Trends in Radiopharmaceuticals (ISTR-2019)

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TRENDS IN RADIOPHARMACEUTICALS (ISTR-2019)

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PROCEEDINGS SERIES

TRENDS IN RADIOPHARMACEUTICALS (ISTR-2019)

PROCEEDINGS OF AN INTERNATIONAL SYMPOSIUM HELD IN VIENNA, 28 OCTOBER–1 NOVEMBER 2019

INTERNATIONAL ATOMIC ENERGY AGENCY
VIENNA, 2020

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FOREWORD

The International Symposium on Trends in Radiopharmaceuticals (ISTR-2019), organized by the IAEA and held in Vienna on 28 October–1 November 2019, was the first IAEA symposium on the topic of radiopharmaceuticals held in 15 years. The symposium attracted nearly 400 participants from 71 Member States and 9 organizations. The aims of the symposium were to review the latest advances in radiopharmaceutical sciences worldwide, to identify trends and to serve as a global forum to enable scientists and professionals working in the field to formulate views and discuss priorities and directions for future work. ISTR-2019 also provided a platform for collaboration and for addressing common problems in the use of radiopharmaceuticals worldwide.

This publication contains the highlights and main takeaways of the symposium, as well as a summary of each session and the side events. The supplementary files available on-line contain the book of abstracts, which includes information on the symposium's organization and logistics, a detailed programme and all the abstracts of the oral and poster presentations.

The IAEA gratefully acknowledges the cooperation and support of the organizations and individuals involved in this conference, in particular N.V. Ngjeqari (Albania), N. Ramamoorthy (India) and J. Vera Araujo (Venezuela). The IAEA officer responsible for this publication was J. Osso Junior of the Division of Physical and Chemical Sciences.

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1. INTRODUCTION

Application of nuclear science and technology in health care management is a primordial area of the 'nuclear programme' in almost all countries. Among such applications, the field of nuclear medicine (NM), which involves the use of radiopharmaceuticals (RPh), for a variety of diagnostic uses and certain specific therapies, has been a key element of nuclear applications in health care. Several of the NM procedures using RPh have become a well-established, widely practised branch in medicine in a number of countries, including many developing nations. The IAEA's strong support in multiple ways has been a crucial factor in the adoption of the use of RPh and practice of NM by several of its Member States (MS).

The use of RPhs is an important tool not only for management of diseases and dysfunctions (clinical NM), but also for better understanding human diseases and developing effective treatment options (medical research), such as in the case of neurology. In this context, there is continuous, impressive progress in NM which is invariably and intricately linked to the development of new RPhs and efficient production of relevant radioisotopes (RI).

Clinical NM practices were largely based on the use of ^{131}I, ^{99m}Tc, ^{201}Tl and ^{89}Sr for a long time until the end of 1980s. Introduction of ^{153}Sm in the late 1990s as an effective alternate to ^{89}Sr was subsequently an important development. The launch of ^{177}Lu, as an ideal complement to ^{131}I-based therapy, was the next significant milestone in NM. In parallel, the well-known merits of PET based imaging procedures (higher resolution and better quantification) and scope to use biological molecules as markers (analogue of glucose, amino acids, drugs, etc.) labelled with ^{18}F, have been effectively harnessed by the multi-disciplinary researchers, with maximum contributions in cancer care.

The International Symposium on Trends in Radiopharmaceuticals (ISTR) is an IAEA organized event. Its main objective was to provide scientists and professionals working in the fields of production of RI and RPhs an international forum for discussing the most recent developments in the field. The previously held conferences at the IAEA devoted to the field of RPhs are:

- Modern Trends in Radiopharmaceuticals for Diagnosis and Therapy, Lisbon, Portugal, 30 March -3 April 1998, Proc. of Symp. -IAEA-TECDOC-1029 (1998);
- Therapeutic Applications of Radiopharmaceuticals, Hyderabad, India, Jan 18-22, 1999, Proc. of Symp. IAEA-TECDOC-1228 (2001);
- International Symposium on Trends in Radiopharmaceuticals (ISTR-2005), IAEA, Vienna Nov 14-18, 2005 - IAEA Conf. Proc. Series 2 Volumes (2007).

As seen in the above, the last symposium was held 15 years before the ISTR-2019. As requested by several MSs and due to the wide positive feedback from participants, the Section aims to host ISTR regularly every four years to continue to bring scientists and other professionals in the field together.

1.1.SUMMARY OF THE SYMPOSIUM

The ISTR-2019 was a well-attended event with the participation of 71 MSs and 9 organisations; nearly 400 participants – out of which 48% were women delegates – attended. The ISTR-2019 was convened in Vienna by the IAEA from 28 October to 01 November 2020. There were 83 oral presentations delivered in 17 topical sessions (including two parallel sessions, namely,

clinical advances in NM and IAEA Technical Cooperation (TC) Success Stories). There were two poster sessions, during which 157 poster papers were presented. Two side events were organized, one by a MS (India) and another one by the Conference Secretariat (entitled 'Women in Radiopharmaceutical Sciences: Challenges and Opportunities'). A working lunch was sponsored by one industrial partner (company). Thirty-three exhibitors from the industry, national centres and professional bodies attended the meeting. The high-quality displays of their technology, products, services and documents enriched the participants with a large volume of useful, technical and professional information.

The Acting Director General of the IAEA in 2019, Mr. Feruta, opened the Symposium. In his address, he cited the various types of roles played by the IAEA and its multiple programmes of support and services to MS under the Nuclear Applications (NA), Safety & Security (NS), and Technical Cooperation (TC) departments. Deputy Director General, Head of the Department of Nuclear Sciences and Applications (NA), Ms. Mokhtar, outlined the roles and deliverables in human health, medical isotopes, RPhs and their contributions towards attaining the United Nations Sustainable Development Goals (UN-SDGs). The Director of the Division of Human Health (Dir-NAHU) of NA, Ms. Abdel-Wahab, gave brief remarks on the clinical roles of RPhs and NM practices. The Director of Physical and Chemical Sciences (Dir-NAPC) of NA, Ms. Denecke, gave welcoming remarks and also highlighted and acknowledged the considerable efforts undertaken by the ISTR-2019 secretariat team. The symposium was organized by the Radioisotope Production and Radiation Technologies section. The Section Head, Mr. Osso Junior, served as the scientific secretary of the ISTR-2019.

The keynote talk delivered by Ms. Suzanne Lapi, from the United States of America, was titled 'From isotopes to images: radioactive materials as tools in medicine'. Her speech was focused on new PET tracers, viz. ^{89}Zr (3.27d; 22.3% β^+ & 76.6% EC), ^{45}Ti (3.08h; 85% β^+ & 15% EC), and ^{68}Ga (68.3 min). The successful use of ^{68}Ga–PET has led the researchers to explore and harness the utility of other (radiometal) PET tracers with relatively longer half-lives. Ms. Lapi gave an example of using one monoclonal antibody (mAb) as a vector for HER2 positive breast cancer PET-imaging to demonstrate the impact made in clinical management of patients. ^{89}Zr appears to be well suited for immuno-targeted (slow kinetics) PET imaging, apart from offering scope for pre-targeting with mAb followed by ^{89}Zr-chelator binding and PET imaging.

The salient points emerging from ISTR-2019 are briefly described in this section. More detailed session-by-session summary is given in the next part of the report. Research reactors (RRs) continue to be the major source of RIs, not only for medical uses but also for industry and research. Reactor produced RIs such as ^{131}I, ^{99}Mo/^{99m}Tc, ^{153}Sm, and ^{177}Lu have been substantially supplemented by the cyclotron produced RIs, especially positron emitters. Considerable progress has been made in RI production technologies as well as in evolving needs-based, alternate technology options for key RIs, for example, ^{99}Mo/^{99m}Tc and ^{68}Ga.

Significant achievements in the production of radiometals using liquid targets in accelerators were presented, especially of ^{68}Ga from ^{68}Zn targets in medical cyclotrons (MCs). The experience gained in Portugal in GBq (Curie) level production of Good Manufacturing Practice (GMP) grade ^{68}Ga, at a very low cost is impressive. The news of daily production and distribution of ^{68}Ga was noteworthy.

There is growing interest in the theranostic approach, that is, using the same vector molecule targeted to the disease lesion for delivering the diagnostic RI for imaging (mostly by PET) and

therapeutic RI (typically beta emitters; and recently also alpha emitters) for targeted radionuclide therapy.

Thanks to the recent improvements in MCs and the potential utility of linear accelerators for radioisotope production, better access is envisaged to several RIs, including ^{68}Ga and ^{64}Cu and new ones like ^{89}Zr and ^{45}Ti. High power electron linac option has also been pursued (for photo-nuclear reactions) and led to increased availability of new beta emitters for theranostic use, including ^{47}Sc and ^{67}Cu.

The use of PET and MC linked radiopharmacy services has grown phenomenally during the past two decades. An important paradigm shift has taken place, where 110 min half-life of ^{18}F is not a hindrance for its wider distribution and use. Consequently, ^{68}Ga (68.3 min), another positron emitter RI proposed for PET since 1970s, has now become a daily utilised RI in numerous centres around the world. Its availability from a ^{68}Ge–^{68}Ga generator and versatility of its M(III) chemistry have rendered it very attractive and made it one of the most common RI in PET-NM procedures. PET tracers beyond those of ^{18}F and ^{68}Ga are increasingly being investigated and many of them have entered the clinical arena, e.g. ^{64}Cu products. Interest in radiometal positron emitters, with relatively long half-lives (several hours to a few days), has also been growing. As a result, many novel RIs, such as ^{89}Zr, ^{45}Ti, and $^{43/44}$Sc are attracting researchers' attention. ^{45}Ti may prove to be a welcome addition to PET tracers, thanks to its three hour half-life, 85% positron emission and straightforward production by (p,n) reaction on natural scandium target (which is mononuclidic ^{45}Sc). Products of ^{45}Ti would be capable of replacing and/or complementing some of the ^{68}Ga products now in regular clinical use. The therapeutic counterpart RIs in some of the above cases, namely, ^{67}Cu and ^{47}Sc, have also been studied extensively.

Despite the superiority of PET tracers, there is continuing relevance of ^{99m}Tc RPhs, especially considering advances in imaging instrumentation, such as the launch of an ultra-high resolution, fast acquisition system and G-SPECT. The same can be said of ^{123}I (thirteen hour half-life, Eγ 159 keV) products too.

Advances in identifying suitable vector molecules to target lesions and coupling them with diagnostic and therapeutic RIs have led to development of uniquely paired RPhs and, in turn, impressive progress in theranostic approaches in recent years. Considerable advances are evident in the development of novel chelators and linkers for ensuring ease and simplicity of radiometal conjugation.

The scope for deriving practical benefits of the high-linear energy transfer based, targeted alpha therapy has been demonstrated. First with ^{223}Ra (for metastatic bone pain palliation, prostate cancer cases in particular) and more importantly with ^{225}Ac for castration resistant cases of prostate cancer. Thus, a major highlight of ISTR-2019 was the session covering the production and quality control (QC) of alpha emitters, ^{225}Ac in particular.

Regarding the volume of practices, it is estimated that every second, there is one SPECT imaging being done, and every ten seconds, one PET imaging study and one radionuclide-based therapy (RNT) procedure are being done somewhere in the world.[1]

[1] The information given is an estimate which is based on the information available in this publication "Advanced Radiation Technology, Ed. N. Ramamoorthy, World Nuclear University, London, UK (2019)".

Clinical advances in the use of RPhs were covered by presentations from the NM Section of the IAEA and by two experts from the MD Anderson Cancer Centre, United States of America. These presentations endorsed the invaluable roles of the new RPh products, PET tracers in oncology and neurology, and in radionuclide therapy, including alpha therapy.

Regulatory requirements governing the production of RPhs were discussed based on the World Health Organization (WHO) guidelines, EU stipulations and the U.S. Food and Drug Administration (US-FDA), as well as the health regulations in Kazakhstan. Emphasis on quality assurance (QA), QC and preclinical testing is a crucial feature in RPh production. The education, training and certification requirements for radiopharmacy installation and operation were also covered and the TC-IAEA support was acknowledged in this context.

The experience gained in setting up radiopharmacy installations for SPECT and PET products was shared through five presented cases, which included facilities set up with IAEA help as well as in the private sector.

The IAEA support in the form of databases to serve RI production planning was covered in three presentations devoted to: IAEA RR database, Medical Cyclotron Directory, and web-tool for calculation of yield and purity of RIs. The success stories of TC-IAEA support were presented by Argentina (PET tracer production), Cuba (^{99m}Tc generator production facility) and Kazakhstan (Gel generator for ^{99m}Tc).

There were several references to the participation in IAEA Coordinated Research Projects (CRPs) (both concluded and ongoing) and the progress made by many participants from different countries. The IAEA CRPs dealing with alternative production options for ^{99}Mo and ^{99m}Tc, production of ^{64}Cu and its products and direct production of ^{68}Ga by ^{68}Zn(p,n) reaction were among the highlighted ones. In addition, there were a number of poster presentations covering results reported by some CRP participants and their experience.

The concluding session included a presentation on ISTR-2019 highlights by the rapporteur. The IAEA Scientific Secretary of ISTR-2019 made a presentation acknowledging one and all for the successful conduct of the symposium. The participants conveyed overwhelming appreciation to the IAEA and ISTR-2019 Secretariat team for the impressive range of professional information and knowledge shared at the ISTR-2019.

1.2. OBJECTIVES AND STRUCTURE OF THESE PROCEEDINGS

The expanded topics covered at the ISTR-2019 included, inter alia, development, production, and uses of diagnostic, therapeutic and theranostic RIs and RPhs, regulatory and licensing aspects, education, training and certification requirements. ISTR-2019 provided a befitting opportunity for multi-disciplinary researchers, medical scientists and other experts to present and discuss their recent research findings. The event helped to strengthen existing collaborations and to establish new contacts for future collaborations, to address needs-based developments of diagnostic and therapeutic products, and to further expand the worldwide use of RPhs and NM procedures, including the recently emerging ones.

The topical sessions of the ISTR-2019 are listed below, summaries of which are found in the following section, where they provided a good coverage of all currently relevant areas:

— Production of medical radioisotopes – Research Reactors;

— Production of medical radioisotopes – Accelerators;
— Production of medical radioisotopes – Generators (Focus on ^{99}Mo);
— Production of radiopharmaceuticals – Theranostic;
— Production of radiopharmaceuticals – SPECT;
— Production of radiopharmaceuticals – PET;
— Production of radiopharmaceuticals – Therapy;
— Clinical advances in nuclear medicine;
— Quality assurance, quality control and pre-clinical evaluation;
— Health regulations – Production of radiopharmaceuticals;
— New trends in radiopharmaceuticals – Chemistry;
— Production of alpha emitters and radiopharmaceuticals;
— Emerging radioisotopes for radiopharmacy;
— Radiopharmacy installations in industrial, hospital and centralized facilities;
— Education in radiopharmacy (including e-learning, certification and training methodologies for professionals involved);
— IAEA Technical Cooperation Success Stories;
— IAEA Databases and APPs.

2. SUMMARY OF SESSIONS

2.1. SESSION 1 - PRODUCTION OF MEDICAL RADIOISOTOPES: RESEARCH REACTORS

RRs continue to be the major source of RI production, not only for medical uses but also for industry and research, as highlighted in many presentations and several posters. An overview on the status and challenges, mostly due to ageing reactors, underlined the vital roles of RRs, with a focus on securing supplies of ^{99}Mo/^{99m}Tc and initiatives taken by the Nuclear Energy Agency - Organization for Economic Cooperation & Development (NEA- at the OECD) through the High-Level Group on the Security of Supply of Medical Radioisotopes (HLG-MR) (involving IAEA cooperation). The emerging alternate routes for ^{99}Mo and ^{99m}Tc production would provide a much-needed diversity in sourcing supplies. These will supplement (but not replace) the existing commercial supplies of fission produced ^{99}Mo and alumina column chromatography generators of ^{99m}Tc.

The national experience of Poland in the large-scale RI production at the Maria reactor highlighted the importance of IAEA support. The RPh-NM share was reported just 1% of the global pharma industry. An IAEA–CRP named ‘Therapeutic Radiopharmaceuticals Labelled with New Emerging Radionuclides (^{67}Cu, ^{186}Re, ^{47}Sc)’ (F22053) has catalysed recent developments in the production of real theranostic RIs, namely $^{44/47}$Sc and $^{64/67}$Cu.

Much progress in supplementing and expanding production of ^{99}Mo and ^{177}Lu was reported. The production and processing capacity enhancement reported for ^{99}Mo are: ANSTO to 3.5kCi; Curium to 5kCi; IRE +50%. RRs currently producing or planning to produce ^{99}Mo are: MURR-USA, FRM2-Germany, and JHR-France. Updates on the plans for installation of new RRs in Europe, e.g. Pallas-NL, Myrrah-Belgium, offer optimism, if not promise, as RR sources for medium-term to long-term future in production of RPhs.

There were many papers on the production and use of ^{177}Lu and the impact of ^{176}Lu enriched target material purity on ^{177}Lu production and resulting specific activity. This can be viewed as an indicator of the expanding production scale of carrier-added ('ca') ^{177}Lu. There is a choice between 'ca' vis-à-vis no-carrier-added ('nca') ^{177}Lu, the latter obtained from the decay of the precursor nuclide ^{177}Yb. It is known that ^{177}Lu of over 740 GBq (20 Ci)/mg specific activity will suffice for most clinical applications, including those involving peptide-conjugates. At the same time, 'nca' ^{177}Lu may yet be necessary to meet specific national regulations governing the discharge limits of radioactivity in effluents in some countries. The choice of production option for ^{177}Lu of required specific activity will be dictated by ease of access to and cost of (i) ^{176}Lu enriched target and very high neutron flux; (ii) ^{176}Yb enriched target and radiochemical processing for separation of ^{177}Lu from Yb.

2.2. SESSION 2 - PRODUCTION OF MEDICAL RADIOISOTOPES: ACCELERATORS

Charged particle accelerators, proton cyclotrons in particular –that include compact MCs– are extensively deployed for regular production of a variety of RIs, especially positron emitters. An overview of the field was presented, highlighting the production routes of the less-commonly used (so called 'non-standard') positron emitters, e.g. ^{86}Y, ^{64}Cu, and ^{89}Zr, using low-energy accelerators, and of therapeutic RI, e.g. ^{67}Cu, ^{225}Ac, ^{47}Sc, ^{193m}Pt, and ^{117m}Sn, in medium-energy accelerators.

The production of radionuclides of metallic elements - viz. ^{89}Zr, $^{43/47}$Sc, ^{52}Mn, and ^{45}Ti, in the TR-24 MCs at University of Alabama at Birmingham (UAB), USA, is based on unique procedures adopted in the design and preparation of solid pellet targets and separation methods. UAB's MC of Ep 18 MeV is used for the production of ^{89}Zr and ^{45}Ti, using mono-nuclidic targets in both cases and Al foil for energy degradation.

The highlight of the session was the progress and notable achievements in the production of radiometals using liquid targets, especially of ^{68}Ga from enriched ^{68}Zn target in MC. The experience gained in Portugal in tens of GBq (curie level) production of GMP grade ^{68}Ga, at very low cost too, is significant. This signals the end of the monopoly of ^{68}Ge–^{68}Ga generator suppliers.

The use of ^{68}Ga for PET/CT has rapidly grown over the world and its use is now second only to ^{18}F. Hence, the ^{68}Zn(p,n) route of production in MC (Ep 13-14 MeV) is becoming well-established (with IAEA support in technology evaluation through a CRP called 'Production of cyclotron-based Gallium-68 radioisotope and related radiopharmaceuticals'[2]) and is acknowledged as an important advancement; e.g. in Canada, yields of 33.3 GBq (0.9 Ci) from 6 mm target and 144.3 GBq (3.9 Ci) from 10 mm target (shelf-life 5 h) were achieved. Both solid target and liquid target are developed and deployed for Ci level production of ^{68}Ga. In the USA, for GBq (Ci) level production, a target design and processing method are being patented.

Shipments of ^{68}Ga to NM sites around MC centres are nowadays routine, similar to that of ^{18}F products. Analysing the pros and cons of this development is helpful. Ease of access to ^{68}Ga using MC and ending monopoly of sourcing of ^{68}Ga are attractive features. On the other hand, the advantage to generator sources of ready access to ^{68}Ga, even without MC on-site, becomes lost. However, ^{68}Ge production is limited to a few centres and it is not readily commercially

[2] More information can be found at https://www.iaea.org/projects/crp/f22073

available for users other than specific contractual procurers, namely, industrial manufacturers of ^{68}Ge–^{68}Ga generators.

Interest in the use of longer-lived positron emitters to match certain physiologic parameters and slow delivery vector molecules is growing. ^{89}Zr and ^{45}Ti are under active consideration in this context, and presentations of such included at the ISTR-2019. These RIsy are produced using mononuclidic target elements, Y and Sc, respectively (no enriched target required). At the University of Alabama at Birmingham, USA, 18 MeV MC has been used with energy degradation Al foils; typical yields of RI reported are:

— ^{89}Y(p,n)^{89}Zr, Ep 13 MeV, 3 h, 40uA, 2.6 GBq (70 mCi);
— ^{45}Sc(p,n)^{45}Ti, Ep 13-14MeV, 0.5 h, 10uA, 2.3 GBq (63 mCi).

The scope of radiometals production in a 30 MeV cyclotron was reported (RFT-30 machine in RoK), with the focus on ^{89}Zr, ^{68}Ge, ^{44}Sc, and ^{67}Cu, along with respective target details and processing methods.

Deferoxime (DFO) is a popular chelator molecule in use with ^{89}Zr; for example, ^{89}Zr-DFO-Trastuzumab has been used in breast cancer cases for immuno-PET imaging. Research and development (R&D) on other chelators is also prevalent. PSMA-11 inhibitor-binder ligand used with ^{68}Ga has also been used with ^{45}Ti for prostate cancer metastases in PET imaging.

The presentation of experience at the Canadian TRIUMF accelerator facility on the production and application of ^{225}Ac and/or ^{213}Bi included an overview of the targeted alpha therapy concept as well as an outline for future plans.

2.3. SESSION 3 - PRODUCTION OF RADIOISOTOPES: GENERATORS (FOCUS ON ^{99}Mo)

IAEA activities to foster the sustainable supply of ^{99}Mo remain important and attractive for many MSs; there is room for more participants to contribute. The session reminded participants of safeguards related aspects due to the use of enriched ^{235}U targets. IAEA has run CRPs to evaluate options for production of ^{99}Mo and ^{99m}Tc in accelerators. They required very highly enriched ^{100}Mo targets to meet the radionuclidic purity specifications.

The largest ^{99m}Tc consumer country, USA, has taken up several measures for domestically securing ^{99}Mo supplies. In particular, new ways of producing ^{99}Mo and ^{99}Mo-^{99m}Tc generators are being successfully developed in USA. New initiatives such as accelerator-based production of ^{99}Mo opened up new opportunities. Progress by several companies offer new solutions but mostly limited to the USA.

Other generator systems were discussed in a presentation from Troitsk, Russia, mainly with the perspective of producing the parent radionuclides by using large facilities, such as the high energy proton accelerator at the Institute for Nuclear Research in Troitsk, Russia. The availability of ^{82}Sr–^{82}Rb generators has significantly increased and several clinical trials were initiated. ^{82}Rb is in considerable demand for myocardial perfusion PET imaging, especially in the aftermath of the 2008–2010 crisis in ^{99}Mo/^{99m}Tc supplies. ^{225}Ac can be produced in Troitsk, but with 0.2% of ^{227}Ac impurity. Hence, this can rather be used for the ^{225}Ac-^{213}Bi generators instead of direct use of ^{225}Ac in patients.

A quasi-generator system utilizing accelerator produced ^{47}Ca as a parent for ^{47}Sc was presented by the Institute of Nuclear Chemistry and Technology, Poland. However, the small difference in half-life of ^{47}Ca (4.5 d) and ^{47}Sc (3.35 d) and the very low natural abundance of ^{46}Ca (0.004 %) would be adverse factors in this approach.

2.4. SESSION 4 - PRODUCTION OF RADIOPHARMACEUTICALS: THERANOSTIC

The growing interest in the theranostic approach, that is, using the same vector molecule targeted to the disease lesion for delivering the diagnostic RI for imaging (mostly by PET) and therapeutic RI (usually beta emitters and alpha emitters) for targeted therapy, is driving considerable R&D efforts in many countries.

Interest in the potential strength of mAb (despite slow kinetics) for highly selective and specific targeted imaging is reviving due to using longer lived ^{89}Zr (78.4 h) as a nearly ideal RI for labelling mAb. Examples of ^{89}Zr labelled antibodies for cancer imaging are:

(a) ^{89}Zr-DFO-Trastuzumab for imaging HER2+ tumours or for following-up response to inhibitor therapy of gastric cancer; and
(b) ^{89}Zr-DFO-HuMAb-5B1 for targeting the carbohydrate antigen CA19.1 over-expressed by pancreatic tumours.

To address the slow kinetics with antibodies, pre-targeting is also pursued as a solution, e.g. using tetrazine for in-vivo click chemistry, and ^{64}Cu / ^{18}F for labelling for PET.

Rich experience and expertise are now available in many centres in the production of ^{68}Ga-DOTATATE and ^{177}Lu-DOTATATE for treatment of neuroendocrine tumours (NET). There is a choice of ‘manual-processing’, ‘automated module’ or ‘kit-based’ procedures available.

RPhs for targeting PSMA in prostate cancer patients by using paired RI, ^{68}Ga (for PET imaging) and ^{177}Lu (for therapy), are of very high interest currently. Recently, targeting PSMA with radiotherapeutic agents labelled with alpha emitter ^{225}Ac is emerging as a superior alternative to ^{177}Lu.

Focus on the ‘isotope on line separation device’ (ISOLDE) technology – a strategy for isolating isotopes generated in situ, based on their mass difference and applying the technique of ‘laser resonance ionization’ for evaporating nuclides from an irradiated sample – is essential when dealing with the production of unconventional (exotic) RIs in an isotopic mixture. In other words, this is an attempt to enrich isotopes of elements in situ, as they are being generated by spallation reaction or similar. Such innovative sourcing of RIs is however unlikely to make an impact on clinical practices in the near future.

^{64}Cu (12.7 h, 17% positron emission) is envisaged to emerge as a theranostic nuclide (akin ^{131}I), as it can be used for both (PET) imaging and for therapy (beta emitter). Also, ^{67}Cu can be used for therapy, keeping ^{64}Cu for PET imaging alone. ^{64}Cu can be produced preferably in MC using enriched ^{64}Ni target [^{64}Ni(p,n)] and in RRs using enriched ^{64}Zn target [^{64}Zn(n,p)] with lower yields. An IAEA–CRP named ‘Copper-64 Radiopharmaceuticals for Theranostic Applications,’ has been dedicated to the production and application of ^{64}Cu-theranostic RPhs since 2016[3]. Furthermore, copper is involved in human biochemical processes so that interest

[3] More information can be found at https://www.iaea.org/projects/crp/f22067.

in ^{64}Cu based RPh has been accordingly quite high, although until recently no major impact has been made in NM practices. ^{64}Cu in a simple divalent inorganic form, $CuCl_2$, has been recently shown to be useful for imaging many tumours. Several other ^{64}Cu products are under investigation. For example, production and radiolabelling of an antibody against the class of glycoproteins 'mucins', expressed by breast cancer cells –radio-conjugate ^{64}Cu-NOTA-Anti-MUC1– has been prepared and characterized. Pre-clinical results were done in animal models and presented by a research group from Iran.

2.5. SESSION 5 - PRODUCTION OF RADIOPHARMACEUTICALS: SPECT

This session emphasised the continuing importance, relevance and value of ^{99m}Tc RPhs, especially in light of advances in imaging instrumentation. For example, the launch of an ultra-high resolution, fast acquisition system, G-SPECT, by a European company, as well as advances in chemistry approaches for linking Tc with biologically sound vector molecules; e.g. use of macrocyclic ligand NODAGA as chelator for Tc and Re; tricarbonyl chemistry aided conjugation to antagonist peptides to use with ^{99m}Tc and ^{188}Re. There is merit to revisit certain ^{99m}Tc RPhs to perform clinical trials again, e.g. ^{99m}Tc-Teboroxime for myocardial perfusion imaging, as well as support resurgence of R&D. Consequently, a natural poser will be to use ^{123}I products and superior SPECT systems. Now that over 1 300 MC centres are in operation across the world (IAEA cyclotron database, presented in Session 14) and the capacity to distribute short-lived RI is available, revisiting ^{123}I (13 h) based RPhs may be warranted.

Based on the success of PSMA targeting agents and PET imaging in prostate cancer patients, development of a SPECT agent, ^{99m}Tc based binder to PSMA –called HYNIC-iPSMA– is of interest in Mexico. It has also been used with therapeutic nuclides ^{177}Lu and ^{225}Ac by using another linker DOTA (*M- DOTA-HYNIC-iPSMA). Another reported use was the synthesis and biological evaluation of ^{99m}Tc based integrin targeting agents by using RGD peptide linker conjugate.

The session had two general presentations, one covering many of the issues faced by developing countries in providing/availing expert NM and radiopharmaceutical resources, and the other on the rich 60-year experience with indigenous radiopharmaceutical programme in Brazil and its future plans for expansion.

2.6. SESSION 6 - PRODUCTION OF RADIOPHARMACEUTICAL: THERAPY

This session attempted to cover RPhs for both the established metastatic bone pain palliation applications and the targeted therapy for tumours.

The success of using ^{89}Sr for bone pain palliation in terminal cancer patients could not be expanded to many parts of the world due to the need to import the product at high cost. At the University of Missouri, Columbia, USA, scientists investigated the use of phosphonate conjugated radiometal (^{153}Sm) to enhance uptake at tumour met sites to mitigate pain. The resultant, FDA approved ^{153}Sm-EDTMP has been used widely since the late 1990s, as ^{153}Sm can be more easily produced than ^{89}Sr. Thanks to the IAEA CRP support, the analogous product ^{177}Lu-EDTMP has been developed and launched about ten years ago, where clinical trials were

also facilitated[4]. Its usage has been expectedly on the rise, as the longer half-life of ^{177}Lu helps shipping products to NM centres in even remote locations. Furthermore, the lower range beta emitters (^{153}Sm, ^{177}Lu) offer greater advantages for bone pain palliation in terms of lower bone marrow toxicity and, in turn, enables delivery of higher dose to tumours. In case of preferred prolonged delivery of radiation dose to bone mets, ^{170}Tm-EDTMP (^{170}Tm, 120 d) can be considered. Mixed RI therapy approach is also possible.

The emergence of the use of ^{223}Ra as an alpha emitter and strontium analogue is an important addition to the session topic. The initial excitement of superior longevity in patients treated with ^{223}Ra could not be realised when applied in larger groups of patients. Selection of patients is a crucial factor for both alpha therapy and beta therapy.

The successful use of peptide based targeted therapy (PRRT) of neuro-endocrine tumour (NET) mets and of enzyme inhibitor ligand based targeted therapy for prostate cancer mets, both using ^{177}Lu, has also led to harnessing high-linear energy transfer alpha emitter or Auger electron emitter RIs. The most widely used therapeutic counterpart for ^{68}Ga remains ^{177}Lu, while recent advances in radionuclide production methods have made ^{225}Ac, ^{213}Bi and ^{161}Tb available as alternatives to ^{177}Lu. This has created interesting opportunities to treat mets with a short-range alpha and/or Auger and conversion electron emissions.

A later section of the report is devoted to alpha emitters, while certain subtle aspects covered in the current session are outlined here. This refers to the challenge with (multiple) alpha emitters like ^{225}Ac (10 d) undergoing a series of decay with the (likely) release of its daughter nuclide(s) from the chelator; this can result in normal tissue toxicity. For example, Francium (Fr) is a potassium analogue, and ^{221}Fr (4.9 min), decay product of ^{225}Ac, can be taken up in normal tissues including myocardium. Consequently, an option to use separated ^{213}Bi (46 min), in place of ^{225}Ac, has been proposed by some researchers. ^{213}Bi is a mono alpha emitter, but its kidney burden is higher; hence, pre-targeting type approach may be a solution for its future use. The use of Auger electron emitter ^{161}Tb resulted in more tumour regression and longer survival, compared to that of ^{177}Lu.

Other presentations in this session described three methods and products, two from India and one from Malaysia. Development of a robust kit method to prepare ^{188}ReN-DEDC/lipiodol in a hospital radiopharmacy, free of glacial acetic acid (glacial acetic acid can result in failures of synthesis, if volume is not tightly controlled) was reported from India. Oxalic acid was used in this method to eliminate the use of glacial acetic acid. This method allowed variation in the radioactive solution volume up to 5 mL (cf. 3 mL with traditional preparation) and faster kinetics of reaction – within 5 minutes compared to 30 minutes with glacial acetic acid. This study was meant to develop import substitution, as an alternative to labelled microspheres or use of HDD/lipiodol with various radionuclides.

^{90}Y–acetate obtained from high level liquid waste from a two-stage supported liquid membrane (SLM)-based ^{90}Sr/^{90}Y generator of India was used to prepare ^{90}Y-DOTATATE and evaluated in SSTR2 positive tumour cells, in comparison to ^{68}Ga-DOTATATE and ^{177}Lu-DOTATATE. Comparable radiolabelling and uptake were observed.

[4] IAEA-CRP named 'Evaluation of the Biological Safety and Clinical Efficacy of ^{177}Lu-EDTMP for Bone Pain Palliation in Metastatic Prostate Cancer (Phase I/II Clinical Trial)'. More information can be found at https://www.iaea.org/projects/crp/e13033

In Malaysia, polystyrene microparticles containing ^{152}Sm were prepared and irradiated to produce ^{153}Sm labelled product for evaluation for hepatic embolization, as an alternative to the imported ^{90}Y microspheres. No degradation upon irradiation and no RI impurities were found in the study.

2.7. SESSION 7 - PRODUCTION OF RADIOPHARMACEUTICAL: PET

This session presented glimpses of some of the advances and trends involving mainly products of ^{18}F, ^{68}Ga and ^{124}I. Apart from several ^{18}F labelled organic molecules under development and/or in regular use and continual development of ^{18}F radiolabelled NOTA/NODAGA peptides via Al^{18}F, the success in targeting PSMA in prostate cancer patients with ^{68}Ga labelled binder molecules has led to researchers exploring ^{18}F based binder molecules to target PSMA. Some novel synthesis of ^{18}F-binder-PSMA via click chemistry was presented by an expert from the Netherlands. In another presentation a researcher from Thailand reported that ^{18}F-PSMA-1007, with a shelf life of 8 h, allowed PET imaging of 8 patients as compared to only 3 with ^{68}Ga-PSMA-11.

Cyclotron production of ^{124}I for PSMA binder radiolabelling was reported by Saudi Arabia, with high radiolabelling yields, very high purity and specific activity.

With growing use of ^{68}Ga peptide conjugates, automated formulation methods for ^{68}Ga-DOTATOC and DOTATATE developed in Innsbruck, Austria, were described. The use of SSTR antagonist ligands for targeting neuroendocrine tumours and of ^{68}Ga PSMA binder conjugate for molecular diagnosis of prostate cancer was also cited. Fibroblast activation protein linked to ^{68}Ga (^{68}Ga-FAPI) has been used to diagnose more than 20 human cancers.

^{64}Cu labelled MeCOSar-Tyr3-octreotate (^{64}Cu-SARTATE) – a new product developed due to the success of ^{68}Ga-DOTA-Octreotate or ^{68}Ga-DOTATATE – was evaluated for PET imaging in Australia for the localization of SSTR-positive NETs and dosimetry planning for personalized peptide receptor radionuclide therapy (PRRT, PRRNT). The rationale was to take advantage of the longer half-life of ^{64}Cu (12.7 h), compared to that of ^{68}Ga (68 min), to better match with bio-kinetics and personalised dosimetry for therapy.

2.8. SESSION 7(A) - CLINICAL ADVANCES IN NUCLEAR MEDICINE

This session featured three presentations, one by the Head of the NM program of the IAEA and two by experts from the MD Anderson Cancer Centre (MDACC), USA.

The presentation by the IAEA expert gave an overview of the importance of NM imaging, considering its great economic impact on the world market of diagnostic imaging. The relevance of NM is with respect to (i) diagnostic imaging in patients with diseases related to high risk of mortality (e.g. cancer and vascular) and (ii) patient treatment, advancing further with development of the therapeutic options using alpha emitting RPhs. The IAEA program also aims to facilitate access to the various services and supporting tools of EANM (European Association of Nuclear Medicine), for education and training, regulatory aspects, quality audit of clinical practice (QUANUM), economic aspects and reimbursement. The IAEA program on NM strives to contribute to UN-SDG ‘3: Good Health & Well-Being’, specific goal ‘3.4: by 2030, reduce by one third premature mortality from NCD (non-communicable disease) through prevention & treatment and promote mental health & well-being’.

The NM physician from MDACC described the evaluation in NM applications, stressing the metabolic content of the information for diagnostic imaging and the (detective) mechanism of action of the target therapy. NM has thus become a very important discipline with an essential role in patients' management. He showed the range of the important achievements of NM, thanks to the technology SPECT, PET, hybrid instruments, radiopharmaceutical developments in the diagnosis and therapy, integration with other medical disciplines, and the inclusion in the guidelines.

The radiopharmacy scientist from MDACC showed the general organization and the intense activities of their Cyclotron Unit. A list of the various RPhs in their pipeline for diagnostic imaging for current clinical use and those still under research were presented. The novel alpha emitters of interest for therapy currently under investigation open the horizons for novel therapeutic approaches in the area of oncology.

2.9. SESSION 8 - QUALITY ASSURANCE, QUALITY CONTROL, AND PRE-CLINICAL

The requirements and recommendations for QC of RPhs prepared in a hospital setting were described by an expert from South Africa, along with a clear differentiation in the (IAEA) level of operation, limited requirements for level 2 and higher for level 3. There was also emphasis in the need for validation of methods developed and on the recent EDQM technical guideline for validation of RPhs. A simple, nice description of QA and QC was cited by this expert: 'Managing Quality is QA; Verifying Quality is QC'.

Development and preclinical evaluation of ^{64}Cu RPhs were summarized by an expert from the University of Missouri, USA. The successful outcome of a recent IAEA CRP on ^{64}Cu was emphasised, as mentioned earlier. Developments, especially for receptor targeting peptides, were shown with the recent advent of highly stable chelators for ^{64}Cu and promising results with bombesin antagonists and divalent probes in a preclinical setting.

An expert from Canada presented results of producing ^{68}Ga in a cyclotron by using an in-house preparation of ^{68}Zn solid target. Very high yields of ^{68}Ga meeting the requirement of the European Pharmacopoeia up to 5 h post production were reported. Validation of production of ^{68}Ga-DOTATE was achieved, resulting in yields of 16 GBq ^{68}Ga-DOTATATE. Permission by Health Canada to use this ^{68}Ga production for clinical use was recently granted.

An EANM presentation explained the changes in Europe related to animal experimentation with a new directive 2010/63/EU, where reduction, refinement and replacement are core aims. An initiative of EANM to survey the consequences for the NM development was presented.

An expert from Germany gave an overview of the development and improvement of ^{18}F ligands for α 7-adrenoreceptors, which are involved in several pathologies related to neuroinflammation (stroke, neurodegeneration etc.). The ^{18}F-DBT-10 showed promising results related to affinity and selectivity for the target and, in an animal stroke model, excellent visualisation of the delineation of the stroke region by Micro-PET; the product is awaiting clinical translation.

2.10. SESSION 9 - HEALTH REGULATIONS: PRODUCTION OF RADIOPHARMACEUTICALS

This session showcased the main features of requirements of WHO, EU and US-FDA, as well as in two national cases, Kazakhstan and Estonia.

WHO has an International Pharmacopoeia that contains entries on RPhs. The guidelines on GMP for RPh, prepared in collaboration with the IAEA, was presented at ISTR-2019. This included general overview of GMP and main principles of GMP that are applicable to both hospital and centralized production and industry. The document will be ready by May 2020. All WHO publications are freely accessible via the Internet.

In Europe, there are different regulatory foundations; also, differences exist between industrial and in-house production regulations. Countries have European or national legislations. EU legislation includes directives and regulations. RPhs, radionuclide generators, kits, and radionuclide precursors are defined as medicinal products within the EU directive 2001/85/EC. These directives also implement the requirement for GMP and marketing authorisation (MA) for these products, which need to be manufactured according to regulations applicable for drug production. Regulations are in the 10 volumes of Eudralex; Vol. 4 is dedicated to GMP guidelines.

The European Pharmacopoeia (Eur. Ph., EP) is under the Council of Europe and comprises chapters and monographs. The European Pharmacopoeia has a legal status and plays an important role in defining quality standards. The provision of extemporaneous preparations, magistral preparations under national level exemptions (no MA needed) has enabled development of evaluation of certain new RPhs.

In USA, the FDA has specific laws for medicinal products (caveat: similar words can have a different meaning in different guidelines) and provides recommendations and guidance as part of its regulatory function. In case of issues with cases, the FDA can provide a private meeting to offer advice. US Pharmacopoeia (USP) is under the auspice of a non-profit organization. US Nuclear Regulatory Commission (NRC) is important for RPhs with respect to radiation safety aspects.

In Kazakhstan, GMP certification is practised since 2015 for RPhs. They have harmonized regulatory requirements with that of EU. Their national pharmacopoeia includes monographs on RPhs.

The presentation from Estonia cited gaps between legal acts, which should be addressed and overcome in their country.

2.11. SESSION 10 - NEW TRENDS IN RADIOPHARMACEUTICALS: CHEMISTRY

Development of new chelating agents for ^{64}Cu, ^{89}Zr and ^{68}Ga in Canada were presented, involving cyclic and acyclic chelators derivatized with *N*-hydroxy-*N*-methyl succinamide pendant arms and synthesized in multiple steps starting with a nonadecane, cyclen and spermine backbones. The newly synthesized ligands showed fast complexation and better stability, and were found useful as chelating agents for the development of radiotracers, including antibodies as a vector molecule.

A review was given by an expert pharmacist from USA on the theranostic radionuclide pairs, with a focus on discussing the development of mAb with ^{124}I (for PET) and ^{131}I (for therapy). Some unique applications, including ones for paediatric patients were shown – e.g. Neuroblastoma (NB) and Diffuse Intrapontine Glioma (DIPG) (rare though; ^{124}I-8H9) –with the caveat that all promising findings may not necessarily be applicable in regular clinical use.

Another expert from USA discussed the use of the macrocyclic ligand NODAGA as a chelating agent for complexing technetium and rhenium using tricarbonyl chemistry. The chelating agents were conjugated to antagonist peptides and used for making stable complexes of ^{99m}Tc and ^{188}Re.

A presentation from Germany cited the tracers useful for brain cancer imaging and the shift from ^{11}C to ^{18}F products. FET, FACH, and F-Fluspidine were also cited as the development of novel strategies (e.g. click chemistry; cross-coupling reaction) for developing radiotracers, taking advantage of the different receptors present in brain cells. Some of the new tracers, when fully developed, could be useful for imaging glioma, multiforme.

The IAEA had conducted a CRP F22064 on 'Nanosized delivery systems for radiopharmaceuticals'[5][1]. The CRP related work on radioactive gold nanoparticles in nanomedicine carried out at University of Missouri, USA was presented. The importance of carrier-added radionuclides for the preparation of such RPhs was cited in this presentation. ^{198}Au/^{199}Au nanoparticles were prepared and injected loco-regionally at the tumour site and they did not drain away from the injection site.

2.12. SESSION 11 - PRODUCTION OF ALPHA EMITTERS AND RADIOPHARMACEUTICALS

This session was a major highlight of ISTR-2019, dedicated to the production and QC of alpha emitters, ^{225}Ac and ^{213}Bi in particular. The most relevant players currently are: the European Commission (EC) through its Joint Research Centre Karlsruhe (JRC-Karlsruhe); US-DOE - BNL; US-DOE – ORNL; US-DOE – LANL; CNL-Canada; and RF-IPPE/JSC. The presentation from JRC-Karlsruhe described various production methods of ^{225}Ac, their advantages and disadvantages, as well as the practical advantages of opting to use ^{225}Ac over ^{213}Bi.

The presentation from US-DOE-BNL outlined the activities of Tri-Lab system in US - ORNL; LANL; BNL; 4-stage plan was described, which included upgrade of facilities and scaling up of ^{225}Ac production capabilities to multi-Ci level. RI separation challenges were cited, especially for the ^{232}Th (p, spallation) route. Currently, ^{225}Ac is made available in fairly large quantities (obtained from the decay of legacy stock of ^{229}Th), through the US-DOE Isotope Program.

The Canadian CNL and TRIUMF facility presented their key activities, including current supply of ^{225}Ac from ^{229}Th-^{225}Ac generator (222 to 370 MBq/month or 6 to 10 mCi/month). CNL presented plans to produce ^{225}Ac from ^{232}Th with 520 MeV proton accelerator and expects to produce up to 1.85 TBq (50 Ci) of ^{225}Ac per year.

[5] More information can be found at https://www.iaea.org/projects/crp/f22064

The CNEA in Argentina presented status of their Alpha Project. Using ^{226}Ra target and proton cyclotron, they aim to produce 37 GBq/year (1 Ci/year). This is estimated to be adequate to meet the envisaged demands in the region. The support of the IAEA and EC-JRC is essential for the project progress.

The following information on ^{225}Ac [9.92 d; E α 5.9 MeV (4 α); ^{221}Fr - ^{217}At - ^{213}Bi, 46 min] is noteworthy:

- Current supplies are: US-DOE Isotope Program (33GBq); RF-IPPE/JSC (22GBq); EC-JRC (11GBq); CNL-Canada (2.5-4.5GBq) - separation from (legacy) old stocks of ^{229}Th (from ^{233}U) - total 66 GBq/year. While this is a significant quantity, the envisaged demand and potential to treat patients in several countries would warrant establishing a much higher production capacity worldwide. Accordingly, large-scale production plan/projects (involving very large budget outlay) are underway, such as in the USA, Canada and Russia.
- ^{232}Th (p, spallation) with high-energy proton accelerators: 0.2% ^{227}Ac (21.8y) co-production is inevitable; other challenges concern separation (from close to 400 activation products) and purification of ^{225}Ac and gaining access to proton-linac facility.
- ^{226}Ra (p,2n) in cyclotrons and ^{226}Ra (γ,n) in electron accelerators; ^{226}Ra (n,2n) ^{225}Ra in high energy neutron sources: some challenges are targetry development and encapsulation of target material, ^{226}Ra stock, co-production of ^{222}Rn and addressing safety issues; etc.

2.13. SESSION 11(A) - IAEA TC SUPPORT: SUCCESS STORIES

The TC programme is a major means of direct support to interested IAEA's MSs. TC places specific emphasis in the area of human health to achieve socioeconomic impact in IAEA's MSs and plays a decisive role in addressing the issues and challenges in the area of radiopharmacy. The IAEA is also devoting much resource to address MS needs in cancer control. The presentation by TC Africa Division covered the support provided in the area of radiopharmacy, citing examples of significant achievements in the area of human resources development for radiopharmacy and strengthening their regulatory framework.

Three typical success cases were showcased, as highlighted by the respective national representatives present at the ISTR-2019:

- Cuba will produce GMP grade ^{99}Mo-^{99m} Tc generators of 8–74 GBq capacity by modernising production line with the help from IAEA-TC project. This timely support made clinical NM services sustainable.
- The Institute of Nuclear Physics (INP) in Kazakhstan developed and set up a facility of GMP grade gel generator for ^{99m}Tc by utilising natural molybdenum irradiation at their WWT-K research reactor with a neutron flux of $2x10^{14}$ $n \cdot cm^{-2} \cdot s^{-1}$. This was made possible by both TC support and a CRP by facilitating sharing of knowledge and expertise.
- La Fundación Centro Diagnóstico Nuclear (FCDN) in Argentina is successfully producing new PET tracers, fifteen new ^{18}F based and one ^{68}Ga based tracer, all made possible through TC support and IAEA collaboration.

2.14. SESSION 12 - EMERGING RADIOISOTOPES FOR RADIOPHARMACY

The presentations in this session were on the new PET tracers beyond ^{18}F and ^{68}Ga, with focus on production of ^{64}Cu, and on potential pairs of RI for theranostics, e.g. ^{67}Cu and ^{64}Cu, ^{47}Sc paired with $^{43/44}Sc$. The Canadian efforts at TRIUMF facility for production of non-conventional medical RI using variety of nuclear reactions and different accelerators provided a nice backdrop.

The production of ^{64}Cu that has both diagnostic and therapeutic potential simply as cupric chloride to target a multitude of cancers, was a major highlight presented by the Mexican team. This was supported by interesting diagnostic images, obtained with ^{64}Cu chloride administered to patients with prostate cancer, glioblastoma and pulmonary cancer.

Initial efforts at Legnaro Nuclear Centre in Italy to produce ^{67}Cu for therapy in a high-energy, high-current cyclotron included use of an interesting approach of multi-foil targetry for sustaining a high proton flux. This was aimed at meeting the requirement of the appropriate incident energy of projectiles for the specific nuclear reaction and, in turn, RI production.

Reactor production of ^{47}Sc by neutron irradiation of enriched ^{46}Ca and separation systems studied in Poland and cyclotron production of ^{47}Sc by irradiation of either titanium or vanadium target in Italy were also discussed.

2.15. SESSION 13 - RADIOPHARMACY INSTALLATIONS

This session highlighted the experience gained in setting up radiopharmacy installations for SPECT and PET products. There were five presented cases, two based on the experience from IAEA supported facilities (^{99m}Tc generator production facility; PET radiopharmacy), two based on the experience of MSs (Australia - SPECT product facility in hospital setting; India - PET product facility for commercial supplies) and one from a medical university in Japan operating two MCs.

The IAEA helped to set up a medium size ^{99m}Tc generator facility in the Philippines. Using this experience, an attempt was made in the 1st presentation to demystify meeting the needs of GMP - Quality Management System (QMS) elements. In western countries a $^{99}Mo/^{99m}Tc$ generator is considered a 'medicinal product'. The production of $^{99}Mo/^{99m}Tc$ generators should be according to GMP. The GMP is followed to control and document all steps in the production process to ensure reproducibility and traceability. It is designed to minimize the risks. Quality assurance (QA) helps to prevent mistakes and defects in the manufactured products and avoid problems when delivering products or services to customers.

The Australian hospital based experience shared in the 2nd presentation highlighted the essential elements of SPECT radiopharmacy lab to offer the best patient care: duly qualified personnel and training; facilities and infrastructure; standard operational procedures (SOPs) for all duties; purchase of materials to be a registered as products; QA and QC; waste management; and documentation (mandatory for GMP). At the international level, standardization and harmonization are difficult due to the diverse practice environment; however, one can use the operational guidance on hospital radiopharmacy published by the IAEA [2].

A successful experience of installing a MC–PET radiopharmacy facility in the private sector in India was shared in the 3rd presentation. Large scale, daily production of [^{18}F] FDG for local

use and distribution is a regular feature and is found financially viable. These services have brought down the cost of PET-CT study for clients in centers. The facility has the capability to prepare other ^{18}F RPhs using fluoride chemistry and ^{13}N-ammonia for cardiac studies. The presentation highlighted the IAEA technical reports, such as 'Cyclotron produced radionuclides: Guidelines for Setting up a Facility and Guidelines on Facility Design and Production of FDG [3]'.

The 4th presentation was on the IAEA experience for setting up a PET radiopharmacy facility. Reference was made to the relevant IAEA technical reports: 'Cyclotron produced radionuclides: Guidelines for Setting up a Facility [4]'; 'Guidelines on Facility Design and Production of FDG [3]'; and 'Strategy for Clinical Implementation and Quality Management of PET tracers [5]'. The presentation emphasized practical tips, such as what is needed to plan and implement a PET Radiopharmacy project: (i) seeking expert advice from the IAEA and/or from professional experts; (ii) not relying solely on the equipment manufacturer's advice; and (iii) carefully selecting the contractor(s). The production of PET RPhs should comply with the codes of GMP; one can see Eudralex for GMP guidelines[6].

The 5th and final presentation was from Fukushima Medical University, Japan. They operate two cyclotrons (middle sized cyclotron and MP-30) for research and clinical applications routinely. Their focus is in using the alpha emitter ^{211}At. This advanced clinical research center has two ongoing projects to translate targeted alpha therapy scope to clinical use.

2.16. SESSION 14 - IAEA DATABASES AND APPS

The IAEA supports in the form of web-based databases the RI production planning. This session covered three presentations by professional experts of the IAEA of their services.

The Medical Isotope Browser[7] is a new tool developed by the IAEA Nuclear Data Section in 2019. This allows to directly predict the production yield of medical isotopes on the basis of user inputs and the level of radionuclidic impurities as well. A few examples were demonstrated.

The IAEA's Research Reactor database (RRDB)[8] contains technical information of over 840 RRs, including subcritical assemblies, in 69 countries, out of which 97 RRs are engaged in RI production. This database will be updated soon in collaboration of non-commercial shared information.

The participants of ISTR-2019 received an introduction to the new IAEA database 'Cyclotrons used for Radionuclide Production[9]' developed by the IAEA Radioisotope Products and Radiation Technology Section. This is a directory that includes more than 1 200 cyclotrons worldwide used for RI production, mainly medical isotopes. The IAEA requests cyclotron users to update the existing information as well as send entries of new facilities frequently.

[6] More information can be found at https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-4/2008_09_annex3_en.pdf
[7] More information can be found at https://www-nds.iaea.org/relnsd/isotopia/isotopia.html
[8] More information can be found at https://nucleus.iaea.org/RRDB/RR/ReactorSearch.aspx?rf=1
[9] More information can be found at https://nucleus.iaea.org/sites/accelerators/Pages/Cyclotron.aspx

2.17. SESSION 15 - EDUCATION IN RADIOPHARMACY

Important advances are evident in addressing radiopharmacy education requirements, including with the help of the IAEA in many regions. For example, an ARCAL project on education in radiopharmacy will be starting in 2020 for countries in Latin American region. In the African region, Morocco has established a master's degree in radiopharmacy. This will also be valuable for education in French speaking African countries. Furthermore, under the auspices of IAEA, an e-learning course in radiopharmacy is being developed and will be tested in some MSs. The IAEA TC support for the above was cited in the session on 'TC support success stories'.

The EANM has implemented recertification process for EANM Radiopharmacy Certificate holders. It also offers higher level interactive course on GMP.

3. SIDE EVENTS

3.1. WORLD NUCLEAR UNIVERSITY OLYMPIAD FINALS

The ISTR-2019 hosted a special event, the final stage of the World Nuclear University (WNU) Nuclear Olympiad. The WNU based in the UK has been supporting training and leaderships in nuclear sciences. This support includes, among other courses, a two-week school on radiation technology, which provides a good coverage of RPhs related management aspects. In addition, WNU organizes the Nuclear Olympiad, which is an international challenge for undergraduate and graduate students on effective public communication on nuclear science and technology. This is a unique opportunity for university students to showcase originality, creativity, and knowledge on nuclear sciences and applications and how these enhance quality of life. During the ISTR-2019 four finalist groups from different countries presented their reports to compete for the first place. The panel of judges consisted of prominent researchers attending the conference as well as IAEA professionals. The winners were a group of five students from the Nuclear Technology Development Centre at the Brazilian Nuclear Energy Commission. The prize for winning the Nuclear Olympiad 2019 was the full paid participation in the WNU short course 'The World Nuclear Industry'.

3.2. WOMEN IN RADIOPHARMACEUTICAL SCIENCES: CHALLENGES AND OPPORTUNITIES

The side event event 'Women in Radiopharmaceutical Sciences. Challenges and Opportunities' took place on 30 October 2019. Ways of strengthening women's representation in Radiopharmaceutical Sciences in the IAEA and in its MSs were the topic of a panel led discussion. The event was opened by Deputy Director General of NA, IAEA. A video, prepared during the ISTR-2019 conference asking the participants about gender parity challenges, was shared with the audience. The number of attendees was approximately 80 persons. Panelists were five ladies and one gentleman, experts in the field of radiopharmacy. The event was moderated by the President of Women in Nuclear Global, Ms. G. Voigt. One of the outcomes of the event was the launch of the network of Women in Radiopharmaceutical Sciences, as part of Women in Nuclear Global. The gender champion of the network is the experienced radiopharmaceutical scientist of the IAEA, Ms. A. Korde. The network was initiated to address the underrepresentation of female scientists in the radiopharmaceutical field.

3.3. RADIOPHARMACEUTICALS FOR HEALTHCARE IN INDIA: CONTRIBUTIONS OF THE DEPARTMENT OF ATOMIC ENERGY

A second side event entitled 'Radiopharmaceuticals for Healthcare in India: Contributions of Dept. of Atomic Energy' was organized by the Indian mission on 29th October 2019. The event showcased the contributions of the Department of Atomic Energy (DAE) constituent units, such as Bhabha Atomic Research Centre (BARC), Board of Radiation and Isotope Technology (BRIT) and Radiation Medicine Centre (RMC), towards the growth of nuclear medicine in India. The event consisted of talks covering the role of DAE in growth of NM in India, highlighting the R&D activities in the field of radiopharmaceuticals, indigenous production and supply of RIs, and RPhs, human resources development for NM as well as patient services offered at the constituent units of DAE. The talks were followed by a question and answer session and the event was appreciated by the scientific community; nearly 60 delegates attended the event.

4. CONCLUSIONS AND OVERALL FINDINGS

This section contains a summary of overall observations, main developments, and trends derived and/or inferred from ISTR-2019, as well as important points of general nature. The key message from ISTR-2019 is that the medical specialty driven by the trio, RI-RPh-NM, is growing and making excellent advances. RPh-NM combo is truly making a difference to patient management and treatment outcome by providing significant additional value in a number of clinical conditions. The major contributions in recent times are in terms of the use of RPhs for PET/CT imaging in diagnostics, and for targeted tumour therapy (especially in patients of NET, prostate cancer). The use of PET tracer for diagnostic or prognostic imaging is invariably a vital element in treatment of cancer patients currently in most parts of the world. RPh based on not only radiolabelled organics, but also radiometal labelled vector-ligand conjugates, dominate the field.

The RI and RPh coverage at ISTR remained predominantly focused on cancer care, though not intended to be so. Coverage of pertinent advances in RI-RPh products for neurology, cardiology and some other areas would have presented a more holistic picture of RPh-NM contributions.

^{225}Ac for alpha therapy and radiometal PET tracers ^{45}Ti and ^{89}Zr, stood out as the emerging key RI (beyond ^{68}Ga and ^{64}Cu) of high interest and potential utility. The proven prospect of facile production of ^{45}Ti and ^{89}Zr using natural targets in existing MCs is the major driver cum rationale for considering further research efforts towards the development of RPh based on these RI. In line with much acclaimed support of the IAEA for its CRPs on ^{64}Cu and ^{68}Ga, among others, it would be beneficial if similar coordinated research efforts under the IAEA auspices would continue to be available to foster and catalyse the production and utilisation of the emerging alpha emitting and PET tracer RIs.

There are concerns due to the lack of accessibility and availability of many useful products in some countries, apart from the issue of their high cost in many cases. Many national centres and entrepreneurs in developing MS face difficulties for obtaining raw materials, including radiochemicals and enriched targets, to sustainably run their national programme to supply RI and RPh to NM centres. The high cost of imaging instrumentation, compounded by the

continual upgrades and frequent launch of further advanced systems (though welcome for image quality, dose reduction, etc.), poses serious challenges to policy makers and finance managers in making funding decisions and budget allocations.

Demands on MC industry will change with the requirement of solid and dedicated liquid target stations to be an essential part of new MC establishments, in order to enable production of many RI of emerging importance, e.g. ^{45}Ti, ^{64}Cu, ^{68}Ga, and ^{89}Zr. It will not be sufficient to just have water target stations for ^{18}F production (apart from gas targets) as the sole or main focus of MC facilities. Also, targetry systems need to be highly 'operator-friendly' to enable reusing the precious enriched target material. MC of Ep >13 MeV energy (variable, preferably) would be in demand, for adopting (p,2n) and (p,n) reaction options for more RI production; i.e. MC of 10–11 MeV is no more likely to be attractive. The simplicity of compact, fixed-energy proton accelerator, cyclotron, has to make way for needs-based alterations/additions, to avail the required incident energy of projectiles on the target(s) for medical RI production.

There is an urgent need for achieving convergence on radiation dosimetry and safety aspects, especially of new RI used, or proposed, for targeted therapy and for theranostics. High energy gammas are present in the decay scheme of many RI under exploration. Positron emission is often only a certain % of the decay of some RI. These impact radiation dosimetry aspects. Thus, it is imperative to take the entire decay scheme of RI into consideration for dosimetry, efficacy and safety purposes. Also, dose to non-target tissues found inevitable, but tolerable with diagnostic dose of RPh, may not be necessarily acceptable when administering therapeutic dose of the same vector-based RPh.

Securing sustainable supplies of medical RI necessitate constant vigilance on the associated socio-economics and operational viability considerations. Enhancing and diversifying options for security of supplies –learned the hard way during and beyond ^{99}Mo/^{99m}Tc supply crisis – form an important lesson for stakeholders dealing with similar key RI needs. For example, the current level of ^{225}Ac availability can help treat only a few thousands of patients every year, while the projected needed doses are for up to half a million patients per year. It would be essential to plan and institute a sustainable economic model in the production and distribution of this important therapeutic RI. The reported project outlays of advanced countries indicate a very high cost for this product.

There is an inevitable need for several enriched targets for RI production, while their reliable availability and cost remain permanent points of concern. In some cases, recycling of such targets is technologically feasible, but certain regulatory issues need to be addressed. Also, commercial interests of large industries dealing with RI and RPh supplies have been known to directly prevent enriched target vendors in making supplies to any others beyond them. It would be worthwhile to engage with them, with the help of the IAEA and national health authorities, to work out possible solutions, without affecting anyone's interests.

There were a number of key phrases, values and take-away home messages cited at ISTR-2019. The following is a short list to give a flavour of such messages articulated at ISTR-2019 (sound-bites):

- "Addressing clinical needs be the primary goal;
- Case for objectively marketing NM-RPh values;
- Selection of the right patient for the right therapy:
- Enable personalised medicine;

— ‘4-A concept’: availability, accessibility, affordability, and appropriateness. This is valid for both NM procedures and RI-RPh products;
— Remain engaged with all the relevant regulators and in a timely manner;
— Every promising result may not necessarily turn out to become a success story. There is need for caution in projecting roles and values of RPh and NM applications to end users and policy-makers, among others”.

RECOMMENDATIONS

The participants of ISTR-2019 requested the IAEA to consider the following:

(1) To continue to foster medical RI and RPh programmes in support of MS, as well as to sustain and further strengthen the support measures;
— To continue addressing the needs for education modules, programmes with certificates and regulatory aspects of radiopharmacy:
(2) To facilitate achieving greater harmonisation – convergence in regulations in the field of RPh – of both pharma-related aspects and of radiation safety;
(3) To seek and support timely inclusion in clinical guidance – standard of care practices, as many of the relevant developments of RPh-NM procedures in clinical management of patients, including the recently proven/emerging roles;
(4) To provide forum to stakeholders to continually address the security and sustainability of supplies of medical RI and RPh; capacity building in the supply chain management;
(5) To make ISTR a quadrennial series event (next ISTR in 2023).

Two other logistical requests were made for consideration in future events of ISTR related to the need for: (i) more space for poster paper displays and (ii) avoiding parallel sessions.

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ABBREVIATIONS

NM	Nuclear Medicine
CRP	Coordinated Research Project
DFO	Deferoxime
FDA	Food and Drug Administration USA
GMP	Good Manufacturing Practice
ISTR	International Symposium on Trends in Radiopharmaceuticals
mAb	Monoclonal antibodies
MC	Medical cyclotrons
MDACC	MD Anderson Cancer Centre
mets	Metastases
MS	Member States
NA	Nuclear Applications
NET	Neuro endocrine tumours
QA	Quality Assurance
QC	Quality Control
R&D	Research and development
RI	Radioisotopes
RPh	Radiopharmaceuticals
RR	Research Reactors
TC	Technical Cooperation
WNU	World Nuclear University

ANNEX: BOOK OF ABSTRACTS

The Book of Abstracts is available in the supplementary electronic files, containing:

- Detailed information of the purpose, objectives, structure and topics covered in the symposium, as well as logistical parameters;
- Scientific committe and scientific secretary members;
- Exhibitors information;
- Detailed programme of the Symposium;
- Abstracts of all participants of oral and poster presentations organized by session;
- IAEA recent publications related to this symposium.

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