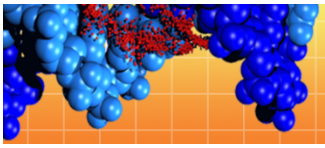

CENTER FOR BIOINFORMATICS & COMPUTATIONAL BIOLOGY

BIOINFORMATICS 2015 SPRING SEMINAR SERIES

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MONDAY, April 13, 2015
3:30pm
DBI Room 102

A mechanical "clock" serves as a master regulator of lung branching morphogenesis

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ABSTRACT: Branching morphogenesis is a developmental program used by many organs, including the lung, kidney, prostate, and mammary gland, to create ramified networks of epithelial tubes that support the flow of fluid and air. Development of the lung is dynamic, highly regulated, and stereotyped, leading to an airway architecture that is conserved within a given species and critical for survival. Interestingly, although the architecture of the airways is optimized for efficient conduction of air, development occurs with a fluid-filled lumen. Whereas almost all contemporary studies focus on the molecular and genetic programs active during branching morphogenesis of the lung, clinical observations and large animal models suggest a critical role for the (dynamic) regulation of mechanical forces, e.g. transmural pressure, in the developing lung. To investigate the role of transmural pressure in branching morphogenesis, I discuss the development of a microfluidic device to culture and apply dynamically-controlled transmural pressures within murine embryonic whole lung explants. This new approach permits the branching process to be imaged dynamically at multiple length and time scales under defined mechanical conditions over days of organ development. Using this microfluidic device along with newly developed measurement techniques and quantitative frameworks to describe the airway architecture, I discuss how lumenal fluid flows, generated by pressure-dependent airway smooth muscle contractions, drive branching morphogenesis. Together, my results demonstrate a novel physical mechanism through which lung branching morphogenesis – the temporal and spatial regulation of billions of individual cells - is mechanically regulated in normal development. These studies 1) suggest that lumenal fluid forces may be critical for sculpting the airway architecture, ultimately leading to enhanced convection of air through the mature airway tree and 2) point to additional studies to determine how mechanical forces integrate into the molecular and genetic programs that control morphogenetic processes in developing tissues.