submitted and abstract and presented his/her work.

R13DK089764-01 Hammes (PI) 2010-2012
National Institutes of Health
"The Biology of Integrated Nuclear and Extranuclear Steroid Signaling"
This grant helps fund a FASEB Summer Research Conference on steroid signaling. The funds are used to bring in young investigators and trainees to the meeting. In fact, we were able to use this support to assist in travel for every trainee who submitted and abstract and presented his/her work in 2010 and hope to do so again in 2012.