BIOGRAPHICAL SKETCH

Steering Committee, Senior Trainer

NAME: Abbott, David H.

eRA COMMONS USER NAME (credential, e.g., agency login): DAVIDABBOTT1

POSITION TITLE: Professor

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	COMPLETION DATE	FIELD OF STUDY
University of Edinburgh, Scotland	BSc	1975	Biological Sciences
University of Edinburgh, Scotland	PhD	1979	Zoology
University of Wisconsin, Madison, Wisconsin	Postdoc	1979-81	Repro. Physiology

A. PERSONAL STATEMENT

I would be delighted to serve as a Faculty Trainer in this iPEnd T32 postdoctoral Training Program application. I have over 40 years of experience in mentoring and training undergraduate, graduate and medical students, as well as medical residents, fellows and junior faculty. I have mentored two MD Fellows on the Pediatric Endocrinology/Diabetes T32 Training Program (PI: Allen) in the Department of Pediatrics (Drs. Nicol and Henrichs), both of whom went on to attain faculty positions at other institutions, two MD Fellows in the Department of Medicine (Drs. Bruns and Bandharu), and an African-American MD Fellow in the Department of Ob/Gyn (Dr. Salih), and I currently mentor two MS students, Ms. Hutcherson and Ms. Willging, on the NICHD-supported Endocrinology and Reproductive Physiology T32 Training Program (PI: Bird). I also sponsor ~12 research undergraduate students each year, and usually 1/year is supported by a competitive research award. I believe that mentoring of young investigators (pre- and post-doctoral) needs to be an integral part of any thriving biomedical research laboratory. Mentees benefit from in-depth experience gained from employing investigative techniques to develop animal models of female reproductive pathophysiology so as to elucidate pathogenic mechanisms underlying a variety of reproductive and metabolic health disorders commonly found in adolescent girls and women. In the last 20 years, as a result of a continuing, long-standing and highly productive collaboration with Drs. Dumesic (Ob/Gyn, UCLA) and Levine (Neuroscience, UW Madison; Director of the Wisconsin National Primate Research Center, WNPRC), my laboratory developed two nonhuman primate models for polycystic ovary syndrome (PCOS): 1) prenatally androgenized (PA) and 2) naturally occurring, hyperandrogenic female monkeys. PA monkeys became the vanguard for a multitude of animal and human studies aimed at determining developmental origins of this most common cardiometabolic endocrinopathy in girls and women. PA monkeys express a multitude of PCOS-like reproductive and metabolic pathophysiological traits prepubertally and in adulthood following gestational exposure to androgen excess and transient maternal hyperglycemia. Our most recent work identifies metabolic dysfunction as a key initial abnormality in early developmental origins of PCOS-like traits and shows that the aberrations in female infants are not as anticipated at metabolomic and epigenetic, as well as endocrinological levels. Our discovery of naturally occurring hyperandrogenic female monkeys that exhibit a combination of PCOS-like traits has not only reinforced this pathogenic understanding, but through whole genome sequencing of individual monkeys, and employing a well-annotated rhesus monkey genome, we are piecing together a genetic-epigenetic pathogenesis for PCOS that is eminently testable. I am more than willing to translate such metabolic and endocrinological insights gained from our PCOS-like monkey models to enable mentored research and career development in child health. Currently, as part of P50 and R01 NIH grants, I am collaborating with Dr. Levine, in silencing gene expression for estrogen receptor alpha (ERα) and for key steroidogenic enzymes, CYP17A1 and CYP19A1, in the ventromedial and arcuate nuclei of the hypothalamus in adult female rhesus monkeys using viral vector technology, to induce obesity and insulin resistance accompanying diminished energy expenditure (thermogenesis), as well as PCOS-like neuroendocrine and menstrual cycle dysfunction. The aims are to establish (1) ERα as the ER regulating metabolic, sexual and pituitary-ovarian function in female primates, including women (a parallel study is underway in adult female marmoset monkeys), and (2) altered hypothalamic production of testosterone and/or estradiol as key pathogenic component(s) contributing altered neuroendocrine control towards PCOS-like metabolic and reproductive dysfunction. We have a well-established, characterized and tractable colonies of

~300 marmosets and ~1200 rhesus macaques at 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 investigation of the cellular and molecular mechanisms that mediate the metabolic, neuroendocrine and behavioral actions of androgens and estrogens in the primate brain, as well as dysfunction in ovaries, pancreas and adipose depots and how such pathogenic function manifests during childhood.

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-	Senior Scientist, Wisconsin National Primate Research Center
1992-1998	Associate Professor, Department of Obstetrics and Gynecology and Wisconsin National Primate Research Center
1993-	Faculty Trainer, Endocrinology/Reproductive Physiology T32 Training Program
1998-	Professor, Department of Obstetrics and Gynecology and Wisconsin National Primate Research Center
2007-	Faculty Trainer, Childhood Diabetes Clinical & Molecular Research T32 Training Program

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
2009-2016	Board, AE-PCOS Society
2014-2017	Member, Annual Meeting Steering Committee, Endocrine Society

Honors

1990	Co-recipient, Laurent-Perrier Champagne Award for Wild Game Conservation
2012-2016	President-Elect AE-PCOS Society (2012-13), President (2013-14), Past President (2014-16)

C. CONTRIBUTIONS TO SCIENCE (trainees are underlined)

(169 peer-reviewed publications, **h-index=64**. In last 5 years, h-index=34, 5-6 publications/year; cited >700 times/year, >12,200 total).

Neural mechanisms converting low female social status into infertility. My lab, concurrently with that of Barry Keverne, ScD FRS FMedSci (University of Cambridge), was the first to publish on social dominance-mediated suppression of female primate reproduction. I then led several teams to undertake a systematic and comparative approaches 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

hypogonadotropic 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.
b. **Abbott DH**. 1984. Behavioral and physiological suppression of fertility in subordinate marmoset monkeys. *Am. J. Primatol*. 6:169-186.
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.
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. PMID: 18945663, PMCID: PMC2592602

Translational insight into pathogenic mechanisms underpinning polycystic ovary syndrome (PCOS) from basic scientist-clinician collaborative development of comprehensive nonhuman primate models. Between 1997 and 2005, together with my clinical colleague Daniel Dumesic, MD (University 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 identification of spontaneously occurring, hyperandrogenic female monkeys exhibiting PCOS-like traits with origins in developmental programming.

[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. **Abbott DH,** Dumesic DA, Eisner JR, Colman RJ, Kemnitz JW. 1998 Insights into the development of PCOS from studies of prenatally androgenized female rhesus monkeys. *Trends in Endocrinology and Metabolism 9:62-67.*

b. **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.
c. 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. PMID: 25207967, PMCID: PMC4160158
d. **Abbott DH,** Rayome BH, Dumesic DA, Lewis KC, Edwards AK, Wallen K, Wilson ME, Appt SE, Levine JE. 2017. Clustering of PCOS-Like Traits in Naturally Hyperandrogenic Female Rhesus Monkeys. *Hum Reprod.* 32: 923-936. PMID: 28333238, PMCID – Journal in Process

Causal mechanisms impairing female sexual function. Personally-distressing female sexual dysfunction has insidious negative effects in women's health, is prevalent (6-12% of women in their reproductive years), yet there is only one FDA-approved therapeutic, in contrast to >26 for male erectile dysfunction. There are two additional FDA-approved therapeutics related to sexual dysfunction in women, but both ameliorate only painful sexual intercourse with men. My lab published the only nonhuman primate preclinical study contributing to the single FDA-approved therapeutic for women targeting marked absence of desire or interest in sexual activity regardless of context. Diminished frequency (low social status) or quality (PCOS) of female sexual activity has been a constant component of my basic research interests in women's health. We were the first to demonstrate (1) aspects of female primate sexual behavior that remain susceptible to testosterone-mediated developmental programming in the neonatal period, (2) how GnRH I and GnRH II engage neural components of female primate sexual initiation, (3) serotonin's complex role in stimulating negative and positive aspects of female primate sociosexual behavior, and (4) combining MRI and PET neuroimaging in a nonhuman primate model to identify potential neural circuits mediating the behavioral effects of the only FDA-approved therapeutic for female sexual dysfunction, flibanserin.

a. **Abbott, DH.** 1984. Differentiation of sexual behavior in female marmoset monkeys. *Prog. Brain Res*. 61:349-358.
b. Barnett DK, Bunnell TM, Millar RP, **Abbott DH**. 2006. Gonadotropin-releasing hormone II stimulates female sexual behavior in marmoset monkeys. *Endocrinology* 147:615-623.
c. Aubert Y, Gustison ML, Gardner LA, Bohl MA, Lange JR, Allers KA, Sommer B, Datson NA, **Abbott DH**. 2012. Flibanserin and 8-OH-DPAT implicate serotonin in association between female marmoset monkey sexual behavior and changes in pair-bond quality. *J Sex Med.* 9:694-707. PMID: 22304661, PMCID: PMC5898967
d. Converse AK, Aubert Y, Allers KA, Sommer B, **Abbott DH**. 2015. Flibanserin-stimulated partner grooming reflects brain metabolism changes in female marmosets. *J Sex Med.* 12:2256-2266. PMID: 26635207, PMCID: PMC5681869

My Bibliography at NCBI:
https://www.ncbi.nlm.nih.gov/sites/myncbi/david.abbott.1/bibliography/50214987/public/?sort=date&direction=ascending

D. ADDITIONAL INFORMATION: RESEARCH SUPPORT AND/OR SCHOLASTIC PERFORMANCE
Ongoing Funding

R01 DK121559-01A (Levine, PI) 07/01/19 – 06/30/23[4]
NIH/NIDDK
Neurosteroid Regulation of Adiposity, Glucose Homeostasis and Energy Expenditure in Primates.
Dr. Abbott is Co-I, and co-responsible with Dr. Levine for day-to-day management of proposed research, especially for neurosurgical approaches, phenotypic testing and analyses.
[4]Perfect score in Study Section, Council approval for funding given May, 2019.

P51 OD011106-53 (Mailick, PI) 05/01/17 – 04/30/22
NIH/OD
Wisconsin National Primate Research Center
Dr. Abbott is part of the Behavioral Services Unit improving and refining social environments of laboratory housed nonhuman primates. Role: Co-Investigator

P50 HD044405 (Dunaif, PI) 07/01/13 – 06/30/18[1]
NIH/NICHD
Specialized Center of Research (SCOR): Genes, androgens and intrauterine environment in PCOS
In Subproject #3, Dr. Abbott is 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-Investigator, Subproject III [1]*2-years of bridge funding approved until 06/30/19.*

P50 HD028934 (Marshall, PI) 04/01/14 – 03/31/19[2]
NIH/NICHD
National Center for Translational Research in Reproduction and Infertility (NCTRI): Clinical and Basic Studies in Polycystic Ovarian Syndrome
Project II: Hypothalamic Steroid Receptors and the Pathogenesis of PCOS
Studies related to this project make use of viral vector-mediated gene silencing and a validated nonhuman primate model of androgen induced reproductive PCOS phenotypes to address major gaps in our understanding of the mechanisms that mediate the pathogenesis of PCOS.
Role: Co-Investigator, Project II [2]*1-year of bridge funding approved until 03/31/20.*

P50 HD071836 (Stouffer, PI) 09/01/17 – 08/31/18[3]
NIH/NICHD
National Center for Translational Research in Reproduction and Infertility (NCTRI): Androgen Excess as a Mechanism for Adipogenic Dysfunction in PCOS Women
In Subproject #4, Dr. Abbott is ensuring completion of the urinary hormone analyses, including determination and interpretation of urinary pregnanediol glucuronide values. Twenty-four samples will be analyzed from each of 36 patients. Sample collection frequency was designed to confirm presence or absence of ovulatory menstrual cycles in study participants and to provide an estimate of menstrual cycle duration.
Role: Co-Investigator, Project 4. [3]*1-year no cost extension until 08/31/19.*

T32 HD041921 (Bird, PI) 05/01/19 – 04/30/24
NIH/NICHD
Endocrinology-Reproductive Physiology Training Grant
Dr. Abbott is one of the faculty mentors and lecturers in ERP courses. He currently mentors two MS students (B. Hutcherson ['04-present, minority]; M. Willging ['19-present]).
Role: Faculty Trainer

T32 DK077586 (Allen, PI) 06/01/14 – 05/31/19
NIH/NIDDK
Childhood Diabetes Clinical & Molecular Research Training Program (CDCMRT)
Dr. Abbott is one of the research mentors. He has successfully mentored two fellows (L. Nicol, MD, 2007-2010; K. Henrichs, MD, 2011-2014) through to faculty appointments. *Revised competitive renewal currently in submission.*
Role: Faculty Preceptor

Recently Completed Funding

R21 HD084992 (Levine, PI) 01/01/16 – 12/31/17
NIH/NICHD
Neuroestrogen Restraint of GnRH in Juvenile Female Primates
Dr. Abbott is Co-I responsible for MRI-guided neurosurgical infusion of gene silencing viral vector specific for aromatase and neuroendocrine assessment of the monkeys.