Intense post-accelerated 11C beams for hadrontherapy: Treatment and at the same time 3D dose mapping by PET imaging

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Abstract

Hadrontherapy was introduced in the USA some decades ago and has by now widespread throughout the world, as seen with the design and construction of CNAO, HIT, PROSCAN, MedAustron and Etoile treatment centers. Accelerator laboratories, such as GANIL, CERN-ISOLDE and SPES, producing post-accelerated radioactive ion beams for fundamental research have in parallel been also multiplied. Here we propose to fully replace or combine carbon therapy treatments based on 12C ions with treatments using a post-accelerated 11C PET radioactive ion. This has the advantage to provide a beam for treatment and at the same time, to collect informations during or just after, on the 3D distribution of the implanted ions by PET imaging using, i.e. PET-CT scanners in the treatment rooms. This approach has already been tested at NIRS in Japan and can be seriously envisaged, notably because of the recent progresses made on 11C ion production and post-acceleration techniques. Furthermore, it presents a much higher sensitivity and flexibility than the so-called “in-beam hadrontherapy PET imaging” in the focus in the recent years.
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1 Introduction

Hadrontherapy was first proposed in 1946 by Prof. Wilson and later applied in Berkeley in 1954 [1]. Since then, thousands of patients have been treated and new hadrontherapy centers have appeared for treatments with protons and carbon ions, using cyclotrons or combined Linac injector/synchrotron accelerators. Beam energies from 60 to 400 MeV/n span the required ion penetration ranges in living tissues, positioning Bragg Peak depths from about 1 to 25 cm. One of the recent facilities under construction, MedAustron, aims at producing protons and $^{12}$C$^{6+}$ ion as 1Hz-$4 \times 10^7$ ion spills delivered in several treatment rooms [2].

The first online mass separated (ISOL) radioactive ion beam was produced at the Niels Bohr Institute in 1951, for the separation of short lived neutron-rich Kr isotopes. The ISOL principle is based on the production of radioisotopes by interaction of a primary driver with a thick target, and by “online” formation of secondary radioactive ion beams (RIB) from the released isotopes, which are purified by mass selection in a dipole magnet. Post-accelerated radioactive beams for fundamental nuclear and astrophysical studies were produced much later, by fragmentation of a high energy beam in 1985 in Berkeley [3] and by post-acceleration of a low-energy ISOL beam in a cyclotron at CRC in Louvain-La-Neuve in 1989 [4]. For instance, $10^7$ $^{11}$C ions/s at 10 MeV energy were then delivered, an intensity which has recently become available at ISAC at TRIUMF [5]. Today several facilities produce post-accelerated radioactive beams for fundamental studies and applications, one of those being REX-ISOLDE soon upgraded to HIE-ISOLDE at CERN [6].

A first proposal to accelerate radioactive ions at even higher energies and intensities was done within the beta-beams project to probe oscillation properties of relativistic neutrinos. Pulsed $10^3$pps of $^8$He and $^{18}$Ne up to Lorentz boost of $\gamma=100$ have been proposed [7]. Intense production of $^8$He and $^{18}$Ne ions was conceptually proposed and partly experimentally verified [8].

Here, we discuss the replacement or combination of the stable light ions used in hadrontherapy – such as $^{12}$C or exploratory ions presently under investigation – with PET emitters of the same chemical element, as tested at NIRS. This feature enables an important new functionality for such treatments: it allows monitoring the exact profile and dose of the irradiation protocol, by in-situ or immediate post-treatmentPET/CT or PET/MRI imaging. This becomes today within reach at CERN, thanks to the recent progresses made for the production of $^{11}$CO$^+$ ion beams [9] and thanks to proven post-acceleration of pure $^{10}$C$^{3+}$ beams in the REX-ISOLDE Linac [10].

2 ISOL accelerated radioactive ion beams facilities for fundamental studies

Isotope production and post-acceleration at operating ISOL facilities presently span a range of different approaches. The SPIRAL facility in GANIL in France uses two Cyclotrons CSS1&2 in series to accelerate stable ion beams that are delivered and fragmented onto a graphite target, part of so-called target and ion source units (Ensemble Cible-Source or ECS, in French), in a shielded cave shown in Fig. 1. The produced isotopes diffuse into an ECR ion source, are ionized, extracted at 10 to 30 keV, mass-separated and injected into the CIME cyclotron [11]. Typical $10^8$ $^{15}$O$^+$ /s are produced with 5% target extraction and ionization efficiency, and are post-accelerated in the CIME cyclotron with 10-20% efficiencies leading to 1-2 $10^7$ $^{15}$O$^+$ /s at 1-20 MeV/n [12]. $^{11}$C radioactive ion beams are not available because the adopted graphite production target does not release the produced chemically identical $^{11}$C isotopes. Despite this, recent investigations of the CO and CO$_2$ molecules ionization and charge breeding efficiencies have recently been undertaken. These molecular forms are particularly useful for C ion beam formation, since they are chemically inert and volatile at room temperature. Ionization and charge breeding efficiencies from 2 to 10% were obtained for charge states of 2-4 [13].
The production and acceleration scheme at LISOL at the CRC, Louvain-La-Neuve, followed a similar approach up until it shut down in 2010. A proton or light ion beam, i.e. $^3$He, was produced in the Cyclone 30 cyclotron, impinged onto a target connected to an ECR source, further mass-separated and post-accelerated in a second Cyclone 44 cyclotron, as shown on Fig. 2. $^{15}$O$^{2+}$ beams where produced with 300 µA, 30 MeV protons onto LiF solid powder targets, 7 $\times$ 10$^{11}$ pps were extracted from the target with 25% efficiencies, and 3.5 $\times$ 10$^9$ $^{15}$O$^{2+}$/s low energy beams produced from the ECR source. A post-accelerated beam of 6 $\times$ 10$^7$ $^{15}$O$^{2+}$/s at 10-29 MeV could be delivered, as well as 1 $\times$ 10$^7$ $^{11}$C$^+$ at 6-10 MeV [4].

A different production and post-acceleration scheme has successfully been introduced and used at CERN-ISOLDE, where the REX-ISOLDE Linac post-accelerator can essentially accelerate all the available low energy radioactive ion beams from ISOLDE up to 3MeV/n, and after the ongoing HIE-ISOLDE upgrade, to 5.5-10 MeV/n, with overall efficiencies of 1 to 20 %. The scheme is based on a 1+→ n+ charge breeding of the 30-60 keV low energy beams from the ISOLDE mass spectrometers before post-acceleration in a short Linac. This is done with a trapping/bunching/breeding platform that combines a Penning Trap (REX-Trap), an electron beam ion source (REX-EBIS), a high voltage platform and a mass separator before injection in the REX-ISOLDE Linac, as shown on Figure 3. REX-ISOLDE has already been used to accelerate $^{10}$C radioactive ion beams. The low-energy charge breeding, molecular break-up and C$^{3+}$ and C$^{4+}$ Linac injection efficiencies were measured at 8.6% with
$^{13}$CO$^+$ ion beam from ISOLDE. Moderate pulse intensities of $2 \times 10^7$ $^{13}$C$^{3+}$ were produced. Typically 50 Hz, 30 $\mu$s pulse characteristics are used. **REX-EBIS** has already reached $6 \times 10^8$ Li$^+$ pulse intensities, approaching the space charge limitations of REX-TRAP, showing no limitations in delivering up to $10^{10}$ ions/s. Other **EBIS** sources have reached even higher intensities, that is $3 \times 10^9$ Au$^{32+}$/pulse at BNL [9]. The present REX-Linac routinely reaches 80-90% transmission efficiencies.

**Fig. 2:** Layout of the LISOL facility in CRC-Louvain La Neuve before its shutdown in 2010 [4].
Fig. 3: Layout of the CERN-ISOLDE facility, including the REX-ISOLDE Linac (top) and details of the layout of the REX-ISOLDE layout until 2012 [14].

A further scheme of post-acceleration has recently been proposed at ISAC2 at TRIUMF, in which the mass separated low energy ion beams are charge-bred into an ECRIS breeder, before injection in a superconducting Linac [15]. However at the moment large beam contaminants coming from the rest gas and insufficient further mass selection and purification has prevented its use for an extensive physics program.

3 Hadrontherapy facilities

The layouts and operational parameters of hadrontherapy facilities have been reviewed in different publications [1,2]. We take here an example of a facility under construction, MedAustron. It will provide both proton and carbon beams, in Wiener Neuerstadt in Austria. It is made of several low energy beam lines where ECR ion sources inject the beam at 8 keV/n first into a Linac, up to 7 MeV/n, which is afterwards injected into - and accelerated within - a synchrotron. Different energies for proton and stable $^{12}$C beams are accessible to fulfill the treatment needs. The layout and beam characteristics are shown in Fig. 4 and Table 1, reprinted from Ref [2].
Fig. 4: MedAustron facility layout (top): ion source hall (IH), synchrotron hall (SH) and irradiation rooms (IR); Details of the source and low energy injection beamlines in the Linac (bottom) [2].

Table 1: Main characteristics of the Medaustenon facility [2].

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Synchrotron circumference</td>
<td>77.6 m</td>
</tr>
<tr>
<td>Number of dipoles</td>
<td>16</td>
</tr>
<tr>
<td>Energy range [MeV/n]</td>
<td>$p_e: 60$-$250$ (800)</td>
</tr>
<tr>
<td></td>
<td>$C^{6+}: 120$-$400$</td>
</tr>
<tr>
<td>Max. number of ions per spill</td>
<td>$p_e: 1 \times 10^{10}$</td>
</tr>
<tr>
<td></td>
<td>$C^{6+}: 4 \times 10^8$</td>
</tr>
<tr>
<td>Spill duration</td>
<td>1.0(0.1) - 10 s</td>
</tr>
<tr>
<td>Repetition rate</td>
<td>&lt; 1.0 Hz</td>
</tr>
<tr>
<td>Intensity variation (min:max)</td>
<td>1:100</td>
</tr>
<tr>
<td>Horizontal tune</td>
<td>1.666</td>
</tr>
<tr>
<td>Vertical tune</td>
<td>1.72</td>
</tr>
<tr>
<td>Field size (fixed beam lines)</td>
<td>$200 \times 200$ mm²</td>
</tr>
<tr>
<td>Beam FWHM at IC</td>
<td>4, 6, 8 or 10 mm</td>
</tr>
<tr>
<td>Lateral beam position precision at IC</td>
<td>0.3 mm</td>
</tr>
<tr>
<td>Time to move between spots</td>
<td>&lt; 200 $\mu$s</td>
</tr>
</tbody>
</table>

4 An ISOL accelerator chain suited for hadrontherapy

Before discussing the motivation to use radioactive ions in hadrontherapy centers, let us briefly see if this could in principle be feasible. Looking at the MedAustron layout which accelerates for treatment
protons and $^{12}$C ions, two modifications can be made. A first one is to fit a dedicated extension hosting a PET isotope production medical cyclotron and a pneumatic isotope samples transport system to inject regular $^{13}$CO$_2$ batches in a dedicated ECR sources. The second one is the replacement of one of the injector source branch with a full chain of ISOL isotope beam production and purification elements, and a charge breeding stage, for instance similar to the REX-ISOLDE functional elements. In the following we provide the motivation to use PET isotopes for treatments and a more detailed view of the required isotope production elements.

4.1 PET isotopes, treatment and dosimetry

PET imaging classically refers to diagnostics based on chemicals carrying a radioisotope emitting positrons. The positron, when it disintegrates by collision with an electron, emits 2 photons in opposite directions. The detection of the simultaneous emission of the 2 photons allows mapping an envelop where the emitting radioisotope is localised. Both the energy of the emitted positrons, the isotope half-life, and the type of chemical carrier will drive the choice of the isotopes. Currently, the most used is $^{18}$F, used in FDG as a glucose analog and oxygen metabolism marker. However other isotopes are increasingly used, for instance $^{11}$C or $^{68}$Ga, which can be produced on hospital sites, from generators or with small medical cyclotrons. In Table 2, we provide a non-exhaustive list of light PET radioisotopes.

<table>
<thead>
<tr>
<th>isotope</th>
<th>Half-life [min.]</th>
<th>Mean Energy [MeV]</th>
<th>Range [mm]</th>
<th>Fraction $\beta^+$ [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{11}$C</td>
<td>20</td>
<td>0.39</td>
<td>1.3</td>
<td>99.8</td>
</tr>
<tr>
<td>$^{13}$N</td>
<td>10</td>
<td>0.49</td>
<td>1.8</td>
<td>99.8</td>
</tr>
<tr>
<td>$^{15}$O</td>
<td>2.0</td>
<td>0.74</td>
<td>3.2</td>
<td>99.9</td>
</tr>
<tr>
<td>$^{18}$F</td>
<td>110</td>
<td>0.25</td>
<td>0.7</td>
<td>96.7</td>
</tr>
<tr>
<td>$^{44}$Sc</td>
<td>235</td>
<td>0.63</td>
<td>2.5</td>
<td>94.3</td>
</tr>
<tr>
<td>$^{64}$Cu</td>
<td>762</td>
<td>0.28</td>
<td>0.8</td>
<td>17.6</td>
</tr>
<tr>
<td>$^{68}$Ga</td>
<td>68</td>
<td>0.83</td>
<td>3.8</td>
<td>89.1</td>
</tr>
</tbody>
</table>

The application of these isotopes for medical imaging is driven by their suitability for production, handling, synthesis of the biomolecule, and of course the proper biofunctional imaging. They are injected in blood vessels, the agent will accumulate in the targeted tissues, and a PET scan will be realised.

Here, we propose to directly use these PET isotopes as ion beams within hadrontherapy protocols to obtain a 3D mapping of the treatment dose, as already investigated at NIRS in Japan. This is done by either a complete replacement of the stable isotope with the radioactive counterpart of the same chemical element if it can be produced at high enough intensities. If the intensity of the PET isotope beam is not high enough, it can be combined with the stable ion beam. This can be done, for instance, by sequences of stable and PET beam irradiations during a single protocol. Interestingly, while activation and contamination are important issues in the operation and maintenance of Radioactive Ion Beam facilities, most of the PET isotopes under consideration present short half-lives and stable decay daughter products. If a significant fraction is lost in specific site of the machine, so-called hot spots, the typical cooling time is a small multiple of their half-lives.

We consider in the present case the treatments by $^{12}$C ions and study the possibility to combine or replace it with $^{11}$C PET ions treatment and dose mapping. Attempts have already been made to use this method by identifying the activity produced by nuclear interaction, named in-beam PET [16]. The in-beam PET approach exploits the properties of protons and Carbon ion beams to produce, i.e. $^{15}$O and $^{11}$C by interaction with H$_2$O comprised in living tissues. Presently, the interpretation is difficult because of the low production rates, the different types of isotopes that contribute to the PET signal,
and the reaction cross-sections that change with the projectile energy when it is stopped in the living tissues as shown on Fig. 5.[16].

![Graphs showing activity and energy deposition in model systems.](image)

**Fig. 5**: Top: In-beam PET activity and energy deposition in model systems [16]. Bottom: Comparison of energy deposition dE/dX for 11/12C implanted ions simulated by Fluka, as proposed here at 210MeV/n and 200MeV/n in soft tissue.

11C and 12C ions have different masses. The 11C beam energy needs to be adapted to obtain a matching stopping profile in the tissue. Corrections of the order of a few percent are required to obtain a Bragg peak position within 1 mm of the reference 12C ion beam. Indeed, there might be a slight mismatch since the electronic and stopping power functions do not adopt simple analytical functions of Z and N parameters. Since the PET imaging resolution in large bodies is of the order of 2 mm, this precision lies within an acceptable range.

Presently, 11C PET imaging is done by injection of biomolecules. Typical activities of 200-700 MBq are used in PET imaging protocols, which corresponds to a total of 2-7 \(10^{11}\) 11C injected isotopes. Of
this amount some fraction only will effectively accumulate in the tissue. In the present case where $^{11}$C isotopes are directly implanted, a localised and lower dose will effectively result from the treatment session, which may correspond to about 1-50 MBq ($10^5$-$5 \times 10^{10}$ implanted ions in a treated volume of several cm$^3$) implanted $^{11}$C ions.

### 4.2 ISOL $^{11}$C PET isotope beam production

A most important point, focus of the present discussion, is the reliable, stable, intense and economically viable production of $^{11}$C ions. Two methods of production can be envisaged. A first one builds up on the methods already extensively developed with compact PET cyclotrons using 10-20 MeV protons. 30 GBq batches can be produced every 30 minutes using $^{14}$N(p,$\alpha$)$^{11}$C reactions in high pressure N$_2$ gas targets [17]. However this can’t be directly connected to typical ion sources for radioactive ion beam production, since the source operating pressure is several orders of magnitude lower, a fraction of mBar, than the required target gas pressure [18]. In PET-compound synthesis modules, the N$_2$ target bulk is released through a selective trapping column which retains the produced $^{11}$CO$_2$. This column can in turn be heated to gradually release the $^{11}$CO$_2$ for injection in the ion source at relevant operating pressures. Continuous $^{11}$CO$_2$ delivery can be obtained by using two extraction ports of a single cyclotron and target modules in a sequential mode. This leads to an average injection rate of $3 \times 10^{10}$ $^{11}$CO$_2$/s in an ECR source used for $^{12}$C beam production. Taking an average 5% ionization efficiency using an ECR ion source, 30% for mass separation, capture and post-acceleration in a Linac, and an overall 20% multi-turn injection and extraction efficiency in the synchrotron, an intensity of $1 \times 10^8$ $^{11}$C ions/pills can be delivered at 1 Hz. This intensity is appropriate for imaging using $^{11}$C as a tracer, in combination with a more intense $^{12}$C ion beam used for treatment, or eventually alone for both imaging and treatment.

A second route has recently been used at CERN-ISOLDE, exploiting spallation reactions $^{19}$F(p,X)$^{11}$C and $^{23}$Na(p,X)$^{11}$C on a molten fluoride target made of a NaF:LiF eutectic and combined with a VADIS 1+ ion source [19]. The pulsed 1.4GeV Proton Synchrotron Booster is of course not a particularly suitable driver for $^{11}$C production. $8 \times 10^8$ $^{11}$CO$^+$/µ$_C$ ISOL beam intensities were produced with an overall 5% extraction and ionization efficiency of the produced isotopes [9]. The driver could for instance be replaced with a more conventional 30 MeV, 1.2 mA proton commercial cyclotron and the target design evolved to cope with the 36kW beam power, a factor 4 higher than the power used on targets operated at the CRC-Louvain-La-Neuve [4]. To reach more interesting in-target production rates, higher proton energies of 70 MeV would lead to $4 \times 10^{11}$/s, that translates into $2 \times 10^{10}$ CO$^+$/s and $2.3 \times 10^8$ $^{11}$C$^6+/spills$ at 1 Hz. This intensity, still slightly lower than the nominal $4 \times 10^8$ requested for MedAustron, is appropriate using $^{11}$C alone for both imaging and treatment. Other drivers can also be envisaged, such as cyclotrons or Linacs with higher energies to better exploit the production cross-section peaking above 200 MeV proton energy [20].

### Table 3: Main Parameters for $^{11}$C ion production

<table>
<thead>
<tr>
<th>Method</th>
<th>Cyclotron (protons)</th>
<th>Target</th>
<th>Reaction</th>
<th>Charge breeding strategy (ion sources)</th>
<th>In-target prod. [pps]</th>
<th>Efficiencies: Ion./post-accel./inj+ej.</th>
<th>$^{11}$C/spills (1Hz)</th>
<th>Refs.</th>
</tr>
</thead>
<tbody>
<tr>
<td>PET prod (batch)</td>
<td>22</td>
<td>N$_2$ (&gt;1 atm)</td>
<td>$^{14}$N(p,$\alpha$)$^{11}$C</td>
<td>ECRIS 0 → n$^+$</td>
<td>$3 \times 10^{10}$</td>
<td>5%/30%/20%</td>
<td>$1 \times 10^8$</td>
<td>13/4/112</td>
</tr>
<tr>
<td>REX-ISOLODE (ISOL)</td>
<td>70</td>
<td>NaF-LiF eutect.</td>
<td>$^{19}$F(p,2$\alpha$)$^{11}$C</td>
<td>VADIS +EBIS 1+ → n$^+$</td>
<td>$4 \times 10^{11}$</td>
<td>5%/8%/20%</td>
<td>$2.3 \times 10^8$</td>
<td>9/10/2</td>
</tr>
</tbody>
</table>
4.3 Other accelerator components for injection in the hadrontherapy Linac

The layout of the low energy part of the accelerator chain before injecting in the Linac will adopt a scheme similar to what has been successfully operated in the existing ISOL facilities or used to inject stable $^{12}$C ions in hadrontherapy facilities. If neutral $^{11}\text{CO}_2$ molecules are directly injected in an ECR source [13], mass separation, beam cooling is required prior to injecting in the Linac. The quality and versatility of the $\mathbf{1+\to n+}$ charge breeding and beam injection scheme has been demonstrated at REX-ISOLDE. Comparison of the cost, efficiencies, maintenance and operational requirements will likely be the driver for suitable technical solutions.

5 Outlook

We have discussed here the possible use PET isotopes in hadrontherapy centers to complete or replace treatments with stable ions. It would present the advantage to precisely map by PET–scan the deposited ion pattern in the tissues. While more work is required to precisely define a technical and cost-effective solution, already part of the required components are operational in Radioactive Beam facilities or at commercial medical PET cyclotrons. Tests have already been done at NIRS on the feasibility of this approach. Future tests could take place to qualify some of the technical choices, for instance within the forthcoming CERN-MEDICIS and HIE-ISOLDE facilities.

Finally, very prospective lines of investigation could lie in the exploration of production and post-acceleration of other PET isotopes, and even of radioisotopes that could combine treatment by ion implantation and subsequent radioactive decay.

6 Acknowledgements

We wish to thank L. Penescu and A. Fabich for input on the baseline efficiencies of the Medaustron facility; We wish to thank F. Wenander and K. Noda-san for making us aware of previous tests done on treatment and imaging done with post accelerated $^{11}$C ions, as well as discussions with A. Ferrari. Finally, we thank U. Amaldi for fruitful exchanges on possible future routes in this direction.

7 Abbreviations

**RIB**: Radioactive Ion Beams

**ISOL**: Isotope mass separation online, first introduced at the Niels Bohr Institute, and today used to produce Radioactive Ion Beam in different Laboratories across the world, for instance at CERN-ISOLDE. The second complementary technique is the so-called in-flight fragmentation technique, such as FAIR at GSI.

**EBIS**: Electron Beam Ion Source

**ECRIS**: Electron Cyclotron Resonance Ion Source

**REX-ISOLDE**: Reacceleration Experiment: Linac post-accelerator for RIBs at CERN-ISOLDE, that comprises a low-energy stage for low energy beam cooling REX-Trap, a charge-breeder REX-EBIS, a pulsed high voltage platform for ion injection at a defined speed in the Linac RFQ. HIE-ISOLDE oversees the upgrade of the post-accelerator with superconductive cavities.

**PET**: Positron Emission tomography, a medical imaging technique which exploits the positron emission of radioisotopes and subsequent photons from the positron-electron annihilation in living tissues. The most used PET agent today is FDG, exploiting $^{18}\text{F}$ produced in small commercial cyclotrons.
**PET-CT** scanner: medical imaging device in which a functional imaging obtained by **PET** is combined with conventional X-ray Computed Tomography for precise localisation.

**VADIS**: Versatile Arc Discharge Ion Source, efficient Forced Electron Beam Induced Arc Discharge (FEBIAD) type ion source.

### References


