BIOGRAPHICAL SKETCH

NAME	POSITION TITLE
Dong, H. Henry	**Associate Professor**
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EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	YEAR(s)	FIELD OF STUDY
Uppsala University, Uppsala, Sweden	Ph.D.	1995	Molecular & Cell Biology
Yale University, New Haven, Connecticut	Postdoctoral	1998	Molecular, Cellular and Developmental Biology

A. Personal Statement:

My research goal is to dissect the insulin-signaling cascade for better understanding the molecular basis that links insulin resistance to metabolic disease in obesity and diabetes. I have been focusing on studies of FoxO1, a key transcription factor that mediates insulin action on the expression of genes involved in diverse functions including cell metabolism, growth, proliferation, differentiation, oxidative stress and aging. In this project, I focus on studies of FoxO1 function in β-cell compensation, an adaptive mechanism of β-cells for overcoming insulin resistance in order to maintain normal blood sugar homeostasis in obese subjects. Our central hypothesis is that FoxO1 integrates insulin signaling to target genes in β-cells, contributing to β-cell compensation for insulin resistance and oxidative stress. I conceived this concept from our studies of FoxO1 in β-cell function, showing that FoxO1 gain-of-function in β-cells are associated with increased β-cell compensation for fat-induced insulin resistance as well as for chemical-elicited oxidative stress, suggesting that FoxO1 is a positive regulator of β-cell compensation. In this project, we propose delineate FoxO1 signaling in five distinct pathways in governing: **1)** β-cell mass, **2)** insulin synthesis/secretion, **3)** glucose sensing, **4)** oxidative stress, and **5)** β-cell survival/apoptosis. Our objective is to understand the mechanisms by which FoxO1 promotes β-cell compensation for insulin resistance and oxidative stress. This project dwells on the PI's long-standing interest and expertise in FoxO1 signaling, availability of relevant animal models and adenoviral vectors encoding FoxO1, or its constitutively active allele, or its specific siRNA for achieving FoxO1 gain- vs. loss-of-function in primary islets.

B. Positions and Honors:

Positions and Employment

2009-present: Associate Professor with Tenure, Department of Pediatrics, Children's Hospital of Pittsburgh, and Department of Pathology, University of Pittsburgh School of Medicine, Pittsburgh, PA.
2004-2009: Assistant professor at Department of Pediatrics, Children's Hospital of Pittsburgh, University of Pittsburgh School of Medicine, Pittsburgh, PA
2001-2004: Assistant Professor at Department of Gene & Cell Medicine. Mount Sinai School of Medicine, New York University, New York, NY.
2001-2004: Assistant Professor at Division of Diabetes and Aging, Department of Geriatrics, Mount Sinai School of Medicine, New York University, New York, NY.
2000-2003: Metabolism & Blood Chemistry Core Director of the JDRF center at Mount Sinai School of Medicine, New York University, New York, NY.
1998-2001: Instructor at Institute for Gene Therapy & Molecular Medicine, Mount Sinai School of Medicine, New York University. New York, NY.

Awards and Honors:

2006-2010 American Diabetes Career Development Award
2004-2006 Beta-Cell Replacement Award from American Diabetes Association
2002-2003 American Diabetes Association Travel Award
1997-1998 Postdoctoral fellowship from Howard Hughes Medical Institute, Yale University, New Haven
1995-1997 Postdoctoral fellowship from Yale University, New Haven, CT.

1993-1995 Predoctoral stipend from Swedish Cancer Society, Stockholm, Sweden
1989-1993 Predoctoral fellowship from National Science Foundation, Stockholm, Sweden

Committees and study sections served:

NIH NIDDK, Cellular Aspects of Diabetes and Obesity (CADO) Study Section 2014, Ad hoc member
NIH NIDDK, Cellular Aspects of Diabetes and Obesity (CADO) Study Section 2013, Ad hoc member
NIH NIDDK, Diabetes, Endo & Metab Disease B Subcommittee (DDK-B) Study Section 2013
NIH NIDDK, Endocrin, Metab, Nutrition & Reproductive Science (EMNR) Study Section 2013
NIH NIDDK, Cellular Aspects of Diabetes and Obesity (CADO) Study Section 2012, Ad hoc member
NIH NIDDK, Integrative Physiology of Obesity & Diabetes Study Section (IPOD) 2011, Ad hoc member
NIH NIDDK, Cellular Aspects of Diabetes and Obesity (CADO) Study Section 2011, Ad hoc member
AHA, Ad hoc member of American Heart Association Lipid Panel Grant Study Section 2010
AAD Abstract reviewer of the 66th, 67th, 68th and 69th Scientific Session of American Diabetes Association.
ADA Ad hoc member of ADA grant study section 2007-2008
Study-section member of ADA-Takeda Pharmaceuticals Beta Cell Award, 2007
Chairperson, Section of FoxOs in Insulin Action, 66th ADA Scientific Session, 2006, Washington DC
Ad hoc member of ADA grant study section 2005-2006
Ad hoc member of JDRF grant study section 2005-2006
Pittsburgh University Obesity & Nutrition Research Center (ONRC) Review Panel
Canadian Alberta Heritage Foundation for Medical Research Review Panel 2006-2007

Membership in Academics:

2007-present: Member of American Heart Association
1999- present: Member of American Diabetes Association
2003- present: Invited member of New York Academy of Sciences
2000- 2002 Member of American Society of Gene Therapy
2000- 2003 Member of IACUC (Institutional Animal Care and Use Committee)

Extramural Responsibilities Served:

Reviewer of J. Clinical Investigation
Reviewer of Cell Metabolism
Reviewer member of Diabetes
Reviewer member of Diabetologia
Reviewer member of Diabetes Care
Reviewer member of Endocrinology
Reviewer of Trends in Endocrinology & Metabolism
Reviewer of FASEB J
Reviewer member of Atherosclerosis, Thrombosis and Vascular Biology
Reviewer member of Molecular Cellular Biology
Reviewer of Am. J. Transplantation
Reviewer of J. Applied Physiology
Reviewer member of Metabolism
Reviewer member of Medical Science Monitor
Reviewer member of Journal of Mol. Medicine
Reviewer member of Transplant International
Reviewer of European Journal of Pharmacology
Reviewer of Proteomics
Reviewer of Metabolic Syndrome and Related Disorders

C. Selected peer-reviewed publications (*out of 53 peer-reviewed articles*).

Most relevant to the current application:

1. Kim DH, Perdomo G, Zhang T, Slusher S, Phillips BE, Fan Y, Giannoukakis N, Gramignoli R, Strom S, Ringquist S and **Dong HH**. FoxO6 integrates insulin signaling to gluconeogenesis in the liver. ***Diabetes.*** 60:2763-2774. 2011.
2. Kamagate A, Kim DH, Zhang T, Slusher S, Gramignoli R, Strom SC, Bertera S, Ringquist S, **Dong HH.** Forkhead box O1 links hepatic insulin action to endoplasmic reticulum stress. ***Endocrinology***. 2010

151:3521-3535. PMID: 20501674. 2010

3. Su D, Coudriet GM, Kim DH, Lu Y, Perdomo G, Qu S, Slusher S, Tse HM, Piganelli J, Giannoukakis N, Zhang J, **Dong HH**. FoxO1 links insulin resistance to proinflammatory cytokine IL-1β production in macrophages. ***Diabetes*****.** 58: 2624-33, 2009.
4. Kamagate A., Qu S., Perdomo G., Kim DH., Slusher S. Meseck, M and **Dong HH**. FoxO1 mediates insulin-dependent regulation of hepatic VLDL production. ***J. Clin. Invest.*** 118:2347-2364. 2008.
5. Altomonte, J., Cong, L., Richter, A., Harbaran, S., Xu, J., Nakae, J., Meseck, M., and **Dong HH.** Foxo1 mediates insulin action on apoC-III and triglyceride metabolism. ***J. Clin. Invest.*** 114:1493-1503. 2004

Additional recent publications of importance to the field:

1. Kim DH, Zhang T, Lee S, Calabuig-Navarro V, Yamauchi J, Piccirillo A, Fan Y, Uppala R, Goetzman E, **Dong HH.** FoxO6 Integrates Insulin Signaling with MTP for Regulating VLDL Production in the Liver. ***Endocrinology.*** 2014 Jan 17:en20131856. [Epub ahead of print]. 2014.
2. Xiao G, Zhang T, Yu S, Lee S, Calabuig-Navarro V, Yamauchi J, Ringquist S, **Dong HH.** ATF4 deficiency protects against high fructose-induced hypertriglyceridemia in mice. ***J Biol Chem.*** 2013 Jul 25. [Epub ahead of print]. PMID: 23888053. 2013.
3. Cifareli V, Lee S, Kim DK, Zhang T, Kamgate A, Slusher S, Bertera S, Luppi P, Trucco T and **Dong HH,** FoxO1 mediates the autocrine effect of endothelin-1 on endothelial cell survival. ***Mol. Endocrinology***. 152:3521-3535. 2012.
4. Yang S, Xu H, Yu S, Cao H, Fan J, Ge C, Fransceschi RT, **Dong HH**, Xiao G. Foxo1 mediates insulin-like growth factor 1 (IGF1)/insulin regulation of osteocalcin expression by antagonizing Runx2 in osteoblasts. ***J Biol Chem.*** 286:19149-58. 2011.
5. Perdomo G, Kim DH, Zhang T, Qu S, Thomas EA, Toledo FG, Slusher S, Fan Y, Kelley DE, **Dong HH**. A role of apolipoprotein D in triglyceride metabolism. ***J Lipid Res***. 51:1298-1311. 2010.
6. Al-Masri M, Krishnamurthy M, Li J, Fellows GF, **Dong HH**, Goodyer CG, Wang R. Effect of forkhead box O1 (FOXO1) on beta cell development in the human fetal pancreas. ***Diabetologia*****.** 53:699-711 2010.
7. Qu S., Su D., Altomonte J., Kamagate A., He J., Perdomo G., Tse T., Jiang Y., and **Dong HH.** PPAR-α mediates the hypolipidemic action of fibrates by antagonizing FoxO1. ***Am J Physiol Endocrin & Metab*****.** 292:E421-434. 2007.
8. Qu S., Perdomo G., Su D., D'Souza FM, Shachter NS and **Dong HH.** Effects of apoA-V on HDL and VLDL metabolism in APOC3 transgenic mice. ***J Lipid Res***. 48:1476-1487. 2007.
9. Su D., Zhang N., He J., Qu S., Slusher S., Bottino R., Bertera S., Bromberg J. and **Dong HH.** Angiopoietin-1 production in islets improves islet engraftment and protects islets from cytokine-induced apoptosis. ***Diabetes*****.** Vol. 56:2274-83. 2007.
10. Qu S., Altomonte J., Perdomo G., He J., Fan Y., Kamagate A., Meseck M. and **Dong HH.** Aberrant FoxO1 function is associated with impaired hepatic metabolism. ***Endocrinology*****.** 147:5641-5652. 2006.
11. Zhang N., Su D, Qu S, Tse T, Bottino R, Balamurugan AN, Xu J, Bromberg JS and **Dong HH.** Sirolimus is associated with reduced islet engraftment and impaired β-cell function. ***Diabetes*** 55:2429-2436. 2006.
12. Zhang, N., Richter, A., Suriawinata, J., Harbaran, S., Altomonte, J., Cong, L., Zhang, H., Song, K., Meseck, M., Bromberg, J., and **Dong, H.** (2004). Elevated VEGF production in islets improves islet graft vascularization. ***Diabetes***. 53:963-970.
13. Altomonte, J., Richter, A., Harbaran, S., Nakae, J., Meseck, M., Accili, D. and **Dong H.** (2003). Inhibition of Foxo1 function is associated with improved fasting glycemia in diabetic mice. ***Am. J. Physiol. Endocrin & Metab.*** 285. E718-728.
14. Puigserver P, Rhee J, Donovan J, Yoon J.C., walkey C.J., Oriente F, Kitamura Y., Altomonte J., **Dong H**., Accili D. and Spiegelman B.M. (2003). Insulin-dependent hepatic gluconeogenesis through FoxO1/PGC1α interaction. ***Nature*****.** 423, 550-555.

D. Research Support

Active grants:

FoxO6 in Glucose Metabolism
R01 NIDDK, 2010-2014

NIH-NIDDK DK087764
Principal investigator: **H. Henry Dong**
This project is to investigate the role of forkhead box O6 transcription factor in glucose metabolism in liver.

FoxO1 in Beta-Cell Compensation
R01 NIDDK, 2014-2017
NIH-NIDDK DK098437
Principal investigator: **H. Henry Dong**
This project is to characterize genetic factor(s) that are responsible for coupling beta-cell compensation with nutrient signals to understand the underlying mechanism of beta-cell failure in diabetes.

Accomplished grants:

Foxo1 in Triglyceride Metabolism
R01 DK066301-01A3,
Year 2006-2011
NIH-NIDDK
Principal investigator: **H. Henry Dong**
This project is to define the role of FoxO1 in glucose and lipid metabolism in health and disease in multiple animal models.