AN ACCELERATOR BASED BNCT FACILITY:THE SPES PROJECT AT INFN LEGNARO

A. Pisent, J. Esposito on behalf of SPES-BNCT collaboration

INFN - Laboratori Nazionali di Legnaro, I-35020 Legnaro (PD), Italy

ABSTRACT

An advanced Exotic Ion Beam facility, named SPES (Study and Production of Exotic Species), that will allow a frontier program in Nuclear and Interdisciplinary Physics has been proposed at LNL. The proton beam, delivered by the first elements of the linac, will be in particular available for research in the Boron Neutron Capture Therapy (BNCT) field. The first step of the SPES project, including the thermal neutron facility for BNCT study, is presently under construction.

Introduction

In the last years the availability of new intense radioactive ion beams (RIB) has been recognized as a fundamental tool for future research in Nuclear Physics. In view of the next generation European facility EURISOL an important role for RIB's physics will be played by European national laboratories, with facilities like SPES (Study and Production of Exotic nuclear Species) at LNL (Laboratori Nazionali di Legnaro). This facility, with an intermediate size between existing first generation facilities and 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, detectors..) in view of the European project. A first design report of SPES was published in '99 (ref. [1]) while a detailed Technical Design Report has been published in 2002 [2].

Recently the INFN has decided the construction of a first phase of SPES, corresponding to the first part of the driver linac, equipped with a neutron source for interdisciplinary applications. This facility will be characterized by relatively moderate size and cost and will deliver intense neutron beams. It will allow significant experiments and activities in both fundamental and applied nuclear physics (medicine, biology and Solid State); in particular, it will represent an attractive accelerator-based source for BNCT.

The BNCT project will use an intense 5 MeV proton beam to produce fast neutrons, which will be properly thermalised. The thermal neutrons will be used for dosimetric, microdosimetric and radiobiological studies as well as for the skin melanoma treatment. Moreover it will be a test bench for an accelerator based BNCT facility which, respect to a reactor based system, is in perspective more practical for the hospital application of the treatment.

SPES facility at LNL

SPES is a new generation ISOL facility proposed at LNL, able to represent a competitive intermediate step between the existing facilities, like SPIRAL and CERN-ISOLDE and the longer-range European facility EURISOL.

The scheme of principle of an ISOL (Ion Selection On Line) facility is the following: a primary accelerator induces a nuclear reaction in a target (nuclear fission in a natural uranium target in our case), producing unstable nuclei. During their short life-time, they are ionized, selected with a magnetic spectrometer, reaccelerated and sent into an experimental apparatus. In this way it is possible to study the nuclei proprieties that are not present in common world and that, even if produced artificially, due to their short life-time, cannot be used as a target. Therefore the ISOL method allows to extend the knowledge of nuclear structure to exotic compounds and to study

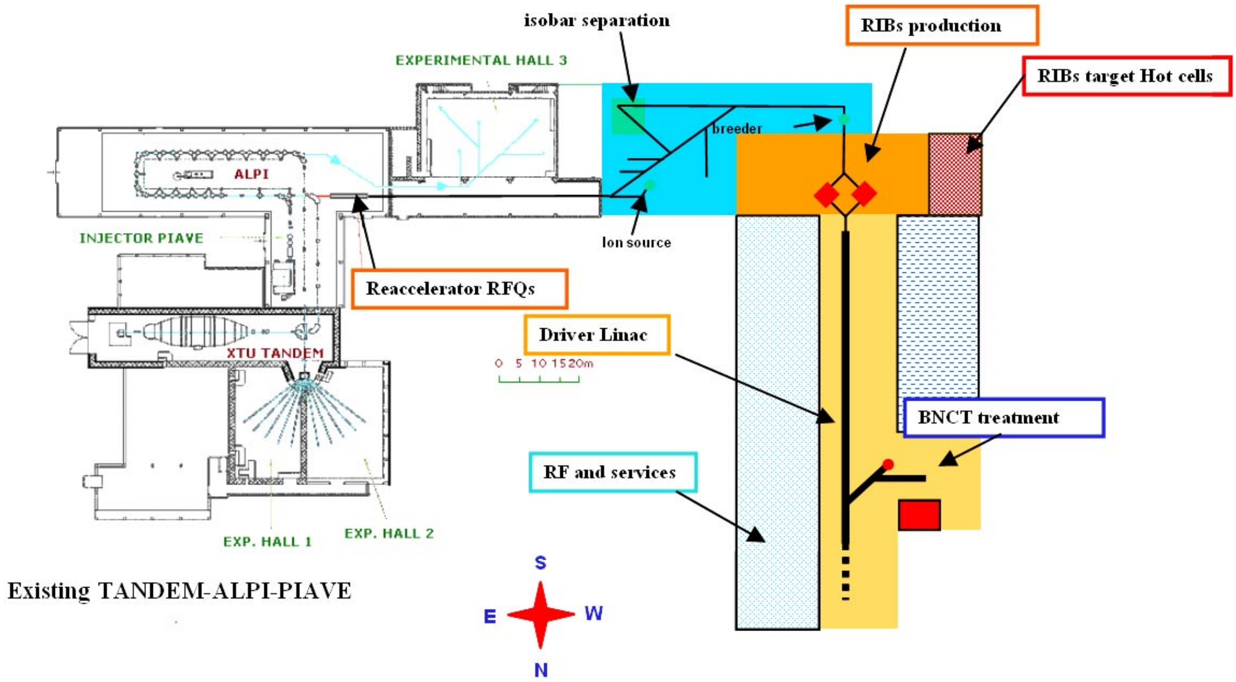

Figure 1. Layout of the SPES facility and integration with the existing PIAVE-ALPI complex

conditions that are relevant for the understanding of the early stage of the Universe and for the nucleo-synthesis which happened after the Big Bang.

Fig. 1 shows a schematic layout of the facility, connected with the existing LNL complex. The main new construction is the driver-linac and RIB production building, west of TANDEM-ALPI complex. Integrated in the same building there will be a part dedicated to the interdisciplinary applications and to the BNCT research. The three experimental halls presently used at LNL will all be reached by accelerated RIBs.

The driver linac design is based on independently phased superconducting cavities, 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 source TRIPS[3] and the RFQ[4] (Radio Frequency Quadrupole), both developed within the TRASCO research program, for nuclear waste transmutation purpose. The source TRIPS is being commissioned at LNS, the other Nuclear Physics Laboratory of INFN, while the RFQ is under construction at LNL (Fig. 2).

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 necessity to keep beam losses below 1%; this implies the requirement to keep 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. In Fig. 2 the hart of the accelerator is shown, with the six accelerating structures and the pumping system mounted together. The beam is accelerated through the symmetry axis of the quadrupole. The first module during the RF measurements after brazing is also shown.

The source and the RFQ, installed at LNL, will represent a unique facility, able to deliver 30 mA, 5 MeV beam. This proton source will be used as a stand alone system for the BNCT facility.

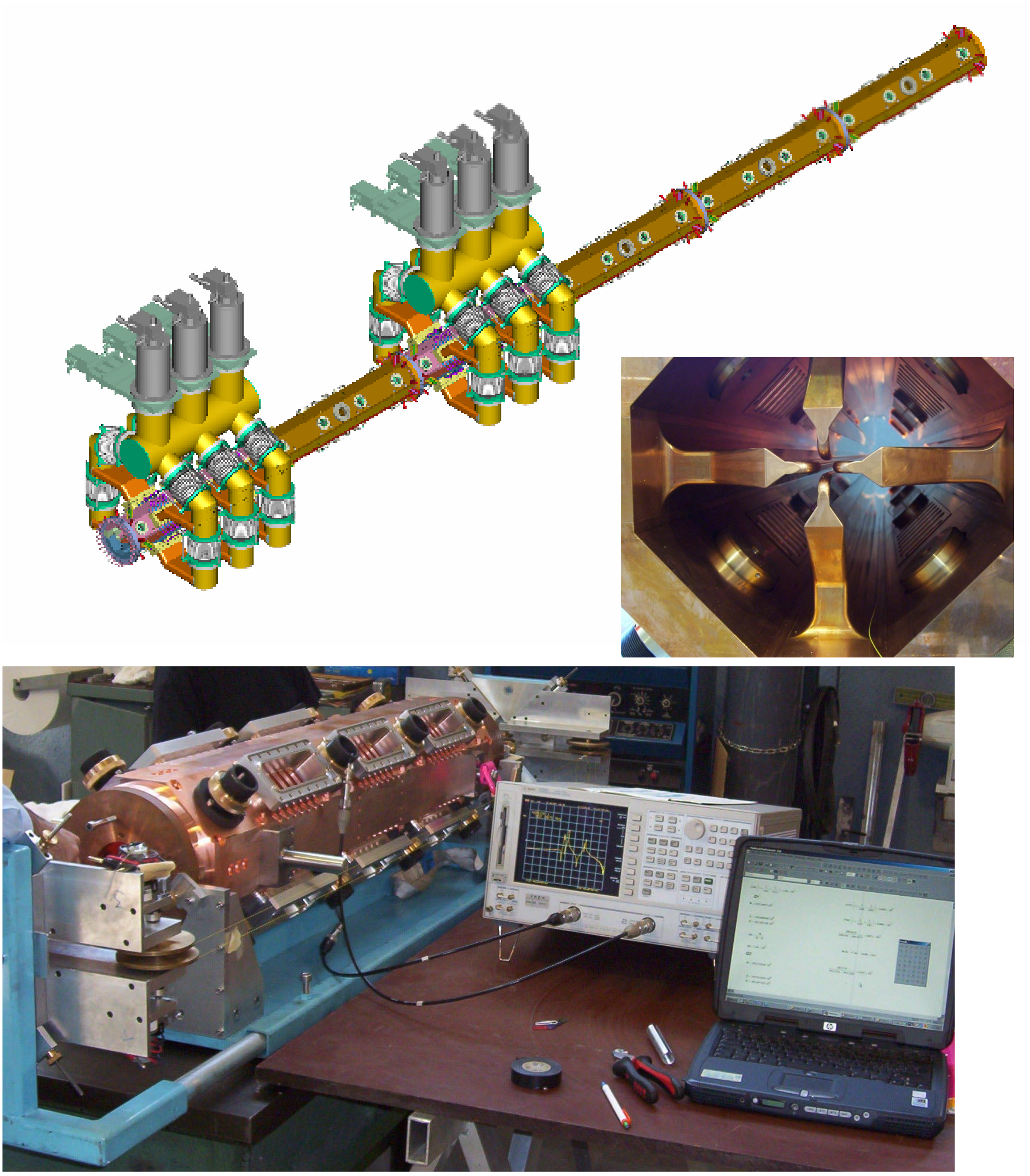

Figure 2. The accelerating structure TRASCO RFQ (5 MeV, 30 mA). Scheme of the 7.13 m long structure, quadrupole cross section and view of the first module during low power RF measurements after the brazing..

The approved initial phase of SPES

Taking into account the main boundaries of restricted financial resources available for scientific research in Italy, and at LNL in particular, taking advantage from the European framework for the development of RIBs in the other main laboratories, like GSI and GANIL, it was decided to start the SPES FI (Fase Iniziale). It will be a first, significative step towards SPES and EURISOL project, a very good test for the high intensity community (ADS), as well as the main provider in support to the community of interdisciplinary physics and medical users.

The facility, approved and funded by INFN will include:

1. the completion and installation of the 5 MeV, 30 mA proton injector;
2. the development and construction of the thermal neutron facility for BNCT;
3. the development and realization of the superconducting proton linac up to 20 MeV ,
4. the continuation of the R&D program on RIB production targets.

In Fig. 3 a schematic lay-out of SPES-FI is shown, with the ion source TRIP, the TRASCO RFQ, and the transport line that allows to deliver the beam either to the superconducting linac or to the BNCT complex. This layout is now being tested with extensive beam dynamics simulations.

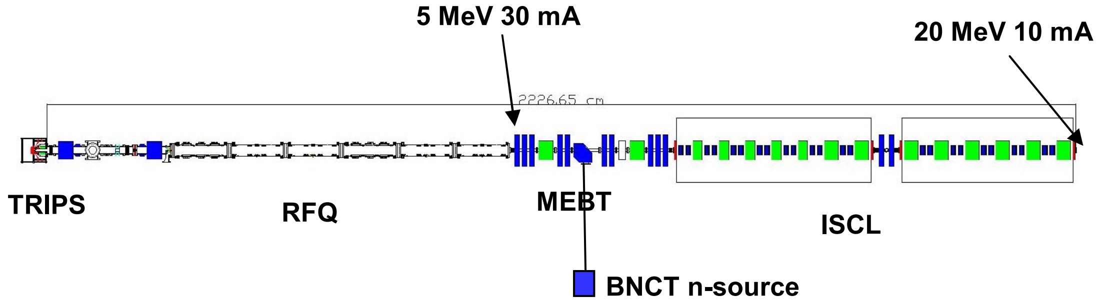

Figure 3. Schematic layout of SPES FI; TRIPS (TRASCO Ion Source), RFQ (Radio Frequency Quadrupole) is the first accelerating stage, the MEBT (Medium Energy Beam Transfer) transfer the beam to the ISCL (Independent Superconducting Cavity Linac), composed by two cryostats, or to the BNCT facility, the thermal neutron source dedicated to the medical experimental program.

The SPES-BNCT research program

The main interdisciplinary user of the facility is the BNCT application. The irradiation facility will exploit the intense proton beam provided by the first SPES acceleration step, the RFQ, through (p,n) reaction on the Be target. The source neutron spectrum will then be slowed down to the thermal energy range by a proper moderator device in order to supply, at the irradiation beam port, a thermal neutron flux level at least of $10^9 cm^2 s^{-1}$ 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, formed by medical doctors, biologists, physicists, nuclear engineers, has gathered around SPES-BNCT project. The researchers involved belongs to different institutions (like IOV, Istituto Oncologico Veneto, Padova University, Milan Polytechnic, Molteni Pharmaceuticals, ENEA, INFN) aimed at the experimental program of an advanced radiotherapy application of skin melanoma treatment using SPES beam, combined with phototherapy approach.

The main items of our research program are the development of the neutron irradiation facility, the new boron carrier compound and the development of a new on-line biological dose monitoring in both tumor and healthy tissues.

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 thermal neutron source setup driven by the 7 MV (3 μA 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 aiming at the optimization design a compact size facility. It should fulfill a high thermal neutron flux requirement, at the irradiation port, lying on the side surface, consistent with neutron economy constraints. The irradiation facility basically consist of an inner D_2O tank, arranged around the ion beam target, which is the first moderator stage, then surrounded by a

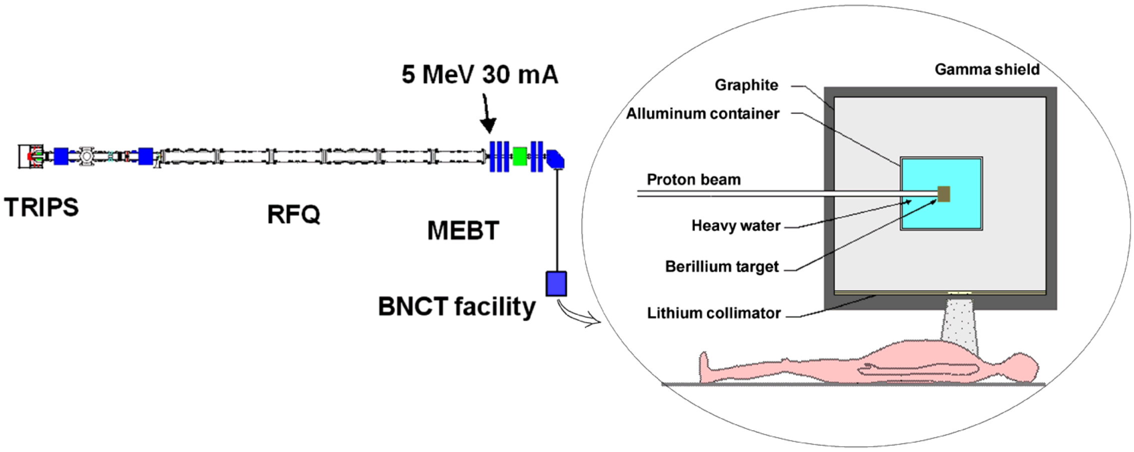

Figure 4. Schematic layout of SPES-BNCT irradiation facility

Reactor Grade (RG) graphite, which acts as a second moderator structure. The proof of principle layout is reported in Fig.4. A series of experimental tests were already performed at the CN demonstration facility[8], in order to have a beam spectrum characterization of thermal 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.

The neutron converter design

As a general rule the target device 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 target 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 $\leq \sim 0.7$ KWcm^{-2}, in order to make use of reliable and already proven target cooling system, would be required.

In collaboration with the STC Sintez of Efremov Institute in S. Petersburg, we have designed a preliminary, high-power, beryllium target prototype. The peculiar target profile shape, shown in Fig.5 has been selected in order to have an approximately constant power density distribution on the

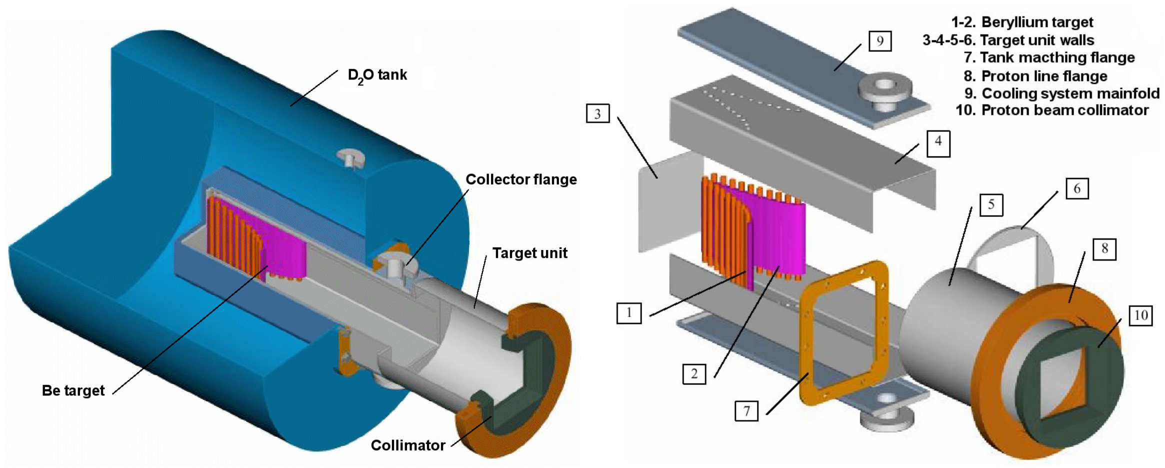

Figure 5. Preliminary Be target design of SPES-BNCT facility: (left) assembly with I moderator stage, (right) exploded view of target unit cooling system

full beryllium target surface. 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 consideration relating the fluid cooling capability, the cooling system simplicity as well as the economic has led to chose light (or heavy) water as the target coolant. 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, which unwanted component needs to be reduced to an extent as low as possible. A further technological effort is therefore under way to develop and test new brazing alloys able to provide a reliable beryllium-aluminum target.

Studies to develop a new boron-loaded phthalocyanine

Interesting perspectives are opened by the observation that a single compound (e.g. a porphyrin or a phthalocyanine) can act as both 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 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 is being developed in order to define the modalities which could promote a synergism between the two different therapeutic approaches. In order to investigate this possibility, a boron phthalocyanine (B-Pc) has been synthesised by Molteni Pharmaceuticals (Florence, Italy). The first step in a sequence, which will be subsequently developed through *in vitro and in vivo* studies, has been the determination of the photosensitizing activity of B-Pc toward a model substrate such as N-acetyl-tryptophanamide (NATA): this amino acid is characterised by a high level of photosensitivity. The photooxidative degradation of NATA can be readily measured by following the fluorescence emission of tryptophan. Our photokinetic studies show that tryptophan is photooxidized with a rate constant of the order of 10^4 s^{-1}, as it is typical of other photosensitizers presently used in clinical practice.

TEPCs design and construction

Radiation dosimetry, which plays a fundamental role to directly monitor the quality of therapeutic neutron beams, is quite complex in BNCT treatment because of the large LET spectrum in the irradiated tissues. Living cells therefore experience radiation events with a high 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, the radiation LET spectrum is different at different depths in tissue. The LET spectrum can even change with the time, since the accelerator-based BNCT beam features can not be assumed constant in time. An accurate monitoring, providing the relative doses of all these components, has then been taken into account. Therefore the BNCT facility will be equipped with tissue-equivalent proportional counters (TEPC), which we have already used to monitor the quality of therapeutic neutron beams[9].

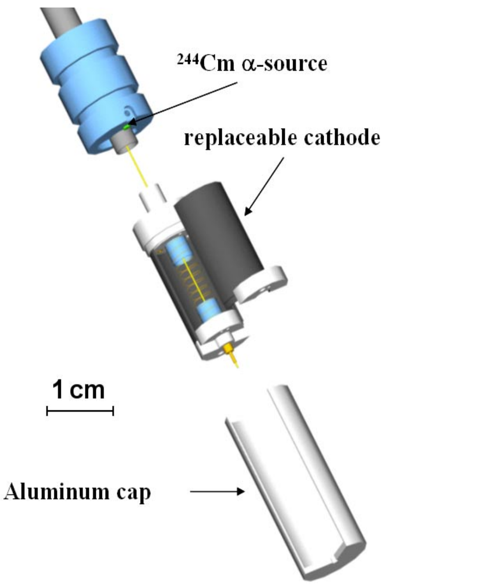

Figure 6. The LNL TEPC exploded view with replaceable cathode walls

A first TEPC prototype, shown in Fig. 6, which sensitive volume is a right cylinder with a height and diameter of 13 mm, has been designed and constructed. The diameter of the anode wire is 100 µm with a helicoidal grid of 6 mm. This detector is able to monitor the fluctuation of the absorbed energy, namely the microdosimetric spectra, both in a 1 µm and in a 50 nm size site (at density of 1g/cm^3), which are respectively of chromosome and of mitochondrion typical sizes. Moreover the LNL-TEPC has been properly designed to provide an easy tissue equivalent cathode walls replacement, with ones loaded at increasing ^{10}B concentration, simulating different tissue boron uptake conditions. At last detector, with and without ^{10}B loaded cathode walls, can also be used to perform thermal neutron flux estimation, as well as to predict the RBE factors for healthy and tumor tissue.

Preliminary TEPCs in air measurements have already been performed in a mixed radiation field (gamma, fast and slow neutrons) both at the LNL BNCT demonstration facility, with a 5 MeV, low current (1µA), proton beam on a thick beryllium target and at the thermal column of TAPIRO ENEA reactor. The preliminary absorbed and biological dose-rate profiles vs. depth, are shown in Fig. 7[10] . All data are scaled to the without ^{10}B dose rate value at the minimum of depth. Dose rate without ^{10}B is almost constant with the depth, decreasing only slowly. Biological dose rate follows the same trend, since RBE is almost constant with the depth. When 100 ppm ^{10}B content is used, the dose rate shows a peak at the depth of about 0.5 g/cm^2. The dose peak follows the thermal neutron flux profile, which has a maximum at that depth. Biological dose-rate, also in this case follows the trend, since the RBE is almost constant with the depth.

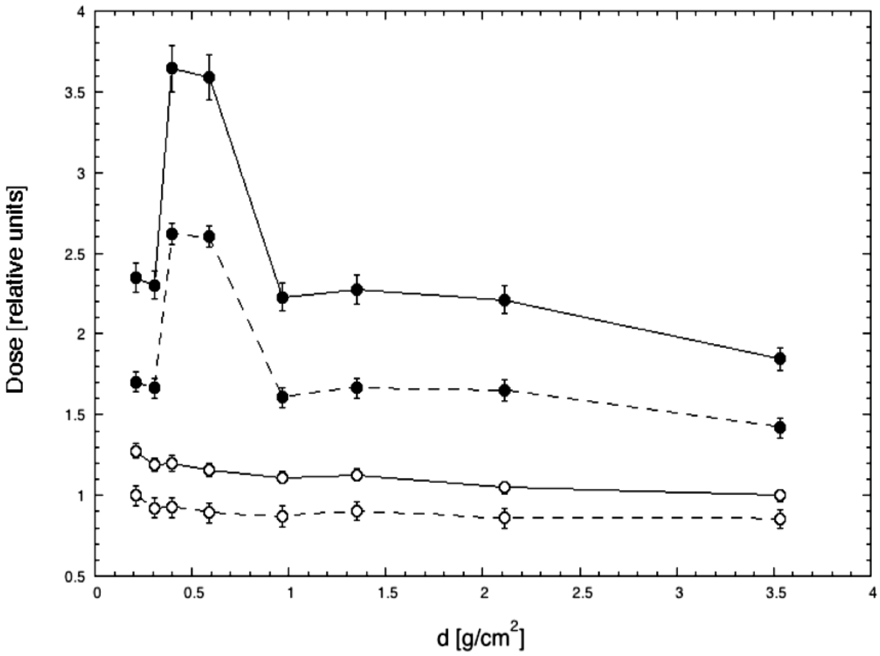

Figure 7. Experimental TEPCs depth-dose profile measurements at the TAPIRO thermal column: absorbed dose (dashed line) and biological dose (full line) variations with polyethylene thickness. Open circles: data without ^{10}B. Full circles: data with 100 ppm of ^{10}B.

In spite of the small sensitive volume, the TEPC external size (Fig. 7), is not suitable to monitor the beam in a water phantom or, in future, inside the patient body. A quite tiny TEPC version, 2.7 mm external diameter, less than 1 mm^3 of sensitive volume is therefore being developed. Thus they could be easily inserted inside the body tissue to locally monitor the intense radiation field coming from the BNCT facility which will be used to treat the skin melanoma. The sketch of this mini-counter is shown in Fig. 8. The counter cathode will be of ^{10}B loaded, tissue-equivalent plastic. In order to assess the proper quantity of boron to add and the monitoring procedures, we will study the microdosimetric spectra collected with cathode at different ^{10}B concentrations. First measurements have already been performed, with a mini-TEPC having a sensitive volume of 1 mm of diameter, by the therapeutic proton beam of the Centre Antoine-Lacassagne in Nice.

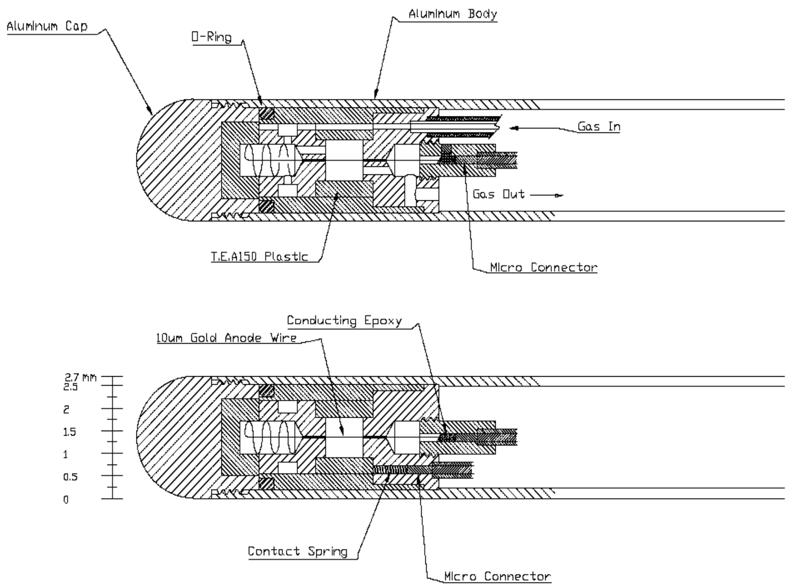

Figure 8. Cutaway views of the mini-TEPC designed and constructed at LNL.

Perspectives

An accelerator based BNCT experimental facility will be built at LNL in the next five year. In the meantime an intense scientific program is pursued for the optimization of the neutron field, the development of a better ^{10}B carrier molecule and a better microdosimetry. The main next steps therefore will be the neutron converter prototype construction and test with 150 kW electron beam, the design of the final irradiation facility and the construction of a new mini TEPC for monitoring and processing microdosimetric data in high flux radiation fields. Moreover the remodeling of TAPIRO thermal irradiation facility, in order to minimize the gamma ray contamination for in vitro and in vivo studies, as well as the feasibility of a new boron compound with 60 ^{10}B atoms clusters will be carried on.

References

[1] SPES Study Group "Project Study of an advanced facility for Exotic Beams at LNL" LNL-INFN (REP) 145/99 report

[2] SPES Technical design report (A. Bracco and A. Pisent editors) LNL-INFN(REP) 181/2002 and http://www.lnl.infn.it/~spes/

[3] G. Ciavola, L. Celona, S. Gammino: "First Beam from the TRASCO Intense Proton Source (TRIPS) at INFN-LNS" Proceedings of the 2001 Particle Accelerator Conference, Chicago, June 18 - 22, 2001

[4] A. Pisent, et al. "TRASCO RFQ", Proceedings of the XX International Linac Conference, Monterey, California, August 21 - 25,p. 902 (2000).

[5] S.Agosteo et al. Advances in the INFN-Legnaro BNCT Project for Skin Melanoma. Proceedings of the international physical and clinical workshop on BNCT. Held in Candiolo (Torino) on the 17th of Febbruary 2001.

[6] U. Amaldi, M. Silari, Eds., The TERA Project and the Centre for Oncological Hadrontherapy, 2nd edn, INFN-LNF Frascati (Roma), 1995

[7] S. Agosteo et al., An accelerator-based thermal neutron source for BNCT: Advances in Neutron Capture Therapy, Vol. 1, (1997) pp 483-489;

[8] S. Agosteo et al Characterization of an accelerator- based neutron source for BNCT of explanted livers, Rad. *Prot. Dos. 70, 559-566, (1997)*

[9] P. Colautti, N.Brassart, V.Conte, M.Guli, G.Tornielli, J. Herault, G.Magrin, L. de Nardo and P.Chauvel. Microdosimetric Measurements in the Fast Neutron Therapeutic Beam of Nice. Physica Medica 14, 55-62 (1998)

[10] L. De Nardo, E. Seravalli, G. Rosi, J. Esposito, P. Colautti, V. Conte and G. Tornielli, BNCT microdosimetry at the Tapiro reactor thermal column, Proc. 9th Neutron Dosimetry Symposium, Delft, The Netherlands Sept. 28, Oct., 3 2003 To be published on Rad. Prot. Dos.