



# Dr. Jeffery R. Barrow

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**Location: Merrill-Cazier Library room 154**  
**March 26, 2009 from 3:30 – 4:30 PM**

## ***How do genes make stuff: Regulation Wnt5a and proximodistal patterning in the limb.***

My laboratory focuses on finding the mechanisms whereby genes regulate the size and shape of three dimensional structures. To address this big question we are studying the embryonic limb the premier model for understanding how an organ develops in three dimensions.

It has been well established that members of the fibroblast growth factor (FGF) family secreted from the apical ectodermal ridge (AER) along the distal margin of the limb are both necessary and sufficient for outgrowth and patterning of the limb. Despite numerous years of research, it remains unclear how these ectodermal FGFs signal outgrowth to the adjacent limb mesenchyme although recent loss and gain of function studies suggest that it is not by promoting cell proliferation or cell survival. In an attempt to better understand the underlying mechanisms, we have generated data that suggest that signals from the AER recruit cells in directional fashion toward the AER. Similarly, we have found that labeled cells in regions of limb buds where the AER has been removed exhibit random growth. To determine how the AER promotes directional outgrowth, we have found that the AER and its associated Fgfs are both necessary and sufficient to activate expression of the signaling factor, Wnt5a, in gradient fashion in the adjacent limb mesenchyme. Previous studies from others have suggested that Wnt5a signals through  $\beta$ -catenin independent pathways to regulate directional cell movements and cell divisions in extending the embryonic axis of lower vertebrates. Similarly, we propose that the Wnt5a gradient in the limb mesenchyme is essential for directional outgrowth of the embryonic limb. Consistent with this hypothesis, it has been reported that Wnt5a<sup>-/-</sup> mouse embryos have severely shortened limbs. Furthermore, we have found that limb mesenchyme is recruited directionally to ectopic sources of Wnt5a in the embryonic limb. In addition, cultured limb cells appear to migrate chemotactically to sources of Wnt5a. Taken together, it appears that the AER invokes directional outgrowth of the adjacent limb mesenchyme by secreting Fgfs which in turn activate a gradient of Wnt5a expression in the mesenchyme. Wnt5a in turn signals directional outgrowth of the mesenchyme. From these data, we propose a model that the AER promotes outgrowth of the limb by recruiting adjacent limb mesenchyme cells toward it. We also propose that the size and shape of the AER in turn determines the size and shape of the limb bud. The shape of the limb bud dictates the pattern of the limb.

**Refreshments will follow in the Biotechnology Building Lobby**

Seminar