WORLD COUNCIL ON ISOTOPES
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WORLD COUNCIL ON ISOTOPES
Newsletter

Promotes safe and environmentally sound use of isotope technologies for global wellbeing

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2020 June
Vol.9 – Issue 6

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01.Lead Article

1. Radioisotopes for Nuclear Medicine, beyond the standard 'trio' (^{131}I, ^{99m}Tc, ^{18}F): Impressions from the IAEA event 'ISTR-2019'

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Introduction

The IAEA convened the International Symposium on Trends in Radio pharmaceuticals (ISTR-2019) from October 28 to November 1, 2019 in Vienna. This well-attended event enabled exchanges on many important developments and of new knowledge, as brought out by the rapporteur, while presenting the salient highlights of ISTR-2019 at the concluding session of ISTR-2019 (1). Another presentation on 'Insights into ISTR-2019' at the Annual Conference of the Society of Nuclear Medicine, India (SNMICON-2019) in December 2019 also showcased the select highlights of ISTR-2019.

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The e-book of ISTR-2019 proceedings will be available soon (2). Also, an overview of ISTR-2019 was reported on by Mr. Ira Goldman in the WCI Newsletter earlier this year (3). Apart from this, during 2019, the IAEA supported the World Nuclear University (WNU) in publishing a book on 'Advanced radiation technology', in connection with the 'WNU Radiation Technology School' held in Obninsk in October 2019. This book contains four chapters dealing with the current status of medical isotopes and radiopharmaceuticals (4). The present article is based on an analysis of the discussions at the above events concerning the radioisotopes (RI) for nuclear medicine[2], as they underpin the development and availability of radiopharmaceuticals (RPh) for nuclear medicine (NM) practices. The focus in the article is on the RI products beyond the well-established trio, ^{131}I, (^{99}Mo/)^{99m}Tc and ^{18}F. RPh aspects per se are not covered, except when making needs-based comments in select sections.

RI production sources: research reactors, (medical) cyclotrons, other accelerators

Production of RI for RPh-NM applications is well distributed, currently between research reactors (RR) and 10-30 MeV medical cyclotrons (MC). The impressive growth in the number of MC in operation (over 1200)[3] spread across many regions of the world is the most welcome feature. In addition, a few high-energy (60-70 MeV) cyclotrons (e.g. in France, Italy (project stage), South Africa, USA) and (30-100 MeV) electron accelerators (Linac) are engaged in the production of RI including ^{67}Cu, ^{47}Sc and related R&D. The prospect of producing RI in large, high-energy (proton) accelerators is also being harnessed, e.g. at the ^{82}Sr parent radionuclide for the ^{82}Rb generator at the Institute for Nuclear Research in Troitsk, Russia; and at the ^{225}Ac at TRIUMF, Canada. Yet, the RRs remain the backbone for large-scale production of many RI of importance, not only for NM, but also for other applications, such as in industry, tele-therapy, brachytherapy etc. However, transfer of target samples, daily or frequently in and out of high-flux positions in RR may not be feasible in many cases. This is a constraint in RR production of RI, which has a short half-life (e.g. ^{64}Cu,^{166}Ho). In the case of MC or other accelerators, routine production of long-lived RI requiring long periods of irradiation may be challenging. The prospect of deploying photo nuclear reaction as a source for RI is also under exploration and electron accelerator facilities in Canada (e.g. upcoming ARIEL facility) and a project in India (SAMEER, Mumbai) will be watched with interest in this context. Updates on RR projects (e.g. Pallas, Myrrah) showed additional (and replacement) capacities for RI production in the long term (not in near future).

[2] Professional views of the author, not necessarily those of the IAEA/WNU/WCI.

[3] https://nucleus.iaea.org/sites/accelerators/Pages/Cyclotron.aspx

RI for Diagnostic Imaging

Most of the reported developments are in the case of cyclotron produced RI, almost exclusively positron emitters (for PET/CT imaging, beyond use of ^{11}C,^{13}N,^{15}O,^{18}F). The use of PET tracers for cancer mets-imaging is invariably a key step nowadays in the workups of cancer patients in a number of countries. Many PET tracers like radio labelled organics and radio metal linked to targeting vector-ligand conjugates are in use. Starting from the keynote address at ISTR-2019 by Dr. S. Lapi, USA, on 'From isotopes to images: radioactive materials as tools in medicine', made several presentations which were devoted to such PET tracers, including and beyond ^{18}F products - e.g. ^{68}Ga (68.3 min), ^{64}Cu (12.7 h), ^{89}Zr (3.27 d) and ^{45}Ti (3.08 h). ^{68}Ga and ^{64}Cu have already been under active consideration by several groups. The proven prospect of facile production of ^{45}Ti (5) and ^{89}Zr (described later) using natural targets in existing MC should be a major driver for further research and development of RPh based on these RI.

Gallium-68: The use of ^{68}Ga (68.3 min, 89% β+), obtained from ^{68}Ge-^{68}Ga generators (known since 1970s itself), for PET/CT imaging of mets and other lesions has expanded in many parts of the world; it is now a regular complement to the use of ^{18}F, and this is also due to the versatility of Ga(III) chemistry. Consequently, two developments are notable, in terms of exploring and harnessing: (i) other radio metal PET tracers with a relatively longer half-life; (ii) additional sources for availing of ^{68}Ga - beyond the traditional ^{68}Ge-^{68}Ga generator option [dependent on the limited sources engaged in the production of ^{68}Ge (271d; dependent on long durations of irradiation of ^{69}Ga target in cyclotron)].

Direct production of ^{68}Ga by ^{68}Zn(p,n) reaction in MC has made considerable progress, including under a CRP of IAEA (Production of cyclotron-based Gallium-68 radioisotope and related radio pharmaceuticals)[4]. Both solid and liquid targets have been deployed with excellent results (2). Experience gained in Portugal at the GBq (Curie) level, GMP-compliant production of ^{68}Ga, using liquid targets and at a lower cost too, is impressive. The Canadian experience and results of producing ^{68}Ga in a cyclotron by using in-house made ^{68}Zn solid targets are: yield of 33-144 GBq from 6-10 mm targets, with a shelf-life of 5 h. ^{68}Ga product meets the specifications of the European Pharmacopoeia. Also, validation of production of ^{68}Ga-DOTATATE (yield of 16 GBq) was reported. Approval has been granted by Health Canada to use this ^{68}Ga production route for clinical use. The reports on daily production of ^{68}Ga at MC and its wide distribution are noteworthy. They also signal the end of the monopoly of ^{68}Ge-^{68}Ga generator suppliers. Diversified sources are essential for key RI for sustainability and the security of supplies (lesson learnt in the

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4 https://www.iaea.org/projects/crp/f22073

case of $^{99}Mo/^{99m}Tc$).

Zirconium-89: Positron emitter RI with relatively longer half-life such as ^{124}I, ^{64}Cu, and ^{89}Zr are better suited for clinical PET/CT imaging with radio labeled monoclonal antibodies (MAb) or similar vectors, which have long biological circulation and target localization time. ^{89}Zr (3.27d, 22.8% positron emission with maximum energy of 0.9 MeV) is of great potential in this context, as it scores over ^{64}Cu in terms of a much longer half-life and over ^{124}I in terms of better scope for applying pre-targeted strategy. For example, ^{89}Zr-Deferoxime - Trastuzumab has been used in breast cancer cases for PET imaging. ^{89}Zr is highly attractive for immuno-targeted PET/CT imaging, including for pre-targeting with MAb followed by ^{89}Zr-chelator for binding in vivo and imaging.

An important practical merit is that ^{89}Zr is produced using natural yttrium target (mononuclidic ^{89}Y). At the University of Alabama in Birmingham (UAB), USA, 18 MeV MC has been used with energy degradation Al foils; typical yield reported (2): $^{89}Y(p,n)^{89}Zr$, Ep 13 MeV, 3 h, 40uA, 2.6 GBq. Irradiation for longer durations, say, 6-9 hours (when MC is not engaged in production of key daily needs such as ^{18}F, ^{68}Ga) with a 50-80 uA current will yield a few tens of GBq of ^{89}Zr, which is an adequate batch-size for weekly production and supply for clinical use. In Italy, a sputtered ^{89}Y target was used at TR-19 cyclotron with 12.5 MeV protons (20-60 µA for 0.5-4 h).

Titanium-45: ^{45}Ti features a 3.08 h half-life and 85% positron emission with maximum energy of 1.04 MeV. More importantly, its production by (p,n) reaction on natural scandium targets (mononuclidic ^{45}Sc) renders it very promising for PET/CT imaging (5). Products of ^{45}Ti would be capable of replacing and/or complementing some of the ^{68}Ga products now in regular clinical use; for example, there may be ^{45}Ti-UBI for infection imaging.

The cross-section for the $^{45}Sc(p,n)^{45}Ti$ reaction is of the order of 200-400 mb depending on the incident energy, Ep 12-14 MeV. At UAB-USA, 18 MeV MC was used with energy degradation Al foil; with a typical yield reported: $^{45}Sc(p,n)^{45}Ti$, Ep 13-14MeV, 0.5 h, 10uA, 2.35 GBq (2). Irradiation for a couple of hours with a 50-80 uA current will yield over 50 GBq ^{45}Ti, a fairly large quantity for clinical use. The prevailing daily distribution chain of ^{18}F-FDG can be leveraged for supplying ^{45}Ti products. It is important to avoid (p,2n)reaction on ^{45}Sc, as it will result in the production of the long-lived ^{44}Ti (60 y) isotopic impurity. Using less than 14 MeV of incident proton energy on a ^{45}Sc target for a short duration (1-2 h) of MC irradiation will be adequate to minimize, if not avoid, the formation of ^{44}Ti traces. ^{45}Ti merits more attention of the managers of both existing and proposed MC facilities for production and of research to develop clinically relevant products for imaging. Although not an M(III) metal tracer, ^{45}Ti appears to be far superior to $^{43/44}Sc$ for regular use in NM.

Copper-64: ^{64}Cu (12.7 h, 17.8% positron emission with maximum energy of 0.65 MeV) under investigation for over three decades is re-emerging for PET/CT imaging and also as a theranostic nuclide (like ^{131}I). As one can use it for PET imaging as well as for therapy (39% beta minus decay, 0.58MeV) (6). One can also use it for PET imaging alone and its analog ^{67}Cu (61.8h, 100% beta, minus decay of 0.39-0.57 MeV) for therapy.

^{64}Cu is produced in MC using enriched ^{64}Ni targets and ^{64}Ni(p,n) reaction. It can also be produced in reactors using enriched ^{64}Zn target and ^{64}Zn(n,p) fast neutron reaction, but in lower yields. IAEA ran a CRP on 'Copper-64 Radio pharmaceuticals for Theranostic Applications'[5] showcasing the R&D efforts on ^{64}Cu and its RPh. ^{64}Cu as $CuCl_2$, in simple inorganic form, has been successfully used in recent years for imaging many tumours and this has increased the interest of the use of ^{64}Cu further.

<u>*Rubidium-82*</u>: ^{82}Rb (75s, potassium analog) obtained from the ^{82}Sr-^{82}Rb generator is finding a niche for PET imaging of myocardial perfusion, especially after the ^{99}Mo/^{99m}Tc supply crisis, and the increasing popularity of PET use, which has better quantification capability. It has thus become a regular feature of nuclear cardiology procedures in a few developed countries. It may remain so until the launch of a superior alternative. However, production of ^{82}Sr (25d; by spallation reaction) remains limited to a few centers precluding its wider deployment. The Institute for Nuclear Research of Russian Academy of Sciences in Moscow reported using its 160 MeV proton accelerator for a new design of ^{82}Sr/^{82}Rb generator of high activity (up to 160 mCi; 30L max. eluent) for cardiac imaging. Each generator is suitable for about 600 patients (2). Though not a positron emitter, a mention of the good old $^{201}TlCl$ is deemed desirable. ^{201}Tl's superior features in vivo as true marker of myocardial perfusion renders it still the preferred choice for SPECT imaging in select NM centers (4). This is also a reminder of the basis of the 30 MeV design feature of MC in the 1980s and 1990s, which was required to perform a (p,3n) reaction for ^{201}Tl production!

<u>*Iodine-123/124, Scandium-43/44 and others*</u>: There is a very long history of efforts to utilize ^{123}I (13.3 h, E 159 keV) and ^{124}I (4.18 d, 25.6% positron emission). The emergence of high-resolution PET/CT imaging as a regular feature of NM services, combined with revived exploration of MAb as a vector for tumors has led to using ^{124}I-MAb for PET imaging, including a pre-targeting approach (and with ^{131}I for therapy). The unique benefit of the ^{124}I-8H9 (antiglioma MAb) application, including in pediatric patients, was shown by MSKCC, USA; e.g. in Diffuse Intrinsic Pontine Glioma (DIPG) or brain stem glioma (a rare condition, difficult to treat) (2).

The recent advances in the launch of ultra-high resolution SPECT systems (aimed mainly to sustain continued benefit from ^{99m}Tc-based products), after getting established, may also

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5 https://www.iaea.org/projects/crp/f22067

lead to revisiting ^{123}I (for all its known merits of being an excellent label for several organic compounds, biochemicals and pharmaceuticals) for regular clinical use in the future. Production of ^{123}I [^{123}Te(p,n)/^{124}Te(p,2n)] and ^{124}I [^{124}Te(p,n)/^{125}Te(p,2n)] is feasible using enriched tellurium targets in low-medium energy MC available in numerous centers.

Interest in positron emitters with a relatively longer half-life and M(III) chemistry features are driving studies on ^{43}Sc (3.9h, 88% positron emission), ^{44}Sc (3.97h, 94.3% positron emissions, daughter nuclide of ^{44}Ti of 60y half-life) and also on therapeutic analog ^{47}Sc (3.35d). ^{43}Sc which is produced from calcium targets irradiated with alphas or protons and ^{44}Sc by the decay of its precursor nuclide ^{44}Ti, which is obtained by (p,2n) reactions on mononuclidic ^{45}Sc targets. The latter requires a long duration of irradiation in view of the 60y half-life of ^{44}Ti. Due to the greater ease of production, ^{45}Ti (though not M(III) metal) will score higher than $^{43/44}$Sc. Further, if required, ^{68}Ga and ^{47}Sc can be the RI pair for theranostic use.

Low-energy accelerators can be used for the production of less-commonly known positron emitters (cited often as 'non-standard', a nomenclature to be discouraged), e.g. ^{86}Y (14.7h, for dosimetry purposes in using pure beta emitter ^{90}Y), ^{52}Mn, etc. UAB-USA has designed and used solid pellet targets in TR-24 MC for production and separation of radionuclides with metallic elements - viz. ^{43}Sc, ^{52}Mn ^{55}Co, ^{89}Zr and ^{45}Ti. In the Republic of Korea, 30 MeV cyclotron (RFT-30 machine) is used for radio metal production, with focus on ^{68}Ge, ^{44}Sc and ^{89}Zr (also ^{67}Cu for therapy) (2).

There are numerous other RI of various elements under exploration, of Fe, Mn, Se, As, etc. This is quite understandable to show the vast range of RI feasibility. However, unless backed by extremely relevant clinical needs and/or research, enhancing the inventory of RI alone, it may not necessarily be productive, except for addressing academic R&D goals.

RI for Therapy

Targeted radionuclide therapy (RNT) is gaining larger clinical acceptance based on the success when using *M-peptide-linker conjugate (e.g. *M(III)-DOTATATE) for neuro endocrine tumors, and recently *M - PSMA-binder-ligand conjugate for prostate cancer. This is leading to the growing adoption of the theranostic approach involving the same vector molecule (e.g. peptide, enzyme inhibitor) targeted to the disease lesion for delivering the diagnostic RI for imaging (mostly PET/CT, e.g. ^{68}Ga), and therapeutic RI - beta emitters (^{177}Lu,^{90}Y) and alpha emitters (^{225}Ac) - for targeted RNT.

Reactors have remained the primary source for therapeutic RI, while entry of ^{225}Ac (discussed later) will open up the avenue of accelerators as an additional source. In assessing RI features for theranostics, caution is necessary on the radiation dose burden to the excretory and non-target tissues, based on the pharmaco-kinetics of the *M-RPh as well as considering the entire decay scheme of the given RI. The permissible/tolerable dose burden to excretory organs (mostly kidneys, bladder) and non-target tissues in the corresponding diagnostic RI-RPh may become the dose-limiting factor with the therapeutic RI dose of the same vector-based RPh.

Palliative treatment of terminal cancer patients suffering from intractable pain from diffused bone mets is a regular procedure in NM therapy (though the volume is much smaller compared to the number of cases handled with external beam therapy in radiation oncology). ^{89}Sr as $SrCl_2$ and ^{153}Sm (also ^{177}Lu) as EDTMP complex remain the mainstay for this purpose. The alpha emitter ^{223}Ra (11d) (analog of Ca, Sr) showed promising findings (higher longevity) in initial studies on prostate cancer patients, however, this could not be established when applied to a larger group of patients.

Lutetium-177: Production and use of ^{177}Lu (6.7d, 0.5MeV) formed the theme of many papers, an indicator of the expanding scale of utilization of ^{177}Lu, both for the carrier-added ('ca') product obtained by $^{176}Lu(n,\gamma)$ reaction, and the no-carrier-added ('nca') ^{177}Lu obtained from the decay of the precursor nuclide ^{177}Yb. There was also coverage of the impact of ^{176}Lu enriched target material purity on ^{177}Lu production and resultant specific activity (2). The twin advantages - viz. highest specific activity and no long-lived contaminant 177mLu - in opting for 'nca' ^{177}Lu are well-recognized. Yet, ^{177}Lu of over 740 GBq/mg specific activity will suffice for most clinical applications, including those involving peptide-conjugates. Scope for production using enriched ^{176}Lu targets in high-flux reactors would be important, keeping in mind the very high cross-section of 2100 b of $^{176}Lu(n,\gamma)$ reaction.

Hard beta emitters ^{90}Y, ^{188}Re: The choice of a hard beta emitter RI to complement the pair of ^{177}Lu for therapy and ^{68}Ga for PET/CT imaging, can be well met by ^{90}Y (66h, 2.27MeV). Though ^{188}Re (17h, 2.12MeV) is in use in some NM centers due to the commercial availability of the ^{188}W-^{188}Re generator, the superior chemistry match of ^{90}Y to complement ^{177}Lu and ^{68}Ga with the same vector molecules is the important feature in favor of ^{90}Y. Further, ^{90}Y can be also relatively more widely produced and distributed to even distant locations. India cited use of ^{90}Y acetate sourcing from ^{90}Sr (recovered from high-level liquid waste from reprocessing spent fuel) and the separation of ^{90}Y based on an indigenous technology using supported liquid membrane. A neutron flux level of 10e15 required for production of ^{188}W (69.4d) by successive neutron capture reaction on enriched ^{186}W targets is a distinct limitation for its wide-scale production, apart from the need for entirely different vectors and linker molecules. Carrier-added ^{166}Ho (26.8h, 1.85MeV) produced in RR by $^{165}Ho(n,\gamma)$ reaction (mononuclidic element target) which may be another (limited) choice.

Miscellaneous others: Search on other theranostic pairs is driving efforts to demonstrate the utility of ^{67}Cu (2.58d), ^{47}Sc (3.35d) among others. Initial efforts at Legnaro Nuclear Centre in Italy to produce ^{67}Cu for therapy in high-energy, high-current cyclotron included use of multi-foil targetry for sustaining high proton flux and meeting the requirement of the appropriate incident energy of projectiles for the specific nuclear reaction, and in turn, multiple RI production (2). The interesting case of simultaneous production of different RI would need further investigations and validation.

Cyclotron production of ^{47}Sc by irradiation of either titanium or vanadium targets is notable, as shown in Italy, for example. Reactor production of ^{47}Sc by neutron irradiation of enriched ^{46}Ca and radiochemical separation may not be a practical option for a large quantity of therapy doses, due to the inherent disadvantage of the 0.004% natural abundance of ^{46}Ca.

Merits of RNT using the Auger (and conversion) electron emitter RI are well acknowledged and efforts are underway to harness the same, for example with the use of ^{161}Tb (6.9d) produced by reactor irradiation of ^{160}Gd (2). There are other RI candidates too (e.g. ^{165}Er), while it may take considerable time before it can be ready for regular clinical use. Despite persistent efforts by promoters, there has been no success in the use of ^{117}mSn (13.6d, a low-energy conversion and Auger electron emitter) and also ^{211}At (7.2h, alpha emitter), for different reasons. Some typical causes for the lack of an RI impact are the highly specific requirements for production, nuclear characteristics beyond desired features, limitation to a link with vector molecules and the inability to be available from larger number of centers. Better alternatives are known.

Alpha emitters - Actinium-225 and Bismuth-213: Interest in using alpha emitters for high LET based efficacious therapy has moved beyond the R&D level to clinical utility (4). This is mainly due to the initial success of $^{223}RaCl_2$ in patients with prostate cancer (later findings have not been encouraging) and more importantly the results with the use of ^{225}Ac linked (in place of ^{177}Lu) to PSMA-binder conjugate, in treating mets in patients of castration resistant prostate cancer (a large fraction of prostate cancer cases).

^{225}Ac for alpha therapy [10 d; E 5.9 MeV; sequential decay products, ^{221}Fr (4.9 min) - ^{217}At (32.3 milli second) - ^{213}Bi (46 min)] turned out to be the most popular topic at ISTR-2019. Current supplies of ^{225}Ac (65-70 GBq/year, adequate for a few thousand patients) are by separation from (legacy) old stocks of ^{229}Th (decay of ^{233}U), the US-DOE Isotope Program (33GBq), the Russia-IPPE/JSC (22GBq), EC-JRC (11GBq) and Canada-CNL (2.5-4.5 GBq) (2). The main methods for ^{225}Ac production are from thorium and ^{226}Ra.

- Thorium targets with a high-energy proton linac [^{232}Th(p, spallation)] option: 0.2% ^{227}Ac (21.8y) co-produced contaminant is inevitable. Also, there are challenges concerning the separation from close to 400 activation products and the purification of ^{225}Ac.

- Radium-226 (alpha active) target based options in: cyclotrons by [^{226}Ra(p,2n)], or electron accelerators by [226Ra(γ,n)225Ra decay], or a high-energy neutron source facility by [^{226}Ra(n,2n)225Ra decay]. Challenges are with the targetry development with encapsulation of ^{226}Ra, availability of ^{226}Ra stock, ^{222}Rn release and radiation safety.

DOE-USA is pursuing a Tri-Lab system, involving ORNL, LANL, BNL (having high-energy accelerators and other infrastructure) for the upgrade of facilities and the scaling up of ^{225}Ac production capabilities to the multi-curie level. One of the plans in Canada (CNL-TRIUMF) is to produce ^{225}Ac from ^{232}Th with a 520 MeV proton accelerator, up to 1.85TBq (^{50}Ci) of ^{225}Ac per year. CNEA-Argentina has a project for using 226Ra target in a proton cyclotron, aiming to produce 37 GBq/year, adequate to meet the envisaged regional demands.

In the case of sequential alpha decay, as in ^{225}Ac, release of daughter nuclide due to it facing recoil energy (much higher than the energy of the chemical bond of the nuclide) from the chelator-target-specific-vector conjugate is quite likely to occur. This can lead to normal tissue toxicity; for example, ^{221}Fr (4.9min); the decay of the product of ^{225}Ac being potassium analogue. Upon release it can be taken up in myocardium.

An alternate option is to use separated ^{213}Bi (46min), in place of ^{225}Ac, but one then loses the advantage of alpha cascade for RNT and a longer half-life of ^{225}Ac favorable for its wide distribution. The ^{225}Ac-^{213}Bi generator option can be cited in favor of distribution logistics. On the other hand, the 46min half-life of ^{213}Bi will be the constraint in its separation, compounding to the RPh form, QC testing, transport, etc.

Perspectives: Impressions and Reflections

The valuable roles of the established RI-trio of ^{131}I, (^{99}Mo/)^{99m}Tc, ^{18}F, further supplemented in the last decade by ^{177}Lu for RNT (RI-quartet now), provide the strong foundation for the RPh-NM field. It is heartening to note that there will be booster supplements in the near future, in terms of ^{225}Ac for alpha therapy, and radio metal tracers ^{68}Ga, ^{64}Cu, ^{89}Zr and ^{45}Ti for PET imaging. Targeted therapy with RI-RPh has much higher clinical value, and accordingly, reliable availability of ^{90}Y and ^{225}Ac (apart from ^{131}I,^{177}Lu), be it from national centers or commercial entities, will be a major need when harnessing them for therapy in NM.

The current level of ^{225}Ac availability is adequate to treat only a few thousand patients every year, while the projected need for doses is up to half a million patients per year. It is essential to have an expansion of production options, capacity additions and the reported large-scale production projects/plans underway in some countries like in the USA and Canada which are thus extremely encouraging.

The role of MC-linked radio pharmacy services has been continually growing for nearly 15 years (2,4). The 110 min half-life of ^{18}F has not proven a hindrance for its wide distribution for clinical use. This paradigm shift is important and has led to fostering regular distribution of other similar short-lived RI products. For the availing of radio metal positron emitters, demands on the MC industry will be changing. Requirement of solid and dedicated liquid target stations will be an essential part of new MC establishments, in order to enable production of ^{45}Ti, ^{64}Cu, ^{68}Ga, ^{89}Zr and ^{124}I. It will not suffice to have only water targets for 18F production and gas targets in the MC facilities. MC of Ep >13 MeV energy (preferably variable) will be more in demand, for adopting (p,n) or (p,2n) reaction options for more RI production. MC of 10-11 MeV will become less attractive. There will be a trade-off of the simplicity of compact, fixed-energy proton cyclotron, in seeking needs-based alterations-additions to the MC, to avail the required incident energy of projectiles on the targets for medical RI production. Targetry systems need to also be more amenable to enable recovery and the reuse of the precious enriched target material.

The mature MC industry, already credited with ensuring a very high degree of robustness of MC operation, can surely meet these emerging needs. Also, greater scope for entrepreneurial ventures running MC facilities for commercial services can be envisaged, for the daily production of 18F, ^{68}Ga and (hopefully soon) ^{45}Ti, and weekly production of ^{89}Zr, and ^{124}I. The frequency of ^{64}Cu production can be twice or three times a week. When a rugged encapsulated ^{226}Ra targetry becomes available, 18-30 MeV MC can also be deployed for the production of ^{225}Ac for therapy.

The demand for several enriched targets for RI production needs to be addressed, as there are challenges in ensuring their reliable availability at affordable cost (4). Recycling of enriched targets is technologically feasible in many cases, subject to regulatory issues being satisfactorily addressed.

In the decay scheme of some of the emerging RI of interest, it is common to find positron emission being only a partial branch of decay. Some RI emit high energy gamma rays, too (e.g. ^{64}Cu). These have an impact on radiation dosimetry computations. It is imperative to take the entire decay scheme of RI into consideration for dosimetry, efficacy and safety purposes. Hence, striving for a convergence of views (if not harmonization), on radiation dosimetry and safety aspects of the identified RI for targeted therapy and for theranostics, will help send an unequivocal message to medical authorities and national regulators of radiation safety and pharmaceutical aspects.

Reiterating the need for security of supply of key medical RI is necessary and there are calls for attention to the associated techno-economic viability and societal health care aspects (learnt the hard way during ^{99}Mo/^{99m}Tc supply crisis over a decade ago!). Expansion and diversification of production options for key RI is an important lesson learnt for sustainable and back-up supplies. It is necessary to evolve a viable economic model for the production and supply of ^{225}Ac for therapy, in light of the reported huge costs of the ongoing/planned projects. Envisaged large volume utilization of ^{225}Ac may help lower its cost. It is important to ensure that ^{225}Ac does not become too expensive to be affordable at NM centers, particularly in developing countries.

Concluding Remarks

The history of growth of NM has clearly shown the trend that only those radioisotopes meeting two key requirements, viz. nuclear characteristics well-matched for imaging or therapy, and 'adequately satisfactory logistics' of production and availability (i.e. amenable to facile supply chain management), can be successful for large-scale clinical use. Shining examples of success are ^{99m}Tc and ^{18}F (cf. lack of success of ^{123}I in the past). Development of organ-specific or lesion-specific RPh based on such RI becomes a natural sequel. The recent success of ^{177}Lu for therapy (against the lack of success of ^{117m}Sn, ^{211}At) is also citable in this context. Now, one can extrapolate the prospect of success in the near future to a few more positron emitters - ^{68}Ga due to diversified ease of access and proven utility for imaging lesions; ^{45}Ti, ^{89}Zr producible with natural elemental targets in a large number of MC and the promising scope to develop RPh; ^{64}Cu, ^{124}I for all their known merits and in the light of the increasing number of MC and PET in use. A much desired new entrant will be ^{225}Ac, due to the high potential of targeted alpha therapy, as soon as any one of the projects underway is completed and large-scale production-supply of ^{225}Ac gets started.

Ultimately, obtaining recognition for RI-RPh product/procedure - including the recently proven/emerging roles of NM - is by its inclusion in Clinical Guidance - Standard of Care practices for management of patients. A concise list of RI-RPh products and (clinical) indications will give much higher strength in seeking such recognition by the larger medical community, compared to having far too many RI-RPh products vying in vain to get recognized. Applying simultaneously a 'sun-set' clause for the 'unfavorable RI' (either restricted accessibility or redundant in the face of superior alternates or prohibitively expensive) would enhance the credibility and real values of RPh-NM.

This article has been prepared during COVID-19 pandemic and the associated lockdown restrictions affecting normal life in most parts of the world. So, it would only be appropriate to conclude with a comment on the potential vulnerability of RI-RPh supplies and disruptions of NM services. Normal means of transport for RI-RPh shipments involves air (international and national) and road (inter-city and intra-city) services. In view of the lack of, or grossly reduced, transportation options for RI-RPh supplies since March 2020 in a number of countries, NM services to patients dependent on daily and weekly supplies of RI-RPh have been affected to varying degrees across the world. MC-based supplies have been perhaps relatively less affected.

Many NM centers are striving to deliver limited services to meet the most pressing needs, namely, for cancer and cardiac patients. The availability of diversified sources of RI-RPh supplies, preferably spread across multiple regions, will be of help in obtaining at least partial supplies during any crisis situation. The inherent vulnerability of NM due to the inevitable dependence on frequent, timely supplies of the perishable RI-RPh has thus come out in the open. It is a wake-up call to all the relevant stakeholders to consider addressing this additional factor, as a part of strengthening the supply chain management practices for key RI-RPh products.

Acknowledgements

This article is a 'by-product' of recently completed tasks for the IAEA's ISTR-2019 and the WNU book 'Advanced Radiation Technology'. I thank Dr. Joao Osso, IAEA and Dr. Patricia Wieland, WNU for assigning me the role of Rapporteur and Editor, respectively.

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02. Isotope-related News

Radiation effective for PPE, but not masks, says IAEA

Radiation is an "effective and established" tool to sterilize personal protective equipment (PPE) that is in high demand during the COVID-19 pandemic, except for respiratory face masks as it weakens their filters, the International Atomic Energy Agency (IAEA) said yesterday.

The IAEA has reviewed findings from five institutions that tested the use of ionizing radiation - gamma and electron beams - to sterilize used respiratory masks, such as models N95 and FFP2 commonly worn by medical personnel.

To read more please visit:
https://world-nuclear-news.org/Articles/Radiation-effective-for-PPE-but-not-masks-says-IAE
Source: WNN

IRE supplies a first commercial batch of LEU-based Mo-99

The Institute for radio elements (IRE), one of the leaders in the production of Molybdenum-99 (Mo-99), the most widely used radio-isotope in nuclear medicine for diagnosis, announced today that the company produced its first commercial Mo-99 Low Enriched Uranium (LEU) batch for the US market.

This conversion to LEU represents a key milestone for IRE in the global commitment to end the civil use of High Enriched Uranium (HEU) for the production of Mo-99 medical isotopes. This demonstrates its unique capacity to carry out advanced R&D activities, while maintaining during the last two years its highest production output to serve the global market during temporary or unplanned outages of some alternative suppliers of medical radioisotopes. It achieves the first step of the complex development of an entirely new industrial process to supply healthcare professionals with Mo-99.

To read more please visit:
https://www.ire.eu/media-room/news/ire-supplies-a-first-commercial-batch-of-leu-based-mo-99
Source: IRE ELIT

CNNC breakthrough reduces cancer treatment costs

The first batch of domestically produced strontium-89 nuclides developed and produced by the Nuclear Power Institute of China -- a unit of China National Nuclear Corporation -- was delivered to Chengdu Gaotong Isotope Co Ltd on April 25, according to CNNC reports.

Experts said that relevant indicators showed the nuclides were at internationally advanced levels, marking the breakthrough where China has successfully developed key technologies for the entire process of research and development, reactor operations, irradiation and production in the strontium-89 nuclide area -- and additionally it has capacity to supply strontium chloride.

To read more please visit:
http://en.cnnc.com.cn/2020-04/28/c_481592.htm
Source: CNNC

NorthStar construction, growth strong amid COVID-19

Company growth at NorthStar Medical Radioisotopes remains uninterrupted by COVID-19, according to CEO Steve Merrick.

Work continues at the headquarters on a new electron accelerator production building to expand capacity of the company's non-uranium domestic supply of molybdenum-99 (Mo-99). "Construction has continued without interruption," Merrick said.

The accelerator project coincides with the isotope processing facility that saw construction in 2019. The processing facility, built directly next to the in-progress accelerator building, will help the company avoid shipping delays between irradiation and processing of Mo-99. Equipment installation at the processing facility remains underway, Merrick added.

To read more please visit:
https://www.beloitdailynews.com/news/local-news/northstar-construction-growth-strong-amid-covid-19/article_019adae5-b527-5743-9966-b28724a8fc83.html
Source: Beloit Daily News

NRC issues operating license application review schedule for SHINE

SHINE Medical Technologies LLC announced today that the U.S. Nuclear Regulatory Commission (NRC) expects to make a final determination regarding the issuance of an operating license to SHINE by October 2021. SHINE's application for a license to operate the medical isotope production facility that it is building in Janesville, Wis., was accepted and docketed by the NRC last October.

"The review schedule established by the NRC for our application reflects the quality of our submission, our effective engagement with NRC staff, and the diligence and hard work of the entire SHINE team," said Greg Piefer, chief executive officer of SHINE. "The review schedule also reflects a very well on prepared and engaged NRC staff. SHINE will continue to work with the NRC to advance the review of SHINE's operating license application."

To watch the webinar please visit:
https://wisconsintechnologycouncil.com/nrc-issues-operating-license-application-review-schedule-for-shine/
Source: Tech Council News

ARTMS Closes a US$19 Million Series A Financing with Deerfield and GHS Fund

ARTMS Inc. a global leader in developing technology that transforms the production of the world's most-used diagnostic imaging isotopes, announced that it has raised US$19 million in Series A financing. The investment was led by New York based Deerfield Management Company with continued investment from Vancouver based seed investor GHS Fund (Quark Venture LP and GF Securities).

"We are thrilled to have this significant investment with such knowledgeable, high-caliber investors. This funding gives us the financial flexibility to leverage our QUANTM Irradiation SystemT (QISTM) technology and partner with customers to revolutionize the nuclear medicine industry by enabling global access to cyclotron-produced medical isotopes," says Charles S. Conroy, Chief Executive Officer of ARTMS Inc.

To read more please visit:
https://www.aithority.com/technology/life-sciences/artms-closes-a-us19-million-series-a-financing-with-deerfield-and-ghs-fund/
Source: AIT News Desk

SNMMI Advocates for Access to Diagnostic Radiopharmaceuticals through COVID-19 and Beyond

This week SNMMI and its coalition partners sent a letter imploring Congress to take immediate action to ensure patient access to FDA-approved diagnostic radiopharmaceutical drugs that aid in the detection of cancer, cardiovascular conditions and neurological disorders. Mounting evidence shows that COVID-19 infection damages not only the respiratory system, but also the heart and other organ systems. Furthermore, the long-term effects of this disease are still unknown. Patients who survive COVID-19 will need access to the best care available, and nuclear medicine is an essential part of that care.

To read more please visit:
https://www.snmmi.org/NewsPublications/NewsDetail.aspx?ItemNumber=33861
Source: SNMMI

F-18 flortaucipir PET and postmortem assessment of Alzheimer disease neuropathologic changes

Visual reads of [18F]flortaucipir positron emission tomography (PET) scans may accurately support a pathological diagnosis of Alzheimer's disease (AD) according to a recent article published on JAMA Neurology. In this diagnostic study of 82 individuals with or without dementia, visual reads of F-18 flortaucipir PET scans corresponded with postmortem Braak stages V and VI levels of cortical neurofibrillary tangles and high levels of AD neuropathological change. Therefore, PET may increase the diagnostic accuracy and confirm the underlying neuropathologic changes of AD.

To read more please visit:
https://jamanetwork.com/journals/jamaneurology/fullarticle/2764329
Source: JAMA

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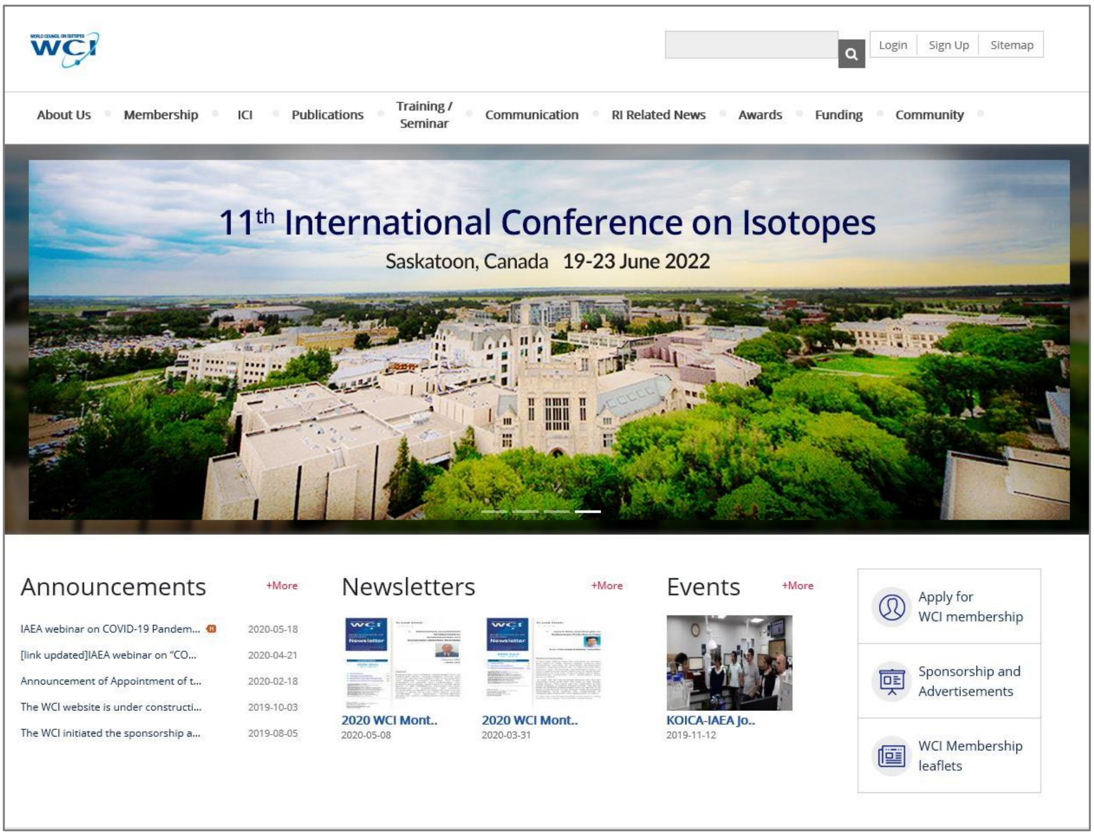
03. Sketches from the Secretariat

3-1. WCI website (www.wci-ici.org) has been upgraded

The WCI website has been totally rebuilt in a significant upgrade as a platform for the exchange and dissemination of information of interest to the global isotope related communities since 2019. It now features additionally created menus, updated information, an improved layout and designs making it a mobile-friendly site with responsive web design. This upgrade has the objective to make access to information easier to allow our members to keep in touch with the global radioisotope communities. The WCI website has been upgraded with the contributions of the financial support from the Government of the Republic of Korea and the administrative support from Korean Association for Radiation Application (KARA).



The upgrade includes the creation of additional menus and sub-menus, information updates, and design improvements. Additional menus and sub-menus contain links to other organizations, ICI Photos and ICI Materials. Information updates feature messages from the Presidents, the Organization, Training/Seminar pages etc. Finally, the design improvements deal with funding etc.

The WCI Secretariat will continue to improve its website to share radioisotope related information with the global radioisotope communities. For more information, please visit the WCI website(www.wci-ici.org).

3-2. The IAEA invited the WCI members to join on the webinar "COVID-19 Pandemic: Radiation Sterilization of PPE" on Thursday, May 21, 2020, 14.00 – 15.30 CET (Vienna time).

The International Atomic Energy Agency (IAEA) informed the WCI Secretariat that the IAEA held the webinar "COVID-19 Pandemic: Radiation Sterilization of PPE" on Thursday, May 21, 2020, 14.00 – 15.30 CET (Vienna time) , and requested the WCI Secretariat disseminate this information to the WCI members.

The webinar had the format of a virtual town-hall meeting, in which an international panel of experts answer questions related to how radiation can be used to sterilize new and used personal protection equipment during the COVID-19 pandemic. The IAEA is committed to supporting member states in the proper use of Radiation Technologies during current COVID-19 pandemic.

The webinar addressed practical considerations and challenges:

1. Current status of radiation sterilization of PPE worldwide
2. PPE reprocessing techniques
3. Reprocessing of respiratory masks by radiation: issues and challenges

4. Prospects of radiation sterilization of PPE

This webinar also functioned as a platform to share and exchange experience and best practice and offered a question and answer session with experts.

For more information, please visit the website:
https://iaea.webex.com/iaea/onstage/g.php?MTID=e72a30d613ccca44deb8b01afcc6a4df5

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04.Future Conferences and Events

The SNMMI 2020 Annual Meeting– Virtual Edition

- Date: July 11 - 14, 2020
- Venue: On-line
- Website: https://am.snmmi.org/imis/SNMMI-AM/Home/SNMMI-AM/Home.aspx

This innovative virtual experience will take place on Saturday, July 11 through Tuesday, July 14, and feature an exceptional program highlighted by some of the hottest topics in nuclear medicine and molecular imaging, including a science pavilion featuring the latest scientific research, an interactive virtual exhibit hall, networking events, and even some special surprises!

ICIGSIG 2020

- Date: July 23 – 24, 2020
- Venue: Berlin, Germany
- Website: https://waset.org/isotope-geology-and-stable-isotope-geochemistry-conference-in-july-2020-in-berlin

The International Research Conference is a federated organization dedicated to bringing together a significant number of diverse scholarly events for presentation within the conference program. Events will run over a span of time during the conference depending on the number and length of the presentations. With its high quality, it provides an exceptional value for students, academics and industry researchers.

RRFM2020

- Date: October11 - 15, 2020
- Venue: Helsinki, Finland
- Website: https://www.euronuclear.org/rrfm-2020-helsinki/

RRFM, the European Research Reactor Conference, is the annual gathering of the research reactor community in Europe. In 2020, we invite you to Helsinki, Finland. The conference program will revolve around a series of plenary sessions dedicated to the latest global developments with regards to research reactor technology and management. One of our keynote speeches will provide insights into the TRIGA fuel production restart at the Framatome CERCA facility. So, mark your diary, block 22 – 26 March in your agenda and join us in Finland!

EANM 20

- Date: October17 – 21, 2020
- Venue: Vienna, Austria
- Website: https://eanm20.eanm.org/

With more than 150 Sessions, the EANM Annual Congress is the most valuable Nuclear Medicine Meeting worldwide. Each year, nearly 7,000 participants have the possibility to network, socialize and discuss the newest trends and findings in the field of Nuclear Medicine. The EANM is proud of receiving approximately 2,200 abstracts annually from all over Europe and overseas. 180 exhibiting companies, covering an area of nearly 4,000 s.q.m. present their newest technologies.

17th International Conference on Cancer Science and Radiation Oncology

- Date: March 15 – 16, 2021
- Venue: Zurich, Switzerland
- Website: https://radiationoncology.alliedacademies.com/

The 17th International Conference on Cancer Science and Radiation Oncology is aimed at creating a platform to express and exchange the thoughts and ideas on recent advancements in cancer treatment. The main focus of the conference will be on developing or innovating new techniques and methodologies for the next generation of cancer treatment.

RAP 2021

- Date: May 31 – June 4, 2021
- Venue: Thessaloniki, Greece
- Website: http://rap-conference.org/20/index.php

The latest coronavirus related developments could have an effect on planning for our conference. It is not certain that existing restrictions regarding public meetings and travel will be lifted in time for our participants to organize their attendance at RAP 2020. In addition, even if formal restrictions are lifted, the disruptions of work and private plans due to the current coronavirus measures may prevent many participants in realizing their original plans and coming to Thessaloniki in the first week of June.

IRRMA 2021

- Date: June 4 – 9, 2021
- Venue: Moscow, Russia
- Website: http://www.lnf.infn.it/conference/irrma2021/

The International Topical Meeting on Industrial Radiation and Radioisotope Measurement Applications is a triennial event organized for the purpose of bringing together scientists and engineers from around the world who share an interest in radiation and radioisotope measurement applications.

IsoEcol 2021

- Date: June 20 – 26, 2021
- Venue: Gaming, Austria
- Website: https://sites.google.com/view/isoecol2020/

The 12th International Conference on the Applications of Stable Isotope Techniques to Ecological Studies will be held in the beautiful town of Gaming, Austria, organized by the Inter-University Center for Aquatic Ecosystem Research WasserCluster Lunz in cooperation with the International Atomic Energy Agency (IAEA) from June 20-26 , 2021. The conference venue is at the historic Kartause (Charter house) in Gaming (pronounced Gah-ming), approximately 2 hours from Vienna by car or public transportation.

ARIS 2021

- Date: September 5 - 10, 2021
- Venue: Palais des Papes, Avignon, France
- Website: https://indico.in2p3.fr/event/19688/

ARIS 2020, the fourth international conference on Advances in Radioactive Isotope Science, will be held in France's beautiful city of Avignon from 14-19 June 2020. ARIS is the flagship conference for rare isotope science, born from the merger of the international conferences 'Exotic Nuclei and Atomic Masses' and 'Radioactive Nuclear Beams'.

IRPA 15

- Date: January 18 – 22, 2021
- Venue: Seoul, Republic of Korea

•Website: https://www.irpa2020.org/

IRPA's International Congresses are a major event in the world of radiation protection, and are held every four years. IRPA15 in Seoul, January 2021, will be the first such congress to be held in Asia since the Hiroshima congress in 2000, and will be a great opportunity for radiation protection professionals from Asia and around the world to meet and discuss the key issues of our time.

NRC 10

- Date: August 25 – 30, 2024
- Venue: Brighton, UK
- Website: https://www.rsc.org/events/detail/38385/10th-international-conference-on-nuclear-and-radiochemistry-nrc10

We will host another high quality scientific program giving an excellent overview of the state of the art modern nuclear and radiochemistry. All aspects of the field will be covered: from nuclear fuel cycle to radiopharmaceutical chemistry, from environmental radioactivity to transactinide chemistry etc.

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WCI Monthly Newsletter

Call for Articles

The WCI Secretariat provides its Monthly Newsletter to about 1,600 subscribers worldwide. The WCI monthly newsletter is a communication channel for the dissemination of information among members and other interested parties in the field of isotope and radiation related technologies. For more and better information on isotopes production and application, the WCI Secretariat is cordially inviting your valuable contributions.

1. Contents

WCI Monthly Newsletter covers the following and contributions are welcome for any of the following topics:

- **Lead article**: National policies, R&D outcomes, views of experts, current issues, innovative technologies in the field of radiation and radioisotopes
- **Conference report**: Report on relevant conferences
- **Future Conferences**: Any events (conferences/seminars/workshops) related to the field of radiation and radioisotopes

* Presenting events through the WCI Newsletter allows wider audiences to be informed, thereby potentially increasing participation.

- **Isotope-related news**: latest news related to the radiation and radioisotopes
- **My biz on isotopes**: topics that demonstrate the cross-cutting and interdisciplinary technologies of WCI member organizations (Please refer to the previous edition (2016 Vol. 5 Issue 2) for more details)

* This column is an excellent opportunity to raise the profile of an organization and explore business opportunities with other WCI members.

2. Requirements

The article provider should be a member of the WCI. (To join us, please visit www.wci-ici.org and sign up online. There is no membership fee.) The writer should be a professional working in the field of isotope production or the application of isotopes or radiation.

3. Format

All articles should be written in English. The length of article should be within 4 pages (A4, Verdana with 10 font size and 1.5 line spacing). Images may be included.

All submissions meeting the above requirements should be submitted to secretary@wci-ici.org

4. Deadline

Articles received by the WCI Secretariat via email before the **25th** of the month will be considered for the next upcoming newsletter.

5. Others

The WCI Publication Committee Chair will review articles for possible inclusion in the newsletter. Articles might be edited according to our own format. The WCI Secretariat will make payment for **your lead article.** It is KRW 100,000 per page A4 size (equal to US$85-95 per page)