SORBONNE
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CHINA SCHOLARSHIP COUNCIL

Appel à projets
Campagne 2022
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Title of the research project :

Silica coated gold nanorods for laser-induced gene therapy

Thesis supervisor (HDR) :

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Research Unit

Name : Laboratoire de Réactivité de Surface

Code *(ex. UMR xxxx)* : UMR7197

Doctorate School

Thesis supervisor's doctorate school (candidate's futur doctoral school) : ED397- Physique et Chimie de Matériaux

PhD student currently supervised by the thesis supervisor (number, year of the first inscription) :

1-2019(ANR,&B.Gallas) 1-2020(CSC,&M.Salmain) 1-2021(ED,&A. Wilson)

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Joint supervisor :

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Research Unit

Name : Laboratoire Lumière, Matière et Interfaces (LuMIn)

Code *(ex. UMR xxxx)* : FRE2036

École doctorale

Joint supervisor's doctorate school : ED573

Or, if non SU : ED Interfaces (univ. Paris Saclay)

PhD student currently supervised by the joint supervisor (number, year of the first inscription) :

1, 2018

Joint supervisor :

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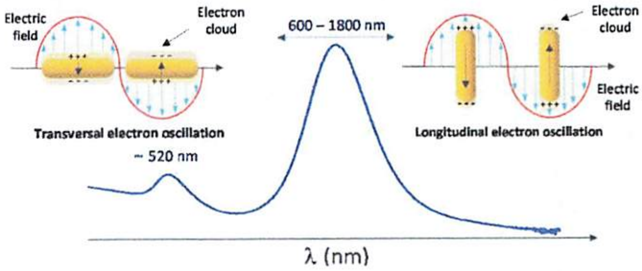
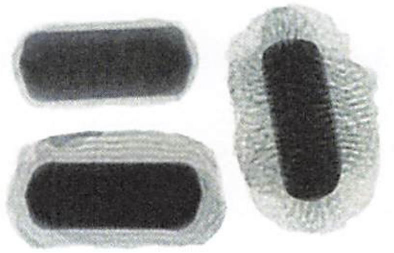
Description of the research project (*ENGLISH*):

1) Study context

Gold nanorods (AuNRs) are now, and over several decades, established as central items for biological applications including biosensing, drug delivery and photothermal therapy. Their ability to absorb light upon irradiation originates from the collective oscillation of electrons in the conduction band of the gold surface; it results in two localized Surface Plasmon Resonance (LSPR) bands called the transversal and longitudinal bands, t-LSPR and l-LSPR, respectively; they correspond to the resonance along the short and long axes of the particle, respectively. [1-2] *The position of l-LSPR band can be finely tuned from 600 and up to 1800 nm by controlling the particle aspect ratio.* [3] *This versatility is of high interest for biomedical applications such as photothermal therapy or drug delivery because of the minimal absorption of blood and human tissues in this region.* [4] *The extensive development of synthesis protocols enables the preparation of particles with desired and controlled properties, mainly using cetyltrimethylammonium bromide (CTAB) as surfactant, surface stabilizer, and shape inducing agent. However, the cytotoxicity of CTAB and its interferences with biological processes, restrict the biomedical applications of AuNRs in photothermal therapy or drug delivery.* [5] *Besides the damaging effect of CTAB, one major drawback of AuNRs application in photothermal therapy, is that they are not stable under irradiation and reshape into spherical nanoparticles.* [6] *In addition, the presence of CTAB limits the accessibility to gold surface and strongly inhibits the grafting of biomolecules such as oligonucleotides for gene therapy.* [1] *To overcome these limitations, the growth of a silica shell on AuNRs, also referred as silica coating, is the most promising route and has expanded tremendously over the last decade as it allows to eliminate or screen CTAB while preserving AuNRs' shape and therefore, their optical properties. Our group has recently reported a versatile method for the synthesis of core-shell AuNR@SiO_2 nanoparticles with tailored shell thickness and porosity to adapt it to the desired biological application.* [7] *We intend in this project to use this technology for gene delivery by laser-induced photothermal conversion, with precise nanoscale thermal management as well as in vitro and in vivo assessments.*





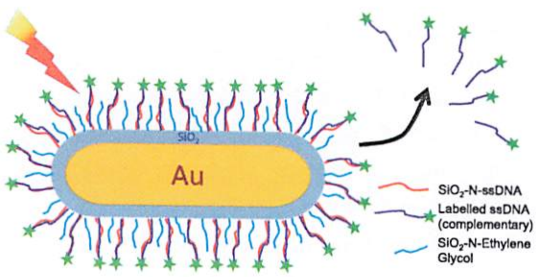
2) Methodology to reach the scientific objectives

This PhD project is co-supervised by Souhir Boujday at Sorbonne University and by Bruno Palpant at ENS Paris Saclay.

1. Synthesis of gold nanorods, silica coating. *The candidate will synthesize AuNRs with proper aspect ratio by the seed-mediated method. Centrifugation-redispersion cycles will refine the shape distribution. A silica layer (1- 10 nm thick), either dense or porous, will then be initiated and developed on the AuNR surface following the previously mentioned protocols. These protocols lead to the complete removal of CTAB (toxic) with resulting reproducible and stable colloidal particles. The multiple* *steps of synthesis and coating with SiO_2 will be assessed and quantified relying on the characterization platforms available at LRS, UV-vis spectroscopy, DLS and zetametry, Raman, XPS and Electron microscopy. The input of porosity to further protect the oligonucleotides from nucleases will be explored.*

2. Biofunctionalization and ssDNA grafting. *Once the synthesis and silica coating protocols mastered by the PhD student, a relevant sequence of single strands DNA for intracellular delivery with a generic therapeutic interest, selected and provided by Paris Saclay will be attached or embedded within the porosity. The AuNR@SiO_2 surface will be functionalized as to optimize DNA grafting by condensation of silanes.*

3. Photo-induced oligonucleotide release: analysis and optimization. *The cellular toxicity and cellular uptake of AuNR@SiO_2 will be assessed and optimized. The laser-induced release of fluorescence-labeled DNA from duplex dsDNA grafted onto AuNPs will be quantified. We will study the complete denaturation of dsDNA strands thanks to the dependence of the emitted intensity on the fluorophore-AuNP distance, in vitro and then in cellulo.*



4. In vivo assessment of the therapeutic relevance of the functionalized nano-objects. *The validation of our NPs for targeted gene delivery will start with assessing their biodistribution in blood and different tissues (liver, spleen, kidney) including tumors after intravenous injection, as well as their potential toxic effects using mice xenografted with human breast cancers. We will then demonstrate and improve the efficiency of the light-induced ON release in vivo. NP biodistribution will be determined by the absolute quantification of gold in tissues (ICP-MS), and by their cell and sub-cellular localization.*

3) References (colored for the host-group)

1. Pellas, V.; Hu, D.; Mazouzi, Y.; Mimoun, Y.; Blanchard, J.; Guibert, C.; Salmain, M.; Boujday, S., Gold Nanorods for LSPR Biosensing: Synthesis, Coating by Silica, and Bioanalytical Applications. *Biosensors* **2020,** *10* (10).
2. Pérez-Juste, J.; Pastoriza-Santos, I.; Liz-Marzán, L. M.; Mulvaney, P., Gold nanorods: Synthesis, characterization and applications. *Coordination Chemistry Reviews* **2005,** *249* (17), 1870-1901.
3. Link, S.; Mohamed, M. B.; El-Sayed, M. A., Simulation of the Optical Absorption Spectra of Gold Nanorods as a Function of Their Aspect Ratio and the Effect of the Medium Dielectric Constant. *The Journal of Physical Chemistry B* **1999,** *103* (16), 3073-3077.
4. Weissleder, R., A clearer vision for in vivo imaging. *Nature Biotechnology* **2001,** *19* (4), 316-317.
5. Jia, Y. P.; Shi, K.; Liao, J. F.; Peng, J. R.; Hao, Y.; Qu, Y.; Chen, L. J.; Liu, L.; Yuan, X.; Qian, Z. Y.; Wei, X. W., Effects of Cetyltrimethylammonium Bromide on the Toxicity of Gold Nanorods Both In Vitro and In Vivo: Molecular Origin of Cytotoxicity and Inflammation. *Small Methods* **2020,** *4* (3), 1900799.
6. Albrecht, W.; van de Glind, A.; Yoshida, H.; Isozaki, Y.; Imhof, A.; van Blaaderen, A.; de Jongh, P. E.; de Jong, K. P.; Zečević, J.; Takeda, S., Impact of the electron beam on the thermal stability of gold nanorods studied by environmental transmission electron microscopy. *Ultramicroscopy* **2018,** *193*, 97-103.
7. Pellas, V.; Blanchard, J.; Guibert, C.; Krafft, J.-M.; Miche, A.; Salmain, M.; Boujday, S., Gold Nanorod Coating with Silica Shells Having Controlled Thickness and Oriented Porosity: Tailoring the Shells for Biosensing. *ACS Applied Nano Materials* **2021**.

4°) Profile of the Applicant (skills/diploma…)

The applicant must have solid skills in Materials Science. He/She must have a taste for nanoparticles synthesis and materials surface functionalization and interest in the biological interfaces. Experimental skills in materials characterization techniques such as XPS, Raman or SEM/TEM will be appreciated.

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