was also diminished. In addition, there were increased apoptosis and decreased proliferation in the PSM of double mutant embryos. These results indicate that *Wnt5a* and *Wnt11* signaling regulates somitogenesis and somite patterning by regulating *Notch* and *Shh* expression and is required for cell proliferation and survival in the PSM.

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Program/Abstract # 394
BMP signaling through ACVR1 is crucial for establishment of the left–right asymmetry via proper formation of node cilia in the mouse
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BMPs have multiple functions including their role in the establishment of left–right patterning in vertebrate development. Recently, we discovered that BMP type I receptor Acvr1 (also known as Alk2) in the epiblast is required for proper left–right patterning using chimeric mouse embryos. To address further how Acvr1 is involved in the process of the establishment of left–right asymmetry, we utilized a conditional gene inactivation strategy to rescue the gastrulation defects of the Acvr1 null mutation. Mosaic inactivation of Acvr1 mutants in the epiblast by using Mox2-Cre (Acvr1:Mox2-Cre) resulted in abnormal heart looping and bilateral expression of left side markers such as Nodal in the lateral plate mesoderm. Acvr1:Mox2-Cre embryos displayed a deformed node structure with abnormal cilia development that resulted in a defect of a cilia-driven leftward flow in the extracellular fluid. Interestingly, Acvr1:Mox2-Cre embryos also displayed abnormal cilia development in a ventral part of the neural tube. Furthermore, mouse embryonic fibroblasts deficient in Acvr1 fail to form the primary cilium, when stimulated by serum starvation. These observations suggest that BMP signaling through ACVR1 is essential for proper development of primary cilia during mouse development and ACVR1 plays a crucial role in formation of node cilia to establish a left–right asymmetry in the mouse.

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Program/Abstract # 395
Endoderm function in left–right development in mice
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The development of left–right (LR) asymmetry is an integral part of the organization of the body plan. Nodal and Lefty2 are the earliest known asymmetric markers expressed at E8.5 in the left lateral plate mesoderm (LPM). However, the initial symmetry breaking event occurs at E8.0 in the mouse node, and involves the leftward flow of extra-embryonic fluid over the node surface known as 'nodal flow'. It is currently not known how this asymmetric LR signal generated in the node transfers to the left LPM. Recent studies have shown upregulated calcium signaling in endoderm cells preferentially in the left side of the node, indicating possible involvement of endoderm in the leftward migration of the LR signal. This study explores the functional requirement of the endoderm layer in LR asymmetry generation using mutants defective in endoderm development in mice. Sox17, a HMG-box transcription factor is required for endoderm formation in mice and other species. Sox17 expression in migrating lateral endoderm cells and node precursors during early gastrulation, and in close proximity to the node at early somite stages suggests possible roles in LR signal transfer. Mice embryos mutant for Sox17 were found to show loss of asymmetric gene expression in the LPM as well as defects in heart looping morphogenesis. Current studies investigate the state of symmetry breaking event in the mutant node and the level of calcium signaling in the endoderm. It is expected that these studies will contribute significantly to our understanding of the establishment of LR asymmetric gene expression and consequent asymmetric development of heart and internal organs.

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Program/Abstract # 396
Endoderm cell signaling networks during liver and pancreas specification
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During embryonic development, the liver and pancreas arise from the anterior foregut endoderm, and genes specific for these tissues are activated by gradients of FGF and BMP proteins secreted from adjacent mesodermal cells. How these extracellular signals activate tissue specific gene programs in different endoderm domains and which signal transduction pathways they employ are, however, not well understood. We have recently shown that hepatic gene induction is elicited by the FGF/MAPK pathway in the prospective hepatic endoderm domain (Calmont et al., 2006). We are now investigating the roles of BMP, TGFb, and p38 MAPK pathways in the activation of the pancreatic and hepatic gene programs. In our experimental approach we use immunohistochemistry with phospho-specific antibodies, specific signaling pathway inhibitors on embryo cultures and conditional inactivation of *Smad4* gene in the endoderm, to elucidate the pattern of expression and biological role of the pathways of interests. By examining diverse signal pathways activations in the foregut domain, superimposed upon our previously determined fate map (Tremblay et al., 2005), we are developing a temporal map of the signaling networks that lead to foregut patterning and liver and pancreas specification.

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Program/Abstract # 397
Notch pathway mutants display craniofacial birth defects and disrupt expression of the pharyngeal arch gene *Barx1*
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Notch signaling is required for craniofacial development. Alagille syndrome, caused by *JAG1* haploinsufficiency in humans, is

characterized by small maxilla and mandible, and *Jag2* null mice have been reported to display severe craniofacial defects. Previously, we obtained significant correlations between decreased hard palate length and mandible height to mandible length ratios in the skeletons of *Dll3-Notch1* double heterozygous mice. Based on these findings, we are analyzing the skeletons of other notch pathway mutants, namely $Dll3^{tm1Rbe/tm1Rbe}$ and $Lfng^{tm1Rjo/tm1Rjo}$, for craniofacial anomalies. In addition, we used microarrays to identify candidate genes that may be down or up-regulated in Dll3 and *Notch1* null embryos during early craniofacial development. 31 genes displayed more than two-fold decreases in mutant embryos, including *Barx1*, a negative regulator of wnt signaling, and the notch pathway gene *Id4*. *Barx1* is expressed in pharyngeal arch 1 and 2 at 9.5@@dpc, and quantitative PCR confirms that expression levels are decreased in *Notch1* and *Dll3* embryos. We are analyzing changes of *Barx1* and *Id4* and other down-regulated genes in the frontonasal prominence and pharyngeal arches of notch mutant embryos.

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Program/Abstract # 398

_O_-Fucose modification is essential for patterning mesoderm in the mouse embryo

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Thrombospondin type 1 repeat (TSR) superfamily members regulate diverse biological activities ranging from cell motility to inhibition of angiogenesis. TSRs are structurally similar to Notch epidermal growth factor repeats. Given the importance of *O*-fucose in modulating Notch receptor function, we predicted that *O*-fucosylation of TSRs will be developmentally significant. Here we demonstrate that mouse *p*rotein *O*-*fu*cosyl*t*ransferase-*2* (POFUT2) specifically adds *O*-fucose to TSRs, and is essential for normal gastrulation. Although early post-implantation allocation of embryonic and extra-embryonic tissues and establishment of anterior/posterior asymmetry occur independent of POFUT2 function, defects in tissue organization and patterning appear after the onset of gastrulation (E6.5). The laterally expanded primitive streak of *Pofut2* mutants resulted in an abundance of mesoderm at the expense of ectoderm derived tissues. Expression of *Snail1* and *Flk1* throughout the mesenchyme suggests that mesoderm is comprised solely of proximal endothelial/blood progenitors. In contrast, teratomas derived from *Pofut2* mutant embryos contain diverse tissues of mesoderm and ectoderm origin, suggesting that *Pofut2* mutant defects are non-cell autonomous. Combined, these results provide evidence that *O*-fucosylation of TSR protein(s) is essential for remodeling or turnover of extracellular matrix, cell-matrix interaction, and/or regulation of signal pathways that are essential for establishing normal patterning within the mouse gastrula.

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