EUROPEAN SYNCHROTRON RADIATION FACILITY

INSTALLATION EUROPEENNE DE RAYONNEMENT SYNCHROTRON

Experiment Report Form

	Experiment title: **"Intracerebral delivery of gold nano particules for synchrotron stereotactic radiotherapy".**	**Experiment number**: MD355
Beamline:	**Date of experiment**: from: Feb 2nd 2009 to: Feb 7th 2009	**Date of report**: 27 February 2009
Shifts: 12	**Local contact(s)**: **Hélène Elleaume**	*Received at ESRF:*

Names and affiliations of applicants (* indicates experimentalists):

Dr. ELLEAUME Hélène*, Dr. ADAM Jean François*, BESSE Sébastien*, BOBYK Laure*, EDOUARD Magali*, Pr ESTEVE François*, Pierre DEMAN*,Mathias VAUTRIN*.
Laboratory INSERM U836 Equipe 6 Grenoble - Institute of Neuroscience ID17 Medical Beamline E.S.R.F. BP 220, 38043 - Grenoble France.

DILMANIAN Avraham
Laboratory Brookhaven National Laboratory (Bld 490) Medical Department Upton, New york 11973-5000 USA.

Dr. SMILOWITZ Henry
Laboratory Dept of Pharmacology University of Connecticut Health Center 263 Farmington Ave. Farmington, CT 06030 USA

Jean LAISSUE Laboratory Institute of Pathology University of Bern Murtenstrasse 31, P.O. 62 CH-3010 BERN Switzerland.

Jim HAINFELD Laboratory NANOPROBES 95 Horseblock Road Yaphank, NY 11980-9710 USA

Aim:

The purpose of this study was to determine whether the efficacy of heavy-atom-enhanced Synchrotron Stereotactic Radiotherapy (SSR) could be improved in the F98 rodent glioma model, by using gold nanoparticles injected intra cerebrally by convection-enhanced delivery methods.

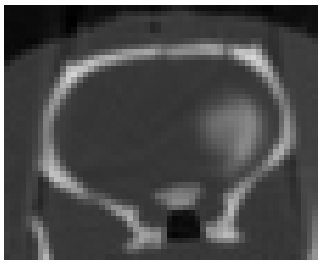
Preliminary results (MD355):

We carried out a preliminary study in February 2009, using intracerebral nanoparticles delivery in association with synchrotron Stereotactic radiotherapy for the treatment of F98 glioma bearing rats. We do not have the final results of this study since the animals have been treated only one month ago. However, we have obtained important information regarding the gold nanoparticles bio-distribution, toxicity and preliminary survival results.

Imaging – Gold quantification:

Two rats bearing F98 glioma were imaged with 3D computed tomography every 10 min for more than 2 hours to determine the gold nanoparticles bio-distribution after intracerebral delivery with convection-enhanced delivery. From the CT imaging it is possible to quantify the intracerebral gold concentration. The gold nanoparticles were infused in 20 µL of PBS over 40 minutes (Au concentration: 100 mg/mL). This experiment demonstrate that very high concentrations of gold nanoparticles could be obtained in the rats' brains for a long duration, suitable for gold-enhanced radiotherapy. However the toxicity was important after intracerebral infusion of gold at this concentration and we had to decrease the amount of gold nanoparticles injected for the therapy experiment. The concentration was divided by 2 and the infused volume was also decreased (5 µL instead of 20 µL).

A)



B)

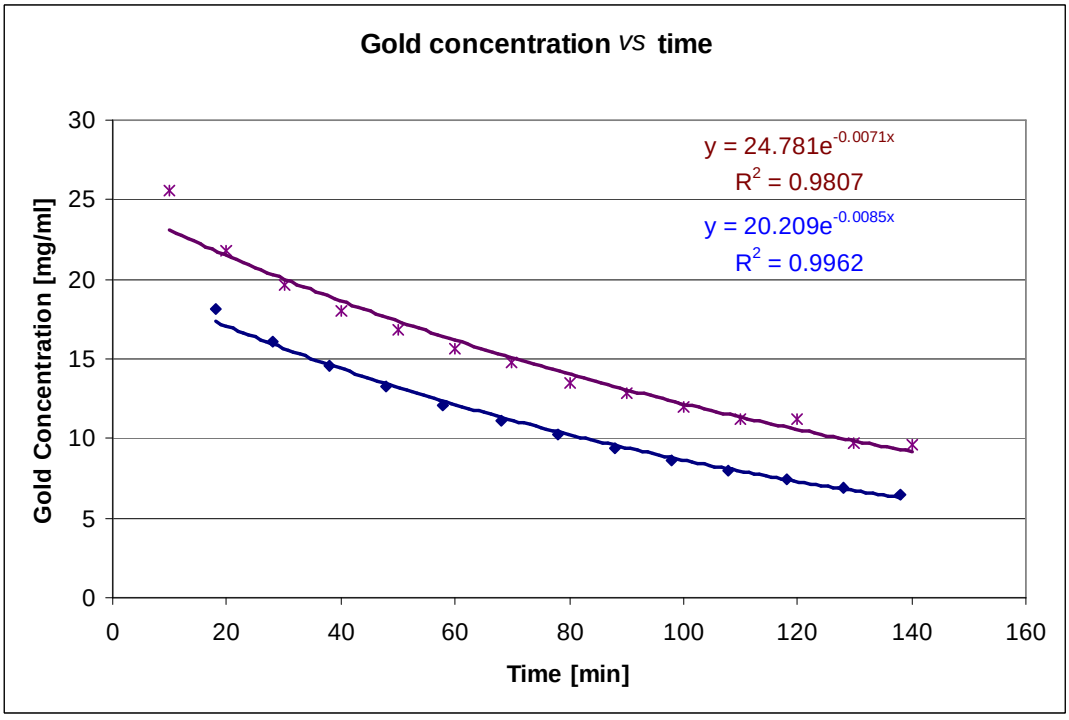


Figure1: A) Gold distribution in a F98 glioma bearing rats 10 min after gold nanoparticles intra tumoral delivery.
B) Gold concentration versus time measured over time in two animals

Therapy study:

The rats were divided into 4 experimental groups: “untreated animals”, “irradiation alone 15 Gy delivered in a single fraction”, “Gold alone”, “Gold + irradiation”.

For all irradiated groups, the irradiation was performed on day 14.
The gold nanoparticles were injected into the tumor by convection-enhanced delivery methods few minutes before irradiation (Gold nanoparticles concentration 50 mg/mL - 5 µL infused by convection-enhanced delvery at a rate 0.5 µL/min).

Tumor imaging:
All rats were imaged at the ESRF on day 14^{th} after tumor inoculation with monochromatic computed tomography at ID17 after injection of a contrast agent intravenously for assessing the tumor presence.

The irradiation setup, described in the previous publications (Adam 2003), was used. The rats were positioned vertically and irradiated in stereotactic conditions with the beam restricted to the tumor dimensions with monochromatic x-rays tuned above the gold K-edge .

The preliminary survival rates, as currently available, are reported in Table 1 (End of February 2009; i.e. one month after tumor inoculation).

Group	Survival rate one month after tumor inoculation
Untreated	31 %
Gold nanoparticles (50 mg/mL - 5 microL)	0 %
Irradiation alone (15 Gy)	63 %
Combined treatment	67 %

Table 1: Survival results after gold –enhanced synchrotron stereotactic radiotherapy.

Conclusions:

Encouraging results were obtained and we would like to further investigate the therapeutic efficacy of this treatment. We do not have the final results of this study since the animals have been treated only one month ago. However, we have obtained important information regarding the gold nanoparticles bio-distribution, toxicity and preliminary survival results.

References

. Adam J.F., Elleaume H., Joubert A., et al. Synchrotron radiation therapy of malignant brain glioma loaded with an iodinated contrast agent: first trial on rats bearing F98 gliomas. Int J Radiat Oncol Biol Phys 2003; 57(5): 1413-1426.