Proposal Code MD- 487
Proposal Title: Optimization of IdUrd synchrotron stereotactic radiotherapy.

Scientists involved: **Laure Bobyk, Jocelyne Gracia-Chantegrel, Pr. François Estève, Dr. Hélène Elleaume, Dr. Jean-Luc Ravanat**

Aims of the experiment and scientific background

Heavy-atom-enhanced SSR is a new radiation therapy treatment that involves selective accumulation of high-Z elements in tumors, followed by stereotactic irradiation with x-rays from a synchrotron source. For instance *in vitro* studies have demonstrated that cells pre-treated with non-radioactive IUdR had a higher sensitization factor than cells irradiated alone and that the optimal energy was 50 keV (Karnas 1999, Corde 2004). IUdR is known as an effective radiosensitiser, when it is incorporated into cellular DNA. Theoretical studies confirm that such an approach should be highly efficient at least if sufficient amounts of Iodine are incorporated in the nucleus (Karnas 2001). In addition, iomeron, an iodine-containing contrast agent has been also shown to efficiently sensitize cells to radiation (Adam et al. 2005, Adam et al. 2006). The objective of the experiment was to evaluate if a combination of both IUdR and iomeron could be use to improve the SSR treatment.

Results

Experiments were performed on F98 cells grown in a medium enriched with IUdr. The amounts of incorporated IUdr were determined subsequently to DNA extraction and digestion by HPLC coupled to tandem mass spectrometry. Cells containing or not IUdr were then irradiated at 50 kev in the presence or not of iomeron and the cell viability was assessed by measuring the ability of the cells to form colonies.
As already observed (MD 394) when about 2% of IUdr is incorporated into the DNA of F98 cells, compared to normal cells, a significant increase in the dose enhanced Factor (DEF) was observed as determined by the clonogenic assay. A similar observation was made for cells irradiated in the presence of iomeron. Such results confirm the radiosensitization effect of both IUdr when incorporated into DNA, and iomeron.
Interestingly, in addition to cell survival, radiation-induced DNA damage was also evaluated in irradiated cells using the comet assay allowing direct determination of the number of strand breaks. Again, when cells were grown in the presence of IUdr, an increase in DNA damage was observed, and interestingly no significant variation in the number of DNA strand breaks were observed in cells irradiated in the presence of iomeron, compared to cells irradiated without iomeron. Such a result suggests that iomeron-induced cell death is not mediated by DNA damage.

Moreover, when cells having incorporated IUdr were irradiated in the presence of iomeron, an additive effect was observed as determined using the clonogenic assay.
In conclusion, our results suggest that the combine use of IUdr and iomeron should be use to improve the efficacy of SSR treatment. An experiment on an animal model is now required to evaluate the efficacy of such treatment that should allow a reduction of the applied dose, thus minimising the side effect of the irradiation.

Reference.

Adam J.F.,Biston M.C.,Joubert A. Charvet, A.-M., Le Bas J.F., Esteve F., Elleaume H., Enhanced delivery of iodine for synchrotron stereotactic radiotherapy by means of intracarotid injection.

International Journal of Radiation Oncology Biology Physics, Mar 2005.
Adam J.F., Joubert A, Biston M.C., Charvet A.-M et al. Prolonged survival of Fischer rats bearing F98 glioma after iodineenhanced synchrotron stereotactic radiotherapy. Int. J. Radiation Oncology Biol. Phys., Vol. 64, No. 2, pp. 603–611, 2006.

Corde S., Joubert A., Adam J.F., et al. Synchrotron radiation-based experimental determination of the optimal energy for cell radiotoxicity enhancement following photoelectric effect on stable iodinated compounds. Br J Cancer 2004; 91(3): 544-551.

Karnas, S.J., et al., Optimal photon energies for IUdR K-edge radiosensitization with filtered x-ray and radioisotope sources. Phys Med Biol, 1999. 44(10): p. 2537-49.

Karnas, S.J., et al., Monte Carlo simulations and measurement of DNA damage from x-ray-triggered auger cascades in iododeoxyuridine (IUdR). Radiat Environ Biophys, 2001. 40(3): p. 199-206.