Master thesis proposal

Light-induced delivery of therapeutic oligonucleotides with gold nano-objects

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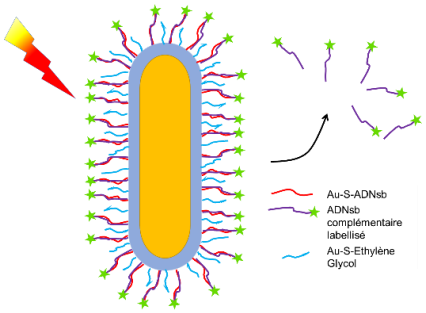
Background

Most dysfunctions in cancer cells result from the expression of mutated genes or deregulated genes that overexpress proteins. Gene therapy can revolutionize cancer treatment by turning off a defective gene using an oligonucleotide (DNA, RNA). However, delivery of the oligonucleotide into the specific cells, tissues or organ is challenging. Using gold nanoparticles (AuNPs) as a DNA/RNA cargo represents an attractive strategy. Illuminated at a particular wavelength they behave like tiny converters of light into heat thanks to the *localized surface plasmon resonance*. When illumination is achieved by ultrashort laser pulses, the photo-induced heating is brief, intense and very confined around the nano-objects. Our project offers to improve the efficiency of DNA delivery in biological cells and its quantitative control by grafting oligonucleotides onto AuNPs and then triggering the delivery by photothermal effect induced by laser pulses (Figure). This project has been awarded a financial support from *Institut d'Alembert* in ENS Paris-Saclay.



Work plan

AuNPs covered with a thin layer of silica (AuNR@SiO_2) are synthesized by our partners in *Laboratoire de Réactivité de Surface* (LRS), Sorbonne University, Paris. These nano-objects are functionalized with DNA after selecting a relevant sequence for intracellular delivery.

1. **Study of the localized photothermal effect.** We will accurately assess the thermal topography around nanoparticles for optimal release under biological conditions. For this, we will explore the distance dependence of temperature at nanometer resolution (using different conjugate oligonucleotides as a temperature probe), varying both the energy and duration of the laser pulse. In parallel, LuMIn will develop a numerical approach to determine the topography of the heating induced by continuous or pulsed irradiation around a set of AuNPs in a cell.
2. **Study of the photo-induced release.** We will quantify the laser-induced release of fluorescence-labeled DNA from duplex dsDNA grafted onto AuNPs. 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*.

Related references

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2. *Pulsed-laser irradiation of multifunctional gold nanoshells to overcome trastuzumab resistance in HER2-overexpressing breast cancer*, T. Nunes *et al.*, *Journal of Experimental & Clinical Cancer Research* **38**, 306 (2019).
3. *High-resolution AFM structure of DNA G-wires in aqueous solution*, K. Bose, C. J. Lech, B. Heddi, A. T. Phan, *Nature Commun.* (2018), **9**, 1959.
4. *Selection, characterization, and application of DNA aptamers for detection of Mycobacterium tuberculosis secreted protein MPT64*, M. Sypabekova; A. Bekmurzayeva; R. Wang; Y. Li; C. Nogues; D. Kanayeva. *Tuberculosis* (2017), 104,70-78