



## Dennis Warner

### Assistant Professor

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### Research Activities:

Much of my research activities during 2007-2008 focused on the TGF $\beta$  and Wnt signaling pathways and their role in developmental processes during formation of the secondary palate. Defects in development of the secondary palate lead to clefts, which affect approximately 1 in 700 births. TGF $\beta$  and Wnt are both large families of cytokines with diverse functions in embryonic and adult tissues. From earlier in vitro studies on primary cultures of embryonic mouse palate mesenchymal cells, we demonstrated that TGF $\beta$ 1 and Wnt-3a cooperate to induce gene transcription. To follow up this observation, we obtained a grant from the American Cleft Palate Foundation to perform high-density microarrays to identify genes whose regulation is uniquely regulated by both TGF $\beta$ 1 and Wnt-3a in combination, using a mouse model, which is very useful because of the similarities to human palate development. Indeed, these experiments have led to a collection of genes that are regulated by TGF $\beta$  and Wnt, and not seen with either cytokine alone. These data provide a foundation for further analysis of the intersection of these two pathways as it pertains to the normal sequence of events required for proper palate development. We have also performed a comprehensive analysis of the expression of other Wnts in the developing mouse palate, an area that is only now beginning to be explored in detail, and have found several display interesting patterns of expression, suggesting specific roles. We are now in a position to determine the functional role of this large family of proteins. Significant progress has been made on the analysis of a protein identified by us (PRDM16) as being involved in the TGF $\beta$  signaling pathway, and, when mutated, can lead to cleft palate in mice. There is also evidence in humans linking mutations of PRDM16 to cleft palate. PRDM16 is a transcription factor that has been recently demonstrated to be a protein that can direct cell differentiation. We obtained a grant from the Kentucky Science and Engineering Fund to further study the role of PRDM16 in crucial cellular/developmental processes necessary for proper palate development, such as cell proliferation, synthesis of extracellular matrix, and fusion of the nascent palatal shelves. We are currently in the process of further characterizing the genes regulated by PRDM16 and its possible role in palatal bone formation.

### Grants Funded:

**Role:** Principal Investigator

**Title:** Gene Discovery in Orofacial Tissue

**Funding Agency:** American Cleft Palate Foundation

**Direct Costs Funded:** \$10,000

**Role:** Principal-Investigator

**Title:** PRDM16: A Novel Zinc Finger Protein Linked to Palatal Clefting

**Funding Agency:** Kentucky Science and Engineering Foundation

**Direct Costs Funded:** \$18,191

### Peer-reviewed Publications:

**Warner DR**, Horn KH, Mudd L, Webb CL, Greene RM, Pisano MM. PRDM16/MEL1: A Novel Smad Binding Protein Expressed in Murine Embryonic Orofacial Tissue. *Biochimica et Biophysica Acta-Molecular Cell Research* 1773:814-820 (2007).

**Warner DR**, Greene RM, Pisano MM. (2007) "PRDM16-Target Assessment" Targeted Proteins Database.

P. Mukhopadhyay P, Webb CL, **Warner DR**, Greene RM, Pisano MM "BMP Signaling Dynamics in Embryonic Orofacial Tissue. *Journal of Cellular Physiology* 216:771-779 (2008).

**Warner DR**, Smith IV HS, Webb , Greene RM, Pisano MM "Expression of Wnts in the Developing Murine Secondary Palate" *International Journal of Developmental Biology*, in press.

