BIOGRAPHICAL SKETCH

NAME: **Burks, Deborah Jane** eRA COMMONS USER NAME: DBURKS	POSITION TITLE: Senior Group Leader, Prince Felipe Research Center, Valencia, Spain
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EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
David Lipscomb College, Nashville, TN	B.S.	1982	Biology
Vanderbilt University, Nashville, TN	Ph.D.	1990	Pharmacology
Duke University, Durham, NC	Postdoctoral Training	1990-1994	Cell Biology
Joslin Diabetes Center, Harvard University Medical School, Boston, MA	Postdoctoral Training	1995-1999	Insulin Signaling in Metabolic Diseases

A. PERSONAL STATEMENT

For the last 20 years, my research has focused on how defects in insulin/IGF-I receptor signal transduction underlie diabetes and neurodegeneration. When evidence emerged very recently to link Zika infection with microcephaly in newborns, we began to relate this developmental impairment to the phenotype caused by loss of insulin receptor substrate 2 (IRS2). Deletion of *Irs2* in mice causes progression to diabetes in adults, but independently of this, it impairs embryonic brain development: Irs2-deficient mice are born with microcephaly. During my postdoctoral training at the Joslin Diabetes Center, I contributed to discoveries that fundamentally changed the perception of the role of insulin signaling in human metabolic diseases. These observations regarding IRS2 had such impact because they were related to the development and function of physiological systems where insulin action was not yet fully appreciated: pancreatic beta cell biology, gonadal function, retinal photoreceptor survival, and embryonic brain development. As senior group leader at the Prince Felipe (CIPF) Center in Spain, my research interests have expanded to include IRS2 function in the maintenance and differentiation of stem cells. As PI of a series of Spanish national grants, I have defined IRS2 signals as critical regulators of hippocampus-dependent learning and memory. Our observations regarding the specific requirement for IRS2 in the proliferation of neuronal progenitors and neurite sprouting form the groundwork for the current proposal. I have served as co-PI of several European Union consortium projects which developed tools for stem-cell research. As a result of these collaborative European grants, I value frequent communication between project partners as key to the completion of research aims. Although the current application is oriented towards the new field of Zika-mediated microcephaly, the central hypothesis is directly related to my prior work. Our laboratory has the technical experience and tools to assess whether Zika infection alters insulin-mediated signaling. I believe my expertise, multi-disciplinary training, and project leadership skills are assets that position us to elucidate the role of insulin signaling in Zika-associated pathologies. This innovative project requires a multi-PI, cross-discipline strategy.

1. Withers DJ*, Burks DJ*, Towery HH, Altamuro SL, Flint CL, White MF. *IRS-2 coordinates IGF-I receptor-mediated beta cell development and peripheral insulin signaling.* Nature Genetics. 1999; 23: 35-40. *co-first authors.

2. Burks DJ, Font de Mora J, Schubert M, Withers DJ, Myers MJ, Towery H, Altamuro SA, Flint CA, White MF. *IRS-2 pathways integrate female reproduction and energy homeostasis*. Nature. 2000; 407(6802):377-82.
3. Schubert M*, Brazil DP*, Burks DJ*, Kushner J. A., Ye J., Flint C., Farhang-Fallah J., Dikkes P., Warot X. M., Rio C., Corfas G, White M. *Insulin receptor substrate-2 deficiency impairs brain growth and promotes tau phosphorylation.* J of Neuroscience. 2003; 23(18):7084-7092.
4. Martín E, Sánchez-Perez A, Trejo JL, Cano-Jaimez M, Pons S, Menes L, White MF, Burks DJ. *Insulin Receptor Substrate-2 is Required for NMDA-Receptor Dependent Long-term Potentiation*. 2012. Cereb Cortex. 22(8):1717-27.

B. POSITIONS

Positions

1999-2001	Research Assistant Professor, Joslin Diabetes Center, Harvard University, Boston, MA
2000-2001	Invited Professor, Department of Anatomy, University of Salamanca, Salamanca, Spain
2001-2004	Junior Investigator, Ramon y Cajal Program, Neuroscience Institute, University of Salamanca, Salamanca, Spain
2004-present	Principal Investigator, Molecular Basis of Disease Program, Centro de Investigación Principe Felipe, Valencia, Spain
2013-2014	Visiting Professor, McWhorter School of Pharmacy, Birmingham, Alabama

Professional Memberships

2006-	Spanish Society for Biochemistry and Molecular Biology
2008-	American Association of Diabetes
2010-	Spanish Society of Diabetes
2012-	European Association of Diabetes

C. CONTRIBUTIONS TO SCIENCE

Throughout the distinct stages of my scientific career, my interests have focused on the molecular basis of human diseases, particularly on the role of receptor signal transduction pathways as they represent optimal targets for therapeutic strategies. I would like to highlight my contributions to four key areas of insulin signaling that are relevant to our current application on Zika virus complications. Understanding how the ZIKV virus subverts cellular machinery in different types of cells is critical to the design and development of effective pharmacological interventions in infected patients.

C1) Defined structure-function relationships for insulin receptor substrate (IRS) protein domains in insulin signaling.

IRS1 and IRS2 are key targets of the insulin receptor tyrosine kinase. Tissues from insulin-resistant and diabetic humans exhibit defects in IRS-dependent signaling, implicating their dysregulation in metabolic diseases. Tyrosine phosphorylation of IRS by insulin/IGF receptors generates binding sites for SH2-domain proteins, including the regulatory subunits of PI3-Kinase which determine AKT activation. IRS1 and IRS2 are large proteins that contain highly similar pleckstrin homology (PH) and phosphotyrosine-binding (PTB) domains. My postdoctoral work (Dr. Morris White, Joslin Diabetes Center) and early career contributions helped define the functions of the PH and PTB domains of IRS proteins: both are required for efficient coupling to the activated receptors. These studies contributed to our recognition that IRS1 and IRS2 have distinct signaling capacities. My experience in protein-protein interactions and my knowledge of the structural/regional features within the IRS proteins are strong assets for the current application which aims to test whether Zika-host interactions impair IRS2 signals in neuronal cells. Recently, Zika domains NS4A and NS4B were demonstrated to impair PI3-kinase/AKT activity (Liang et al., 2016). One possibility is that these domains interact directly with activated IRS2 within

cells and target this molecule for degradation. If true, this hypothesis would provide one explanation for Zika-mediated microcephaly since loss of IRS2 in mice produces microcephaly in mice and impairs neuronal progenitor proliferation *in vitro*.

--Burks DJ, Pons S, Towery H, Smith-Hall J, Myers MG, Jr., Yenush L, White MF. *Heterologous PH domains do not mediate coupling of IRS-1 to the insulin receptor.* J Biol Chem 1997; 272; 27716-27721.
--Burks DJ, Wang J, Towery H, Ishibashi O, Lowe D, Riedel H, White MF. *IRS pleckstrin homology domains bind to acidic motifs in proteins.* J Biol Chem 1998; 273: 31061-31067.
--Kido Y, Burks DJ, Withers D, Bruning JC, Kahn CR, White MF, Accili D. *Tissue-specific insulin resistance in mice with mutations in the insulin receptor, IRS-1, and IRS-2.* J. Clin. Invest. 2000; 105: 199-205.
--Garcia-Barrado MJ, Iglesias-Osma MC, Sanz S, Viedma-Moreno V, Pastor MF, Prieto-Martin A, Carretero J, Moratinos J, and Burks DJ. *Differential Sensitivity To Adrenergic Stimulation Underlies The Sexual Dimorphism In The Development Of Diabetes Caused By Irs-2 Deficiency*. Biochem Pharmacol. 2011. 81(2):279-88.

C2) Demonstrated the specific requirement for IRS2-mediated signaling in endocrine pancreas development and hypothalamic regulation of body weight and reproduction. The discovery of IRS2 revealed a family of signaling scaffold proteins. I began my postdoctoral training in Dr. White's lab (Joslin Diabetes Center) around this time and was fascinated by the question of potential functional differences between IRS1 and IRS2, given that they are highly similar and ubiquitously expressed. To define the functional differences, we developed knockout mice of the different IRS proteins and obtained surprising results. Mice deficient for IRS1 were reduced in overall size but displayed improved metabolism and longevity. In sharp contrast, IRS2 mice developed progressive diabetes due to impaired development and expansion of pancreatic beta cells. This was a profound confirmation of the functional differences between IRS1 and IRS2 and moreover, was the first indication that these insulin signaling molecules were key regulators of developmental pathways. Subsequently, I made other novel observations that expanded the importance of IRS signaling. Irs2-deficient females are infertile and develop moderate obesity. These studies generated a paradigm shift in the field as it linked IRS2 signals to hypothalamic regulation of reproduction and appetite regulation which were novel concepts in the early 2000s. Subsequent studies have demonstrated that IRS2 is not only required for female reproduction but also for testicular development: Irs2-deficient male gonads are reduced by 30% in size. Interestingly, recent studies have linked Zika to testicular damage (Govero et al, 2016). Publications generated from these studies are highly cited in the field of diabetes and metabolism. These contributions are very relevant to the current application as they demonstrate expertise in IRS animal models and multi-disciplinary training.
--Withers DJ*, Burks DJ*, Towery HH, Altamuro SL, Flint CL, White MF. *IRS-2 coordinates IGF-I receptor-mediated beta cell development and peripheral insulin signaling*. Nature Genetics 1999; 23: 35-40.
--Burks DJ, Font de Mora J, Schubert M, Withers DJ, Myers MJ, Towery H, Altamuro SA, Flint CA, White MF. *IRS-2 pathways integrate female reproduction and energy homeostasis.* Nature. 2000; 407(6802):377-82.
--Burks DJ, White MF. *The role of IRS proteins in beta cell physiology.* Diabetes. 2001; 456: 120-125.
--Hennige AM, Burks DJ, Ozcan U., Kulkarni R. N., Ye J., Park S., Schubert M., Fisher T. L., Dow M. A., Leshan R., Zakira M., Mossa-Basha M., White MF. *Up-Regulation of insulin receptor substrate-2 in pancreatic beta cells prevents diabetes.* J of Clin Invest. 2003;112:1521-1532.
-- Griffeth R, Carretero J, Burks DJ. *IRS2 is Essential for testicular development.* PLOS One. 2013; 8(5): e62103.

C3) Identified a unique role for IRS2 in brain development and C4) in the proliferation and differentiation of neuronal stem cells. My contributions in this area are directly related to the present

application and form the basis of the hypothesis regarding the potential relationship between Zika-induced microcephaly and impaired IRS2 signaling. Genetic ablation of *Irs2* in mice causes progression to diabetes in adults, but independently of this phenotype, it impairs embryonic brain development. Irs2-deficient mice are born with a 40% reduction in brain size. The small brain phenotype can be detected as early as day embryonic day 14 and reflects a proportionate, global reduction in brain size. I also contributed to the discovery that IRS2 signals are essential for the development and function of retinal photoreceptors. Studies from my group have demonstrated that adult Irs2 null mice display defects in learning and memory and our published studies implicate IRS2 signaling in mechanisms of synaptic plasticity. More recently, our efforts have focused on characterization of IRS2's role in neuronal progenitor cells. Although it stimulates growth of different types of cells, the effects of insulin on adult neural stem cells have not been well characterized. Neurospheres isolated from brains of adult Irs2-deficient mice display significantly reduced expansion**,** reduced diameter, and accelerated exhaustion compared to cultures derived from control mice (see Preliminary Results for complete description of this submitted paper).

--Bruning JC, Gautam D, Burks DJ, Schubert M, Gillette J, Orban PC, Krone W, Muller-Weiland D, Kahn CR. Role of the brain insulin receptor in control of body weight and reproduction. Science. 2000; 289 (5487):2122-5.

--Schubert M*, Brazil DP*, Burks DJ*, Kushner J. A., Ye J., Flint C., Farhang-Fallah J., Dikkes P., Warot X. M., Rio C., Corfas G, White M. Insulin receptor substrate-2 deficiency impairs brain growth and promotes tau phosphorylation. J Neuroscience. 2003; 23(18):7084-7092. Co-first authors.

--Trejo JL, Carro E, and Burks DJ. *Experimental Model Systems for Understanding the Role of IGF-I and Its Receptor During Embryonic Development.* Adv Exp Med Biol 2005; 567:27-53.

--Yi X, Schubert M, Peachey NS, Suzuma K, Burks DJ, Kushner JA, Suzuma I, Cahill C, Flint, CL, Dow MA, King GL, and White MF. Insulin receptor substrate-2 is essential for maturation and survival of photoreceptor cells. J Neuroscience. 2005; 25:1240-48.

--Martín E, Sánchez-Perez A, Trejo JL, Cano-Jaimez M, Pons S, Menes L, White MF, Burks DJ. *Insulin Receptor Substrate-2 is Required for NMDA-Receptor Dependent Long-term Potentiation*. 2012. Cereb Cortex. 22(8):1717-27.

--Chirivella L, Cano-Jaimez M, Pérez-Sánchez F, Herraez L, Carretero J, Fariñas I, Burks DJ, Kirstein M. *IRS2 signalling is required for the development of a subset of sensory spinal neurons.* Eur J Neurosci. 2012. 35(3):341-52.

--Bertero A, Madrigal P, Galli A, Hubner NC, Moreno I, Burks D, Brown S, Pedersen RA, Gaffney D, Mendjan S, Pauklin S, Vallier L. *Activin/Nodal signaling and NANOG orchestrate human embryonic stem cell fate decisions by controlling the H3K4me3 chromatin mark.* Genes Dev. 2015 Apr 1;29(7):702-17.

D. RESEARCH SUPPORT, Last Three Years

Ongoing Grants: National and International Support

Project Title: The Role of IRS2 Signals in the Endocrine Pancreas.
Funding Source: National Diabetes Network (CIBERDEM), National Health Institute Carlos III
Role: PI
Funding Period: 2012-ongoing, renewable.

Project Title: Development and Testing of Anti-diabetic Drugs in the IRS2 Mouse Model.
Role: PI
Funding Source: Biotech Company
Funding Period: 2016-2018

Project Title: European Consortium for the Early Treatment of Diabetic Retinopathy: Neurodegeneration as an early event in the Complications of Diabetes.
Role: Co-PI
Funding Agency: European Union, Seventh Framework Programme
Funding period: 2011-2017

Completed Grants

Project Title: The Regulation of Progenitor Cells by Insulin/IRS2 Signaling: Implications for Metabolic Diseases
Role: PI
Funding Agency: Spanish Science Ministry (MINECO), Grant Reference SAF201/28331
Funding period: 2013-2016

Project: INNOVALIV: Innovative Strategies to generate Human Hepatocytes for Cell therapy
Role: Co-PI
Funding Agency: Seventh Framework Programme, European Union
2011-2015

Project: Analysis of IRS2 pathways as a link between diabetes and neurodegenerative diseases
Role: PI
Funding Agency: Spanish Science Ministry (MINECO), Grant Reference SAF2008/00011
2009-2012