

In Vivo Assessment of Metal Organic Framework (MOFs) for the Future use as Delivery Agents for Drugs to Treat PAH

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Extended Abstract

Pulmonary arterial hypertension (PAH) is a progressive, debilitating and fatal condition with no cure. However small molecule drugs, including sildenafil, selexipag and bosentan, have been developed and are used to treat PAH but do not offer a cure and life expectancy, even on medication, is only between 2-5 years after diagnosis. All PAH drugs are ubiquitous dilators and their therapeutic dose is severely limited by their systemic side-effects [1]. We are working on the hypothesis that current PAH-drugs could be used more effectively at higher local (to the lung) concentrations if delivered selectively using a nanomedicine approach. We suggest that if toxicological limitations of nanomedicines can be overcome their use in PAH to delivery current drugs to the lung could turn this fatal disease to a chronic drug-managed condition. One nanoparticle that we are interested in is from the Materials of Institute Lavoisier (MIL), the so called MIL-89. MIL-89 is an iron based metal organic framework (MOF). MIL-89 is a good candidate for delivery of drugs because (i) it can be tailored to accommodate different drugs including those with the molecular weights of current PAH-medications (MW; 300-500) [2], (ii) it is biocompatible and biodegradable [3]; (iii) it has a large internal surface area and high drug loading capacity; (iv) it is thermally and mechanically stable; and (v) it promises a long drug release-period with the ability to incorporate different functional groups [2, 4-5]. We have previously shown that MIL-89 at concentrations up to 10µg/ml is non-toxic to human lung cells including those from patients with PAH. In the current study we have investigated the effects of MIL-89 in rats *in vivo* for markers of toxicity. MIL-89 at 50mg/kg was administered (i.p.) for two weeks at days 0, 1, 3, 7, 10 and 14. At each time point rats were weighed, killed, plasma and tissues collected. MIL-89 had no effect on body weight, lung oedema or on plasma markers of organ failure. Importantly, histological analysis showed that MIL-89 reached our target organ of interest, the lung. These observations are consistent with our previous *in vitro* studies showing that MIL-89 is non-toxic in cellular models relevant to PAH and suggest that this particular MOF is tolerated short term *in vivo* and accumulates in lung tissue and that this work with MOFs will offer interests to the researchers in the field of drug-delivery development using nanotechnology.

References:

- [1] S. L. Archer, *et al.*, "Basic science of pulmonary arterial hypertension for clinicians: new concepts and experimental therapies," *Circulation*, vol. 121, no. 18, pp. 2045-66, 2010.

- [2] P. Horcajada, *et al.*, "Porous metal-organic-framework nanoscale carriers as a potential platform for drug delivery and imaging," *Nat. Mater.*, vol. 9, no. 2, pp. 172-8, 2010.
- [3] R. C. Huxford, *et al.*, "Metal-organic frameworks as potential drug carriers," *Curr. Opin. Chem. Biol.*, vol. 14, no. 2, pp. 262-8, 2010.
- [4] G. Ferey, *et al.*, "A chromium terephthalate-based solid with unusually large pore volumes and surface area," *Science*, vol. 309, no. 5743, pp. 2040-2, 2005.
- [5] P. Horcajada, *et al.*, "Metal-organic frameworks as efficient materials for drug delivery," *Angew. Chem. Int. Ed. Engl.*, vol. 45, no. 36, pp. 5974-8, 2006.