Program/Abstract # 234
Genetic and phenotypic characterization of a novel mouse model of cleft palate
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Orofacial clefting is one of the most common birth defects in humans, affecting approximately 1 in 700 live births. This frequency likely stems from the complexity of craniofacial morphogenesis, which requires precise regulation of gene expression changes, alterations in cell physiology and morphogenic movements. Although an increasing number of genes have been linked to cleft lip and cleft palate, the mechanisms governing orofacial malformations remain unclear. Phenotype-driven approaches, such as N-ethyl-N-nitrosourea (ENU) mutagenesis and spontaneous mutants, provide an unbiased strategy to identify novel genes and pathways important for the etiology of cleft palate. We have recently identified a novel ENU-induced recessive mouse mutation, clfp4, which displays cleft secondary palate, omphalocele and skeletal malformations with high penetrance. While simultaneous presentation of orofacial clefting and body wall defects is observed in human syndromes, there are few mouse models that recapitulate these phenotypes. Preliminary mapping data places the mutation at the distal end of Chromosome 10, a region where this combination of phenotypes has not been reported. Thus, clfp4 likely represents a new model of craniofacial/body wall birth defects. We are currently conducting a high-resolution mapping cross to further narrow the critical interval harboring the causative gene and will utilize array-based capture and next-generation sequencing technology to identify the causative mutation. This work will improve our understanding of the molecular networks that regulate normal palate development and body wall fusion.

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Program/Abstract # 235
Cognitive and behavioral effects of mid pregnant (day 14) folinic acid supplementation on mice as illustrated by T-Maze and water maze performance
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The role of folate in the 1-carbon pathway is well understood. Necessary for metabolism and rapid cell division and growth, increased folate levels have been recommended to women who plan to become or are pregnant. The supplementation of folic acid has been shown to be a means of limiting birth defects associated with folate deficiency, such as neural tube defects. Something which has not been adequately researched is whether there are any adverse cognitive or behavioral effects associated with inconsistent administration of folic acid supplementation. In these experiments, we examined the cognitive, behavior and motor skills of mice whose mothers had received different levels of folinic acid for two days in mid-pregnancy (days 12–13). Dams were then assigned to two groups – those to be sacrificed on E14 for embryonic analysis and those allowed to go to term for cognitive and motor studies. Preliminary data show that the different levels of folinic acid administered in utero have profound effects on the performance of neonatal and juvenile mice. Mice treated at days 12–13 of gestation with high concentrations of folinic acid were not active or curious in the T-Maze, displayed aggression and lacked direction in the MWM. Our results demonstrate the possibility that inconsistent administration of folate supplements by pregnant women could negatively affect the developing fetus and later lead to cognitive, motor and behavioral deficits.

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Program/Abstract # 236
Molecular and morphological changes in development associated with alterations in 1-carbon metabolism during late pregnancy (day 17) in ICR mice
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