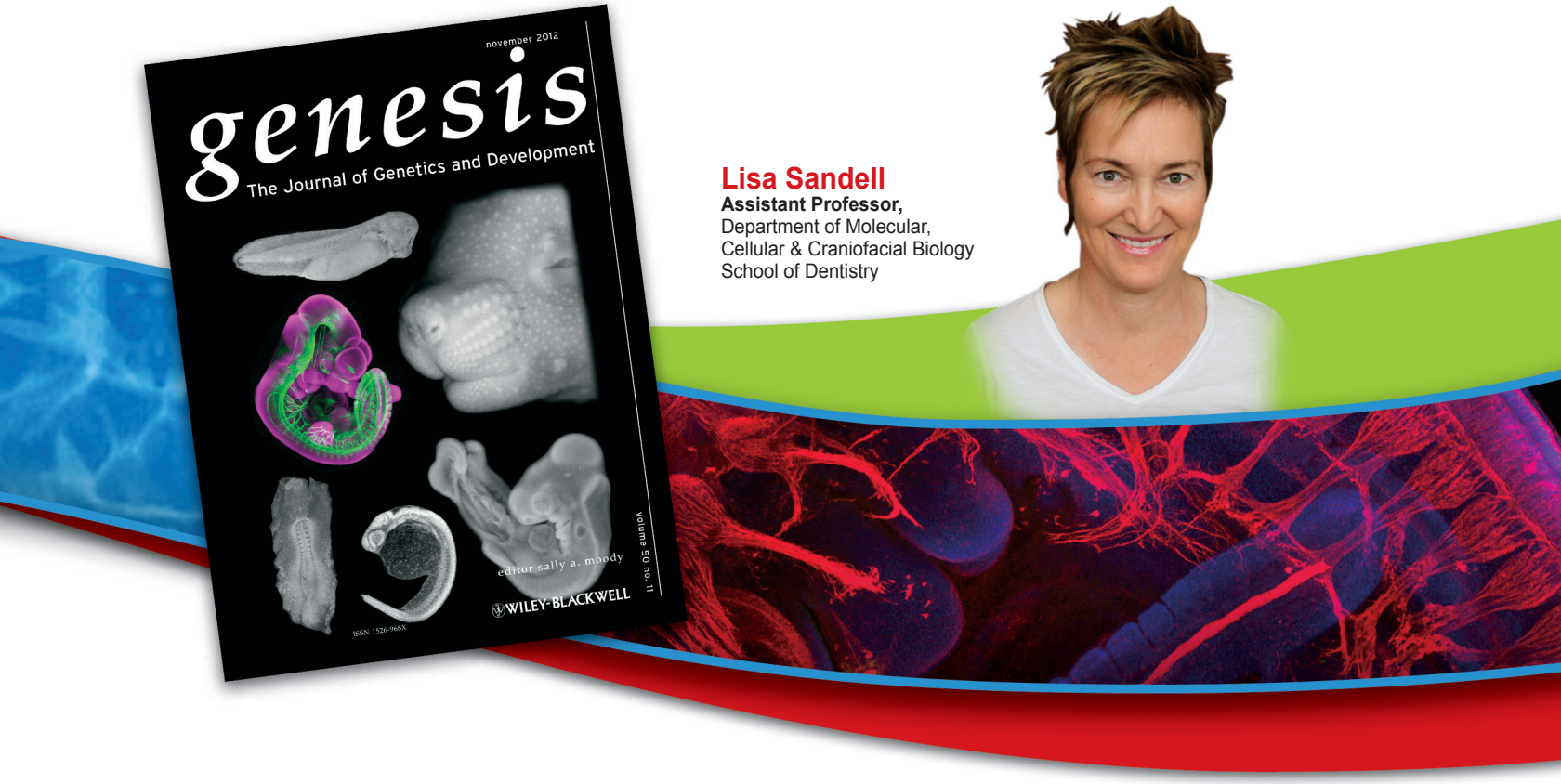

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Congenital heart disease is a serious human health issue, affecting as many as 1% of live births. The cause of most heart abnormalities is unknown, reflecting the deficiencies of our understanding of environmental agents, genetic factors, and gene-environment interactions that contribute to cardiac birth defects. One molecule that is clearly essential for heart development is Retinoic Acid (RA), the active derivative of Vitamin A. Precise regulation of RA is critical - excess or insufficiency can cause cardiac birth defects. Despite its well-established importance, the molecular mechanisms regulating RA within an embryo are largely unknown. Vitamin A is metabolized into RA in two steps, the first of which has been historically attributed to alcohol dehydrogenases (ADH). In a surprising discovery that has cast doubt on the role of ADH enzymes, I have recently identified that RDH10, a short chain dehydrogenase/reductase, is essential for catalyzing the first step Vitamin A metabolism. Preliminary examination of embryos with a point mutation in Rdh10 suggests that these embryos have severe cardiac abnormalities. Current gaps in understanding include: How is metabolism of Vitamin A into RA regulated? Do Vitamin A metabolism defects caused by Rdh10 mutation produce cardiac abnormalities, and, if so, by what molecular mechanism? Do alcohol-metabolizing enzymes play a role in synthesis of RA and does alcohol exposure contribute to heart defects by disrupting RA homeostasis? To address these issues I have developed a series of Rdh10 mutant mice and have made reporter mice for detection cell populations critical for heart development. I have also developed imaging techniques for visualizing molecular changes within the developing mouse heart. The major hypothesis of this proposed research is that RDH10 is essential for cardiac development because it is a key control point for regulating embryonic RA production. The results of this study will shed light on the mechanism of Vitamin A metabolism, its regulation, and its role in embryonic heart development and will clarify potential overlap between that process and other metabolic pathways. Importantly, they will help rationally inform preventive and therapeutic approaches aimed at reducing or ameliorating congenital heart defects.

Publications:

F1000Prime RECOMMENDED

Sandell LL, Kurosaka H, Trainor PA. Whole mount nuclear fluorescent imaging: Convenient documentation of embryo morphology. Genesis. (2012) Genesis 50(1) DOI: 10.1002/dvg.22344

Sandell LL , Lynn ML , Inman KE , McDowell W , Trainor PA , RDH10 Oxidation of Vitamin A Is a Critical Control Step in Synthesis of Retinoic Acid during Mouse Embryogenesis. PLoS ONE 7(2): e30698. (2012). doi:10.1371/journal.pone.0030698

Krysten M. Farjo, Gennadiy Moiseyev, Olga Nikolaeva, **Lisa L. Sandell**, Paul A. Trainor, and Jianxing Ma. RDH10 is the primary enzyme responsible for the first step of embryonic retinoic acid synthesis. Developmental Biology 357(2): 347-55, (2011). PMCID: PMC316459

Lisa Sandell and Daisuke Sakai. Mammalian Cell Culture. Current Protocols - Essential Laboratory Techniques. Curr. Protoc. Essential Lab. Tech. 5:4.3.1-4.3.32. John Wiley & Sons (2011). DOI: 10.1002/9780470089941.et0403s5

Sandeep Kumar, **Lisa L. Sandell,** Paul A. Trainor, Frank Koentgen, and Gregg Duester. Alcohol and Aldehyde Dehydrogenases: Retinoid Metabolic Effects in Mouse Knockout Models. Biochimica et Biophysica Acta (BBA) – Molecular and Cell Biology of Lipids, (2011). PMCID: PMC3161159

Lisa L Sandell, Angelo Iulianella, Kristin R Melton, Megan Lynn, Macie Walker, Kimberly E. Inman, Shachi Bhatt, Margot Leroux-Berger, Michelle Crawford, Natalie Jones, Jennifer Dennis and Paul A Trainor. A phenotype driven ENU mutagenesis screen for identifying novel alleles with functional roles in early mouse craniofacial development. Genesis, 49 (4), 342-359, (2011). PMID:21305688

Thomas J. Cunningham, Christina Chatzi, **Lisa L. Sandell,** Paul A. Trainor, and Gregg Duester. Rdh10 Mutants Deficient in Limb Field Retinoic Acid Signaling Exhibit Normal Limb Patterning but Display Interdigital Webbing. Developmental Dynamics, 240 (5), 1142-1150, (2011). PMCID: PMC3081420

External Professional Activities

Invited speaker:
American Association of Anatomists/Experimental Biology conference 2012

Participant:
Gordon Research Conference – Craniofacial Morphogenesis and Tissue Regeneraton

Invited speaker:
Seminar Series, University of Cincinnati, Department of Biology