REPORT for MD90 Experiment

1. Introduction

Previous experiments (Corde et al. Cancer Res. 2003) have shown that synchrotron photoactivation of cis-platinum (PAT-Plat) consists in an excess of DNA single- and double-strand breaks, probably due to an excess of radiation dose delivered to the close vicinity of DNA. Recently, thank to the efforts of U647 INSERM and the support of ESRF, another publication in Cancer Research has been accepted (Biston et al., Cancer Res, 2004, 64, 2317-2323).

As specified in this MD90 proposal, we endeavoured to optimize PAT-Plat by:
1) using new platinum-containing agents to increase the therapeutic index
2) applying this technique to human tumors (nude mice).

Unfortunately, for technical reasons, the use of human tumor xenografted-mice was not possible since the project of L2 facility, required for such experiments and foreseen some months ago was not still accepted.
Consequently, we deliberately focused the beamtime to the first point: to measure the benefit of carboplatinum experiment in *in vitro* (DNA breaks measurement) and *in vivo* experiments (survival of rats bearing gliomas)

2. Sample preparation and irradiations conditions

For in vitro experiments, equal amounts of F98 rodent cells were submitted to lysis after different treatment to cis-platinum, carboplatinum and/or synchrotron radiation (from 30 to 85 keV) amd thereafter embedded in agarose plugs (neutral matrix). Yields of DNA double-strand breaks was assessed in pulsed-field gel electrophoresis.

For survival of rats bearing F98 gliomas, please see previous reports and proposals

Both *in vitro* and *in vivo* set-ups were already developed in routine at ID17 (see previous proposals) and irradiation conditions were applied successfully.

3. Results and conclusions

An extra-number of more slowly repaired DSB was observed when irradiating carboplatinum-treated F98 cells at 78.8 keV but not at 40 keV, confirming the efficiency of PAT with platinum-containing agents. Furthermore, we observed that yields of PAT-Plat induced DSB were proportional to the concentration of platinum atoms, whatever the drugs.

Conversely, while carboplatinum decreased also the DSB repair rate, cisplatinum appeared to be more efficient to inhibit DSB repair process, at equal concentrations. Again, with carboplatinum the PAT-Plat-induced DSBs provides an abnormally large yield of very short DNA fragments (less than 100 kb), confirming our work hypothesis that PAT-Plat emits electrons at the close vicinity of the cis-platinum DNA-adducts.

For in vivo preliminary experiments, at the present days, one more month is required to establish clearly the conclusions of the *in vivo* experiments and to evaluate quantitatively the benefit of the use of carboplatinum. However, we observed that more rats survive with higher

concentrations of carboplatinum and that cis-platinum presents the inconvenient to increase the yields of early death (maybe due to higher toxicity than carboplatinum).