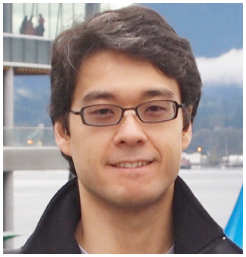
2012 Abstracts



Kenny Schlosser, PhD

Ottawa Hospital Research Institute
Ottawa, Ontario, Canada

Role of Extracellular Circulating MicroRNAs in Idiopathic Pulmonary Arterial Hypertension

Idiopathic pulmonary arterial hypertension (IPAH) is characterized by a deterioration of the underlying structure of the lung vasculature, and the resulting increase in pulmonary vascular resistance leads to right heart failure and premature death. Despite improvements in treatment, the overall prognosis for IPAH remains poor with no known cure. Although the precise cause of IPAH remains unclear, there is increasing interest in small non-coding RNA molecules known as microRNAs (miRNAs). MiRNAs associate with specific protein complexes and control gene expression by directing the translational inhibition or degradation of target messenger RNAs. To date, over 1000 highly conserved mammalian miRNAs have been annotated, and many have been shown to act as key regulators of fundamental biological processes, including cell proliferation, apoptosis, and inflammation; these processes have all been implicated as possible pathobiologic mechanisms of IPAH. MicroRNAs have traditionally been thought to exist and function exclusively within cells; however, stable extracellular miRNAs have recently been discovered in the blood, which has led to speculation of an entirely new type of paracrine and/or hormonal function. These circulating miRNAs have been isolated from blood plasma under both normal and pathophysiological conditions, including various cancers and cardiovascular disease, but their identification and functional significance in lung vascular diseases like IPAH have not been investigated. We hypothesized that IPAH is associated with aberrant levels of circulating

Kenny Schlosser, PhD

miRNAs which reflect disease-specific mechanisms of vascular injury and/or remodeling. We aim to 1) characterize the global plasma miRNome of a cohort of IPAH patients, 2) identify specific plasma miRNAs with aberrant expression patterns that are conserved between human IPAH and the SU5416/hypoxia rat model, and 3) determine if these miRNAs play a causal, adaptive, or bystander role in the development of PAH, by evaluating the effects of both miRNA inhibition and supplementation in the experimental PAH model. The characterization of these circulating miRNAs may provide new biomarkers of PAH, insight into novel mechanisms underlying the pathobiology of this disease, and potential targets for therapeutic intervention.