

TEXAS TECH UNIVERSITY
Department of Mechanical Engineering



Targeted Inhalable Drug Delivery Systems for Respiratory Diseases

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Abstract: Pulmonary arterial hypertension (PAH) is a debilitating and deadly disease of the pulmonary circulation; although relatively rare, PAH affects persons of every ethnic group, race, gender, and age, including newborns. Current anti-PAH medications (prostacyclin analogs, endothelin receptor antagonists, and phosphodiesterase-5 inhibitors) require cumbersome intravenous and subcutaneous injections, lack pulmonary selectivity, suffer from instability, produce systemic side effects, and fail to cure the underlying cause of the disease. Because PAH pathophysiology is entwined with multiple cellular and molecular pathways, single-drug therapy only modestly improves pulmonary hemodynamics and fails to restrain disease progression. Various combinations of anti-PAH drugs have recently been studied, but patient outcomes remain disappointing. Being predominantly vasodilators, the currently approved drugs do not reverse pulmonary vascular remodeling and abate right heart dysfunction, a major cause of deaths in PAH. We propose to circumvent indwelling catheter- and needle-based administration of drugs, intensify pulmonary selectivity, and reverse the pathogenesis of the disease to improve patient outcomes by formulating a combination of two drugs in nanocarriers equipped with a pulmonary homing device. We hypothesize that *inhalable and targetable nanoparticles containing a vasodilator and an antioxidant ameliorate pulmonary vasoconstriction, reverse pulmonary arterial remodeling, and abate right heart enlargement and failure in PAH*. We tested this hypothesis by developing a targetable nanocarrier-based combination therapy that simultaneously targets two pathways of PAH pathogenesis: oxidative stress and Rho-kinase pathways. The system consists of nanoparticles containing Cu/Zn superoxide dismutase, a superoxide scavenger, and fasudil, a Rho-kinase inhibitor and potent vasodilator. The outer surface of the particles was coated with a cyclic peptide, CAR (CARSKNKDC), which accumulates preferentially in the hypertensive pulmonary arteries of PAH rats. We have used various cellular, intact organ and rodent models of PAH to generate preclinical data—stepping-stones for development of an efficacious drug therapy—and address an unmet medical need. The proposed delivery system will reduce the systemic exposure of drugs, reverse heart dysfunction, eliminate the need for catheters and needles, enhance patient compliance, ease economic burdens, free patients from discomfort, and cure the underlying causes of this deadly disease.

Bio: Dr. Fakhrul Ahsan is a University Distinguished Professor in the Department of Pharmaceutical Sciences at the Texas Tech University Health Sciences Center School of Pharmacy in Amarillo, Texas. He is also the Program Advisor for the Graduate Program in Pharmaceutical Sciences at the TTUHSC School of Pharmacy. He holds a Master of Pharmacy Degree from the University of Dhaka in Bangladesh, and a Ph.D. in Pharmaceutics from Complutense University of Madrid. Dr. Ahsan's research revolves around the development of novel formulations for the pulmonary delivery of small- and large-molecular-weight therapeutic agents. One of his major research interests is the development of inhalation formulations for the treatment of pulmonary arterial hypertension. He has published 66 papers in first-tier drug delivery journals, 91 abstracts related to respiratory drug delivery, and authored six book chapters. By the end of 2015, his work had been cited over 2,500 times and he had acquired an H-index of 27. He is a reviewer of numerous internationally reputed journals, and a member of the Editorial Boards of the *European Journal of Pharmaceutical Sciences* and the *Journal of Pharmacy and Pharmaceutical Sciences*, he was an Associate Editor of the *Journal of Drug Targeting*. Dr. Ahsan has received three NIH-R15s and one R01 grant. He has been serving as an *ad-hoc* member of various NIH study sections for about eight years. Texas Tech University Health Sciences Center recognized his excellence as an educator and investigator by awarding him with the President's Young Investigator Award.



Monday, February 15, 2016
Livermore Center 101 | 2:00 – 3:00 pm
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