PROPOSAL FOR A COMMITTEE V
open CALL

NEPTUNE:
Nuclear process-driven Enhancement of Proton Therapy UNrav Eled

June 11, 2018

Principal investigator:

G Cuttone (INFN-LNS)

Working Packages responsibles

WP1, modelling: A Attili (RM3) and GAP Cirrone (LNS)

WP2, imaging and quantification: R Faccini (RM1) and S Bortolussi (PV)

WP3, microdosimetry: S Agosteo (MI)

WP4, radiobiology: L Manti (NA)

WP5, experimental activities: C La Tessa (TIFPA)

CALL type	Open
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Principal investigator	G Cuttone (INFN-LNS)
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Abstract

Protontherapy is an important radiation modality that has been used to treat cancer for over 60 years. In the last 10 years, clinical proton therapy has been rapidly growing with more than 80 facilities worldwide [1]. The interest in proton therapy stems from the physical properties of protons allowing for a much improved dose shaping around the target and greater healthy tissue sparing. One shortcoming of protontherapy is its inability to treat radioresistant cancers, being protons radiobiologically almost as effective as photons. Heavier particles, such as ^{12}C ions, can overcome radioresistance but they present radiobiological and economic issues that hamper their widespread adoption. Therefore, many strategies have been designed to increase the biological effectiveness of proton beams. Examples are chemical radiosensitizing agents or, more recently, metallic nanoparticles. The goal of this project is to investigate the use 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 [2], where a significant enhancement of biological effectiveness was achieved by the p-^{11}B reaction. Clinically relevant binary approaches were first proposed with Boron Neutron Capture Therapy (BNCT), which exploits thermal neutron capture in ^{10}B, suitably accumulated into tumour before irradiation. The radiosensitising effects due to the presence of ^{10}B will be compared to those elicited by p-^{11}B, using the same carrier and relating the observed effects with intracellular ^{11}B and ^{10}B distribution as well as modelled particle action and measured dose deposition at the micro/nanometer scale. Moreover, the p-^{19}F 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.

1 Scientific proposal status-of-the art and main goals

1.1 Status of the art

Cancer therapy is a multi-modality approach including surgery, chemotherapy (systemic or targeted), radiation (by external beams or through radionuclide incorporation) and immunotherapy. Conventional radiotherapy is typically administered using external photon or electron beams. The concept of using protons in radiotherapy has been around for more than 60 years, but remained confined to research laboratories until the 1990s. Since then, clinical proton therapy has been growing rapidly counting nowadays more than 80 facilities worldwide [1]. The rationale underlying the use of protons in radiotherapy stems from their physical properties, i.e. the inverted dose-depth profile as described by the Bragg curve, which grants a much improved dose shaping around the target and greater sparing of healthy tissue/organs at risk. In the last decades, research efforts in the field of conventional radiotherapy have reduced the dosimetric gap between photons and protons in terms of tumour conformation. Nevertheless, significant accomplishments have marked advances in proton therapy over the same period. Although it can be envisaged that technological developments will continue to improve the dose profiling achievable with photon therapy, the latter cannot be expected to fully match the dosimetric advantage offered by protons since the integral dose difference cannot be overcome. This is of particular relevance, for instance, for paediatric cancers, where the overall integral dose released to the healthy tissue and/or sensitive organs is by far too large to yield acceptable second cancer risks even by one of the most advanced conventional radiotherapy approaches, Intensity Modulated RadioTherapy (IMRT) [3]. In addition, as we are just starting to use the dose-shaping capabilities of Intensity Modulated Proton Therapy (IMPT), the advantage in dose profiling offered by proton therapy is likely to increase. However, one of the shortcomings of proton therapy resides in its limited capability to locally control radioresistant cancers. Radiobiologically, protons are almost as effective as photons. This is because the biological outcome of cellular irradiation strongly depends on the physical

pattern of energy deposition at the nanoscale level (e.g. DNA). The greater the ionisation density (described by the Linear Energy Transfer-LET), the more severe and less repairable the induced damage is as a result of a higher degree of spatio-temporal clustering of DNA lesions. This, in turn, is translated into a greater Relative Biological Effectiveness (RBE), e.g. more cell killing per radiation dose. Cancer cell resilience to radiation is a manifold process (driven by genetic make-up, hypoxia, etc) leading ultimately to treatment failure. Heavier particles such as ^{12}C ions can overcome such radioresistance because they are densely ionising. Several radiobiological uncertainties, concerning the late effects of sublethally damaged healthy cells and cell signalling-mediated modifications of the tumour microenvironment, persist that, coupled with economical issues, hamper ^{12}C-based hadrontherapy wider adoption [4, 5]. In the last years, therefore, many strategies have been designed with the aim of increasing the biological effectiveness of light hadron beams. Possible methodologies investigated chemical radiosensitizing agents or, more recently, electromagnetic-driven enhancement of local dose through high-Z metallic nanoparticles. All these approaches additionally attempt to exploit energy-dependent mechanisms in order to differentiate conveniently between healthy tissue (entrance channel) and tumor (target). As far as local enhancement of a primary incident radiation beam is concerned, Boron Neutron Capture Therapy historically represents the first *binary* treatment approach, exploiting a nuclear fusion reaction, namely n+^{10}B, in the attempt to increase the energy released within the tumour [6, 7, 8]. In this project, we will investigate new *binary* approaches to improve the proton therapy effectiveness. The main concept at the base of such techniques is the exploitation of nuclear reactions triggered by the protons themselves and able to generate short-range high-LET particles, causing a highly local damaging action. The recent data published in [2] show, in fact, that a significant enhancement of protons biological effectiveness can be achieved by exploiting the p-^{11}B reaction: using a carrier also known in BNCT, i.e. sodium borocaptate (BSH) an increase in cell killing and DNA damage was measured at the mid-SOBP of a clinical proton beam. The maximum cross section for such a reaction occurs at low proton energy, corresponding to the tumour region

where the incident proton beam slows down. This would in principle eliminate the constraint of a differential uptake of the carrier between normal and cancer cells as needed in the BNCT because of the n-^{10}B reaction being triggered by thermal neutrons.

The promising results obtained with the p-^{11}B reaction prompted the interest in the investigation of another proton-driven reaction, i.e. p-^{19}F, the rationale for which being twofold: the production of high-LET particles similar to the p-B reaction products (which would enhance proton biological effectiveness) and the high selectivity to tumors if attached to a ^{19}F carrier, such as. the FDG-3 enzyme (minimizing detrimental effects on healthy tissues). If proven pre-clinically viable, these innovative approaches will not only lead to extend the range of tumours curable with proton therapy but also act as a driving force toward hypofractionation, with consequent relevant societal impact.

1.2 Main goals and methodology approach

Charged particle inverted dose-depth profile represents the physical pillar of protontherapy. Reduced integral dose to healthy tissues entails lessened risk of adverse effects. On the other hand, there is no obvious radiobiological advantage in the use of protons since their LET in the clinical energy range (a few keV/micron) is too low to achieve a cell killing effect significantly greater than in conventional radiotherapy. A well-known relationship links physical radiation quality (LET) and its biological effectiveness (RBE). As ionization density increases, so does damage complexity, because multiple locally damaged sites arise, among which double-strand breaks (DSB). Highly spatio-temporally related DSB are poorly repairable and lead to increased cell death. Historically, the first approach to predict a tumour-confined increase of radiobiologically effective dose by irradiation with a primary beam is Boron Neutron Capture Therapy (BNCT), which exploits the n + ^{10}B $\rightarrow \alpha$ + ^{7}Li reaction, occurring with a cross section of 3837 barn. Here, thermal neutrons trigger short-range high-LET particles. In this case, the dose deposited in the tumour is mainly due to the neutron capture reaction in ^{10}B, while surrounding tissues potentially healthy are substantially spared. In light of this, two other

binary approaches have been proposed that exploit the $p + {}^{11}B \rightarrow 3\alpha$ and $p + {}^{19}F \rightarrow \alpha + {}^{16}O$ reactions. A schematic representation of this new approach is reported in Figure 1.1.

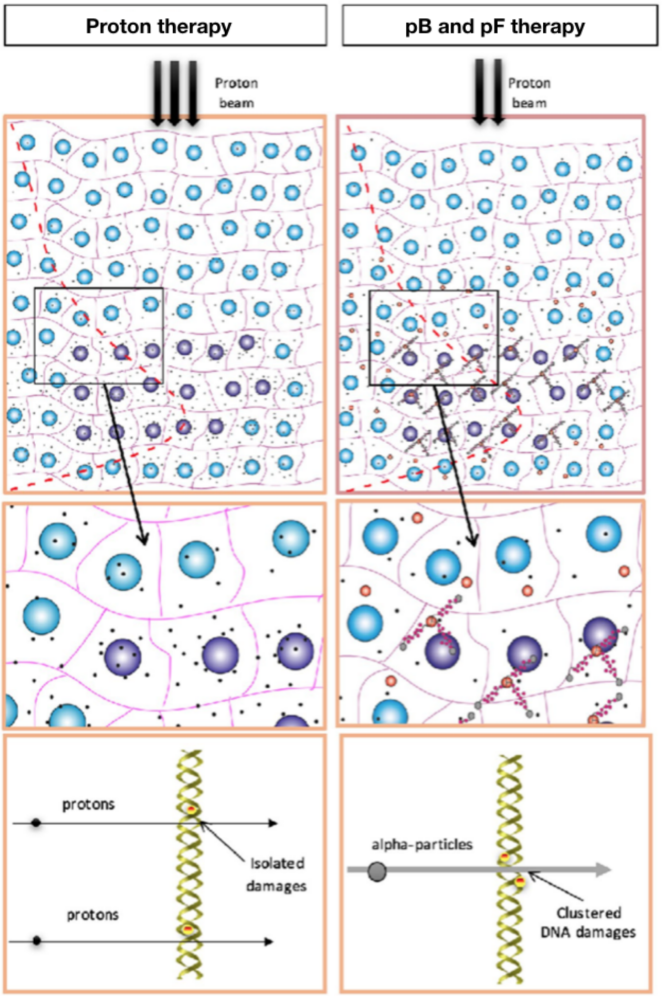


Figure 1.1: Schematic representation of *conventional* radiotherapy by low-LET proton beams (left) and the rationale for boron/fluorine-enhanced protontherapy (right)

1.2.1 Physical considerations about the PBCT

The proton-boron nuclear reaction considered is formalized as $p + {}^{11}B \rightarrow 3\alpha$. It has a positive Q-value (8.7 MeV) and is referred to as *proton-boron fusion reaction*. This reaction has gathered

interest because of the process ability to produce copious numbers of alpha particles in an exothermic reaction. According to the literature, the p-B nuclear fusion reaction shows three resonant energies and can be described as a two-step reaction in which three alphas are produced. A proton interacting with a ^{11}B nucleus induces the formation of a $^{12}C^*$ compound nucleus formed in the 2- or 3- excited state. ^{12}C* then decays in one alpha particle and one ^{8}Be that, in turn, immediately decay in two secondary alpha particles. The emitted alpha particles exhibit a wide energy spectrum with a predominant energy around 4 MeV. Such a reaction has been considered very attractive for the generation of fusion energy without producing neutron-induced radioactivity. As said above, the p-B fusion reaction is expected to play a strategic role in medical applications improving the effectiveness of protontherapy. The relevance of this method stems from the fact that the fusion reaction cross section becomes significantly high at relatively low incident proton energy, i.e. around the Bragg peak region. In light of this, we proposed to exploit the p + ^{11}B $\rightarrow 3\alpha$ reaction, whose cross section resonates at 675 keV as reported in Figure 1.2.

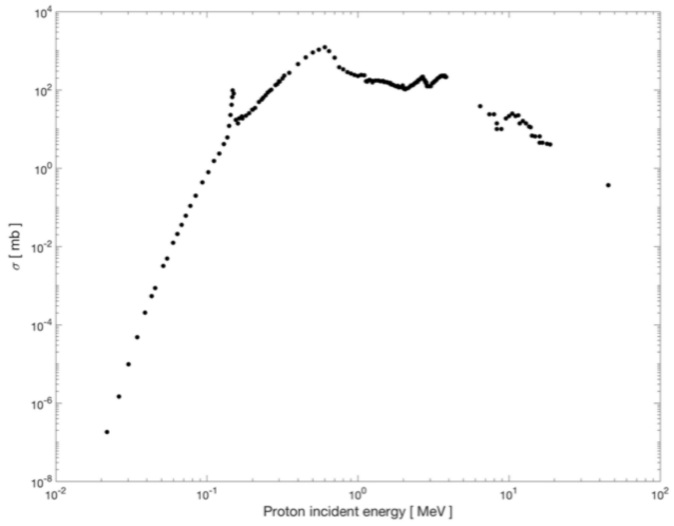


Figure 1.2: Experimental cross sections. Proton-^{11}B total reaction cross section for the most probable α_1 channel decay (from EXFOR database).

In protontherapy such energies are those of protons as they slow down across the tumour region. The latter eliminates the requirement for selective boron uptake by cancer cell as alpha particles will be not generated, in principle, in healthy tissues where incident proton energy is too distant from that of the cross-section maximum; together with the growing number of protontherapy centers, this elegantly bypasses the main drawbacks of BNCT. Using a compound employed in BNCT, BSH or sodium borocaptate ($Na_2B_{12}H_{11}SH$), we experimentally demonstrated for the first time that proton biological effectiveness is indeed augmented by the presence of the ^{11}B carrier [2]. Specifically, we exposed cancer cells at the 60-MeV CATANA protontherapy beamline (LNS-INFN) and measured an increase in cell death in BSH-treated samples: the dose-modifying factor (DMF) for 10% level of cell survival was about 1.46; that is, the presence of BSH reduced the dose of protons necessary to kill 90% of cells by almost a 0.7-fold factor. Moreover, BSH-treated cells following proton irradiation yielded a significantly higher proportion of complex-type Chromosome Aberrations (CA) compared to cells irradiated in the absence of ^{11}B. Such CA represent a hallmark of high-LET radiation exposure, strongly implying the observed enhancement of proton-induced cell killing be due to the densely ionising alpha particles generated by the p-B reaction.

1.2.2 Physical consideration on p-^{19}F

The p-F reaction could have an application similar to that suggested for p-B. In Figure 1.3 the scheme of the reaction of protons with ^{19}F nuclei is shown. The physical effectiveness in terms of cross sections for producing low energy recoil particles is in fact comparable. Specifically, as visible in Figure 1.4, the two processes are behaving similarly in an energetic region where the protons are mainly distributed in the Bragg peak region, with a cross section close to 1 barn, and both are decreasing at increasing energy, although for the latter literature data are incomplete. The specific advantage of considering the p-F reaction, is that these nuclei can be carried by several bio-compatible molecules. One example is the ^{19}F-FDG (unmarked fluoro-deoxy-D-glucose), which is basically a substitute of glucose, with an OH group replaced

by an F nucleus, hence with a high sustainability in tissues. In fact, FDG, especially in its marked ^{18}F form, is a commonly used tracer in Positron Emission Tomography (PET). In low concentrations, because of the presence of the marked isotope, it is widely used as a functional PET-based imager of metabolic activity for tumor delineation (see e.g. [9]). In its normal form (^{19}F), it is also used as NMR (Nuclear Magnetic Resonance) probe [10]. Thus, the possibility to increase the concentration, especially in the isomer 3-FDG (F replacing the OH in position 3 instead of 2) up to 5 mg/g should lead to larger yields, overruling small differences in cross sections.

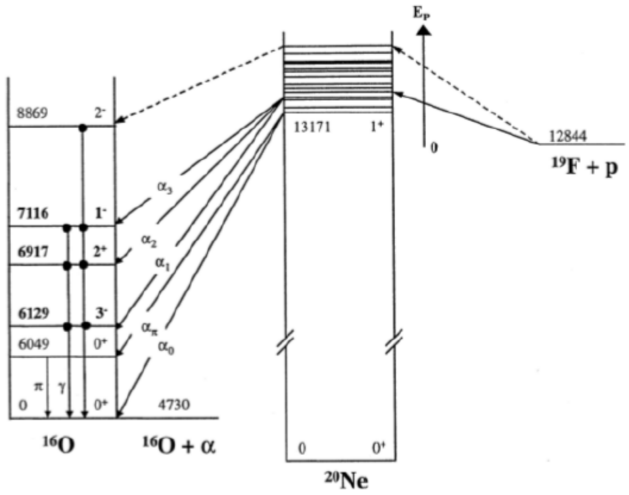


Figure 1.3: Scheme of the ^{19}F+p reaction.

Another relevant difference with the p-B process is that the peak of the energy spectrum of the generated alphas is shifted to higher values (up to 13 MeV) thus generating secondary tracks able to traverse multiple cells. Thus, despite a production of a lower number of alphas per event (3 particles are produced in the p-B reaction) the killing action of the p-F generated particles can be larger. As a further advantage, this molecule, can potentially used for beam monitoring through the specific gamma emission, as being explored in a parallel project by one of the coworkers. Although measurements (already performed and currently ongoing) demonstrated a significant increase in the primary proton beam radiobiological effectiveness,

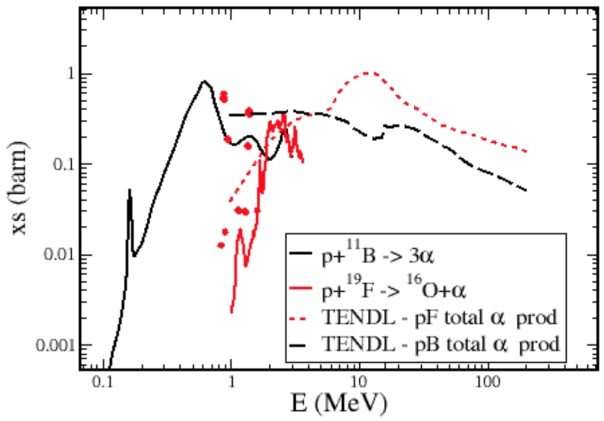


Figure 1.4: Comparison of cross sections for alpha production of the 2 different processes exploited in the NEPTUNE project.

the precise interpretation of such results is still lacking.

1.2.3 Physical consideration on BNCT

Boron Neutron Capture Therapy is based on the reaction of low-energy neutrons with ^{10}B producing two high-LET, short-range particles: a ^{7}Li ion and an alpha particle. The particles coming from the neutron capture in ^{10}B have two possible energies: alpha can be emitted at 1.47 MeV (94%) or 1.78 MeV (6%) and ^{7}Li at 0.84 MeV (94%) or 1.01 MeV (6%). Dose deposited by BNCT entails a complex evaluation because it depends on four different radiation components: products of neutron capture in ^{10}B, protons coming from neutron capture in nitrogen, neutron scattering in hydrogen and gamma radiation coming from neutron capture in hydrogen and from the primary beam. Thus, the total absorbed dose is contributed to by different components, which have in fact different effects in biological tissues. Typically, dose in BNCT is given by a weighted sum, using as weights the RBE values obtained by radiobiological experiments for each component.

1.2.4 Radiobiology and microdosimetry

The observed increase in the amount of BSH-associated cell death and DNA damage in proton-irradiated cells cannot be explained simply considering the calculated yield of the produced secondary, and such a possibility can be reasonably expected for p+^{19}F, too. Strong circumstantial evidence in fact points to the high-LET alpha-particles generated in the p-B reaction being responsible for the observed effect as shown, for example, by the increased proportion of complex-type chromosome aberrations per radiation dose measured in the BSH-treated samples compared to samples irradiated by protons only. However, the magnitude of the increase in cell killing does not quantitatively reconcile with the excess absorbed dose expected on the basis of the calculated number of alpha-particles yielded for the reaction cross section at the used proton energies. It is therefore important to invoke other physical and/or biological factors. It is currently accepted that it is exceedingly simplistic to interpret radiation biological action at the DNA level, i.e. on a submicrometric scale, solely on the basis of macroscopic concepts like the absorbed dose or the average LET distributions. This is due to the intrinsically inhomogeneous nature of energy deposition events along radiation tracks, which becomes more significant as ionization density increases. Moreover, the increased biological effectiveness (RBE) of high- versus low-LET radiation is thought to stem from the increased severity of DNA damage, and thereof poor repairability, resulting from a greater number of clusters of ionization events. This leads to DNA clustered lesions (CL), which encompass locally multiply damaged sites the cellular repair system fails to restore. Therefore, micro- and nano-dosimetric approaches are needed to take into account such effects because for the close relationship between the induction of CL and the degree of ionization clustering in sub-micrometric volumes, microdosimetry and nanodosimetry measurements may help to understand whether the measured ionization-cluster distribution under the experimental conditions of cellular irradiation is consistent with the observed enhancement in the biological effects for varying concentrations of boron and fluorine. An additional insight that may arise from radiobiology studies concerns the possible contribution of the so-called non-targeted

effects. The long-standing DNA-centric tenet of radiation cellular effects arising only if a cell is physically *hit* by radiation has been disputed in the last 20 years by a wealth of in vitro and in vivo evidence for so-called non-targeted phenomena, e.g. the bystander effect. In the latter, cells that have not been traversed directly by radiation tracks may manifest cytogenetic damage, even at later times among their progeny (radiation-induced genomical instability), such effects being peculiarly observed at very low doses, i.e. when a small fraction of a cell population is bound to be actually irradiated assuming a Poisson probability distribution of nuclei traversals. Therefore, understanding of the processes associated with the binary strategies studied here requires multi-level experimental and theoretical approaches to fill the conceptual gap between the underlying physics and the biological outcome.

1.2.5 Fluorinated compounds imaging techniques

Based on the experience from BNCT, it is safe to assume that also boron/fluorine-mediated radiosensitization will depend critically on the carrier concentrations that can be achieved in the target nuclei. Hence, following a punctual determination of the carrier accumulation within the cellular samples subject to irradiation to determine in vitro enhancement of proton biological effects, when the techniquel enters clinical routine, such carrier concentration will have to be ascertained in vivo on a patient-by-patient basis. This calls for the development of imaging techniques optimized for the tracers of interest. Furthermore, knowledge of the bio-kinetics of the pharmaceuticals allows to optimize the time between preparation of the cell culture and irradiation. We plan to setup tests to assess the biokinetics of tracers on mice models of pancreas tumors. To this aim, PET/SPECT imaging would allow to test concentrations up to ~ 10-16 Moles/ml, while those required for sensitization are eleven orders of magnitude larger. We therefore suggest to exploit the fact that the gyromagnetic factor of ^{19}F is close ^{1}H to perform Magnetic Resonance Imaging (MRI) of the distribution of ^{19}F. The absence of intrinsic ^{19}F signals in living tissues allows indeed in vivo visualization of fluorinated tracers, with a signal-to-noise ratio (SNR) close to that of ^{1}H MRI, even with only

~ 1mMole/ml. Nonetheless, the limit of MRI with ^{19}F is the relatively high concentrations required to have a good SNR. Since the limiting factor is the electronic noise of the RF emitting and receiving coils and the corresponding readout chain, this project can give a significant contribution. We therefore propose to develop a test stand for SNR optimization in ^{19}F MRI, exploiting the expertise in RF antennas from accelerator physics, in low signals detection in high background from gravitational waves studies and in multivariate analysis applied to imaging from high-energy physics experiments.

1.3 Research group description

Neptune is based on eight participating Units and five Working Packages (WP). A representation of the conceptual links and workflow between such WP is reported in Figure 1.5.

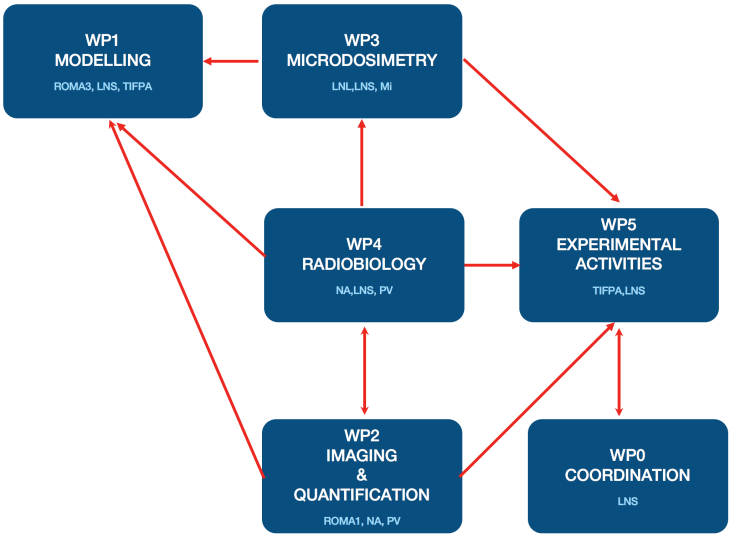


Figure 1.5: Sketch of project WP and their relations: the arrows direction indicates the correct information flux.

The role in the Project of the participating Units is detailed in the following sections. Neptune will focus on the characterization of the p-^{11}B and the p-^{19}F reactions in all their relevant aspects: from modelling (using analytical and Monte Carlo approaches), to microdosimetry and radiobiology. In parallel, novel imaging technologies needed for the tracer biodistribu-

tion studies will be developed. It is readily seen as such tasks, organized in WPs, are closely connected: verification of the methodology feasibility for possible clinical applications requires radiobiological demonstration of the enhancement of proton biological effectiveness by quantifying the excess cell death and DNA damage caused by the p-B and p-F reactions (WP4 where INFN-NA and INFN-LNS are involved), such data feeding and being crucially interpreted by the modellization studies based on the cross section-dependent expected yield of alpha particles (WP1, where INFN-LNS, INFN-RM3 and INFN-TIFPA are involved) for the measured optimal intracellular concentration of the boron and fluorine carriers (WP2 where INFN-RM1, INFN-PV and INFN-NA are involved); the latter, in turn, will be used to verify the accumulation pattern in the organ of choice for imaging purposes using an ex-vivo system (WP2), which mirrors that used in vitro (WP4). Moreover, since the working hypothesis at the core of the binary approaches here investigated is that the secondary ions produced by the nuclear reactions bring about their action by causing highly localized clustered DNA lesions, WP4 will measure clustered damage-specific biomarkers to provide indirect proof that the observed effects are ascribable to such damage clustering, which must reflect a distribution of the ionization events at the sub-micrometric scale as measured by WP3 (where INFN-MI, INFN-LNL and INFN-LNS are involved). The WP5 (INFN-TIFPA) will coordinate all experimental and theoretical activities.

1.4 External contributes

The project involves national and international universities and research institutions: the Institute of Molecular Bioimaging and Physiology (IBFM), the Institute for Microelectronics and Microsystems (IMM) and the Institute for Complex System (ISC) of the CNR; the University of Wollongong (UoW), Australia; the University of Naples (UNINA), the University of Campania (UNICAMPANIA); the Istituto Superiore di Sanità (ISS), the Treatment Planning and Computational Dosimetry group of CNEA, Argentina and, finally, the Bruno Kessler Foundation (FBK) of Trento. IBFM will be involved in radiobiology, contributing to the study of direct and indirect

effects of ionizing radiation. The UoW will support this project in Monte Carlo simulations on micro- and nano-scales with Geant4 and Geant4-DNA. UNICAMPANIA and UNINA will perform radiobiology studies to determine data to better understand the processes involved in particle interaction. ISC will contribute to the monitoring of the pharmacokinetics and tissues uptake of ^{11}B and ^{19}F enriched carriers. Moreover, the ISC will study together with the INFN Sapienza new strategies to improve the signal-to-noise ratio of NMR images realized using the ^{19}F signal. The CNEA will give its contribute in the simulation of BNCT dose components and in the connection between BNCT and proton-B/F issues. The ISS will be involved in the molecule quantification on in vivo model. The UoW and the FBK will be involved in the WP3 (microdosimetry) for the simulation studies of boron and fluorine ions implantation on CR39 nuclear track detectors. The CR39 Boron/Fluorine doped will be used as a new and innovative detector for alphas measurement. IMM and UoW will realise a complementary ad-hoc microdosimetric detector equipped with a 11B-enriched slice that will act as converter in the p-11B reaction. The detector of UoW will be offered at a discounted price (see offer) and the UoW guarantees all the necessary support for the data taking and analysis.

1.5 Past or current projects fundend on similar topics

Neptune is conceived within a line of research in medical physics that INFN has been funding for years. The Committee V, in particular, funded, in the last years, projects able to catalyze and improve the knowledge in the medical physics field. Among these, TPS (Treatment Planning System) and RDH (Research and Development in Hadrontherapy) MOVE-IT (Modeling and Verification for Ion beam Treatment planning)were/are mainly devoted to the development of computational approaches for the evaluation of the radiobiological damage with ion beams and to the corresponding verification. The MITRA, NADIR, NIRVANA and MC-INFN projects investigated the Monte Carlo aspects related to the microdosimetric calculations and measurements. Finally, MIMO-BRAGG and ETHICS were two radiobiological-addressed experiments focused on the studies of the heavy ion and proton damage on tumour and healthy tissues.

The first of the binary therapies ever studied is BNCT, studied in Pavia Unit since the Eighties. Neptune aims at widening research in the field of innovative radiotherapies based on binary approaches, with the idea of harmonizing the efforts of the scientific community in Italy. Following is a list of projects funded in the last 5 years. They are all related to BNCT and to developments useful also in other applications, such as imaging for diagnosis.

- INFN project NEU_BEAT, 2016-18 funded by MAECI-MOST - Scientific and technological cooperation agreement between Italy and China (NEUtron BEam for cAncer Therapy)
- Dipartimenti d′Eccellenza: Dept of Physics, University of Pavia
- INFN - CNS5: BEAT_PRO 2017-to date (BEAm Tailoring and PRocedures Optimization for BNCT)
- INFN - CNS5 young grant experiment 3CATS - 2017-18
- INFN *Progetto Premiale* MUNES (MUltidisciplinary NEutron Sources)
- INFN- CNS5 NETTUNO 2014-16 (NEutron capture therapy of Thoracic TUmours with New fOrmulations)
- INFN - CNS5 experiment WIDET 1 2012-2013 (WIDESpread tumours BNCT)

Figure 1.6 show the overview of the main internal and external projects funded in the last ten years on topics related to the NEPTUNE call.

1.6 Description of the impact and effects of this research

Neptune will offer the opportunity to explore a number of physical, chemical and radiobiological aspects associated to the processes induced by charged particle beams, permitting to deepen our understanding from different perspectives, which are particularly relevant for potential future clinical applications. Our research may pave the way towards similar binary approaches where other nuclear reactions will be studied to either potentiate the action of

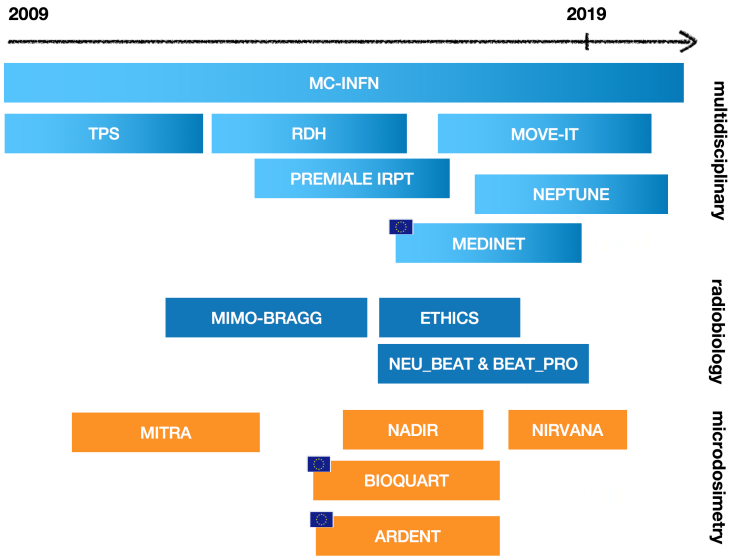


Figure 1.6: Projcts funded internally and externally the CSN5 and related to the topics of NEPTUNE; The different research fiels are also indicated.

primary external beams or exploit them to improve medical imaging, or both, as is the case proposed by us. Establishing nuclear reaction-based binary approaches as a clinically viable strategy to potentiate proton radiobiological effectiveness would have, in fact, a profound scientific and social impact, in addition to being an elegant example of bringing together apparently distant fields such as nuclear physics and radiotherapy. Much is still needed to fully understand particle radiobiology. Independent research lines, based on Monte Carlo simulations and on experiments investigating radiation chemistry (e.g. intra-track generation of reactive oxygen species or ROS) as well as biomolecular pathways set in motion by the interaction of ionising radiation with living matter point to the role played by the physical processes underlying the energy deposition patterns and how these influence the biological outcome of cellular irradiation. The Project will constitute an important advance because it will entail the elaboration of models capable of explaining the observed enhancement of a low-LET radiation by high-LET secondary products. Models will have to take into account the expected yield of high-LET particles, the measured ^{11}B/^{19}F concentrations and the radio-biological parameters derived from experimentally constructed dose-response curves, and

reconcile them within micro/nano dosimetric considerations. From a social viewpoint, the potentialities of a more effective protontherapy (PT) are self-evident: this would enormously benefit patients because it will allow to extend PT to include diseases that currently suffer from poor prognosis and also allow to improve the treatment of those for which PT protocols are already in place without increasing the risk of recurrences/complications. Increasing biological effectiveness in proton therapy will be of interest also from a ballistic physical point of view for those situations where the tumour is placed close to organ(s) at risk and the use of other particle beams that produce projectile fragmentation (e.g. ^{12}C ions) would cause unwanted dose deposition eliciting several side effect. Skull base and cervical spine chordoma, soft tissue and bone sarcoma, skull base meningioma, paranasal sinus carcinoma, uveal melanoma, thoracic spine-sacrum tumours are clinical examples of tumors where PT ensures a dosimetric superiority over photon beams, through reduction of the integral dose and the dose to organs at risk. In a future scenario where proton therapy will have greater biological effectiveness, the current resistance to its extended clinical use will be certainly overcome, thanks also to the greater diffusion of hypofractionated treatment protocols. Pediatric tumors of the central nervous system (medulloblastoma, ependymoma, dysgerminoma, glioma), pediatric rhabdomyosarcomas, located in the head-neck region (in the parameningeal or orbitary region), in the genito-urinary region (bladder-prostatic or para-testicular), Ewing's sarcomas and also pediatric tumors of the renal and pararenal region (Wilms and neuroblastoma), are all examples of tumors to be treated only with PT, if clinical-biological gain couples with the current one, of a more strictly dosimetric type. On these grounds, it is evident that the cost impact of such a new approach could be enormous: the possibility to use proton beams also for radioresistant tumors avoiding more complex technique and/or therapy, will be extremely advantageous from both economically and clinically .

1.7 Risk assessment and risk reduction

1.7.1 WP1 (modelling) and WP3 (microdosimetry)

The main risk related to these WPs is that the detectors will not be able to reproduce the field of secondary alphas, due to the low count of these particles. The contingency plan is to increase the ^{11}B concentration in the detectors converter with respect to those already available. To achieve this goal the steps are: 1) MC simulations for calculating the concentration giving a measurable count rate; 2) perform irradiation with a silicon microdosimeter coupled to a pure B target and compare results with Monte Carlo.

1.7.2 WP2 (imaging and quantification)

The imaging activities of WP2 have two main objectives: developing a technique to estimate the concentration of Boron and Fluorine carriers and optimizing the MRI with ^{19}F for to future bio-kinetic studies. The main risk related to the concentration is that the chosen tracers release a signal difficult to detect with ^{19}F-MRI. This can be either caused by the uptake mechanism or by the experimental conditions. For instance, BSH is known not to enter the glioblastoma cells, making the NMR relaxation times difficult to detect. As a mitigation, different tracers can be developed by the chemists included in the team, that can enhance the signal by adding ^{19}F atoms to the composite, or try other carriers (fluorinated boronophenylalanine for Boron or penta-fluorinated phenylalanine for Fluorine carrier). The ex-vivo tests are planned to take place at the Istituto Superiore di Sanità with implantation of the tumors in the pancreas. As a contingency plan, the CAPIR facility in Catania is available. The ^{19}F-NMR electronic and signal processing optimization will bring together the expertise available within INFN to build an open-access system where optimization studies can be carried out. We identified a low field (0.25T) system on which both the antenna and the receiver can be implemented. The risk is that the state-of-the-art benchmarks are achieved with industrial devices for which implementation details are protected. On the other side, we have the support of one of the

producing company (Bruker) supporting us in the project. As a mitigation, we will make all the necessary arrangements with the company to obtain the needed information.

1.7.3 WP4 (radiobiology)

The radiobiological experiments planned in the WP4 are exposed to the typical risks related with the use of biological systems (contamination resulting in the partial or total loss of samples, lack of reproducibility leading to insufficient statistical robustness). Indeed, delivery of meaningful results strongly depends on beam time availability to adequately repeat measurements. The contingency plan is to envisage multiple replicates treated as independent samples within each experimental session and to use alternative facilities. The variability of biological response may also result in sub-optimal uptake or exceedingly high cytotoxicity of one or both the carriers, a risk that is shared with WP2 . Risk reduction may be achieved using alternative compounds such as BPA (for ^{11}B), and ^{19}F-labelled phenylalanine as highlighted above for WP2.

1.8 Link with future regional/national/european and international tenders

The project is expected to have a very strong and broad impact on the international community engaged in particle therapy research and for INFN, in particular. Specifically, it could help enforce long-term collaboration between several INFN centers and the proton therapy center in Trento, CNAO and LNS, exploiting the use of their growing experimental facilities. Similar facilities are planned e.g. in USA (UniPenn), UK, and Japan, which are in contact with our team and may profit from the advances reached in this project. The topic of improving particle therapy effectiveness , explored by this Project, is highly relevant also in view of European funding. In the framework of the Horizon2020 Programme, translational research in particle therapy has proved particularly successful, as shown by the high rate of recently funded projects , especially those connecting basic physics (nuclear atomic and molecular) to a biomedical improvement. In hadrontherapy , three recently funded calls have special

relevance:

1. 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 special regard to radiosensitization by metallic nanoparticles and targeting the oxygen effect, with particle therapy.

2. Nano IBCT - COST Action (*nanoscale insight in Ion Beam Cancer Therapy*): Focused on describing the mechanisms of dose deposition and biological effectiveness in particle therapy based on fundamental physics interactions.

3. OMA - Marie Curie ITN (*Optimizing Medical Accelerator*) on the advancing of accelerator facilities for biomedical applications.

In conclusion, this project represents an ideal starting point to improve and extend the application of the developed methods in the field of cancer treatment improvement in collaboration with European partners.

2 Project Global Organisation: Working package division

2.1 WP0: project coordination

Responsible: G Cuttone (INFN-LNS)

The objectives of the WG0 are:

1. Coordinate and streamline the Project;

2. Organize project management meetings and workshops to monitor progress of each technical WP and evaluate advancements and risk management;

3. Facilitate flow of information between partners and coordinate all activities according to the work plan;

4. Stimulate Transferable Technology (TT) and patenting

5. Establish an interface with INFN for reporting and administration.

Two tasks have been identified:

1. **T0.1- Management:**

   The Project Coordinator will establish a Management Committee, formed by the WP leaders and Unit coordinators. Periodical meetings will be organized in which team members will be asked to report about the main advancements of the Project. In such meetings, the achievement of key milestones will be critically assessed, particularly with respect to a Risk Management Plan based on what reported. The Committee will be responsible of organizing every year a two-day collaboration meeting in which team members and young researchers will give presentations about performed work. The meeting will include selected invited lectures from prominent scientists in the field, as well as collaborators from international institutes. The intellectual property plan presented below will be re-assessed and implemented to properly manage the results obtained through the Project and the possible industrial/commercial applications. Patenting and non-disclosure agreements will be considered whenever necessary for sensitive data.

2. **T0.2- Dissemination and TT:**

   A results dissemination program addressed both to the scientific community and the broad public will be implemented, which will include: i) Project webpage; ii) Publication in (scientific journals, presentations to international conferences; iii) Information to general public via press releases, interviews and the project webpage.

Milestones		
	Month	Description
M0.1	1-6	WPs management agreement (Report)
M0.2	1-7	Project web-site
M0.3	12	Collaboration meeting
M0.4	24	Collaboration meeting
M0.5	36	Collaboration meeting

Deliverables		
	Month	Description
D0.1	12	Status report
D0.2	24	Status report
D0.3	36	Status report

Personnel		
Name	Title, Institution	FTE(%)
Giacomo Cuttone	Direttore di ricerca, INFN-LNS	50
Pablo Cirrone	Ricercatore, INFN-LNS	10

![h]

2.1.1 Milestones, deliverables and human resources

2.2 WP1: modelling

Responsibles: A Attili (INFN-Roma3); GAP Cirrone (INFN-LNS)

The main aim of the WP1 is the investigation of the radiobiological role of the alpha particles produced in the p+^{11}B→3α and p+^{19}F→^{16}O+α by means of computational modelling. Other reaction channels and the production of all secondary fragments will be evaluated and considered, as well. This task will be carried out via the implementation of three approaches.

First approach The experimental set-up used at INFN-LNS will be simulated with Geant4 [11] to estimate the particle spectra generated by the nuclear reactions. The spectra will be used as an input for the radiobiological simulations based on the microdosimetric kinetic model (MKM) [12], which is currently clinically used in hadrontherapy [13, 14] and BNCT [15]. The MKM has been also implemented in a code by INFN-TO/Roma3 [16]. Links with other WPs:

1. The simulated spectra will be compared with the microdosimetric data (WP3).

2. Information about the B and F cellular uptake (WP2) will enable the survivals calculations to be compared with the measurements (WP4).

Second approach Radiochemical processes could play a relevant role in nuclear-based enhanced proton-therapy [17]. In a refinement of the modelling, a chemical-physics characterization of the reactive species following p+^{11}B and p+^{19}F reactions, will be carried out via two MC codes, Geant4-DNA [18] and TRAX-CHEM [19].

Links with other WPs:

1. The results of the simulations will be compared with the ROS measurements, (WP4).

2. The simulation of the reactive species will be related with the measured rate of DSBs, CAs and foci (WP4) (see Figure 2.1). These results will be used to tune the model to improve the agreement between predictions and observations.

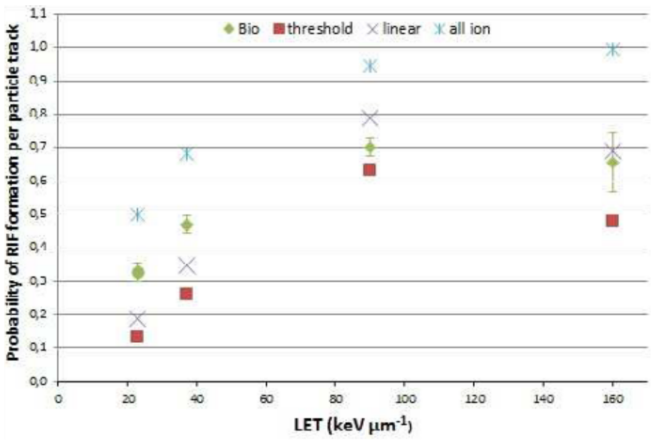


Figure 2.1: Example of radiation-induced foci probability (RIF) per track evaluated via Geant4-DNA simulations with different criteria of DSB formation. Experimental data of 53BP1 foci are reported with green circles for proton and green diamonds for alpha particles. From [51].

Third approach In order to better reproduce the experimental data, other indirect mechanisms such as non targeted effects (NTEs) will be implemented in the MKM [20]. Links with

other WPs: The predictions will be compared with the bystander measurements (WP4).

BNCT simulations The dose delivered to cells will be simulated with MCNP in which the reactor has been modelend and the irradiation position has been fully characterized for neutron flux and for gamma dose. Cell survival experiments are modelled and each dose component calculated in the cell layer, taking into account the boron concentration.

2.2.1 Milestones, deliverables and human resources

Milestones		
	Month	**Description**
M1.1	6-12	Integration of the simulated spectra evaluated in M1.1 in the MKM
M1.2	18-24	Inclusion of the bystander effect in the simulations developed in D1.1 and M1.1
M1.3	24-30	Comparison between simulation data D1.1 and experimental data taken by WP2. Inclusion of the experimental data (cell survival) in the radiobiological simulations
M1.4	24-30	Comparison between simulation data D1.1 and experimental data taken by WP2. Inclusion of the experimental data (cell survival) taken by WP4
M1.5	30-36	Comparison between simulation data D1.1 and experimental data taken by WP2. Inclusion of the experimental data (ROS production) taken by WP4
M1.6	30-36	Comparison between simulation data (D1.1, M1.3, D1.2 and M1.5) and experimental data taken by WP2. Inclusion of the experimental data (cell survival, DSB,CA,foci) taken by WP4
M1.7	30-36	Comparison between simulation data M1.3 and experimental data taken by WP2. Inclusion of the experimental data (cell survival, DSB,CA,foci) taken by WP4

Deliverables		
	Month	**Description**
D1.1	1-6	Implementation of MC simulations (Gean4) for p+11B and p+19F nuclear reaction spectra generated in the experimental setup
D1.2	12-18	Implementation of Geant4-DNA and TRAX-CHEM simulations starting from the spectra obtained in (1.a)

Personnel		
Name	**Title, Institution**	**FTE(%)**
Andrea Attili	Ricercatore, INFN-RM3	40
Pablo Cirrone	Ricercatore, INFN-LNS	10
Giada Petringa	Dottoranda, INFN-LNS	30
Elettra Bellinzona	Assegnista, INFN-TIFPA	20
Francesca Ballarini	Professore Associato, UNIPV - INFN PV	30
Silva Bortolussi	RTDb, UNIPV - INFN PV	10

2.3 WP2: imaging and quantification

Responsibles: R Faccini (INFN-Roma1); S Bortolussi (INFN-PV)

WP2 plans to assess the distribution and kinetics of tracers in cell cultures and mice (**Task 2.1**) models. Coherently with WP4, the B and F carriers are BSH and FDG-3 respectively. The cell line considered is PANC-1. As far as in-vivo tests are concerned, the NA and PV Units will optimize analytical protocols to perform metabolomic studies using Liquid Chromatography with High Resolution Mass Spectrometry and Neutron Autoradiography with CR39 detectors at the TRIGA Mark II reactor, respectively. Measurements of the amount of internalized ^{11}B as a function of the administered BSH will be carried out on DU145 and MCF-10 cells for consistency with [2] and then extended to PANC-1 cells and to FDG-3. Kinetics and cytotoxicity curves will be realized to determine pre-treatment time for optimal uptake, while intracellular localization will provide insights on the cell-killing effects [Postuma, 2016]. As far as ex-vivo tests are concerned, Magnetic Resonance Imaging (MRI) will be applied and the distribution of ^{19}F will be investigated [21, 22]: in absence of intrinsic ^{19}F signals in living tissues allows in vivo visualization of exogenous fluorinated tracers, with a signal-to-noise ratio (SNR) close to that of ^{1}H MRI, even with only ~1.0 mM/ml. The 9.4T scanner with both the ^{1}H and ^{19}F receiving coil for in-vitro samples, present in the joint INFN-Roma/CNR MRI lab of S. Capuani will be used to study the NMR characteristics of the chosen tracers (i.e. molecular stability in tissues, concentrations) and evaluate their spatial distribution mapping in ex-vivo samples on animal models of PANC-1 tumors in pancreas to be performed by the ISS members of the group. The limit of ^{19}F MRI is the high concentrations required to have a good SNR. Since the limiting factor is the electronic noise of the RF emitting and receiving coil [23, 24, 25], we propose to develop a test stand for SNR optimization in ^{19}F MRI (**Task 2.2**). By exploiting the low field scanner (0.35T) and the expertise of the MRI lab [26, 27] the project aims at:

- implementing a new RF antenna at ~20MHz, designed to maximize the emitted signal
- integrating the Software Define Radio (SDR) technology in the receivers to optimize the digital signal processing algorithms for optimal SNR, by exploiting the competence developed for the low signals of Virgo. The option to cool the electronics at 4K will also be considered [28].

In parallel, we will exploit the experience in machine learning of the group to optimize the image analysis (**Task 2.3**), considering the possibility to analyse simultaneously the ^{19}F and ^{1}H images. In particular we propose to implement real time Deep Neural Network approaches on last generation FPGA.

2.3.1 Milestones, deliverables and human resources

Milestones		
	Month	**Description**
M2.1.1	1-36	Measurement of concentrations of borated and fluorinated compounds in in-vitro tests, via neutron autoradiography and LC-HR/MS
M2.1.2	9-28	Ex-vivo test on mice models
M2.2.3	1-12	Implementation of SDR
M2.2.2	1-16	Read out optimization
M2.2.3	13-32	Design of optimized antenna
M2.3.1	17-36	Data analysis
M2.3.2	5-28	Multivariate analysis

Deliverables		
	Month	**Description**
D2.1	1-16	Establishment of a procedure for the measurement of the concentration of borated and fluorinated compound in in-vitro tests (18Months)
D2.2	1-36	Optimization of sensitivity of 19-F MRI by means of hardware and software improvements

Personnel		
Name	**Title, Institution**	**FTE(%)**
Valerio Bocci	Primo Tecnologo - INFN-Roma1	40
Paolo Fresch	Assegnista, INFN-Roma1	10
Silvia Capuani	Ricercatore, CNR-ISC, INFN-Roma1	30
Riccardo Faccini	Prof. Ordinario, Sapienza, INFN-ROma1	20
Sergio Frasca	Professore Associato, Sapienza - INFN-Roma1	30
Stefano Giagu	Professore Associato, Sapienza - INFN-Roma1	10
Andrea Messina	Ricercatore, Sapienza - INFN-Roma1	15
Andrea Mostacci	Professore Associato, Sapienza - INFN-Roma1	20
Dante Rotili	Ricercatore, Sapienza - INFN-Roma1	20
Alessio Sarti	Professore Associato, Sapienza - INFN-Roma1	10
Michela Marafini	Ricercatore, Centro Fermi, INFN-Roma1	20
Marco Vignati	Primo Ricercatore, INFN-Roma1	20
Cecilia Voena	Ricercatore, INFN-Roma1	20
Silvia Bortolussi	Ricercatore (RTDb), UNIPV, INFN-PV	10
Saverio Altieri	Prof. Associato, UNIPV e INFN-PV	10
Ian Postuma	Assegnista, INFN-PV	10
Nicoletta Protti	Assegnista, INFN-PV	10
Cinzia Ferrari	Tecnico (EP) UNIPV	10
Severina Pacifico	Ricercatore UNICAMPANIA, INFN-NA	20
Simona Piccolella	Ricercatore UNICAMPANIA, INFN-NA	20
Francesca Vulcano	Ricercatore, ISS INFN-Roma1	30
Luisa Milazzo	Ricercatore, ISS INFN-Roma1	30
Giampiero Macioce	Tecnico - ISS, INFN-Roma1	30

2.4 WP3: microdosimetry

Responsible: S Agosteo (INFN-MI)

The aim of WG3 is to measure microdosimetric spectra across the proton Bragg peak with detectors with tissue-equivalent (TE) walls/converters unloaded and loaded with boron and fluorine. The microdosimetric spectra will be assessed at the same depths where cells will

be irradiated by WG4, thus providing a physical characterization of the radiation field at cellular dimensions. Proton irradiations will be performed at LNS and TIFPA. Already available microdosimeters will be employed, namely tissue-equivalent proportional counters (TEPCs) and silicon telescopes. The feasibility of employing SiC devices for microdosimetry will also be studied for their better tissue-equivalence and radiation hardness. Moreover, experimental spectra at the nanometric level will be assessed for providing data for modelling (WG1).

Miniature dual-TEPC systems were constructed at LNL [29, 30, 31] for BNCT applications, allowing microdosimetry measurements with excellent spatial resolution in high beam intensity (Figure 2.2) while a dual-TEPC with walls loaded with ^{11}B will be constructed.

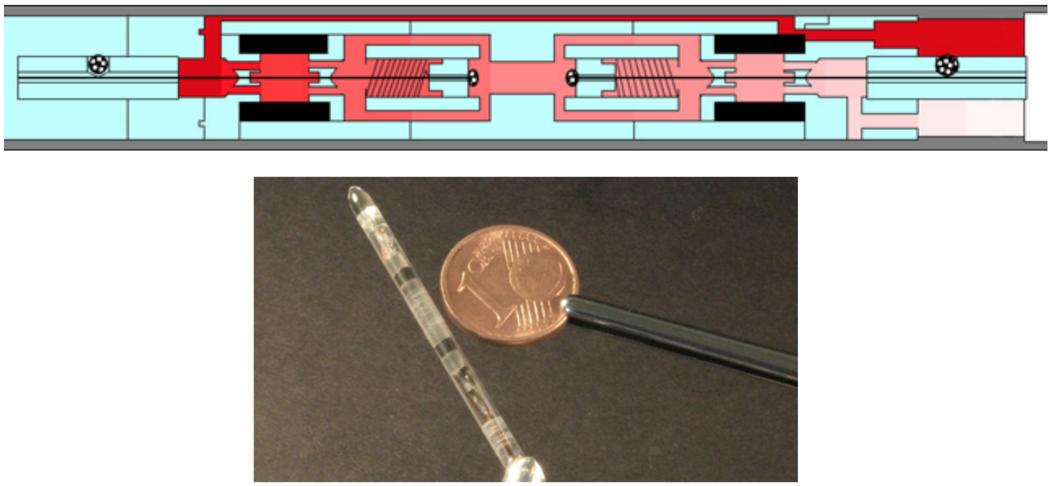


Figure 2.2: Top: Layout of the first mini twin-TEPC constructed at LNL; Bottom: the twin-TEPC inserted inside a transparent plastic sleeve. The two mini TEPCs are visible as small black cylinders.

The silicon microdosimeter is based on the monolithic telescope technology [32]. The standard structure consists of a ΔE stage and an E residual-energy stage about 2 μm and 500 μm in thickness, respectively. The sketch of the device is shown in Figure 2.3. The ΔE stage acts as a solid state microdosimeter, while the E stage gives information on the energy and the type of the impinging particle [33, 34]. It should be mentioned that these telescope devices also allow to discriminate the type of the impinging particle through a scatter-plot.

The contribution of each particle to the microdosimetric distribution can be hence assessed. The silicon detectors will be coupled to boron-loaded (or F loaded) and pure TE plastics. Coupling with a pure boron/fluorine target is also foreseen for maximizing the production of alpha particles from the studied reactions. It should be mentioned that these telescope devices also allow to discriminate the type of the impinging particle through a scatter-plot. The contribution of each particle to the microdosimetric distribution can be hence assessed. The silicon detectors will be coupled to boron-loaded (or F loaded) and pure TE plastics. Coupling with a pure boron/fluorine target is also foreseen for maximizing the production of alpha particles from the studied reactions.

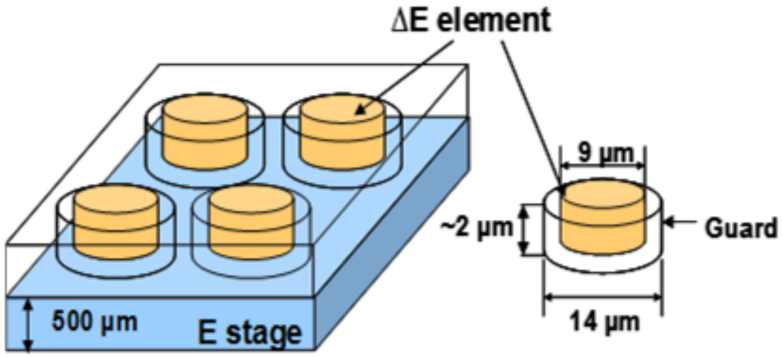


Figure 2.3: Sketch of the segmented telescope.

2.4.1 Milestones, deliverables and human resources

Milestones		
	Month	**Description**
M3.1	1-6	Preliminary measurements with silicon telescopes and TEPCs with available B converters
M3.2	1-6	Design of TE plastics containing B-11 and F for TEPC walls and SiC converts
M3.3	6-12	Continuation of preliminary measurements with silicon telescopes and TEPCs
M3.4	6-12	Comparison between simulation data D1.1 and experimental data taken by WP2. Inclusion of the experimental data (cell survival) taken by WP4
M3.5	12-24	Comparison between simulation data D1.1 and experimental data taken by WP2. Inclusion of the experimental data (ROS production) taken by WP4
M3.6	12-24	Comparison between simulation data (D1.1, M1.3, D1.2 and M1.5) and experimental data taken by WP2. Inclusion of the experimental data (cell survival, DSB,CA,foci) taken by WP4
M3.7	24-36	Measurements with Si telescopes, SiCs with and without F
M3.8	24-36	Measurements with avalanche confinement TEPCs with and without F

Deliverables		
	Month	**Description**
D3.1	12	Microdosimetric spectra from the measurement at LNS with the already available detectors (for WP1 and WP4)
D3.2	12-24	Microdosimetric spectra with the avalanche confinement detectors simulating different site sizes (for WP1)
D3.3	30	Microdosimetric spectra and scatter-plots with F loaded converters

Personnel		
Name	**Title, Institution**	**FTE(%)**
Stefano Agosteo	Professore Ordinario, POLIMI, INFN-MI	30
Davide Bortot	Assegnista, POLIMI, INFN-MI	30
Giovanni D'angelo	Tecnico, POLIMI, INFN-MI	50
Alberto Fazzi	Professore Associato, POLIMI, INFN-MI	30
Davide Mazzucconi	Dottorando, POLIMI, INFN-MI	30
Claudio Pirovano	Tecnico, POLIMI, INFN-MI	50
Andrea Pola	Professore Associato, POLIMI, INFN-MI	20
Valeria Conte	Ricercatrice, INFN-LNL	20
Anna Selva	Assegnista, INFN-LNL	20
Anna Bianchi	Dottoranda, INFN-LNL	20
Pablo Cirrone	Ricercatore, INFN-LNS	10
Giada Petringa	Dottoranda, INFN-LNS	10
Salvatore Tudisco	Ricercatore, INFN-LNS	20
Sebastiana Puglia	Assegnista, INFN-LNS	30
Valentina Scuderi	Associata, INFN-LNS	30
Andrea Attili	Ricercatore, INFN-Roma3	10

2.5 WP4: radiobiology

Responsible: L Manti(INFN-NA)

Focus of this WP is to assess Proton Effectiveness Enhancement (PEE) by p+^{11}B (p-B) and p+^{19}F (p-F), with the final goal of making protontherapy amenable to radioresistant tumours [35].

Task4.1 Cytogenetic damage. After corroborating previous data (Figure 2.4), we shall study radioresistant PANC-1 cells from high-mortality rate pancreatic cancer [36], promisingly treated with ^{12}C ions [37], using BJ fibroblasts as normal cell reference. Cell death, chromosome aberrations (CA) and micronuclei (MN) will quantify proton-induced damage In cells exposed at mid-SOBP (LNS-INFN and TIFPA). Upregulation of apoptosis, whose suppression renders PANC-1 radioresistant [38], will prove radiosensitization by p-B and p-F. BNCT will be tested as a treatment modality for pancreatic cancer. Survival will be evaluated as a function

of dose calculated by Monte Carlo methods.

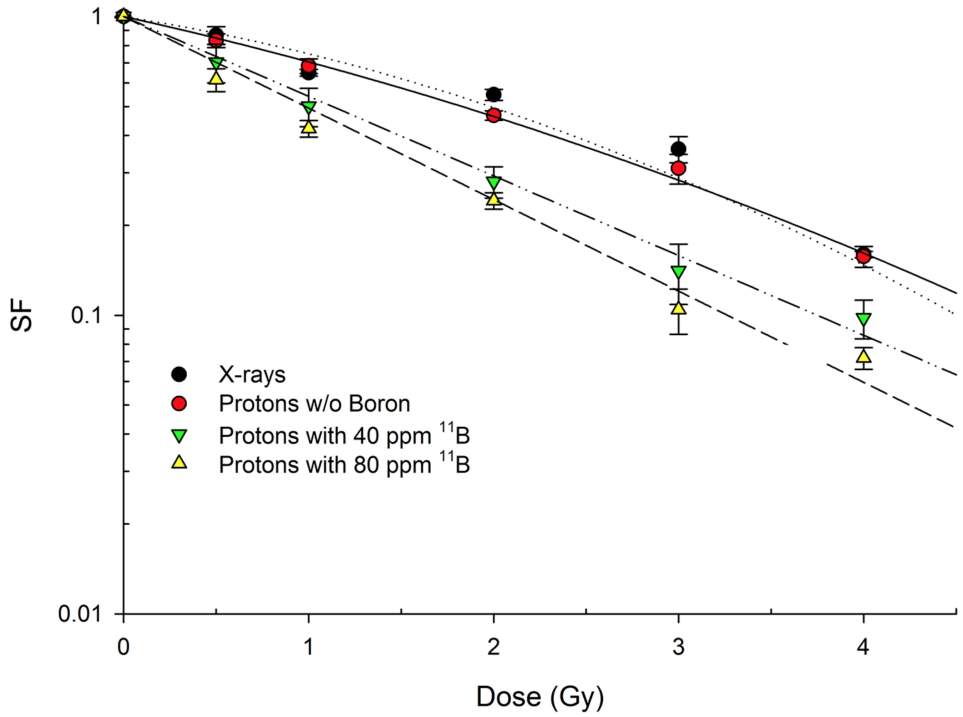


Figure 2.4: BSH enhances proton-induced cell death [2].

Task4.2 Proton energy. In cells exposed along the Bragg curve, no PEE is expected at beam entrance (highest energy), as cross sections are lowest. As protons slow down, a depth-dependent increase in PEE is deemed to occur along the SOBP. Beams from 3-MV and 14-MV Tandem accelerators at CIRCE-UNICAMPANIA and INFN-LNS, with energy close to reaction cross section maxima, will provide mechanistic insights.

Task4.3 High-LET (HL). To causally link PEE to reaction secondaries, HL signatures will be sought. HL causes spatio-temporally clustered lesions (CL) (Figure 2.5), made of double-strand breaks (DSB) and non-DSB lesions, distinctively impacting radiation chemistry and repair pathways.

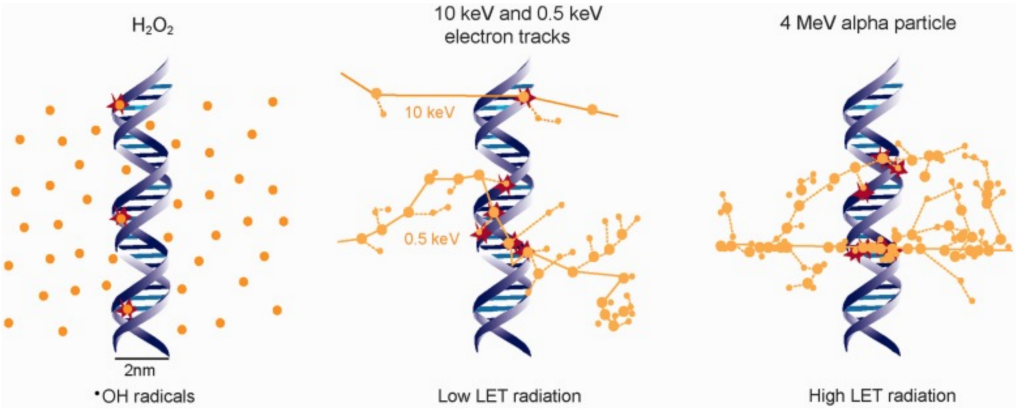


Figure 2.5: DNA damage clusterization [39].

- Intra-track recombination lowers yields of radical species (e.g. OH^*) raising that of molecular products [40]: H_3O^+ was recently identified as an alpha-particle chemical signature [41]. Hence, ROS will be measured at various times after irradiation [42].
- CL are preferentially repaired by ATR-activated Homologous Recombination (HR) [43]. Hence, measurements of ATR/ATM kinase ratio will flag for HR.
- Initial and residual CL will be quantified by colocalization of DSB (gamma-H2AX/53BP1 foci) and non-DSB (OGG1/POLB/XPA) [44]. H2Bub, a newly identified marker for alpha-particle CL [45], will be studied.
- HL specifically causes complex-type CA [46] and peculiarly increases MN frequency [47]: mFISH coupled with MN assay can reveal damage complexity [48]. Premature senescence (PS), which is linked with CL [49, 50], will be quantified by beta-galactosidase assay.

Task4.4 Bystander effects (BE). BE may explain discrepancies between PEE and reaction secondary yields. Factors released by directly proton-irradiated cells in the presence of BSH or ^{19}F-FDG may magnify cytotoxicity. ^{11}B- and ^{19}F-free medium from irradiated cells will

be transferred onto unirradiated cells, which will be assayed for clonogenic death and DNA damage.

2.5.1 Milestones, deliverables and human resources

Milestones		
	Month	**Description**
M4.1	12	Task 4.1 Radiobiological characterization of PANC-1 and BJ cells
M4.2	18	Task 4.2 Irradiations along high-energy proton SOBPs. Studies of ROS, repair pathways and Clustered Lesions (CL) signatures
M4.3	24	Task 4.3 & 4.4 Preliminary irradiations with low-energy monochromatic proton beams and medium-transfer experiment to assess bystander effects
M4.4	30	Task 4.1 & 4.2 Corroboration of data from experiments along SOBP and monoenergetic proton beams. Relationship with modeling results (WP.1)
M4.5	36	Task 4.3 & Task 4.4 Corroboration of data on bystander effect and CL-elicited responses (ROS, repair pathways, foci, micronuclei, chromosome aberrations, senescence). Relationship with micro/ nano dosimetry results (WP3)

Deliverables		
	Month	**Description**
D4.1	6	Corroboration of proton biological enhancement by p-B in previously tested cell systems (MCF-10 and DU145 cells)
D4.2	12	Preliminary results on enhancement of proton beam effectiveness by p-B and p-F on PANC-1 and BJ cells. Testing carrier concentrations from WP2
D4.3	24	Results on high-LET radiation induced CL as effector of proton biological enhancement by p-B and p-F reactions. Cell survival studies with BNCT
D4.4	36	Confirmation of nuclear reaction-driven enhancement of proton biological effectiveness and identification of associated specific CL biomarkers. Elucidation af the underlying biophysical processes and role of bystander effect

Personnel		
Name	**Title, Institution**	**FTE(%)**
Lorenzo Manti	Professore Associato, UNINA, INFN-NA	60
Mariagabriella Pugliese	Professore Associato, UNINA, INFN-NA	30
Chiara Feoli	Specializzanda in Fisica Medica, UNINA, INFN-NA	30
Valerio Ricciardi	Dottorando, UNICAMPANIA, INFN-NA	40
Severina Pacifico	RU, UNICAMPANIA, INFN-NA	10
Simona Piccolella	RU, UNICAMPANIA, INFN-NA	10
Giusi Imma Forte	Ricercatore IBFM-CNR, INFN-LNS	40
Luigi Minafra	Ricercatore IBFM-CNR, INFN-LNS	30
Francesco Paolo Cammarata	Ricercatore IBFM-CNR, INFN-LNS	50
Valentina Bravatà	CTER IBFM-CNR INFN-LNS	30
Giorgio Russo	Ricercatore, IBFM-CNR, INFN-LNS	30
Pietro Pisciotta	Dottorando, UNICT, INFN-LNS	50
Saverio Altieri	Professore Associato, UNIPV, INFN-PV	10
Silva Bortolussi	Ricercatore (RTDb), UNIPV-INFN-PV	10
Nicoletta Protti	Borsista, INFN-PV	10
Ian Postuma	Assegnista, INFN-PV	10
Cinzia Ferrari	Tecnico (EP), UNIPV	10
Agata Scordino	Professore Ordinario,UNICT, INFN-LNS	50
Rosaria Grasso	Ricercatore, UNICT, INFN-LNS	60
Franco Musumeci	Professore Associato,UNICT, INFN-LNS	50
Filippo Torrisi	Dottorando, UNICT, LNS-INFN	50

2.6 WP5: coordination of the experimental activities

Responsible: C La Tessa (INFN-TIFPA)

The aim of this work package is to coordinate all measurement campaigns described in WP2, WP3 and WP4 to ensure a consistency in the methodologies and produce high-quality data. The standardization of the experimental procedures is a key point also for the modeling team (WP1) that minimizes possible discrepancies between measurements and simulations not arising from limitations of the physical or biological models. WP5 will interact with

the experimenters of the other WPs to provide support in designing and optimizing the measurement setup. The criteria and guidelines followed in this process will be also based on the inputs provided by WP1. For the experimental activities, two facilities have been selected as headquarters: LNS (Catania) and TIFPA (Trento). For each test campaign, the WP will recommend the facility that better meets the specific requirements. Additionally, the personnel involved in WP5 will provide on-site support for all operations carried out. A total of 20 hours per year of beam time have been considered as part of the budget allocated to this WP to be used by WP1, WP2, WP3 and WP4.

2.6.1 Milestones, deliverables and human resources

Milestones		
	Month	**Description**
M5.1	1-6	Definition criteria and guidelines to be followed during experimental activities (collaboration with WP1)
M5.2	1-6	Planification of the experimental activity of the following 6 months
M5.3	13-18	Planification of the experimental activity of the following 6 months
M5.4	25-30	Planification of the experimental activity of the following 6 months

Deliverables		
	Month	**Description**
D5.1	6	Report on experimental criteria to be followed
D5.2	12	Summary report of all experimental activities carried out by WP2, WP3 and WP4 within the first year of activities
D5.3	24	Summary report of all experimental activities carried out by WP2, WP3 and WP4 within the first year of activities
D5.4	36	Summary report of all experimental activities carried out by WP2, WP3 and WP$ within the first year of activities

Personnel		
Name	**Title, Institution**	**FTE(%)**
Chiara La Tessa	RTDB, UNI-TRENTO, INFN-TIFPA	20
Marta Rovituso	Assegnista, TIFPA.INFN	30
Giada Petringa	Dottoranda, UNICT, INFN-LNS	10
Antonino Picciotto	Ricercatore, FBK, INFN-TIFPA	30
Sofia Colombi	Dottoranda, UNI-TRENTO, INFN-TIFPA	30

2.7 Financial requests

	ITEM	I anno	II anno	III anno	Totale	GROUP	WP
Personale	2 years of grant on radiobiological modeling and experimental activity	0,00 €	28.500,00 €	28.500,00 €	57.000,00 €	LNS	1 and 5
	2 years of grant on Imaging and quantification	0,00 €	28.500,00 €	28.500,00 €	57.000,00 €	RM1	2
	2 years of grant on experimental microdosimetry	0,00 €	28.500,00 €	28.500,00 €	57.000,00 €	LNL	3
	2 years of grant on radiobiology	28.500,00 €	28.500,00 €	0,00 €	57.000,00 €	NA	4
Missioni	Collaboration Activity at LNS*	2.000,00 €	2.000,00 €	2.000,00 €	6.000,00 €	RM3	1
		2.000,00 €	2.000,00 €	2.000,00 €	6.000,00 €	TIFPA	1
	Collaboration Activity at TIFPA*	2.000,00 €	2.000,00 €	2.000,00 €	6.000,00 €	RM3	1
		2.000,00 €	2.000,00 €	2.000,00 €	6.000,00 €	LNS	1
	Collaboration Activity at RM3*	2.000,00 €	2.000,00 €	2.000,00 €	6.000,00 €	TIFPA	1
		2.000,00 €	2.000,00 €	2.000,00 €	6.000,00 €	LNS	1
	Experimental activity at LNS	2.000,00 €	2.000,00 €	2.000,00 €	6.000,00 €	RM3	1
		5.000,00 €	5.000,00 €	5.000,00 €	15.000,00 €	TIFPA	1 and 5
		2.500,00 €	2.500,00 €	2.500,00 €	7.500,00 €	NA	4
	Experimental activity at LNS (trunk rent included)	6.000,00 €	8.000,00 €	6.000,00 €	20.000,00 €	MI	3
		6.000,00 €	8.000,00 €	6.000,00 €	20.000,00 €	LNL	3
	Experimental Activity at TIFPA	2.000,00 €	2.000,00 €	2.000,00 €	6.000,00 €	RM3	1
		6.000,00 €	6.000,00 €	6.000,00 €	18.000,00 €	LNS	1 and 4
		2.500,00 €	2.500,00 €	2.500,00 €	7.500,00 €	NA	4
	Collaboration Meeting	2.000,00 €	2.000,00 €	2.000,00 €	6.000,00 €	RM3	1
		2.000,00 €	2.000,00 €	2.000,00 €	6.000,00 €	LNS	1, 0 and 4
		2.000,00 €	2.000,00 €	2.000,00 €	6.000,00 €	TIFPA	1 and 5
		1.000,00 €	1.000,00 €	1.000,00 €	€3.000,00	PV	4
		1.000,00 €	1.000,00 €	1.000,00 €	3.000,00 €	NA	4
		2.000,00 €	2.000,00 €	2.000,00 €	6.000,00 €	RM1	2
	Conference Participation	1.500,00 €	1.500,00 €	1.500,00 €	4.500,00 €	LNS	1
		1.500,00 €	1.500,00 €	1.500,00 €	4.500,00 €	TIFPA	5
		1.500,00 €	1.500,00 €	1.500,00 €	4.500,00 €	NA	4
		1.500,00 €	1.500,00 €	1.500,00 €	4.500,00 €	RM1	2
		1.500,00 €	1.500,00 €	1.500,00 €	4.500,00 €	RM3	1
		1.500,00 €	1.500,00 €	1.500,00 €	4.500,00 €	LNL	3
		1.500,00 €	1.500,00 €	1.500,00 €	4.500,00 €	MI	3
		1.500,00 €	1.500,00 €	1.500,00 €	4.500,00 €	PV	4
Inventariabile	Multicore	4.000,00 €	0,00 €	0,00 €	4.000,00 €	RM3	1
	Software Define Radio (SDR)	15.000,00 €	0,00 €	0,00 €	15.000,00 €	RM1	2
	Criogenerator for MRI electronics	0,00 €	20.000,00 €	0,00 €	20.000,00 €	RM1	2
	PC for data acquisition and analysis	2.000,00 €	0,00 €	0,00 €	2.000,00 €	RM1	2
	moderno HPLC per analisi metabolomiche	48.356,69 €	0,00 €	0,00 €	48.356,69 €	NA	2
	CAEN HV 4 channels (see offer)	6.000,00 €	0,00 €	0,00 €	6.000,00 €	MI	3
	2 ORTEC Amplifiers (see offer)	11.500,00 €	0,00 €	0,00 €	11.500,00 €	MI	3
	Microdosimetry detectors for alpha particles measurements FROM UOW (see offer)	30.000,00 €	0,00 €	0,00 €	30.000,00 €	LNS	3
	Stand replacement for motorized fluorescence microscope dedicated to automated search of metaphases and micronuclei	10.000,00 €	0,00 €	0,00 €	10.000,00 €	NA	4
	Ionization chamber for dosimetry for x ray irradiation with radiogen tube of cell cultures as low LET reference	5.500,00 €	0,00 €	0,00 €	5.500,00 €	NA	4
	PhMeter and thermocouple to be used for reagents in cytogentic assay procedures	1.000,00 €	€0,00	€0,00	€1.000,00	NA	4

Consumabile	Tracers for imaging	4.000,00 €	3.000,00 €	3.000,00 €	10.000,00 €	RM1	2
	Material for antenna development	4.000,00 €	3.000,00 €	3.000,00 €	10.000,00 €	RM1	2
	FPGA with PCIe interface fo optimal imaging	0,00 €	5.000,00 €	0,00 €	5.000,00 €	RM1	2
	Solventi ed altri consumabili per HPLC e LC/MS	4.500,00 €	4.500,00 €	4.500,00 €	13.500,00 €	NA	2
	Materiali consumabili per colture cellulari	3.000,00 €	3.000,00 €	1.000,00 €	7.000,00 €	PV	2
	Materiali consumabili per autoradiografia neutronica (CR39, reagenti)	1.500,00 €	1.500,00 €	0,00 €	3.000,00 €	PV	2
	consumables for tests on 40 NOD/SCID mice (animals+plastic+reagent+caratterız. cellulare)	10.000,00 €	10.000,00 €	10.000,00 €	30.000,00 €	RM1	2
	Development and construction of PCBs for low-noise front-end electronics for new configurations of silicon microdosimeters	10.000,00 €	0,00 €	0,00 €	10.000,00 €	MI	3
	Construction of a new preamplifier (low-noise and wide dynamics) for the the multi-shell borated TEPC	0,00 €	7.000,00 €	0,00 €	7.000,00 €	MI	3
	Boron foil (see offer)	710,00 €	0,00 €	0,00 €	710,00 €	MI	3
	TE gas (see offer)	3.000,00 €	0,00 €	0,00 €	3.000,00 €	MI	3
	Borated plastic (see offer)	10.000,00 €	0,00 €	0,00 €	10.000,00 €	LNL	3
	Development and construction of PCBs for SiCs mounting	6.000,00 €	0,00 €	0,00 €	6.000,00 €	LNS	3
	Front-end electronics for SiC microdosimeters	4.000,00 €	0,00 €	0,00 €	4.000,00 €	LNS	3
	Fluorated plastic	0,00 €	10.000,00 €	0,00 €	10.000,00 €	LNL	3
	TE gas (see offer)	3.000,00 €	0,00 €	0,00 €	3.000,00 €	LNL	3
	Laboratory consummables for cell culture, antibodies, kits for DNA damage and ROS quantification	12.000,00 €	6.000,00 €	5.000,00 €	23.000,00 €	LNS	4
	Laboratory consummables for cell culture, apoptosis (caspase) quantification,	14.000,00 €	5.000,00 €	4.000,00 €	23.000,00 €	NA (Caserta)	4
	Laboratory consummables, purchase of cell lines, cell culture media, reagents for DNA damage and senescence, boron carrier	18.000,00 €	18.000,00 €	16.000,00 €	52.000,00 €	NA	4
	Chromosome painting probes, reagents for chromosome (calyculin A) and micronuclei (Cytochalasin B)	10.000,00 €	10.000,00 €	8.000,00 €	28.000,00 €	NA	4
	Liquid nitrogen and C02 for cell cryopreservation & incubator for cell culture, mylar for low-energy proton irradiation	3.000,00 €	3.000,00 €	3.000,00 €	9.000,00 €	NA	4
	Laboratory consummables for cell cultures	4.000,00 €	3.000,00 €	3.000,00 €	10.000,00 €	PV	4
	Laboratory consummables for neutron autoradiography	500,00 €	500,00 €	0,00 €		PV	4
	Beam Time	8.000,00 €	8.000,00 €	8.000,00 €	24.000,00 €	TIFPA	5
	Water equivalent plastic for microdosimetry detectors for alpha particles measurements FROM UOW	0,00 €	4.000,00 €	0,00 €	4.000,00 €	LNS	3
Costruzione apparati	Dedicated support structures for experiments	10.000,00 €	0,00 €	0,00 €	10.000,00 €	TIFPA	6
Altre spese per servizi	Final Machine Learning algorithm on GPU NVIDIA server	0,00 €	0,00 €	2.500,00 €	0,00 €	RM1	2
	Irraggiamenti al reattore TRIGA Mark II	4.000,00 €	4.000,00 €	2.000,00 €	10.000,00 €	PV	2
	Irradiations at TRIGA Mark II reactor	4.000,00 €	4.000,00 €	1.000,00 €	9.000,00 €	PV	4
Software	License renewal software of microscope-connected automated chromosome and micronucleus search and detection	0,00 €	6.000,00 €	0,00 €	6.000,00 €	NA	4
	Training for the use of the mFISH detection program on the automated system by specialist	1.500,00 €	0,00 €	0,00 €	1.500,00 €	NA	4
Totale		I ANNO 380.566,69 €	II ANNO 322.500,00 €	III ANNO 104.500,00 €	TOTALE 925.066,69 €		

2.8 Effort requested in each involved INFN Section

A positive statment from the former Director of each involved INFN Section will be included during the INFN database compilation.

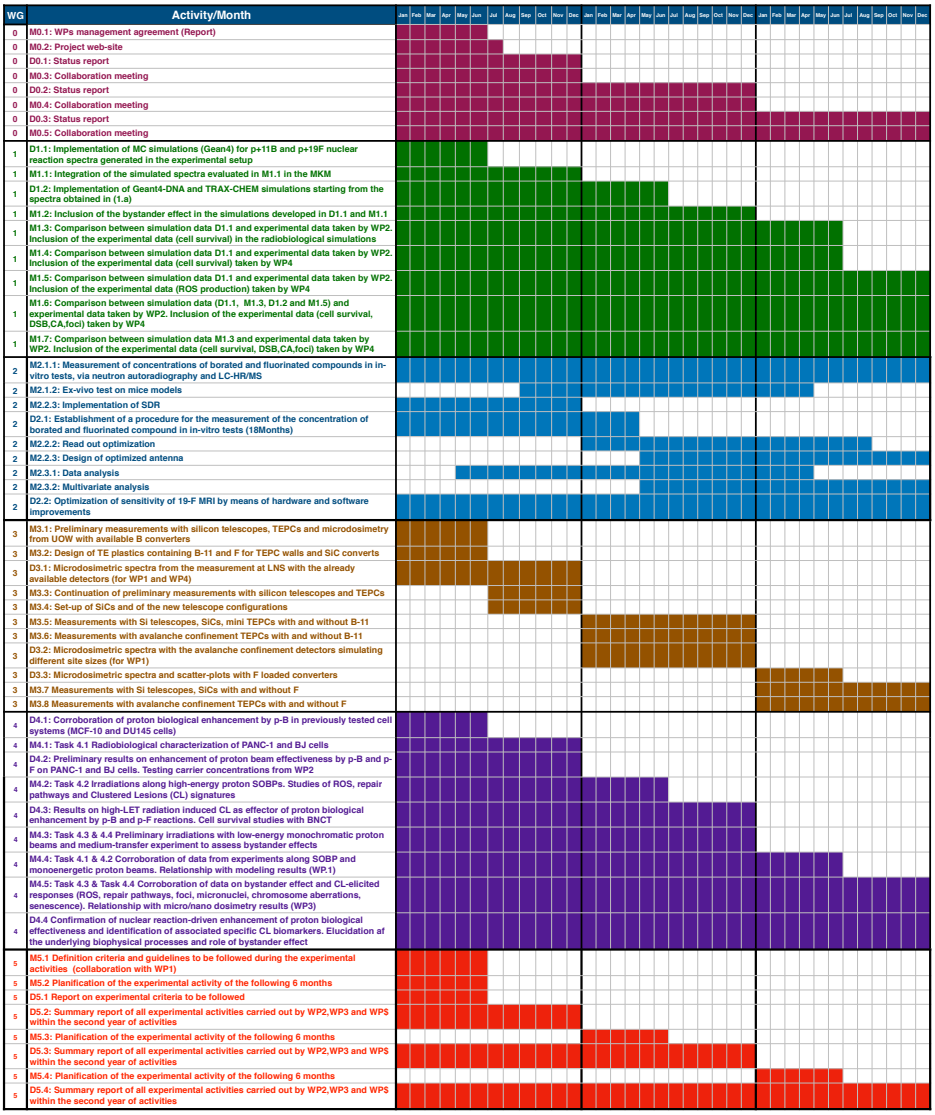
At moment the following involvment are foreseen:

1. **INFN-NA** for the first year: 7 days to the Electronic and Detector Service; 14 days to the Mechanical Workshop. Both will be used for r maintenance/repair of the radiogen tube (SIEMENS Stabilipan II) with which irradiations will be performed to study the radioresponse of the new cell lines (PANC-1 and BJ) foreseen in the project. Low-LET radiation is also the reference radiation in particle radiation studies.

2. **INFN-LNS** support of the vacuum service and electronic and mechanical departments during the available beam runs;

   One beam time (2 BTU = 16 hours) of 62 MeV proton beams guranteed for the preliminary tests

2.9 GANTT chart



2.10 Background Intellectual Property Rights

Many background intellectual properties can be identified. The following is a list, probably not exhaustive. By the way we are fully dispoal to improve it during our activity.

1. The proton-Boron approach is protected by the European EP 3 266 470 A1 submitted by GAP Cirrone (INFN, I), D Margarone (ELI-Beamlines, CZ), L Giuffrida (ELI-Beamlines, CZ) and A Picciotto (FBK, I). Application number 16178280.0 pubblished on January 10, 2018. The patent is reported in the *Patents* section.

2. INFN-LNS: Monte Carlo simulation realized in the framework of the Geant4 toolkit able to fully simulate a passive protontherapy beamline and the connected dose, LET and RBE distributions

3. Monte Carlo algorithms developed using the Geant4 toolkit, connected with the main relevant radiobiological models and able to calculate important radiobiological parameters

4. Capability to design, simulate and realize different passive beam elements to modulate the energy and define the optimal spot, of a clinical proton beam

5. Innovative dosimetric approach to measure the dose realesed to a patient undergoing a radiotherapy session. The system is protected by an Italian patent n 102017000087851 entitled *"Metodo per la misurazione di dosi radioterapiche"*. The patent is reported in the *Patents* section.

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3 Additional documentation

3.1 Endorsemnet declarations

UNIVERSITÀ degli STUDI di CATANIA

CAPiR Center for Advanced Preclinical *in vivo* Research

Delegato Titolare
Stabilimento Utilizzatore Unico e Area Preclinica
CAPiR

Prof.ssa Rosalba Parenti
mail parenti@unict.it tel 0954781134

Catania, 8 giugno 2018

Spett.le OPBA

Oggetto: Lettera di supporto per il bando delle call di Gruppo V: NEPTUNE (Nuclear process driven Enhancement of Proton Therapy UNravEled)

Caro Presidente,
facendo riferimento al progetto NEPTUNE (PI: Giacomo Cuttone – INFN-LNS, Catania, Responsabile di Unità: Lorenzo Manti, Partecipanti locali: Severina Pacifico e Simona Piccolella), esprimo l'interesse del Center for Advanced Preclinical in vivo Center (CAPiR), di cui la sottoscritta è coordinatore scientifico e Titolare delegato del Rettore dell'Università degli studi di Catania, alla partecipazione alla Call in questione per quanto attiene alle attività sperimentali ad essa collegate che si svolgeranno in collaborazione con la Sezione INFN di Catania.

Cordiali saluti,
Rosalba

CAPiR
Università Degli Studi Di Catania,
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Consiglio Nazionale delle Ricerche
ISTITUTO DI BIOIMMAGINI E FISIOLOGIA MOLECOLARE (IBFM)

Il Direttore
Prof.ssa Maria Carla Gilardi

To **Prof. G. Cuttone**
Principal Investigator of the Neptune Proposal
Laboratori Nazionali del Sud
Istituto Nazionale di Fisica Nucleare
Via Santa Sofia, 62
95123 Catania

The Institute of Molecular Bioimaging and Physiology (IBFM) - CNR has a Research Unit in Cefalù (Palermo), whose main topic of Research is Radiobiology. The IBFM research group in Cefalù has been actively collaborating for some years with the research group of the LNS-INFN, in the field of Radiobiology, having previously participated in the INFN CSN5 Calls ETHICS and MoVeIT. The collaboration extends to the preclinical protocol PETS (PrEclinicalhadronTherapyStudies), approved by the Ministry of Health.

Research activities in radiobiology take advantage from the multidisciplinary skills present in the group: i) Cell and Molecular Biology and Animal Science, adopting a proteogenomic approach, to deeply evaluate the main pathways involved in the cell response to stress stimuli induced by radiations; ii) Medical Physics, to study and optimize the physical characteristics of the radiation by both experimental techniques and computer simulations; iii) Engineering, to develop Image processing methods for the definition of the target volume to be treated, and for the follow-up and monitoring of the therapy response.

IBFM expresses strong interest in the NEPTUNE (Nuclear process driven Enhancement of Proton Therapy UNravEled) Call proposal coordinated by Prof. Giacomo Cuttone, within the framework of the INFN Call Group V 2018 and, in case the Project is approved, will give the necessary support to the planned research activities.

In particular, IBFM will be involved in the context of the WP4 (Radiobiology), contributing to the deepening of the direct and indirect effects of ionizing radiation, linked to DNA repair mechanisms and the quantification of reactive oxygen species in response to the Proton treatments proposed in the project.

Maria Carla Gilardi

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Il sottoscritto, La Via Francesco, primo ricercatore del CNR-IMM e responsabile del gruppo di ricerca sulla crescita del carburo di silicio, ritiene che la call dell'INFN: *Nuclear process driven Enhancement of Proton Therapy UNravEled* (**NEPTUNE**) , che prevede l'utilizzo dei rivelatori sviluppati all'interno del progetto **SiCILIA** in collaborazione fra il CNR-IMM e l'INFN come micro-dosimetri, possa essere di grande interesse per lo studio di questi nuovi rivelatori in campo bio-medico. Infatti, da un lato, questo nuovo campo di ricerca potrà avere un notevole impulso grazie alla grande sensibilità e *radiation hardness* di questi rivelatori, inoltre questo tipo di applicazione darà nuovi stimoli per ottenere degli strati epitassiali sempre più perfetti e meno difettosi e per studiare nel dettaglio l'effetto delle radiazioni sulla formazione di difetti cristallini che alla lunga deteriorano le proprietà del rivelatore.

In definitiva si tratta di un progetto interessante per le applicazioni bio-mediche ma che potrà avere anche delle ricadute sia nello sviluppo dei rivelatori in SiC, sia nello studio dell'epitassia del SiC e del danno creato dalle radiazioni utilizzate su questo materiale.

Catania, 29/05/2018 Firma:

Francesco La Via

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To Prof. G. Cuttone
Principal Investigator of the Neptune Proposal
Laboratori Nazionali del Sud
Istituto Nazionale di Fisica Nucleare
Via Santa Sofia, 62
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The CNR Institute of Complex Systems (CNR-ISC) hosts research on complex systems that is systems composed of many elements whose mutual interaction gives rise to unexpected emergent phenomena. The emergence of collective behaviour is certainly not restricted to the physical sciences, but it is ubiquitous in nature, from biology to medical physics. For this reason, the study of complex systems requires a truly interdisciplinary mindset. The great variety of ISC research activities reflects this view of complexity.
Medical physics in our institution is mainly represented by the work of Dr. Silvia Capuani. Silvia Capuani headquarters is in Physics Department of Sapienza University of Rome, where she directs her own research group and holds a NMR laboratory. Her research interests include investigations of NMR Spectroscopy and Imaging in living systems (ex-vivo tissues, in-vivo animal models, humans). Specifically, her research focuses on developing new NMR techniques and innovative NMR diagnostic approaches. She has a PhD in physics and a specialization in medical physics. During her research activity she has established over the years, collaborations with different groups of physicists, such as those of INFN unit of Rome Sapienza, physical chemists, biochemists and clinicians, which are still kept active. She obtained several contracts in public hospitals and research institutions concerning technology transfer in the field of NMR investigation.
In particular, she is an expert in boron neutron capture therapy (BNCT) and has worked with INFN members for several years to develop it. In recent years she has participated to the GAP project (GPU applications project) - Realtime for HEP and Medical Imaging, a project funded under the FIRB-2012 "Futuro in Ricerca" with three research units: INFN (section of Pisa), Rome "Sapienza" and University of Ferrara.
CNR-ISC expresses strong interest in the NEPTUNE (Nuclear process driven Enhancement of Proton Therapy UNravEled) Call proposal coordinated by Prof Giacomo Cuttone, within the framework of the INFN Call Group V 2018 and will give the necessary support to the planned research activities.
In particular, CNR-ISC will contribute to the monitoring of the pharmacokinetics and uptake by tissues of 11B and 19F enriched carriers useful for triggering the nuclear reaction with protons to destroy tumour cells. Moreover the CNR-ISC will study together with the colleagues of INFN Sapienza new strategies to improve the signal-to-noise ratio of NMR images realized using the 19F signal.

CONTI
CLAUDIO
29.05.
2018
12:18:18
UTC

Il Direttore
(Prof. Claudio Conti)
Documento firmato digitalmente

Istituto Superiore di Sanità

Prof. G. Cuttone
Principal Investigator of the Neptune Proposal
Laboratori Nazionali del Sud
Istituto Nazionale di Fisica Nucleare
Via Santa Sofia, 62
95123 Catania

The Department of Oncology and Molecular Medicine of the National Institute of Health (OMM-ISS) has a research group that collaborates with the research of the INFN, already for some years, in the field of Radiobiology, having previously participated in the INFN CSN5 Call ETHICS.

The project will take advantage from the skill of the OMM-ISS research group in the field of cellular and molecular biology, and animal research.

OMM-ISS expresses strong interest in the NEPTUNE (Nuclear process driven Enhancement of Proton Therapy UNravEled) Call proposal coordinated by Prof Giacomo Cuttone, within the framework of the INFN Call Group V 2018 and will give the necessary support to the planned research activities relative to the establishment of an orthotopic pancreatic cancer mouse model.

Dr. Mauro Biffoni
Director
Department of Oncology and Molecular Medicine

DIPARTIMENTO DI CHIMICA
E TECNOLOGIE DEL FARMACO

SAPIENZA
UNIVERSITÀ DI ROMA

To Prof. G. Cuttone
Principal Investigator of the Neptune Proposal
Laboratori Nazionali del Sud
Istituto Nazionale di Fisica Nucleare
Via Santa Sofia, 62
95123 Catania

In the Department of Chemistry and Technologies of Drugs works Dr. Rotili, who has as one of the main research topics the medicinal chemistry development of tracers for imaging and therapeutic purposes.

The Department of Chemistry and Technologies of Drugs expresses strong interest in the NEPTUNE (Nuclear process driven Enhancement of Proton Therapy UNravEled) Call proposal coordinated by Prof. Giacomo Cuttone, within the framework of the INFN (National Institute for Nuclear Physics) Call Group V 2018, and will give the necessary support to the planned research activities of Dr. Rotili.

In particular, in the context of the WP2 (Imaging), Dr. Rotili and his collaborators will be directly involved in the medicinal chemistry development of small molecules containing fluorine (^{19}F) and boron (^{11}B) atoms as enhancers of the biological effectiveness of proton-therapy.

Furthermore, the Department of Chemistry and Technologies of Drugs will allow, in case the project will be funded, Dr. Rotili to be associated with INFN.

Rome, June 5th 2018

Head of Department
Prof. Bruno Botta

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Prof. G. Cuttone
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Milano, 07.06.2018

Dear Prof. Cuttone, Dr. Silvia Capuani, one of Bruker historical users, informed us about the innovative research in the frame of the NEPTUNE project that you coordinate.
Bruker, leader in the field of MR instrumentation and more, is interested in the results of NEPTUNE project within the framework of the INFN Call Group V 2018 and the related planned research activities.
Particular interest falls on monitoring 19F enriched carrier pharmacokinetics and tissue uptake for cancer cells therapy and towards this goal in new strategies to improve the signal-to-noise ratio of 19F MR images, that Dr. Silvia Capuani (CNR-ISC) is studying in a taem with colleagues of INFN Sapienza.

Best regards

Bruker Italia S.r.l.
Dr. Francesco Moneta

Università
degli Studi
della Campania
Luigi Vanvitelli

Dipartimento di
Scienze e Tecnologie
Ambientali Biologiche e
Farmaceutiche

Al Dr. Valter Bonvicini
Presidente della Commissione Scientifica Nazionale V
INFN

Caserta, 22 maggio 2018

Oggetto: Lettera di supporto per il bando delle call di Gruppo V:
NEPTUNE (Nuclear process driven Enhancement of Proton Therapy UNravEled)

Caro Presidente,

facendo riferimento al progetto NEPTUNE (PI: Giacomo Cuttone – INFN-LNS, Catania, Responsabile di Unità: Lorenzo Manti, Partecipanti locali: Severina Pacifico e Simona Piccolella), esprimo l'interesse del Dipartimento di Scienze e Tecnologie Ambientali Biologiche e Farmaceutiche (DISTABiF) da me diretto per la partecipazione alla Call in questione per quanto attiene alle attività sperimentali ad esse collegate che si svolgeranno in collaborazione con la Sezione INFN di Napoli.

Cordiali saluti

Il Direttore
Prof. Paolo Vincenzo Pedone

UNIVERSITÀ DEGLI STUDI DI NAPOLI FEDERICO II

Al Dr. Valter Bonvicini
Presidente della Commissione Scientifica Nazionale V
INFN

Napoli, 21 maggio 2018

Oggetto: Lettera di supporto per il bando delle call di Gruppo V:
NEPTUNE (Nuclear process driven Enhancement of Proton Therapy UNravEled)

Caro Presidente,

facendo riferimento al progetto NEPTUNE (PI: Giacomo Cuttone – INFN-LNS, Catania, Responsabile Locale: Lorenzo Manti), esprimo l'interesse del Dipartimento di Fisica "E. Pancini" da me diretto per la partecipazione alla Call in questione per quanto attiene alle attività sperimentali ad esse collegate che si svolgeranno in collaborazione con la Sezione INFN di Napoli.

Cordiali saluti

UNIVERSITÀ DEGLI STUDI DI NAPOLI FEDERICO II Dipartimento di Fisica

Il Direttore
Prof. Leonardo Merola

CENTRE FOR MEDICAL RADIATION PHYSICS
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22nd May 2018

Dr G Cuttone,
Director
INFN-LNS,
Via S Sofia 62, 95123-Catania (I)

Dear Dr Cuttone,

I am writing this letter to support the "NEPTUNE" project, which is dedicated to the study of proton-Boron and proton-Fluorine reaction to enhance the radiobiological effectiveness (RBE) of proton therapy.

The Centre for Medical Radiation Physics (CMRP) will provide support for this project as follows:

- Monte Carlo simulations on micro- and nano-scales with Geant 4 and Geant –DNA to predict deposited ionizing energies on cellular and DNA levels and related to that radiation damage in biological cells
- Provide innovative radiation detection instrumentation for microdosimetry allowing modelling of boron isotopes uptake on a cellular level and RBE evaluation
- Provide CMRP PhD students and researchers for collaborative experiments on the beamline at INFN
- Accepting INFN students and researchers for collaborative research at CMRP

I look forward to productive research collaboration.

Anatoly Rozenfeld, Ph.D.
Distinguished Professor of Medical Physics
Director, Centre for Medical Radiation Physics
University of Wollongong

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and Applications

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Trento, 10.6.2018

Al Presidente della
Commissione Scientifica Nazionale V
INFN
Dr. Valter Bonvicini

Oggetto: Progetto NEPTUNE

Caro Valter,
in relazione al progetto NEPTUNE presentato come Call della Commissione V (responsabile nazionale: Dr. Giacomo Cuttone, LNS Catania; responsabile locale per TIFPA: Prof. Chiara La Tessa), ti comunico il mio parere positivo sull'iniziativa, e in particolare assicurarti che nulla osta per quanto riguarda l'utilizzo di risorse e/o strumentazione del TIFPA per lo svolgimento del progetto.

Cordiali saluti,

Il Direttore TIFPA

(Prof. Marco Durante)

INFN Joint Initiative with Trento University, Bruno Kessler Foundation and Trento APSS

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FONDAZIONE BRUNO KESSLER
CMM CENTER FOR MATERIALS AND MICROSYSTEMS

Dr. G. Cuttone,
Director
INFN-LNS,
Via S. Sofia 62,
95123-Catania (I)

Dear Dr. Cuttone,

I am writing this letter to corroborate the "NEPTUNE" project, which is dedicated to the experimental and simulation study of proton boron and proton fluorine nuclear reaction to enhance the protontherapy effectiveness in the radiobiological framework.

In this context, the Micro-Nano Facility division of the Fondazione Bruno Kessler will provide support on the following aspects:

- Monte Carlo simulations on boron and fluorine ions energy and dose distribution in the CR39 nuclear tracks detectors used for dosimetry analysis.
- Ion implantation experimental campaign on CR39 nuclear tracks detectors for dosimetry preparatory analysis on alpha particles generation during the proton therapy experiments.
- In addition to the above points, MNF group will evaluate the possibility to use SIMS (Secondary Ion Mass Spectrometry) techniques to measure the physical parameters of the ion implantation.

Sincerely Yours,

3.2 Curriculum Vitae

3.2.1 WP0 leader: Giacomo Cuttone

Giacomo Cuttone (Catania, 18/02/1960) Nuclear Physicist with specialization in Accelerator Physics. He got the Degree in Physic on april 1983 at the Catania University. Researcher at INFN Laboratori Nazionali del Sud (LNS) of Catania since may 1985. In 1995 he was First Researcher and in 2002 Research Director. He was part of Superconducting Cyclotron (CS) project at INFN and, since the beginning of his research activity, participating to its design and realization. He was head of the cyclotron operations at LNS in 1994-1998. He is among the proponents of the EXCYT project at LNS for the production of exotic beams. Within this project he had the responsibility of extracting high-intensity beam from the CS and he participated in the definition and development of low intensity diagnostic devices. Since July 2002 up to 2008 he was chair of INFN EXCYT national project. During the period covered under his direction, the project had its successful conclusion with the production and first nuclear physic experiment with ^{8}Li radioactive beam. Since 1996 he was Head of Protontherapy scientific activities at the LNS. He is the head of the LNS protontherapy facility (CATANA). It is the first and actually the unique Italian protontherapy facility for ocular melanoma treatments in operation. Since 2002 up to now about 500 patients has been successfully treated. He was President of the Executive Committee of the European Integrated Project MAESTRO funded for five years 2005-2009 by EU under the Sixth Framework Program on the "Combating Cancer". Under this project, among other he was in charge of the working group for the study and development of a program of quality assurance in protontherapy. He contributed to study, design and develop a superconducting cyclotron for protons and ions for applications in hadrontherapy. He is the unique Italian member of the Particle Therapy Cooperative Group (PTCOG) Steering Committee. He was appointed as a member of the OECD Working Group on Nuclear Physics representing INFN. In this context he was the coordinator of the sub-group on the activities of applied nuclear physics and its interconnections with other scientific fields. He

was member of the EURISOL site panel contributing to the definition of the site requirements for the facility installation. He participates in the development of an experimental program of measurements for the study of nuclear fragmentation for applications in hadrontherapy and to validate the physical models implemented in Monte Carlo like Geant4. This aim represent nowadays is main research interest with experimental programs carried out at LNS and GSI In this lab, he is the spokesperson of an international collaboration, constituted by INFN, GSI, CEA, IN2P3, ESA and University of Valencia, that will carry out approved experiments with the Music-Aladin-TOF-LAND detection setup at GSI. He was the spokesperson of the INFN GEANT4 collaboration and member of the Geant4 steering board. He was President of the INFN Applied Physic National Commission (CSN5) in 2008-2011. He was member of the SPES steering committee at LNL. He is member of the selection panel of the NupNET European Project and in charge for INFN of the Accelerators WP of the European Project EurisolNET. Moreover he is member of the industrial applications of future accelerators WP for the PP TIARA. In August 2009 he was selected by the INFN search Committee for the LNL Director Selection. He didn't accept this invitation being President of CSN5 since less than one year. He was national chair of many INFN experiments for new detectors R&D, new accelerators, hadrontherapy, dosimetry and novel imaging techniques. He was member of the scientific committees and organizing committee of national and international conferences. He presented invited talks in international conferences and national and international workshops. He is referee of experiments and scientific articles in international journals. He is Professor of Accelerator Physics at the Physics Faculty, at the Medical Physics School and at Physics Phd School of the Physic Department of the Catania University since 2003. Since 2011 August 1st until now, he is Director of the Laboratori Nazionali del Sud in Catania. He was the Scientific Chair of the PON projects Km3NeT-Italia and EMSO-Medit, funded by the Italian Minister of Education, University and Research (MIUR) for the realization of the submarine high energy neutrino telescope (Km3NeT project) in Capo Passero (Italy) and for its applications in Geophysics, Vulcanology and Marine Biology. The total budget for the project was 21 M euro.

He is the Italian Delegate of Horizon2020-Euratom, appointed by MIUR at UE in Bruxelles. He is the INFN coordinator of the scientific committee of the INFN-Egypt Scientific Accademy (ASRT).He is part of the bilateral scientific committee of INFN with CNR and INGV.He was Coordinator of the project Idmar (interdisciplinar Sea laboratory) Funded in pofesr 14-20 Sicilian region for 40M euro He is the coordinator of the contract (2.4 M euro) for the realization of the research and preclinical beam line ELIMED in Prague, in the framework of the ELI Esfri Project. He is principal investigator of the *Grande Rilevanza Project* Italia-Serbia funded by the Italian Minister of Foreign Affairs (MAECI) on Biophysical study of the effects induced by carbon ion beams and secondary particles produced by nuclear fragmentation. He is author of more than 200 papers on scientific journals and member of scientific and advisory committee of International conference. He had tens invited talks at national and international conference and workshop.

Pubblications

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3.2.2 WP1 leader: G A Pablo Cirrone

Dr. Cirrone Giuseppe Antonio Pablo was born in Catania on August 20, 1974.

He received his Master Degree in Nuclear Physics on April 1998 discussing a thesis on the application of the plastic scintillators in medical physics. In 1998 entered in the Medical Physics school of the Florence University where he get his degree as Qualified Medical Physicist in 2000 discussing a work thesis on the use of the natural and synthetic diamond as dosimetric system for ionizing radiation. In 2000 he started the PhD course at the Catania University .The PhD work was completely dedicated to the use and application of the Monte Carlo approach in proton and ion therapy. He get his PhD title in 2003 discussing a thesis on the use of the Monte Carlo Geant4 code in hadrontherapy applications.

Dr. Cirrone is expert of the use of proton and ion in radiation treatment and of absolute and relative dosimetry in electron, photon and ion beam. He is expert of the development and test of detectors for medical applications. He is expert of the development and use of Monte

Carlo-based techniques for the simulation of problems related to the medical physics and nuclear fields. He is expert in the beamline transport and diagnostic of laser-driven ion beams. Since 2002 he belongs to the Geant4 Collaboration being responsible for the development and maintenance of an example for the simulation of iontherapy related problems. Since 2006 is member of the Geant4 Steering Board as responsible of the "Advanced Examples" working group and since 2008 is responsible of the validation activity of the Geant4 "Low Energy" working Group. Since 2007 he is the responsible of the protontherapy beam line and of the interdisciplinary beam-line at the Laboratori Nazionali del Sud of INFN coordinating and supporting various experimental Groups. In 2006 he was local spokesperson of the PRIMA INFN project dedicated to the development and design of a proton computed tomography. In 2010 was local spokesperson of the LILIA INFN project dedicated to the study and detection of proton beams accelerated by high power ladder beams to be used in medical application. Since 2012 he is responsible of the ELIMED (ELI-Beamline MEDical applications) project. ELIMED will realize a Users? transport beamline and associated diagnostic for laser-accelerated beams. The beamline is being installed at ELI-Beamlines (Prague, CZ) in these months (June - December 2018). At moment, he is the local Coordinator of the multidisciplinary Committee of INFN and since 2007 is National Responsible of the MC-INFN, a project funded by the V Committee of INFN and dedicated to the Monte Carlo software development for radiation transport.

He is President of the Technical Board of the COMETA consortium, a National research Institution dedicated to the high performance computing and related applications. He was a member of the scientific committees and organization of national and international conferences. He presented reports in international conference and national and international workshops. He was a referee of experiments and scientific articles in international journals.

Pubblications

1. Cirrone G.A.P., Manti L, Margarone D, Petringa G, Giuffrida L, Minopoli A, Picciotto A, Russo G, Cammarata F, Pisciotta P, Perozziello FM, Romano F, Marchese V, Milluzzo G,

Scuderi V, Cuttone G, Korn G (2018). First experimental proof of Proton Boron Capture Therapy (PBCT) to enhance protontherapy effectiveness. SCIENTIFIC REPORTS, vol. 8, ISSN: 2045-2322, doi: 10.1038/s41598-018-19258-5

2. Russo AD, Schillaci F, Pommarel L, Romano F, Amato A, Amico AG, Calanna A, Cirrone G.A.P., Costa M, Cuttone G, Amato C, De Luca G, Flacco FA, Gallo G, Giove D, Grmek A, La Rosa G, Leanza R, Maggiore M, Malka V, Milluzzo G, Petringa G, Pipek J, Scuderi V, Vauzour B, Zappala E (2017). Characterization of the ELIMED prototype permanent magnet quadrupole system. JOURNAL OF INSTRUMENTATION, vol. 12, ISSN: 1748-0221, doi: 10.1088/1748-0221/12/01/C01031

3. Scuderi V, Milluzzo G, Alejo A, Amico AG, Booth N, Cirrone G.A.P., Doria D, Green J, Kar S, Larosa G, Leanza R, Margarone D, McKenna P, Padda H, Petringa G, Pipek J, Romagnani L, Romano F, Schillaci F, Borghesi M, Cuttone G, Korn G (2017). Time of Flight based diagnostics for high energy laser driven ion beams. JOURNAL OF INSTRUMENTATION, vol. 12, ISSN: 1748-0221, doi: 10.1088/1748-0221/12/03/C03086

4. Cirrone G.A.P., Cuttone G, Raffaele L, Salamone V, Avitabile T, Privitera G, Spatola C, Amico AG, Larosa G, Leanza R, Margarone D, Milluzzo G, Patti V, Petringa G, Romano F, Russo A, Russo A, Sabini MG, Schillaci F, Scuderi V, Valastro LM (2017). Clinical and Research Activities at the CATANA Facility of INFN-LNS: From the Conventional Hadrontherapy to the Laser-Driven Approach (vol 7, 223, 2017). FRONTIERS IN ONCOLOGY, vol. 7, ISSN: 2234-943X, doi: 10.3389/fonc.2017.00247

5. Amako K, Dotti A., Cirrone G.A.P., and the Geant4 Collaboration (2015). Recent developments in Geant4. ANNALS OF NUCLEAR ENERGY, ISSN: 0306-4549, doi: 10.1016/j.anucene.2014.08.021

6. Cirrone G.A.P., Romano F, Scuderi V, Amato A, Candiano G, Cuttone G, Giove D, Korn G, Krasa J, Leanza R, Manna R, Maggiore M, Marchese V, Margarone D, Milluzzo G, Petringa G, Sabini MG, Schillaci F, Tramontana A, Valastro L, Velyhan A (2015). Transport and

dosimetric solutions for the ELIMED laser-driven beam line. NUCLEAR INSTRUMENTS & METHODS IN PHYSICS RESEARCH. SECTION A, ACCELERATORS, SPECTROMETERS, DETECTORS AND ASSOCIATED EQUIPMENT, vol. 796, p. 99-103, ISSN: 0168-9002, doi: 10.1016/j.nima.2015.02.019

7. Cirrone G.A.P., Cuttone G, Romano F, Schillaci F, Scuderi V, Amato A, Candiano G, Costa M, Gallo G, Larosa G, Korn G, Leanza R, Manna R, Maggiore M, Marchese V, Margarone D, Milluzzo G, Petringa G, Tramontana A (2015). Design and Status of the ELIMED Beam Line for Laser-Driven Ion Beams. APPLIED SCIENCES, vol. 5, p. 427-445, ISSN: 2076-3417, doi: 10.3390/app5030427

8. Chaudhary P, Marshall TI, Perozziello FM, Manti L, Currell FJ, Hanton F, McMahon SJ, Kavanagh JN, Cirrone G.A.P., Romano F, Prise KM, Schettino G (2014). Relative Biological Effectiveness Variation Along Monoenergetic and Modulated Bragg Peaks of a 62-MeV Therapeutic Proton Beam: A Preclinical Assessment. INTERNATIONAL JOURNAL OF RADIATION ONCOLOGY BIOLOGY PHYSICS, vol. 90, p. 27-35, ISSN: 0360-3016, doi: 10.1016/j.ijrobp.2014.05.010ù

9. Agosteo S, Anania MP, Caresana M, Cirrone G.A.P., De Martinis C, Delle Side D, Fazzi A, Gatti G, Giove D, Giulietti D, Gizzi LA, Labate L, Londrillo P, Maggiore M, Nassisi V, Sinigardi S, Tramontana A, Schillaci F, Scuderi V, Turchetti G, Varoli V, Velardi L (2014). The LILIA (laser induced light ions acceleration) experiment at LNF. NUCLEAR INSTRUMENTS & METHODS IN PHYSICS RESEARCH. SECTION B, BEAM INTERACTIONS WITH MATERIALS AND ATOMS, vol. 331, p. 15-19, ISSN: 0168-583X, doi: 10.1016/j.nimb.2013.12.035

10. Rossomme S, Marinelli M, Verona-Rinati G, Romano F, Cirrone G.A.P., Kacperek A, Vynckier S, Palmans H (2017). Response of synthetic diamond detectors in proton, carbon, and oxygen ion beams. MEDICAL PHYSICS, vol. 44, p. 5445-5449, ISSN: 0094-2405, doi: 10.1002/mp.12473

3.2.3 WP1 leader: Andrea Attili

General information

Name: Andrea Attili

Address: Via della Vasca Navale, 84, 00146 Roma RM

+39 0657337287

e-mail: attili@to.infn.it

Education

- 2003

  Ph.D in Physics – Università degli Studi ?Roma Tre?, Roma (Italy) ?Study of the glass transition of a supercooled liquid mixture in bulk and confined phases? Sup.: Prof. M. Rovere, Dr. P. Gallo.

- 1998

  Graduated in Physics – Università degli Studi ?Roma Tre?, Roma (Italy) ?Studio delle correlazioni angolari tra fotoelettrone ed elettrone Auger (APECS): un esperimento su Cu(111) con radiazione di sincrotrone? (?Study of the angular correlations between photo- and Auger-electron (APECS): an experiment on CU(111) using synchrotron radiation?) Sup.: Prof. G. Stefani. Final grade: 110/110 cum laude.

Research activities

Key-words of the research activity:

- Medical physics in particle therapy.
- Dosimetry, treatment planning and Q.A.
- Monte Carlo simulations and radiobiological modelling in particle therapy.
- Experimental and theoretical study of condensed matter physics.

- 2011-2018

  Research activity in medical physics

  Researcher, permanent position at INFN (Istituto Nazionale di Fisica Nucleare), Sezione di Torino (Italy). INFN Research Projects:

  - Development of a novel Treatment Planning System for oncological treatment with proton and carbon ion beams – Implementation and clinical validation of a treatment planning system (TPS) for hadrontherapy in collaboration with an industrial partner (Ion Beam Application, IBA, Belgium).
  - Research and development in hadrontherapy (RDH) – Responsable of the working package related to the study of advanced treatment planning systems for ion beam therapy and radiobiological modelling.
  - Innovative Radio- and Particle-Therapy (IRPT) – Responsable of the working package related to the study of advanced treatment planning systems for ion beam therapy and radiobiological modelling
  - Modeling and verification for Ion beam Treatment planning (MoVeIT) – study of advanced treatment planning systems for ion beam therapy and radiobiological modelling.

- 2006-2010 Research activities in medical physics

  Researcher, temporary position at INFN (Istituto Nazionale di Fisica Nucleare), Sezione di Torino (Italy). Research activities:

  - Implementation of radiobiological models for hadrontherapy – I investigated and extended different radiobiological models for the evaluation of cell survival after exposition to carbon ions and protons beams.
  - Study of a treatment planning system for hadrontherapy – Study of fast algorithms, to be used in the optimization procedure of treatment planning with light ions beams and protons, for the evaluation of the biological effects of the irradiation.

- 2005-2006 Research activities in medical physics

  Temporary position, Università degli Studi di Torino, Department of Experimental Physics, Torino (Italy). Scientific referee: Prof. C. Peroni. Research activities: Study of the acquisition and data on-line processing of a monitoring system of therapeutic ion beams – The activity is associated to the realization of the Beam Monitor System (BMS) used in the Centro Nazionale di Adroterapia Oncologica (CNAO) in Pavia (Italy)

- 2004-2005 Research activities in bioinformatics

  Temporary position, Università ?La Sapienza?, Department of Biochemical Sciences, Roma (Italy). Scientific referee: Prof. A. Tramontano. Research activities:
  Realization of ?machine learning? automatic techniques for the prediction of the quality of proteins structural models – I developed neural networks and original specific algorithms to correlate and to predict the quality of macromolecules models, to be intended as the weighted distance between the putative 3D structure of the models and the experimental data of the real proteins. Development of relational databases to be used for the classification of proteins based upon specific domains; I obtained the classification through the use of original data-mining programs and of procedures for the automatic creation of databases.

- 2000-2003 Research activities in condensed matter physics (Ph.D. thesis)

  Ph.D. grant, Università ?Roma Tre?, Department of Physics, Roma (Italy). Scientific Referee: Prof. M. Rovere and P. Gallo. Research activities:

  - Modeling and simulation of supercooled liquids; I investigated the dynamics of liquids confined in amorphous gels through Molecular Dynamics (MD) simulations. I verified the possibility of using the 'Mode Coupling Theory' (MCT) for predicting the dynamical properties of supercooled systems even in condition of tight confinement.

– Study of the glass-transition in supercooled liquids; I investigated the thermodynamics of supercooled liquids down to glass-transition, at the Kauzmann temperature, through the analysis of 'inherent structures' (IS) and of vibrational normal modes of the disordered system

Grants, Prizes and public competitions

- 2010 Winner (first on the list) in the public competition for a permanent research position at Istituto Nazionale di Fisica Nucleare (INFN), Area Fisica Applicata.
- 2009 Winner (third on the list) of a grant fund in the regional competition ?I3P - Startup Piemonte 2009?, for the presentation of a business plan for a hi-tech startup enterprise (I-SEE, Internet Simulation Evaluation Evision)
- 2000 Winner (first on the list) in the national competition for a Ph.D. Physics grant (XV Ciclo). Università ?La Sapienza?, Roma (Italy).
- 2000 Winner in the national competition for a Ph.D. Physics grant (XV Ciclo). Università ?Tor Vergata?, Roma (Italy).
- 2000 Winner (first on the list) in the national competition for a Ph.D. Physics grant (XV Ciclo). Università ?Roma Tre?, Roma (Italy).
- 1998 Prize for ?Young scientific authors?, assigned by Istituto Nazionale per la Fisica della Materia (INFM) for the work ?Angular Correlations in Auger Photoelectron Coincidence Spectroscopy? presented at the INFM National Meeting.
- 1997 Istituto Nazionale per la Fisica della Materia (INFM) study grant for the work related to the thesis in Physics at carried out at Elettra Synchrotron Light Laboratory, Trieste (Italy).

- 1994-1996 Study grants for assistant to faculty didactic laboratories for the courses of ?Esperimentazioni di Fisica I? and ?Esperimentazioni di Fisica II?, Physics Department, Università degli Studi ?Roma Tre?, Roma (Italy).

Pubblications

1. Strigari, L., Torriani, F., Manganaro, L., Inaniwa, T., Dalmasso, F., Cirio, R., and Attili, A. (2018). Tumour control in ion beam radiotherapy with different ions in the presence of hypoxia: an oxygen enhancement ratio model based on the microdosimetric kinetic model. Physics in Medicine and Biology, 63(6), 065012. https://doi.org/10.1088/1361-6560/aa89ae

2. Manganaro, L., Russo, G., Bourhaleb, F., Fausti, F., Giordanengo, S., Monaco, V., ? Attili, A. (2018). ?Survival?: a simulation toolkit introducing a modular approach for radiobiological evaluations in ion beam therapy. Physics in Medicine and Biology, 63(8), 08NT01. https://doi.org/10.1088/1361-6560/aab697

3. Strigari, L., Ferrero, V., Visonà, G., Dalmasso, F., Gobbato, A., Cerello, P., ? Attili, A. (2017). Targeted dose enhancement in radiotherapy for breast cancer using gold nanoparticles, part 2: A treatment planning study. Medical Physics, 44(5), 1993?2001. https://doi.org/10.1002/mp.12178

4. Manganaro, L., Russo, G., Cirio, R., Dalmasso, F., Giordanengo, S., Monaco, V., ? Attili, A. (2017). A Monte Carlo approach to the microdosimetric kinetic model to account for dose rate time structure effects in ion beam therapy with application in treatment planning simulations. Medical Physics, 44(4), 1577?1589. https://doi.org/10.1002/mp.12133

5. Russo, G., Attili, A., Battistoni, G., Bertrand, D., Bourhaleb, F., Cappucci, F., ? Marchetto, F. (2016). A novel algorithm for the calculation of physical and biological irradiation quantities in scanned ion beam therapy: the beamlet superposition approach. Physics in Medicine and Biology, 61(1), 183?214. https://doi.org/10.1088/0031-9155/61/1/183

6. Polster, L., Schuemann, J., Rinaldi, I., Burigo, L., McNamara, A. L., Stewart, R. D., Attili, A., ? Paganetti, H. (2015). Extension of TOPAS for the simulation of proton radiation effects considering molecular and cellular endpoints. Physics in Medicine and Biology, 60(13), 5053?5070. https://doi.org/10.1088/0031-9155/60/13/5053

7. Strigari, L., Attili, A., Duggento, A., Chiaravalloti, A., Schillaci, O., and Guerrisi, M. G. (2015). Quantitative analysis of basal and interim PET/CT images for predicting tumor recurrence in patients with Hodgkin?s lymphoma. Nuclear Medicine Communications, 37(1), 1. https://doi.org/10.1097/MNM.0000000000000399

8. Cometto, A., Russo, G., Bourhaleb, F., Milian, F. M., Giordanengo, S., Marchetto, F., ? Attili, A. (2014). Direct evaluation of radiobiological parameters from clinical data in the case of ion beam therapy: an alternative approach to the relative biological effectiveness. Physics in Medicine and Biology, 59(23), 7393?7417. https://doi.org/10.1088/0031-9155/59/23/7393

9. Russo, G., Attili, A., Bourhaleb, F., Marchetto, F., Peroni, C., Schmitt, E., and Bertrand, D. (2011). Analysis of the reliability of the local effect model for the use in carbon ion treatment planning systems. Radiation Protection Dosimetry, 143(2?4), 497?502. https://doi.org/10.1093/rpd/ncq407

10. Pardo, J., Donetti, M., Bourhaleb, F., Ansarinejad, A., Attili, A., Cirio, R., ? Sacchi, R. (2009). Heuristic optimization of the scanning path of particle therapy beams. Medical Physics, 36(6Part1), 2043?2051. https://doi.org/10.1118/1.3121506

3.2.4 WP2 leader: Riccardo Faccini

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EDUCATION AND EMPLOYMENT

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2017 - Full Professor

2012 - Associate Professor

2009 - Chisesi-Tomassoni Prize Sapienza Univ. of Rome

2002 - ’12 Ricercatore at the University of Rome La Sapienza, department of Physics

2000 - ’02 Research grant with Istituto Nazionale di Fisica Nucleare, Rome

1998 - 2002 Research Assistant at University of California San Diego

Nov. 94 -Jun. 98 Graduate school in Physics at the University of Rome, La Sapienza. Ph.D. thesis on Measurement of sin2hw in hadronic decays of the Z boson with the L3 experiment at LEP? Awarded the PhD title on June 9th 1998.

Sep 89 - Jul. 94 Undergraduate school at the University of Rome, La Sapienza. Laurea thesis on Ricerca del Bosone di Higgs a LEP200

BIBLIOMETRIC PARAMETERS

H-Index (ISI): 63

Total citations: 20,165

Total Pubs: 748

COORDINATING/COMMITTEE EXPERIENCES

2017- Deputy Dean, Faculty of Science

2015- Member of the editorial board of Scientific Reports

2015- Director of the PhD school of Accelator Physics

2013- PI of the INFN research projects CHIRONE/CHIR2

2011- PI of the Applied Radiation Physics Group (ARPG http://arpg-serv.ing2.uniroma1.it/arpg-site/)

2015-17 Member of the Product Quality committee of "La Sapienza"

2012-14: Member of the Research Committee of "La Sapienza"

2010-2012 Principal investigator of the PlasmonX experiment

2009 - '14 Coordinator of the didactics of the Dept. of Physics of Sapienza

2009 -'12 PI of the Rome SuperB group

2007 -'09 - PI of the Rome BaBar Group

2004 - 06 Physics Analysis Coordinator of the BaBar experiment (600 collaborators)

1999 - 2004 Coordinator of the Charmonium (1999-2002) and Semileptonic (2003-2004) Analysis Working Groups of the BaBar experiment.

1999 - 2002 Coordinator of the analysis effort leading to the first observation of CP violation in B decays (100 people) with the BaBar experiment

1995 - 1997 Contact person for the L3 experiment (150 people) of the CERN committee on the search for anomalous four-jet events.

REASERCH ACHIEVEMENTS

My research activity has spanned several aspects of data analysis and detectors for particle physics. In particular my carreer started in large high energy physics experiments and then (after 15 years) turned towards applications of the techniques that I had learned to know. In the following details can be found, where the large collaborations mentioned are:

* the SuperB project: an experiment that intended to study Flavour Physics at very high luminosity, but that was not eventually funded

* the BaBar experiment at the Stanford Linear Accelerator Center: an experiment to study CP violation and B physics in B meson decays

* the L3 experiment at the CERN of Geneva: a LEP experiment for precise measurements of electroweak parameters and search for physics beyond the Standard Model.

Details:

- 2011-today – a Novel Radio-guided surgery technique – Development of an intraop-

erative probe for the detector of tumor residuals. Activity financed by IIT in a joint grant with Sapienza. Partnership with the Istituto Neurologico Carlo Besta, the IEO, the Policlinico Gemelli of Rome, and the Ospedale Pediatrico Bambin Gesú.

- 2011-today — Hadron-therapy dosimetry — Measurement of the products of the interactions of ions with the patient during hadrotherapy and development of an innovative detector for dosimetry.

- 2013 — Low energy neuclar reactions – Verification of a measurement of Low Energy Nuclear Reactions

- 2009-2011 — Laser Plasma Acceleration, Spectrometer – Development of a spectrometer to measure the spectrum of the electrons generated in the interaction of a ultra-high power laser with plasma (PlasmonX experiment).

- 2008-2012 - SUPERB - Convener of the Spectroscopy and Exotica WG of the SuperB collaboration. I coordinated the activities towards the assessment of the physics reach of SuperB in the study of the heavy quarkonium spectroscopy and of the direct searches of exotic particles. As PI of the Rome group, involved in the design of the electromagnetic calorimeter of the SuperB experiment (crystal choice, test-beams, electronics and mechanics)

- 2007-2014 - BABAR, spectroscopy - The large number of exotic charmonium states observed was a hint of the existence of a new kind of matter never observed before: bound states of four quarks or of two quarks and a gluon. The plethora of measurements had to be systematized with a joint experimentalists-theorists work. I have therefore created a collaboration with theory colleagues to review the observations and the interpretations in a consistent way. Few individual papers where published, but above all a review. In this context in 2008 I designed, coordinated, and studied an energy scan of the PEP-II accelerator at the Stanford Linear Accelerator Center. The scan was finalized to the

search for exotic bottomonium. This run represents the most accurate such scan, twenty times better than the previous existing ones. No exotic state was unfortunately found.

- 2005-2006 - BABAR, Physics Coordinator - CKM Physics Coordinator of the BaBar Experiment (600+ collaborators) in 2005-2006. During my term the experiment produced in excess of 70 papers, observed for the first time several new quark bound states and refined significant the bounds on the possible physics beyond the Standard Model involving the low energy processes BaBar can study. Following this experience I was the chair of the 2008 edition of the most outstanding workshop on the physics of BaBar, the CKM workshop. In this role I was able to coordinate the activity of 150+ people towards the realization of a Phys. Repts. which is the current reference paper on the topic.

- 2002-2005 - BABAR, Unitarity triangle - I developed a novel measurement of the CKM matrix angle gamma based on B decays to non CP-eigenstates. The technique, that required several ancillary measurements, is now well established. Also, I developed an innovative technique for the study of B meson decays in high luminosity B-factories that allows to perform inclusive measurements in large background environments (Recoil Physics method). Its first application, was to the measurement of the b?u transitions.

- 1999-2002 - BABAR, sin2beta, CP violation- The measurement of the CP violating quantity sin2beta was the flagship analysis of the BaBar experiment. Its measurement corresponded to the first observation of violation of the CP parity in B decays and was critical in the assessment of the mechanism that lead from the Big-Bang (when matter and anti-matter were present in equal parts) to the current universe, where anti-matter is highly suppressed. I was first coordinator from the start of the experiment of the working group devoted to the reconstruction of the events needed for such measurement and then I was the first sin2beta coordinator, i.e. the coordinator of a group of about 100 physicists that performed the first observation of CP violation in B decays.

- 1998-2000 - BABAR, detector & Software - commissioning of the drift chamber and

development of the code for the reconstruction of secondary vertices. I also designed and implementated the data format that summarized all the information needed for the analysis of the data.

- 1996-1998 - L3, electromagnetic calorimeter- responsible for the installation and running of an electromagnetic calorimeter made of lead and scintillating fibers filling the gaps in the L3 electromagnetic calorimeter.
- 1996-1998 - L3, sin2theta_w - My PHD thesis was on the development of a novel analysis technique that allowed to measure the electroweak mixing angle theta_w in hadronic Z decays. This measurement required particular care and ad-hoc techniques because of the relatively poor performances of the tracking system of the experiment.
- 1994-1998 - L3, Higgs Boson - I searched for the Higgs boson decays into bottom quarks by optimizing the possible discrimination power obtainable by reconstructing the jets, in particular by exploiting the possibility to identify the hadrons containing bottom quarks by their long decay time. Although the Higgs boson was not found, a competing experiment claimed the observation of a particle decaying into the same final state I was searching without evidence. After two years of intense cross checks and devoted data taking it was proven that the signal actually did not exist.

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FUNDS

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Funds (in kEuro) administered (from Sapienza, INFN and IIT) as PI:

* BaBar 1061

* SuperB 129

* PlasmonX 289

* ARPG (medical physics) 350

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- Technology Transfer Patent RM2013A000050 (deposited in 2013) "SONDA DI RIVELAZIONE DI RADIAZIONE BETA- PER LA IDENTIFICAZIONE INTRAOPERATORIA DI RESIDUI TUMORALI" ? Extended to PCT (deposited in 2014)

- Outreach: 2016- ideator and coordinator of the LAB2GO project for the requalification of high school physics laboratories (www.roma1.infn.it/LAB2GO)
  2014- Coordinator of the panel on education of the Osservatorio Scienza per la Societa' of the Rome Municipality
  2012- ideator, coordinator, and author of the only podcast of physics in italian, www.fisicast.it
  2011- Active in PLS, Olimpiadi di Fisica, Incontri di fisica INFN

- Journals: reviewer of Phys. Rev. Lett. and Physics Letters.

- Teaching courses: Statistics for Particle Physics since 1999, Programming (6CFU) since 2007, Didactics of physics for the TFA (A059 – 4 CFU) and Medical Physics (6CFU) since 2014. Few other courses as assistant tutor of tens of Laurea theses and 10 Ph.D. theses

Pubblications

1. Rucinski A., et al(2018), Secondary radiation measurements for particle therapy applications: charged particles produced by He-4 and C-12 ion beams in a PMMA target at large angle, PHYSICS IN MEDICINE AND BIOLOGY, vol. 63, p. 055018

2. Venditti I., et al (2017). Y3+ embedded in polymeric nanoparticles: Morphology, dimension and stability of composite colloidal system. COLLOIDS AND SURFACES. A, PHYSICOCHEMICAL AND ENGINEERING ASPECTS, vol. 532, p. 125-131

3. Mancini-Terracciano Ca., et al (2017). Feasibility of beta-particle radioguided surgery for a variety of nuclear medicine radionuclides. PHYSICA MEDICA, vol. 43, p. 127-133.

4. Marafini M., et al(2017). Secondary radiation measurements for particle therapy applications: Nuclear fragmentation produced by 4He ion beams in a PMMA target. PHYSICS IN MEDICINE AND BIOLOGY, vol. 62, p. 1291-1309

5. Donnarumma R., et al (2016). A novel radioguided surgery technique exploiting beta-decay. PHYSICA MEDICA, vol. 32, p. 104-105

6. Russomando A., et al (2016). An Intraoperative - Detecting Probe for Radio-Guided Surgery in Tumour Resection. IEEE TRANSACTIONS ON NUCLEAR SCIENCE, vol. 63, p. 2533-2539

7. Solfaroli Camillocci E., et al(2016). First ex vivo validation of a radioguided surgery technique with beta- radiation. PHYSICA MEDICA, vol. 32, p. 1139-1144

8. Battistoni G., et al. (2015). Measurement of charged particle yields from therapeutic beams in view of the design of an innovative hadrontherapy dose monitor. JOURNAL OF INSTRUMENTATION, vol. 10

9. COLLAMATI F., et al .(2015). Toward Radioguided Surgery with beta(-) Decays: Uptake of a Somatostatin Analogue, DOTATOC, in Meningioma and High-Grade Glioma. THE JOURNAL OF NUCLEAR MEDICINE, vol. 56, p. 3-8

10. Camillocci Solfaroli E., et al, (2014). A novel radioguided surgery technique exploiting - decays. SCIENTIFIC REPORTS, 4, 4401

3.2.5 WP2 leader: Silva Bortolussi

Place and date of birth: Latisana, UD, 08 November 1978

Home address: via Colombarolo 7, 27028 San Martino Siccomario, Pavia, Italy

Contact:

Office location: Department of Physics, room 1-38, via Bassi 6, 27100 Pavia

E-mail address: silva.bortolussi@pv.infn.it silva.bortolussi@unipv.it

Telephone: +39 0382 98 76 35

website: https://www.bnct.it

Present Position:

Senior Researcher (RTDb) at Department of Physics, University of Pavia

Past Positions:

Fixed-Term Researcher at INFN

Fixed-Term Researcher at University of Pavia

Post-doc at INFN and at University of Pavia.

Research interests:

S.B. research interests are in the field of nuclear physics applied to medicine and biology, in particular in Boron Neutron Capture Therapy (BNCT). She performs computational dosimetry by Monte Carlo calculations of neutron and gamma transport, and treatment planning simulations, with particular interest in new models to express BNCT dose in photon-equivalent units. She specialized in performing boron concentration measurements in biological samples by alpha spectrometry and neutron autoradiography, especially finalized to assess the feasibility of BNCT for different kinds of tumours, and to test the effectiveness of new boron carriers. Presently, she is devoting many efforts for the realization of a new BNCT facility for clinical trials based on the use of a proton accelerator. In particular, she collaborates in the design of suitable neutron beams based on the evaluation of the dosimetric performances in relevant clinical scenarios. She manages international collaborations especially in Latin America and in China, where she has spent research periods, given lectures in summer school programs at

Universities, organized students exchange and supervised PhD. She is active in fund raising and technology transfer activities, being PI and local responsible of a number of national and international grants in the field of BNCT, and managing relationship with industries and funding bodies. She is co-author of a deposited patent. She coordinates outreach activities such as European Researchers Night in Pavia, and gives seminars and conferences for non-technical public.

Teaching:

Chair of the course "Simulations in bio-sanitary field", for the MSc in Physics, University of Pavia (http://fisica.unipv.it/dida/Insegnamento.php?id=24768). Chair of the course "Experimental Physics" for the BSc in Biotechnology, University of Pavia (http://genmic.unipv.eu/site/home/didattica/arti
-FISICA SPERIMENTALE-CORSO B). Intensive Course on Monte Carlo for medical physics 30/10-18/11 2015, University of Campinas, Brasil. Summer School Intensive Course on Monte Carlo for medical physics, July 2018, Nanjing University of Astronautics and Aeronautics, Nanjing, China.

Education:

June 2015 Master Executive in Open Innovation and Knowledge Transfer (110/110 cum laude) MIP, Milan Polytechnic, II level Master Thesis "A Successful External Funds Service", Supervisor Dr M. Arena (Milan Polytechnic), Tutors Dr V. Vercesi (INFN, Unit of Pavia) and Dr B. Chiucconi (University of Macerata)

January 2008 Ph.D. in Physics, University of Pavia, Italy Thesis "Boron Neutron Capture Therapy of Disseminated Tumours", supervisor Prof S.Altieri (University of Pavia), Referee Dr R.Moss (JRC, Petten, The Netherlands)

May 2004 Master of Science in Physics (110/110 cum laude), University of Trieste, Italy Thesis "Una originale configurazione del campo neutronico per una migliore uniformità della dose nell'organo espiantato", supervisor prof L.Bertocchi (University of Trieste) co-supervisors, Prof. T.Pinelli and Prof S.Altieri (University of Pavia)

July 1997 Secondary School degree (60/60), Liceo Scientifico E.Majorana, San Vito al Tagliamento, Pordenone, Italy

Awards, Grants and Honors

Fairchild Award for young researchers, at 11th International Congress of Neutron Capture Therapy (ICNCT), Japan, 2006

Award for young researchers in the field of tumours of young age "Giovanni Carcea", Crotone, 2012

Secretary General of International Society on Neutron Capture Therapy (ISNCT)

Delegate for Pavia University at the Latin America Working Group - COIMBRA Group

President of Organizing Committee of 8th YBNCT, September 2015, Pavia, Italy

Member of Organizing Committee of 13th ICNCT, November 2008, Florence, Italy

Member of Scientific Committee of 14th, 15th and 16th ICNCT (2010 Argentina, 2012 Japan and 2014 Finland, respectively).

Member of Scientific Committee of 7th Young researcher BNCT meeting, 2013, Granada, Spain.

Member of Executive Board of Italian Society of Research in Radiation (SIRR) 2011-2013: Principal Investigator of the project "La terapia per cattura neutronica: una nuova prospettiva per il trattamento dell'osteosarcoma" funded in the call FIRB-Futuro in Ricerca 2008.

Other Funded Projects:

- 2018-2021 Participant in the project "Dipartimento di Eccellenza", Dept of Physics, University of Pavia, in the part dedicated to medical physics
- 2017 and 2018 Coordinator of a project funded by CUIA (Consorzio Università Italia Argentina) for the organization of a workshop in Buenos Aires.
- 2017-2019 PI of INFN project BEAT_PRO
- 2016-2018 local responsible of MAECI project NEU_BEAT, executive programme of

scientific and technological cooperation between Italy and China 16-18

- 2014-2016 participant in Project PIP, CONICET, Argentina.
- 2014-2016 participant in Project PICT "Terapia por Captura Neutrónica en Boro (BNCT) para un tratamiento novel de metástasis múltiples en pulmón: estudio de BNCT ex-situ en oveja y estudio de BNCT in-situ en rata", CONICET, Argentina.
- 2013-2016: local responsible of the INFN experiments NeTTuNO and NeuTargs
- 2013-2015: participant in INFN "progetto premiale" MUNES "Multidisciplinary Neutron Source"
- 2012-2014: local responsible of the project: "Boron Neutron Capture Therapy (BNCT) in cutaneous recurrences of breast cancer: the diagnostic and therapeutic utility of 18F-FBPA PET/CT" funded by Italian Ministry of Health in the scheme "ricerca finalizzata 2010"
- 2011-2012 participant in CARIPLO project "Characterization of boron carrying magnetic nanoparticles for MRI assisted BNCT (Boron Neutron Capture Therapy)"
- 2011-2012 participant in INFN experiment MIMO-BRAGG
- 2011-2013 participant in INFN experiment ARCO
- 2009-2012 participant in INFN experiment Widest1
- 2007-2008 participant in INFN experiment Widest
- 2007-2008 participant in PRIN 2006 "Trattamento metastasi polmonari mediante cattura neutronica: studi preliminari"
- 2007-2008 participant in INFN experiment ELBA
- 2005-2006 participant in PRIN 2004 "Misura di assorbimento del boro in tessuto polmonare di ratto affetto da tumore"

- 2006-2010 participant in an International FIRB project 2004 "Studi proteomici e farmacocinetici in relazione alla terapia antitumorale BNCT
- 2004-2006 participant in INFN experiment TAoRMINA3

National and International Congresses contributions: 12
Seminars/invited presentations: 10 international, 5 national
Invited talk in plenary sessions (international congresses): 2
Pubblications in Proceedings: 17
Abstract to national and international congresses: more than 40

Guest Editor of Special Issue of Applied Radiation and Isotopes 67(7-8), 2009 (Int. Conf. 13th ICNCT, Firenze Nov 2008).
Reviewer for Medical Physics, Applied Radiation and Isotopes and others.

Research Visiting Periods Abroad:

- 2007 Host: Dr Marcelo Miller, Departamento de Instrumentacion y Control - CNEA, Buenos Aires, Argentina
- 2009 Host: Dr Marcelo Miller, Departamento de Instrumentacion y Control - CNEA, Buenos Aires, Argentina
- 2010 Host: Dr Sara J. González, Grupo de Dosimetría Computacional y Treatment Planning - CNEA, Buenos Aires, Argentina
- 2011 Host: Dr Sara J. González, Grupo de Dosimetría Computacional y Treatment Planning - CNEA, Buenos Aires, Argentina
- 2014 Host: Dr Sara J. González, Grupo de Dosimetría Computacional y Treatment Planning - CNEA, Buenos Aires, Argentina

- 2015 Host: Dr Sara J. González, Grupo de Dosimetría Computacional y Treatment Planning - CNEA, Buenos Aires, Argentina
- 2015 Host: Prof. Sandro Guedes, Physics Institute, University of Campinas, Brasil
- 2016 Host: Dr Sara J. González, Grupo de Dosimetría Computacional y Treatment Planning - CNEA, Buenos Aires, Argentina
- 2017 Host: Dr Sara J. González, Grupo de Dosimetría Computacional y Treatment Planning - CNEA, Buenos Aires, Argentina
- 2018 Host: Prof. Xiaobin Tang, Nanjing University of Areonautics and Astronautics, Nanjing, China

Research Products

(From Sopus database)

Publications: 61

Citations: 522

h-index: 12

Pubblications

1. S. Bortolussi, I. Postuma, N. Protti, L. Provenzano, C. Ferrari, L. Cansolino, P. Dionigi, O. Galasso, G. Gasparini, S. Altieri, S.-I. Miyatake and S.J. González, Understanding the potentiality of accelerator based-boron neutron capture therapy for osteosarcoma: dosimetry assessment based on the reported clinical experience, Radiation Oncology 2017 12:130
2. González SJ, Pozzi ECC, Monti Hughes A, Provenzano L, Koivunoro H, Carando DG, Thorp SI, Casal MR, Bertolussi S, Trivillin VA, Garabalino MA, Curotto P, Heber EM, Santa Cruz GA, Kankaanranta L, Joensuu H, Schwint AE. Photon iso-effective dose for cancer

treatment with mixed field radiation based on dose-response assessment from human and an animal model: clinical application to boron neutron capture therapy for head and neck cancer. Phys Med Biol. 2017, 62(20):7938-7958.

3. S. Bortolussi, N. Protti, M. Ferrari, I. Postuma, S. Fatemi, M. Prata, F. Ballarini, M.P. Carante, R. Farias, S. J. González, M. Marrale, S. Gallo, A. Bartolotta, G. Iacoviello, D. Nigg, S. Altieri, Neutron flux and gamma dose measurement in the BNCT irradiation facility at the TRIGA reactor of the University of Pavia, NIMB, 2018, 414:113-120

4. I. Postuma, S.Bortolussi, N.Protti, F.Ballarini, P.Bruschi, L. Ciani, S.Ristori, L.Panza, C.Ferrari, L.Cansolino, S.Altieri ?An improved neutron autoradiography set-up for 10B concentration measurements in biological samples?, reports of practical oncology and radiotherapy, 21(2), 2016, 123?128

5. R.O. Farías, S.Bortolussi, P.R. Menéndez, S.J. González, Exploring Boron Neutron Capture Therapy for non-small cell lung cancer, Physica Medica, 30(8), 2014, 888?897

6. S.Bortolussi and S.Altieri ?Boron Concentration Measurement in Biological Tissues by Charged Particles Spectrometry?, Rad. Env. Biophys, (2013) 52:493?503

7. L. Cansolino, A.M. Clerici, C. Zonta, P. Dionigi, G. Mazzini, R. Di Liberto, S. Altieri, F. Ballarini, S. Bortolussi, M.P. Carante, M. Ferrari, S.J. González, I. Postuma, N.Protti, G.A. Santa Cruz and C. Ferrari ?Comparative Study of the Radiobiological Effects Induced on Adherent vs Suspended Cells by BNCT, Neutrons and Gamma Rays Treatments? Appl Radiat Isot, 2015 106:226-32

8. M.A.Gadan, S.Bortolussi, I.Postuma, F. Ballarini, P.Bruschi, N.Protti, D. Santoro, S.Stella, L.Cansolino, A.Clerici, C.Ferrari, A.Zonta, C. Zonta and S.Altieri, ?Set-up and calibration of a Method to Measure 10B Concentration in Biological Samples by Neutron Autoradiography?, Nucl. Meas. Meth. B 274 (2012) 51?56

9. S.Bortolussi, J.G.Bakeine, F.Ballarini, P.Bruschi, M.A.Gadan, N.Protti, S. Stella, A.Clerici, C.Ferrari, L.Cansolino, C.Zonta, A.Zonta, R.Nano and S.Altieri, ?Boron uptake measurements in a rat model for Boron Neutron Capture Therapy of lung tumours?, Appl. Rad. Isot., 69 (2011) 394?398

10. C. Ferrari, J. Bakeine, F. Ballarini, A. Boninella, S. Bortolussi, P. Bruschi, L. Cansolino, A.M.Clerici, P. Dionigi, N. Protti, S. Stella, A. Zonta, C. Zonta and S. Altieri. Experimental and theoretical studies for Boron Neutron Capture Therapy down to cellular level: Boron uptake/washout and cell death, Rad. Res., 2011, vol. 175, 452-462.

3.2.6 WP3 leader: Stefano Agosteo

Stefano Giulini Castiglioni Agosteo is a full professor in the field of Nuclear Measurements and Instrumentation at the Politecnico di Milano. Since 1992 he has been collaborating with the TERA program for constructing a hadrontherapy centre in Italy, presently operating in Pavia (CNAO). He has been involved mainly in the radiation protection aspects of the hadrontherapy centre and in the design of an accelerator-based neutron source for boron neutron capture therapy (BNCT). Since 1996 S. Agosteo has been collaborating with the radiation protection group of CERN. In the period 1996-2000, this collaboration aimed at measuring the neutron spectra in the SPS experimental halls and the neutron yield from targets of different materials bombarded by protons and lead ion beams with momenta higher than 40 GeV/c. Other topics in the framework of this collaboration were: the calculation of attenuation curves in concrete of secondary radiation from high and intermediate energy charged hadrons on targets of various materials; the characterization of high-energy neutron detectors. His research interests are also focussed on radiation dosimetry, microdosimetry and neutron spectrometry. In particular, the research in the field of microdosimetry is addressed to the assessment of radiation quality of hadrontherapy fields. He was responsible (at the local and/or national level) for several research programs of the INFN in the field of BNCT, neutron spectrometry with silicon detectors, silicon microdosimetry and microdosimetry at the nanometric level.

Presently he is the local responsible (INFN-MI) for the INFN NIRVANA (Nuovi Rivelatori per Nanodosimetria) project, aiming at studying new detectors for nanodosimetry.. He is a full member of the Working Group 6 'Computational Dosimetry' of the EURADOS, the European Radiation Dosimetry Group. He acted as the scientist in charge for the Politecnico di Milano of the ARDENT ITN Marie Curie project, funded by the EU under contract PITN-GA-2011-289198-ARDENT. In the period 2010-2017 he acted as the Chairman of the MSc Course in Nuclear Engineering of the Politecnico di Milano. He is a member of the PhD Council in Energy and Nuclear Science and Technology of the Politecnico di Milano. He is a corresponding member of the Istituto Lombardo Accademia di Scienze e Lettere. He is a member of the Editorial Board of Radiation Measurements and he acts as a reviewer for several international journals.

Pubblications

1. S. Agosteo, M. Silari, L. Ulrici, Instrument Response in Complex Radiation Fields, Radiation Protection Dosimetry, 137 (2009) 51-73 doi: 10.1093/rpd/ncp186.

2. A. Wroe, R. Schulte, A. Fazzi, A. Pola, S. Agosteo, A. Rozenfeld, RBE Estimation of Proton Radiation Fields Using a ?E-E Telescope, Medical Physics 36 (2009) 4486-4494.

3. S. Agosteo, Overview of Novel Techniques for Radiation Protection and Dosimetry, Radiation Measurements 45 (2010) 1171-1177.

4. S. Agosteo, G.A.P. Cirrone, P. Colautti, G. Cuttone, G. D'Angelo, A. Fazzi, M.V. Introini, D. Moro, A. Pola, V. Varoli, Study of a silicon telescope for solid state microdosimetry: preliminary measurements at the therapeutic proton beam line of CATANA, Radiation Measurements 45 (2010) 1284-1289. doi: 10.1016/j.radmeas/2010.06.051.

5. S. Agosteo, A. Pola, Silicon microdosimetry, Radiation Protection Dosimetry 143 (2011) 409-415, doi: 10.1093/rpd/ncq408.

6. S. Agosteo, A. Fazzi, M.V. Introini, A. Pola, A.B. Rosenfeld, R. Shulte, A. Wroe, Study of

a monolithic silicon telescope for solid state microdosimetry: Response to a 100 MeV proton beam, Radiation Measurements 46 (2011) 1529-1533.

7. S. Agosteo, G.A.P. Cirrone, G. D?Angelo, A. Fazzi, M.V. Introini, A. Pola, Feasibility study of radiation quality assessment with a monolithic silicon telescope: Irradiations with 62 AMeV carbon ions at LNS-INFN Radiation Measurements 46 (2011) 1534-1538.

8. S. Agosteo, A. Fazzi, M.V. Introini, M. Lorenzoli, A. Pola, A telescope detection system for direct and high resolution spectrometry of intense neutron fields, Radiation Measurements 85 (2016) 1-17. http://dx.doi.org/10.1016/j.radmeas.2015.12.005/1350-4487/

9. D. Bortot, A. Pola, S. Agosteo, S. Pasquato, D. Mazzucconi, A. Fazzi, P. Colautti, V. Conte, A novel avalanche-confinement TEPC for microdosimetry at nanometric level, Radiation Measurements 103 (2017) 1-12.

10. D. Mazzucconi, D. Bortot, A. Pola, S. Agosteo, S. Pasquato, A. Fazzi, P. Colautti, V. Conte, Monte Carlo simulation of a new TEPC for microdosimetry at nanometric level: Response against a carbon ion beam, Radiation Measurements 113 (2018) 7-13.

3.2.7 WP4 leader: Lorenzo Manti

General information:

Name: Lorenzo Manti

Phone numbers: +39081676262 (office); +39081676219 (lab)

e-mails: manti@na.infn.it; lorenzo.manti@unina.it

Current position

Associate Professor of Applied Physics, Department of Physics, University of Naples Federico II, Via Cintia, Complesso Universitario di Monte S. Angelo, Naples 80126, Italy

Education and career:

- 1994: Degree in Physics (first class with honours) at the University of Naples Federico II.
- 1995: MSc in Radiation Biology (grant from European Radiation Protection Education and Training Action-ERPET), St. Bartholomew?s Hospital Medical, University of London, UK
- 1996: Bursary, TERA (TERapia con Adroni) project, Gray Laboratory, London, UK
- 2001: PhD in Radiation Biology (grant from Cancer Research Wales), School of Bio-Sciences, University of Wales, Cardiff. UK.
- 2002: Research contract, Radiation Biophysics Laboratory, Department of Physical Sciences, University of Naples Federico II, Italy
- 2002- 2017 Researcher, Department of Physical Sciences, University of Naples Federico II, Italy.
- 2007, October Visiting Scholar, Institute for Environmental Medicine, University of Philadelphia, US
- 2011, March Visiting Research Fellow, School of Medicine, Dentistry and Biomedical Sciences, Queen's University, Belfast, UK
- 2017- present Associate Professor, University of Naples Federico II, Italy

Main research activity and interests

- Charged particle radiation biology
- Non-cancer late effects in hadrontherapy

- Radiation-induced chromosome aberrations and premature cellular senescence
- Radiation-induced genomic instability and cellular radiosensitivity
- Tumour radiosensitization
- Radiobiology of laser-generated particle beams

Principal Investigator (PI) or local coordinator of funded research projects

- 2008-09: 'Effects of radiofrequency microwaves (UMTS signal) on the progeny of human cells damaged by ionising radiation', in collaboration with the Department of Engineering and Telecommunications and approved in 2009 by the local government (Regione Campania) funding Office.
- 2009: Italian National Institute of Nuclear Physics (INFN)-funded project BIORT on the radiobiological properties of Intra-Operatory Radiotherapy.
- 2010:INFN-funded project ARCAICA on the adaptive response to mobile telephony radiofrequency fields induced by ionizing radiation.
- 2012-13: INFN-funded project MIMO-BRAGG on the induction of cytogenetic damage by various ions and modelization of track-structure role.
- 2013-15 INFN-funded PLASMA_med (Proton LASer-driven beam transport, diagnostic and MEdical Applications). Local coordinator
- 2015- present INFN-funded project ETHICS ?Pre-clinical Experimental and THeoretical studies to Improve treatment and protection by Charged particleS: Understanding the underlying action mechanisms on normal cells by charged particles used in medicine to reduce the risks for human health?.

Participation to other research projects

I have worked on the following Italian National Institute of Nuclear Physics (INFN)-funded projects:

- Molecular and cellular effects of various LET carbon ions (Grant ATER.BIOR, 2002).
- Biological effects of heavy ions from the cosmic radiation field for astronauts? radiation protection (Grant SHIELD, 2003-2006) in collaboration with NASA
- Late effects of heavy ions in in vitro biological systems of interest in hadrontherapy (Grant ETIOPE, 2006-2008)
- Physical characterization for radiation protection purposes of novel shielding materials (kevlar and nextel) to be used for space exploration (Grant SPADA, 2007-2009)
- Radiosensibilization of radioresistant gliomas by concomitant use of high-LET ion radiation (carbon ions) and chemotherapy (Grant TPS, 2010-12)

Academic and non-academic responsibilities

- 2017-present President of the European Radiation Research Society (ERRS), www.errs.eu
- 2017-present Member of the Departmental Committee for Outreach and Scientific divulgation, Physics Dept., University of Naples Federico II
- 2016-present: Editorial Board of Frontiers Public Health
- 2016-present: Review Editor of the Frontiers journals collection
- 2016-present: Member of the Teaching Council, PhD School in Mathematics, Physics and Applied Engineering, Università della Campania 'Luigi Vanvitelli', Caserta, Italy

- 2015: Referee for the European Metrology Programme for Innovation and Research (EMPIR)-Call 2015
- 2014-present: Editorial Board of International Journal of Radiology
- 2014-present: Faculty Member of training course Molecular Mechanisms of Radiation Carcinogenesis, European Joint Programme CONCERT, Helmholtz-Center e Technical University, Munich, Germany
- 2009-present: Member of the Teaching Council, Medical Physics School, University of Naples Federico II, Naples, italy
- 2004-2017: Associate member, Radiation Research Society (RRS)
- 2007-2012 Coordinator of the Teaching Laboratories, Physical Sciences Department, University of Naples Federico II
- 2003-2012 Chief-Editor of the official magazine by the Italian Society for Radiation Research (Società Italiana per la Ricerca sulle Radiazioni-SIRR)

Responsibilities in scientific/organizing committees:

- 14th International Congress of Radiation Research (ICRR), Warsaw, Poland (2011)
- 39th Annual Meeting of the European Radiation (ERRS), Vietri sul Mare, Italy (2012)
- 40th Annual ERRS Meeting, Dublin, EIRE (2013)
- 41st Annual ERRS Meeting, Rhodes, Greece (2014)
- 15th ICCR Meeting, Kyoto, Japan (2015)
- 42nd Annual ERRS Meeting, Amsterdam, The Netherlands (2016)

- 43rd Annual Meeting of the ERRS and 20th Annual Meeting of the German Society for Biological Radiation Research (GBS), Essen, Germany (2017).

Reviewer for the following journals:

- Nature-Scientific Reports
- Frontiers in Oncology
- Frontiers in Immunology
- Oncotarget
- International Journal of Radiation Oncology, Biology, Physics
- Mutation Research-Genetic Toxicology and Environmental Mutagenesis
- PLoS One
- Radiation and Environmental Biophysics
- International Journal of Radiation Biology
- Radiation Research
- Nuclear Instruments and Methods in Nuclear Physics B
- British Journal of Radiology
- Central European Journal of Biology
- Journal of Radiation Research
- International Journal of Hygiene and Environmental Health
- Physica Medica

- Life Sciences in Space Research
- JINST-Journal of Instrumentation
- Journal of Inflammation
- Journal of Biotechnology
- Environmental Engineering and Management Journal
- Translational Cancer Research

Teaching duties

- 1996-2000 University of Cardiff, UK
- Biostatistics and Applications of Computing Sciences for the Analysis of Experimental Data
- Applied Mathematics for Biological Sciences
- 2001-Present University of Naples Federico II, Italy
  Bioinformatics (curriculum in Health Biotechnologies)
  Laboratory of General Physics (curriculum in Environmental Sciences)
  Laboratory of General Physics (curriculum in Chemistry)
  General Physics (curriculum in Physics)
  Radiation Biology (MSc in Health Physics and PhD in Physics)
  Biophysics (curriculum Physics degree)
  Radiation biophysics (MSc in Physics)

Supervisor of 50 final year theses for the achievement of the degree in Physics, in Biological Sciences and Environmental Sciences. Supervisor of 1 PhD thesis in Physics. Currently

supervising 1 BSc student and 1 PhD student in Physics. External referee for 2 PhD theses in Physics

Author of over 50 papers in peer-reviewed journals and over 100 conference proceedings.

Pubblications

1. Manti L., Jamali M., Prise K. M., Michael B. D., Trott K. R., Genomic instability in Chinese hamster cells after exposure to x-rays, neutrons or alpha?particles of different LET. Radiat. Res., 147, 22-28 (1997).

2. Manti L., Davies H. E., Venables S., Bowen I. D., Court J. B., Correlation between the clonogenic initial slope and the response of polykaryon-forming units: the behavior of strains defective in Xrcc5 and ATM and the heritability of small variations in radioresponse. Radiat. Res., 154, 650-658 (2000).

3. Manti L., Durante M., Grossi G., Ortenzia O., Pugliese M., Scampoli P., Gialanella G., Measurements of metaphase and interphase chromosome aberrations transmitted through early cell replication rounds in human lymphocytes exposed to low-LET protons and high-LET 12C ions. Mutat. Res, 596, 151-165 (2006).

4. Belli M., Bettega D., Calzolari P., Cherubini R., Cuttone G., Durante M., Esposito G., Furusawa Y., Gerardi S., Gialanella G., Grossi G., Manti L., Marchesini R., Pugliese M., Scampoli P., Simone G., Sorrentino E., Tabocchini M. A., Tallone L., Effectiveness of monoenergetic and spread-out Bragg peak carbon ions for inactivation of various normal and tumour human cell lines. J. Radiat. Res., 49, 597-607 (2008).

5. Manti L., D?Arco A., Cooperative biological effects between ionizing radiation and other physical and chemical agents Mutat. Res. Rev., 704, 115-122 (2010).

6. P. Chaudhary, T. Marshall, L. Manti, F.J. Currell, S.J. McMahon, J.N. Kavanagh, G.A.P. Cirrone, F. Romano, K.M. Prise, G. Schettino, RBE variation along monoenergetic and

modulated Bragg peaks of a 62 MeV therapeutic proton beam: a pre-clinical assessment. Int. J. Radiat. Oncol. Biol. Phys. 90, 27-35 (2014) Savage K I, Gorski JJ, Barros EM, Irwin GW, Manti L, Powell AJ, Pellagatti A, Lukashchuk N, McCance DJ,

7. McCluggage WG, Schettino G, Salto-Tellez M 1, Boultwood J, Derek J. Richard DJ, McDade SS, Harkin D P, Identification of a BRCA1-mRNA splicing complex required for efficient DNA repair and maintenance of genomic stability. Mol. Cell, 54, 445-459 (2014)

8. L. Manti, F. M. Perozziello, M. Borghesi, G. Candiano, P. Chaudhary, G.A.P. Cirrone, D. Doria, D. Gwynne, R. Leanza, K. M. Prise, L. Romagnani, F. Romano, V. Scuderi, A.Tramontana The radiobiology of laser-driven particle beams: focus on sub-lethal responses of normal human cells. JINST, 12, C03084 (2017)

9. J. Vohhodina, E. Barros, A. L. Savage, F. Liberante, L. Manti, P. Bankhead, N. Cosgrove, A. F. Madden, D. P. Harkin, K.I. Savage, The RNA processing factors THRAP3 and BCLAF1 promote the DNA damage response through selective mRNA splicing and nuclear export, Nucleic Acids Res, 45, 12816-12833 (2017)

10. G.A.P. Cirrone, L. Manti, D. Margarone, G. Petringa, L.Giuffrida, A. Minopoli, A. Picciotto, G. Russo, F. Cammarata, P. Pisciotta, F. M. Perozziello FM, F. Romano, V. Marchese, G. Miluzzo, V. Scuderi, G. Cuttone, G. Korg. First experimental proof of the Proton Boron Capture Therapy (PBCT) to enhance protontherapy effectiveness. Sci. Rep., 8, 1141 (2018)

3.2.8 WP5 leader: Chiara La Tessa

Dr. Chiara La Tessa has been working in physics research since 2003. Her activities have included experiments, data analysis as well as theoretical investigations and Monte Carlo simulations. Since the master thesis she has been involved in research programs merging fundamental physics, biology and medical fields. Her research has been focused on the physics of radiation-matter interaction and its applications to cancer therapy (mainly using

charged particles) and radiation protection in space, keeping a close interest in radiation biology. In the past 9 years, she has been working in physics laboratories where, together with carrying on a research program, she has coordinated and supervised the daily activities, maintenance and development of the facilities and beam lines. For 2 years, dr. La Tessa was tenured and leader of the radiation physics group at GSI (Darmstadt, Germany) and for 3 and half years worked as one of the coordinators of the NASA Space Radiation Laboratory (NSRL) at Brookhaven National Laboratory (Upton, NY, USA). She is currently on a tenure track at the Department of Physics of the University of Trento (Italy), a position received by direct appointment. Dr. La Tessa is also associated (con incarico di ricerca) to the Italian Institute of Nuclear Physics (INFN) and one of the coordinators of the experimental room located in the Trento protonterapy center (Italy).

Key-words of the research activity:

- Experimental and theoretical study of particle interaction with matter
- Radiation biophysics
- Nuclear fragmentation
- Medical physics in particle therapy
- Dosimetry and microdosimetry
- Radiation protection in space
- Monte Carlo simulations

2003-2007:PhD student within the department of Applied Physics at Chalmers University of Technology (Göteborg, Sweden). During the PhD project, she studied the process of nuclear fragmentation using both an experimental and theoretical approach. She performed measurements in collaboration with the Life science division at Lawrence Berkeley National

Laboratory (LBNL) (CA, USA) and learned the tools for the data analysis. Dr. La Tessa studied the fragmentation cross section systematics, focusing on validating the weak and strong factorization properties. She became an advanced user of the PHITS Monte Carlo transport code and also developed a semiempirical model based on the weak factorization property and able to predict projectile partial charge-changing cross sections for heavy ions.

2007-2009:Postdoctoral fellow at the University "Tor Vergata" (Rome, Italy). The research of the group she joined, focused on a project called ALTEA (Anomalous Long Term Effect on Astronauts) whose goal was to characterize the radiation field inside the ISS (International Space Station) and in particular to study the phenomenon of light flashes perceived by astronauts during their permanence in space. Her main task within the project was to be in charge of the simulations using different Monte Carlo codes (PHITS and GEANT4).

2009-2011:Postdoctoral fellow at GSI Helmholtzzentrum für Schwerionenforschung GmbH (Darmstadt, Germany)

2011-2013: Tenured and group leader at GSI Helmholtzzentrum für Schwerionenforschung GmbH (Darmstadt, Germany) When dr. La Tessa joined the Biophysics group at GSI, she used my expertise in experimental and theoretical nuclear physics to tackle several scientific challenges in the field of radiotherapy. Her primary interest was to study the physical processes that change the composition and spatial distribution of the primary beam when interacting with the patient?s body and how these changes effect the dose distribution. To do so, she experimentally characterized the interaction of light ions (Protons, Helium, Lithium, Carbon, Oxygen) with elemental and tissue-like materials. She also performed a comprehensive study of the 3D dose profile both inside and outside the tumor volume for innovative radiation therapies both with photons (IMRT) and ions (Protons and Carbon ions passively delivered or scanned). Dr. La Tessa performed this research as a participant to the European project FP7

(grant agreement No: 231965) called ALLEGRO. Exploiting nuclear fragmentation, she also worked on developing a technique alternative to Positron Emission Tomography (PET) for real-time monitoring of the irradiated volume position during a radiation treatment with ions. She also dedicated my research to space radioprotection by testing and optimizing shielding materials for applications in orbiting stations, spacecraft and permanent human bases on other planets. The study included dosimetry and microdosimetry measurements as well as a physical characterization of the mixed radiation field created by fragmentation of the primary ions inside the shield. This study was part of the ESA funded project entitled ROSSINI (grant agreement No: SGI-TASI-PRO-0026) of which Dr. La Tessa was a coapplicant. During her work at GSI she mainly gained expertise in detector developments, experimental techniques, electronics and advanced data analysis.

2013-2016:Associate physicist and facility coordinator of the NASA Space Radiation Laboratory (NSRL) within the Collider-Accelerator Department at Brookhaven National Laboratory (BNL). At NSRL, Dr. La Tessa was in charge of the operation support to users in the areas of biology and physics. The job consisted of advising and supporting the users in various aspects concerning the design and realization of their experiments. It also had a technical side, which includes beam line maintenance, upgrade, beam setting and dosimetry. She also carried on my work on the nuclear interactions, performing experiments to characterize fragmentation and scattering of projectiles of interest both for space and ion therapy research. She became a co-Principal Investigator of the Transport Codes and Measurements Phase III Project funded by NASA SRPE and based at NSRL. The goal of the experiment was to provide double differential isotopic charge-changing cross sections for benchmarking deterministic and Monte Carlo codes of interest for NASA. In 2013, Dr. La Tessa joined the Radiation Research Society (RADRES), where she became the group leader for physics of the Early Career Investigators (ECI) and a member of the program advisory committee. In 2018, she has been elected Counselor-at-Large of the RADRES.

2016-present: Tenure track for associate professor (RTDB) at the University of Trento (Italy) Her research activities at the Physics Department in Trento, have been centered on two topics: radiotherapy and space radioprotection. In 2017, dr. La Tessa became associated to the INFN and appointed as one of the coordinators of the TIFPA-INFN experimental room in the Trento Protontherapy center, which has been fully operational and open to external users since 2016. In 2017, the facility has been selected as one of the core facilities of the ESA-IBER program. She am currently among the participants of the INFN CSN3 project "FOOT - Fragmentation of The Target".

Awards

- 1st prize at the Young Scientist Oral Presentation Award at the Heavy Ion in Therapy and Space Symposium, Cologne, Germany, July 6th ? 10th 2009.
- Zeldovich Medal for COSPAR Scientific Commission F, 39th COSPAR Scientific Assembly, July 14th ? 22nd 2012, Mysore, India.
- June 2015 CSWP woman physicist of the month.
- ECI travel grant award for participating to the 63rd (Cancun, Mexico, 2017) and 64th (Chicago, IL, US, 2018) Radiation Research Society (RADRES) Annual meeting.

Side appointments to scientific activities

- Counselor-at-Large for the Radiation Research Society (RADRES) (2018-2021).
- Member of the PhD program committee at the Department of Physics of the University of Trento (Italy) (2017-present).

- Member of the European Space Agency (ESA) topical team "Space Radiation Research"(2016-present).
- Member of the Steering Committee for the European call in Hadron Physics INFRAIA-01-2018-2019: "Integrating Activities for Advanced Communities".
- Member of the INFN 2015 and 2016 committee awarding the funding for six projects presented by young researchers.
- Member of the INFN 2016 committee awarding twelve postdoctoral fellowships to foreign researchers.

Referee for the following journals: Physics in Medicine and Biology, Physica Medica, British Journal of Radiology, Radiation Oncology, Radiotherapy and Oncology, Advances in Space Research, Radiation Measurements, Radiation Research, Medical Physics, IEEE Transaction on Nuclear Science.

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Pubblications

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2. C. La Tessa, L. Sihver, C. Zeitlin, J. Miller, S. Guetersloh, L. Heilbronn, D. Mancusi, Y. Iwata and T. Murakami, Test of weak and strong factorization in nucleus-nucleus collisions at several hundred MeV/nucleon, Nucl. Phys. A 791, 434-450(2007).

3. C. La Tessa, L. Di Fino, M. Larosa, K. Lee, D. Mancusi, D. Matthiä, L. Narici and V. Zaconte, Simulation of ALTEA calibrationdata with PHITS, FLUKA and GEANT4, Nucl. Instrum. Meth. B 267, 3549-3557(2009).

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8. M. Rovituso, C. Schuy, U. Weber, S. Brons, M. A. Cortés-Giraldo, C. La Tessa, E. Piasetzky, D. Izraeli, D. Schardt, M. Toppi, E. Scifoni, M. Krämer, M. Durante, Fragmentation of 120 and 200 MeVu1 4He ions in water and PMMA targets, Phys. Med. Biol. 62, 1310-1326(2017).

9. F. Tommasino, M. Rovituso, S. Fabiano, S. Piffer, C. Manea, S. Lorentini, S. Lanzone, Z. Wang, M. Pasini, W. J. Burger, C. La Tessa, E. Scifoni, M. Schwarz, M. Durante, Proton beam characterization in the experimental room of the Trento Proton Therapy facility, NIMA 869, 15-20 (2017).

10. M. Rovituso, C. La Tessa, Nuclear interactions of new ions in cancer therapy: impact on dosimetry, Transl. Cancer Res. 6, S914-S933(2017).

3.3 Patents

(19) Europäisches Patentamt
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Remarks:
Claim 18 is deemed to be abandoned due to non-payment of the claims fee (Rule 45(3) EPC).

(54) **DEVICE AND METHOD FOR IMAGING AND ENHANCED PROTON-THERAPY TREATMENT USING NUCLEAR REACTIONS**

(57) The present invention provides a device, a system and a method for cancer therapy based on proton boron nuclear fusion reaction and simultaneous prompt gamma-ray imaging. The invention is based on the use of an incoming energetic proton beam interacting with a mixture of ^{11}B and ^{10}B isotopes to achieve simultaneity of the clinical irradiation and imaging, as well as to enhance the biological dose released into the cancer cells. The device is specifically adapted to performing such treatment.

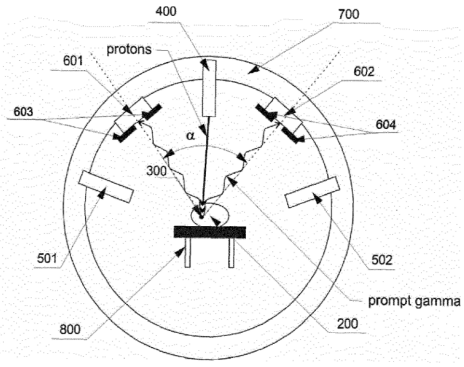

Fig. 2

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