Program/Abstract # 417
Molecular characterization of *C. elegans* gene ZK1010.3, a homologue of human frg-1
Qian Liu, Peter L. Jones
Department of Cell and Dev. Biol. Univ. of Ill., Urbana, IL, USA

FSHD is an autosomal dominant myopathy characterized by progressive atrophy of skeletal muscles. FSHD region gene 1 (*FRG1*) is a leading candidate gene for FSHD pathology. Overexpressing FRG1 in mouse skeletal muscle or *Xenopus* tadpoles results in an FSHD-like phenotype. We analyzed expression of endogenous *C. elegans* FRG1 (Zk1010.3) and found that early in development FRG1 is a nuclear protein, in adult animals the endogenous FRG1 protein was primarily cytoplasmic, indicating a developmental regulation of subcellular localization and potentially multiple roles for FRG1 in muscle development. Misexpression of FRG1 by either RNAi knockdown or transgenic overexpression disrupts the normal growth rate. Overexpression of FRG1 also affected adult animals, which displayed disrupted ventral body wall muscles and shifted FRG1 subcellular localization predominantly to the nucleus through all developmental stages yet appeared to enhance cytoplasmic actin bundling. Our results support a disease model that overexpression of FRG1 leads to FSHD pathology.

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Program/Abstract # 418
The role of Sprouty1 in cardiac fibroblasts and epicardium
Markus Bussen, Gail R. Martin
Department of Anatomy and Program in Developmental Biology, University of California, San Francisco, CA 94158, USA

Sprouty1 (*Spry1*) encodes a protein that modulates RAS/MAPK pathway activity downstream of receptor tyrosine kinase activation. *Spry1* null mice develop cardiac hypertrophy. A detailed expression analysis has revealed that *Spry1* is expressed in the epicardium, the outermost layer of the heart, on embryonic day (E) 12.5, and is not detected in cardiomyocytes. At E14.5, *Spry1* expression can be found in cardiac fibroblasts (CF) and the smooth muscle cell (SMC) of the coronary vessels. *Spry1* expression in these non-myocyte populations is maintained during adulthood. Since Sprouty genes are known to function intracellularly, these data indicate that *Spry1* function is required in the epicardium and/or its derivatives to prevent hypertrophy of cardiomyocytes. We suggest that the cardiac hypertrophy phenotype in *Spry1* null mice is due to a defect in CFs that causes an increase in the amount of extracellular matrix (ECM) in the myocardium and/or a change in ECM composition. In support of this hypothesis, we have data suggesting that there is excess collagen deposition in *Spry1* null hearts resulting from an upregulation of the SOX9 and SLUG in CFs. Preliminary data, using a conditional gene targeting strategy that specifically inactivates *Spry1* in CFs and SMCs, indicate that cardiac hypertrophy is caused by the lack of *Spry1* in these cell populations.

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Program/Abstract # 419
Control of embryonic stem cell proliferation and migration can be controlled in vivo by pharmacological modulation of endogenous ion channels
Douglas J. Blackiston[a], Michael Levin[a,b]
[a]*Center for Regenerative and Dev. Biol., Forsyth Institute, Boston, MA, USA*
[b]*Department of Biol., Tufts Univ., Medford, MA, USA*

Voltage gradients across cells, and the underlying ion transporters giving rise to membrane potential, are important regulators of a variety of developmental processes including cell specification, differentiation, and migration. These processes in turn regulate many morphogenetic events including embryonic development and regeneration. Here, we report that altering the membrane potential of *Xenopus laevis* embryos during neurulation through molecular or pharmacological treatments leads to a striking hyper-pigmentation in embryos. This hyper-pigmentation is characterized by 1) a significant increase in number of melanocytes, 2) dendritic and abnormal melanocyte morphology, and 3) invasiveness of pigment cells to areas normally devoid of pigmentation including neural tissues and internal organs. We find these effects to be non-cell autonomous and can be induced through disruptions of either potassium or chloride ion gradients, suggesting a general membrane potential mechanism as opposed to specific ion channel signaling. These data demonstrate the importance of membrane potential during development as an important regulator of cell division and behavior, and show the potential for modulation of embryonic stem cell development, in vivo, using small molecule drugs to tune membrane potential. Progress in this field may yield profound insight into cancer and regenerative medicine.

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