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

A Pisent, P. Colautti, J Esposito, L. De Nardo, V. Conte, D. Agosteo, G. Jori, P.A. Posocco, L.B. Tecchio, R. Tinti, G. Rosi

INFN-LNL, Legnaro (Padova), Italy,

Physics Department, Padova University, Italy

Nuclear Engineering Department, Milano Polytechnic, Italy

Biology Department, Padova University, Italy

ENEA (FIS-NUC) Bologna, Italy

ENEA (FIS-ION) Roma, Italy

Abstract In the framework of an advanced Exotic Ion Beam facility project, named SPES (Study and Production of Exotic Species), that will allow a frontier program 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 Enea-Casaccia TAPIRO reactor.

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1. Introduction
The new facility proposed for LNL, named SPES (Study and Production of Exotic Species), is based on the use of a new high intensity linac as a primary linac and of the existing superconducting linac ALPI as post accelerator. The main exotic beam production mechanism is the fission induced in a $^{238}$U target, in uranium carbide chemical form; the nominal fission rate is few $10^{13}$ s$^{-1}$, while the beam power on target is few 100 kW. A general description of the facility can be found in [1].

This linac, operating at 352.2 MHz, is based on a normal conducting RFQ followed by an independently phased superconducting cavities linac (ISCL), for a proton beam current of 5 mA. Moreover the superconducting linac, with the construction of a second RFQ, has the capability to accelerate deuterons and light ions at the same energy per charge; this allows an upgrade with an important boost of the radioactive ion beam intensity. The main linac components are the off resonance rf source TRIPS[2], the TRASCO RFQ[3] and the ISCL. The first part of the linac (up to 20 MeV), indicated as SPES-1 in Fig.1, has recently been funded.
The source and the RFQ have been developed within the TRASCO research program, aimed to the development of a high intensity linac for nuclear waste transmutation. The source TRIPS, built and commissioned at LNS, has been recently transferred to LNL, while the RFQ is under construction. The RFQ is a 7.13 m long accelerating structure composed by six modules fed by one high power klystron. The construction of this high intensity accelerator implies many technological challenges; for example in the construction of the cavity one has to fulfil very severe mechanical tolerances (around 0.02 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 2.

The source and the RFQ will represent a unique facility, able to deliver 30 mA 5 MeV beam. The main interdisciplinary user of the 5 MeV facility is the Boron Neutron Capture Therapy (BNCT). The 30 mA proton beam through (p,n) reaction on $^9$Be and a neutron moderator (mainly heavy water and graphite), generates the neutron flux of thermal neutrons (about $2.5 \times 10^{10}/(s \ cm^2)$) required for the therapy. Accelerator based neutron sources with these characteristics are not at present available worldwide, and the BNCT results are since now based on the use of nuclear reactors. Therefore this facility will represent an attractive accelerator based thermal neutron beam facility for dosimetric, microdosimetric and radiobiological studies, as well as for BNCT application to skin melanoma. Further more it will be a fundamental test bench for an operative accelerator-based BNCT facility concept, with a possible spin-off in a hospital based system.

The BNCT application will be the main interdisciplinary user of the SPES-1 facility thus exploiting the intense proton beam provided by the first SPES accelerating step, the RFQ, through (p,n) reaction on the Be target. The neutron source spectrum provided 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 $10^9 \ cm^{-2} s^{-1}$ required for patient treatment. The LNL-BNCT facility is foreseen to explore the treatment of extended skin melanoma with such a therapeutic modality [4]. 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. THE SPES-BNCT RESEARCH PROGRAM

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2.1 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 (3 \( \mu \)A max.), CN Van de Graaff accelerator, according to the constraints requested by the TERA program [5] aiming at an hospital-based centre of hadrons therapy in Italy. Preliminary MCNP computer code simulation trials [6] were performed in order to obtain an optimized design of a compact size facility able to fulfill a high thermal neutron flux requirement, at the irradiation port, lying on the side surface, consistent with neutron economy constraints. The demonstration facility basically consists of an inner D2O 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 [7] in order to provide a beam spectrum characterization of neutrons emerging both from \( ^{9}\text{Be}(d,n)^{10}\text{B} \) and \( ^{9}\text{Be}(p,n)^{9}\text{B} \) reactions, induced respectively by 7 MeV

Figure 2 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.
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.

2.2 The neutron converter design
A R&D effort is simultaneously being 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. As a general rule the target design is closely linked with the design of the neutron beam shaping and filtering assembly, which must take into account the geometry of the neutron converter and the effect of the support structure on the neutron and gamma transport. Different engineering as well as operative and safety issues concerning the neutron generator have thus to be carefully assessed, depending on the main SPES project constraints. A detailed knowledge about both double differential neutron yielding at the given ion beam energy and the proper solutions for target cooling are, among them, the most important items under investigation. The beam target 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 $\leq 0.7$ 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[8]. The target main structural components, reported in figure 6, are based on a zirconium alloy ($Zr + 2.5\%$ Nb), while the neutron converter exploits the tile concept, i.e. beryllium tiles which are brazed on a 10 mm outer diameter, 1mm thickness, cooling pipes. These latter are produced by casting of bronze (CuCrZr) alloy onto 0.3 mm thickness SS pipe with the following quenching and ageing manufacturing process. Such a composite pipe structure allows for the application of the well-developed Be-Cu joint technology, thus avoiding the corrosion of copper alloy by the coolant. The target profile, has been selected in order to meet the design criteria to provide an approximately 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 design takes into account the requirement to have a removable target unit from the BNCT facility for easy inspection as well as maintenance purposes. Some concern relating the cooling fluid capability, the cooling system simplicity as well as the economic has led light water to be chosen as coolant for both the target and the related collimator. A detailed coupled thermal-mechanical analysis has been also been performed to assess the maximum...
working temperatures, the related mechanical stresses and deformations both under static and cycling loading operating conditions, and estimation of the target lifetime as well. The steady state thermal

Figure 4: At left density power distribution (kW/cm$^2$) at the target on a plane perpendicular to the beam line, at the center the Beryllium converter profile (units are in mm) and at right the construction details. analysis results, reported figure 7, shows the maximum temperature on the beryllium hitting surface (673 °C) and of zirconium collectors (21 °C) are well below the correspondingly melting points.

On the other hand the stress intensities calculated at loading stage in all structural parts have revealed within the allowable design limits. Several mock-ups have been manufactured and tested at the High Heat Flux (HHF) Tsefey e-beam facility at the Efremov Institute under different power density levels, up to 1.1 kWcm$^{-2}$. All inspected samples revealed a good brazing quality with a uniform brazing layer. The joint between tiles and cooling pipes was not damaged during the tests and no any visible cracks and erosions have finally been observed inside Be thickness. The first, full-scale target prototype, shown in figure 8, constructed by the end of 2004, has successfully passed the preliminary series of both operative and critical e-beam power test conditions on March 2005. The technology to braze a beryllium layer on a bulk copper support and heat sink material, already proven in the framework of ITER project, has however the drawback of a too high prompt gamma ray contamination at the irradiation port. This represents an unwanted component and needs to be reduced to an extent as low as possible. A further technological effort is therefore 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.

Figure 5 Target prototype final assembly (left) and surface visual inspection after the first electron beam power test performed at the HHF facility (right).
2.3 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 tumor cells and a cell photosensitize. 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 euplastic diseases based on the ability of tumor tissues to retain some photosensitizes with a certain degree of selectivity; hence, photo activation of the photosensitize by visible or near infrared radiation leads to tumor necrosis by the production of catatonic species. Since the selective and homogenous 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 10B-enriched carbora-containing phthalocyanine (B-Pc) has been at the purpose synthesized by Molten Pharmaceuticals (Florence, Italy) and in vitro studies, performed during the first investigation stage, revealed the carbora-carrying phthalocyanine was efficiently accumulated by B16F1 melanoma cells with induced extensive cell mortality after a red light irradiation. Moreover (B-Pc), once injected to C57BL/6 mice bearing a subcutaneous melanoma, photosensitized an important tumor response, provided the irradiation with 600-700 nm light was performed 3 hr after phthalocyanine administration. The first, in vivo BNCT study [9] was also performed at the original thermal irradiation facility (at present dismantled) of TAPIRO research reactor, which is located at the ENEA Acacia research center near Rome. Irradiation of the (B-Pc) loaded melanoma bearing mice with thermal neutrons at 24 h after injection led to a significant delay in tumor growth 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 5.

2.4 Development on the new TEPCs for dosimetry and beam quality monitoring

Radiation dosimetry is quite complex in BNCT treatment because of co-presence of different radiation components 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 (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 with the time, since the accelerator-based BNCT beam features can not be assumed constant in time. A detailed beam quality monitoring, providing the relative contribution of all dose components,
has therefore to be been taken into account. The total absorbed dose can be divided in the main three components having different biological effectiveness: the gamma dose, the neutron dose and the BNC dose, that means the dose arising from alpha and lithium ions of the \( ^{10}\text{B(n, } \alpha\text{)}^7\text{Li} \) reaction. Still now, three different detectors are used to assess the three dose components: a gamma detector, a fast neutron detector and a thermal neutron detector. Our aim is having a single detector able to measure contemporary the all three components and their qualities. The experience gained in the last years led us to select the tissue-equivalent proportional counters (TEPC), which have been proved to be able to measure the absorbed dose and its quality with high accuracy both for high energy [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 an easy tissue equivalent A-150 plastic cathode shells replacement, with different \(^{10}\text{B}\) concentration ranging from 0 to 100 ppm, was constructed. Thanks to its large sensitive volume (2.3 cm\(^3\)), the counter is able to measure in relatively weak radiation fields as those ones available at Legnaro laboratories. Similar measurements were performed inside the irradiation cavity of TAPIRO ENEA fast reactor 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. The new counter is made of two cylindrical TEPCs with two cathode walls, both of them are of A-150 plastic; however one of them is loaded with 50 ppm of \(^{10}\text{B}\). Each TEPC design follows the main project lines already published [16]. Having two TEPCs in the same counter satisfies the requirement to get all dosimetric data (gamma dose, neutron dose, BNC dose, plus their quality and the total radiation field quality) just in one measurement. A cutaway view of the new twin TEPC is reported in figure 13. The twin TEPC has two sensitive cavities of 0.9 mm diameter each (0.6 mm\(^3\)). The two TEPCs are flowed with tissue-equivalent propane-based gas mixture. They can

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Figure 6  (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.

Figure 7 Cutaway view of the new-mini-TEPC designed and constructed at LNL.
operate at gas pressures between 63 and 1260 mbar, corresponding to simulated sites of 0.1-2.0 µm of diameter (when scaled at density of 1 g/cm³). A picture of the twin TEPC with electrical as well as vacuum and gas flowing connections is shown in figure 14. The counter has been used to perform first microdosimetric measurements at the HYTHOR thermal column recently installed at the TAPIRO reactor, which first two microdosimetric spectra collected, are shown in figure 15. The microdosimetric spectrum is basically the pulse height spectrum of a gas spectrometer calibrated in lineal energy, weighted with the lineal energy value y and normalized to unity. Therefore, the area under the curve is the relative contribution to the absorbed dose due to y-events of the interval taken into account. Different radiation contributions to the absorbed dose can be distinguished. Events less than 20 keV/µm are mainly due to electrons, set in motion by gamma rays. Events in between 20 and 150 keV/µm are mainly due to protons, set in motion by fast and slow neutrons, as well as by 580 keV protons of the thermal neutron reaction 14N(n,p)14C. Events bigger than 150 keV/µm are mainly due to alpha particles and heavier recoils, set in motion by fast neutrons. When 10B is added in the TEPC wall, events bigger than 150 keV/µm are due also to alpha and lithium ions of the thermal neutron reaction 10B(n, α)7Li. Moreover, because the ions trajectories inside the two 0.9 mm sensitive volumes can cover a large distribution of possibilities (from 0 to 1.27 mm), both proton and heavier ions give rise also to small pulses, which give rise in the microdosimetric spectrum to long tails towards low y-value. A precise evaluation of the different absorbed dose components is feasible. More details about are published elsewhere [15]. The spectra of figure 15 have been further normalized to the without-10B total absorbed dose D0. Therefore, the area under the 10B curve for a given y logarithmic interval minus the area under the without-10B curve for the same y logarithmic interval is the percentage increasing of the absorbed dose in the given y interval, when 50 ppm of 10B are added. Figure 15 shows that the gamma dose does not change significantly when 50 ppm of 10B 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 10B thermal neutron capture reactions.

![Figure 8 Absorbed dose distributions per logarithmic increment of lineal energy measured inside the irradiation vavity of HYTHOR BSA by the twin TEPC. The spectra are normalized to the without-10B total absorbed dose. The simulated site size is 1 µm.](image-url)
3. Conclusions
The approved project for the development of LNL, SPES-1, includes a neutron source, based on a high intensity proton accelerator, suitable for BNCT tests. Therefore the linac is under construction, a prototype of the high power converter made in beryllium has been tested with e-beam of nominal power density, a low power demonstration facility was tested at CN accelerator (INFN-LNL), a microdosimeter prototype have been built and tested with thermal neutrons at TAPIRO reactor (ENEA Acacia). Moreover an intense research program is being carried out by an interdisciplinary group, including “in vitro” and “in vivo” tests of new boron carrier molecules under thermal neutrons irradiation at the TAPIRO reactor (ENEA-Acacia).

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