



Douglas Darling, Ph.D.

Professor

Department of Periodontics,
Endodontics & Dental Hygiene
School of Dentistry

Research Activities

We are studying the molecular basis for trafficking of secreted proteins within the cell during regulated secretion. Secretory proteins synthesized in the major salivary glands, including the parotid glands, are primarily stored in dense-core secretory granules and released in response to external stimuli (regulated or stimulated secretion). Parotid salivary proteins are secreted apically, primarily by the regulated secretory pathway. Understanding how sorting occurs in salivary glands would contribute to the correct targeting of therapeutic transgenes. To study the molecular basis for trafficking, we use a proteomics approach to define proteins in the secretory granule membrane, and systems biology approaches to define regulatory pathways. We hope to define the developmental mechanisms that create the secretory pathways.

In addition, our laboratory is interested in the regulation of gene transcription in eucaryotic cells. We are investigating the molecular mechanism of action of the zfh family of transcription factors. We have isolated cDNA and genomic clones of the Zfh1/Zfhx1a/ZEB1 transcription factor. ZEB1 is essential for life as well as T-cell development, craniofacial development, and skeletal patterning. ZEB1 is a SMAD-binding protein, and therefore is part of the TGFbeta family signaling mechanism. Current projects investigate the role of ZEB1 and related genes in early development, and the molecular interactions that underlie those roles. We focus on development of the eye, which has specific defects in ZEB1-mutant mice that mimic birth defects in some human babies. In addition, we are studying the molecular basis for cleft palate in ZEB1 knock-out mice.

Grants Funded

Role: Principal Investigator

Title: Selective Aggregation and Sorting of Salivary Protein

Funding Agency: National Institutes of Health, NIDCR

Direct Costs Funded: \$875,000

Role: Principal Investigator

Title: Ocular Defects Caused by TCF8/Zfhx1a Mutation

Funding Agency: NIH/ NEI

Direct Costs Funded: \$275,000

Role: Co-Investigator

Title: Oral H. pylori Prevalence in Intellectually/Developmentally Disabled Adults

Funding Agency: NIH/NIDCR

Direct Costs Funded: \$275,000



Role: Principal Investigator
Title: Identifying Periodontal Antigens By Protein Microarray
Funding Agency: NIH/NIDCR
Direct Costs Funded: \$275,000

Role: Co-Investigator; PI Ken Ramos
Title: Center for Environmental Genomics and Integrative Biology (CEGIB)
Funding Agency: NIH/NIEHS
Direct Costs Funded: \$3,000,000

Role: Principal Investigator
Title: Mathematical Model of Parotid Acinar Differentiation
Funding Agency: NIH/NIDCR
Direct Costs Funded: \$1,900,000

Peer-reviewed Publications

S.G. Venkatesh, J. Tan, S.U. Gorr and **D.S. Darling** (2007) Isoproterenol Increases Sorting Of Parotid Gland Cargo Proteins To The Basolateral Pathway. *Am J Physiol Cell Physiol*. 293: C558 - C565. PMID: 17537806, PMCID: PMC2084485.

Manavella PA, Roqueiro G, **Darling DS**, and Cabanillas AM. (2007) The ZFH1A gene is differentially autoregulated by its isoforms. *Biochem. Biophys. Res. Commun.* 360(3): 621-626. PMID:17610840. doi:10.1016/j.bbrc.2007.06.088

Kitchens DH, Binkley CJ, Wallace DL, **Darling DS**, (2007) Helicobacter pylori Infection in Intellectually and Developmentally Disabled Persons: A Review. *Special Care in Dentistry*. 27 (4):127-33, PMID:17972442.

Liu Y, Costantino ME, Durango-Montoya D, **Darling DS**, and Dean DC (2007): The zinc finger transcription factor ZFH1A is linked to cell proliferation through the Rb/E2F pathway. *Biochem. J.* 408(1): 79-85. doi:10.1042/BJ20070344. PMID:17655524. PMCID: PMC2049079.

Kowase T, Walsh HE, **Darling DS**, and Shupnik MA (2007) Estrogen Enhances GnRH-Stimulated Transcription of the LH Subunit Promoters via Altered Expression of Stimulatory and Suppressive Transcription Factors. *Endocrinology*, 148: 6083 – 6091. doi:10.1210/en.2007-0407. PMID:17823254.

Liu Y, El-Naggar S, **Darling DS**, Higashi Y, and Dean DC (2008) Zeb1 links epithelial-mesenchymal transition and cellular senescence. *Development* 135, 579-588. doi:10.1242/10.1242/dev.007047. PMID: 18192284.

Jin JZ, Li Q, Higashi Y, **Darling DS**, and Ding J (2008) Analysis of Zfh1a mutant mice reveals palatal shelf contact-independent medial edge epithelial differentiation during palate fusion. *Cell and Tissue Research*, 333:29-38. doi: 10.1007/s00441-008-0612-x

Singh M, Spoelstra NS, Jean A, Howe E, Torkko KC, Clark HR, **Darling DS**, Shroyer KR, Horwitz KB, Broaddus RR, and Richer JK (2008) ZEB1 expression in type I vs type II endometrial cancers: a marker of aggressive disease. *Mod Pathol*. 21(7): 912-23. PMID 18487993.

Liu Y, Peng X, Tan J, **Darling DS**, Kaplan HJ, and Dean DC (2008) Zeb1 Mutant Mice as a Model of Posterior Corneal Dystrophy. *Invest. Ophthalmol. Vis. Sci.*, 49: 1843 - 1849. DOI: 10.1167/iovs.07-0789.