Cisplatin-Based Metal Organic Framework Nanoparticles for Targeted Drug Delivery and Tumor Imaging

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Abstract:

Nanoscale metal organic framework (NMOF) particles are nanoparticles composed of an amorphous framework constructed from an organic linker ligand and a metal ion. These nanoparticles are excellent candidates for use in drug delivery due to their biodegradability, tunable size and high loading capacity. In this study, we synthesized novel NMOFs based on the anti-cancer drug cisplatin with high payload (83%). A targeted near-infrared (NIR) molecular probe was also incorporated into this nanoparticle to achieve NIR imaging capability and targeted drug particle delivery. The anticancer effect of the nano-construct was demonstrated on cancer cells and the targeted delivery of this nano-theranostic agent was evaluated both *in vitro* and *in vivo*.

Introduction:

Metal organic frameworks are materials composed of metal ions coordinated with organic linker ligands. When shrunk down to the nanoscale, the potential for drug delivery applications arise [1]. The drug can be directly loaded into the porous in the framework or alternatively the framework can be constructed with the drug acting as the organic linker. By building the framework from the drug itself, one can increase the payload of the particle while decreasing the overall unwanted material. However, not all drugs can be used in the framework directly in this fashion. For example, a stringent requirement is that the metal ions should form the framework with the desired drug.

In this project, we constructed MOF nanoparticles based on the anti-cancer drug cisplatin with a simple nanoprecipitation method. Different nanoparticle sizes were obtained when using different precipitation procedures. To achieve the controlled drug delivery and imaging capability, we coated the amorphous prodrug nanoparticle with polymer and silica shells, at the same time, an integrin targeted imaging probe LS301 was incorporated to achieve the targeted tumor imaging. The morphologies and sizes were characterized via electron microscopes and dynamic light scattering. *In vitro* and *in vivo* studies were also conducted to confirm the targeted imaging capability and therapeutic effect.

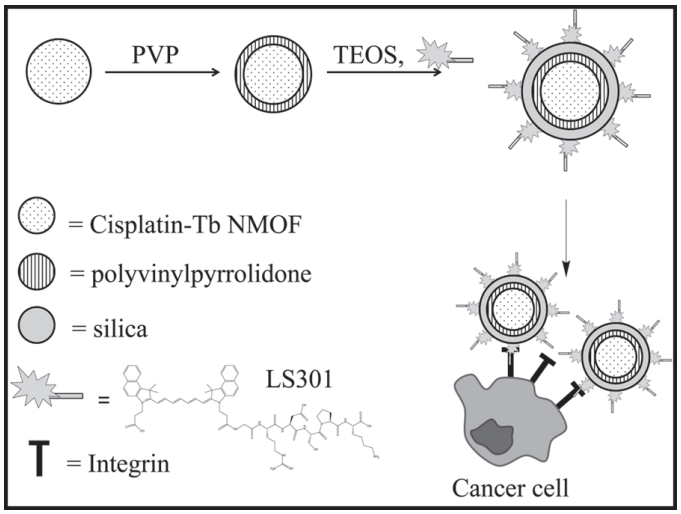

Figure 1: Coating scheme for nanoscale metal organic framework particles.

Experimental Procedure:

A disuccinatocisplatin (DSCP) salt was first synthesized [1]. Methanol was added to the mixture of DSCP prodrug NPs with terbium salt to form the NMOF construct through the nanoprecipitation process [2]. By modifying method to precipitate the prodrug NPs, we were able to obtain particles with different sizes. Polyvinylpyrrolidone (PVP) and silica shells were coated onto this NMOF construct subsequently to achieve the controlled the drug release. At the same time, NIR imaging probe cypate-cyclic GRD (LS301) [3] was also incorporated into the nano-construct to make it capable for targeted tumor imaging (Figure 1).

Results and Conclusions:

The particles were characterized by scanning electron microscopy (SEM), transmission electron microscopy (TEM), and dynamic light scattering (DLS) to determine the morphology and size. Figure 2a shows a SEM image of NP1-uncoated, and

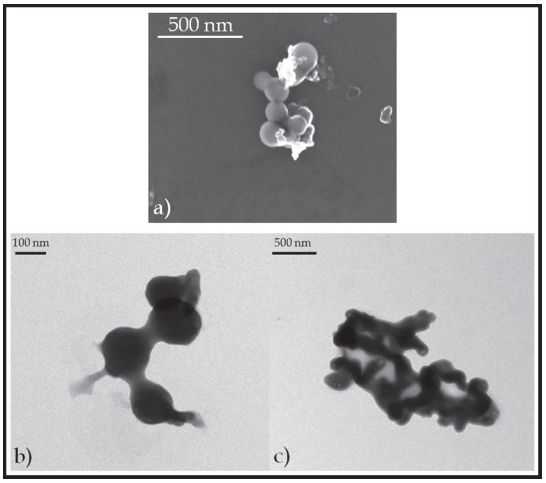

Figure 2: a) SEM image of NP1-uncoated. b) TEM image of NP2-uncoated. c) TEM image of NP1-silica/probe.

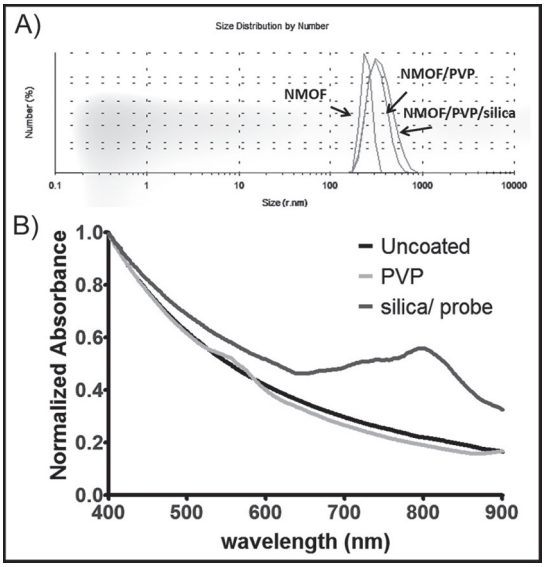

Figure 3: a) Graph of size distribution of uncoated, PVP coated and silica/probe coated NP1 determined by DLS. b) Normalized absorbance of bare, PVP and silica/probe coated NP1.

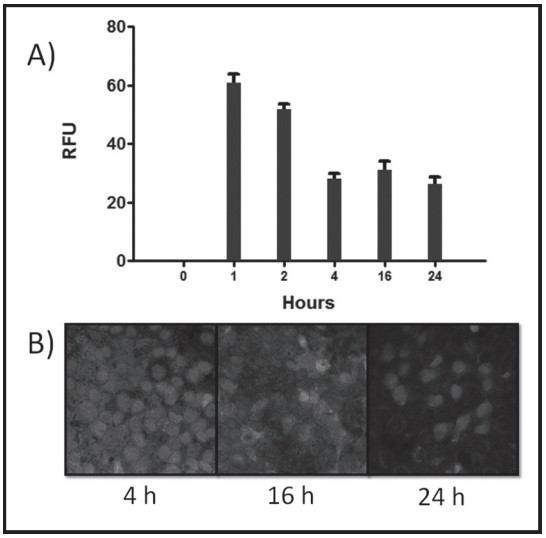

Figure 4: a) Relative fluorescence of cells at various time points during the internalization study. b) Representative images of the fluorescence of LS301 and nuclear stain during internalization at various time points.

Figure 2b and c shows a TEM image of NP2-uncoated and NP1-silica/probe. The DLS results demonstrating the change in size as a function of time during the coating procedure can be seen in Figure 3a. The absorption (Figure 3b) and emission spectra were recorded on a spectrophotometer and spectrofluorometer, respectively for NP1 uncoated, PVP-coated and silica coated NPs. NP1-silica/probe sample exhibited an emission peak around 800 nm that indicates the targeted imaging probe LS301 was successfully incorporated into the nano-construct.

The internalization of the silica-probe coated NP1 was investigated in A431 cancer cells. The relative fluorescence of the NMOF particles at different time point is shown in Figure 4. The high intensity of fluorescence after one hour shows that NP1 rapidly internalized in the cells. Following this peak intensity, the fluorescence intensity gradually decreased with time until it plateaued after four hours. This decrease in fluorescence was probably caused intracellular degradation of the particles, which was accompanied by the drug release. The observed fluorescence enhancement at one hour incubation could be attributed to sequestration of the dye in the silica shell [4]. Subsequent degradation of the silica shell resulted in the release of the LS301 molecular probe, with the attendant loss of fluorescence enhancement by the silica shell.

Conclusions and Future Work:

To summarize, we successfully synthesized a high payload cisplatin-based NMOF anti-cancer drug construct with targeted tumor imaging capability. The controlled drug delivery and targeted tumor imaging were demonstrated in both *in vitro* and *in vivo* studies. In the future, more drugs or co-drug will be examined to form this kind of NMOF construct to explore the better drug delivery and therapeutic effect.

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