Ministero dell'Istruzione dell'Università e della Ricerca

Dipartimento per la formazione superiore e per la Ricerca
Direzione Generale per il Coordinamento, la promozione e la valorizzazione della Ricerca

PRIN: PROGETTI DI RICERCA DI RILEVANTE INTERESSE NAZIONALE – Bando 2017
Prot. 2017XKWWK9

PART A

1. Action line

South line/Linea Sud

2. Research project title

PBCT Proton Boron Capture Therapy

3. Duration (months)

36 months

4. Main ERC field

PE - Physical Sciences and Engineering

5. Possible other ERC field

LS - Life Sciences

6. ERC subfields

1. PE2_3 Nuclear physics
2. PE6_12 Scientific computing, simulation and modelling tools
3. LS7_7 Radiation therapy

7. Key Words

nº	Testo inglese
1.	applied physics
2.	radiotherapy
3.	medical physics
4.	nuclear physics
5.	applications of physics in biology
6.	Protontherapy enhancement

8. Principal Investigator

CUTTONE (Surname)	**GIACOMO** (Name)
Dirigente di ricerca (Category)	
18/02/1960 (Date of birth)	**CTTGCM60B18C351G** (Personal identification code)
Istituto Nazionale di Fisica Nucleare (University)	
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9. List of the Research Units

nº	Associated Investigator	Category	University/ Research Institution	Registered office (address)	Does operating office coincide with	Operating office (address)	Contract of availability	Declaration of availability of	e-mail address

					registered office?		of operating office	the operating office and copy of contract	
1.	CUTTONE Giacomo	Dirigente di ricerca	Istituto Nazionale di Fisica Nucleare	Via Enrico Fermi, 40 - Frascati (Roma) (RM)	no	City: Catania (CT) Address Via S Sofia 63	lease		cuttone@lns.infn.it
2.	MANTI Lorenzo	Professore Associato (L. 240/10)	Università degli Studi di Napoli Federico II	C.so Umberto I, 40 - NAPOLI (NA)	no	City: Napoli (NA) Address Via Cinthia 26	property		manti@na.infn.it
3.	PACIFICO Severina	Ricercatore confermato	Università degli Studi della Campania "Luigi Vanvitelli"	Viale Abramo Lincoln n.5 - CASERTA (CE)	no	City: Caserta (CE) Address Via Vivaldi 43	property		severina.pacifico@unina2.it
4.	PARENTI Rosalba	Professore Associato confermato	Università degli Studi di CATANIA	P.zza dell'Universita',2 - CATANIA (CT)	no	City: Catania (CT) Address Via S Sofia Sofia 97	property		parenti@unict.it
5.	RUSSO Giorgio	Ricercatore	Consiglio Nazionale delle Ricerche	Piazzale Aldo Moro, 7 - Roma (RM)	no	City: Cefalù (PA) Address Contrada Pietrapollastra - Pisciotto	free availability		giorgio-russo@cnr.it

10. Brief description of the research proposal

The PBCT project aims at establishing the p+11B3 (p-B) reaction as a novel strategy to enhance protontherapy effectiveness. The reaction effects will be investigated in human glioma cells both in in-vitro and in-vivo models, in conjunction with boron uptake and metabolization studies. Analytical models will link the observed radiobiological results with the physics underlying the reaction. First proposed by Do-Kun et al. [1] but in vitro experimentally proved by Cirrone et al [2], the rationale for PBCT lies in the high radiobiological effectiveness of the short-range alpha particles generated in the p-B reaction. Except for the superior ballistic precision at conforming the dose to the cancer volume, protontherapy lacks a distinctive clinical advantage over conventional radiotherapy, protons being almost as effective as photons/electrons at damaging DNA. Thus, PBCT could treat radioresistant cancers (e.g. gliomas), for which protons are currently of no avail. Moreover, locally increasing the biological effective dose to tumors would allow a major shift towards hypofractionation regimes, improving protontherapy cost-effectiveness. The final aim of this project is, therefore, to prove the viability of PBCT, paving the way for the first clinical trials on patients.

11. Total cost of the research project, per single item

Associated Investigator	item A.1	item A.2.1	item B	item C	item D	item E	sub-total	item F	Total

CUTTONE Giacomo	105.133	85.200	114.200	95.000	0	20.000	419.533	34.882,56	**454.415,56**
MANTI Lorenzo	40.833	75.000	69.500	10.000	0	20.000	215.333		**215.333**
PACIFICO Severina	25.000	25.000	30.000	0	0	20.000	100.000		**100.000**
PARENTI Rosalba	51.660	75.000	75.996	0	0	30.000	232.656		**232.656**
RUSSO Giorgio	38.119	71.400	65.711	0	0	20.000	195.230		**195.230**
Total	**260.745**	**331.600**	**355.407**	**105.000**	**0**	**110.000**	**1.162.752**	**34.882,56**	**1.197.634,56**

- item A.1: Enhancement of months/person of permanent employees
- item A.2.1: Cost of contracts of non-employees, specifically to recruit
- item B: Overheads (flat rate equal to 60% of the total cost of staff, A.1 + A.2.1, for each research unit)
- item C: Cost of equipment, instruments and software
- item D: Cost of consulting services and similar
- item E: Other operating costs
- item F: Prize (automatically calculated as 3% of total cost of the project)

PART B

B.1

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1. Abstract

Cancer therapy is a multi-modality approach including surgery, systemic or targeted chemotherapy, radiation (by external beams or through radionuclide incorporation), and immunotherapy. Radiotherapy is typically administered using external photon or electron beams. Protontherapy has been around for more than 60 years, but remained confined to research laboratories until the 1990s. Since then, clinical protontherapy has been growing rapidly counting nowadays more than 80 facilities worldwide. The interest in protontherapy stems from the physical properties of protons allowing for a much improved dose painting around the target and greater sparing of healthy tissue.

In the last decades, research efforts in the field of photon-based radiotherapy have reduced the dosimetric gap between photons and protons in terms of tumour conformation. Nevertheless, significant advances have been made in protontherapy 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 by one of the most advanced conventional radiotherapy approaches, Intensity Modulated RadioTherapy (IMRT), is by far too large to yield acceptable second cancer risks. In addition, as we are just starting to use the dose-shaping capabilities of Intensity Modulated ProtonTherapy (IMPT), the advantage in dose profiling offered by proton therapy is likely to increase.

The advent of conformal radiotherapy techniques, such as proton/ion therapy (commonly referred to as hadrontherapy), has also lead to the possibility of increasing the dose per fraction for many treatment regimes/pathologies. Not only dose hypofractionation is of potential clinical advantage but it also entails a greater cost-effectiveness reducing the burden on patients who, for example, could undergo a one-week treatment compared to a “conventional” five-week course.

If it is true that reducing the risk of long-term adverse effects is a tenet of modern radiotherapy, locoregional tumour control, hence avoidance of disease recurrence, is arguably its chief priority. However, one of the shortcomings of protontherapy resides in the fact that it is not suitable to treat radioresistant cancers. Radiobiologically, protons are, in fact, 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 parameter 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, leads to 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 poor local tumour control. Heavier particles such as carbon ions can overcome such radioresistance because they are densely ionising but they present a series of radiobiological and economical issues that still hamper their widespread adoption. In the last years, therefore, many strategies have been designed with the aim of increasing the biological effectiveness of proton beams (i.e using radiosensitising agents or exploiting the action of nanoparticles).

In this project, the possibility to increase protontherapy biological effectiveness with the aid of a nuclear fusion reaction, namely p+11B3 or p-B, will be investigated both analytically and experimentally. The

rationale is two-fold: the alpha-particle emitted possess high LET and short range, allowing in principle a highly local damaging action; the maximum cross section in the the p-B reaction occurs at low proton energies (i.e. less than 1 MeV), corresponding to the tumour region in a typical proton therapy scenario. Very recent data published in [15] by our group show that a significant enhancement of proton RBE can be achieved by p-B. If proven pre-clinically viable, this innovative approach will allow to extend the range of tumours curable by protontherapy acting as a driving force toward hypofractionation, with consequent relevant societal impact.

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2. Detailed description of the project: targets that the project aims to achieve and their significance in terms of advancement of knowledge, state of the art and proposed methodology

Clinical background and motivation of the investigated disease

This project concerns the possibility of using protontherapy for a neoplastic disease not treated with this radiotherapy modality: high-grade glioma (HGG). With an essentially locoregional natural history, HGG, which includes glioblastoma multiforme and anaplastic astrocytoma and tends to relapse locally, without distant localizations. Average survival is about 1 year, after standard treatments, involving maximal safe resection and/or radiation/chemotherapy (1,2). There is a clear relationship between survival and radiation dose, with doses of 60 Gy providing the best survival (3). The pattern of recurrence typically affects a 2-cm area around the initially treated target (4), so that improving overall survival requires an increase of local control. Conventional photon beam radiotherapy has failed to give such a result, both through dose escalation trials (5) and use of altered fractionations (6). Modern radiotherapy techniques have also been tested, such as brachytherapy, IMRT, Volumetric-Modulated Arc Therapy and Stereotactic RadioTherapy, but none was able to significatively improve patients' overall survival (7-8).

Protontherapy has demonstrated to give optimal clinical results, thanks to the highly focused dose deposition in tumours located close to critical organs with reduced tolerance to radiation, and it is a promising candidate in the attempt to increase local control in HGG. Hence, the possibility to increase proton RBE by means of the p-B reaction represents an attractive prospective towards a positive outcome of such a devastating disease. Moreover, the local increase in dose in principle allowed by PBCT would allow hypofraction. This, in turn, leads to an increase in cell death, because of the overall higher dose per fraction delivered, reducing accelerated tumor cell repopulation and shortening the overall treatment time.

Rationale for the enhancement of protontherapy using the proposed p-B reaction

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 at mid-Spread-Out Bragg Peak, SOBP) is too low to achieve a cell killing effect significantly greater than in conventional radiotherapy. This currently prevents protontherapy from being useful against intrinsically radioresistant cancers. A well-known relationship links physical radiation quality (LET) and its biological effectiveness (RBE), based on the notion that cellular lethality increases with the degree of DNA damage clustering, i.e. complexity, which reflects the nanoscale mode of radiation action. 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 (9). Therapeutic 12C ion beams show an LET at mid-SOBP of about 50 keV/micron, conferring these particles a greater RBE for tumour cell killing, which is the radiobiological justification for their use against radioresistant cancers. However, 12C-based hadrontherapy struggles to establish itself to the same extent of protontherapy. Firstly, thorough radiobiological knowledge of late effects is still lacking (10): greater RBE at cell killing when lethal doses per fraction are used is likely to translate also in an increased effectiveness at causing sub-lethal damage at the low dose incurred by normal cells in the plateau region of the 12C Bragg curve. This may increase the health risk in patients. In addition, unlike protons, 12C ions yield a non-negligible dose deposition beyond the SOBP (11) due to nuclear fragmentation. Finally, economical issues encumber this form of hadrontherapy (12).

In this context, strategies combining greater RBE while maintaining reasonably low-dose levels in healthy tissues are desirable. 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+10B +7Li reaction. Here, thermal neutrons trigger short-range high-LET particles. In fact, BNCT has been proposed as an effective treatment for gliomas (13). However, it requires: a) neutrons, whose availability and dosimetry are not trivial; b) selectivity in boron uptake by tumour cells only. In light of this, another binary approach has been proposed that exploits the p+11B3 reaction (14), whose cross section resonates at 675 keV. 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 (Na2B12H11SH), we experimentally demonstrated for the first time that proton biological effectiveness is indeed augmented by the presence of the 11B carrier (15). 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 CAs compared to cells irradiated in the absence of 11B. Such CAs represents a hallmark of high-LET radiation exposure (16), strongly implying the observed enhancement of proton-induced cell killing be due to the densely ionising alpha particles generated by the p-B reaction.

Physical considerations about the PBCT

The proton-boron nuclear reaction considered is usually formalized as p+11B 3. It has a positive Q-value (8.7MeV) and is often 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 (17). According to the literature, the p-B nuclear fusion reaction shows three resonant energies and can be described as a two-step reaction (18). A proton interacting with a 11B nucleus induces the formation of a 12C* compound nucleus formed in the 2- or 3- excited state. If the 12C* nucleus is formed in its 2- state, it will decay to the first 2+ state of 8Be emitting one alpha-particle with l=3. If the 12C* nucleus is formed in its 3- state, then the primary alpha particle can be emitted either with l=1 from the decay to the first 2+ 8Be excited state, or with l=3 from the decay to the 0+8Be ground state. In either case, the remaining 8Be (2+ or 0+) nucleus immediately decays into two secondary alpha particles with l=2. Alpha particles emitted in the first stage present a well-defined energy distribution and are commonly referred to as 0 and 1 if the 8Be 2+ or the 0+ states are populated, respectively. Few authors report that a very unlikely fourth channel, characterized by a maximum cross section of 10b in the 2.0–2.7MeV energy range, can be also populated (19). In this case, the 12C* directly breaks into three particles skipping the intermediate 8Be stage, resulting in a continuous energy distribution. The emitted alpha particles exhibit a wide energy spectrum with a predominant energy around 4MeV. 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 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. Actually, in conventional protontherapy, the proton beam is typically slowed down inside the tumour thickness (the Bragg peak region). Thus, most of the beam energy is delivered to the tumour cells. Assuming that a given concentration of 11B nuclei is present preferentially in the tumour volume, fusion reaction events can be triggered by the incoming slow protons generating a relevant yield of highly DNA-damaging alpha particles localized in the tumour region.

Target 1 - Advanced boron concentration measurements
Accurate measurements of boron concentration at cell level are fundamental as they represent, together with alpha-particle yield calculation, the physical base for rigorous explanation and modelisation of the observed effect. In BNCT the measurement of 10B atoms is an ongoing challenge. In fact, when a high ratio of free-to-bound pool occurs, a severe loss of boron atoms between drug administration time and BNCT initiation occurs, defining BNCT failure. It would be highly advantageous for BNCT using a boron compound capable of delivering higher boron bound pool concentrations to tumour cells. In this context, HPLC-based analytical tools in BNCT were widely investigated to unravel free/bound ratio, as well as, instability and degradation mechanisms of boron compounds (20, 21). Tandem mass spectrometry technique was also verified as a performant approach for reproducible and quantitative detection of boron compounds (22), and for characterizing specific molecular 10B-containing compounds. Thus, hyphenated ultra-performance liquid chromatography-high resolution mass spectrometry techniques (UPLC-HRMS) will be applied in the PBCT project to achieve new insights into cellular distribution of 11B atoms through metabolomics workflows. Analytical protocols will be optimized to realize both targeted and untargeted metabolomics exploration of treated cells, previously subjected to metabolic activity quenching and intracellular metabolites extraction (23). Studies, taking into account mass spectral fragmentation, and detectability of boron compounds such as and/or their derivatives, will be properly rationalized to strictly define 11B-metabolic fate. The main goal is designing and developing a UPLC-HRMS nontargeted global fingerprinting approach also applicable to preclinical samples. To the latter purpose, investigation of homogenization and extractive procedures will be optimized, using tissue amounts as small as possible. In a complementary and supplementary scenario, alpha spectrometry and neutron autoradiography will be also applied. These techniques allow to emphasize the boron biodistribution in tissues, almost at a cellular level (down to 1 ppm). Neutron autoradiography is based on the neutron irradiation of borated sample deposited on a solid state nuclear track detector (e.g. CR-39). Charged particles generated by the capture reaction in 10B leave latent tracks made visible through chemical etching. Parameters such as irradiation and etching time can be tuned to obtain an imaging of the boron concentration in samples or a map of separate tracks that can be digitally counted. For tissue sections from tumour biopsies, imaging can be coupled to a quantitative measurement of boron concentration by means of alpha spectrometry, by irradiating thin tissue sections and by detecting the charged particles generated by the neutron capture with a silicon detector. Furthermore, neutron autoradiography of a contiguous section allows weighting the contribution of tumour and normal tissues to the final boron concentration value. The values of 10B concentration give information about 11B concentration when samples are treated with formulations containing natural-abundance boron.

Target 2 - Computational and experimental evaluation of alpha particle dosimetric contribution
The radiobiological data reported by Cirrone et al (15) suggest that the reaction may be responsible for the observed increase in the biological effectiveness of a clinical proton beam. Nevertheless, is impossible to provide a simple analytical computation able to explain these results, for instance by correlating the biological effect with the mere total number of -particles expected to be generated. Therefore, micro- and nano-dosimetric approaches must be taken into account to reconcile the underlying physics with the effects arising at cellular level. Therefore, a more precise evaluation of real actual boron density inside cells, must be addressed.
The main purpose of this target will be the combined use of Monte Carlo simulations and analytical approaches to simulate the irradiation set-up, the alphas generated in the reaction and to develop a model able to reconcile those with the observed biological damage. The whole experimental set-up, including the physical characteristics of the beam, will be simulated using the Geant4 toolkit (24). The number of lesions will be calculated by a model based on the local-effect track-structure applied to a realistic mixed field that include primary and secondary particles (25). In parallel, simulations will be carried out with the BIANCA model/code, which can also simulate chromosome aberrations in addition to cell death (26).
An important part of this target will be dedicated to the experimental RBE prediction. This issue will addressed by using advanced solid-state microdosimetry technology invented and developed at CMRP UOW (27). Such microdosimetry is based on innovative Silicon On Insulator radiation detectors with array of 3D sensitive volumes with size matching typical biological cells allowing to measure stochastically deposited ionizing energy from secondary and primary radiation event by event.

Target 3: In vitro radiobiological studies
Cell radiosensitivity measurements are essential to ascertain the expected increase in proton biological effectiveness by p-B reaction. Furthermore, analysis of structural chromosomal aberrations (CAs) is instrumental to indirectly prove that such an effect is due to the high-LET alpha particles generated by the reaction. Therefore, aim of T3 is the study of the in-vitro radioresponse of cell lines irradiated with clinical and monoenergetic proton beams in the presence of the 11B concentrations as determined in T1. The results will feed the analytical and modelling part developed in T2, in terms of the correlation of the observed effect with the expected yield of alpha particles and thereof dosimetry, as well as providing useful preparatory information for carrying out the pre-clinical part envisaged by T4.
A pre-requisite for the clinical exploitation of the p-B reaction to potentiate protontherapy is the assessment that given concentration(s) of 11B result in a magnification of proton-induced lethal cellular damage. Cell death will be quantified by the clonogenic assay, the golden standard for measuring cellular radiosensitivity in vitro (28). Clonogenic dose-response curves, whose parameters alpha and beta are of well-known clinical usefulness (29), will be derived for cancer cells. CAs will be studied in genomically stable normal cells by Fluorescence In-Situ Hybridization (FISH) techniques; particularly, multicolour(m)-FISH karyotyping will allow to detect complex CAs, a powerful cytogenetic signature of high-LET radiation exposure (30). Other endpoints investigated will be micronucleus formation and premature cellular senescence.
Importantly, cellular irradiations will be performed at various depths of clinical proton SOBP to study the dependence of the radiosensitization effect by the p-B reaction upon the energy of the incident proton beam. Monochromatic low-energy protons, available at the 3-MV Tandem accelerator of the CIRCE laboratory (Università della Campania L.Vanvitelli), will provide insights on the biophysical mechanisms in the proximity of the cross section maximum for the p-B reaction.

Target 4: In vivo pre-clinical studies
T4 will investigate the effect of the p-B reaction in human glioma cell in-vivo models. To obtain “in vivo biological validation of the radiobiological model”, immortalized glioblastoma cell line will be inoculated in immunodeficient nude mice. The animals will be randomized in four experimental groups:
1) Control group (untreated);
2) Treatment with Boron;
3) Treatment with Protons;
4) Combined Treatment with Proton + Boron.
They will be sacrificed to study the doseeffect curves of tumour reduction and to analyze the cellular and molecular mechanisms induced by the treatment with an OMICS approach. On tumour masses will be also performed histological analysis. Part of the irradiated tumour will be used to quantify cell death as assessed by clonogenic assay, similar to what done in T3, since the in-vivo behaviour of irradiated cells may significantly differ due to intercellular signalling.
MicroPET/CT analysis will be performed to monitor tumour growth. Micro-PET (Positron Emission Tomography) studies will serve to investigate changes in the rate of cell proliferation in murine tumour model before and after protontherapy with/without boron. In particular, PET scans using 18F-FET will be performed before and after the irradiation in control group and in both treated groups. For each PET examination, automatic and operator-independent regions of interest will be obtained to delineate the tumours using ad-hoc developed tool. Consequently, Standardized Uptake Value (SUV), Metabolic Tumor Volume (MTV) and Total Lesion Proliferation (TLP) will be calculated and assessed. Nevertheless, SUV measurements are strongly affected by the partial volume effect (PVE). Hence, PVE correction

will be carried out using recovery coefficient methodology. Preliminary PET experiments using phantoms containing spheres of different volumes will be mandatory.

Target 5: Towards clinical trial
The clinical development of protontherapy requires further in vivo experimental evaluations, such as those proposed in this project. In the neuro-oncology field, with particular reference to glioblastoma multiforme (GBM), there are two-fold high expectations and clinical needs: the search for biomarkers that can guide clinical choices and act as a driving force for new molecules; on the other, the development of new methods of selective irradiation of neoplastic cells.
The most important prognostic biomarker in clinical use for GBM is methylation of the O-6-methylguanine-DNA methyltransferase (MGMT) promoter, which has a predictive value for outcome and benefit from combined radiochemotherapy with the cytostatic agent temozolomide (TMZ). GBMs are also characterized by epidermal growth factor receptor (EGFR) amplification and/or EGFR overexpression, p-16 deletion, mouse double minute 2 homologue (MDM2) amplification and/or MDM2 overexpression, isocitrate dehydrogenases (IDH1-2) mutations, loss of heterozygosity (LOH) of chromosome 10, co-deletion of 1p/19q. These genetic and molecular alterations will help in future clinical trials to stratify patients affected by glioblastoma to receive a more aggressive treatment.
The possibility of increasing the relative biological efficacy of proton beams through the interaction with 11B will open new scenarios in the radiation treatment of GBM. A future clinical trial can explore the possibility to expose the tumor volume to higher Gray equivalent (GyRBE) doses, up to 90 GyRBE, by dose-escalation study and hypofractionation regimen studies

3. Project development, with identification of the role of each research unit with regards to expected targets, and related modalities of integration and collaboration

UNIT 1: Laboratori Nazionali del Suf of INFN
LNS Laboratory (Laboratori Nazionali del Sud) of the INFN (Istituto Nazionale di Fisica Nucleare) is the Principal Investigator institute.
INFN-LNS represents a consolidated Italian research institution, well established in the national and international scientific field. INFN-LNS hosted the first proton therapy facility in Italy and it is still one of the few centres in the world to carry out eye clinical proton therapy. Within the INFN- LNS there are consolidated competences related to the clinical dosimetry, development of detectors for hadrontherapy; to the characterization and validation of hadrontherapy treatment plannings and to the Monte Carlo simulations. Recently, LNS has strengthened the radiobiology laboratory offering a full support for in-vitro studies; this permitted the realisation of many radiobiology projects to study the effect of ion beams on tissues and the development of many collaborations with different international research groups. In the last years, at LNS has been developed a laboratory dedicated to radiobiologically studies in-vivo, as well. Starting since 2016 at LNS the first Proton Therapy Animal Facility on the national territory dedicated to small animals treatment, is active.
INFN-LNS will coordinate the participating Units and will be involved in different aspects of the project:
The study of the nuclear reaction involved in the investigated effect and the development of experimental procedures dedicated to the measure of alpha spectra;
The development of a dedicated Monte Carlo simulation of the whole irradiation set-up; The Monte Carlo will permit the realistic estimation of the generated alphas, the evaluation of the relevant radiobiological quantities and of the alpha-induced damage and, finally, the optimisation of the irradiation procedures.
The definition of the dosimetric procedures for the in-vitro and in-vivo irradiations

UNIT2: CNR
The Institute of Molecular Bioimaging and Physiology - National Research Council (IBFM–CNR) carries out its activities at the Giglio Hospital in Cefalù.
The IBFM diagnostics and research activities are strongly translational, with the overall objective of cancer studying and care, using advanced biomedical technologies involved in pathology, proteogenomics, and biomedical imaging. The IBFM researchers are physicists, biologists, engineers, and radio-chemists who work together, ensuring the convergence of multidisciplinary expertise on the issues under study.
In this project the IBFM Unit will monitor the radiation response in murine tumour model using PET imaging. In particular, in-vivo parameters will be extracted using ad-hoc developed tool to assess functional changes in follow-up examinations.
The aim is to evaluate the potential usefulness of PET imaging with [18F]FET considering its ability to assess the therapy efficacy early predicting tumour response and, consequently, allowing the discrimination of mouse responders from non-responders to treatment.

UNIT 3: University of Naples
The Physics Department of the University of Naples offers a wide range of expertise and resources, both in terms of research topics and laboratories. Its research activities cover the whole spectrum of physical sciences, from theoretical to applied physics, attracting public funds with a number of highly competitive projects at national and international level. Particularly close are the links with other Universities as well as Research Institutions such as INFN and CNR. Within the Department, the Radiation Biophysics Group represents one of the very few University-based laboratories with a long-standing research record in radiobiology. Peculiar attention has been traditionally devoted to the study of charged particles' biological effects of interest in hadrontherapy. In this project, the Unit will be involved in the in-vitro and in-vivo experimental part, playing a pivotal role in quantifying the boron-assisted enhancement of proton biological effectiveness at cellular and molecular level by means of clinically relevant endpoints (e.g. cell death, DNA damage, etc). The aim is to elucidate the biophysical mechanisms underlying the boron-driven enhancement of proton RBE by experimentally correlating its magnitude with physical parameters at play in the p-B reaction such as the energy of the incident proton beam. Hence, cellular radioresponse in the presence of the boron-carrier will be evaluated along clinical SOBPs as well as for monoenergetic beams.

UNIT 4: University of Campania
The Department of Environmental, Biological and Pharmaceutical Sciences and Technologies of the University of Campania "Luigi Vanvitelli" is a prestigious research centre that brings together a wide range of qualified multi-disciplinary activities, which make use of the synergies between the various skills of the researchers present and the instrumental equipment implemented. The main research lines of interest, related to the project, concern "omics" application and its focus on the study of pools of molecules in biological samples. In particular, metabolomics analyses through advanced analytical tools as high-resolution mass spectrometry (HRMS) and nuclear magnetic resonance (NMR) are commonly carried out in a both supplementary and complementary approach.
In the PBCT project, the Unit will perform UHPLC-HRMS measurements to unravel boron concentrations in biological samples and potentially reconstruct its metabolic fate. Exploratory metabolomics experiments will involve the examination of a series of non-target metabolites, looking for those with statistically significant variations in their abundance within a set of samples experiments compared to control samples, also determining their chemical structure. The phase of interpretation allows the researcher to link the metabolite to the physiological condition or biological process.

UNIT 5: University of Catania
The research unit possesses the necessary skills and expertise to approach the different aspects inherent to research plan, including cellular and molecular analyses in the different pathophysiological conditions to be tested both in vitro (Laboratorio di Fisiologia Molecolare e Cellulare), and in vivo models (Center for Advanced Preclinical in vivo Research, CAPiR), as well as the analyses in which histopathological/immunohistochemical and radiotherapy skills are requested during and after the radiation therapy. Anatomic Pathology section will perform all the histological and immunohistochemical examinations of neoplastic tissues with special emphasis on the morphological changes and expression of several bio-markers. Vascularization pattern of tumors, tumor necrosis and reparative processes will be also studied. Healthy tissues surrounding tumors will be tested morphologically and immunohistochemically to assess the potential effects of radiation therapy in macroscopically normal tissues. Radiotherapy section also has over 15 years experience in the clinical treatment of orbital tumors with proton beams in collaboration with INFN-LNS. This allowed to develop a pioneering expertise in Italy, before the current greater spread of proton therapy in clinical practice.

Unit Integration

The project consists of five well-defined Targets, each of which is under the responsibility of a specific Unit. From what said above, it is evident the degree of integration between all Units. One intrinsic characteristic of the PBCT project is clearly its multidisciplinarity that can be faced only adopting a cross-thematic approach. The project, in fact, has to deal with multi-facet scientific aspects belonging to several fields, from physics and biochemistry to biology and medicine, which are tightly interconnected: thus, evaluation of the involved reaction at micro- and nanodosimetric scale, alongside Monte Carlo and analytical simulations (T2), must be related, on one side, to the quantification of the Boron uptake (T1) and, on the other side, to the biological response of the cellular systems in vitro (T3); moreover, development of specific imaging approaches and the results from the in-vivo preclinical studies (T4) will be fundamental for a proper design of clinical trials (T5).
The following list summarise the the activities that will be performed of each of the participating Unit:
INFN-LNS: study of the reaction, Monte Carlo and analytical modelling of the radiobiological effects of the produces alphas; Microdosimetric evaluations related to the produced alphas and measure of alphas with dedicated microdosimetry (in collaboration with the UOW); irradiation set-up and absolute dosimetry for samples irradiation.
UNINA, University of Caserta, CNR (also in Collaboration with University of Pavia): in-vitro studies and quantification of the Boron uptake inside cells.
UNICT, CNR: In-vitro studies and quantification of the Boron uptake inside cells: In-vivo studies

The level of complexity of the proposed topics of research implies that the involvement of other research groups other than those directly listed above (project Units) is necessary and will decisively contribute to the achievement of the proposed objectives in the scheduled time. In view of the multidisciplinary nature of the project, such external collaborating groups, from different national and international institutions, necessarily belong to diverse areas. To the PBCT project will be also give their contribute researchers from the INFN Section of Pavia (with their expertise in the Boron uptake evaluation), from the TIFPA Section of Trento (for the irradiation with high energy proton beams); from the University of Wollongong (Australia) with their expertise in capability into realise microdosimetry for the alpha particle measurements and for the related biological effect.

4. Possibile application potentialities and scientific and/or technological and/or social and/or economic impact of the project

Improvement of scientific knowledge (application to other diseases)
Establishing the p-B reaction as a clinically viable strategy to potentiate proton radiobiological effectiveness would have a large scientific and social impact, in addition to being an elegant example of bringing together apparently distant fields such as nuclear physics and radiotherapy.
Our project will offer the opportunity to explore a number of aspects that would usually remain distinct while shedding light onto a deeper understanding of charged particle radiobiology. In fact, completely independent research lines concur with the notion that the biological outcome of cellular DNA irradiation is strictly governed by the physics underlying the energy deposition pattern, as is the case, for example, of Monte-carlo simulations, on one side, and of experiments based on the biochemical phosphorylation gamma-H2AX histone assay, on the other side. Scientifically, the PBCT project will therefore constitute an important advance as far as the mode of action of radiation at the nanoscale level is concerned because it entails the elaboration of a model capable of explaining the observed enhancement of a low-LET radiation by the p-B reaction. Such a model will have necessarily to take into account the expected yield of high-LET particles, the measured 11B concentration and the radiobiological parameters derived from experimentally constructed dose-response curves, and reconcile them within micro/nanodosimetric considerations. Additionally, our research may pave the way towards similar binary approaches where other nuclear reactions will be studied to either potentiate the action of primary external beams or exploit them to improve medical imaging, or both, as is the case with our approach.
From a social viewpoint, the potentialities of rendering protontherapy more effective are self-evident: this would enormously benefit patients because not only will it allow to extend protontherapy to include diseases that currently suffer from poor prognosis but it will also allow to improve the treatment of those for which protontherapy protocols are already in place without increasing the risk of sequelae.

Clinical and economical Impact
Protontherapy has demonstrated to give optimal clinical results in tumors located close to critical organs with reduced tolerance to radiation. Skull base and cervical spine chordoma, soft tissue and bone sarcoma abutting CNS structures, skull base meningioma, paranasal sinus carcinoma, uveal melanoma, thoracic spine-sacrum tumours are clinical examples of tumors where protontherapy ensure a dosimetric superiority over photon beams, through reduction of the integral dose and the dose to organs at risk.
Clinical advantages are, unfortunately, limited in particularly radioresistant tumors, like high grade gliomas, where the increasing effectiveness obtained from the proton-boron reaction is expected to traslate in a clinical gain.
In a future scenario where proton therapy will have greater biological effectiveness, the current resistance to its extended clinical use will certainly be overcome, thanks also to the greater diffusion of hypofractionated treatment protocols.
The potential clinical impact is considerable, both as regards the tumors currently treated with protontherapy, and for others. 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 protontherapy, if the clinical-biological gain joins the current one, of a more strictly dosimetric type.
The clinical impact of a biologically more effective protontherapy in adulthood is, if possible, even greater. Just think about the potential application of hypofractionated protocols, on the model of what

happens in the current clinical practice of stereotactic body radiotherapy, for non-small cell lung cancer, for pancreatic carcinoma (whose incidence is increasing), for primary or secondary tumors of the liver and for tumors of the genito-urinary region.
Premising this, is evident that, consequentially, the cost impact of a such new approach could be enormous: the possibility to use proton beams also for radioresistant tumour avoiding the use of more complex technique and/or therapy, will be extremely advantageous from both an economic and clinical point of view

5. Costs and fundings, for each research unit (automatically calculated)

nº	Associated or principal investigator	Total cost (euro)	Co-funding (item A.1) (euro)	MIUR funding (other items) (euro)
1.	CUTTONE Giacomo	454.415,56	105.133	349.282,56
2.	MANTI Lorenzo	215.333	40.833	174.500
3.	PACIFICO Severina	100.000	25.000	75.000
4.	PARENTI Rosalba	232.656	51.660	180.996
5.	RUSSO Giorgio	195.230	38.119	157.111
	Total	**1.197.634,56**	**260.745**	**936.889,56**

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B.2

1. PI's Curriculum Vitae

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 Li8 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€.

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€

He is the coordinator of the contract (2.4 M€) 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.

1.a National and international grants (as Principal Investigator)

Responsible of INFN experiments at LNS:
TRON 1990-1991: Realization of control systems for accelerators based on transputer technology
LIDIA 1993: Realization of advanced beam diagnostic systems for high intensity ions beams
MOPI 2004-2005: Realization of a real time system for lateral beam profiling acquisition
PRIMA (Proton Imaging) 2006-2008
CONRAD 1999-2002: realization of detectors for dosimetry in the field of advanced conformal techniques
TPS (Treatment Planning System) 2009-2012
FRAG (FRAGmentation) 2010-2012
IRPT (Innovation in Radio and Particle-therapy): MIUR National Relevant project
IDEA 1994-1995: New diagnostic equipments for low intensity ion beams
ELDE 1996-1998: New materials for electrostatic deflectors for high intensity cyclotrons
CANDIDO (CAN we Do a DIamond Dosimetry?) 1998-2000
EXCYT 2002-2006: National facility for radioactive beams
MOBIDIC (MOdulated Beams of Ions Delivered by Infn Cyclotron) 2007-2008
CASCADE (CAtana SCintillatore Array DEtector) 1997-1998
GEANT4 (GEometry ANd Tracking) 2004-2010
DORA (Diagnostica Ottica Real time per Adroterapia) 2000-2003
MC-INFN (Monte Carlo - INFN) 2005-2007
Responsible of International experiments at LNS:
PI of KM3NET (Cubic Kilometre Neutrino Telescope) project - PON 2007-2013 e POR Pofesr regione siciliana 2017-2020
PI of AISHA (Advanced Ion Source for Hadron Therapy) - POR Pofesr Regione siciliana 2007-2013
ESA grant: ESA-BIORAD
ENVISION (European NoVel Imaging System for ION therapy): funded by the European Community (Settimo Programma quadro)
Chairman of the MAESTRO proj.(Methods and Advanced Equipment for Simulation and Treatment in Radio Oncology): funded by the European Community (Sesto Programma quadro)
Coordinator of the Italian Health Minister committee on “Status and Perspectives of Protontherapy in Italy”
PI of MAECI Grande Rilevanza Project ITALIA-SERBIA
PI administrative of ELIMED (ELI-Beamlines MEDical and multidisciplinary applications) 2014-2018

1.b National and international acknowledgments

Scientific Responsible of CATANA (Centro di AdroTerapia e Applicazioni Nucleari Avanzate) from 1996 to now

Responsible of R&D projects for the operator-machine interaction in the framework of the realisation and installation of the superconducting cyclotron.

Responsible of “Computer Control” division at LNS (1990-1992)

Responsible of transfer activity at LNS (1999) “trasferimento tecnologico e formazione esterna” at LNS (1999)

Official Geant4 collaboration member from 2003 to now

Scientific Responsible of the collaboration between LNS and Vinca Institute from 2003 to now

Scientific committee member of PTCOG from 2008 to now

Coordinator of the project Idmar (interdisciplinar Sea laboratory) Funded in pofesr 14-20 Sicilian region for 40M€

MIUR delegate for H2020-EURATOM from 2013 to now

2. Principal scientific publications of PI

1. Allison J, Amako K, Apostolakis J, Arce P, Asai M, Aso T, Bagli E, Bagulya A, Banerjee S, Barrand G, Beck BR, Bogdanov AG, Brandt D, Brown JMC, Burkhardt H, Canal P, Cano-Ott D, Chauvie S, Cho K, Cirrone GAP...(2016). Recent developments in GEANT4. NUCLEAR INSTRUMENTS & METHODS IN PHYSICS RESEARCH. SECTION A, ACCELERATORS, SPECTROMETERS, DETECTORS AND ASSOCIATED EQUIPMENT, vol. 835, p. 186-225, ISSN: 0168-9002, doi: 10.1016/j.nima.2016.06.125 - **Articolo in rivista**
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3. Keta O, Todorovic D, Popovic N, Koricanac L, Cuttone G, Petrovic I, Ristic-Fira A (2014). Radiosensitivity of human ovarian carcinoma and melanoma cells to gamma-rays and protons. ARCHIVES OF MEDICAL SCIENCE, vol. 10, p. 578-586, ISSN: 1734-1922, doi: 10.5114/aoms.2014.43751 - **Articolo in rivista**
4. Kraan AC, Battistoni G, Belcari N, Camarlinghi N, Cirrone GAP, Cuttone G, Ferretti S, Ferrari A, Pirrone G, Romano F, Sala P, Sportelli G, Straub K, Tramontana A, Del Guerra A, Rosso V (2014). Proton range monitoring with in-beam PET: Monte Carlo activity predictions and comparison with cyclotron data. PHYSICA MEDICA, vol. 30, p. 559-569, ISSN: 1120-1797, doi: 10.1016/j.ejmp.2014.04.003 - **Articolo in rivista**
5. Romano F, Cirrone GAP, Cuttone G, Di Rosa F, Mazzaglia SE, Petrovic I, Fira AR, Varisano A (2014). A Monte Carlo study for the calculation of the average linear energy transfer (LET) distributions for a clinical proton beam line and a radiobiological carbon ion beam line. PHYSICS IN MEDICINE AND BIOLOGY, vol. 59, p. 2863-2882, ISSN: 0031-9155, doi: 10.1088/0031-9155/59/12/2863 - **Articolo in rivista**
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12. G. Cuttone, G.A.P. Cirrone, Di Franco G, V. La Monaca, S. Lo Nigro, J. Ott, S. Pittera, Privitera G, L. Raffaele, A. Reibaldi, M.G. Sabini, V. Salamone, M. Sanfilippo, C. Spatola, and L.M. Valastro (2011). CATANA protontherapy facility: The state of art of clinical and dosimetric experience. THE EUROPEAN PHYSICAL JOURNAL PLUS, vol. 126: 65 DOI: 10.1140/epjp/i2011-11065-1, p. 2-7, ISSN: 2190-5444, doi: 10.1140/epjp/i2011-11065-1 - **Articolo in rivista**

13. Ristic-Fira A, Koricanac L, Zakula J, Keta O, Iannolo G, Cuttone G, Petrovic I (2011). PROTON INACTIVATION OF MELANOMACELLS ENHANCED BY FOTEMUSTINE. RADIATION PROTECTION DOSIMETRY, vol. 143, p. 503-507, ISSN: 0144-8420, doi: 10.1093/rpd/ncq527 - **Articolo in rivista**

14. Cirrone GAP, Cuttone G, Di Rosa F, Pandola L, Romano F, Zhang Q (2010). Validation of the Geant4 electromagnetic photon cross-sections for elements and compounds. NUCLEAR INSTRUMENTS & METHODS IN PHYSICS RESEARCH. SECTION A, ACCELERATORS, SPECTROMETERS, DETECTORS AND ASSOCIATED EQUIPMENT, vol. 618, p. 315-322, ISSN: 0168-9002, doi: 10.1016/j.nima.2010.02.112 - **Articolo in rivista**

15. Menichelli D, Bruzzi M, Bucciolini M, Candiano G, Cirrone GAP, Capineri L, Civinini C, Cuttone G, Lo Presti D, Marrazzo L, Pallotta S, Randazzo N, Sipala V, Talamonti C, Valentini S, Pieri S, Reggioli V, Brianzi M, Tesi M (2010). Characterization of a Silicon Strip Detector and a YAG:Ce Calorimeter for a Proton Computed Radiography Apparatus. IEEE TRANSACTIONS ON NUCLEAR SCIENCE, vol. 57, p. 8-16, ISSN: 0018-9499, doi: 10.1109/TNS.2009.2031869 - **Articolo in rivista**

16. Petrovic I, Ristic-Fira A, Todorovic D, Koricanac L, Valastro L, Cirrone P, Cuttone G (2010). Response of a radioresistant human melanoma cell line along the proton spread-out Bragg peak. INTERNATIONAL JOURNAL OF RADIATION BIOLOGY, vol. 86, p. 742-751, ISSN: 0955-3002, doi: 10.3109/09553002.2010.481322 - **Articolo in rivista**

17. Sipala V., Bruzzi M., Bucciolini M., Candiano G., Capineri L., Cirrone G. A. P., Civinini C., Cuttone G., Lo Presti D, Marrazzo L., Mazzaglia E., Menichelli D., Randazzo N., Talamonti C., Valentini S. (2010). A proton imaging device: Design and status of realization. NUCLEAR INSTRUMENTS & METHODS IN PHYSICS RESEARCH. SECTION A, ACCELERATORS, SPECTROMETERS, DETECTORS AND ASSOCIATED EQUIPMENT, vol. 612, p. 566-570, ISSN: 0168-9002, doi: 10.1016/j.nima.2009.08.029 - **Articolo in rivista**

18. Vecchio S, Attanasi F, Belcari N, Camarda M, Cirrone GAP, Cuttone G, Di Rosa F, Lanconelli N, Moehrs S, Rosso V, Russo G, Del Guerra A (2009). A PET Prototype for "In-Beam" Monitoring of Proton Therapy RID C-4085-2009. IEEE TRANSACTIONS ON NUCLEAR SCIENCE, vol. 56, p. 51-56, ISSN: 0018-9499, doi: 10.1109/TNS.2008.2008306 - **Articolo in rivista**

19. Attanasi F, Belcari N, Camarda M, Cirrone GAP, Cuttone G, Del Guerra A, Di Rosa F, Lanconelli N, Rosso V, Russo G, Veechio S (2008). Preliminary results of an in-beam PET prototype for proton therapy RID C-4085-2009. NUCLEAR INSTRUMENTS & METHODS IN PHYSICS RESEARCH. SECTION A, ACCELERATORS, SPECTROMETERS, DETECTORS AND ASSOCIATED EQUIPMENT, vol. 591, p. 296-299, ISSN: 0168-9002, doi: 10.1016/j.nima.2008.03.076 - **Articolo in rivista**

20. 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, Publiese M, Scampoli P, Simone G, Sorrentino E, Tabocchini MA, Tallone L (2008). Effectiveness of Monoenergetic and Spread-Out Bragg Peak Carbon-Ions for Inactivation of Various Normal and Tumour Human Cell Lines RID C-4085-2009 RID A-4487-2012 RID F-3799-2010 RID A-4035-2010. JOURNAL OF RADIATION RESEARCH, vol. 49, p. 597-607, ISSN: 0449-3060, doi: 10.1269/jrr.08052 - **Articolo in rivista**

3. Hindex of PI (only for the scientific fields in which the use of the H-index is usually adopted)

H-Index	Source
24	WoS

4. Associated investigators' Curriculum Vitae

1. MANTI Lorenzo

General information
Place and date of birth: Naples, Italy, 27th September 1966
Phone numbers: +39081676262 (office); +39081676219 (lab)
e-mails: manti@na.infn.it
lorenzo.manti@unina.it

Academic position
Associate Professor of Applied Physics at Department of Physics, University of Naples Federico II, 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 BioSciences, University of Wales, Cardiff. UK.
2002: Research contract, Radiation Biophysics Laboratory, Department of Physical Sciences, University of Naples Federico II, Italy
2002- 2017 Assistant Professor of Applied Physics at the 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- Associate Professor the Department of Physics, University of Naples Federico II, Italy

Main research activity and interests
• Radiation biology
• Non-cancer late effects in hadrontherapy
• Radiation-induced chromosome aberrations and premature cellular senescence
• Radiation-induced genomic instability and cellular radiosensitivity (cell death mechanisms)
• Tumour radiosensitization
• Radiobiological effects of laser-generated particle beams
• Biological cooperative effect; interactions between non-ionising and ionising radiations on DNA damage induction

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. PI
2009: Italian National Institute of Nuclear Physics (INFN)-funded project BIORT on the radiobiological properties of Intra-Operatory Radiotherapy. PI
2010: INFN-funded project ARCAICA on the adaptive response to mobile telephony radiofrequency fields induced by ionizing radiation. PI
2012-13: INFN-funded project MIMO-BRAGG on the induction of cytogenetic damage by various ions and modelization of track-structure role. PI
2013-15 INFN-funded PLASMA_med (Proton LASer-driven beam transport, diagnostic and MEdical Applications). Local coordinator
2015- present INFN-funded project L3IA. 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". PI

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)

I have also taken part in the following funded research projects
Italian Space agency (ASI)-funded project "Study of the effects of shielding on several biological systems in order to develop the existing models and codes of radiation transport and interaction with space radiation" (2000-2003).
Italian Ministry of Education and Research-funded "Biophysical studies of nuclear fragmentation of heavy ions at energies of interest for particle-based radiotherapy and space radiation protection" (2004-05)

Academic and non-academic responsibilities

2017-present President of the European Radiation Research Society (ERRS), www.errs.eu
2017: Academic Co-Editor, Cancers, Special Issue on "Selected papers from the Joint 43rd ERRS and 20th German Society for Biological Radiation Research (GBS) Annual Meetings"
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 group of journals
2016-present: Member of the Teaching Council, PhD School in Mathematics, Physics and Applied Engineering, Università della Campania "Luigi Vanvitelli" (formerly Seconda Università di Napoli-SUN), 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-presente: 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-present: 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 Rocerca sulle Radiazioni-SIRR)

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 49 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 MSc student and 1 PhD student in Physics.

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

2. PACIFICO Severina
Dr PhD SEVERINA PACIFICO

PERSONAL INFORMATION
Severina, Pacifico; Born in Caserta, Italy 16.09.1977, married, three daughters
URL for web site: https://www.researchgate.net/profile/Severina_Pacifico
Researcher unique identifier(s): Scopus Author ID 8698605300

CURRENT POSITION
2010/17 Permanent Researcher of Organic Chemistry at University of Campania Luigi Vanvitelli, Italy. (Career Breaks 27/11/2012- 27/04/2013, Maternity)

EDUCATION
2003 Degree with distinction in Biological Sciences, University of Campania Luigi Vanvitelli, Italy.
2003/07 PhD in Computational Biology, University of Campania Luigi Vanvitelli, Italy.

Fellowships
2008 Post-doctoral fellowships at University of Naples Federico II, Italy.

SUPERVISION OF PHD AND GRADUATE STUDENTS
2010-2017 Tutor of 50 Master Thesis in Pharmacy, 4 Master Thesis in Biology, 2 Master Thesis in Food and Human Nutrition Sciences, 16 Bachelor Thesis in Biological Sciences and 3 Bachelor Thesis in Biotechnology
2014 Tutor of 1 PhD Thesis in PhD Program “Resources and Environment”
2016 Co-Tutor of 1 PhD Thesis in PhD Program “Biomolecular Sciences”

TEACHING ACTIVITIES
2008/09; 2009/10 Teaching contract of Natural Products Chemistry for Biology bachelor course

2009/10 Teaching contract of Pharmacognosy & Phytochemistry for Pharmacy degree course
2010/11; 2011/12 Regular Teacher of Pharmacognosy & Phytochemistry for Pharmacy degree course

2012/13-2017/18 Regular Teacher of Organic Chemistry II for Pharmacy degree course
2012/13; 2013/14 Regular Teacher of Pharmacognosy for Pharmacy degree course
2014/15; 2016/17 Regular Teacher of Phytochemistry & Pharmacognosy for Pharmacy degree course
2017/18 Regular Teacher of Food Chemistry for Food Science and Human Nutrition degree course

Member of PhD course in Environment Design and Innovation

EDITORIAL WORK
From 2016 Member of Editorial Board of Food Research International (Elsevier, ISSN 0963-9969)
http://www.journals.elsevier .com/food-research-international/editori al-board
2010/17 Peer reviewer for the following peer-reviewed international journals African Journal of Pharmacy and Pharmacology, Biotechnology and Biomaterials, Biotechnology and Bioprocess Engineering, Chemical Engineering Research and Design, European Journal of Nutraceuticals & Functional Foods, Food Science e Technology International, Nutrition, Food Research International, Food Chemical and Toxicology, Journal of Human and Ecological Risk Assessment, Journal of Cytology & Histology, Journal of Biomedical Materials Research: Part A, Journal of Agricultural and Food Chemistry, Food and Bioproducts Processing, Toxicological & Environmental Chemistry, Molecules, Plants, Plants Food for Human Nutrition, International Journal of Preventive Medicine, Food Chemistry, NeuroChemistry International, Journal of Functional Foods
2015 Peer reviewer for the evaluation of a research project for the Israeli Ministry of Science, Technology and Space
2010 Peer reviewer for the evaluation of a research project in the context of “2010 Regular Research Funding Competition” of the Chilean “National Fund for Scientific and Technological Development (FONDECYT)”.

BRIEF TRACK-RECORD
Dr. Pacifico’s research activity resulted in 89 publications (in international peer reviewed refereed journals), 4 chapters in international books, and communications in national and international conferences. The research interest, in the field of Natural Products and Food Chemistry primarily aims to 1) the phytochemical study of medicinal and/or edible plants; 2) the chemical characterization of secondary metabolites by spectroscopic (UV, IR, NMR) and spectrometric techniques; 3) LC-MS/MS metabolic profiling and fingerprinting of natural extracts; 4) the evaluation of antioxidant, chemopreventive and neuroprotective properties of natural products (phytocomplexes and secondary metabolites therein).

3. PARENTI Rosalba

Name: Rosalba Parenti
Place and Date of birth: Catania, December 23-1965
Present address: Department of Biomedical and Biotechnological Sciences, Physiology Section, University of Catania Torre Biologica, Via Santa Sofia, 89 - Catania 95123 E-mail: parenti@unict.it

Actual position: Associate Professor of Physiology, University of Catania, Italy.

Education:
1989 - Advanced degree in Pharmacy
1995 - PhD in “Neurosciences " University of L'Aquila.
1996 - Assistant Professor of Physiology, University of Catania, Italy (BIO/09)
2003 - Associate Professor of Physiology (BIO/09).

Assignments and roles
- 2008-2009: Vice-Director of the Department of Physiological Sciences.
- 2009-2010: Director of the Department of Physiological Sciences.
- 2008 to present: Member of Società Italiana di Fisiologia.
- 2010: Supervisor animal research of the UniCT.
- 2010: Member of Institutional animal care and use committee (I.A.C.U.C.)
- 2011: Regional Supervisor (Sicilia) of the European Biomedical Research Association.
- 2012: Member of Academic Senate of the UniCT
- 2014: Vice-Director, Department of Biomedical and Biotechnological Sciences, UniCT
- 2007-2015/ 2017: Member Board of PhD in "Biotechnology"
- 2009-to present: Delegate of the Rector of the University of Catania as "Titolare dello SUU e Area Preclinica del CAPiR (Center for Advanced Preclinical in vivo Research)"

Teaching Activities:
- 1996/to present: Physiology for "Corso di Laurea in Farmacia" - University of Catania.
- 2000/2011: Biology for "Corso di Laurea in Farmacia" - University of Catania.
- 2012 to present: Physiology for "Corso di Laurea in Medicina e Chirurgia" - University of Catania.
- 2016 to present: Physiology for "Corso di Laurea in Biotecnologie Mediche" - University of Catania.
- 2011 to present: Physiology for third level Degree in "Hospital Pharmacy".

Research experience:
1987 to present - Department of Physiological Sciences (now "Biomedical and Biotechnological Sciences") University of Catania.University of Catania.
1994 - Ecole Normale Superieure - Developpment et evolution du systeme nerveux - Equipe atipe niveau 3 - CNRS URA - Paris).
1998 - International Institute of Genetic and Biophysic. CNR, Napoli.
2005-2007 - Functional Genomic Center – Institute of Neurological Sciences. CNR, Catania.

Scientific Interests
- Neuroscience: Anatomo/functional organization of the SNC; Neurodegeneration/neuroprotection; Neuroiflammation; Development; Gap Junctions.
- Ontogeny/Cancer: Oncofetal proteins; Experimental cancer models for antitumoral therapies; Cancer Biomarkers; Drug Delivery
- Regenerative Medicine: In vitro and in vivo models for bone/cartilage regeneration

Member of research centers:
- Research Center "Farmacologia Oculare - CERFO", UniCT.
- Research Center "Prevenzione, Diagnosi e Cura dei Tumori - C.R.S.Pre.Di.C.T." UniCT.
- Research Multidisciplinary Center "Diagnosi e Terapia delle Malattie Rare", UniCT
- Research Multidisciplinary Center "Tecniche e Chirurgie Mini-invasive", UniCT.

Main Research project responsibilities
- 2008. PRIN "Espressione del recettore per la transferrina di tipo I (TfR1) mRNA e analisi delle sue isoforme proteiche per l'identificazione di potenziali biomarker di tumori tiroidei ".
- 2008. Progetto di ricerca d'Ateneo ORCT073103 dal titolo "Azione neuroprotettiva dell'emeossigenasi-1 in modelli di sofferenza cerebrale".
- 2009. "Allestimento di modelli sperimentali di xenotrapianto di cellule staminali neoplastiche umane, utili per lo studio delle terapie antitumorali" da: Società Casa di Cura Musumeci - Gecac S.r.l. nell'ambito del programma di ricerca denominato "Identificazione e produzione di cellule staminali neoplactiche utilizzabili come strumento per lo studio dell'efficacia dei prodotti terapeutici antitumorali" ai sensi del Decreto Ministeriale N. 593 08/08/2000, protocollo MUR 1557/2004.
- 2013. "Identificazione di signature (parametri e profili) per il supporto alla definizione di metodologie innovative ed il proof of concept di un sistema di procedure di medicina traslazionale personalizzata (patient driven)" da: Economicti Research S.r.l. nell'ambito del Piano di sviluppo di filiera denominato "Smart Grid:Power & ICT - POR FESR 2007/2013 Sicilia.
- 2013. Responsabile Corso di formazione specilistica di ricercatori dal titolo "Nuove figure di specialisti di tecnologie avanzate per l'identificazione e analisi di biomarcatori nel settore oncologico" da: Società Nerviano Medical Sciences S.r.l. nell'ambito del Progetto di Ricerca industriale e formazione PON01_02418.
- 2014. FIR "Correlation between DOR agonist effects and release of pro-inflammatory cytokines. A new interpretative key for improvement of neuropathic pain symptoms".
- 2015. Responsabile del contratto di attività formative specialistica di Fisiologia Cellulare. CNR-ISN - progetto di formazione nell'ambito "DNA on Dick: Piattaforma e kit diagnostici per la salute dell'uomo in ambito oncologico, neurologico e infettivologico e delle malalttie legate alla povertà", progetto cod.: CTN01_00177_817708 nell'ambito del PON "Ricerca e competitività 2007-2013.
- 2016: "Sistemi per il trasporto ed il rilascio di farmaci in Oncologia - OR 3.1 - 3.1a / 3.1b" per UNICT. Progetto di ricerca "Drug delivery: veicoli per un'innovazione sostenibile" - PON03PE_00216_1 - settore Salute Dell'uomo/Scienze Della Vita, di cui è Soggetto Attuatore il Distretto ad Alta Tecnologia Biomedico, Sicilia.
- 2017: "Valutazione in vitro di sostanze naturali per coadiuvare la rigenerazione osteo-cartilaginea" affidato da Bionap srl.
- 2017: "Valutazione di molecole bioattive da usare come immunostimolanti ed immunomodulanti" affidato da Etna Biotech s.r.l..

Reviewer Activities and editorial committees
- Guest Editor: Special Issue "Immunomarkers in human developing and pediatric neoplastic tissues" by Gaetano Magro, Giuceppe Musumeci & Rosalba Parenti in "Acta Histochemica" - Elsevier.
- Member of Editorial Board: "Frontiers Physiology"; "The Open Access Journal of Science and Technology" Sections i) Neuroscience; ii) Physiology; iii) Cell Biology; "American Research Journal of Biosciences"; "Mediterranean Journal of Biosciences"; "International Journal of Pediatricc & Neonatal Care".
- Reviewer: Journal of Cellular Physiology; Regenerative Medicine; Oxidative Medicine and Cellular Longevity; The American Journal of the Medical Sciences; Biology of the Cell; BioMed Research International; Current Medicinal Chemistry; Future Oncology; ISRN Neuroscience; Oncotarget; Plos One; Disease Markers; Scientific Literature; Pharmacology and Toxicology; Translational Cancer Research; Journal of Drug Design and Development; Oncology Reports; Molecular Medicine Reports; International Journal of Oncology.

4. RUSSO Giorgio

Name: Giorgio Russo
Institution:Institute of Molecular Bioimaging and Physiology (IBFM), Cefalù Support Unit (U.O.S) National Research Council (CNR)
Address: Contrada Pietrapollastra Pisciotto, 90015 Cefalù (PA), Italy
Phone: 0039 347 30 10 337
e-mail: giorgio-russo@cnr.it

October 2003: Master degree in Nuclear Physics, University of Catania disputing an experimental thesis on the development of a Monte Carlo Simulation of an Hadrontherapy Beam Line;
July 2007: Qualification in Medical Physics, University of Catania, disputing an experimental thesis on a Monte Carlo simulation of a clinical treatment using the Leksell Gamma Knife;
November 2009: Qualification in Radioprotection Expert at high level for the protection against the risks from the ionizing radiation

Position: Researcher

Responsibilities

Head of “Medical Physics and Bioimaging processing” Laboratory of IBFM-CNR
Qualified Expert in Radioprotection at the National Institute for Nuclear Physics - Catania Unit
Qualified Expert in Radioprotection at the National Institute for Nuclear Physics - Laboratori Nazionali del Sud (LNS)
Qualified Expert in Radioprotection at the Institute of Molecular Bioimaging and Physiology - Cefalù Support Unit
Member of the Monte Carlo Geant4 Collaboration
Member of the PhD School of the Physics department, University of Catania, Italy
Teacher of “Advanced Techniques of Physics applied to Medicine”, University of Catania, Italy
Member of the Medical Physics School of the University of Palermo, Italy
CNR Head of the Catania Animal Facility Collaboration between University of Catania, IBFM-CNR, Cannizzaro Hospital, LNS-INFN. The collaboration involves on the preclinical studies using hadrontherapy and molecular imaging.
CNR Head of the Scientific Collaboration between IBFM-CNR and LNS-INFN. The collaboration involves on the Monte Carlo simulation and radiobiological studies in hadrontherapy.
CNR Head of the Scientific Collaboration between IBFM-CNR and Cannizzaro Hospital. The collaboration involves on the molecular images analysis for oncological and neurological diseases.

Responsibilities in Research Projects

2017: “An Innovative Diagnostic method”, funded by Italian National Institute of Nuclear Physics (INFN), Principal Investigator (PI)
2014: “Italian Molecular Imaging Network”, funded by The Italian Ministry of Education, Universities and Research (MIUR), Local Coordinator.
2011 - 2013: “Development of a platform technology for the non-invasive treatment of Oncological and infectious diseases based on the use of focused ultrasound”, funded by The Italian Ministry of Education, Universities and Research (MIUR), Local Coordinator.

Skills

His research interests include the development and implementation of elaboration methods to biomedical imaging, the Monte Carlo simulations in radiotherapy. His most recent research activity has been dedicated to the dosimetric studies for the preclinical hadron therapy applications, with experimental measurements and Monte Carlo – GEANT4 simulations, and to the PET/CT image analysis for the treatment response and radiotherapy planning.
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 of the analysis of PET/CT images, quantification of the radiotracer uptake, for oncological and neurological disease.
He is author of 82 pubblications. Supervisor of 2 final-year theses for the achievement of the degree in Physics. Supervisor of 2 thesis in Medical Physics. Currently supervising 1 MSc student and 1 PhD student in Physics

5. Principal scientific publications of associated investigators

1. **MANTI Lorenzo**

1. Cirrone, G. A. P., Manti, L., Margarone, D., Petringa, G., Giuffrida, L., Minopoli, A., Picciotto, A., Russo, G., Cammarata, F., Pisciotta, P.,...(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 - **Articolo in rivista**
2. Manti L., Perozziello F.M., Borghesi M., Candiano G., Chaudhary P., Cirrone G.A.P., Doria D., Gwynne D., Leanza R., Prise K. M., Romagnani L., Romano F., Scuderi V., Tramontana A. (2017). The radiobiology of laser-driven particle beams: focus on sub-lethal responses of normal human cells. JOURNAL OF INSTRUMENTATION, vol. 12, p. C03084, ISSN: 1748-0221, doi: 10.1088/1748-0221/12/03/C03084 - **Articolo in rivista**
3. Petringa G., Cirrone G.A.P., Caliri C., Cuttone G., Giuffrida L., Larosa G., Manna R., Manti L., Marchese V., Marchetta C., Margarone D., Milluzzo G., Picciotto A., Romano F., Romano F.P., Russo A.D., Russo G., Santonocito D., Scuderi V. (2017). Study of gamma-ray emission by proton beam interaction with injected Boron atoms for future medical imaging applications. JOURNAL OF INSTRUMENTATION, vol. 12, p. C03049, ISSN: 1748-0221, doi: 10.1088/1748-0221/12/03/C03049 - **Articolo in rivista**
4. Petringa, G., Cirrone, G. A. P., Caliri, C., Cuttone, G., Giuffrida, L., La Rosa, G., Manna, R., Manti, L., Marchese, V., Marchetta, C.,...(2017). Prompt gamma-ray emission for future imaging applications in proton-boron fusion therapy. JOURNAL OF INSTRUMENTATION, vol. 12, p. C03059, ISSN: 1748-0221, doi: 10.1088/1748-0221/12/03/C03059 - **Articolo in rivista**
5. Scampoli Paola, Carpentieri Carmela, Giannelli Marco, Magaddino Vera, Manti Lorenzo, Moriello Carmen, Piliero Maria Antonietta, Righi Sergio, Di Martino Fabio (2017). Radiobiological characterization of the very high dose rate and dose per pulse electron beams produced by an IORT (intra operative radiation therapy) dedicated linac. TRANSLATIONAL CANCER RESEARCH, vol. 6, p. S761-S768, ISSN: 2218-676X, doi: 10.21037/tcr.2017.05.21 - **Articolo in rivista**
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6. Hindex of associated investigators (only for the scientific fields in which the use of the H-index is usually adopted)

nº	Surname Name	H-Index	Source
1.	MANTI Lorenzo	14	Scopus
2.	RUSSO Giorgio	10	WoS
3.	PARENTI Rosalba	18	Scopus
4.	PACIFICO Severina	21	Scopus

7. Main staff involved (max 10 professors/researchers for each research unit, in addition to the PI or associated investigator), highlighting the time commitment expected

List of the Research Units

Unit 1 - CUTTONE Giacomo

Personnel of the research unit

nº	Surname Name	Category	University/ Research Institution	e-mail address	Months/person expected
1.	CUTTONE Giacomo	Dirigente di ricerca	Istituto Nazionale di Fisica Nucleare	cuttone@lns.infn.it	6,0
2.	CIRRONE Giuseppe	Ricercatore	Istituto Nazionale di Fisica Nucleare	cirrone@lns.infn.it	6,0

Unit 2 - MANTI Lorenzo

Personnel of the research unit

nº	Surname Name	Category	University/ Research Institution	e-mail address	Months/person expected
1.	MANTI Lorenzo	Professore Associato (L. 240/10)	Università degli Studi di Napoli Federico II	manti@na.infn.it	5,0
2.	PUGLIESE Mariagabriella	Professore Associato (L. 240/10)	Università degli Studi di Napoli Federico II	pugliese@na.infn.it	2,0

Unit 3 - PACIFICO Severina

Personnel of the research unit

nº	Surname Name	Category	University/ Research Institution	e-mail address	Months/person expected
1.	PACIFICO Severina	Ricercatore confermato	Università degli Studi della Campania "Luigi Vanvitelli"	severina.pacifico@unina2.it	6,0

Unit 4 - PARENTI Rosalba

Personnel of the research unit

nº	Surname Name	Category	University/ Research Institution	e-mail address	Months/person expected
1.	PARENTI Rosalba	Professore Associato confermato	Università degli Studi di CATANIA	parenti@unict.it	4,0
2.	MAGRO Gaetano Giuseppe	Professore Associato confermato	Università degli Studi di CATANIA	g.magro@unict.it	2,0
3.	SPATOLA Corrado	Ricercatore a t.d. - t.pieno (art. 24 c.3-a L. 240/10)	Università degli Studi di CATANIA	cor_spatola@hotmail.com	3,0
4.	CALABRESE Giovanna	Assegnista	Università degli Studi di CATANIA	soniacalabrese@hotmail.com	12,0

Unit 5 - RUSSO Giorgio

Personnel of the research unit

nº	Surname Name	Category	University/ Research Institution	e-mail address	Months/person expected
1.	RUSSO Giorgio	Ricercatore	Consiglio Nazionale delle Ricerche	giorgio-russo@cnr.it	5,0
2.	FORTE Giusi Irma	Ricercatore	Consiglio Nazionale delle Ricerche	giusi.forte@ibfm.cnr.it	4,0

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8. Major new contracts for staff specifically to recruit

nº	Associated or principal investigator	Number of contracts RTD expected	Number of research grants expected	Number of PhD expected	Predictable overall time commitment (months)
1.	CUTTONE Giacomo	0	2	0	36
2.	MANTI Lorenzo	0	2	0	36
3.	PACIFICO Severina	0	1	0	12
4.	PARENTI Rosalba	0	2	0	36
5.	RUSSO Giorgio	0	2	0	36
	Total	**0**	**9**	**0**	**156**

9. Statement by the Principal Investigator

Con la sottomissione della presente proposta, consapevole della responsabilità civile e penale, attesto l'assenza di duplicazione degli obiettivi e dei contributi richiesti con altri progetti in corso o già conclusi

"I dati contenuti nella domanda di finanziamento sono trattati esclusivamente per lo svolgimento delle funzioni istituzionali del MIUR. Incaricato del trattamento è il CINECA - Business Unit MIUR. La consultazione è altresì riservata agli atenei e agli enti di ricerca (ciascuno per le parti di propria competenza), al MIUR - D.G. per il Coordinamento e lo Sviluppo della Ricerca - Ufficio V, al CNGR e ai CdS. Il MIUR potrà anche procedere alla diffusione dei principali dati economici e scientifici relativi ai progetti finanziati".

Date 27/03/2018 ore 16:49