RESEARCH

Generation of radio nuclides [^{64}Cu, ^{62}Cu, ^{18}F, ^{11}C] through the giant dipole mechanism

Yogendra N Srivastava[1*†], John Swain[1†], Allan Widom[1†], Georges de Montmollin[2†], Pierre-Alain Tercier[3†], Olivier Pisaturo[3†] and Fréderic Miéville[3†]

*Correspondence: yogendra.srivastava@gmail.com
[1] Physics Department, Northeastern University, 112 Dana Research Building, 02115, Boston, MASS, USA
Full list of author information is available at the end of the article
†Equal contributor

Abstract

1 Background

We describe the generation of radio nuclides -needed for imaging and treatment in nuclear medicine- through the giant dipole mechanism and electro-strong interactions.

2 Method

Electron accelerators routinely available in radiation oncology departments when suitably modified can be used for this purpose. The method is applied to the particularly important case of (i) Copper radio nuclides(RI) [^{62}Cu, ^{64}Cu] that are of interest both for imaging and cancer treatment, as well as (ii) for the production of the imaging RI ^{18}F and ^{11}C together.

3 Results

Experimental data that show the feasibility of the scheme are presented here through the production of radio nuclides [^{62}Cu & ^{64}Cu] when a sample of pure Copper was irradiated by a beam of 22 MeV electrons from the accelerator facility in the radiation oncology department of the Swiss Fribourg hospital. Firm evidence of RI production is provided through the measurements of the radiation from the two Copper RI and the two measured life-times are within 2% of their expected values. Also presented -to our knowledge for the first time- are experimental results about the production of the much sought after RI ^{18}F along with another ^{11}C in one shot, through a non-cyclotron or a nuclear reactor source.

4 Conclusion

Our results confirm the hypothesis that upon suitable modifications, electron accelerators available at medical radiation oncology centers, can indeed be used to produce *the required amounts* of radio nuclei *in situ* locally, *when needed*. It should reduce the cost of production as well as that of transport and at the same time avoid the use of nuclear reactors [or cyclotrons] that (may) suffer from the production of unwanted nuclear waste. For the future, a scaled up RI production through high intensity electron machines can allow us to develop a novel strategy: pinpoint a tumor through an RI with a chelated material accompanying it to fight the tumor -in real time- with less cumbersome biological assays.

Keywords: gdr;e-s;imaging;RI

Content

A brief outline of the subject matter of this paper.

5 Introduction

The Canadian particle accelerator centre TRIUMF produces about half of the world's medical radionuclides. This activity is aptly summarized by its nuclear medicine team: *Radionuclide production is indeed true alchemy, that is, converting the atoms of one element into those of another*[1]. TRIUMF has also been trying to channel the means of such nuclear transmutations and production of medical nuclides towards particle accelerators (protons, electrons), away from their traditional sources of production viz. nuclear reactors so as to avoid the well known perils of the latter [2].

Quite independently, there have been studies of nuclear transmutations triggered by *smart materials* (such as, piezo-electrics, ferro-magnetics) under severe stress [3],[4],[5],[6],[7],[8], and of pyro-electrics undergoing changes in temperature [9],[10]. The underlying *electro-strong* (ES) theory describing phenomena for materials under stress is based on the well known giant dipole resonances (GDR) that is briefly described in Sec. (5.1). In Sec. (6.1), we apply the formalism towards the production of the radionuclide ^{64}Cu, that is useful both for imaging as well as for treatment of cancer. Needless to say that the method is applicable to other nuclei and is not limited to Cu such as production of the highly useful nuclides ^{18}F & ^{11}C that we discuss later in Sec. (6.5). While the above appears eminently satisfactory, there remains the practical and economically burdensome problem of separating the wanted isotope say ^{64}Cu from the overwhelming background of the original Copper (^{63}Cu,^{65}Cu). A simple alternative method is described in Sec. (6.4) that obviates this problem and conveniently removes a possible obstacle against the proposed method.

In Sec. (7), we describe extensive experimental results about the production of Copper radionuclides ^{62}Cu, ^{64}Cu; Fluorine ^{18}F and Carbon ^{11}C obtained by the medical physics group at Fribourg hospital in Switzerland using their 22 MeV electron accelerator. Clear evidence is found for the production of ^{62}Cu and ^{64}Cu through their radioactive decays that agree with the theoretical predictions. Analogous results are presented for the production of both ^{18}F and ^{11}C together from the same target.

Sec. (8) closes the paper with some concluding remarks along with a few words about the prospects for the future.

5.1 GDR and *electro-strong* theory

Photo- and electro-disintegration techniques have been traditionally used for studying giant dipole resonances and through them nuclear structure. More recently,

through laser and *smart* material devices, electrons have been accelerated in condensed matter systems up to several tens of MeV. The possibility of inducing electro-disintegration of nuclei through such devices has been explored in [3],[4],[5],[6]. It involves a synthesis of electromagnetic and strong forces in condensed matter via giant dipole resonances to give an effective *electro-strong interaction* - a large coupling of electromagnetic and strong interactions- in the tens of MeV range. For a discussion of processes induced by electro-weak reactions, see,[11],[12]. Applications of both electro-weak and electro-strong processes can be found in two recent papers[13],[14].

In the present work, we consider nuclear transmutation experiments that utilize electro-strong interaction processes induced by the synthesis of electro-magnetic (EM) & strong forces, for the production of radio isotopes (RI) needed for nuclear medicine. If the effective electron flux lies within $10^{(12\div 15)}$/sec., then the expected rate of RI production would be $10^{(10\div 13)}$/sec., corresponding to an RI activity around $(0.05 \div 50)\ GBq/mg$. See, [15] for further details.

Over several decades, virtual photons from electron scattering as well as Bremsstrahlung photons have been routinely used to cause nuclear photo-disintegration via the generation of giant dipole resonances (GDR) in the intermediate state. The reactions studied extensively are with production of one or two neutrons such as

$$\begin{aligned} A + \tilde{\gamma} &\rightarrow\ n + A^{*} \\ A + \tilde{\gamma} &\rightarrow\ (n+n) + A^{**} \end{aligned} \tag{1}$$

where $\tilde{\gamma}$ is the virtual photon from electron scattering and the final nuclei A^{*} stand for the disintegration product collectively. Of course, their counterpart nuclear breakup reactions $A(\gamma, n)A^{*}$ and $A(\gamma, nn)A^{**}$ from real Bremsstrahlung photons (γ) have also been of continued interest and study. Typically, GDR's are in the $(10 \div 20))$ MeV range for heavy nuclei and $(15 \div 25)$ MeV for light nuclei. Detailed compendia of such data exist[16] given their importance for a variety of practical applications.

In the above mentioned type of accelerator experiments, it is rather hard to study directly the final nuclei produced A^{*}, A^{**} given their very low velocity and hence an exceedingly low probability for their escape. The object here is complementary, that is the development of detailed & systematic chemical procedures establishing the nature of the final nuclei produced. GDR induced neutron production probabilities from a variety of materials are quite high in the range of $(10^{-3} \div 10^{-2})$ per electron on thick targets.

Fission is often only considered for nuclei heavier than iron, which sits at the bottom of the binding energy curve - anything lighter than iron needs energy to be supplied to get it to split into lighter nuclei. Very little seems to have been done by way of analysing the decay products of GDR-excited nuclei other than to count the neutrons released. At higher energies (1.5 GeV and over) one sees a wide variety of decay products[17] but if one just has enough energy to excite the GDR, there seems to be little known.

Now if tens of MeV are present in simple condensed matter systems, and with the giant dipole resonances available, endothermic fission reactions may be more

interesting and more common than has been typically thought. Looking for new elements or new isotopes not present originally would indicate the occurrence of nuclear reactions in addition to the simple detection of neutrons (many of which may be too slow to make it to detectors, but which could reveal themselves through transmutations). We emphasize that since the processes considered here, unlike earlier electroweak low energy nuclear reactions, are not suppressed by the Fermi constant, the scale at which transmutations occur could be very large - on the order of 10^{-3} or more per energetic electron as discussed above.

Of course, one can also expect increased rates for exothermic fission reactions, such as increased rates of spontaneous nuclear fission processes. Whatever nuclei are produced, they may in turn undergo further reactions such as decays (weak or strong, or through emission of gamma rays) and may absorb neutrons such as those produced in the initial GDR decay. These might be revealed via chemical means, or via neutron activation, electron microscopy elemental analysis, X-ray fluorescence, or other techniques. The central point here is that if electrons are accelerated to tens of MeV in condensed matter systems, then one expects both endothermic and exothermic nuclear fission processes as well as the appearance of new nuclei due to further reactions of the decay products including further decays and/or the absorption of produced neutrons.

After the generic discussion of GDR and ES interactions presented in this section, we turn in the next section to (two) explicit examples where a photon of a definite energy impinges on a specific material to produce a particular radio nuclide along with the production of a low energy neutron.

6 Method

Below we describe two different methods for the generation of radio isotopes.

6.1 GDR method I for ^{64}Cu,^{62}Cu production

As shown below, ^{63}Cu and ^{65}Cu are the two naturally occurring stable isotopes of Copper and the short half-life isotope ^{64}Cu is one of the radio-isotopes wanted in nuclear medicine both for imaging and for treatment of cancer, due to its decays both via β^+ and β^- modes and producing benign elements such as Nickel and Zinc.

$$\begin{aligned}
(1)^{63}Cu : \textbf{Stable} : \text{natural concentration} = 69.15\%; \\
Z = 29;\ N = 34; J^P = 3/2^-; \\
(2)^{65}Cu : \textbf{Stable} : \text{natural concentration} = 30.85\%; \\
Z = 29;\ N = 36; J^P = 3/2^-; \\
(3)^{64}Cu : \textbf{Unstable}; \text{Half} - \text{life} = 12.7\ hours; \\
N = 35; J^P = 1^+; \\
\text{decays via } (i)\beta^+ \text{ (positron) (61\%) into } {}^{64}Ni; \\
(ii)\beta^- \text{ (electron) (39\%) into} {}^{64}Zn.
\end{aligned} \tag{2}$$

6.2 Production of RI ^{64}Cu via GDR:

Our proposed method I for producing this RI using an electron machine via one-photon exchange GDR process producing a single neutron is schematically as fol-

lows:

$$\begin{aligned} e(p_1;s_1) \rightarrow e(p_2;s_2) + \gamma^*(E_\gamma;k_\gamma); \\ E_\gamma = (E_1 - E_2);\ k_\gamma = |\mathbf{p}_1 - \mathbf{p}_2| \\ \gamma^* + {}^{65}Cu \rightarrow \left({}^{65}Cu\right)^* \rightarrow {}^{64}Cu + n; \end{aligned} \tag{3}$$

- 1. Clearly, only the stable $A = 65$ Copper (and not the other, more than twice more abundant $A = 63$ Copper) can produce the wanted radio isotope $A = 64$ along with a single neutron.
- 2. Spin parity considerations seem to favour this channel. The initial nuclear ground state of ${}^{65}Cu$ has $J^P = 3/2^-$ and the initial photon has $J^P = 1^-$. The final state nuclear ground state ${}^{64}Cu$ has $J^P = 1^+$ and the final neutron has $J^P = 1/2^+$.
- 3. According to the compilation of GDR cross-sections on nuclei[16], the parameters for the required process are as follows

$$\begin{aligned} \gamma^* + {}^{65}Cu \rightarrow \left({}^{65}Cu\right)^* \rightarrow {}^{64}Cu + n; \\ \text{Peak photon energy } E_\gamma(peak) \sim 18\ MeV; \\ \text{Cross} - \text{section at the peak :} \\ \sigma_{(max)} \sim 150\ \text{milli} - \text{barns}. \end{aligned} \tag{4}$$

  Of course, the above cross-section should be multiplied by 0.3 for the *measurable* cross-section since a given piece of Copper has only 30% of ${}^{65}Cu$ in it. Thus, approximately 45 milli-barns may be expected as the peak cross-section for producing ${}^{64}Cu$ nucleus.
- 4. Very useful estimates of the number of neutrons produced per electron in the initial electron-energy interval of interest here $(10 \div 20)$ MeV can be found in [18]. Roughly speaking, for a Copper target of thickness between $(1 \div 4)$ radiation lengths [corresponding to the material thickness $(13 \div 53)\ gm./cm^2$], the number of neutrons/electron ranges between $(2 \div 7)\ \times 10^{-4}$ for an incident electron energy ~ 20 MeV. To within a factor of two, we should expect the same ratio for the number of ${}^{64}Cu$ produced per electron of about 20 MeV.

6.3 **Production of RI ${}^{62}Cu$ via GDR:**

There is also a shorter lived radio isotope of Copper ${}^{62}Cu$ that can be GDR produced along with a neutron by ${}^{63}Cu$:

$$\begin{aligned} {}^{62}Cu : \textbf{Unstable};\ \text{Half} - \text{life} = 9.67\ minutes; \\ Z = 29; N = 33; J^P = 1^+; \\ \text{decays via } \beta^+ \text{ (positron) } into\ {}^{62}Ni; \\ \text{with emission energy } E = 1315\ KeV. \end{aligned} \tag{5}$$

Its [98% decay] into positrons renders this RI as an excellent candidate for imaging and relabeling of molecules, whereas its almost total disappearance within less than an hour, renders Cu^{62} of less practical and more restricted use for treatment than Cu^{64} [19].

6.4 GDR method II for ^{64}Cu,^{62}Cu production

The objective here is to find stable isotopes of an element with a certain charge (Z_{parent}) that can - always through the GDR mechanism- produce the sought for radio nuclide(s) of charge ($Z_{daughter} \neq Z_{parent}$) different from that of the parent nucleus. Of course, since $\Delta Z \neq 0$, the rest of the final state would have to have a non-vanishing charge and thus cannot be a single neutron. While this implies a reduction in the nuclide production cross-section, it has the distinct advantage that expensive isotope separations would not be required. With suitable amounts of extra parent material, higher electron luminosity and increased bombardment time, the problem of reduction in the cross-section can be largely circumvented.

Let us apply the above towards producing Copper radio nuclides (charge $Z = 29$) through the bombardment of a parent nucleus Zinc (charge $Z = 30$). There are the following 4 stable isotopes of Zinc of relevance here:

$$\begin{aligned}
(i)^{64}Zn: &\quad \text{natural concentration } = 49.2\%;\\
(ii)^{66}Zn: &\quad \text{natural concentration } = 27.7\%;\\
(iii)^{67}Zn: &\quad \text{natural concentration } = 4\%;\\
(iv)^{68}Zn: &\quad \text{natural concentration } = 18.5\%.
\end{aligned}$$

For the purpose at hand, let us consider the following GDR-induced final state reactions.

$$\gamma^* + {}^{68}_{30}Zn \rightarrow p + {}^{67}_{29}Cu; \tag{6}$$
$$\gamma^* + {}^{66}_{30}Zn \rightarrow d + {}^{64}_{29}Cu; \tag{7}$$
$$\gamma^* + {}^{66}_{30}Zn \rightarrow n + p + {}^{64}_{29}Cu; \tag{8}$$
$$\gamma^* + {}^{64}_{30}Zn \rightarrow d + {}^{62}_{29}Cu; \tag{9}$$
$$\gamma^* + {}^{64}_{30}Zn \rightarrow n + p + {}^{62}_{29}Cu. \tag{10}$$

In [20], the production of the nuclide ^{67}Cu through the proton mode as well as the production of nuclides ^{64}Cu and ^{62}Cu, via both the deuteron and the (np) modes have been measured. They find that the deuteron production in the threshold region is anomalously "large". At 22 MeV, the production cross-section for the nuclide ^{67}Cu from Zinc [Eq.(6)] is 18 milli-barns[16]. On the other hand, at similar energies, the peak production cross-sections for the nuclides ^{64}Cu,^{62}Cu through the d and (np) modes, are about 3 milli-barns, a factor of about six smaller. However, folding in the natural concentrations of the various Zinc isotopes, the effective production cross-sections of ^{67}Cu:^{64}Cu:^{62}Cu should be roughly (3.33:0.83:1.48) milli-barns respectively. For proton associated photo-production of ^{67}Cu, see [21].

A chemical separation of the produced Copper nuclides from Zinc was already performed in [20] quite successfully. The details can be found in Appendix of [20].

Presently, more modern chemical methods can be employed for this purpose[22], [23].

6.5 Simultaneous electro-production of ^{18}F & ^{11}C radio-nuclides

As a proof of concept experiment for the production of another much sought after tracer radio nuclide, we chose to investigate the production of ^{18}F using an electron accelerator (and as we shall see in the following, we use a solid target in contrast to an aqueous solution used routinely). In the detailed review [23] published by IAEA [International Atomic Energy Agency, Vienna, Austria], regarding the medical applications of radio nuclides, it is stated that the present medical *demand for* ^{18}F *far exceeds its availability*. Thus, it is definitely worthwhile to experiment with alternative methods -such as the one presented here- for its production specially since we can produce it in tandem with another medically important radio isotope ^{11}C. So far as we are aware the particular method described here has not been attempted before.

Let us recall some well-known facts about stable fluorine and its one isotope relevant for medicine:

$$\begin{aligned}
&(1)^{19}F : \textbf{Stable} : \text{natural concentration} = 100\%; \\
&\qquad\qquad Z = 9;\ N = 10; J^P = 1/2^+; \\
&(2)^{18}F : \textbf{Unstable}; \text{Half} - \text{life} = 109.74\ minutes; \\
&\qquad\qquad Z = 9; N = 9; J^P = 1^+; \\
&\text{decays via } (i)\beta^+ \text{ (positron) } (96.9\%) \text{ into } {}^{18}O; \\
&\qquad (ii)\text{electron capture } (3.14\%) \text{ into} {}^{18}O.
\end{aligned} \tag{11}$$

Due to its fast decay rate, the "shelf life" of ^{18}F -limited to two half-lives- is only about 4 hours and distribution of such radio isotopes presents logistical problems. It is for this reason that IAEA[23] recommended establishment of centralized production facilities. This 2009-report also noted [*vedi* Sec.(8.2)[23]]:

the possibility of large scale production of radio isotopes from photons seemed very unlikely a decade ago, while now that possibility seems, at least at the proof-of-concept level, highly probable.

Given the technical advances made in the decade after the above report was published, it is our proposal to establish and equip radiation oncology departments towards *in situ* production of short-lived radio nuclides employing their in-house electron accelerators (suitably modified for this purpose).

^{18}F production mechanisms used in the past have been reviewed in [24, 25, 26]. The two major nuclear reaction processes invoked for this purpose are

$$\begin{aligned}
&(i)\ \ p + {}^{18}O \rightarrow n + {}^{18}F;\ [\text{incident proton energy } (11 \div 17)\ MeV] \\
&(ii)\ \ d + {}^{20}Ne \rightarrow \alpha + {}^{18}F;\ [\text{incident deuteron energy } (8 \div 14)\ MeV]
\end{aligned} \tag{12}$$

While the proton-initiated process has a larger cross-section, it requires "enriched" water ($H_2{}^{18}$O), that is cumbersome (and expensive) as the latter constitutes only

(approximately) 2% of ordinary water ($H_2{}^{16}$O). Also, as noted by Cole *et al* [26], fluorine in the aqueous state generated via process (i) must be de-solvated & activated by treatment with a chelator [Kryptofix 2.2.2] to bind the potassium and "free" the fluoride ions for direct nucleophilic labeling reactions. Process (ii) on the other hand, produces $[^{18}\mathrm{F}]\mathrm{F}_2$ that can be directly used for electrophilic labeling.

It should also be noted that any hadronic initiated radio nuclide production process (initiated say by a proton or a deuteron beam) can give rise to unwanted radio nuclides if the target has contamination from heavier materials. For example, Fig.(1) in Hess *et al* in[27], shows production of an undesired radio isotope ^{55}Co (half-life 17.54 hours) due to the presence of iron in their aluminum foil target ($Al_2\ {}^{18}O_3$) that was irradiated by a proton beam.

The GDR process for the production of ^{18}F that we have extensively experimented with and that we are advocating is to irradiate polytetrafluoroethylene $[(C_2F_4)_n]$ -commonly known as Teflon- by an electron beam. There are 2 fluorine atoms for each carbon atom; by weight about 76% fluorine and 24% carbon and the substance is rather light (density = 2.2 gm/cm^3). The chosen target material has the great advantage of not only producing ^{18}F (from the parent ^{19}F) but also ^{11}C from its parent ^{12}C:

$$\begin{aligned} &\gamma^* +^{19} F \rightarrow n +^{18} F; \\ &\gamma^* +^{12} C \rightarrow n +^{11} C. \end{aligned} \tag{13}$$

As both produced radio nuclides are of medical imaging interest, this reaction is unique in this respect and offers a distinct advantage over previous methods.

7 Results

The experiments were performed at the radiation oncology site of the Fribourg Hospital using a medical linear accelerator (TrueBeam 2.7MR2 from Varian).
The setup for the generation of copper radio nuclides was the following:

- A (10×10) cm Copper (Cu) plate of thickness 0.5 mm was placed under a broad electron beam (at 22 MeV).
- The Copper plate was centered in the beam [produced through a (15×15) cm applicator]. The plate was placed at a source-surface distance (SSD) of 100 cm.
- The plate lay on the treatment couch (carbon fiber) to reduce any other contribution to the measured activation.
- A maximum dose rate (1000 Monitor Units / min = 1000 MU/min) was chosen, corresponding to 10 Gy/min at 100 cm SSD.
- Then the Copper target was irradiated for 20 minutes thus totaling $20,000$ MU.
- As soon as the beam was stopped (after $20,000$ MU), the chronometer was started to measure the activity (γ radiation) expected from the production and decays of radio nuclides Cu^{62} and Cu^{64}. The detector employed was a NaI(Tl) 2.0" x 2.0" crystal γ-scintillation detector.

The setup for the generation of RI ^{18}F & ^{11}C using Teflon (C_2F_4) targets was as follows:
Two sets of measurements were made with Teflon. Sample weighing 13.105(10) gms. was irradiated with 10,000 MU of the 22 MeV electron beam. To alleviate excessive intensity of the source and the dead time of our detector, a second sample 2 of Teflon weighing 3.205 gms was irradiated with only 4,000 MU by the same electron beam.
For both Teflon experiments, the technique was to place the target in front of the detector for 24 hours after having stopped the short irradiation. Zero time is the time when the beam stopped. A few minutes later the measurement started taking into account this zero time (starting point of the time scale). The software PRA.exe accumulated all the events with the time of appearance. Thus, after the measurement, it became feasible to analyze the spectrum (from 0 to 4 MeV) by focusing on a single part. Clearly the interesting part for both isotopes ^{11}C and ^{18}F lies in the annihilation peak area (511 keV).
Each Teflon target was irradiated at 1,000 MU/minute under the broad beam of 22 MeV electrons (Applicator 15 × 15). A short time (∼ 2 minutes) later, they were deposed in front of the detector for 24 hours one after the other.
In the following, we present a brief account of the experimental results and their analysis of relevance to the present paper. First a model for the expected production rates of Cu RI are presented followed by its implications for the experimental data.Then, we discuss the observed spectra from ^{11}C & and ^{18}F.

7.1 Theoretical model production rates for Cu RI

Under the hypotheses that

- 1. A copper slab composed of N_o atoms is entirely irradiated by an electron flux rate $\dot{\phi}$ for a time T_{irr};
- 2. The copper slab is uniquely composed of the stable isotopes ^{63}Cu & ^{65}Cu, whose natural abundances are $(1 - f_{65})$ & f_{65} respetively;
- 3. Upon radiation N_{62} atoms of ^{62}Cu & N_{64} atoms of ^{64}Cu are produced via GDR processes

$$\begin{aligned} \gamma +^{65} Cu \rightarrow (^{65}Cu)^* \rightarrow n +^{64} Cu;\ \text{a cross} - \text{section}\ \sigma_{64};\\ \gamma +^{63} Cu \rightarrow (^{63}Cu)^* \rightarrow n +^{62} Cu;\ \text{a cross} - \text{section}\ \sigma_{62}; \end{aligned} \tag{14}$$

- 4. ^{62}Cu decays with a half-life of $\frac{ln2}{\lambda_{62}}$ sec. and ^{64}Cu decays with a half-life of $\frac{ln2}{\lambda_{64}}$ sec.

Under the above hypotheses, we have the following linear rate equations -during irradiation:

$$\begin{aligned} \frac{dN_{65}}{dt} &= -\dot{\phi}\sigma_{64}N_{65};\\ \frac{dN_{64}}{dt} &= \dot{\phi}\sigma_{64}N_{65} - \lambda_{64}N_{64}; \end{aligned} \tag{15}$$

and

$$\begin{aligned} \frac{dN_{63}}{dt} &= -\dot{\phi}\sigma_{62}N_{63}; \\ \frac{dN_{62}}{dt} &= \dot{\phi}\sigma_{62}N_{63} - \lambda_{62}N_{62}. \end{aligned} \tag{16}$$

Their solutions -during the irradiation- are

$$\begin{aligned} N_{65}(t) &= f_{65}N_0 e^{-\dot{\phi}\sigma_{64}t}; \\ N_{64}(t) &= \Big(\frac{\dot{\phi}\sigma_{64}}{\dot{\phi}\sigma_{64} - \lambda_{64}}\Big)(f_{65}N_0)\Big[e^{-\lambda_{64}t} - e^{-\dot{\phi}\sigma_{64}t}\Big]; \end{aligned} \tag{17}$$

and

$$\begin{aligned} N_{63}(t) &= (1 - f_{65})N_0 e^{-\dot{\phi}\sigma_{62}t}; \\ N_{62}(t) &= \Big(\frac{\dot{\phi}\sigma_{62}}{\dot{\phi}\sigma_{62} - \lambda_{62}}\Big)[(1 - f_{65})N_0]\Big[e^{-\lambda_{62}t} - e^{-\dot{\phi}\sigma_{62}t}\Big]. \end{aligned} \tag{18}$$

After the irradiation, the electron flux $\dot{\phi} = 0$ and hence, the populations of RI's vary only due to their radio-active decays. Thus, the solutions for $t > T_{irr}$ simplify to

$$\begin{aligned} N_{65}(t \geq T_{irr}) &= f_{65}N_0 e^{-\dot{\phi}\sigma_{64}T_{irr}}; \\ N_{64}(t > T_{irr}) &= \Big(\frac{\dot{\phi}\sigma_{64}}{\dot{\phi}\sigma_{64} - \lambda_{64}}\Big)(f_{65}N_0)\Big[1 - e^{-(\dot{\phi}\sigma_{64} - \lambda_{64})T_{irr}}\Big]e^{-\lambda_{64}t}; \\ N_{63}(t \geq T_{irr}) &= (1 - f_{65})N_0 e^{-\dot{\phi}\sigma_{62}T_{irr}}; \\ N_{62}(t > T_{irr}) &= \Big(\frac{\dot{\phi}\sigma_{62}}{\dot{\phi}\sigma_{62} - \lambda_{62}}\Big)[(1 - f_{65})N_0]\Big[1 - e^{-(\dot{\phi}\sigma_{62} - \lambda_{62})T_{irr}}\Big]e^{-\lambda_{62}t}. \end{aligned} \tag{19}$$

The activity of the two RI isotopes are obtained upon multiplying their respective numbers (produced) by their decay constants:

$$\begin{aligned} A_{64}(t \leq T_{irr}) &= \Big(\frac{\dot{\phi}\lambda_{64}\sigma_{64}}{\dot{\phi}\sigma_{64} - \lambda_{64}}\Big)(f_{65}N_0)\Big[e^{-\lambda_{64}t} - e^{-\dot{\phi}\sigma_{64}t}\Big]; \\ A_{64}(t \geq T_{irr}) &= \Big(\frac{\dot{\phi}\lambda_{64}\sigma_{64}}{\dot{\phi}\sigma_{64} - \lambda_{64}}\Big)(f_{65}N_0)\Big[1 - e^{-(\dot{\phi}\sigma_{64} - \lambda_{64})T_{irr}}\Big]e^{-\lambda_{64}t}; \end{aligned} \tag{20}$$

and

$$A_{62}(t \leq T_{irr}) = \Big(\frac{\dot{\phi}\lambda_{62}\sigma_{62}}{\dot{\phi}\sigma_{62} - \lambda_{62}}\Big)[(1 - f_{65})N_0]\Big[e^{-\lambda_{62}t} - e^{-\dot{\phi}\sigma_{62}t}\Big];$$

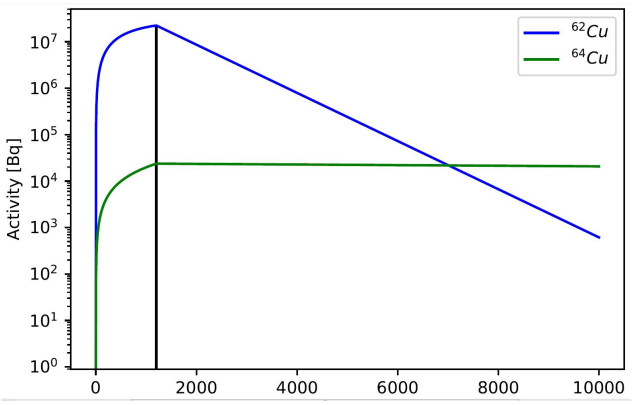

Figure 1 Activity of ^{62}Cu (blue) and ^{64}Cu (green) as a function of time. The black vertical line represents the moment when the electron beam has been switched off.

$$A_{62}(t \geq T_{irr}) = \Big(\frac{\dot{\phi}\lambda_{62}\sigma_{62}}{\dot{\phi}\sigma_{62} - \lambda_{62}}\Big)[(1 - f_{65})N_0]\Big[1 - e^{-(\dot{\phi}\sigma_{62} - \lambda_{62})T_{irr}}\Big]e^{-\lambda_{62}t}. \tag{21}$$

The activities of ^{62}Cu & ^{64}Cu are shown in Fig.(1). Fig.(2) shows the theoretical versus the experimentally measured total activity.

7.2 Comparison with experimental data of CU RI

The parameters employed are as follows.

$$\begin{aligned} N_o &= 4.33 \times 10^{23}; \\ \sigma_{62} = 200\ millibarn; \sigma_{64} &= 20\ millibarn; \\ f_{65} &= 0.3085; \\ \dot{\phi} &= 8.06 \times 10^8/cm^2/sec.; \\ \lambda_{62} = 1.19 \times 10^{-3}/sec.; \lambda_{64} &= 1.52 \times 10^{-5}/sec. \end{aligned} \tag{22}$$

and in view of the geometrical acceptance of the setup, the global sensitivity has been set at 40%.

As can be seen, our theoretical expressions describe the data quite well. The uncertainties associated with the cross-sections[16] as well as a lack of knowledge of the sensitivity of the measurement device helps in fine tuning the theoretical model.

7.3 Measured spectra of ^{18}F and ^{11}C from Teflon

For the generation of ^{18}F and ^{11}C, two samples of Teflon were irradiated by the electron beam as described above. The two measured spectra are shown in Fig.(3) and Fig.(4).

It is clear from Fig.(3) and Fig.(4). that there is a lot of background radiation in the spectra from post-irradiation conditions.

The strategy from previously performed experiments prompted us to concentrate on the region of the annihilation peak and evaluate the time dependency of events

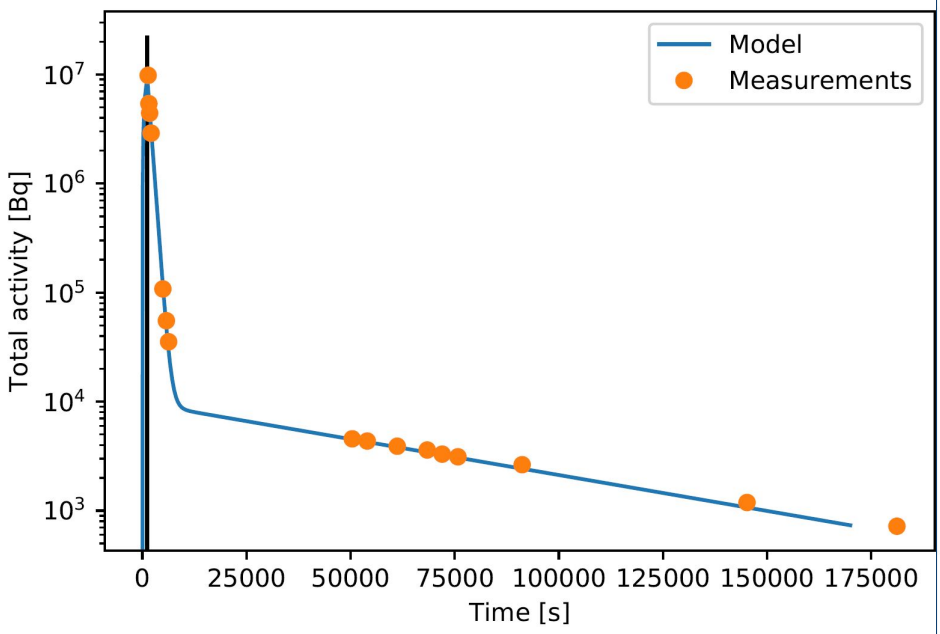

Figure 2 Theoretical vs measured total activity of Cu RI (in Bq) as a function of time.

with in that special portion of the spectrum. The zoomed spectra are presented in Fig.(5) and Fig.(6). The fitted function for the observed activity is

$$Activity(t) = A_o e^{-\lambda_A t} + B_o e^{-\lambda_B t} + \text{background};$$
$$\lambda_A = \frac{ln2}{T_{1/2A}}; \lambda_B = \frac{ln2}{T_{1/2B}}; \tag{23}$$

that includes two different decays (A & B) along with a background.
The effect of dead time -only necessary for the first target- can be taken into account by the following equation:

$$Activity_{deadtime}(t) = Activity(t) e^{-Activity(t)\tau}. \tag{24}$$

The counts of events are plotted for each of those zoomed spectra as well as the fitted decay in Fig.(7) & Fig.(**??**).
The counts (and associated error) during one minute were taken for the whole range of 24 hours and just divided by 60 to get counts per second.

The agreement between the theoretical expressions and the experimental data on Cu, C & F RI bolsters our confidence in the here proposed electro-production method of radio nuclides.
Further details about the experiment and data analysis are available through the corresponding author.

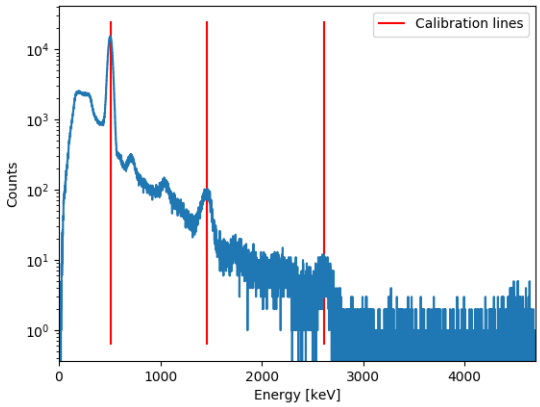

Figure 3 The spectrum of Teflon target number 1 after irradiation. The annihilation peak (511 keV) is very visible

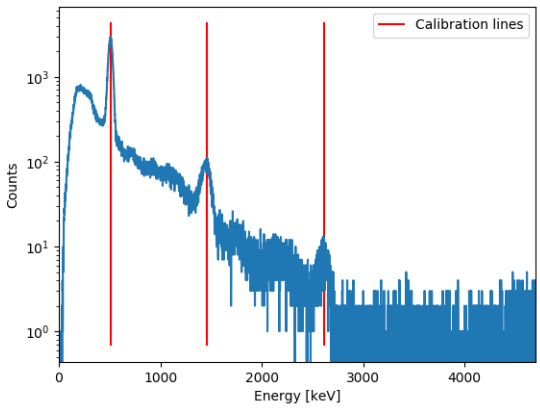

Figure 4 The spectrum of Teflon target number 2 after irradiation. The annihilation peak (511 keV) is again very visible

8 Conclusions and future prospects

We proposed that electron accelerators (in the energy range $15 \div 25$ MeV) that are by now commonly available at medical centres throughout the world be used -rather than nuclear reactors- to locally produce medically needed radio nuclides.
The theoretical basis for the proposal is anchored upon the well studied phenomena of giant dipole resonances in nuclei and that of electro-strong interactions.
We applied the scheme towards the production of radio nuclides ^{64}Cu & ^{62}Cu, along with a neutron, at the electron accelerator running at 22 MeV at the radiation oncology division of the Fribourg Hospital in Switzerland. The experimental data from the bombardment of a Copper slab confirmed production of both Copper radio isotopes in agreement with the theoretical expectations, thus proving the feasibility of the method.
A different method is proposed that avoids a separation of radio isotopes of Copper

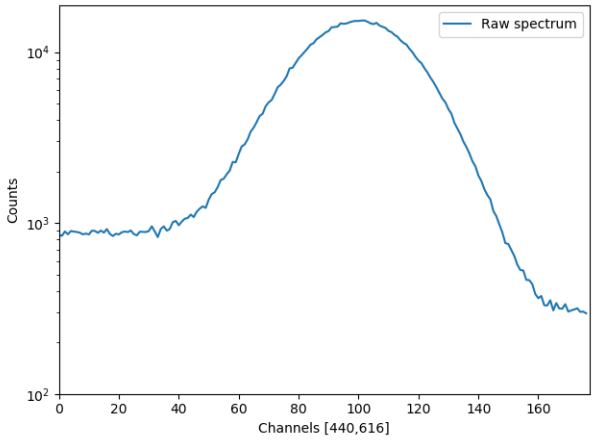

Figure 5 The zoomed spectrum of target number 1 (13.105 g) after irradiation (annihilation peak).

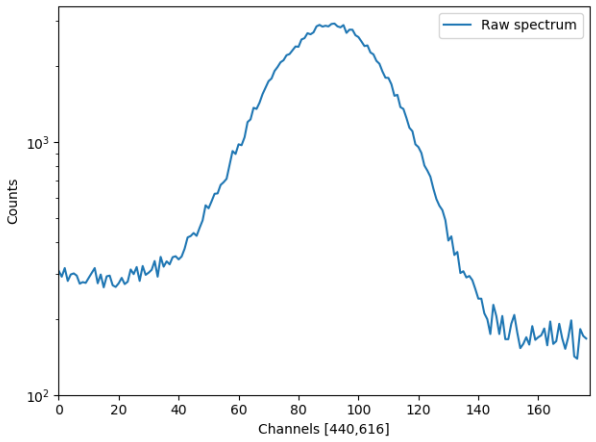

Figure 6 The zoomed spectrum of target number 2 (3.205 g) after irradiation (annihilation peak).

from the large background of stable Copper. It involves using Zinc as the nucleus to be irradiated that can produce -albeit with a reduced probability- various Copper nuclides either accompanied by a proton or with final states of a deuteron or an (np) pair. Thus, the extraction of sought for Copper nuclides from a background of Zinc is reduced to a simpler problem of elemental separation.
We also applied the proposed electron beam method towards the production of ^{11}C & ^{18}F simultaneously using a Teflon target. So far as we are aware, it is the first time that two different medically needed RI have been produced together. Again, the method works as verified by a successful theoretical analysis of the experimental data.

An apparent objection to RI electro-production is that an expensive & cumbersome isotope separation would be required. However, for both Copper and Fluorine possible strategies exist to circumvent it. Let us consider Copper:

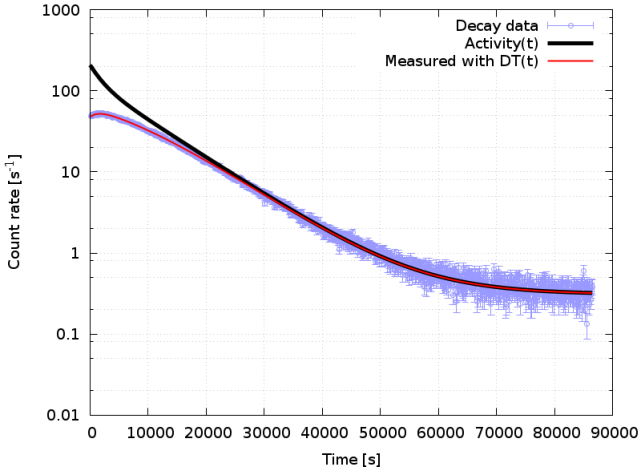

Figure 7 The decay data and a fit to the activity for Teflon sample 1. See text for detail.

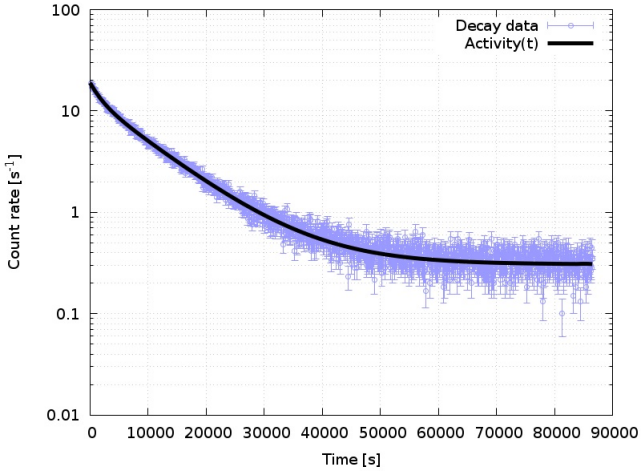

Figure 8 The decay data and a fit to the activity for Teflon sample 2. See text for detail

- 1. humans have $(1.4 \div 2.1)$mg/Kg of Copper in their body;
- 2. Normal human dietary intake is $(0.6 \div 2)$ mg of Cu/day. Thus, a given dose of $[^{62}Cu/^{64}Cu]Cl_2$ solution injected into the body may contain safely up to say 2 mg of normal Cu in $CuCl_2$;
- 3. For imaging purposes, typically $(350 \div 850)$ MBq of radiation is required;
- 4. To produce 1 GigaBq (at production), we need to produce 0.084 nanograms of ^{62}Cu and 6.62 nanograms of ^{64}Cu;
- 5. Thus, to be on the safe side, the electron beam radiation must be strong enough to convert about 3 parts per million of the parent Cu nuclei to deliver 1 GigaBq of ^{64}Cu radiation. The requirement is much less severe (by over a factor of a hundred) for ^{62}Cu.

Can the above be achieved? The answer is yes as shall be shown momentarily by a simple calculation.

There is another apparent objection to extra copper in the body of cancer patients. As is well known, Cu^{+} migrates undesirably into the nucleus of a tumor leading to angiogenesis (formation of new blood cells)[28][29]. However, what was discovered about a decade ago has been well summarized by Wang *et al* [30]:

- 1. Organic chelators of copper can passively reduce cellular copper and serve the role as inhibitors of angiogenesis;
- 2. Moreover, they can also actively attack cellular targets such as proteasome, which plays a critical role in cancer development and survival;
- 3. The discovery of such molecules initially relied on a step by step synthesis followed by biological assays;
- 4. Today high-throughput chemistry and high-throughput screening have significantly expedited the copper binding molecule discovery to turn *cancer-promoting* copper into *anti-cancer* agents [31].

A true blessing in disguise for our proposal: We can use Cu RI for imaging a tumor and properly chelated left-over normal Copper as an anti-tumor agent.

Having established the positive aspect of properly chelated normal copper to accompany the RI copper, let us now return to compute the electro-production rates of these RI $[^{62}Cu/^{64}Cu]$:

Consider a LINAC with a current I. Then, the rate of electron injection into the LINAC would be

$$\dot{N}_e = (\frac{I}{e}) \approx \quad (6 \times 10^{18}/sec) \times (\frac{I}{Amp}) \tag{25}$$

If there is a fraction $[f(t_{rad}) \sim (10^{-4} \div 10^{-3})]$ of neutrons/electron, for a Cu target of radiation thickness t_{rad}, the neutron production rate becomes

$$\dot{N}_n = f(t_{rad}) \times (6 \times 10^{18}/sec) \times (\frac{I}{Amp}). \tag{26}$$

For the electron energy range $[15 \div 22$ MeV] under consideration, there is practically only a single production channel. Thus, Eq.(26) gives the total production rate for $[^{62}Cu$ & $^{64}Cu]$.

Ignoring decays during irradiation, the number of ^{64}Cu produced in a time (ΔT) is given by

$$\begin{aligned} N(64) &= (\Delta T) f_{64}(t_{rad})(6x10^{18}/sec)(I/Amp) \\ Activity(64) &= (\Delta T/hour)[\frac{f_{64}}{10^{-4}}](I/Amp)[4.72 \times 10^{13}]Bq; \end{aligned} \tag{27}$$

and similarly

$$\begin{aligned} N(62) &= (\Delta T) f_{62}(t_{rad})(6 \times 10^{18}/sec)(I/Amp); \\ Activity(62) &= (\Delta T/hour)[\frac{f_{62}}{10^{-4}}](I/Amp)[3.73 \times 10^{15}]Bq \end{aligned} \tag{28}$$

These are very encouraging numbers since:

- 1. A properly designed Copper target (mass < 1 gram) irradiated for one hour in a 1 Mega Watt LINAC can produce about 470 samples of ^{64}Cu of 1 GigaBq dosage each accompanied by about 2 milligram of natural Copper;
- 2. Local production would increase substantially the shelf life of the radio-isotope;
- 3. 1 GigaBq of ^{64}Cu accompanied by 2 milligrams of natural Copper chelated say with disulfiram (DSF) has the attractive property of injecting: an anti cancer agent (DSF)-Cu complex along with its partner ^{64}Cu through its two-photon decay non-invasively signaling -in real time- precisely where the drug went i.e., into the tumor and when.

An exciting possibility for the future indeed.

9 Discussions

As medical facilities are more likely to have an electron accelerator rather than a nuclear reactor as well, we expect that in the future radio nuclides shall be locally produced if and when needed through the GDR mechanism avoiding some of the problems associated with nuclear reactors. It is to be also hoped that producers of medical electron accelerators would in the future bear special attention in their designs to this new venue of nuclear medicine. For instance, an increased electron luminosity, suitably modified photon beam apertures and inclusion of chemical separation kits can surpass the present method over competing schemes.

Declarations:

Ethics approval and consent to participate
Does not apply.

Consent for publication
Does not apply.

Availability of data and material
Further details about the data presented in this paper can be found at the link: http://www.lenr-cities.ch/Radiation.

Competing interests
The authors declare that they have no competing interests.

Funding
Does not apply.

Authors' contributions
JS, YS, AW developed the basic idea and the theory behind the experiments.YS & AW wrote the paper. PT, OP and FM, three members of the Fribourg medical physics group performed the experiments. G de M, CEO of LENR-Cities Suisse, provided support and general supervision of the project.

Acknowledgements
YS would like to thank the Department of Physics and Geology, University of Perugia, Italy for their hospitality.

Author details
[1] Physics Department, Northeastern University, 112 Dana Research Building, 02115, Boston, MASS, USA. [2] LENR-CITIES Suisse Sárl, Rue Charles-Knapp 29, Ch-2000 Neuchatel, Switzerland. [3] Radiation Oncology Department, hôpital fribourgeois, CH-1708 Fribourg CH, Chemin des Pensionnats 2-6, 1752 Villars-sur-Glâne, CH-1708 Fribourg, Switzerland.

References

1. Medical Isotope Production at TRIUMF -from Imaging to Treatment. https://www.triumf.ca
2. Ruth, T.J.: The uses of radiotracers in the life sciences. Rep. Prog. Phys. **72**, 016701 (2009)
3. Swain, J., Widom, A., Srivastava, Y.: Electrostrong nuclear disintegration in condensed matter. arXiv: 1306.5165v1 [nucl-th] (2013)
4. Widom, A., Swain, J., Srivastava, Y.: Neutron production from the fracture of piezoelectric rocks. J. Phys. G. Nucl. Part. Phys. **40**, 015006 (2013)
5. Srivastava, Y.N., $et.\ al.$: Induction of nuclear reactions through piezo-electrics and other means. Key Engineering Materials **543**, 68 (2013)
6. Widom, A., Swain, J., Srivastava, Y.N.: Photodisintegration of the iron nucleus in fractured magnetite rocks with magnetostriction. Meccanica **50**, 1205 (2015)
7. Carpinteri, A., Lacidogna, G., Manuello, A. (eds.): Acoustic, Electromagnetic, Neutron Emissions from Fracture and Earthquakes. Springer, ??? (2015)
8. Carpinteri, A., Borla, O.: Fracto-emissions as seismic precursors. Engineering Fracture Mechanics **177**, 230 (2017)
9. Naranjo, B., Gimzewski, J., Putterman, S.: Observation of nuclear fusion driven by a pyro-electric crystal. Nature (London) **434**, 1115 (2005)
10. Geuther, J., Danon, Y., Saglime, F.: Nuclear reactions initiated by a pyro-electric accelerator. Phys. Rev. Lett. **96**, 054803 (2006)
11. Cirillo, D., Widom, A., Srivastava, Y., Swain, J., $et.\ al.$: Experimental evidence of a neutron flux generation in a plasma discharge electrolytic cell. Key Engineering Materials **495**, 104 (2012)
12. Cirillo, D., Widom, A., Srivastava, Y., Swain, J., $et.\ al.$: Water plasma modes and nuclear transmutations on the metallic cathode of a plasma discharge in an electrolytic cell. Key Engineering Materials **495**, 124 (2012)
13. Widom, A., Srivastava, Y.N., Swain, J., de Montmollin, G., Rosselli, L.: Reaction products from electrode fracture and coulomb explosions in batteries. Engineering Fracture Mechanics **184**, 88–100 (2017)
14. Widom, A., Srivastava, Y.N., Swain, J., de Montmollin, G.: Tensile and explosive properties of current carrying wires. Engineering Fracture Mechanics **197**, 114 (2018)
15. Ejiri, H., Daté, S.: Coherent photo-nuclear reactions for isotope transmutation. arXiv: 1102.4451 (2011)
16. Varlamov, A., Varlamov, V., Rudenko, D., Stepanov, M.: Atlas of giant dipole resonances, parameters and graphs of photonuclear reaction cross-sections. INDC(NDS)-394 (1999)
17. Fulmer, C.B.: Photo-nuclear reactions in iron and aluminum bombarded with high energy electrons. Phys. Rev. **C2**, 1371 (1970)
18. Barber, W., George, W.: Neutron yields from targets bombarded by electrons. Phys. Rev. **116**, 1551 (1951)
19. Evangelista, L., Luigi, M., Cascini, G.: New issues for copper-64: from precursor to innovative pet tracers in clinical oncology. Current Radiopharmaceuticals **6**, 000–000 (2013)
20. Goldemberg, J., Marquez, L.: Measurements of (γ, d) and (γ, np) reactions in the threshold region. Nuclear Physics **7**, 202 (1958)
21. Starovoitova, V., Grimm, T., Cole, P.: Accelerator-based photoproduction of promising beta-emitters cu67 and sc47. J. of Radioanalytical and Nuclear Chemistry **305**, 127 (2015)
22. Dasgupta, A., Mausner, L., Srivastava, S.: A new separation procedure for copper 67 from proton irradiated zinc. Int. J. of Radiation: Applications and Instrumentation. Part A. Applied Radiation and Isotopes **42**, 371 (1991)
23. Cyclotron Produced Radionuclides: Principles and Practice; Technical Reports Series No. 465, Vienna(2009). https://www-pub.iaea.org
24. Jacobson, O., Chen, X.: Pet designated flouride-18 production and chemistry. Curr Top Med Chem. **10**, 1048 (2010)
25. Jacobson, O., Kiesewetter, D.O., Chen, X.: Fluorine-18 radiochemistry, labeling strategies and synthetic routes. Bioconjugate Chem. **26**, 1 (2015)
26. Cole, E.L., Stewart, M.N., Littich, R., Hoareau, R., Scott, P.J.H.: Radiosyntheses using fluorine-18: the art and science of late stage fluorination. Curr Top Med Chem. **14**, 875 (2014)
27. Hess, E., Takács, S., Scholten, B., Tárkányi, F., Coenen, H., Qaim, S.: Excitation function of the ^{18}o(p,n)^{18}f nuclear reaction from threshold up to 30 mev. Radiochim. Acta **89**, 357 (2001)
28. Jullien, A., Gateau, C., Lebrun, C., Kieffer, I., Testemale, D., Delangle, P.: d-penicillamine tripodal derivatives as efficient copper(i) chelators. Inorg. Chem. **53**, 5229 (2014)
29. Tegoni, M., Valensin, D., Toso, L., Remelli, M.: Copper chelators: Chemical properties and bio-medical applications. Curr Med Chem. **21(33)**, 3785 (2014)
30. Wang, F., Jiao, P., Qi, M., Frezza, M., Dou, Q.P., Yan, B.: Turning tumor-promoting copper into an anti-cancer weapon via high-throughput chemistry. Curr Med Chem. **17(25)**, 2685 (2010)
31. Asahi, H., Tolba, M.E.M., Tanabe, M., Sugano, S., Abe, K., Kawamoto, F.: Perturbation of copper homeostasis is instrumental in early developmental arrest of intraerythrocytic plasmodium falciparum. BMC Microbiol. **14**, 167 (2014)

Figures