Department of Pharmacology
Application
Thomas Collum Butler Fellowship
(Deadline: MONDAY, December 14, 2009)

I. Name: Nicole M. Vincent Jordan

Mentor: Gary Johnson, PhD

Graduate Program/Entering Date: Pharmacology, Fall 2007

II. Brief Statement of Research Interests (1 page maximum):

Trophoblast stem (TS) cell lineage commitment decisions from multipotent to mature, differentiated trophoblast require morphological and functional changes characteristic of developmental epithelial-mesenchymal transition (EMT). A mechanistic understanding of epigenetic reprogramming inducing EMT is critically important for understanding the network of changes contributing to developmental disorders central to dysregulated EMT.

Targeted inactivation of the serine-threonine protein kinase MAP3K4 in mice results in severe developmental dysregulation, including neural tube closure, skeletal patterning, craniofacial and placental defects characterized by trophoblast hyperinvasiveness. In contrast to wild-type TS (TS^{WT}) cells, TS cells isolated from genetically engineered mice with a mutant MAP3K4 (TS^{KI4}) exhibit hallmarks of stable EMT, including decreased expression of the epithelial marker E-cadherin, increased expression of mesenchymal markers N-cadherin and vimentin, and increased cellular invasiveness. Further characterization of TS^{KI4} cells demonstrates selective loss of histone H2A and H2B acetylation with no demonstrable change in the acetylation levels of histones H3 and H4. Genome-wide chromatin immunoprecipitation coupled to high throughput sequencing (ChIP-seq) and gene array identify the coordinated loss of H2B lysine 5 acetylation (H2BK5Ac) with the repression of a network of genes critical to the maintenance of the epithelial phenotype. Therefore, the goal of my dissertation research is to elucidate the signaling network impacted by epigenetic and transcription factor changes contributing to dysregulated developmental EMT in TS^{KI4} cells.

Using ChIP-seq, mRNA-seq and bioinformatics analysis, this research goal will be accomplished by the following two specific aims: 1) Define the gene expression profiles coordinately regulated by loss of H2A/H2B acetylation and loss of H3K27 tri-methylation (H3K27me3) in TS^{KI4} cells; 2) Define the gene expression profiles controlled by dysregulated AP-1 transcription factor activation in TS^{KI4} cells. It is hypothesized that the induction of EMT in TS^{KI4} cells results from genome-wide changes mediated by coordinated loss of the repressive modification H3K27me3 with loss of H2A and H2B acetylation and by dysregulation of the AP-1 transcription factor repertoire, known to be regulated by MAPK signaling. To date the epigenetic and transcriptional regulation of stem cell plasticity and the mechanisms by which stems cells execute defined gene expression programs essential to cellular specification during development are poorly understood. A greater understanding of how signaling mechanisms mediate chromatin organization responsible for global gene expression patterns regulating developmental EMT is important for understanding the developmental disorders involving tissue remodeling.

III. State How Your Work Relates to Developmental Disabilities (1 paragraph):

Epithelial-mesenchymal transition (EMT) is a fundamental developmental program critical for the formation of developing organs during embryogenesis. Dysregulated activation of the EMT program can lead to numerous developmental defects, such as mesoderm, heart valve, craniofacial and placental malformations. Relevant to EMT, we previously characterized the developmental dysregulation of a genetically engineered MAP3K4-inactive (KI4) mouse, which exhibits neural tube (rachischisis) and mesoderm (omphalocele) closure defects, as well as craniofacial (neural crest) and placental implantation (trophoblast) abnormalities. Trophoblast stem cells isolated from the placentas of KI4 mice (TS^{KI4} cells) exhibit stable EMT, characterized by loss of the epithelial marker E-cadherin, increased cellular invasiveness, and increased expression of the mesenchymal markers N-cadherin and vimentin. Therefore, TS^{KI4} cells provide a novel system for elucidation of the molecular mechanisms and signaling networks contributing to EMT, thereby providing a greater understanding of the pathogenesis of developmental disorders involving tissue remodeling.

IV. List Publications, Abstracts, Awards:

Publications:

Abell A.N.*, **Jordan N.V.***, Huang W., Johnson N.L., Granger D.A., Mieczkowski P.A., Leping L., Johnson G.L. (2009) Epigenetic regulation of developmental epithelial-mesenchymal transition in trophoblast stem cells. Submitted.

Guerrier S., Coutinho-Budd J., Sassa T., Gresset A., **Jordan N.V.**, Chin K., Jin W.L., Frost A., Polleux F. (2009) The F-bar domain of srGAP2 induces membrane protrusions required for neuronal migration and morphogenesis. Cell, 138(5): 990-1004.

Abell A.N., Granger D.A., Johnson N.L., **Vincent-Jordan N.**, Dibble C.F. Johnson G.L. (2009). Trophoblast stem cell maintenance by fibroblast growth factor 4 requires MEKK4 activation of Jun N-terminal kinase. Mol Cell Biol., 10: 2748-61.
Abstracts:

*Denotes shared first authorship.

Abstracts:

Jordan N.V., Abell A.N., Granger D.A., Johnson N.L., Johnson G.L. (October 2009). MEKK4-dependent epigenetic regulation of developmental EMT in trophoblast stem cells. *2009 UNC Pharmacology Department Research Retreat*.

Jordan N.V., Abell A.N., Granger D.A., Johnson N.L., Johnson G.L. (September 2009). MEKK4-dependent epigenetic regulation of developmental EMT in trophoblast stem cells. *4th International Conference on Epithelial-Mesenchymal Transition*.

Awards:

2009 – UNC Pharmacology Research Retreat Poster Award
2009 – 4th International Conference of Epithelial-Mesenchymal Transition Travel Award
2007 – Pharmacology NIH Training Grant GM007040
2005 – Graduate, Indiana University, Magna Cum Laude
2004 – Phi Beta Kappa, Indiana University
2003 – Ira Lee Summer Research Grant, Indiana University
2002 – Chemistry Department Award, Academic Scholarship, Indiana University
2001 – Dean's List, Indiana University

2001 – Hutton Honor's College Award, Academic Scholarship, Indiana University
2001 – Faculty Award, Academic Scholarship, Indiana University
2001 – Gill Academic Scholarship in Science, Indiana University
2000 – Intel International Science and Engineering Fair, 3rd Place Award in Microbiology

RETURN APPLICATION TO: Kathy C. Justice (kcj@med.unc.edu), Student Services Manager, Pharmacology Graduate Studies, CB#7365, Rm#4017 Genetic Medicine Bldg. (by December 14, 2009).