**Leveraging molecular order of highly porous metal organic**

**framework (MOF) nanoparticles for pulmonary drug delivery**

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**Introduction.** Pulmonary diseases such as lung cancer, influenza, tuberculosis, cystic fibrosis, and chronic obstructive pulmonary diseases (COPD) cause millions of global deaths each year [1]. Despite considerable benefits, most of these respiratory diseases are not treated through an inhaled treatment owing to formulation challenges surrounding inhaled therapeutics [2]. Metal-organic frameworks (MOFs), coordination compounds of metals and ligands, offer promise as nanoparticle drug delivery vehicles due to their cargo-loading capacity, tunable pore size, and potential biocompatibility [3]. Additionally, we hypothesize that the low porosity will allow for MOFs to be easily delivered as aerosols, improving dispersion and lung penetration. To establish the utility of MOF nanoparticles as pulmonary drug delivery carriers, we seek to evaluate a zirconium chloride-based MOF, UiO-66, over a range of particle sizes and porosities (as measured by framework defectiveness). In this work, we characterize both their physical properties and biocompatibility to validate the application of these particles for pulmonary drug delivery.

**Methods.** UiO-66 nanoparticles were synthesized under acid-free conditions, with water content, synthesis time, and ratio between ligand and metal reactants controlled to modulate the particle size [4]. This approach enabled generation of UiO-66 nanoparticles of tunable defectiveness, measured by thermogravitational analysis (TGA). Crystallinity was confirmed for all samples using X-ray diffraction (XRD). The cargo-loading capacity and kinetic release profile were characterized for a model cargo, rhodamine B (RITC), using fluorescent measurements. Particle sizing was performed using scanning electron microscopy (SEM), dynamic light scattering (DLS), and next generation impactor (NGI). Biocompatibility was assessed using both *in vitro* and *in vivo* assays. Cell viability and uptake *in vitro* was established for each particle type in murine-derived alveolar macrophages (MH-S) and A549 epithelial cells. Pulmonary inflammatory responses following treatment of UiO-66 nanoparticles in C57BL/6 mice were also assessed 24 hrs following orotracheal instillation.

**Results and Discussion.** Monodisperse UiO-66 nanoparticles were successfully fabricated with geometric radii between 30-120 nm. Cargo-loading capacity was highly dependent on framework defectiveness, with maximum RITC loading capacities achieved as much as determined double the UiO-66 framework by mass. Uniquely, UiO-66 nanoparticles achieved high stability in neutral pH conditions, but rapidly degraded in less than 24 hrs in acidic buffer conditions, a desirable characteristic for drug release *in vivo*. RITC loading was found to have significant impact on the aerodynamic diameter of the resultant MOFs; interestingly, RITC loading decreased the mass median aerodynamic diameter (MMAD) as compared to unloaded samples. All UiO-66 samples were found to be highly biocompatible via both *in vivo* and *in vivo* assays, with no acute toxicity or inflammatory response observed via cytokine release, cell infiltration, and histology.

**References.** [1] World Health Organization. Fact sheet N°310. 2010. [2] Weers, J.G. *J Aerosol Med Pulm Drug Deliv*. 2010. 23 Suppl 2, S5-23. [3] Rocca, J.D. *Acc Chem Res*. 2011. *44* (10), 957-968. [4] Decker, G., Stillman, Z.S., Attia, L., Fromen, C.A., Bloch, E.,*Chem Mater* 2019. *31* (13) 4831-4839.