Scholarly Activities:

Birth defects are an enormous human health care issue, occurring in approximately 3.0% of all live births. The high prevalence of birth defects reflects the complexity of embryonic development wherein a single fertilized egg becomes a multicellular embryo that progressively builds itself into an organism with all the needed structures and organs of an individual. This self-building process is largely dependent upon a progressive program orchestrated by cell-cell communication that is mediated by a handful of molecular signals. Because these signaling molecules are so critical for regulating development, disturbances to the signaling pathways are often associated with birth defects.

One of the key signaling molecules used to direct many aspects of embryonic development is Retinoic Acid, a diffusible hormone-like molecule generated by enzymatic metabolism of dietary Vitamin A. During embryonic development, Vitamin A must be converted into Retinoic Acid at precise times and places, in order for proper development to occur. In humans and other species excessive or deficient levels of RA, whether by diet or genetic perturbation, each result in a variety of birth defects including cardiac abnormalities, ear, eye, organ, and gland defects, and orofacial clefts. Despite the fact that it has been clear for decades that deficiency of Vitamin A causes birth defects, we know almost nothing about the etiology of birth defects that result from insufficient Retinoic Acid.

Our research aims to elucidate how regulated production of Retinoic Acid controls embryo development, and, importantly, how disruption of the process may be responsible for a variety of birth defects. Our approach is based upon the examination of mice in which the gene encoding the enzyme RDH10 is inactivated, a condition which blocks the conversion of Vitamin A into Retinoic Acid.

We are currently investigating how deficient Vitamin A metabolism causes cleft lip and palate. Results of our analysis will help guide recommendations for nutrition during pregnancy so that cases of cleft lip and palate resulting from dietary factors may be prevented. We are also investigating how deficient Vitamin A metabolism impacts growth and development of salivary glands. Results of this analysis may elucidate methods for promoting regeneration in damaged or aging adult salivary glands.

Additionally, as part of our study to determine how deficient Vitamin A metabolism impacts development of the ear, we have made new discoveries about the progression of normal ear development in a healthy embryo. Using novel imaging techniques that facilitate visualization of embryonic structures we have determined that the precursors of neurons of the inner ear nerve and the precursors of Schwann cells that myelinate the nerve migrate and develop in tandem from the earliest stages of cranial nerve development.

Grants:

Role: *Subproject Director:*
P20 Director: *RM Greene*
Subproject Title: *Role of Vitamin A Metabolism in Congential Heart Defects*
P20 Title: *"Molecular Determinants of Developmental Defects"*
Funding Agency: *NIH (NIGMS) COBRE 9P20GM103453*

Publications (2013-2014):

Cunningham Thomas J, Zhao X, **Sandell** Lisa L, Evans Sylvia M, Trainor Paul A, Duester G. Antagonism between Retinoic Acid and Fibroblast Growth Factor Signaling during Limb Development. Cell Reports 3: 1503-1511. (2013)

Hadel DM, Keller BB, **Sandell** LL. Confocal imaging of whole vertebrate embryos reveals novel insights into molecular and cellular mechanisms of organ development. in SPIE BiOS (eds. AM Rollins, CW Lo, SE Fraser), pp. 895302-895302-895307. International Society for Optics and Photonics, San Francisco. (2014)

Sandell LL. Neural Crest Cells in Ear Development. in NEURAL CREST CELLS Evolution, Development and Disease (ed. PA Trainor), pp. 167-188. Academic Press, London. (2014)

Sandell LL, Butler Tjaden NE, Barlow AJ, Trainor PA. Cochleovestibular nerve development is integrated with migratory neural crest cells. Dev Biol 385: 200-210. (2014)

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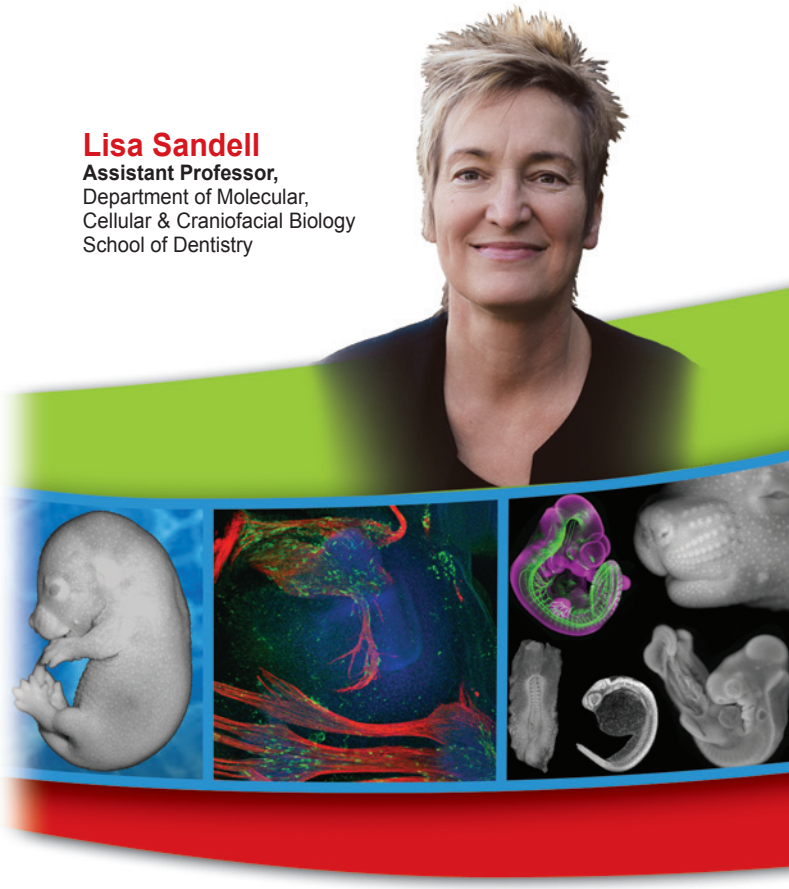

External Professional Activities

Society for Craniofacial Genetics & Developmental Biology – member, Annual Meeting Session Chair
Society for Developmental Biology – member
American Association of Anatomists - member

Invited Speaker, Research!Louisville
Invited Speaker, Seattle Children's Research Insititute, Seattle, WA
Invited Speaker, BiOS/SPIE, Optical Methods in Developmental Biology II, San Francisco, CA
Invited Speaker, Craniofacial Research Symposium, Cincinnati, OH