

Abstract

Developing new methodologies for cancer diagnosis and therapy involves the need to minimize current therapies secondary effects. In this field, nanotechnology brings out the opportunity to design and manufacture vehicles for therapeutic and/or diagnostic agents, which may be selectively targeted to the pathological tissue and respond under specific stimuli that allow to accurately control the systems biological activity.

In this context, this doctoral thesis tackles the design, synthesis and biological validation of metalorganic nanoparticle-based systems (nanoMOFs). The general aim is the study and evaluation of nanoMOFs potential as structural components of vehicles for biomedical use, mostly to drug intracellular diffusion and clinical imaging improvement. This rationale leads to two main challenges:

Developing stable systems based on Fe^{3+} nanoMOFs for intracellular diffusion of antitumor drugs.

Developing stable systems based on Fe^{3+} and Gd^{3+} nanoMOFs to obtain novel contrast agents that can enhance magnetic resonance imaging.

In order to address the first challenge, we have prepared camptothecin (CPT) controlled release materials based on amino group functionalized nanoMOFs, MIL-100(Fe) and MIL-101(Fe), where CPT is covalently bonded over amino groups by amidation or click chemistry. CPT-loaded MIL-101(Fe) derivatives have shown improved cell internalization due to their positive ζ potential and a strong response to acid pH, increasing drug discharge over 2-4 fold at pH 5, which promotes intracellular release by endosomolytic activity. Overall, these nanoMOFs provide an appropriate vehicle for safe CPT diffusion, with good potential at *in vivo* use.

With regards to our second challenge, we have developed different contrast agents for magnetic resonance imaging based on a Prussian Blue analogue, $\text{Gd}(\text{H}_2\text{O})_4[\text{Fe}(\text{CN})_6]$, that is able to increase both longitudinal (T_1) and transversal relaxivity (T_2). By reaction of $\text{Gd}(\text{H}_2\text{O})_4[\text{Fe}(\text{CN})_6]$ with silicate in alkaline medium we have obtained Gd-Si oxide monodispersed nanoparticles keeping the pristine morphology, with T_1 y T_2 *in vitro* values higher than Gd^{3+} chelate commercial solutions. Moreover, we have obtained a novel hybrid material by $\text{Gd}(\text{H}_2\text{O})_4[\text{Fe}(\text{CN})_6]$ nanoparticle covering with a thin silica layer, by silicate hydrolysis and polymerization at neutral pH. Such material presented T_1 values one order higher than Gd^{3+} chelate based systems and a positive contrast much stronger in magnetic resonance images *in vitro* and *in vivo*, due to the synergetic effect between Fe^{3+} and Gd^{3+} magnetic centers closely connected through cyano-bridge bonds in an extremely dense structure. Furthermore, these nanoparticles present a very homogeneous composition and a constant Gd:Fe atomic ratio, providing excellent signal reproducibility.