PhD Thesis title: 'Photo-activation Therapy with Nanoparticles: Modeling at a Sub-Micrometer Level and Experimental Comparison'

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ABSTRACT:

An innovative approach using X-ray interactions with heavy elements seems to open a promising way for the treatment of resistant cancers, such as high-grade gliomas. Such a technique is developed at the medical beam line of ESRF using monochromatic X-rays in the 25-90 keV range for the treatment of brain tumors. The use of gold nanoparticles (AuNP) to treat mice bearing subcutaneous tumors led to encouraging results. However, the physical processes and biological impact of the photon activation of nanoparticles are not yet well understood. The experimental results cannot be explained by macroscopic dose calculations. The aim of this work was to evaluate, at the sub-cellular level, the dose enhancement in presence of nanoparticles and the properties of the secondary electrons production using Monte Carlo simulations. At first, simulations were performed using a cell geometry, in order to compare the simulated data to the experiments realized on the ID17 beamline of ESRF. Clonogenic assays have been performed on F98 cells to measure the "Sensitizer Enhancement Ratio" for an irradiation of 4 Gy (SER_{4Gy}) in the presence of gadolinium, for several beam energies (25 to 80 keV). These experimental and numerical studies were done to evaluate the influence of the gadolinium location within the cell and its shape (nanoparticles or contrast agent). On the other hand, a comparative study has been performed to evaluate the behavior of a nanoparticle under irradiation at a nanometer scale. Electron spectra have been studied for two heavy elements - gold and gadolinium - and several beam energies ranging from 25 keV to 2 MeV. Experiments have shown that gadolinium nanoparticles (GdNP) incubated for 5 h with the cells were strongly effective compared to non-incubated nanoparticles and contrast agent, for the same concentration of gadolinium. Radiosensitivity could possibly be explained by a biological action of GdNP on the cell cycle. Another reason could be attributed to the important dose enhancement factor (DEF) calculated in the vicinity of GdNP, highlighted from two-dimension DEF maps. The DEF can reach two orders of magnitude within the proximity of few nanometers from the GdNP surface and is mainly due to high-linear energy transfer electrons (< 5 keV). By modeling the case of nanoparticles randomly distributed on the cell membrane (closest to the experimental case), we showed that a good correlation exists between the SER_{4Gy}

and the membrane DEF. On the other hand, the comparison of the two elements showed that GdNP could produce more electrons (of lower energy) than AuNP (with same mass), but that the local DEF due to AuNP was more important. Interesting results were obtained by comparing the local DEF with experimental results on plasmid DNA. However, it seems important to carry on these studies by taking into account the post-irradiation chemical processes through modeling.

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