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Progress on the accelerator based SPES-BNCT project at INFN Legnaro

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Abstract. In the framework of an advanced Exotic Ion Beam facility, named SPES (Study and Production of Exotic Species), that will allow a frontier program both in nuclear and interdisciplinary physics, an intense thermal neutron beam facility, devoted to perform Boron Neutron Capture Therapy (BNCT) experimental treatments on skin melanoma tumor, is currently under construction based on the SPES proton driver. A vast radiobiological investigation in vitro and in vivo has started with the new ^{10}B carriers developed. Special microdosimetric detectors have been constructed to properly measure all the BNCT dose components and their qualities. Both microdosimetric and radiobiological measurements are being performed at the new HYTHOR beam shaping assembly at the Enea-Casaccia TAPIRO reactor.

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1. Introduction

In the last years the availability of new, intense, Radioactive Ion Beams (RIB's) has been recognized as a fundamental tool for future research in nuclear physics of exotic, unstable nuclei not present in the common world, that are relevant for the understanding of the early stage of the Universe. In view of the next generation European facility EURISOL an important role for RIB's physics will be played by European national projects like SPES at LNL (Laboratori Nazionali di Legnaro). This facility, having an intermediate size between existing, first generation, GANIL-SPIRAL and CERN-ISOLDE ones and the longer-range EURISOL, will allow, together with an extensive physics program in the field of nuclear and interdisciplinary physics, to boost the technological development (accelerator, production targets and detectors) in view of the European project. A first design report of SPES was published in '99 [1] while a detailed Technical Design Report (TDR) has been published in 2002 [2]. The construction of the first stage of SPES project, named SPES-1, including the RFQ equipped with an intense neutron source, as well as the first part of the superconducting proton linac up to 20 MeV and the R&D on RIB's production targets has been approved by the INFN board on 2004. It will be a first, remarkable step towards SPES and EURISOL projects, and a test bench for the high intensity community (ADS), as well as the main provider in support to the community of interdisciplinary physics and medical users. Due to the relatively small size and affordable cost it will also deliver intense neutron beams for experimental activities in both fundamental and applied nuclear physics (medicine, biology and solid state). On the other hand it will represent an attractive, accelerator-based, thermal neutron beam facility for dosimetric, microdosimetric and radiobiological studies, as well as for the BNCT application of skin melanoma treatment. Furthermore it will be a fundamental test bench for an operative, accelerator-based BNCT facility concept, which could provide in perspective a possible spin-off in a hospital institution instead of the more complex, even low power, dedicated reactor-based systems.

2. The approved starting stage of SPES Facility at LNL

The main new construction relying the SPES facility is the driver-linac and RIB's production building, which will be connected with the already existing both TANDEM-ALPI complex. Integrated in the same building, there will also be a section mainly dedicated to the interdisciplinary applications and to the BNCT research. The driver linac design is based on the Independently phased Superconducting Cavities (ISC), which extend to high intensity proton linacs the technology developed for heavy ion boosters, like ALPI. The injector linac components are the off-resonance RF proton source TRIPS [3] already constructed at LNS, the other INFN Nuclear Physics Laboratory, and the RFQ [4] (Radio Frequency Quadrupole) under construction at LNL, both developed within the TRASCO research program, for nuclear waste transmutation purpose. The RFQ is a 7.13 m long structure composed by six modules resonating at 352 MHz, fed by one high power klystron. The main technological challenge of this accelerator comes from the main constraint to keep beam losses below 1% which implies the requirement to fulfill very severe mechanical tolerances (around 0.01 mm) in the geometry of the structure, realized in ultra-pure copper, while operating with a very high RF power dissipation. A sketch of the accelerator including the six accelerating structures mounted together and the first module during the RF measurements after brazing treatment is shown in Figure 1. The source and the RFQ, installed at LNL, will represent a unique facility, able to deliver 30 mA, 5 MeV beam which will be used as a stand alone system for the BNCT facility as well. A schematic layout of SPES-1 with the ion source TRIP, the TRASCO RFQ, and the transport lines to both the superconducting linac and the BNCT facility is shown in Figure 2. This layout is now being tested with extensive beam dynamics simulations.

Fig. 1. The TRASCO RFQ (5 MeV, 30 mA). Layout of the 7.13 m long accelerating structure on the support system, the main cooling pipes connections, quadrupole cross section and view of the first module constructed ready for low power RF measurements after the brazing thermal treatment.

2.1. The SPES-BNCT reserch program

The BNCT application will be the main interdisciplinary user of the SPES-1 facility, thus exploiting the intense proton beam provided by RFQ, the first accelerating step of SPES facility. The neutron source spectrum provided through (p,n) reaction on the Be target will then be slowed down to the thermal energy range by a proper spectrum shifter device, in order to supply, at the irradiation beam port, a thermal neutron flux level at least of $10^9 \mathrm{cm}^{-2}\mathrm{s}^{-1}$ requested for patient treatment. The LNL-BNCT facility is foreseen to explore the treatment of extended skin melanoma with such a therapeutic modality [5]. An interdisciplinary research group has been gathered around SPES-BNCT project, formed by medical doctors, biologists, physi-

Fig. 2. Schematic layout of SPES-I; TRIPS (TRASCO Ion Source), RFQ (Radio Frequency Quadrupole) is the first accelerating stage, the MEBT (Medium Energy Beam Transfer) transfer the beam to the ISCL (Independent Superconducting Cavity Linac), composed by two cryostats, or to the BNCT facility, the thermal neutron source dedicated to the medical experimental program.

cists, nuclear engineers belonging to different institutions (Veneto regional center for skin melanoma, Padova University, Milan Polytechnic, Molteni Pharmaceuticals, ENEA, INFN) aimed at the experimental program of an advanced radiotherapy application of skin melanoma treatment. The main items of the research program are being mainly focused on the neutron irradiation facility design, the development of a new boron carrier and a new, on-line, biological dose monitoring in both tumor and healthy tissues.

2.1.1. The thermal facility modeling

The SPES-BNCT facility design will exploit the experience gained, in the last years, at the INFN-LNL, with the experimental, low power, thermal neutron source facility driven by the 7 MV (3μA max.) CN Van de Graaff accelerator, according to the constraints requested by the TERA program [6] aiming at an hospital-based centre of hadrons therapy in Italy. Preliminary MCNP computer code simulation trials [7] were performed in order to obtain an optimized design of a compact size facility able to fulfill a high thermal neutron flux required at the irradiation port, consistent with neutron economy constraints. The demonstration facility basically consists of an inner D_2O tank arranged around the ion beam target which is the first moderator stage, then surrounded by a Reactor Grade (RG) graphite which acts as a second spectrum shifter structure. A series of experimental tests were performed [8] in order to provide a beam spectrum characterization of neutrons emerging both from ^{9}Be(d,n)^{10}B and ^{9}Be(p,n)^{9}B reactions, induced respectively by 7 MeV deuterons and 5 MeV protons on a thick beryllium target. A schematic proof-of-principle layout sketch of the final beam shaping assembly (currently at the neutronic design stage) and the RFQ driver is reported in Figure 3.

Fig. 3. Schematic layout of SPES-BNCT irradiation facility

2.1.2. The neutron converter design

A RD effort has simultaneously been carried out in order to select the proper neutron source target type consistent with the SPES design specifications. After extensive MCNPX simulation trials on the same demonstration facility modeling, beryllium has revealed as a whole the best solution, taking into account the neutron yielding performance, as well as the related target engineering know-how. The neutron design is, in particular, a key point because of the high thermal power load in operating conditions (150 kW). A target beam spot area, which should keep the surface heat load to a level as low as 0.7 $\mathrm{kWcm^{-2}}$, in order to make use of reliable and already proven target cooling system, would be required. After both neutronic as well as technological feasibility studies lasted two years, an original, improved, stage II beryllium-based target concept, shown in Figure 4, has thus been designed, in collaboration with the STC Sintez of Efremov Institute in S. Petersburg, as the best neutron converter solution.

The target main structural components are based on a zirconium alloy while the neutron converter exploits the tile concept, i.e. beryllium tiles which are brazed on a 10 mm outer diameter, 1 mm thickness, cooling pipes. Such a composite pipe structure allows for the application of the well-developed Be-Cu joint technology developed in the framework of ITER project on next fusion reactor, thus avoiding the corrosion of copper alloy by the coolant. Finally the peculiar target profile

Fig. 4. Be neutron converter final design for BNCT facility: (left) assembly with I moderator stage (right) target plug system

has been selected in order to meet the design criteria to provide a constant power density distribution on the full beryllium target surface (along beam axis direction), while getting the neutron yielding volume as close as possible to the ideal point-like source. The first, full-scale target prototype, shown in Figure 5, constructed by the end of 2004, has successfully passed the preliminary series of both operative and critical e-beam full power tests on March 2005.

Fig. 5. Target prototype final assembly (left) and surface visual inspection after the first electron beam power test performed at the HHF facility (right).

On the other hand a further technological effort is under way to develop and test a new, reliable, neutron converter made of a solid Be block only. A first full-scale prototype following the new concept has recently been constructed and positively passed the preliminary pressure and He leakage tests, thus proving the proper manufacturing process adopted.

2.1.3. The new thermal spectrum shifter for *in vivo* test at TAPIRO reactor

Due to the lack of an intense enough thermal neutron source available at the LNL, a scientific collaboration has started between ENEA and INFN in the framework of the Italian BNCT research program [9], to carry out a radiobiological study on a subcutaneous melanoma tumor model implanted in laboratory mice at the low-power (5 kW), TAPIRO research fast reactor, located at the ENEA Casaccia Centre near Rome. These in vivo experiments are a fundamental test bench in order to assess pharmacokinetics, uptake effectiveness, as well as tumor damage following BNC nuclear process of the new boron compounds which have been selected. The original thermal irradiation facility, at present dismantled, has nonetheless revealed to drive both the unwanted non-thermal and gamma dose components inside the irradiation cavity to an extent which heavily limits both in vitro and in vivo experimental tests of any boron compound. A new request, focused on the assessment to provide a better thermal neutron beam quality, has therefore arisen and an extensive MCNPX beam shaping assembly modeling thus started at LNL which final solution based on an original, hybrid, neutron spectrum shifter configuration is reported in Figure 6. The new facility HYTHOR (**HY**brid **T**hermal spectrum s**H**ifter Tapir**O** **R**eactor) has the main advantage to provide an high, thermal neutron flux level uniformly distributed inside the irradiation cavity with a very low gamma background. A comparison of main parameters calculated between the original and the new HYTHOR thermal column is at last reported in Table 1.

Fig. 6. The new HYTHOR thermal beam shaping assembly designed and constructed at LNL: main features (left) and after installation inside the irradiation cave of TAPIRO reactor with the removable irradiation cavity inserted (right).

As can be observed HYTHOR is able to provide the best thermal flux performance with the unwanted dose component well below the recommended limits of $2{\cdot}10^{-13}$ $\mathrm{Gycm^{-2}}$. Preliminary beam characterization measurements performed so far inside the Bi shielded irradiation cavity with the standard foil activation technique confirmed the calculation results within 15% uncertainties. Additional benchmark trials already planned by fall 2005 will provide further confirmation.

Table 1. Beam performance comparison between the old (ENEA) and the new, HYTHOR, thermal BSA designed and assembled at LNL (MCNPX calculation)

Main Parameters	Original ENEA thermal column	HYTHOR (LNL)
$\Phi_{th(E<0.4eV)}$ ($cm^{-2}\mathrm{s}^{-1}$)	$2.00\cdot10^9$ ±0.1%	$3.50\cdot10^9$ ±0.1%
Φ_{total} ($cm^{-2}\mathrm{s}^{-1}$)	$2.30\cdot10^9$ ±0.1%	$3.75\cdot10^9$ ±0.1%
Φ_{th}/Φ_{total}	0.88	0.92
$\dot{K}_{n(epi-fast)}/\Phi_{th}$ ($Gy\cdot\mathrm{cm}^{-2}$)	$1.00\cdot10^{-13}$ ±2.1%	$0.15\cdot10^{-13}$ ±4.1%
$\dot{K}_{\gamma}/\Phi_{th}$ ($Gy\cdot\mathrm{cm}^{-2}$)	$3.60\cdot10^{-13}$ ±0.4%	$0.85\cdot10^{-13}$ ±0.4%

2.1.4. Studies to develop a new boron-loaded carrier

Interesting perspectives are opened by the new concept to use a single compound (e.g. a porphyrin or a phthalocyanine) which can act both as a boron carrier to tumour cells and a cell photosensitizer. Therefore, a tumor lesion could be treated by two different modalities, such as BNCT and photodynamic therapy (PDT). PDT is a promising experimental treatment for neoplastic diseases based on the ability of tumour tissues to retain some photosensitizers with a certain degree of selectivity. Hence, photoactivation of the photosensitizer by visible or near infrared radiation leads to tumor necrosis by the production of cytotoxic species. Since the selective assimilation of a boron compound into the tumor cells is one of the main requirements of boron neutron capture therapy (BNCT), a specific research line has started at the Biology Department of Padua University in order to assess the modalities which could promote such a different therapeutic approach. A novel ^{10}B-enriched carboranyl-containing phthalocyanine (B-Pc) has been at the purpose synthesized by Molteni Pharmaceuticals (Florence, Italy) and in vitro studies, performed during the first investigation stage, revealed the carboranyl-carrying phthalocyanine was efficiently accumulated by B16F1 melanotic melanoma cells with induced extensive cell mortality after a red light irradiation. The first, in vivo BNCT study [9] were also performed on (B-Pc) loaded melanoma bearing mice at the original thermal column (at present dismantled) of TAPIRO research reactor which preliminary results led to a significant tumour growing delay, compared with control untreated ones [9]. A new version of boron phtalocianine with two carborane groups placed in axial position has been recently synthesized and, although carries only 20 boron atoms, the half of previous version, first experimental in vitro studies have shown an uptake effectiveness inside the cell even better than the former one. A sketch of the two new molecules is reported in Figure 7.

Fig. 7. The new boron loaded phtalocianine molecules synthesized with different carborane groups in planar and axial position developed by Molteni Pharmaceuticals.

2.1.5. Development on the new TEPCs for dosimetry and beam quality monitoring

Radiation dosimetry is quite complex in BNCT treatment because of different radiation components contribution with different biological effectiveness. Living cells experience in fact radiation events with a large LET spreading, ranging from few tenth of keV/μm (2.2 MeV gamma rays), to about 300 keV/μm (^{7}Li ions of 870 keV of energy). Moreover, since the neutron spectrum changes with the depth, radiation components relative yield changes with depth in tissue. The radiation field can even change depending on the accelerator-based BNCT beam features which can not be assumed constant in time. A detailed beam quality monitoring, providing the relative contribution of all absorbed dose components, (gamma, neutron and the BNC ones) having different biological effectiveness has therefore to be been taken into account. Still now, three different detectors are being used to assess the different dose components contribution, while our aim is to use a single detector able to perform the same measures simultaneously. The experience gained in the last years led us to select the tissue-equivalent proportional counters (TEPC), which have proven to measure the absorbed dose and its quality with high accuracy both for high [10] and low energy [11] neutrons, as well as for fast neutron therapeutic beams [12] and BNCT applications [13], [14]. A first TEPC prototype with changeable, tissue equivalent A-150 plastic cathode shells, loaded with different ^{10}B concentration ranging from 0 to 100 ppm, was constructed. Due to its large sensitive volume (2.3 cm^3), the counter may be used in relatively weak radiation fields only, as those ones available at Legnaro labs. Similar measurements were also performed inside the irradiation cavity of former TAPIRO thermal column at very low (20 W) power level [15]. In order to prevent pile-up event distortions in microdosimetric spectra, a much smaller counter has been designed, which cutaway view is reported in Figure **??**, made of two cylindrical TEPCs with two A-150 plastic cathode walls, one of them being loaded with 50 ppm of ^{10}B [16]. The main requirement to get all dosimetric data (gamma, neutron and BNC dose, plus their qualities parameters, as well as the total radiation field quality) just in one measurement only, can thus be fulfilled. The twin TEPC has two sensitive cavities of 0.9 mm diameter each (0.6 mm^3) which are flowed with tissue-equivalent propane-based gas mixture. They can operate at gas pressures between 63 and 1260 mbar, corresponding to simulated site sizes ranging between 0.1-2.0 μm of diameter (when scaled at density of 1 g/cm^3). A prototype of the twin TEPC constructed, with electrical as well as vacuum and gas flowing connections visible, is shown in Figure 8. The counter has been used to perform first microdosimetric measurements at the new HYTHOR thermal column recently installed at the TAPIRO reactor, which first two microdosimetric spectra collected, are shown in Figure 9.

Fig. 8. Cutaway view of the new-mini-TEPC designed and constructed at LNL.

More details about a precise evaluation of the different absorbed dose components are published elsewhere [15]. Figure **??** shows that the gamma dose does not change significantly when 50 ppm of ^{10}B are added, but the absorbed dose of events between 20 and 500 keV/μm increases of a factor 3.9. This increase can only be due to helium and lithium ions emerging from the ^{10}B thermal neutron capture reactions.

Fig. 9. (left) The twin TEPC prototype: the two TEPCs are inserted inside the top of the 2.7 mm titanium long sleeve. (right) The twin TEPC passing through the duct of the irradiation cavity door of HYTHOR BSA. The slim sleeve with the two TEPCs is emerging out of the door left side. The aluminum box containing front-end electronics, vacuum and gas ports as well as electrical connections is placed on a shelf on the door right side.

Fig. 10. Absorbed dose distributions per logarithmic increment of lineal energy measured inside the irradiation vavity of HYTHOR BSA by the twin TEPC. The spectra are normalised to the without-10B total absorbed dose. The simulated site size is 1μm.

3. Conclusions

An accelerator-driven,thermal neutron beam facility is scheduled to be constructed at LNL in the next five years in the framework of SPES project, mainly dedicated to perform BNCT experimental investigations. The next milestone will therefore be focused on a new series of operative as well as critical thermo-mechanical test under

150 kW electron beam of the two neutron converter prototypes already constructed. Moreover the final beam shaping assembly neutronic design, as well as the new, twin-mini, TEPC tests for monitoring and processing microdosimetric data in high flux radiation fields are currently under way. On the other hand the biochemical research for new boron-porphyrines carriers will also be investigated. This research aims to find an alternative drug, which is more efficient and selective than the actual drugs used in BNCT. First measurements with the twin TEPC have pointed out the feasibility to perform a full BNCT dosimetry with a single detector. A single mini counter, which includes two tissue-equivalent gas spectrometers, can measure gamma, neutron and BNC doses and their qualities in the intense BNCT radiation field simultaneously. Additional tests are being carried out in order to get such a detector fully characterized for all the dose components with 5% or less of accuracy response.

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Notes

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