Mise en place et étude de l'environnement dosimétrique pour la radiothérapie préclinique à ultra-haut débit de dose (FLASH) avec les faisceaux proton et alpha d'ARRONAX

End-to-end dosimetry for preclinical proton and alpha with Ultra-High Dose Rate (FLASH) irradiation at ARRONAX

Lab / team: SUBATECH / PRISMA

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Context / Expected social and economic impact and outcomes of the PhD (1/2 page)

Radiation therapy consists in delivering ionizing radiation to the tumor while avoiding the surrounding normal tissue. Treatment efficacy is often limited by the resistance of tumors and the treatment toxicity for healthy organs. Then prescription must represent a trade-off between risks and benefits. Among the recent developments in the field of preclinical radiotherapy, the remarkable sparing of normal tissue obtained after irradiation at ultra-high dose rate (UHDR) without efficiency loss on tumor, the so-called FLASH effect, is really promising. However, the mechanisms involved in the FLASH effect remain unknown and required preclinical investigations in physic, biology and radiation chemistry. From medical, nuclear and instrumentation physics points of view, several challenges must be met (beam delivery, dose measurement and beam monitoring, innovative detection techniques, etc.) to be able to investigate this effect and drive the biological and chemical studies. All this investigations will give a better understanding of the FLASH effect with the objective to determine the optimal parameters providing the maximal sparing effect on normal tissues. Moreover, the new detection techniques developed and characterized in UHDR conditions could be used in clinical FLASH radiotherapy.

Scientific goals, position with regard to the state of the art, originality, continuity with previous works (if any, indicate new goals) or new subject (1-2 pages max)

FLASH radiotherapy is one of the most promising technique in the treatment of cancer. Due to production facilities, the FLASH effect is mainly studied with electrons despite their small penetration depth (few cm). Protons combine several advantages: ballistic with the Bragg peak, a large penetration depth and the possibility to create UHDR beams. FLASH proton therapy is therefore most suitable for clinical applications.

The ARRONAX Cyclotron is the ideal device for FLASH preclinical hadrontherapy investigation. Alpha (67.4MeV) and proton (68MeV) energy are adapted to preclinical irradiations. The ARRONAX cyclotron is one of the few devices in the world allowing a high flexibility in the beam parameters from conventional dose rate (2Gy/min) to UHDR (60kGy/s). A home-made pulsing chopper-based system was developed and validated in order to adjust the duration of the irradiation and the frequency rate of the pulse repetition, allowing an easy shift between conventional and UHDR irradiations and a flexible beam structure. The beam structure (number of pulses, pulses width, pulse and mean dose rate) plays an important role in the FLASH effect and will be investigated. Moreover, the capability to produce FLASH alpha beams will allow evaluating the impact of particle type and linear energy transfer (LET). Dose measurement and beam monitoring is the major challenge due to beam characteristics in UHDR conditions (> 40Gy/s with very short pulses (ms)).

The goal of this work is to develop an end-to-end dosimetric environment for a proton and alpha beam in UHDR conditions at ARRONAX facility.

This environment will be tailored to the requirement of biological studies on cells and small animals as well as of radiation chemical studies.

Classical detector used in conventional dose rate, such as ionization chambers, are dose rate dependent and thus not suitable in UHDR conditions. In a previous investigation, we shown the dose rate dependency of two classic radiochromic films in UHDR proton and alpha beams. A new film, OC-1, was investigated and found to be dose rate independent in these conditions (Villoing et al. 2022). Films allows 2D dose measurement but are limited by their indirect reading. Beam monitoring requires fast and accurate detectors independent of dose rate. In a previous thesis, Flavien Ralite developed innovating methods for online dosimetry in hadrontherapy (Ralite 2021). These methods are based on light detection in transparent media and on bremsstrahlung detection in opaque media. They have to be adapted in the UHDR context, particularly, in term of temporal resolution and dose rate dependency.

Until now, biological models in ARRONAX experiments were cells and zebrafish embryos likened to water. The understanding of biological FLASH mechanisms requires more realistic models, such as mice. These models requires sophisticated dose calculations taking into account tissues densities and composition. Dose distribution in mice will be calculated with a Monte Carlo (GATE) model of the beamline and validated by measurements.

Currently, biological and chemical studies in FLASH are performed in the "plateau" of the proton and alpha beams with ARRONAX beams. LET investigation will require a spread-out Bragg peak (SOBP). Method used in conventional dose rate are not applicable in FLASH due to the very short beam-on-time. A ridge filter will be designed based on Monte Carlo (GATE) simulations and validated by measurements.

The "FLASH team" in Nantes involves medical physicists, radiobiologists and physicians from ICO, physicists and radiochemists form ARRONAX and SUBATECH. We also collaborate with the "Laboratoire de Physique de Clermont" (LPC) with the objective to model the FLASH effetc in GEANT4-DNA. The work of simulation with GATE made during the PhD will be shared with the LPC as input data for Geant4-DNA.

Villoing et al. Proton beam dosimetry at ultra-high dose rates (FLASH): Evaluation of GAFchromic (EBT3, EBT-XD) and Orthochromic (OC-1) film performances. Med. Phys. 49(4), 1-14, 2022

Ralite Flavien. Développement de méthodes innovantes de dosimétrie en ligne pour l'hadronthérapie et la radiobiologie. Thèse de doctorat sous la direction de Vincent Métivier et Charbel Koumeir, soutenue le 18/11/2021.

Required skills for the applicant, scientific relevance of the advisors with regard to the topic, complementarity if relevant (1/2 page max)

This PhD combines experimentation and simulation. The applicant should have a Master in nuclear and/or medical physics. Knowledge in Monte Carlo simulation will be appreciated.

FLASH investigation involves different areas such as physic, radiobiology, radiochemistry and medicine. The applicant will have to adapt to a multidisciplinary team.

Good English languages skills will be an advantage.