Silica Nanoparticle – photoinduced CO releasing molecule – sugar conjugates: towards a new approach for the treatment of liver cancer.

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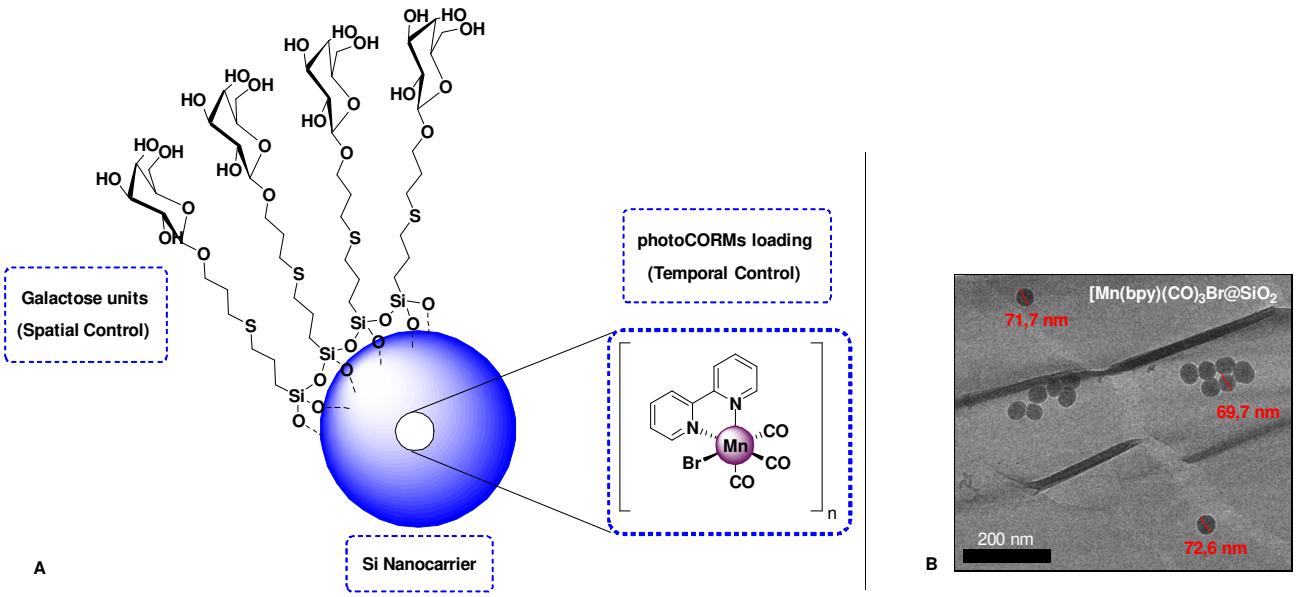
Nowadays, cancer is considered as the leading cause of death in developed countries. Among them, liver cancer is among the most frequent cancers with a poor prognostic. The major subtype of liver cancer, that is hepatocellular carcinoma (HCC), is the third most common cause of death by cancer and the fifth most common malignancy worldwide with over 700 000 new cases per year. To manage HCC, systemic conventional chemotherapy becomes the only alternative but shows limited efficacy because of multidrug resistance and severe side effects. In order to overcome the multidrug resistance of HCC, an ubiquitous cell poison such as carbon monoxide (CO) could be considered as an alternative therapeutic agent. CO has been recognized for a long time as a dangerous gas to mammals. Its high toxicity is mainly due to the high affinity of CO for iron in hemoglobin leading to the fast and nearly irreversible formation of carboxyhemoglobin. More generally all hemoproteins including vital enzymes involved in oxidative phosphorylation are sensitive to CO. On the other hand, CO has a vital role in organisms and is produced endogenously by heme oxygenase during heme catabolism. Studies revealed that CO plays a pivotal role as a gaseous signaling neurotransmitter. It is now well admitted that CO has a very promising therapeutic potential according to the dose. In its gaseous state, CO is very difficult to administer and the dose difficult to control. To overcome this issue, Carbon Monoxide Releasing Molecules (CORMs) have emerged as a suitable mode of administration of CO. Even more efficient are CORMs delivering CO upon a given external stimulus, such as visible light, i.e. PhotoCORMs.

PhD program:

On this basis, the objective of the PhD thesis is first to design a novel series of manganese(I)-based photoCORMs, whose excitation wavelength (from the visible to the near IR region) will be tuned by modifying the coordination sphere. These PhotoCORMs will next be encaged within silica nanoparticle-based (SiNPs) nanocarriers for the selective delivery of a **toxic dose** of CO to HCC cells. These SiNPs find increasing utility as drug delivery systems due to their ease of synthesis, size control and porosity, biocompatibility and versatile surface chemistry. **Spatial control** of CO delivery will be ensured by decorating the SiNPs with galactose ligands to take advantage of their affinity for ASGP-R, overexpressed in HCC cells. This will allow multivalent presentation of the sugar entities to the surface of HCC cells thus increasing the efficiency of their cell uptake. Preliminary experiments have been performed to prove the feasibility of our approach. The PhotoCORM $[Mn(bpy)(CO)_3Br]$ was successfully incorporated into SiNPs and galactose units (GAL) were successfully grafted all around the surface (scheme 1).



Scheme 1: A Encapsulation of photoCORMs into a poly-galactosylated silica nanoparticle; **B** TEM image of encapsulated photoCORM $[Mn(bpy)(CO)_3Br]$.

A significant part of the project will be devoted to the thorough characterization of the nano-objects by complementary analytical studies (TEM, DLS, Zeta potential measurement, IR spectroscopy). The amount of PhotoCORM incorporated into the SiNPs will be determined by assay of Mn and Si with ICP-OES. The knowledge of this parameter is essential to be able tightly control the dosage of the CO released from the PhotoCORMs. Next, the amount of CO released from the SiNPs upon light irradiation will be measured by gas chromatography and the kinetics of CO release will be monitored by in-situ IR spectroscopy. The amount of GAL entities grafted to the SiNPs surface will be determined by an enzymatic assay.

Once the multifunctional nanoobjects fully characterized, we will perform cell uptake studies on the HCC cell model HepG2. We will take advantage of the luminescence properties of the rhenium analogues of the PhotoCORMs to track the nanoparticles within cells by fluorescence microscopy. Control experiments will be performed on HeLa cell line that does not express ASGP-R and/or with SiNPs lacking the galactose units. Cell viability studies will be performed in the dark or after light irradiation to investigate the (photo)cytotoxic properties of the various nanosystems. Finally, and in the view to produce nanomedicines for in vivo studies, PEG substituents will be introduced at the surface of the galactose-decorated, PhotoCORM-loaded SiNPs to increase their blood circulation time by delaying opsonization and evading macrophages clearance.

To conclude, this PhD proposal aims at furnishing a proof-of-concept for the development of a cytotoxic nanomedicine dedicated to hepatocellular carcinoma treatment, combining galactose-derivatized silica nanoparticles with encapsulated manganese-based PhotoCORM for the targeted delivery of CO. To the best of our knowledge, there is no previous example of PhotoCORMs encapsulation within SiO_2 nanoparticles decorated with carbohydrate vectors giving us new avenues to develop this promising strategy for anticancer therapy.

Expected student profile:

The PhD candidate must have a MSc degree in molecular chemistry (or equivalent). He/she should have strong skills in organic and organometallic chemistry with a knowledge in material chemistry. Experience in nanoparticles preparation and/or characterization will be an asset. A strong motivation to work at the interface between several disciplines is expected. Autonomy, curiosity and open-mind are also welcome. The candidate should apply according to the procedure described in this link (http://ed406.sorbonne-universite.fr/fr/contrats-doctoraux.html).