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Technical note

Characterisation of a β detector on positron emitters for medical applications

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ABSTRACT

Purpose: Radio Guided Surgery (RGS) is a technique that helps the surgeon to achieve an as complete as possible tumor resection, thanks to the intraoperative detection of particles emitted by a radio tracer that bounds to tumoral cells.

In the last years, a novel approach to this technique has been proposed that, exploiting β^- emitting radio tracers, overtakes some limitations of established γ-RGS.

In this context, a first prototype of an intraoperative β particle detector, based on a high light yield and low density organic scintillator, has been developed and characterised on pure β^- emitters, like ^{90}Y. The demonstrated very high efficiency to β^- particles, together with the remarkable transparency to photons, suggested the possibility to use this detector also with β^+ emitting sources, that have plenty of applications in nuclear medicine. In this paper, we present upgrades and optimisations performed to the detector to reveal such particles.

Methods: Laboratory measurement have been performed on liquid ^{68}Ga source, and were used to validate and tune a Monte Carlo simulation.

Results: The upgraded detector has an ~80% efficiency to electrons above ~110 keV, reaching a plateau value of ~95%. At the same time, the probe is substantially transparent to photons below ~200 keV, reaching a plateau value of ~3%.

Conclusions: The new prototype seems to have promising characteristics to perform RGS also with β^+ emitting isotopes.

1. Introduction

Radio Guided Surgery (RGS) is a technique that helps the surgeon to achieve an as complete as possible tumor resection [1]. The technique is based on the administration to the patient, before surgery, of a radio pharmaceutical that bounds to tumoral cells. The emitted radiation is revealed by a dedicated detector, named *probe*, that guides the surgeon towards tumor remnants.

In the last years, a novel approach to this technique has been proposed [2] that, exploiting β^- emitting radio tracers, overtakes some limitations of established γ-RGS [3,4]. In fact, electrons with ~1 MeV energy penetrate only few millimetres of human tissue, while about 1/3 of 144 keV photons (emitted by the commonly used ^{99m}Tc) traverse more than 8 cm, making γ-RGS hardly applicable in context characterised by elevated background coming from healthy tissue.

In this framework, an intraoperative detector to reveal β particles

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has been designed and developed, based on a high light yield and low density organic scintillator to achieve high efficiency to electrons while retaining low sensitivity to photons.

The effectiveness of RGS based on beta radiation has been demonstrated and tested on ex vivo specimens of cerebral [5–7] and intestinal neuroendocrine tumors [8] after administration of ^{90}Y-DOTATOC. In case of pure beta- emitters as ^{90}Y the abundance of electrons with respect to a negligible amount of photons mainly due to bremsstrahlung (ecc.) makes the beta radiation well detectable and identifiable. Nonetheless, the promising test results previously obtained suggest a study of feasibility of RGS also in case of PET radiotracers. In fact, using β^+ emitters, a high background of 511 keV photons is expected but the high beta detection efficiency and the remarkable photon transparency of the detecting probe [9] could lead to a sufficient signal to noise ratio, eventually allowing the performing of RGS.

This possibility could indeed remarkably increase the number of application fields of β-RGS. In fact, the main limitation of the proposed technique is due to the lack of radio tracers that can be marked with pure β^- emitting isotopes, that in turn implies a limited number of tumors to which the technique can be applied.

On the contrary, being sensitive also to β^+ emitters would allow to exploit the vast majority of radio tracers that are currently used in nuclear medicine for PET exams, such as ^{18}F ($\tau_{1/2} = 110$ min, endpoint 0.633 MeV) or ^{68}Ga ($\tau_{1/2} = 68$ min, endpoint 1.9 MeV), and which already have numerous application cases.

This interest in extending RGS application fields is also demonstrated by a recent prospective study [10] that aimed to assess the possibility to use ^{68}Ga-DOTATATE to guide the resection of abdominal Neuro Endocrine Tumors. However, in this case a commercial γ detector has been used to reveal annihilation photons instead of primary decaying positrons. As a result, despite overall positive conclusions, authors found a 25% (33/133) of false positives cases (i.e. samples identified as "diseased" by the probe but found healthy at the post operation histological exam), the majority of which coming from pancreas, liver and gastro-intestinal tract, i.e. organs characterised by an elevated level of physiological uptake of radio tracers.

Moreover, it has been recently demonstrated by our team that ^{68}Ga-PSMA, an innovative radio pharmaceutical that is gaining more and more interest in the staging of prostate cancer [11], has an uptake good enough to perform β-RGS in lypmhoadenectomy in case of prostatic surgery [12].

The first prototype of β probe, that has been used both for ex-vivo tests [5] [7] and for the aforementioned feasibility study on PSMA, had demonstrated an efficiency to electrons greater than 70% above 540 keV, being very inefficient to electrons below ~300 keV [13]. This threshold, however, is too high to allow at all any application involving ^{18}F. Notwithstanding its higher endpoint energy, also the use of ^{68}Ga is hindered. In fact, even neglecting the attenuation effect of the traversed tissue, only 80% of positrons are emitted above this threshold.

Moreover, it has to be stressed that the proposed RGS technique, while leveraging on the locality of the electron emission to gain sensitivity, has in this very aspect also a possible limitation. In fact, the interposition of even small layers of healthy tissue between the tumor and the detector could diminish the energy of the emitted particle, and eventually absorb it, possibly preventing the lesion to be detected.

To face these issues, in the last years further studies on the detector have been carried on to increase the sensitivity to low energy β particles, aiming at a new device able to efficiently detect low energy (~100 keV) electrons, both to use lower end point β decaying nuclides and to detect deeper tumors.

In this paper, we present modifications and optimisations to the detector aimed at improving its capability of detecting β^+ particles, together with its characterisation by means of experimental measurements on ^{68}Ga liquid source and Monte Carlo simulations, leading to an evaluation of the efficiency to both β and γ particles.

It has to be recognised that the idea of using β^+ emitters in Radio Guided Surgery, directly detecting positrons, is not indeed new. However, with respect to already proposed approaches [14–20], the detector studied in this paper does not require the subtraction of the annihilation photons' background, thanks to its intrinsic low sensitivity to such a contribution. As a result, the here proposed approach would allow to develop a much simpler, smaller and handier tool, being these crucial aspects when dealing with intra operative detectors.

2. Materials and methods

2.0.1. Detector

The core of the β^- detecting probe is represented by a cylindrical (6 mm in diameter and 3 mm in height) scintillator, made of commercial mono-crystalline para-terphenyl (doped with 0,1% in mass of (E,E)-1,4-Diphenyl-1,3-butadiene). This material has been found to be an optimal candidate for low energy electron detection [9], being a non hygroscopic organic scintillator with high light yield (~140% of anthracene [21]) and low density (1.23 g/cm^3).

A thickness of 3 mm for the scintillator has been found to be an optimal compromise between gamma rejection and β sensitivity in case of ^{68}Ga. In fact, if on one side a smaller thickness would result in an even smaller sensitivity to photons, it would also imply a reduced sensitivity to high energy, Minimum Ionizing, β particles, that would release a smaller amount of energy in the detector. It has in fact to be noted that about 50% of electrons from this isotope have more than $1 MeV$ of energy.

Differently from previous prototypes of the probe [21], where the active material was encapsulated in a black ABS (Acrilonitrile Butadiene Stirene) absorber, in the used detector, light collection has been improved both surrounding the crystal with a 1 mm thick white diffusing Delrin ring and covering the front face with two 4 μm layers of a reflective alluminized mylar film. The light tightness of this assembly was then achieved adding an external black PVC (Poly Vinyl Cloride) ring covered, on the front face, by a 15 μm layer of Alluminum.

However, the more substantial improvement to the light collection efficiency is given by the use of a 3×3 mm^2 Silicon photomultiplier (SiPM SensL C-series 30035, in an SMT package), instead of the 1×1 mm^2 MicroFC 10000 Series in a TO18 package, used in the first realization of the probe.

The adoption of a wider sensor and the improve in its optical coupling with the crystal increase by a factor ~9× the geometrical acceptance of the light sensor, making it sensitive to the light emitted in any point of the crystal.

This aspect was indeed the main limitation to the efficiency of the first probe design, while the new prototype is optimized and improved to increase the light collection efficiency. This results in an increasing of the detector sensitivity, thus reducing the impact on the detection of scintillation light attenuation also in case of distant emission points.

The detector is housed in a "pen-like probe", with an aluminum cylindrical body. Portable electronics, based on an Arduino Due board equipped with a custom analog shield providing signal conditioning and trigger logic, was used for the readout [22].

2.0.2. Source

The ^{68}Ga has been provided by *Radio Farmacia of Policlinico Gemelli, Roma*, in liquid form inside a graduated syringe. Total volume was:

$$V_{Ga} = (3.2 \pm 0.1) \text{ mL},$$

with a total activity at the time of supply of:

$$A_{Ga} = (1.26 \pm 0.06) \text{ MBq}.$$

To perform measurements, started after about 4 h from the source supply, a volume of

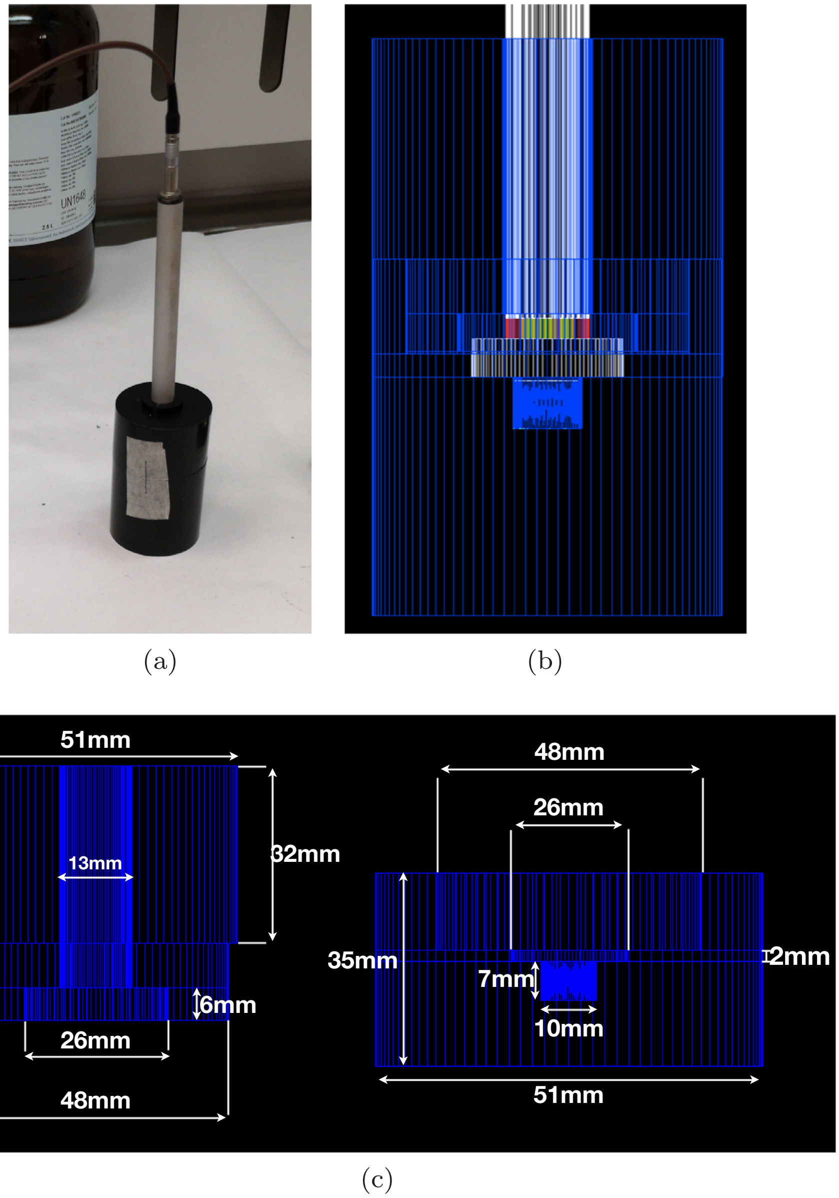


Fig. 1. a) PVC holding structure developed to house both the source and the probe. b) Geant4 reconstruction of the support: in blue the holding structure, in white the probe Alluminum case, in red and yellow the two layers of PVC and Delrin for lateral shielding, in gray the 5.5 mm plastic absorber between the source and the detector. c) Sizes of two parts of the support.

$$V_{Source} = (0.500 \pm 0.005)\ \text{mL}$$

of ^{68}Ga was extracted by means of a smaller (1 mL) syringe.

2.0.3. Experimental setup

Both the source and the probe were housed in a PVC holder designed to protect the operator from the radio-activity, get control of relevant geometric parameters like source-probe distance and centring, have the possibility to insert an absorber for particle selection, and, finally, to provide a structure with well known geometrical and physical parameters (volumes position, shapes and density). Having a precise awareness of the whole setup is in fact fundamental to develop the corresponding Monte Carlo simulation in Geant4 [23], which is needed for example to evaluate the actual flux of annihilation photons that may give a signal inside the crystal. The holder is shown in Fig. 1 along with its modelisation in the Monte Carlo.

2.0.4. Performed measurements

Once the dedicated area of the PVC support had been filled with the V_{Source} of ^{68}Ga, data were taken in two different configurations: with and without interposing between the source and the detector a 5.5 mm PVC absorber. This thickness has been chosen based on the Monte Carlo simulation, as sufficient to stop all positrons from reaching the detector, thus allowing to assess the performances of the detector with photons. In all these measurements, the source-probe distance was kept constant (d = 5.5 mm), whether the absorber was present or not. In each of the two configurations, rates were taken as a function of time for about 1 h.

Intrinsic detector noise measurements have been taken at regular interval times during data acquisition, averting the probe from the source, and have been found to be of the order of few CPSs.

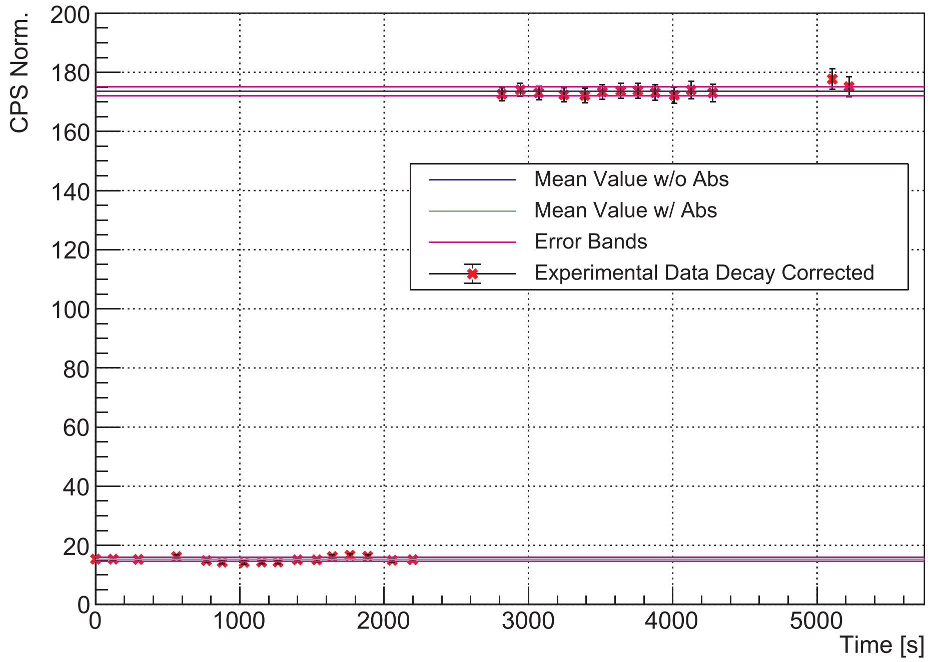


Fig. 2. Counts obtained on ^{68}Ga with and without the PVC absorber between the probe and the detector, normalised for the physical decay time.

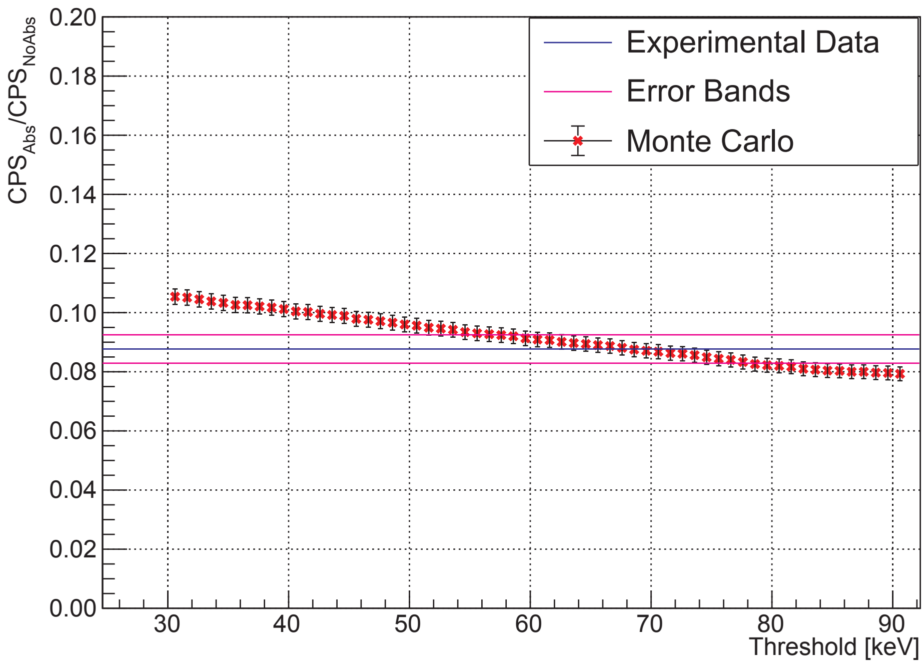


Fig. 3. Ratio of Monte Carlo expected rates on ^{68}Ga with and without the PVC absorber between the probe and the detector, as a function of the deposited energy threshold. Error bars represent the Poissonian fluctuation of each rate value.

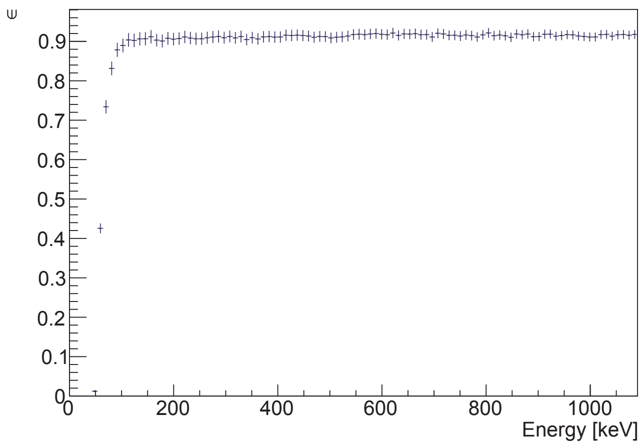
3. Results

3.0.5. Counts with and without absorber

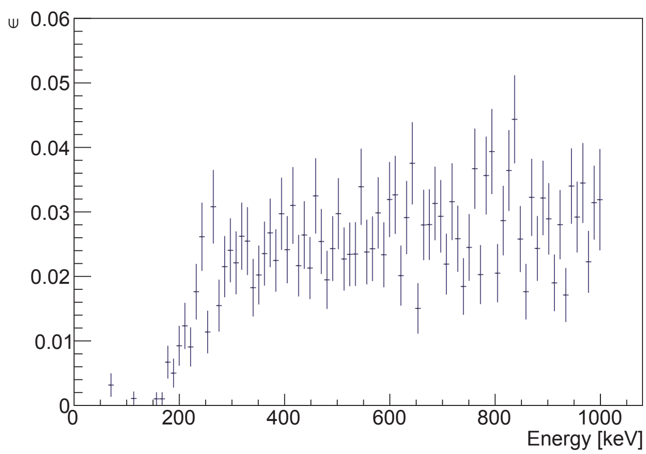
Fig. 2 shows the counting rates measured at different times on the ^{68}Ga source with and without the interposition of the 5.5 mm PVC absorber between the source and the detector. Since the measurement lasted ~$1.3 \times \tau_{Ga^{68}}$, we reported the measurements after correcting for the decay exponential. Data have also been subtracted with their respective intrinsic noise counts. Error bars represent the Poissonian fluctuation of each rate value, while error bands have been obtained as $(R_{Max} - R_{Min})/\sqrt{12}$.

3.0.6. Determination of the effective threshold on collected energy

A detailed Monte Carlo simulation of the experimental setup has been developed in Geant4 to evaluate the energy deposition inside the detector. In particular, all the described volumes and physical processes of interest have been implemented, with the exception of scintillation, which is expected not to play a significant role given the reduced size of the detector in spite of a massive impact in term of CPU time. A production threshold of 0.1 *mm* has been set in Geant, i.e. no secondary particle that is able to travel less than this distance is generated in the simulation, while its energy is locally released. However, in order to compare the simulated and the data counting rates, a threshold in



(a)



(b)

Fig. 4. Efficiency curve for electrons (a) and photons (b), as described in the text.

deposited energy (E_{dep}) must be found, to mimic the effect of the hardware threshold.

To this aim, results from Fig. 2 were used to extract the ratio between counts with and without absorber. It has to be noted that this approach allows also to get rid of the dependence on the absolute activity of the source, which was characterised by the most significant uncertainty. This ratio has been found to be:

$R = CPS_{Abs}/CPS_{NoAbs} = 8.77 \pm 0.41\%.$

The Monte Carlo simulation is then used to correlate the measured value of R with E_{Thr}, as shown in Fig. 3. We can thus estimate:

$E_{Thr} = (70 \pm 10)$ keV.

3.0.7. Efficiency curves

After the Monte Carlo tuning described above, the simulation can be used to asses the performances of the detector also in other experimental situations. In particular, to obtain efficiency curves on both electrons and photons, we simulated two different configurations.

It has to be remembered that the expected typical application scenario for this detector is the one in which the probe is used (either in "open" or in "laparoscopic" surgery) to detect small tumor remnants, immersed in an almost isotropic photon background, coming from all the healthy organs nearby.

In this view, to evaluate the efficiency to beta particles, the detector has been placed in contact with a 12 mm diameter source layer of isotropic electrons having a flat energy distribution in the 0 − 3 MeV range, to mimic the signal coming from the tumor.

On the other hand, to evaluate the efficiency to background photons, a spherical γ source with a radius of 8 cm has been placed centred in the detector, again with a flat spectrum in the 0 − 1 MeV, and isotropic angle distribution. In this case, the idea is that when using a β^+ radio tracer, annihilation photons are expected to come almost isotropically from each direction around the detector.

To obtain the efficiency curves, the fraction of primary particles that originated an event that gave a "detected" signal ($E_{dep} > E_{Thr}$) in the active area of the detector has been evaluated, for each energy bin. In order to factorise out the geometrical efficiency, that is expected to vary from an application case to the other, the normalisation has been done with respect to particles having at least one "Monte Carlo step" into the active area of the detector.

Results are shown in Fig. 4, and suggest that the probe has an ~80% efficiency to electrons above ~110 keV, reaching a plateau value of ~95%. At the same time, the probe is substantially transparent to photons below ~200 keV, reaching a plateau value of ~3%.

4. Conclusions

To develop an innovative approach to Radio Guided Surgery, a β detector has been proposed and characterised on pure β^- emitters. Elevated sensitivity to electrons, together with its substantial transparency to photons, had been demonstrated, suggesting the possibility to use it also with β^+ emitters. In this paper, we presented hardware upgrades of the first generation detector aimed at optimising it to reveal positrons, while retaining scarce sensitivity to photons. This new detector has been characterised with a liquid Gallium-68 β^+ source, that allowed to tune a dedicated Monte Carlo simulation, finding the threshold in energy deposition that corresponds to the hardware one. The thus validated simulation was then used to obtain efficiencies for both electrons and photons.

The efficiency curves show that the probe starts to have good sensitivity to electrons above ~110 keV. This is indeed a step improvement with respect to the first generation detector, that was substantially blind to electrons below ~300 keV [13]. At the same time, the efficiency on photons remains very small, with a plateau value of ~3%.

This improved detector seems to be a very promising tool in view of a possible extension of Radio Guided Surgery that uses β^+ emission in cases characterised by a good enough demonstrated uptake of the radio pharmaceutical. In particular, even if the tests presented in this paper have been performed with a ^{68}Ga source, the β efficiency curve seems to suggest that also the detection of ^{18}F could in principle be feasible. It is worth mentioning again that this could be an impressive boost to the factual usefulness of the proposed RGS technique, having ^{68}Ga and particularly ^{18}F a vast variety of applications. To this aim, a dedicated experimental campaign on liquid ^{18}F is foreseen in the near future.

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