The project *NEPTUNE*

(**N**uclear process-driven **E**nhancement of **P**roton **T**herapy **UN**ra**V**eled)

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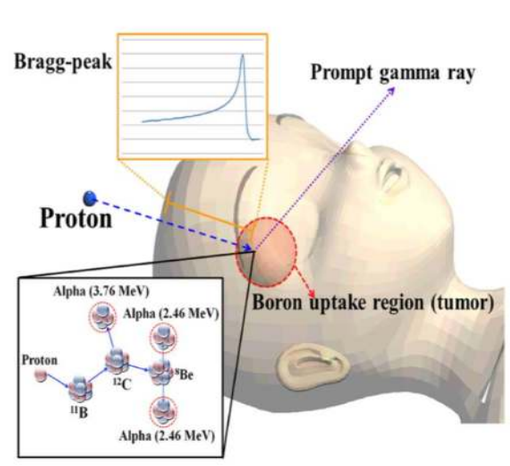
The **goal of this project** is to investigate the enhancement of biological effectiveness of proton beams by means of nuclear reactions, triggered by protons, generating short-range high-LET alpha particles inside the tumours, thereby allowing a highly localized DNA-damaging action.

Specifically, we intend to **consolidate** and **explain** the promising results recently published in [1], achieved by the p+^{11}B → 3α reaction (Proton Boron Capture Therapy, PBCT) as a new binary approach with respect to BNCT (n-^{10}B reaction).

The radiosensitising effects in BNCT will be compared to those elicited by PBCT, using the same carrier and relating the observed effects with intracellular ^{11}B and ^{10}B distribution.

Moreover, the p+^{19}F → ^{16}O+α reaction, which also generates secondary particles potentially leading to local enhancement of proton effectiveness, will be investigated.

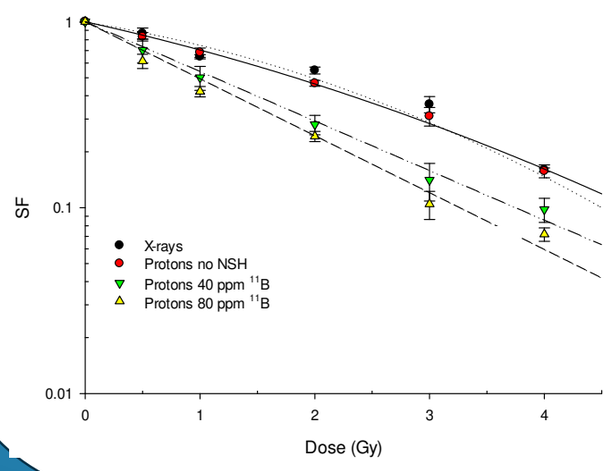


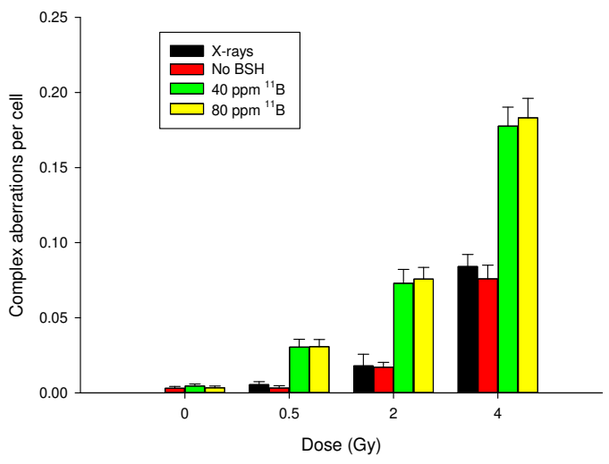
The in-vivo imaging of ^{11}B and ^{19}F carriers will be studied, in particular by optimizing ^{19}F-based magnetic resonance.

First **experimetal results** from measures performed at INFN-LNS in the Ocular Facility CATANA in a clinical SOBP configuration [1]:

- **Proton biological effectiveness is enhanced** by cell treatment with boron carrier BSH
- **Dose-modifying factor** (DMF_{10}) for clonogenic survival is about **1.5** at mid-SOBP (dose-averaged proton LET ~5 keV/mm)

  DMF is sensitive to position along SOBP, i.e. to variation of cross section with incident proton energy.
- **Chromosome aberration data** correlate with enhanced BSH-mediated radiosensitivity.





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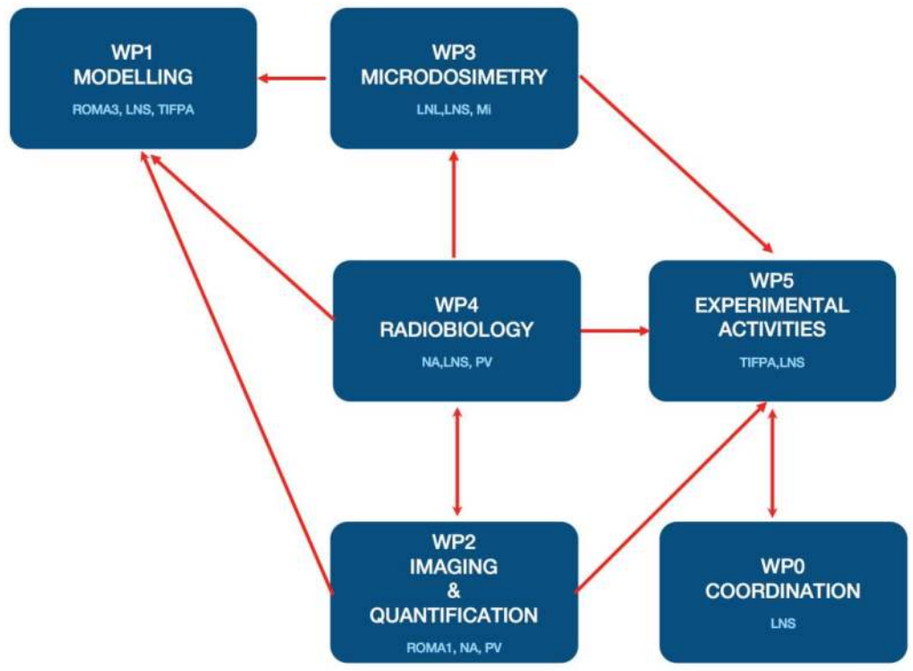
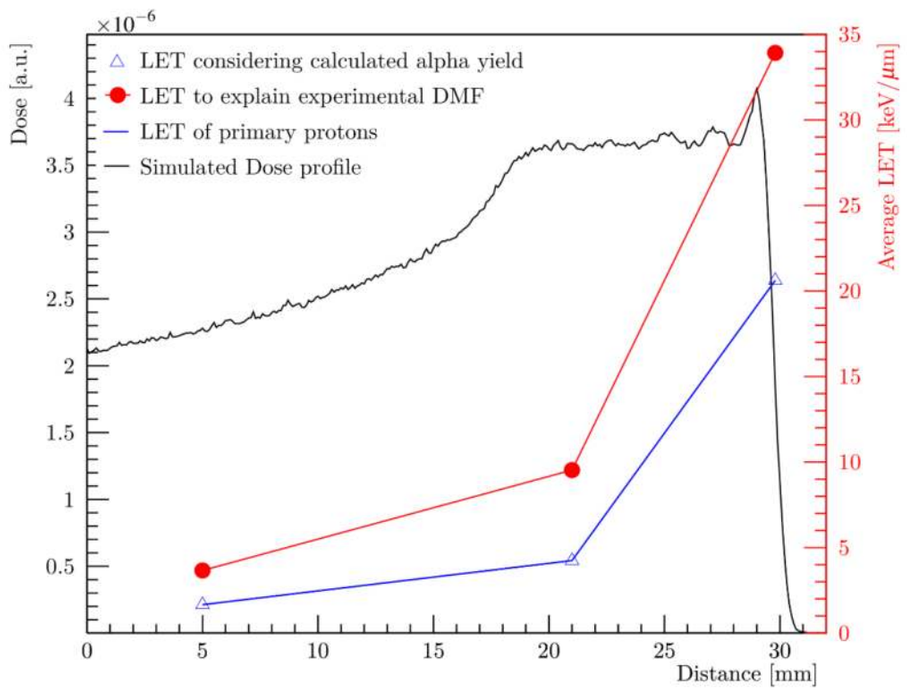


Discrepancy between **analytical calculation** and observed **RBE enhancement [2]**

Experimental results on RBE enhancement [1], seem to fall short of an immediate justification by estimations merely based on analytical and Monte Carlo evaluations of classical dosimetric quantities such as integral dose, LET, and RBE.
The total number of alpha particles generated and estimated on the basis of the well-known total production cross-section of the p-B reaction, does not explain the experimental results in terms of an average LET increase and, hence, with a corresponding RBE enhancement.
If classical radiobiological models are applied, in order to reach the observed DMF values, one would require a number of alpha particles larger by a factor of 10^5 with respect to the calculated yield. In the future, a micro and nano dosimetric approach should be taken into account as it may give experimental informations about the number and quality of high-LET particles produced, and may also take into account the biological effects of a local huge dose deposit able to explain part of the discrepancy.
Different biological effects, like the creation of free radicals and bystander effect, could also contribute to the explanation of the effect experimentally observed.



[1] GAP Cirrone et al., Sci Rep. 2018 Jan 18;8(1):1141
[2] G.A.P. Cirrone et al., *RAD journal*, 3(3):147–151, 2018