## BIOGRAPHICAL SKETCH

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NAME: David H. Abbott

eRA COMMONS USER NAME (credential, e.g., agency login): davidabbott1

POSITION TITLE: 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)* | Completion Date MM/YYYY | FIELD OF STUDY |
|---|---|---|---|
| University of Edinburgh, Scotland | B.Sc. | 1975 | Biological Sciences |
| University of Edinburgh, Scotland | Ph.D. | 1979 | Zoology |
| University of Wisconsin, Madison, Wisconsin | Postdoc | 1979-81 | Repro. Physiology |

### A. Personal Statement

I would be delighted to serve as a Co-Investigator in Dr. Kapur's proposal. I have been collaborating with Dr. Kapur and her colleague Dr. Patankar, over the last 8 years on a variety of ovarian-related projects, and have aided in the development of the current proposal and components of the supporting preliminary data. I bring to this effort over 30 years of experience employing rodent, primate and exotic species models of female reproductive endocrinology to determine pathophysiological mechanisms underlying a variety of reproductive health disorders commonly found in women. As a result of long-standing and highly productive collaborations, my lab developed a comprehensive nonhuman primate model for polycystic ovary syndrome (PCOS), the prenatally androgenized female rhesus monkey, that has been the vanguard for a multitude of animal and human studies aimed at determining developmental origins of this most common endocrinopathy in women. Our most recent work identifies metabolic dysfunction as a key initial abnormality in early developmental origins of PCOS-like traits and shows that the initial aberrations are not as anticipated at metabolomic and epigenetic, as well as endocrinological levels. Our rodent and marmoset monkey models reflect environmental inhibition of ovarian function that helped mechanistic understanding of diminished follicle development. My lab has developed a suite of expertise for utilizing the marmoset monkey as a model for ovarian-related research, including aspects of social regulation of ovulation and gonadal regulation of adrenocortical steroidogenic function. We have a well-established, characterized and tractable colony of ~300 marmosets at the Wisconsin National Primate Research Center (WNPRC) nicely adapted to biomedical procedures, and supported by animal and veterinary staff steeped in species-specific expertise. Together with Assay and Pathology Services, joint WNPRC and Institute of Clinical and Translational Research (CTSA-based) resources, the combined facilities and expertise will enable my lab to fully engage the proposed aims. I am more than willing to continue translating expertise gained from developing marmoset monkey models to this application and the systematic examination of contributions from the fallopian tube to ovarian cancer. As a Senior Scientist at the Wisconsin National Primate Research Center (WNPRC), I enable preferential access for Drs. Kapur and Patankar to WNPRC resources and to a network of my collaborators across campus, the US and internationally.

1. Dumesic DA, Patankar M, Barnett DK, Lesnick TG, Hutcherson BA, **Abbott DH**. 2009 Early prenatal androgenization results in diminished ovarian reserve in adult female rhesus monkeys. *Hum Reprod.* 24:3188-3195. (PMCID: PMC2777787)
2. Roti Roti EC, Leisman SK, **Abbott DH**, Salih SM. 2012. Acute Doxorubicin insult in the mouse ovary is cell- and follicle-type dependent. *PLoS ONE.* 7:e42293. (PMCID: PMC3410926)

3. Roti Roti EC, Ringelstetter AK, Kropp J, **Abbott DH**, Salih SM. 2014. Bortezomib prevents acute Doxorubicin ovarian insult and follicle demise, improving the fertility window and pup birth weight in mice. *PLoS ONE* 9:e108174. (PMCID: PMC4176970)
4. Salih SM, Ringelstetter AK, Elsarrag MZ, **Abbott DH**, Roti Roti EC. 2015. Dexrazoxane Abrogates Acute Doxorubicin Toxicity in Marmoset Ovary. *Biol Reprod.* 2015 92:73. (PMCID: PMC4367967)

## B. Positions and Honors

**Positions and Employment**

| | |
|---|---|
| 1981-1984 | Research Associate, Department of Anatomy, University of Cambridge, England. |
| 1984-1990 | Research Fellow and Unit Head, Institute of Zoology, MRC/AFRC Comparative Physiology Research Group, Zoological Society of London, England. |
| 1990- | University of Wisconsin - Madison, Wisconsin, USA. |
| 1990-1992 | Visiting Associate Professor, Department of Obstetrics and Gynecology and Wisconsin National Primate Research Center |
| 1990-1999 | Chair, Physiological Ethology Research Group, Wisconsin National Primate Research Center |
| 1991- | Faculty Member, Wisconsin National Primate Research Center |
| 1992-1998 | Associate Professor, Department of Obstetrics and Gynecology and Wisconsin National Primate Research Center |
| 1993- | Faculty Member, Endocrinology/Reproductive Physiology Training Program |
| 1998- | Professor, Department of Obstetrics and Gynecology and Wisconsin National Primate Research Center |

**Other Experience and Professional Memberships**

| | |
|---|---|
| 1995- | Editorial Board, Psychoneuroendocrinology |
| 2003-2008 | External Advisory Board, European Union Consortium investigating fetal programming of metabolic, endocrinological, behavioral and neural function |
| 2006- | Editorial Board, Neuroendocrinology |
| 2007- | Ad hoc Member, NIH IPOD, ICER and ad hoc Study Sections |
| 2008- | Editorial Board, Int. J of Obesity |
| 2009- | Board, AE-PCOS Society |
| 2014- | Annual Meeting Steering Committee, Endocrine Society |

**Honors**

| | |
|---|---|
| 1990 | Co-recipient, Laurent-Perrier Champagne Award for Wild Game Conservation |
| 2012-2015 | President-Elect AE-PCOS Society (2012-13), President (2013-14), Past President (2014-15) |

**C. Contribution to Science** (146 peer-reviewed publications, **h-index = 44**. In last 3 years, 5-8 publications/year; cited over 400 times/year).

**1.** I led several teams to undertake a systematic and comparative approach to determining neuroendocrine mechanisms mediating anovulation in socially subordinate females by studying, for the most part, two mammalian species that exhibit this trait to an extreme degree, the common marmoset (*Callithrix jacchus*), an arboreal, anthropoid primate from northeastern Brazil and the naked mole-rat (*Heterocephalus glaber*), a subterranean, caviomorph rodent from East Africa. We found surprising similarities in rank-related infertility among subordinate females of both species, even though these species are well separated by phylogeny, ecology and geography. We demonstrated that social status almost completely determines ovarian function: a single dominant female ovulates and produced offspring, while most, if not all, subordinates are anovulatory. We implicated inhibited hypothalamic secretion of gonadotropin releasing-hormone (GnRH) as the probable cause of hypogonadotropic anovulation from social and neuroendocrine manipulations of female subordinates. At least for naked mole-rats, we confirmed hypogonadotrpic anovulation as a naturally-occurring condition, from our field studies of free-living colonies in Kenya. We considered that dominance-driven harassment of subordinates exploits generalized inhibitory reproductive responses that most vertebrate species show to chronic physiological stress. This pivotal concept, however, was to undergo a drastic re-evaluation following my move to the University of Wisconsin-Madison. There results with marmosets consistently suggested involvement of specific, and perhaps novel, neuroendocrine mechanisms in social suppression of ovulation

and not generalized stress. Experimental behavioral studies demonstrated that a majority of female marmosets do not even contest for dominance status. In established social groups, overt harassment of subordinate female marmosets and elevations in circulating cortisol and adrenocorticotropin (ACTH) concentrations were not found. Circulating cortisol levels were, in fact, suppressed. Studies employing discrete ablations of olfactory epithelia and detailed chemical analyses of individual female scent suggested that associative learning of olfactory (and visual) cues from a subordinate female's specific dominant female provided psychological conditioning of the neural mechanisms inhibiting gonadotropin secretion. Direct hypothalamic measurement of GnRH, from development of a push-pull perfusion system, provided no evidence of reduced or disrupted GnRH release from the hypothalamus in anovulatory subordinates and, instead, suggested that disruption or inhibition of GnRH-induced gonadotropin secretion from the pituitary formed the basis of socially-induced hypogonadotropic anovulation. Taken together, these developments suggested that subordinate status in marmoset monkeys is a stable physiological and behavioral alternative to dominant status and does not engender physiological stress. Subordinate females are, however, exquisitely sensitive to changes in their social environment and can rapidly engage ovulatory function in the absence of higher-ranking females. Such results are consistent with current reproductive skew theory prediction that a large proportion of female marmosets (and naked mole-rats) opt to curtail reproduction until conditions favorable for reproduction prevail (dominance status and presence of subordinates to raise offspring).


**a.** **Abbott DH**, Hearn JP. 1978. Physical, hormonal and behavioural aspects of sexual development in the marmoset monkey, Callithrix jacchus. *J Reprod Fertil.* 53:155-66. **201 citations.**

**b.** **Abbott DH**. 1984. Behavioral and physiological suppression of fertility in subordinate marmoset monkeys. *Am. J. Primatol*. 6:169-186. **207 citations**.

**c.** **Abbott DH**, Keverne EB, Bercovitch FB, Shively CA, Mendoza SP, Saltzman W, Snowdon CT, Ziegler TE, Banjevic M, Garland T Jr. and Sapolsky RM. 2003. Are subordinates always stressed? A comparative analysis of rank differences in cortisol levels among primates. *Horm. Behav.* 43:67-82. **263 citations**.

**d.** Saltzman W, Digby L, **Abbott DH.** 2009 Reproductive skew in female common marmosets: What can proximate mechanisms tell us about ultimate causation? *Proc Biol Sci* 276:389-399. (PMCID: PMC2592602)


2. Between 1997 and 2005, together with my clinical colleague Daniel Dumesic, MD (Univeristy of California, Los Angeles, CA), I initiated the breakthrough experiments in nonhuman primates to identify fetal origins of polycystic ovary syndrome (PCOS), a familial infertility disorder affecting ~15% of women with accompanying 50-80% obesity, double the risk of type 2 diabetes and a tripled risk of gestational diabetes. The work was heralded as groundbreaking translational research, nationally and internationally, as exemplified by clinical research leaders in the field, Andrea Dunaif, MD (Northwestern University, Chicago, IL), Jeffrey Chang, MD (University of California, San Diego, CA), Richard Legro, MD (Penn State College of Medicine, Hershey, PA) and Stephen Franks, MD (Imperial College London, UK) stating "the insight that prenatal exposure to androgens can reproduce most of the features of the human syndrome in primates has led to a paradigm shift in concepts about the pathogenesis of the disorder" [1]. I have attracted multiple NIH grants in support of the collaborative, team-science approach needed to address this multi-faceted translational effort, including R01, R21 and U01 grants, as well as subprojects in P50 (Northwestern University), U54 (now P50s, University of Virginia and Oregon Health Sciences University) and P51 (Wisconsin National Primate Research Center) grants totaling $5.9 million in direct costs (3 are still active). We now focus on molecular mechanisms in our monkey models related to gene candidates for PCOS, including a population of naturally occurring hyperandrogenic female monkeys.

Citation: [1] *Polycystic Ovary Syndrome: Current Controversies from the Ovary to the Pancreas.* Editors: Dunaif A, Chang RJ, Franks S, Legro RS. Humana Press, Towata, NJ. 2008, Preface, p. vii.


a. Eisner JR, Dumesic DA, Kemnitz JW, **Abbott DH**. 2000. Timing of prenatal androgen excess determines differential impairments in insulin secretion and action in adult female rhesus monkeys. *J. Clin. Endocrinol. Metab.* 85: 1206-1210. **103 citations**

b. **Abbott DH**, Dumesic DA, Franks S. 2002. Developmental origin of polycystic ovary syndrome - a hypothesis. *J Endocrinol.* 174:1-5. **218 citations**

c. **Abbott DH,** Barnett DK, Bruns CM, Schramm RD, Dumesic DA. 2005. Androgen excess fetal programming of female reproduction: a developmental etiology for polycystic ovary syndrome? *Human Reproduction Update* 11:357-374. **198 citations**
d. Wood JR, Dumesic DA, **Abbott DH**, Strauss JF. 2007. Molecular abnormalities in oocytes from women with polycystic ovary syndrome revealed by microarray analysis. *J Clin. Endocrinol Metab* 92:705-713. **125 citations**
e. Keller E, Chazenbalk GD, Aguilera P, Madrigal V, Grogan T, Elashoff D, Dumesic DA, **Abbott DH.** 2014. Impaired preadipocyte differentiation into adipocytes in subcutaneous abdominal adipose of PCOS-like female rhesus monkeys. *Endocrinology.* 155:2696-703. (PMCID: PMC4060192)
f. Nicol LE, O'Brien TD, Dumesic DA, Grogan T, Tarantal AF, **Abbott DH**. 2014. Abnormal infant islet morphology precedes insulin resistance in PCOS-like monkeys. *PLoS One.* 9:e106527. (PMCID: PMC4160158)

**Complete List of Peer-Reviewed Published Work in PubMed:**
http://www.ncbi.nlm.nih.gov/pubmed/?term=abbott+dh

**D. Research Support**

**Ongoing Research Support**

P51 OD011106-53 (PI: MR Mailick) 07/02/13 – 04/30/17 1.20 calendar
NIH/OD Yr 53 Direct: $7,098,330
Wisconsin National Primate Research Center
Dr. Abbott forms part of the Behavioral Enrichment Unit.
Role: Co-I

P50 HD044405-12 (PI: A Dunaif) 07/01/13 – 06/30/17 1.80 calendar
NIH/NICHD $231,473
Genes, androgens and intrauterine environment in PCOS
In Subproject #3 in this competitive renewal, Dr. Abbott will be collaborating with Dr. Jon Levine (Subproject PI and Associate Director of the P50) to investigate the contribution of hypothalamic estrogen resistance in the pathogenesis of obesity, insulin resistance and PCOS in marmoset monkeys, a new nonhuman primate model for PCOS in humans.
Role: Co-I, Subproject III

P50 HD028934-21 (PI: JC Marshall) 04/01/14 – 03/31/19 1.50 calendar
*Converted from U54 to P50, Fall 2014*
NIH/NICHD $231,712
Clinical and Basic Studies in Polycystic Ovarian Syndrome (RFA-HD-14-017)
Project II: Hypothalamic Steroid Receptors and the Pathogenesis of PCOS
Studies related to this project will make use of viral vector-mediated gene silencing and a validated nonhuman primate model of androgen induced reproductive PCOS phenotypes to address these major gaps in our understanding of the mechanisms that mediate the pathogenesis of PCOS.
Role: Co-I, Project II

T32 HD041921-11 (PI: IM Bird) 05/01/14 – 04/30/19
NIH/NICHD $172,704
Endocrinology-Reproductive Physiology Training Grant
Dr. Abbott is one of the faculty mentors and he lecturers in ERP courses. He currently mentors two students (B. Hutcherson for MS [04-present, minority]; M. Kraynak for PhD [13-present]).
Role: Trainer

T32 DK077586-06A1 (PI: MJ MacDonald) 06/01/14 – 05/31/19
NIH/NIDDK $118,290
Childhood Diabetes Clinical & Molecular Research Training Program (CDCMRT)
Dr. Abbott is one of the research trainers. He has successfully mentored two fellows (L. Nicol, MD, 2007-2010; K. Henrichs, MD, 2011-2014) through to faculty appointments.

Role: Trainer

**Completed Research Support**

3P51 RR000167-48S1 (PI: M Cadwallader) 10/01/09-04/30/12
NIH/NCRR
Revision Award: Determining PCOS-like traits in macaques and newborn human infants.
This competitive supplement is to characterize naturally occurring PCOS in monkeys and a newborn biomarker for PCOS in humans. Dr. Abbott leads this effort.
Role: **Named Co-I**

No agency number available (PI: **DH Abbott**) 11/1/09-12/31/12
Viamet Pharmaceuticals
Identification of novel inhibitors of gonadal and adrenal steroid production in macaque monkeys.
The goals of this project are to identify mechanisms of action of various androgen biosynthesis inhibitors.
Role: PI