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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 TGFß, 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.

Publications:

Singh S., C.L. Webb, R.M. Greene, **M.M. Pisano**. 2011. Arsenate-induced apoptosis in murine embryonic maxillary mesenchymal cells via mitochondrial-mediated oxidative injury. Birth Defects Res. A. 88:25-34.

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Warner D, P. Mukhopadhyay, G. Brock, V. Pihur, **M.M. Pisano**, R.M. Greene. 2011. TGFß and Wnt-3a interact to induce unique gene expression profiles in murine embryonic palate mesenchyme cells. Repro. Tox. 31:128-133.

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Mukhopadhyay P., G. Brock, S. Appana, C. L.Webb, R.M. Greene, **M.M. Pisano**. 2011. microRNA gene expression signatures in the developing neural tube. Birth Defects Res. A. 91:744-762.

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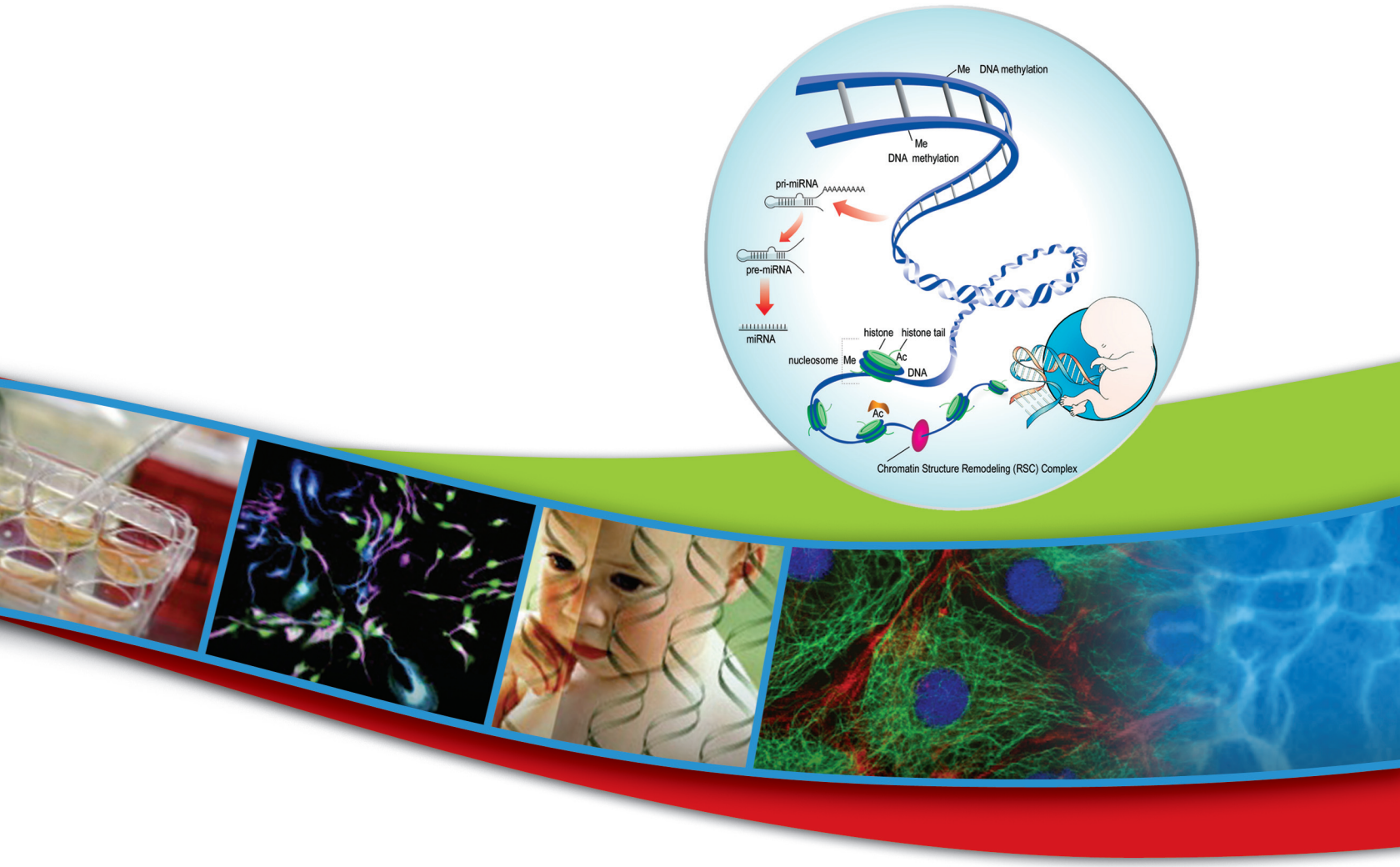
Green M.L., A.V. Singh, L.B. Ruest, **M.M. Pisano**, R.A. Prough, T.B. Knudsen. 2011. Differential programming of p53-deficient embryonic cells during rotenone block. Toxicology 290:31-41.

Warner D., C.L. Webb, R.M. Greene, **M.M. Pisano**. 2011. Altered signal transduction in Folr1-/- mouse embryo fibroblasts. Cell Biol. Int. 35:1253-1259.



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Mukhopadhyay P., C.L. Webb, **M.M. Pisano**, R.M. Greene. 2012. Strain-specific modifier genes governing craniofacial phenotypes in ski-null mice. Birth Defects Res. A. 94:162-175.

Warner D.W., P. Mukhopadhyay, C.L. Webb, R.M. Greene, **M.M. Pisano**. 2012. Chromatin immuno-precipitation-promoter microarray identification of genes regulated by PRDM16 in murine embryonic palate mesenchymal cells Exper. Biol. Med. 237:387-394. Special feature on EurekAlert!

Canales L., J. Chen, E. Kelty, S. Musah, C. Webb, **M.M. Pisano**, R.E. Neal. 2012 . Developmental Cigarette Smoke Exposure Alters Liver Proteome Profiles In Low birth weight Pups. Toxicol. 300:1-11.

Rekha J, J. Chen, L. Canales, T.M. Birtles, **M. M. Pisano**, R.E. Neal. 2012. Developmental Cigarette Smoke Exposure Alters Kidney Proteome Profiles. Toxicol. 299: 80-89.

Seelan R.S., P. Mukhopadhyay, **M.M. Pisano**, R.M. Greene. 2012. Developmental epigenetics of the murine secondary palate. ILAR Journal, special issue "Epigenetics – From Mice to Men." 53:240-248.

Amos-Kroohs RM, M.T, Williams, A.A. Brauna, D.L. Graham, C.L. Webb, T.S. Birtles, R.M. Greene, C.V. Vorhees, **M.M. Pisano**. 2013. Neurobehavioral phenotype of C57BL/6J mice prenatally and neonatally exposed to cigarette smoke. Neurobehav. Teratol Toxicol. 35:34-45.

Luijten M, A.V. Singh, C. Bastian, A Westerman, **M.M. Pisano**, J.L.A. Pennings, A. Verhoef, M.L. Green, A.H. Piersma, A. de Vries, T.B. Knudsen. 2013. 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 G.N., P. Mukhopadhyay, V. Pihur, R.M. Greene, **M.M. Pisano**. 2013. MmPalateMiRNA, an R Package Compendium Illustrating Analysis of miRNA Microarray Data. Source Code in Biol. and Med. 8(1)1 [Epub ahead of print].

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P. Mukhopadhyay, F. Rezzoug, J. Kaikaus, R.M. Greene and **M.M. Pisano**. 2013. Alcohol modulates expression of DNA methyltransfereases and Methyl CpG/CpG domain-binding proteins in murine embryonic fibroblasts. Repro. Toxicol. 94:162-175.

R.S. Seelan, P. Mukhopadhyay, D.R. Warner, C.L. Webb, **M.M. Pisano**, R.M. Greene. 2013. Epigenetic Regulation of Sox4 During Palate Development. Epigenomics – 5:131-146.

Seelan R., S.N. Appana, P. Mukhopadhyay, D.R. Warner, G.N. Brock, **M.M. Pisano**, R.M. Greene. Developmental profiles of the murine palatal methylome. Birth Defects Res. A Apr 3. doi: 10.1002/bdra.23126. [Epub ahead of print].

Editorships and Awards:

Greene R.M. and **M.M. Pisano**. Guest Editors, Epigenetic Processes in Development, Birth Defects Research A: Clinical and Molecular Teratology, (edit. DM Juriloff), Wiley-Blackwell, Hoboken, NJ (2011).

The Society for Experimental Biology and Medicine's "Best Clinical/Preclinical and Translational Paper of 2013" for Warner et al., Cell Tissue Res. 351:445-52.

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PI: M. Michele Pisano
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PI: Robert M Greene
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PI: Robert M. Greene
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PI: Robert M. Greene
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External Professional Activities:

Editorial Board: Reproductive Toxicology
Editorial Board: Developmental Biology Journal
Editorial Board: Conference Papers in Molecular Biology

Advisory Board: Genome Canada Funded Center, "Four Dimensional Modeling of Genetic Disease"

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Member: Physician Champion Network of Kentucky