Interestingly, cardiac myocytes transfected with Daam1 siRNA contract at a rate approximately three times higher than control treated myocytes, suggesting that Daam1 regulates cardiac contractility. Thus, Daam1 regulates cardiomyocyte cell–cell interactions and may be required for late stage remodeling in the heart.

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Program/Abstract # 130
LR asymmetric morphogenesis of heart looping
Shanhong Cheng, Brad Graham, Ranajeet Sound, Gary Schoenwolf, Yukio Saijoh
Department of Neurobiology and Anatomy, University of Utah, USA

Establishment of left right (LR) axis formation is required for correct positioning and function of internal organs. Our long-term goal is to reveal the mechanism of how LR asymmetric signals regulate LR asymmetric morphogenesis. Our previous work has revealed the significance of the Nodal-signaling pathway in the establishment of the LR asymmetry, which is required for the correct positioning and morphogenesis of internal organs. However, the cellular and molecular mechanisms by which LR signals bring about asymmetric organ development are unknown. We are investigating how LR signals regulate cell behaviors in asymmetric heart looping morphogenesis. The heart is the first organ to exhibit LR asymmetry, and its looping morphogenesis is readily accessible in culture. The left and right primordial heart fields migrate and fuse to form a single heart tube that subsequently loops rightward. Looping morphogenesis is achieved by rotation of the heart tube exerted by the out flow tract rotation and overriding of left caudal rudiments. We focus on cellular behaviors in these events and have analyzed cell movement by dye labeling and morphological changes by time lapse imaging, cell proliferation, and gene expression in the chick and mouse. Our cell tracing experiments showed changes in cell positions from mediolateral to anteroposterior orientation, and significant cell cluster extension during migration, which could be major forces for looping morphogenesis. Based on these data, we will discuss how LR signals regulate LR asymmetric looping of the heart.

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Program/Abstract # 131
Inturned PCP effector gene is required for cilia biogenesis and mouse embryonic development
Aimin Liu [a], Huiqing Zeng [a], Weisheng Wu [a], Aaron Wynkoop [a], Lee Niswander [b], Aimin Liu [b]
[a] *Department of Biology, Pennsylvania State University, University Park, PA, USA*
[b] *Department of Pediatrics, UCHSC, Aurora, CO, USA*

Cilia are cell surface organelles required for mammalian embryonic development and multiple adult physiological functions. Recent protein localization studies indicated that some proteins regulating the planar cell polarity (PCP) pathway are localized to the axonemes and basal bodies of the primary cilia. However, the functional significance of this connection between cilia and PCP regulation has yet to be corroborated in mammals. The inturned PCP effector (Intu) gene was originally identified in the fruit flies based on its role in regulating the formation and polarity of wing hairs. In the current study, we take both forward and reverse genetic approaches to study the function of Intu in the mouse. Double-thumb (Dtm), a hypomorphic mutant allele of Intu generated by chemical mutagenesis, exhibits polydactyly and behavioral defects including circling and head bobbing. We also generated a null Intu mutant through gene-targeting in mouse embryonic stem (ES) cells, and found that the complete loss of Intu function results in multiple developmental defects including neural tube defects, spinal cord patterning defects and severe polydactyly. Our scanning electron microscopic study indicated that cilia biogenesis is disrupted by the mutation in Intu. In conclusion, our study provided the first evidence in the mouse that a PCP effector gene is required for ciliogenesis and embryonic development.

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Program/Abstract # 132
Patterning of the mouse embryonic germ layers: The Townes and Holtfreter cell sorting experiments revisited
Robert Moore [a,b], Kathy Q. Cai [b], Xiang-Xi Xu [a,b]
[a] *Department of Medical Oncology, Fox Chase Cancer Center, Philadelphia, PA, USA*
[b] *Department of Medicine, UM/Sylvester Comprehensive Cancer Center, Miami, FL, USA*

The experiments undertaken by Townes and Holtfreter described that cells dissociated from the embryonic germ layers segregated homotypically once homogeneously mixed. Subsequently, Steinberg pioneered the differential adhesive hypothesis (DAH) to explain these and other patterning phenomena. We have revisited these issues using embryoid bodies derived from mouse embryonic stem (ES) cells where nascent endoderm is distributed, initially internally but eventually sorts to the spheroid surface. Wild type and E-cadherin null ES cells were used to generate chimeric embryoid bodies to probe the relative importance of adhesion and differentiation for the partitioning of endoderm to surface. When undifferentiated wild type and undifferentiated E-cadherin null ES cells were mixed, the resulting cell aggregates consisted of a core of highly adhesive wild type cells surrounded by E-cadherin null cells, consistent with the DAH. Both ES cell types were also differentiated into primitive endoderm-like cells by exposure to retinoic acid and then mixed with undifferentiated counterparts. We observed that endoderm cells always sorted to the surface to form an endoderm layer irrespective of their E-cadherin status or that of their undifferentiated counterparts. Thus, the sorting of primitive endoderm from pluripotent ES cells contradicts the DAH. We propose that the autonomous ability of endoderm cells to generate apical polarity, rather than differential adhesive affinity, governs the developmental restriction of primitive endoderm cells to a superficial layer.

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Program/Abstract # 133
Sequential roles of Wnt signaling/β-catenin in mouse ventral dermal development
Radhika Atit [a], Jennifer Ohtola [a], John Myers [a], Batool Akhtar-Zaidi [a], Diana Zuzindlak [a], Pooja Sandesara [a], Susan Mackem [a,b,c,d]
[a] *Department of Biology, Case Western Reserve University, OH, USA*
[b] *Laboratory of Pathology, National Cancer Institute, Bethesda, MD, USA*
[c] *Department of Genetics, Case Western Reserve University, OH, USA*
[d] *Department of Dermatology, Case Western Reserve University, OH, USA*