After Experiment Report:

1. Proposal number: 2008A1863
2. Title of experiment: Micro-beam dose enhancement using gold-nanoparticles: validated using cancers cell cultures and polymer gels
3. Name and affiliation of the project leader: Moshi Geso, RMIT University,
4. Beam line used: BL28B2
5. Research Summary:

Microbeam dose measurements and enhancement with gold nanoparticles using PAG and biological cells

Microbeam radiotherapy “MRT” encompasses delivery of parallel plane beams of micrometers in size (about 25 μm) and spaced by much larger non irradiated spaces (about 200 μm). MRT have been proven to be a highly interesting radiotherapy technique which promises large benefits upon its clinical application. Moreover, it raises very many challenging radiobiological questions. However, radiation dose required for delivery of MRT procedure with its full radiobiological and rdaiotheraputic benefits is prohibitively high and it requires microdosimetry techniques for its quantification. In general, micordosimetry is being used to measure the stochastic distributions of energy deposited by radiations in microscopic sites and its measurement reliability is considered to be a serious challenge for all the known dosimetry techniques. Therefore MRT could profit immensely from radiation dose measurement techniques.

MRT’s nature of possessing high dose gradients means that it is difficult to accurately determine the dose distribution. Current techniques employed for dose measurement include Metal-Oxide Semiconductor Field Effect Transistor “MOSFET”s and radiochromic films; however, currently no method is completely satisfactory. Additionally, the predicted dose distribution of MRT has been simulated using Monte Carlo techniques. These dosimetry techniques have been employed with limitations to determine mainly the ratio of the dose at the peak (irradiated areas) to the low dose (minimum values at the non irradiated areas) at the valleys and this is termed peak to valley ratio. This value of the peak-valley-ratio is critical for the effectiveness of the MRT technique’s validity.

One feature of this work aimed at attempting to use Polyacrlyamide Gel “PAG” dosimeters for capturing the dose at the peaks of the microbeams and the dose at valley. Polymer gels are normally monomers which get converted into polymers via the free radicals generated by irradiation. The polymers are further linked via some special types of cross linkers to form gigantic molecules. This process affects the gels magnetic and optical properties. The change in their magnetic characteristics can be detected by MRI scanning with spatial resolution about a millimeter. However, such a resolution is not adequate for microbeam dosimetry. Therefore, we used the change in their optical properties as a means for dose extraction. And this change in optical property of PAGs is detected by Raman spectroscopy. Raman spectroscopy can analyze dose measurements with about a micrometer resolution. This attempt stemmed from our pioneered work to extend the applicability of PAGs to minefields in radiotherapy(1).

The experimental set up for PAGs irradiation at SPring-8 and their Raman spectroscopy output is depicted in figure 1-a. The gel dosimeters were prepared in Australia and transported to the SPring-8 site in Japan. Then they were irradiated at the beam line BL28B2 with 100-150 kV x-ray beam that is collimated through special type microbeam slits adequate for delivery of MRT beam. The irradiated gels were transported back to Australia for Raman spectroscopy scanning. The outcome of this section comprises validity of PAG dosimeters for dose determination of the microbeam and an approximate estimation of the ratio of the peak-to-valley dose and the results are validated against radiochromic film and MOSFET type dosimeters previously documented in literature.

The other feature of this work focused on discovering means of enhancing the dose delivered by microbeams. Radiation dose enhancement is always a desirable issue in radiobiology and radiotherapy in general and of course much more so in the high dose gradient MRT technique. This research also aimed at investigating the microbeam dose enhancement using gold nanoparticles "AuNPs" as extension to our previous work(2) with x-ray tube beams. This approach (dose enhancement) was validated by two ways; one through employing PAGs and the other one through cell culture studies. Dose enhancement by metallic nanoparticles has been found to be more effective at low (kilovoltage) ranges of x-ray energies which encompasses that of the microbeam (about 100-150 kV). A typical experimental set up for cell culture irradiation by microbeams with a depicted outcome showing dead cells aligning the irradiated areas are displayed in figure 1-b. The irradiation with microbeam was accomplished with cells (Bovine endothelial type) incubated with various concentrations of AuNPs (of about 2 nm in size) ranging from 0 and up to about 2 mM. The cells were fixed at different time intervals after irradiation. The fixed cells were then transported to Australia for immunohisto-chemistry investigations to determine the rate of the depleted gaps filling and the level of the cells' stress and their relation- ships with the AuNPs. The outcome will determine the effects of the inclusion of the gold nanoparticles in the target on the cells growth and their signaling after irradiation. The results beside their value in Microbeam radiotherapy will shed light on many radiological and molecular biology issues such as cells signaling and so called bystander effect. Moreover, an attempt was made to determine the cells viability with and without the existence of the nanoparticles in the culture to augment our previous findings(2) and the results are depicted in figure(2). The histogram clearly indicated the influence of the AuNPs on the effective dose delivered to the cells in the culture. The data from the analysis of the PAGs and the cell cultures studies will conclude the full effects of the AuNPs on the microbeam dosimetry.

The basis of the AuNPs effects on the dose is also studied theoretically and the underpinning explanation for such effects is vital for the data analysis and the plans for further studies in this area. Incubation of the cell culture (or PAGs) with the metallic nanoparticles leads to additional interaction of x-rays with the high atomic number target atoms. At these energies (around 100-150 kV) most of the x-ray photons will interact with the gold atoms through Compton and photoelectric effects. Generation of large number of Auger electrons is also anticipated, which will end up losing their energy locally hence enhancing the overall dose deposited at the target.

Dose enhancement factor "DEF" is defined as;

$$DEF = 1 + \frac{c_{nano} \int_{E_0}^{E_{\max}} \Psi(E) \left(\frac{\mu_{en}}{\rho} \right)_{nano,E} dE}{\int_{E_0}^{E_{\max}} \Psi(E) \left(\frac{\mu_{en}}{\rho} \right)_{water,E} dE}$$

Where c represents the mass composition of the nanoparticles in the target and it is assumed to be small compared to one for the above relationship to hold.
Ψ is the photon energy fluence and $(\mu en/\rho)$ is the mass-energy absorption coefficient and E refers to the x-photon energy.
It should be noted that the above equation is derived under the condition of negligible weight of gold to that of the cells culture.

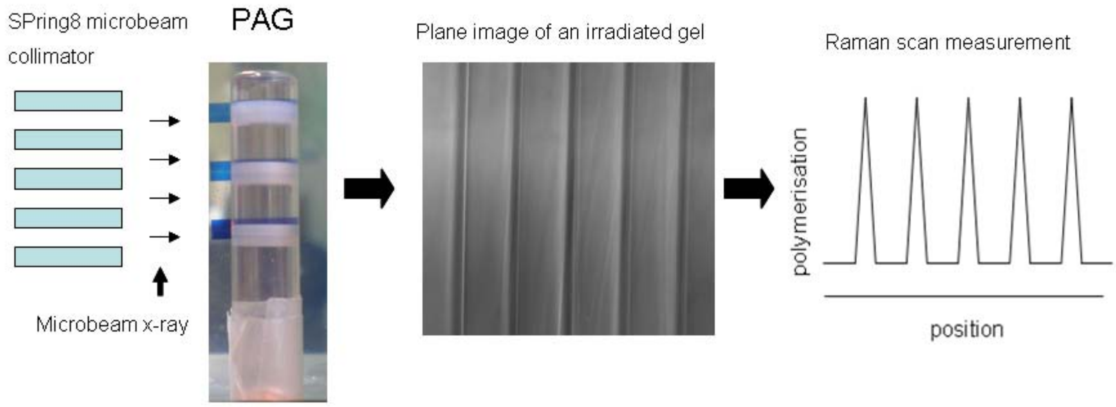


Figure-1a: Experimental set up of gels irradiation at BL28E2 beam line and the outcome.

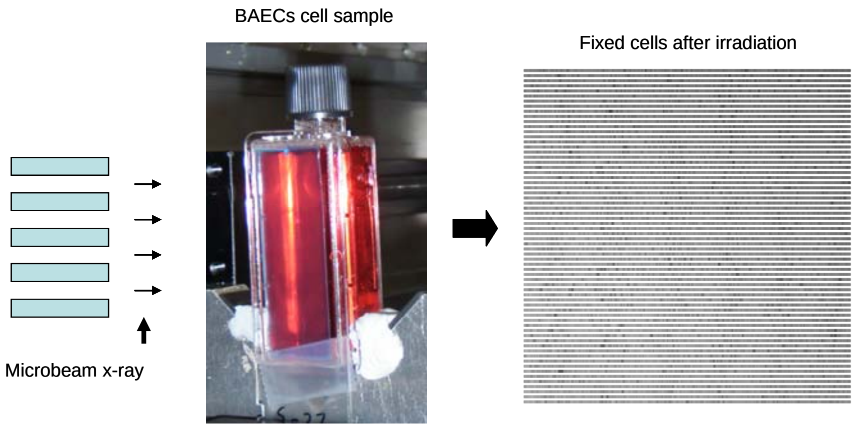
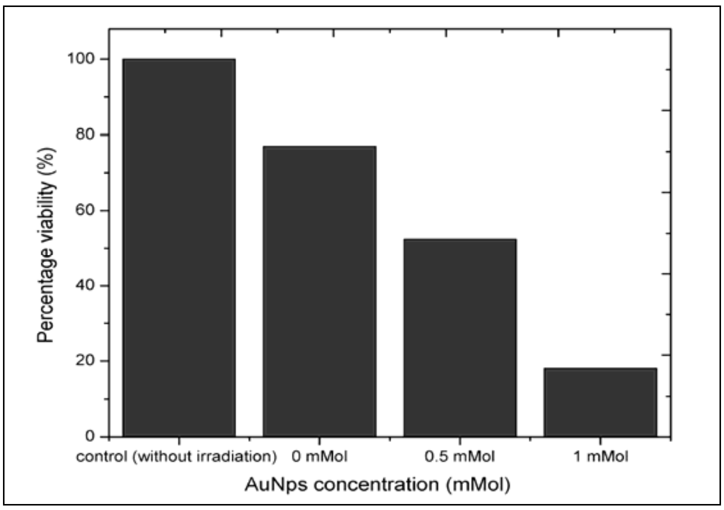


Figure-1b: Experimental set up for cell culture irradiation with microbeam



Figure(2):Cell survival with and without gold nanoparticles

References:

1. a-Wong C.,J., et al. Moshi Geso*, 2009"Small field size dose profiles measurements using gel dosimeters, gafchromic films and microTLD dosimeters », Radiaiton Measurements, Vol. 44, issue #3, pages:249-256. b- M. Geso*, T. Ackerly, S. Brown, Z. Chua, C. He, C. J. Wong, C. E. Powell, A. Ho, G. Qiao, D. H. Solomon, W. Patterson, and J. M. Droege, "Determination of dosimetric perturbations caused by aneurysm clip in Stereotactic Radiosurgery using gel phantoms and EBT-Gafchromic films," Medical Physics, vol. 35, pp. 744-752, 2008.
2. Rahman W.,et al. and M.Geso*, "Enhancement of radiation effects by gold nanoparticles for superficial radiation therapy", Nanomedicine:Nanotechnology, Biology, and Medicine 5(2009)136-142.