MoVe IT

Modeling and **Ve**rification for **I**on beam **T**reatment planning

INFN CSN5 "Call 2017" Project proposal

Short Abstract

The **MoVe IT** project is aimed at developing **innovative modeling for biologically optimized treatment planning with ion beams** and dedicated plan **verification devices** allowing its validation accounting for a high complexity of physical and biological effects. The main effects that will be explored and implemented are the biological impact of **target nuclei fragmentation, relative biological effectiveness (RBE)** and **intra-tumor heterogeneity**. The radiobiological implementation in research treatment planning system (TPS) will be coupled with design of patented tools for in-vitro and in-vivo irradiation, the development and update of the 3 complementary Italian **facilities** for experiments on therapeutic ion beams, and advanced models for related risk estimation (**NTCP**) and tumor control assessment (**TCP**).

1 Table of Contents

1 SCIENTIFIC PROPOSAL

1.1 State of the Art and Background

Translational research in hadrontherapy, after providing in recent years successful insights in the specific radiation damage mechanisms and allowing impressive technical developments, is now coming to a maturity where further advances require a large interdisciplinary and multicentric coordination. In particular, in order to translate basic physics and radiobiology research in an improved clinical outcome, a treatment planning system (TPS), governing the delivering of the particles for a therapeutic irradiation session, should be flexible enough to incorporate the changes provided by the new models in a research-oriented way. The preclinical testing of an improved TPS also requires dedicated devices for its verification, in particular for the on-line characterization of the irradiation beams and with an advanced level of dosimetry. Several aspects in this connection are now coming to a time point requesting a specific research effort, which can be faced with present INFN expertise and ion beam facilities, supported by selected international partners.

1.1.1 RBE and nuclear fragmentation

Among the several radiobiological parameters which are subject of study in particle therapy, the relative biological effectiveness (RBE) is certainly the most discussed. While for heavier ions, the need of explicit RBE models is well established, several years of debate are running about its use in the case of protons.

Because of the large variability of this effect, and the consideration of other sources of comparable large uncertainty (e.g. positioning of the patient, CT calibration and other sources of range uncertainty) clinical standard was set on a conservative choice, i.e. on choosing a constant factor of 1.1 for proton RBE, scaling the physical dose, and reducing its potential with the additional choice of conservative margins for planning.

Recently, also thanks to technical improvements reducing the other types of uncertainty, this position has been again challenged. Intense research in this field demonstrated that the variation of RBE as a function of linear energy transfer (LET), also in the range of LET for protons, shows an evident systematics, when looking to large pools of data [1–3] (see Fig.1a), which could be relevant at least on a dosimetric level. Even though supported by several studies, it is still not clear whether this aspect is relevant for clinical practice. Considering the limited increase of LET with depth for protons, it is generally assumed that possible increase in RBE could play a role only at the distal fall-off of a spread-out Bragg peak (SOBP). However, it was shown that also when this effect mostly concerns a very limited part of the target, for a combination of energy straggling and increase of LET, it induces an extension in the range of “biologically effective” dose which may be critical for close-by organs at risks (fig.1b) [4]

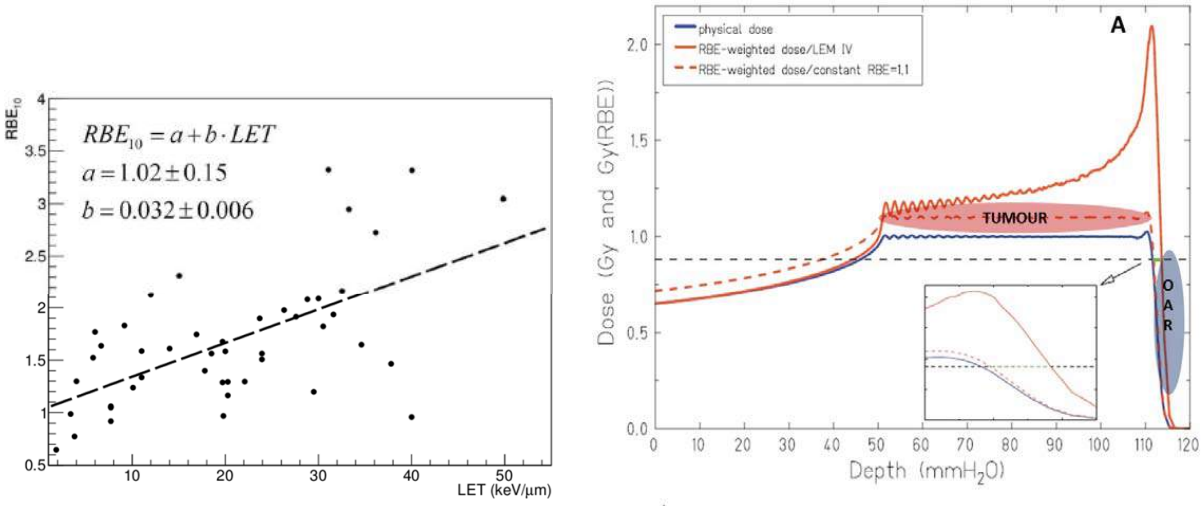


Fig. 1: a) Systematics in proton RBE (10% survival) vs LET in vitro data as extracted from the PIDE database [2] and reported in a recent review [3]. b) The Impact of a variable RBE description in proton therapy, with special regard to a "biological range" extension effect at the end of the target (from Ref. [4])

Moreover, apart from the primary beam, the irradiation field is characterized by the presence of recoil target fragments, having high charge and low residual energy. Those fragments introduce high LET components, which can be associated to an increase in RBE. This is expected to play a role mainly in the entrance channel, where an increase in RBE up to about a 10% has been estimated, as due to secondary fragments. While for heavier ions the largest impact of nuclear fragmentation is related to the quite abundant projectile fragments (see fig.2), detected by several experiments, and whose experimental biological effect is accounted in most of the advanced TPS, in the case of protons the only source of fragments poses critical detection challenges (fig.3).

At present, no experiment has been able to resolve this contribution and no full account for target fragments in proton therapy is available. The FOOT experiment which has been proposed and planned in INFN CSN3, based on a challenging inverse kinematics approach, is promising to shed unprecedented light in this process.

In general, the problem of assessing the clinical impact of the RBE of protons is becoming in latest years a really hot topic [1]. In order to estimate a clinical effect, a dosimetric assessment may be not sufficient. In order to translate a dose into a quantitative indication of clinical outcomes, the implementation of models on the probability of risk induction for healthy tissues/organs at risk, characterized from the normal tissue complication probability (NTCP) is needed, and this is now felt as a priority in the particle therapy community.

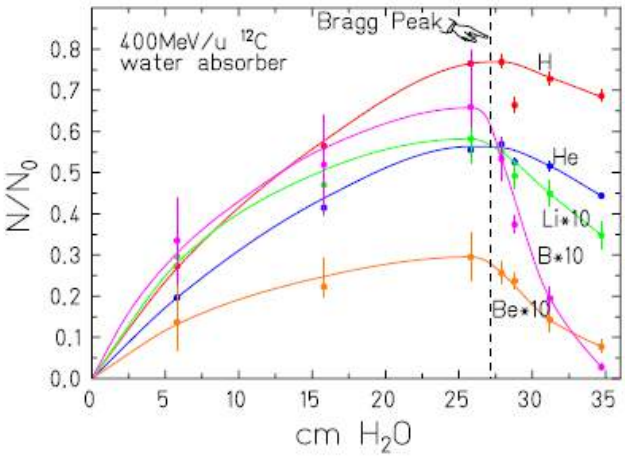
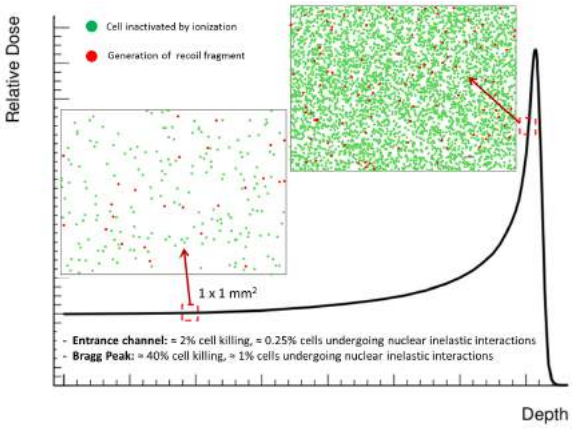


Fig. 2 : Build-up of projectile nuclear fragments in a therapeutic carbon ion beam [24].



Fragment	E (MeV)	LET (keV/µm)	Range (µm)
^{15}O	1.0	983	2.3
^{15}N	1.0	925	2.5
^{14}N	2.0	1137	3.6
^{13}C	3.0	951	5.4
^{12}C	3.8	912	6.2
^{11}C	4.6	878	7.0
^{10}B	5.4	643	9.9
^{8}Be	6.4	400	15.7
^{6}Li	6.8	215	26.7
^{4}He	6.0	77	48.5
^{3}He	4.7	89	38.8
^{2}H	2.5	14	68.9

Fig. 3: Panel a: Impact of ionization and target fragmentation in different regions of a Bragg curve, for a proton beam penetrating in water. It is shown roughly that the relative contribution of target fragments, as compared to primary ionization, to a biological effect (cell killing) changes from an almost 10% in the entrance region down to a 2.5% in the target. [3] Panel b, expected results from target fragmentation in terms of the different related quantities (E, LET range) according to calculations with the formula of ref. [25]

1.1.2 Intra-tumor heterogeneity

Another key challenges in modern radiotherapy (RT) is the possibility to adapt the treatment to patient- and tumour-specific features, i.e., to perform what is known as adaptive treatment planning.

Therefore, knowledge about patient and/or tumour specific alterations may be used to modify and improve the treatment. By including the above information I the plan optimization, a real inverse treatment planning could be achieved. While to this date these concepts have mostly been used for temporal variation of the shape and absolute position of the target volume, considered to be homogeneous, only limited studies have tried to exploit this to biological variations within the tumour.

In fact, the present standard of care in RT is based on the conventional postulate that tumours are homogenous entities, and, therefore, the dose distribution delivered must be as uniform as possible across the tumour volume. Clearly, this assumption may not provide the best tumour control probability (TCP) and the lowest normal tissue control probability (NTCP, see below) for many solid cancers.

Heterogeneity is emerging as an important prognostic factor, and targeting multiple tumour compartments is a possible solution to fight radioresistance and achieve sustainable responses.

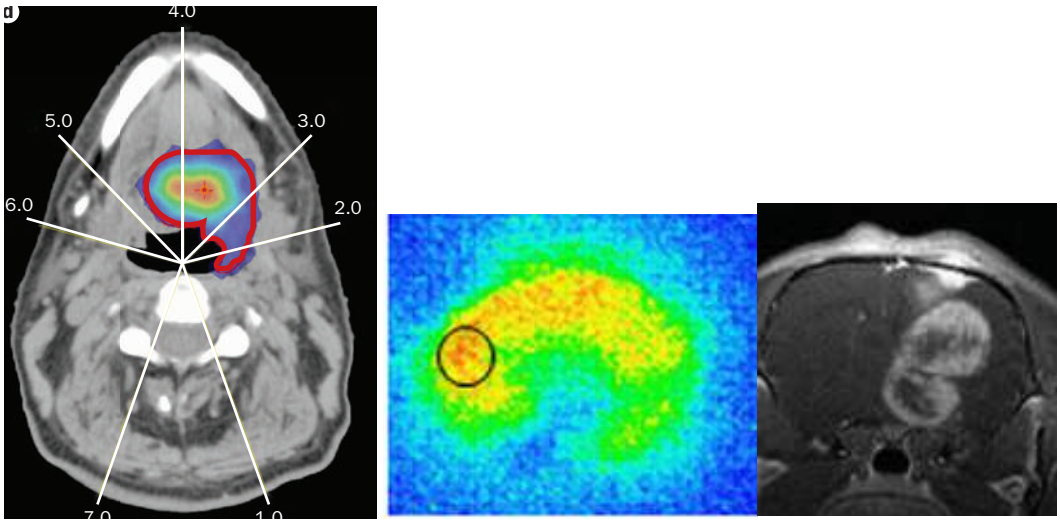


Fig.4 : Different types of intra-tumor heterogeneities revealed with up-to date imaging techniques: a) PET (18F-AZA tracer) imaging correlated to inhomogeneous oxygen distribution (hypoxia), in human head and neck cancer b) 64Cu –ATSM tracer PET image showing a peak concentration of stem cells in a murine tumor c) MRI imaging showing a differential concentration of a radiosensitizer in a murine model.

These different regions respond in general to radiation in different way, not only depending on the concentration of the specific agent of inhomogeneity, but also on the LET of the radiation in that specific position. Particle therapy, then, offers the LET and its related biological effect dependence as an additional degree of freedom for tuning a treatment.

Ion beam radiation, thus, allows in principle a larger flexibility and a higher potential for achieving an efficient adaptive treatment planning, especially thanks to the spatial selectivity

offered by its ballistic properties, inverse depth-dose profile and reduced multiple scattering, and the possibility of pencil beam scanning.

The most important among these sources of heterogeneity is probably hypoxia, i.e. regions with incomplete oxygenation, showing a strongly increased radioresistance quantified by the oxygen enhancement ratio (OER). Among the several physical and radiobiological peculiar advantages of particle beams there is the lower sensitivity to the presence of molecular oxygen (reduced OER) for increasing LET (see fig.5).

Recent advances on functional imaging (mostly with PET techniques, but several different techniques are being proposed including MRI, fluorescence, Cerenkov radiation) also thanks to advanced computational analyses of the data, are promising to supply three-dimensional maps of morphological and functional characteristics of the tissues with increasing resolution, allowing insight in these features. The X-rays community then started to consider this information for performing inhomogeneous irradiations with a technique called dose painting [5].

In our previous work we have started including the OER optimization in an ion beam treatment planning [6] and explored, beyond the dose painting approach, other adaptive methods exploiting the ion beam features like LET painting [7] and Kill painting [8]. We've also shown that ions like Oxygen beam may have a better impact on overcoming hypoxia, also when considering the trade off of a lager fragmentation and then higher RBE in the entrance channel [9–11].

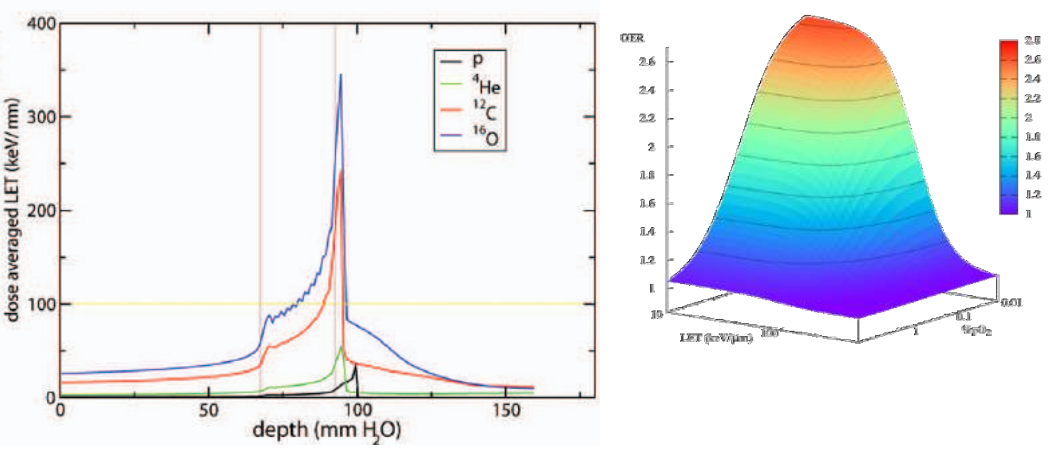


Fig. 5: Dose averaged LET profiles for different ions as compared to a threshold value (yellow) [9] where a substantial reduction of the OER can be verified (see right panel), for any level of oxygen concentration [8]

However this field is just at the beginning and several steps are missing for realizing a full exploitation of ion beams for heterogeneous tumors, including different types of heterogeneity different particles, potentially used in combination [11], etc.

Also in this case, despite pure radiation biophysical modelling, basic nuclear physics, in describing the full fragmentation spectra of the "new" ions and thus the actual voxel by voxel LET distribution, plays a very important role.

1.1.3 NTCP and TCP modeling

In the framework of the technological advances of modern RT such as hadrontherapy, mathematical models of radiobiological effects (intended as "macroscopic" modeling of clinical outcomes in opposition to basic radiobiology) potentially play an essential role. Radiotherapy treatment plan assessment relies on an implicit estimation of the tumor control probability (TCP) and normal tissue complication probability (NTCP) arising from a given dose distribution. NTCP and TCP are both primarily dose-volume based models. In RT planning, the 3D dose distribution in a given organ structure, target volume or critical structure, is summarized in a graphical 2D format by dose-volume histogram (DVH). A DVH is a histogram relating the radiation dose to a structure volume. A potential application of radiobiological modeling to radiotherapy is the optimization of treatment plans trough the determination of TCP and NTCP values using models that include both clinical data and dose-volume information. The plan optimization process is then performed by a fine tuning of trade-offs between those values.

The use of NTCP models may help to identify the optimal plan that minimizes radiation-induced side effects for individual patients [12]. In particular, NTCP models can be used as scorers in order to quantify the advantages expected from hadrontherapy in view of the improved physical selectivity. This is extremely relevant due to the current lack of randomized clinical trials, which hinders an easy and robust identification of patient categories that might clearly benefit from these types of treatments.

Generally, NTCP models attempt to reduce complicated dosimetric and anatomic information to a single risk measure. Modeling of NTCP has been performed with different techniques for many organs and end-points [13–15]. In these models, organ functional architecture, with respect to dose-volume tolerance characteristics and volume effect, has been described as either "serial" or "parallel" by using the electrical analogy. The phenomelogical Lyman-Kutcher-Burman (LKB) approach [16], in particular, is the most well-known and traditionally accepted methods for predicting toxicity after radiation treatment. This model is uniquely based on dose-distribution and fractionation information. However it has been reported how radiotherapy outcomes may

also be affected by multiple factors other than the dose. A different modeling philosophy has been successfully proposed based on multivariable logistic modeling [17].

TCP models formulation rely on the assumption that tumor control requires the killing of all tumor stem cells by the radiation treatment and Poisson statistics are employed to calculate the proportion of the various tumor types in which every stem cell is inactivated as a function of dose [18]. For these TCP values to predict clinical response accurately, the values of intrinsic radiosensitivity of the stem cells and their total number in the tumor (i.e., the cells that must be inactivated) should be known. These parameters are not usually determined for individual tumors but reasonable estimates are available for populations of like tumors in different patients. Inter-tumor heterogeneity should be also taken into account when modeling the radiation response of groups of human cancers. This heterogeneity arises from distributions in clonogen intrinsic radiosensitivity, oxygenation status, growth fraction and possibly other factors. In addition, host factors such as immune response can also play a role. TCP models are particularly important for determining the effectiveness of novel fractionation schemes or the effect of departures from homogeneous irradiation.

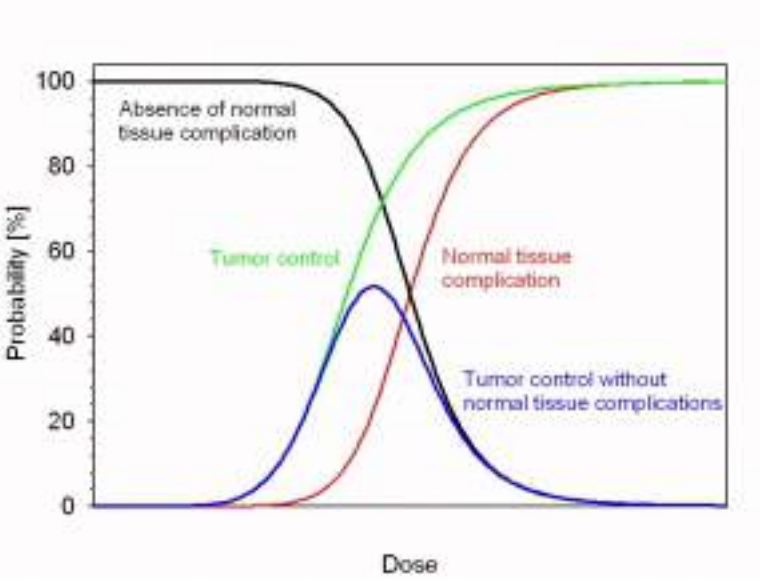


Fig. 6: Dependence of TCP and NTCP on dose. The probability of tumor control without normal issue complications receives its maximum in the so-called "therapeutic window. (from dkfz.de)

1.1.4 Beam Monitoring

The accurate beam characterization at the irradiation lines is important both for in-vitro and in-vivo experiments. The use of ionization chambers is a consolidated technology for beam monitoring in charged particle facilities. These detectors are characterized by good transparency, relatively simple construction and good long term stability. However, beam monitoring with gas

detectors has several drawbacks: the sensitivity is quite low, limiting the minimum detectable particle flux, the detector response is quite slow and the dependence on beam quality factors such as beam energy, fluence, fluence rate etc. needs to be fully characterized and calibrated frequently with reference dosimeters. A detector capable of single particle counting would overcome all these limitations.

In this respect, planar silicon detectors may offer a viable alternative to gas detectors: they have very good sensitivity to a single particle, excellent space resolution and limited thickness. Recently, new technological developments towards the future LHC experiments have been presented which increase considerably the performance of these sensors.

One of the innovative designs, developed by CNM (Barcellona) within RD50 CERN collaboration, are the Low Gain Avalanche Detectors (LGADs) where a moderate (≈10) internal charge multiplication is achieved in n-in-p sensors by the strong E field induced by an additional p+ doping layer implanted at few μm depth. The increased Signal/Noise allows designing very thin LGADs specifically optimized for high resolution time measurements and very short collection time (Ultra Fast Silicon Detectors – UFSD) [19] . With sensors as thin as 50 μm, a time resolution at the level of few tens of picoseconds with a charge collection time of about 1 ns have been achieved in the INFN project UFSD (CSN5). With an appropriate segmentation, single particle counting from few Hz up to hundreds of MHz are feasible, as needed for beam characterization purposes at the irradiation facilities. In addition, the excellent time resolution opens the possibility of the beam energy measurement with time-of-flight technique.

1.2 Objectives, Originality and Innovation

The Project aims at developing and testing innovative treatment planning models for particle therapy, accounting for a higher complexity of biophysical processes and to allow its verification on a multi-scale level.

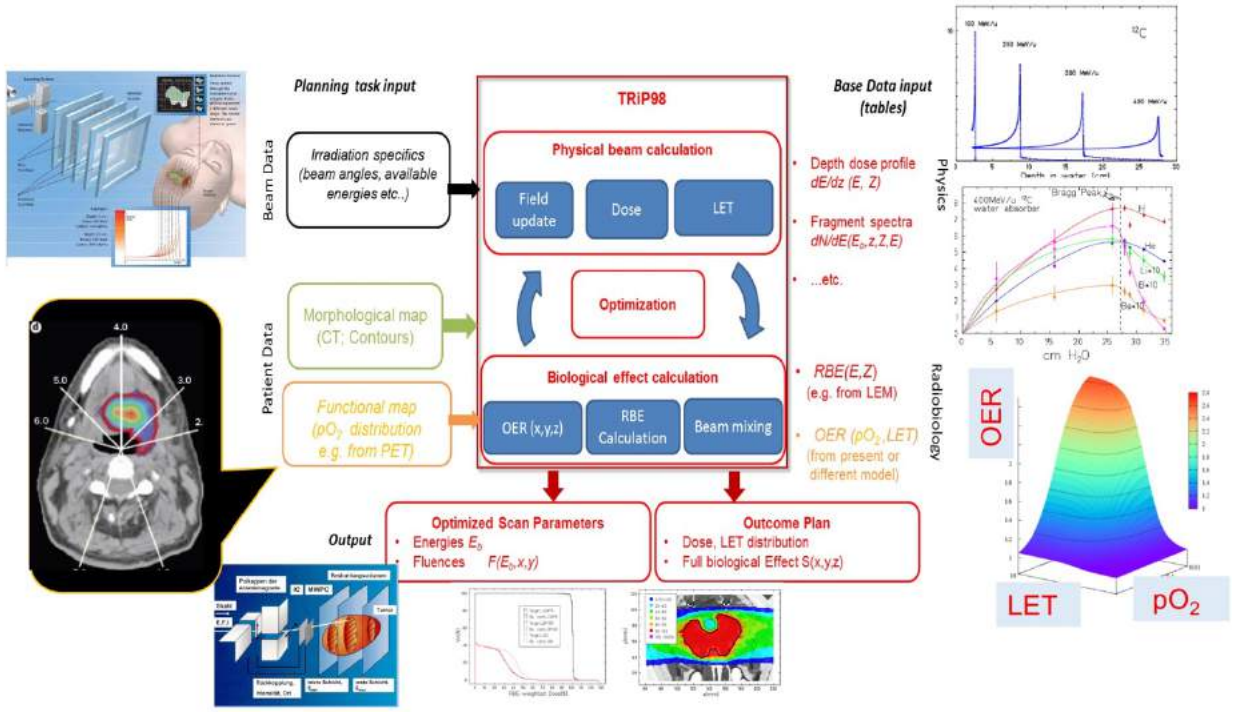


Fig.7 : TRiP98 structure, including recent implementations.

The TPS modelling part is based on the use of TRiP98 (Treatment Planning for Particles) [11,19] the first TPS for actively scanned heavy ions which, after serving the GSI pilot project on carbon ion therapy, is at the basis of the systems used in all the heavy ions treatment centers in Europe (HIT, MIT, CNAO, Med-Austron) and China (SPHIC), and now used as a research tool in several institutions,, including Lyon, Krakow, Marburg, Aarhus, beyond GSI and TIFPA. The first TRiP98 paper [20] was recently selected by Physics in Medicine and Biology Editorial board as the most important paper in ion beam therapy of all times appeared in the journal, and among the 25 most influential in overall the journal topics.

The modular structure of the code (see fig.7) allows gradual advancing of the physical and biophysical models, and its optimization module allows already to keep into account several features for biologically adapted inverse planning.

In collaboration with GSI, the TIFPA researchers will be able to use in TRiP98 the LEMIV version of the LEM code which has been shown to be especially suitable for proton biological effect description.

In addition the project will involve for some applications a INFN developed outstanding software, the code RPlanIT, which comes form a fork of the more known PlanKIT, a treatment planning kernel originally developed by INFN-Torino in collaboration with IBA. The latter offers among other features the possibility to use different biophysical models (e.g. the

microdosimetric kinetic model (MKM)), and, being fully programmable by the users, great flexibility for complex analysis including robustness tests.

The envisaged key issues that will be addressed are:

- explicit RBE description of proton beams, including impact of full nuclear fragmentation
- accounting for different models for the effects of hypoxia and possibly other sources of intra-tumor eterogeneity with different ions.

Among the introduced innovations in this modelling part of the project, there is the definition of a new optimization quantity in the planning task, going beyond the conventionally used absorbed dose, or purely RBE-weighted dose, but introducing an ”isoeffective dose in the local microenvironment” keeping into account all the possible sources of biological effectiveness, due to both the beam and the target local features.

For the fragmentation part, the project will offer an immediate application of cross section data arising from the FOOT experiment (see previous section). Such data were never available before. Being the resulting fragment spectra quite different in shape, variability, energy range distribution as compared to o the spectra normally accounted for fragments stemming from the projectile, their implementation will open new challenges, especially as far as the weighting of the biological effect, which also peaks at very low energies, and evaluating its impact.

The quantification of the impact of the different approaches developed in this project, will be linked to NTCP and TCP analysis, allowing translation of the dosimetric analysis to a clinical impact.

Opening the way to perform an end-point based treatment planning, where NTCP, TCP or their combination (like different metrics of the therapeutic ratio see fig.6) is directly taken into account in the optimization, will introduce another powerful novelty, since this task was never realized for particle beams, accounting for all the above mentioned biological effects.

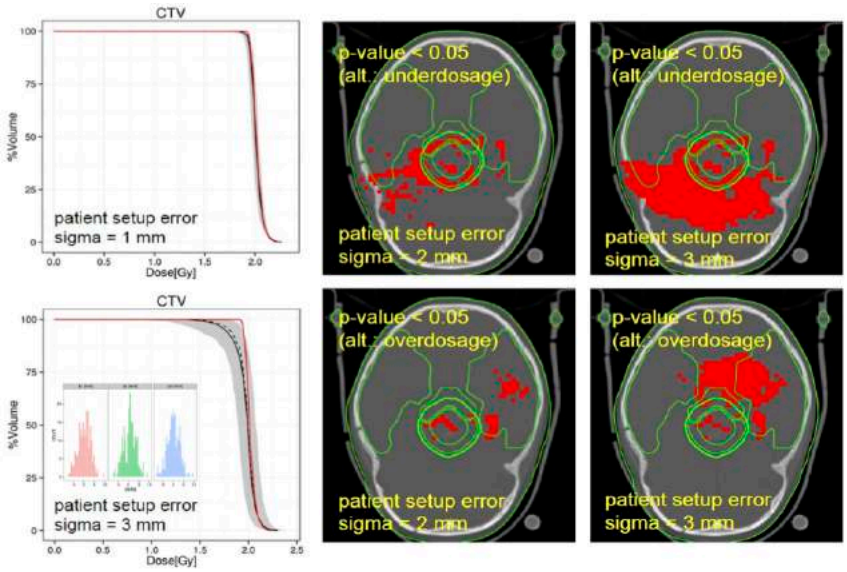


Fig. 8: Example of underdosage/overdosage analysis performed with RPlanIT for a given setup error distribution

The new concepts, introduced in this modelling part, will require a new dosimetry, which will be able to return a verification of a biological effect, in its complexity as planned and predicted by the TPS models.

Firstly, this will need an intense work in setting up facilities, and related target station able to offer a great variety of specific verification tests. These facilities are providing complementary energies and particle types, and all of them are linked to therapeutic centers, offering potential immediate translation of the advances in a clinical environment, and fundamental feedback on needs and feasibility from the clinical experts. Basic physical dosimetry, but allowing new features, like analysis of beam fluences and energy at the same time will be a relevant task in this context.

Thus, based on the team expertise on this topic, our project will invest on the development of innovative devices allowing the simulation of phantom patient geometries, where the different effects (RBE, OER) may be detected efficiently.

While a large part of the project implementation will be devoted to in vitro dosimetry, an important part of it will be dedicated to in vivo verification, namely

- NTCP analysis of the impact of variable RBE account on a mouse model
- TCP and molecular level analysis of irradiated mices for a given tumor line with possible hypoxic areas

Among the aims of this project there is also to perform a large-scale *in silico* study of the clinical impact of variable RBE in Proton therapy, based on the TPS models managed in the consortium, mentioned above. This analysis will be carried on based on real patient plans provided by the

Trento Proton Therapy Center (TPTC), beside additional literature data. This will offer a possible answer or at least fundamental indications to a long standing open question, and suggest specific clinical trials which could be likely be performed in the TPTC itself.

The project has then a high interdisciplinary level, ranging from basic physics measurements, biophysical modeling to clinical testing and promises to initiate larger term collaborations between the involved partners which will deliver breakthrough in the field of hadrontherapy.

1.3 Relevance for INFN and INFN-CSN5 Mission

A recent INFN workshop "La Radiobiologia in INFN" held in Trento, 12-13 May 2016, (https://agenda.infn.it/conferenceOtherViews.py?view=standard&confId=11036) overviewed the research and the outstanding results accomplished in recent years in INFN, namely in CSN5, in the field of radiobiology with a focus to particle therapy. It was very clear, at the same time, that it should be given a new momentum with larger interdisciplinary involvement at the present stage, for further advances and that several new challenges are opened which can be faced with the INFN expertise and the collaboration of selected external partners.

The large impact of **inter-disciplinary applications in medicine and biology** in the present project, represents a follow-up of this conference, joining most of the INFN groups having contributed to the field, and at the same time a very direct fulfilment of one of the core missions of INFN-CSN5.

A high level of translational research starting from basic physics and reaching biological and clinical endpoints is stemming from this project. Treatment planning implementation offers the way to test the input models, originated e.g., from basic physics cross sections, in a macroscopic measurable quantity with a biological effect (e.g. clonogenic survival at different positions of a beam).

Joining advanced physical dose and biological effect measurements with ion beams, will allow unprecedented control in **optimizing radiation therapy**, contributing to one of the key missions related to the biomedical applications of INFN-CSN5 research.

In summary all the following aspects of INFN-CSN5 mission will be greatly impacted by the MoVe IT project:

- ✓ *Detectors development* - including bio-radiation detectors, i.e., not only upgrade of specific detectors for particle tracking and energy deposition, but also extending the concept of radiation measurements with advanced tools for measuring a biologically effective dose, coupled to pure physical adsorbed dose detecting devices.
- ✓ *Accelerators beamline development:* Tuning of the final part of a beamline, including specific target stations for experiments, scattering devices and energy degraders, allowing to fully exploit the different accelerator facilities and provide a feedback for their upgrade. Part of the project is the development of novel devices for the on-line measurement of the beam fluence, profile and energy, complementing and extending the information form existing monitor detectors, mainly based on ionization chambers

- ✓ *Advanced Computation*, stimulating the advances in both analytical and Monte Carlo calculations for dose planning. Interaction with the MC-INFN project will give additional momentum to this point.
- ✓ *Interdisciplinary research for Medical Applications*, as mentioned above.
- ✓ *Transferable technology* (TT) output beyond scientific publications: delivering patents, infrastructures, and a worldwide unique network of INFN irradiation facilities for TPS verification in hadrontherapy

In addition, in a more general INFN context, the connection with the experiment of CSN3 FOOT, is offering an application to basic research in the field of nuclear physics, translating directly its impact in technical advances for healthcare applications.

For the above mentioned reasons, the topics addressed by this Project are of central relevance for the Scientific Mission of INFN-CSN5 in particular and of INFN in general.

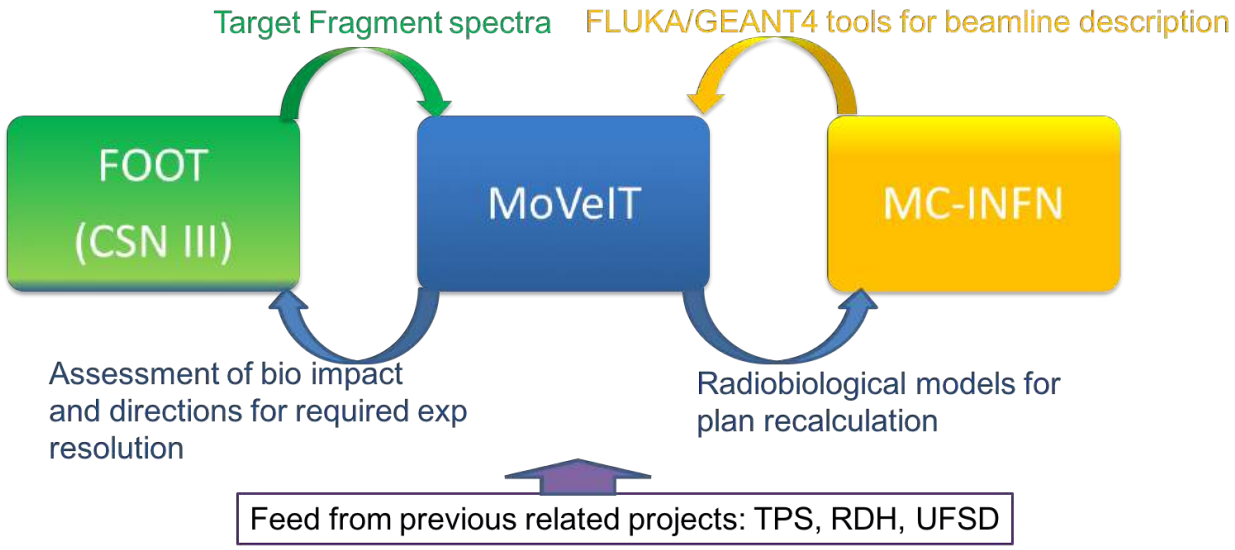


Fig. 9: Role of MoVe IT in the interaction with different INFN projects

1.4 INFN-CSN5 participating units and their role

The role in the Project of the participating Units is detailed in the following sections.

1.4.1 INFN Trento Institute for Fundamental Physics and Applications

The INFN-TIFPA Unit will coordinate the whole project and will work specifically on different parts of it: First, they'll work on the biophysical modelling and implementation in treatment planning in WP1, in collaboration with the GSI group. In combination with APSS proton therapy center and INFN-NA they'll perform a large in silico analysis of the impact of RBE account in proton therapy on patient data.

Then a major task will be developing of specific biological dosimetry devices, in collaboration with BIOTech and CIBIO, allowing biological effect measurements with a high resolution, e.g for a biological range verification in proton beams, and of testing of hypoxia adapted treatment plans.

Finally, they'll be involved in the upgrade of TIFPA facility, in collaboration with LNS and in all the irradiations with high energy protons in the physics and radiobiology lines.

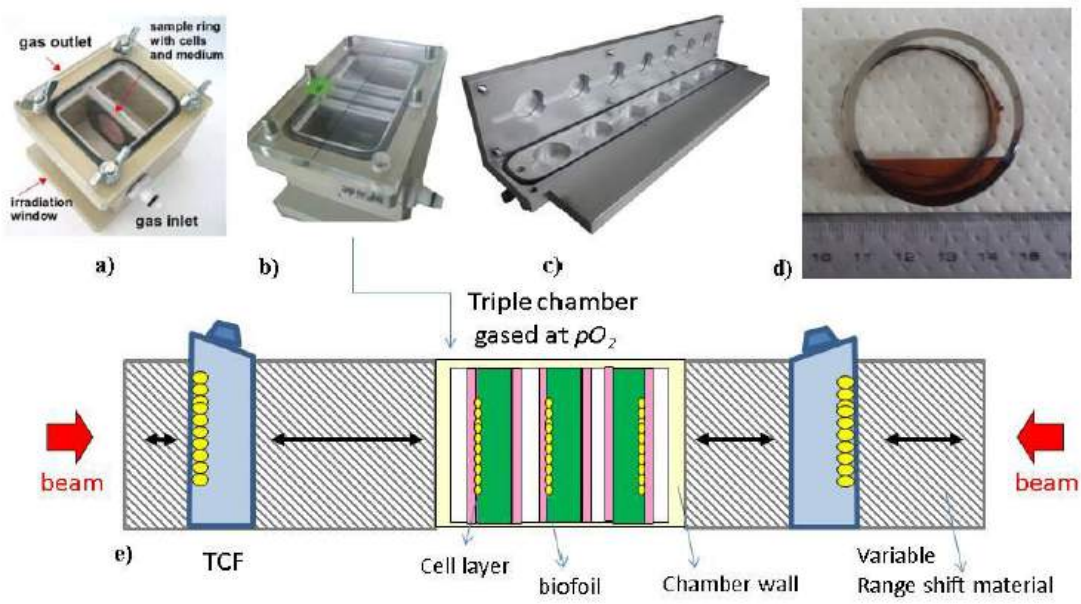


Fig. 10: bio-phantom devices for conditioned hypoxia measurements [8]

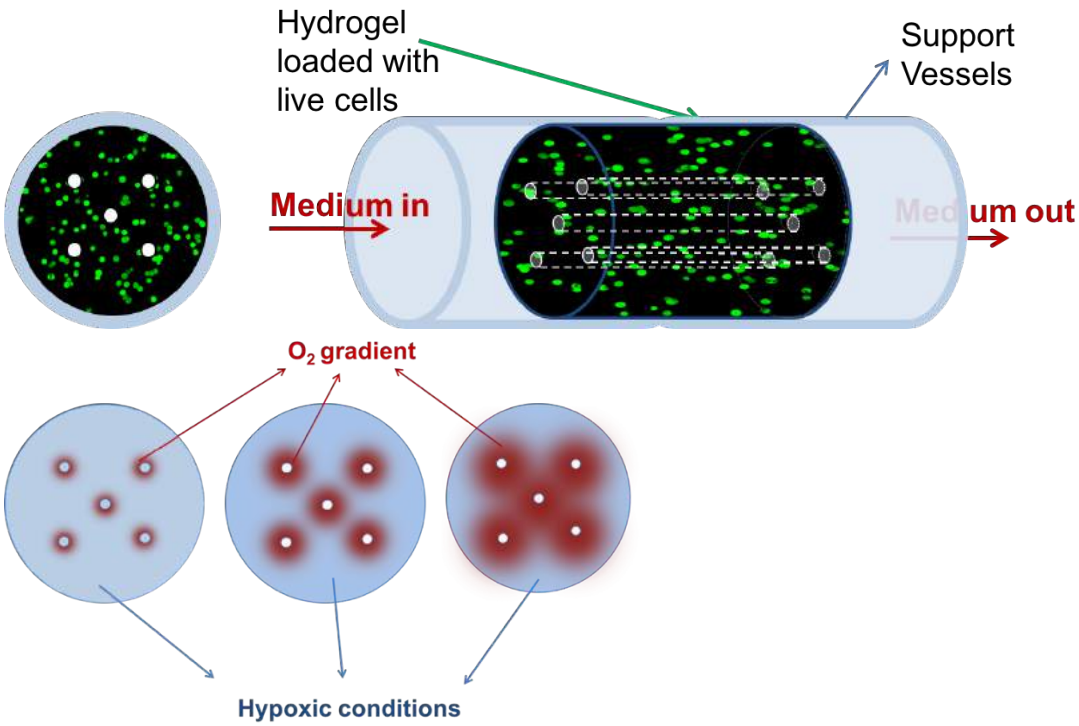


Fig. 11: Planned devices for irradiation phantoms with simulated hypoxic conditions allowing realistic cell communication between different regions

1.4.2 INFN Torino

The INFN-TO Unit, which has a wide expertise in development of hardware and software for hadrontherapy applications, will be primarily responsible for two different tasks: the implementation of the radiobiologcal models in RPlanIT in the context of WP1 and the development of specific detectors for the on-line measurement of the beam characteristics during the irradiation (number of delivered particles, beam profile and beam energy).

Regarding the first task, the INFN-TO Unit will work in parallel and in synergy with the INFN-TIFPA group, both extending their TPS RPlanIT to implement the new models developed and handling the commissioning of the software. This will provide a useful crosscheck of the results obtained with an implementation alternative to TRiP98. Andrea Attili, the first developer of RPlanIT and its previous versions, will lead this activity together with Lorenzo Manganaro.

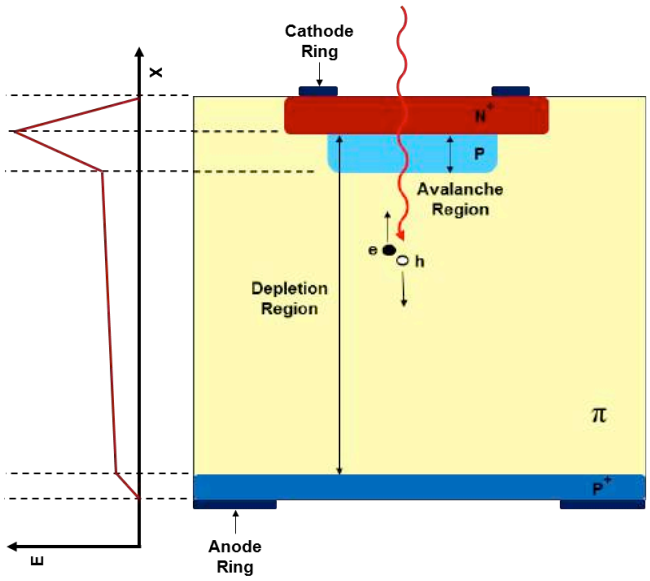


Fig. 12: Low-Gain Avalanche Detectors (LGADs) are innovative detectors developed within the RD50 CERN collaboration which feature a moderate (≈10) internal charge multiplication achieved through an additional p+ doping layer few microns depth. The increase signal-to-noise ratio allows designing very thin Ultra Fast Silicon Detectors (UFSD) designed for fast signal collection times, high rates and very good time resolution.

Both the in-vitro and in-vivo irradiation tests foreseen in the project need an accurate and precise control of the beam distribution, in particular of the number of delivered particles and of the beam position and profile. In the second task, new strip silicon sensors, based on the design of Ultra-Fast Silicon Detectors (UFSD, see Fig.12) [19] already financed by the INFN CSNV, will be developed to measure directly

profiles, complementing the information from ionization chambers usually used in the irradiation lines, which are unable to provide these measurements at low fluxes.

Another device to be developed within the project will use the excellent timing capabilities of UFSD sensors to provide an on-line measurement of the beam energy using time-of-flight techniques. For both the projects dedicated VLSI chips for the read-out electronics will be designed and developed.

1.4.3 INFN Laboratori Nazionali del Sud

The Laboratori Nazionali del Sud will be primarily leading and coordinate the upgrade of the facilities.
The LNS team developed advanced tools in GEANT4 for describing the beamline components including all the parts of a target station, producing a customized version of the public advanced GEANT4 example “Hadrontherapy” [21,22]. In collaboration with the TIFPA team, the hadrontherapy class will be expanded in order to account for the TIFPA lines at Trento PTC.

Radiobiological quantification of the beam, i.e. LET and RBE maps, including specific target stations, will be finally performed in combination with the developments from WP1.

In addition, the Catania group will bring the expertise of its members associated to CNR-IBFM, on molecular level analysis and in vivo irradiation which will be fundamental for a verification of the TPS models at a preclinical level.

In the framework of the project a tool that will be able to evaluate the biological parameters starting to the event-by-event track of each particle, will be developed. The target, corresponding to the sensitive detector, will be voxelized to collect information about the secondary particle produced and their released energy. The scheme representing the main logical steps to calculate the RBE inside the Geant4 application, is reported in Figure 13.

2.

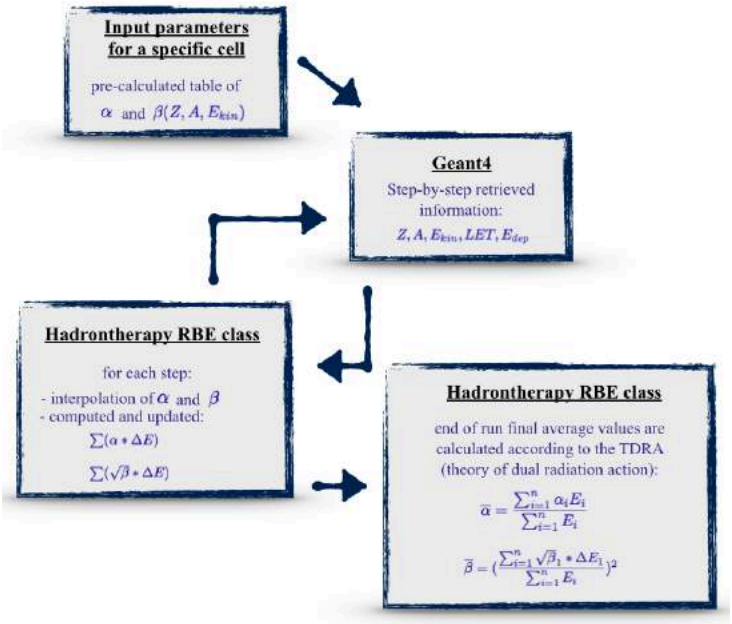


Fig. 13: Simplified scheme of the RBE computation that will be implemented in Geant4

1.4.4 INFN Napoli

The contribution of INFN-NA, will be on three different parts of the project. The group guided by L. Cella, in strict cooperation with CNR –IBB, will provide an essential expertise for NTCP modelling, thanks to their internationally recognized work the field. Her guide, in combination with the APSS team, for investigating those clinical cases where an impact of explicit RBE in proton plans can be relevant, will be fundamental. Dose-response modeling of brain organs-at-risk involved in intracranial tumor irradiation such as the visual pathway tolerance and neurocognitive impairment will be approached. A special focus will be devoted to radiation-induced spinal cord myelopathy. This radiation complication is one of the most dreaded negative

outcomes for both patients and radiation oncologists. For the cervical cord data, a value of α/β = 0.87 Gy (95% CI 0.54–1.19 Gy) has been reported (Schultheiss TE (2008), The radiation dose-response of the human spinal cord. Int J Radiat Oncol Biol Phys 71:1455–1459). With a so low α/β value, a potential clinical impact of an advanced RBE description is expected.

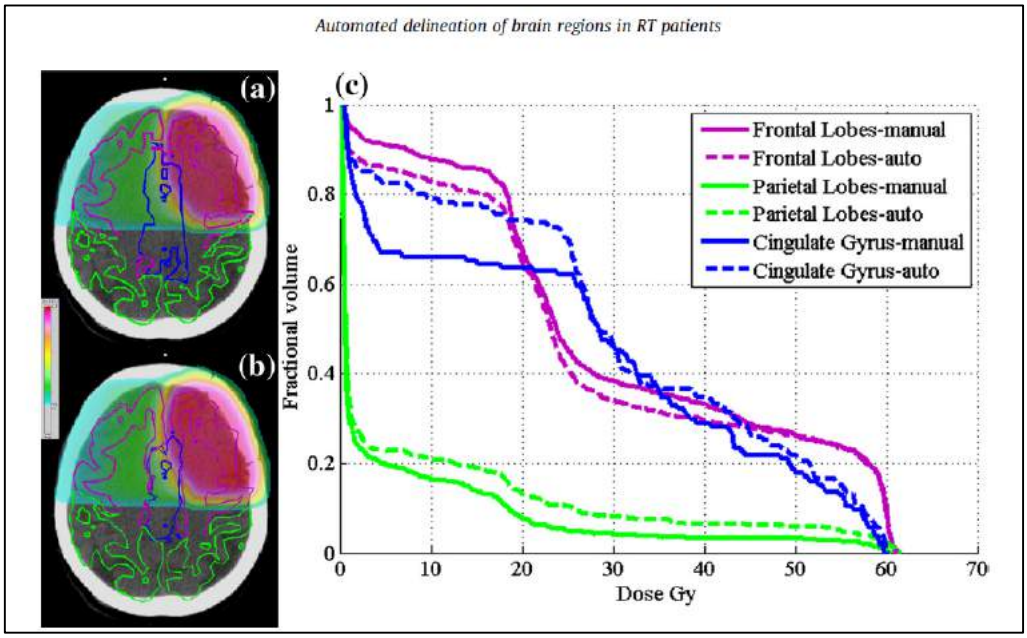


Fig. 14. Dose distributions and dose–volume histograms (DVHs) relative to the automated atlas-based magnetic resonance imaging segmentation (MRI-ABAS) tool for brain substructures delineation and for dose-volume information extraction implemented at IBB-CNR for NTCP modelling: the automated RT contours (a) are compared with manual delineation RT contours (b) on axial CT images. In (c) the DVHs of cingulate gyrus, frontal and parietal lobes for the automated RT contours (dashed lines) and for the manual delineation contours (solid lines) are reported (Conson M., Radiother Oncol. 112 2014).

Fig. 15: Exposition of a mouse sample in the CATANA line at LNS

1.4.5 INFN Milano

The group lead by G. Battistoni at INFN-MI will act in the project on different levels. First, they will represent the major link with the FOOT experiment (CSN III) together with part of the TIFPA team, overviewing the exchange of information between the two projects. Moreover because of their longstanding cooperation with CNAO, and especially for their leading role in supervising the establishment of the experimental facility in the framework of IRPT project, their task will be analogous of that one of TIFPA with the APSS protontherapy facility in coordinating all the activities related to CNAO. Finally their world-leading expertise as developer of the FLUKA MC code, and the experience deriving from the TPS and RDH experiments of CNS V, will provide the necessary competence for generating the appropriate MC tools for beamline description and will provide another fundamental link with the activities of the CSN V experiment MC-INFN focused on the development of the major Monte Carlo codes in the INFN context.

1.5 External Institutions Involved

1.5.1 CNAO – Centro Nazionale di Adroterapia Oncologica

The Centro Nazionale di Adroterapia Oncologica is one of the first (the second in order of opening time) worldwide centers for actively scanned carbon ion therapy. CNAO is also a center for research and most of this is performed in strict collaboration with INFN. In particular, INFN

and CNAO have started, with the funding of IRPT project, the construction of a new beam line dedicated to experimental activity in a dedicated area. In the future, beyond protons and Carbon beams, new ion will be available. Priorities will be 4He and 16O.

The experimental area, to be completed within 2017, will allow to carry on different kind of experiments and tests, radiobiology being one of the main interests. CNAO has also experimental radiobiologists in its staff and a laboratory specifically equipped for their activity exists. At CNAO there are other research activities in progress which are closely related to the goals of the present proposal, such as those concerning Treatment Planning, development of Monte Carlo verification of plans (based on FLUKA code) and its coupling with new radiobiological models. Again, many of these researches are in collaboration with INFN and this occurred so far mostly through the RDH and MC-INFN experiments in CSN V.

1.5.2 GSI Helmholtz Center for Heavy Ions Research

The Biophysics department at GSI is a world leader in a broad range of aspects of heavy ion biophysics and ion beam therapy, from modeling of ion beam radiation effects to first development of treatment planning for particles. These leading research activities, among other outstanding results, were substantial for the success of the Carbon therapy pilot project, held there from 1999 to 2007, when 440 patients were treated with scanned carbon ions.

GSI researchers, including the founder of the TRiP98 code, Michael Kraemer, and of the author of the LEM model in its various versions (I-IV), Michael Scholz, long-standing collaborators of the TIFPA team, will offer their support and advise in any activities including TRiP and LEM.

A special agreement is presently in play for the use of TRiP98 at TIFPA, under particular conditions.

1.5.3 APSS – Trento Protontherapy Center

The Trento Proton Therapy Centre (TPTC, part of Agenzia Provinciale per i Servizi Sanitari - APSS), where patients are treated since the end of 2014, will be an essential strategic partner. In particular, the in silico study on proton RBE impact will be carried on based on real patient plans provided by the TPTC. The team of clinicians and medical physicists of TPTC will strongly support this study, contributing with their medical expertise to the definition of possible strategies for future clinical trials. Obviously, the TPTC is a natural candidate for the eventual execution of such clinical trials.

1.5.4 CNR –IBFM Cefalu'

The CNR-IBFM is from a long time collaborating in synergy with INFN-LNS unit.

The main activities of this unit will be focused on molecular characterization of the targets including hypoxia biomarkers, by microarray and pathway analysis in in-vitro models developed in WP3 task 2. Moreover, in-vivo experiments will be performed on mouse models in order to validate treatment plans from WP1 and TCP and NTCP measurement for protons treatments. Furthermore, molecular analysis will be used to study mouse tissue response, by genomics and proteomics methods.

1.5.5 CNR- IBB Naples

The research activities of the Institute of Biostructure and Bioimaging (IBB) of the National Research Council are mainly devoted to translational research to develop new tools for prevention, diagnosis, and targeted therapies. The IBB investigators involved in the research proposal have intensively worked on development of models for prediction of radiation induced normal tissue effects using novel predictive approaches. The main activities of the IBB group will be focused on the extension of NTCP models developed for patients receiving conventional RT to hadrontherapy, NTCP model validation against collected toxicity data as well as TCP parameters estimation for heterogeneous hypoxic tumors

1.5.6 Parthenope University Naples

The Università degli Studi di Napoli "Parthenope" is an innovative center of higher education offering high-quality teaching and research in Economy, Engineering and Science and Technologies. In particular, the Department of Science and Technology (DiST) offers scientific expertise and training in Ecology, Biology, Energy, Microbiology, Chemistry and Biochemistry, Environmental Impact Assessment. DiST is a part of a network of relevant and highly qualified international researches institutions (IGB, CNR, Stazione Zoologica Anton Dohrn, University of Naples Federico II), offering collaborations and expertise sharing and facilities including libraries and laboratories (biochemical, proteomic, molecular biology, histology, cytology). DiST has a Biology laboratory with facilities and devices for histology and molecular biology investigation.

1.5.7 Catania University

Catania University The Catania University is from a long time collaborating in synergy with INFN-LNS unit. The Unit directed by Prof. Rosalba Parenti of the Laboratory of Molecular and Cellular Physiology (Department of Biomedical and Biotechnological Sciences- University of Catania) will provide an essential expertise for In vivo Experimental Design and preclinical imaging. Specifically, studies will be performed at SUU-Preclinical Center of the University of Catania, by using the most advanced molecular vision technologies including PET; X-RAY/Optical Imaging; Ultrasound High-frequency; Optical Coherence Tomography. In the proposed project, PET/CT quantitative 3D

tomographic imaging through radiotracers, obtained from the Cannizzaro Hospital, can provide deep insight into the underlying mechanisms of studied pathology. In particular, the above described technologies will allow the assessment of the effects of ion beams treatment and the effectiveness of new therapeutic tools.

1.5.8 UT Southwestern– Dallas (USA)

UT Southwestern is the Medical Center in Dallas, Texas, renowned for their high-quality scientific activity leading to 6 Nobel prizes. UT Southwestern recently received an NCI grant for the construction of the first heavy ion therapy center in US. They have launched an extensive pre-clinical research study in radiobiology and treatment planning, with several points in common with MoVeIT

1.5.9 Trento University (CIBIO and BIOtech departments)

The Centre for Integrative Biology (CIBIO) is a new interdisciplinary Centre at the University of Trento, one of the top-ranked academic institutions in Italy. CIBIO is the first initiative in molecular medicine and biotechnology in Trentino, an autonomous province of Italy characterised by a high lvel of public investmentin innovation and research.

The mission of the centre is to promote an integrative view of fundamental biological processes and of their derangement in disease, whereby basic science co-exists with biomedical oriented translational approaches.

Research at CIBIO covers topics all emphasising experimental analysis at the various levels of biological organisation and focusing on four major research programmes: Cancer Biology & Genomics, Cell & Molecular Biology, Microbiology & Synthetic Biology, and Neurobiology & Development.

As a new centre, CIBIO has acquired state-of-the-art equipment covering all the tools necessary for biomedical projects to be carried out with the required level of technological sophistication with commonly shared instrumentation facilities operated by dedicated staff scientists, including: High-Throughput/High Content Screening Facility, Next Generation Sequencing Facility, Microarray Facility, Cell Analysis and Separation Facility, Advanced Imaging Facility and Bioanalytical Mass Spectrometry Facility.

BIOtech is part of the Department of Industrial Engineering at the University of Trento and is active in two main areas: Tissue and cell dynamics, and Biophysics.

Tissue and cell dynamic compartment addresses material and devices that can promote tissue repair and regeneration, following tissue engineering and regenerative medicine approaches.

Recent activities of the group regarded protein-based materials, smart hydrogels, bioreactors, cells-biomaterials interaction, protein adsorption, nanobiomaterials and nanotechnologies for imaging and therapy of tumors, matrices and substrates for cell encapsulation and growth.

Facilities comprise electron microscopy (SEM, AFM), confocal microscopy, cell culture laboratories, polymer processing machines, mechanical characterization, spectroscopic techniques and a wide range of other apparatus for materials characterization.

1.5.10 FBK – Fondazione Bruno Kessler (Trento)

FBK has a long standing collaboration with the INFN group of Torino for the development of ultrafast Silicon detectors within the INFN UFSD project. The design of the silicon sensors envisaged in this project will benefit from the synergy with the UFSD activity, including the contribution of FBK which will provide assistance in the detector design and tests at Trento.

FBK is one of the founding institutes of TIFPA from 2015.

1.6 Other INFN National Commissions (CSNs) involved

As mentioned above, the present project will have a strong interaction with CSN III, through the FOOT experiment. The connection with this experiment, and the activity carried in Group III, will be assured by several consortium members who are participants in the latter experiment. The responsible of this interaction will be Prof. G. Battistoni (INFN-MI).

1.7 Cofinancing private and public bodies

A certain amount of co-financing for covering namely Consumables/Instrumentation related expenses is envisaged.

INFN-TO will make use of some of the laboratory instrumentation and setup used for the development and test of UFSD sensors financed by the UFSD-ERC project of the INFN. The strong synergy with UFSD will make it possible to include at no cost few test structures of interest for MoVeIT in engineering runs already foreseen by UFSD. Moreover, the community involved with the UFSD development has expressed a strong interest in investigating the application of this novel technology to medical environment and will co-finance half of the costs for two engineering runs foreseen by this project (see attached letter from Nicolo Cartiglia).

he IBFM CNR will contribute to the project with our man power getting involved our researchers for the biological and physical issues; and with our instruments for the

biological analysis. Routinely, IBFM researchers work at LNS – INFN laboratories into the common project for medical physics and radiobiological studies. The Catania University will contribute to the project getting involved the preclinical advanced molecular vision technologies, in particular the PET/CT system to visualize the hypoxia area and to the treatment monitoring.

In addition a separate proposal to the Trentino region for financing a pencil beam scanner for TIFPA experimental room has been prepared.

1.8 Project Implementation

1.8.1 Team Expertise and Infrastructures

The present consortium gathers most of the INFN groups with largest involvement in Particle Therapy. The specific skills of different groups and the involved infrastructures are highly complementary, covering all the needs of the present project, together with the precious support of the external partners.

Remarkably, the three involved facilities have at disposal a wide range of energies and ions of interest for the research activities here proposed.

The research team based at **INFN-TIFPA** has outstanding expertise in radiobiology with a focus on ion beam irradiation, biophysical modelling for hadrontherapy, biological dosimetry and technical implementation.

The group members have been working for several years in different and very advanced particle therapy centers around the world, like the Helmholtzzentrum für Schwerionenforschung (GSI) in Darmstadt, Germany and the National Institute of Radiological Sciences (NIRS) in Chiba, Japan, and they have strong collaborations with many research institutes, Universities and particle therapy centers around the world (Colorado State University (CSU), USA, Heidelberg Ion therapy Center (HIT) in Germany, Centro Nazionale di Adroterapia Oncologica (CNAO) in Pavia, Italy).

The PI at GSI was deputy of the modelling group, led by Michael Kraemer, and has contributed substantially to the new improvements of the research version of the treatment planning software (TPS) TRiP98. Among these new improvements there are modeling of new ion beams (He,O), hypoxia adaptive planning and detector response simulations

The unit is strictly linked to the experimental room at the Trento proton therapy center, whose development is under TIFPA responsibility. The facility allows the use of accelerated protons in the range 70 – 235 MeV and offers two beamlines, one dedicated to basic physics experiment (30 deg) and the orther foreseen for radiobiological irradiations (0 deg). In the latter different methods are planned for broad beam irradiation. The initial solution will be oriented to passive

scattering device, while on a longer term, a separate application has been already prepared for funding and installing a pencil beam nozzle, analogous of that one of the therapy rooms.

In addition a multi-functional laboratory is annexed to the experimental cave, allowing direct processing of the samples.

Moreover the group has access to the laboratory of the Centre for Integrative Biology (CIBIO) in Trento and frequent availability of beam time for experiments at GSI, HIT and NIRS.

The group, after several seminal contributions and reviews in the field of particle therapy and ion beam induced radiation damage in general [3,21–23] firstly explored the field of the intra-tumour heterogeneity for ion beams [6,8,11]

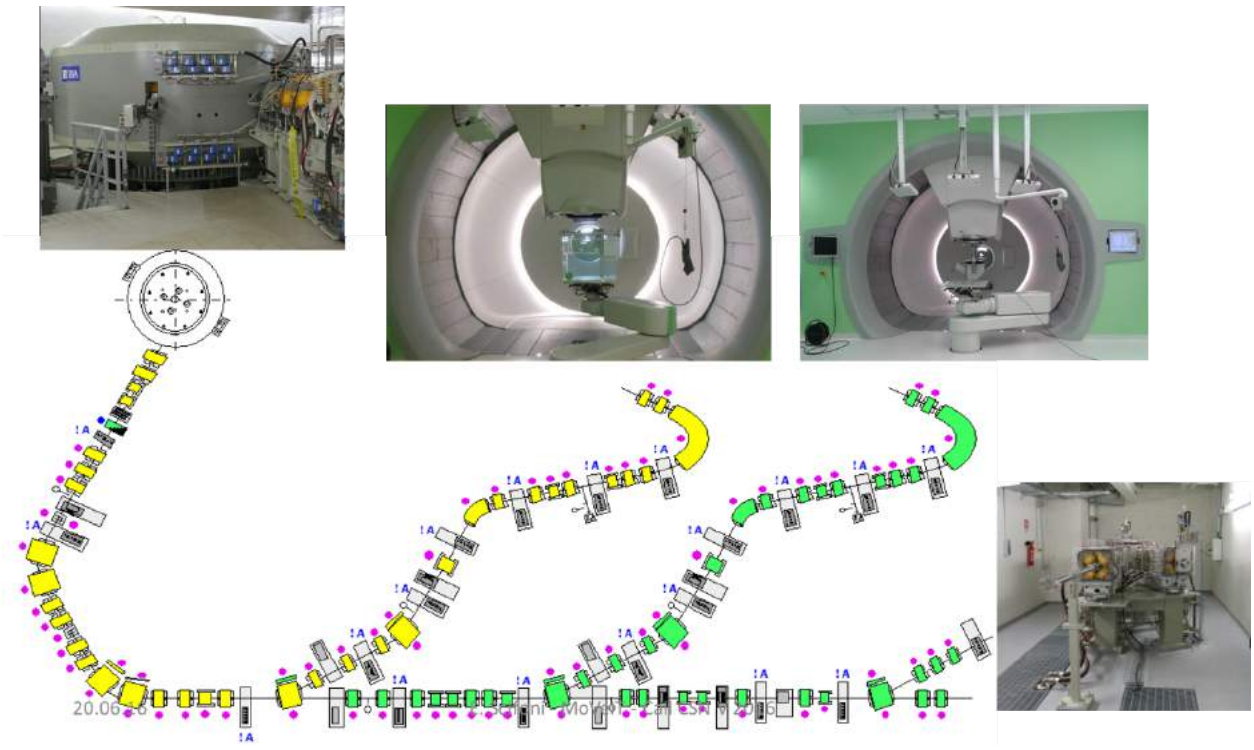


Fig.16. : Sketch of the Trento Proton Therapy Center, including the TIFPA experimental cave (on the right), presently in development phase. The two lines at 0 and 30 degrees are visible

The research team of **INFN-LNS** has great experience in to the design, simulation, development and realisation of clinical transport beamlines for proton beams and general proton and carbon irradiation beamline for multidisciplinary applications (biological and detector irradiations, etc.).

The Laboratori Nazionali del Sud (National Southern Laboratories) of INFN (LNS) is a well-established European ion beam research infrastructure covering nuclear physics, materials analysis, medical physics, development and test of detectors for absolute and relative dosimetry, radiobiology, environmental and cultural heritage applications.

The basic equipment that will be put at disposal of the Move-IT project consist of two irradiation beamlines lines, located in two different irradiation room, where samples irradiations with proton and ion beams can be easily performed.

The first is the clinical beamline, also refereed as CATANA beamline and regularly used for the patients protontherapy treatments. The CATANA beamline is exclusively dedicated to in-air irradiation with 62 MeV proton beams. Here pristine and clinically modulated proton beams can be delivered with a maximum spot-size of 40 mm in diameter and a transversal dose homogeneity better than 5%. Beam dose-rate can vary from 0.1 to 70 Gy/min. Also lower and higher dose rate can be obtained but, in this case, specific dosimetric/diagnostic devices must be adopted.

The second is the so-called 'zero-degree' beamline. Here all the ion beams accelerated by the LNS Superconducting Cyclotron can be transported. This beamline is equipped with systems able to perform the absolute dosimetry of proton and carbon beams while an effort is needed to improve the relative dosimetry measurements devices.

At the 'Zero-degree' beamline, the possibility to irradiate in vacuum is also feasible.

The following table reports the list of potential ion of interest available at INFN-LNS with the corresponding energies inside the two described beamlines

The ions of potential interest and corresponding energies are listed in the following table.

Ion	Energy [MeV/A]
1H	62,80
4He	25, 62, 80
12C	23, 62, 80
16O	21, 25, 55, 62, 80
18O	15, 55
20Ne	20, 40, 45, 62
40Ar	15, 20, 40

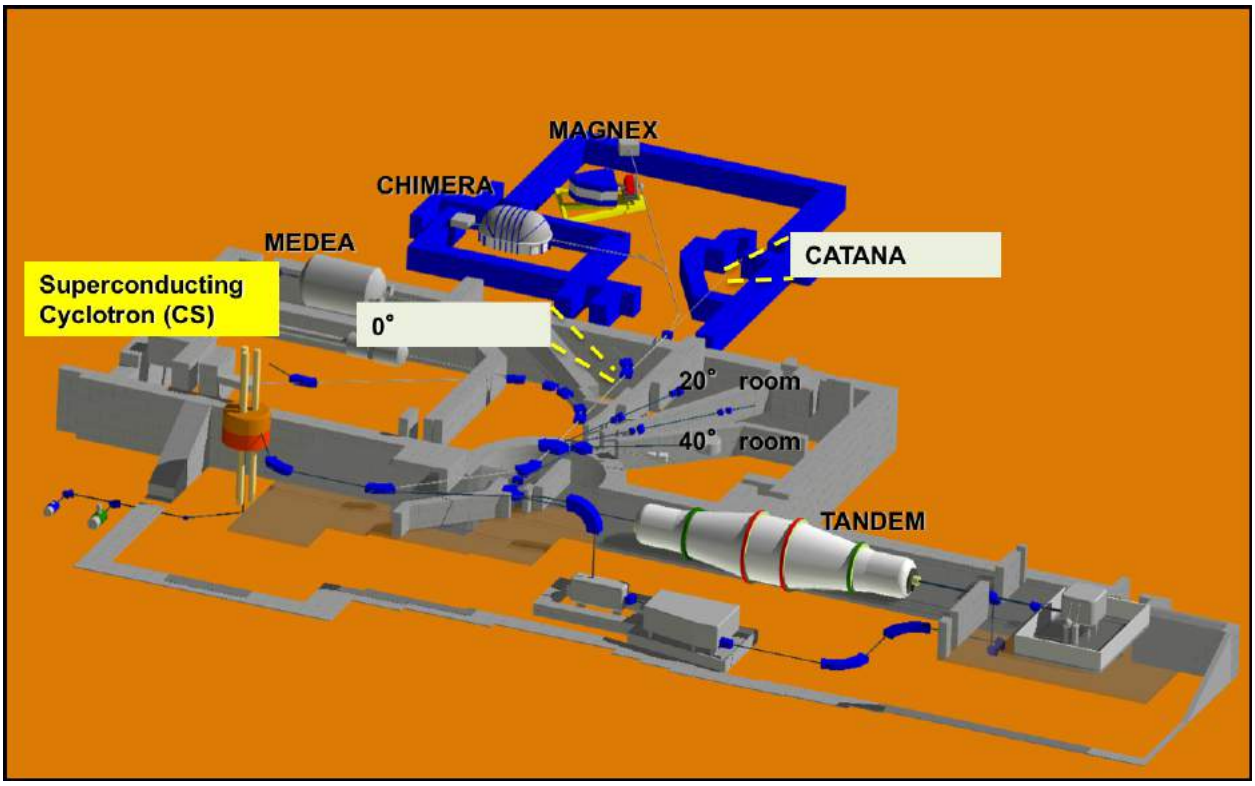


Fig. 17: Sketch of the LNS facility , including the CATANA and the 0 degree line.

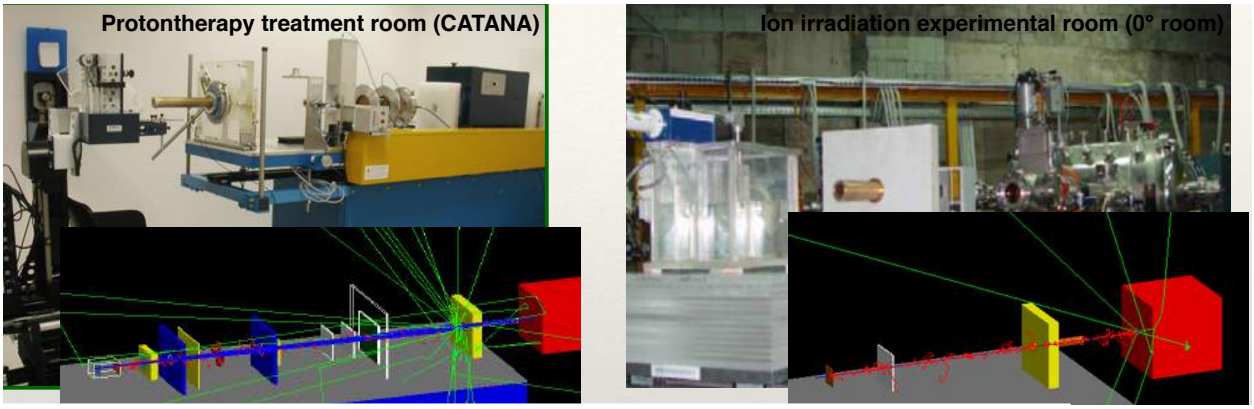


Fig.18 : Simulation classes prepared with GEANT4 of the 2 beamline at LNS

The group is strictly interacting with the IBFM-CNR (Cefalù Unit) and the Catania University having advanced expertise for in vivo and molecular biomarker analysis. This research team works in the field of radiobiology for the development of new therapeutic approaches combined with ionizing radiation and drugs/molecules by using in-vitro and in-vivo models with proteogenomic technologies in order to identify new biomarkers of

radiosensitivity/radioresistance to treatments. Moreover, the Unit will perform the animal PET imaging analysis taken advantage from the clinical experiences on the clinical PET/CT image analysis. The research team is multidisciplinary, including qualified persons in the fields of cell and molecular biology, animal science, medical phisics and imaging analsys.

The research team based at **INFN-NA** will bring their expertise in NTCP analysis, with all the medical physics team infrastructures at CNR-IBB, and in vivo analysis with related laboratories for histological investigations.

The Research team at **INFN-MI** is responsible for the establishment of the Experimental room at CNAO, and represents the major reference point for it. Beyond this, the Milano group has experience and competences in Monte Carlo calculation for hadrontherapy. In particular they can contribute with the know-how related to the FLUKA code, which is the main simulation tool in use at CNAO.

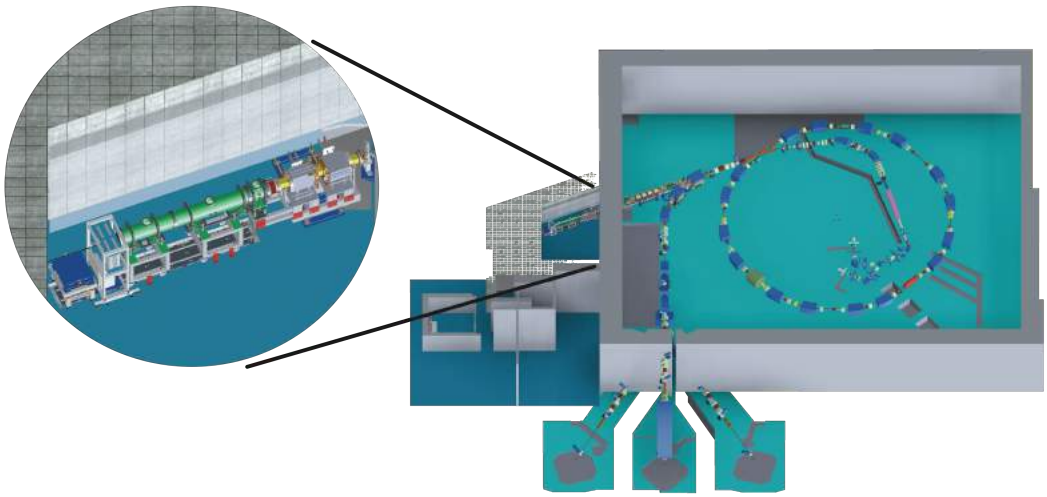


Fig.19 : Sketch of the Experimental cave which is planned at CNAO

The members of the **INFN-TO** group have a longstanding experience on the development of detectors and microelectronics for beam monitoring applications [27,28] and for dose profile measurements , and on the development of TPS software [29] for particle therapy. They are collaborating in the development of UFSD sensors, and will use the expertise gained in the past years, and their strict contacts with external institutions (FBK, CNM, Santa Cruz) and groups (CERN RD50), to adapt these novel detectors forthis project.

Among the infrastructures of the INFN-TO division which are available to the project are the already existing laboratory setup used for the UFSD development and characterization. These include the simulation software, a fully controlled LabView setup of several instruments (oscilloscopes, pico-laser. HV and LV power supplies), a micrometric 3D positioning table and automatic parameter analyser. Moreover, the INFN-TO division provides access to a pool for the design of microelectronics devices and to the mechanical and electronic workshops.

1.8.2 International collaborations

The **INFN-TIFPA Unit** has longstanding and intense collaboration with three of the most important particle centers around the world: the Helmholtz center for heavy ions research (GSI), Darmstadt, Germany and the National Institute of Radiological Sciences (NIRS), Chiba, Japan and Heidelberg Ion Therapy center (HIT). Other more recent collaborations include Dallas Particle Therapy center which is presently under construction and which is highly interested in testing the tools developed in this project, especially concerning the biological dosimetry.

1.8.3 Project feasibility and sustainability

As detailed below, the preliminary results obtained by the participating Units in the respective research fields pose a solid basis for the implementation of the Project, in terms of feasibility and sustainability.

Previous results on advanced treatment planning and biological dosimetry verification have been done by researchers of **INFN-TIFPA Unit** at GSI, HIT the National Institute of Radiological Sciences in Chiba, Japan.

Researchers of the group largely contributed to biophysical modeling of ion beams, helping to emphasize the importance of a complete RBE description, not only for heavy ions, but also for proton beams, in contrast to the usually accepted constant factor (RBE = 1.1) adopted in therapy centers. Moreover TIFPA members contributed to a seminal work illustrating for the first time on quantitative basis the relevance of a “biological range” extension, due to this effect, through model studies [4,25] The proton beam radiobiology in general was also widely covered by the group members [3].

The group also pioneered the account of hypoxia in treatment planning, new ion beams biophysical description and possible combination of the latter [8,11].

The contribution of the **INFN-TO** group will be also essential in this field, thanks to their longstanding experience as developers of PlanKIT [29].

The great expertise of **INFN-NA** in NTCP modeling, supported by APSS team will assure the complementary need for clinical –relevant assessments.

As far as facility upgrade and target station realization, the group at **INFN-LNS** and **INFN-MI** can warrantee a success thanks to the outstanding results already gained in the respective centers both in hardware and in software realization, including highly detailed Monte Carlo implementation. As mentioned in WP description, the translation of these results, to facilities with different characteristics (e.g. range of energy) will be definitely feasible. Here, the **INFN-TO** task for realizing innovative detectors, is also assured by the world-reknown work done by this partner realizing outstanding devices like the TERA chip family, the Dose Delivery System of CNAO and the leading role in the development of UFSD detectors.

The results of preliminary *in vivo* experiments with protons performed by **INFN-LNS** team and **IBFM-CNR** team can be reassumed in three macro part: the dosimetric, the Monte Carlo simulation and the experimental part.

It was determined a well define dosimetric protocol that explicate the steps that it must be followed to perform a precise small animal proton irradiation and to achieve a high conformal dose to the target. Moreover, it was designed and developed a precise and consistent small animal homemade positioning and holding system at INFN-LNS in Catania (Italy) and it will be used to guarantee a precise and consistent animal positioning. Finally, it was developed an accurate Monte Carlo simulation using Geant4 code to simulate the treatment in order to choose the best animal position and to accurately perform all the necessary dosimetric evaluations.

The Geant4 application developed can be used, beyond than for choosing the best setup of small animal irradiation, also to realize dosimetric studies and its peculiarity consists on the possibility to introduce the real target composition as target in the simulation using the DICOM micro-CT image. This application was fully validated comparing its results with the experimental measurements. The latter were performed at the CATANA (Centro di AdroTerapia e Applicazioni Nucleari Avanzate) facility at INFN-LNS irradiating both PMMA and water solid phantom.

1.8.4 Human and Instrumental resources along the project

The research team is based on **51** members (of which 3 are technicians), for a total Full Time Equivalent (FTE) of **22.5** over the entire 3-years duration of the project.

In addition to these staff members, 4 postdocs to be hired on 2-years contracts are requested, who will work 100% on the project, thus contributing for an **additional** 8/3=**2.6** FTE overall the project, for a cumulative value of **25.1** FTE.

The distributions of team members and of their relevant FTEs among the 5 participating Units are reported in **Table I**.

#	Unit	Researchers	Technicians	Tot. members	Tot. FTE
1	INFN-TIFPA	9	1	**10**	**3.9**
2	INFN-LNS	16	2	**18**	**6.3**
3	INFN-TO	9		**9**	**7.3**
4	INFN-NA	7		**7**	**4.1**
5	INFN-MI	7		**7**	**0.9**
	Total	**48**	**3**	**51**	**22.5**

Table I: distribution of man-months allocated to the Project.

Further details about the Units organization (coordinators, WP involvement, team members) are reported in **Section 2**

The major instrumental resources, include the 3 ion beam facilities, the detectotor and biological laboratories, the use of the software TRiP98 and RPlanIT, as fully detailed above, in the infrastructures section (2.8.1)

1.9 Risk Assessment and Alternative Plans

The Project has been well calibrated on the accessible resources, however some possible and not fully predictable events could hinder the proposed plans. The facilities wre the experimental tests are supposed to occur, are the more impacted by this possible problems. We considered however possibl solutioms for thiese issues:

- CNAO's commissioning and radioprotection authorization for new Ions: The Radioprotection authorization for the use of new ions (Helium, Oxygen) in CNAO could take longer than expected, despite our network partners are already making efforts to speed up this process. In the case when the Irradiations with O and He beams will be not possible in time for the duration of the project, alternative solution can be the use of the HIT facility at Heidelberg (Germany), a facility with very similar characteristics as compared to the ones envisaged at CNAO. Moreover the TIFPA researchers have a long standing experience of irradiations and of previous plan verification exactly at the Heidelberg facility.

- Failure of Cofinancing of the pencil beam scanning at TIFPA: The implementation of a pencil beam nozzle at the TIFPA facility will allow maximum flexibility in the planning of proton beams for biological targets. The huge cost connected with this technical device (1.7 MEUR) could not be accounted in the present proposal and has been allocated to a different proposal. In case the latter expected funding will not be realized, there are several solutions for

alternative plans. Most irradiations will be realized with the passive scanning system and only those who really require an advanced modulation of the field could be either performed in the Gantry rooms of the APSS center, either with the proton beam at CNAO.

- Radiation resistance of silicon detectors exposed to therapeutic beams. The main risk in the use of UFSD silicon detectors for beam monitoring is related to the high radiation doses from therapeutic beams. The design of UFSD sensors has not been optimized yet for radiation resistance, and the measurements performed up to now indicate a stable behavior up to 1014 neq/cm2 for 300 um thick detectors (this corresponds to a few hours of a therapeutical proton pencil beam with an current of 1 nA and a FWHM of ~ 1 cm); at higher doses the internal gain of the sensors decreases and it is necessary to raise the bias voltage to keep a stable signal level. It is expected that the use of thinner sensors (50 um thickness) will decrease the trapping probability in the sensors, therefore extending the operative time. Intense work is currently going on in the UFSD community to increase the radiation resistance of the sensors. Several approaches as alternative dopants and doping profiles are being investigated with the expectation to reach a stable behavior up to >1015 neq/cm2 fluences in the next 1 or 2 years. Alternative designs for planar silicon sensor based on the current studies for the High Luiminosity-LHC will be considered as a backup solution in case the preliminary irradiation tests of UFSD sensors with therapeutical beams will show disappointing results.

1.10 Impact on Global Research and Horizon2020

The project is expected to have a very strong and broad impact on the international community researching in particle therapy, and for INFN in particular.

Specifically, it could help to enforce long-term collaboration between several INFN centers and the proton therapy center in Trento, CNAO and LNS, exploiting the the use of their growing experimental facilities.

Similar facilities are planned e.g. in USA (UniPenn), Europe (Krakow) and Japan, which are still in contact with our team and they may profit of the advances reached in this project.

The topics in adaptive particle therapy explored by the Project are highly relevant also in the framework of **European funding**.

In the framework of the **Horizon2020** Programme, several recently funded Calls demonstrate that Translational research in particle therapy, has been highly funded, especially those activities connecting basic physics (nuclear atomic and molecular) to a biomedical improverment. For the case of Hadrontherapy two recently funded calls have special relevance:

- ARGENT - Marie Curie ITN ("Advanced radiotherapies generated by nanoprocesses and technologies") based on the translation to clinical relevant implementations of basic physics research in radiotherapy, with a special regard to radiosensitization by Metallic nanoparticles and oxygen effect, with particle therapy.

- Nano IBCT –COST Action ("nanoscale insight in Ion Beam Cancer Therapy"): Focused in describing the mechanisms of dose deposition and biological effectiveness in particle therapy based on fundamental physics interactions.
- OMA – Marie Curie ITN ("Optimizing Medical Accelerator") on the advancing of accelerator facilities for biomedical applications

We remark that the development of novel silicon detectors with excellent timing capabilities is the subject of an ERC grant of the EU (UFSD ERC) to the INFN. Medical application of this technology is potentially eligible for future H2020 calls.

Therefore, the Project represents an ideal starting point to extend the application of the developed methods and devices in the field of TPS improvement and verification, in collaboration with European partners.

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