Novel cancer therapies:
Combination of MRT with gold nanoparticles and radio-sensitizing drugs.

REPORT of MD1039

Introduction: Our laboratory is investigating how to improve the treatment of mice, harboring the B16F10 melanoma tumor, by the use of Synchrotron microbeam radiation. This experimental radiotherapy technique is based on a single fraction of spatially distributed synchrotron x-ray microbeams. This type of irradiation has proven to be more successful than the delivery of a single dose of conventional radiotherapy in our (Potez et. al. 2017) and several other laboratories. The temporal fractionation of MRT – administered through several ports – and its combination with homogeneous irradiation is also under investigation. The aim of this project was to increase the effectivity of single applications of Microbeam Radiation Therapy (MRT) by combining it with gold nanoparticles (AuNPs). We tested whether a priming low-dose of microbeam irradiation was able to promote vascular permeability and thus the extravasation of AuNPs into the tumor mass prior to the delivery of the therapeutic high dose of MRT.

The experiment MD1039, was our first beamtime at the ESRF that included the use of gold-nanoparticles (AuNPs) as an adjuvant agent for the treatment of melanomas implanted into the ear of mice. The main objective was: *"Using Gold nanoparticles to increase the effect of the dose of MRT deposited in the melanoma tumour"*

Methods: Mice were subjected to different combinations of therapies between 8-10 days after tumor implantation. Microbeam irradiation was delivered as a low-dose priming modality and as a therapeutic high dose – in the MRT mode - in the biomedical beamline ID 17 of the European Synchrotron. The purpose of the low-dose priming irradiation was to evaluate its ability to induce vascular permeability, while the purpose of the high dose MRT was to halt the growth of the melanoma. The array was composed by 50um wide beamlets separated by 200um on center. Peak doses were 150Gy and 400Gy respectively. The animal model employed was C57BL/6J female mice implanted with 120,000 B16.F10 melanoma cells in their ears. 40 mg per mouse of 15nm AuNPs were administered via tail-vein. Tumor growth was recorded daily. The uptake of AuNPs by the tumors was also analyzed to determine the best time at which the high-dose of MRT should be delivered after the administration of AuNPs. The time of euthanasia was directly linked to the integrity of the tumor, which we used to estimate the median survival times.

Results: Can AuNPs improve the treatment of melanoma when combined with MRT? The answer is yes. The data showed that mice subjected to the AuNPs injection, before their melanoma was treated with 400 Gy of MRT, displayed a delay in tumor grow beyond of what was achieved by the mice that did not receive AuNPs before MRT. The data also showed that the administration of AuNPs after the delivery of the priming low-dose, 48h before the high-dose of MRT, delayed the tumor growth even further. The survival data show that the MRT treated mice lived for much longer than the control and the group that received AuNPs died at a later point.

The dose-boosting effect of AuNPs can also be observed when a priming low-dose microbeam irradiation is employed. The administration of AuNPs immediately after the delivery of the priming low-dose delayed the tumor growth compared to when AuNPs were not present. Moreover, the survival data show statistically significant differences between groups receiving: no irradiation (Control); a single therapeutic-MRT; a combination of priming dose and therapeutic MRT without AuNP; and triple combination of priming, AuNPs, and therapeutic-MRT. Consequently, the administration of AuNPs in combination with a priming- and therapeutic-MRT induced a Median Survival Time (MST) of 39.5 days, the highest of this project. Falling behind is the combination of priming dose and therapeutic MRT without AuNP with 29 days of MST, and the groups that received a single dose of therapeutic-MRT.

It was interesting to observe the ability of the priming low-dose microbeam irradiation to delay the tumor growth in relation to the control.

Conclusions: We can conclude that AuNPs increased the effect of the therapeutic high-dose of MRT (400 Gy) but that the boosting effect is highly dependent on the delivery of a priming low-dose of MRT. Administration of AuNPs prior to the therapeutic MRT is able to increase the MST by 1 day, but when a priming dose is given 45min before the AuNPs injection, the MST increased by 10 days. Suggesting that the priming-MRT dose is inducing vascular permeability that allows a larger extravasation of AuNPs (from the blood vessels into the tumor stroma), which in turn enhanced even more the therapeutic high-dose of MRT.