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Simulations and tests for metabolic radiotherapy with ^{188}Re

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^{188}Re is a beta and gamma emitter used in metabolic radiotherapy. SCINTIRAD is a multidisciplinary collaboration that aims at determining the radio-response of ^{188}Re in cells "in vitro" and the biodistribution in different organs of mice "in vivo", and studying the therapeutic effect on liver and other tumours induced in mice. Several tumour cell lines have been treated "in vitro" with a ^{188}Re solution. The dosimetry of ^{188}Re used to target the different lines of cancer cells has been evaluated using GEANT4, and preliminary results are presented. Studies to optimize the imaging of ^{188}Re "in vivo" have also continued, including the characterization of H8500 Flat Panel PMT and of $LaBr_3$ crystals, and the development of dedicated electronics.

1. Introduction

SCINTIRAD [1] is a multidisciplinary collaboration that aims at determining the radio-response of Rhenium-188, a β^- and γ emitter used in metabolic radiotherapy. Both the response with cells "in vitro" and the biodistribution in different organs of mice "in vivo", and the therapeutic effect on liver and other tumours induced in mice have been studied. ^{188}Re is a promising candidate for the application in Nuclear Medicine [2]. Its chemical properties, similar to the widely used congener Technetium-99m, permit to use all the informations on the biodistribution of ^{99m}Tc-radiopharmaceuticals for the research of useful ^{188}Re-radiotherapeuticals.

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^{188}Re decays to ^{188}Os (70%) or ^{188}Os* (30%) with a half-life of about 17 hours, via the emission of β-ray, the most frequent transition (70%) having a maximum energy of 2.12 MeV (0.78 MeV average energy). At the maximum energy, the electron is absorbed within a radius of 11 mm in biological tissues. In addition, ^{188}Os* emits promptly (0.69 ns) a γ-ray, mainly in the line at 155 keV (so that about 15% of the original ^{188}Re decays end up with the emission of a 155 keV photon) but with the photon spectrum extending up to about 2 MeV. While the beta emission is fundamental for therapeutic purposes, the gamma rays can be detected to evaluate the biodistribution of the radionuclide and for a real-time SPECT monitoring of regional drug concentration during radiation therapy.

Hyaluronic Acid (HA) is a molecule already adopted as suitable vector of chemiotherapeutic drugs [3]. ^{99m}Tc-HA labeling procedure and biodistribution studies have been previously reported in literature [4]. HA has also been adopted as vector for ^{188}Re. Preliminary results on the effect of a ^{188}Re-perrhenate solution on a series of tumor cell lines obtained in vitro have been presented in [5]. The dosimetry of ^{188}Re used to target the different lines of cancer cells has been evaluated using a MonteCarlo simulation based on GEANT4 [6], and the preliminary results obtained are presented in Section 2.

The different emission properties of ^{188}Re, compared to ^{99m}Tc, which emits just one single γ-ray at a fixed energy of 140 keV, imply a different design of the imaging camera, to cope with the higher image background due to both β-rays interference, given the secondary interactions those electrons can generate everywhere in the FOV, and higher energies γ-rays, given their higher penetration compared to the ones from the main line. Ongoing developments of the studies aimed at optimizing the imaging of ^{188}Re "in vivo" are presented in Section 3, including the characterization of the photomultiplier and of the scintillator, as well as the development of dedicated electronics.

2. Dose calculation using a GEANT4 simulation

In [5] preliminary results were obtained on the radio-response of ^{188}Re-perrhenate in a panel of human tumour cell lines treated "in vitro". The cell cultures were deposited inside the (darkest) wells of the experimental setup, as shown in Fig. 1. Active wells were interleaved by empty holes filled with water, acting as absorbing medium, to simplify the evaluation of the dose. Inhibition of cell proliferation, induction of micronuclei and apoptosis have been considered as measures to ascertain the sensitivity to the β-emission of ^{188}Re. Cells were incubated with ^{188}Re-perrhenate and harvested 48 or 72 hours later for evaluation of inhibition of cell growth by means of MTT assay [5].

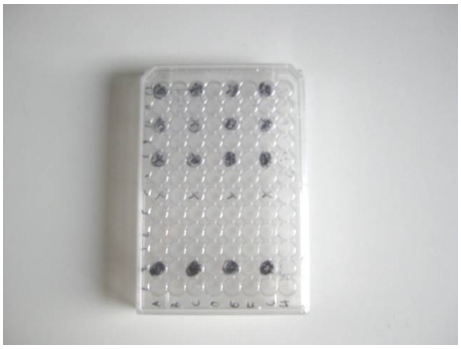

Figure 1. A picture of the wells used to assess biological response to ^{188}Re of a set of human tumour cell lines. The darkest wells contains the biological material. The cells in the top three rows are filled with a solution with an initial activity of, respectively from top to bottom, 50, 100 and 150 μCi/cc; the lowest row is a control one and does not contain ^{188}Re

The experimental setup was reproduced using a simulation based on the GEANT4 MonteCarlo program [6]. The model is shown in Fig. 2. It consisted of a grid of 5 × 7 cylindrical wells disposed adiacent to each other, as in the real experiment. Wells were 6 mm height, with a 3.5 mm inner radius and 4.5 mm outer radius. The inner volume was filled either with water, or with a solution containing water and ^{188}Re. In the wells containing the radioactive solution, the 6 μm height layer at their bottom (this height corresponds to the average height of culture cells) represents the biological material which was irradiated.

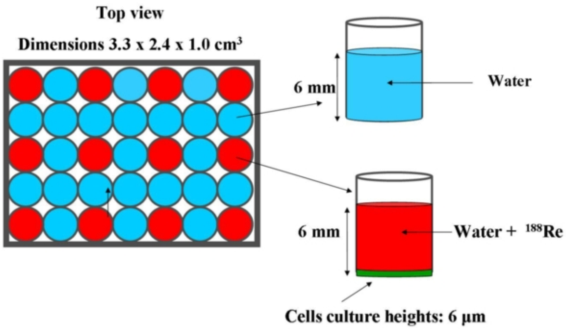

Figure 2. The modellization used for the GEANT4 simulation of the experimental setup used to assess biological response to ^{188}Re of a set of human tumour cell lines.

GEANT4 provides methods to decay ^{188}Re with its specific lifetime and spectra of the decay products. Figure 3 shows an example of such an event: the visible ^{188}Re decay products (photons and electrons) are propagated inside the simulated material, and undergo there all the interactions requested by the user. To calculate the total dose absorbed by the cells, a computation of the average dose per ^{188}Re decay was carried out using a large sample of similarly simulated events: at this point, the dose corresponding to a given initial activity inside the active wells can be inferred by a simple rescaling.

Being the volume of the radioactive solution contained within each well of 0.23 cc, considering that the lifetime of ^{188}Re is 24.5 hours, and

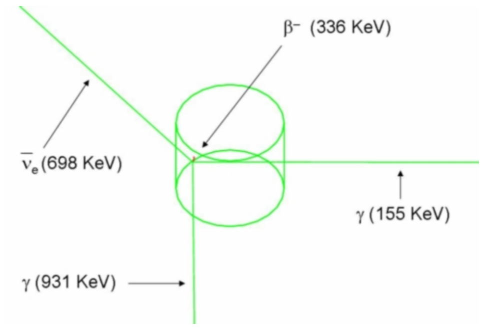

Figure 3. Example of a decay simulated with GEANT4: ^{188}Re decays β^- into ^{188}Os$^*_{2,3}$; ^{188}Os$^*_{2,3}$ decays promptly into the first excited state ^{188}Os$^*_{2,5}$ and the 931 keV photon; ^{188}Os$^*_{2,5}$ in its turn further decays into ^{188}Os and the 155 keV photon.

using the formula $A(t) = dN/dt$, the total number of decays inside the solution contained in a single cell in 48h (72h) is calculated as $3.2 \cdot 10^{10}$ ($3.6 \cdot 10^{10}$), when the initial activity in the solution is 50 μCi/cc. The GEANT4 simulation estimates an average energy deposition in the biological sample of about 280 eV per event. Therefore, the dose absorbed in 48h (72h) by each of the cell cultures deposited in the wells when the activity of the radioactive solution is 50 μCi/cc can be estimated as being approximately 6.3 Gy (6.9 Gy). Doses two and three times that large correspond, respectively, to the wells in the experimental setup filled with an initial activity of 100 μCi/cc and 150 μCi/cc.

It has been verified with the same GEANT4 simulation that having the wells filled with the absorbing medium interleaved with the activated ones is able to reduce the dose received from the nearby active cells to a negligible level. This is shown in Fig. 4, where the average dose deposited per event in the nearby wells when only one of them is activated is calculated using 10^8 simulated events: values below 10 meV are obtained with this setup, to be compared to the average energy deposition of 280 eV for a ^{188}Re decay inside the same well.

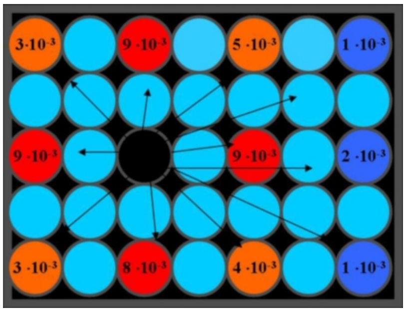

Figure 4. Average dose, in eV, deposited in the nearby cells when only one of them in the setup is activated

3. Development of the $LaBr_3$ camera

To evaluate the biodistribution of ^{188}Re labeled radiopharmaceuticals in small animals, a gamma-camera with YAP as scintillating crystal is presently used by the collaboration [7]. In order to improve spatial and energy resolution, and thus improve also the separation of the 155 keV photon of ^{188}Re from the background, non pointing photons, two new gamma-cameras will be positioned at 90 deg around the animal. Each camera will consist of one planar crystal of $LaBr_3$:Ce [8], 50×50 mm^2 wide and 4 mm thick, read out by a H8500 Hamamatsu Flat-Panel PMT [9], with a glass window 1.8 mm thick connecting the two devices. The front-end electronics for the 64 channels of the H8500 has been designed using MPX-08 chips [10]. The whole system will be mounted on a rotating support, in order to produce tomographic images.

The linearity of the energy response was verified experimentally with three radioactive sources (^{241}Am, ^{57}Co, ^{99m}Tc), all having the energy of the radiated photon within the range of interest.

Energy resolutions obtained with this setup in a preliminary stage is shown in Fig 5: on top, the spectrum obtained with the 59.5 keV line of ^{241}Am, where a FWHM of about 24% was achieved; below, the spectrum of the higher energy 140 keV photon of ^{99m}Tc is shown, with a FWHM of about 10%.

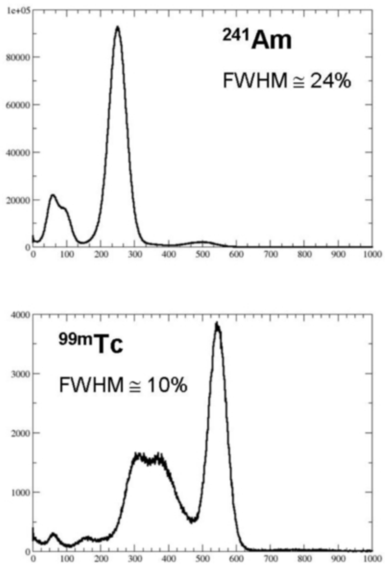

Figure 5. Energy spectra of a ^{241}Am source (top, $E_\gamma = 59.5$ keV) and a ^{99m}Tc source (bottom, $E_\gamma = 140$ keV), as obtained with the $LaBr_3$ crystal readout by the flat panel and the front-end electronics described in the text.

4. Conclusions

Different aspects of metabolic radiotherapy with ^{188}Re have been studied. The dosimetry of panels of tumour cell lines irradiated with a ^{188}Re solution has been evaluated using GEANT4. Progress has also been made towards the use of the 155 keV photon from ^{188}Os* decay: an energy resolution of 10% has been obtained with ^{99m}Tc and a LaBr3:Ce scintillating crystal viewed by a H8500 flat panel photomultiplier.

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REFERENCES

1. A. Antoccia et al., Nucl. Phys. B (Proc. Suppl.) 150 (2006) 411.
2. J.S. Wang et al., Eur. J. Nucl. Med. 23 (1996) 13; S. Banerjee et al., Nucl. Med. Commun. 22 (2001) 1101; E. Savio et al., BMC Nucl. Med. `http://www.biomedcentral.com/14171_2385/1/2` ; E. Dadachova et al., Nucl. Med. Biol. 29 (2002) 13; J.C. Paeng, J. Nucl. Med. 44 (2003) 2033; J.M. Jeong and J.K. Chung, Cancer Biother. Radiopharm. 18 (2003) 707; C. Spitzweg and J.C. Morris, Thyroid 14 (2004) 424; A. Boschi et al., Nucl. Med. commun. 25 (2004) 691; R. Frier, Mini Rev. Med. Chem. 4 (2004) 61; K. De Ruyck et al., J. Nucl. Med. 45 (2004) 612; G. Wunderlich et al., Appl. Radiat. Isot. 62 (2005) 745; J. Shukla et al., Pharmazie 60 (2005) 583; B. Lambert et al., J. Nucl. Med. 46 (2005) 1326; A. Kumar et al., Eur. J. Gastroenterol. Hepatol. 18 (2006) 219; E. Garin et al., Nucl. Med. Commun. 27 (2006) 363; B. Lambert et al., Eur. J. Nucl. Med. Mol. Imaging 33 (2006) 344.
3. R. Rossin et al., In vivo Biodistribution Studies on Hyaluronan Butyrate by Means of 99mTc Direct Labelling and YAP Camera, In: Technetium, Rhenium and Other Metals in Chemistry and Nuclear Medicine (M. Nicolini, U. Mazzi Eds.), pp 689-693, SGEditoriali, Padova, 2002.
4. M.C. Giron et al., YAP-Camera Device for Biodistribution Studies in Mice of 99mTc-Radiotracers, Poster at the 6th Int. Symp. on Technetium in Chemistry and Nuclear Medicine, Brixen, Italy, 2002.
5. A. Antoccia, et al., 188Rhenium induced cell death and apoptosis in a panel of tumor cell lines, Nucl. Instrum. Meth. 571A (2007) 471.
6. S. Agostinelli et al, GEANT4: a simulation toolkit, Nucl. Instrum. Meth. A506 (2003) 250
7. A. Antoccia, et al., A YAP camera for the biodistribution of ^{188}Re conjugated with Hyaluronic-Acid in "in vivo" systems, Nucl. Instrum. Meth. 571A (2007) 484.
8. R. Pani, et al., Lantanum scintillator crystals for gamma ray imaging, Nucl. Instrum. Meth. 567A (2006) 294.
9. `http://www.hamamatsu.com`
10. `http://www.novarad.com`