Committee Charges for 2008-2009:
1. To develop and publish standardized methods for calculating internal radiation doses from diagnostic and therapeutic radiopharmaceuticals
2. To compile and disseminate supporting data needed to implement such methods, including radionuclide decay properties and emissions, energy absorbed fractions, and anatomic models
3. To develop and publish software tools that implement MIRD calculations and models
4. To assess and publish dosimetry for new radiopharmaceuticals
5. To develop methods for correlating dose with response to evaluate the relevance of factors, in addition to absorbed dose, that influence biological response from internal emitters
6. To address other critical and timely dosimetry issues that may impact the practice of nuclear medicine

Progress of Charge/Objectives/Goals since report of January 2009 (attached):
1. MIRD Pamphlet No. 21 – A generalized schema for radiopharmaceutical dosimetry: standardization of nomenclature, J Nucl Med. 2009 Mar;50(3):477-84 has been published. This report reconciles the MIRD and ICRP system of equations for internal dosimetry.

MIRD Dose Estimate Report No. 20: Radiation absorbed Dose Estimates for $^{111}$In- and $^{90}$Y-Ibritumomab Tiuxetan (Zevalin™). J Nucl Med 2009 Apr;50(4):644-52 for the first FDA-approved targeted radiotherapeutic combination, $^{111}$In- and $^{90}$Y-Ibritumomab Tiuxetan (Zevalin™). This report provides an independent and authoritative estimation of the dosimetry associated with this therapeutic agent.

2. MIRD Radionuclide Data and Decay Schemes (description and sales figures provided in Jan ’09 report)

3. The MIRD Committee has met with the two interns and projects for each have been assigned. Ann McAnn (formerly Larkin) is developing an internet-based teaching module to illustrate and provide a hands-on demonstration of Pamphlet 20 results. Recognizing that some of the concepts related to biological effects are well established in external radiotherapy but less so in nuclear medicine therapy, the Committee felt it important to introduce these concepts in a manner that would allow individuals to try out “what if” scenarios as a step to understanding how radiobiological modeling can impact therapeutic nuclear medicine.

The Committee hopes to generate such modules for selected future pamphlets as a way of teaching and disseminating the content of these pamphlets. We hope to include such modules on the SNM web site and possibly as stand-alone teaching modules that may be marketed at the Society’s discretion. This project has just been initiated and we do not have a time-line as to likely completion date – this will depend upon funds available and the time available to the intern for this project. To allow completion of these projects, the internship duration will be extended beyond two years.

The second intern, Ande Bao, will be working on the dosimetry of $^{177}$Lu-EDTMP for bone pain palliation. The IAEA currently has a program promoting this radionuclide for bone pain palliation in developing countries and there may be some support for this project from the IAEA. Dr. Zanzonico was asked by IAEA to write imaging and dosimetry protocols for the radiopharmaceutical.

4. The abridged version of MIRD Pamphlet No. 22 - Radiobiology and Dosimetry of Alpha-Particle Emitters for Targeted Radionuclide Therapy, has been accepted for publication by JNM. The Committee is planning on making the entire version available via the SNM website and possibly also preparing a monograph of the entire document for sale by SNM.

6. Working with the MIRD Committee, Ted Treves has organized a CE session on pediatric nuclear medicine imaging for the Toronto ’09 SNM annual meeting. The Committee will continue to work with Dr. Treves to establish well-founded pediatric dosing guidelines.

**Pediatric Radiopharmaceutical Dosimetry Symposium - Part I**

**Pediatric Radiopharmaceutical Dosimetry Symposium - Part II**

Dr. Joseph Rajendran, Chairman of the Nuclear Oncology Council, working with MIRD has organized a joint Nuclear Oncology Council/MIRD CE Session - Patient-Specific Dosimetry for Systemic Radionuclide Therapy: Opportunities to Personalize Treatment to be held in Toronto.

**Patient-Specific Dosimetry for Systemic Radiotherapy: Opportunities for Personalizing Cancer Therapy**

The 3rd International Symposium on Radionuclide Therapy and Radiopharmaceutical Dosimetry (ISRTRD)/Alpha Symposium (http://isrtrd2009.labworks.org) has drawn a surprising large number of registrants; 359 as of Monday, 5/11/09. About one third of these are non-member registrations, suggesting that the program has brought in a large number of attendees that would not otherwise attend SNM. Registration will be closed at 389 because of room capacity issues. As noted in the Jan ’09 report, the purpose of the meeting is to establish a dialogue between physicians and physicists involved in dosimetry, accordingly, the format of the abstract sessions is to have an invited physician speaker launch each session, moderate the session, and then also participate in a discussion at the end of the session. All of the sessions have been designated CE sessions by SNM. The structure for the alpha portion of the program is different and conforms to the precedent set by prior alpha meetings. The meeting will start on Saturday with the alpha symposium portion of the meeting (which ends on Sunday) and continue through Wednesday. SNM has assigned CE credits to every session of this meeting. A handouts for the alpha portion of the program is attached. The rest of the program is summarized in a second attachment that we may also be handing out at the meeting.

—George Sgouros, PhD, Chair, SNM MIRD Committee
Program and Abstracts

6th Symposium on Alpha-Emitting Radionuclides in Therapy

In conjunction with the 3rd International Symposium on Radionuclide Therapy and Radiopharmaceutical Dosimetry

Hosted as part of the SNM 2009 Annual Meeting
June 13-17, 2009
Toronto, Canada

Sponsored by:
European Commission – Joint Research Centre – Institute for Transuranium Elements
US Department of Energy
Medical Internal Radiation Dose (MIRD) Committee
SNM – Advancing Molecular Imaging and Therapy
Program and Abstracts of the

6th Symposium on Alpha-Emitting Radionuclides in Therapy

Held in conjunction with the 3rd International Symposium on Radionuclide Therapy and Radiopharmaceutical Dosimetry (ISRTRD) at the SNM 2009 Annual Meeting

June 13-17, 2009, Toronto, Canada
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<tr>
<th>Time</th>
<th>Session</th>
<th>Speaker</th>
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<tr>
<td>8:20 AM</td>
<td><strong>Welcome &amp; Introduction</strong> George Sgouros, PhD</td>
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<td>8:30 AM</td>
<td><strong>Whys and Wherefores of Alpha Particle Therapy</strong> S. James Adelstein, MD, PhD</td>
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<td>9:00 AM</td>
<td><strong>Alpha-Particle Immunotherapy with Bi-213 and Ac-225-Antibodies</strong> David A. Scheinberg, MD, PhD</td>
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<td>9:30 AM</td>
<td><strong>Astatine-211 Labeled Targeted Radiotherapeutics: Prospects and Problems</strong> Michael R. Zalutsky, PhD</td>
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<td>10:00 AM</td>
<td><strong>Clinical Development of Bone-Seeking $^{213}$Ra (Alpharadin®): Current Status</strong> Oyvind S. Bruland, MD, PhD</td>
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<td>10:30 AM</td>
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<td>10:45 AM</td>
<td><strong>Bi-213-DOTA-Substance P for the therapy of malignant Glioma</strong> Flavio Forrer, MD, PhD</td>
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<td>11:15 AM</td>
<td><strong>Advances in Targeted Alpha Therapy for Metastatic Melanoma</strong> Barry Allen, PhD</td>
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<td>11:45 AM</td>
<td><strong>Astatine-211 for Ovarian Cancer</strong> Lars Jacobsson, PhD</td>
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<td>12:30 PM</td>
<td>Lunch</td>
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<td>1:30 PM</td>
<td><strong>Bismuth-213 in Radioimmunotherapy of Infectious Diseases</strong> Ekaterina A. Dadachova, PhD</td>
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<td>1:50 PM</td>
<td><strong>Radioimmunotherapy with Alpha-Emitters as Conditioning for Nonmyeloablative Hematopoietic Cell Transplantation</strong> Brenda Sandmaier, MD</td>
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<td><strong>Therapeutic Studies with $^{212}$Pb or Moby Dick</strong> Martin Brechbiel, Ph.D</td>
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<td>2:30 PM</td>
<td><strong>Locoroegional Bi-213-Radioimmunotherapy</strong> Reingard Senekowitsch-Schmidtke, MD, PhD</td>
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<td>3:00 PM</td>
<td><strong>Supply of Actinium-225 from Oak Ridge National Laboratory – an Experimental and Theoretical Perspective</strong> Saed Mirzadeh, PhD</td>
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<td>3:30 PM</td>
<td><strong>Production and Pre-Clinical Testing of Ac-225/Bi-213 and U-230/Th-226</strong> Alfred Morgenstern, PhD</td>
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<td>4:00 PM</td>
<td><strong>Alpha-Emitters for Oncology</strong> Nikolay A. Nerozin, PhD</td>
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<td>4:20 PM</td>
<td><strong>Advances in Dosimetry and Radiobiology of Alpha Particle Emitters</strong> Roger W. Howell, PhD</td>
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*Sponsored by NorthStar Medical Radioisotopes, LLC*
Summary
Techniques for calculating absorbed dose for cell, pre-clinical animal studies as well as for clinical trials will be reviewed and practical approaches for implementing alpha-particle dosimetry in a clinical setting will be discussed.

Educational Objectives
Upon completion of this activity, the participant will be able to:
1. Explain what microdosimetry is and why it is needed in some cases for alpha-particle emitters.
2. Explain how to perform alpha-particle dosimetry at the cell level and for pre-clinical animal studies.
3. Describe how the decay scheme of alpha-emitters can impact toxicity and influence the dosimetry calculations for clinical trials.

10:30 AM - 11:30 AM Alpha Dosimetry - In Vitro, Clinical & Pre-Clinical
George Sgouros, PhD; John Roeske, PhD; Roger W. Howell, PhD

11:30 AM - 12:00 PM Panel Discussion - Dosimetry/Radiobiology in Targeted Alpha Therapy - How Best to Implement Clinically?
George Sgouros, PhD; John Roeske, PhD; Roger W. Howell, PhD.
John L. Humm, PhD
Sunday, June 14, 2009

ISRTRD/ALPHA Session 1: Clinical & Pre-clinical Studies

Moderators: Roy H. Larsen, PhD; Martin Brechbiel, Ph.D

CME: 1.5 VOICE: 1.5
CPE: 1.5 [210-000-09-324-L04] CAMPEP: 1.5

No. 35 Clinical development of bone-seeking $^{223}$Ra (Alpharadin$^B$): Current status
12:45 PM Oyvind Bruland; 1. University of Oslo, Department of Oncology, The Norwegian Radium Hospital, Oslo, Norway.

No. 36 Radioimmunotherapy of human bladder cancer in a nude mouse model comparing $^{213}$Bi-213-anti-EGFR-MAb and Th-226-anti-EGFR-MAb
12:57 PM Birgit Pfost; Alfred Morgenstern; Christof Seidl; Frank Bruchertseifer; Michael Autenrieth; Christos Apostolidis; Kamel Abbas; Reingard Senekowitsch-Schmidtke; 1. Dept. Nuclear Medicine, Technische Universitaet Muenchen, Munich, Germany; 2. EC, JRC, Inst. Transuranium Elements, Karlsruhe, Germany; 3. Dept. Urology, Technische Universitaet Muenchen, Munich, Germany; 4. EC, JRC, Inst. Health Consumer Protect., Ispra, Italy.

No. 37 Determination of Kidney Dose Distributions Using Autoradiography and HpGe Spectroscopy of Kidney After Injection of $^{225}$Ac-HuM195
1:09 PM Jazmin Schwartz; J, Jaspreet ; S. Ruan; S.M. Larson; D. Scheinberg; J.L. Humm; 1. MSKCC, NY, NY, United States; 2. Pfizer, New London, CT, United States.

No. 38 An alpha-Particle Emitting Radiopeptide ($^{213}$Bi-DOTA-PESIN) for therapy of Prostate Cancer
1:21 PM Damian Wild; Michael Frischknecht; Alfred Morgenstern; Frank Bruchertseifer; Julie Boisclair; Anne Provencher-Bolliger; Helmut Maecke; 1. University Hospital Basel, Division of Radiological Chemistry, Basel, Switzerland; 2. Institute of Transuranium Elements, Karlsruhe, Germany; 3. Novartis Pharma, SP&A/Investigative and Regulatory Pathology, Basel, Switzerland.

No. 39 Preliminary studies using $^{211}$At-Labeled Anti-PSMA MAb for treatment of metastatic prostate cancer in a mouse model
1:33 PM D. Scott Wilbur; Donald Hamlin; Holly Nguyen; Hirohisa Nakamae; Ming-Kuan Chyan; Robert Vessella; Brenda Sandmaier; 1. University of Washington, Department of Radiation Oncology, Seattle, WA, United States; 2. University of Washington, Department of Urology, Seattle, WA, United States; 3. Fred Hutchinson Cancer Research Center, Clinical Research Division, Seattle, WA, United States.

No. 40 An astatine-211 labeled PSMA inhibitor for targeted alpha-particle radiotherapy of prostate carcinoma
1:45 PM Ganesan Vaidyanathan; Ronnie Mease; Donna Affleck; Ying Chen; Philip Welsh; Marc Hens; Martin Pomper; Michael Zalutsky; 1. Duke University, Durham, NC, United States; 2. Johns Hopkins University, Baltimore, MD, United States.
Sunday, June 14, 2009

ISRTRD/ALPHA Session 2: Radiochemistry/Development Studies

Moderators: Michael R. Zalutsky, PhD, Reingard Senekowitsch-Schmidtke, MD, PhD

CME: 1.5  VOICE: 1.5
CPE: 1.5 [210-000-09-159-L04]  CAMPEP: 1.5

No. 97  4:15 PM  Assessment of long term radiotoxicity after treatment with the low dose rate α-particle emitting radioimmunoconjugate $^{227}$Th-rituximab Jostein Dahle; Thora Jonasdottir; Helen Heyerdahl; Jahn Martin Nesland; Jorgen Borrebaek; Anne Kristine Hjelmerud; Roy Larsen; 1. Norwegian Radium Hospital, Department of Radiation Biology, Oslo, Norway; 2. Norwegian School of Veterinary Science, Department of Companion Animal Clinical Sciences, Oslo, Norway; 3. Rikshospitalet University Hospital, Division of Pathology, Oslo, Norway; 4. Algeta ASA, Oslo, Norway.

No. 98  4:27 PM  Targeted therapy of breast cancer with low dose rate alpha-particle-emitting $^{227}$Th-trastuzumab Jostein Dahle; Cecilie Krogh; Nasir Abbas; Anne Kristine Hjelmerud; Jorgen Borrebaek; Aasmund Larsen; Roy Larsen; Oyvind Bruland; 1. Norwegian Radium Hospital, Department of Radiation Biology, Oslo, Norway; 2. Norwegian School of Veterinary Science, Department of Companion Animal Clinical Sciences, Oslo, Norway; 3. Rikshospitalet University Hospital, Division of Pathology, Oslo, Norway; 4. Algeta ASA, Oslo, Norway.

No. 99  4:39 PM  Isolation and Protein Labeling of At-211 from Irradiated Bismuth Targets using a Modified Wet Chemistry Approach D. Scott Wilbur; Donald Hamlin; Ming-Kuan Chyan; Brenda Sandmaier; 1. University of Washington, Department of Radiation Oncology, Seattle, WA, United States; 2. Fred Hutchinson Cancer Research Center, Clinical Research Division, Seattle, WA, United States.

No. 100  4:51 PM  Inorganic Nanoparticle Monoclonal Antibody Conjugates Saed Mirzadeh; Jonathan Woodward; Robert Standaert; Sheng Dai; Adam Rondinone; Stephen Kennel; 1. Oak Ridge National Laboratory, Nuclear Science and Technology Division, Oak Ridge, TN, United States; 2. ORNL, Chemical Sciences Division, TN, United States; 3. University of TN Graduate School of Medicine, Department of Medicine, Knoxville, TN, United States; 4. ORNL, Life Sciences Division, TN, United States.

No. 101  5:03 PM  Modeling biological response to nonuniform distributions of radioactivity in three dimensional tissues Roger Howell; Prasad Neti; 1. UMDNJ-New Jersey Medical School, Department of Radiology, Newark, NJ, United States.

No. 102  5:15 PM  Dosimetry for $^{223}$Ra and its daughters Cecilia Hindorf; Sarah Chittenden; Anne-Kirsti Aksnes; Val Lewington; Chris Parker; Glenn Flux; 1. ENVN, Imagerie Medicale, Nantes, France; 2. Royal Marsden Hospital, Physics, Nuclear Medicine, Urology, Sutton, United Kingdom; 3.Algeta ASA, Oslo, Norway.
No. 1818 **In vitro cytotoxicity of low dose-rate radioimmunotherapy by the α-emitting radioimmunoconjugate $^{227}$Th-rituximab** Jostein Dahle; Cecilie Krogh; Katrine Melhus; Jorgen Borrebaek; Roy Larsen; Yngve Kvinnslund; 1. Norwegian Radium Hospital, Department of Radiation Biology, Oslo, Norway; 2. Algeta ASA, Oslo, Norway; 3. Nordic Neurolabs, Bergen, Norway.

No. 1819 **Treatment of HER2-expressing breast cancer and ovarian cancer cells in vitro with low dose rate alpha-particle-emitting $^{227}$Th-trastuzumab** Cecilie Krogh; Hans Magnus Hopen; Jorgen Borrebaek; Aasmund Larsen; Roy Larsen; Jostein Dahle; 1. Norwegian Radium Hospital, Department of Radiation Biology, Oslo, Norway; 2. Algeta ASA, Oslo, Norway.

No. 1820 **Treatment of mice with SKBR-3 breast cancer or SKOV-3 ovarian cancer xenografts with low dose rate alpha-particle-emitting $^{227}$Th-trastuzumab** Nasir Abbas; Oyvind Bruland; Anne Hjelmerud; Jorgen Borrebaek; Aasmund Larsen; Roy Larsen; Jostein Dahle; 1. Norwegian Radium Hospital, Radiation Biology, Oslo, Norway; 2. Rikshospitalet University Hospital, Department of Oncology, Oslo, Norway; 3. Algeta ASA, Oslo, Norway.

No. 1821 **An improved labeling method for Thorium-227 labeled antibodies for targeted alpha therapy** Jorgen Borrebaek; Aasmund Larsen; Ellen Brevik; Jostein Dahle; Nadir Abbas; Anne Kristine Hjelmerud; 1. Algeta ASA, Oslo, Norway; 2. Institute for Cancer Research, Department of Radiation Biology, Oslo, Norway.

No. 1822 **Matched Pair Imaging for Peptide Targeted Melanoma Alpha-Particle Therapy** Xiuli Zhang; Yubin Miao; Said Figueroa; Darrell Fisher; Timothy Hoffman; Herbert Moore; Richard Testa; Thomas Quinn; 1. University of Missouri, Columbia, MO, United States; 2. Truman Veterans Administration Hospital, Columbia, MO, United States; 3. Pacific Northwest National Laboratory, Richland, WA, United States; 4. AlphaMed Inc, Acton, MA, United States.

No. 1823 **Alternate Methods for Production of Ac-225** James Harvey; George Messina; Glenn Isensee; Phil Horwitz; Dan McAlister; 1. NorthStar Medical Radioisotopes, LLC, Madison, WI, United States; 2. PG Research Foundation, Darien, IL, United States.

No. 1824 **Automated Radionuclide Separation System (ARS2) for Producing Short-Lived Daughter Radioisotopes for Nuclear Medicine** James Harvey; George Messina; Glenn Isensee; Phil Horwitz; Dan McAlister; 1. NorthStar Medical Radioisotopes, LLC, Madison, WI, United States; 2. PG Research Foundation, Darien, IL, United States.

No. 1825 **Quantitative $^{18}$F-fluoride PET to monitor response in skeletal metastases from prostate cancer treated with AlpharadinTM ($^{223}$Ra-chloride)** Gary Cook; Glenn Flux; Chris Parker; Sue Chua; Anne-Kirsti Aksnes; Val Lewington; 1. Royal Marsden NHS Foundation Trust, Sutton, United Kingdom; 2. Algeta, Oslo, Norway; 3. .
ABSTRACTS

Whys and Wherefores of Alpha Particle Therapy

S. James Adelstein
Harvard Medical School, Boston MA, USA

Since the 1920s, the hope has been expressed that “heavy elements emitting radiations of molecular dimensions” could be used for cancer therapy. There are a number of reasons for believing that alpha-particle emitting radionuclides would serve this purpose.

Alpha-particles create a high ionization density in biological material. They produce severe damage to DNA, there is little DNA repair, and few cellular traversals are required to sterilize cells. Alpha-particles have a short-range (50-100μm) relative to most beta-particle emitters and a cross-fire confined to nearby cells or clusters of malignant ones. The biological response to alpha-particles is not oxygen dependent and, thus, less affected by non-uniformities in tumor oxygenation. A consistent bystander effect has been demonstrated for alpha-particles, which could amplify their effect by damaging cells that have not been hit directly.

The utility of alpha-particles has been demonstrated in cell cultures and in animal models, thus verifying their promise for treating cancer. On the other hand, these particles can also inflict severe damage to normal tissues. Avoiding this consequence, by the design of highly specific carriers, remains a challenge to their clinical utilization.
To enhance the potency of native antibodies and avoid nonspecific cytotoxicity seen with β-emitting radio-immunoconjugates, the α-emitting radiometal $^{213}$Bi and the alpha particle isotope generator Ac-225 were conjugated to various antibodies with bifunctional chelates and tested in different cancer systems in models and in patients. Preclinical data showed activity in disseminated leukemia models, solid tumor xenografts, vascular targeting models and in IP and IT applications. Ac-225 was 1000 times more potent and more toxic than B-213. The feasibility, safety, and antileukemic activity of $^{213}$Bi-HuM195 alone were shown in a phase I trial. Because of the short-range (50-80 µm) and high linear energy transfer (8400 keV) of α particles, radioimmunotherapy with $^{213}$Bi is ideally suited for the treatment of residual disease. To determine the effects of $^{213}$Bi-HuM195 against cytoreduced disease, we treated 31 patients with cytarabine 200 mg/m²/day for 5 days followed by $^{213}$Bi-HuM195 in a phase I/II trial. During the phase I portion of the study, cohorts of 3-6 patients were treated with 18.5, 27.75, 37, and 46.25 MBq/kg. Prolonged myelosuppression with grade 4 leukopenia > 35 days was the most common dose-limiting toxicity. The maximum tolerated dose (MTD) was 37 MBq/kg. Extramedullary toxicity was primarily limited to ≤ grade 2 events, including infusion-related reactions; however, grade 3/4 liver function abnormalities were seen in four patients. Significant reductions in marrow blasts were seen at all dose levels, and clinical responses were observed in 6 of the 25 patients who received doses of at least 37 MBq/kg (2 CR, 2 CRp, 2 PR). Pharmacokinetic and biodistribution studies suggested that saturation of all available CD33 sites by $^{213}$Bi-HuM195 was possible after cytoreduction with cytarabine. Single doses of Ac-225-HuM195 has now been used in 11 patients In a phase 1 dose-escalation trial that is ongoing. 3 patients each have been treated at 0.5, 1.0 and 2.0 uCi per kg and 2 patients at 4uCi per kg. No acute toxicities were seen. One of 2 patients evaluable for neutropenia developed an ANC <500/µL. Grade 4 thrombocytopenia was seen in both patients who were evaluable. Five patients had neutropenic fever and 1 patient died of infectious complications. One patient with a prior history of fungal hepatitis developed a grade 3 elevation in alkaline phosphate lasting 6 days after receiving 1 µCi/kg of $^{225}$Ac-HuM195. No other grade 3-4 extramedullary toxicities were observed. No evidence of radiation nephritis has been seen, with follow-up to 10 months. Antileukemic effects included elimination of peripheral blood blasts in 6 of 10 evaluable patients and dose-related reductions of >33% of bone marrow blasts in 5 of 9 evaluable patients at 4 weeks following treatment. One patient had 3% bone marrow blasts after therapy. This trial is ongoing.
Astatine-211-Labeled Targeted Radiotherapeutics: Problems and Prospects

Michael R. Zalutsky
Departments of Radiology, Radiation Oncology and Biomedical Engineering, Duke University, Durham, NC, USA

The heavy halogen $^{211}$At was first proposed for use in $\alpha$-particle targeted radiotherapy more than 30 years ago and continues to be one of the most promising radionuclides for this purpose. Although its 7.2-h half life is not ideal for intravenously administered whole antibodies, it is compatible with the pharmacokinetics of antibody fragments, peptides, aptamers and organic molecules. Its diverse chemistry allows its incorporation into a wide array of targeting vehicles, relying on its chemical similarity to iodine to provide a useful point of departure. On the other hand, the relatively low carbon-astatine bond strength is challenging. In common with the other $\alpha$-emitters being discussed at this symposium, lack of reliable availability is one of the biggest hurdles in the use of $^{211}$At for targeted radiotherapy. However, in the case of $^{211}$At, it is not a question of production cost or availability of target material, because $^{211}$At can be produced in reasonable yield from natural bismuth targets. Rather, the difficulty is the lack of cyclotrons equipped with the medium energy $\alpha$-particle beams required for its production. If the infrastructure for producing $^{211}$At is to be improved to the stage where $^{211}$At-labeled radiopharmaceuticals can have a meaningful impact, several developments must occur. First, the ability to produce clinically relevant levels of $^{211}$At that can be shipped to remote locations in chemically tractable form must be demonstrated. Approaches under consideration include compensating for radiolysis-mediated effects and the consideration of alternative chemistries. Second, strategies for compensating for heterogeneities in dose deposition must be developed, hopefully in a way that is compatible with approval for human use. And third, it is essential that more clinical trials be performed with $^{211}$At-labeled therapeutics, particularly in settings of minimum residual disease where the radiobiological advantages of $\alpha$-particles can be best exploited. Our own efforts in that regard will be to acquire the remaining data needed to initiate clinical evaluation of meta-$^{211}$Atastatobenzylguanidine and $^{211}$At-labeled trastuzumab in patients with neuroblastoma and breast cancer neoplastic meningitis, respectively. In conclusion, the major barrier in moving $^{211}$At-labeled targeted radiotherapeutics from appealing concept to practical treatment is the limited availability of the radionuclide. Hopefully, advances in radiochemistry and the results clinical trials at multiple institutions will provide a compelling rationale for the construction of more cyclotrons capable of producing $^{211}$At.
Clinical Development of Bone-Seeking $^{223}$Ra (Alpharadin$^R$): Current Status

Øyvind S. Bruland
Department of Oncology. The Norwegian Radium Hospital, University of Oslo, N-0310 Oslo, Norway.

The bone-seeking, alpha-particle emitting radiopharmaceutical Alpharadin$^R$ – $^{223}$RaCl$_2$ ($t_{1/2} = 11.4$ days) is under clinical development as a novel treatment for skeletal metastases from breast and prostate cancer. This presentation will address selected aspects of the pre-clinical research and review the current status of clinical trials in patients with skeletal metastases from hormone refractory prostate cancer (HRPC).

Phase-1 studies (1,2) showed that toxicity is generally low, the treatment seems therapeutically beneficial for the patients and that repeated dosing is feasible. In a randomized phase 2 trial involving 64 patients with HRPC cancer and painful skeletal metastases who received 4 monthly injections of $^{223}$Ra or saline as an adjuvant to external beam radiotherapy, a 4.5 months difference in survival was observed (3). Median overall survival was 46.4 weeks in the placebo group and 65.3 weeks in the Alpharadin group (HR 2.103, $p=0.017$). 30% of the patients were alive at 24 months in the latter group compared to 13% that received placebo. A phase-3 study is currently recruiting, and other phase-1 and 2 trials are completed and under analysis. For a complete outline of the clinical program – see www.clinicaltrial.gov/ct2/results?term=radium-223

Bi-213-DOTA-Substance P for the therapy of malignant Glioma

Flavio Forrer
Nuclear Medicine,
University Hospital Basel, Switzerland

Critically located gliomas of the brain represent a therapeutically challenging subgroup of brain intrinsic neoplasms. Therapeutic standard recommendations such as radical resection followed by combined radiochemotherapy often cannot be applied in the treatment of these tumors. A radical therapeutic approach and the preservation of functions are two contrary goals in these cases. The feasibility and low toxicity of targeting malignant gliomas with local injection of beta-radiation emitting ${}^{90}$Yttrium-DOTA (Thi$^8$,Met(O$_2$)$_{11}$)substance P has successfully been shown by our group in an adjuvant as well as in a neoadjuvant setting [1,2]. However, in critically located tumors, the mean tissue range of 5 mm of Yttrium-90 may lead to serious damage of adjacent, functionally critical areas of the brain. In contrast, the alpha-radiation emitting radionuclide Bismuth-213 with its mean tissue range of 81 µm may have a more favourable toxicity profile. Therefore we evaluated local radiopeptide therapy using $[^{213}$Bi]-DOTA (Thi$^8$,Met(O$_2$)$_{11}$) substance P in patients with critically located high and low grade gliomas as the primary therapeutic modality.

In our pilot study, we included 5 patients with critically located gliomas without previous treatment. Two patients had a glioblastoma multiforme (GBM, WHO grade IV), one patient suffered from an anaplastic astrocytoma (WHO grade III) and two patients had a WHO grade II astrocytoma. After implantation of intratumoral catheter systems, local injections with Indium-111 Substance P were performed in order to prove specific binding of the radiopharmaceutical in the tumor and to estimate the radiation absorbed dose in the tumor. Afterwards totally 30 to 60 mCi Bismuth-213 labelled substance P was injected over the same catheter systems. Besides feasibility and toxicity, further endpoints of the study were the functional outcome and progression free survival of the patients.

Targeted radiopeptide therapy using $[^{213}$Bi]-DOTA (Thi$^8$,Met(O$_2$)$_{11}$) substance P was feasible and well tolerated by all patients. Absorbed dose estimations were available in 4 patients. The calculated absorbed dose in the tumor ranged from 44 to 584 Gy/GBq. No additional neurological deficit was observed. Repetitive MR-imaging was suggestive of radiation-induced necrosis and demarcation of the tumors, which was validated by subsequent resection.

Targeted local radiotherapy using $[^{213}$Bi]-DOTA (Thi$^8$,Met(O$_2$)$_{11}$) substance P may represent an innovative and effective treatment strategy for critically located malignant gliomas. Patients with smaller and symptomatic tumors may be the subgroup with the highest benefit; primarily non-operable gliomas may become resectable in the course of this treatment, thereby possibly improving the prognosis.

References

Advances in Targeted Alpha Therapy for Metastatic Melanoma

Barry J Allen
Centre for Experimental Radiation Oncology,
St George Hospital Cancer Care Centre
Gray St, Kogarah 2217, NSW
Australia

Targeted alpha therapy (TAT) is a developing experimental cancer therapy based on the cytotoxic properties of the high linear energy transfer (~ 100 keV/µm) and low range (20-80 µm) of alpha particles. Monoclonal antibodies are labeled with alpha emitting radioisotopes to form the alpha-immunoconjugate (AIC), which can be highly lethal to targeted cancer cells but spare normal tissue.

Our research and development program for metastatic melanoma has passed from test tube to bedside. Phase 1 clinical trials have been completed for intralesional therapy and are well advanced for systemic therapy of metastatic melanoma. A biological dosimeter has been developed based on the measurement of micronuclei in lymphocytes.

The melanoma systemic trial demonstrated that alpha therapy could regress solid tumours. This effect was ascribed to a process called Tumour Anti-Vascular Alpha Therapy (TAVAT), which has the potential to change outcome in end-stage disease. Intravenous injections of up to 25 mCi of the 213Bi-9.2.27 alpha immunoconjugate have not caused any adverse events of any level. However, promising therapeutic responses have been observed in the 38 patients treated so far, being 10% partial response, 40% stable disease, and 10% long term survival at 2-5 years.

References
This review will cover the efforts in Gothenburg, “from bench to bedside,” to evaluate the potential of $^{211}$At radioimmunotherapy in the treatment of small tumor deposits of ovarian cancer in the abdominal cavity.

The lifetime risk of ovarian cancer is 1%–2% in European and American women. Despite seemingly successful surgery followed by chemotherapy, most patients will relapse, most frequently in the abdominal cavity, and succumb to the disease. Despite newer systemic chemotherapy regimens, the outcome has not improved over the past decade. Radioimmunotherapy with various $\beta$-emitters has displayed promising results, though an international Phase III trial of $^{90}$Y-labeled antibody showed no improvement in time to relapse or survival. This disappointing result might be explained by the long range of $\beta$-emitters, which results in poor irradiation of tumors less than a few millimeters in size. In treating small tumors, the short range and high LET of $\alpha$-emitters such as $^{211}$At offer a significant advantage by more effectively irradiating targeted small cell clusters.

For about 10 years the PET and Cyclotron Center in Copenhagen has regularly delivered $^{211}$At to the research group in Gothenburg. Astatine is isolated from the irradiated target by dry distillation, a quick and effective process done in a few minutes with 80% recovery. The $^{211}$At-labelling method, recently improved, now gives stable radiochemical yields of 70%–80%, even at high activities, with the antibody conjugate’s tumor-cell binding ability essentially preserved. The activity of an antibody batch of 0.1–0.5 mg is approximately 300–500 MBq, sufficient for extensive animal experiments or for treatment of a single patient.

The therapeutic effect has been studied in a series of experiments in vitro and in nude mice with ip growth of microscopic ovarian cancer tumors. A number of parameters related to the injected antibody conjugate and stage of tumor growth have been investigated. Studies of toxic effects for bone-marrow, kidneys, and the peritoneal membrane indicate that microscopic tumors smaller than approximately 0.1 mm are likely sterilized without any serious organ toxicity. Tumor cure probability decreases with increasing tumor size.

Dosimetry, based on biokinetic modeling and a Monte Carlo program, indicates that an absorbed dose of approximately 20 Gy is needed for tumor eradication in nude mice. The tolerance level (mean absorbed dose) is estimated to be approximately 0.5 Gy for bone-marrow and 10 Gy for kidneys. For the peritoneal membrane preliminary results indicate a tolerance level of more than 25 Gy. Comparisons with low-LET $^{60}$Co irradiation for tumor-growth inhibition and bone-marrow toxicity both resulted in RBE $\approx 5$.

Based on the promising results of the animal studies, a clinical Phase I study of 9 patients was started in 2005. Thirty to 120 MBq of $^{211}$At-MX35 F(ab′)$_2$ was administered i.p. in 1.1–2.2 L of fluid (Extraneal). Dosimetric calculations were mainly based on the $^{211}$At activity in samples of peritoneal fluid, blood, and urine 0–48 h post injection. Gamma camera imaging did not reveal uptake in any major organs except the thyroid. The thyroid uptake was reduced by potassium perchlorate or potassium iodide in the last four patients. No adverse effects of the treatment were observed subjectively or in the laboratory parameters. In conclusion, therapeutic absorbed doses of $^{211}$At in microscopic tumor clusters in the abdominal cavity are achievable without significant toxicity.
Bismuth-213 in Radioimmunotherapy of Infectious Diseases

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There is a clear need for new approaches to therapy of infectious diseases due to increasing number of immunosuppressed individuals in whom antimicrobial therapies are not effective; growing prevalence of diseases caused by highly resistant microorganisms, some of which are not susceptible to any currently available antimicrobial agents; and a dearth of new antimicrobial drugs in the development pipeline. To further complicate matters new microbes are regularly identified and for many there are no available therapies and there is the specter of biological weapons. Several years ago we performed proof-of-principle experiments in the murine Cryptococcus neoformans infection aimed at demonstrating the usefulness of radioimmunotherapy (RIT) in treatment of infection. One of the therapeutic radionuclides investigated for RIT of infection was $^{213}$Bi which was selected for two main reasons: powerful alpha-emission which would allow for the destruction of radiation-resistant microbial cells and short physical half-life which would allow for the delivery of cytocidal radiation doses within the time-span which matches the doubling time of microorganisms (20 – 120 min for bacteria and fungi, respectively). Since then we have extended the applications of $^{213}$Bi-labeled antibodies to RIT of other fungal (H. capsulatum), bacterial (S. pneumoniae and B. anthracis) and viral (HIV-1) infections. Antibody-targeted alpha radiation was also effective against fungal biofilms. We investigated the choice of antibodies with different isotypes or size as delivery vehicles for $^{213}$Bi, the mechanisms of action of RIT on microbes and the safety issues of RIT treatments. Most recently we have demonstrated by performing repeated infection of mice with RIT-treated C. neoformans that RIT did not produce radiation resistant microbial cells and can be administered several times if needed for complete elimination of microbial load. RIT also proved to be more efficient in killing C. neoformans cells in vitro and in vivo than conventionally used anti-fungal drug Amphotericin B. RIT with $^{213}$Bi-armed antibodies evolves into the efficient anti-infectious diseases modality.
Radioimmunotherapy with Alpha-Emitters as Conditioning for Nonmyeloablative Hematopoietic Cell Transplantation

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Allogeneic hematopoietic cell transplantation (HCT) is an important treatment modality for patients with both malignant and nonmalignant hematologic disorders. However, its utility in patients has been limited by complications related to the toxicity of the conditioning regimens used. One strategy to decrease toxicity of conditioning regimens for HCT has been the use of radiation targeted systemically with radionuclide-labeled monoclonal antibodies (MAb). While MAb labeled with β-emitting radionuclides have shown some efficacy, a more promising alternative is the use of α-particle emitters. In contrast to β-emitting radionuclides, the high linear energy transfer and short particle range of α-particles makes them particularly attractive for killing hematopoietic cells in the blood and marrow. We initially investigated bismuth-213 (213Bi)-labeled anti-CD45 MAb to replace total body irradiation (TBI) as nonmyeloablative conditioning for HCT. In other studies we used an anti-TCRαβ MAb to selectively target T cells. These approaches for conditioning successfully allowed sustained engraftment of major histocompatibility (MHC)-matched allogeneic marrow in the canine model. In the MHC-haploidentical model, the CD45 MAb coupled to 213Bi allowed only transient donor engraftment in the majority of the animals, probably due to surviving host NK cells. These results, along with the fact that 213Bi currently has a very high cost and limited availability, led to a decision to investigate another alpha-emitting radionuclide, astatine-211 (211At), for this application. We hypothesized that the longer half-life of 211At (t1/2 = 7.2 h vs. 46 min for 213Bi) might allow more time for the labeled MAb to target and kill T and NK cells. Such a result might provide a more durable donor engraftment after HCT with MHC-haploidentical donors. As an initial step in the transition to 211At, we compared 211At and 213Bi on the same MAb for their ability to target hematopoietic cells in the mouse model. In the experiments, a rat anti-murine CD45 MAb was conjugated with the appropriate labeling moiety and was labeled with either 213Bi- or 211At. Groups of mice were evaluated for their myelosuppression and non-hematological toxicity after receiving varying quantities of radioactivity (2, 10, 20 or 50 μCi) on various quantities (2, 10 or 40 μg) of MAb. Biodistribution studies showed that the spleen contained the highest concentration of radioactivity irrespective of the radionuclide used. However, the highest spleen concentrations were observed for 211At-labeled MAb. It seems likely that the higher spleen concentrations were due to the longer half-life of 211At, which could permit better localization of isotope before decay. At the highest dose given of 213Bi, severe but transient hepatic toxicity was noted. However, 211At-labeled MAb did not show hepatic toxicity. No renal toxicity was observed in either 213Bi or 211At groups. All mice injected with 20 or 50 μCi 211At, but none with the same quantities of 213Bi, had lethal myeloablation. Calculations estimated that the radiation absorbed doses per unit administered activity (cGy/μCi) to the spleen were 18 to 25 times the 213Bi dose when 211At was used. These data suggest that smaller quantities of 211At-labeled anti-CD45 antibody are sufficient to achieve myelosuppression and myeloablation with less non-hematological toxicity compared with 213Bi labeled MAb. Currently, toxicity studies are being carried out in the canine model.
Therapeutic Studies with $^{212}\text{Pb}$, or Moby Dick.

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The use of targeted $\alpha$-particle radiation therapy continues to remain an attractive therapeutic modality for the eradication of residual or metastatic disease. The fundamental physical properties of the applicable radionuclides, $^{212}\text{Bi}$, $^{213}\text{Bi}$, $^{212}\text{Pb}$, $^{211}\text{At}$, $^{225}\text{Ac}$, i.e. high-LET combined with short path length emissions provide both advantages and limitations to their range of use. Each is also complicated with physical properties that involve variables such as short (or long) half-live, limited availability, limited production, high cost, decay product daughters, and other properties. Our lab has explored the use of all in various arenas and we currently focus on the use of $^{212}\text{Pb}$ targeted by the monoclonal antibodies trastuzumab, cetuximab, and panitumumab which provide delivery to HER2 and EGFR, respectively.

Studies from this laboratory previously demonstrated the efficacy of $^{213}\text{Bi}$ or $^{212}\text{Pb}$-trastuzumab for treatment of disseminated peritoneal disease establishing maximum effective doses for $^{213}\text{Bi}$ (500 $\mu$Ci) and $^{212}\text{Pb}$ (10 $\mu$Ci) in an i.p. disseminated tumor model (LS-174T). Those investigations have been extended to develop multi-modality treatment regimens, i.e., combining chemotherapeutics with targeted $\alpha$-particle radiation therapy. Gemcitabine (GEM), taxol and carboplatin have all been evaluated at various stages for their ability to potentiate targeted $\alpha$-particle radiation therapy in both single and multi-dosing regimens. For example, 2 cycles of $^{212}\text{Pb}$-trastuzumab with a GEM given 24 hr prior to and 1 week after targeted $\alpha$-particle radiation therapy with that component being administered on a 3 week interval provided the greatest benefit. Additionally, studies have been executed to empirically define order of administration of the components of these regimens with regard to the nature of the radionuclide. These studies will be presented in perspective to their $^{213}\text{Bi}$ counterparts, where possible, along with the results of those completed and ongoing studies targeting EGFR.

Call me Ishmael.


Locoregional Bi-213-Radioimmunotherapy
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The poor prognosis of cancer with early tumor cell dissemination into the peritoneal cavity as observed in gastric, colon and ovarian cancer can be attributed to insufficient passage of systemically applied drugs to intraperitoneally located tumor cells. The short range of α-emitters coupled to an appropriate carrier targeting tumor specific structures makes them powerful tools particularly for elimination of intraperitoneally disseminated single tumor cells or small tumor cell clusters especially after locoregional application.

We have established a model for intraperitoneally disseminated gastric cancer using human HSC45-M2 gastric cancer cells expressing mutant d9-E-cadherin that mimics the clinical situation in human gastric cancer as to intraperitoneal tumor spread. At 24 h after cell inoculation, tumor cells are still in the peritoneal cavity as single cells or small tumor cell clusters. At day 8 after tumor cell inoculation macroscopic tumor nodules in the mesenterium and the peritoneal serous membrane mimic advanced micronodular peritoneal carcinomatosis. 45 min after i. p. injection of a monoclonal antibody specifically targeting d9-E-cadherin labelled with Bi-213 (Bi-213-d9MAb) 40% ID/g could be detected in tumor tissue. For optimization of radioimmunotherapy with Bi-213-d9MAb mice were injected intraperitoneally with 0.37, 1.85, 7.4 or 22.2 MBq. Controls were treated with saline or native d9MAb.

Mice injected with saline or native d9MAb at day 1 after tumor cell inoculation showed a median survival of 19 or 38 days, respectively. Application of 1.85 MBq was most efficient in terms of survival. At the end of the observation period (300 d) almost 90% of the mice were still alive and showed no signs of disease. Therapy at day 8 was less effective. Toxic side effects were negligible at therapeutically efficient Bi-213 activities. Reduction of leucocyte counts, induction of chromosomal aberrations in bone marrow cells and kidney toxicity were observed only after application of 22.2 MBq. The efficacy of Bi-213-d9MAb therapy could also be visualized non-invasively via bioluminescent imaging after i. p. inoculation of HSC45-M2 cells stably transfected with firefly luciferase.

We further established models of peritoneal carcinomatosis caused by ovarian carcinoma, pancreas- as well as colon carcinoma. For treatment of these tumors we used a DTPA-chelated dimer of the vascular tumor-homing peptide F3 forming stable complexes with $^{213}$Bi ($^{213}$Bi-DTPA-[F3]$_2$). $^{213}$Bi-DTPA-[F3]$_2$ binds nucleolin on the surface of tumor cells and is subsequently internalized into the nucleus. $^{213}$Bi-DTPA-[F3]$_2$ accumulated in intraperitoneally growing tumors with an uptake of 30% ID/g at 45 min after injection. Treatment studies revealed that $^{213}$Bi-DTPA-[F3]$_2$ blocks the growth of small intraperitoneal tumors and reduces the growth of advanced tumors. Consequently, the survival of mice was significantly increased by this treatment compared to mice treated with $^{213}$Bi-DTPA or PBS. As $^{213}$Bi-DTPA-[F3]$_2$ did not show toxic side effects it may also emerge as an effective tool in the treatment of peritoneal carcinomatosis.

We have also established an orthotopic human bladder carcinoma xenograft mouse model to evaluate therapeutic efficacy of intravesically instilled Bi-213-anti-EGFR-MAb. EJ28-luc cells (stably transfected with luciferase) were instilled in the bladder after gentle electrocautery. Tumor growth was monitored via non-invasive bioluminescence imaging. Controls had to be sacrificed due to progressive tumor burden between 20 and 69 days after cell instillation. Groups that underwent Bi-213-anti-EGFR-MAb therapy showed significantly longer survival ($p<0.01$): Following intravesical instillation of 0.925 MBq of the radioimmunoconjugate 1 h or 7 d after tumor cell inoculation mice survived longer than 300 d without any signs of tumor in 90% or 80% of cases, respectively. Therapeutic instillation of 0.37 MBq of Bi-213-anti-EGFR-MAb 1 h after cell instillation was as successful as application of 0.925 MBq. Intravesical therapy with 0.37 MBq 7 d after cell instillation was less effective than 0.925 MBq, only 50% survived longer than 300 d. Signs of nephrotoxicity could not be observed. Moreover, a striking 100% response rate of the tumor to α-radioimmunotherapy might provide urothelial carcinoma patients with a promising treatment option and should therefore be the aim of future translational research.
Supply of Actinium-225 from Oak Ridge National Laboratory – an Experimental and Theoretical Perspective

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Actinium-225 is currently obtained from the decay of 7430-y ²²⁹Th through the 15-d ²²⁵Ra intermediate radionuclide. A stock of purified ²²⁵Ra further provides a continuous but, of course, declining supply of ²²⁵Ac over a 45-days period. While the bulk of ²²⁵Ac, freshly separated from ²²⁹Th (up to ~60 mCi/batch), has been typically provided to the Memorial Sloan Kettering Cancer Center in support of AML human trial, smaller batches of ²²⁵Ac (20 mCi and less) from the decay of ²²⁵Ra have been supplied to a number of research institutes and universities throughout U.S., as well as Europe and Australia. The current ORNL ²²⁹Th supply is about 150 mCi, and is currently processed every 60-days. The initial purification of ²²⁹Th from waste material began at ORNL in 1995, and since then the separation process has been refined and expanded to a projected production level of ~700 mCi of ²²⁵Ac in 2009. A brief description of the chemical separation of ²²⁵Ra and ²²⁵Ac from ²²⁹Th, separation of ²²⁵Ac from ²²⁵Ra, and steps to improve the ²²⁵Ac quality will be discussed. A comparison between experimental and theoretical yields also will be presented, together with projected increase in yield by adapting a 30-day processing campaign.
Production and Pre-Clinical Testing of Ac-225/Bi-213 and U-230/Th-226

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The production of Ac-225/Bi-213 at the Institute for Transuranium Elements (ITU) is based on radiochemical extraction from a Th-229 source. The process consists of a combination of ion exchange and extraction chromatography, is quality controlled using alpha- and gamma spectrometry and ICP-MS and yields an Ac-225 product of >99.99% radiochemical purity.

More recently the alpha cascade emitters U-230/Th-226 have been identified as promising novel isotopes for application in targeted alpha therapy (TAT). U-230 ($t_{1/2} = 20.8$ days) is a pure alpha emitter generating a highly cytotoxic cascade of five alpha particles with a cumulative energy of 33.6 MeV. The short-lived daughter nuclide Th-226 ($t_{1/2} = 31$ min) is decaying through a rapid cascade of three further alpha emitting daughter isotopes (Ra-222, Rn-218, Po-214) with half-lives of 164 µs - 38 s. Overall the decay of Th-226 is generating a cascade of 4 alpha particles with a cumulative energy of 27.7 MeV. Th-226 is available via a radionuclide generator loaded with its mother nuclide U-230.

For the production of U-230/Th-226 three cyclotron driven processes have been developed to date. The processes are based on irradiation of Th-232 or Pa-231 targets according to the reactions $^{232}$Th(p,3n)$^{230}$(β$^-$)U-230, $^{231}$Pa(p,2n)U-230 and $^{231}$(d,3n)U-230 followed by radiochemical isolation of carrier-free U-230. Cross sections and thick target yields for these reactions will be presented in the energy relevant for production of U-230. Selected examples of pre-clinical in vitro studies comparing the cytotoxicity of Th-226- and Bi-213-labelled radioconjugates will be given.
Alpha-Emitters for Oncology

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Basic methods of Ac-225 and Ra-224 production are presented, and the method of these isotopes production from long stored U-233/U-232 is briefly described. Equipment and techniques of the isotope quality control are presented. End product Ac-225 and Ra-224 are described from the point of view of their application in nuclear medicine. Finally, the IPPE ability to supply Ac-225 and Ra-224 to clinics and hospitals are reviewed.
Advances in Dosimetry and Radiobiology of Alpha Particle Emitters

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In therapeutic nuclear medicine with alpha particle emitters, prediction of biological responses in tumor and normal tissues relies on calculation of the absorbed dose. Absorbed dose specification is complex due to the wide variety of radiations emitted, heterogeneity in activity distribution, biokinetics, etc. Following the administration of a radiopharmaceutical, the radioactivity is taken up by the various organs within the body and the radioactivity is then eliminated through both biological clearance and physical decay. A general formalism was developed by the Medical Internal Radiation Dose (MIRD) Committee of the Society of Nuclear Medicine to calculate absorbed doses from tissue incorporated radioactivity. Conventional organ absorbed dose estimates assumed that the radioactivity was distributed uniformly throughout the organ and the mean absorbed dose to the organ was calculated. However, there have been dramatic improvements in MIRD dosimetry models that reflect the substructure of organs as well as tissue elements within them. These models rely on improved nuclear medicine imaging capabilities that facilitate determination of activity within the voxels that represent tissue elements about 0.2 - 1 cm³. However, even these improved approaches assume that all cells within the tissue element (represented by the voxel) receive essentially the same absorbed dose. The tissue element may be comprised of a variety of cells having very different radiosensitivity, and sometimes, depending on the radiopharmaceutical, very different degrees of incorporation of radioactivity. Accordingly, the absorbed dose delivered to the various cells in the tissue element may differ markedly as well as their response. Therefore, a combination of voxel dosimetry and dosimetry at the cellular and multicellular levels will be required to accurately predict biological response to alpha particle emitting radiopharmaceuticals.

The extent that nonuniform distributions of radioactivity within a small tissue element impact the absorbed dose distribution, and ultimately the biological effect, is strongly dependent on the number, type, and energy of the radiations emitted by the radionuclide. Alpha-particle emitting radionuclides of therapeutic interest, and their radioactive daughters, often emit not only alpha particles, but also gamma-rays, x-rays, beta particles, internal conversion electrons, and low-energy Auger electrons. The range of the emitted alpha particles in biological tissues is 40-100 μm, Auger electrons deposit their energy within subcellular dimensions. Energetic beta emitters have a greater degree of cross-irradiation because their mean range in tissue is at least several hundred μm. Nevertheless, nonuniform distributions of therapeutic alpha emitters invariably leads to nonuniform dose distributions that are delivered by radiations with various relative biological effectiveness (RBE). Interestingly, the RBE can depend on whether the dose to a given cell arises from radioactive decays within itself (self-dose) or decays in surrounding cells or other parts of the body (cross-dose). Cellular response to self-dose delivered by a radiopharmaceutical can be different than its response to cross-dose from the same radiopharmaceutical. In addition, nonuniform dose distributions may also lead to bystander effects which can have an impact on the response of both tumor and normal tissues.

This CME lecture will summarize these concepts in the context of MIRD dosimetry and experimental models that have been designed to specifically address the issues cited above.
Clinical development of bone-seeking $^{223}$Ra (Alpharadin): Current status. O. S. Bruland*; University of Oslo, Department of Oncology, The Norwegian Radium Hospital, Oslo, Norway

Objectives: The bone-seeking, alpha-particle emitting radiopharmaceutical Alpharadin$^R$ – $^{223}$RaCl$_2$ ($t_{1/2} = 11.4$ days) is under clinical development as a novel treatment for skeletal metastases from breast and prostate cancer. Methods: This presentation will address selected aspects of the pre-clinical research and review the current status of clinical trials in patients with skeletal metastases from hormone refractory prostate cancer (HRPC). Results: Phase-1 studies (1,2) showed that toxicity is generally low, the treatment seems therapeutically beneficial for the patients and that repeated dosing is feasible. In a randomized phase 2 trial involving 64 patients with HRPC cancer and painful skeletal metastases who received 4 monthly injections of $^{223}$Ra or saline as an adjuvant to external beam radiotherapy, a 4.5 months difference in survival was observed (3). Median overall survival was 46.4 weeks in the placebo group and 65.3 weeks in the Alpharadin group (HR 2.103, p=0.017). 30% of the patients were alive at 24 months in the latter group compared to 13% that received placebo. A phase-3 study is currently recruiting, and other phase-1 and 2 trials are completed and under analysis. Conclusions: For a complete outline of the clinical program – see www.clinicaltrial.gov/ct2/results?term=radium-223 1. Nilsson S, et al., Clin Cancer Res 2005;11 (12): 4451-59 2. Bruland ØS, et al., Clin Caner Res 2006;12: 6250s-57s 3. Nilsson S, et al., Lancet Oncology 2007;8: 587-94

Objectives: Transurethral resection of urothelial cancer still results in high recurrence rates. In new concepts for therapy of disseminated tumor cells α-emitter immunoconjugates are applied. Therefore the aim of this study was to compare the therapeutic efficacy of Bi-213- and Th-226-anti-EGFR-MAb in an orthotopic EGFR-overexpressing bladder carcinoma model. Methods: 2x10^6 luciferase transfected EJ28 cancer cells were instilled into the bladders of female swiss nu/nu mice following urothelial electrocautery. 10 tumor-bearing mice each were intravesically instilled with 0.925 MBq of Bi-213-MAb or 0.37 MBq Th-226-MAb 1h, 7d and 14d after cell inoculation; controls received PBS. Tumor development and therapy response was imaged via bioluminescence imaging and survival observed up to 300d. Results: Mice of the control group reached a median survival of 41d. Bi-213-anti-EGFR therapy prolonged survival >300 d in 90%, 80% and 40% of animals treated 1h, 7d and 14d after cell instillation, respectively. Therapy with Th-226-MAb starting 10/2008 turned out to be as effective as Bi-213 therapy: 90% of animals of each group treated 1h, 7d and 14d after cell inoculation are still alive without signs of toxicity. Conclusions: Both α-emitter-anti-EGFR conjugates effectively eradicated disseminated tumor cells. Thus, therapy using Th-226-anti-EGFR might be a very promising supplement and/or alternative to Bi-213-anti-EGFR in treatment of urothelial cancer.

Objectives: A major concern of using $^{225}$AcHuM195 is renal toxicity from the 3 α-emitting daughters released from the decay of $^{225}$Ac. We determined the dose distribution of $^{225}$Ac and its daughters in kidney after administration $^{225}$AcHuM195 antibody. Methods: Mice injected with 600 nCi of $^{225}$AcHuM195 antibody were sacrificed at 24, 96, and 144 hr. The kidneys were removed immediately. Ten sections were collected from one kidney from each animal and imaged by digital autoradiography (DAG). Exposures (EXP) were performed immediately after sectioning (EXP 1 hr), and 24 hr after sectioning (EXP 16-30 hr). The 1st image shows total activity distribution mainly from the daughters that translocate there. By the start of 2nd EXP all daughters had decayed, and the $^{225}$Ac parent was in equilibrium with the newly generated daughters, which remained at the parent's location. A HpGe detector was used to resolve $^{225}$Ac activity contribution from that of its daughters by measuring emitted γ's (218 & 440 keV) in the second kidney. Known activity standards were measured by DAG and spectroscopy. Results: DAG images and spectra from the HpGe were calibrated with the respective standards. The dose to the cortex was calculated using the DAG as 27.3 Gy from $^{225}$Ac and 4.6 Gy from $^{213}$Bi and for the medulla were 17 Gy ($^{225}$Ac) and 6.5 Gy ($^{213}$Bi). The WK doses from the spectroscopy were determined to be 17.4 Gy ($^{225}$Ac) and 8.7 Gy ($^{213}$Bi). Conclusions: Doses from $^{225}$AcHuM195 and its daughters were estimated for different regions of the kidney and found to be highly tissue-dependent, and not easily determined from average dose calculations over the kidney as a whole.

Objectives: Overexpression of GRP receptors in a variety of human carcinomas including prostate cancer provides an attractive target for internal radiotherapy. The goal of this study was to compare the therapeutic efficiency of $^{213}$Bi- vs. $^{177}$Lu-DOTA-PESIN in a prostate cancer mouse model (PC-3 tumor model). Methods: For therapy efficiency and toxicity studies mice were injected with $^{213}$Bi- or $^{177}$Lu-DOTA-PESIN, whereas control groups were left untreated. The maximum tolerated dose (MTD), biodistribution, and dosimetry of each agent was determined as well. Results: Both radiopeptides tested in this study showed rapid blood clearance and tumor uptake. One hour after injection of $^{213}$Bi- or $^{177}$Lu-DOTA-PESIN the PC-3 tumor uptake was 9.0 %IA/g and 11.6 %IA/g, respectively (P=0.2). The MTD of $^{213}$Bi-DOTA-PESIN and $^{177}$Lu-DOTA-PESIN was 5x5 MBq and 4x28 MBq, corresponding to kidney doses of 6 and 6.7 Gy. The tumor response rate (initial tumor size: 6-9 mm) and kidney toxicity are shown in the table below. Dose limiting organ was the kidneys; other organs did not show toxicity. At MTD, $^{213}$Bi-DOTA-PESIN was significantly more effective than $^{177}$Lu-DOTA-PESIN. Conclusions: These preclinical data show that alpha-therapy with $^{213}$Bi-DOTA-PESIN is more effective than beta-therapy and represents a new approach for treating prostate cancer. Due to its short physical half-life, $^{213}$Bi appears to be especially suitable for the use in conjunction with fast-clearing peptides.

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<th>$^{177}$Lu-DOTA-PESIN (n≥10)</th>
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<td>4x28 MBq</td>
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<td>Kidney toxicity (Grade 0 – 5)</td>
<td>0 – 5</td>
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**Objectives:** The objective of the research was to demonstrate that PSA levels can be reduced in a mouse model for prostate cancer skeletal metastases after treatment with a $^{211}$At-labeled anti-PSMA monoclonal antibody (MAb).

**Methods:** Four groups of 18 SCID mice were implanted with C4-2B human prostate cancer cells into the tibia. MAbs (107-1A4 & MOPC-21) were modified with maleimide-closo-decaborate(2-) for labeling with $^{211}$At. Blood was monitored weekly for PSA levels (n=13/group). Five remaining mice per group had blood draws weekly to evaluate CBC, liver enzymes, bilirubin, urea and creatinine. The study used 4 MAb (10 μg each) treatment groups. Grp 1: unmodified anti-PSMA MAb, 107-1A4; Grp 2: non-specific MAb, MOPC-21 labeled with 10 μCi $^{211}$At; Grp 3: 107-1A4, 10 μCi $^{211}$At; and Grp 4: 107-1A4, 1 μCi $^{211}$At.

**Results:** All groups had a large variation in PSA values. The specific MAb, [At]107-1A4 (10 μCi/10 μg), had the lowest avg PSA values, with the avg PSA values in other groups being: Grp2<Grp4~Grp1. When the PSA values were evaluated relative to the initial PSA value, the avg values (± std dev) were: Grp 1: 7.9±10x; Grp 2: 3.6±3.5x; Grp 3: 2.0±1.5x; and Grp 4: 6.1±4.3x. No toxicity was noted from the treatment by blood analyses.

**Conclusions:** Treatment with 10 μCi $^{211}$At-labeled 107-1A4 dramatically decreased average blood PSA values without toxicity. 

**Research Support:** These studies were funded by the Pacific NW Prostate Cancer SPORE (P50-CA97186) and the Fred Hutchinson Cancer Research Center.
An astatine-211 labeled PSMA inhibitor for targeted alpha-particle radiotherapy of prostate carcinoma. G. Vaidyanathan¹, R. C. Mease², D. J. Affleck¹, Y. Chen², P. Welsh¹, M. Hens¹, M. G. Pomper², M. R. Zalutsky¹; ¹. Duke University, Durham, NC 2. Johns Hopkins University, Baltimore, MD

Objectives: Urea-based prostate-specific membrane antigen (PSMA) inhibitors labeled with $^{18}$F, radioiodine and radiometals are promising agents for imaging prostate cancer (PCa). Because of their low molecular weight and rapid normal tissue clearance, these molecules might be ideal for selectively delivering the 7.2-h half life $\alpha$-particle emitter $^{211}$At to PCa cells. Methods: The target compound, 2-[3-[5-(4-[211]Atastato-benzoylamino)-1-carboxy-pentyl]-ureido]-pentanedioic acid (ABCPUP) and its $^{131}$I-labeled analogue, CIBPUP were synthesized in two steps from a protected tin precursor. Their uptake was determined in a paired-label study with PSMA positive PC3 PIP and PSMA negative PC3 FLU cells. Results: After a 10 min reaction, the average radiochemical yields for the astatination of tin precursor was 78.3 ± 12.2% (n = 4), which was comparable to radioiodination yields (76.5 ± 7.4%; n = 2); deprotection was quantitative. The uptake (% input dose per $5 \times 10^5$ cells) of both ABCPUP and CIBPUP in PIP cells increased with time (4.9 ± 0.3% and 19.3 ± 0.9% for ABCPUP and 5.0 ± 0.3% and 22.3 ± 1.1% for CIBPUP at 30 min and 4 h, respectively; p < 0.05 for ABCPUP versus CIBPUP). The uptake of both tracers was reduced to less than 4% of controls when co-incubated with 2-PMPA, an inhibitor of PSMA. For both tracers, the absolute uptake in FLU cells ranged from 0.01 – 0.04%. Conclusions: Substitution of $^{211}$At for iodine in this compound did not result in any alteration in specificity of its binding to PCa cells. ABCPUP warrants further evaluation as a targeted radiotherapeutic for the treatment of PCa. Research Support: NIH grants CA42324, CA92871.
Assessment of long term radiotoxicity after treatment with the low dose rate \(\alpha\)-particle emitting radioimmunoconjugate \(^{227}\text{Th}\)-rituximab. J. Dahle\(^1\), T. Jonasdottir\(^2\), H. Heyerdahl\(^1\), J. Nesland\(^3\), J. Borrebaek\(^4\), A. Hjelmerud\(^4\), R. Larsen\(^1\); 1. Norwegian Radium Hospital, Department of Radiation Biology, Oslo, Norway 2. Norwegian School of Veterinary Science, Department of Companion Animal Clinical Sciences, Oslo, Norway 3. Rikshospitalet University Hospital, Division of Pathology, Oslo, Norway 4. Algeta ASA, Oslo, Norway

**Objectives:** To evaluate possible late side effects of \(^{227}\text{Th}\)-rituximab, the long-term radiotoxicity was investigated. **Methods:** BALB/c mice were injected with saline, cold rituximab or 50, 200 or 1000 kBq/kg \(^{227}\text{Th}\)-rituximab and followed for up to one year. In addition, nude mice with Raji xenografts treated with 50, 200, 400, 600 or 1000 kBq/kg \(^{227}\text{Th}\) rituximab were also included in the study. Toxicity was evaluated by measurements of mouse body-weight, white blood cell (WBC) and platelet counts, serum clinical chemistry parameters and histological examination of tissues. **Results:** Only the 1000 kBq/kg dosage resulted in decreased body-weight. There was a significant but temporary decrease in WBC and platelet count in mice treated with 1000 and 400 kBq/kg \(^{227}\text{Th}\)-rituximab. Therefore, the no-observed-adverse-effect-level (NOAEL) was 200 kBq/kg. The maximum tolerated activity was between 600 and 1000 kBq/kg. No significant signs of toxicity were observed in histological sections in any examined tissue. The maximum tolerated dose to bone marrow was estimated to be 3.6 Gy. **Conclusions:** Therapeutic relevant dose levels of \(^{227}\text{Th}\)-rituximab were well tolerated in mice. Bone marrow suppression, as indicated by decrease in WBC count, was the dose limiting radiotoxicity. These toxicity data together with anti-tumor activity data in a CD20 positive xenograft mouse model, indicate that therapeutic effects could be obtained with relatively safe dosage levels of the radioimmunoconjugate. **Research Support:** The study was supported by the Norwegian Research Council and the Norwegian Cancer Society as well as Algeta ASA.
Targeted therapy of breast cancer with low dose rate alpha-particle-emitting $^{227}$Th-trastuzumab. J. Dahle$^1$, C. Krogh$^1$, N. Abbas$^3$, A. Hjelmerud$^1$, J. Borrebaek$^2$, A. Larsen$^2$, R. Larsen$^1$, O. Bruland$^3$; 1. Norwegian Radium Hospital, Department of Radiation Biology, Oslo, Norway 2. Algeta ASA, Oslo, Norway 3. Rikshospitalet, Department of Oncology, Oslo, Norway

Objectives: The purpose of this study was to explore the potential of a low dose rate alpha-particle emitting radioimmunoconjugate; $^{227}$Th-trastuzumab (Herceptin), as a novel treatment of metastatic breast cancer. Methods: Two HER2-expressing breast cancer cell lines, BT-474 and SKBR-3, as well as the HER2-negative cell line MCF-7 were incubated with 0-20 kBq/ml of $^{227}$Th-Herceptin and cell bound activity was measured. Cell survival, growth rate and induction of apoptosis were studied. Mice with subcutaneous SKBR-3 tumor xenografts were treated with 200, 400 and 600 kBq/kg of intravenously injected $^{227}$Th-trastuzumab, non-specific $^{227}$Th-rituximab or cold trastuzumab and the growth of the tumors were followed for up to 4 months. The toxicity of the treatment was evaluated by monitoring blood cell counts. Results: The therapeutic effect on cells in culture depended both on differences in growth rate of the cell lines and on differences in binding of $^{227}$Th-trastuzumab. High in vitro growth-rate correlated with weaker therapeutic effect. Single injection of 200 kBq/kg $^{227}$Th-trastuzumab resulted in a growth delay of 54 or 51 days in growing to 500 mm$^3$ as compared with untreated mice or mice treated with cold Herceptin, respectively. There was a dosage dependent increase in therapeutic effect. Hematological toxicity to blood was modest and temporary. Conclusions: This study shows a therapeutic effect of low dose-rate alpha-particle radioimmunotherapy against breast cancer cells and warrants further in vivo studies with repeated dosing. Research Support: This work was supported by The Norwegian Research Council, The Norwegian Cancer Society, Helse SørØst and Algeta ASA.
Isolation and Protein Labeling of At-211 from Irradiated Bismuth Targets using a Modified Wet Chemistry Approach. D. Wilbur*1, D. K. Hamlin1, M. Chyan1, B. M. Sandmaier2; 1. University of Washington, Department of Radiation Oncology, Seattle, WA 2. Fred Hutchinson Cancer Research Center, Clinical Research Division, Seattle, WA

Objectives: The objectives were to improve consistency and yields of $^{211}$At isolated from irradiated targets using a modified wet chemistry approach, and to demonstrate protein labeling. Methods: The large quantity of Bi metal used in our irradiations required modification of the literature reports for wet chemistry isolation of $^{211}$At. Bi metal was dissolved in a minimum amount of HNO$_3$ (15 mL with rinse). The HNO$_3$ was removed by distillation. The residue was dissolved in 8M HCl and transferred to another vial (10 mL HCl with rinse). The HCl solution was extracted with diisopropyl ether (DIPE; 8mL)-rinsed with 8M HCl (3mL). Two mL of 4N NaOH was added to the DIPE layer. The NaOH layer was separated and the DIPE was rinsed with 0.5mL H$_2$O. The volume of the NaOH solution was reduced by distillation. To the residue was added 1mL of H$_2$O. The resultant aqueous $^{211}$At solution was brought to near neutral with 8N HCl (slightly basic). The $^{211}$At was reacted with chloramine-T to label antibodies conjugated with a closo-decaborate(2-) derivative. Results: Isolation of the $^{211}$At was accomplished in ~80% recovery (decay corrected) from the wet chemistry process. The overall time was approximately 2.5 h from dissolution of target to obtaining labeled MAbs. Labeled MAbs were obtained in 66-71% yield after purification. Conclusions: The modified wet chemistry isolation approach provides more consistent and higher recovery yields than the dry distillation approach. Further optimization of recovery yields and minimization of time required is on-going. Research Support: These studies were supported by grants from the National Institutes of Health (CA118940 and CA113431).
Inorganic Nanoparticle Monoclonal Antibody Conjugates. S. Mirzadeh *1, J. Woodward2, R. F. Standaert4, S. Dai2, A. J. Rondinone2, S. J. Kennel3; 1. Oak Ridge National Laboratory, Nuclear Science and Technology Division, Oak Ridge, TN 2. ORNL, Chemical Sciences Division, TN 3. University of TN Graduate School of Medicine, Department of Medicine, Knoxville, TN 4. ORNL, Life Sciences Division, TN

Objectives: We used a model system of radiolabeled quantum dots to document the competition between efficient vascular targeting and interaction of NP with the reticuloendothelial (RE) system. Such a nanoparticle system may be useful for delivery of $^{225}$Ac.

Methods: CdTe($^{125m}$Te)-NP capped with ZnS were derivitized with mercaptoacetic acid and conjugated to MAb201B that binds to murine thrombomodulin expressed in the lumen of lung blood vessels. The MAb targeted NP were tested in vivo by SPECT/CT imaging, autoradiography and std organ biodistribution. Biodistribution was also determined in mice depleted of phagocytic cells by clodronate-loaded liposomes.

Results: NPs-MAb 201B retained $^{125m}$Te and antibody activity and accumulated in lung (>400 %ID/g) within 1 h of iv injection, where control antibody-NPs did not. In a few hours, a large fraction of lung-targeted NPs redistributed to spleen and liver or excreted. Removal of NPs from circulation by phagocytic cells was confirmed by comparing biodistribution of targeted NPs in normal mice vs those depleted of phagocytic cells. In clodronate liposomes-treated mice, loss of the targeted NP from lung was inhibited by several fold at 24 h, while accumulation in liver and spleen remained constant.

Conclusions: Result indicates that targeting of NPs preparations is a competition between the effectiveness of the targeting agent and the natural tendency for RE uptake of the particles.
Modeling biological response to nonuniform distributions of radioactivity in three dimensional tissues. R. W. Howell*, P. V. Neti; UMDNJ-New Jersey Medical School, Department of Radiology, Newark, NJ

Objectives: Our experimental studies on the lethality of radionuclides in multicellular clusters showed that many variables are involved in the response of cell populations. Variables include radiation characteristics, geometry of the cell population, %cells labeled, activity distribution among the labeled cells, cellular self- and cross-dose, and biological uptake and clearance of the radiochemical. Initially we modeled the survival of a 3D cell population with a semi-empirical approach that took into account the cellular self- and cross-dose and %cells labeled. This approach achieved some success within 1-2 logs of kill, however, it could not explain saturation in the survival curves. Here we create a multicellular dosimetry model to investigate how the response of a 3D cell population depends on the %cells labeled, detailed geometry of the cluster, and activity distribution among the labeled cells. Methods: Multicellular clusters are modeled as $4 \times 10^6$ spherical cells in close-packed cubic geometry. Cells are arranged to simulate different cone and paraboloid geometries. Activity is distributed among a defined percentage of cells according to a log normal or Poisson distribution. Self- and cross-dose cellular S values are calculated for $^{131}$I and $^{210}$Po. Self- and cross-doses are tallied for target cells and a Monte Carlo approach is used to determine whether a given target cell survives. The surviving cells are tallied and used to create survival curves. Results: Preliminary calculations indicate that two-component survival curves can be observed when radioactivity is log normally distributed among the labeled cells. Conclusions: The response of 3D cell populations can be modeled using the present theoretical multicellular dosimetry approach. Research Support: The project described was supported in part by Grant Number R01CA083838 from the National Cancer Institute. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Cancer Institute or the National Institutes of Health.
Dosimetry for $^{223}\text{Ra}$ and its daughters. C. Hindorf$^1$, S. Chittenden$^2$, A. Aksnes$^3$, V. Lewington$^2$, C. Parker$^2$, G. F. Flux$^2$; 1. ENVN, Imagerie Medicale, Nantes, France 2. Royal Marsden Hospital, Physics, Nuclear Medicine, Urology, Sutton, United Kingdom 3. Algeta ASA, Oslo, Norway

Objectives: $^{223}\text{Ra}$ decays to stable lead via a relatively complicated decay chain ($^{223}\text{Ra}\rightarrow^{219}\text{Rn}\rightarrow^{215}\text{Po}\rightarrow^{211}\text{Pb}\rightarrow^{211}\text{Bi} \rightarrow^{207}\text{TI} \rightarrow^{207}\text{Pb}$). All radionuclides in the chain except $^{215}\text{Po}$ and $^{207}\text{TI}$ emit photons which therefore presents the possibility of measuring the pharmacokinetics for each daughter separately. The aim of this study was to investigate the dosimetry for $^{223}\text{Ra}$ with these separate measurements.

Methods: Six patients with bone metastases from prostate cancer received two $^{223}\text{Ra}$ Cl$_2$ administrations (100 kBq/kg, twice the normal clinical amount) delivered by intravenous injection six weeks apart. Pharmacokinetics were followed for one week following administration using whole body measurements, scintillation camera imaging and blood sampling. Complete faecal and urine collection was performed up to 48 h after administration. The activity of $^{223}\text{Ra}$, $^{223}\text{Ra+219}\text{Rn}$, $^{211}\text{Pb}$ and $^{211}\text{Bi}$ was measured for the whole body, urine and faecal samples and $^{223}\text{Ra}$ and $^{211}\text{Pb}$ were measured for the blood samples. Imaging was performed with energy windows enabling separate quantification of $^{223}\text{Ra}$ and $^{223}\text{Ra+219}\text{Rn}$. Results: The absorbed whole-body dose was 0.190 Gy (range: 0.142 Gy – 0.541 Gy) when the daughters were assumed to follow $^{223}\text{Ra}$ and 0.188 Gy (range: 0.140 Gy – 0.516 Gy) when the pharmacokinetics for the daughters were considered separately. Conclusions: It is possible to measure whole-body pharmacokinetics for the daughters of $^{223}\text{Ra}$. The whole body absorbed dose in this case is similar to the absorbed dose calculated assuming that the daughters have the same pharmacokinetics as $^{223}\text{Ra}$.
1818 - **In vitro cytotoxicity of low dose-rate radioimmunotherapy by the α-emitting radioimmunoconjugate** $^{227}$Th-rituximab. J. Dahle$^1$, C. Krogh$^1$, K. Melhus$^1$, J. Borrebaek$^2$, R. Larsen$^1$, Y. Kvinnsland$^3$; 1. Norwegian Radium Hospital, Department of Radiation Biology, Oslo, Norway 2. Algeta ASA, Oslo, Norway 3. Nordic Neurolabs, Bergen, Norway

**Objectives:** To determine if the low dose-rate alpha particle-emitting radioimmunoconjugate $^{227}$Th-DOTA-rituximab can be used to inactivate lymphoma cells growing as single cells and small colonies. **Methods:** CD20-positive lymphoma cell lines were treated with $^{227}$Th-rituximab for 1-5 weeks. To simulate the in vivo situation with continuous but decreasing supply of radioimmunoconjugates from the blood pool, the cells were not washed after incubation with $^{227}$Th-rituximab, but half of the medium was replaced with fresh medium and the cell concentration was determined every other day after start of incubation. A microdosimetric model was established to estimate the average number of hits in the nucleus for different localizations of activity. **Results:** There was a specific targeted effect on cell growth of the $^{227}$Th-rituximab treatment. Although the cells were not washed after incubation with $^{227}$Th-rituximab the average contribution of activity in the medium to the dose was only 6%, while the average contribution from activity on the cells' own surface was 78%. The dose-rates after incubation with 800 Bq/ml $^{227}$Th-rituximab varied from 0.01-0.03 cGy/min. The average delay in growing from $10^5$ to $10^7$ cells per ml was 17.3 days when the cells were incubated with 800 Bq/ml $^{227}$Th-rituximab while it was 10.9 days when the cells were irradiated with 6 Gy of X-radiation. The relative biological effect of the treatment was estimated to be 2.9-3.4. **Conclusions:** The low dose-rate radioimmunoconjugate $^{227}$Th-rituximab is suitable for inactivation of single lymphoma cells and small colonies of lymphoma cells. **Research Support:** The study was supported by the Norwegian Research Council and the Norwegian Cancer Society as well as Algeta ASA.
1819 - Treatment of HER2-expressing breast cancer and ovarian cancer cells in vitro with low dose rate alpha-particle-emitting $^{227}$Th-trastuzumab. C. Krogh¹, H. Hopen¹, J. Borrebaek², A. Larsen², R. Larsen¹, J. Dahle¹; 1. Norwegian Radium Hospital, Department of Radiation Biology, Oslo, Norway 2. Algeta ASA, Oslo, Norway

**Objectives:** The purpose of this study was to evaluate the cytotoxic effect of the internalizing low dose rate alpha-particle emitting radioimmunoconjugate $^{227}$Th-trastuzumab (Herceptin) on HER2-expressing cells in vitro. **Methods:** Three HER2-expressing cell lines, BT-474 (breast), SKBR-3 (breast) and SKOV-3 (ovarian), as well as one HER2-negative breast cancer cell line (MCF-7) were incubated with 0-20 kBq/ml of $^{227}$Th-trastuzumab or non-binding $^{227}$Th-rituximab. Cell associated activity was measured at several time points after start of incubation and average numbers of alpha-particle decays per cell were estimated. Survival, growth rate as well as induction of apoptosis were studied. **Results:** $^{227}$Th-trastuzumab was internalized into the HER2 expressing cells. SKBR-3 cells bound more $^{227}$Th-trastuzumab than BT-474 cells and SKOV-3 cells bound least, while the MCF-7 cells bound essentially nothing. The growth rates of the cells were different, with SKOV-3 growing faster than SKBR-3, and BT-474 growing slowest. There was a dosage dependent decrease in survival of the HER2-positive cell lines treated with $^{227}$Th-trastuzumab, while there was no effect on MCF-7 cells and no effect of non-binding $^{227}$Th-rituximab on the HER2 positive cells even for the highest dosage. The cytotoxic effect of $^{227}$Th-trastuzumab was highest for BT-474 cells followed by SKBR-3 cells and SKOV-3 cells. **Conclusions:** Therapeutic effect of $^{227}$Th-trastuzumab on cells in culture depended on growth rate of the cells. A high growth-rate reduced the effectiveness of the low dose-rate radioimmunotherapy in this study. **Research Support:** This work was supported by The Norwegian Research Council, The Norwegian Cancer Society and Algeta ASA.
1820 - Treatment of mice with SKBR-3 breast cancer or SKOV-3 ovarian cancer xenografts with low dose rate alpha-particle-emitting $^{227}$Th-trastuzumab. N. Abbas$^1$, O. Bruland$^2$, A. K. Hjelmerud$^1$, J. Borrebaek$^3$, A. Larsen$^3$, R. Larsen$^1$, J. Dahle$^1$; 1. Norwegian Radium Hospital, Radiation Biology, Oslo, Norway 2. Rikshospitalet University Hospital, Department of Oncology, Oslo, Norway 3. Algeta ASA, Oslo, Norway

**Objectives:** The purpose of this study was to compare therapeutic effects of the low dose rate alpha-particle emitting radioimmunoconjugate $^{227}$Th-trastuzumab on two HER2-expressing cancers. **Methods:** Biodistribution of $^{227}$Th-trastuzumab in mice with SKBR-3 or SKOV-3 xenografts was determined and compared with biodistribution of $^{227}$Th-rituximab. Mice with subcutaneous xenografts were treated with 200, 400 and 600 kBq/kg of intravenously injected $^{227}$Th-trastuzumab, NaCl (control), cold trastuzumab or non-specific $^{227}$Th-rituximab and the growth of tumors were followed. Toxicity was monitored by repeated blood cell counting. **Results:** $^{227}$Th-trastuzumab was stable in vivo. The area under curve for tumor uptake was similar but the peak in tumor uptake was at 4 days after injection for SKBR-3 while it was at 7 days for SKOV-3. Cold trastuzumab and non-specific $^{227}$Th-rituximab had no effect on the tumor growth; whereas $^{227}$Th-trastuzumab resulted in significant growth delay as compared with control mice for both tumors. The delay in growing to 500 mm$^3$ after injection of 200 kBq/kg $^{227}$Th-trastuzumab was 54 days for SKBR-3 and 10 days for SKOV-3. There was a dosage dependent increase in therapeutic effect but also in toxicity. **Conclusions:** A difference in therapeutic effect of $^{227}$Th-trastuzumab when treating SKBR-3 and SKOV-3 tumors was observed, which may be related to differences in growth, antigen expression and kinetics in the tumor uptake of $^{227}$Th-trastuzumab. **Research Support:** This work was supported by The Norwegian Research Council, The Norwegian Cancer Society and Algeta ASA.
1821 - An improved labeling method for Thorium-227 labeled antibodies for targeted alpha therapy. J. Borrebaek¹, A. Larsen¹, E. Brevik¹, J. Dahle², N. Abbas², A. Hjelmerud²; 1. Algeta ASA, Oslo, Norway 2. Institute for Cancer Research, Department of Radiation Biology, Oslo, Norway

Objectives: Targeted alpha therapy with thorium-227 labeled antibodies has shown promising results in tumor models in vivo. We describe a new method for thorium-227 labeling, using antibodies pre-conjugated with the bifunctional chelator p-SCN-Bn-DOTA, and compared this with the previously used pre-chelation method. The aim was to improve labeling efficiency, yield, stability, immunoreactivity and to keep a favorable biodistribution profile and high tumor uptake. Methods: mAb’s were conjugated with p-SCN-Bn-DOTA and chelated with thorium-227. In vitro stability was evaluated by incubating the labeled conjugates in serum, purifying the protein by size exclusion at different timesteps and measuring the immunoreactivity on cells. In vivo biodistribution and tumor uptake of $^{227}$Th-p-SCN-Bn-DOTA-mAb were determined using normal and tumor xenografted mice. Results: The new method labeled p-SCN-Bn-DOTA-mAb with 60-80% radiochemical yield. The in vitro stability data showed a protein fraction yield of 80-90% and an immunoreactivity of 60-70% after 14 days of incubation, which were comparable to the old labeling method. Results in vivo indicated a similar biodistribution profile and tumor uptake as obtained with the pre-chelation method. Conclusions: The new labeling method using pre-conjugated p-SCN-Bn-DOTA-mAb showed significantly higher thorium-227 labeling efficiency compared to the old method (1-10% Efficiency). Pre-conjugation of the antibody is a more convenient labeling approach, facilitating use of freeze-dried p-SCN-Bn-DOTA-mAb kits for labeling. The in vitro stability was high, and mouse xenograft data showed an acceptable biodistribution profile and tumor uptake.
Objectives: The goal of the study was to develop and validate the peptide Pb-203-DOTA-Re(Arg11)CCMSH as a matched pair imaging agent for the α-particle emitting Pb-212-DOTA-Re(Arg11)CCMSH melanoma therapeutic. A matched-pair imaging agent is critical for determining tumor uptake, patient specific dosimetry and the proper therapeutic dose administration. Methods: DOTA-Re(Arg11)CCMSH was labeled with the γ-emitting radionuclide Pb-203 in 0.5 M NH₄OAc (pH 5.4) at 85°C for 30 min, followed by HPLC purification. The pharmacokinetics and SPECT imaging properties of Pb-203-DOTA-Re(Arg11)CCMSH were examined in B16/F1 melanoma bearing mice. Results: Pb-203 and Pb-212 labeled DOTA-Re(Arg11)CCMSH displayed receptor-mediated tumor uptake of 11.25±1.52%ID/g and 11.87±3.24 %ID/g at 2 h post-injection (pi). Except for the kidneys, non-target organ uptakes were low (< 1 %ID/g) at 2, 4 and 24 h pi. The renal uptake for the Pb-203 and Pb-212 labeled peptides was 7.78±1.42 %ID/g and 7.31±1.26 %ID/g at 2 h pi. Both peptides exhibited rapid clearance, with ~89% of the radioactivity in the urine 2 h pi. Melanoma lesions were visualized with Pb-203-DOTA-Re(Arg11)CCMSH via SPECT imaging 2 h pi. Conclusions: Pb-203-DOTA-Re(Arg11)CCMSH displayed nearly identical tumor uptake values and clearance kinetics as the Pb-212 therapeutic agent. Moreover, Pb-203-DOTA-Re(Arg11)CCMSH was able to detect melanoma tumors using SPECT imaging, demonstrating its utility as a matched pair imaging agent to support targeted α-particle therapy. Research Support: NIH R42CA85106, R44CA114920
**Objectives:** Ac-225 and its daughter Bi-213 have become increasingly important in clinical research covering various diseases. The current US production of Ac-225 is limited to about 600mCi annually from the Oak Ridge National Laboratory. This current production is mostly committed to current researchers and the need exist to produce more Ac-225 to support and encourage further clinical efforts using this radioisotope. While sources are limited of the stock material used to produce Ac-225, there are options available to meet this need. **Methods:** Ac-225 (10.0days) 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: 1) chemical extraction of Ac-225 from old LWBR 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, and 5) LINAC production. **Results:** NorthStar has efforts underway in all five of the methods mentioned. While challenges exist with all, the efforts are beginning to bare fruit and each effort will be reviewed. **Conclusions:** NorthStar has successfully produced Ac-225 from LWBR fuel stocks and has worked with Oak Ridge National Laboratory to demonstrate enhancements to the current production methods that would increase the amount of Ac-225 produced annually. Continuing efforts in the other listed production routes are on-going.
**1824 - Automated Radionuclide Separation System (ARS2) for Producing Short-Lived Daughter Radioisotopes for Nuclear Medicine.** J. Harvey¹, G. Messina¹, G. Isensee¹, P. Horwitz², D. McAlister²; 1. NorthStar Medical Radioisotopes, LLC, Madison, WI 2. PG Research Foundation, Darien, IL

**Objectives:** Numerous challenges face clinicians and researchers who work with radioisotopes. One of those challenges is to be able to regularly and consistently produce the radioisotope of interest in the clinical setting if that radioisotope is short-lived and derived from a parent radionuclide. The ARS2 is a new instrument designed to meet that challenge. **Methods:** The ARS2 provides a platform for reliably and consistently producing a short-lived daughter radioisotope. The system consists of three main sections: 1) instrument body housing necessary pumps, valves, and controlling electronics, 2) an external interface to communicate with the instrument, and 3) a disposable kit providing necessary chemistry supplies to affect the desired radioisotope production. **Results:** The ARS2 can be configured for many radioisotope pairs such as Ac-225/Bi-213, W-188/Re-188 and Ge-68/Ga-68 to name a few. Once an ARS2 is configured at the factory, it is dedicated to that radioisotope pair and cannot be inadvertently used to generate a different pair. It provides the desired daughter radionuclide in a realible, consistent, and reproducible form. Further, since it is microprocessor controlled, the ARS2 will run mostly hands off reducing worker dose and thus improving worker safety. **Conclusions:** The ARS2 meets in increasing challenges in nuclear medicine of producing a consistent and realible short-lived daughter radioisotope. As the use of radioisotopes increases the value of the ARS2 to handle higher levels of radioactivity allows clinicians and researchers to use those levels safely.
**1825 - Quantitative $^{18}$F-fluoride PET to monitor response in skeletal metastases from prostate cancer treated with Alpharadin ($^{223}$Ra-chloride).**

G. Cook¹, G. F. Flux¹, C. Parker¹, S. Chua¹, A. Aksnes², V. Lewington¹; ¹ Royal Marsden NHS Foundation Trust, Sutton, United Kingdom ² Algeta, Oslo, Norway

**Objectives:** $^{99m}$Tc-MDP bone scintigraphy is insensitive for monitoring treatment response in skeletal metastases. In a pilot study we assessed the accuracy of quantitative $^{18}$F-fluoride PET in patients with skeletal metastases from prostate cancer receiving $^{223}$Ra-chloride radionuclide therapy. **Methods:** Five patients with skeletal metastases from prostate cancer and no soft tissue disease received 100 kBq/kg $^{223}$Ra-chloride therapy at 0 and 6 weeks and had whole body $^{18}$F-fluoride PET scans at baseline, 6 and 12 weeks with concurrent PSA measurements. Qualitative comparison of PET scans was performed blinded to PSA results. Quantitative comparison was made measuring SUVmax in 5 lesions in each patient. The mean of the 5 SUVmax measurements in each patient was used as a quantitative measure of global metastatic activity at each time point. **Results:** Three patients showed a PSA response (-40%, -31%, -27%) whilst 2 patients showed modest increases (+10%, +17%). Qualitative assessment of $^{18}$F-fluoride scans recorded stable disease in each case. However, quantitative assessment showed agreement with PSA response with 3 responders (-52%, -75%, -49%) and 2 with minimal change (+12%, -16%). Changes in SUV correlated with PSA temporally and in relation to overall response ($r = 0.86$). **Conclusions:** Quantitative $^{18}$F-fluoride PET is more accurate than qualitative scan comparison in assessing response in bone metastases in patients with prostate cancer treated with $^{223}$Ra-chloride, correlating closely with PSA response. The method has potential to specifically monitor skeletal response to systemic treatments in patients with mixed skeletal and soft tissue metastases.
ISRTRD PROGRAM

Monday, June 15
8:00 AM-9:30 AM  701B
ISRTRD Refresher Course Thyroid Dosimetry/Radiobiology & Imaging Quantitation
Sponsored by the MIRD Committee and ISRTRD

| CME: 1.5 | VOICE: 1.5 |
| CPE: 1.5 [210-000-09-165-L04] | CAMPEP: 1.5 |

Summary
Recent developments in thyroid dosimetry and radiobiology, including the use of recombinant human TSH and its impact on dosimetry and radioiodine kinetics. In a follow-up session, imaging/dosimetry for targeted radionuclide therapy will be covered with an emphasis on quantitative imaging techniques and dose calculation approaches. The variation and possible sources of errors in performing such calculations will also be discussed.

Educational Objectives
Upon completion of this activity, the participant will be able to:
1. List the various approaches for determining the administered activity used to treat thyroid cancer patients.
2. Discuss the impact of rhTSH on thyroid dosimetry and treatment planning.
3. Discuss the importance of quantitative imaging for targeted therapy.
4. List approaches for performing quantitative imaging.
5. Discuss the role of absorbed dose calculations for targeted radionuclide therapy and also the methods used.
6. List the sources of error and uncertainty in absorbed dose calculations and also know their magnitude.

Organizers: Manuel Bardies; Michael Lassmann, PhD; George Sgouros, PhD
Moderator: Stephen R. Thomas, PhD

8:00 AM - 8:20 AM  Thyroid Dosimetry/Radiobiology
Michael Lassmann, PhD; George Sgouros, PhD

8:20 AM - 8:40 AM  Imaging/Dosimetry for Targeted Radionuclide Therapy: Quantitative Imaging for Targeted Radionuclide Therapy
Irene M. Buvat, PhD

8:40 AM - 9:00 AM  Absorbed Dose Calculations for Targeted Radionuclide Therapy
Sven-Erik Strand, PhD

9:00 AM - 9:20 AM  Quantifying Sources of Variation and Errors in Clinical Dosimetry
Manuel Bardies

9:20 AM - 9:30 AM  Panel Discussion
Monday, June 15
10:00 AM-11:30 AM
ISRTRD -Thyroid Dosimetry/Radiobiology

Sponsored by the MIRD Committee and ISRTRD

CME: 1.5 VOICE: 1.5
CPE: 1.5 [210-000-09-173-L04] CAMPEP: 1.5

Summary
The clinical aspects of radioiodine therapy for thyroid cancer will be reviewed.

Educational Objectives
Upon completion of this activity, the participant will be able to:
1. Understand the clinical aspects of radioiodine therapy of thyroid cancer
2. Understand the role of dosimetry in radioiodine therapy of thyroid cancer

Organizer: George Sgouros, PhD
Moderators: Dunstana Melo, PhD; Paul Ladenson, MD

10:00 AM  Thyroid, Clinical  Paul Ladenson, MD

10:24 AM  **131I-iodide dose reconstruction for hyperthyroid patients**
D Melo; P. Zanzonico; A. A. Brill; M. Stabin; P. Vicini; A. Bouville; B. Moroz; D. Kwon; S. Simon; National Cancer Institute 1. National Cancer Institute, Division of Cancer Epidemiology and Genetics, Bethesda, MD, United States; 2. Memorial Sloan-Kettering Cancer Center, New York, NY, United States; 3. Vanderbilt University, South Nashville, TN, United States; 4. University of Washington, Seattle, WA, United States.

10:36 AM  **124-I PET-Based 3D-RD Dosimetry for a Pediatric Thyroid Cancer Patient: Real-Time Treatment Planning**
Robert Hobbs; Martin Lodge; R Wahl; Mehrbod Javadi; Steve Cho; David Chien; Marge Ewertz; Paul Ladenson; George Sgouros; 1. Johns Hopkins University, Baltimore, MD, United States.

10:48 AM  **123I, 131I, 99mTc and 211At induced thyroid stunning (reduced iodide transport and NIS mRNA expression) in vitro**
Eva Forssl-Aronsson; Charlotta Lundh; Ulrika Lindencrona; Per Postgard; Therese Carlsson; Mikael Nilsson; 1. University of Gothenburg, Dept of Radiation Physics, Gothenburg, Sweden; 2. University of Gothenburg, Dept of Medical Chemistry and Cell Biology, Gothenburg, Sweden.

11:00 AM  **Radiation Safety Evaluation for Patients with 131I Therapy**
Lu Ke-yi; Li Xian-feng; Hu Guang; Liu Jian-Zhong; Li Si-Jin; 1. First Hospital of Shanxi Medical University, Dept of Nuclear Medicine, Taiyuan, China.

11:12 AM  Panel Discussion
ISRTRD PROGRAM

Monday, June 15
12:30 PM-2:00 PM 701B
ISRTRD - Radionuclide Therapy/Dosimetry of Hepatocellular Carcinoma
Sponsored by the MIRD Committee and ISRTRD

CME: 1.5  
CPE: 1.5 [210-000-09-191-L04]

Summary
The clinical aspects of hepatocellular carcinoma with radionuclides will be reviewed.

Educational Objectives
Upon completion of this activity, the participant will be able to:
1. Explain how radionuclides are used to treat hepatocellular carcinoma.
2. List the radiolabeled agents used to treat this disease.

Organizer: George Sgouros, PhD
Moderator: Pat B. Zanzonico, PhD
Co-Moderator: Jean-Luc Raoul, MD, PhD

12:30 PM - 12:50 PM  Treatment of Hepatocellular Carcinoma With Radionuclides
Jean-Luc Raoul, MD, PhD

No. 208 12:54 PM  Hepatic dosimetry for holmium-166 poly(L-lactic acid) microspheres: MIRD and beyond
Mark Konijnenberg; Maarten Vente; Tim de Wit; Hugo de Jong; Fred van het Schip; Frank Nijsen; 1. Covidien, Research & Development, Petten, Netherlands; 2. University Medical Center Utrecht, Department of Radiology and Nuclear Medicine, Utrecht, Netherlands.

No. 209 1:06 PM  Comparison of three radiation dosimetry models for Yttrium-90 microsphere radioembolotherapy
S. Cheenu Kappadath; William Erwin; Pritesh Mutha; Shashank Prasad; Ravi Murthy; 1. UT MD Anderson Cancer Center, Houston, TX, United States.

No. 210 1:18 PM  Y-90 microsphere dosimetry in hepatic malignancies
Stefan Mueller; Verena Hartung; Stephen Moore; Monia Hamami; Andreas Bockisch; 1. Universitaetsklinikum Essen, Nuklearmedizin, Essen, Germany; 2. Brigham & Women's Hospital, Harvard Medical School, Radiology, Boston, MA, United States.

No. 211 1:30 PM  Analysis of resected hepatic tumor and normal tissues regarding heterogeneity in specific radioactivity following pre-surgical radioembolization with 90Y resin microspheres
Jonas Hogberg; Peter Gjertsson; Ragnar Hultborn; Magnus Rizell; Olof Henriksson; Ola Nilsson; Johanna Svensson; Jakob Himmelman; Peter Bernhardt; 1. Sahlgrenska University Hospital, Dept of Med Physics and Med Engineering, Gothenburg, Sweden; 2. Sahlgrenska University Hospital, Dept of Clinical Physiology, Gothenburg, Sweden; 3. Sahlgrenska University Hospital, Dept of Oncology, Gothenburg, Sweden; 4. Sahlgrenska University Hospital, Dept of Surgery, Gothenburg, Sweden; 5. Sahlgrenska University Hospital, Dept of Radiology, Gothenburg, Sweden; 6. Sahlgrenska University Hospital, Dept of Pathology, Gothenburg, Sweden.

1:42  Panel Discussion
Monday, June 15
4:30 PM-6:00 PM 701B

ISRTRD - Bone Pain Agents / Marrow Dosimetry
Sponsored by the MIRD Committee and ISRTRD

| CME: 1.5       | VOICE: 1.5       |
| CPE: 1.5 [210-000-09-212-L04] | CAMPEP: 1.5 |

Summary
The clinical aspects of bone pain palliation using radionuclides will be reviewed.

Educational Objectives
Upon completion of this activity, the participant will be able to:
1. Discuss the clinical use of different radionuclides in bone pain palliation.
2. List the various clinical applications, side effects, and possible role of combination therapy in bone pain palliation.
3. Examine the role of patient-specific dosing for administration of agents for bone pain palliation.

Organizer: George Sgouros, PhD
Moderators: Giuliano Mariani, MD; Neeta D. Pandit-Taskar, MD

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<th>Time</th>
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<tr>
<td>4:30 PM</td>
<td>Bone Pain - Clinical</td>
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<td>Neeta D. Pandit-Taskar, MD</td>
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No. 267 4:54 PM  
**Image-based skeletal dosimetry models for the ICRP reference pediatric series**  

No. 268 5:06 PM  
**Effect of chemotherapy on the spatial distribution of stem cells in human bone marrow**  

No. 269 5:18 PM  
**THE SPATIAL PROFILE OF BLOOD VESSELS AND HEMATOPOIETIC STEM CELLS WITHIN THE MARROW CAVITIES OF THE HUMAN SKELETON**  
Vincent Bourke; Christopher Watchman; Arnaud Dieudonne; Wesley Bolch; 1. University of Arizona, Tucson, AZ, United States; 2. University of Florida, Gainesville, FL, United States.

No. 270 5:30 PM  
**Patient specific 3-D Radiobiological Dosimetry (3D-RD) for 153Sm-EDTMP therapy of osteosarcoma**  
Srinivasan Senthamizhchelvan; Robert Hobbs; Sebastien Baechler; H Song; Bin He; Eric Frey; Cindy Schwartz; David Loeb; George Sgouros; 1. Johns Hopkins University, Baltimore, MD, United States; 2. University of Lausanne, University Institute of Radiation Physics, Switzerland; 3. Alpert Warren Medical School, Brown University, Providence, RI, United States.

No. 271 5:42 PM  
**A novel SPECT/CT voxel-based dose calculation method for targeted radionuclide therapy**  
Justin Mikell; Oleg Vassiliev; William Erwin; Todd Wareing; Gregory Failla; John McGhee; Rodolfo Nunez; Naoto Ueno; Radhe Mohan; Firas Mourtada; 1. UT MD Anderson Cancer Center, Houston, TX, United States; 2. Transpire Inc., Gig Harbor, WA, United States.

5:54 Brief Panel Discussion
Tuesday, June 16
7:30 AM-9:00 AM
ISRTRD Refresher Course - Computational Phantoms for Imaging & Dosimetry
Sponsored by the MIRD Committee and ISRTRD

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<td>CPE: 1.5 [210-000-09-219-L04]</td>
<td>CAMPEP: 1.5</td>
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Summary
New developments in computational phantoms for imaging and dosimetry will be reviewed.

Educational Objectives
Upon completion of this activity, the participant will be able to:
1. Demonstrate how computational phantoms may be used in imaging and dosimetry.
2. Explain the potential impact that newer generations of computational phantoms will have on patient radionuclide dosimetry.

Organizer: George Sgouros, PhD
Moderator: Yuni K. Dewaraja, PhD

7:30 AM - 9:00 AM New Dosimetry Models - BM, Pediatric & Customizable Phantoms
Wesley E. Bolch, PhD; Eric C. Frey, PhD
Tuesday, June 16
9:45 AM-11:15 AM
ISISRD - Radioimmunotherapy of Lymphoma

Sponsored by the MIRD Committee and ISISRD

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**Summary**
The treatment of lymphoma using radioimmunotherapy will be reviewed.

**Educational Objectives**
Upon completion of this activity, the participant will be able to:
1. Examine the role of radioimmunotherapy in the treatment of lymphoma.
2. Explain how dosimetry can be used to optimize radioimmunotherapy treatment of lymphoma.
3. Describe the results and status of current and ongoing lymphoma radioimmunotherapy trials.

Organizer: George Sgouros, PhD
Moderators: Sven-Erik Strand, PhD; Richard L. Wahl, MD

| 9:45 AM | RIT of Lymphoma, Clinical
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<td>Richard L. Wahl, MD</td>
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<tr>
<th>No. 377</th>
<th>10:09 AM</th>
<th><strong>Quantitative SPECT/CT for radioimmunotherapy (RIT) treatment planning: comparison of tracer and therapy dosimetry</strong> Yuni Dewaraja; Anca Avram; Matthew Schipper; Scott Wilderman; Kenneth Koral; Denise Regan; Mark Kaminski; 1. University of Michigan, Ann Arbor, MI, United States; 2. Innovative Analytics, Kalamazoo, MI, United States.</th>
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<td>No. 378</td>
<td>10:21 AM</td>
<td><strong>Evaluation of quantitative 90Y bremsstrahlung SPECT based on patient studies</strong> David Minarik; Katarina Sjogreen Gleisner; Michael Ljungberg; 1. Lund University, Medical Radiation Physics, Lund, Sweden.</td>
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<td>No. 379</td>
<td>10:33 AM</td>
<td><strong>Computation of equivalent uniform dose for regressing tumors in radioimmunotherapy using quantitative 3D SPECT/CT imaging data</strong> Scott Wilderman; Pete Roberson; Hanan Amro; Yuni Dewaraja; 1. University of Michigan, Nuclear Engineering, Radiology, and Radiation Oncology, Ann Arbor, MI, .</td>
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<tr>
<td>No. 380</td>
<td>10:45 AM</td>
<td><strong>A comparison of pharmacokinetic curves from quantitative planar and SPECT imaging of 111-In labeled antibodies</strong> Michael Ljungberg; Katarina Gleisner Sjogreen; 1. Medical Radiation Physics, Lund University, Lund, Sweden.</td>
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<th>No. 377</th>
<th>10:57 AM</th>
<th><strong>Quantitative SPECT/CT for radioimmunotherapy (RIT) treatment planning: comparison of tracer and therapy dosimetry</strong> Yuni Dewaraja; Anca Avram; Matthew Schipper; Scott Wilderman; Kenneth Koral; Denise Regan; Mark Kaminski; 1. University of Michigan, Ann Arbor, MI, United States; 2. Innovative Analytics, Kalamazoo, MI, United States.</th>
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11:09 **Panel Discussion**
Tuesday, June 16  
12:30 PM-2:00 PM | 701B

**ISRTRD - Targeted, Diagnostic and Therapeutic Agents**

Sponsored by the MIRD Committee and ISRTRD

| CME: 1.5 | VOICE: 1.5 |
| CPE: 1.5 [210-000-09-256-L04] | CAMPEP: 1.5 |

**Summary**

Recent developments in pretargeting and engineered and low-molecular-weight agents in radionuclide therapy will be reviewed.

**Educational Objectives**

Upon completion of this activity, the participant will be able to:

1. List new approaches for targeted radionuclide therapy.
2. Review the implications of such developments for dosimetry and treat planning.

Organizer: George Sgouros, PhD

Moderators: Edward B. Silberstein, MD; John M. Pagel, MD, PhD

12:30 PM - 12:50 PM | Pretargeting & Low-Molecular-Weight Targeted Agents

**No. 444**

| 12:54 PM | Dosimetry evaluation in a phase I study of intravenous 131I-TM601 in patients with recurrent or refractory somatic and/or cerebral metastatic solid tumors | S Shen; John Fiveash; Jeffrey Raizer; Neil Senzer; Thomas Gribbin; Nicholas Avgeropoulos; Stewart Spies; Amy Bock; Carolyn McGarry; Alison O'Neill; 1. Univ Alabama, Birmingham, AL, United States; 2. Northwestern Univ, Chicago, IL, United States; 3. Mary Crowley Cancer Res Ctr, Dallas, TX, United States; 4. Lack's Cancer Ctr, Grand Rapids, MI, United States; 5. Florida Hosp Cancer Ins, Orlando, FL, United States; 6. TransMolecular Inc, Cambridge, MA, United States. |

**No. 445**


**No. 446**

| 1:18 PM | Radiation dosimetry of 68Ga-NOTA-RGD, PET agent for angiogenesis imaging in humans | Joong Hyun Kim; Jae Sung Lee; Keon Wook Kang; Ho-Young Lee; Tae-You Kim; Jae Min Jeong; June Chung; Myung Lee; Dong Soo Lee; 1. Seoul National University, Department of Nuclear Medicine, Seoul, South Korea; 2. Seoul National University, Department of Internal Medicine, Seoul, South Korea. |

**No. 447**

| 1:30 PM | Biodistribution and radiation dosimetry of angiogenesis marker [F-18]RGD-K5 measured using human PET | Mohan Doss; R. Katherine Alpaugh; Jian Q. Yu; 1. Fox Chase Cancer Center, Philadelphia, PA, United States. |

**No. 448**

| 1:42 PM | Biodistribution and dosimetry of [C-11] PK-11195 PET imaging in children and adults | Ajay Kumar; O Muzik; Diane Chugani; P Chakraborty; Harry Chugani; 1. Dept of Pediatrics and Neurology, School of Medicine, Wayne State University, PET Center, Children Hospital of Michigan, Detroit, MI, United States. |

1:54 | Brief Panel Discussion |
ISRTRD PROGRAM

Tuesday, June 16
2:30 PM-4:00 PM 701B

ISRTRD - Radiopeptides

Sponsored by the MIRD Committee and ISRTRD

| CME: 1.5 | VOICE: 1.5 |
| CPE: 1.5 [210-000-09-272-L04] | CAMPEP: 1.5 |

Summary
Recent developments and clinical results in radiopeptide therapy are reviewed.

Educational Objectives
Upon completion of this activity, the participant will be able to:
1. Examine how radiopeptides are used in cancer therapy.
2. Describe developments in the dosimetry associated with radiopeptide therapy.

Organizer: George Sgouros, PhD
Moderators: Marta Cremonesi, PhD; Francois Jamar, MD, PhD

2:30 PM - 2:50 PM
Radiopeptide Therapy
Francois Jamar, MD, PhD

No. 498 The Use of 3D Patient-Specific Radiobiological Dosimetry for Kidneys in Peptide Receptor
2:54 PM Radionuclide Therapy S Baechler; R Hobbs; A Bischof-Delaloye; A Boubaker; B He; E Frey; G Sgouros; 1. University Hospital Center and University of Lausanne, Switzerland; 2. Department of Radiology, Johns Hopkins University, Baltimore, MD, .

No. 499 Lutetium-177 Octreotate Radiopeptide Therapy of Endocrine Cancer: Tumor and Critical
3:06 PM Organ Dosimetry Paul Brayshaw; Phillip Claringbold; J Turner; 1. University of Western Australia, Fremantle Hospital, Fremantle, WA, Australia.

No. 500 Estimation of absorbed dose to the kidneys after treatment with 177Lu-DOTA-octreotate
3:18 PM Maria Larsson; Peter Bernhardt; Gertrud Berg; Johanna Svensson; Hakan Ahlman; Bo Wangberg; Eva Forssell-Aronsson; 1. University of Gothenburg, Department of Radiation Physics, Gothenburg, Sweden; 2. University of Gothenburg, Department of Oncology, Gothenburg, Sweden; 3. University of Gothenburg, Department of Surgery, Gothenburg, Sweden.

No. 501 A comparison of different image-based methods for kidney dosimetry in patients treated with 177Lu-DOTATATE
3:30 PM Mattias Nickel; Michael Ljungberg; Katarina Sjogreen-Gleisner; 1. Lund University, Clinical Sciences, Medical Radiation Physics, Lund, Sweden.

No. 502 Bone Marrow Dosimetry after [Lu-177-DOTA0,Tyr3]octreotate
3:42 PM Flavio Forrer; Eric Krenning; Peter kooij; Mark Konijnenberg; Dik Kwekkeboom; 1. Erasmus MC, Nuclear Medicine, Rotterdam, Netherlands; 2. Tyco Healthcare, Research and Development, Mallinckrodt Medical BV, Petten, Netherlands.

3:54 Brief panel discussion
ISRTRD PROGRAM

Wednesday, June 17
7:30 AM-9:00 AM

ISRTRD Refresher Course - Patient-Specific Dosimetry

Sponsored by the MIRD Committee and ISRTRD

**Summary**
Recent advances in patient-specific dosimetry will be reviewed.

**Educational Objectives**
Upon completion of this activity, the participant will be able to:
1. Explain what patient-specific dosimetry means and how it is applied.
2. List the advantages and disadvantages of this approach to patient dosimetry.
3. Understand future developments in patient-specific dosimetry

Organizer: George Sgouros, PhD
Moderator: Stephen C. Moore, PhD

7:30 AM - 9:00 AM  **Patient-Specific Imaging-Based Treatment Planning**
George Sgouros, PhD; Michael Ljungberg, PhD; Glenn Flux, PhD
# ISRTRD PROGRAM

**Wednesday, June 17**

**9:45 AM-11:15 AM**

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**Summary**

Dose-response studies in radionuclide therapy are reviewed. The role of radiobiological modeling in obtaining dose estimates that correlate with response is discussed.

**Educational Objectives**

Upon completion of this activity, the participant will be able to:

1. Describe clinical and pre-clinical studies investigating the relationship between absorbed dose and tumor or normal tissue response.
2. List radiobiological models with an impact may improve upon the dose-response relationship.
3. Examine the potential role of dose rate, RBE, and dose heterogeneity for radiation dose response.

**Organizer:** George Sgouros, PhD  
**Moderator:** Joseph A. O'Donoghue, PhD

**9:45 AM –10:05: AM**  **Concepts of Radionuclide Dose/Response Relationships in Normal Organs and Malignancies**  
Ruby Meredith, MD, PhD

**10:09 AM**  **Iodine-125 radioprobing study of the structure of human telomeric DNA**  
Timur Gaynutdinov; Ronald Neumann; Igor Panyutin; 1. NIH, Clinical Center, Radiology and Imaging Sciences, Bethesda, MD, United States.

**10:21 AM**  **Assessment of photon and electron internal organ dose for the University of Florida hybrid computational phantoms of the ICRP 89 reference male and female 1, 5, and 10-year-old**  
Choonsik Lee; Daniel Lodwick; Wesley Bolch; 1. University of Florida, Department of Nuclear and Radiological Engineering, Gainesville, FL, United States.

**10:33 AM**  **Image registration in the context of 3D SPECT dosimetry for radionuclide therapy**  
Katarina Sjogreen Gleisner; Michael Ljungberg; 1. Lund University, Medical Radiation Physics, Lund, Sweden.

**10:45 AM**  **Aortic Wall Modeling/Dosimetry in Lymphoma Patients Treated with Radioimmunotherapy**  
Robert Hobbs; Sebastien Baechler; Srinivasan Senthamizhchelvan; H Song; Bin He; Eric Frey; R Wahl; H Jacene; George Sgouros; 1. John Hopkins University, Baltimore, MD, United States; 2. University Institute of Radiation Physics, University of Lausanne, Switzerland

**10:57**  **Panel Discussion**