PhD position in instrumentation

Development of a dosimetry system to track alpha particles in *in vitro* assays for Targeted Alpha Therapy

Description:
Targeted alpha therapy (TAT) is a treatment modality in which a labelled α-emitting radioisotope is injected into the patient. The labelled molecules specifically target tumour cell biomarkers. As a result, the dose deposition produced by the decay of the radioisotopes is concentrated in close proximity to the tumour cells, especially in the case of α-emitters. The favourable properties of α-particles (short range, high linear energy transfer, potent cytotoxicity) explain the increasing development and use of TAT [1].

Like any new treatment, TAT requires preclinical studies to evaluate the efficacy of new molecules and to compare results with other existing modalities. In vitro experiments are part of this research. They consist of exposing cells cultured in a dish to labelled radioisotopes diluted in culture medium. In this type of experiment, biological effects (such as survival rate) are usually correlated with the injected activity. Although this may be relevant for β-emitters (due to the millimetre range of β-particles), it is not for the quantitative assessment of α-emitting radioisotopes. Moreover, to compare the efficiency of TAT with other treatments, such as external beam radiotherapy or β-emitting targeted radiotherapy [2], knowledge of the absorbed dose in cells is much more relevant. The dose calculation is usually performed with the MIRD formalism [3], [4], [5] and, in the case of in vitro experiments, depends on the spatial distribution of the radioisotopes in the culture medium and the thickness of the cells.

An innovative method was successfully developed and tested during a preclinical evaluation of ^{212}Pb-VCAM-1 [6] to provide reliable and accurate dose measurements during *in vitro* experiments [7]. This method is mainly based on the measurement of the energy spectrum of α-particles emitted from the culture medium through a 2.5 µm Mylar wall using silicon detectors and a deconvolution method based on Monte Carlo simulations, developed to determine the spatial distribution of the radioisotopes in the culture medium and the dose deposited in the cells [8].

This method has been shown to improve the determination of the spatial and temporal distribution of radioisotopes in *in vitro* experiments. However, the precise and accurate quantification of the biological effect of alpha particle irradiation requires further investigations and development, in particular with regard to the cell geometry model which can strongly influence the fraction of energy absorbed by the cells.

The first part of this thesis will therefore deal with the modelling of cells in in vitro configurations. This study will require the acquisition of cell images and/or the use of existing images. It will then be necessary to determine a relevant geometry to be implemented in the simulations, the variability of this geometry and the impact of this variability in terms of absorbed dose.

The second part of the PhD thesis will concern the evolution of the detection system. Indeed, the current detection system provides a dose averaged over the whole culture well. For alpha particles, especially for low activities, it may be necessary to obtain a high resolution 2D spatial distribution at the cell level to observe stochastic dose deposition mechanisms. To address this, a new detection system based on the use of a scintillator coupled to a microscopic imaging system will be developed and investigated.

Finally, the use of different commercially available scintillators and imaging systems will be compared and optimized to find the better match in terms of scintillation and detection efficiency. Monte Carlo simulations will also be performed to optimize the setup configuration. A prototype will then be implemented and characterized with alpha emitting sources. Once the prototype implemented, its function response will be determined in different irradiation configurations and used to perform dosimetric evaluation of alpha irradiations at the cellular level.

This project will be done at GANIL, in the frame of its research program on the production and dosimetry of innovative medical radioisotopes. GANIL has also important skills in nuclear instrumentation and preclinical dosimetry [9], [10], [11], [12], [13] and already developed collaborations with other laboratories (ISTCT, CLCC François Baclesse, Cyceron, LPC Caen…) in interdisciplinary domains.

Expected skills:

The student must have a formation in nuclear physics with a good knowledge of the detection of radiations and their interactions with matter. Knowledge in radiotherapy and dosimetry would be a plus.
The student will participate to the prototype implementation. He/she will perform experimental characterizations and evaluations as well as Monte Carlo simulations and data analysis. The candidate must thus have an interest for experimentation as well as simulation and will have to develop skill in instrumentation, programming and Monte Carlo simulations.
The candidate will need to be able to work in an interdisciplinary domain with people from other research fields such as biology, medical physics or medicine.

Contact: Anne-Marie FRELIN
Phone: +33 (0)2 31 45 45 30
mail: anne-marie.frelin@ganil.fr

GANIL, BP 55027, 14076 Caen France

References

[1] F. Guerard, J. Barbet, J. F. Chatal, F. Kraeber-Bodere, M. Cherel, et F. Haddad, « Which radionuclide, carrier molecule and clinical indication for alpha-immunotherapy? », *Q. J. Nucl. Med. Mol. Imaging Off. Publ. Ital. Assoc. Nucl. Med. AIMN Int. Assoc. Radiopharmacol. IAR Sect. Soc. Of*, vol. 59, n° 2, p. 161-167, juin 2015.
[2] N. Falzone *et al.*, « Dosimetric evaluation of radionuclides for VCAM-1-targeted radionuclide therapy of early brain metastases », *Theranostics*, vol. 8, p. 292-303, janv. 2018.
[3] W. E. Bolch, K. F. Eckerman, G. Sgouros, et S. R. Thomas, « MIRD Pamphlet No. 21: A Generalized Schema for Radiopharmaceutical Dosimetry—Standardization of Nomenclature », *J. Nucl. Med.*, vol. 50, n° 3, p. 477-484, 2009, doi: 10.2967/jnumed.108.056036.
[4] C.-Y. Huang, S. Guatelli, B. M. Oborn, et B. J. Allen, « Microdosimetry for Targeted Alpha Therapy of Cancer », *Comput. Math. Methods Med.*, vol. 2012, p. 153212, 2012, doi: 10.1155/2012/153212.
[5] M. Šefl, K. P. Brabcová, et V. Štepán, « Dosimetry as a Catch in Radiobiology Experiments », *Radiat. Res.*, vol. 190, n° 4, p. 404-411, 2018.
[6] A. Corroyer-Dulmont *et al.*, « VCAM-1 targeted alpha-particle therapy for early brain metastases », *Neuro-Oncol.*, vol. 22, n° 3, p. 357-368, mars 2020, doi: 10.1093/neuonc/noz169.
[7] A.-M. Frelin-Labalme *et al.*, « Radionuclide spatial distribution and dose deposition for in vitro assessments of 212 Pb-αVCAM-1 targeted alpha therapy », *Med. Phys.*, vol. 47, n° 3, p. 1317-1326, mars 2020, doi: 10.1002/mp.13969.

[8] A. Doudard *et al.*, « Application of a new spectral deconvolution method for in vitro dosimetry in assessment of targeted alpha therapy », *Med. Phys.*, vol. 50, n° 6, p. 3762-3772, juin 2023, doi: 10.1002/mp.16279.
[9] C. Le Deroff, A.-M. Frelin-Labalme, et X. Ledoux, « Characterization of a scintillating fibre detector for small animal imaging and irradiation dosimetry », *Br. J. Radiol.*, vol. 90, n° 0, p. 20160454, 2017, doi: 10.1259/bjr.20160454.
[10] C. Le Deroff, A.-M. Frelin, et X. Ledoux, « Energy dependence of a scintillating fiber detector for preclinical dosimetry with an image guided micro-irradiator. », *Phys. Med. Biol.*, vol. 64, n° 11, p. 115015, mai 2019, doi: 10.1088/1361-6560/ab1854.
[11] C. Le Deroff, E. A. Pérès, X. Ledoux, J. Toutain, et A.-M. Frelin-Labalme, « In vivo surface dosimetry with a scintillating fiber dosimeter in preclinical image-guided radiotherapy », *Med. Phys.*, vol. 47, n° 1, p. 234-241, janv. 2020, doi: 10.1002/mp.13903.
[12] A.-M. Frelin, V. Beaudouin, C. L. Deroff, et T. Roger, « Implementation and evaluation of respiratory gating in small animal radiotherapy », *Phys. Med. Biol.*, vol. 63, n° 21, p. 215024, oct. 2018, doi: 10.1088/1361-6560/aae760.
[13] A.-M. Frelin *et al.*, « Development of a three-dimensional scintillation detector for pencil beam verification in proton therapy patient-specific quality assurance », *Med. Phys.*, sept. 2024, doi: 10.1002/mp.17388.