4° INCONTRO SULL'ECOSISTEMA TOSCANO PER L'INNOVAZIONE - SPOKE 1

giovedì 12 dicembre 2024 - giovedì 12 dicembre 2024

CNR - Area della Ricerca di Pisa

Scientific Program

Project Management

The *Advanced radiotherapies and diagnostics in oncology*-SPOKE 1 aims at a comprehensive translational (from bench to bedside) approach to advanced radiotherapy, from the models to the clinics, including the most advanced tools and methods based on ionizing radiation known to date, from innovative external beam generators to radiotracers and radiopharmaceuticals (available at CNR and UNIPI), for a step change in diagnostics and therapy of tumors. CPFR center at UNIPI/AOUP, equipped with a world-unique electron Linac, will perform fundamental studies to understand the radiobiological mechanism underlying Flash effect and pre-clinical studies finalized to realize the first clinical trials on skin cancer with low energy (<10 MeV).

Subproject 1.1

Innovative approaches to radiotherapy oncology and radiation sources
For the clinical translation of the FLASH effect, it is mandatory to achieve dose delivery parameters and to monitor and control dose delivery in regimes that are not accessible with current conventional clinical devices. We will address the characterization and deployment of novel available sources to investigate fundamental radiobiological processes and to enable the development of preclinical and clinical studies. A new generation of LINAC providing FLASH electron beam by radiofrequency acceleration technique (Electron FLASH) up to 9 MeV will be available at the CPFR center from June 2022.

Subproject 1.2

Simulations, molecular mechanisms validation and riadiobiological effect modelling

The underlying cellular mechanism of the differential effects of UHDR in cancer vs normal tissues are not fully understood. This issue will be addressed with a multi-scale and multi-methodological computer simulation and modelling approach. This in silico analysis will constitute a conceptual and quantitative bridge between the sub-project 1 and 3, with the general aim of clarifying the connections between the physical parameters of the radiation and the radiobiological effects in vitro.

Subproject 1.3

Radiobiological effects of ionizing radiation: in vitro (cell culture) and in vivo

Overall goal of the present sub-project is to evaluate FLASH radiobiological effects in vivo in acute conditions in normal and tumor tissues using two innovative devices: a) electron accelerator specially made for in vivo research on flash radiotherapy, with a triode-cannon, and a complete control and manipulation of the beam (device parameters: dose-per-pulse up to 40 Gy, dose-rate up to 10000 Gy/s and instantaneous dose-per-pulse 10^7Gy/s continuously). b) The experimental Laser-Linac source delivers ultrashort, VHEE pencil-beam like electrons (100-250 MeV) with ultra-high dose-rate, exceeding 1E10 Gy/s (for devices detail see WP1). To optimize the clinical translation of the FLASH effect, in vivo studies are required as use of various cell lines led to inconsistent results in reproducing the effect.

Subproject 1.4

FLASH radiotherapy: preclinical

To warrant an actual clinical translation of the results obtained in sub-project 3 profiling long term effects of FLASH radiotherapy in preclinical models is a mandatory requirement. Overall goal of the present sub-project is to evaluate how FLASH radiotherapy impacts on the cure, i.e., tumor growth of melanoma and glioblastoma and on potential damaging effects on brain function, cardiovascular system, and metabolism in comparison with conventional radiotherapy. The data obtained here aimed at understanding the spatial dynamics of the flash effect (volume effect, adjacent fields) will pave the way for the optimization of the VHEE.

Subproject 1.5

FLASH radiotherapy: from preclinical to clinical

The aim of this sub-project is to acquire preclinical data in vivo and to adapt the ElectronFlash LINAC for the clinical use to further explore the potential of EF, in a feasibility and safety study of FLASH-RT in patients with skin cancer. This perspective is of extraordinary interest since, beyond the pure dermatological application, the skin represents an organ at risk for radiotherapy in general and therefore a specific dermatological trial would offer relevant information for the progress of all clinical studies. Moreover, the combination of Flash-RT with chemotherapy, targeted therapy and immunotherapy will be investigated in pre-clinical tests.

Subproject 1.6

***In situ* advanced diagnostics of radiation deposition and conformality**

FLASH ready VHEEs are expected to be available as pencil beams with a few millimeters size. In order to allow the irradiation of the typical tumor volumes, efforts have to be made to optimize the tumor coverage, and the effects of spatial fractionation need to be fully understood. On the other hand, the use of pencil beams will allow a fine tuning of the radiation dose conformality, provided that suitable radiation delivery strategies are developed. These issues will be addressed within this subproject, initially by means of Monte Carlo simulations. The laser-driven VHEE beams developed at CNR-INO within subproject 1 will then be used to demonstrate the possibility of advanced dose conformality capabilities. The extremely hypofractionated regime envisaged for FLASH treatments requires control imaging systems able to check the compliance of the treatment plan in vivo with high accuracy and during the very short irradiation time. The aims of this sub-project are to develop two innovative control imaging systems.

Subproject 1.7

Synthesis and production of "tumor targeted" radionuclides, radiotracers and radiopharmaceuticals for experimental studies

The global aim of this sub-project is the development and production of new agents for nuclear molecular imaging studies and drug development of new theranostics. The specific objectives of the radiochemical research concerns: i) the synthesis of radiotracers with high specific activity for developing new imaging biomarkers; ii) implementation of new methods for the synthesis of peptides with direct 18F-labeling approaches; iii) production of PET radiotracers for preclinical and translational studies of FLASH radiotherapy; iv) the validation of proof-of-concept studies of new therapeutic/theranostic approaches; v) enhancing the validation with GLP approach applied to the development of new chemical entities and preclinical imaging.

Subproject 1.8

Synthesis and production of "tumor targeted" radionuclides, radiotracers and radiopharmaceuticals for clinical use

The general objective of sub-project 8 is to make available radiopharmaceuticals for oncological diagnostics to THE for clinical applications. The radiopharmaceuticals will be produced in the "Officina Farmaceutica" (OF) of CNR-IFC in Pisa, the only one Italian site of a public institution authorized by AIFA to produce radiopharmaceuticals according to GMP (Good Manufacturing Practice). The organization chart reflects the regulation 219/06 for pharmaceutical preparations. Two "Qualified Persons" have been authorized by AIFA to release drugs for human use. OF already produces some authorized radiopharmaceuticals for specific companies and tightly collaborates with Toscana Gabriele Monasterio Foundation for production and testing of new radiopharmaceuticals to be used in pre-clinical and clinical studies of phase 1, 2 and 3.