The following action is requested by the School of Medicine regarding the promotion of Maureen Gannon, PhD as Associate Professor of Medicine on the basic scientist track, (tenure) of the full-time faculty of the Vanderbilt School of Medicine effective January 1, 2008 until December 31, 2010.

Academic career:
Dr. Gannon was recruited by Vanderbilt and joined the faculty of the Division of Diabetes, Endocrinology and Metabolism, Department of Medicine, in 2001.

She received a M.S. in Biology at Adelphi University in New York and a B.S. in Biology from Molloy College in New York, where she graduated Magna Cum Laude. In May, 1996, Dr. Gannon received a Ph.D. in Cell Biology from Cornell University in New York. Her postdoctoral training includes a fellowship here at Vanderbilt in Cell Biology from 1996-2001.

Consistency and importance of research theme:
The over-riding theme of Dr. Gannon’s laboratory is the “cellular and molecular regulation of pancreas organogenesis”. Diseases of the pancreas are some of the most debilitating and life threatening, including diabetes, pancreatitis and pancreatic cancer. Aspects of the work performed in Dr. Gannon’s laboratory have implications for all of these diseases.

The exocrine tissue (acinar and ductal cells) accounts for ~98% of adult organ mass; endocrine cells comprise 1-2% of the organ. It remains unclear whether a single progenitor cell can give rise to all differentiated pancreatic cell types. Dr. Gannon’s laboratory is interesting in understanding:
- how multipotent pancreatic progenitor cells are allocated to exocrine vs. endocrine lineages during development
- how exocrine and endocrine cells are generated in the appropriate proportions
- how the different endocrine cell types are generated in the appropriate proportions
- how these cells communicate with one another to form a functional organ
- how these cell types are maintained/generated throughout the life of the organism

The model system Dr. Gannon uses to address these questions is the mouse. Many genes identified in the mouse as playing an important role in pancreas development and mature organ function play identical roles in humans. Dr. Gannon’s laboratory has engineered mice with cell type- or tissue-specific over-expression of transgenes using well-characterized promoter elements. In addition, she has utilized both global gene inactivation as well as conditional gene inactivation (Cre/lox) to assess the requirement for a particular gene in some aspects of pancreas development and/or function. Thus, gene expression can be either increased or decreased to determine the effects that this manipulation has on events during embryonic development (overall organ growth, lineage allocation, proliferation, terminal differentiation) or in the adult (cell survival, mature function,
cell turnover, whole animal physiology). What follows is a summary of the current projects in Dr. Gannon’s laboratory.

1. **Function of HNF6 in pancreatic lineage specification and differentiation**

HNF6 (OC-1) is a member of the one-cut family of transcription factors. Although first identified in liver, HNF6 is also expressed in the pancreas. HNF6 is expressed throughout the early pancreatic bud epithelium, but becomes specifically down-regulated in the endocrine lineage by late gestation. Expression in ducts and acinar cells is maintained throughout the life of the organism. HNF6 directly activates the promoter of the pro-endocrine gene, neurogenin3 (ngn3) and is essential for generation of pancreatic endocrine cells during embryonic development. Global gene inactivation results in a dramatic decrease in endocrine cells.

Dr. Gannon’s research team found that HNF6 protein is no longer detected once cells begin to express hormones defining a particular endocrine lineage. To address the hypothesis that HNF6 was solely required for initiation of the endocrine program by direct activation of the ngn3 promoter, Dr. Gannon’s lab generated mice carrying floxed HNF6 alleles, allowing for conditional inactivation using Cre/lox. Specifically, ngn3-Cre transgenic mice were used to inactivate HNF6 early in cells thought to be committed to the endocrine lineage. The results of these studies showed conclusively that HNF6 is NOT required for terminal differentiation of pancreatic endocrine cells or for mature beta cell function. However, lineage-tracing analyses revealed that the duration of HNF6/Ngn3 co-expression affected pancreatic lineage allocation. An increased proportion of cells in which the ngn3-Cre was activated (and thus HNF6 was inactivated), differentiated into exocrine rather than endocrine cells. These studies demonstrated that, 1. ngn3-expressing cells do not represent a strict endocrine progenitor, 2. sustained HNF6 expression in ngn3+ cells may be required to fully commit a multipotent progenitor to the endocrine lineage and, 3. HNF6 is not required for further events in endocrine/beta cell differentiation once cells have irreversibly committed to the endocrine lineage. These results demonstrated that maintained expression of HNF6 in differentiated endocrine cells is not required.

As a postdoctoral fellow, Dr. Gannon used an endocrine-specific fragment of the pdx1 promoter to direct HNF6 expression to endocrine cells for the life of the organism. HNF6 transgenic animals show defects in islet development and function: endocrine clusters fail to migrate away from the ductal epithelium and remain closely adhered to the ducts. Islets fail to form the characteristic architecture (beta cells at the core and other endocrine cells types at the periphery). Maintenance of HNF6 expression in the endocrine lineage also resulted in dramatically impaired glucose-stimulated insulin secretion and diabetes. Now, in her own laboratory, Dr. Gannon has followed up on these initial observations and has determined that the major cause of the impaired insulin secretion in HNF6 transgenic animals is a failure in beta cell terminal differentiation. Electron microscopic analyses of beta cells from these animals revealed a dramatic decrease in insulin granule biosynthesis, with insulin protein being "trapped" in the secretory pathway (ER and Golgi). The critical beta cell transcription factor, MafA, was undetectable during development and after birth. Thus, these results support a scenario where down-regulation of HNF6 in cells committed to the endocrine lineage is necessary for the different lineages to be generated in the appropriate proportions, and also to allow for terminal differentiation of beta cells.

To begin to elucidate the mechanisms whereby maintained HNF6 expression causes defects in islet morphogenesis and function, Dr. Gannon’s laboratory recently performed whole genome microarray analyses comparing gene expression profiles between wild type and HNF6 transgenic islets at perinatal stages. This study identified candidate gene products and cellular pathways that may be involved in this process. Importantly, gene products involved in cell adhesion, migration, extracellular matrix remodeling, and proliferation were altered in HNF6 transgenic pancreata,
revealing specific candidates that can now be analyzed directly for their role in islet morphogenesis. Expression of gene products known to be involved in vesicle biosynthesis, trafficking, and membrane fusion was altered in HNF6 transgenic pancreata, providing candidate genes whose altered expression may contribute to the insulin secretory defect in these animals described above. Expression of MafA was reduced five-fold, in agreement with our immunohistochemical analysis.

These gene expression data are of great value to the beta cell biology community, and should facilitate analysis of the role that these new candidate genes play in normal islet development and mature beta cell function. This information is crucial given the push to direct the differentiation of stem or progenitor cells towards the beta cell lineage for potential use in the treatment of diabetes. For example, these studies revealed that HNF6 over-expression results in down-regulation of a TGF-beta response gene, connective tissue growth factor (CTGF). CTGF is known, in other cellular systems to be important for cell adhesion, migration, extracellular matrix remodeling, and proliferation…processes involved in normal islet development and altered in the HNF6 transgenic islets. Dr. Gannon’s research team is currently pursuing an analysis of the role that CTGF plays in islet development. Prior to her work, CTGF was only known to play a role in disease states such as pancreatitis and pancreatic cancer, but had never been described in normal pancreas development.

In addition to understanding the role that HNF6 plays in specification and differentiation of pancreatic endocrine cells, Dr. Gannon has performed analyses to better determine the function of HNF6 in the exocrine pancreas. To this end, HNF6 was conditionally inactivated in the entire pancreas using pdx1Cre. The developmental phenotype of HNF6Δpanc pancreata is nearly identical to that reported for the global knockout of HNF6; however, the early lethality associated with global HNF6 inactivation does not occur in HNF6Δpanc animals. Dr. Gannon has discovered that HNF6Δpanc pancreata show increased duct cell proliferation, squamous cell metaplasia and acinar-to-ductal metaplasia…all pre-neoplastic conditions. In addition, HNF6Δpanc pancreata have dilated ducts due to loss of primary cilia and display fluid filled cysts and morphological changes associated with pancreatitis. They also observe increased expression of markers of pancreatitis, including MMP7, P8, and CTGF, and a dramatic decrease in the Prox1 transcription factor, known to be important for normal pancreas development. Thus, these studies have established a link between HNF6 and two devastating human diseases: pancreatitis and pancreatic cancer.

2. Regulation of embryonic and postnatal beta cell mass
Beta cell mass is dynamic, increasing during pregnancy and the insulin resistance associated with obesity. Since diabetes results from an absolute (Type 1) or relative (Type 2) inadequate functional beta cell mass, genes and pathways involved in maintaining or augmenting beta cell mass are candidates for being affected in diabetic individuals. Functional analysis of these genes may lead to new strategies for increasing existing beta cell mass in diabetic patients and/or facilitate the production of beta cells in vitro from stem or progenitor cells.

Dr. Gannon’s laboratory has recently begun studying genes involved in the genesis and maintenance of beta cell mass. Using conditional gene inactivation, she discovered that the Foxm1 transcription factor is essential for the maintenance of postnatal beta pancreas, Dr. Gannon found that Foxm1 is highly expressed in developing endocrine cells and at much lower levels in ducts and acini. Using the Cre/lox system, her team inactivated Foxm1 specifically in the pdx1 expression domain. Beta cell mass was normal at birth as was overall growth and development of the pancreas. As Foxm1Δpanc animals aged, however, they progressed from glucose intolerance to frank diabetes (by 9 weeks of age). Defects in glucose homeostasis were caused by a selective decrease in beta cell proliferation and a loss of beta cells over time.
Dr. Gannon’s results suggest that Foxm1 is required during normal beta cell turnover to maintain beta cell mass in the adult. These results also suggest that Foxm1 is dispensable for endocrine progenitor and/or beta cell proliferation during embryogenesis and that pathways or mechanisms for embryonic beta cell replication (or neogenesis) may differ from those utilized in the adult (replication of existing beta cells).

The Gannon lab is currently using the floxed allele of Foxm1, in combination with various standard and inducible Cre transgenic lines, to analyze the role of Foxm1 in beta cell proliferation response to known stimuli (diet induced obesity, pregnancy, growth factors, injury). These studies will determine whether all stimuli of beta cell proliferation converge on Foxm1 or whether Foxm1 is required for beta cell proliferation only under certain circumstances. Interestingly, the data emerging from these studies suggest that the latter is true. Loss of Foxm1 prevents the increase in beta cell proliferation and beta cell mass expansion that normally occurs during pregnancy. Indeed, Foxm1 mutant females display gestational diabetes despite being euglycemic as virgins. In contrast, beta cell proliferation and beta cell mass regeneration following partial pancreatectomy is only partially impaired in the absence of Foxm1. Thus, it seems that Foxm1 is absolutely essential during pregnancy, but may be compensated for, in part, in response to an injury model. The Gannon lab has shown that Foxm1 is dispensable for embryonic beta cell proliferation. Since beta cell mass regeneration after partial pancreatectomy is thought to be due to reactivation of the embryonic program of beta cell neogenesis, it may be that neogenesis does no require Foxm1 in the adult either.

Dr. Gannon is also continuing her analysis of CTGF function during pancreas development. The lab has found that CTGF is expressed in ducts and beta cells but not acinar cells during development. CTGF expression in beta cells is extinguished soon after birth, but is maintained in ducts and blood vessels throughout the life of the organism. Interestingly, Dr. Gannon has found that CTGF is re-expressed in maternal islets during pregnancy, a time of beta cell mass expansion and that CTGF heterozygotes have impaired glucose tolerance. In the absence of CTGF, islet morphogenesis is perturbed. In addition, there is a dramatic decrease in embryonic beta cell proliferation and insulin-positive cells. Thus, Dr. Gannon’s team has identified CTGF as one of only a few factors (Pdx1, p27, and PERK) reported to be required for embryonic beta cell proliferation.

Dr. Gannon has generated a conditional allele of CTGF in collaboration with Regeneron Pharmaceuticals to allow for inactivation in specific cell types at specific developmental and postnatal time points. Mice carrying the floxed CTGF allele have already been bred with mice in which CTGF can be inactivated specifically in islet endocrine cells or pancreatic epithelial cells.

Since becoming an independent investigator, Dr. Gannon has been very successful in obtaining extramural funding (a Pilot and Feasibility grant from the Beta Cell Biology Consortium, 2 RO1’s, a JDRF Career Development Award, and a JDRF Research Award).

**Quality and originality of scientific work:**
Since becoming a faculty member, Dr. Gannon has authored 16 peer reviewed original research publications, one book chapter, and three peer reviewed review articles. In addition, Dr. Gannon has three other manuscripts that have already been submitted for publication and are in the process of being revised for resubmission.

Dr. Gannon was the first to show that inactivation of HNF6 specifically in multi-potent pancreatic progenitors using Cre-lox technology alters allocation of progenitors to the endocrine lineage (ie, a greater proportion of progenitors are diverted to the exocrine lineage). In addition, she has shown that failure to down-regulate HNF6 in differentiated endocrine cells defective insulin granule...
biosynthesis and loss of the beta cell transcription factor, MafA, resulting in diabetes. Dr. Gannon is the first person to describe the expression and function of CTGF in the developing pancreas, and in embryonic beta cell proliferation. Her lab was also the first to demonstrate that the positive cell cycle regulator, Foxm1, is dispensable for embryonic beta cell proliferation but is absolutely essential for maintenance of postnatal beta cell mass. Inactivation of Foxm1 in the pancreas results in a dramatic decrease in proliferation of mature beta cells and a gradual decrease in beta cell mass, leading to diabetes. The results from Dr. Gannon’s laboratory have implications for beta cell function and maturation in situations such as directed differentiation of ES cells toward a beta cell fate. In addition, her studies suggest that defects in beta cell proliferation may predispose some individuals to diabetes, and provide a potential therapeutic target for augmenting beta cell mass.

**Significant publications:**


   In this collaborative effort with her postdoctoral mentor, Dr. Gannon described the generation and characterization of a tamoxifen-inducible islet-specific Cre deleter line of mice. In this line of mice, an islet-specific fragment of the *pdx1* promoter (identified and characterized by Dr. Gannon as a postdoctoral fellow) was used to drive expression of a fusion protein between Cre recombinase and the estrogen receptor ligand binding domain. Dr. Gannon’s laboratory has entered into several productive collaborations with other laboratories in the field using these mice (including Al Powers, Vanderbilt; Batrton Wicksteed, University of Chicago; Vincent Poitout, University of Montreal; Beatriz Sosa-Pineda, St. Jude’s Children’s Research Hospital).


   In this study Dr. Gannon showed that the Foxm1 transcription factor, a known positive cell cycle regulator, is highly expressed in mouse embryonic endocrine cells and early postnatal islets, but declines as animals age. Pancreas-wide inactivation of Foxm1 using Cre-lox technology had no effect on beta cell mass at birth (suggesting redundant or parallel pathways regulating beta cell proliferation during embryogenesis). Rather, loss of Foxm1 resulted in a specific and dramatic decrease in adult beta cell proliferation, a subsequent decline in beta cell mass over time, and ultimately diabetes. Foxm1 joins a growing list of cell cycle regulators (cdk4, Cyclin D2, E2F) that exhibit diabetes due to defects in maintenance of postnatal beta cell mass when broadly inactivated. Taken further, expansion of immature beta cells during directed differentiation of ES cells may require stimulation of as yet unknown cell cycle regulators, while expansion of mature beta cells obtained from adult sources may be possible with activation of Foxm1.


   This publication represents a thorough analysis of the HNF6 transgenic line Dr. Gannon generated as a post-doctoral fellow. Here, Dr. Gannon’s team showed that continued expression of HNF6 in developing beta cells resulted in a dramatic decrease in the transcription factor, MafA, a marker of mature beta cells. In fact, the phenotype of animals over-expressing HNF6 is remarkably similar to the phenotype of MafA null mutant mice. Maintenance of HNF6 in the beta cell lineage
resulted in severe defects in insulin granule biosynthesis and thus a loss of stimulation of insulin secretion in response to elevated glucose (and other stimuli). These studies have a direct relevance to efforts using directed differentiation to generate beta cells and/or islets from ES cells. Although HNF6 is an important factor to initiate the endocrine differentiation program, it clearly needs to be down-regulated prior to terminal differentiation in order for beta cells to become fully mature and glucose responsive. Indeed, culturing of human islets (a standard procedure prior to islet transplantation) results in up-regulation of HNF6, with potentially deleterious functional consequences for these transplanted islets. These studies highlight the need for a thorough understanding of the temporal regulation of factors involved in normal islet/beta cell development in order to maximize differentiation from stem cell sources.


This paper demonstrates Dr. Gannon’s unique ability to collaborate with leaders in the field of pancreas/endoderm development. This study was initiated in Dr. Gannon’s laboratory to understand the functional significance of three highly conserved regions within the pdx1 promoter. Pdx1 is essential for early pancreatic bud development and for later beta cell function in both mice and humans. Dr. Gannon’s laboratory identified a 300bp region of the pdx1 promoter (Area III) that was responsible for early expression of pdx1 throughout the pancreatic buds. They identified a potential binding site for another critical pancreatic transcription factor complex, PTF1, within Area III. In collaboration with Dr. Roland Stein’s lab (Vanderbilt), Dr. Gannon’s team demonstrated that PTF1 can bind to Area III of the pdx1 promoter and that transcriptional activation through Area III is dependent on an intact PTF1 site. She also collaborated with Dr. Ken Zaret (Fox Chase Cancer Center), to definitively show that PTF1 regulates the pdx1 gene in the embryonic pancreas in vivo. These studies are the first to show an interaction between two critical regulators of pancreatic bud development.


This paper is a Preview for a research article from Helena Edlund’s laboratory that appeared in the March 2007 issue of the journal, Cell Metabolism. Dr. Edlund is one of the foremost researchers in the field of pancreas development and diabetes. Dr. Gannon was invited by the editorial office to write this review for a top-tier journal. This invitation signifies her recognition as an expert in the field of pancreas development and function. The article from the Edlund lab describes, for the first time, the role of BMP signaling in beta cell function. These studies revealed that BMP4 and its receptor act in an autocrine loop within the beta cell to augment glucose-stimulated insulin secretion. In addition, these studies showed that addition of exogenous BMP4 can improve glucose homeostasis in a mouse model of Type 2 diabetes. In her review, Dr. Gannon put these findings within the context of the field as a whole, discussed shortcomings and caveats of the study, and speculated about the therapeutic potential for augmenting BMP signaling in diabetic patients.

Productivity:
Dr. Gannon has established significant professional collaboration with faculty and staff at Vanderbilt in several different departments (Surgery, Cell and Developmental Biology, Molecular Physiology and Biophysics). In addition, she has maintained and cultivated long-term collaborations with investigators in other institutions: Dr. Robert Costa, University of Illinois at Chicago (10 years); Dr. David Brigstock, The Ohio State University (3 years); Dr. Karen Lyons, UCLA (3 years); Dr. Adolfo
Garcia-Ocana, University of Pittsburgh (3 years); Dr. Aris Economides, Regeneron Pharmaceuticals (3 years).

Dr. Gannon currently holds one RO1 on the role of HNF6 in pancreas development (which has been submitted for competitive renewal). Dr. Gannon’s results showing a genetic link between HNF6, TGF-beta, and CTGF will form the basis for the renewal application. Dr. Gannon also holds an RO1 for her studies on Foxm1 function in beta cell replication and regeneration. She has a third major grant from the JDRF addressing the role of CTGF in beta cell differentiation and proliferation.

**Independence:**
Dr. Gannon has shown great novelty in her research and has unequivocally established her scientific independence. The current projects ongoing in her lab were all originated by her since she started her own laboratory. She has competed for and successfully received significant extramural funding.

**Evidence of contribution to education and teaching; awards:**
Since joining our faculty in 2001, Dr. Gannon has contributed greatly to the education programs of our Division and the Department of Medicine. Her teaching has included lab supervision and instruction of PhD students. Three of her students successfully defended their theses and graduated in 2007: Elizabeth Tweedie Ables, Peter Wiebe, and Laura Wilding Crawford. Currently she supervises three PhD students, all of which have passed their Qualifying Exam. One of these is an MD/PhD student. She has had one postdoctoral fellow complete her training in the Gannon lab (Dr. Hongjie Zhang, 2002-2007) and another recently arrive (Dr. Renuka Menon). In addition, Dr. Gannon has supervised many rotation students as part of the Interdisciplinary Graduate Program (IGP).

Dr. Gannon has also lectured for the IGP Core Course, Genetics section; the IGP Core Course, Endocrinology section (2003-2004); and Molecular Development Biology Course since 2001. Dr. Gannon was the course director for the Molecular Developmental Biology Course from 2003-2006 and was the course director for Tutorials in Physiology from 2001-2003. She also contributes regularly to Endocrine Grand Rounds, Molecular Physiology and Biophysics department seminars, and our Division’s fellows research Conference. She also lectured during Department of Medicine Grand Rounds in 2003. Dr. Gannon has also been a member of the Graduate Executive Council for the Department of Molecular Physiology and Biophysics since September 2006. In this capacity, she participates in decisions regarding the instruction and training of PhD students in this department as well as being chair of several Qualifying Exam and thesis committees.

Dr. Gannon’s excellence in teaching was recognized in the 2007 Division of Diabetes, Endocrinology and Metabolism Teaching Award.

Dr. Gannon was co-founder and co-chair of the Vanderbilt University Association of Postdoctoral Fellows in the Life Sciences in 1998 and in 1997 was organizer of the first annual Developmental Biology Retreat here at Vanderbilt.

Also, Dr. Gannon was one of the key organizers of the 2004 and 2007 meetings here on campus entitled: Frontiers in Genome Engineering: Building a Better Mouse.
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