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Enriching Research in Pulmonary Vascular Medicine

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2015 ABSTRACT

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Development of microRNA-based therapeutic strategies for pulmonary arterial hypertension.

Introduction:

Pulmonary arterial hypertension is a disease characterized by the vascular remodeling of the pulmonary arterioles, leading to increased pulmonary vascular resistance and right ventricular failure. A number of microRNAs have emerged as promising therapeutic targets, but significant hurdles remain before they can be pursued in clinical studies.

Background:

Pulmonary arterial hypertension (PAH) is a disease of exceedingly high mortality with limited therapeutic modalities. Work from the Chun (mentor) laboratory and others have identified key microRNAs involved in the disease pathogenesis, including miR-424, miR-503, miR-204, miR-130, miR-301, miR-21, miR-145, and miR-124. Although these studies have all identified novel pathways in experimental models with strong translational applicability to human disease, a number of limitations prevent advancement of a microRNA based therapeutic strategy in PAH. First, there is currently no standardized delivery strategy for the microRNA mimics or antagonists to the pulmonary vascular cells. Second, although each of these studies have demonstrated varying degrees of therapeutic efficacy for the specific microRNAs of interest, a direct comparison of efficacy using a standardized delivery technique and disease models has never been investigated. The current proposal will identify an effective delivery strategy for oligonucleotide based therapy to the pulmonary vasculature. It will then utilize this strategy to compare the efficacy of targeting candidate microRNAs known to be involved in the pathogenesis of PAH, to identify the best therapeutic targets for development of early clinical trials. We will utilize novel, vascular targeting nanoparticle based delivery strategies, in conjunction with robust experimental rodent models of pulmonary hypertension, to pursue these studies.

Hypothesis and Objectives:

We hypothesize that a nanoparticle based approach for delivery of microRNA mimics or antagonists is an effective strategy for treatment of pulmonary arterial hypertension. We will determine the most effective delivery strategy and identify the strongest microRNA candidate(s) with the goal of developing early clinical studies.

Specific Aim 1:

Develop and identify the optimal nanoparticle composition and delivery strategy for targeting oligonucleotides to the pulmonary vasculature. We will test the efficacy of modified nanoparticle compositions to achieve selective delivery of microRNA mimics or antagonists in vitro to primary cells of the pulmonary vasculature.

Specific Aim 2:

Identify the microRNA targets with the most effective therapeutic efficacy in rescuing preclinical models of pulmonary hypertension. We will utilize the optimal nanoparticle composition identified in Specific Aim 1 to test the efficacy of targeting multiple microRNA candidates in vivo, using the monocrotaline and the SU-5416/hypoxia models of pulmonary hypertension.

Specific Aim 3:

Evaluate the feasibility of combining microRNA targets to augment therapeutic efficacy. We will determine if a combination of the best microRNA mimics/antagonists (identified in Aim 2) can achieve an additive or synergistic effect to augment therapeutic efficacy.