



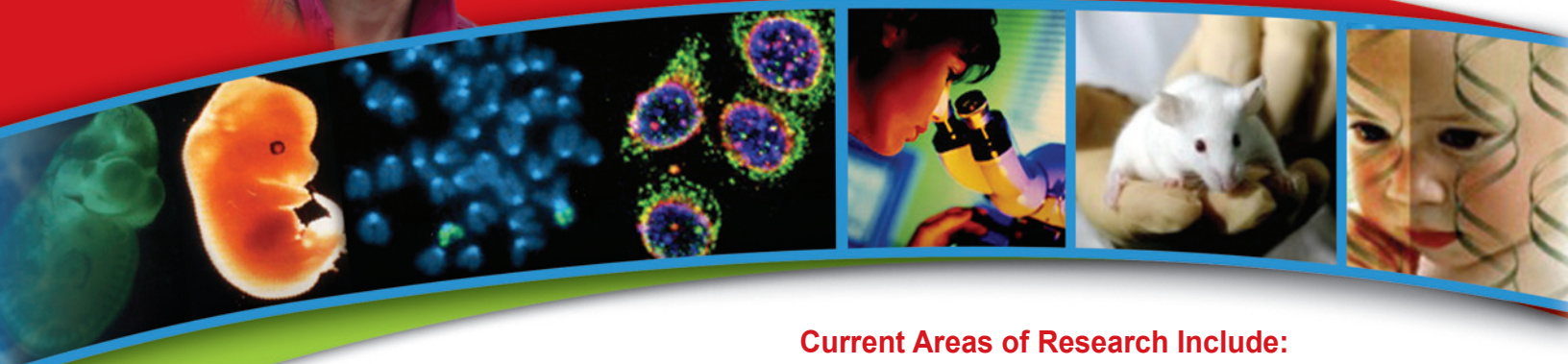
M. Michele Pisano, Ph.D.

University Scholar

Professor, Molecular, Cellular and Craniofacial Biology

Professor, Pharmacology and Toxicology

Research Director: Molecular Craniofacial Development



Scholarly Activities:

Molecular genetic and epigenetic mechanisms of development, and developmental toxicology. Birth defects and congenital developmental disabilities constitute an underappreciated global pandemic. Eight million infants are born with birth defects each year – nearly forty percent of these infants and children die before the age of 5. Despite unprecedented strides in medicine and healthcare, birth defects remain the leading worldwide cause of infant mortality and childhood morbidity. These statistics notwithstanding, public health efforts in the United States and globally have failed to categorize the prevention and treatment of birth defects as national health priorities. Even international agencies such as the World Health Organization and the United Nations have failed to evolve an appreciation for the magnitude of the human health crisis associated with birth defects and developmental disabilities. In June of 2006, the United Nations General Assembly adopted a declaration urging the nations of the world to strengthen their battle against AIDS – a disease termed by then UN Secretary-General Kofi Annan as the “greatest challenge of our generation”. Indeed, 3 million adults and children die from AIDS annually – a sobering statistic, but one that is exceeded by the 3.3 million infants and children that die annually from birth defects and congenital developmental disabilities. Even in the United States, a country with one of the most advanced healthcare systems in the world, a child is born with a birth defect and two babies with low birthweight – every three minutes. Moreover, despite unprecedented intellectual and technological strides in the biomedical sciences, including sequencing of the human genome and advances in prenatal care/diagnostics – the overall incidence of birth defects and developmental disabilities is not declining and the underlying causes of nearly 70 percent of all birth defects remain unknown. In view of this, *the research activities in our laboratory seek to provide a better understanding of the molecular, genetic, and epigenetic basis of normal development, as well as elucidate the genes and molecules that when altered result in the genesis of birth defects and infant low birthweight.* Particular focus is centered on prenatal, maternal and child health issues relevant to the state of Kentucky. A combination of unique characteristics in the state, including socio-economic factors and an unusually high percentage of women who continue to smoke and drink during their pregnancy, contribute to an increased prevalence of major birth defects such as oro/facial clefting, neural tube defects, fetal alcohol- and maternal diabetes-induced embryopathies, as well as infant low birthweight and developmental disabilities.

Current Areas of Research Include:

- Role and interplay of TGF β , BMP and Wnt signaling pathways in development of the mammalian lip and palate.
- Epigenetic underpinnings of mammalian craniofacial development: defining the contribution and integration of microRNAs, DNA methylation and histone modifications in orchestrating development of the neural tube and morphogenesis of the orofacial region (lip and palate).
- Variants in microRNAs and gene-specific methylation as risk factors for orofacial clefting (cleft lip and palate) and neural tube defects.
- Epigenetic modifications of cranial neural crest progenitor (stem) cells and their role in the genesis of craniofacial anomalies.
- Role of maternal nutrition and in utero nutrient deficiencies in congenital craniofacial anomalies.
- Molecular and cellular mechanisms underlying pre/postnatal cigarette smoke exposure-induced neurodevelopmental and behavioral defects.
- Environmental epigenetics of in utero cigarette smoke or alcohol exposure and effects on craniofacial development and the genesis of craniofacial anomalies.
- Animal models and biomarkers of cigarette smoke's developmental toxicity

Grants:

PI: MM Pisano

PI: RE Neal

Title: “Developmental Cigarette Smoke Exposure: Biomarkers of Neurotoxicity”

Funding Agency: NIH (NIDA) R21-DA027466

Co-I: MM Pisano

PI: RM Greene

Title: “Transcriptional Coactivators and Pregnancy Outcomes”

Funding Agency: NIH (NICHD) R01- HD053509

PI: RM Greene

Co-I: MM Pisano

Title: “Nutritional Epigenetics and Orofacial Development”

Funding Agency: NIH (NICHD) R01-DE018215-05

Subproject Director: MM Pisano

P20 Director: RM Greene

Subproject Title: “Pre- and Postnatal Tobacco Smoke Exposure: Effects on Neurocognitive Development”

P20 Title: “Molecular Determinants of Developmental Defects”

Funding Agency: NIH (NIGMS) COBRE 9P20GM103453

Mentor: MM Pisano

Co-Mentor: RM Greene

Trainee: SC Smith

Title: Epigenetic and Developmental Consequences of Environmental Tobacco Smoke Exposure”

Funding Agency: NIEHS T32 ES011564 (PI: D Hein)

Training Grant and Center Grant Co-I or Faculty Mentor:

NIH/NIEHS Training Grant (T32 ES011564), Mentor; "Molecular Epidemiology and Mechanisms of Occupational/Environmental Diseases", PI - D. Hein; (2004-2014).

NIH/NIEHS Training Grant (T35 ES014559), Mentor, "Summer Environmental Health Sciences Training Program", PI - R. Prough; (2006-2016).

NIH/NIEHS Center Grant (P30-ES014443), Research Faculty; "Center for Environmental Genomics and Integrative Biology", PI - K. Ramos; (2007-2013)

Publications (2013-2014):

Amos-Kroohs RM, Williams MT, Brauna AA, Graham DL, Webb CL, Birtles TL, Greene RM, Vorhees CM, **Pisano MM**. Neurobehavioral phenotype of C57BL/6J mice prenatally and neonatally exposed to cigarette smoke. *Neurobehavior Teratology Toxicology* 35:34-45 (2013).

Luijten M, Singh AV, Bastian C, Westerman A, **Pisano MM**, Pennings JLA, Verhoef A, Green ML, Piersma AH, de Vries A, Knudsen TB. Altered developmental programming of the mouse mammary gland in female offspring following perinatal dietary exposures. *Plos ONE* February 2013 | Volume 8 | Issue 2 | e556.

Brock GN, Mukhopadhyay P, Pihur V, Webb CL, Greene RM, **Pisano MM**. 2013. MmPalateMiRNA, an R Package Compendium Illustrating Analysis of miRNA Microarray Data. *Source Code in Biology and Medicine* 8:1-20 (2013).

Warner DR, Wells JP, Greene RM, **Pisano MM**. Gene expression changes in the secondary palate and mandible of PRDM16^{-/-} mice. *Cell and Tissue Research* 351:445-452 (2013)

Mukhopadhyay P, Rezzoug F, Kaikous J, Greene RM, **Pisano MM**. Alcohol modulates expression of DNA methyltransferases and Methyl CpG/CpG domain-binding proteins in murine embryonic fibroblasts. *Reproductive Toxicology* 37:40-48. (2013).

Seelan RS, Mukhopadhyay P, Warner DR, Webb CL, **Pisano MM**, Greene RM. Epigenetic Regulation of Sox4 During Palate Development. *Epigenomics* 5:131-146 (2013).

Seelan RS, Appana SN, Mukhopadhyay P, Warner DR, Brock GN, **Pisano MM**, Greene RM. Developmental profiles of the murine palatal methylome. *Birth Defects Research A* 97:171-186 (2013).

Liu Y, Mukhopadhyay P, **Pisano MM**, Lu X, Huang L, Lu Q, Dean DC. Repression of Zeb1 and hypoxia cause sequential MET and induction of Aid, Oct4, and Dnmt1, leading to immortalization and multipotential reprogramming of fibroblasts in spheres. *Stem Cells* 31:1350-1362 (2013).

Seelan RS, Smolenkova I, Andres S, Wittliff JL, Mukhopadhyay P, Warner DR, **Pisano MM**, Greene RM. Epigenetic Analysis of Laser Capture Microdissected Fetal Epithelia. *Analytical Biochemistry* 443:68-74 (2013).

Green ML, **Pisano MM**, Prough RA, Knudsen TB. Release of targeted p53 from the mitochondrion as an early signal during mitochondrial dysfunction. *Cellular Signalling* 25:2383-2390 (2013).

Neal RE, Chen J, Rekha J, Jang H, Brock GN, Abomoelak B, Greene RM, **Pisano MM**. Developmental cigarette smoke exposure: Hippocampus proteome and metabolome profiles in low birthweight pups. *Toxicology* 317:40-49 (2014).

Warner DR, Mukhopadhyay P, Brock GN, Webb CL, **Pisano MM**, Greene RM. MicroRNA expression profiling of the developing murine upper lip. *Development Growth and Differentiation* 56:434-447 (2014).

Warner DR, Greene RM, **Pisano MM**. PRDM16 in Development and Disease. *Human Genetics and Embryology* 4:1-4 (2014).

Jin JZ, Warner DR, Lu Q, **Pisano MM**, Greene RM, Ding J. Deciphering TGFβ3 function in medial edge epithelium specification and fusion during mouse secondary palate development. *Developmental Dynamics* 243:1536-1543 (2014).

Greene, RM and **Pisano MM**. "Perspectives in orofacial cleft research III: Molecular mechanisms" in *Comprehensive Cleft Care, 2nd Edition*, Edit. Lossee, JE and Kirschner, RE; McGraw-Hill Inc., New York. (2015).

Seelan RS, Mukhopadhyay P, Warner DR, Appana SN, Brock GN, **Pisano MM**, Greene RM. Methylated microRNA genes of the developing murine palate. *microRNA* 3:160-173 (2015).

External Professional Activities (2013-2014):

Awards:

The Society for Experimental Biology and Medicine's "Best Clinical/Preclinical and Translational Paper of 2013" for Warner et al., *Cell Tissue Res.* 351:445-452.

Editorial Boards:

Developmental Biology Journal
Conference Papers in Molecular Biology
Reproductive Toxicology
International Journal of Embryology

Invited Ad Hoc Panel Member/Reviewer:

NIH Population Sciences and Epidemiology (PSE) Integrated Review Group, Special Emphasis Panel for RFA on Epigenetic, Social, Behavioral and Environmental Interactions, 2013.

NIH Risk, Prevention and Intervention for Addiction (RPIA) Review Panel, RFA for P50 Centers of Excellence - Tobacco Centers of Regulatory Science for Research Relevant to the Family Smoking Prevention and Tobacco Control Act, 2013.

NIH Infectious Disease, Reproductive Health, and Asthma/Pulmonary Conditions (IRAP) Review Panel, 2013.

NIH Special Emphasis Panel for Tobacco Control Regulatory Research (RFA-OD-13-010 and -011 RFA for), 2014.

Professional Affiliations:

Society for Developmental Biology
 American Cleft Palate Craniofacial Association
 Physician Champion Network of Kentucky

Ad Hoc Manuscript Reviewer:

Wellcome Trust; Austrian Science Foundation; Toxicology; Differentiation; Epigenomics; Epigenetics; Gene; J. Cell. Physiol.; In Vitro, Cell. Devel. Biol.; Develop. Dynamics; Lab. Investigation; Birth Defects Research. Pt. A.; Birth Defects Research. Pt. B; Intl. J. Dev. Biol.;

