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"Evaluating nanocomposite microparticles for the delivery of therapeutics for pulmonary arterial hypertension"

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Pulmonary arterial hypertension (PAH) is a chronic, incurable, and life-threatening disease that is characterized by abnormally high blood pressure in the arteries leading from the heart to the lungs. Patients often suffer from chest pain, shortness of breath, fainting, dizziness, and in many cases heart failure and ultimately death. The therapies currently approved to treat PAH are most commonly available in oral or intravenous form, but often result in undesirable systemic side effects. An effective treatment needs to be designed to deliver targeted therapeutics to the lung periphery to ensure maximum localized bioavailability and to decrease the side effects associated with systemic delivery. The goal of our research is to develop and evaluate dry powder aerosols comprised of nanocomposite microparticles (nCmP) containing the newly-investigated PAH drug tacrolimus to be delivered directly to the lung and surrounding arteries. These particles are designed to overcome mucociliary clearance in the lung and to avoid alveolar macrophages to allow for longer retention time in the lungs. The production of these aerosols began with synthesizing the biodegradable polymer, acetalated dextran (Ac-Dex), with an appropriate cyclic acetal conversion (65-75%). Then using a single emulsion evaporation method, Ac-Dex was used to form nanoparticles, which were characterized for their size, charge, and drug encapsulation. The final step of synthesizing the nCmP was spray drying a solution of nanoparticles suspended with mannitol (an excipient) in water. The nanoparticles were successfully

optimized to be of appropriate size to avoid macrophage uptake (150 - 230 nm). The drug-loaded particles had an encapsulation efficiency of 32.7%, resulting in a drug loading of 32.75 µg tacrolimus/mg acetalated dextran. The nanoparticles were loaded with the fluorescent dye FITC to verify their successful encapsulation into the microparticles. We were able to demonstrate the successful synthesis and the morphology of the dry nCmP using confocal fluorescence and scanning electron microscopy. The development of the nCmP could lead to the improved treatment of PAH for many patients afflicted by this life-threatening disease.