Program/Abstract # 357
Analysis of cardiovascular anomalies in the Ts65Dn mouse model for Down syndrome
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The Ts65Dn mouse is the most-studied murine model for Down syndrome (DS) or trisomy 21. Homology between triplicated murine genes and genes on human chromosome 21 (Hsa21) correlates with the shared anomalies of Ts65Dn mice and DS patients. Congenital heart defects occur in approximately 50 percent of DS individuals and we have worked to characterize cardiovascular anomalies observed in Ts65Dn neonates. Vascular abnormalities were identified in 17 percent of trisomic neonates by examination of gross anatomy. We found right aortic arch with Kommerell’s diverticulum, interrupted aortic arch and persistent truncus arteriosus. Intracardiac defects were detected using staining with hemotoxylin and eosin, and Masson’s trichrome. We have identified interventricular septal defects and broad foramen ovale in trisomic neonates. Additionally, immunohistochemistry indicates abnormal muscle composition in the cardiac valves of trisomic neonates. These findings suggest that the gene imbalance in Ts65Dn disrupts crucial pathways in cardiac development.

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Program/Abstract # 358
Guidance molecules in organogenesis: Slit signaling in Drosophila hindgut development
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The alimentary canal in the Drosophila embryo is comprised of three regions, the foregut, midgut and hindgut. The most posterior section, the hindgut, forms by invagination of ectoderm, DNA endoreplication and convergent extension. The hindgut is subdivided into the small intestine, large intestine and rectum. The large intestine contains three morphologically and molecularly distinct cell populations. These are described as dorsal, ventral and boundary cells. The presence of guidance cues that lead migrating cells to their points of attachment has been shown in the CNS and somatic muscle systems in Drosophila. Specifically, the ECM protein, Slit, and Roundabout (Robo) family of receptors function in both systems to repel the migrating cells. Slit, Robo and Robo2 are also expressed in the hindgut. At this time in development, the cells of the hindgut have already been determined. Dorsal, ventral and boundary cells are correctly specified in slit loss of function mutants as shown by immunohistochemical stainings using cell-specific markers. Moreover, in slit loss of function mutants, lumen defects as well as defects in overall cell shape are seen using EM and immunohistochemistry. We suggest a novel role for Slit in lumen formation and cell shape regulation in the Drosophila hindgut.

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and underscores a novel function of non-canonical Wnt signaling in the endoderm.

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Program/Abstract # 360  
Zebrafish enteric neuron formation corresponds to smooth muscle development
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Multipotent enteric precursors from the vagal neural crest migrate through the pharyngeal arches into the digestive system and migrate to the posterior of intestine. During migration, precursors proliferate and differentiate into diverse neurons and glia that populate the entire digestive system. Previously, the zebrafish digestive system has been shown to be homologous to other vertebrates. In this work, we further characterize zebrafish enteric development. We have previously found that increases in differentiated zebrafish enteric neurons are completed by 98 hpf. Here we show that development of this system progresses through distinct steps beginning with a rapid proliferative phase during migration of enteric precursors. Proliferation then slows and is combined with a relatively slow phase of enteric neural differentiation. This slow phase of enteric neural differentiation corresponds to formation of circular smooth muscle during the first half of the third day. Longitudinal muscle develops during the last half of the third day and appears to be fully formed by the beginning of the fourth day. As the longitudinal smooth muscle matures, a rapid phase of enteric neural differentiation begins. During this time, we observe differentiation of the final two thirds of enteric neurons. Formation of the enteric neurons and intestinal smooth muscle appears to be coordinated and reciprocal interactions between the tissues may be needed to complete development. Further analysis of digestive mutants or embryos manipulated by morpholino will unravel the extent of the interdependence of the two tissues during development.

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Program/Abstract # 361  
Expression profiling the developing mammalian enteric nervous system identifies novel markers and candidate Hirschsprung disease genes
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The enteric nervous system (ENS) is composed of neurons and glial cells, organized as interconnected ganglia within the gut wall, which control its persistaltic and secretory activity. The Ret receptor tyrosine kinase is expressed throughout enteric neurogenesis and is required for normal ENS development; humans with mutations in the RET locus have Hirschsprung disease (HSCR—an absence of ganglia in the colon) and mice lacking Ret have total intestinal aganglionosis. Using RNA from wild type and Ret mutant (aganglionic) gut tissue and DNA microarrays, we conducted a differential screen for ENS expressed genes and identified hundreds of candidate ENS expressed genes. This screen was robust and sensitive; all 47 analyzed genes are expressed in the ENS, including some expressed in only subpopulations of ENS cells. Many novel genes for studying ENS development were identified, including genes with human homologues mapping to previously identified HSCR susceptibility loci, thus representing excellent candidates for HSCR disease genes. The success of this screen has sparked a range of research extensions: mice mutant for the candidate HSCR disease genes are being examined for ENS defects; zebrafish TILLING mutants are enabling cross-species screens for ENS development regulators; and finally, transgenic mouse tools are now being used in novel ways to isolate ENS stem cells/progenitor cells, which may have applications in stem cell replacement therapies in HSCR models.

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Program/Abstract # 362  
Mouse mutagenesis for targeting mutations causing abnormal diaphragm development
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Defects in diaphragm development are devastating birth defects in humans. Congenital posterolateral diaphragmatic hernias occur in 1/3000 live births and have an overall mortality near 50%. The pathogenesis of these defects is poorly understood. Mouse models of abnormal diaphragm development are needed for the study of diaphragmatic embryogenesis. Mouse mutagenesis with ethynitrosourea (ENU) is a valuable tool for modeling specific defects in organogenesis. Although induced mutations are random, screening may be performed to target organs of interest. As part of an ongoing ENU mutagenesis screen, embryos were specifically examined for defects in diaphragm development. From this screen, over 2000 embryos were screened in late embryogenesis, and three new mouse models were recovered. The “Overgrown” mutation causes muscle overgrowth onto the central tendon. Mice with the “Heartburn” mutation have a hiatal hernia, and some also have separate posterior diaphragmatic defects. A third line has a left sided posterior diaphragmatic hernia. To map these mutations, a whole-genome SNP genotyping panel is being used to identify regions of retained homozygosity of A/J strain genome (the mutagenized strain) in mutant animals. The “Overgrown”