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DiGeorge syndrome/velo-cardio-facial syndrome (DGS/VCFS; 22q11.2 deletion syndrome) is the most common microdeletion syndrome in humans with an estimated incidence of 1/4000. Typical features of this syndrome are cardiovascular defects such as interrupted aortic arch, outflow tract defects, thymus and parathyroid hypo- or aplasia as well as submucous cleft palate. The TBX1 gene within the 22q11.2 region deleted in affected individuals encodes a T-box transcription factor. Heterozygosity of Tbx1, the mouse homologue of TBX1, results in mild defects dependent on genetic background, whereas complete inactivation results in severe malformations in multiple tissues, indicating that embryonic development is highly sensitive to Tbx1 gene dosage. We report here that loss of function mutations in two Sprouty genes, which encode feedback antagonists of receptor tyrosine kinase (RTK) signaling, phenocopy many defects associated with the syndrome in the mouse. A stepwise reduction of Sprouty gene dosage resulted in different phenotypes emerging at specific steps, suggesting that the threshold up to which a given developmental process can tolerate increased RTK signaling is different. Tbx1 heterozygosity significantly exacerbated the severity of all these defects, which correlated with a substantial increase in RTK signaling. We conclude from these observations that TBX1 functions as an essential component of a buffering mechanism that protects the embryo against perturbations in RTK signaling that may lead to developmental defects characteristic of DGS/VCFS.

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Program/Abstract # 408
Reciprocal rescue of sensory cell cilia defects by CEP290 and BBS6 (MKKS) alleles

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Ciliopathies are developmental disorders that arise due to defects in cilia biogenesis and function, and affect various sensory systems including the auditory system. Involvement of multiple syndromic ciliopathy genes, whose protein products are thought to function as macromolecular complexes in both cilia and basal bodies, implicate dynamic regulation of ciliary protein interactions. Mutations in CEP290 (also known as NPHP6 or BBS14), have been found to cause several ciliary disorders [Leber congenital amaurosis (LCA), Senior–Loken syndrome, Joubert syndrome, nephronophthisis (NPHP), Meckel–Gruber syndrome (MKS) and Bardet–Biedl syndrome (BBS)]. Little is known about the function of CEP290, or how this protein interacts with other cilia-related proteins complexes. An initial finding of variants of MKKS (also known as BBS6) in LCA patients led to an exploration of epistatic interactions between CEP290 and MKKS. We found that the DSD domain of CEP290, which is deleted in a mouse model (Cep290rd16) of LCA, directly interacts with MKKS, and that pathogenic variants of MKKS disrupt this interaction. Mice with either Cep290rd16/rd16 or Mkksko/ko genotypes exhibit structural and functional auditory, photoreceptor, and olfactory deficits. Unexpectedly, Cep290rd16/rd16; Mkksko/ko double mutants actually show a degree of functional and/or morphological rescue in all three sensory systems by comparison with either single mutant. Morphological analysis suggests that improved ciliogenesis forms the mechanistic basis for this functional rescue. Our data demonstrate reciprocal modifier effects between the CEP290 DSD domain and MKKS that provides insight into the regulation of cilia formation and function.

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Program/Abstract # 409
Shwachman Diamond Syndrome is a p53-independent ribosomopathy

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Mutations in the human Shwachman–Bodian Diamond Syndrome (SBDS) gene cause chronic neutropenia, exocrine pancreas dysfunction and skeletal defects. Although the precise cellular function of SBDS is unknown, it has been implicated in ribosome biogenesis. Diseases that affect ribosome biogenesis, termed ribosomopathies, are generally understood to do so through a p53-dependent mechanism. We used morpholino knock-down of the zebrafish orthologue of SBDS to recapitulate the disease phenotype. Loss of SBDS in zebrafish resulted in a loss of neutrophils, a small exocrine pancreas and a disrupted skeletal architecture. Unlike other ribosomopathies, we have demonstrated that loss of p53 does not rescue the SBDS MO mediated phenotype. We conclude Shwachman Diamond Syndrome is a p53-independent ribosomopathy.

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Program/Abstract # 410
BMP signaling as a context-dependent regulator of myocardial proliferation and apoptosis: Relevance to congenital heart defects and adult heart disease

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Acquired heart disease in adults is a leading cause of disability and death, while cardiac malformations are a leading cause of prenatal and neonatal death. Organogenesis of the heart involves a complex contribution of multiple cell types from several sources, and the heart must become functional well before its development is complete. An understanding of the extracellular signals that regulate heart development will help clarify how the heart is constructed, and may prove useful in elucidating molecular pathways relevant to adult heart disease and its treatment. We have used mouse models to probe the roles of Bone Morphogenetic Protein (BMP) signaling in heart development and disease. Several tissue-specific genetic ablations and in vitro explant culture experiments demonstrate a direct requirement for BMP signaling in regulating myocardial differentiation and proliferation in extracardiac progenitors. Later, BMP signaling is necessary within the heart for cardiomyocyte proliferation. We further find that BMP antagonism by Noggin is necessary to keep myocardial proliferation in check during embryogenesis. Thus, BMP signaling and its antagonism balance myocardial proliferation in the embryonic ventricles. In the adult heart, BMP signaling increases in myocardium that has become ischemic upon cardiac artery blockage (myocardial infarction). We find that BMP promotes apoptosis in infarcted heart tissue. Genetic or pharmacological reduction of BMP activity reduces apoptosis and the extent of myocardial damage after injury. Our findings shed new light on the regulation of normal mammalian heart development and its

anomalies, and suggest potential therapeutic approaches to adult heart disease.

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Program/Abstract # 411
Poster: TGF-beta signaling reduces FGF-10 in hypoxic newborn mouse lung during the critical period of lung development
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Introduction: We have recently shown that excessive transforming grow factor (TGF-β) signaling mediates hypoxia-induces inhibition of alveolar development and abnormal pulmonary arterial remodeling in the newborn lung, producing a phenotype that mimics bronchopulmonary dysplasia (BPD) in preterm infants. The mechanisms by which excessive TGF-β signaling inhibits alveolar septation are not known. Fibroblast growth factor (FGF)-10 is a critical modulator of early lung development and in the saccular stage but its role in alveolar septation has not been defined. It has been shown that the FGF-10 promoter contains a TGF-β response element. *Objective*: We hypothesized that excessive TGF-β signaling in the newborn hypoxia-induced mouse lung inhibits alveolar septation via reduction of FGF-10. *Methods*: In vivo: Wilde type C57BL/6 were exposed to air or hypoxia (12% O2) from birth to two weeks (the critical period of lung development) and evaluated for FGF-10 and TGF-β mRNA and protein. Inhibition of TGF-β signaling was achieved by administration of TGF-β neutralizing antibody (ID11) to WT mice or 20 ug/g ZnSO4 given intraperitoneally daily to DNIIR pups (an inducible dominant-negative mutation of the TGF-β type II receptor) and exposed to hypoxia or air from birth to 14 days of age. In vitro: Newborn Lung Fibroblasts and Pulmonary Microvascular Endothelial Cells (PMVEC) were exposed to air or hypoxia for 24 h. FGF-10 mRNA and protein were evaluated in cell lysates. *Results*: Hypoxia reduces FGF-10 mRNA in both in vivo (Fig. 1) and in vitro studies (Fig. 3). Pups receiving the TGF-β neutralizing antibody (ID11) had increased FGF-10 and better lung development (Fig. 1). FGF-10 staining was not significantly decreased in DNIIR hypoxic mice compared to air control (Fig. 2). *Conclusion*: These results suggest that hypoxia-induced increased TGF-β signaling may reduce FGF-10, which may contribute to impairment of lung development. *Future experiments*: Additional studies are in progress to inhibit FGF-10 signaling in vivo, to determine if FGF-10 is necessary for alveolar septation.

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Program/Abstract # 412
A mouse model for juvenile hydrocephalus
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Juvenile hydrocephalus, the accumulation of cerebrospinal fluid (CSF) in the ventricles of the brain, causes significant morbidity among human children affecting roughly 1 in 500 newborns. The disease manifests due to overproduction, decreased absorption, or restricted flow of CSF. Few genetic causes of this disease are known, and therefore animal models can prove beneficial in identifying candidate genes. The Juvenile hydrocephalus (Jh) mouse line contains a transgenic integration on mouse chromosome 9. Homozygous Jh mice exhibit hydrocephalus by two weeks of age and few survive beyond eight weeks. This phenotype represents a novel cause of the disease since no known hydrocephalus mutations map to the region. Analysis of the integration site showed disruption of an uncharacterized gene, I11. Preliminary data suggests that a transgene carrying a functional copy of I11 can rescue the Jh phenotype. However, the predicted protein product of I11 has no recognizable functional domains and its role in CSF maintenance is unknown. Future research will focus on definitively establishing the role of I11 in hydrocephalus and dissecting its function.

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Program/Abstract # 413
Characterization of zebrafish orthologues of the human B3GALTL gene involved in Peters-Plus syndrome
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Purpose: Peters-Plus Syndrome (PPS) is an autosomal recessive disorder characterized by ocular anterior segment dysgenesis (primarily Peters' anomaly), short stature and brachydactyly along with additional variable features. Mutations in Beta-1,3-glucosyltransferase (B3GALTL) gene were shown to explain 100% of classic PPS cases. No animal models have yet been developed. This study aims to characterize zebrafish orthologues of B3GALTL in terms of sequence, expression pattern and function. *Methods*: Zebrafish orthologues of human B3GALTL were identified using database analysis, RT-PCR and sequencing; expression was analyzed using RT-PCR and in situ hybridization; knockdown was performed via injection of morpholino oligomers targeting zebrafish B3GALTL genes followed by RT-PCR transcript analyses. Gross morphological analysis of morphants was done using alcian blue staining and histology. *Results*: Two orthologues of human B3GALTL gene were identified: B3GALTLA and B3GALTLB. Each is expressed early in development. In situ hybridization showed distinct expression patterns for B3GALTLA in the brain, lens, retina, and other structures. Knockdown of one or both genes produced zebrafish with phenotypes similar to PPS. Alcian blue staining revealed defects in craniofacial cartilage formation. Histology and brightfield examination showed cornea and brain malformations, curved and short trunks, enlarged heart, and fin abnormalities. Semi-quantitative RT-PCR data confirmed morpholino efficiency. *Conclusion*: Zebrafish B3GALTLA and B3GALTLB are essential for normal embryonic development and have conserved function with the human gene. A zebrafish model of PPS is being developed to study mechanisms of this debilitating condition.

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Program/Abstract # 414
The planarian *Schmidtea mediterranea* as a free-living model for understanding and controlling flatworm parasites
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Schistosomiasis is a tropical disease caused by flatworm parasites (*Schistosoma*) that affects hundreds of millions of people in the developing world. Although only a single drug (praziquantel) is available to treat this disease, the complicated life cycle of this parasite, that involves both mollusc and vertebrate hosts, impedes efforts to uncover and validate novel therapeutic targets. Thus, we are