Introduction

Pulmonary Physiological Barrier Limitations
Drug delivery tenants have recently been applied to the aerosol delivery of therapeutics to the lungs to treat a wide variety of pulmonary diseases, including lung cancer, cystic fibrosis, asthma, COPD, etc. Despite these advances, the drug delivered to the lungs has to overcome a multitude of barriers including:

- **Aerosolization:** the size of the particles must allow for delivery to the site of action within the lungs (from upper to lower airways)
- **Formulation:** poorly-water soluble drugs are often challenging to formulate

- **Physiological:** aerosolized particles and/or drugs must be able to penetrate barriers in the lungs such as mucus, surfactant, cells, and tumor tissue.

Dry Powder Aerosol Nanocomposite Microparticles
Aerosolized dry powder particles can be engineered to be delivered to various locations in the lungs to deliver therapeutics, where larger particles deposit in the upper airways and smaller particles in the lower airways. Nanocomposite microparticles (nCmP) involve the incorporation of smaller, drug-loaded nanoparticles (NP) into a larger microparticle with or without an excipient. Once the nCmP impact on pulmonary tissue, the dissociate, releasing the loaded NP.

In addition to be able to overcome physiological barriers, nCmP can also overcome some common aerosolization barriers including:

1. **Tissue targeting:** the size of the nCmP can be tuned to allow for deposition in any part of the lung
2. **Phagocytosis:** particles that can be effectively aerosolized to the alveoli (2.5 μm in diameter) are also uptaken easily by alveolar macrophages. The NP released from the nCmP overcome this mechanism.
3. **NP Delivery:** while NP can effectively penetrate barriers, aerosolized NP are too small to impact on the surface of the lungs, whereas nCmP are not.

Cell-Penetrating Nanocomposite Microparticles for Pulmonary Hypertension Applications

- **Background:** Pulmonary hypertension (PAH) is a chronic, incurable cardiovascular disease characterized by increased blood pressure in the pulmonary arteries. Current therapies given systematically are expensive and result in undesired side effects, limiting the frequency of doses.
- **Tacrolimus (TAC):** immunosuppressant recently found to be useful in treating PAH as it reverses the BMP-2 mutation associated with certain types of PAH.

- **Formulation:** PVA-coated NP were loaded with TAC via emulsion/solvent evaporation. NP were then mixed with mannitol during the spray drying process to form nCmP.

- **Analysis:** size, drug loading and release, stability, aerosolization

- **Conclusions:** drug-loaded NP and nCmP were successfully formulated that can control drug release following effective deposition to the lower lungs.

Tumor-Penetrating Nanocomposite Microparticles for Lung Cancer Applications

- **Background:** Survival rates for patients diagnosed with lung cancer has not increased in the recent past. Aerosol therapeutics offer the advantage of localized treatment for a wide variety of cancers that affect the lungs.

- **Tumor Penetration:** the peptide iRGD (CRGDRGDC) is known to enhance tumor penetration via the following mechanism: iRGD homes to integrins via RGD present in the peptide and then iRGD-conjugated cargos are uptaken by cells and tumor tissue via the neuropilin-1 pathway.

- **Formulation:** NP were loaded with paclitaxel (PTX) and were then mixed with mannitol during the spray drying process to form nCmP.

Air-Grown Tumor Spheroids

Air-grown tumor spheroids better mimic physiological tissue. We have developed these spheroids for the evaluation of aerosol anti-cancer therapeutics.

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nCmP can control the release of AZI and RAP and be effectively deposited on the lower regions of the lungs (Stages 3-7)