Applied Radiation and Isotopes 165 (2020) 109247

Contents lists available at ScienceDirect

Applied Radiation and Isotopes

journal homepage: http://www.elsevier.com/locate/apradiso

BNCT research activities at the Granada group and the project NeMeSis: Neutrons for medicine and sciences, towards an accelerator-based facility for new BNCT therapies, medical isotope production and other scientific neutron applications

I. Porras [a,*], J. Praena [a], F. Arias de Saavedra [a], M. Pedrosa-Rivera [a,b], P. Torres-Sánchez [a], M. P. Sabariego [a], J. Expósito-Hernández [c], J.M. Llamas-Elvira [d], A. Ramírez-Navarro [d], A. Rodríguez-Fernández [d], J.M. Osorio-Ceballos [e], C. Ruiz-Ruiz [f], M.J. Ruiz-Magaña [f]

[a] Departamento de Física Atómica, Molecular y Nuclear, Universidad de Granada, Granada, Spain
[b] Institut Laue-Langevin. Grenoble, Rhône-Alpes, France
[c] UGC de Oncología, Hospital Universitario Virgen de las Nieves, Granada, Spain
[d] UGC de Medicina Nuclear, Hospital Universitario Virgen de las Nieves, Granada, Spain
[e] Servicio de Radiofisica y Protección Radiológica, Hospital Universitario Virgen de las Nieves, Granada, Spain
[f] Departamento de Bioquímica y Biología Molecular III e Inmunología, Universidad de Granada, Granada, Spain

ARTICLE INFO

Keywords:
Neutron capture therapy
Nuclear cross section
Radiobiology
Neutron beams
Radioisotope production

ABSTRACT

The Granada group in BNCT research is currently performing studies on: nuclear and radiobiological data for BNCT, new boron compounds and a new design for a neutron source for BNCT and other applications, including the production of medical radioisotopes. All these activities are described in this report.

1. Introduction

Boron Neutron Capture Therapy (BNCT), which has recently shown very promising results (Barth et al., 2012), is now facing a renaissance with the introduction of a new generation of accelerator based BNCT centers expected soon (Kreiner et al., 2016).

The Granada group started a few years ago a strong activity in BNCT research, being the first one in Spain. This group is formed by researchers of the Departments of Atomic, Molecular and Nuclear Physics, Biochemistry and Molecular Biology and Immunology of the University of Granada, and of the University Hospital "Virgen de las Nieves" in Granada, and sustains collaborations with international research institutions as the Institute Laue-Langevin (ILL) of Grenoble (France), the European Center for Nuclear Research (CERN) of Geneva (Switzerland), and with national institutes as the National Accelerator Center of Seville or the Institute for Material Sciences of Barcelona.

The aim of this research activity is to pursue improvements for this very promising form of radiotherapy in whose potential we believe. The research lines include:

- the reduction of uncertainties for improving the accuracy of the treatment planning,
- the design of the optimal neutron beam for BNCT from a particle accelerator,
- the search of new boron compounds which may improve the selectivity, and
- exploring new avenues as the use of another cooperative isotope as a neutron capturer or the application of neutron guides for a potential BNCT-based radiosurgery with cold or thermal neutrons.

As a side project, and from a relevant exchange of ideas with the physicians at the Department of Nuclear Medicine, we studied the possibility of producing medical radioisotopes from an accelerator suitable for BNCT, with the aim of increasing the potential applications of a new

* Corresponding author.
E-mail address: porras@ugr.es (I. Porras).

https://doi.org/10.1016/j.apradiso.2020.109247
Received 8 October 2019; Received in revised form 24 April 2020; Accepted 26 May 2020
Available online 6 July 2020

facility. This has produced stimulating results that shows the possibility of producing new radiopharmaceuticals for advanced diagnostic methods.

The main goal of this project has led to the conceptual design of a multi-purpose facility which will allow performing BNCT clinical trials as well as other scientific applications. Our aim is to incorporate in the future clinical trials the results from our research, which will be discussed in this review, as well of the most recent advances from the very active BNCT community.

2. Reducing uncertainties in BNCT treatment planning

The analysis of the current data from BNCT clinical trials shows a clear improvement of the treatment outcome with the delivered dose. In order to optimize the treatments, it is a key task to reduce the uncertainties associated with the determination of the dose at the organs of risk. We have studied some of these sources of uncertainty.

2.1. Nuclear data for Monte Carlo simulations for BNCT. measurements at n_TOF (CERN)

BNCT treatment planning has made use of Monte Carlo simulations for the neutron transport and for the calculation of the physical dose delivered both at tumor and at normal tissues. In the reference dose calculations of Goorley et al. (2002), the spectral neutron flux that is obtained by codes like MCNPX (Pelowitz, 2005) at any point in the phantom is integrated with cross-section dependent kerma factors in order to obtain the physical dose.

Currently, in BNCT the physical dose is calculated as the sum of three contributions: the neutron dose D_n, the boron dose, D_B, and the gamma dose, D_γ. The neutron dose is usually separated as: the fast dose D_f, from the secondary particles (mainly hydrogen recoils) produced by neutrons with energy above 0.5 eV and the thermal dose D_t, for neutrons with energy below 0.5 eV (Goorley et al., 2002; IAEA, 2001). The latter is dominated by the ^{14}N (n,p) reaction and sometimes it is also called the nitrogen dose (Joensuu et al., 2003). The gamma dose is delivered by any photons from the own beam contamination as well as the 2.224 MeV photons from the hydrogen capture of thermal neutrons inside the phantom.

The International Commission on Radiation Units and Measurements (ICRU) recommends for conventional radiotherapy that the uncertainties of every step of the treatment should be kept well below 5% (ICRU, 1978). For BNCT, we have examined the role of the knowledge of the cross sections as possible sources of uncertainty in the determination of the prescribed dose. In clinical trials, the dose delivered to a ^{10}B loaded tumor is due to ^{10}B $(n,\alpha)^7$Li, whose cross section is very well known (it is a standard reference), being much higher than the sum of all the other reactions. However, for the delivered dose to the normal tissue, which is a limiting factor in the treatment planning for the organs at risk, the other components are very important. As said above, the ^{14}N $(n,p)^{14}$C reaction dominates the thermal dose. There is a fair amount of experimental data on this reaction, with cross section spanning over several different energy ranges. However, the existing discrepancies are important and relevant for BNCT dosimetry and also for astrophysics (element nucleosynthesis) (Praena et al., 2017). From 61 meV to 35 keV, there is only one differential measurement, Koehler and O'Brien (Koehler et al., 1989), therefore the evaluations are based on it, but its extrapolation to thermal energy does not match the most recent results of Wagemans et al. (2001). There are discrepancies at the thermal point of about 50% in the experimental values reported in EXFOR database (Zerkin and Pritychenko, 2018). This uncertainty has important consequences in BNCT because of the crucial importance of the ^{14}N $(n,p)^{14}$C reaction on the delivered dose to normal tissue.

For this reason a proposal for the measurement of this cross section for thermal and epithermal energies at the neutron time of flight (n_TOF) facility at CERN was presented and approved by the INTC committee in 2017 (Praena et al., 2017), and some months later the experiment was performed, with all the support of the n_TOF collaboration (The n_TOF collaboration).

The n_TOF facility at CERN in Geneva makes use of the PS high-energy proton beam to produce a broad energy range neutron beam via spallation into a lead target. The generated neutrons are guided through beam pipes to two experimental areas (EAR-1 and EAR-2) located 185 and 20 m away from the target, respectively. At these locations, samples are placed at the neutron beam and the reaction products are detected. Provided the long path lengths, the energy of the neutrons can be obtained with high precision from the detection time of flight at the experimental areas.

The measurement of the ^{14}N $(n,p)^{14}$C reaction was carried out during September–October 2017 at the EAR-2. Two detection systems were used; one of them based on MicroMegas detectors, which are charged particle gaseous detectors with a high neutron and gamma transparency. These features allow using them at in-beam conditions, which further improves the geometrical detection efficiency. The other detection system was based on Double-Sided Silicon Strip Detectors (DSSSD), which can provide information on the angular distribution of the reaction products, and also profits from a reduced background due to their off-beam positioning. Fig. 1 shows both detection systems.

The preliminary results from the measurement report a slightly lower value for the thermal cross-section compared to the reference evaluations. The energy region accessed with the MicroMegas setup ranged from the thermal point to 60 keV. Along this region, the $1/v$ relation for the cross-section was verified, in good agreement with previous measurements and evaluations. Fig. 2 shows the measurement compared with the ENDF evaluation and the previous data in the same energy range.

Also, we have measured two neutron capture reactions on ^{35}Cl: (n,p) (Praena et al., 2017) and (n,γ) (Porras et al., 2018a). This is an element especially present in brain and skin, and it can play a non-negligible role in neutron transport and delivered dose. We have estimated with Monte Carlo simulations the role of these reactions and we have found that the photons of up to 8.5 MeV emitted by the radiative capture of ^{35}Cl, at the concentration typical in brain, may account at certain depths (between 3 and 5 cm) of up to 12% of the total dose in normal brain, in the absence of boron, as illustrated in Fig. 3. The measurement of this reaction, performed in n_TOF at the experimental area EAR-1 with C_6D_6 liquid scintillators, is under analysis.

2.2. Radiobiological data for BNCT treatment planning

The different dose components of BNCT may have different biological effectiveness due to differences in their linear energy transfer. Therefore, a "biological" or "weighted" dose (D_W) is defined as the sum of the dose components weighted with different factors *wi* (Goorley et al., 2002; IAEA, 2001), previously called relative biological effectiveness (RBE) factors (Coderre and Morris, 1999):

$$D_W = w_f D_f + w_t D_t + w_\gamma D_\gamma + w_B D_B \quad (1)$$

The quantity D_w is interpreted as the equivalent photon dose which produces the same effect than the BNCT procedure and is expressed in Gy-Eq or Gy(W). The weighting factors *wi* are defined as the ratio of the reference photon irradiation dose and the value of the physical dose component which is needed to produce the same effect.

The weighting factors w_i are a major source of uncertainty in the estimation of the treatment outcome of BNCT, for different reasons: (i) they are dose-dependent and cannot be strictly applied to other dose components than those for which were obtained, (ii) the current values used were obtained for brain tumor therapy, and because of a lack of knowledge for other tissues, they are also used for other type of tumors, (iii) the thermal and fast dose values, which were not possible to separate in previous experiments, are assumed to take the same value, and

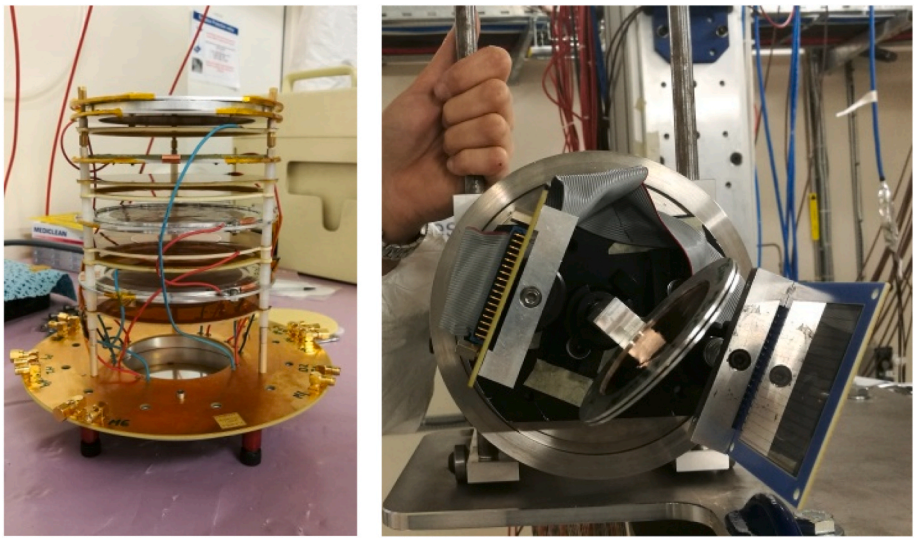

Fig. 1. The two detection systems used for the measurement of the ^{14}N $(n,p)^{14}$C reaction at n_TOF. The picture on the left shows the MicroMegas setup and the picture on the right shows the DSSSD setup.

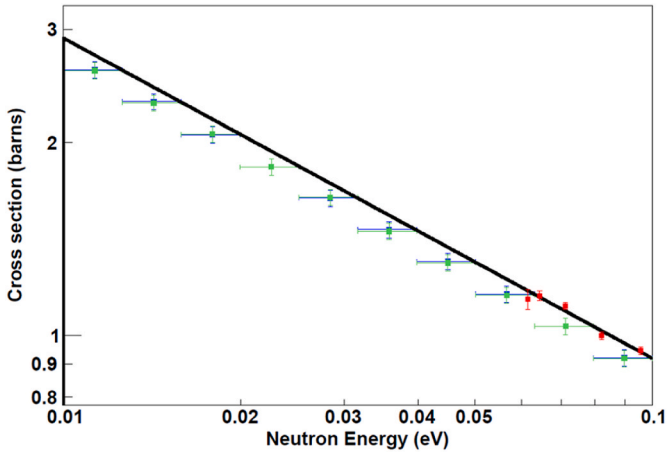

Fig. 2. Preliminary estimations of the cross-section of the 14N (n,p)14C reaction (green dots) in the thermal region, compared to the ENDF-8 evaluation in black and previous measurements data (Koehler et al., 1989) in red. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

(iv) the gamma dose is assumed to be 1, although there is some evidence of the need of a dose reduction factor due to the smaller dose rate for this component in BNCT in comparison to conventional radiotherapy.

Our group is performing research towards overcoming these drawbacks. A resolution for most of them consists of adopting the formalism of the photon isoeffective dose developed by González and Santa Cruz (Gonzalez and Santa Cruz, 2012). In this formalism the photon isoeffective dose D_R is obtained from the resolution of the equation:

$$\sum_{i=1}^{4}\alpha_i D_i + \sum_{i=1}^{4}\sum_{j=1}^{4} G_{ij}(\theta)\sqrt{\beta_i\beta_j}D_iD_j = \alpha_R D_R + G(\theta')\beta_R D_R^2 \quad , \tag{2}$$

where α_i, β_i are the coefficients of the Linear-Quadratic model for the dose component D_i $(i = f, t, \gamma, B)$ and $G(\theta)$ denoted the Lea-Catcheside time factor. However this formalism requires accurate values for all the coefficients. For example, the β_i coefficients on which the synergies between different types of radiation strongly depend, are small and difficult to extract accurately from mixed-field measurements (quasi-linear dependence errors).

For obtaining the coefficients accurately, the optimal data should come from irradiations from different beams where the set of values $(D_t, D_f, D_\gamma, D_B)$ are linearly independent. We have designed an experimental campaign for in-vitro samples at three facilities: a pure low energy neutron beam, as the cold neutron line PF1b of the Institute Laue-Langevin (ILL) of Grenoble (France) with different conditions for the cells, an epithermal neutron beam as the accelerator-based neutron source HispaNoS of the National Accelerator Center of Seville (CNA) and a hospital LINAC for conventional radiotherapy. The different type of irradiations and the dominating components of the dose delivered are displayed in Table 1.

We have started the radiobiology measurements at ILL with a pure cold neutron beam and the first results have been published (Pedrosa-Rivera et al., 2020a).

Additionally, we have proposed a simplified formalism for a first order approximation of the photon isoeffective dose, based on new weighting factors, defined as the ratio of the alpha coefficients of the different radiations: $W_i = \alpha_i/\alpha_p$. This formalism (Pedrosa-Rivera et al., 2020b) can be summarized in the Equations:

$$W_f D_f + W_t D_t + \left(D_\gamma + \frac{D_\gamma^2}{\alpha_p/\beta_p}\right) + W_B D_B = \begin{cases} D_p + \dfrac{D_p^2}{\alpha_p/\beta_p} & (3a) \\ n\left(d_p + \dfrac{d_p^2}{\alpha_p/\beta_p}\right) & (3b) \end{cases}$$

where D_p is the approximation to a single-fraction photon isoeffective dose, and n stands for the number of sessions of dose d_p of a fractionated photon isoeffective treatment. The new weighting factors, which are true constants, can be estimated from the previous ones or can be measured from radiobiology measurements.

In addition to the suitability of the PF1b line at ILL for radiobiology measurements, this facility is very adequate for in-vitro tests of new boron compounds. We have started in vitro studies of boron rich compounds, which will include uptake measurements for different cell lines, both tumor and normal, using both ICP-AES at UGR and boron autoradiography under collaboration with the group of Pavia (Italy). The response of cells cultured with the boron compounds and the CBE measurement will be performed at the PF1b neutron line at ILL, for which a proposal has been approved (Porras et al., 2018b). A high neutron flux (thermal capture equivalent flux above 2×10^9 n/(s cm^2)) guarantees accurate measurements in a short time (irradiations of a few minutes). A class 2 biological laboratory has been installed in the same

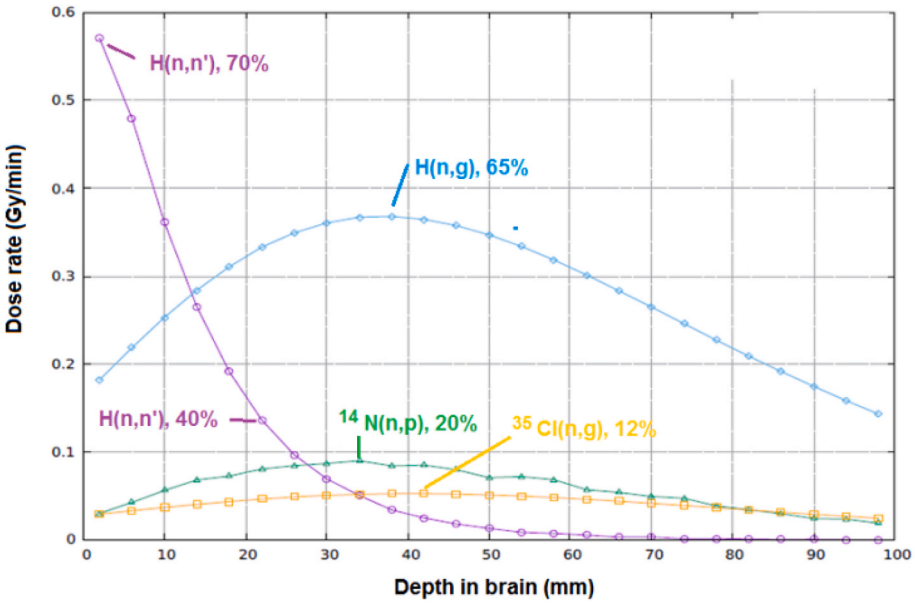

Fig. 3. Dose components due to the most relevant individual reactions, in brain tissue, as a function of depth, estimated with Monte Carlo simulations.

instruments hall, which makes possible processing the cells just after the irradiation. We are open to establish collaborations for testing new boron compounds at this facility.

3. Potential new strategies

3.1. Sulfur-33 as a cooperative capturer for BNCT

We have performed preliminary studies on potential use of ^{33}S as an additional neutron capturer for enhancing BNCT, the reason being the important role played by sulfur in biochemistry and the enhanced high sulfur concentrations (of the order of mg/g) found in different tumors, addressed to an enhanced synthesis of glutathione (Gamcsik et al., 2012). ^{33}S is one of the few isotopes in the nuclear chart for which the dominant neutron capture reaction leads to alpha emission instead to photon emissions. However, its cross section was assumed to be more than three orders of magnitude smaller than that of boron, although there were no previous experimental data below 10 keV and important discrepancies were found between reported data above this quantity. For this reason our group performed recently measurements of this cross section at CERN and ILL. Two measurements were performed at n_TOF (CERN), at experimental areas EAR-1 and EAR-2, for measuring the epithermal and thermal region respectively, and another measurement at the thermal energy was performed at the PF1b line at ILL.

The results, illustrated in Fig. 4, show that there is a 1/v dependence on the cross section at energies below 10 keV and a high resonance, with peak value above 25 b at 13.5 keV (Praena et al., 2018). However the thermal cross section value extracted from the experiments is still below 1 b. Therefore, the potential use of ^{33}S in BNCT depends on the possibility of using neutron beams with a high component at such energy, which would lead to resonance captures from primary neutrons before thermalization and would enhance the dose at small depths (Porras et al., 2014).

3.2. Neutron-guided BNCT

Cold neutrons, those arising from a moderator at low temperatures, have a large wavelength and can be guided and focused through guides and lenses at large distances. At these guides, those low energy neutrons impinging on the walls at small angles travel by zig-zag or Garland reflections while those of higher energies cross the walls and are lost from the beam. This feature allows also focusing the beam enhancing the neutron flux in a small surface, of submilimeter size (the size of a catheter that can be inserted into the body).

Such neutrons, when entering a boron-loaded tissue would produce a very high local dose, as the capture cross sections increases with decreasing energy (1/v) behaviour. Although it would be a very poorly penetrating beam, it would have the ability of be directed to a particular spot, which could be appropriate for some radiosurgery applications. We are conducting basic studies by means of simulations with the code McStas (Lefmann and Nielsen, 1999) (used for guiding cold neutrons) and MCNPX (Pelowitz, 2005) (for the transport in the tissue and the evaluation of the delivered dose) for studying this challenging potential application.

In Fig. 5, it is illustrated the concentration produced for a cold neutron beam of 1 meV in a focusing guide of 2 m length, starting from a section of 10 × 10 cm to a 5 × 5 cm exit one (Porras et al., 2020). In the figure we have plotted that ratio between the dose that would be delivered to a phantom of a standard soft tissue in tumor (assumed loaded with a concentration of boron of 35 ppm) and the maximum value of the dose produced at normal tissue (for which a boron concentration of 10 ppm is assumed). Regions where this ratio is less than one are not coloured.

4. NeMeSis: an accelerator-based facility for BNCT and other scientific applications

The project NeMeSis (Neutrons for Medicine and Scientific applications) is based on an electrostatic accelerator able to produce a proton beam of 2.1 MeV at a current of 30 mA, which is already available in the market (Neutron Therapeutics and Inc). In our design, a solid lithium target on a copper backing refrigerated by microchannels designed in collaboration with the Laboratori Nazionale di Legnaro (Italy) (Mastinu et al., 2015) will be used for the neutron production. Preliminary estimations with the ANSYS code and tests under the proton accelerator of Birmingham show that this system is able to dissipate power up to 3 kW/cm^2. The idea is to make use of a low cost target that can be replaced frequently, which would avoid blistering problems. Our estimations of a beam shape assembly which is currently under optimization would produce a pure epithermal neutron beam, as the low proton energy would produce neutrons up to a maximum energy of 0.35 MeV, which require less moderation than most options conceived for BNCT.

Table 1
In-vitro experiments planned and relative role of the dose components.

Setup	D_t	D_f	D_γ	D_B
Pure cold neutron beam[a] with no gamma contamination and minimal culture medium	Dominant	0	Small	0
Pure cold neutron beam[a] with no gamma contamination and minimal culture, with boron	Important	0	Small	Different values (can be dominant)
Pure cold neutron beam[a] with no gamma contamination and large culture medium	Relevant	0	Relevant (can be dominant)	0
Pure cold neutron beam[a] with no gamma contamination and large culture medium, with boron	Relevant	0	Relevant (can be dominant)	Different values (can be dominant)
Epithermal beam[b] and minimal culture medium	Small	Dominant	Small	0
Epithermal beam[b] and minimal culture medium, with boron	Small	Dominant	Small	Different values (can be dominant)
Epithermal beam[b] and large culture medium	Relevant	Relevant	Relevant	0
Epithermal beam[b] and large culture medium, with boron	Relevant	Relevant	Relevant	Different values (can be dominant)
Hospital linac[c] at dose rate similar to the BNCT gamma component	0	0	Dominant	0

[a] Cold neutron beam correspond to that of the PF1b line at ILL.
[b] Epithermal beam refers to the one produced by the 7Li (p,n) reaction near the threshold at CNA, Seville and.
[c] Hospital Linac is the Elekta Versa HD™ accelerator at the Granada University hospital "Virgen de las Nieves".

This neutron beam will be used for performing clinical trials for the treatment of brain tumors (including GBM) and recurrent head and neck cancers. In addition to this, we plan to perform the previous studies required for other applications such as the treatment of liver metastases of colorectal cancers without autotransplantation (due to the expected penetrability of the beam), soft tissue sarcomas, some type of lung tumors, local recurrences of breast or pancreatic cancers.

In this facility the production of medical radioisotopes for diagnosis will be also pursued. In particular our group has recently studied the production of very short lived PET radioisotopes (^{11}C, ^{13}N and ^{15}O) with a deuteron beam (Arias de Saavedra et al., 2018) that could be extracted from a second line from the same accelerator used for the neutron beam production for BNCT. In addition to this, the production of radioisotopes by neutron capture as ^{99}Mo (parent of ^{99m}Tc, for which there are several supply concerns (European Nuclear Society)) can be explored from the epithermal flux from the lithium target. This is feasible when the neutron capture resonance integral in the epithermal range is specially large, as in the case of ^{98}Mo (50 times larger than the thermal value). All these are very interesting possibilities to explore because any of them may make a BNCT facility more sustainable and therefore more attractive for investments.

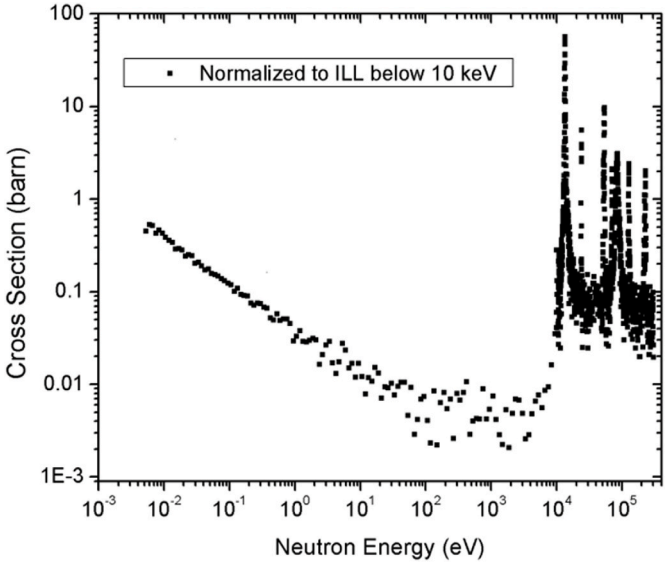

Fig. 4. Cross section values for the ^{33}S (n,α) reaction measured at n_TOF and normalized to the thermal value from the ILL measurement. High resonances in the epithermal region have been confirmed.

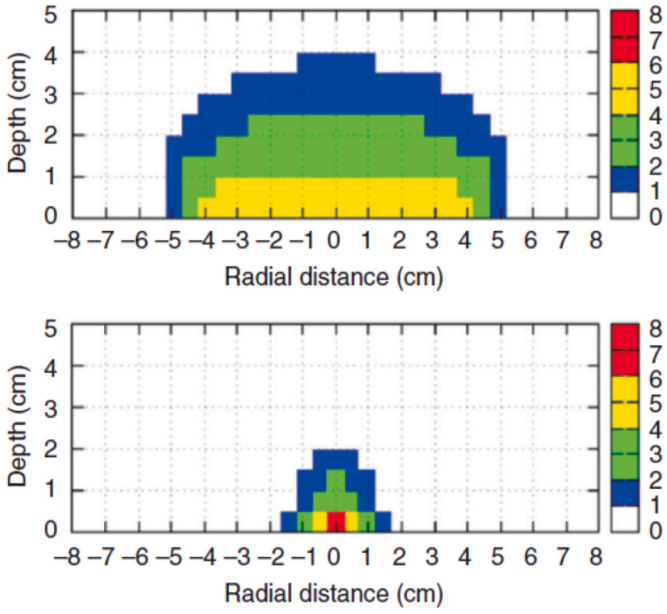

Fig. 5. Ratio of dose at tumor with respect to the maximum dose at normal tissue produced by an original cold beam of 10 × 10 cm (above) and the result of focalizing the beam at 5 × 5 cm (below).

The scheme of the NeMeSis facility is sketched in Fig. 6.

We intend to perform the preliminary studies for using the facility towards other scientific applications. Neutrons are very important as a tool for very different fields of science and technology, ranging from the study of radiation damage in circuits, radiation protection for space missions or neutron scattering, which has a great amount of applications in material sciences and structural biology. This latter possibility would require the use of a neutron cooler (e.g. moderator of liquid deuterium at 25 K) in order to produce a cold neutron beam similar to those of existing facilities.

Granada is the official European candidate for the facility IFMIF-DONES (Irradiation of Fusion Materials International Facility – Demo Oriented Neutron Source), which is aimed to produce a huge neutron

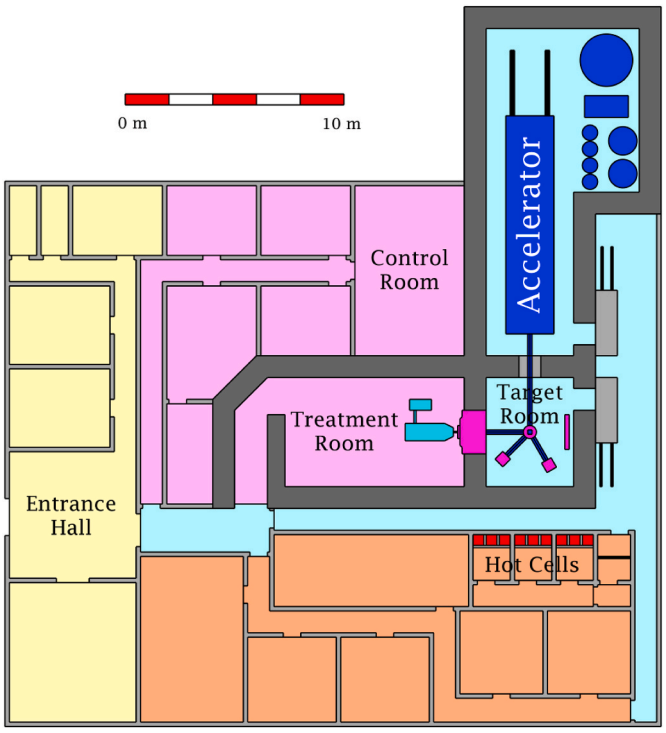

Fig. 6. Scheme of the facility: from the accelerator hall up to three beams will be extracted in the target area: (i) the one transporting protons to the beam shape assembly inserted in the shielding next to the treatment room, (ii) a second beam of protons will impinge another lithium target inside a moderator containing the target for radioisotope production by neutron capture, and (iii) a deuteron beam will hit the targets for PET radioisotope production. Also shown are the hot cells for radiopharmaceutical production.

flux in order to test materials for the future DEMO fusion reactor. It is planned to accelerate deuterons up to 40 MeV with a current of 125 mA and using a liquid lithium target in order to produce an unprecedented neutron flux (Ibarra et al., 2019). This is a long term project that could benefit from the previous construction and use of the NeMeSis facility, since this would allow conducting preliminary studies of neutron applications that could be performed in a future to the neutron source DONES.

5. Conclusions

The activities on BNCT research of the Granada group have been described. They are possible thanks to collaboration with different groups. In particular we want to stress the potential use of two international facilities for basic research: (i) the neutron time of flight at CERN, of which we are part of the collaboration, and which is optimal for neutron cross section measurements, and (ii) the Institute Laue-Langevin where a biology laboratory has been installed close to a very clean low energy neutron beam, perfectly suitable for radiobiology studies and in-vitro test of boron compounds, for which we have proposals already accepted. We are open to collaborations with other groups with the same research interest.

With respect to clinical BNCT research, it is our aim is to build a facility that would allow performing clinical trials in a future. We are optimizing an accelerator-based design that will expand the type of cancers treated with BNCT. In addition to this, this facility intends to be a prototype of theranostic facility where the production of radioisotopes will allow developing new nuclear medicine procedures.

Our group is honored to host the next International Congress on Neutron Capture Therapy, which will be the 19th edition and will take place in Granada, Spain in June 2021 (www.icnct19. org).

Declaration of competing interest

The authors declare there is no conflict of interests in this work.

Acknowledgements

We acknowledge financial support for this work from the *Asociación Española Contra el Cáncer* (AECC), project PS16163811PORR (with donations from Bridgestone-FirstStop Spain), the Spanish MINECO under contract FIS2015-69941-C2-1-P, Junta de Andalucía under contract P11-FQM-8229, the Campus of International Excellence BioTic (P-BS-64) and the donors of the University of Granada Chair *Neutrons for Medicine*: the Spanish *Fundación ACS*, *Asociación Capitán Antonio*, *La Kuadrilla de Iznalloz and Sonriendo se Puede Ganar*.

References

Arias de Saavedra, F., Porras, I., Praena, J., 2018. Routes for the production of isotopes for PET with high intensity deuteron accelerators. Nucl. Instrum. Methods Phys. Res. A 887, 50–53.
Barth, R.F., Vicente, M.G., Harling, O.K., et al., 2012. Current status of boron neutron capture therapy of high grade gliomas and recurrent head and neck cancer. Radiat. Oncol. 7, 146–166.
Coderre, J.A., Morris, G.E., 1999. The radiation biology of boron neutron capture therapy. Radiat. Res. 151, 1–18.
European Nuclear Society. The medical isotope crisis. http://www.euronuclear.org/1-information/news/medical-isotope-crisis.htm.
Gamcsik, M.P., Mohit, S., Kasibhatla, S., et al., 2012. Glutathione levels in human tumors. Biomarkers 17, 671–691.
Gonzalez, S.J., Santa Cruz, G.A., 2012. The photon-iso-effective dose in boron neutron capture therapy. Radiat. Res. 178, 609–621.
Goorley, J.T., Kiger III, W.S., Zamenhof, R.G., 2002. Reference dosimetry calculations for neutron capture therapy with comparison of analytical and voxel models. Med. Phys. 29, 145–156.
Iaea, 2001. Current Status of Neutron Capture Therapy. IAEA-TECDOC-1223. International Atomic Energy Agency, Vienna, Austria).
Ibarra, A., Arbeiter, F., Bernardi, D., et al., 2019. The European approach to the fusion-like neutron source: the IFMIF-DONES project. Nucl. Fusion 59, 6.
Icru, 1978. Dose Specification for Reporting External Beam Therapy with Photons and Electrons ICRU Report, vol. 29. Bethesda, MD, USA).
Joensuu, H., Kankaanranta, L., Seppälä, T., et al., 2003. Boron neutron capture therapy of brain tumors: clinical trials at the Finnish facility using boronophenylalanine. J. Neuro Oncol. 62, 123–134.
Koehler, P.E., et al., 1989. ^{14}N(n ,p)^{14}C cross section from 61 meV to 34.6 keV and its astrophysical implications. Phys. Rev. C39, 1655.
Kreiner, A.J., Bergueiro, J., Cartelli, D., et al., 2016. Present status of accelerator-based BNCT. Rep. Practical Oncol. Radiother. 21, 95–101.
Lefmann, K., Nielsen, K., 1999. McStas, a general software package for neutron ray-tracing simulations. Neutron News 10, 20–23.
Mastinu, P., Martín-Hernández, G., Praena, J., 2015. Micro-channel–based high specific power lithium target. Il Nuovo Cimento 38C, 193. https://doi.org/10.1393/ncc/i2015-15193-y.
Neutron Therapeutics, Inc. http://www.neutrontherapeutics.com/technology/.
Pedrosa-Rivera, M., Ruiz-Magaña, M.J., Porras, I., et al., 2020a. Neutron radiobiology studies with a pure cold neutron beam. Nucl. Instrum. Methods B 462, 24–31.
Pedrosa-Rivera, M., Praena, J., Porras, I., et al., 2020b. A simple approximation for the evaluation of the photon isoeffective dose in Boron Neutron Capture Therapy based on dose independent weighting factors. Appl. Radiat. Isot. 157, 109018.
Pelowitz, D.B., 2005. MCNPX Users Manual Version 2.5.0 - LA-CP05-0369. Los Alamos National Laboratory.
Porras, I., Sabaté-Gilarte, M., Praena, J., et al., 2014. 33S for neutron capture therapy: nuclear data for Monte Carlo calculations. Nucl. Data Sheets 120, 246–249.
Porras, I., Wright T, T., Bennett, S., et al., 2018a. Measurement of the 35Cl(n,γ) Cross Section at N_TOF EAR1. Proposal to the ISOLDE and Neutron Time-Of-Flight Committee. CERN Document Server. http://cds.cern.ch/record/002299695.
Porras, I., Arias de Saavedra, F., Benoit, B., et al., 2018b. Radiobiology in Vitro Measurements for Boron Neutron Capture Therapy. Institut Laue-Langevin (ILL). https://doi.org/10.5291/ill-data.3-07-376.
Porras, I., 2020. Applications of neutron optics to biomedicine: BNCT. In: Calvo, M.L., Alvarez-Estrada, R.F. (Eds.), Advances in Neutron Optics: Fundamentals and Applications in Materials Science and Biomedicine. CRC Press, Boca Raton, FL, USA. https://doi.org/10.1201/9780367816056.
Praena, J., Porras, I., Sabaté-Gilarte, M., et al., 2017. The ^{14}N(n, p)^{14}C and ^{35}Cl(n, p) ^{35}S Reactions at n_TOF-EAR2: Dosimetry in BNCT and Astrophysics. Proposal to the ISOLDE and Neutron Time-Of-Flight Committee. CERN Document Server. https://cds.cern.ch/record/2266484.
Praena, J., Sabaté-Gilarte, M., Porras, I., et al., 2018. Measurement and resonance analysis of the 33S(n,α)30Si cross section at the CERN n_TOF facility in the energy region from 10 to 300 keV. Phys. Rev. C97, 064603.
The n_TOF collaboration at CERN. https://ntof-exp.web.cern.ch/ntof-exp/.

Wagemans, J., et al., 2001. Experimental determination of the 14N(n, p)14C reaction cross section for thermal neutrons. Phys. Rev. C61, 064601.
www.icnct19.org.
Zerkin, V.V., Pritychenko, E., 2018. The experimental nuclear reaction data (EXFOR): extended computer database and Web retrieval system. Nucl. Instrum. Methods Phys. Res. A 888, 31–43.