Application of nanoMOF to lung drug delivery: role of physico-chemical features on their interaction with cancer cells

Description of the scientific background

Metal Organic Frameworks (MOFs) are hybrid materials formed by the self-assembly of metal connecting points (ions or clusters) and bridging organic ligands leading to the creation of three-dimensional networks with high and regular porosities. Nanometric MOF hold interesting properties for drug delivery applications such as easy functionalization, biodegradability, important porosity (up to 4000 m^2g^{-1}) and large pore size.[1] Recently it has been discovered that Iron-carboxilated nanoMOF, composed if iron(III) octaedra trimers and trimesate anions display a unique pH-responsiveness and reversible aggregation behavior.[2] Thus, while stable at acidic pH values, they form aggregates at the neutral pH of the blood, with an adequate size to be retained within the lung capillaries. Such property has been exploited for the delivery of the anticancer drug gemcitabine monophosphate to this tissue. Aggregates were present in the lung as fast as 5 minutes post injection, by then in less than 24h, they completely disappeared, and the release of the drug payload occurred following particle degradation and surface charge changes. (Figure 1) As results, an impressive antitumor efficacy was observed in an experimental model of metastatic lung carcinoma compared to the free drug.

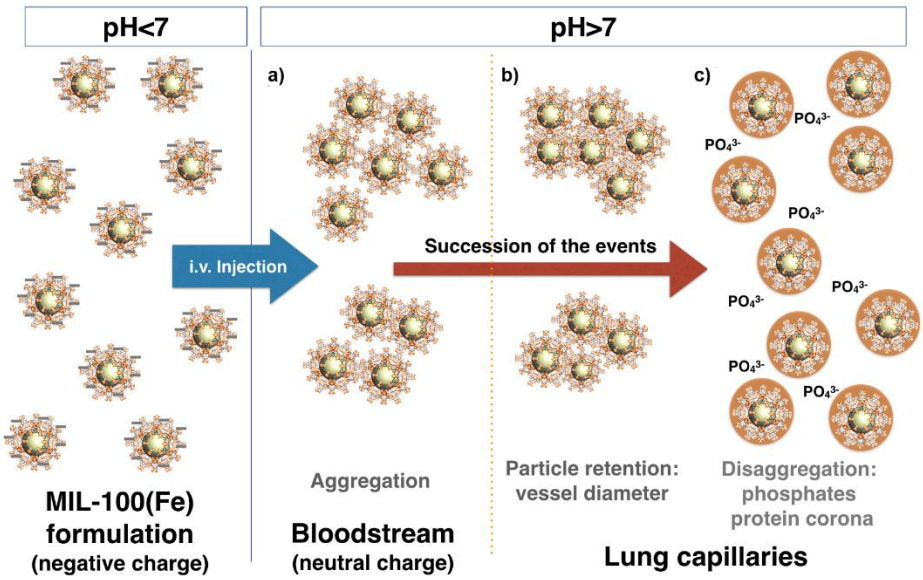

Figure 1. Schematic representation of nanoMOF reversible aggregation in vivo.

[1] Horcajada P et al. Porous metal–organic-framework nanoscale carriers as a potential platform for drug delivery and imaging. Nature Materials 2009;9:172

[2] Simon-Yarza T et al. A Smart Metal–Organic Framework Nanomaterial for Lung Targeting. Angewandte Chemie International Edition 2017;56:15565-9.

Description of the aim of the project

The aim of this project is to understand in vitro how the physico-chemical properties of nanoMOFs influence the specific interaction with the cancer cells.

Description of the organization of the projects

A small library of iron trimesate mesoporous MIL-100(Fe) nanoMOF displaying different physico-chemical properties will be prepared through microwave assisted or room temperature green synthesis. We intend to investigate three main parameters: size, shape (spherical or faceted) and surface functionalization. Surface modification with various biomolecules will be performed either covalently (*e.g.,* phosphate β-cyclodextrin) or non-covalently (*e.g.,* heparin, PEG-Graft-fast). Gemcitabine monophosphate, a major anticancer drug will then be encapsulated into the MOFs according to a "green" impregnation method. Fluorescently labeled (*e.g.,* furazan, bodipy) nanoMOFs will be prepared by simple impregnation methods. Capacity of these nanoMOF to interact with lung cancer cells will be evaluated in vitro on a 3D tumor model of lung cancer in collaboration with a Post-Doc researcher already working on this topic.

Expected results

These studies will allow to generate new knowledge on the factors which play a crucial role in *(i)* the penetration/accumulation of the nanoMOFs through the whole tumor tissue and *(ii)* the effectiveness of treatments resulting from a better drug availability in the tumor.

Required Skill

- Experience working in a laboratory environment and familiarity with basic techniques for formulation and characterization of drug delivery systems
- Good organizational skills
- Data exploitation
- Report writing

Stage length: 6 months, January-July 2019

Institution Institut Galien Paris-Sud, UMR CNRS 8612. http://www.umr-cnrs8612.u-psud.fr/

Some of the experiences will be performed at the Institut des Matériaux Poreux de Paris
http://www.chimie.ens.fr/?q=fr/node/4765

Supervisor(s) of the project

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