NEPTUNE

Nuclear process-driven Enhancement of Proton Therapy UNravEled

CALL CNS 5

Preventivi 2019 – Nuova Iniziativa

Responsabile Nazionale: G. Cuttone – Responsabile locale: S. Bortolussi

Research area: Multidisciplinary

Sezioni Participanti: LNS (6.5), Napoli (2.2), Roma1 (3.55), Roma3 (0.5), LNL (0.6), Milano (2.4), Pavia (1.3), TIFPA (1.3)

Totale: 18.35

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OPEN

First experimental proof of Proton Boron Capture Therapy (PBCT) to enhance protontherapy effectiveness

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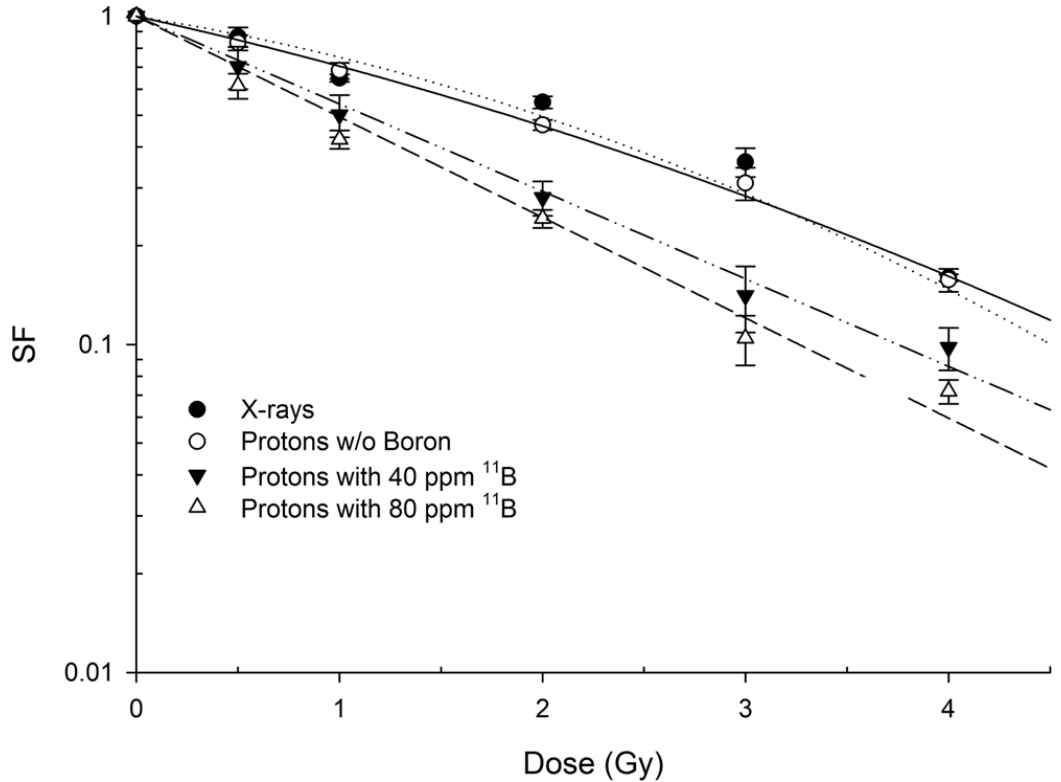
"… we exploited the $p + {}^{11}B \rightarrow 3\alpha$ reaction to generate high-LET alpha particles with a clinical proton beam. To maximize the reaction rate, we used sodium borocaptate (BSH) with natural boron content.

Boron-Neutron Capture Therapy (BNCT) uses ^{10}B-enriched BSH for neutron irradiation triggered alpha particles.

We recorded significantly increased cellular lethality and chromosome aberration complexity. .."

diverse misure *in vitro* confermano che in presenza di BSH ($Na_2B_{12}H_{11}SH$) c'è maggior danno cellulare, rispetto a irraggiamento con soli protoni.



However….

“ The radiobiological data reported in this work suggest that the p + $^{11}B \rightarrow 3\alpha$ reaction as being responsible for the observed increase in the biological effectiveness of a clinical proton beam. **However desirable, we cannot currently provide a simple analytical computation able to explain our results**, for instance by correlating the biological effect with the total number of α-particles that can be expected to be generated under our experimental conditions.”

Conti di dosimetria **non** supportano la conclusione che la reazione p + $^{11}B \rightarrow 3\alpha$ sia la (sola) responsabile dell’effetto: data la sezione d’urto di cattura del p sul Boro-11 (~1 barn) e la fluenza di protoni (dell’ordine di 10^8 p/cm^2), la dose aggiuntiva dovuta alle particelle alfa generate è dell’ordine di 10^{-7} Gy, e il numero di particelle alfa generate nella flask è dell’ordine di 100.
Inoltre l’effetto non sembra cambiare significativamente raddoppiando la concentrazione di boro nella flask.

Precedenti

AIP ADVANCES **6**, 095119 (2016)

The investigation of physical conditions of boron uptake region in proton boron fusion therapy (PBFT)

Joo-Young Jung,[1,2] Do-Kun Yoon,[1] Heui Chang Lee,[3,4] Bo Lu,[2,a] and Tae Suk Suh[1,b]

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[2]*Department of Radiation Oncology, University of Florida, Gainesville, Florida, USA*

[3]*J. Crayton Pruitt Family Department of Biomedical Engineering, University of Florida, Gainesville, Florida, USA*

[4]*Weldon School of Biomedical Engineering, Purdue University, West Lafayette, Indiana, USA*

"An effective proton boron reaction required the boron concentration to be equal to or greater than 14.4 mg/g"

www.impactjournals.com/oncotarget/ Oncotarget, 2017, Vol. 8, (No. 24), pp: 39774-39781

Clinical Research Paper

Comparison between proton boron fusion therapy (PBFT) and boron neutron capture therapy (BNCT): a Monte Carlo study

Joo-Young Jung[1,2,*], Do-Kun Yoon[1,*], Brendan Barraclough[2,3], Heui Chang Lee[3,4], Tae Suk Suh[1] and Bo Lu[2]

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[*] These authors have contributed equally to this work

"The boron concentration was set at 1.04 mg/g"

However, the concentration used in the Sci. Rep. experiments was ~10-100 times lower (80 ppm = 0.08 mg/g)…

Razionale

- INFN impegnato su diverse attività legate a **radioterapie innovative**.
- La possibilità di ottenere un enhancement dell'effetto terapeutico tramite somministrazione di ^{11}B e irraggiamento protonico potrebbe avere un impatto nella diffusione della protonterapia **(precisione balistica dei protoni + elevata efficacia biologica delle particelle α)**
- È necessario **investigare i meccanismi** per capire quale/i sia/no la/le causa/e dell'effetto osservato
- È sfruttabile l'esistente **esperienza in ambito BNCT**: misura del boro intracellulare, dosimetria in campo misto, simulazione & modellistica, radiobiologia.

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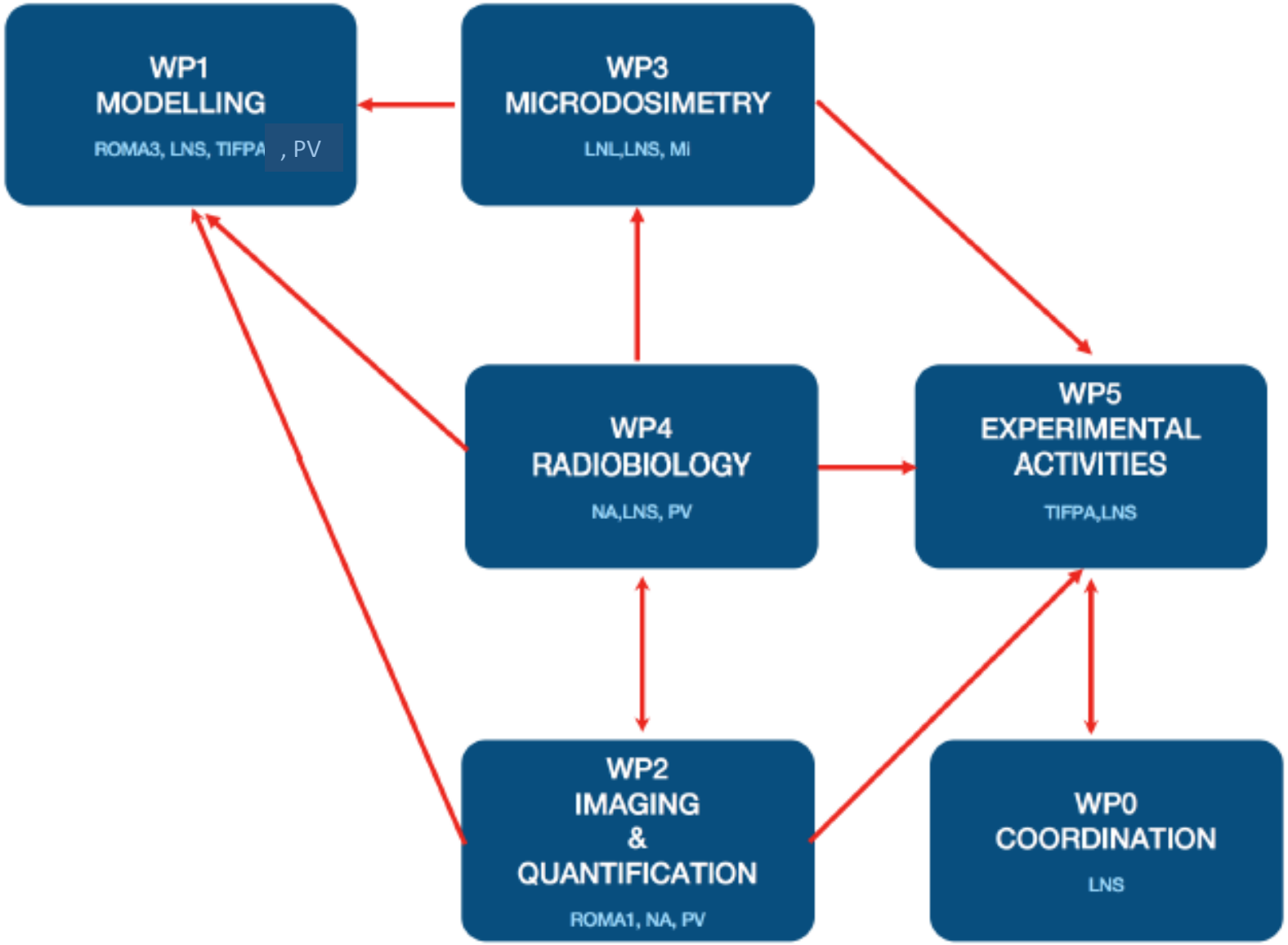
- La call mira a studiare meccanismi di base che permettano di capire interazione di campi misti a livello cellulare per modellizzare effetti osservati macroscopici.
- In questo progetto si mettono a sistema le competenze di molti gruppi che si dedicano a radioterapia con particelle e a modellizzazione in radiobiologia.


WP1
MODELLING
ROMA3, LNS, TIFPA , PV
WP3
MICRODOSIMETRY
LNL,LNS, MI
WP4
RADIOBIOLOGY
NA,LNS, PV
WP5
EXPERIMENTAL
ACTIVITIES
TIFPA,LNS
WP2
IMAGING
&
QUANTIFICATION
ROMA1, NA, PV
WP0
COORDINATION
LNS

Attività di Pavia – WP2 (**Roma1, PV**, NA)

- misura del boro intracellulare in colture cellulari trattate allo stesso modo che per irraggiamento con p+ *(gli esperimenti fatti finora assumono uguale concentrazione nelle cellule e nel mezzo di coltura, ma l'esperienza BNCT insegna che non è così)*

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

Attività di Pavia - WP4 (**NA**, LNS, PV)

- Confronto tra gli effetti di BNCT e quelli di p+^{11}B su linee cellulari, *a parità di dose assorbita* per chiarire i meccanismi

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

Attività di Pavia - WP1 (**Roma3, LNS**, PV, TIFPA)

- modellizzazione teorica/computazionale dell'effetto

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

Anagrafica PV 2019

- Silva Bortolussi, *RTDb* 30%
- Saverio Altieri, *PA* 10%
- Ian Postuma, *assegnista INFN* 20%
- Nicoletta Protti, *borsista INFN* 10%
- Cinzia Ferrari, *tecnico UniPV* 20%
- Francesca Ballarini, *PA* 30%
- Valerio Vercesi 10%

- TOT FTE 1.3

Richieste PV per il triennio 2019-2021
⇒ *per il 2019 si può assumere il totale/3*

- Consumabili (colture cellulari, misura boro) 21.0 kEuro
- Collaboration meetings 3.0 kEuro
- Partecipazioni congressi 1.5 kEuro
- Servizi 19.0 kEuro

- TOTALE 44.5 kEuro

⇒ totale 2019 ~ 15 keuro

Back-up slides

*Altri WP - WP3 Microdosimetry (**MI**, LNL, LNS, Roma3)*

- misura di spettri microdosimetrici lungo il SOBP (alle stesse profondità a cui verranno posizionate le cellule nel WP4), usando detectors tessuto-equiv (alcuni dei quali già usati in passato per BNCT) in presenza o meno di Boro

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

*Altri WP – WP5 Coordination of experimental activities (**TIFPA**, LNS)*

- coordinare le misure descritte in WP2/WP3/WP4 assicurando consistenza e standardizzazione delle metodologie, e fornire assistenza in loco durante le misure

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 WP5 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