REPORT ON JOINT IAEA-JRC WORKSHOP

"SUPPLY OF ACTINIUM-225"

IAEA, Vienna

October 2018

OUTLINE

EDITORS

JOAO ALBERTO OSSO JUNIOR[1], VALERIIA STAROVOITOVA[1], AMIRREZA JALILIAN[1], ARUNA KORDE[1], ALFRED MORGENSTERN[2], FRANK BRUCHERTSEIFER[2], ALBAN KELLERBAUER[2]

[1]INTERNATIONAL ATOMIC ENERGY AGENCY (IAEA); DEPARTMENT OF NUCLEAR SCIENCES AND APPLICATIONS; DIVISION OF PHYSICAL AND CHEMICAL SCIENCES; RADIOISOTOPE PRODUCTS AND RADIATION TECHNOLOGY SECTION; VIENNA; AUSTRIA

[2]EUROPEAN COMMISSION; JOINT RESEARCH CENTRE (JRC); DIRECTORATE FOR NUCLEAR SAFETY AND SECURITY; KARLSRUHE; GERMANY

1. SUMMARY

In October 2018, the IAEA and the Joint Research Centre (JRC) of the European Commission held a two-day workshop on demand and supply of ^{225}Ac. The worldwide need for ^{225}Ac for targeted alpha therapy was clearly demonstrated in several presentations and estimates of demand were given. To meet this demand three main production routes were discussed in detail, including "milking" of stockpiled ^{233}U, spallation of ^{232}Th with high energy proton accelerators, and production of ^{225}Ac from ^{226}Ra with either proton cyclotrons or electron linacs. The advantages and disadvantages of each of the production methods as well as ^{225}Ac supply projections were presented. Numerous speakers from national laboratories, research institutes, and private companies from the United States (US), Canada, Germany, Russia, and other countries shared their most recent results and exchanged the ideas. More than 70 participants from 17 different Member States attended the workshop, which provided them a unique opportunity to discuss their work face-to-face, strengthen the existing collaborations and establish new ones. The workshop addressed the problem of establishing the reliable supply of ^{225}Ac.

2. BACKGROUND AND PURPOSE OF THE WORKSHOP

In 2017, a Practical Arrangement (PA) was signed between the IAEA and The European Commission on Cooperation on Nuclear Science Applications. One of the scopes of this PA is the production and development of the α-emitter ^{225}Ac for medical application. On 11 May 2017 a side event on the EU-IAEA cooperation in nuclear science applications was held at the IAEA, followed by a meeting between Mr Joao Osso Jr., Head of the IAEA Radioisotope Products and Radiation Technology Section, and Mr Alfred Morgenstern, Project Leader at the JRC, was conducted. The meeting concluded that the first step of the cooperation should be the implementation of a workshop on "Supply of Ac-225". The purpose of this event would be to bring together producers, distributors, and users of ^{225}Ac and to discuss the status of ^{225}Ac production and steps necessary to provide its stable and reliable supply.

3. AGENDA AND LIST OF PARTICIPANTS

WORKSHOP ON "SUPPLY OF ACTINIUM-225"

VIENNA INTERNATIONAL CENTER - ROOM M2-
9-10 OCTOBER 2018

DAY 1: TUESDAY OCT. 9th

9:00 - 9:20	**Welcome Session** • *Joao Osso, IAEA* • *Aldo Malavasi, DDG-NA* • *Maria Betti, Director JRC* • *Jehanne Gillo, Director DOE*
9:20 - 9:40	**Opening Statements** • *Joao Osso, IAEA* • *Alfred Morgenstern, JRC*
9:40 - 10:00	**Session 1: Clinical Applications of Ac-225** • *TBD general*
10:00 - 10:30	**Coffee Break** 
10:30 - 12:10	**Session 1.1: Clinical Applications of Ac-225 Reports** **Moderator: TBD** • *Clemens Kratochwil, University Hospital Heidelberg* • *Mike Sathegke, University of Pretoria* • *Leszek Krolicki, Medical University Warsaw* • *Mattias Eiber, Technical University Munich* • *Joseph Jurcic, University of Columbia*
12:10 - 12:30	**Session 1.2: Alpha-radiopharmaceuticals: from bench to bed experience** • *Juergen Gay, Bayer*
12:30 - 14:00	**Lunch Break** 
14:00 - 14:20	**Session 2: Production of Ac-225** • *Alfred Morgenstern, JRC*

14:20 - 15:30	**Session 2.1: Production of Ac-225 from Th-229** **Moderator: Frank Bruchertseifer** • *Saed Mirzadeh, ORNL* • *Frank Bruchertseifer, JRC* • *Nikolay Nerozin, IPPE* • *Patrick Causey, CNL* • *Kenneth Czerwinski, Terrapower*
15:30 - 16:00	**Coffee Break** 
16:00 - 16:40	**Session 2.1: Production of Ac-225 from Th-229 (discussions)** **Moderator: Frank Bruchertseifer**
16:40 - 17:30	**Session 2.2: Production of Ac-225 from photonuclear reactions** **Moderator: Joao Osso, IAEA** • *Valeria Starovoitova, IAEA* • *Paul Schaffer, TRIUMF* • *Sergey Chemerisov, ANL*
17:30 - 19:30	**Reception** 

DAY 2: WEDNESDAY OCT. 10th

9:00 - 10:30	**Session 2.3: Production of Ac-225 from Th-232 spallation** **Moderator: Wolfgang Runde** • *Saed Mirzadeh, ORNL* • *Cathy Cutler, BHNL* • *Kevin John, LANL* • *Boris Zhuikov, Institute for Nuclear Research* • *Paul Schaffer, TRIUMF* • *Thierry Stora, CERN* • *Jim Harvey, NorthStar*
10:30 - 11:00	**Coffee Break** 
11:00 - 11:30	**Session 2.3: Production of Ac-225 from Th-232 spallation (discussions)** **Moderator: Wolfgang Runde**

11:30 - 12:30	**Session 2.4: Production of Ac-225 from Ra-226** **Moderator: TBD** • *Alfred Morgenstern, JRC* • *Jan Stursa, NPI Rez* • *Oscar Pozzi, CNEA* • *Kyo Chul Lee, KIRAMS* • *Viplav Gupta, DKFZ* • *Herrmann Schweickert, Zyklotron AG Karlsruhe* • *Jun Hatazawa, Osaka University* • *Dennis Elema, SCK-CEN*
12:30 - 14:00	**Lunch Break**
14:00 - 15:00	**Session 2.4: Production of Ac-225 from Ra-226 (discussions)** **Moderator: TBD**
15:00 - 15:30	**Session 2.5: DOE Isotope Program: Focus on Ac-225** • *Jehanne Gillo, DOE*
15:30 - 16:00	**Coffee Break and Adjourn Meeting for non- IAEA-JRC Participants**
16:00 - 17:30	**Session 3: Discussions and preparation of report** • *IAEA+JRC*
17:30	**Adjourn Meeting** **END**

	Country	***Name***	***Email***
1	***Argentina***	*Mr Oscar Rodolfo Pozzi*	pozzi@cae.cnea.gov.ar
2	***Belgium***	*Mr Jean Geets*	Jean-Michel.Geets@iba-group.com
3	***Belgium***	*Mr Dennis Ringkjobing Elema*	dennis.elema@sckcen.be
4	***Canada***	*Mr Eric Burak*	burak@fusionpharma.com
5	***Canada***	*Mr Patrick Causey*	patrick.causey@cnl.ca
6	***Canada***	*Mr Robert Holmes*	robert.holmes@cnl.ca
7	***Canada***	*Mr Jacob Vienneau*	jacob.vienneau@cnl.ca
8	***Canada***	*Mr Paul Schaffer*	PSchaffer@triumf.ca
9	***Cuba***	*Mr Rene Leyva Montana*	rene@centis.edu.cu
10	***Cuba***	*Ms Mariela León Pérez*	mariela@centis.edu.cu
11	***Czech Republic***	*Mr Jan Kozempel*	jan.kozempel@fjfi.cvut.cz
12	***Czech Republic***	*Mr Ondrej Lebeda*	lebeda@ujf.cas.cz
13	***Czech Republic***	*Mr Jan Stursa*	stursa@ujf.cas.cz
14	***Finland***	*Mr Ari Virtanen*	ari.virtanen@iyu.fi
15	***France***	*Mr Richard Zimmermann*	rgz@morphopharma.com
16	***Germany***	*Mr Frank Bruchertseifer*	frank.bruchertseifer@ec.europa.eu
17	***Germany***	*Mr Roberto Caciuffo*	Roberto.Caciuffo@ec.europa.eu
18	***Germany***	*Mr Matthias Eiber*	matthias.eiber@tum.de
19	***Germany***	*Mr Jürgen Gay*	
20	***Germany***	*Mr Viplav Gupta*	v.gupta@dkfz-heidelberg.de
21	***Germany***	*Mr Richard Henkelmann*	richard.henkelmann@itg-garching.de
22	***Germany***	*Mr Alban Kellerbauer*	a.kellerbauer@mpi-hd.mpg.de
23	***Germany***	*Mr Klaus Kopka*	k.kopka@dkfz-heidelberg.de
24	***Germany***	*Mr Clemens Kratochwil*	Clemens.Kratochwil@med.uni-heidelberg.de
25	***Germany***	*Mr Alfred Morgenstern*	Alfred.MORGENSTERN@ec.europa.eu
26	***Germany***	*Mr Oliver Neels*	o.neels@dkfz-heidelberg.de
27	***Germany***	*Mr Franz Oberdorfer*	franz.oberdorfer@zyklotron-ag.de

28	***Germany***	*Mr Hermann Schweickert*	hermann.schweickert@zyklotron-ag.de
29	***Japan***	*Mr Jun Hatazawa*	hatazawa@tracer.med.osaka-u.ac.jp
30	***Japan***	*Mr Tatsuya Higashi*	higashi.tatsuya@qst.go.jp
31	***Japan***	*Mr Kotaro Nagatsu*	nagatsu.kotaro@qst.go jp
32	***Korea, Republic of***	*Mr Seung Dae Yang*	sdyang@kaeri.re.kr
33	***Korea, Republic of***	*Mr Kyo Lee*	kyochul@kirams.re.kr
34	***Korea, Republic of***	*Mr Sang-Moo Lim*	smlim328@kcch.re.kr
35	***Netherlands***	*Mr Klaas Bakker*	k.bakker@nrg.eu
36	***Poland***	*Mr Leszek Krolicki*	leszek.krolicki@wum.edu.pl
37	***Poland***	*Ms Renata Mikolajczak*	Renata.Mikolajczak@polatom.pl
38	***Russian Federation***	*Mr Stepan Khamianov*	skhamyanov@ippe.ru
39	***Russian Federation***	*Mr Valery Radchenko*	vradchenko@triumf.ca
40	***Russian Federation***	*Ms Olga Valzdorf*	OVValzdorf@isotop.ru
41	***Russian Federation***	*Mr Boris Zhuikov*	bz@inr.ru
42	***South Africa***	*Mr Martin Magwaza*	martin@bgmpharma.co.za
43	***South Africa***	*Mr Brian Mphahlele*	brian.mphahlele@necsa.co.za
44	***South Africa***	*Mr Machaba Sathekge*	mike.sathekge@up.ac.za
45	***Switzerland***	*Mr Adrian Merlo*	adrian.merlo@bluewin.ch
46	***Switzerland***	*Mr Thierry Stora*	thierry.stora@cern.ch
47	***United States***	*Ms Rebecca Abergel*	abergel@berkeley.edu
48	***United States***	*Ms Alison Armour*	AArmour@Endocyte.com
49	***United States***	*Mr Roy Brown*	Roy.BROWN@curiumpharma.com
50	***United States***	*Mr Erik Chelius*	ErikChelius@Endocyte.com
51	***United States***	*Mr Sergey Chemerisov*	chemerisov@anl.gov
52	***United States***	*Ms Cathy Sue Cutler*	ccutler@bnl.gov
53	***United States***	*Mr Ken Czerwinski*	kczerwinski@terrapower.com
54	***United States***	*Mr Marc Garland*	Marc.Garland@science.doe.gov
55	***United States***	*Ms Jehanne Gillo*	jehanne.gillo@science.doe.gov
56	***United States***	*Mr James Harvey*	jharvey@northstarnm.com
57	***United States***	*Mr Kevin John*	kjohn@lanl.gov
58	***United States***	*Mr Joseph Jurcic*	jgj2110@cumc.columbia.edu
59	***United States***	*Ms Ourania Kosti*	okosti@nas.edu
60	***United States***	*Mr Richard McKannay*	rhm@isoflex.com
61	***United States***	*Mr George Messina*	gmessina@northstarnm.com

62	***United States***	*Mr Wolfgang Runde*	runde@lanl.gov
63	***United States***	*Mr John Vincent*	jvincent@ionetix.com
64	***United States***	*Mr Henry Padgett*	henry.padgett@cardinalhealth.com
65	***IAEA***	*Mr Joao Alberto Osso Jr*	J.A.Osso-Junior@iaea.org
66	***IAEA***	*Mr Amir Jalilian*	A.Jalilian@iaea.org
67	***IAEA***	*Ms Aruna Korde*	A.Korde@iaea.org
68	***IAEA***	*Ms Valeriia Starovoitova*	V.Starovoitova@iaea.org
69	***IAEA***	*Mr Arjan Koning*	A.Koning@iaea.org
70	***IAEA***	*Mr Francesco Giammarile*	F.Giammarile@iaea.org
71	***IAEA***	*Ms Vojna Ngjeqari*	V.Ngjeqari@iaea.org

4. SUMMARY OF PRESENTATIONS (ABSTRACTS)

Clinical Applications of Ac-225

C. Kratochwil

University Hospital Heidelberg, Department of Nuclear Medicine, Heidelberg, Germany

Clinical need: Until now, in Heidelberg, 25 patients with neuroendocrine tumors and one patient with melanoma have been treated with ^{213}Bi-DOTATOC or ^{213}Bi-cMSH, respectively. In addition, 38 patients with neuroendocrine tumors and 200 patients with prostate cancer have been treated with ^{225}Ac-DOTATOC and ^{225}Ac-PSMA-617. For all mentioned radiopharmaceuticals also beta-emitting counterparts based on ^{90}Y or ^{177}Lu are available. In brief, in comparison to these historical controls our experience with the related alpha-therapies consistently demonstrates a gradual and clinically interesting improvement of response rates and deepness of response (radiological and tumor-markers).

Quantitative demand: Our treatments have been given in fractionated doses over several cycles; the summed treatment activities are about 30-50 MBq ^{225}Ac per patient. Worldwide 80,000 patients die from prostate-cancer each year and would have been possible candidates for alpha-radiation therapies; however, the remaining demand, once a ^{177}Lu-radioligand has been established, for a particular indication is hard to predict. Nevertheless, several promising shuttle molecules are currently under development and, if directly approved as alpha-emitter labeled therapeutics, success in 2-3 epidemically less important tumor entities could drive a quantitative similar clinical need.

Qualitative issues: Impurities from long half-life nuclides are typically not relevant for the patient's safety, but environment protection and waste disposal can be a relevant issue. In Germany, the general exemption level for ^{227}Ac is 1kBq, which would be 0.0001% of a 10 MBq ^{225}Ac patient dose; but for radiopharmaceuticals exceptions are possible. For example, the general exemption level for ^{227}Th is 10kBq but clinically approved ^{223}Ra can contain up to 0.5% ^{227}Th and 0.004% ^{227}Ac in a 6 MBq ^{223}Ra dose. Regulations may vary between different countries but according to the physician's personal opinion, producers should try to keep their ^{227}Ac impurities <0.01% of ^{225}Ac.

^{225}Ac-PSMA-617 in advanced prostate cancer

M. Sathekge

Steve Biko Academic Hospital, University of Pretoria, South Africa

The limited effective therapies available for castration-resistant prostate cancer (mCRPC) despite the high mortality and morbidity associated with this aggressive disease emphasizes a need for continued effort to broaden treatment options available for this phase of the disease. Targeted radionuclide therapy technique has been successfully used in the treatment of different cancers including differentiated thyroid carcinoma and metastatic neuroendocrine neoplasms. The prostate cancer cells express the prostate-specific membrane antigen (PSMA) on its surface. Higher level of PSMA expression is found in metastatic and castration-resistant forms of prostate cancer. PSMA has been targeted for imaging and therapy of prostate cancer. The earlier experience with PSMA-based radioligand therapy (RLT) was with the use of Luttetium-177 (^{177}Lu), a beta emitter. The effectiveness of ^{177}Lu-PSMA RLT has been shown in several studies with tolerable side effects. Up to about 30% of patients will, however, not respond to ^{177}Lu-PSMA RLT.

Fortunately, ^{225}Ac- Prostate-specific membrane antigen (PSMA)-617, initially developed and characterised at JRC Karlsruhe in 2013, is a highly promising novel compound for therapy of prostate cancer. A remarkable therapeutic efficacy has been demonstrated in heavily pre-treated metastatic castration-resistant prostate cancer (mCRPC) patients, with xerostomia as the main side effect in Heidelberg, Germany. The excellent results have since led to University of Pretoria exploring the impact of ^{225}Ac-PSMA-617 in both heavily and less heavily pre-treated patients and also addressing the major challenge of ^{225}Ac-PSMA-617 therapy of damage to the salivary glands.

Conclusions/lessons from our experience:

Efficacy:
- Tumor shrinkage
- Symptom relief and QoL improvement
- Biomarker reduction
- Impact on survival

Tolerability:
- Nephro and Hematological toxicity well tolerated (limited/none)
- Xerostomia (mainly G1)

Interdisciplinary approach is essential for the implementation of ^{225}Ac-PSMA-617:
- Indicated for extensive skeletal metastases – not suitable for ^{177}Lu-PSMA and for patients not qualifying for other conventional therapies or refuse conventional therapies
- Determine the activity/dose (de-escalation approach)
- Need for a prospective Phase Trial I/II
- Explore cyclotron-based production of ^{225}Ac

Targeted alpha therapy of glioblastoma multiforme: clinical experience with ^{225}Ac-Substance-P

L. Krolicki[1], F. Bruchertseifer[2], J. Kunikowska[1], H. Koziara[3], B. Królicki[3], M. Jakuciński[4], D. Pawlak[5], C. Apostolidis[2], R. Rola[6], A. Merlo[7], A. Morgenstern[2]

[1] *Department of Nuclear Medicine, Medical University of Warsaw, Warsaw, Poland*

[2] *European Commission, Joint Research Centre, Karlsruhe, Germany*

[3] *Department of Neurosurgery, Institute of Oncology, Warsaw, Poland*

[4] *Department of Nuclear Medicine, Brodnowski Hospital, Warsaw, Poland*

[5] *Radioisotope Centre POLATOM, National Centre for Nuclear Research, Otwock, Poland*

[6] *Department of Neurology, Military Institute of Aviation Medicine. Warsaw, Poland*

[7] *University of Basel, Switzerland*

Treatment of patients with recurrent glioma is very limited and the overall survival from the diagnosis (for GBM) is 6-9 months. Introduction of new options of treatment is critically important for this group of patients. Gliomas are characterized by a high expression of receptors for Substance –P (SP), regardless of the histological grading. Therefore, SP labeled with alpha emitters was used for local application into the tumour. Local application reduces systemic adverse effects of the drug as well as the protective effect of the Blood-Brain-Barrier. Moreover, alpha rays have many advantages: tissue range is less than 100 μm; hypoxia and cell cycle are not critical to the effect of radiation. Initially, ^{213} Bi was used for labeling of SP; bismuthium is convenient for labeling of peptides, and short T1/2 of ^{213}Bi ($T_{1/2}$ = 46 min) is beneficial for radiation protection. Currently, 225Ac was introduced. It seems that a diverse range of energy, as well as longer T1/2 (10 days) should favor a better distribution of the radiopharmaceutical into the tumor.

Twenty-one patients with histologically confirmed recurrence of the glia tumor grade II-IV were treated (grade II - 1 patient, grade III - 8 patients, grade IV - 12 patients). All patients received a standard treatment (surgery + radio-chemo-therapy). When a recurrence/progression was diagnosed, an intracavitary/intratumoral injection of 20-40 MBq ^{225}Ac-SP was applied every 2 months (1-7 injections). Monitoring of toxicity and overall survival was indicated as the first goal of the study.

Results: PFS ranges between 2.4 up to 17.6 months, OS from primary diagnosis ranges between 7.9 up to 114.7 months, OS from diagnosis of recurrence – 4.7 up to 41.4 months, and OS from start of radioisotopic treatment – 1.7 up to 35.0 months.

Intracavitary/intratumoral injection of ^{225}Ac-substance P is tolerated well. Only mild temporary adverse effects (edema, epileptic seizures, aphasia) were observed. It seems that the presented method using 225Ac is promising and requires further clinical trials.

Safety and Efficacy of Ac-225-PSMA-617 In mCRPC After Failure of Lu-177-PSMA

M. Eiber, A. Morgenstern

Department of Nuclear medicine, Klinikum rechts der Isar, TUM, München, Germany

Despite several new agents have been approved in the last years metastatic castration resistant prostate cancer (mCRPC) is still a major medical challenge. The beta-emitter 177Lu-PSMA radioligand therapy (RLT) is applied under compassionate use in several countries but its antitumor effect can decrease over time. Preliminary data exist on the treatment with Actinium-225-PSMA (Ac-225-PSMA) as alpha-emitter. The aim of this retrospective analysis was to investigate safety and efficacy of Ac-225-PSMA-617 RLT in mCRPC after failure of Lu-177-PSMA.

Fifteen 15 mCRPC patients (mean age of 72, range 48 - 84) who underwent Ac-225-PSMA-617 RLT between 10/17 to 06/18 were included in the analysis. All patients were previously treated with second line antihormonal treatment (80% abiraterone, 87% enzalutamide), chemotherapy (93% docetaxel, 53% Cabazitaxel) and showed progression after treatment with Lu-177-PSMA. A baseline PSMA-PET/CT exhibited high PSMA-expression in the majority of tumor lesions and patients were treated in 8 weekly until progression or relevant side effects. Each cycle was following by restaging PSMA-PET/CT after 6 weeks. Prostate-specific antigen (PSA) and blood cell count were measured every 2 weeks.

We report safety data, antitumor response with prostate specific antigen (PSA) declines and radiographic tumor response as well as clinical outcome with changes in Eastern Cooperative Oncology Group (ECOG) performance status and pain severity. Hematological and non-hematological side effects were graded using CTCAE criteria.

Fifteen patients underwent a median of 24 cycles of Ac-225-PSMA-617 (range: 1-3) with a mean dose of 9 MBq Ac-225-PSMA617. 7 patients received only 1 cycle, 6 patients 2 cycles and 2 patients 3 cycles. The baseline PSA was 758 ng/ml (range 49 – 4073). 10/15 patients showed any PSA-decline, 5/15 a PSA-decline of ≥50% and 3 patients no PSA-decline at any time. Grade 1-2 xerostomia occurred in 14 and 1 patient, respectively. 5/15 patients requested to stop treatment due to xerostomia. Two patients developed grade 2 renal insufficiency, 4 patients grade 3-4 anemia, 2 patients grade 3 thrombocytopenia.

In this small cohort Ac-225-PSMA-617 RLT showed antitumor effect in mCRPC after Lu-177-PSMA failure. However, treatment had to be stopped in one third of the patients due to xerostomia.

Alpha-Particle Therapy for Acute Myeloid Leukemia

J. Jurcic

Columbia University, Irving Medical Center, New York, NY, USA

Radioimmunotherapy represents an attractive strategy to deliver radiation selectively to tumor and other target organs while minimizing toxicity to normal tissues. Leukemia is ideally suited to this approach because of the easy accessibility of malignant cells in the blood and bone marrow and its well-defined antigenic targets. Because α-particles have a shorter range and higher linear energy transfer than β-particles, targeted α-particle therapy offers the potential for more efficient tumor cell killing while sparing surrounding normal cells. We developed a first-generation α-emitting construct for the treatment of acute myeloid leukemia (AML), ^{213}Bi-lintuzumab, which targets the myeloid cell-surface antigen CD33. An initial phase I clinical trial conducted in 18 patients with relapsed and refractory AML provided proof-of-principle that systemically administered targeted α-particle therapy was feasible, safe, and had anti-tumor activity in humans[1].

We subsequently showed that cytarabine followed by ^{213}Bi-lintuzumab produced remission in 33% of patients with newly diagnosed patients with AML who could not tolerate intensive chemotherapy and patients with untreated relapsed AML[2]. A more potent second-generation construct containing ^{225}Ac, a radiometal that generates 4 α-particle emissions, was then developed[3]. A phase I study demonstrated that a single dose of ^{225}Ac-lintuzuamb was safe at doses of 111 kBq/kg or less and resulted in reductions in bone marrow leukemia cells in 67% of patients with relapsed or refractory AML[4]. Based on these findings, fractioned doses of ^{225}Ac-lintuzumab (18.5-74 kBg/kg/fraction) were combined with low-dose cytarabine in a phase I trial conducted in older patients with AML. Five of 18 patients (28%) had objective response[5]. Although a maximum tolerated dose was not reached, 74 kBk/kg/fraction was chosen as the phase II dose to limit myelosuppression. In a subsequent phase II study conducted in older AML patients, objective responses were seen in nine of 13 patients (69%)[6]. ^{225}Ac-lintuzumab has shown significant activity in AML both alone and in combination with chemotherapy.

Future development of ^{225}Ac-lintuzumab includes combinations with standard chemotherapy and novel targeted agents, as well as treatment for minimal residual disease and conditioning before hematopoietic cell transplantation.

[1] Jurcic JG *et al. Blood* 2002; 100:1233-1239
[2] Rosenblat TL *et al. Clin Cancer Res* 2010; 16:5303-5311
[3] McDevitt MR *et al. Science* 2001; 294:1537-1540
[4] Jurcic JG *et al. Blood* 2011; 118:768
[5] Jurcic JG *et al.* SNMMI 2017; Abstract 456
[6] Finn LE *et al. Blood* 2017; 130:2638

United States Department of Energy Production of Actinium-225 from Thorium-229

M. Garland

DOE Isotope Program, U.S. Department of Energy, Washington, DC, USA

The United States Department of Energy (DOE) recovered approximately 140 mCi of thorium-229 (Th-229) from legacy uranium-233 processing solutions in the 1990s and stores the Th-229 in four fractions (cows) in a hot cell at the Oak Ridge National Laboratory (ORNL) for the provision of actinium-225 (Ac-225). Since 1997, DOE has supplied the majority of Ac-225 used in medical application research, either as dried Ac-225 nitrate or loaded on an actinium-225/bismuth-213 generator. Typically, DOE produces 700-900 mCi per year depending on customer demand, with a maximum capability of approximately 1,000 mCi per year. ORNL is currently conducting the 144th production campaign and made over 200 shipments to researchers last year. Separation of Ac-225 from Th-229 cows provides pure Ac-225 (no other Ac isotopes) and is decoupled from active production by irradiation of targets. Anion and cation exchange chromatography is used for the separation and purification of Ac-225 with steps to first separate the Ac-225 and Ra-225 from the Th-229, and the separation of Ac-225 from bulk radium performed in a hot cell due to the radiation dose associated with the Th-228 (the decay chain results in Ra-224 in the radium fraction) that is also present in the Th-229 cows. The separated Ac-225 is taken to a glovebox line for final purification and packaging for shipment to customers. The radium pool that remains in the hot cell is processed periodically while the Ra-225 continues to decay to useful amounts of Ac-225. In addition to necessitating a hot cell to store and process >100 mCi of Th-229, there is a practical limit of 100 mCi of Ac-225 in the glovebox line due to dose limitations to the radiochemists performing glovebox operations.

To increase the amount of Th-229 available for Ac-225 production, DOE is conducting research and development on reactor production of Th-229 by irradiation of radium-226 (Ra-226) targets in the High Flux Isotope Reactor (HFIR). Due to the triple neutron capture required to transform Ra-226 into Th-229, a high flux reactor is required to achieve reasonable Th-229 yields. Projections are that up to 23 mCi of Th-229 per gram of Ra-226 will be produced in one year of irradiation in HFIR (six reactor cycles of approximately 25 days each). Test irradiations to optimize target design and measure yields will be performed through 2019 and production will commence upon successful completion of the research and development. It is expected that tens of grams of Ra-226 could be irradiated on an annual basis to produce hundreds of mCi of Th-229 per year. Each Ci added to the Th-229 cows will provide at least 70 Ci of pure Ac-225 per year.

Production of Actinium-225 from Thorium-229 at JRC Karlsruhe

A. Morgenstern, F. Bruchertseifer

European Commission, Joint Research Centre, Directorate for Nuclear Safety and Security, Karlsruhe, Germany

JRC Karlsruhe started the production of ^{225}Ac through radiochemical extraction from ^{229}Th at the beginning of the 1990's and has been the first laboratory to produce ^{225}Ac / ^{213}Bi for clinical application. The ^{229}Th source available at JRC Karlsruhe consists of 215 mg (≈ 1,7 GBq) of ^{229}Th yielding a total annual production of approximately 13 GBq of ^{225}Ac in up to 24 production cycles. The maximum activity available in a single batch is typically ≈ 1.3 GBq. The process used for the separation of ^{225}Ac from ^{229}Th is a two-step process based on the combination of ion exchange and extraction chromatographic processes. The ^{229}Th source, containing an approximately 150 fold excess of natural ^{232}Th, is stored as a batch adsorbed on anion exchange resin in 8 M HNO_3. At regular time intervals, typically every 8-9 weeks, ^{225}Ra and ^{225}Ac are separated from ^{229}Th / ^{232}Th using anion exchange in nitric acid media. In the second step of the separation process, ^{225}Ac is separated from ^{225}Ra and residual traces of ^{229}Th / ^{232}Th by extraction chromatography using UTEVA and DGA resins. The ^{225}Ra fraction is stored for subsequent extractions of ^{225}Ac in 2-3 week intervals. The separation process has a yield exceeding 95% and is quality controlled by alpha and gamma spectrometry as well as ICP-MS. The resulting ^{225}Ac product is carrier-free with a radiochemical purity of > 99.98% containing < 2 x 10^{-5} of ^{225}Ra and < 9 x 10^{-5} of ^{233}U / ^{229}Th relative to the activity of ^{225}Ac. To date JRC Karlsruhe has prepared > 500 batches of ^{225}Ac / ^{213}Bi, with a total of > 300 GBq ^{225}Ac for preclinical and clinical research conducted in house or in collaboration with partners in Europe, Africa, Asia, Australia and North and South America. ^{225}Ac is prepared as dried nitrate or chloride, or loaded on a radionuclide generator made from AG MP-50 cation exchange resin. The generator can be loaded with activities up to 4 GBq Ac-225 and shown to allow yields of ^{213}Bi elution of 76±3 % and a breakthrough of ^{225}Ac of 59±60 ppb for > 50 elutions performed during several weeks.

Current Status and Perspective of Actinium-225 Production at JSC "SSC RF – IPPE"

N.A. Nerozin, S.V. Khamianov, V.V. Shapovalov, S.V. Tkachev

JSC "SSC RF – IPPE", Obninsk, Russia

Alpha-emitting radionuclides are highly promising products for radiation therapy. They demonstrate a huge potential for treating a wide spectrum of malignant diseases because, having been delivered to tumor cells, they destruct them while lesion of neighboring organs is minimal. JSC "SSC RF – IPPE" has been engaged in activities on ^{225}Ac extraction from ^{229}Th and ^{225}Ac purification since 2002. 150 mCi of ^{229}Th have been produced by processing ^{233}U. By present day more than 2Ci of ^{225}Ac were supplied to medical institutions which developed methods of therapy of various diseases worldwide, mainly in the USA and Germany. The concentration of Th-228, Th-229 is <0.007 %A and that of Ra-224, Ra-225 is <0.02%A in the supplied product. The total concentration of inactive impurity cations is <0.3 μg/mCi, and they are Ca, Mg, and Al for the most part. The production capacity of JSC "SSC RF – IPPE" is about 420 mCi/year of ^{225}Ac with 5 days pre-calibration from a delivery date.

An alternative to the abovementioned technology can be Th-229 production from Ra-228. The Project main goal is to develop a new process for gettingTh-229 radioisotope that is the raw material for the production of Ac-225 radioisotope. The proposed process bases on Th-229 production from the irradiated Ra-228. Ra-228 is accumulated in natural thorium (Th-232) decay (in the nature Ra-228 accompanies Th-232 in the ratio of ≈0.4 mg per 1 ton of ^{232}Th (^{228}Ra /^{230}Th ≈ $2\cdot10^{-5}$). The other alternative for getting sizeable amounts of ^{229}Th is based on the application of a radionuclide from uranium decay chain - ^{230}Th ($T_{1/2}$ = 75 thousand years). In the nature Th-230 accompanies uranium-238 in the ratio of 20 g per 1 ton of ^{238}U (^{230}Th/^{238}U ≈ $2\cdot10^{-5}$). ^{230}Th is recovered from the Earth's interior when mining uranium ore. When uranium is separated ^{230}Th with the other daughter products is sent to waste piles. A large stock of ^{230}Th has been accumulated in waste piles of separation plants as a result of production of the enriched ^{235}U.

Preliminary evaluations show that considerable amounts of ^{229}Th can be obtained by the following nuclear reactions:

1. ^{230}Th(n,2n)^{229}Th - ^{230}Th irradiation by fast neutrons in a nuclear reactor;
2. ^{230}Th(p,pn)^{229}Th - ^{230}Th irradiation by protons in a cyclotron;
3. ^{230}Th(γ,n)^{229}Th – ^{230}Th irradiation in a linear accelerator of electrons;
4. ^{230}Th(p,2n)^{229}Pa (1.4d)→^{299}Th – ^{230}Th irradiation by protons in a cyclotron.

Calculations and theoretical studies demonstrate that the photonuclear reaction on Th-230 will be the most promising method.

Production of a Thorium/Actinium Generator at the Canadian Nuclear Laboratories

P. Causey

Canadian Nuclear Laboratories, Chalk River, Canada

The therapeutic potential of alpha emitting radioisotopes for the treatment of metastatic cancers has been demonstrated in a clinical setting. At the Canadian Nuclear Laboratories (CNL), Chalk River ON., work is being conducted to produce an isotope generator using ^{233}U as source material to construct a Th/Ac generator, which is to be used to provide a regular supply of ^{225}Ac. A limited and controlled supply of aged ^{233}U from previous fuel development programs is available at CNL. Work is continuing to manually process the remaining stockpile of ^{233}U to increase the size of the generator, such that a supply of ^{225}Ac is readily available to support internal and collaborative efforts pertaining to preclinical TAT research within CNL and with external academic investigators.

A thorium fraction containing primarily the desired isotope (^{229}Th) has been isolated through a combination of anion exchange and extraction chromatographic techniques. Similarly, following implementation of a modified Eichrom® method for the extraction of Actinium, purified ^{225}Ac was isolated and labeled to an anti-epidermal growth factor receptor (EGFR) antibody. ^{225}Ac-DOTA-nimotuzumab is a potential radioimmunotherapeutic agent against EGFR positive cancers.

Currently, the ^{233}U source material has been processed and characterized by alpha spectroscopy and mass spectroscopic methods. In addition, the solution of dissolved ^{233}U and daughter isotopes have been radiochemically separated, to yield a supply of ^{229}Th that has been similarly characterized. Regular milking of the generator has yielded MBq quantities of purified ^{225}Ac. Furthermore, in an effort to increase the performance of the Th/Ac generator, an automated system is being integrated into the process, which will improve the regular milking of the system. The resulting ^{225}Ac was used to label DOTA-nimotuzumab with a radiochemical yield of 25% (95% radiochemical purity upon purification) and a specific activity of 0.03 MBq/µg.

To support internal and collaborative research programs in Targeted Alpha Therapy, CNL has recently constructed a 10 mCi scale Th/Ac generator to regularly provide access to this valuable isotope. The recent results pertaining to this area of the research will be presented.

Production of ^{225}Ac from ^{229}Th

K. Czerwinski

TerraPower LLC, Bellevue, WA, USA

The presentation provides an overview of TerraPower, LLC, the company directions, and the activities related to generation of ^{225}Ac from ^{229}Th. TerraPower is a nuclear technology company located in Bellevue, Washington, USA. The company uses mission driven innovation to develop nuclear based technology with a positive societal impact. Reduction of CO_2 emission in electricity generation is an ongoing effort that is address through the development of novel fast reactors; the traveling wave reactor and the molten chloride fast reactor. The medical application of radioisotopes is pursued by TerraPower as another beneficial use of nuclear technology. TerraPower capabilities for medical isotope efforts primarily engaged the developed radiochemistry expertise within the company. TerraPower was founded in 2007 by Bill Gates, who is the company chairman. TerraPower has the largest private section advanced fast reactor staff in the United States. The company has a history of research collaboration and currently manages over 80 contracts and agreement with the US Department of Energy, university, and global government entities. TerraPower has a range of capabilities related to medical isotopes. The company currently has a specific radioactive material license to work with medical isotopes, including ^{229}Th and ^{255}Ac. Protocols and material work plans have been developed within the radioactive materials license. Relevant studies related to ^{229}Th recovery and the generation of ^{225}Ac are going at TerraPower and cooperating universities.

The ^{229}Th to be obtained by TerraPower have been identified from ^{233}U stock within the US Department of Energy and include medical isotope applications[1]. These identified stocks have around 45 g of ^{229}Th. Routes for the separation of ^{229}Th from the ^{233}U by ion exchange has been documented in the literature, with specific mention of this specific ^{233}U material[2]. The amount of ^{232}U in the ^{233}U is up to 220 ppm, resulting in a potential handling gamma dose from the ^{208}Tl daughter. The expected ^{225}Ac product from TerraPower is expected to include the nitrate or chloride compound[3] or generators from the decay of ^{225}Ra to ^{225}Ac[4,5]. TerraPower expects to provide material to the radiopharmaceutical community by 2020 from ^{229}Th.

[1] Forsberg and Lewis, Uses For Uranium-233: What Should Be Kept for Future Needs, ORNL-6952, 1999.
[2] Laue and Nash eds.; ACS Symposium Series, Ch. 13 (Du et.al.), 2003.
[3] Morgenstern et. al., Curr. Radiopharm, 2012
[4] Włodzimirska et. al., Radiochim. Acta, 2003
[5] McAlister and Horwitz, Radiochim. Acta., 2011

High-Purity Ac-225 Production from Ra-226 using a Superconducting Electron Linac

V. N Starovoitova, T. L. Grimm, A. K. Grimm, W. C. Peters, M. A. Zamiara

Niowave Inc, Lansing, MI, USA

Niowave is operating a closed-loop cycle to domestically produce high-purity Ac-225 and other alpha emitters from Ra-226 using a superconducting electron linear accelerator. The commercial-scale system will produce 10 Ci per week of Ac-225 from a nitrate-based solution of Ra-226. The electron beam impinges on a photon converter to irradiate the Ra-226, inducing a photon-neutron reaction to Ra-225, which decays to Ac-225. Ac-225 is eluted continuously from the target vessel then centrifugal contactors are used to harvest and purify Ac-225 through a separation cascade.

Unlike other production methods, including proton linacs (spallation of Th-232) and proton cyclotrons (Ra-226 bombardment), Niowave's method does not generate any Ac-227 contamination in the Ac-225 product. Niowave's superconducting linacs can handle higher production output (>500 Ci per year using a 20 MeV, 210 kW beam) than any other method. Demonstration-scale production of 10 mCi batches of Ac-225 at Niowave's HQ has begun and will be complete in April 2019. Niowave is in a unique position to quickly take the lead in alpha-emitters for cancer therapy because they have expertise in superconducting electron linacs and an NRC materials license to possess and irradiate Ra-226 while capturing gaseous radioisotopes and progeny. This presentation will focus on Niowave's scale up plans to full production including radium acquisition, NRC and FDA licensing strategies, and a path to profitability.

Production of Ac-225 from photonuclear reactions: TRIUMF ARIEL

P. Schaffer

TRIUMF, Vancouver, BC, Canada

From its inception, the Life Sciences division at TRIUMF has leveraged the laboratory's extensive particle accelerator expertise and infrastructure to explore novel technology to produce a wide variety of isotopes. While access to TRIUMF's 13 to 500 MeV proton cyclotrons has led to the routine production of a number of isotopes and radiopharmaceuticals, anticipated access to a new 10mA, 30 MeV elinac has led to the postulated development of a number of new radionuclides, including ^{225}Ac via the ^{226}Ra(γ,n)^{225}Ra $\rightarrow$ ^{225}Ac transformation. A summary of TRIUMF's efforts to build the elinac within TRIUMF's new Advanced Rare IsotopE Laboratory (ARIEL) will be discussed along with some of the key challenges and advantages of high power, large-scale photonuclear isotope production.

Photonuclear Capabilities at Argonne National Laboratory

S. Chemerisov, J. Nolen, J. Song, D. Rotsch, A. Brown and K. Hafidi

Argonne National Laboratory, Lemont, IL, USA

Argonne's Low Energy Accelerator Facility (LEAF) has become a part of the DOE Isotope Program. Facility is currently used to produce Cu-67 therapeutic radioisotope for distribution through National Isotope Distribution Center (NIDC). Actinium-225 is a potential future isotope for the production at the LEAF through the photonuclear reaction. The Radium-226 (γ, n) Radium-225 reaction threshold is 6.4 MeV, the maximum cross section of the reaction is 532 mb at energy 13.75 MeV. Radium-225 decays with half-life of 14.9 days, producing Actinium-225. LEAF recently upgraded electron linac is capable to deliver 20 kW electron beam at 40 MeV beam energy to the target making it suitable for efficient production of isotopes through photonuclear pass way. Laboratory Directed Research Development (LDRD) funded project culminated in design of the optimized target for production of Actinium-225. Demonstration of Actinium-225 production at LEAF is planned for the end of 2018. Following production scale-up will yield 1-2 Ci/week production of Actinium-225 by the end of 2020.

This work was supported by Office of Science, Office of Nuclear Physics Isotope Program, and Argonne National Laboratory under U.S. Department of Energy contract DE-AC02-06CH11357.

US DOE Tri-Lab Production Effort to Provide Accelerator-Produced ^{225}Ac for Radiotherapy

J. Kevin[1] and C. Cutler[2]

[1] - *Los Alamos National Laboratory, Alamos, NM, USA*
[2] -*Brookhaven National Laboratory, Upton, NY, USA*

The current availability of accelerator produced Ac-225 from the US Department of Energy Isotope Program's Tri-Lab (ORNL, BNL, LANL) Research and Production Effort to Provide Accelerator-Produced ^{225}Ac for Radiotherapy will be presented. Additional details will be presented on recent production improvements and ongoing plans for further scaling up our operations. In addition, impacts associated with the radionuclidic quality of the accelerator-produced ^{225}Ac product, concentrating on the ^{227}Ac by product, will be provided. Specifics regarding preparations for Current Good Manufacturing Practices (CGMP) level of processing, development of a supporting Drug Master File (DMF) and details of routine material availability will also be discussed.

US DOE – United States Department of Energy, Office of Science, Office of Nuclear Physics

BNL – Brookhaven National Laboratory

LANL – Los Alamos National Laboratory

NIDC – National Isotope Development Center

ORNL – Oak Ridge National Laboratory

Production of Ac-225 from Th-232 metallic targets on 160 MeV proton beam at Institute for Nuclear Research (Moscow-Troitsk)

B.L. Zhuikov, S.V.Ermolaev, E.V.Lapshina, A.N.Vasiliev, A.A.Kobtsev

Institute for Nuclear Research of Russian Academy of Sciences, Troitsk, Moscow, Russia

Since 2006 a method for producing ^{225}Ac via irradiation of metallic natural thorium targets at 160 MeV high current proton beam has been developing at the Institute of Nuclear Research of Russian Academy of Sciences (INR). Several Russian institutions are also involved: Lomonosov Moscow State University (Chemical Faculty), Karpov Institute of Physical Chemistry, and LUCH Scientific Production Association.

Production cross-sections have been accurately measured below 143 MeV and demonstrated that high amounts of ^{225}Ac may be produced. The most efficient target consists of 3 mm metallic Th-plate incapsulated into niobium shell (15-30 g). A good contact of niobium target windows and metallic Th-surface is provided by diffusion welding, which includes simultaneously high temperature and pressing with several tons press in high vacuum.

The first stage of chemical recovery consists of consequent dissolution of niobium window and metallic thorium. In the next step we used liquid-liquid extraction in HDEHP to remove the main part of Th from 0.1 M nitric solution. Afterwards we used liquid chromatography with consequently DGA-, Ln- and TRU-Resins produced by TrysKem® company. These processing remove ^{232}Th as well as stable elements and radioactive element from the solution. The only radionuclide impurity in the final product is 0.2% of ^{227}Ac, and this restricts direct application of ^{225}Ac in medicine. Total chemical yield is more than 85%.

The developed targetry (two 3 mm targets with slanted 27^{o} beam) and the described chemistry procedure will be able to produce about 2 Ci of ^{225}Ac per 10-day irradiation at 100 μA beam of INR linac after 10-day decay.

INR has produced few tens of mCi in a target but stopped production since the hot cell production facility is not available anymore. This problem may be solved in collaboration with different producers. Two new types of ^{225}Ac/^{213}Bi-generators are under development in order to minimize the effect of ^{227}Ac-impurity and radiation impact in high activity ^{225}Ac generator.

Production of Ac-225 from Th-232 spallation: TRIUMF 500 MeV Cyclotron, Isotope Production Facility

P. Schaffer

TRIUMF, Vancouver, BC, Canada

TRIUMF has begun production of Ac-225 by the irradiation of thorium metal with 480 MeV protons and has developed new methods for separating Ac from these targets. Irradiated thorium was dissolved in a combination of nitric and hydrofluoric acids; after which the majority of thorium was removed by addition hydrogen peroxide, forming a thorium peroxide precipitate which is easily filtered with minimal Ac or Ra losses. The filtrate was subjected to ion exchange and extraction chromatography resins to isolate Ac and Ra from remaining trace Th quantities and other spallation products. This approach provided two Ac-225 products with different impurity profiles: directly-produced Ac-225, which contained long-lived Ac-227; and Ac-225 produced from decay of Ra-225 fraction, which was virtually Ac-227 free. Both Ac-225 fractions were then subjected to labeling experiments on known (i.e. DOTA) and novel (i.e. macropa, octapa, pypa) and subjected to seven-day stability studies in human serum and La challenge. Future efforts will focus on increasing irradiation frequency and duration to afford greater quantities of Ac-225 with and without Ac-227.

TRIUMF has also initiated a capital upgrade project funded by Canada Foundation for Innovation which will see a new proton beamline and remote-operated parasitic isotope production target installed as part of the emerging Advanced Rare IsotopE Laboratory (ARIEL). Irradiations with TRIUMF's existing infrastructure have yielded ~370 MBq (~10 mCi) per run, with a goal of increasing to >3.7 GBq (>100 mCi)/run in the new facility. Higher level processing will be pursued via strategic partnerships.

CERN-MEDICIS: Prospects for the Production of ^{225}Ac

T. Stora

CERN, Genève, Switzerland

CERN is one of the largest international particle physics research laboratories with an annual number of visiting scientists of about 12,000. Within a large set of active experimental collaborations taking beam from the accelerator complex, the ISOLDE facility has been operating for more than 50 years and is capable to produce today a large variety of radioactive ion beams used for fundamental research in nuclear physics and for applications. The CERN-MEDICIS project was initiated in 2013 and started with the construction of an extension of the existing Class A Laboratory to exploit the otherwise lost protons with targets irradiated in the ISOLDE HRS beam dump, to safely perform isotope collection with a dedicated mass separator and to handle open radioactive sources for subsequent shipping to collaborating medical partners. The building was completed for the restart of the accelerator and experimental facilities after the first CERN Long Shutdown in 2015. Currently regular 500MBq-range isotope collections and distribution to partner institutes of the MEDICIS Collaboration are performed[1].

2018 was the first year of operation of the facility. It notably includes the first uranium target operation; the production of radiolanthanides such as ^{149,152,155}Tb, ^{165}Tm from tantalum targets; high specific activity ^{169}Er separated from an imported external $^{168/169}$Er source produced at Institut Laue Langevin ILL[2]; the production of activities up to 100 MBq EOB, and the radiochemical purification done at partner institutes. As CERN enters its second Long Shutdown, the MEDICIS facility will undergo installation and completion of the laser ion source and a radiochemistry laboratory. It will resume its operation with external sources provided by RNMC, ILL or ARRONAX in 2019 and 2020.

The production of implanted sources of ^{225}Ra/Ac/Fr, with no neighbouring masses contaminants, has been achieved previously at ISOLDE from ThC_x and UC_x targets, and is the subject of further developments[3]. Production rates of ^{225}Ac, ^{225}Ra, ^{225}Fr equal to 1.5 10^9, 3.0 10^8 and 3.8 10^7pps resp., for a standard Uranium Carbide ISOLDE target geometry can be found in the new ISOLDE Yield Database[4]. From these data and those published by Guglielmetti et al.[5], a yearly production of 3.4GBq of mass separated ^{225}Ra/Ac sources, with an integrated 4.5 10^{19} proton on target delivered to MEDICIS could be envisaged during CERN accelerators operational years. Prospects for further increase would be associated with the development of a laser ion source and with future proton beam intensity upgrades.

---

[1] dos Santos Augusto R. M. et al. "CERN-MEDICIS: a new facility." *Applied Sciences* 4.2 (2014): 265-281

[2] R. Formento Cavaier "Very high specific activity Er-169 production at MEDICIS from external ILL target", MEDICIS Project MED-011, http://cds.cern.ch/record/2632033.

[3] F. Bruchertseifer, T. Stora, et al. Radium and Francium beam tests to produce 225Ac/213Bi generators at CERN-MEDICIS, CERN-INTC-2015-052 http://cds.cern.ch/record/2059859. K. Dockx et al., CERN-INTC-2017-016, http://cds.cern.ch/record/2241281.

[4] J. Ballof et al, The upgraded ISOLDE yield database, subm. EMISXVIII proc. https://isoyields2.web.cern.ch

[5] A. Guglielmetti et al., New measurement of exotic decay of 225Ac by 14C emission, EPJ A12, 383 (2001).

Progress Towards an Alternative Method for Production of Ac225

J. T. Harvey

NorthStar Medical Technologies, LLC, Beloit, WI, USA

Ac-225 and its daughter Bi-213 have become increasingly important in clinical research for potential treatment of various diseases. The current US production of Ac-225 is limited to about 900 mCi annually from Oak Ridge National Laboratory. While there are limited sources of the stock material used to produce Ac-225, there are options available to meet this need. NorthStar has previously described a high-energy proton spallation of Th-232 approach. This route is capable of supplying daily quantities equivalent to the current annual supply. This presentation will describe the current development effort that is underway started in 2017 and continuing.

Cyclotron production of ^{225}Ac via the ^{226}Ra(p,2n)^{225}Ac reaction

A. Kellerbauer, F. Bruchertseifer, A. Morgenstern

European Commission, Joint Research Centre, Directorate for Nuclear Safety and Security, Karlsruhe, Germany

The irradiation of a Ra-226 target with medium-energy protons is a very promising route to the production of Ac-225 due to its large cross-section and the availability of hundreds of suitable cyclotron facilities worldwide. This technique was first experimentally investigated at JRC Karlsruhe more than 15 years ago. Both thin and thick targets containing radium chloride were manufactured, irradiated at a proton cyclotron facility, and dissolved for analysis.

Thin targets were produced by evaporating 12.5 µg of $RaCl_2$ onto a thin foil and welding the foil into a silver capsule to produce a gas-tight container. The target was placed into a water-cooled holder and irradiated at up to 28 MeV energy at the Karlsruhe cyclotron.[1] Following the dissolution of the target layer, the produced nuclides were chemically separated using Ln-spec and Sr-spec chromatography columns. In this way, the cross-section of the reaction was quantified at three irradiation energies and compared to a calculation of the excitation function using the statistical-model code ALICE. The maximum cross-section was found to be 710(70) mb at a proton energy of $\approx$16.8 MeV.

For production testing, thick target pellets were prepared from 30 mg radium within a 300 mg barium chloride matrix. Three thick targets were irradiated with currents ranging from 20 to 50 µA, yielding 141 to 485 MBq of Ac-225, demonstrating the validity of the process on production scale.[2]

Considering the large quantities of radium required for a production target, the safe handling of radium, the management of radon emanations and the gas-tight containment of helium gas build-up are currently the main challenges on the way to routine production. JRC Karlsruhe has begun a new radium target development program with two main objectives: First, to improve and complete the earlier measurement of the excitation function, and secondly, to better address the challenges related to the use of radium as target material.

[1] C. Apostolidis, R. Molinet, J. McGinley *et al.*, "Cyclotron production of Ac-225 for targeted alpha therapy," Appl. Radiat. Isot. **62** (2005) 383, doi:10.1016/j.apradiso.2004.06.013.
[2] A. Morgenstern, K. Abbas, F. Bruchertseifer and C. Apostolidis, "Production of alpha emitters for targeted alpha therapy," Curr. Radiopharm. **1** (2008) 135, doi:10.2174/1874471010801030135.

Cyclotron production of ^{225}Ac via the ^{226}Ra(p,2n) reaction

O. Lebeda, J. Štursa

Nuclear Physics Institute of the CAS, Řež, Czech Republic

A nuclear reaction ^{226}Ra (p,2n) seems to be favourable for direct cyclotron production of ^{225}Ac. However, calculated and the only available experimental[1] cross-sections of the ^{226}Ra (p,2n) reaction show systematic difference. Obviously, there is a need for a more accurate measurement with small beam energy steps to obtain precise knowledge of the excitation function course. The only relevant isotopic impurity in the product is ^{226}Ac ($T_{½}$ = 29.37 h, β^- 83 %, EC 17 %) resulting in fast decay chain of ^{226}Th and in ^{226}Ra. It doesn't represent any significant problem, taking into account both the decay products and rapid activity drop in time in comparison with ^{225}Ac.

Major problem of any production of ^{225}Ac based on ^{226}Ra target is target radioactivity and particularly continuous emanation of ^{222}Rn. It means that it is highly desirable to minimize the target mass. We consider as acceptable handling max. ca 50 mg of ^{226}Ra. Assuming only small beam energy loss of 1 MeV in the target (± 0.5 MeV around the maximum of the excitation function, i.e. 15.5→14.5 MeV), the required amount of ^{226}Ra in a perpendicular target of 8 mm diameter is below 50 mg. Expected activity of ^{225}Ac after 1 d irradiation with 50 μA proton beam is ca 2.6 GBq. In 10 days of cooling time, the activity ratio of ^{226}Ac and ^{225}Ac drops to 2.3×10^{-3}.

Due to high radium reactivity, a suitable chemical form is very important. Very probably, simple inorganic salt like chloride is the compound of choice. It hasn't surprisingly many drawbacks in comparison to metallic radium that has anyhow very low thermal conductivity of 18.6 W $m^{-1}K^{-1}$.

Routine production of ^{225}Ac assumes solving of the following issues:

- Applying the target layer has to be solved. Uniformity of the target layer should be checked.
- Vacuum-tight encapsulation should provide good heat exchange between the target and the capsule
- Cooling: 4π water cooling, He/water cooling?
- Recycling the ^{226}Ra seems to be well feasible
- The process has to be fully automated
- Management of emanation and long-lived deposit

A dedicated workplace for the target manufacturing, irradiation and processing, well separated from other activities of the cyclotron site is to be established, appropriately air-conditioned and protected from the ^{222}Rn release to the surrounding atmosphere. Risk associated with ^{226}Ra handling indicates limits of the processed mass depending on the workplace equipment, technology implemented and security measures.

[1] Apostolidis et al., Appl Radiat Isot. 2005 62(3):383-7

Alpha Project: Argentina Project for Developing Production of Ac-225 and Bi-213 and Corresponding Radiopharmaceuticals for Targeted Therapy

O. R. Pozzi

National Atomic Energy Commission (CNEA), Ezeiza Atomic Centre, Argentina

The Alpha Project of the National Atomic Energy Commission of Argentina (CNEA) is a local project for the development of the production of Ac-225 and Bi-123 from Ra-226 target via Ra-226(p,2n)Ac-225 reaction in medium-low energy cyclotron. The main goal of the Alpha Project is to secure the regional supply of Ac-225 in order to provide for future treatment of cancer patients and to support the R&D for new applications. To fulfill the goals of the project a new dedicated nuclear facility is being built in Argentina and expected to become fully operational in 2020-2021. It has been designed to deal with Ra-226 targets and it will have several radiochemical labs containing one multipurpose hot cell, five hot cells dedicated to Ac-225 processing, and one GMP hot cell. This installation will also have a pilot plant for production of small batch of radiopharmaceutical, initially under local GMP condition but capable to be upgraded to more demanding international GMP regulation.

The irradiation of the Ra-226 target will be made in the cyclotron "Cyclotron Corporation CP42" (25-42 MeV) located at the Ezeiza Atomic Center of CNEA using the fully automated irradiation station with a target holder specifically designed to work with sealed Ra-226 targets and 4π water cooling. Ii will be tested with a 60 mg of $RaCl_2$ dummy in the next few months. Theoretical models predict the cooling time should be at leasr 240 hrs (one $T_{1/2}$ of Ac-225) before processing the target. This will decrease the Ac-226 activity to < 0.3% of its initial value and provide Ac-226/Ac225 ration to be < 0.005. This cooling time will also result in decay of the Ac-226 daughters. According to the yield calculations for the preliminary target designed to run at lower density current (< 100 μA/cm^2), with 58 mg $RaCl_2$ irradiated 4 hrs. x 50 μA at 24-10 MeV will be able to produce 335 mCi EOB per batch, and 167.5 mCi after cooling time of 240 hrs. A production target capable to withstand 200 μA will require a bigger amount of $RaCl_2$ (230mg for 2 cm^2) with 24 hrs. x 50 μA irradiation at 24-10 MeV will result in 1.34 Ci of Ac-225 EOB per batch, and 670 mCi after 240 hrs. of cooling. Assuming an average dose of 0.5 mCi/patient, this amount will be enough for 1340 patient (losses for purification are not considered). Using this assumption one cyclotron running once a week, 4 weeks/month, 11 month/year will be able to produce 29.5 Ci/year of Ac-225, which is enough for almost 59,000 patient/year.

This production method based on the Ra-226(p,2n)Ac-225 based in cyclotrons has several advantages. It produces Ac-225 of high radionuclide purity; it is suitable for local and regional markets where Ac-225 production can be adjusted depending on the needs; it can produce on demand up to ~30 Ci/year using only one non-dedicated cyclotron working once a week; and it fulfils the goals set for the Alpha Project to secure the Ac-225 supply for our country and the region.

Ac-225 Production at KIRAMS

K. C. Lee

Korea Institute of Radiological & Medical Sciences (KIRAMS), Seoul, South Korea

KIRAMS is planning to complete the production setup of At-211 / Ac-225 and routinely produce therapeutic radionuclides within next 10 years. Half-life of Ac-225 is 10 days, and it is obtained by purification of previously mentioned nuclear waste Th-229. Another method to obtain Ac-225 is the accelerator nuclear reaction (p,2n) using Ra-226, and I will introduce Ac-225 production plan using Ra-226.

To overcome the radiation handling regulation to use Ra-226 for Ac-225 production we are planning to do the following remodeling of the facilities:

● We will use a single exhaust for the room, with a differential pressure to prevent the spread of potential contamination.

● Targeting and separating materials will be passed through the pass-box. In other words, the material movement line and the workers line will be clearly distinguished.

● We will use two separate glove boxes: one to open Ra-226 seeds and prepare the target; and another one for irradiated target separation and purification.

● We will establish a dedicated storage room for radioactive materials and radioactive waste storage

In the previously reported method of producing Ac-225 using Ra-226, a solid target was used. However, since we have a small amount of Ra-226 available in Korea, we will try to produce Ac-225 considering the use of liquid targets similarly to F-18 production. To conclude, we will produce Ac-225 using the liquid Ra-226 target after getting the certification within 2019.

Medical Cyclotron Production of Actinium-225 – A Technical Report

V. Gupta, K. Kopka

German Cancer Research Center (DKFZ), Heidelberg, Germany

The hottest topic currently in the field of targeted alpha therapy (TAT) in Nuclear Medicine is the treatment of cancer cells by the application of ^{225}Ac based radiotracers which has shown very promising results over the last decades. Due to highly challenging and costly production routes of ^{225}Ac, the world is lacking its supply (current 4 GBq[1]) against its current demands ($\geq$ 5 – 8 TBq). A rough estimation for late stage prostate cancer patients is shown below (note that 1,4 million cases in 2013 with 293,000 deaths worldwide only due to prostate cancer are reported[2]):

*One patient (avg. 70 kg)/year needs = 100 kBq * 70 kg * 4 (cycles) =* ***28 MBq.*** *(dose = 100kBq/kg)*
For ***100,000*** *patients = 28 MBq * 100,000 =* ***2,800 GBq (ca. 75 Ci)***

Apart from various production methods of ^{225}Ac (via. nuclear reactors, different mass separation techniques, photon irradiation etc.), there exists a highly efficient production route via ^{226}Ra(p,2n)^{225}Ac by using medical cyclotrons (15-30 MeV), with a high reaction cross-section of 710 mb at 16.8 MeV proton energy[3]. Hence, instead of producing ^{225}Ac in bulk quantities (ca. 1-2 TBq) in some big national centers (BNL, TRIUMF, DOE) and transporting the product worldwide, cyclotron possessing centers globally can produce a fair amount of ^{225}Ac (ca. 10-50 GBq) that could be sufficient to serve in their own vicinity. It could not only help to meet global demands but also solve the issues like transportation, large handling of radioactive ^{226}Ra, disposal problem, impurities (undesirable ^{227}Ac) and so on. Nevertheless, the challenges associated with its production i.e. rare availability of ^{226}Ra, effective handling of ^{222}Rn gas ($T_{1/2}$ = 3.8 d) – a decay product of ^{226}Ra, local and global radiation safety regulations, highly efficient target design etc. have to be thoroughly investigated and effectively solved.

Cyclotron production of ^{225}Ac can be a breakthrough due to its abundant availability globally (ca. 500 cyclotrons).Since, medical cyclotrons in various research centers and PET clinics are heavily engaged with routine productions of PET nuclides, therefore with the help of radiation safety authorities and local governing bodies, *dedicated separate facilities* with modern equipment (hot cells, separate cyclotron and target stations, competent individuals etc.) are needed country wise to ensure the continuous and abundant supplies of ^{225}Ac.

[1] Technical Meeting on "Alpha emitting radionuclides and radiopharmaceuticals for therapy", IAEA Vienna 2013
[2] Chen et al. Sci. Rep. 7, 40003; (2017)
[3] Apostolidis et al., Appl Radiat Isot. 2005 62(3):383-7

SCK•CEN – Production of Therapeutic Radioisotopes

D. Elema

SCK•CEN, the Belgian Nuclear Research Centre, Mol, Belgium

The Belgian Nuclear Research Centre (SCK•CEN) has more than 750 employees who devote themselves every day to developing peaceful applications of ionizing radiation. SCK•CEN has a long history of performing irradiations in its BR2 reactor for medical radioisotope production for diagnostic and therapeutic applications. SCK•CEN has been recognized for its expertise and performs a variety of activities (research, services and education) that are linked to medical applications of ionizing radiation and the use of medical radioisotopes. In 2016 SCK•CEN set a new strategic goal to become a world-class center of excellence for research and manufacturing in the field of radiopharmaceuticals.

By combining existing medical related activities at SCK•CEN within radiochemistry/radiopharmacy, radiobiology and dosimetry in one dedicated program the goal is to become an even stronger player within the field of radiopharmaceutical research (pre-clinical studies) as well as a recognized supplier of medical radioisotopes.

SCK•CEN also has deep know-how on handling of alpha emitters and has the necessary infrastructure. SCK•CEN has recently engaged in developing advanced capabilities for the production of radioisotopes to support the development of new radiopharmaceuticals through contract research. It has recently been announced that SCK•CEN will join the network of Global Morpho Pharma as shareholder, innovation partner and therapeutic medical radionuclides manufacturer. The main focus will initially be on the production and distribution of industrial quantities of non-carrier added Lutetium-177 (*nca* Lu-177) and Actinium-225 free of long-lived impurities. These medical radionuclides are instrumental for a novel class of cancer therapeutics currently under clinical development or already commercially available. SCK•CEN and IRE ELiT (the innovation subsidiary of IRE) are furthermore joining forces within the network to establish a reliable supply of GMP grade *nca* Lu-177 in Europe and beyond.

Additionally, SCK•CEN possesses a large stock of ^{226}Ra and is currently focusing on making this material available for ^{225}Ac production. SCK•CEN plans to develop targets suited for ^{225}Ac production through the (gamma,n) photon route and the (p,2n) proton route.

5. HIGHLIGHTS OF PRESENTATIONS

5.1. Medical Uses of ^{225}Ac

To date approximately 700 patients have received a total of >1500 treatments with ^{225}Ac- or ^{213}Bi-labeled radioconjugates for therapy of prostate cancer, glioma, neuroendocrine tumors, leukemia, Non-Hodgkins Lymphoma, malignant melanoma and bladder cancer. The clinical tests have been conducted using ^{225}Ac or ^{225}Ac / ^{213}Bi radionuclide generators produced and quality controlled at JRC Karlsruhe or ORNL. The radionuclides obtained from both sites have high radionuclidic and chemical purity, afford high labelling yields and have been found safe for administration to humans by well-trained physicians following established protocols for radiolabeling and quality control.

Radioimmunotherapy with ^{213}Bi and ^{225}Ac

The pioneering first-in-human clinical investigations of ^{213}Bi-labeled antibodies were conducted for therapy of leukemia, melanoma and Non-Hodgkins Lymphoma. Based on the promising results of two studies investigating the safety and therapeutic efficacy of the ^{213}Bi-labeled anti-CD33 antibody lintuzumab for therapy of leukemia, a clinical study investigating the ^{225}Ac labelled analogue is currently ongoing. A recent pilot study on the locoregional treatment of bladder cancer (carcinoma in situ) using a ^{213}Bi-labelled anti-EGFR monoclonal antibody has been conducted in collaboration of JRC Karlsruhe and Technical University Munich, Germany.

Peptide receptor alpha therapy with ^{213}Bi and ^{225}Ac

Targeted peptide receptor alpha therapy with ^{213}Bi / ^{225}Ac has been clinically tested for treatment of brain tumors, neuroendocrine tumors and prostate cancer. Important advantages of utilizing low molecular weight ligands as targeting vehicles for ^{213}Bi and ^{225}Ac include fast tumor uptake and rapid clearance of unbound conjugates from circulation. Internalizing ligands are particularly advantageous for application in combination with ^{225}Ac in order to harness the multiple alpha particles emitted in its decay chain.

The introduction of ^{225}Ac-PSMA617 for therapy of metastatic castration resistant prostate cancer constitutes a major advancement in targeted alpha therapy. ^{225}Ac-PSMA617 was first developed and characterized at JRC Karlsruhe in 2013 and clinical testing was started in collaboration with University Hospital Heidelberg in 2014. Within the last 5 years, more than

350 patients suffering from advanced prostate cancer have received treatment with ^{225}Ac-PSMA617 within compassionate use programs conducted in collaboration of JRC Karlsruhe with hospitals in Heidelberg, Munich and Pretoria. The remarkable therapeutic results obtained with ^{225}Ac-PSMA617 have strongly triggered global interest in medical application of actinium-225. Prospective clinical studies for regulatory approval of this promising compound are highly warranted.

5.2. ^{225}Ac Production Methods

Several ^{225}Ac production methods exist nowadays, including its extraction from the ^{233}U, spallation of ^{232}Th, and irradiation of ^{226}Ra targets. Each of these methods has advantages and disadvantages and all three methods are being pursued in various research facilities around the world.

Extraction from ^{233}U

One of most straightforward methods to produce ^{225}Ac is to extract it from ^{233}U as a product of its alpha decay chain:

$$\mathbf{^{233}U}\ (T_{1/2} = 1.6\times10^{5}\ \text{a}) \rightarrow \mathbf{^{229}Th}\ (T_{1/2} = 7.9\times10^{3}\ \text{a}) \rightarrow \mathbf{^{225}Ra}\ (T_{1/2} = 15\ \text{d}) \rightarrow \mathbf{^{225}Ac}$$

Significant amounts of ^{233}U were stockpiled in the USA and Russia between the 1950s and the 1970s. In the late 1990s, several ^{229}Th sources were made from ^{233}U stocks. One of these sources is currently kept in the US (5.5 GBq, 150 mCi, at Oak Ridge National Laboratory), another one in Germany (1.7 GBq, 46 mCi, at JRC Karlsruhe). A similar ^{229}Th source was prepared and has been used in Russia (5.5 GBq, 150 mCi, at Leipunskii Institute for Physics and Power Engineering). The separation of ^{225}Ac from Th-229 is rather straightforward and is performed 6–12 times per year. The resulting product is not contaminated by other actinium radioisotopes. However, the amount of ^{225}Ac one can obtain is limited by ^{229}Th activity. As of today, only 63 GBq (1.7 Ci) of ^{225}Ac can be produced world-wide every year using the existing ^{229}Th sources, which is not enough to cover all the demand for ^{225}Ac and ^{213}Bi. More ^{229}Th could be prepared from the still existing legacy stock of ^{233}U. This approach is currently being investigated by TerraPower, Inc.

Spallation of ^{232}Th

The limited amount of ^{225}Ac produced annually is sufficient for pre-clinical or clinical trials, but is not enough for commercial product development, including licencing and approval. According to recent estimates, the minimum required annual production of ^{225}Ac is ≈100–

200 Ci/a, assuming 1 mCi per patient and 100,000–200,000 patients per year. To address the ever-increasing demand for ^{225}Ac, alternative production methods have been investigated by many groups. Spallation of heavy elements by high-energy protons is a commonly used reaction for the production of isotopes for nuclear physics research. As of today, several high energy proton accelerator facilities exist and operate worldwide, including BNL, LANL, TRIUMF, INR, iThemba, Arronax, and others. Theoretically, any heavy element can be used for ^{225}Ac production, but thorium is the best choice due to its thermomechanical properties, high spallation cross-section, and no co-production of fissile ^{235}U and ^{239}Pu. Spallation of natural thorium, which is mostly ^{232}Th, results in a significant yield of ^{225}Ac (and ^{225}Ra, which can be used to extract further ^{225}Ac after its decay) from several channels:

$$\mathbf{^{232}Th}(p,x)\mathbf{^{225}Ac}$$

$$\mathbf{^{232}Th}(p,x)\mathbf{^{225}Ra}\ (T_{1/2} = 15\ \text{d}) \rightarrow \mathbf{^{225}Ac}$$

^{232}Th is relatively abundant, inexpensive, and easy to work with. However, during the spallation, a variety of other products are formed. While most of them are short-lived and can be separated from the final product, one of the contaminants of concern is ^{227}Ac. By the end of bombardment, the typical activity ratio of ^{227}Ac to ^{225}Ac is ≈0.2%. This long-lived radioisotope ($T_{½}$ = 22 a) cannot be easily separated from ^{225}Ac. ^{227}Ac increases the toxicity of the ^{225}Ac radiopharmaceutical and creates a problem patient waste handling. Therefore, production of clinical-grade ^{225}Ac by spallation of thorium is challenging. Nevertheless, this method is being pursued by the several US DOE National Laboratories, TRIUMF, INR, CERN, and NorthStar Medical Technologies.

Production from ^{226}Ra

The third production method, which has recently raised a lot of interest, is the production of ^{225}Ac from ^{226}Ra ($T_{1/2}$ = 1.6×10^3 a) targets using low-energy accelerators, either proton or electron, via the following reactions:

$$\mathbf{^{226}Ra}(p,2n)\mathbf{^{225}Ac}$$

$$\mathbf{^{226}Ra}(\gamma,n)\mathbf{^{225}Ra}\ (T_{1/2} = 15\ \text{d}) \rightarrow \mathbf{^{225}Ac}$$

This approach has several advantages. First, low-energy accelerators are more readily available than the high-energy proton beams required for spallation. In addition, both reactions result in a very high specific activity of ^{225}Ac as the amount of co-produced ^{227}Ac is negligible. The

disadvantages of these production methods come from the ^{226}Ra target material. Due to its high radiotoxicity and its decay to ^{222}Rn gas, target manufacturing, irradiation, processing, and recycling is rather complicated. Historically, sealed ^{226}Ra sources were used to treat cancer; however, after safer radioisotopes became widely available, many radium sources were just left to decay in storage, many of them for decades. According to the IAEA estimates, about 1 kg (1000 Ci) of ^{226}Ra currently exists in the world in the form of radium needles for brachytherapy. In many countries, special programs exist to eliminate these sources, and their recycling into ^{226}Ra targets could be very beneficial. Using electron linacs for photonuclear production is currently investigated by ANL, TRIUMF, and Niowave, Inc. Production of ^{225}Ac with low-energy cyclotrons is more common and has been pursued by JRC, NPI Rez, CNEA, KIRAMS, DKFZ, Zyklotron AG Karlsruhe, SCK-CEN, and Osaka University, among others.

6. CONCLUSIONS

- The workshop proved to be a highly successful event attended by more than 70 participants from 17 Member States.
- The need for ^{225}Ac was clearly established and several production methods were discussed. It was emphasized that diversity of production methods is highly desirable to ensure ever-rising demand.
- ^{225}Ac extraction from ^{233}U stockpiles was shown to be not sufficient for the market, unless the legacy stock of ^{233}U, currently overseen by the US DOE, is used for this production method.
- ^{227}Ac contamination of ^{225}Ac produced via thorium spallation was acknowledged and addressed by both the medical researchers and the radioisotope producers.
- Challenges related to handling ^{226}Ra targets were discussed in detail. Radiation safety (especially release of ^{222}Rn gas) during the target production, irradiation, and recovery was also addressed.
- The US DOE Isotope Program's support and involvement in various production routes was clearly demonstrated. Their efforts are invaluable and greatly appreciated by the participants.
- The IAEA and JRC will continue their support of this program by organising conferences, workshops, and other events. For example, the 11th International Symposium on Targeted Alpha Therapy will be held on April 2-4, 2019 in Ottawa, Canada and the International Symposium on Trends in Radiopharmaceuticals (ISTR-2019) will take place in October 2019 at the IAEA headquarters in Vienna.

Recognizing the growing attention on targeted alpha therapy using ^{225}Ac, a two-day technical workshop on "Supply of Actinium-225" was held in October 2018 with more than 70 participants from over 17 different Member States attending. The impressive results of clinical studies conducted thus far and the global need for ^{225}Ac for targeted alpha therapy was clearly demonstrated by several presenters from the medical and radiopharmaceutical communities. To meet this demand, three main production routes were discussed in detail, including "milking" of stockpiled ^{233}U, spallation of ^{232}Th with high energy proton accelerators, and production of ^{225}Ac from ^{226}Ra with either proton cyclotrons or electron Linear Accelerators. The advantages and disadvantages of each of the production methods as well as ^{225}Ac supply projections were presented. Numerous speakers from national laboratories, research institutes, and private companies from the US, Canada, Germany, Russia, and other countries shared their most recent

results and exchanged ideas. This meeting provided all the participants a unique opportunity to discuss their work face-to-face, strengthen the existing collaborations and establish new ones and proved to be extremely useful in addressing the problem of establishing the reliable supply of ^{225}Ac.

The joint IAEA-JRC workshop on “Supply of Actinium-225” provided physicists, chemists, and medical researchers an international forum for discussing the most recent developments related to ^{225}Ac demand and supply. Two major topics were covered during the workshop: production of ^{225}Ac, and its medical applications. Experts from all over the world met and discussed their most recent work. This meeting helped maintain existing and establish new collaborations to address the problem of short supply and high demand of ^{225}Ac suitable for therapy.

7. RECOMMENDATIONS

- The demand for therapeutic alpha-emitters, including ^{225}Ac, continues to grow. At the same time, no clear solution to the highly limited supply exists today. We recommend to continue the IAEA's support in resolving this challenge by organizing conferences, workshops, and other international events to periodically review the progress and the issues.
- Several production methods are currently being developed and each of them has its own advantages and drawbacks. We recommend to further develop all the methods to provide diversity of the supply. We also recommend to create a network of suppliers to provide fast and accurate exchange of information related to these production methods.
- Using ^{226}Ra as target material can reduce the burden of old radium needles in many hospitals worldwide. We recommend to investigate the possibility to "recycle" such needles for the ^{226}Ra target preparation.
- At the same time, production, irradiation, and recovery of ^{226}Ra targets requires special attention to radiation safety issues, especially concerning ^{222}Rn. We recommend to review these issues and prepare guidelines to address them.
- Lack of experimental cross-section data is one of the hurdles in the area of photonuclear production of ^{225}Ac from ^{226}Ra. We recommend to conduct these measurements at some of the Member State facilities.
- IAEA should promote activities related to the safety aspects of the different routes for ^{225}Ac production and the dosimetry of ^{225}Ac containing radionuclidic impurities. Activities related to the production and use of other potential alpha emitters should be promoted as well.