Report of the MD164 Experiments.

There is now a large body of evidence that the combination of radiotherapy with treatment to halogenated chemotherapeutic agents improves the prognosis of a number of malignancies more than radio- and chemo-therapy alone by providing synergetic anti-cancer effects (1, 2 and references herein). Since 5 years, Grenoble Hospital research team and, thereafter, U647 Inserm unit, have developed an innovating radio-chemotherapy approach consisting in irradiating cells treated to cis-platinum at the Pt K-edge (78.4.keV) to produce additional irreparable damage in tumor cells throughout an enhanced photoelectric effect. Synchrotrons display very high dose rate and easily monochromatizable radiation that makes theoretically possible such phenomenon, called photoactivation therapy (PAT). By using cisplatinum as heavy element-containing vector, we called ``PAT-Plat`` such promising medical applications of synchrotron.

In the frame of the previous experiments, here are the main milestones:
- LS1698: first measurement of DNA breaks in treated cells and first molecular model for PAT-Plat.
- LS2100 and LS2121: first preclinical assays on rats bearing glioma
- MD18 and MD35: series of preclinical assays
- MD40: PAT-Plat provides specific small DNA fragments
- MD70: PAT-Plat effect requires H1 histone protein
- MD90: Advantages of carboplatinum both *in vitro* and *in vivo*

PAT-Plat with tyrosine kinase inhibitors (PhD student mainly involved: Zuzana Bencokova)
Since some tyrosine and serine kinases have been shown to participate in the DNA repair recombination pathways, we proposed to ask whether some kinase inhibitors used extensively in clinic impact both *in vitro* (DNA and cells) and *in vivo* (rats bearing gliomas) upon the PAT-Plat response, notably by limiting the RAD51-dependent recombination pathways (4, 5). A series of shifts have been used therefore in preparation of nude mice and modified PAT-Plat treatments. *To add wortmanin and/or herceptin during treatment was shown to increase the number of unrepaired DNA breaks sensored by the phosphorylation of H2AX in vitro, suggesting an enhancement of the therapeutic index. With regard first results about the survival of rats bearing brain tumors and treated to PAT-Plat +wortmannin (PAT-Plat W) and PAT-Plat+herceptin (PAT-Plat H), 100% of PAT-Plat W, 50% of PAT-Plat W, 33% of PAT-Plat H treated rats are still surviving after 100 days post-treatment.*.

To add wortmanin and/or herceptin during treatment was shown to increase the number of unrepaired DNA breaks sensored by the phosphorylation of H2AX in vitro which may protract survival of rats bearing glioma, suggesting an enhancement of the therapeutic index. *Specific experiments about dosimetry have also been also performed to secure the set-up of irradiation for nude mice.*

Potential targeted genetic statuses (PhD student mainly involved: Jérôme Gastaldo). BRCA1 was shown to be required for the PAT-Plat effect, we propose to investigate *in vivo* (nude mice bearing human tumors) PAT-Plat responses of human tumor models of different origin (notably breast, ovarian and skin cancers) expressing differentially the BRCA1 protein The first application of PAT-Plat on nude mice bearing the human breast MDA tumor resulted in the disappearance of the tumor in *100% of PAT-Plat treated mice whereas tumors are still increasing in mice treated to other control treatments (irradiation or cisplatin alone) after 100 days post-treatment.*

All these encouraging results require additional beamtime experiments to verify the reproducibility and to provide a more general insight for the questions asked. Anew proposal (MD202) has been recently accepted to this aim.