Subject 2 : **In situ Evaluation of the efficiency of grafted nanoparticle under extreme electron dose rates**

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As part of the study of nanoparticles (NPs) used in radiotherapy as radioenhancers to increase the effects of radiation on tumor cells, it is a key issue to monitor their effect in real time, by fast and non-intrusive methods. This close monitoring protocol proposed in this project is the first step for prediction of the radioenhancement efficiency and the evaluation of the locally delivered dose in presence of NPs. Thus, the development of a new nanodosimetric tool and method to ensure the standardization and transferability of solutions to the clinic is a major step to develop new strategies for cancer radiation therapies.

The hypotheses of this project are the following. The team at ISMO has designed a multifunctional platinum NP (NP-Pt) grafted with Rhodamine-B (RhB) molecules. The RhB fluorescence of the transplanted NP-Pt was used first to track it until internalization in the target cell. Exploiting the fluorescence lifetime (�) of the RhB grafted to the NP-Pt (NP-Pt-RhB) opens new possibilities to carry out monitoring of NP-Pt effects on local dose delivery in the tumor cells and in-vivo. It is well known that the fluorescence lifetime (�) provides information on the environment of the fluorescence emitter (RhB) because charge transfers or reactions allow the excited state to relax by non-radiative pathways. Thus, modifications of the environment, due to pH modification, application of an electric field or high temperature or production of byproducts, lead to � variations.

Upon irradiation, the environment of the tumor target cells changes. It instantly produces a strong field of ionized molecules (mainly those of water) and very quickly generates the production of free radicals. These species affect the relaxation of the excited states of a dye molecule such as RhB. The interaction of the fluorescence emitter with radicals "quenches" the fluorescence. Hence, measurement of � gives access to the local chemical composition, effectiveness and local dose delivery induced by radiation.

A new modality in radiation therapy is the FLASH using ultra high dose rates. The new laser-plasma driven electron accelerators, can reached a dose rate about 109-12 Gy/s, several orders of magnitude higher than the dose rate used for conventional treatment (in the range of 1Gy/min). The fundamental processes responsible for the FLASH effect are under investigation and not elucidated at that time. These specific extreme dose rate particle sources could be used to elucidate the FLASH effect.

The objective of this training project is to probe the capability of NP-Pt tagged with RhB to enhance the effect of the beam coming from the laser-plasma driven electron accelerator, and to use this protocol to characterize and quantify their efficiency to improve radiation effects when submitted to extreme dose rate electron bunches such as FLASH. It includes measurements and in-depth analysis of the of NP-PtRhB fluorescence intensity to probe in real time the fast chemical changes in cells and determine the local dose deliver. We plan to measure the fluorescence yields in different cell lines (HeLa, PC3, U87 glioblastoma, BxPC3 pancreas, fibroblast) cultivated in classical monolayer culture mode (2D).

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