Program/Abstract # 195
Role of xSyndecan4 in non-canonical Wnt signaling
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The non-canonical or β-catenin independent Wnt signaling pathway regulates convergence and extension movements in vertebrate embryos and planar cell polarity. Recently in our laboratory, we have demonstrated that a cell surface heparan sulphate proteoglycan, Syndecan4 (xSyn4), is critical for *Xenopus laevis* gastrulation and is a component of the non-canonical Wnt signalling pathway. We have found that xSyn4 is expressed in the same tissues and interacts functionally and biochemically with Frizzled-7 (xFz7) and Dishevelled (xDsh). Furthermore, xSyn4 is necessary and sufficient to activate translocation of xDsh to the plasma membrane. In this work we have used methodologies such as GST-pulldown and immunoprecipitation in HEK293T cells in order to investigate the interaction between xSyn4, xDsh and xFz7. We have observed that xDsh and xFz7 interact with xSyn4 cytoplasmic domain. Also, we have found that xSyn4 stability is regulated by activation of the non-canonical Wnt pathway in a proteasome dependent manner and that the cytoplasmic domain is required for such effect.

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Program/Abstract # 196
A bimodal modulator in canonical Wnt signal transduction
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The Wnt family of secreted ligands plays critical roles in embryonic development and cancer formation. In canonical Wnt signaling, β-catenin is a key component of the pathway for transducing the signal from the cytoplasm to the nucleus and regulating Wnt-responsive genes by binding to a member of the TCF/LEF transcription factors. Here we show that a DNA binding protein has a bimodal activity in canonical Wnt signaling. When we have knocked down the protein expression by morpholino antisense oligo (MO), TOPFlash reporter activity is significantly reduced in *Xenopus* embryo. While modest exogenous expression has additive effect on reporter activity when coinjected with Wnt-8 or β-catenin, a higher amount of mRNA injection results in inhibition of canonical Wnt signaling. Lef1 activity is reduced by the MO, suggesting that it functions at the transcription level. These results provide a novel insight into a regulation of TCF/LEF activity.

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Program/Abstract # 197
A role of Diversin subcellular localization in modulating Wnt signaling
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Wnt proteins are secreted glycoproteins that play crucial roles in cell proliferation, cell fate specification and morphogenetic processes in early embryos. Molecular mechanisms, by which distinct beta-catenin-dependent and beta-catenin-independent pathways are activated in Wnt responding cells, are not well understood. The ankyrin-repeat protein Diversin has been implicated in different Wnt pathways and associates with critical Wnt pathway regulators including Dishevelled, CK1-epsilon and Axin. Here we show that Diversin is localized to the centrosome and this localization depended on the C-terminal domain of Diversin. This centrosomal distribution is altered in ectodermal cells stimulated with specific Wnt ligands. Also, Diversin was recruited to the cell membrane by Frizzled receptors, and this regulation required the ankyrin-repeat domain of Diversin. We will present the comparison of signaling activities of wild type Diversin and the Diversin constructs lacking centrosomal localization. Our data support the hypothesis that the regulation of Diversin subcellular distribution is critical for different Wnt signaling outcomes.

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Program/Abstract # 198
Cardiomyocyte-specific loss of neurofibromin promotes cardiac hypertrophy and dysfunction through activation of the fetal gene program
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Neurofibromatosis type I (NF1) is a common autosomal dominant disorder with a broad array of clinical manifestations, including benign and malignant tumors, osseous dysplasias, and characteristic cutaneous findings. NF1 patients also have an increased incidence of cardiovascular diseases, including obstructive vascular disorders and hypertension. The disease gene, NF1 encodes neurofibromin, a ubiquitously expressed protein that acts, in part, as a Ras-GAP (GTPase activating protein), downregulating the activity of activated Ras protooncogenes. In animal models, endothelial and smooth muscle expression of the disease gene is critical for normal heart development and the prevention of vascular disease, respectively. To examine the role of NF1 in the adult heart, we generated mice with homozygous loss of the murine homolog Nf1 in myocardium (Nf1mhcKO). These mice have normal embryonic cardiovascular development, but have marked cardiac hypertrophy in the adult. This hypertrophic response appears to be mediated through activation of a fetal gene program. Interestingly, this activation may not be regulated solely though attenuation of Ras activity, and preliminary work in our laboratory has suggested novel cell signaling pathways through which this, and other neurofibromin-mediated responses, may be acting.

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Program/Abstract # 199
Nf1 is required for early murine lens development
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Human neurofibromatosis 1 (NF1) is an autosomal dominant genetic disease characterized by multiple discrete dermal neurofibromas as well as optic and other central nervous system gliomas. Neurofibromin, the protein product of the NF1 gene has been shown to function as a Ras-GTPase activating protein (GAP). In addition to this tumor suppressor role, neurofibromin may also regulate adenylyl-