10th International Symposium on Targeted Alpha Therapy

Ishikawa Ongakudo : Hougaku Hall, Kanazawa, Japan
May 30 – June 1, 2017

^{149}Tb ^{225}Ac ^{212}Bi

^{211}At 金沢 日本 ^{212}Pb

^{223}Ra ^{213}Bi ^{227}Th

^{226}Th

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10th International Symposium on Targeted Alpha Therapy

ISHIKAWA ONGAKUDO
Kanazawa, Japan
May 30 – June 1, 2017

Organizers:

Seigo Kinuya
Kohshin Washiyama
Kanazawa University
Kanazawa, Japan

Alfred Morgenstern
Frank Bruchertseifer
European Commission
Joint Research Centre
Directorate for Nuclear Safety and Security
Karlsruhe, Germany

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The 10th International Symposium on Targeted Alpha Therapy marks the 20th anniversary of a successful series of international symposia on this topic initiated by the Joint Research Centre of the European Commission, including meetings in Karlsruhe (1997, 2000), Heidelberg (2002), Düsseldorf (2004), Aachen (2007), Toronto (2009), Berlin (2011), Oak Ridge (2013) and Warsaw (2015).

The symposium is kindly supported by:

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Program of the

10th International Symposium on Targeted Alpha Therapy

ISHIKAWA ONGAKUDO, Kanazawa, Japan
May 30 – June 1, 2017

Tuesday May 30, 2017

18:00 – 21:00 WELCOME RECEPTION AND REGISTRATION
Shiinoki Cultural Complex（しいのき迎賓館）

Wednesday May 31, 2017

8:30 – 8:45 WELCOME / INTRODUCTION
Seigo Kinuya / Kohshin Washiyama
Kanazawa University
Alfred Morgenstern
European Commission, Joint Research Centre, Directorate for Nuclear Safety and Security

SESSION Ia CLINICAL EXPERIENCES
Moderator: Alfred Morgenstern, Brenda Sandmaier

8:45 – 9:05 **Efficacy of ^{225}Ac-labeled anti-CD33 antibody in acute myeloid leukemia (AML) correlates with peripheral blast count**
Mark Berger[1], Joseph Jurcic[2] and David Scheinberg[3]
[1]Actinium Pharmaceuticals, Inc.; [2]New York Presbyterian - Columbia University Medical Center; [3]Memorial Sloan Kettering Cancer Center

9:05 – 9:25 **^{213}Bi-anti-EGFR-MAb therapy of recurrent bladder cancer – a pilot study**
K. Scheidhauer[1], C. Seidl[1], F. Bruchertseifer[2], C. Apostolidis[2], M. Autenrieth[3], F. Kurtz[3], T. Horn[3], M. Schwaiger[1], J. Gschwend[3], C. D'Alessandria[1], C. Pfob[1], R. Senekowitsch-Schmidtke[1], A. Morgenstern[2]
[1]Dept. Nuclear Medicine, Technische Universität Muenchen, Munich, Germany; [2]European Commission, Joint Research Centre, Directorate for Nuclear Safety and Security, Karlsruhe, Germany; [3]Dept. Urology, Technische Universität Muenchen, Munich, Germany

9:25 – 9:45

Targeted alpha therapy of glioblastoma multiforme: clinical experience with ^{213}Bi- and ^{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, Directorate for Nuclear Safety and Security, Karlsruhe, Germany; [3] Department of Neurosurgery, Institute of Psychiatry and Neurology, 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

9:45 – 10:05

Dosimetry and Biodistribution of ^{203}Pb-AR-RMX in Patients with Somatostatin Expressing Neuroendocrine Tumors. A Clinical Exploratory Study.

E. S. Delpassand[1], T. A. Stallons[2], M. Hamidi[3], L. Bolek[3], M. Ali[3], G. Vahdati[3], A. Saidi[2], F. Rojas-Quijano[4], P. Jurek[4], G. Kiefer[4], B. He[5], M. Ghaly[5,6], E. Frey[5,6], G. Sgouros[5,6], J. Torgue[2], I. Tworowska[1]

[1] RadioMedix Inc., USA; [2] AREVA Med LLC., USA; [3] Excel Diagnostics and Nuclear Oncology Center, USA; [4] Macrocyclics Inc., USA; [5] Rapid LLC., USA; [6] Johns Hopkins University, USA

10:05 – 10:30 *Coffee break*

SESSION Ib CLINICAL EXPERIENCES - PROSTATE
Moderator: Seigo Kinuya, Christof Seidl

10:30 – 10:50

^{225}Ac-PSMA-617: PSMA targeting alpha-radiation therapy of patients with metastatic castration resistant prostate cancer (mCRPC)

C. Kratochwil[1], F. Bruchertseifer[2], F. L. Giesel[1], C. Apostolidis[2], U. Haberkorn[1], A. Morgenstern[2]

[1] Department of Nuclear Medicine, University Hospital Heidelberg, Germany; [2] European Commission, Joint Research Centre, Directorate for Nuclear Safety and Security, Karlsruhe, Germany

10:50 – 11:10

Radium-223 (Ra-223) in asymptomatic metastatic castration resistant prostate cancer (mCRPC) patients treated in an international early access program (iEAP)

Wim Oyen,[1] Fred Saad,[2] Silke Gillessen,[3] Daniel Heinrich,[4] Daniel Keizman,[5] Joe M. O'Sullivan,[6] Joan Carles,[7] Manfred Wirth,[8] Kurt Miller,[9] Liping Huang,[10] Monica Seger,[10] Sten Nilsson,[11] Axel Heidenreich[12]

[1]The Royal Marsden NHS Foundation Trust and The Institute of Cancer Research, Sutton, UK;
[2]University of Montreal Hospital Center, Montreal, Canada;
[3]Kantonsspital St Gallen, St Gallen, Switzerland; [4]Akershus University Hospital, Lørenskog, Norway; [5]Meir Medical Center, Kfar-Saba, Israel; [6]The Centre for Cancer Research and Cell Biology, Queen's University Belfast, and the Northern Ireland Cancer Centre, Belfast, Northern Ireland; [7]Vall d' Hebron University Hospital, Vall d'Hebron Institute of Oncology, Barcelona, Spain; [8]University Hospital Carl-Gustav Carus, Dresden, Germany;
[9]Charité University Medicine Berlin, Berlin, Germany; [10]Bayer HealthCare Pharmaceuticals, Whippany, New Jersey, USA;
[11]Karolinska University Hospital, Stockholm, Sweden;
[12]University Hospital Cologne, Köln, Germany

11:10 – 11:30

Changes in alkaline phosphatase (ALP) dynamics and overall survival (OS) in metastatic castration-resistant prostate cancer (mCRPC) patients treated with radium-223 in an international early access program (EAP)

Wim Oyen,[1] Fred Saad,[2] Silke Gillessen,[3] Axel Heidenreich,[4] Daniel Keizman,[5] Joe M. O'Sullivan,[6] Joan Carles,[7] Manfred Wirth,[8] Kurt Miller,[9] Giuseppe Procopio,[10] Monica Seger,[11] Sten Nilsson,[12] Daniel Heinrich[13]

[1]The Royal Marsden NHS Foundation Trust and The Institute of Cancer Research, Sutton, UK; [2]University of Montreal Hospital Center, Montreal, Canada; [3]Kantonsspital St Gallen, St Gallen, Switzerland; [4]University Hospital Cologne, Köln, Germany; [5]Meir Medical Center, Kfar-Saba, Israel; [6]The Centre for Cancer Research and Cell Biology, Queen's University Belfast, and the Northern Ireland Cancer Centre, Belfast, Northern Ireland; [7]Vall d' Hebron University Hospital, Vall d'Hebron Institute of Oncology, Barcelona, Spain; [8]University Hospital Carl-Gustav Carus, Dresden, Germany;
[9]Charité University Medicine Berlin, Berlin, Germany; [10]Fondazione IRCCS - Istituto Nazionale dei Tumori - S.C. Medicina Oncologica 1, Milan, Italy; [11]Bayer HealthCare Pharmaceuticals, Whippany, New Jersey, USA; [12]Karolinska University Hospital, Stockholm, Sweden;
[13]Akershus University Hospital, Lørenskog, Norway

LUNCH SYMPOSIUM supported by FUJIFILM RI Pharma Co., Ltd.
Moderator: Kunihiko Yokoyama (Public Central Hospital of Matto Ishikawa PET Center, Matto, Japan)

11:40 – 12:10 **Diagnosis and therapy for bone metastatic prostate cancer**
Atsushi Mizokami
Department of Integrative Cancer Therapy and Urology Kanazawa University, Graduate School of Medical Science, Kanazawa, Japan

12:20 – 13:20 *Working Lunch /* POSTER SESSION I

SESSION IIa PRECLINICAL STUDIES
Moderator: Ekaterina Dadachova, Jean-Pierre Pouget

13:20 – 13:40 **Reduction of radiation exposure to the large intestine during ^{223}Ra alpha therapy with oral administration of barium sulfate**
S. Hanadate[1,2], K. Washiyama[3], M. Yoshimoto[4], H. Matsumoto[5], A.B. Tsuji[2], T. Higashi[2], Y. Yoshii[2]
[1]Toho University, Chiba, Japan; [2]National Institute of Radiological Sciences, National Institutes for Quantum and Radiological Science and Technology, Chiba, Japan; [3]Kanazawa University, Kanazawa, Japan; [4]Exploratory Oncology Research & Clinical Trial Center, National Cancer Center, Chiba, Japan; [5]Nihon Medi-Physics Co., Ltd., Chiba, Japan

13:40 – 14:00 **Pharmacokinetic profiling and therapeutic efficacy of alpha-emitter labeled anti-PD-L1 antibodies in an immune competent transgenic breast cancer model**
Jessie R. Nedrow[1], Anders Josefsson[1], Sunju Park[1], Tom Bäck[2], Robert F. Hobbs[1], Cory Brayton[1], Frank Bruchertseifer[3], Alfred Morgenstern[3], and George Sgouros[1]
[1]Johns Hopkins University, School of Medicine, Baltimore, MD, USA; [2]The Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden; [3]European Commission, Joint Research Centre, Directorate for Nuclear Safety and Security, Karlsruhe, Germany

14:00 – 14:20 **Novel IgG to melanin shows promise for radioimmunotherapy of metastatic melanoma**
Ekaterina Dadachova[1], Ekaterina Revskaya[2], Arthie Jeyakumar[2], Zewei Jiang[2], Frank Bruchertseifer[3], Alfred Morgenstern[3], David Rickles[4]
[1]University of Saskatchewan, SK, Canada; [2]Albert Einstein College of Medicine, New York, USA; [3]European Commission, Joint Research Centre, Directorate for Nuclear Safety and Security, Karlsruhe, Germany; [4]RadImmune Inc., Los Angeles, USA

14:20 – 14:40 **Involvement of direct and indirect (bystander) cytotoxic effects in alpha-RIT of small volume peritoneal carcinomatosis using ^{213}Bi- and ^{212}Pb-labeled mAbs**

Riad Ladjohounlou[1,2,3,4], Alexandre Pichard[1,2,3,4], Vincent Boudousq[1,2,3,4], Salomé Paillas[1,2,3,4], Catherine Lozza[1,2,3,4], Sara Marcatili[5], Manuel Bardiès[5], Nicolas Chouin[6], Frank Bruchertseifer[7], Alfred Morgenstern[7], Julien Torgue[8], Isabelle Navarro-Teulon[1,2,3,4] and Jean-Pierre Pouget[1,2,3,4]

[1]IRCM, Institut de Recherche en Cancérologie de Montpellier, Montpellier, F-34298, France. [2]INSERM, U1194, Montpellier, F-34298, France. [3]Université de Montpellier, Montpellier, F-34090, France. [4] Institut régional du Cancer de Montpellier, Montpellier, F-34298, France. [5]UMR 1037 INSERM/UPS, Centre de Recherche en Cancérologie de Toulouse, Toulouse F-31062, France; [6]AMAROC, ONIRIS, Nantes 44300, France; [7]European Commission, Joint Research Centre, Directorate for Nuclear Safety and Security, Karlsruhe, Germany ; [8] AREVA Med, 4800 Hampden lane, Bethesda, MD 20814, USA

14:40 – 15:00 **Preclinical evaluation of anti-HER2 2Rs15d nanobody labeled with ^{225}Ac**

M. Pruszyński[1], M. D'Huyvetter[2], E. Cędrowska[1], T. Lahoutte[2], F. Bruchertseifer[3], A. Morgenstern[3]

[1]Institute of Nuclear Chemistry and Technology, Warsaw, Poland; [2]In Vivo Cellular and Molecular Imaging (ICMI) Lab, Vrije Universiteit Brussel, Brussels, Belgium; [3]European Commission, Joint Research Centre, Directorate for Nuclear Safety and Security, Karlsruhe, Germany

15:00 – 15:30 *Coffee break*

SESSION IIb PRECLINICAL STUDIES
Moderator: Michael R. Zalutsky, Yasushi Arano

15:30 – 15:50 **Preclinical evaluation of astatinated nanobodies for targeted alpha therapy**

Yana Dekempeneer[1,2], Matthias D'Huyvetter*[1], Emma Aneheim[3], Catarina Xavier[1], Tony Lahoutte[1,4], Tom Bäck[3], Holger Jensen[5], Vicky Caveliers[1,4], Sture Lindegren[3]*

[1]Laboratory of In Vivo Cellular and Molecular Imaging, Vrije Universiteit Brussel, Brussels, Belgium; [2]Belgian Nuclear Research Center (SCK•CEN), Mol, Belgium; [3]Targeted Alpha Therapy group, University of Gothenburg, Gothenburg, Sweden; [4]Nuclear Medicine Department, UZ Brussel, Brussels, Belgium; [5]Cyclotron and PET Unit, Copenhagen, Denmark

15:50 – 16:10 **Development of α-emitting [^{211}At]-*meta*-astatobenzylguanidine (^{211}At-MABG) as a novel therapeutic agent for malignant pheochromocytoma**

Yasuhiro Ohshima[1], Sudo Hitomi[2], Shigeki Watanabe[1], Kotaro Nagatsu[2], Atsushi Tsuji[1], Tetsuya Sakashita[1], Atsuo Waki[2], Keiichiro Yoshinaga[2], Tatsuya Higashi[2] and Noriko S. Ishioka[1]
[1]Quantum Beam Science Research Directorate, National Institute for Quantum and Radiological Science and Technology, Takasaki, Japan.
[2]National Institute of Radiological Sciences, National Institutes for Quantum and Radiological Science and Technology, Chiba, Japan

16:10 – 16:30 **Directing alpha-emitting conjugates to cancer chromatin via PARP-1**

[1]Mehran Makvandi, [1]Catherine Hou, [1]Kuiying Xu, [1]Redmond-Craig Anderson, [1]Laura Puentes, [1]Samuel Sander Effron, [1]Robert H Mach, [1,2]John M Maris, and [1]Daniel A Pryma
[1]University of Pennsylvania, Perelman School of Medicine, Department of Radiology and Division of Nuclear Medicine;
[2]Children's Hospital of Philadelphia

16:30 – 16:50 **Locoregional α-radioimmunotherapy against peritoneal metastasis of gastric cancer**

Huizi Keiko Li[1,2)], Yukie Morokoshi[2)], Sumitaka Hasegawa[2)]
[1]Graduate School of Medical and Pharmaceutical Sciences, Chiba University, Japan; [2]Radiation and Cancer Biology Team, NIRS, QST, Japan

16:50 – 17:10 **A comparative evaluation of ^{225}Ac vs ^{213}Bi as therapeutic radioisotopes for targeted alpha therapy**

Barry J Allen
Faculty of Medicine, University Western Sydney, NSW Australia

17:10 ADJOURN

19:00 – 22:00 SYMPOSIUM BANQUET DINNER
ANA CROWNE PLAZA KANAZAWA, 16-3 Showa-machi, Kanazawa

Thursday June 1, 2017

SESSION III DOSIMETRY AND INSTRUMENTATION
Moderator: George Sgouros, Kohshin Washiyama

8:30 – 8:50 **Optimization of the patient dosimetry in alphatherapy**

Benabdallah Nadia[1], Bernardini Michela[2], Franck Didier[1], de Labroille-Vaylet Claire[3,4], Bolch Wesley E.[5] and Desbrée Aurélie[1]
[1]IRSN, Institute for Radiological Protection and Nuclear Safety, Paris, France; [2]HEGP, Hôpital Européen Georges Pompidou, Paris, France; [3]UPMC, University of Paris 06 Biophysics; [4]Hôpital Trousseau, Paris, France; [5]Department of Biomedical Engineering, University of Florida, Gainesville, USA

8:50 – 9:10 **Correspondence between alpha-particle emitter dosimetry and normal organ toxicity**

Anders Josefsson[1], Jessie R. Nedrow[1], Robert F. Hobbs[2], Tom Bäck[3], Sunju Park[1], Frank Bruchertseifer[4], Alfred Morgenstern[4] and George Sgouros[1]
[1]Russell H. Morgan Department of Radiology and Radiological Science, Johns Hopkins University, School of Medicine, Baltimore, MD, USA; [2]Department of Radiation Oncology and Molecular Radiation Sciences, Johns Hopkins University, School of Medicine, Baltimore, MD, USA; [3]The Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden; [4]European Commission, Joint Research Centre, Directorate for Nuclear Safety and Security, Karlsruhe, Germany

9:10 – 9:30 **High-resolution Alpha Camera imaging as a tool for developing Targeted Alpha Therapy**

T. Bäck[1], N. Chouin[2], S. Lindegren[1], E. Aneheim[1], H. Jensen[3], A. Hallqvist[4], P. Albertsson[4], and S. Palm[1]
Departments of [1]Radiation Physics and [4]Oncology, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden; [2]LUNAM Université, Oniris, AMaROC , Nantes, France; [3] PET and Cyclotron Unit, Department of Clinical Physiology and Nuclear Medicine, Copenhagen University Hospital, Copenhagen, Denmark

9:30 – 9:50 **Experimental Alpha Microdosimetry using Fluorescent Nuclear Track Detectors**

Jasper J.M. Kouwenberg[1], Adrie J.J. Bos[2], Antonia Denkova[1]
[1]RadioIsotopes for Health, Delft University of Technology, Delft, the Netherlands; [2]Fundamental Aspects of Materials and Energy, Delft University of Technology, Delft, the Netherlands

9:50 – 10:20 *Coffee break*

SESSION IV NANOCARRIERS
Moderator: Saed Mirzadeh, Sture Lindegren

10:20 – 10:40 **Lanthanum phosphate nanoparticles as carriers for ^{225}Ac, ^{223}Ra and ^{225}Ra for targeted alpha therapy**

S. Mirzadeh[1], J. V. Rojas[1†], M. F. McLaughlin[2††], J. D. Woodward[1], D. Robertson[2], and S. J. Kennel[3]
[1]Nuclear Security and Isotope Technology Division, Oak Ridge National Laboratory, Oak Ridge, TN 37831; [2]Department of Chemistry and University of Missouri Research Reactor, University of Missouri, Columbia, MO 65211; [3]Graduate School of Medicine, University of TN, Knoxville, TN 37920; †Current address: Department of Mechanical and Nuclear Engineering, Virginia Commonwealth University, Richmond, VA 23228; ††Current address: Baylor College of Medicine, Houston, TX 77030

10:40 – 11:00 **Nanocarriers of ^{223}Ra for TAT**

Ján Kozempel, Martin Vlk, Petra Mičolová, Ekaterina Kukleva, Pavel Nykl and Michal Sakmár
Department of Nuclear chemistry, Faculty of Nuclear Sciences and Physical Engineering, Czech technical university in Prague, Břehová 7, 115 19 Prague 1, Czech Republic

11:00 – 11:20 **Gold nanoparticle– conjugates as a carrier for ^{211}At in alpha particle therapy**

P.Koźmiński[1], Ł.Janiszewska[1], M.Pruszyński[1], B.Wąs[3], J.Jastrzębski[2], J.Choiński[2], A.Stolarz[2], M.Sitarz[2], K.Szkliniarz[3], J.Grobelny[4], G.Celichowski[4], A.Bilewicz[1]
[1]Institute of Nuclear Chemistry and Technology; [2]Heavy Ion Laboratory, Warsaw University; [3]Institute of Nuclear Physics, Cracow; [4]Department of Materials Technology and Chemistry, University of Lodz

11:20 – 11:40 **Assessing ^{225}Ac-Polymersomes for Targeted Radionuclide Therapy**

R.M. de Kruijff[1], S. Heskamp[2], A. van der Meer[1], J. Kouwenberg[1], G. Torrelo Villa[1], A. Morgenstern[3], F. Bruchertseifer[3], P. Sminia[4], A.G. Denkova[1]
[1]Radiation Science and Technology, Delft University of Technology, Delft, the Netherlands; [2]Radiology and Nuclear Medicine, Radboud University Medical Centre; Nijmegen, the Netherlands; [3]European Commission, Directorate for Nuclear Safety and Security, Karlsruhe, Germany; [4]VUmc Cancer Centre Amsterdam, De Boelelaan 1118, 1081 Amsterdam, the Netherlands

LUNCH SYMPOSIUM supported by Bayer Yakuhin, Ltd.

Moderator: Makoto Hosono (Radiology, Faculty of Medicine and Atomic Energy Research Institute at Kindai University, Osaka, Japan)

11:50 – 12:20 **Radium-223 From Bench to Bedside, and Future Directions for Targeted Alpha Therapy**

Joe O'Sullivan
Radiation Oncology, Queen's University Belfast and Clinical Director at The Northern Ireland Cancer Centre, Belfast, UK

12:30 – 13:30 Working Lunch / POSTER SESSION II

SESSION Va RADIOCHEMISTRY AND NUCLIDE PRODUCTION

Moderator: Gilles Montavon, Valery Radchenko

13:30 – 13:50 **Exploration of the chemistry of astatine; from basic research towards applied questions**

G. Montavon[1], C. Alliot[2], J. Champion[1], N. Galland[3], N. Guo[1], R. Maurice[1], D.-C. Sergentu[1,3], D. Teze[1,3]
[1]SUBATECH, UMR CNRS 6457, 44307 Nantes Cedex 3, France; [2]GIP ARRONAX, F-44817 Saint-Herblain, France; [3]CEISAM, UMR CNRS 6230, 44322 Nantes Cedex 3, France

13:50 – 14:10 **Progress in the [^{211}At]-astatination of antibodies by nucleophilic approaches using aryliodonium salts precursors**

François Guérard[1], Laurent Navarro[1], Cyrille Alliot[1,2], Martin W. Brechbiel[3], Michel Chérel[1] and Jean-François Gestin[1]
[1] Centre de Recherche en Cancérologie Nantes-Angers (CRCNA), Unité INSERM 892 - CNRS 6299, Nantes 44007 (France). [2] Arronax GIP, Nantes 44817 (France). [3] Radioimmune & Inorganic Chemistry Section, Radiation Oncology Branch, National Cancer Institute, National Institutes of Health, Bethesda, Maryland 20892 (USA)

14:10 – 14:30 **Quality Assurance and Labeling Chemistry Qualification for cGMP Production of Astatine-211-Labeled anti-CD45 Antibodies**

D. S. Wilbur[1], Y. Li[1], D.K. Hamlin[1], M.-K. Chyan[1], A.L. Wooten[1], E. F. Dorman[1], R. Storb[1,2], O.W. Press[1,2] and B.M. Sandmaier[1,2]
[1]University of Washington; [2]Fred Hutchinson Cancer Research Center, Seattle, WA, USA

14:30 – 14:50 **Development of effective chelators for Th-227 to be used in Targeted Thorium Conjugates**

Olav B Ryan[1], Alan Cuthbertson[1], Gunnar Herstad[2], Derek Grant[1] and Roger M Bjerke[1]
[1]Bayer AS, Oslo, Norway; [2]Synthetica AS, Oslo, Norway

14:50 – 15:10 **Spectroscopic and computational studies of actinium coordination chemistry**

Benjamin W. Stein[1], Maryline G. Ferrier[1], Stosh A. Kozimor[1], Eva R. Birnbaum[1], Jonathan W. Engle[1,2], Kevin D. John[1], John M. Berg[1], Juan S. Lezama Pacheco[3]

[1] Los Alamos National Laborary, Chemistry Division, Los Alamos, New Mexico 87545, USA; [2] University of Wisconsin, Madison, Wisconsin 53711, USA; [3] Stanford University, Stanford, California 94305, USA

15:10 – 15:40 *Coffee break*

SESSION Vb RADIOCHEMISTRY AND NUCLIDE PRODUCTION
Moderator: Frank Bruchertseifer, Jonathan Engle

15:40 – 16:00 **A Novel Micro-Actinium-225/Bismuth-213 Biomedical Generator System**

Davern S.M. [1], O'Neil D.W.[3]., Hallikainen H.[4], Allman S[2]., Millet L.J.[5], Retterer S.T.[2], Doktycz M.J.[2], Standaert R.F.[2], Boll R.A.[1], Van Cleve S.[1], DePaoli D.W.[1],and Mirzadeh S[1].

Divisions of [1]Nuclear Security & Isotope Technology and [2]Biosciences, Oak Ridge National Laboratory, Oak Ridge, TN 37831-6229. [3]Oak Ridge Associated Universities, Oak Ridge TN 37830, [4]Arizona State University, Tempe, AZ 85281. [5]Joint Institute of Biological Sciences, University of Tennessee and Oak Ridge National Laboratory, TN 37831 USA.

16:00 – 16:20 **US DOE Tri-Lab Research Effort to Provide Accelerator-Produced ^{225}Ac for Radiotherapy: 2017 Update**

Kevin D. John (LANL), Ethan R. Balkin (US DOE), Eva R. Birnbaum (LANL), Rose A. Boll (ORNL), Mark Brugh (LANL), Jason Cooley (LANL), Roy Copping (ORNL), Cathy S. Cutler (BNL), David L. Denton (ORNL), Michael E. Fassbender (LANL), Kevin Felker (ORNL, NIDC), Mitch D. Ferren (ORNL, NIDC), Jonathan M. Fitzsimmons (BNL), Justin R. Griswold (ORNL), John W. Krueger (ORNL), Tara Mastren (LANL), Leonard F. Mausner (BNL), Dmitri G. Medvedev (BNL), Saed Mirzadeh (ORNL), Karen E. Murphy (ORNL), F. Meiring Nortier (LANL), Allison C. Owens (ORNL), Dennis R. Phillips (US DOE), Wolfgang H. Runde (LANL, NIDC), Daniel W. Stracener (ORNL), Lance E. Wyant (ORNL)

16:20 – 16:40 **Production of a Thorium/Actinium Generator at the Canadian Nuclear Laboratories**

P. Causey[1], D. Bureau[1], K. Leeder[1], R. Perron[1], S.V. Hartimath[2], H. Fonge[2]

[1] Canadian Nuclear Laboratories, Chalk River, Canada; [2] University of Saskatchewan, Saskatoon, Canada

16:40 – 17:00 **Progress Toward an Alternate Method for Production of Ac-225**
James Harvey[1], Thomas Kroc[2]
[1]NorthStar Medical Radioisotopes, LLC, Madison, WI, USA
[2]Fermi National Accelerator Laboratory, Batavia, IL, USA

17:00 – 17:15 SYMPOSIUM CLOSURE

Friday June 2, 2017

12:45 – 18:00 TRIP TO SHIRAKAWA-GO WORLD HERITAGE SITE

Poster SESSION I

Initial Experience of Ra-223 at the Japan Community Healthcare Organization (JCHO) Tokyo Shinjuku Medical Center

Nobuko Utsumi, Hiromasa Kurosaki
Department of Radiology, JCHO Tokyo Shinjuku Medical Center, Tokyo, Japan

Methods of survey and decontamination of radium-223 dichloride for radionuclide therapy in clinical facilities

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Biodistribution, dosimetry and imaging of ^{225}Ac-DOTA-anti-PD-L1-BC in a murine immunocompetent transgenic breast cancer model

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Reducing renal uptake of free ^{213}Bi associated with the decay of ^{225}Ac-labeled radiopharmaceuticals

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How biodistribution, toxicity, and chelation of accelerator-produced actinium-225 will determine its fate in targeted alpha therapy

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Preclinical studies of ^{211}At in Multiple Myeloma

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Experimental alpha-radioimmunotherapy against liver metastasis of gastric cancer

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Synthesis and radiotherapeutic effect of two I-131 or At-211 labelled radioprobes for melanoma with overexpressed metabotropic glutamate receptor 1

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Comparison of pharmacokinetics between meta-benzylguanidine labeled with radioactive iodine, bromine and astatine

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^{203}Pb-AR-RMX conjugates for image guided TAT of neuroendocrine tumors (NETs)

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^{225}Ac-DOTA-Substance P as a potential radiopharmaceutical for targeted alpha therapy of glioblastoma multiforme

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Assessment of ^{213}Bi-anti-EGFR-MAb treatment response in malignant cancer cells

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Cytotoxicity evaluation using α-particle emitting radionuclides ^{211}At conjugated antibody

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Biodegradable polymersomes as carrier for alpha radionuclide therapy

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Barium ferrite nanoparticles labeled with ^{223}Ra:
a new potential radiobioconjugate for internal alpha therapy

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The impact of tumor burden on the absorbed dose to the kidneys from Actinium-225 labeled antibody therapy in a murine model and predicted dosimetric impact for human clinical use

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Biokinetic modelling for optimization of intraperitoneal targeted alpha therapy of disseminated ovarian cancer

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Absorbed dose evaluation for the normal neighboring organs on thyroid gland of hyperthyroidism for iodine-131 radionuclide therapy using the Monte-Carlo based PHITS code combined with voxel phantom data for the application of targeted alpha therapy

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How should we normalise dose in TAT for cancer?

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Poster SESSION II

Development of a scintillator based Compton camera for targeted α-particle radiotherapy

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Individual Alpha Particle Measurement using FNTD and SIM Super-Resolution Microscopy

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Radioisotope Production and Dynamic Multi-Isotope Imaging of the ^{225}Ac Decay Chain

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Chemical Purification of Actinium-225 from Proton-Irradiated Thorium Targets

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Behavior of Ac, Th and Ra on cation exchange resin in hydrochloric and trichloroacetic acids: Towards an alternative separation strategy for ^{225}Ac from irradiated thorium targets

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Radiochemical separation of ^{224}Ra from ^{232}U or ^{228}Th sources for ^{224}Ra/^{212}Pb/^{212}Bi generator

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Solution thermodynamics and kinetics of Th(IV) complexation by bare and conjugated Me-3,2-HOPO-based ligands

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Development of a resin-supported bifunctional reagent to simplify labeling of ^{211}At

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Isolation of ^{211}At using an anion-exchange column method

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Development of a ^{211}Rn/^{211}At Generator based on Dry-Chemistry

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Wet chemistry of radon and astatine for the development of a ^{211}Rn/^{211}At generator

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Laboratory automation employed in the purification of astatine-211 from dissolved bismuth targets: Development, optimization, and performance validation of the fluidic system

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Realizing Clinical Trials with Astatine-211: Radiopharmaceutical Chemistry

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Isolation of alpha-emitting radionuclides for nuclear medicine in JSC "SSC RF – IPPE"

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Production of Actinium-225 at Oak Ridge National Laboratory

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Reactor Production of ^{229}Th via Neutron Capture of ^{228}Ra Target

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Astatine-211 production using the C70XP

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The Production of ^{211}At at Fukushima Medical University

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The ultimate ^{225}Ac---->^{213}Bi generator

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SESSION I

CLINICAL EXPERIENCES

Efficacy of Ac-225-labeled anti-CD33 antibody in acute myeloid leukemia (AML) correlates with peripheral blast count

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Objectives: Actimab-A, composed of Ac-225 conjugated to the anti-CD33 monoclonal antibody lintuzumab, demonstrated safety and efficacy against AML in two phase 1 trials. To determine predictors of response, we correlated efficacy outcomes with differences in patient characteristics, disease characteristics, level of leukemic burden, and treatment regimen.

Methods: In the first phase 1 trial, relapsed and refractory AML patients were treated with a single infusion of Actimab-A without concomitant anti-leukemic therapy. Administered activity levels ranged from 18.5 to 148 kBq/kg, with 111 kBq/kg established as the maximum tolerated dose (MTD). In the second trial, newly diagnosed AML patients were treated with two equal fractionated doses of Actimab-A after receiving low dose cytarabine (LDAC) in an attempt to reduce disease burden. Total administered activities ranged from 37 to 148 kBq/kg, and the MTD was not reached. Subgroups were analyzed based on patient characteristics (age), disease characteristics (disease status [newly diagnosed vs. relapsed/refractory AML], primary vs. secondary AML following a prior hematologic disorder, cytogenetic/molecular genetic risk category), disease burden (bone marrow blast percentage, peripheral blood blast count), and treatment regimen (administered activity, dose fractionation, prior cytoreduction). Analyses were conducted to establish whether patients with objective responses achieving at least complete response with incomplete blood count recovery (CRi) differed from patients who did not achieve at least a CRi.

Results: There were no statistically significant differences in efficacy outcomes with respect to age, disease characteristics, bone marrow blast percentage, dose fractionation, or prior cytoreduction. Peripheral blood blast count (number of circulating blasts/μL of peripheral blood), however, was a highly significant predictor of objective response. Among 36 patients across all dose levels with available data treated in these two trials, 8/19 patients (42%) with peripheral blood blast counts < 200/μL responded, compared with 0/17 with blast counts ≥ 200/μL (P=0.002). To confirm these findings, we analyzed whether peripheral blood blast burden exhibited a similar correlation when the efficacy endpoint was broadened to include all patients who had ≥ 50% reduction in bone marrow blasts. The difference remained statistically significant, with 12/15 evaluable patients (75%) with blast counts < 200/μL having ≥ 50% decrease in bone marrow blasts and 4/16 evaluable patients (25%) with blast counts ≥ 200/μL having a comparable response (P=0.002). In addition, we observed a trend toward increased response rates with higher administered activities, which became more prominent when outcomes were adjusted for peripheral blood blast burden.

Conclusions: These findings indicate that baseline peripheral blast count is a strong predictor of response. The difference in response rates is likely due to decreased marrow targeting in patients with higher circulating blast counts because subsaturating antibody doses were administered in these trials.

Bi-213-anti-EGFR-MAb therapy of recurrent bladder cancer – a pilot study

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Objectives: Following transurethral resection of non-muscle-invasive bladder cancer (carcinoma in situ) and subsequent chemotherapy and treatment with Bacillus Calmette–Guérin (BCG), up to 40% of patients relapse within 5 years and need complete bladder excision. Therefore, new therapeutic strategies to combat tumor recurrence are needed. Because treatment of mice bearing intravesical human bladder cancer xenografts with Bi-213-anti-EGFR-MAb turned out highly efficient, the aim of this pilot study was to evaluate feasibility, safety and therapeutic efficacy of the α-emitter radioimmunoconjugate in recurrent bladder cancer patients.

Methods: The alpha-emitter Bi-213 was eluted from a Ac-225/Bi-213 generator system and coupled to the anti-EGFR-MAb (cetuximab, Merck, Germany) via the chelating agent CHX-A"-DTPA. 12 patients (10 m, 2 f) suffering from carcinoma in situ bladder cancer that had shown no response to BCG treatment were intravesically applied with 366-821 MBq (9.9 – 22.2 mCi) of Bi-213-anti-EGFR-MAb in 40 ml of PBS. Distribution of Bi-213-anti-EGFR-MAb was monitored by SPECT/CT. Treatment was terminated by emptying of the radioimmunoconjugate from the bladder up to 120 min after injection. Efficacy was evaluated via endoscopy and histology after eight weeks, and then six-monthly.

Results: All patients (pts) showed excellent toleration of the treatment without any side effects. SPECT/CT monitoring clearly revealed location of the Bi-213-anti-EGFR-MAb immunoconjugate in the bladder. Up to now (10 pts), treatment resulted in a documented complete eradication of tumor cells in three patients (CR is lasting 2.1 yrs, resp. 3.2 yrs, 1 pt with relapse after six months) and progressive tumor growth in seven patients.

Conclusion: Intravesical instillation of Bi-213-anti-EGFR-MAb is a promising, well tolerated therapeutic option for treatment of in situ bladder cancer after BCG failure and can help to avoid or postpone radical bladder surgery. A follow up study is planned to investigate further improvement of therapeutic efficacy through dose escalation and repeated treatments.

Targeted alpha therapy of glioblastoma multiforme: clinical experience with ^{213}Bi- and ^{225}Ac-Substance P

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Background and Objectives:
Glioblastoma multiforme (GBM), the most common primary brain tumor in adults, has a very poor prognosis with a median overall survival of 14.6 months despite of aggressive therapy. Targeted alpha therapy (TAT) with the short range, high LET alpha emitters ^{213}Bi and ^{225}Ac offers the potential for selective irradiation of tumors and minimizing damage to adjacent regions of the brain. The low-molecular weight peptide carrier substance P is targeting NK 1 receptors, which are consistently over-expressed on GBM cells. We report our clinical experience with ^{213}Bi-DOTA-Substance P (^{213}Bi-SP) and ^{225}Ac-DOTAGA-Substance P (^{225}Ac-SP) in patients with recurrent GBM.

Methods:
Histologically confirmed recurrence of GBM after standard therapy (surgery, radio- and chemotherapy) was diagnosed in all patients. The group receiving ^{213}Bi-SP included patients with primary GBM (n=18) and secondary GBM (n=7) while ^{225}Ac-SP patients had primary GBM (n=5). Following intracavitary or intratumoral insertion of 1 or 2 catheter systems, patients were treated with 1–7 doses of about 2 GBq ^{213}Bi-SP or 1-4 doses of 10 MBq ^{225}Ac-SP in intervals of typically 2 months. ^{68}Ga-SP was co-injected with the therapeutic doses to assess biodistribution using PET/CT. Therapeutic response was monitored with repetitive MRI.

Results:
Treatment with up to 11 GBq ^{213}Bi-SP or 40 MBq ^{225}Ac-SP was tolerated well with only mild transient adverse reactions. PET/CT of co-injected ^{68}Ga-SP showed high retention of the radiolabelled peptide at the tumour site. In patients with primary GBM treated with ^{213}Bi-SP the PFS from start of TAT was 3.7 months. The median overall survival after primary diagnosis was 21.5 months (8-36 months) and the median survival from the diagnosis of the recurrence was 9 months (3-30 months). In patients with secondary GBM treated with ^{213}Bi-SP median progression free survival was 13.6 months. Median overall survival from the first diagnosis was 46.8 months. Follow up of patients treated with ^{225}Ac-SP is ongoing.

Conclusion:
Treatment of recurrent GBM with ^{213}Bi-SP and ^{225}Ac-SP is safe with a favorable toxicity profile. Tumor control could be achieved predominantly in patients that received multiple doses of TAT. Interim survival analysis indicates a prolongation of median survival after therapy with ^{213}Bi-SP compared to standard therapy alone. Targeted alpha therapy with ^{213}Bi-SP and ^{225}Ac-SP may evolve as a promising novel option for treatment of GBM.

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Dosimetry and Biodistribution of ^{203}Pb-AR-RMX in Patients with Somatostatin Expressing Neuroendocrine Tumors. A Clinical Exploratory Study.

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Background and Objective: The primary objective of the first-in-human open-label, single-dose, diagnostic study of ^{203}Pb-AR-RMX (IND 130690) was assessment of the dosimetry and biodistribution of the radiotracer in patients with somatostatin expressing neuroendocrine cancers. The ^{203}Pb-AR-RMX served as a surrogate for ^{212}Pb-labeled AR-RMX designed for targeted alpha particle therapy (TAT) of neuroendocrine cancers. The secondary objective of this exploratory study was intra-subject comparison of distribution of ^{203}Pb-AR-RMX to organ distribution of the currently available somatostatin receptor imaging agents, such as ^{111}In-Octreoscan or ^{68}Ga-DOTATATE.

Methods: Five patients with histologically and/or clinically confirmed NET and prior somatostatin analogue scans (positive or negative) were enrolled in the exploratory phase I clinical trial. All patients completed 4 cycles of ^{177}Lu-DOTATATE PRRT. The whole body as well as SPECT/CT images of the abdomen of patients were acquired and complete dosimetry calculation were performed after iv administration of 5 mCi (+/-10%) of ^{203}Pb-AR-RMX. ^{68}Ga-DOTATATE PET/CT scans were also performed as per expanded access IND 117289. Alternatively, ^{111}In-Octreoscan was also acquired as part of standard of care for NETs patients. The PK and safety assessment of ^{203}Pb-AR-RMX was completed by collection of patient's blood and urine samples up to 48h post injection. Dosimetry calculations were performed using custom RAPID reconstruction software.

Results and Discussion: The distribution and excretion characteristics of ^{203}Pb-AR-RMX were very similar to PK properties of ^{68}Ga-DOTATATE and ^{177}Lu-DOTATATE. No acute or delayed hematological or renal toxicity was observed. The pharmacokinetic and biodistribution data of whole body and SPET/CT imaging studies were used to calculate the ^{203}Pb-AR-RMX organ absorbed dose and also the expected tissue absorbed doses for ^{212}Pb-AR-RMX. Spleen receives the highest absorbed dose of ^{212}Pb-AR-RMX and as expected kidneys are the doses limiting organs for TAT. Detailed dosimetry of the investigational agent will be presented.

The eIND clinical studies of ^{203}Pb-AR-RMX confirmed favorable PK characteristics, dosimetry, and sensitivity of lesion detection in NETs patients. The pre-clinical efficacy, toxicity and dosimetry studies of ^{212}Pb-AR-RMX are on-going and will provide guidance on design of the first in human TAT clinical studies of ^{212}Pb-AR-RMX in NETs patients. ^{212}Pb-AR-RMX has a potential to advance radionuclide therapy of NETs and improved efficacy of PRRT by delivering therapeutic radiation dose precisely to SSTR2-(+) neuroendocrine cancer cells.

^{225}Ac-PSMA-617: PSMA targeting alpha-radiation therapy of patients with mCRPC

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Purpose: To evaluate the potential of PSMA targeting ^{225}Ac-PSMA617 as a promising new treatment option for poor prognosis advanced stage mCRPC (metastatic castration-resistant prostate cancer) patients. An appropriate starting activity for clinical application of ^{225}Ac-PSMA617 was defined by preliminary dosimetry modeling. The treatment protocol was further refined by an empirical dose escalation during "compassionate use" in a first group of advanced stage patients. The derived "standard operation procedure" was used to treat a larger group of patients, which now has >6 months of follow up. Here we report our clinical observations in regard to anti-tumor activity as well as acute and mid-term toxicities experienced with this new concept of mCRPC therapy.

Methods: A dosimetry estimate was calculated based on time-activity-curves derived from serially performed ^{177}Lu-PSMA-617 scans extrapolated to the physical half-life of ^{225}Ac, assuming instant decay of instable daughter nuclides. First patients (n=14) were treated with escalating activities between 50 kBq/kg BW and 200 kBq/kg BW and administration intervals of either 2 or 4 months. Adverse events were used to define the maximum tolerated dose. Based on this preliminary clinical experiences a standard protocol was defined and used for therapy of a second group of patients (n=28). PSA and radiological response were used to evaluate anti-tumor activity. Hematological toxicity and clinical side-effects were evaluated every 4 weeks.

Results: Assuming a relative biological effectiveness of 5, a mean dose of 2.3 Sv for salivary glands, 0.7 Sv for kidneys and 0.05 Sv for red marrow were estimated for 1 MBq of ^{225}Ac-PSMA617; comparable to an activity of 1 GB of ^{177}Lu-PSMA617. First clinical experience revealed that severe xerostomia became dose-limiting before relevant hematological toxicity was observed. 100kBq/kg BW ^{225}Ac-PSMA617 administered every 2 months was used as a first clinical standard protocol. From n=28 patients "intention-to-treat", finally n=20 were treated "per-protocol" and n=15 of them (75%) demonstrated a PSA and radiological response after a follow-up period of 6 months. Complete remission was observed in n=4 patients (20%). Due to early progression n=3 patients discontinued therapy at an earlier time-point, n=5 patients discontinued due to xerostomia. No grade-3/4 hematological toxicity was observed for patients with grade-0/1 values at baseline, regardless of the extent of bone involvement.

Conclusions: A standard treatment activity of 100kBq/kg BW administered every two month is associated with remarkable anti-tumor activity and tolerable side-effects. Hematological toxicity is moderate even in cases of diffuse type bone(marrow) infiltration. Further research should be focused to ameliorate off-target radiation affecting salivary glands.

Radium-223 (Ra-223) in asymptomatic metastatic castration resistant prostate cancer (mCRPC) patients treated in an international early access program (iEAP)

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Background: Ra-223, a targeted alpha therapy, is currently used to treat mCRPC patients (pts). To investigate Ra-223 when used early in the disease course, we analyzed safety and efficacy in mCRPC pts with no symptoms at baseline treated in an iEAP.

Methods: This was a prospective, single-arm phase 3b study of mCRPC pts (malignant lymphadenopathy not exceeding 6 cm was allowed, visceral disease was excluded). Pts received Ra-223, 55 kBq/kg IV, every 4 weeks for up to 6 cycles. Co-primary endpoints were safety and overall survival (OS). Post hoc analyses were performed according to asymptomatic or symptomatic disease status at baseline. Asymptomatic was defined as no pain and no opioid use at baseline.

Results: 708 pts received ≥1 Ra-223 injection: 548 (77%) were defined as symptomatic and 135 (19%) were defined as asymptomatic. Asymptomatic pts had more favorable baseline characteristics than symptomatic pts (Table). Fewer asymptomatic pts had received prior abiraterone (34 pts, 25% vs 190, 35%), enzalutamide (5 pts, 4% vs 43, 8%) and prior docetaxel (70 pts, 52% vs 339, 62%). More asymptomatic pts received 6 cycles of Ra-223 (96, 71% vs 300, 55%). Adverse events (AEs) were reported for fewer pts with asymptomatic vs symptomatic disease: any grade, 61% vs 79%; grade 3/4, 29% vs 40% and serious AEs, 22% vs 38%. OS was longer in asymptomatic pts and ALP normalization was more common (Table).

Conclusions: Asymptomatic pts were more likely to have a better prognosis and to complete all 6 cycles of Ra-223. Ongoing first-line combination studies (ERA-223: NCT02043678 and PEACE-3: NCT02194842) may show whether Ra-223 administered early in the disease course will lead to better outcomes.

	Asymptomatic pts N=135	**Symptomatic pts** N=548
Baseline characteristics		
ECOG PS, n (%)		
0	76 (56)	176 (32)
1	52 (39)	293 (53)
≥2	7 (5)	79 (14)
ALP (U/L), n	133	545
Median	127.0	168.0
PSA (µg/L), n	134	543
Median	113.0	154.6
Outcome		
Overall survival		
Events, n (%)	27 (20)	192 (35)
Median, months (95% CI)	20.5 (20.5–NR)	13.5 (11.7–17.1)
ALP normalization, n (%)	71	342
Yes	42 (59)	116 (34)
No	29 (41)	226 (66)

NR=not reached.

Changes in alkaline phosphatase (ALP) dynamics and overall survival (OS) in metastatic castration-resistant prostate cancer (mCRPC) patients treated with radium-223 in an international early access program (EAP)

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Background: Identifying a reliable marker of efficacy for radium-223 dichloride (Ra-223) would aid in the clinical management of mCRPC patients (pts). In exploratory analyses of mCRPC pts with symptomatic bone metastases treated with Ra-223 in the ALSYMPCA trial, OS was significantly longer in pts with a confirmed decline in ALP levels from baseline at week 12, compared with pts without a confirmed ALP decline. Here, we present data on ALP dynamics and OS and time to first symptomatic skeletal events (SSE) in pts treated with Ra-223 in an international EAP.

Methods: This was a prospective single-arm phase IIIb study of CRPC pts with symptomatic or asymptomatic bone metastases (no visceral disease) recruited from 14 countries. Pts received Ra-223 55 kBq/kg IV, every 4 weeks for up to 6 cycles. Co-primary endpoints were safety and OS. Exploratory analyses investigated whether a confirmed decline (any magnitude) in ALP levels was associated with OS and time to first SSE.

Results: 696 pts received at least one Ra-223 cycle. Of those, 398 (57%) pts had a confirmed decline in ALP and 298 (43%) had no confirmed ALP decline. Key baseline characteristics are shown (Table). More pts with a confirmed ALP decline (374, 94%) received 5–6 Ra-223 injections than those with no ALP decline (99, 33%). Hazard ratios (HR) for confirmed ALP decline at week 12 vs no decline suggest a strong association of ALP decline with both longer OS (HR 0.299, 95% CI 0.227–0.395) and longer time to first SSE (HR 0.474, 95% CI 0.340–0.662) (Table).

Conclusions: In this EAP, which is relevant for pts currently treated in clinical practice, decline in ALP was associated with longer OS and time to first SSE.

	Confirmed ALP decline	
Parameter	**Yes,** N=398	**No,** N=298
Baseline characteristics		
ECOG PS, n (%)		
0	170 (43%)	91 (31%)
1	189 (47%)	159 (53%)
≥2	39 (10%)	48 (16%)
Pain*, n (%)	380	287
Mild	217 (57%)	153 (53%)
Moderate-severe	79 (21%)	79 (28%)
None	84 (22%)	55 (19%)
ALP (U/L), n	398	296
Median	149.0	148.5
PSA (µg/L), n	398	295
Median	117.2	202.0
Hemoglobin (g/dL)		
Median	12.4	11.8

	Confirmed ALP decline	
Parameter	**Yes,** N=398	**No,** N=298
Efficacy outcome		
Overall survival		
Events, n (%)	86 (22%)	124 (42%)
Median, months	NR	10.0
95% CI	NA	8.6-11.5
Hazard ratio†	0.299	
95% CI	0.227-0.395	
Time to first SSE		
Events, n (%)	76 (19%)	67 (22%)
Median, months	17.5	NR
95% CI	17.0-18.1	NA
Hazard ratio†	0.474	
95% CI	0.340-0.662	

*Measured from the brief pain inventory short form.
†Calculated from Cox proportional hazards model.
NR/A=not reached/available.

SESSION II

PLECLINICAL STUDIES

Reduction of radiation exposure to the large intestine during ^{223}Ra alpha therapy with oral administration of barium sulfate

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Background and Objective: Alpha therapy with Radium-223 dichloride ($^{223}RaCl_2$) is used for the treatment of patients with castration-resistant prostate cancer, symptomatic bone metastases without known visceral metastatic disease. ^{223}Ra is a calcium analogue, which forms complexes with hydroxyapatite in activated osteoblastic regions near metastases. From clinical studies, intravenous injection of $^{223}RaCl_2$ caused gastrointestinal disorders, such as nausea, abdominal discomfort and diarrhea as the most frequent adverse events due to radiation exposure. Here, we proposed a novel strategy to reduce accumulation of ^{223}Ra in the large intestine by oral administration of barium sulfate ($BaSO_4$) known as a coprecipitating agent of Ra.

Methods: $^{223}RaCl_2$ (10 kBq/mouse) was intravenously injected in ddY mice with or without oral administration of $BaSO_4$ (150 mg/mouse) at 1 h before injection of $^{223}RaCl_2$. The biodistribution was examined at 1, 2, 4, 6, and 24 h after $^{223}RaCl_2$ injection. In addition, for laxative treatment, 50% glycerin enema solution (0.3 mL) was administered rectally at 3 h after $^{223}RaCl_2$ injection, with or without $BaSO_4$ administration in a manner described above, and the biodistribution was studied at 1 h after glycerin enema (4 h after $^{223}RaCl_2$ injection). The organs of interest, including blood, liver, kidney, small intestine, large intestine, spleen, and femur, were collected and weighed; and urine and feces were also collected. Radioactivity was counted with a γ-counter.

Results: $BaSO_4$ significantly reduced ^{223}Ra accumulation in the large intestine at 1, 2 and 4 h after $^{223}RaCl_2$ injection ($P < 0.05$). ^{223}Ra activity was slightly increased in the urine and feces in the $BaSO_4$ group at 24 h after $^{223}RaCl_2$ injection, compared to the control group. Glycerin enema decreased ^{223}Ra accumulation in the large intestine to a similar level of $BaSO_4$. However, no additional effect of glycerin enema to $BaSO_4$ was observed.

Conclusions: These results demonstrated that use of $BaSO_4$ was effective to reduce ^{223}Ra accumulation in the large intestine during $^{223}RaCl_2$ therapy and glycerin enema would help to clear $BaSO_4$ from the body without lessening the effect of $BaSO_4$. This method could be useful to reduce adverse events on $^{223}RaCl_2$ therapy.

Pharmacokinetic profiling and therapeutic efficacy of alpha-emitter labeled anti-PD-L1 antibodies in an immune competent transgenic breast cancer model

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Background. Programmed cell Death Ligand 1 (PD-L1) is part of an immune checkpoint system that is essential for preventing autoimmunity. Tumor cells have developed the ability to co-opt these immune checkpoints to suppress anti-tumor immunity. PD-L1 is expressed on tumor cells, tumor associated macrophages (TAMs) and other cells within the microenvironment of the tumor. Immunotherapy using anti-PD-L1 antibody has shown promising anti-tumor effect against a number of cancers including breast cancer, and is currently used in several clinical trials. Furthermore, studies have shown that anti-PD-L1 targeted immunotherapy synergizes with radiation therapy. The aim of this study was to investigate if the therapeutic efficacy of anti-PD-L1 targeted immunotherapy is enhanced when combined with the alpha-particle emitting radiotherapeutic nuclide Actinium-225(^{225}Ac) in a murine immunocompetent metastatic breast cancer model.

Methods. For pharmacokinetics studies, 8-12 week old healthy female *neu*-N mice bearing NT2.5 tumors were injected with ^{111}In-DTPA-anti-PD-L1-BC (0.37 MBq) at antibody concentrations of 1-10 mg/kg, and ^{225}Ac-DOTA-anti-PD-L1-BC (15 kBq, 3-mg/kg). *Ex vivo* biodistributions were performed at 1, 6, 24, 72, and 144 hours post-injection. For therapeutic efficacy studies, groups of mice (n=8-10) with disseminated disease were injected intravenously 3 days post the LCV injection with either ^{225}Ac-DOTA-anti-PD-L1-BC (15 kBq, 3-mg/kg), unconjuageted antibody (3-mg/kg), or saline. Max-tolerated dose studies were performed at 15 – 44 kBq (3-mg/kg).

Results. Radiolabeling of ^{225}Ac-DOTA-anti-PD-L1-BC conjugate was done with a radiochemical purity >95%. The pharmacokinetic profiles suggested administration of the anti-PD-L1 antibody at 3-mg/kg. The pilot therapeutic study demonstrated that the group receiving a single dose of 15 kBq of ^{225}Ac-DOTA-anti-PD-L1-BC (3 mg/kg) had significant increases in median survival (63 days, $p \geq 0.05$) when compared to the saline control group (44 days). MTD studies demonstrated that doses up to 37 kBq were well tolerated over 100 days post-injection of ^{225}Ac-DOTA-anti-PD-L1-BC, with indications of minor liver toxicity post-mortem.

Conclusion. These preliminary studies have also highlighted that alternating the pharmacokinetic profiles of these agents to better match the dynamic nature of PD-L1 expression is key in optimizing the potential of this combined therapy for translation to the clinic. Pilot therapy studies with ^{225}Ac-labeled anti-PD-L1 conjugates are showing promising results for the combination of a therapeutic radionuclide, ^{225}Ac, and anti-PD-L1 immunotherapy. These studies have demonstrated that the delivery of ^{225}Ac, via conjugation to anti-PD-L1 antibodies, to metastatic breast cancer sites has the ability to increase median survival in a metastatic breast cancer mouse model. Furthermore the selected dose of 15 kBq was well tolerated in mice, with the potential to increase the dose administered.

Novel IgG to melanin shows promise for radioimmunotherapy of metastatic melanoma

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Objectives: Despite several novel drugs for metastatic melanoma entering the market in the last few years, there is an enormous need for novel effective treatments that would not rely on patients' specific genotypes, biochemical pathways, microbiomes or the variability of an individual's immune system. Earlier we have conducted a successful Phase 1 Clinical trial in patients with metastatic melanoma of a murine antibody to melanin radiolabeled with beta emitter 188Rhenium (^{188}Re). The trial demonstrated safety and was indicative of the efficacy of the approach targeting melanin with radiolabeled antibodies (1). However, the IgM isotype of that first generation antibody presented an impediment for its humanization and further clinical development. Recently, we have identified an 8C3 murine antibody to melanin of the IgG isotype which is amenable to humanization. The goal of this study was to evaluate the possibility of radiolabeling this new antibody with ^{188}Re and alpha emitter 213Bismuth (^{213}Bi) and to assess its potential as a radioimmunotherapy (RIT) reagent for metastatic melanoma. Methods: Female C57Bl6 mice were injected with highly aggressive B16-F10 murine melanoma cells via tail vain to form metastases like lesions in the lungs. 8C8 was radiolabeled with ^{188}Re or ^{213}Bi "directly' or via CHXA"-DTPA chelating agent, respectively. On day 4 after cells injections the groups of 5-7 mice were treated with either unlabeled 8C3 antibody, or 400 μCi ^{188}Re-8C3 or 400 μCi ^{213}Bi-8C3 mAb, or left untreated. On day 14 after cells injection the mice were sacrificed, their lungs removed and metastases-like lesions enumerated. Results: There was statistically significant (P=0.01) reduction of metastases-like lesions in the lungs of mice treated with either 400 μCi ^{188}Re-8C3 or 400 μCi ^{213}Bi-8C3 mAb in comparison with the untreated controls. The unlabeled 8C3 mAb did not have any effect on the number of the lesions. Conclusion: 8C3, a 2nd generation IgG antibody to melanin, demonstrated impressive results in decreasing melanoma lung lesions in an aggressive murine melanoma model. This novel molecular targeted systemic radiation therapy was not accompanied by any undesirable side effects. We conclude that 8C3 is a promising agent for development into a clinical RIT reagent for patients with metastatic melanoma refractory to standard of care treatments.

References: Klein M. et al. J. Skin Cancer 2013;2013:828329

Involvement of direct and indirect (bystander) cytotoxic effects in alpha-RIT of small volume peritoneal carcinomatosis using ^{213}Bi- and ^{212}Pb-labeled mAbs

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Objectives: We investigated *in vitro* and *in vivo* the relative contribution of direct and indirect (bystander) effects in the therapeutic efficacy of ^{213}Bi- and ^{212}Pb-labeled mAbs used for treating small volume peritoneal carcinomatosis.

Methods: *In vitro*, A-431 cells exposed to increasing activities (0–0.5 MBq/mL; 37 MBq/mg) of either 35A7 (anti-CEA), Trastuzumab (anti-HER2) or PX (non-specific) ^{212}Pb-labeled mAbs while SK-OV-3 expressing MISRII were exposed for 90 min to 0.06-0.5MBq/mL of 16F12 ^{213}Bi-mAb or ^{213}Bi-PX mAb. The relative contribution to cell killing of direct and bystander effects between donor and recipient cells, respectively was assessed using standard medium transfer protocol. Biological end points measured both in donor (direct effect) and in recipient cells (bystander effects) included clonogenic survival and oxidative DNA damage together with protein expression involved signalling pathways involved in tumor cells response. We also assessed the contribution of oxidative stress to both direct and indirect bystander effects.
In vivo, nude mice with intraperitoneal (i.p.) 2-3 mm A-431 tumor cells xenografts were i.p. injected with increasing activities (370–1480 kBq; 37 MBq/mg) of the above mentioned anti-CEA, anti-HER2 or non-specific ^{212}Pb-mAbs. Determination of radioactivity at the tissue level was done using digital micro-autoradiography (DAR) and absorbed doses were calculated. Biological markers including 53BP1, caspase 3 and Ki67 proteins were also determined in tissue by immunohistochemistry.

Results: *In vitro* we showed in donor cells the strong efficacy of ^{212}Pb-35A7 and ^{212}Pb-trastuzumab mAbs and also to a lower extent of ^{213}Bi-16F12 mAb. Significant bystander cytotoxicity was measured in all recipient cells. The complexity of DNA damage (53BP1 foci) observed in donor cells confirmed the high LET cytotoxic effects of ^{212}Pb-mAbs while less complex damage were observed in recipient cells. We showed that p38 and JNK proteins play an essential role in bystander effects through an oxidative stress-mediated formation of membrane lipid rafts.
In vivo, dose distribution was calculated using DAR analysis and voxel dosimetry. Results showed a strong dose gradient for anti-CEA ^{212}Pb-mAbs while it was much more homogeneous for anti-HER2 or for the non-specific ^{212}Pb-mAbs. These results explain the relative higher therapeutic efficacy previously reported *in vivo* for anti-HER2 ^{212}Pb-mAbs compared with anti-CEA ^{212}Pb-mAbs. However, we also observed a similar formation of DNA damage in tissue independently of tumour absorbed doses thereby indicating that bystander effects could also be involved.

Conclusions: Our results showed *in vitro* and *in vivo* the strong contribution of direct effects of ^{212}Pb- and 213Bi-labeled mAbs in killing tumour cells and the involvement of P38 and JNK signalling pathways through oxidative stress induction. Wes showed *in vivo* that heterogeneity in mAbs distribution could be counterbalanced to some extent by the presence of bystander effects.

Preclinical evaluation of anti-HER2 2Rs15d nanobody labeled with ^{225}Ac

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Objectives: Human Epidermal Growth Factor Receptor type 2 (HER2) is overexpressed in a series of human cancer types such as breast, ovarian, colorectal and urothelial carcinomas and is often associated with a higher recurrence rate and a shorter time to relapse. Intact mAbs are not always ideal vectors for radioimmunotherapy due to their slow pharmacokinetic and normal-tissue clearance. Nanobodies (nbs) are small antibody fragments (~15kDa) with beneficial pharmacokinetic properties, and those targeted to HER2 are very attractive vectors for targeted radionuclide therapy (TRT). The aim of this study was to develop and evaluate a potential molecular-targeted drug based on the anti-HER2-Nb labeled with ^{225}Ac.

Methods: The bifunctional chelate *p*-SCN-Bn-DOTA was coupled to anti-HER2 2Rs15d-Nb and the obtained bioconjugate was further labeled with ^{225}Ac. The stability of ^{225}Ac-DOTA-2Rs15d-Nb was determined in PBS, human serum and cell culture medium for up to 10 days at RT and 37^{o}C. Binding specificity, affinity and cell internalization assays were evaluated on SKOV-3 (HER2^{+}) and MDA-MB-231 (HER2^{-}) cells; immunoreactive fraction (IF) by the Lindmo method. Cell viability was assessed using the MTS colorimetric assay. The *in vivo* accumulation of free ^{225}Ac and ^{225}Ac-DOTA as controls was performed on female C57bl/6 normal mice. Finally, the biodistribution of ^{225}Ac-DOTA-2Rs15d-Nb was assessed in the presence or absence of 150mg/kg Gelofusine in female athymic nude Crl:NU-Foxn1^{nu} mice subcutaneously xenografted with SKOV-3 and MDA-MB-231 tumors.

Results: Labeling yield of DOTA-2Rs15d-Nb with ^{225}Ac was high, with an efficiency of *ca*. 90%. TCA precipitation, ITLC, and SDS-PAGE indicated that >95% of radioactivity was protein-associated after purification. Stability in biological solutions, according to ^{225}Ac radionuclide, was above 90% over 10d. ^{225}Ac-DOTA-2Rs15d-Nb bound specifically to HER2^{+} cells with 69-83% IF and a K_D of 4.06 ± 0.45 nM. Blocking of HER2 with 100>excess of cold 2Rs15d-Nb reduced binding almost 30-fold, whereas cold Trastuzumab did not compete to binding sites. Low level of binding (0.3%) was observed for MDA-MB-231 (HER2^{-}) cell line. Internalization assay indicated about 10-25% of initially bound radioactivity was trapped intracellularly for ^{225}Ac-DOTA-2Rs15d-Nb over 24h. Cytotoxicity studies demonstrated that ^{225}Ac-DOTA-2Rs15d-Nb significantly reduced SKOV-3 cell viability in a dose dependent manner compare to ^{225}Ac-DOTA as a control. No significant differences in cytotoxicity were noticed in MDA-MB-231 cells for ^{225}Ac-DOTA-2Rs15d-Nb and ^{225}Ac-DOTA. Tumor uptake in SKOV-3 xenografted mice was high and specific (~5%), whereas in MDA-MB-231 was below 0.5% already 1h p.i.. Kidney accumulation was reduced almost 3-fold by coinjection of ^{225}Ac-DOTA-2Rs15d-Nb with 150 mg/kg Gelofusine.

Conclusions: ^{225}Ac-DOTA-2Rs15d-Nb showed strong *in vitro* therapeutic potential and high tumor uptake *in vivo*. Therefore, this radiobioconjugate is a promising agent that warrants further *in vivo* evaluation and TRT in SKOV-3 xenografted mice.

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Preclinical evaluation of astatinated nanobodies for targeted alpha therapy

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Introduction: The use of nanobodies (Nbs) as vehicles in targeted radionuclide therapy has gained traction due to their excellent *in vivo* properties, high affinity and fast clearance kinetics. Moreover, Nbs show good tumor penetration due to their small size and conformational structure. This study investigates a novel molecular targeted therapy which combines the α-particle emitter Astatine-211 (^{211}At) and the HER2-targeting 2Rs15d-Nb to selectively kill HER2$^+$ metastases. To achieve astatinated 2Rs15d-Nbs, two different radiochemical methodologies were validated using three different prosthetic groups. In the "random labelling method", the primary amines of lysines on the Nb surface are used as conjugation sites. The "site-specific labelling approach" aims at obtaining a homogeneous tracer population with a fixed conjugation. Here the prosthetic group is conjugated to the carboxyl-terminal cysteine of 2Rs15d-His6-Linker-Cys. The different conjugates were evaluated for their binding specificity, immunoreactivity and degree of internalisation in HER2$^+$ SKOV-3 cells.

Materials & Methods: 2Rs15d-Nb was randomly labelled with ^{211}At via the prosthetic groups N-succinimidyl-3-(trimethylstannyl) benzoate (**m-eATE**) (2), N-succinimidyl3-[^{211}At]astato-4-guanidino-methylbenzoate (**SGMAB**) (3), while 2Rs15d-His6-Linker-Cys was site-specifically labelled using N-[2-(maleimido)ethyl]-3-(trimethylstannyl)benzamide (**MSB**) (4). The radiochemical purity (RP) was determined by instant thin-layer chromatography (iTLC), via co-precipitation with human serum albumin using 20% trichloroacetic acid and with size exclusion fast protein liquid chromatography (FPLC). Next, the immunoreactive fraction (IRF) was evaluated on HER2$^+$ SKOV-3 cells using the Lindmo assay. Their specificity of binding was measured with and without a 100-fold excess of unlabelled Nb. Here, 20 nM of ^{211}At-labelled Nbs were incubated with the cells during 1 h at 4°C, after which unbound Nb was washed away using ice-cold PBS. The bound fraction was collected using 1 M NaOH (15 minutes at 37°C). Finally, the degree of internalization in HER2$^+$ SKOV-3 cells was evaluated over 24h. The cells were exposed to 0.1 M glycine-HCl (pH 2.8) (5 minutes at 4°C) to collect the membrane-bound fraction. The internalized fraction was collected using 1 M NaOH.

Results: Radioastatination of 2Rs15d using m-eATE and a specific activity of 118.66 MBq/mg resulted in a radiochemical yield (RCY) of 55% and a RP of 99%. The use of SGMAB with a specific activity of 68.66 MBq/mg resulted in a RCY of 28% and a RP of 99%. Finally, the site-specific labelling with MSB using a specific activity of 270.77 MBq/mg resulted in a RCY of 52% and a RP > 91%. FPLC of the three astatinated Nbs showed that the ^{211}At-activity peak overlaps well with the conjugated Nb peak of the UV-chromatogram. The IRF of astatinated SGMAB- and me-ATE-Nb was 66% and 42% respectively. Furthermore, binding to HER2 could be blocked ($p<0.0001$) for the three different astatinated Nbs, confirming its specificity of binding. The internalized fractions were 24.54%, 11.77%, 25.04% at 1h and 18.15%, 10.87%, 9.54% at 24h for astatinated Nbs using MSB, SGMAB and me-ATE respectively.

Conclusion: Taken together, both strategies can be used successfully for ^{211}At-labeling of the anti-HER2 2Rs15d Nb. All three ^{211}At-labeled Nb conjugates bind to and internalize into HER2$^+$ SKOV-3 cells efficiently. The planned *in vivo* evaluation in mice with HER2$^+$ SKOV-3 tumor xenografts will allow us to confirm the present data and will give more insight in the biodistribution of the different ^{211}At-labeled Nb conjugates.

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Development of α-emitting [^{211}At]-*meta*-astatobenzylguanidine (^{211}At-MABG) as a novel therapeutic agent for malignant pheochromocytoma

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Beta-emitting [^{131}I]-*meta*-iodobenzylguanidine (^{131}I-MIBG) has been used in the treatment of malignant pheochromocytoma (PCC). However, the rates of complete remission after treatment with ^{131}I-MIBG were quite low in previous clinical studies, indicating that clinical therapeutic effect of ^{131}I-MIBG is still insufficient. Alpha-particle has shorter path-length and deposits higher energy in tissues than β-particle. These properties enable α-emitters to strongly suppress the growth of tumor cells. Astatine-211 (^{211}At) is an α-emitting halogen and has a suitable half-life for cancer therapy ($t_{1/2}$=7.2 h). Therefore, [^{211}At]-*meta*-astatobenzylguanidine (^{211}At-MABG) may potentially suppress the growth of malignant PCC. However, no therapeutic studies of ^{211}At-MABG in malignant PCC have been reported. In this study, the therapeutic effects of ^{211}At-MABG was investigated using rat PCC models both *in vitro* and *in vivo*.

^{211}At was produced via the ^{209}Bi(α,2n)^{211}At reaction and was isolated through dry distillation. ^{211}At-MABG was synthesized by astatination of *meta*-trimethylsilylbenzylguanidine hemisulfate in the presence of *N*-chlorosuccinimide as an oxidant. Cellular uptake and tumor suppressive effects of ^{211}At-MABG were examined using a rat PCC cell line, PC12. Biodistribution and therapeutic effects of ^{211}At-MABG were examined using mice bearing PC12 as the *in vivo* study.

^{211}At-MABG was highly taken up into PC12 cells through the norepinephrine transporter (NET). Clonogenic growth of PC12 was significantly suppressed by the treatment with 0.2 kBq/mL ^{211}At-MABG compared to the control ($P<0.0001$). DNA double-strand breaks, cell cycle arrest at the G2/M phase and cell death were observed after ^{211}At-MABG treatment. *In vivo* biodistribution studies showed that ^{211}At-MABG was highly distributed and was retained in tumors (29.1 ± 9.3% injected dose per gram of tissue (%ID/g) at 1 h, 16.4 ± 5.7 %ID/g at 24 h post-injection). The radioactivity in normal organs except for adrenal and stomach was time-dependently cleared. Furthermore, the tumor size was significantly reduced by the single administration of ^{211}At-MABG (555 kBq/head) compared to the control group (relative tumor volume at day 7: 0.54 ± 0.12 (^{211}At-MABG) vs.1.82 ± 0.60 (Control), $P<0.01$). The ^{211}At-MABG treatment group did not show any weight reduction compared to the control group at day 7 ($P=0.881$).

^{211}At-MABG highly accumulated in tumor cells via NET both *in vitro* and *in vivo*, and exhibited a strong therapeutic effect in a PCC-bearing mice model without an associated weight reduction. Furthermore, α-irradiation dependent DNA damage, cell cycle arrest and cell death were involved in antitumor effects of ^{211}At-MABG. Taking these results into account, ^{211}At-MABG might be an attractive therapeutic agent for the treatment of malignant PCC. At present, dose-escalation experiment with ^{211}At-MABG is being addressed.

Directing alpha-emitting conjugates to cancer chromatin via PARP-1

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Introduction: Poly(ADP-ribose) Polymerase 1 (PARP-1) is a guardian of genomic stability and plays critical roles in DNA damage response, cell cycle, epigenetics, and inflammation. PARP-1 is the second most abundant nuclear protein next to histones and offers a unique target for the delivery of alpha emitting radionuclides directly to chromatin maximizing radiobiological effects. High-risk neuroblastoma is a deadly pediatric malignancy that overexpresses PARP-1 and approximately 80% of patients succumb to their disease. By utilizing the overexpression of PARP-1 we aim to selectively target high-risk neuroblastomas for the delivery of alpha particles directly to cancer chromatin.

Methods: Astatine-211 was produced on a JSW BC3015 cyclotron at 28.5 MeV via the Bi-209(α,2n)At-211 nuclear reaction. Astatine-211 was isolated by dry distillation and radiochemically functionalized onto a small molecule PARP inhibitor to afford ^{211}At-MM4. Using a panel of neuroblastoma cell lines, the pharmacology and cytotoxicity of ^{211}At-MM4 was evaluated in vitro. Next, protein analysis was performed by Western to evaluate expression of classical and alternative non-homologous end joining proteins. In addition, PARP-1 expression and DNA damage were assessed in response to therapy. Furthermore, in vivo therapy studies with PET/CT imaging of PARP-1 were performed to assess therapeutic efficacy and predictive capabilities of companion diagnostics.

Results: IMR-05, SK-N-SH, and NLF were the most sensitive cell lines evaluated and Be-2-c was the most resistant cell line. All cell lines evaluated were high-risk neuroblastomas and baseline Western protein analysis did not reveal specific pathway dependence for classical or alternative non-homologous end joining defined by protein expression. Response to therapy showed significant increases in DNA damage measured by gH2AX. Interestingly PARP-1 expression was upregulated post therapy in the resistant cell line Be-2-c. IMR-05 was the most sensitive cell line in vitro and was translated to in vivo models where therapeutic efficacy was shown. PET/CT imaging of PARP-1 post therapy showed low tumor uptake and was indicative of response.

Conclusion: ^{211}At-MM4 is a small molecule PARP inhibitor functionalized with an alpha emitting radionuclide astatine-211 that can effectively deliver alpha-particles to the nucleus of cancer cells. The neuroblastoma cell lines evaluated showed differential sensitivities and in vitro results translated into in vivo models. Furthermore we have characterized a novel therapy for high-risk neurobalstoma and aim for future clinical translation.

Locoregional α-radioimmunotherapy against peritoneal metastasis of gastric cancer

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Gastric cancer is one of the main causes of cancer related death. It is curable at early stage, however it often be found at late stage with metastasis existence because of the asymptomatic. Patients with peritoneal metastasis of gastric cancer (PMGC) have extremely poor prognosis, however, no effective therapeutics has been established. About 20% of GC is reported as HER2-overexpressed (HER2+), and trastuzumab, a humanized anti-HER2 monoclonal antibody, has been clinically used for the treatment of HER2+ PMGC.
As radioimmunotherapy (RIT) has huge advantages in targeting metastatic cancer and the physical characteristics of alpha-emitter providing effective cell killing effects, α-RIT is expected as a novel promising treatment for metastasis. Astatine 211 (^{211}At) is one of the attractive alpha-emitter for clinical use. In this study, we investigated the cell cytotoxicity to GC cell lines and evaluated the therapeutic efficacy of locoregional α-RIT with ^{211}At -trastuzumab against HER2+ PMGC in preclinical mice model. We will discuss the possibility of α-RIT with ^{211}At -trastuzumab as a novel effective therapeutics for HER2+ PMGC.

A comparative evaluation of Ac225 vs Bi213 as therapeutic radioisotopes for targeted alpha therapy

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Abstract

The Ac225:Bi213 generator is the mainstay for preclinical and clinical studies of targeted alpha therapy for cancer. Both Ac225 (4 alpha decays) and Bi213 (one alpha decay) are being used to label targeting vectors to form the alpha immunoconjugate for cancer therapy. This paper considers the radiobiological and economic aspects of Ac225 versus Bi213 as the preferred radioisotope for preclinical and clinical TAT. The in vitro and in vivo evidence and the role of DNA repair processes is examined. The maximum tolerance dose (MTD) and therapeutic gain (TG) are endpoints for comparison. Ac225 has the higher therapeutic gain, when normalised to equal alpha production. However, slow repair of DBSs effects reduce this advantage. Comparisons are made for the specific energy deposition in targeted and non-targeted cells, for endothelial cells by direct or indirect targeting, the need for sparing agents to save critical organs and cost considerations for preclinical and clinical trials and clinical use. Overall, Ac225 is found to have the better or equal performance to Bi213 at a much lower cost.

SESSION III

DOSIMETRY AND INSTRUMENTATION

Optimization of the patient dosimetry in alphatherapy

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In nuclear medicine, the injected activity needs to be personalized for each patient, in order to minimize the absorbed dose to the organs at risk (OAR) and maximize the absorbed dose to the tumors. For alpha-particle emitting radiopharmaceuticals, the dosimetry is especially challenging because of the short range of alpha particles. The aim of this work was to develop tools to optimize patient-specific dosimetry in alphatherapy. To that aim, the study focus on ^{223}Ra-dichloride (Xofigo®) which is the first alpha-emitter radiopharmaceutical that has received approval for the treatment of patients with castration-resistant prostate cancer metastasized to bones.

First, quantitative imaging must be performed to characterize the macroscopic biodistribution of the radiopharmaceutical in the patient body. The range of alpha particle prevents them from being detected. However, ^{223}Ra emits useful photons with a probability of emission permitting their detection by gamma camera. As SPECT imaging gives a better quantification than planar imaging, the possibility of quantitative SPECT imaging of ^{223}Ra was investigated for the first time. Several phantoms studies were performed in order to determine the best collimator, energy setting and the best reconstruction parameters for SPECT/CT imaging, according to the MIRD Pamphlet No. 23. Quantification accuracies of approximately 4% for a 5.6mL sphere containing 20kBq/mL can be expected. This protocol has been implemented in a new clinical trial for treatment of patients with bone metastases in renal cell carcinoma.

Then, as bone marrow is an OAR for these treatments, the dose to this region is needed. However, bones have a heterogeneous and complex structure where the two radiosensitive tissues, endosteum and red bone marrow, are described at a microscopic scale. Moreover, current dose models do not account for energy or bone-site dependence as shown by alpha-particle absorbed fractions given in ICRP Publication 30. Using the most realistic voxelized model of the skeleton for adult male, developed by the University of Florida, and MCNP6 Monte Carlo code, the doses per units of cumulated activity have been calculated. These doses have been determined for several source tissues such as the trabecular bone, the inactive marrow or the cortical bone. Differences, up to 50% when considering the trabecular bone surface as source and red bone marrow as target, were observed between our model and the ICRP Publication 30. Furthermore, the marrow cellularity is dependent of the age. In order to optimize the dosimetry, the evolution of alpha absorbed fraction to the red bone marrow with the marrow cellularity was investigated.

Finally, the short range of alpha-particles relative to the typical scale of human organ dimensions can lead to a highly non-uniform irradiation of the target volume. The microdistribution of ^{223}Ra must be known to correlate absorbed dose to therapeutic response. As it is not possible to determine these parameters in humans, microdistribution of ^{223}Ra was investigated in skeletally mature mice and metastasis models, using autoradiography.

Therefore, this study investigates different aspects of the ^{223}Ra dosimetry and offers tools to optimize dosimetry for other alpha emitters.

Correspondence between alpha-particle emitter dosimetry and normal organ toxicity

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Objectives

The objective of dosimetry is to guide the design and implementation of radiopharmaceutical therapy, either on a patient population basis, or if the variability is sufficiently high, on an individual patient basis. Key to this is that absorbed dose estimates predict likely toxicity and tumor response to treatment. It is not possible to administer a tracer level of activity in alpha-particle emitter therapy to obtain the pharmacokinetics required for dosimetry, therefore, preclinical microscale dosimetry studies must be combined with macroscopic whole-organ dosimetry. We illustrate this approach for an antibody that targets the immune checkpoint inhibitor, PD-L1 which we have investigated as a means of alpha-particle emitter delivery in a combined immunological and alpha-particle emitter targeting strategy.

Methods

Healthy *neu*-N mice were injected intravenously with 15, 22, 30, 37 and 44 kBq of ^{225}Ac-anti-PD-L1-BC (3mg/kg). The study was ended and the mouse sacrificed when one of the following conditions were met: *1)* Greater than 20% weight loss *2)* Evidence of pain/distress *3)* 100 day endpoint. At time of sacrifice: spleen, liver, kidneys and thymus were removed, weighed and sent for histopathology. *neu*-N mice were injected intravenously with 67 kBq of ^{225}Ac-DOTA-anti-PD-L1-BC (3mg/kg) and sacrificed for α-Camera imaging to determine activity distributions within liver, spleen, kidneys and thymus. Whole organ dosimetry was performed only considering alpha-particles, contribution from gamma and beta-particles were neglected. Actinium-225 and daughters were assumed to deposit their energy locally. The mean absorbed dose $\overline{D}$ was calculated as: $\overline{D} = \tilde{A} \cdot \Delta \cdot \emptyset / m$ where $\tilde{A}$ the time integrated activity, Δ the mean energy per nuclear transition, $\emptyset$ the absorbed faction and m the mass of the organ.

Results

Liver and spleen received the highest mean absorbed doses: 738 and 615 mGy/kBq, respectively; the kidneys received 138 mGy/kBq with 86.6 mGy/kBq due to free ^{213}Bi. A radiation dose of 18-23 Gy to the whole kidney gives 5% risk of injury in 5 years. Uniform distribution of ^{225}Ac-anti-PD-L1-BC was seen in the liver, but a non-uniform distribution was found in the kidneys, spleen and thymus. Bismuth-213 accumulates in the renal cortex adding to a more non-uniform dose distribution. Given the relatively uniform microscale distribution within the liver we expect from macrodosimetry that the liver will be the dose-limiting organ. At 37 kBq and above significant liver toxicity was noted, including a significant reduction in liver mass and weight loss. In this case, the macrodosimetry is consistent with the observed MTD. However, the activity distribution in the kidneys, spleen and thymus was non-uniform. Correspondingly, only the highest administered activity led to a significant reduction in spleen weight and the thymus seemed to be insensitive to administered activity. The threshold for renal toxicity corresponds to 130-170 kBq administered activity and the renal toxicity indicated by mass reduction occurred at far lower administered activities. In the case of kidneys, 63% of the absorbed dose is due to free ^{213}Bi, which is predominantly localized in the renal cortex.

Conclusions

These results highlights the importance of dosimetry calculations that account for the microscopic localization of alpha-particle emitters within the normal tissues.

High-resolution Alpha Camera imaging as a tool for developing Targeted Alpha Therapy

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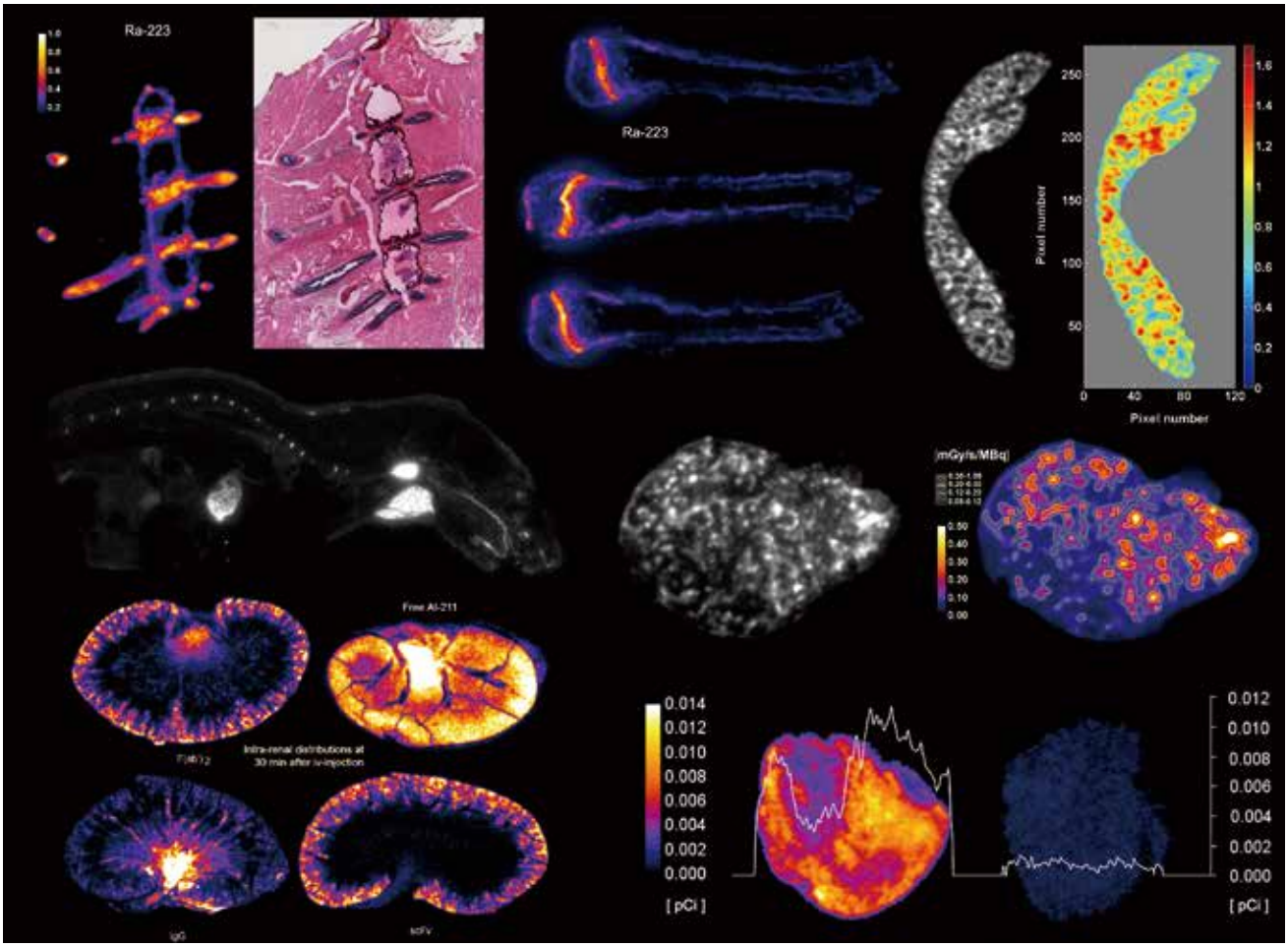
Targeted alpha therapy (TAT) attracts increased interest, particularly for treatment of metastatic cancer. Before its full clinical potential can be realized, however, many of the current gaps of knowledge must be overcome.

The often missing information relates to the highly localized, and often very heterogeneous, alpha-particle radiation energy distribution. The concept of mean absorbed dose to whole organs will therefore in many cases be misleading when evaluating, for example, dose-response relationships. Instead, the dosimetry from alpha-particle irradiation must be derived for the small-scale (sub-organ) level. This can be achieved using small-scale imaging of alpha-particle decay and dosimetric modelling.

The alpha camera imaging system was developed to provide high-resolution quantitative imaging of alpha particles in tissue. The key elements of this system have been previously published. Here, an updated overview of the alpha camera imaging platform and results from a wide range of collaborative and published studies will be provided. Distribution data will be presented from imaging of several alpha-emitters including Ra-223, Th-227, Bi-213 and At-211. Several different issues of TAT will be addressed. Examples of such issues include intra-tumoral and intra-renal distribution; PRIT vs RIT; uniform vs non-uniform uptake in normal organs; and bone marrow imaging. Illustrative examples will be presented of how alpha camera imaging can be used for small scale 3D- dosimetry using voxel dose-kernel computations. The capability of quantum detection and imaging, i.e. single-event imaging of individual alpha particles will also be shown.

Importantly, preliminary imaging results will be presented for the first two patients of an ongoing bone biopsy study on patients being treated with Ra-223 chloride for treatment of castration resistant metastatic prostate cancer. This biopsy study aims to derive small-scale experimental data on the Ra-223 uptake profile and distribution in skeletal tumor lesions in the bone and marrow compartments.



Experimental Alpha Microdosimetry using Fluorescent Nuclear Track Detectors

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The dosimetry of alpha-particle emitters is challenging because of the stochastic nature of energy deposited in small, subcellular targets. We present a novel, experimental method employing Al_2O_3:C,Mg Fluorescent Nuclear Track Detectors (FNTD) to derive the specific energy distribution of cell nuclei. The distributions matched closely with their analytically derived counterpart[1] and the method was successfully adjusted to comply with the most recent microdosimetry kinetic models[2]. For U87 cells irradiated with a collimated americium-241 source, the survival slope based on the absorbed dose yielded $\alpha_D = 1.88 \pm 0.14$ Gy^{-1}. Using the method, the microdosimetric survival slope, domain radius and effective nucleus radius[2] were determined at respectively $\alpha_z = 2.25 \pm 0.19$ Gy^{-1}, $r_d = 0.31 \pm 0.06$ μm and $r_d = 7.2 \pm 1.1$ μm. This data was used to show that the common 20% standard deviation rule for microdosimetry requirement is not effective for alpha radiation. This method avoids the need for complex Monte Carlo simulation and assumptions regarding the radiation field or cell geometry and is therefore far less susceptible to bias and easier to apply.

In addition, simulations of the fictive scenario of americium-241 isotopes evenly distributed in the cytoplasm in a 3D cell culture were used to estimate the error in survival resulting from neglecting microdosimetry. The absolute difference in expected surviving fraction for $\alpha_D = 1.88$ and the absorbed dose versus $\alpha_z = 2.25$ in the microdosimetric survival equation were found as 3.3E-3 and 4.2E-4 at an absorbed dose of respectively 2 and 6 Gy. These small differences illustrates that the contribution of microdosimetry is, at this point, far below those of cell cycle RBE, OER and the targeting efficiency uncertainty of alpha radionuclide carriers. Extensive research of microdosimetry for survival prediction is therefore discouraged as long as biological uncertainties persist.

Figure 1: (left) Slice of 3D fluorescence scan of U87 cell. (middle) Segmented version of left image. (right) Specific energy distribution for given cell. Histogram indicates the FNTD method, while the black line is the analytically derived distribution.

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SESSION IV

NANOCARRIERS

Lanthanum phosphate nanoparticles as carriers for ^{225}Ac, ^{223}Ra and ^{225}Ra for targeted alpha therapy

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In-vivo generator radionuclides, such as ^{225}Ac, ^{223}Ra, and ^{225}Ra are of special interest for target alpha therapy as they emit multiple α-particles during their decay. Utilizing appropriate carriers capable of retaining both the parent radioisotope as well as daughter products is important for the effective delivery of the radioisotope to the tumor site while mitigating global *in vivo* radiotoxicity. In this work, $LaPO_4$ core and core+2 shells nanoparticles (NPs) (NPs with 2 layers of cold $LaPO_4$ deposited on the core surfaces) were synthesized containing either ^{223}Ra or ^{225}Ra/^{225}Ac and the retention of the parents and daughters within the NPs *in vitro* was investigated.

XRD and TEM analysis revealed that the NPs crystallized with mean diameters of 3.4 and 6.3 nm for core and core+2 shells, respectively. The core $LaPO_4$ NPs retained up to 88% of ^{223}Ra over 35 days. In the core+2 shells NPs, the retention of ^{223}Ra and its daughter, ^{211}Pb, was improved to >99.9% over 27 days. The retention of ^{225}Ra/^{225}Ac parents was >99.98% and ~80% for the ^{221}Fr and ^{213}Bi daughters over 35 days for the core+2 shells NPs.

Conjugation of $LaPO_4$ NP's to mAb 201B was achieved using a lipoamide polyethylene glycol (dPEG)-COOH linker with gold-coated $La_{0.5}Gd_{0.5}\{^{225}Ac\}PO_4$ NPs. The conjugates showed an antibody–mediated uptake of 30% injected dose/organ in the target lung, vasculature which was enhanced to 47% when the reticuloendotheilial system was temporarily paralyzed. Further, the core-shell NPs retained a large fraction of the daughter products at the target site without compromising the tumoricidal properties of the α-radiation; retention of the ^{213}Bi daughter in endothelial tissue was over 70% at 1 h and about 90% at 24 h post-injection. In a model of lung metastases, treatment of mice with lung-targeted $La\{^{225}Ac\}PO_4$ NPs reduced EMT-6 lung tumor colonies significantly over control treatments.

In conclusion, the high *in vitro* retention of both parents and daughters suggest that $LaPO_4$ NPs are potentially effective carriers of Ac and Ra isotopes, and the NPs-antibody construct is indeed stable in vivo with very high antibody–directed uptake.

Nanocarriers of ^{223}Ra for TAT

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Objectives

Our research was focused on the development of novel nuclear-recoil-resistant carriers of ^{223}Ra based on selected nanomaterials and their stability testing. The retention of ^{223}Ra in such carriers would enable us to develop advanced targeted nanoconstructs for targeted cancer therapy.

Methods

Several nanomaterials were tested as possible vehicles of ^{223}Ra, including the hydroxyapatite, and TiO_2. In house prepared ^{227}Ac/^{227}Th/^{223}Ra generator served as a ^{223}Ra source. Elution of ^{223}Ra was performed by 0.8M HNO_3 an CH_3OH (8:2). A source of ^{99m}Tc was the ^{99}Mo/^{99m}Tc DRYTEC™ generator (GE Healthcare, Ltd) and was eluted with 0.9% NaCl. Radionuclidic purity of the eluates was determined by high resolution gamma-spectrometry and in the case of ^{223}Ra also alpha spectrometry was employed.
The radiolabelling of nanoparticles was performed employing two different strategies; the surface and the intrinsic (volume) labelling. Further, ^{99m}Tc was also used as a diagnostic counter-part to ^{223}Ra.
In vitro stabilities were evaluated by contacting 1 mg of labelled nanomaterials with biological matrices or a physiological saline. Samples were measured every half-life of the corresponding radionuclide. *In vivo* stabilities were tested on outbred male athymic CD1-Foxn^{1nu} mice (Charles River) bearing HT-29 xenografts. Approx. 200 kBq of ^{223}Ra/mice in 50 μL of physiological saline was applied to each mice *intra*-tumorally and the activity distribution was determined *ex vivo*. All animal experiments were conducted in accordance with animal protection act and were approved by the Ministry of Health of the Czech Republic (Approval No.: 46/2014).

Results

Labelling yields for ^{223}Ra and ^{99m}Tc under optimal conditions exceeded 95%. *In vitro* stability tests showed acceptable stabilities of some nanoconstructs in physiological saline, bovine plasma, serum and albumin solution. The released radioactivity was measured every half-life of radionuclide (^{223}Ra – 11.4 days and ^{99m}Tc – 6.1 hours) and was followed-up for 5 half-lives.
In vivo stability tests showed that the best results were obtained with [^{223}Ra]TiO_2. Over 98 % of the activity remained in the place of application within the period of the study (14 days) for [^{223}Ra]TiO_2.

Conclusions

Good labelling results encourage us for further development and testing of ^{223}Ra labelled nanoconstructs, eventhough some Ra release would be probably always present.

Gold nanoparticle– conjugates as a carrier for ^{211}At in alpha particle therapy

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Introduction: Among the others α-emitting radionuclide ^{211}At has attractive properties for use in targeted radionuclide therapy, especially for small tumours and cancer metastasis. ^{211}At is produced via ^{209}Bi(α,2n)^{211}At nuclear reaction and has a 7.2 h half-life - a sufficient time for its production, synthetic chemistry, transportation and medical application. However, many astatine compounds that have been synthesized are unstable in vivo, providing motivation for seeking other ^{211}At labeling strategies. In our work we propose to utilize formation of strong bond between metallic gold and astatine to bind the ^{211}At to two biomolecules, peptide substance P and trastuzumab.

Materials and methods: The gold nanoparticles with diameter of 5 nm were synthesized by Turkevich methods. The nanoparticles were characterized by SEM, STEM and DLS technique. The obtained gold nanoparticles were conjugated to substance P 5-11 (short peptide fragment having high affinity to NK1 receptors on the glioma cells) and trastuzumab (antibody having affinity to Her2 receptor). In first step polyethylene glicol with disulfide or thioctic acid with N-succinimidyl ester as a linkers were conjugated with biomolecules. After twenty four hours product was purified, lyophilized and spontaneously bound to gold nanoparticles. The obtained bioconjugates were labelled with ^{211}At produced in cyclotron at the Heavy Ion Laboratory, University of Warsaw. Before labeling astatine was reduced to At^- using 0.01 M Na_2SO_3 solution. Stability of the obtained radiobioconjugates were tested in biological fluids: sodium chloride, cysteine, glutathione and human serum for 2, 4 and 19 hours.

Results: The Au- PEG-Substance P (5-11) and Au- PEG-trastuzumab bioconjugates were successfully synthesized. The HPLC analysis has shown that bioconjugates are covalently attached to the gold surface. using the thiol approach. The labeling yield of ^{211}At was higher than 99%. The ^{211}At bioconjugates were very stable in human blood serum and cerebrospinal fluid. Less than 0.1% of the ^{211}At radioactivity was found in solution. Also agglomeration of the nanoparticles was not observed. In-vitro biological studies indicate that ^{211}At- Au- PEG-Substance P (5-11) radiobioconjugate exhibits high affinity and cytotoxicity to the human glioma T98G cell line while ^{211}At-Au- PEG-trastuzumab to the SKOV3 ovarian cell line.

Conclusion: We have shown that gold nanoparticles labelled with ^{211}At functionalized with substance P and trastuzumab presents a prospective solution for the use of the ^{211}At as a therapeutic tool for targeting glioma cells and HER2 positive breast and ovarian cancers.

This work was supported by National Science Center of Poland (Grant 011/01/M/ST406756).

Assessing ^{225}Ac-Polymersomes for Targeted Radionuclide Therapy

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To use longer-lived alpha-emitting radionuclides like ^{225}Ac (with multiple alpha particles emitted in its decay chain) in targeted alpha therapy (TAT), it is essential to deal with the recoil problem. One way to do this, is to incorporate the mother nuclide in a nanocarrier, allowing the alpha particles to damage surrounding tumour tissue, but keeping the radioactive daughter nuclides inside. In the present study, polymersomes (nanocarriers composed of amphiphilic block copolymers) have been used to retain the harmful daughters. Ideal vesicle designs were simulated with the Geant4 Monte Carlo simulation package, and the recoil retention of ^{221}Fr and ^{213}Bi was determined in different designs. The best design was subsequently synthesized in the lab, and daughter retention has been compared to the simulations.

We have determined the uptake of polymersomes in cells, where the vesicles accumulate in the cytoplasm of a U87 glioma cell. Subsequent in vitro studies have been done in 3D spheroidal tumour models, which are a great intermediary between cell monolayer studies and in vivo studies. We found that within a day after exposure the polymersomes are found mainly in the outer layers but after just a few days they have distributed themselves evenly throughout the spheroid. With ^{225}Ac encapsulated in the aqueous cavity, the polymersomes appear to have enormous therapeutic potential, where a decrease in spheroid growth rate has been observed at just 0.1 kBq of ^{225}Ac added. Spheroidal tumours start to shrink significantly at about 1 kBq of activity, and higher activities cause the complete destruction of the spheroid. Using the same amount of ^{225}Ac coupled to DTPA has a slightly reduced effect on the spheroid, as compared to when ^{225}Ac is encapsulated in polymersomes, likely because it does not diffuse as well through the spheroid as ^{225}Ac in polymersomes does. Based on previously established pharmacokinetics of the polymersomes, preliminary recoil retention studies have been attempted in vivo, showing the potential of the polymersomes in TAT. Nevertheless more studies are necessary to fully evaluate the recoil fate when using polymersomes.

Concluding, polymersomes are versatile nanocarriers, which are capable of retaining ^{225}Ac daughters to a great extend, even in small vesicles. Their distribution throughout the tumour spheroid causes complete destruction of the tumour at already very low amounts of ^{225}Ac. In vivo recoil retention requires further studies.

SESSION V

RADIOCHEMISTRY AND NUCLIDE PRODUCTION

Exploration of the chemistry of astatine; from basic research towards applied questions

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^{211}At is considered as one of the most promising radionuclides for targeted alpha therapy. Most of the currently labelling protocols are developed based on iodine chemistry and lead to the formation of astatobenzoate-labelled compounds. Such labelling is unstable, contrary to the iodine case, when the carrier molecule is metabolized. Its limited availability and poorly known basic chemistry hamper the development of specific protocols for At-211. Our aims at exploring the fundamental chemistry of astatine following a methodology centered on the following questions.

(i) ***How to get information at the molecular level?*** Different molecular modelling tools were developed and take into account relativistic effects. They notably allow to define the structure of the molecules and to quantify the formation of the compounds, parameters which can be compared with experimental values.

(ii) ***What are the astatine forms available for the labelling;*** the dual experimental / theoretical approach was used to evidence the species existing in aqueous solution as function of the pH and Eh. In agreement with the trend expected in the halogen series, At^- was evidenced by ion-exchange chromatography and electromobility measurements. Its range of existence is however limited with the presence of two At species at the oxidation states +I (At^+) and +III (AtO^+). Astatine is the only halogen which can form stable cationic forms. This clearly shows the limit of the analogy generally made with iodine.

(iii) ***What it the reactivity of astatine species?*** Astatine cationic species can interact with inorganic or organic ligands to form complexes. The first experimental evidence of the formation of a halogen bond between lewis bases and AtI species was recently shown.

(iv) ***How to explain the in-vivo unstability and what parameter can be improved?*** We attribute the deastatination mechanism of astatobenzoate-labelled compounds to oxidative dehalogenation in biological compartments, in particular lysosomes. An apparent correlation has been evidenced between *in vivo* stability of ^{211}At-labeled compounds and the At−R (R = C, B) bond enthalpies obtained from relativistic quantum mechanical calculations, *i.e.* the higher the stability, the higher the bond energy.

(v) ***Can we imagine an in silico screening in order to develop new labelling strategies?*** Relativistic density functional theory was used to predict the narrow experimental domain in which it may be possible to detect the heaviest possible trihalogen species, $IAtBr^-$. This work shows the capability of the molecular modelling tools to predict astatine reactivity. Calculations are ongoing in order to propose possible alternative labelling protocols, the objective being to increase the bond strength energy as compared to that of C-At_{aryl} bond.

The purpose of this presentation is to give an overview of the results obtained within the framework of this work started about 10 years ago.

Progress in the [^{211}At]-astatination of antibodies by nucleophilic approaches using aryliodonium salts precursors

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Background and Objectives: Aryliodonium salts have recently emerged as versatile precursors for the synthesis of ^{18}F-radiolabeled compounds for PET imaging.[1,2] However, little is known about the applicability of these reagents for labeling with the heaviest radiohalogen astatine, whose isotope 211At is promising for targeted α therapy.[3] In this study, we develop a new radiolabeling approach using aryliodonium salts chemistry based of our recent discovery of the unique reactivity of astatine with these compounds.[4]

Methods: First, parameters of radio-iodination and astatination reaction (solvent, temperature, duration and counter-ion of iodonium) were studied on model compounds. Bifunctional iodonium salts were then designed, allowing the synthesis of [^{125}I]-SIB and [^{211}At]-SAB, two prosthetic groups widely used for radio-iodination and astatination of biomolecules. Both [^{125}I]-SIB and [^{211}At]-SAB were conjugated to the multiple myeloma targeting mAb 9E7.4 (anti-CD138). Conjugation yields and resulting immunoreactivity were compared with the conventional arylstannane chemistry approach.

Results and Discussions: Initial reaction parameters studies highlighted a striking difference of reactivity between radio-iodide and astatide that could not be anticipated from the trends observed within the halogen series. Not only the astatination reaction was highly efficient at much lower temperature than iodination, but it appeared solvent and counter-ion independent (not iodination). Astatination of an antibody with specifically designed iodonium salts outperformed conventional arylstannane chemistry approaches in terms of global efficiency and consistency (global yields of 43 ± 2 % vs 20 ± 5% from arylstannane chemistry) with excellent preservation of immunoreactivity of the IgG with both radionuclides and less concerns regarding the toxicity of precursors and side products. The radiochemical yield improvements was mainly due to the absence of a need of purification by HPLC as in stannane chemistry, the aryliodonium salts being highly retained on short silica cartridge, and the high reproducibility was attributed to the use of astatine in the highly stable At^- form instead of the At^+ form needed for electrophilic astatodestannylation that is difficult to control.

In comparison with the conventional arylstannane approach, aryliodonium salts appear as more efficient precursors for preparation of radio-iodinated and astatinated compounds. Furthermore, they allow simpler purification procedures (easy transfer to automation and clinical use), with the additional advantage of a much lower toxicity, which is of primary importance for human use. Most of all, the unexpected reactivity of astatine we unveiled highlights that a lot is still to be discovered about the chemistry of this radioelement which remains to date largely unexplored.[5]

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Quality Assurance and Labeling Chemistry Qualification for cGMP Production of Astatine-211-Labeled anti-CD45 Antibodies

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Objectives: The objective of this research effort was to set up controls and procedures to translate the production of ^{211}At-labeled anti-CD45 antibodies from benchtop to cGMP patient preparations. That translation requires assurance of the identity, purity, non-pyrogenicity and sterility of the labeled product being produced under cGMP conditions. It also requires demonstration of three consecutive ^{211}At antibody labeling reactions that meet release criteria.

Methods: The ^{211}At used for labeling was produced on a Scanditronix MC50 in the Medical Cyclotron Facility at UW. After irradiation, ^{211}At was separated from the bismuth target using a wet chemistry isolation approach in a non-cGMP facility. Radionuclidic identity, chemical species identity, and radionuclidic purity were evaluated, and documented on a certificate of analysis for release of the isolated ^{211}At. Radionuclidic identity of ^{211}At was confirmed by High-Purity Germanium (HPGe) spectrometry and radio-HPLC. Radiochemical purity was obtained by radio-HPLC analyses. The ^{211}At was transferred to the cGMP facility and used for radiolabeling the anti-CD45 antibody BC8, preconjugated under cGMP conditions with a *closo*-decaborate(2-) reagent. Three consecutive ^{211}At-labeling procedures were conducted to demonstrate reproducibility for meeting the release criteria of the labeling procedure. Radiochemical purity and stability of the ^{211}At labeled product was obtained by radio-ITLC. Pyrogenicity was obtained using an Endosafe PTS system. Sterility testing was conducted following USP guidelines. Immunoreactivity of the final product was assessed by FACS and radiolabeled cell binding.

Results: Quantities of ^{211}At up to 4.7 GBq (128 mCi) were produced during the studies, and up to 2.8 GBq (75 mCi) were isolated from the wet chemistry procedure (3-hour procedure; avg. 78% yield) to demonstrate that level of production could be accomplished. Three consecutive ^{211}At-labeling runs were conducted with 1.1 GBq (31 mCi) to 1.5 GBq (41 mCi) Na[^{211}At]At labeling of 8 mg BC8-B10 to provide 0.67 – 1.19 GBq (18 – 32 mCi) of ^{211}At-BC8-B10, for 45 – 78% isolated radiochemical yield. These ^{211}At-labeled antibodies were 98% pure by radio-ITLC, had <0.50 EU/mL in the endotoxin test and were found to be sterile. The labeled antibodies passed the release criteria of retaining >50% immunoreactivity (62-83%) by cell binding or FACS. Stability of four preparations containing 25 mg/mL ascorbate, with specific activities ranging from 59 – 159 MBq/mg (1.6 – 4.3 mCi/mg), was high (96%) over a 21-hour time period. Immunoreactivity in those preparations at ~6 hours post labeling was high (88-98% by FACS).

Conclusions: It was demonstrated that quantities of ^{211}At required for the anticipated highest level of patient doses could be produced. The transfer of labeling method from laboratory to cGMP facility was successful with demonstration of three consecutive preparations of ^{211}At-BC8-B10 that met the criteria to release them for patient administration.

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Development of effective chelators for Th-227 to be used in Targeted Thorium Conjugates

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Objective

The clinical development of targeted radioimmunotherapies (RIT) for the treatment of cancer utilizing the high linear energy transfer (LET) of alpha-particles has, to a large extent, been limited by the availability of suitable radionuclides on a commercial scale. More recently, with the approval in May 2013 of Xofigo for the treatment of castration resistant prostate cancer (CRPC), a commercial production line for the alpha-emitting radionuclide radium-223 (Ra-223) was established. However, although the inherent bone-seeking characteristics of Ra-223 make it well suited for the targeting of bone metastases in CRPC, the paucity of efficient chelator systems limits its use in radioimmunotherapy. By utilizing the same actinium-227 generators as used in the manufacture of Ra-223, highly purified thorium-227 (Th-227) may be produced. Unlike Ra-223, Th-227 exists in the 4+ oxidation state and forms stable complexes with chelators such as 1,4,7,10-tetraazacycloododecane- N, N', N'', N'''-tetraacetic acid (DOTA). However, in order to achieve sufficient labeling of DOTA-coupled antibodies, the complexation step must either be performed as a two-step process or directly at elevated temperatures. The harsh conditions used for direct labeling are not always compatible with the stability of complex biological macromolecules such as antibodies. In addition the slower complex formation rates affect radiolabeling yield, efficiency and specific activity. Therefore, there remains a need for alternative chelators which complex thorium-227 in near quantitative yield at ambient temperature in aqueous solutions.

Methods

Examples of synthesis of chelator, conjugation to monoclonal antibody, as well as, radiolabelling with Th-227 and *in* vivo data in mice will be presented.

Results

To this end we have developed an octadentate chelator utilizing the 3-hydroxy-N-methyl-2- pyridinone moiety, abbreviated Me-3,2-HOPO, reported previously to form extremely stable thorium complexes. By conjugation to monoclonal anitbodies, this chelator enables the development of Targeted Thorium Conjugates (TTC's) for the targeted alpha therapy of various cancer types. *In vivo* studies in tumor bearing mice demonstrate the potential for such a strategy.

Conclusions

We report herein on the development of a class of effective chelators for Th-227. These could allow the development of Targeted Thorium Conjugates (TTCs) to enable use of targeted alpha therapies to treat various cancers

Spectroscopic and computational studies of actinium coordination chemistry

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Actinium-225 (t1/2=10 d) is an extremely promising isotope for the treatment of metastatic cancers. During the decay of Ac-225 and daughters, a total of 4 alpha particles are emitted, which gives Ac-225 uniquely high cytotoxicity. However, the use of Ac-225 has been hindered by both the limited understanding of the fundamental chemistry of Ac and the insufficient supply. Currently, Ac-225 is produced via thorium-229 generators which are derived from legacy uranium-233 sources which is a material of proliferation concern. At Los Alamos National Laboratories (LANL), we have been part of the Tri-Lab project to develop an accelerator production capability using the proton irradiation of natural thorium. In addition to the production aspects, we have also been engaged in a cutting-edge research program focused on developing a wide variety of spectroscopic and physical techniques to interrogate the chemistry of Ac. Contrary to Ac-225, whose short half-life requires tracer level studies, Ac-227 (t1/2=22 y) is available in microgram amounts which enables the use of traditional chemical techniques (albeit with several challenges). With our stock of ~10 mCi (~150 ug) of Ac-227 we have developed multiple spectroscopic and theoretical approaches to help understand Ac coordination chemistry, including X-ray absorption fine structure (XAFS), electronic absorption, nuclear magnetic resonance (NMR), and fluorescence spectroscopies. The experimental results have been unraveled within the context of advanced molecular dynamics-density functional theory (MD-DFT) calculations.

While Ac-227 has a much lower specific activity than Ac-225, the strong alpha/beta/gamma emissions of the daughter products have necessitated the development of careful handling protocols, both at LANL and at the Stanford Synchrotron Radiation Laboratory (SSRL). Additionally, the limited supply of Ac-227 necessitates full recovery of all material, which rules out any destructive measurements. Overcoming these challenges has resulted in many firsts, including the first XAFS and NMR measurements of Ac containing compounds. We have found these techniques to be complementary and very useful to our program of understanding Ac coordination chemistry both with simple ligands (e.g. chloride and aqua) and popular chelators (e.g. DOTA). Finally, we will discuss the development of some new chelator frameworks designed to provide enhanced spectroscopic handles to help determine the utility of particular functional groups in Ac chelator development.

A Novel Micro-Actinium-225/Bismuth-213 Biomedical Generator System

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Targeted alpha-therapy (TAT) employs targeting agents, e.g. monoclonal antibodies to deliver highly energetic alpha particles to cancer cells for their destruction, while minimizing collateral damage to adjacent normal cells. Bi-213, one of the most commonly used alpha-emitters in TAT, has a half-life of 45.6 minutes, and is available from the decay of Ac-225 ($t_{1/2}$=10 d) in a generator system. Microfluidic "lab-on-a-chip" technology allows many chemical processes to be scaled to the micro- or nano-scale. Miniaturization conserves valuable reagents, reduces workers' exposure to radiation and allows for the production of valuable chemicals, including radiotherapeutic agents on a scale suitable for research or individual doses. An Ac-225 generator using BioRad MP50 cation-exchange resin in a chromatographic column format is typically used to produce Bi-213. In this study, microfluidic devices analogous to these large, resin filled columns have been used to separate Bi-213 from Ac-225. In this proof of concept study, microfluidic devices were loaded with MP50 resin (50-70 μm) with bed volumes in the range of 10 – 100 μL and were loaded with μCi to mCi quantities of Ac-225. Similar to macro-generators, Bi-213 is eluted from micro-generators with 0.1 M KI/0.1 M HCl with an overall yield of ~75% (decay corrected to start of Bi elution), and Ac-225 breakthrough of ~$2x10^{-3}$%. Further, Bi-213 from micro-generators has been shown to efficiently label a diethylenetriaminepentaacetic acid (DTPA)-conjugated monoclonal antibody. Work to optimize these devices is ongoing, and future work will examine incorporation of on-chip labeling and separation of labeled antibody from free Bi-213.

US DOE Tri-Lab Research Effort to Provide Accelerator-Produced ^{225}Ac for Radiotherapy: 2017 Update

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A general overview and update of the US Department of Energy Isotope Program's Tri-Lab (ORNL, BNL, LANL) Research Effort to Provide Accelerator-Produced ^{225}Ac for Radiotherapy will be presented with focus on accelerator-production and final product isolation methodologies. In addition, impacts on the radionuclidic quality of the accelerator-produced ^{225}Ac product as well as the product quality with respect to a ^{225}Ac /^{213}Bi generator application will be presented. Specifics regarding ongoing evaluations of the accelerator-produced ^{225}Ac by independent end-users related to pre-clinical dosimetry and toxicity studies and broad logistical challenges associated with the accelerator-based production approach 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

LA-UR-17-21018

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

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Objectives

The therapeutic potential of alpha emitting radioisotopes for the treatment of metastatic cancers has been demonstrated in the clinic. 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. Locally at CNL, a limited and controlled supply of aged ^{233}U from previous fuel development programs is available. Work is underway 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 the CNL and with external academic investigators.

Methods

A thorium fraction containing mostly 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 potential radioimmunotherapeutic agent against EGFR positive cancers.

Results

As of now, 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.

Conclusions

To support internal and collaborative research programs in Targeted Alpha Therapy, CNL has recently constructed a pilot 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.

Progress Toward an Alternate Method for Production of Ac-225

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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. Ac-225 (10.0 days) is a decay product of Th-229 (7,340 yrs). The source of the US supply of Th-229 is legacy stocks of U-233 (>150,000 yrs). U-233 though is a highly controlled material as it is considered a proliferation risk, thus making use of U-233 extremely limited. Nevertheless, there are possible paths to increased Ac-225 production. Those are/ were : 1) chemical extraction of Ac-225 from old Light Water Breeder Reactor fuel stocks, 2) chemical extraction of Th-229 from legacy U-233 materials, 3) enhanced production methods for extraction of Ac-225 from current Th-229 materials, 4) cyclotron production, 5) electron accelerator production and 6) high-energy proton spallation of Th-232. 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 annnual supply. This talk will describe the current development effort that is underway during 2017 toward a goal to continuing development efforts to approach 100mCi+ of Ac-225 per run by the end of 2018, with the ultimate target to achieve sufficient capability in the future to meet market demands.

POSTER SESSION I

Initial Experience of Ra-223 at the Japan Community Healthcare Organization (JCHO) Tokyo Shinjuku Medical Center

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Introduction: Prostate tumors are initially dependent on androgens for their growth which can be controlled by treating patients with either surgical castration or with medical castration using luteinizing-hormone releasing agonists or antagonists (androgen-deprivation therapy), which is regarded as a standard of care for patients with advanced or metastatic disease in this setting. However, for many patients, the disease progresses and is commonly referred to as a castration-resistant prostate cancer (CRPC). The majority (90%) of patients with CRPC have radiological evidence of bone metastasis. Recently, the bone-targeting agent radium-223 dichloride (Ra-223) has been added as an option for treating metastatic CRPC (mCRPC). We report our initial experience of using Ra-223 at the Japan Community Healthcare Organization (JCHO) Tokyo Shinjuku Medical Center.

Materials and methods: Between August 2016 and February 2017, 14 patients diagnosed as mCRPC were treated with Ra-223 at the JCHO Tokyo Shinjuku Medical Center. They all presented with multiple (extensive) and symptomatic bone metastasis. Each patient received Ra-223 at a dose of 50 kBq per kg of weight intravenously every 4 weeks up to 6 times. Blood tests were taken after each injection, and computed tomography (CT) after around 3rd injection of Ra-223. Acute toxicity was assessed according to the CTCAE ver. 4.0.

Results: At the time of February 10, 2017, 5 patients had completed treatment after receiving 6 doses of Ra-223, and 5 patients had been under medical treatment. 5 of 14 patients had their treatment interrupted, of which the general condition of 2 patients degraded, another experiencing increasing pain, and 2 patients confirmed to have new visceral metastases. We evaluated the change of in levels of PSA, ALP, BAP, and 1CTP throughout the treatment. Among 8 patients who had completed 4 doses Ra-223 and discontinuity of 5th injection had not been decided by February 10, the PSA levels were reduced (-25%) in the 4 patients after 4 doses of Ra-223. As for bone markers, Ra-223 reduced (-25%), the ALP levels in 4 patients, BAP levels in 6 patients, and 1CTP levels in 4 patients. Among such 8 patients, the PSA levels increased (+25%) in 4 patients, though the ALP levels increased (+25%) in only 1 patient and no patient was observed whose BAP and 1CTP levels increased (+25%). During the treatment, no grade 3 or worse acute toxicity was observed.

Conclusion: Ra-223 therapy was well tolerated, but 35% of the patients were dropped during the therapy judged by clinical assessment. In line with other reports, Ra-223 didn't seem to reflect the effect of Ra-223 directly, and Ra-223 could reduce the bone markers such as ALP, BAP, and 1CTP. Further study is needed to decide which type of mCRPC patients would respond well to Ra-223, and what data item is most effective to evaluate the effect of Ra-223.

Methods of survey and decontamination of radium-223 dichloride for radionuclide therapy in clinical facilities

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Background and Objective: Radium-223 dichloride (Ra-223), a bone-seeking α -emitting radiopharmaceutical for radionuclide therapy, was developed and already incorporated in the management of castration-resistant prostate cancer with bone metastases (mCRPC). Considering the impact of Ra-223 for mCRPC and potentially other bone metastatic diseases, issues concerning radiation control for Ra-223 still require investigation including monitoring using conventional detectors and radioactive decontamination in nuclear medicine facilities. We therefore conducted experiments on monitoring and decontamination of Ra-223, and constructed procedures and standards for handling Ra-223 in clinical facilities.

Methods: Ra-223 emits photons as γ-rays and characteristic X-rays that are detected by conventionnal GM detectors and NaI(Tl) scintillator detectors. Our studies consisted of 2 parts, 1) Measuremts with survey meters for Ra-223, and 2) Decontamination. 1) We made a mock contamination source, and conducted spectrum analysis of Ra-223 emission using High Purity Germanium detectors (HP-Ge), and then clarified characteristics of conventional GM detectors and NaI(Tl) scintillator detectors as well as a dedicated ZnS(Ag) α detector for measuring Ra-223 by considering parameters of time constant, distance, and speed. 2) Decontamination effciencies were measured by dropping Ra-223 on materials including linoleumn, and decontaminating by swab technique with parameters as follows; with or without drying of materials, swab paper soaked with cleaners such as EDTA and commercially available cleaners, and swabbing pressure.

Results: Regarding monitoring of Ra-223, photon spectrum was analyzed with HP-Ge, and then conventional GM detectors and NaI(Tl) scintillator detectors were more efficient than a dedicated ZnS(Ag) α detector which showed remarkably decreasing counting rates with increasing source to detector distance. In decontamination of materials, drying of materials diminished decontamination rates, which suggested necessity of rapid coping in case of contamination.

Conclusions: Ra-223 dichloride should be handled in nuclear medicine facilities according to standard procedures for radiation protection. Characterizing survey detectors for responses to α particles is critical for optimization of measurements. Rapid decontamination of materials before getting dried out and use of appropriate cleaners were recommended in case of contamination.

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Biodistribution, dosimetry and imaging of ^{225}Ac-DOTA-anti-PD-L1-BC in a murine immunocompetent transgenic breast cancer model

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Objectives
The recent development of immunomodulatory agents have brought immunotherapy up as a possible treatment against various types of cancers. This treatment approach is based on tumors avoiding immune system recognition by co-opting immune checkpoints intended to prevent autoimmunity. One of the immune checkpoint mediators is the Programmed Cell Death protein 1 (PD-1) receptor. PD-1 interacts with Programmed cell Death Ligand 1 (PD-L1). PD-L1 is expressed on a variety of tumor cells, tumor associated macrophages and other cells in the tumor microenvironment. Clinical trials of anti-PD-L1 antibodies have yielded promising results in patient populations, which have exhausted all other conventional therapeutic options. In addition a number of studies have shown the potential of combined immune checkpoint inhibition therapy and external beam radiotherapy. In this study we examine the feasibility of a ^{225}Ac-labeled anti-PD-L1 antibody to deliver an alpha-particle emitting radionuclide in a murine immunocompetent transgenic breast cancer model.

Methods
The animals used in this study was 4-7 weeks old *neu*-N mice, which were injected subcutaneously with NT2.5 cells ($1x10^6$) in the right flank. Following a growth period of 4 weeks, the tumor-bearing mice were injected intravenously with ^{225}Ac-DOTA-anti-PD-L1-BC (15 kBq) at 3 mg/kg. At 1, 6, 24, 72, and 144 hours post-injection the mice were sacrificed. The blood, heart, lungs, liver, spleen, kidneys, stomach, intestine, bone, thymus, muscle, tumor, and brown adipose tissue were harvested, weighed, and measured for biodistribution data. Normal tissue and tumor mean absorbed doses were calculated using the ^{225}Ac-DOTA-anti-PD-L1-BC biodistribution data. The α-Camera was used to image the distribution and activity concentrations of ^{225}Ac-DOTA-anti-PD-L1-BC within the normal tissues (liver, spleen, kidney and thymus) and tumor.

Results
The highest calculated mean absorbed dose for ^{225}Ac-DOTA-anti-PD-L1-BC for the normal tissues were liver, spleen, thymus, kidneys, blood and tumor with 738, 615, 282, 138, 80.4 and 141 mGy/kBq, respectively. The mean absorbed dose to the kidneys from free ^{213}Bi was 86.6 mGy/kBq, which accounted for 62.6% of the total dose. The α-Camera images of ^{225}Ac-DOTA-anti-PD-L1-BC showed a relatively uniform activity distribution in liver and kidneys. The spleen showed a non-uniform distribution with hotspots up to 3 times higher concentrations in the white pulp regions. The white pulp regions predominately comprises of lymphocytes, antigen-presenting cells, and macrophages in addition to T- and B-cells. The thymus showed uptake with up to 3 times higher activity concentrations in peripheral regions identified as the cortex, associated with CD4/CD8-double negative thymocytes with high expression of PD-L1. The tumors showed heterogeneous distribution with activity concentrations up to 3 times higher in the immature stroma mainly along the peripheral areas of the tumor.

Conclusions
Findings presented in this study are supportive of combining immune checkpoint therapies, including anti-PD-L1 therapy, with targeted radionuclide therapy. The developed agent ^{225}Ac-DOTA-anti-PD-L1-BC, was well-tolerated at the activity and antibody concentration selected with the liver receiving the highest radiation dose. This agent is able to deliver targeted radiation to both primary and metastatic sites, helping to prepare the tumor's microenvironment for immune checkpoint therapy.

Reducing renal uptake of free ^{213}Bi associated with the decay of ^{225}Ac-labeled radiopharmaceuticals

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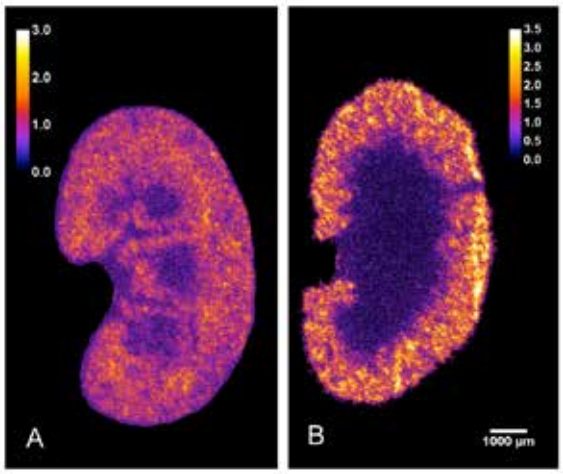
Background. Alpha-emitting radionuclides provide cytotoxic agents that are considered impervious to conventional cellular resistance mechanisms such as effusion pumps, signaling pathway redundancy, and cell cycle modulation (e.g., cell dormancy, G1/G0 or G2/M block). Actinium-225 is a promising α-emitting radionuclide due to its net decay of four α-particles. The longest-lived progeny of ^{225}Ac, bismuth-213 concentrates in the kidneys. Depending upon tumor burden, and the accessibility of tumor cells the percent tumor uptake of IV-administered radiolabeled antibody in humans is typically of the order of a few percent or less. This means that the majority of antibody-bound ^{225}Ac decays would occur in the circulation and lead to eventual renal toxicity as has been observed in pre-clinical studies The objective of this work is to evaluate the potential to reduce renal uptake of free ^{213}Bi by exploiting the mechanism associated with bismuth uptake.

Methods. Neu-N mice (5-7 weeks) that were either pre-treated with bismuth citrate or received no pre-treatment were administered free ^{213}Bi. At 5, 30 and 60 minutes post-injection the mice were sacrificed and renal uptake was determined. In addition, alpha camera images were obtained to compare the microscale distribution and dose in mice receiving pre-treatment or no treatment.

Results. Mice pre-treated with bismuth citrate demonstrated significant reduction in renal uptake of ^{213}Bi compared to mice not receiving pre-treatment. There was a 63% reduction in the renal absorbed dose in mice pre-treated with bismuth citrate (1.52 mGy/kBq). Alpha camera images demonstrated similar distribution of free ^{213}Bi, but with a dramatic reduction in signal in the renal alpha camera image in the mice receiving bismuth citrate.

Conclusion. The results presented here supports the potential of bismuth citrate pre-treatments to block renal accumulation of free bismuth-213 associated with the decay of actinium-225 radiopharmaceuticals. We demonstrated that the reduction in free ^{213}Bi in the kidneys translates to a significantly lower renal absorbed dose, lowering the potential of long-term renal toxicity. Future experiments will evaluate the impact of the bismuth citrate pre-treatment in mice administered the ^{225}Ac labeled radiopharmaceutical, ^{225}Ac-DOTA-7.16.4.



Alpha camera images of mouse renal slices 30 minutes post-injection of free ^{213}Bi (0.45-0.74 MBq). (**A**) Mouse was pre-treated with cold bismuth 2 hours pre-injection of free ^{213}Bi.
(**B**) Mouse received no pre-treatment

How biodistribution, toxicity, and chelation of accelerator-produced actinium-225 will determine its fate in targeted alpha therapy

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Targeted alpha-particle therapy holds tremendous potential as a cancer treatment, since it offers the potential of delivering a highly cytotoxic dose to targeted cells while minimizing damage to the surrounding healthy tissue, due to the short range and high linear energy transfer of alpha particles. A few actinide isotopes have recently emerged as promising short-lived radionuclides that emit multiple α particles in their decay chains, dramatically increasing the potential delivered dose. In particular, Ac-225 can act as an in vivo alpha-generator radionuclide and is of great interest for new therapeutic applications. To create a targeted alpha therapeutic, one must assemble 3 basic parts: a targeting moiety, a radionuclide chelating ligand, and an appropriate radionuclide such as Ac-225. Though sound in theory, and despite promising therapeutic potential established in pre-clinical and clinical studies, such designs have been slow to emerge. Reasons for this protracted development are many, including limited supply of the radioisotope, insufficient understanding of its biodistribution and biodosimetry, poor retention of alpha-emitting daughter products at the target site, as well as inadequate chelation, one of the major drawbacks.
To seek further development of Ac-225 bioconjugate therapeutics, ongoing efforts aim at addressing all of those limitations. Our approach is to clearly delineate the biodistribution of Ac-225, its short-lived daughter products, and potential trace contaminants such as Ac-227 that may be co-produced in new larger-scale accelerator-derived processes. The biokinetics of unchelated (in citrate solutions), chelated (with classic macrocyclic, amino-polycarboxylic acids, or new hydroxypyridinone ligands under development), and bio-conjugated Ac-225 and Ac-227 were determined in mice. Comparisons of the distribution profiles and resulting dosimetry will be presented and discussed with the perspective of a pressing need for the development of new targeted alpha-therapy strategies.

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Preclinical studies of ^{211}At in Multiple Myeloma

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Background and Objectives: Multiple myeloma (MM) treatments, such as high-dose melphalan therapy plus autologous stem-cell transplant (ASCT), or regimens incorporating the novel agents bortezomide, thalidomide and lenalidomide, substantially increase the rate of Complete Response (CR) that is associated with longer patient survival. Thus, maintaining the CR status by improving the minimal residual disease (MRD) after induction therapy is a key goal for MM management. Here we address the question of radioimmunotherapy (RIT) efficacy in MM MRD treatment in mice with a low tumor burden. Alpha emitters are particularly well-adapted to this approach because the short range of alpha particles enables localized irradiation of tumor cells within the bone marrow and a cytotoxic effect on isolated cells due to the high LET of alpha particles. The CD138 antigen was used as a target because of its strong expression on myeloma cells in 100% of patients.

Methods: Intravenous injection of 10^6 5T33 mouse myeloma cells into the Syngeneic mouse strain C57 Kalrwij resulted in a rapid invasion of the marrow and limb paralysis, as illustrated by fluorescence imaging with luciferase-transfected 5T33 cells. RIT was performed 10 days after 5T33 cell engraftment with an IV injection of an anti-mouse CD138 9E7.4 monoclonal antibody radiolabeled with ^{211}At at activities of 370, 55, 740 and 1.11 kBq. A blood cell count was performed in order to monitor hematological toxicity.

Results and Discussions: The groups treated with 740 kBq exhibited a median survival greater than 150 days compared to 43 days in the control untreated group. The highest activity (1.11 kBq) showed short-term toxicity while the lowest activity (370 kBq) gave results similar to the controls. With activities of 740 kBq, mice exhibited a transient hematological toxicity.
This study demonstrates promising therapeutic efficacy of ^{211}At-labeled anti-mCD138 for the treatment of residual disease in the case of MM, with only moderate and transient toxicity.

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Experimental alpha-radioimmunotherapy against liver metastasis of gastric cancer

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Gastric cancer (GC) is one of the main causes of cancer related death worldwide. Liver metastasis is often found at late stage of GC. The prognosis of patients with liver metastasis is extremely poor due to lack of effective therapeutics. HER2 is a reliable marker of some population of GC (20-30%) and is thus a potential target for the treatment of liver metastasis of GC. We established a mouse model of liver metastasis of HER2-positive GC to investigate the therapeutic efficacy of anti-HER2 antibody (trastuzumab) armed with alpha-emitter astatine-211. In this symposium, we will discuss the therapeutic efficacy of experimental alpha-radioimmunotherapy against liver metastasis of gastric cancer in a mouse model.

Synthesis and radiotherapeutic effect of two I-131 or At-211 labelled radioprobes for melanoma with overexpressed metabotropic glutamate receptor 1

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Metabotropic glutamate receptor 1 (mGluR1) is found ectopically in various kinds of cancers, such as melanoma and breast cancer. It has been reported that overexpressed mGluR1 exhibited oncogenic characteristics that independently trigger melanocyte tumorigenesis. Further, inhibition or inactivation of mGlu1 was demonstrated to prevent growth and progression of melanomas. Emipirical data indicate that mGlu1 is a promising molecular imaging target and could be applied for the diagnosis and personalized treatment of melanomas. Recently, we developed 4-[^{18}F]fluoro-*N*-[4-(6-(isopropylamino)pyrimidin-4-yl)-1,3-thiazol-2-yl]-*N*-methylbenzamide ([^{18}F]FITM) and its other halogen-substituted analogs as PET probes for in vivo imaging of mGluR1 in melanoma [1,2]. In this study, we radiosynthesized 4-[^{131}I]iodo ([^{131}I]**1**)- or 4-[^{211}At]astato ([^{211}At]**1**)- *N*-[4-(6-(isopropylamino)pyrimidin-4-yl)-1,3-thiazol-2-yl]-*N*-methylbenzamide as two target-radionuclide-therapy probes and evaluated their antitumoral effects on mice bearing B16F10 melanoma.

Unlabeled **1** and its tin precursor for the present radiosynthesis were prepared according to the method reported by our laboratory [2,3]. Radiosynthesis of [^{131}I]**1** was performed by reaction of tin precursor with [^{131}I]NaI (280 MBq in 0.5 M NaOH) in the presence of 30% H_2O_2 at room temperature for 2 h. After purification and formulation, [^{131}I]**1** was obtained in 45 ± 20% radiochemical yield (n > 3, based on the total [^{131}I]NaI). The molar radioactivity and radiochemical purity of [^{131}I]**1** were 40 ± 4 GBq/μmol and >99% at the end of synthesis. Treatment the B16F10-bearing mice with [^{131}I]**1** at 18 MBq and 9 MBq in 2 doses/mouse significantly reduced the tumor volumes ($P < 0.05$), compared to the untreated group, whereas treatment with [^{131}I]NaI or unlabeled **1** did not show significant antitumoral effect ($P > 0.05$). PET with [^{18}F]FITM further confirmed reduced uptake of radioactivity in the [^{131}I]**1**-treated B16F10 tumor. ^{211}At for radiolabeling was produced using a remotely controlled versatile system developed in house [4]. [^{211}At]**1** was successfully synthesized by the reaction of tin precursor with ^{211}At in the presence of *N*-chlorosuccinimide at room temperature for 1 h. The radiochemical conversion of [^{211}At]**1** exceeded 40%. Optimized radiosynthesis and radiotherapy by [^{211}At]**1** for melanoma are in progress.

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Comparison of pharmacokinetics between meta-benzylguanidine labeled with radioactive iodine, bromine and astatine

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Meta-benzylguanidine that is a functional analogue of norepinephrine transporter (NET) accumulates in NET-expressing tumors, such as pheochromocytoma, paraganglioma, and neuroblastoma. The analogue labeled with radioisotopes have been used for the current radionuclide therapy (^{131}I labeled meta-benzylguanidine: ^{131}I-MIBG), studied as a PET tracer (^{76}Br-MBBG), and MABG labeled with an α emitter of ^{211}At is one of promising targeted α-particle radiotherapy (TAT). The comparative study of pharmacokinetics between meta-benzylguanidine labeled with radioactive iodine, bromine and astatine may help predict a potential of TRT using elements with the same characteristics. In the case of halogens, a growing body of data on ^{123}I/^{125}I/^{131}I-labeled compounds (peptides, antibody and so on) might be an important finding for ^{211}At-TAT in future. Here, we show the comparison of pharmacokinetics on MIBG, MBBG and MABG.

Biodistribution of MIBG, MBBG and MABG were collected from the previous papers (Paper **A** of Vaidyanathan *et al.*, Nucl. Med. Biol., 1996; Paper **B** of Watanabe *et al.*, J. Nucl. Med., 2010) and unpublished data (Paper **U**, data from Dr. Y. Ohshima). The paper **A** (**A**) reported the biodistribution of ^{211}At-MABG and^{131}I-MIBG in nude mice bearing SK-N-SH human neuroblastoma xenografts. The paper **B** did that of ^{77}Br-MBBG and ^{125}I-MIBG in PC-12-bearing nude mice. The paper **U** (**U**) is of ^{211}At-MABG in PC-12-bearing nude mice. Percent injected doses per gram (%ID) were compared 1 hour after injection, and biological uptake and clearance were analyzed by mono-exponential fitting using data at one hour later. Interestingly, in spite of the difference of bearing cells and radioisotopes, biodistributions in %ID of MIBG, MBBG and MABG showed the similar trend in normal organs. The %ID of cancer tissue depended on the bearing cell line. The biological uptake rates of tumor were in almost the same range, 0.55 h^{-1} at ^{211}At-MABG (**A**), 0.82 h^{-1} of ^{77}Br-MBBG and 0.69 h^{-1} of ^{125}I-MIBG, 0.30 h^{-1} of ^{211}At-MABG in **U**. On the other hand, the clearance curves demonstrated the biphasic change in most of normal organs. For example, the short clearance rates of liver are 1.65 h^{-1} and 0.9 h^{-1} of ^{211}At-MABG (**A**) and (**U**), 1.0 h^{-1} of ^{131}I-MIBG. The long ones were 18.7 h^{-1} (^{211}At-MABG in **A**), 13.2 h^{-1} (^{211}At-MABG in **U**) and 11.1 h^{-1} (^{131}I-MIBG). These clearance rates were within a factor of 2. Clearance parameters of the paper **B** were excluded, because of a short time of a sampling period. Taken together, these results demonstrate that MIBG, MBBG, MABG in nude mice bearing NET-expressing cell line show a similar pharmacokinetics on biological uptake and clearance at one hour later, with in a factor of 2, suggesting that accumulation in tumors of this analogue labeled with radioactive halogens depends not on a slow response, but on the initial events of a considerable early stage (within 1 hour of injection).

^{203}Pb-AR-RMX conjugates for image guided TAT of neuroendocrine tumors (NETs)

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Background and Objective: The incidence of neuroendocrine tumors (NETs) has been increasing worldwide during the last 20 years due to improved surveillance and diagnosis of this disease. Most NETs strongly express somatostatin receptors (SSTRs) which provides basis for therapy using somatostatin-derived peptides. The peptide receptor radionuclide therapy (PRRT) for SSTR NETs has emerged more than 15 years ago. The ^{90}Y/^{177}Lu-PRRT has shown to induce objective response in 30-45% of metastatic NETs patients with hematologic/renal toxicity reduced by dose fractionation. The complete response to therapy is rare due to the heterogeneity of NETs; advanced stage of disease at the time of diagnosis; and patient resistance to nonradioactive octreotide and ^{90}Y/^{177}Lu-PRRT developed during the therapy. The ¬targeted-alpha-emitter-therapy (TAT) of NETs can overcome these limitations. It can enhance the therapeutic response of patients and decrease side-effect and overcome patient resistance of ^{90}Y/^{177}Lu-PRRT without significant acute and mid-term toxicity. The RadioMedix and AREVA Med teams together have recently developed several novel ^{203}Pb-peptide derivatives targeting SSTR(+)cancer cells, ^{203}Pb-AR-RMX. ^{203}Pb is a gamma-emitter (279keV;t1/2=51.9h), suitable for SPECT imaging. The ^{203}Pb is a match surrogate for ^{212}Pb-TAT because both isotopes share identical chemical properties. The objectives of these studies were: (1) to evaluate the SSTR-targeting properties of ^{203}Pb-AR-RMX; (2) to determine their pharmacokinetics and bioD in vivo in SSTR-overexpressing xenographs; and (3) to select lead candidate for further e-IND clinical studies.

Methods: AR-RMX conjugate was manufactured under GMP by Macrocylics. The agent was characterized by HPLC-chromatography and LC-MS analysis. The ^{203}Pb-radiolabeling of AR-RMX was carried out under mild conditions. The SSTR-binding properties of AR-RMX were determined in the cellular uptake/ competition studies in AR-42J cancer cells. The competition studies were performed by co-incubation of tested agent with SSTR-specific ligands in cancer cell lines.

Results and Discussion: The ^{203}Pb-AR-RMX-15, shows high selectivity toward SSTR in cellular uptake studies and tumor-specific accumulation and retention in AR42J xenograph mice. Tumor uptake of ^{203}Pb-AR-RMX-15 was >14.4 %ID/g at 1h post injection and it remained at this level at least for 24h. The kidneys accumulation of ^{203}Pb-AR-RMX-15 was >13 %ID/g at 1h and varies in different strains of mice but decreased progressively over the 24h. The kidney uptake of agent is similar to previously observed for octreotate labeled with other isotopes. The tumor uptake is significantly higher possible as a result of the change of charge of the agent. Preliminary studies of ^{203}Pb-AR-RMX-15 showed that its kidney retention can be reduced by >32% by co-injection of positively charged amino acids. ^{203}Pb-AR-RMX-15 has shown >98% radio/chemical stability up 7 days post-formulation; no bone marrow uptake of agent was observed in bioD studies done up to 24h post-injection. These results allow us to hypothesize that the therapeutic dose of ^{212}Pb-AR-RMX-15 is expected to be significantly higher than the dose limiting activity.

The ^{203}Pb-AR-RMX-15 showed promising results in vitro and in vivo studies and has been selected for validation in e-IND clinical studies (IND 130690). Our “theranostics” approach using ^{203}Pb/^{212}Pb-PRRT has a potential to advance image-guided therapy that can detect and deliver therapeutic radiation dose precisely to SSTR(+)NETs.

^{225}Ac-DOTA-Substance P as a potential radiopharmaceutical for targeted alpha therapy of glioblastoma multiforme

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Objectives: Gliomas, particularly WHO grade IV glioblastoma multiforme (GBM) are one of the most common and aggressive primary types of the cancer of the central nervous system and are composed of morphologically diverse population of cells in the tumour mass. Despite all current forms of treatment such as advanced surgery techniques, radiation therapy and chemotherapy, the life expectancy of patients diagnosed with GBM is 12 to 15 months displaying the worst median overall survival among all human neoplasms. Targeted alpha therapy has been shown to overcome chemo- and radioresistance *in vitro* and thus presents a promising new approach for therapy of GBM. The findings that high affinity Substance P receptor NK1 is high consistently expressed in primary malignant gliomas and in the intratumoral and peritumoral vasculature makes this receptor a very attractive target for glioma cancer therapy.

Methods: In this study, a protocol for the synthesis of SP labelled with the alpha emitter ^{225}Ac was developed. The effects of ^{225}Ac-DOTA-SP were investigated on human glioblastoma cell lines (T98G, U87 MG, U138 MG) as well as GBM stem cells. Expression of NK1 receptors on the cell lines was confirmed by PCR and Western blot analysis.. The receptor affinity of ^{225}Ac-DOTA-SP was determined by saturation binding experiments. Cell viability was assayed using the MTS colorimetric assay and the clonogenic assay. Apoptosis and cell cycle studies of the glioblastoma cells were determined by flow cytometry analysis.

Results: Using optimized labeling conditions for the synthesis, ^{225}Ac-DOTA-SP was obtained with a specific activity of 3.3 MBq/nmol and a purity of > 99 %. Binding affinity studies showed K_d values of 19.2 ± 1.9 nM and B_{max} values of 0.27 ± 0.04 ng/ml. A significant dose-dependent reduction in cell viability (70-80 %) was detected up to 6 days of treatment. Also, colony-forming capacity was inhibited at the lower doses tested. In comparison, treatment with the conventional agent temozolomide showed higher cell viability and colony-forming capacity. ^{225}Ac-DOTA-SP treatment caused induction of late apoptosis pathways without induction of early apoptosis pathways. Cells were arrested to G2/M-phase upon treatment. Increasing doses and treatment time caused additional S-phase arrest. Similar results were obtained using human glioblastoma stem cells, known to show radioresistance.

Conclusions: In summary, our work proves the potential of ^{225}Ac-DOTA-SP for the treatment of glioblastoma and identifies the principal effects on cell viability, clonogenicity, apoptosis, and cell cycle in cancer cell lines and glioblastoma stem cells. Targeted alpha therapy with ^{225}Ac-DOTA-SP is a promising approach for treatment of GBM and warrants further investigation *in vivo*.

Assessment of ^{213}Bi-anti-EGFR-MAb treatment response in malignant cancer cells

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Aim: Evaluation of response to treatment is among the major challenges in oncology. Using a targeted therapy approach with an alpha-particle emitting radionuclide we investigated two different tumor cell lines with regard to alterations in glycolysis as measure of therapy response. Hereby, in vitro assays represent a valuable tool to provide necessary information about therapeutic efficacy.

Methods: To investigate therapeutic efficacy and cellular metabolic changes, treatment of LN18 and EJ28-luc cancer cells with ^{213}Bi-anti-EGFR-MAb (1.48 MBq/ml) was carried out for 3 h. Treated cells and controls were then incubated with ^{13}C-labelled glucose for 18 h followed by isotopologic enrichment analysis of metabolites using mass spectrometry. Moreover, ^{18}F-FDG-uptake assays were performed to evaluate glycolytic turnover.

Results: Treatment of EJ28-luc bladder cancer cells with the ^{213}Bi-anti-EGFR conjugates resulted in a significantly decreased enrichment of the following ^{13}C-labelled amino acids: alanine, aspartate, glutamate, glycine, proline and serine. In contrast, early treatment response assessment with regard to the ^{13}C-glucose enrichment pattern in the glioblastoma cell line LN18 showed an increase in all of the above-mentioned amino acids.

Conclusions: Different responses following ^{213}Bi-anti-EGFR-MAb treatment with regard to ^{13}C glucose enrichment – decrease in EJ28-luc bladder cancer cells and increase in LN18 glioma cells – are indicative of different signalling cascades activated in bladder cancer and glioma cells. To clarify this phenomenon further investigation including other cancer cell lines is mandatory.

Cytotoxicity evaluation using α-particle emitting radionuclides ^{211}At conjugated antibody

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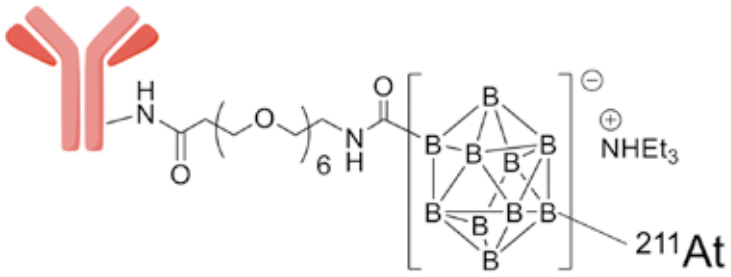
Project Research Center for Fundamental Sciences, Graduate School of Science, Osaka University

The principal aim of this study was development of next-generation internal radiotherapy using ^{211}At conjugated with cancer targeting molecules.
First, we synthesized anti-CD20 antibody conjugated decaborane ($B_{10}H_{14}$) with polyethylene glycol linker[1-5]. ^{211}At was produced by the cyclotron, and then quickly purified and combined to decaborane conjugated antibody. Now we are getting this ^{211}At combined antibody in about 80% yield.
Next, we performed cytotoxicity evaluation of ^{211}At and this antibody using Raji cells (B lymphocyte cell line derived with Burkitt's Lymphoma). As a result, the time- and concentration-dependent cell death were confirmed in both ^{211}At and this antibody. In the immediate future, we plan to examine that the same study with anti-HER2 antibody for breast cancer, and *in vivo* study using some tumor-bearing animals.



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Biodegradable polymersomes as carrier for alpha radionuclide therapy

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Alpha radionuclide therapy is a promising option for cancer treatment. However, how to deliver the alpha radionuclide to the cancer is still under study. A lot of carriers have been studied such as antibody, peptide and nanocarriers. Nanocarriers could be an option owing to they have many advantages. Since biodegradable block copolymer could self-assemble into nanocarriers that have been showing great potentials in diagnostic and therapy[1,2]. In previous study, we have demonstrated polymeric nanocarriers are good option for alpha radionuclide therapy[2]. Here, we have designed and developed iodine-rich biodegradable block copolymer (poly(ethylene glycol)-b-poly(iodine carbonate) PEO-PIC) and radiolabeled with radioiodine (^{125}I) for the in vivo study. The radiolabeling efficiency is 83±8 % by isotopes exchange reaction. The block copolymer could self-assemble into nanoparticles in solution and the size is around 100 nm, which prolong circulation time in vivo. In vivo study shows that the tumor uptake up to 17 %ID/g measured by microSPECT/CT. The results show that the biodegradable nanoparticles have great potential on delivery alpha radionuclide for cancer therapy.

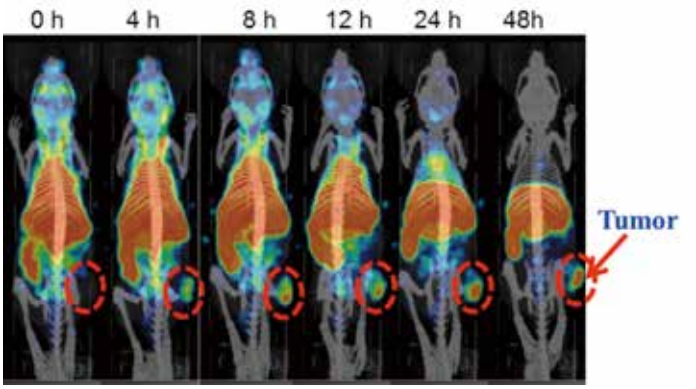

Fig. 1 Distribution and tumor accumulation of nanocarriers in tumor-bearing mice.

Acknowledgements: This work was supported by the China Postdoctoral Science Foundation (2016M591915).

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Barium ferrite nanoparticles labeled with ^{223}Ra: a new potential radiobioconjugate for internal alpha therapy

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Objectives

Alpha particle emitting isotopes are in considerable interest for radionuclide therapy because of their high cytotoxicity and short path length. Unfortunately, many available emitters have certain disadvantages: ^{211}At forms weak bonds with carbon atoms in the biomolecules, ^{212}Bi, ^{213}Bi, ^{211}Pb and ^{226}Th have short half-lives and the decay of ^{225}Ac and ^{223}Ra produces further alpha emitting radionculides that may escape from the radiobioconjugates.

An advantage of ^{223}Ra is that it currently has a higher availability. It is obtained from ^{227}Ac/^{223}Ra generators, wherein ^{227}Ac ($T_{1/2}$=21.8 y) can be produced in research reactors by neutron irradiation of ^{226}Ra targets. Unfortunately, the lack of an appropriate bifunctional ligand for radium has to date hampered the application of ^{223}Ra in receptor targeted therapy. In our studies we investigated barium ferrite ($BaFe_{12}O_{19}$) bioconjugates as vehicles for ^{223}Ra radionuclide for targeted α therapy.

Results and methods

The super-paramagnetic barium hexaferrite nanoparticles labelled with ^{223}Ra were synthesized by a modified autoclave method described by Drofenik et al [1]. To the reaction mixture of $FeCl_3$, $BaCl_2$ and NaOH solutions 2 MBq of ^{223}Ra was added. The solution was stirred in autoclave at 200^{o}C-217^{o}C for 5 h. In order to synthesize a radiopharmaceutical having affinity for Her 2 receptors, the monoclonal antibody trastuzumab was conjugated to the obtained barium ferrite nanoparticles. PEG linker (2000 kDa) comprising the silane group at one end and N-succinimid ester (NHS) at the second was used for synthesis of silane-PEG-trastuzumab radiobioconjugate. The obtained bioconjugate was characterized by transmission emission spectroscopy, thermogravimetric analysis, dynamic light scattering and were tested for stability in biological fluids. The ^{223}Ra labeled $BaFe_{12}O_{19}$ bioconjugate almost quantitatively retains ^{223}Ra, have high receptor affinity towards Her2 receptors expressing ovarian cancer and exhibits high cytotoxic effect *in-vitro*.

Conclusions

Trastuzumab functionalized barium(^{223}Ra) ferrite represents a viable solution for use of the ^{223}Ra *in vivo* a generator as a therapeutic construct for targeting Her2 positive breast and ovarian cancers. The ^{223}Ra radiobioconjugate successfully retain nearly 99% of ^{223}Ra and majority of the daughter products without compromising the tumoricidal properties of the radiation. It is worth to notice, that the release of the decay product from ^{223}Ra might be of limited concern, because 75% of the α-particle are emitted within 4 seconds after the ^{223}Ra decay. In addition, [^{223}Ra]$BaFe_{12}O_{19}$-PEG-trastuzumab have been shown to possess binding properties towards Her2 receptor expressing ovarian cancer cells and exhibits high cytotoxic effect in vitro.

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The impact of tumor burden on the absorbed dose to the kidneys from Actinium-225 labeled antibody therapy in a murine model and predicted dosimetric impact for human clinical use

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Objectives
There has been increasing interest in the use alpha-particle emitting radionuclides to combat cancer, especially in metastasized disease. The short range of the emitted alpha-particles combined with the high LET makes them effective against single cells, cell clusters and solid tumors. Studies have shown that the main part of the absorbed dose to the kidneys when using ^{225}Ac labeled antibodies originates from the free daughter ^{213}Bi, which is generated from ^{225}Ac in the rest of the body. Furthermore, the dosimetry has been well qualitatively characterized using the macro-to-micro (M2M) small scale methodology. In this study we examine how the tumor burden affects the absorbed dose to the kidneys from both the ^{225}Ac labeled antibody and the free daughter ^{213}Bi in a transgenic immunocompetent mouse model applying M2M and extrapolate to human use.

Methods
In this study *neu*-N mice where used. The animals were injected subcutaneously with NT2.5 cells in the right flank 4 weeks prior to experiments to generate the tumors. Healthy non-tumor and the tumor bearing mice were injected intravenously via the tail vein with 37 kBq of ^{225}Ac-7.16.4 and sacrificed 1, 6, 24, 72 and 144 hours after injection. After sacrifice the kidneys were harvested and immediately counted in a gamma well counter for 1 min at the time for a total minimum duration of 4.5 hours. A double exponential expression was fitted to the measured data points to obtain the activity of ^{225}Ac-7.16.4 and free ^{213}Bi per unit mass within the kidneys at sacrifice. Whole organ kidney dosimetry for ^{225}Ac-7.16.4 and free ^{213}Bi was determined using this measured biodistribution data. Actinium-225 and its alpha-particle emitting decay daughters ^{221}Fr, ^{217}At, ^{213}Bi and ^{213}Po were assumed to decay at the same location within the kidneys for ^{225}Ac-7.16.4.

Results
The highest activity concentration of free ^{213}Bi and ^{225}Ac-7.16.4 was 1 hour after injection with 20,400 and 2,050 Bq/g for non-tumor bearing and 16,200 and 2,100 Bq/g for tumor bearing mice, respectively. The ^{225}Ac-7.16.4 cleared from the kidneys for the non-tumor bearing mice with an effective half-life of 75 hours and 78 hours for tumor bearing mice. The absorbed dose to the kidneys for tumor bearing mice from ^{225}Ac-7.16.4 was 73.7 mGy/kBq and 131 mGy/kBq from free ^{213}Bi. For the non-tumor bearing mice the corresponding absorbed dose to the kidneys was 19.3 mGy/kBq and 41.8 mGy/kBq, respectively. Translating to human from the mouse model using linear relationship using respective whole body and kidney weights and a range expected tumor burdens shows a lesser dosimetric impact in humans due to the lower tumor/kidney mass ratio.

Conclusions
This study shows that the tumor bearing mice have a higher kidney absorbed dose compared with the non-tumor bearing mice, due to les free ^{213}Bi from decaying ^{225}Ac-7.16.4 in the tumor. This indicates that the free ^{213}Bi contribution to kidney dose is expected to be less in humans where the tumor burden to kidney mass ratio is much lower than in the murine model, but that tumor burden should be considered when treatment planning.

Biokinetic modelling for optimization of intraperitoneal targeted alpha therapy of disseminated ovarian cancer

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Background: Our group now has more than 20 years' experience in evaluating targeted alpha therapy (TAT) for treatment of disseminated ovarian cancer. Our completed phase I clinical study on ^{211}At-MX35 F(ab')$_2$ showed a high peritoneal retention of the radiolabeled antibody fragment and low absorbed doses to critical organs such as bone marrow and thyroid at therapeutic activity levels. Adverse effects of the radiopharmaceutical were not observed. A retrospective dosimetric study based on this phase I trial was published in 2015. That study included clinical biokinetic data from blood and *i.p*. fluid sampling, urine collection, and scintigraphy from three patients treated intraperitoneally with ^{211}At-MX35 F(ab')$_2$ produced with an improved radiolabeling technique.

Objectives: A biokinetic model is constructed to strengthen a key aspect of TAT, i.e. radiation dosimetry. This is needed to relate observed biological effects to the highly localized energy deposition of alpha particles. The overall aim is to use results from the model to predict clinical outcome and assist in individually optimizing each patient's treatment.

Methods: Our previously developed model, that simulates the biokinetics of various *i.p*. or *i.v*. administered radioimmunoconjugates, is expanded to include the time-dependent transport of mAb from the tumor surface to its inner layers. The model is based on the dynamic modelling software STELLA. It generates results of the time-dependent biodistribution that are used as input for micro- and small-scale dosimetry. A separate, also in-house developed, Monte Carlo computer code for various alpha-particle emitters (e.g. ^{211}At and ^{213}Bi) is used for microdosimetric analysis of microtumors of various sizes.

Results: A physiology-based biokinetic model of the transport of *i.p.* infused antibodies that describes distribution to healthy tissues and binding to microtumors of various sizes has been developed. Together with micro- and small-scale dosimetry, the model predicts the absorbed dose to both tumors and critical healthy tissues for various radionuclides and infused solutions. This tool might be useful for understanding and predicting how variations in administered activity; specific activity; compound stability; administered *i.p.* volume; addition of an osmotic solution (e.g. Extraneal); tumor cell antigen expression etc. will affect efficacy and toxicity. Ideally, the model results could therefore be used to guide and optimize future *i.p.* alpha-particle-emitting radioimmunotherapies.

Conclusion: The presented biokinetic model, based partly on our own clinical data, can generate results useful for optimizing future clinical trials involving intraperitoneal TAT.

Absorbed dose evaluation for the normal neighboring organs on thyroid gland of hyperthyroidism for iodine-131 radionuclide therapy using the Monte-Carlo based PHITS code combined with voxel phantom data for the application of targeted alpha therapy

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Background and Objective: Today to simplify the implementation of absorbed dose calculations using voxel phantom data, the research group for radiation transport analysis in JAEA have promoted to develop the Monte-Carlo based PHITS (Particle Heavy Ion Transport code System) code and to establish the code becoming one of the standardized calculation codes for risk assessment and research field of medical physics. We have collaborated with the PHITS research group to work on the pertinent improvement of the PHITS code that is specialized for medical physics in clinical use. There is, this study will be dedicated to the absorbed dose calculated upon the maximum equal dose distribution at a targeted thyroid gland with Basedow disease in radionuclide therapy of ^{131}I as a β (γ) emitter by PHITS in conjunction with the voxel phantom date of an adult male, and with based on the normalization of the obtained absorbed dose, we have developed a new method becoming possible to simplify the implementation of the absorbed dose calculations for the neighboring risk organs using the formula of Marinelli-Quimby generally in clinical use for the targeted organ of thyroid gland.

Methods: The latest version of PHITS code already released on September 2016 is 2.88 and it becomes available for us to perform the implementations of absorbed dose evaluation of targeted thyroids of ^{131}I β(γ) nuclides delivered on radiopharmaceuticals in radionuclide therapy. In geometrical modeling of a complex structure such as human body the PHITS code can provide valuable insight and assistance for dosimetry of organs of interest including thyroid gland in this work. For the source modeling of beta particle originated from β- decay of ^{131}I, the beta energy spectrum is available by referring to the MIRD Decay Schemes 2nd Edition. Our focused Marinelli-Quimby's formula of ^{131}I in clinical use is expressed as follows,

$$\text{absorbed dose of thyroid gland (Gy)} = \frac{135 \times A \times U \times T_{eff}}{3.7 \times W \times 8 \times 3.7 \times 100},$$

where A (MBq) is a prescription radioactivity of ^{131}I, U(%) is an uptake rate on 24 hours, T_{eff}(day) is an effective half-life of ^{131}I, and W is the targeted thyroid gland of ^{131}I. The simplified suggested method in this study enables us to deduce the absorbed doses the neighboring risk organs with based on the normalization of the obtained absorbed dose of thyroid gland by the formula.

Results and Discussion: Figure 1 shows an example output of the absorbed dose distribution on the coronal cross section, which was calculated by the PHITS code through the total number of history of 1E+7. From all the calculated results with based on the normalization by the Marinelli-Quimby's formula, we can find that the absorbed doses of thyroid gland as a targeted organ is determined to be 334.6 Gy and esophagus, skin, spinal marrow and salivary gland as risk organs are simply obtained to be 2.54, 0.19, 1.27, and 0.02 Gy. In this presentation in detail, it will be stated that we have worked on developing the absorbed dose evaluations associated with a targeted alpha therapy on various voxel phantom organs using the PHITS code via the radiation source section setting up the focused parameter changing a β- emitter to an α- one, ^{223}Ra, ^{211}At, and so on.

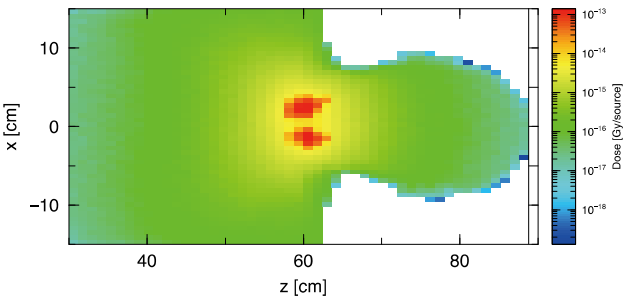

Fig. 1 Absorbed dose distribution on the coronal cross section of the upper half of voxel phantom

How should we normalise dose in TAT for cancer?

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Abstract

Introduction: Conventional dose normalisation in cancer therapy is based on body surface area (BSA), body weight (BWT) or just flat dosing. It is up to the Oncologist to change the dose to suit the patient response. However, the critical parameters for alpha immunoconjugates (AIC) are the drug concentration and area under the clearance curve (AUC). The overall concentration depends on the total body water (TBW) for hydrophilic drugs.

Objective: To achieve personalised medicine by the estimation of patient TBW using fat free mass (FFM) for a more appropriate dose normalisation.

Methods: TBW can be measured directly by dilution methods with D2O and T2O requiring laboratory measurements, as does the AUC, that are not practical for regular treatments. The four compartment model for body composition provides a more simple approach. BWT = FM + FFM; FFM = TBW + PM + BM where FM is the fat mass, FFM is the fat free mass, PM is the protein mass and BM is the bone mass. Body fat can be readily measured by the skin fold technique and more accurately by BIA and DEXA. As bone mass is constant and protein mass varies slowly for chronic patients, then FFM is a measure of TBW.

Conclusion: Phase 1 clinical trials should therefore be expressed in terms of FFM for dose normalisation. Otherwise, one third of patients who are thinner or fatter than the average could be over or under dosed by 10% or more.

POSTER SESSION II

Development of a scintillator based Compton camera for targeted α-particle radiotherapy

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Imaging the radionuclide distribution for targeted α-radiotherapy in cancer is useful for optimizing treatment strategies as well as for determining the suitability of a given agent for a particular patient. A promising radionuclide of ^{211}At and its daughter radionuclide of ^{211}Po emit high-energy photons (570, 687, and 898 keV) at a total intensity of 0.9%. These high-energy photons are not substantially attenuated in the body, and hence, a Compton camera is most suitable for visualizing ^{211}At distribution noninvasively.

We devised a Compton camera to demonstrate therapeutic imaging using the radionuclide of ^{211}At. The Compton camera consisted of two detectors: a scatterer and an absorber. Scintillator material of both the detectors was cerium-doped gadolinium aluminum gallium garnet (GAGG) Ce:$Gd_3Al_2Ga_3O_{12}$. The scatterer was a 20.8 × 20.8 × 5-mm^3 GAGG array block, coupled to a silicon photomultiplier, and partitioned into a 22 × 22 matrix. The size of a single GAGG element of the scatterer was 0.85 × 0.85 × 5 mm^3. The absorber was a 41.7 × 41.7 × 10-mm^3 GAGG array block, coupled to a flat panel type multianode photomultiplier tube, and partitioned into a 44 × 44 matrix. The size of a single GAGG element of the absorber was 0.85 × 0.85 × 10 mm^3. Distance between the front ends of the scatterer and absorber GAGG array blocks was 15 mm. A conventional digital circuit for a positron emission tomography camera was diverted.

In order to test ^{211}At imaging capability of the camera, Compton event data of 20-MBq radioactive solution of ^{211}At was acquired for 10 minutes. The window of the summed deposited energy was set to 570 keV, and the selected events were imaged by backprojection. Using this method, the radioactive source of ^{211}At was clearly imaged.

In conclusion, we have developed a Compton camera and successfully imaged a radioactive source of ^{211}At, and this technique can be useful for targeted α-particle radiotherapy.

Individual Alpha Particle Measurement using FNTD and SIM Super-Resolution Microscopy

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We present a novel, experimental method employing Al_2O_3:C,Mg Fluorescent Nuclear Track Detectors (FNTD) to measure the range, energy and angular distribution of alpha tracks simultaneously. This use of FNTDs for alpha radiation is novel and is the first method to combine measurement of range, energy and angle for individual alpha tracks within a single detector. The FNTDs were irradiated using an Am241 source placed inside the 3D printed honeycomb collimator to limit the maximum angle of particles entering the detector. Detector read-out was done using both Confocal Laser Scanning Microscopy (CLSM) and Super-resolution Structured Illumination Microscopy (SIM), yielding respectively 96 x 96 x 490 nm^3 and 74 x 74 x 110 nm^3 voxels in 98 x 98 x 12 μm^3 volumes. The measured fluorescence spots were reconstructed to tracks and the endpoint of each track was estimated using the fluorescence intensity within the track. For each track, the angle, length and energy could be calculated with good accuracy. The calculated mean energy, angular distribution and dose rate all matched with simulation. The high resolution of SIM allowed for visualization of alpha particle scattering events within the detector. Both read-out methods were used to calculate the amount of scattering of alpha particles within the crystal in the form of the detour factor. The detour factor from SIM approximated the detour factor the closest with 0.988 versus 0.984 from NIST's ASTAR.

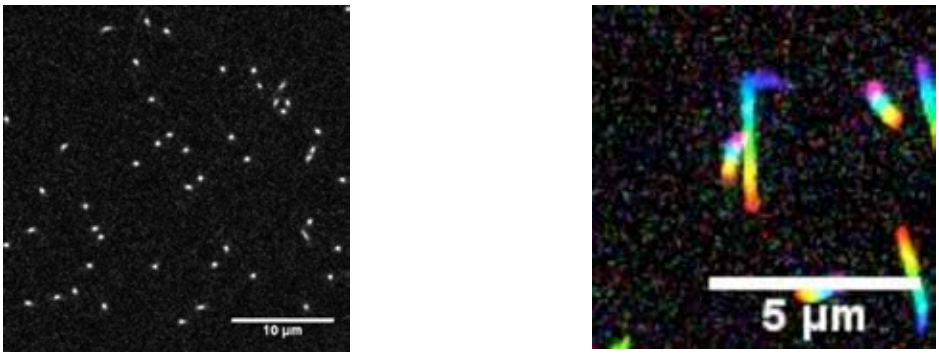

Figure 1: (left) Slice of CLSM scan of FNTD irradiated with Am241. (right) Tracks measured with SIM. The color indicated the depth in the crytal. A clear bend in the center track can be seen indicating a scatter of the particle.

Radioisotope Production and Dynamic Multi-Isotope Imaging of the ^{225}Ac Decay Chain

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Purpose: Effective use of the ^{225}Ac decay chain in targeted alpha therapy requires the retention of both ^{225}Ac and progeny isotopes at the target site. Imaging-based pharmacokinetic tests of these pharmaceuticals must therefore separately yet simultaneously image multiple isotopes that may not be colocalized despite being part of the same decay chain. This work will present results demonstrating the feasibility of quantitative preclinical imaging tests of ^{225}Ac-radiopharmaceuticals via simultaneous, dual-isotope SPECT imaging of two components of the ^{225}Ac decay chain: ^{221}Fr (218 keV) and ^{213}Bi (440 keV). Current and future ^{225}Ac production methods at TRIUMF will also be discussed.

Methods: ^{225}Ac and parent ^{225}Ra were produced using TRIUMF's Isotope Separation OnLine (ISOL) facility[1] by implanting a 28 keV mass 225 ion beam (containing ^{225}Ac and ^{225}Ra ions) into an aluminum target to a depth of 20 nm (simulated with SRIM[2]). Rinsing of the target with 0.1 M HCl post-implantation, followed by ^{225}Ac and ^{225}Ra separation via ion exchange resin (DGA[3]) provides a direct source of ^{225}Ac, plus a ^{225}Ra generator from which ^{225}Ac can be eluted every 17.5 days. Solutions of the ^{225}Ac decay chain in equilibrium were then used to acquire ^{221}Fr and ^{213}Bi images using a VECTor scanner[4] (MILabs), a multi-modality microSPECT/PET/CT imaging system capable of sub-millimeter quantitative SPECT. VECTor's versatility is enabled by interchangeable collimators, two of which were assessed for use in this application: a high-energy (HE) collimator, and a high-sensitivity (HS) collimator. Image quality phantoms were used to assess each collimator's performance in terms of contrast and noise. A hotrod resolution phantom containing clusters of thin rods with diameters ranging between 0.85 and 1.70 mm was used to assess resolution. To demonstrate this method can image dynamic ^{221}Fr and ^{213}Bi activity distributions that are not colocalized, a phantom containing a ^{213}Bi generator[5] (from ^{225}Ac decay) was dynamically imaged immediately after milking the generator, such that the reestablishment of transient equilibrium between ^{225}Ac, ^{221}Fr, and ^{213}Bi could be observed.

Results: While ISOL production runs have yielded up to 18.5 MBq of ^{225}Ac and 7.1 MBq of ^{225}Ra at end of beam, only 3.8 MBq of ^{225}Ac has so far been made available for imaging studies. Image contrast values consistent with expected activity were observed for high activity regions. In hotrod phantom images, the HE collimator resolved all rods for both ^{221}Fr and ^{213}Bi images. With the HS collimator, no rods were resolvable in ^{213}Bi images and only rods $\geq$1.3 mm were resolved in ^{221}Fr images. After eluting the ^{213}Bi generator, images accurately visualized reestablishment of transient equilibrium of the ^{225}Ac decay chain as expected.

Conclusion: A novel imaging method with potential to evaluate the pharmacokinetics of the ^{225}Ac decay chain in vivo has been presented. Results also demonstrate that this method requires the use of a high-performance high-energy SPECT collimator. Current work focuses on development of new ^{225}Ac production methods – via the proton irradiation of thorium at 500 MeV – capable of producing the larger ^{225}Ac quantities required to demonstrate this new imaging method in vivo.

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Chemical Purification of Actinium-225 from Proton-Irradiated Thorium Targets

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Research efforts at three US Department of Energy laboratories, Oak Ridge National Laboratory (ORNL), Los Alamos National Laboratory (LANL), and Brookhaven National Laboratory (BNL), are focused on providing accelerator-produced ^{225}Ac for radioimmunotherapy applications. The actinium is produced via high-energy proton irradiation of thorium targets and must be separated from thorium and a vast suite of fission and reaction by-products. In support of this effort, a series of thorium irradiations and actinium chemical separation campaigns have been performed to demonstrate chemical purification of actinium and evaluate yield and purity. A variety of chemical separations strategies have been developed and evaluated to optimize the challenging separations chemistry associated with this production method. A number of highly purified samples of accelerator-produced ^{225}Ac, ranging in activity from 1–20 mCi, have been provided to a limited number of researchers for evaluation. The results of these recent actinium separation campaigns, the underlying chemical complexities involved, and a reference to evaluations will be presented.

Behavior of Ac, Th and Ra on cation exchange resin in hydrochloric and trichloroacetic acids: Towards an alternative separation strategy for ^{225}Ac from irradiated thorium targets

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Introduction

Actinium-225 ($t_{1/2}$ 9.92 days) is a promising candidate for Targeted Alpha Therapy (TAT) application [1] which can be used directly in combination with antibodies and peptides or as a generator source of ^{213}Bi ($t_{1/2}$ 45.6 min), another promising TAT candidate [2]. Currently, the supply of ^{225}Ac is limited to approx. 63 GBq/year from an aging ^{229}Th stock. Several alternative strategies for production of ^{225}Ac are under development, with the irradiation of thorium with high energy (≥100 MeV) protons being one of the most promising. However, one of the challenges is that the Ac requires isolation from bulk (multi-grams) quantities of thorium and hundreds of co-produced fission products. Several chemical separation strategies have been proposed [3, 4]. In this work we tested an alternative separation strategy for isolation of actinium isotopes from irradiated thorium.

Materials and Methods

Several dissolution tests were performed with different acids, including hydrochloric, trichloroacetic, citric, tartaric and lactic acids. Systematic evaluation of distribution coefficients (K_d) was performed with Ac, Ra and Th radiotracers in systems hydrochloric/ trichloroacetic acids and cation exchange resin. Additionally, dynamic column separation experiments with Ac and Ra radiotracers with bulk thorium mass in trichloroacetic/ hydrochloric acids on cation exchange resin were performed.

Results

Of all tested acids, hydrochloric and trichloroacetic acids showed to be most suitable for thorium dissolution. Distribution coefficients results and dependency of behaviour of tested elements with variation of acids concentrations will be discussed. Dynamic column separation tests showed strong retention of Ac and Ra and negligible thorium retention at the same time in system trichloroacetic acid- cation exchange resin.

Conclusion

Tested systems based on cation exchange resin in hydrochloric and trichloroacetic acids, showed promising conditions for separation of Actinium and Radium isotopes from bulk thorium mass.

Acknowledgments: We thank teams from Phasotron facility at JINR and TRIUMF main cyclotron for performing irradiations.

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Radiochemical separation of ^{224}Ra from ^{232}U or ^{228}Th sources for ^{224}Ra/^{212}Pb/^{212}Bi generator

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Objectives: The use of short-lived radionuclides in nuclear medicine has grown considerably and has led to the development of radionuclide generators that serve as convenient sources of their production. The ^{212}Pb and ^{212}Bi are short-lived α-emitters that are interested from the targeted radionuclide therapy (TRT) point of view. The purpose of the present work was to develop a simple dynamic generator for rapid milking of carrier-free ^{224}Ra from ^{232}U or ^{228}Th sources with a high decontamination factor; and further milking of ^{212}Pb and its daughter ^{212}Bi from the separated ^{224}Ra.

Methods: Commercially available poly(tetrafluroethylene) (PTFE) powder with 40um particle size was impregnated with bis(2-ethylhexyl) phosphate (HDEHP) dissolved in acetone followed by evaporation of solvent on a rotavapor. The glass column was filled with prepared resin and washed with 2L 0.1M HNO_3. Next, ^{232}U or ^{228}Th in 0.1M HNO_3 was loaded on the bed and mother radionuclides extracted on the top of the column at a flow rate of 5 drops/min followed by additional 10mL 0.1M HNO_3 wash. The function of the generator was checked during few months by measuring the breakthrough of ^{232}U or ^{228}Th into ^{224}Ra eluate. Simultaneously the yield of eluted ^{224}Ra was determined as a function of the HNO_3 concentration. The eluted ^{224}Ra was loaded on the column with Dowex50Wx8 (100-200 mesh) and served as a generator for ^{212}Pb and ^{212}Bi. Different concentrations of HCl alone or mixed with NaCl were used to elute either ^{212}Pb or ^{212}Bi.

Results: The carrier-free ^{224}Ra can be eluted from ^{232}U or ^{228}Th generators with 4mL of 0.1M HNO_3. The yield was about 90% of the theoretical value with less than 0.001% of ^{232}U or ^{228}Th breakthrough. The obtained ^{224}Ra can be used as a source of ^{212}Pb and ^{212}Bi. The ^{212}Bi can be eluted from Dowex50Wx8 with 0.5mL of 0.5M HCl, whereas ^{212}Pb can be eluted with 100uL of 2M HCl or 1mL mixture of HCl-NaCl and eluate after buffering can be used for direct labeling with desired bioconjugates.

Conclusions: The elaborated generators of ^{224}Ra separation are simple, operate reliably and are easy to maintain. The elution procedure takes less than 2 min and ^{224}Ra is obtained nearly quantitative with high radionuclide purity. Further long term studies are required on potential radiation damage to obtained resin. The eluted ^{224}Ra can be easily used for obtaining its descendants with high radionuclide purity for further bioconjugate radiolabeling studies.

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Solution thermodynamics and kinetics of Th(IV) complexation by bare and conjugated Me-3,2-HOPO-based ligands

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Among the alpha-emitting radioisotopes envisaged for targeted alpha-therapies (TAT), thorium-227 has caught growing attention due to the relative easiness of its production and its half-life of ~19 days, which is well suited for medical applications. Current developments in ^{227}Th-based therapeutics have the advantage of relying on Th coordination chemistry, thanks to the availability of the natural and weakly radioactive isotope thorium-232. In addition, studies investigating Th-based treatments benefit from extensive knowledge acquired on Th(IV) chemistry in the frame of the nuclear fuel cycles, rare earth element or uranium mining and actinide decorporation studies; a considerable asset over other potential TAT isotopes such as radium-223 and actinium-225.

In this work, the solution thermodynamics of a novel thorium chelator, comprising four 3-hydroxy-N-methyl-2-pyridinone (Me-3,2-HOPO) binding units, a spermine scaffold and one pendant carboxylate arm for conjugation were investigated. The aqueous chemistry of the octadentate Me-3,2-HOPO ligand and its antibody conjugate were evaluated using the spectral properties of the Me-3,2-HOPO binding groups. Ligand protonation constants and stability constants of the complexes formed between the ligand or its bioconjugate, and Th(IV), Zr(IV), Hf(IV), Gd(III), Eu(III), Al(III) and Fe(III) were determined experimentally. The results show a very high affinity of the chelator and its bioconjugate for Th sequestration and an excellent selectivity toward M(IV) over M(III) metal ions. The ligand and its bioconjugate also exhibit fast kinetics of Th(IV) binding, with notable differences with the Zr(IV) and Fe(III) systems. Single X-ray crystallographic data were collected and will be presented. The data obtained with the investigational bare and conjugated Me-3,2-HOPO ligand support the development of this new class of targeted thorium conjugates in the field of oncology.

Development of a resin-supported bifunctional reagent to simplify labeling of ^{211}At

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^{211}At ($T_{1/2}$ = 7.2 h) is well-known as a preferable nuclide to targeted alpha therapy (TAT). ^{211}At must be labeled to a vector such as antibody to be accumulated on tumors. For TAT, labeling should be automated to avoid the radiation exposure of operators. In this work, for future automation, we attempted to develop a new simplified "catch-and-release" labeling procedure of ^{211}At with a resin-supported N-succinimidyl 3-(trimethylstannyl)benzoate (MeATE). MeATE is one of the possible ^{211}At-labeling reagents and is a bifunctional reagent which is substitutable to ^{211}At with trimethylstannyl group, and reactive to an amino group of antibody with active ester structure. In a column procedure with the resin, first, ^{211}At is retained on the resin by the substitution reaction with trimethylstannyl group. Then, after resin-washing, ^{211}At is labeled to antibody by the reaction between active ester and amino groups of antibody. This approach has advantages such that 1) the labeling reaction can be more easily automated by a column flow reaction, 2) an irradiated bismuth target need not to be separated beforehand; bismuth can be separated in the column by the difference of bonding strength between C-At and C-Bi, and 3)both solvents of ^{211}At and antibody can be selected with higher flexibility because each solution is mixed with only the resin. We prepared a silica-based MeATE resin with a commercially available 3-(2-succinic anhydride)propyl-functionalized silica gel. This was selected because of its low, undesirable astatine absorption to the resin. An ^{211}At labeling test was batch-wisely performed with the resin. At first, the resin was soaked with aqueous 1 % acetic acid solution including ^{211}At under an oxidative condition with N-iodosuccinimide (NIS). After quenching of NIS and washing, the resin was mixed with *n*-butylamine, an analogue of lysine residue of antibody. Final ^{211}At-labeled products were identified by HPLC analysis with compared with the UV- or radio-chromatogram of stable iodine isotope or ^{125}I analogue. An objective ^{211}At-labeled compound was obtained with 45 % yield and 84 % radiochemical purity. At present, protein labeling and column flow synthesis experiments are underway.

Isolation of ^{211}At using an anion-exchange column method

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Background:

Astatine-211 (^{211}At), a promising radionuclide for the targeted alpha therapy, is mainly produced via the ^{209}Bi(α ,2n)^{211}At reaction and widely isolated by the dry distillation from an irradiated Bi target. The dry distillation has simple procedures and a wide of solvents are available to recover ^{211}At. However, it has difficulty with low reproducibility when production scale is up. On the other hand, wet isolation requires complicated procedures, but it has high reproducibility.(1) Solid phase extraction (SPE) is one of the practical options for automation of ^{211}At isolation, because it is widely used for the isolation of radionuclides produced by a cyclotron and employed in an automated module such as ^{18}F-FDG synthesis and ^{64}Cu isolation. Therefore, we evaluated an anion-exchange SPE column for ^{211}At isolation.

Method:

Astatine-211 was produced by irradiating alpha beams of 28.1 MeV to a vapor deposited Bi target in QST-Takasaki. After irradiation, Bi deposited on the target surface was dissolved concentrated HNO_3 solution. After diluted with H_2O to adjust 8 M solution, the resulting solution was passed through an anion-exchange SPE column to trap ^{211}At. The column was washed with 2M HCl (x 4), and then trapped ^{211}At was eluted with low concentration of NaOH solutions. An ^{211}At labeled compound, [^{211}At]*N*-Boc-(4-astato)phenylalanine methyl ester, was synthesized by using collected solutions with or without neutralization. Astatination was carried out via the electrophilic destannylation in the presence of oxidizing reagent. Reverse-phase radio high performance liquid chromatography was used for characterization and determination of radiochemical yield (RCY) of the desired compound.

Results and Discussions:

Isolation studies demonstrated that excellent trapping efficiencies (>99%) were observed when loading the 8M HNO_3 solution and reasonable overall efficiencies (39-50%) were obtained by eluting with 0.1M NaOH solution. Residual Bi was completely removed with quite low wash losses of ^{211}At in all cases. In order to validate utility of the isolation method, ^{211}At labeled phenylalanine derivative was synthesized via the electrophilic destannylation. The syntheses afforded excellent radiochemical yield in the presence of oxidizing reagent, chloraminT (RCY: >97%). Interestingly, astatination was also occurred in the absence of oxidizing reagent (RCY: 16%), indicating that reactive species of ^{211}At was present in the collected solution after neutralization. These results showed that the anion-exchange column method has potential but further improvements are necessary for automation of ^{211}At isolation. Results on chemical form of isolated ^{211}At and synthesis of ^{211}At labeled peptides for the targeted alpha therapy will be also presented in this talk.

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Development of a ^{211}Rn/^{211}At Generator based on Dry-Chemistry

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Objectives: In general, the ^{211}At nuclide, a prospective candidate for targeted alpha radiotherapy, has been produced through bombardment of a bismuth target with 28 MeV helium ions in the ^{209}Bi(α, 2n)^{211}At reaction [1]. In contrast, our project is focused on the production in the ^{209}Bi(^{7}Li, 5n)^{211}Rn→^{211}At reaction [2]. This enables us to supply ^{211}At in a ^{211}Rn/^{211}At generator system. The daughter ^{211}At of 7.2 h in half-life is generated through EC decay of the parent ^{211}Rn of 14.7 h, expanding time-frame for transportation and use of ^{211}At. In the project, a chemical procedure based on dry-chemistry as well as that based on wet-chemistry [2] has been studied to develop the ^{211}Rn/^{211}At generator system.

Methods: Radon-211 was produced in the irradiation of a thin bismuth target of approximately 1 mg/cm^2 on an aluminum backing sheet with 60 MeV ^{7}Li^{3+} beams from the JAEA tandem accelerator via the ^{209}Bi(^{7}Li, 5n)^{211}Rn reaction. After the irradiation, the ^{211}Rn was separated from the target and purified in a chemical procedure based on dry-chemistry using an apparatus for the ^{211}Rn/^{211}At generator system. The bismuth target placed in a test tube which is a part of the apparatus was heated up to temperature 520°C by an electric furnace to melt the bismuth target. Radon-211 escaped from the melted bismuth target was transported to a stainless steel tube cooled to the temperature of liquid nitrogen by helium gas stream which circulates through the apparatus. The ^{211}Rn in the apparatus was monitored by lead-shielded GR1-gamma spectrometers. The ^{211}Rn trapped in the stainless steel tube was allowed to stand for over half a day to generate ^{211}At. After removing the helium gas including ^{211}Rn from the stainless steel tube, no-carrier-added ^{211}At deposited on the wall was recovered by rinsing the tube with flowing ethanol. Eluted ethanol was successively collected in three glass vials of 2 mL. Activities of ^{211}At were measured by alpha-ray spectrometry to determine recovery yields. Sources for alpha-ray spectrometry were prepared by depositing a portion of the eluted ethanol including astatine on a silver sheet.

Results and Conclusion: The dry-chemical process, namely, the separation and collection of ^{211}Rn in the apparatus for the ^{211}Rn/^{211}At generator system were accomplished within 15 min. The overall recovery yields of ^{211}At generated from ^{211}Rn (n=3) were approximately 35% in the first fraction of the eluted ethanol of 2mL, 8 % in the second and 1 % in the third. Ethanol easily removes a large portion of astatine generated through EC decay of ^{211}Rn from the stainless steel tube. The results demonstrate that the chemical procedure based on dry-chemistry as well as that based on wet-chemistry [2] could provide the unique ability of the ^{211}Rn/^{211}At generator.

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Wet chemistry of radon and astatine for the development of a ^{211}Rn/^{211}At generator

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Background and Objective: One of the promising nuclides among various alpha emitters is ^{211}At of a half-life of 7.21 h, which gathers much attention in targeted alpha therapy due to its appropriate life and expected chemical properties of the element. In order to improve the availability of ^{211}At, the development of a ^{211}Rn/^{211}At generator has a possibility to provide the nuclides in a wider range of locations distant from accelerator facilities where they are produced. However, especially Rn-chemistry has not been well studied to control its behaviors in the successive chemical processes needed. Therefore, we aim to study wet chemistry processes on Rn with At to realize a ^{211}Rn/^{211}At generator.

Methods: Radon-211 was produced in the irradiation of a stack of bismuth targets of 1.2-1.5 mg/cm^2 with 60 MeV ^{7}Li^{3+} beams from the JAEA tandem accelerator via the ^{209}Bi(^{7}Li,5n)^{211}Rn nuclear reaction. After the irradiation, each target was dissolved in 6 M nitric acid and radon atoms produced in the reaction were extracted to organic phase in the end. After the extraction, each phase was subjected to γ-ray spectrometry with a Ge detector, to determine the extraction yield of ^{211}Rn into the organic phase. The trapped ^{211}Rn was then allowed to stand for over half a day to generate ^{211}At in the organic solvent in a syringe where the solvent was kept away from the air and subject to the subsequent extraction of At. The back-extraction of ^{211}At was performed using alcohols with an oxidizing agent. After the back-extraction, each phase was subjected to the measurements with a liquid scintillation counter (LSC), to determine the amounts of ^{211}At and ^{211}Po and to determine the back extraction yield of ^{211}At. In addition, the extraction yields of ^{211}Rn with ^{211}At into alcohol solutions were also assayed by γ-ray spectrometry with a Ge detector to determine separation factors of At from Rn.

Results and Discussion: The γ-ray measurements revealed that ^{211}Rn was selectively extracted into dodecane after chemical separation from the target, while the other by-products remained in the aqueous solution. The extraction yield of ^{211}Rn in dodecane was estimated to be ca. 80-95%. The LSC measurement revealed that the back extraction yield of ^{211}At generated from the decay of ^{211}Rn was able to be increased to more than 90 % when an oxidizing agent of N-bromosuccinimide (NBS) was added to MeOH or EtOH aqueous solutions although some Rn was mixed into the alcohol solutions. Best performance we attained thus far for MeOH and EtOH solutions were 100vol% and 90vol% with water. The conditions of solvent extraction are acceptable for the At extraction but better systems should be sought for from a viewpoint of minimization of Rn spill.

Laboratory automation employed in the purification of astatine-211 from dissolved bismuth targets: Development, optimization, and performance validation of the fluidic system

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Astatine-211 (^{211}At) is a promising α-emitting isotope that is being evaluated for use in the treatment of blood-borne cancers, such as leukemia and lymphoma, as well as micrometastatic disease. The combination of its short half-life (7.2 h), highly energetic α-emissions (5.87 MeV (^{211}At, 41.8%) and 7.45 MeV (^{211}Po, 58.2%)), and stable antibody labeling chemistries assure a promising future for this isotope.

The University of Washington (UW) is one of only a few U.S. institutions that are capable of routine accelerator-based production of ^{211}At. The UW Scanditronix MC-50 cyclotron utilizes an α-particle beam to bombard high-purity Bi metal (naturally monoisotopic) to form ^{211}At via the ^{209}Bi(α,2n)^{211}At reaction. The UW team has developed a multi-step wet chemical purification process [1] to supply ^{211}At for radiolabeling and oncological research. The process is based on the early solvent extraction studies of Neumann [2], wherein ^{211}At is efficiently extracted from 8 M HCl into diisopropyl ether (DIPE), washed with 8 M HCl, and finally back-extracted into NaOH. The UW ^{211}At isolation process, from target dissolution to final isotope purification, is performed manually in a glovebox.

PNNL is collaborating with UW to streamline the ^{211}At production process through the development of automated modules that can replicate the current manual isolation steps. This includes a flow-based Bi target dissolution cell [3], remotely controlled thermal system to distill away the HNO_3 used to dissolve the target and bring the Bi salts up in HCl acid, and a fluidic system to automate the liquid/liquid extraction process. The ultimate objective is to have a fully automated process replace the manual handling steps. This will ultimately facilitate the preparation of more frequent and higher activity production runs, as the use of this isotope for oncological research and therapy is anticipated to grow in the coming years. Details of the fluidic system and its performance validation testing to date will be presented.

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Realizing Clinical Trials with Astatine-211: Radiopharmaceutical Chemistry

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Background

Despite the consensus around the clinical potential of astatine-211 (At-211), there are only a few research groups that routinely work with the nuclide. There are three main reason for this:

- Availability of the nuclide. Despite a number of globally existing cyclotron capable of producing At-211 very few cyclotron facilities do produce the nuclide.

- Lack of chemical infrastructure. Currently the research groups that do work with At-211 depend on custom systems for recovering At-211. Setting up and implementing such a custom unit require long lead times to provide a proper working system. This means that even though there are cyclotrons capable of producing At-211, there is a lack of research infrastructure that prohibits interested parties to scale up or even start At-211 research.

- Complex At-211 chemistry. Appropriate chemical synthesis methods for stable bonds between At-211 and tumor specific vectors needs to be established.

Aim

Herein we present chemical strategies for overcoming problems in research and clinical trials with At-211, including automation of isolation and work up of At-211 and chemical synthesis of At-211 radiopharmaceuticals.

Method

An automatic system has been assembled by integrating a dry-distillation system with a generic research synthesis module. To simplify the synthesis of At-211-radiopharmaceuticals prefabricated conjugated molecules has been synthesized. This strategy reduce reaction times, increase radiochemical yields and can effortless be adopted for automatic radiochemical synthesis.

Conclusion

By providing a chemistry infrastructure in the form of an automatic system for work up and chemical synthesis of At-211 radiopharmaceuticals, the main obstacles concerning At-211 would be overcome and hence the demand for At-211 research and clinical trials could be significantly enhanced.

Isolation of alpha-emitting radionuclides for nuclear medicine in JSC “SSC RF – IPPE”

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Alpha-emitting radionuclides - very promising radiotherapy means showing tremendous potential in the treatment of a broad spectrum of malignant neoplasms, as being delivered to the tumor cells using a carrier such as peptides, monoclonal antibodies, simple low molecular weight compounds, modular nanotransporters etc., ensure their destruction with minimal damage to the surrounding organs.

For the possibility of their use in nuclear medicine, the alpha-emitting radionuclides must possess a number of properties, such as: clean alpha emitters; have half-lives long enough to allow their selection and delivery to the medical institution, but not long enough to present a danger to the patient; their chemical properties should ensure a strong bond with a variety of media; they must be accessible and affordable. These radionuclides, in particular, are ^{225}Ac and ^{224}Ra.

Since 2002 JSC “SSC RF - IPPE” works on the isolation and purification of ^{225}Ac from ^{229}Th, 150 mCi of which were obtained from the reprocessing of ^{233}U. To date, delivered over 2 Ci ^{225}Ac to the medical facilities, mainly in the US and Germany, which have been developing methods of treatment of various diseases. Delivered product (5-10 mCi ^{225}Ac/ml) does not contain ^{228}Th, ^{229}Th and ^{233}U, as well as any β- and gamma-emitting nuclides impurity, but contain inactive impurity cations (μg/ml) such as: Ca – 1.3×10^{-2}, Mg – 3.0×10^{-3}, Cu – 1.3×10^{-3}, Mn – 1.3×10^{-4} and Al – 2.2×10^{-3}. The production capacity of JSC “SSC RF - IPPE” is about 50 mCi ^{225}Ac/month with calibration on the 5th day from the date of delivery.

In 2007, JSC “SSC RF - IPPE” was created the industrial site on release of ^{224}Ra from ^{228}Th, which, in turn, prepared by reprocessing of ^{232}U followed by held different times. Generator was developed, consisting of a column filled with resin CRF-20T-60 where sorbed ^{228}Th, is used for periodic washing out of ^{224}Ra with subsequent purification of iron cations and other impurities. Designed and certified method allows obtaining high-purity product containing no ^{228}Th, nor any β- and gamma-emitting nuclides impurity. In the final product are found only alpha-emitting radionuclides belonging to chains of ^{228}Th and ^{229}Th decay. Among the inactive impurity cations only Mn and Fe of small amounts (1.3 and 0.13 μg/ml) are present in the final product (0.1 mCi ^{224}Ra /ml). Radionuclide purity and content of inactive impurities of the resulting product allows using its for the development of a number of methods of therapy of cancer. The production capacity of JSC “SSC RF - IPPE” is about 20 mCi ^{224}Ra/month with calibration on the 4th day from the date of delivery.

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Production of Actinium-225 at Oak Ridge National Laboratory

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Background and Objective: Oak Ridge National Laboratory (ORNL) is a major producer of ^{225}Ac and supplies several clinical trials for the treatment of various forms of cancer with this promising radioisotope. Actinium-225 ($t_{1/2}$ = 10.0 days) has nuclear properties well suited for use in targeted alpha therapy, emitting four α-particles in a decay cascade via short half-life daughters. It can be used exclusively as a generator for ^{213}Bi ($t_{1/2}$ = 45.6 min), which is also under evaluation in a number of clinical trials. ORNL has been producing and shipping ^{225}Ac for research and clinical applications since 1997. During the first year of production, a total of 135 mCi was shipped. Since then, production levels have steadily increased such that in 2016 ORNL produced 900 mCi of ^{225}Ac in 15 processing campaigns. From 1997 through the end of calendar year 2016, we have conducted 130 production campaigns and have provided ~9,000 mCi in over 900 shipments. Our objective is to continually investigate processing techniques that will improve production in order to meet the increasing demand for ^{225}Ac using the limited amount of high-purity ^{229}Th currently available. Most recently, we have adjusted our processing schedule for milking ^{225}Ac from the ^{229}Th to every 3 weeks to optimize the balance between the allotted time for ingrowth and the frequency of chemical separations. With this schedule, a minimum of 16 mCi of ^{225}Ac is available for clinical trials on a weekly basis.

Separation and Purification: The chemical separation consists of anion exchange separation using hydrochloric and nitric acids followed by cation exchange separation for the final purification. Gamma spectroscopy is used for quality control analysis of the final product prior to shipping. Mass spectroscopy data has been used to evaluate chemical purities.

Results: Various processing schedules have been used for the production of the ^{225}Ac, depending on the needs of the scientific community, staffing, and funding. This presentation will review various production sequences and present ways to optimize production from our current ^{229}Th cow. Our goal for 2017 is to produce 1000 mCi ^{225}Ac for use in research and clinical trials.

Reactor Production of ^{229}Th via Neutron Capture of ^{228}Ra Target

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As a part of a general program to investigate alternative approaches that can increase the supply of ^{225}Ac for TAT applications, the reactor production of ^{229}Th (parent of ^{225}Ac) has been examined and the production yields for ^{229}Th, ^{227}Ac and ^{228}Th *via* neutron capture of ^{226}Ra targets have been reported (Hogle *et al*, 2016). Ra-228 is an alternative target isotope for the reactor route *via* the ^{228}Ra [n,γ]^{229}Ra ($t_{1/2}$ = 4.0 min, β^-) ^{229}Ac ($t_{1/2}$ = 1.04 h, β^-) ^{229}Th reaction. Ra-228 ($t_{1/2}$ = 5.8 y) is the first α-decay daughter of natural thorium (^{232}Th). It's availability is currently very limited, but it is extremely desirable since access to ^{229}Th by this route requires only a single neutron capture in comparison to the three neutron captures required by ^{226}Ra.
In this work, the production yield of ^{229}Th for the above reaction is reported. Measurements were made based on two ^{228}Ra targets (0.70 and 0.24 μg), each irradiated for 25.5 days. Ra-228 was extracted from ~4.4 kg of aged ^{232}Th by ion-exchange chromatography in 95 column runs. After further purification and removal of >99% of ^{228}Th (β^- decay product of ^{228}Ra), ^{228}Ra was sealed in high-purity quartz ampoules for irradiation, and the precise amount of ^{228}Ra in each ampoule was confirmed by γ-ray spectroscopy. After irradiation, the Ra and Th fractions were isolated, purified, and analyzed by γ-ray spectroscopy. The relative amounts of Th isotopes were determined by mass spectroscopy because quantification of ^{229}Th by γ-ray spectroscopy in the presence of very high activity ^{228}Th is not possible. While ^{228}Ra recovery was >99%, and yield of ^{228}Th and ^{230}Th was within 90% of the theoretical predication, the yield of ^{229}Th at 260 ± 10 Bq/μg of ^{228}Ra is significantly below the expected value of ~1000 Bq/μg. At this time, the cause of the discrepancy is unknown, especially considering that both the ^{228}Ra and ^{230}Th yields were much closer to the expected value. The discrepancy may be due to the extremely high cross section of ^{229}Ac, followed by rapid transmutation of ^{230}Ac to ^{230}Th, or it could be due to high fission of ^{229}Th; therefore, further evaluation of this production route and re-evaluation of the fission cross section of ^{229}Th is necessary.

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Astatine-211 production using the C70XP

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The ARRONAX cyclotron is a high intensity (up to twice 375 µA for protons) and high energy (up to 70 MeV) multiparticle (protons, deuterons, α particles) facility installed in Nantes, France since 2010. One of the reasons to have alpha beams available is to be able to produce Astatine-211. A large R&D effort has also been set starting from beam energy degradation through the target preparation, the set-up of the purification process and the QC method. For the last 2 years, we have been able to produce astatine-211 more than 20 times a year with a total delivered activity of 8 GBq at calibration time. This productions have been used by Subatech laboratory and CRCNA to perform fundamental [1], radiolabeling [2] studies and preclinical work on multiple myeloma.

The target is prepared by bismuth evaporation on aluminum nitride (AlN) support under vacuum. The bismuth thickness has to be at least 25 µm thick to take advantage of the production cross section (zero below 20.7 MeV) and to benefit from the better thermal properties of the support as compare to bismuth.

The delivered alpha beam energy is too high (68 MeV) for optimal astatine-211 production. To minimize the production of astatine-210 which decays to Po-210 (highly toxic radionuclide), the energy has to be less than 28.6 MeV. To decrease the kinetic energy of our projectiles, a cooled carbon degrador has been designed. It allows to put around 20 µA on target with 25% loss coming from angular straggling. With this technique, the beam energy is enlarged and has been defined to still keep the At211/At210 ration below 1E-4 at EOB. This results to a lower production yield than the theoretical one (around 10 MBq/µA.h).

After irradiation, the target is transferred into a glove box to perform a dry-distillation of the target. One challenge was to adapt the process proposed by Lindegren (2001) to our large targets (14 cm^2). By increasing the size of all components, the effects of all parameters (argon flow rate, capillary length, temperature of the cryotrap, …) were more sensitive. They have been optimized and a recovery yield of about 85±5% is obtained on routine. After the dry distillation process, the capillary can be washed with any solvent. In our case we choose $CHCl_3$ as regard of its radiolysis resistance and the possibility to evaporate it to dryness without activity losses. This allows to recover astatine-211 in any solvent whitin a very small volume (few µL).

The quality control of the final solution is performed with HPGe detector and a procedure has been developed allowing determining immediately after production the At-210/At-211 ratio with a high reliability.

At the Arronax facility, we are producing Astatine-211 every two weeks. Irradiation stands for 3 hours and the whole purification process (from target recovery to transport ready) takes 1.5 hour leading to the production of 400MBq at the calibration time. The next step is to automate the process in our radiopharmacy to prepare a clinical trial with this isotope.

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The Production of ^{211}At at Fukushima Medical University

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Background: Advanced Clinical Research Center was established as a part of reconstruction plan in Fukushima Medical University after the earthquake in 2011, and it has been operated since June 2016. Our center owns two types of cyclotrons; a small HM-20SV (Sumitomo Heavy Industries, Ltd.(SHI)), for producing clinically used PET radiopharmaceuticals, and the other MP-30 (p: 15-30 MeV, d: 8-15 MeV, α: 32 MeV, SHI) for producing radionuclides including ^{211}At for targeted α-particle therapy (TAT). ^{211}At has many potential advantages for TAT with its half-life ($t_{1/2}$ = 7.2 hr), high yield of α-particle (100%), and the nature of halogen. Our center would be one of the only five supply bases that can currently produce astatine in Japan. Here we report on experimental production for stable supply of ^{211}At using MP-30 Cyclotron.
Method: ^{211}At was produced by irradiation of natural bismuth (^{209}Bi) metal targets following the nuclear reaction: ^{209}Bi(α, 2n)^{211}At using an MP-30. Our cyclotron has a vertical irradiation system in order to irradiate low melting point materials without processing and also powders such as bismuth. Therefore, we applied a method for ^{211}At production reported by Nagatsu et al., using the encapsulated target coupled with an external vertical beam. We modified details of the method according to the specific features of our cyclotron systems as follows. High-purity ^{209}Bi shots (99.9999%, 6-7 g) were used as the target with no further purification or solidification. The target vessel has V-shaped bottom made of Nb. Bi target in the vessel is covered with an aluminum foil (70 μm, 99%) and sealed with a clipper. The target was irradiated for 8 h with alpha particles initially accelerated at 32 MeV. Beam current used was 20 μA. After irradiation, Bi of the target and Al of the degrader were dissolved with concentrated nitric acid. The production amount of ^{211}At was measured with a germanium semiconductor detector and radioisotope calibrator (^{64}Cu setting).
Results and Discussion: As a result, ^{211}At of *ca*.1.58 GBq (EOB) was obtained. ^{210}At disintegrates into ^{210}Po with strong toxicity. If ^{211}At is used for medical purposes, it is desirable that ^{210}At does not contaminate the manufactured At solution. It was confirmed that ^{210}At was not formed in HPGe. The optimization of irradiation conditions and refining conditions are underway in our facility.

The ultimate ^{225}Ac---->^{213}Bi generator

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Since 1990 there are about 15 international patents covering the major issues involved with realizing the chemistry and the equipment requirements to enable α-particle radioimmunotherapy on a regular basis in hospitals. It is striking that these patents, without exception, fail to address two different aspects needed to enable two requirements for successful α-particle radioimmunotherapy to beat, for example, various types of tumors and their metastases.

One is to ensure that the drug after intravascular administration is distributed homogeneously over the population of tumor cells without needlessly overdosing the drug, in particular in cases of high numbers of antigenic sites on the membrane surface of the tumor cells. The way to cope with this problem is to dilute the drug with the correct amount of non-active targeting subtance (that is: the drug minus the isotope coupled onto it) to ensure a deposit of the amount of active drug molecules (in the order of maximal 10) to kill the cell nucleus and bind non-active targeting substance on essentially all the other active target sites.

The other is to make use of this dilution of the targeting agent to ensure that the confrontation of the ^{213}Bi will result in a highly accelerated (quasi instantaneous) binding of the ^{213}Bi on the high overdose of targeting agent and that, in practise, the binding reaction can be performed in a continuous mode. That will minimize the decay of ^{213}Bi during its concentration by decay of ^{225}Ac and enhance its potential to be used therapeutically in comparison with any step-wise creation-utilization scheme used today.

Continuous operation of a ^{225}Ac---->^{213}Bi generator instead of the usual step-wise operation can reduce the need for ^{225}Ac per unit of ^{213}Bi with a factor of ≈ 5, thereby allowing for a savings in isotope costs of € 20,000 per patient treated, resulting in a total treatment cost for a patient of ≈ € 25,000. This would mean the difference in costs needed to make α-particle radioimmunotherapy economically attractive.

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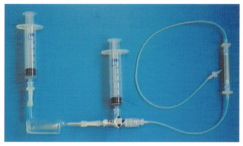

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