BIOGRAPHICAL SKETCH

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NAME: Magnuson, Mark A.

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

POSITION TITLE: Louise B. McGavock Professor of Molecular Physiology Biophysics, Medicine, and Cell and Developmental Biology

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
Luther College, Decorah, IA	B.A.	1975	Biology/Chemistry
University of Iowa, Iowa City, IA	M.D.	1979	Medicine
University of Rochester, Rochester, NY	Resident	1979-1982	Internal Medicine
NIADDK, NIH, Bethesda, MD	Staff Fellow	1982-1985	Molecular Biology
Vanderbilt University School of Medicine, Nashville, TN	Clinical Fellow Senior Fellow	1985-1987 1985-1987	Clinical Endocrinology Molecular Endocrinology

A. Personal Statement

My career has long been focused on genes important for glucose homeostasis. While my early career was focused on the cloning of genes important for glucose metabolism, including *Gck*, my scientific reputation stems largely from our derivation of genetically-altered mouse models, which for years involved the use of Cre/LoxP. The mice we derived were invaluable for determining the cell-specific functions of G*ck, Pck1, PPARγ, Abcc8 (*sulfonylurea receptor), *Rictor, MafA and Insm1*. Beginning around fifteen years ago, our focus shifted to learning more about pancreas/islet development, due to the central leadership role I assumed in the Beta Cell Biology Consortium (BCBC). To facilitate our studies and those of others, we optimized the use of *Recombinase-mediated Cassette Exchange* (RMCE) to efficiently derive many useful alleles. The methods and cell lines that we developed enabled ourselves and others to gain fundamentally important insights into the function of *Ptf1a, Pdx1, Ngn3, Insm1, Nkx2.2, MafA, Oc1, Sox17 and Dll1* in pancreas and/or beta cell development. As a part of this effort, we also derived a number of RMCE-mediated knock-in mice that express fluorescent proteins under the control of key genes, including *Ins2*, as described in this proposal.

My interactions over fourteen years with other scientists in the BCBC had the unforeseen effect on my approach to science. Instead of being content studying individual genes, I began to see that there were larger problems that required a more systems-based approach to be solved. In this regard, my involvement with Dr. Chris Stoeckert (UPenn) and J-P. Cartailler (VU) revealed to me the potential, and in fact need, to incorporate bioinformatics strategies directly into our research. While I may not be very adept at computer programming and data management, I have learned to understand and speak the language. This enables me to communicate with data scientists, and to not only begin to utilize these approaches with confidence, but also to stimulate specific enhancements in the software tools that are required.

I am also committed to undergraduate and graduate education, and participate in the NIH-funded Vanderbilt Medical Scientist Training Program, the Molecular Endocrinology Training Program (Richard O'Brien, PI), the Developmental Biology Training Program (Chris Wright, PI), and the Diabetes and Endocrinology Training Program (Jim May, PI). Prior to leading the BCBC for 14 years, I was the Assistant Vice Chancellor for Research at Vanderbilt during which time I established policies and systems for managing our many outstanding Shared Resources. Currently I direct both the Vanderbilt Center for Stem Cell Biology and the Vanderbilt Transgenic/ES Cell Shared Resource. I've also held key leadership roles in the Vanderbilt Diabetes Research and Training Center, the Vanderbilt-Ingram Cancer Center, and have served on the external advisory boards of several major research Centers and Consortia.

B. Positions and Honors

Academic Positions

1987-1992	Assistant Professor of Molecular Physiology and Biophysics and of Medicine, Vanderbilt University School of Medicine, Nashville, TN
1992-1996	Associate Professor of Molecular Physiology and Biophysics and of Medicine, Vanderbilt University School of Medicine, Nashville, TN
1996-present	Professor of Molecular Physiology and Biophysics, Vanderbilt University School of Medicine, Nashville, TN
1996-present	Professor of Medicine, Vanderbilt University School of Medicine, Nashville, TN
2006-present	Professor of Cell and Developmental Biology, Vanderbilt University School of Medicine, Nashville, TN

Other Experience, Professional Memberships and Advisory Committees

1991-2008	Editorial Board Member for *Diabetes* (1991-1993), *Molecular Endocrinology* (1993-1996), *American Journal of Physiology: Endocrinology and Metabolism* (1995-2000), and *Journal of Biological Chemistry* (1997-2002 and 2003-2008)
2001-2012	Associate Editor for *American Journal of Physiology: Endocrinology and Metabolism* (2001-2004) and *Experimental Biology and Medicine* (2006-2012)
1992-1996	Member, Juvenile Diabetes Research Foundation: Scientific Review Committee
1992-present	NIH - Endocrinology Study Section (1996-2000); Special Emphasis Panels: Identifying Type I and II Diabetes Genes (1992 &1993), Diabetes Interdisciplinary Research Programs (1997), Gene Therapy of Diabetes and its Complications (2001, Chair), Diabetes and Research Training Centers (2002), Beta Cell Biology Consortium U-19s (2001, Chair) and Beta Cell Biology Consortium U-01s (2005); BECON 2003 Symposia *Catalyzing Team Science* (2003, Co-moderator); Planning Meeting for Knockout Mouse Project (KOMP) (2005, Participant); Chair, Steering and Executive Committees of the NIDDK Beta Cell Biology Consortium (2001-2015); Co-Chair of a working group for NIDDK Type 1 Diabetes Research Strategic Plan (2005); NIDDK Advisory Council (2006-2010)
1993-present	Transgenic Mouse/ES Cell Shared Resource: Director (1993-1998 and 1999-present)
1998-1999	Director of Biomedical Sciences, Vanderbilt University School of Medicine
1999-2005	Assistant Vice-Chancellor for Research, Vanderbilt University School of Medicine
2002-2010	Associate Director for Shared Resources in the Vanderbilt-Ingram Cancer Center
2004-present	Director and Faculty Investigator, Vanderbilt Center for Stem Cell Biology
2005-2007	Scientific Advisory Board, Functional Genomics in Engineered ES Cells Consortium (EU)
2006-2012	External Scientific Advisory Board Member, Jonsson Comprehensive Cancer Center, UCLA
2009	Scientific Review Panel, Howard Hughes Medical Institute
2010-2012	Genome Sciences Resource: Interim Director (2010-2011), Scientific Director (2011-2012)
2012-2014	External Advisory Board, Institute for Diabetes, Obesity and Metabolism, University of Pennsylvania, Philadelphia, PA
2012-2015	External Scientific Advisory Board Member, Norris Cotton Cancer Center, Dartmouth-Hitchcock Medical Center
2012-present	External Advisory Committee Member, NHLBI-funded Lung Repair & Regeneration Consortium (LRRC)

Honors

1993	American Society of Clinical Investigation
2005-2010	Earl W. Sutherland, Jr. Professor of Molecular Physiology and Biophysics
2006	Sidney P. Collowick Faculty Research Award, Vanderbilt University Medical Center
2006	Arnold Lazarow Memorial Lecture, University of Minnesota
2011	Louise B. McGavock Chair of Molecular Physiology and Biophysics
2012	Ray A. and Robert L. Kroc Lecture, University of Pennsylvania
2013	Association of American Physicians
2013	Fellow, American Association for the Advancement of Science
2014	Special Award from the NIDDK for Leadership of the Beta Cell Biology Consortium
2015	Distinguished Service Award, Luther College

C. Contributions to Science

1. I cloned glucokinase (*Ggk*) from both rat liver and insulinoma tissue, and discovered there were two cell type specific isoforms due to the use of alternate promoters. Cloning of *Gck* from the rat quickly enabled isolation of the human *GCK* gene and the discovery that mutations within the *Gck* gene cause Maturity Onset Diabetes of the Young, type 2 (MODY-2), persistent hyperinsulinemic hypoglycemia of infancy (PHHI), and permanent neonatal diabetes (PND). This knowledge led several large pharmaceutical companies to explore *GCK* as a drug target for Type 2 diabetes and to identify small molecule activators of the enzyme. After characterizing the upstream *Gck* promoter region, characterizing two *Rfx3*- and *Rfx6*-binding elements, developing tissue-specific gene knockout mice, studying the role of *Gck* regulatory protein in liver, and determining how specific mutations affect both the kinetics and stability of the enzyme, my interests shifted to other topics.

a. M.A. Magnuson and K.D. Shelton; An alternate promoter in the glucokinase gene is active in the pancreatic β cell, *Journal of Biological Chemistry*, 264:15936-15942, 1989.
b. T. L. Jetton, Y. Liang, C.C. Pettepher, E.C. Zimmerman, F.G. Cox, K. Horvath, F.M. Matschinsky, and M.A. Magnuson; Analysis of upstream glucokinase promoter activity in transgenic mice and identification of glucokinase in rare neuroendocrine cells in the brain and gut. *Journal of Biological Chemistry*, 269:3641-3654, 1994.
c. J. Grimsby, R. Sarabu, W.L. Corbett, N-E. Haynes, F.T. Bizzarro, J.W. Coffey, K. Guertin, D.W. Hilliard, R.F. Kester, P.E. Mahaney, L. Marcus, L. Qi, C.L. Spence, J. Tengi, M.A. Magnuson, C.A. Chu, M.T. Dvorozniak, F.M. Matschinsky, J. F. Grippo, Allosteric activation of glucokinase by a novel pharmacological antidiabetic agent, *Science*, 301:370-373, 2003.
d. S. Tornovsky-Babeay*, D. Dadon*, O. Ziv*, E. Tzipilevich, T. Kadosh, R.S-B. Haroush, A. Hija, M. Stolovich-Rain, J. Furth-Lavi, Z. Granot, S. Porat, L.H. Philipson, K.C. Herold, T.R. Bhatti, C. Stanley, F.M. Ashcroft, P. In't Veld, A. Saada, M.A. Magnuson, B. Glaser, Y. Dor. Type 2 diabetes and congenital hyperinsulinism cause DNA doublestrand breaks and p53 activity in beta-cells (*Equal contributors), *Cell Metabolism*, 19:109-21, 2014.

2. I was the first to generate efficient cre driver lines for performing hepatic and pancreatic beta cell-specific gene knock-outs, and have been at the forefront of developing new strategies and approaches for efficiently deriving many other useful lines of mice. The strategies and technology I developed or enhanced led us to derive over a hundred genetically altered mice or mESCs containing different mutations, loxP sites, fluorescent reporters, and components of the Reverse Tetracycline Trans-Activator (rtTA) system. These mice have been used by hundreds, if not thousands, of different laboratories.

a. C. Postic, M. Shiota, K.D. Niswender, T.L. Jetton, K.D. Shelton, J. Lindner, Y. Chen, J. M. Moates, A.D. Cherrington, and M.A. Magnuson, Cell-specific roles of glucokinase in glucose homeostasis as determined by liver and pancreatic β cell-specific gene knock-outs using Cre recombinase, *Journal of Biological Chemistry*, 274:305-315, 1999.
b. Q. Long, K.D. Shelton, J. Lindner, J.R. Jones and M.A. Magnuson, Efficient Recombinase-Mediated Cassette Exchange in mouse embryonic stem cells by staggered positive-negative selection, *Genesis*, 39:256–262, 2004.
c. S.X. Chen, A. Osipovich, A. Ustione, L. Potter, S. Hipkens, R. Gangula, W. Yuan, D. Piston, and M.A. Magnuson. Quantification of factors influencing fluorescent protein expression using RMCE to generate an allelic series in ROSA26, *Disease Models and Mechanisms,* 4:537-47, 2011. **PMCID: PMC3124063**
d. B. Brouwers, G. de Faudeur, A.B. Osipovich, L. Goyvaerts, K. Lemaire, L. Boesmans, E.J.G. Cauwelier, L. Goyvaerts, M. Granvik, V.P.E.G. Pruniau, L. Van Lommel, J. Van Schoors, J.S. Stancill, I. Smolders, V. Goffin, N. Binart, P. in't Veld, J. Declercq, M.A. Magnuson, J.W.M. Creemers, F. Schuit and A. Schraenen. Impaired islet function in commonly used transgenic mouse lines due human growth hormone minigene expression, *Cell Metabolism*, 20:979–990, 2014.

3. As a postdoctoral fellow, I was involved in studies that explored the regulation of phosphoenolpyruvate carboxykinase (*Pck1*). These efforts motivated me to develop mice with a floxed *pck1* allele and to discover that animals lacking hepatic *PEPCK* maintain fasting euglycemia at the expense of severe steatosis, excessive accumulation of TCA cycle intermediates, disruption of hepatic cataplerosis, and the near complete blockage of gluconeogenesis from amino acids and lactate. By developing a series of animals that expressed differing amounts of *PEPCK*, and collaborating with others, we found that changes in protein content only weakly influenced gluconeogenic flux.

a. P. She, M. Shiota, K. Shelton, R. Chalkley, C. Postic and M.A. Magnuson, Phosphoenolpyruvate carboxykinase is necessary for the integration of hepatic energy metabolism*, Molecular and Cellular Biology*, 20:6508-6517, 2000. **PMCID: PMC86125**
b. S.C. Burgess, N. Hausler, M. Merritt, C. Storey, A. Milde, S. Koshy, J. Lindner, M.A. Magnuson, C.R. Malloy and A.D. Sherry, Impaired TCA cycle activity in mouse livers lacking cytosolic phosphoenolpyruvate carboxykinase, *Journal of Biological Chemistry*, 279: 48941-48949, 2004.
c. P. She, S.C. Burgess, M. Shiota, P. Flakoll, E.P. Donahue, C.R. Malloy, A.D. Sherry and M.A. Magnuson, Mechanisms by which liver-specific PEPCK knockout mice preserve euglycemia during starvation, *Diabetes*, 52:1649-1654, 2003.
d. S.C. Burgess, T. He, Z. Yan, J. Lindner, A.D. Sherry, C.R. Malloy, J.D. Browning, M.A. Magnuson, Cytosolic phosphoenolpyruvate carboxykinase does not solely control the rate of hepatic gluconeogenesis in the intact mouse liver, *Cell Metabolism*, 5:313-20, 2007. **PMCID: PMC2680089**

4. While exploring the gene expression differences between pancreatic tumors isolated from mice expressing a GCK-SV40 T antigen transgene, we discovered *Rictor*, a scaffolding protein essential for the function of mTOR complex 2 (mTORC2). By developing mice with a conditional allele for *Rictor,* we established with certainty that mTORC2 catalyzed the phosphorylation of Akt/PKB at Ser473. Our studies and those of others have established the vital importance of *Rictor*/mTORC2 in multiple cell types, including the pancreatic β-cells.

a. Shiota, J-T. Woo, J. Lindner, K.D. Shelton and M.A. Magnuson; Multiallelic Disruption of the *rictor* gene in mice reveals that mTOR complex 2 is essential for fetal growth and viability, *Developmental Cell*, 11:583-589, 2006.
b. D.A. Guertin, D.M. Stevens, M. Saitoh, K. Crosby, K.S. Cormier, D. Mullholland, M.A. Magnuson, H. Wu and D.M. Sabatini. The mTOR complex 2 is required for the development of prostate cancer induced by *PTEN* loss in mice, *Cancer Cell,* 15:148-59*,* 2009. **PMCID: PMC2701381**
c. K.W. Lee, P. Gudapati, S. Dragovic, C. Spencer, S. Joyce, N. Killeen, M.A. Magnuson, M. Boothby. Mammalian target of rapamycin protein complex 2 regulates differentiation of Th1 and Th2 cell subsets via distinct signaling pathways, *Immunity*, 32:743-753, 2010. **PMCID: PMC2911434**
d. Y.Gu, J. Lindner, A. Kumar, W. Yuan, M. A. Magnuson; Rictor/mTORC2 is essential for maintaining a balance between beta cell proliferation and cell size, *Diabetes*, 60:827-37, 2011. **PMCID: PMC3046843**

5. We and others have used mouse alleles we generated to gain important insights into the functional roles of *Ptf1a, Pdx1, Ngn3, Insm1, Nkx2.2, MafA, Oc1, Sox17 and Dll1* in pancreas and/or beta cell development. By working with leading developmental biologists we contributed to the acquisition of knowledge that defined the lineage by which beta-cells are formed, thereby providing knowledge that was essential for making beta cells from pluripotent stem cells by directed differentiation. More recently, we've been using fluorescent protein (FP)-expressing knock-in alleles to analyze the gene regulatory network of pancreatic endocrine progenitor cells and mature pancreatic β-cells by RNA-Sequencing.

a. M.F. Offield, T.L. Jetton, P.A. Labosky, M. Ray, R. Stein, M.A. Magnuson, B.L.M. Hogan, and C.V.E.Wright; Pdx-1 is required for pancreatic outgrowth and differentiation of the rostral duodenum. *Development,* 122:983-995, 1996.
b. J. Burlison, Q. Long, Yoshio Fujitani, C.V.E. Wright and M.A. Magnuson; Pdx-1 and Ptf1a concurrently determine fate specification of pancreatic multipotent progenitor cells, *Developmental Biology*, 316:74-86, 2008. **PMCID: PMC2425677**
c. Choi, M.R-C. Kraus, L.A. Lemaire, M. Yoshimoto, S. Vemula, L.A. Potter, E. Manduchi, C.J. Stoeckert Jr., A. Grapin-Botton, M.A. Magnuson, Dual lineage-specific expression of Sox17 during mouse embryogenesis, *Stem Cells*, 30:2297–2308, 2012. **PMCID: PMC3448801**
d. A.B. Osipovich, R. Gangula, J. Schneider, T. Okubo, Q. Long, S. Hipkens, E. Manduchi, C.J. Stoeckert Jr, S. Takada and M.A. Magnuson. *Insm1* promotes endocrine cell differentiation by modulating expression of a network of genes that includes *Neurog3* and *Ripply3*, *Development,* 141:2939-49, 2014. **PMCID: PMC4197673**

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/1J1b_m-X9h5kv/bibliography/43477457/public/?sort=date&direction=ascending

As of September 27, 2016 my h-index was 81 based on 17665 citations in the ISI Web of Knowledge, and 91 based on 24568 citations in Google Scholar.

A. Research Support

Ongoing Research Support

P60 DK020593-37 (McGuinness) 05/14/2012 – 03/31/2017
NIH/NIDDK (UNIV__VUMC/Powers)
Diabetes Research and Training Center
The Vanderbilt Diabetes Research and Training Center (DRTC), in its 33rd continuous year of operation as a NIH-sponsored Diabetes Center, and seeks to continue its efforts to facilitate the discovery, application, and translation of scientific knowledge to improve the care of patients with diabetes. The Vanderbilt DRTC is an interdisciplinary program involving 98 participating faculty distributed among 18 departments in two schools and four colleges at Vanderbilt and at neighboring Meharry Medical College.

P30 CA068485-21(Hiebert) 09/07/2015-08/31/2020
NIH/NCI (UNIV__VUMC/Pietenpol)
Cancer Center Support Grant
This grant provides support for approximately 12 different Shared Resources, including the Transgenic/ESC Shared Resource. These Shared Resources support the research mission of both VICC and VUMC investigators. Dr. Magnuson serves as the Senior Scientific Director of the Vanderbilt Transgenic/ESC Shared Resource.

Pending Research Support

2 P30 DK020593-38 (McGuinness) 04/01/2017 – 03/31/2022
NIH/NIDDK (UNIV___ VUMC/Powers)
Diabetes Research and Training Center
The Vanderbilt Diabetes Research and Training Center (DRTC), in its 33rd continuous year of operation as a NIH-sponsored Diabetes Center, and seeks to continue its efforts to facilitate the discovery, application, and translation of scientific knowledge to improve the care of patients with diabetes. The Vanderbilt DRTC is an interdisciplinary program involving 98 participating faculty distributed among 18 departments in two schools and four colleges at Vanderbilt and at neighboring Meharry Medical College.

1R01 DK111565-01 (Magnuson) 09/01/2016-08/31/2020
NIH/NIDDK *Gene regulatory network in pancreatic endocrine progenitor cells*
The overall goal of these studies is to extend our knowledge of the gene regulatory network in pancreatic endocrine cells in order to understand how T2D-linked mutations in humans conspire to cause cell failure and dedifferentiation.

Completed Research Support

5 U01 DK089523-05 (Magnuson) 09/20/2010 - 06/30/2016
NIH/NIDDK *Genetic control of pancreatic endocrine cell development (BCBC)*
This project is focused on developing new reagents, datasets and bioinformatics tools necessary for a deeper understanding of the molecular events that occur during 1) normal pancreas development in the mouse, and 2) the trans-differentiation of acinar to beta cells following the forced expression of transcription factors.

U01 DK089570 (Wright) 09/15/2010 - 06/30/2015
NIH/NIDDK *Architecture and communication controlling the efficient generation of beta cells (BCBC)*
This project was focused on generating translationally applicable findings on the development of pancreatic endocrine-fated progenitor cells. Although this project remains active, I no longer receive any support from it. Role: Co-Principal Investigator

U01 DK072473 (Magnuson) 09/10/2010 - 07/31/2015
NIH/NIDDK *Coordinating Center for Beta Cell Biology Consortium (BCBC)*
The mission of the BCBC is to facilitate interdisciplinary approaches that will advance our understanding of pancreatic islet development and function with the long-term goal of developing a cell-based therapy for insulin delivery. Role: Principal Investigator