SOCIETY OF
NUCLEAR MEDICINE
AND MOLECULAR IMAGING

March 10, 2016

Chairman Stephen G. Burns
U.S. Nuclear Regulatory Commission
Mail Stop 0-16G4
Washington, DC 20555-0001

Re: NRC Training and Experience Requirements for Alpha- and Beta-Emitters

Dear Chairman Burns:

The Society of Nuclear Medicine and Molecular Imaging (SNMMI) is greatly concerned over some of the rhetoric being used in the debate on training and experience requirements for Alpha- and Beta-Emitters. SNMMI commends the Nuclear Regulatory Commission (NRC) Advisory Committee on the Medical Uses of Isotopes (ACMUI) Sub-Committee for addressing this important issue in their report submitted on March 10, 2016. Specifically the SNMMI supports the report which:

1. Reports that it is not possible to conclude that the current T&E requirements are the only, or even the principal, cause of the decreased use of radiopharmaceuticals like Zevalin® and Bexxar®, and because of the potential issues raised by the proposed changes in T&E, the subcommittee recommends against the reduction in the number of hours of T&E required.

2. Recommends that the ACMUI establish a standing sub-committee with the specific charge of periodically reviewing the T&E requirements currently in effect and making recommendations for changes as warranted.

As leading experts in this area, we respectfully request a meeting with the Commissioners as soon as possible to discuss the very real risks to reducing the training hours from 700 to 80. While it is true that the NRC requires as little as 80 hours of total training for oral I-131, alpha emitters are a totally different class of therapeutic radionuclides from beta-emitters like I-131 due to the potential for extreme toxicity from internal contamination and difficulty of detecting alpha-particle contamination for those with little training.

SNMMI is one of the largest medical societies serving individuals who perform and interpret advanced diagnostic imaging in nuclear medicine. Our 17,000 members represent radiologists practicing nuclear medicine, nuclear medicine physicians, technologists, physicists, nuclear cardiologists, and molecular imaging researchers. SNMMI is responsible for the promotion of research, technology development, publication of procedure standards, government and inter-societal relations, continuing education, and

community education as it relates to all aspects of positron emission tomography (PET) and general nuclear medicine.

A couple of years ago, SNMMI hosted two joint workshops with the National Cancer Institute (NCI). Both workshops were held at National Institutes of Health (NIH) and the purpose was to find the most productive strategies to ensure the potential benefits of targeted radionuclide therapy (TRT), which includes drugs such as Zevalin ® and Xofigo ®. There was a recognition of the need to discuss the challenges relating to the availability, supporting technology and interdisciplinary training/research. Many of the recommendations made at the workshop were in direct response to the barriers listed by industry representatives. The number of authorized users, however, was not listed among the barriers to adoption. I can assure you that SNMMI and its members have worked hard to ensure that patients receive the right treatment at the right time.

The results of both workshops were published in the *Journal of Nuclear Medicine (JNM)*. For your convenience, I have attached a copy of both articles.

Recommendations from the workshops include:

- The need for evidence-based clinical trials to prove effectiveness
- Developing centers of excellence to coordinate and translate advances from basic science to clinical use
- Increased interaction across the spectrum of stakeholders in targeted therapy
- Increased studies exploring personalized dosimetry
- Easing patient fears of radiation and the work-up needed
- Educating patients showing reduced toxicity than chemotherapy, where applicable
- Increase outreach and training – work with residency review committees across specialties to promote inclusion in training
- Maintenance of certification programs could be offered within and outside of the traditional core of nuclear medicine-oriented professional meetings

One of our biggest concerns is the rhetoric being used to describe the process by which Zevalin, Xofigo, and possibly other drugs, are delivered to the patient. We have heard this clinical process characterized as just “patient-ready doses prepared at, and dispensed from, licensed radiopharmacies.” We think it is essential that the NRC Commissioners understand the full range of activities performed by multiple personnel in the delivery of radioactive therapeutics. As previously stated, alpha emitters are a separate class of therapeutic radionuclides from beta-emitters due to the potential for extreme toxicity from internal contamination and difficulty of detecting alpha-particle contamination for those with little training. Will an authorized user with 80 hours of training be prepared to clean spills, will they understand how to prepare an area of treatment, will they understand safe limits, will they have a dose calibrator in order to reduce the dose if necessary, will they know how to dispose of the tubing, flush the

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IV, dispose of the syringes, will there be competent supervision of technologists and ancillary staff? It isn't as easy as just "pushing a button."

In conclusion, SNMMI does not support training and experience modifications to the NRC's regulation. A reduction to 80 hours would establish requirements at an inappropriate level for an entire class of current and future therapeutics. We respectfully request a meeting at your earliest convenience to discuss this very important issue. Please feel free to contact me directly, or have your staff contact Susan Bunning, Director of Health Policy and Regulatory Affairs, at (703) 326-1182 or sbunning@snmmi.org.

Sincerely,

Hossein Jadvar, MD, PhD, MPH, MBA, FACNM
SNMMI President

CC: Commissioners, Kristine L. Svinicki, William C. Ostendorff, and Jeff Baran

Proceedings of the Second NCI–SNMMI Workshop on Targeted Radionuclide Therapy

Frederic Fahey[1], Katherine Zukotynski[2], Hossein Jadvar[3], and Jacek Capala[4], with input from the organizing committee, contributors, and participants of the second NCI–SNMMI Workshop on Targeted Radionuclide Therapy

[1]Boston Children's Hospital and Harvard Medical School, Boston, Massachusetts; [2]Sunnybrook Health Sciences Centre, University of Toronto, Toronto, Ontario, Canada, and Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts; [3]University of Southern California, Los Angeles, California; and [4]National Cancer Institute, National Institutes of Health, Bethesda, Maryland

In 2013, the Society of Nuclear Medicine and Molecular Imaging (SNMMI) and the National Cancer Institute (NCI) partnered for the first time to host a joint workshop on targeted radionuclide therapy (TRT) (*1*). Broad discussion at that gathering suggested the need for a follow-up workshop bringing together both industry and government agencies in dialogue on educational and regulatory issues emphasizing further development of TRT. The second workshop, in October 2014, included individuals from multiple scientific disciplines, industry, government agencies, and international collaborators. The goal was to review what has been learned to date about the implementation of TRT, discuss the most promising agents moving forward, and investigate a path to bring them to the clinic. Cochaired by Drs. Frederic Fahey and Katherine Zukotynski, the 2-day event assembled a small but diverse group of stakeholders (Fig. 1) for discussion in both structured and open-forum formats. This white paper briefly summarizes the discussion on TRT that took place at the workshop and offers next-step recommendations.

LESSONS LEARNED ABOUT TRT

Through a series of presentations, individuals representing different professional perspectives on TRT offered insight on lessons learned and current challenges.

Radiochemistry

Dr. Cathy Cutler (University of Missouri) reviewed the status of TRT radiochemistry, described the experience at the University of Missouri Research Reactor Center, and explored the potential role of large-animal models in clinical trials of TRT.

Today, therapeutic use of radionuclides represents about 5% of nuclear medicine procedures. The optimal radionuclide for TRT is often target- and vector-dependent. Consideration should be given to decay characteristics (mode of decay, half-life, purity, specific activity), radiolabeling chemistry (simplicity, stability, pharmacokinetics), cost, and ability to access sufficient quantities for clinical trials or routine use. The choice of chelate, method of radiolabeling, time for production and formulation, ability to automate, and methods of purification and quality control are all important. The mode of production can affect sample purity and cost, and the ability to automate manufacturing can affect availability.

The advantages of TRT include the ability to tailor tumor dose versus normal-tissue dose (which is not possible with chemotherapy), selective targeting of disease, and cross-fire irradiation, among others. Cross-fire irradiation allows killing of tumor cells that are not directly targeted, which is important for treating heterogeneous tumor tissue.

Traditionally the Food and Drug Administration (FDA) has mandated large-batch radiopharmaceutical production to ensure uniformity and enable extensive quality control testing. However, few sites have the necessary facilities or expertise. An alternative production method was implemented for ^{131}I-tositumomab (Bexxar; GlaxoSmithKline) and ^{90}Y-ibritumomab tiuxetan (Zevalin; Spectrum Pharmaceuticals, Inc.); kits containing the antibody and radionuclide were shipped to on-site radiopharmacies, which produced the compound as needed. Although this method eliminated large-scale centralized production, access to kits and specialized transportation were problematic. Another alternative was the development of generators. However, access to generators was limited. Finally, the production of medium-sized radiopharmaceutical batches at a limited number of regional centers, similar to the method for manufacturing PET radiopharmaceuticals, has been suggested. This model may be more cost-effective than large-batch production, eliminate reliance on a single site, and enable hospitals and clinics to order a unit dose for administration, which is often preferred.

The University of Missouri Research Reactor Center experience supporting the ^{166}Ho-1,4,7,10-tetraazacyclododecane-1,4,7,10-tetramethylene-phosphonate (DOTMP) clinical trial illustrated challenges associated with radiopharmaceutical production and distribution. The University of Missouri Research Reactor had to process 740–7,400 GBq (20–200 Ci) of ^{166}Ho, produce clinical-grade ^{166}Ho-DOTMP, and access a high-flux region 2–4 d per week for insertion and removal of targets. Dedicated hot cells and a 6-barrel flux trap with tubes that could be removed while the reactor was running were used. A partnership with industry was forged to bolster cGMP experience.

The experience at the University of Missouri with a canine model for testing radioassays illustrated the potential role of

Received Apr. 8, 2015; revision accepted May 11, 2015.
For correspondence or reprints contact: Frederic Fahey, Boston Children's Hospital, 300 Longwood Ave., Boston, MA 02115.
E-mail: frederic.fahey@childrens.harvard.edu.
Published online May 21, 2015.

DOI: 10.2967/jnumed.115.159038

FIGURE 1. Participants of the second NCI–SNMMI Workshop on Targeted Radionuclide Therapy.

large-animal models in TRT clinical trials. To evaluate ^{177}Lu-DOTMP toxicity, researchers from the University of Missouri studied the effects of radiopharmaceutical administration on dogs (*2*). The preliminary findings supported evaluation of the radiopharmaceutical as a potential therapy for primary and metastatic bone cancer in both dogs and humans. Trials in dog models of spontaneously occurring cancers that mimic the human conditions facilitate protocol optimization and translation to humans.

Dr. Cutler concluded her talk by addressing the role of radiobiology in TRT, an important and largely unexplored topic. She suggested that radiochemists have a key role to play in the future of TRT and that collaboration with both physicians and members of the public is needed to demonstrate the success and safety of TRT.

Industry

Dr. Lee Allen and Dr. Rick Satitpunwaycha (Spectrum Pharmaceuticals) provided insight into TRT commercialization challenges, focusing on ^{90}Y-ibritumomab tiuxetan, a CD20-directed regimen available in more than 40 countries and the first radioimmunotherapy to receive FDA approval in the United States.

^{90}Y-ibritumomab tiuxetan may be used to treat relapsed or refractory low-grade, follicular, or transformed B-cell non-Hodgkin lymphoma, including rituximab-refractory follicular non-Hodgkin lymphoma. In describing 2 key studies for FDA approval, Dr. Allen suggested that neither radioimmunotherapy response nor toxicity was an obstacle. The overall response rate of ^{90}Y-ibritumomab tiuxetan was 74% in one study, a single-arm trial of 54 patients with relapsed, rituximab-refractory follicular lymphoma. The overall response rate was significantly higher in a second study, a randomized, open-label multicenter comparison with rituximab in 130 patients with relapsed or refractory low-grade or follicular non-Hodgkin lymphoma (83% vs. 55%, $P < 0.001$). The complete response rates to radioimmunotherapy were also high: 15% in one study and 38% in the other study. Regarding adverse effects, the principal toxicity was prolonged, severe cytopenia. The most common nonhematologic adverse reactions were fatigue (33%), nasopharyngitis (19%), and nausea (18%). In a phase III randomized, controlled trial of ^{90}Y-ibritumomab tiuxetan for consolidation in patients with advanced follicular non-Hodgkin lymphoma, the overall incidence of secondary malignancies was 13% (*3*). Dr. Allen noted that although oncologists are concerned about the potential for secondary malignancies, ^{90}Y-ibritumomab tiuxetan toxicities are manageable, with the advantage of a one-time administration versus multiple cycles of chemotherapy.

However, despite the apparent effectiveness, safety, and convenience of radioimmunotherapy, use is low. ^{90}Y-ibritumomab tiuxetan was used to treat 889 patients in 2010, compared with 551 in 2013, and was projected to be given to approximately 400 patients in 2014. In an effort to augment data, the manufacturer recently initiated 3 randomized clinical trials including ^{90}Y-ibritumomab tiuxetan, all of which have now been terminated because of low patient accrual. For example, the target accrual for a trial of patients with diffuse large B-cell lymphoma was 500, but after 2 y only 70 patients had been enrolled. Indeed, Dr. Satitpunwaycha said GlaxoSmithKline's decision to withdraw ^{131}I-tositumomab from the market in February 2014 was because "use of the regimen has been extremely limited and is projected to decline." Only 55 doses of ^{131}I-tositumomab were sold in North America in 2013.

Recently Spectrum Pharmaceuticals conducted a survey of oncologists that found several possible reasons for low ^{90}Y-ibritumomab tiuxetan use: patient concern about radiation, physician concern about myelodysplastic syndrome, availability of new oral agents, the requirement for platelets to be over 100,000 and bone marrow involvement to be less than 25%, and perception that ^{131}I-tositumomab and ^{90}Y-ibritumomab tiuxetan had been taken off the market.

Dr. Allen and Dr. Satitpunwaycha concluded that several issues need to be addressed for radioimmunotherapy to be adopted into clinical practice, including improving collaboration between physicians to allow easy access to radioimmunotherapy, training physicians to use radioimmunotherapy, bolstering support from opinion leaders, improving ease of assessing patient eligibility and posttherapy follow-up, and resolving reimbursement concerns with the Affordable Care Act. In short, ^{90}Y-ibritumomab tiuxetan may be an effective therapy that is being avoided, at least in part, because of logistic challenges related to access, lack of experience, and competition from newer agents.

Lymphoma Therapy

Dr. Janis O'Malley (University of Alabama at Birmingham) discussed the role of radioimmunotherapy in lymphoma, using the experience with ^{131}I-tositumomab and ^{90}Y-ibritumomab tiuxetan as examples of why effective therapies sometimes fail after reaching the commercial market. Background was provided on the incidence of lymphoma in the United States, prognosis, and management (*4–6*).

Several trials have shown increased survival in patients with lymphoma treated with the anti-CD20 monoclonal antibody (mAb) rituximab, which induces complement-dependent cytotoxicity and antibody-dependent cellular toxicity (*7*). Other immunotherapy agents approved for lymphoma include the anti-CD52 mAbs alemtuzumab and ofatumumab and the anti-CD30 antibody–drug conjugate brentuximab vedotin (*8*). Radioimmunotherapy with mAbs that bind the CD20 and CD30 antigen may be effective for patients with lymphoma. In the phase III FIT trial for patients with previously untreated, advanced follicular lymphoma, median progression-free survival (PFS) was 37 mo in the ^{90}Y-ibritumomab tiuxetan arm, compared with 13.5 mo in controls ($P < 0.001$) (*9*). However, despite their success and the potential for using radioimmunotherapy to target antibody markers beyond CD20 and CD30, Dr. O'Malley noted that these agents have fallen

out of favor with many oncologists. This may be due, at least in part, to concerns about cost, radiation effects, and a perceived lack of data from large randomized trials comparing radioimmunotherapy with nonradioactive lymphoma therapy. There is also concern about a potential negative financial effect from patient referral to a nuclear medicine physician or a radiation oncologist (*10*).

Dr. O'Malley reviewed the experience with ^{131}I-tositumomab since FDA approval in 2003 through discontinuation of sales in February 2014 due to low use and suggested that a possible reason for low use could be the treatment protocol. Multiple visits were needed for dosimetry, in order to determine the administered activity to maximize tumor response and minimize toxicity. Also, the mAb was labeled with ^{131}I, which could result in thyroid exposure, necessitating premedication. The protocol for ^{90}Y-ibritumomab tiuxetan administration is less involved because dosimetry is not required, the therapy can be given on an outpatient basis, and it is well tolerated with no myelotoxicity at the dose ranges that have been studied. However, Dr. O'Malley noted that, despite data supporting radioimmunotherapy and its inclusion in National Comprehensive Cancer Network Guidelines, few oncologists prescribe ^{90}Y-ibritumomab tiuxetan.

Dr. O'Malley concluded her talk with a review of challenges and opportunities for radioimmunotherapy in lymphoma. Large randomized trials are difficult to design, given the rapidly changing available pharmaceuticals, but would bolster existing data. Reimbursement issues need to be addressed, and the misperception that radioimmunotherapy is more expensive than chemotherapy needs to be corrected. Increasing personnel trained to administer radioimmunotherapy could lead to improved access, and advances in dosimetry could maximize the ability to administer treatment early and effectively. Research should be done on additional targets beyond CD20, new labeling agents, and improved antibodies.

Peptide Receptor Radionuclide Therapy (PRRT) of Neuroendocrine Tumors (NETs)

Dr. Richard Baum (Zentralklinik Bad Berka) discussed PRRT in NETs of the pancreas and midgut.

NETs are the second most common gastrointestinal cancer, and although the incidence is low, prevalence is high: approximately 120,000 cases in the United States, 296,000 in Europe, and 2.4 million worldwide. Current FDA-approved therapies for metastatic NET (G1/G2) include somatostatin analogs and tyrosine kinase inhibitor/mammalian target of rapamycin pathway inhibitors at a cost of approximately $4,000 per month. Somatostatin analogs do not produce a complete response and rarely result in partial response. The complete response rate for mammalian target of rapamycin pathway inhibitors is low and may be associated with significant toxicity, including drug-induced death (*11–13*).

Dr. Baum presented findings from the European Neuroendocrine Tumor Society Center of Excellence at Zentralklinik Bad Berka and from German multiinstitutional registry studies. He noted that PRRT improves PFS and overall survival by several years in metastatic or progressive G1–G2 NETs compared with other treatment modalities regardless of previous therapy. Further, the combination of ^{177}Lu- and ^{90}Y-based PRRT (duo PRRT) may be more effective than either radionuclide alone. Thus, in patients with progressive NETs, fractionated, personalized PRRT with lower doses of radioactivity given over a longer period (Bad Berka Protocol) may result in an excellent response even in advanced cases.

A German multiinstitutional registry study with prospective follow-up in 450 patients also indicates that PRRT is an effective therapy for patients with G1–G2 NETs, irrespective of previous therapies, with a survival advantage of several years compared with other therapies and only minor side effects. Median overall survival of all patients from the start of treatment was 59 mo. Median PFS measured from the last cycle of therapy was 41 mo. Median PFS of pancreatic NET was 39 mo. Similar results were obtained for NET of unknown primary (median PFS, 38 mo) whereas NET of the small bowel had a median PFS of 51 mo. Side effects such as nephro- or hematotoxicity were observed in only 0.2% and 2% of patients, respectively.

Patient selection for personalized PRRT (Bad Berka Score) takes into account a multiplicity of factors including standardized uptake values on PET/CT, renal function, hematologic status, liver involvement, extrahepatic tumor burden, and Ki-67 index. More than 9,000 ^{68}Ga PET/CT clinical studies have been done at Bad Berka since 2004. In June 2014 the European Medicines Agency approved for the first time a ^{68}Ga generator, and 8 different ^{68}Ga-labeled radiopharmaceuticals are now in clinical use at the center. Dr. Baum underscored the advantages of ^{68}Ga-somatostatin PET/CT (e.g., using DOTATOC, DOTATATE, or DOTANOC) to determine which patients are most likely to benefit from radionuclide therapy.

Experience with PRRT in Europe dates to 1994, when PRRT with high-dose ^{111}In-octreotide was first performed by Krenning's group in Rotterdam (*14*). The concept has since expanded to centers throughout the world with no commercial support. Established in 2011, the European Neuroendocrine Tumor Society Center of Excellence at Zentralklinik Bad Berka now has more than 1,200 patient visits and administers more than 500 cycles of PRRT every year. Ten physicians at the Center and a dedicated multidisciplinary team of experts in internal medicine; endocrinology; gastroenterology; oncology; abdominal, thoracic, spinal, and heart surgery; radiology; and interventional radiology are directly involved in therapy. An individual treatment plan based on a tumor board consensus is developed for each patient. Four to 6 cycles of PRRT with low to intermediate dosages of radioactivity, and as many as 10 cycles, are administered. For some patients, ^{90}Y and ^{177}Lu are used in combination, given sequentially or concurrently (tandem PRRT). An intraarterial route is used to selectively target liver metastases and large, inoperable primary tumors. All clinical data on PRRT are entered in a prospective clinical database, which now includes more than 1.4 million datasets.

In the Bad Berka experience, which includes treatment of more than 1,251 patients with more than 4,000 therapy cycles, up to 10 cycles of PRRT given over several years were well tolerated by most patients (*15*). With nephroprotection using amino acids, severe renal toxicity can be avoided or reduced. Hematologic toxicity is usually mild to moderate (except for rare cases of myelodysplastic syndrome, which occur in 2%–3%). Although cure of NETs is rarely possible with PRRT, 85% of patients have improvement in clinical symptoms and 95% of underweight patients gain 5% or more of their body mass. In addition, neoadjuvant PRRT can be administered in cases of inoperable NET to render the tumor operable by inducing radiation necrosis, leading to decreased tumor size. In concluding his talk, Dr. Baum emphasized that PRRT should be done at specialized centers because NET patients need individualized interdisciplinary treatment and long-term care. PRRT can be effectively combined with transarterial chemoembolization, radiofrequency ablation,

chemotherapy (e.g., using capecitabine/5-fluorouracil, temozolomide, or doxorubicin), and kinase inhibitors (e.g., everolimus).

Prostate Cancer Therapy

Dr. Fatima Karzai (NCI) presented an overview of prostate cancer therapy, highlighting the role of TRT.

Prostate cancer is the most common malignancy in men, with a lifetime risk of 1 in 6. Age and family history are contributory, and genetic predisposition may play a role in 5%–10% of cases. Distant metastases (most commonly to bone) are present in 4% of cases at diagnosis, and more than 20% of men with prostate cancer will die of the disease. Clinical parameters such as prostate-specific antigen, Gleason score, and time from surgery to biochemical recurrence are used to stratify patients at high risk of cancer-specific mortality after radical prostatectomy.

The changing landscape of prostate cancer treatment in recent years was reviewed, including the use of abiraterone, enzalutamide, and $^{223}RaCl_2$ (an α emitter with a half-life of 11.4 d, also known as Xofigo [Bayer Healthcare Pharmaceuticals]). Dr. Karzai discussed the need for patient selection to tailor treatment for localized prostate cancer (i.e., watch and wait, androgen deprivation therapy, prostatectomy), locally advanced disease (i.e., prostatectomy or radiotherapy with androgen deprivation therapy), and metastatic disease. The role of androgen deprivation with surgical castration or administration of luteinizing hormone–releasing hormone agonists, antagonists, or antiandrogens; chemotherapy; external-beam radiation therapy (EBRT); and immunotherapy was discussed. The different FDA-approved drugs for metastatic castration-resistant prostate cancer (mCRPC) therapy, including docetaxel, sipuleucel-T, abiraterone, cabazitaxel, enzalutamide, and $^{223}RaCl_2$, were reviewed. Docetaxel is associated with increased median survival, quality of life, and pain response in men with mCRPC, but adverse effects include central nervous system toxicity (20%–58%), neutropenia (84%–99%), and pulmonary reactions (41%). Sipuleucel-T, an active cellular immunotherapy, has a median survival benefit of 4.1 mo with adverse effects that include cerebrovascular events in 3.5% of patients (*16*). Abiraterone is a CYP7 inhibitor that blocks androgen synthesis by the adrenal glands, testes, and prostate cancer cells. In clinical trials, an overall survival benefit of 14.8 mo versus 10.9 mo for placebo was demonstrated. Adverse effects include edema (25%–27%), fatigue (39%), and lymphocytopenia (38%). Cabazitaxel, a novel taxane, has shown improved PFS and overall survival in mCRPC compared with mitoxantrone (2.8 and 15.1 mo vs. 1.4 and 12.7 mo, respectively). Adverse effects include fatigue (37%), anemia (98%), and neutropenia (94%). Enzalutamide is a small-molecule androgen receptor antagonist that prevents nuclear translocation and coactivator recruitment. In a phase III study, median survival was 18.4 mo for enzalutamide versus 13.6 mo for placebo. Adverse effects include peripheral edema (15%), fatigue (51%), and neutropenia (15%). Radionuclides have an established role in palliation of metastases from prostate cancer. In phase III trials, ^{153}Sm (a β and γ emitter) and ^{89}Sr (a β emitter) have demonstrated safety and efficacy for pain palliation in patients with mCRPC, and $^{223}RaCl_2$ (received FDA approval in 2013) has been shown to improve overall survival (*17*). In the ALSYMPCA phase III trial, median survival for men with mCRPC treated with $^{223}RaCl_2$ was 14.9 mo, versus 11.3 mo for placebo ($P < 0.001$). Adverse effects associated with $^{223}RaCl_2$ include leukopenia (35%), thrombocytopenia (31%), and neutropenia (18%).

Dr. Karzai concluded her remarks with recommendations on future directions, noting that this is an exciting time to be treating prostate cancer given the rapidly changing landscape of available medications. For example, results from the CHAARTED trial, presented at the 2014 meeting of the American Society of Clinical Oncology, showed a survival impact for androgen deprivation therapy plus docetaxel versus androgen deprivation therapy alone for hormone-sensitive newly metastatic disease, altering the standard of care for these patients (*18*). However, an understanding of mechanisms of resistance to drugs such as docetaxel is of importance in improving outcomes for men with metastatic prostate cancer. Studies are needed to elucidate ways to sequence available agents and determine novel strategies for therapy to overcome resistance.

OPPORTUNITIES

Targets and Targeting Agents

Dr. Janice Reichert (Reichert Biotechnology Consulting LLC) presented an overview of TRT based on business intelligence research available as of September 2014. Her presentation focused on 4 questions: Who is developing relevant biosimilar antibodies that might be amenable to a radiolabeled form? Which TRTs under development use mAbs effective in a cold form? Which cold mAbs have failed in phase II or III trials because of lack of efficacy? Which mAbs have already been labeled with a radionuclide?

Approximately 200 antibodies are currently under investigation in the United States for cancer, 40% of which are noncanonical and have undergone extensive protein engineering and design to enhance functionality. Every year, approximately 50 novel antibodies enter clinical studies in the United States. In addition, some patents for antibody therapeutics first approved in the late 1990s and early 2000s have expired, and thus biosimilar versions of these products are also in clinical development. Three biosimilar mAbs relevant for TRT—bevacizumab, rituximab, and trastuzumab—are in phase III studies with expected completion dates ranging from 2015 to 2017.

Half the clinical trials with novel antibodies are in oncology, and many are terminated because of lack of efficacy. Examples of phase II trial failures include carlumab in prostate cancer, dacetuzumab in diffuse large B-cell lymphoma/chronic lymphocytic leukemia, tigatuzumab in breast cancer, and tovetumab in glioblastoma and non–small cell lung carcinoma (NSCLC). The most recent phase III trial failure was with a fusion protein onartuzumab for gastric cancer; other examples include farletuzumab in ovarian cancer, figitumumab in lung cancer, zalutumumab in head and neck cancer, and zanolimumab in T-cell lymphoma.

Cold molecules currently in phase III studies for which radiolabeling could be considered include bavituximab (NSCLC) and elotuzumab (multiple myeloma). Rilotumumab is being studied commercially (Amgen; gastric cancer) as well as in the government and nonprofit sectors (NCI; NSCLC).

Nine radiolabeled mAbs relevant for TRT are currently in commercially supported studies. Two are in phase I development (^{90}Y-OTSA101, ^{212}Pb-trastuzumab [trastuzumab]), 6 are in phase I/II or phase II development (^{177}Lu-DOTA-HH1 [tetulomab], ^{90}Y-IMMU-102 [epratuzumab], ^{225}Ac-huM195 [lintuzumab], ^{131}I-chTNT-1/B [chTNT], ^{131}I-BC8 [BC8], ^{177}Lu-ATL-101 [J591]), and one is in phase III development (^{90}Y-IMMU-107 [clivatuzumab]). Four mAbs—trastuzumab, epratuzumab, lintuzumab, and

J591—have been studied in cold as well as radiolabeled forms. Adding a radionuclide is only one of many ways to enhance the functionality of mAbs in oncology. Other strategies being tested in clinical studies include glycoengineering and development of antibody–drug conjugates and bispecific antibodies.

Dr. Reichert also urged consideration of molecules in development that are not antibodies, such as the peptibody trebananib, which targets and binds to Ang-1 and Ang-2 and is in a phase III trial for ovarian cancer.

Dr. Reichert concluded her talk with a review of mAbs that incorporate diagnostic radionuclides and a perspective on the best sources of mAbs. The only diagnostic mAb incorporating a radioisotope still on the U.S. market is ^{111}In-capromab (ProstaScint; EUSA Pharma), a murine IgG1κ targeting prostate-specific membrane antigen. Biosimilar antibodies are the best sources of mAbs for TRT, with trastuzumab, bevacizumab, and rituximab projected to enter the market in the European Union or United States in several years. Many options also exist among the cold mAbs that have failed in phase II or III for efficacy or are currently in phase III, with the choice dependent on the target.

Radiochemistry

Dr. Martin Brechbiel (NCI) described the range of available radionuclides and the conjugation chemistry needed for TRT applications.

Most radionuclides are metals, and the importance of choosing an appropriate chelating agent was emphasized. A discussion on classic coordination chemistry criteria ensued, and the importance of considering cavity size versus ionic radius, denticity, donor group character, formation kinetics, and dissociation rates was presented. Dr. Brechbiel suggested that the most effective and easiest way to evaluate a chelating agent is with in vivo biodistribution studies. In vitro studies of thermodynamic stability, acid-catalyzed dissociation, and serum stability to predict failure, also can be performed. Although acyclic compounds such as diethylenetriaminepentaacetic acid tend to have faster formation kinetics and form at room temperature, macrocyclic compounds such as DOTA are more stable but require heating.

A detailed discussion of radionuclides and chelating agents followed, starting with actinium and ending with zirconium. For example, it was noted that actinium is being studied in multicenter phase III trials using different DOTAs, although the radiolabeling efficiency is poor (*19,20*). Several chelating agents exist for ^{212}Bi and ^{213}Bi; however, the clinical use of these radionuclides is challenging because of their short half-lives. Coordination chemistry for copper is well established, whereas for thorium it could be improved. Radiolabeling of ^{89}Zr with desferrioxamine has been studied but is not highly stable, as demonstrated by localization of the uncomplexed element in bone (*21*).

In concluding his remarks, Dr. Brechbiel suggested that most metallic radionuclides of interest for TRT have adequate chelation chemistry but that there are opportunities to fine-tune the science. CHX-A diethylenetriaminepentaacetic acid has proven suitable for in vivo use with ^{111}In,^{86}Y, ^{90}Y, ^{177}Lu, ^{212}Bi, and ^{213}Bi, whereas C-DOTA and other DOTAs are suitable for ^{111}In, ^{86}Y, ^{90}Y, ^{177}Lu, ^{225}Ac, and ^{227}Th. C-NOTA and other NOTAs are suitable for ^{67}Ga, ^{68}Ga, ^{111}In, ^{64}Cu, and ^{67}Cu. Desferrioxamine can be used in vivo with ^{89}Zr, and sarcophagines are suitable for use with ^{64}Cu and ^{67}Cu. Above all, Dr. Brechbiel noted, the choice of chelating agent must be tailored to the TRT application and radionuclide being used.

Radioisotopes and Treatment Planning

Dr. Barry Wessels (University Hospitals of Cleveland) described new methods of evaluating dose–response relationships for combination therapies, based on lessons learned from EBRT. Radiobiology as a game changer in maximizing the time-averaged therapeutic ratio for successful radioimmunotherapy was emphasized.

The principles of molecular radiobiology were reviewed, and the availability of therapeutic radionuclides and associated emission characteristics were discussed. It was noted that availability has not changed substantially in nearly 30 years. The choice of radionuclide for TRT should take into consideration the emitted particle range, carrier uptake nonuniformity, amount of target radiation delivered, and time-averaged therapeutic ratio as a function of physical and biologic half-life. The utility of small-animal SPECT was reviewed. With α-particle dosimetry, the mean dose to macroscopic target volume is not predictive of biologic effect, the mean dose to marrow is not predictive or indicative of therapeutic effect, and the dose to cells is dependent on the spatial distribution of emitters relative to the target cell population.

The importance of dosimetry and development of a suitable treatment plan as with EBRT was emphasized. A computerized tool for multicellular dosimetry (MIRD cell, version 2.0) was highlighted (*22*). Principles of human dosimetry were discussed, underscoring the tenet that calculated dose is not equivalent to biologic dose. It was noted that radiation quality, subcellular distribution, radiosensitivity, dose rate, repair, and repopulation all contribute to absorbed dose. The biologically effective dose quantifies the biologic effect of a radiation therapy. For radioimmunotherapy, fractionation schemes can be converted to biologically effective dose values in grays, which can then be added or subtracted and converted back to biologically equivalent dose schemes.

Turning to advances in dosimetry, Dr. Wessels described SPECT guidance, studies of spheres for selective internal radiation therapy, and patient-specific 3-dimensional radiobiologic dosimetry (3D-RD). It was suggested that SPECT may be helpful for TRT planning. Also, ^{90}Y PET has been used for quantification of liver dosimetry in selective internal radiation therapy. In a pediatric patient with thyroid cancer and lung metastases, more aggressive therapy with ^{131}I is possible using treatment planning with ^{124}I PET-based 3D-RD. A retrospective analysis of conventional dosimetric methodologies yielded absorbed dose estimates consistent with 3D-RD, but the necessary corrections might not have been known without use of the technology in this case.

The advantage of EBRT combined with TRT versus a single agent was discussed. Use of 2 different modalities together could increase the total tolerated radiation dose because each modality is associated with different nontarget organs at risk. Clinical applications could include, among others, paraganglioma (^{131}I-metaiodobenzylguanidine) and lesions of the bone (^{153}Sm-ethylenediaminetetramethylene phosphonate), brain (^{131}I-radretumab), and liver (^{90}Y-microspheres) (*23*).

In concluding his remarks, Dr. Wessels noted that newer methods of combining more accurate dosimetric information with radiobiologic models have led to an increased understanding of TRT dose–response data. Radioimmunotherapy patients are often undertreated because of fear of side effects. Application of the biologically effective dose and equivalent uniform dose radiobiologic model to TRT has been reasonably successful. Using the model within clinically relevant limits can provide guidance on dose–response effects for new fractionation schemes, combination therapy, and clinical trial design.

Nuclear Medicine

Dr. Steven Larson (Memorial Sloan Kettering Cancer Center) reviewed the current status and promise of TRT from the perspective of a nuclear medicine physician. Research at the Memorial Sloan Kettering Cancer Center on a theranostic approach to solid tumors, in particular thyroid cancer, was described.

^{131}I is often used for ablation of well-differentiated thyroid cancer; however, in many patients, the disease progresses after ablation, possibly because of low uptake. There is a high prevalence of *BRAF* mutations in thyroid cancer refractory to treatment with ^{131}I, and inhibition of the oncogene may increase uptake. In a study by Memorial Sloan Kettering Cancer Center researchers, a novel theranostic approach was used in a group of thyroid cancer patients who were refractory to ^{131}I therapy, whereby ^{124}I was used to select those patients (~50%) whose radioiodine uptake could be restored by treatment with selumetinib (a mitogen-activated protein kinase and mitogen-activated protein kinase kinase 2 inhibitor) over a 4-wk treatment. Patients with dramatic improvement in radioiodine uptake (as predicted by ^{124}I PET) were treated, and 5 of 7 had RECIST-based responses to ^{131}I therapy of their thyroid malignancy (*24*). This is an example of precision medicine in which patients who responded could be treated with radioiodine with therapeutic benefit whereas patients with a minimal response could be directed to other therapies and avoid ineffective ^{131}I treatment and side effects. Tumors with *RAS* mutations were particularly susceptible to this strategy.

Moving beyond applications in thyroid cancer, Dr. Larson reviewed work by Memorial Sloan Kettering Cancer Center researchers on theranostic agents for imaging and treating other solid tumors. Radiolabeled 3F8 and 8H9 have been studied in recurrent neuroblastoma. Compartmental intrathecal antibody-based radioimmunotherapy has shown promise in metastatic central nervous system neuroblastoma. Preclinical research is ongoing on multistep targeting, whereby bispecific antibodies serve as targeting vectors for pretargeted radioimmunotherapy (*25*).

Dr. Larson concluded by emphasizing the potential of theranostics to improve patient selection for radioimmunotherapy and predict those likely to enjoy a meaningful response with minimal toxicity. For thyroid cancer, the goal, given the methods currently available, should be cure, not just disease control.

HURDLES AND INCENTIVES

Regulatory Affairs

Dr. Paula Jacobs (NCI) reviewed regulatory requirements for submitting an Investigational New Drug (IND) application to the U.S. FDA (*26*), noting that other countries have similar but not identical requirements and regulatory processes. The elements of an IND were explained, and special issues for metal-containing drugs were described.

The purpose of an IND is to gain exemption from the law requiring an approved marketing application for a drug before transport or distribution across state lines. An IND should be prepared after preliminary in vivo pharmacology and toxicity studies have been completed in animal models. The FDA's assessment of an IND is designed to ensure that a clinical protocol is not unnecessarily risky for the patient population in which it is being tested. The agency has 30 days to review the submission, and applicants can expect to receive "requests for information" that require an immediate response.

Three categories of information are required in an IND: data from animal pharmacology and toxicology studies; specifics on chemistry, manufacturing, and controls; and a detailed protocol for the clinical study. The preclinical data are reviewed for safety, and the clinical investigator's qualifications are evaluated. Efficacy is a secondary concern in early trials. It is important to remember that INDs are "living" documents, that is, an annual report is required, adverse events must be reported, and protocol amendments as well as new protocols must be submitted to the FDA. Investigators submitting INDs are expected to understand the FDA guidance regarding documents and provide a coherent and defensible biologic rationale. Preclinical data must document bioactivity in vitro and in vivo; absorption; distribution, metabolism, and excretion; and toxicology. For radiopharmaceuticals, dosimetry is required. The clinical plan must be relevant and supportable, with a strong emphasis on patient safety, and provide the framework for future research.

The regulatory path is the same for small molecules, most biologicals, and radiolabeled drugs, but the strategy used to apply for an IND may differ depending on the compounds involved, pharmacokinetics, pharmacodynamics, and dose escalation. A new protocol can be filed under an existing IND. Radioactive drugs that have been used in humans but will be studied in a research protocol that does not involve therapy can be approved by an FDA radioactive drug research committee. If a new IND is filed with a letter of agreement associated with another IND, only new information (not in the previously approved IND) need be submitted. All sections must be completed for new, standalone INDs.

Most traditional INDs are investigator-initiated and use a single agent that is expected to proceed to phase III trials and a new drug application (NDA). Extensive preclinical data typically are required, and dose escalation is involved. With an exploratory IND (x-IND, phase 0), up to 5 agents can be explored under a single IND for microdose studies designed to evaluate pharmacokinetics or specific target imaging but not therapeutic effects. A microdose is defined as less than 1/100th of the dose calculated to yield a pharmacologic effect and less than 100 μg of a small molecule or less than 30 nmol of a protein. Fewer preclinical data are expected, and resubmission as a traditional IND is required to continue development if studies done under an x-IND are successful. Of note, an x-IND can also be called an e-IND, which unfortunately is also the terminology for an emergency IND.

Dr. Jacobs provided links to FDA guidance on the IND process and noted that all the information required for an IND except the clinical aspects can be "imported" from another IND by a letter of reference. Details were provided about components of the chemistry, manufacturing, and controls; pharmacology and toxicology; and in vitro and in vivo testing sections. Information required for metal-containing drugs includes data on exchange with biologic metals and protein binding and absorption, distribution, metabolism, and excretion of all components. Robust analytic techniques are necessary to quantify both metal and organic components in biologic matrices. Special concern exists about retained components and metabolites.

It was noted that toxicology studies can be a major barrier to IND filing. FDA guidance typically demands 2 species and multiple studies, which can be expensive, lengthy, and require a lot of material. However, the initial program is negotiable early in the IND process if the proposed program is supported by good science that ensures patient safety. Special characteristics that inform nonsafety evaluations are mass dose; route of administration; frequency of use; proposed test population; biologic, physical, and effective half-lives; data on similar drugs; and specific FDA guidance for the specific drug class.

Dr. Jacobs concluded her remarks with a regulatory affairs perspective on ^{223}Ra-dichloride. In vitro studies in the ^{223}Ra-dichloride NDA documented survival, DNA damage, cell cycle effects, and osteoclast effects. In vivo efficacy data were on dose, mechanism of action, and survival in a model. Absorption, distribution, metabolism, and excretion studies were performed in mice, rats, and dogs. Toxicology studies were performed in mice, rats, and dogs plus local irritation in rabbits. No genotoxicity or reproductive toxicity studies were required.

Dr. Jacob's final message to investigators preparing INDs for the first time was to seek help from someone with experience in the process.

Industry

Dr. David Goldenberg (Immunomedics) provided a personal perspective on hurdles and opportunities for TRT in oncology. Lessons learned from ^{131}I-tositumomab and ^{90}Y-ibritumomab tiuxetan and experience with studies of ^{90}Y-radiolabeled clivatuzumab tetraxetan (^{90}Y-labeled hPAM4 [clivatuzumab]), which has fast track status with the FDA for treatment of pancreatic cancer, were presented.

The pipeline of radiopharmaceutical candidates has declined, from 25 in 2006 to 4 in 2014, only one of which (^{223}Ra-dichloride) is approved for therapy. Prospects for growth lie in personalized medicine and identification of companion diagnostics for TRT. Hurdles faced by the field include specificity of biomarkers, complexity and cost of evaluating combined modalities, and proving to regulatory authorities an improvement in disease management. Collaboration between nuclear medicine physicians and oncologists must be improved; the tumor board concept has potential in that regard. For commercial entities, return on investment and time to market are considerations.

The key lesson learned from ^{131}I-tositumomab and ^{90}Y-ibritumomab tiuxetan is that science and efficacy alone do not guarantee success. An extensive pipeline of therapies is available to oncologists, who are rapidly adopting new modalities such as targeted agents, oral drugs, and combination therapies. To succeed, radiopharmaceuticals must change disease management by distinguishing patients whose tumors are operable versus inoperable and those who will benefit versus will not benefit from specific treatments.

The presentation then turned to the experience with ^{90}Y-clivatuzumab, which has been developed as a fractionated therapy for metastatic pancreatic cancer. A phase Ib trial completed in 2014 showed improved efficacy for a combination with fixed, low-dose gemcitabine versus ^{90}Y-clivatuzumab alone in third-line therapy. An international phase III, multicenter, double-blind trial is ongoing of ^{90}Y-clivatuzumab plus gemcitabine versus gemcitabine alone in that same setting (ClinicalTrials.gov identifier NCT01956812). Patients in the experimental arm are receiving ^{90}Y-clivatuzumab 3 times weekly plus gemcitabine 4 times weekly for multiple cycles. Patients in the active comparator arm are receiving placebo 3 times weekly plus gemcitabine 4 times weekly for multiple cycles. In the clinical studies performed to date, no infusion reactions to ^{90}Y-clivatuzumab have been seen, myelosuppression was manageable, and no other significant adverse effects were reported. A survival analysis has shown improved overall survival (median, 9.3 mo) in 31 patients with previously treated metastatic pancreatic cancer who received multiple cycles of ^{90}Y-clivatuzumab combined with low-dose gemcitabine. The results suggest that radioimmunotherapy has promise as third-line therapy for pancreatic cancer and that multiple cycles are essential.

Other applications of radiopharmaceuticals being explored by Immunomedics include epratuzumab in B-cell tumors, ^{18}F-AlF mAbs and peptides as companion imaging agents, pretargeted immuno-PET and radioimmunotherapy as a bispecific antibody platform, and combinations of antibody–drug conjugates with radioimmunotherapy.

Radiopharmaceuticals

Ms. Sally Schwarz (Washington University) provided an overview of the toxicity testing requirements for INDs submitted to the FDA, which have evolved to mandate additional monitoring, including latent toxicity. The experience with approval of radiotherapeutics from ^{89}Sr-chloride in 1993 to ^{223}Ra-dichloride in 2013 was discussed. The focus was on FDA guidance on pharmacology and toxicology in 2 species.

Acute toxicity testing, based on administration of one or more doses over a period not to exceed 24 h, has been required for pharmaceuticals since 1996. For intravenous drugs, a single route is sufficient; for all other routes, the intended route plus intravenous must be tested. Two mammalian species must be included, with testing in small groups, observation for 14 d after administration, and gross necropsies on all animals.

^{89}Sr-chloride (Metastron; GE Healthcare) was, in 1993, the first radiopharmaceutical submitted for FDA approval as an adjunct to local-field EBRT in mCRPC. Data from the Trans Canada study showed a statistically significant difference ($P < 0.002$) in the number of new painful sites per patient in the placebo group versus the active group (*27*). A statistically significant difference also was demonstrated in median time to further radiotherapy in the 2 groups ($P = 0.006$). ^{89}Sr-chloride was shown to be effective at reducing disease progression and need for analgesic support and improving quality of life, with increased but tolerable hematologic toxicity.

Three years later, ^{211}At toxicity in B63CF mice was documented in preparation for designing future investigations of ^{211}At-labeled therapeutic compounds. In a study by McLendon et al., up to 7,400 kBq (200 μCi) for 80 d was administered to one group, up to 2,960 kBq (80 μCi) was used in the second group, and up to 740 kBq (20 μCi) was administered to the third group (*28*).

More recently, approval in 2013 of ^{223}Ra-dichloride, a first-in-class radiopharmaceutical that selectively targets bone metastases, was based on the results of the randomized phase III ALSYMPCA trial. ^{223}Ra-dichloride was shown to prolong overall survival (3.6-mo advantage; $P = 0.00185$) and time to first symptomatic skeletal event ($P = 0.00046$) versus placebo in patients with mCRPC and symptomatic bone metastases, with toxicity comparable to placebo. A phase I clinical trial in breast and prostate cancer with skeletal metastases demonstrated safety and tolerability at all therapeutically relevant dosages. Data from a phase II trial in advanced breast cancer and progressive bone-dominant disease demonstrated targeting of areas of increased bone metabolism and biologic activity.

Turning to trials of radiopharmaceuticals currently under way, the international multicenter Advanced Accelerator Applications (AAA) ^{177}Lu-DOTATATE trial was approved on the basis of toxicology studies in rats and dogs. A 23-cGy dose limit to the kidneys was established from experience with AAA ^{177}Lu-DOTATATE in EBRT. A phase III randomized trial of $^{223}RaCl_2$ plus abiraterone acetate in mCRPC was begun in March 2014. Subjects in the active arm receive $^{223}RaCl_2$ (50 kBq/kg intravenously) every

4 wk for 6 cycles plus 1,000 mg of oral abiraterone acetate daily plus prednisone/prednisolone until an on-study symptomatic skeletal event occurs. The estimated study completion date is July 2020.

Commenting on the cost of toxicology studies, Ms. Schwarz noted that a single rodent study can cost $70,000–$120,000 and that large-animal models such as swine may be a cheaper alternative that would allow performance of toxicology studies in a single species for a therapeutic IND. A good-laboratory-practice lab should be used. Late toxicity can be determined using EBRT, with latent periods of 3–7 mo for nephritis in rats and 10 mo for renal dysfunction in dogs. Rats and dogs are species appropriate for assessing pulmonary fibrosis, and rabbits and dogs for myocardial fibrosis. Human dosimetry and pharmacokinetics using tracer doses should be determined before initiation of a late radiation toxicity study. Timing of toxicity studies can vary on the basis of risk and benefit, but completion before phase II dose escalation is recommended. The highest mass dose of the nonradioactive compound should be used as the control, and at least 4 dose levels should be included to identify dose-related toxicity.

In concluding her presentation, Ms. Schwarz noted that for TRT to move forward more rapidly, FDA hurdles must be identified and researchers must work together to share toxicity data and possibly use the x-IND concept for radiotherapeutics.

ROUNDTABLE DISCUSSION

Dr. Ulli Köster (Institut Laue-Langevin) and Dr. John Valliant (Centre for Probe Development and Commercialization, McMaster University) led a roundtable discussion with experts Aimal Khan Ahmed (Bayer Healthcare), Jehanne Gillo (Department of Energy), Andreas Kluge (ABX-CRO), Deepa Narayanan (NCI Small Business Innovation Research [SBIR]), and Greg Evans (SBIR). The participants were invited to offer their opinions on a series of questions posed by the cochairs.

The experts were asked, given the state of the field today, what information would need to be presented to a pharmaceutical company to secure an investment in TRT. The panel's consensus was that there is no easy answer, considering the experience with ^{131}I-tositumomab and ^{90}Y-ibritumomab tiuxetan and the need for a return on investment. On a positive note, the opinion was shared that $^{223}RaCl_2$ is likely to play a major role in the oncology portfolio at Bayer Healthcare, given the company's acquisition of Algeta. Licensing of hospitals to administer the product was considered a possible postapproval barrier to adoption of $^{223}RaCl_2$. In this ongoing process, already over 1,400 hospitals have been licensed. This effort can pave the way for future clinical application of other TRT with α emitters. Inadequate reimbursement, given the complexity of the treatment, also is a concern for TRT in general.

TRT as a component of NCI SBIR's funded small-business portfolio then was discussed. The portfolio includes approximately 10–20 active projects involving radionuclides for imaging, versus fewer than 5 for therapy, but there is interest in expanding the offerings. Congress has recently reauthorized the SBIR and Small Business Technology Transfer programs and increased the set-aside percentage for funding of them, in the context of the entire NCI budget.

Only U.S. small business concerns can participate in the SBIR program (http://sbir.cancer.gov/about/eligibility/). The NCI's support for a robust TRT pipeline and encouragement of out-of-the-box thinking to advance the field were emphasized.

The Department of Energy's National Isotope Development Center (http://www.isotopes.gov/) and its role in facilitating production of isotopes and ensuring their availability for medical research were reviewed. The National Isotope Development Center works closely with a representative from the National Institutes of Health to determine the needs of the Institutes for isotopes.

CONSENSUS

Breakout sessions held as part of the NCI–SNMMI workshop included cross-sections of stakeholders and focused on 1 of 4 disease-specific topics: breast cancer, lymphoma and leukemia, lung cancer and neuroendocrine cancer, or prostate cancer. Summaries of the discussions and consensus reached by each group were presented by a rapporteur with a focus on the current state of the art of TRT, clinical indications, apparent strengths and weaknesses, the most promising advances in the field, and challenges to acceptance and incorporation into routine clinical use.

Breast Cancer

Dr. Stanley Lipkowitz (NCI) summarized the results of the breakout group focusing on breast cancer.

The logistics of treatment execution were discussed, and several hurdles to the adoption of TRT were reviewed. For example: short half-lives make radionuclide transportation difficult, protocols requiring dosimetry result in multiple patient visits, coordination of multidisciplinary teams is complicated, loss of revenue and risks associated with radiation are concerns, and competition from other agents works against use of radionuclides in clinical trials and in the commercial setting.

Past experience with TRT suggests that success depends on an effective multidisciplinary team approach. Opportunities exist for radioimmunotherapy in breast cancer. Although there are targeted agents for estrogen receptor–negative and HER2-positive breast cancer, TRT could have a niche as a second- or third-line therapy. Also, the success of current breast cancer therapy has led to increased survival; however, the incidence of brain metastases has also increased. Intrathecal TRT may have an advantage over chemotherapy in this setting.

In conclusion, the breakout group felt the best path forward for TRT in breast cancer was to address unmet therapeutic needs and to encourage the development of multidisciplinary teams to support its administration and management. Research is needed to identify whether the best targeting agents for breast cancer are radiolabeled antibodies, fragments, or peptides.

Lymphoma and Leukemia

Dr. Jeffrey Norenberg (University of New Mexico) presented the results from the breakout group focusing on lymphoma and leukemia.

There are several opportunities for TRT in lymphoma and leukemia. For example, TRT could be helpful in T-cell lymphoma or in bone marrow conditioning or myeloablation before autologous bone marrow transplantation. In leukemia, surface molecules are well characterized and could present potential targets for radioimmunotherapy. Combinations of EBRT and TRT have yet to be studied in clinical trials.

The breakout group discussed the need for development of an economic model to sustain TRT, including well-described roles for oncologists, nuclear medicine physicians, and radiation oncologists; increased interdisciplinary communication; and transparency regarding cost and availability. The need to bolster patient education about available treatment options was mentioned.

Structured training should be made available to all providers involved in radionuclide therapy, including medical oncologists, radiation oncologists, radiochemists, and trainees, and focused specialty meetings should be convened, including cooperation with several professional groups such as the American Society for Radiation Oncology, SNMMI, and American Society of Clinical Oncology. A change in the paradigm at the FDA for INDs and NDAs regarding toxicity of radionuclides versus nonradioactive therapies is needed to fully realize the potential of TRT, and increased engagement of patient advocacy groups could help influence the FDA and payers in that regard.

Lung Cancer and Neuroendocrine Neoplasms

Dr. Shakun Malik (NCI) reported on the breakout group discussion regarding lung and neuroendocrine cancers.

Opportunities exist for epidermal growth factor receptor TRT in lung cancer. Two drugs that target the epidermal growth factor receptor subfamily (erlotinib and afatinib) are approved for first-line therapy of advanced NSCLC. Crizotinib and ceritinib are being studied to target the anaplastic lymphoma kinase gene in NSCLC. Covalent (irreversible) epidermal growth factor receptor inhibitors are being studied to target mutant forms while sparing wild-type, or normal, epidermal growth factor receptor. Most are small fluorinated or chlorinated molecules, suggesting the potential for radiolabeling with isotopes such as ^{18}F or ^{11}C. This strategy would facilitate companion diagnostic imaging and therapy and might enhance potency. Other targets in NSCLC are TTF1 (a specific marker for primary lung adenocarcinoma) and carcinoembryonic antigen. A preliminary study suggests that radiolabeled MOC-31 may be useful in diagnosis and therapeutic management of small cell lung carcinoma (*29*). The results of a phase I dose-escalation study of ^{188}Re-P2045 for TRT in patients with NSCLC or small cell lung carcinoma suggest that further research is warranted (*30*).

Opportunities exist for TRT in NETs. PRRT with ^{177}Lu- and ^{90}Y-octreotide derivatives has been validated in Europe in NETs, as described in Dr. Baum's presentation. Improvements in dosimetry may facilitate FDA approval of clinical trials for new α and β emitters.

The breakout group concluded that the future for TRT in lung cancer and NETs is likely to be in dosimetry as a way to personalize therapy, a theranostic approach, research on α-particle therapy, and potential for orphan drug status. Challenges to TRT include the need for intravenous access versus the oral route of most non-TRT therapies, issues with availability of good laboratory practice–grade peptides, and the cost of an NDA.

Prostate Cancer

Dr. Eric Rohren (M.D. Anderson Cancer Center) summarized the discussion of the breakout group focusing on prostate cancer.

Every year, approximately 220,000 men are diagnosed with the disease in the United States. Twenty percent of deaths due to the disease occur in the 5% of patients who have metastases at diagnosis (http://seer.cancer.gov/statfacts/html/prost.html). Although drug treatments for mCRPC are rapidly expanding, they are having only a limited impact on improving survival curves. Thus, the group saw a significant opportunity for TRT throughout the disease spectrum and particularly in mCRPC.

Hurdles identified for TRT in prostate cancer included tumor heterogeneity, the choice between small molecules and antibodies, the impact of TRT versus other therapies, and the need to increase the profile of TRT among oncologists. Two niches identified for TRT included treatment of men with metastases at diagnosis and imaging and treatment of primary disease, regional nodes, and metastases. Current techniques for imaging nodal metastases are lacking, and radiopharmaceuticals could help determine which patients should receive aggressive treatment. TRT also may have a role in high-grade tumors, for which therapeutic options are limited, as well as in the adjuvant setting in combination with standard treatments. Experience to date with prostate-specific membrane antigen suggests that it may be the best target for radionuclides such as ^{99m}Tc, ^{68}Ga, ^{131}I, ^{177}Lu, and ^{225}Ac.

In order for the field to move forward, Dr. Rohren underscored the need to take a theranostic approach to radiopharmaceuticals, that is, to develop individual agents for both diagnosis and therapy, or in combination with imaging agents. An understanding of their mechanism of action, optimization of dosimetry, and demonstrated efficacy are important to gaining increasing support for TRT from oncologists and their patients.

Other barriers to the success of TRT discussed by the breakout group include the limited support for development of therapies from bench through approval to bedside and lack of messaging. Outreach should be done to increase support from all stakeholders—clinicians, patients, advocacy groups, government agencies, and payers—with a focus on data demonstrating efficacy.

HIGHLIGHTS AND FUTURE DIRECTIONS

Dr. Hossein Jadvar provided an overview of the workshop, emphasizing that the overarching goal of TRT is to deliver timely, cost-effective therapy offering the best possible outcome to patients.

The second NCI–SNMMI workshop expanded on what was accomplished in 2013. The content was disease-focused, and the group of stakeholders was broader, including industry, regulatory, and government colleagues from the United States, as well as European experts.

In the area of preclinical research, optimal combinations of targets, chelates, and radionuclides were discussed. In addition to the existing in vitro and in vivo models, potential exists for validation of new in vivo models in larger animals. Robust, reproducible data are needed, as are dosimetry models for treatment planning in order to comply with regulatory requirements and provide optimal patient care.

Often clinical trials including TRT have suboptimal methodology with nonstandardized endpoint definitions. To advance, appropriately designed large multicenter, randomized trials must be performed. Time is of the essence, and comparison of TRT to current therapies, which are rapidly evolving, is needed. Outcomes such as quality of life should be considered since cancer is increasingly viewed as a chronic disease. TRT may also be helpful early in the course of disease, as in the case of, for example, micrometastases and oligometastatic disease. Novel regimens could include TRT, EBRT, or chemotherapy; multistep targeted chemoradionuclide immunoconjugates; and therapy with different radionuclides in patients who fail initial TRT. The potential for theranostic applications to guide patient selection, identify optimal dose, and assess treatment effectiveness was advocated.

The industry perspective on TRT production and marketing, access to raw materials, regulatory issues, and cost of clinical trials remain concerns. Facilitating dosimetry and TRT implementation is important. Education for patients and providers is needed. The silo mentality of specialties and the inability of specialists to share revenue were identified as impediments to TRT adoption.

There are several barriers in the area of regulation and reimbursement. In the United States, some radionuclides are difficult to access, some are unapproved, and even those that are approved and reimbursable may be underutilized. Although published reports exist on the use of radionuclides for TRT in Europe, the data rarely can be incorporated into applications for approval and reimbursement in the United States. A need was identified to streamline coordination between the FDA and the Centers for Medicare and Medicaid Services such that reimbursement can keep pace with new drug approvals. Also discussed were issues with levels of reimbursement and a potential need to mandate disclosure by providers to patients of all therapeutic options available to them.

Partnership of all stakeholders was underscored as key to the future of TRT. In terms of the overarching government strategy, coordination is needed among the National Institutes of Health, FDA, Nuclear Regulatory Commission, Centers for Medicare and Medicaid Services, and Congress. In academia, a collaborative approach is needed to raise awareness and knowledge of TRT among all professionals. Pharmaceutical companies should be encouraged to view TRT as an important tool in the armamentarium of cancer therapy. Unbiased and accurate patient information about TRT is needed, and a paradigm shift in the practice of TRT to care by multispecialty teams is important. Inclusion of nuclear medicine specialists on tumor boards was discussed as an initial step toward fostering collaborative practice, as was the importance of outreach.

In conclusion, Dr. Jadvar suggested the need for a balanced, unbiased approach to the integration of TRT into the therapeutic algorithm for patients with cancer. Research must be actively pursued so that barriers to the adoption of TRT can be overcome. The key is to demonstrate that—whether given alone, in combination, or sequentially—TRT has an important role in patient care.

CONCLUSION

In summing up, cochair Dr. Zukotynski suggested that the time for TRT is now and that there is a need to bring together professionals from various walks of life to share their expertise on TRT. Dr. Fahey echoed this sentiment and expressed thanks to the workshop organizers and participants for demonstrating their dedication to the specialty. SNMMI's acknowledgment of the importance of TRT is evidenced by its plans to develop a center of excellence that will provide professional networking and educational opportunities in the area while simultaneously serving as a resource for development and implementation of Society policy. The organization also has a role to play in fostering partnerships with organizations such as the American Association of Physicists in Medicine, American Society for Radiation Oncology, and American Society of Clinical Oncology and in collaborating with agencies such as the NCI, FDA, and Department of Energy.

On the basis of the presented discussion and conclusions, the following set of actions is recommended. New research is necessary to determine the most promising approaches for the next generation of targeted radionuclide therapies. This research may involve availability of new raw materials, new or increased supply of therapeutic radionuclides, selection of proper targeting approaches, development of appropriate in vivo models in larger animals, construction of dosimetric models, and, eventually, appropriately designed large multicenter, randomized trials. The ability to fund such research presents a considerable challenge, as do the regulatory issues associated with bringing such novel therapies to the clinic. For these reasons, greater cooperation among all stakeholders is necessary to realize the promises of TRT. Those of different specialties need to work more closely in an open partnership with our international colleagues and industry as well as governmental funders and regulators.

With the 75th anniversary of the first therapeutic use of a radionuclide approaching in 2016, the time may be opportune to increase the profile of TRT.

DISCLOSURE

No potential conflict of interest relevant to this article was reported.

ACKNOWLEDGMENTS

The organizing committee is made up of the following individuals: Frederic Fahey (Boston Children's Hospital, Harvard Medical School); Katherine Zukotynski (University of Toronto and Harvard Medical School); Hossein Jadvar (University of Southern California); Jacek Capala (NCI); C. Craig Hill (NCI); Ulli Köster (Institut Laue-Langevin); Jason Lewis (Memorial Sloan Kettering Cancer Center); Frank I. Lin (NCI); and Bhadrasain Vikram (NCI).

The contributors include Richard Wahl (Johns Hopkins University); Ruby F. Meredith (University of Alabama at Birmingham); Cathy S. Cutler (University of Missouri); Lee Allen (Spectrum Pharmaceuticals); Rick Satitpunwaycha (Spectrum Pharmaceuticals); Janis O'Malley (University of Alabama at Birmingham); Richard Baum (Zentralklinik Bad Berka); Fatima Karzai (NCI); Ekaterina Dadachova (Yeshiva University); Janice Reichert (Reichert Biotechnology Consulting LLC); Martin Brechbiel (NCI); Barry Wessels (University Hospitals of Cleveland); Steven Larson (Memorial Sloan Kettering Cancer Center); Aimal Khan Ahmed (Bayer Healthcare); Paula Jacobs (NCI); David Goldenberg (Immunomedics); Sally Schwarz (Washington University in St. Louis); John Valliant (Centre for Probe Development and Commercialization); Jehanne Gillo (Department of Energy); Andreas Kluge (ABX-CRO); Deepa Narayanan (SBIR); Greg Evans (SBIR); Giuseppe Giaccone (Georgetown University); Martin Pomper (Johns Hopkins University); Stanley Lipkowitz (NCI); Jeffrey Norenberg (University of New Mexico); Shakun Malik (NCI); and Eric M. Rohren (M.D. Anderson Cancer Center).

We gratefully acknowledge the contributions of the following individuals to this work: Anne Hiller, Nikki Wenzel-Lamb, Judy Brazel, and Virginia Pappas (SNMMI), as well as Erica Butler, Ling Lang, and Pat Angelis (NCI).

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Targeted Radionuclide Therapy: Proceedings of a Joint Workshop Hosted by the National Cancer Institute and the Society of Nuclear Medicine and Molecular Imaging

Frederic Fahey[1], Katherine Zukotynski[2], Jacek Capala[3] and Nancy Knight[4], with input from the Organizing Committee, Contributors, and Participants of the NCI/SNMMI Joint Workshop on Targeted Radionuclide Therapy*

[1]Boston Children's Hospital, Boston, Massachusetts, and Harvard Medical School, Boston, Massachusetts; [2]Sunnybrook Health Sciences Centre, University of Toronto, Ontario, Canada, and Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts; [3]National Cancer Institute, Bethesda, Maryland; and [4]University of Maryland School of Medicine, Baltimore, Maryland

The growing interest in targeted radionuclide therapy (TRT) for a broad range of applications is shared by a diverse group of medical professionals, including but not limited to physicians and basic scientists in several fields, as well as members of industry, regulatory bodies, and patients. However, no organizational structure is available to regularly bring these stakeholders together to discuss the latest findings and the most productive strategies to ensure that the potential benefits of TRT are realized.

Recognizing the need for a forum to discuss the advances and challenges of TRT relating to availability, supporting technology, and interdisciplinary training and research, the National Cancer Institute (NCI) and the Society of Nuclear Medicine and Molecular Imaging (SNMMI) hosted a joint workshop on March 18 and 19, 2013, at the National Institutes of Health campus in Bethesda, Maryland (*1*). Plans for the workshop were initiated in 2012 by Dr. Frederic Fahey, SNMMI president, and Dr. Jacek Capala of the NCI, and the 2-d event was cochaired by Dr. Fahey and Dr. Katherine Zukotynski. The event was designed to bring a small but diverse group of stakeholders together (Fig. 1) to discuss contemporary TRT in both structured and open-forum formats, to assess approaches for collaboration, and to evaluate strategies to bring the most promising therapies into routine clinical use. This white paper briefly reviews the discussion on TRT that took place at the workshop and offers next-step recommendations from attendees as summarized in presentations by subject matter experts.

BACKGROUND: RADIONUCLIDE THERAPY, FROM SPECULATIVE TO TARGETED

Historically, reaching a consensus on the advantages, indications, and implementation of radionuclide therapy, radioimmunotherapy, and TRT has been challenging. In the introduction to MIRD pamphlet no. 22, Sgouros et al. pointed out that the use of ^{224}Ra for cancer therapy was suggested by Alexander Graham Bell as early as 1903 (*2,3*). However, despite sporadic applications of both β and α emitters for clinical oncology proposed during the 20th century, only ^{131}I therapy, introduced in 1946 for the treatment of thyroid disease (*4*), has been consistently used. ^{131}I was first used in radioimmunotherapy in 1982 (*5*), and the first trial of an α emitter in TRT was not reported until 1997 (*6*). In the past decade, an increasing number of radionuclide and therapeutic agent combinations have been explored in cancer therapy, with a growing body of literature suggesting their effectiveness. The recent U.S. Food and Drug Administration (FDA) approval of ^{223}Ra-dichloride for castration-resistant prostate cancer has generated significant interest in α emitters as a strategy for cancer therapy among diverse stakeholders, including patients and their families (*7*). The working group at the NCI/SNMMI workshop noted that to foster expanding awareness of TRT across the spectrum of medical disciplines, consensus on a single name by which to refer to these therapies is needed. First, it is important to recall that techniques in which a radionuclide is administered with therapeutic intent may or may not be targeted. For example, radionuclide therapy encompasses everything from ^{131}I thyroid ablation to localized delivery of theranostic agents, with the term *theranostic* implying that the agent has potential for both diagnostic and therapeutic use. Radioimmunotherapy describes targeted therapy with radiolabeled monoclonal antibodies. Molecular targeted therapy describes both radionuclide and nonradionuclide therapy (*8*). TRT describes techniques in which one or more radionuclides, usually but not always incorporated into a conjugate or attached to a ligand, are administered with the goal of providing targeted therapy at the cellular or molecular level.

EXPERT PERSPECTIVES ON THE TRT STATE OF THE ART

Through a series of presentations, individuals representing different professional perspectives on TRT offered a look at the state of the art and current challenges.

A Medical Physicist Perspective

Dr. George Sgouros reviewed the physics of TRT, highlighting the potential of TRT in cancer therapy and emphasizing the role of dosimetry in conducting phase I trials of novel radionuclide agents. TRT delivery, which is not susceptible to the resistance mechanisms seen with chemotherapy, kills targeted cells instead of inhibiting growth or survival pathways and precludes adaptation. Further, TRT can be paired with imaging and other techniques to predict

Received Nov. 12, 2013; revision accepted Nov. 15, 2013.
For correspondence or reprints contact: Frederic Fahey, Children's Hospital, 300 Longwood, Ave., Boston, MA 02115.
E-mail: frederic.fahey@childrens.harvard.edu
*These individuals are listed in the Acknowledgment section at the end of this article.
Published online Jan. 6, 2014

DOI: 10.2967/jnumed.113.135178

FIGURE 1. More than 40 molecular imaging physicians, physicists, oncologists, basic scientists, and others gathered at the National Institutes of Health on March 18 and 19, 2013, for a workshop on targeted radionuclide therapy.

delivery of therapeutic agents to tumor targets and normal organs before therapy administration and thus can be used to guide escalation protocols and treatment planning. These advantages make TRT especially promising in several cancers.

Dr. Sgouros stressed the importance of reassessing dosimetry methods used in TRT, emphasizing the need to adopt methods specific to the therapy being used and geared to evaluating treatment efficacy and toxicity. Current dosimetry methods associated with and appropriate to radioimmunotherapy, for example, are often model-based methods for risk evaluation. In general, these methods are not patient-specific, do not account for nonuniformity, and do not predict toxicity or efficacy. In the context of TRT, Dr. Sgouros recommended moving away from average absorbed dose, noting that a single absorbed dose volume is useful only if it successfully predicts biologic effects. He recommended adoption of patient-specific, 3-dimensional (3D) dosimetry coupled with radiobiologic modeling, where 3D internal dosimetry has the advantages of being patient-specific, using accurate anatomy and activity data, calculating absorbed dose voxel by voxel, and providing output dose as a mean over a chosen volume or dose–volume histogram (*9–11*). Also, 3D radiobiologic dosimetry with Monte Carlo calculations and radiobiologic modeling to predict response from absorbed dose can produce a more faithful prediction of tumor response and toxicity to normal tissue (*12–14*). Dr. Sgouros provided examples of 3D radiobiologic dosimetry capabilities in clinical cases, as well as comparisons with organ mean absorbed doses that were calculated with OLINDA software (*15*). He pointed to the general agreement of these methods and the advantages of 3D radiobiologic dosimetry in real-time treatment planning with patient-specific dosimetry and the potential for additional utility in combined-modality therapy (*16*).

Dr. Sgouros reviewed considerations for α-particle dosimetry and characteristics that distinguish it from β-particle therapy. For example, with α-particle therapy, the mean dose to any macroscopic target volume may not predict overall biologic effect (i.e., some cells may receive no dose, whereas others receive a high dose), such that total effective dose depends on the spatial distribution of activity relative to the target cell population. He illustrated this principle with ^{223}Ra bone dosimetry for the treatment of castration-resistant prostate cancer (with the newly approved agent Xofigo [^{223}Ra-dichloride; Bayer HealthCare Pharmaceuticals]) (*17*) and with ^{213}Bi-labeled monoclonal antibodies in mouse models of breast cancer metastases (*18*). As in other areas of TRT research, pairing preclinical studies with human studies allowed derivation of microscale absorbed dose without human autoradiography. As part of the translation of these studies to clinical use, Dr. Sgouros suggested including absorbed dose as an escalation variable in phase I clinical studies.

Dr. Sgouros concluded his talk by emphasizing the importance of collaboration among various stakeholders in the TRT process to ensure its advancement, citing Mercadante and Fulfaro (*19*): "The decision to use radiopharmaceutical agents should be based on a multidisciplinary plan, involving radiation oncology, nuclear medicine, and medical oncology."

A Radiochemist Perspective

Dr. Michael R. Zalutsky summarized the current status of the radiochemistry underlying TRT. The critical importance of appropriate radionuclide selection to the success of TRT was stressed. Also, a variety of key considerations were discussed, including the need for radionuclide availability at reasonable cost and selection of an appropriate labeling methodology.

Dr. Zalutsky emphasized that improved labeling methodologies would result in more specific and selective tumor targeting and therapeutic efficacy. Criteria to be considered in selecting a labeling method included the need for specific activity, preservation of biologic function, stability in vivo, adaptability to high activity levels, and characteristic tumor-mediated degradation. In a detailed summary of current labeling strategies, Dr. Zalutsky reviewed the process of labeling radiometals (acyclic chelated [diethylenetriaminepentaacetic acid, or DTPA] and macrocycles [DOTA]) and radiohalogens (direct electrophilic [IODO-GEN; Pierce Biotechnology, Inc.] and prosthetic group conjugation [Bolton-Hunter, dehalogenation resistant, and residualizing]). Several challenges associated with conventional radiosynthesis of radiolabeled agents were discussed, and the solid-phase synthesis of ^{211}At-meta-astatobenzylguanidine was presented as an example of a simpler radiochemical approach more suited to routine use. Of note, specific activity poses greater difficulties in TRT than in diagnostic imaging—with diagnostic imaging, acceptable contrast is needed, whereas with TRT, homogeneous delivery of sufficient radionuclide to a target is needed to have the desired therapeutic effect. In a study by Akabani et al. (*20*), although ^{211}At-labeled trastuzumab monoclonal antibody was shown to be effective for treating HER2-positive tumor cells, the specific activity of the agent was an important variable influencing the efficiency of cell killing. The challenges in TRT are compounded by the fact that some molecular targets are expressed at low levels

and most have a high degree of heterogeneity within individual tumors.

Dr. Zalutsky noted the importance of understanding radiotherapeutic agent metabolism in normal tissues and tumors, as well as the nature and disposition of labeled catabolites that are generated, in order to optimize therapy and reduce toxicity. Considerations regarding the biodistribution of labeled catabolites were illustrated with ^{177}Lu- and ^{125}I-labeled agents, and tumor-to-tissue ratios using bone, liver, tumor, blood, spleen, thyroid, and kidneys were shown. Methods for accurately assessing internalization into specific molecular targets were discussed for both research and clinical applications.

Also discussed was an additional factor that can confound radiochemistry at therapeutic dose levels: the effect of radiolysis. Radiation can generate ions, free radicals, and other molecules in a complex process yielding a spectrum of products dependent on type of radiation, dose rate, and presence of trace components. This was illustrated using ^{211}At, where the effects of radiolysis can result in lower labeling yields at higher activity levels and at varying times of day, and poor reactivity in ^{211}At shipped from one site to another. Lack of reliability in the preparation of clinical doses larger than 350 MBq and challenges to commercialization were reviewed. The need to develop approaches to meet these challenges were underlined and illustrated using the synthesis of *N*-succinimidyl 3-^{211}At-astatobenzoate for preparation of clinical doses of ^{211}At-labeled radiopharmaceuticals.

Dr. Zalutsky concluded his talk by suggesting that labeling methods are currently available for most radionuclides of clinical interest for TRT. However, concerted efforts will need to be made to ensure production of labeled compounds at activity levels sufficient for TRT and to address challenges associated with specific activity, radiolysis, and catabolism to maximize effectiveness and safety.

A Nuclear Medicine Physician Perspective

Dr. Richard L. Wahl provided an overview of the history and emerging opportunities in TRT. He began with a review of ^{131}I therapy in thyroid cancer (*21*) and the use of ^{124}I PET/CT as a guide in the diagnosis and treatment of tumors with *BRAF*-activating mutations (*22*). Dr. Wahl then provided an in-depth look at the clinical use of tositumomab and ^{131}I-tositumomab (Bexxar; GlaxoSmithKline), the radiolabeled anti-CD20 monoclonal antibody approved for the treatment of follicular lymphoma. Follicular non-Hodgkin lymphoma (NHL) is the second most common type of NHL and accounts for 25%–40% of all adult lymphoma. The overview included a discussion of CD20 expression in the B-cell life cycle, characteristics and mechanisms of action of the constituent radiolabel and monoclonal antibody, and the treatment regimen currently used (*23,24*). Dosimetry considerations for ^{131}I-tositumomab treatment were reviewed, and the need for an accurate and personalized approach to maximize radiation dose to tumor and minimize patient toxicity was underlined. The concept was discussed that dosimetry studies confirm great variation in antibody clearance among patients, depending on factors such as tumor size, splenomegaly, or the amount of bone marrow involvement. The importance of adjusting the amount of radioactivity given to ensure all patients individually receive a total body dose of 75 cGy was emphasized. The advantages of careful dosimetry calculations allowing physicians to prospectively individualize therapeutic dose were reviewed. The rationale was discussed for administering unlabeled tositumomab before the ^{131}I-labeled antibody, along with the results of clinical studies of ^{131}I-tositumomab in patients treated with rituximab. Data were presented suggesting benefits of ^{131}I-tositumomab retreatment in patients who previously responded to ^{131}I-tositumomab therapy (*25*). The fact that ^{131}I-tositumomab has been shown to have an overall response rate of 95% (complete response, 75%) in patients with previously untreated, advanced-stage, low-grade NHL was discussed (*26*). Studies of up-front radioimmunotherapy plus chemotherapy, the use of ^{131}I-rituximab radioimmunotherapy in relapsed or refractory indolent NHL (*27*), and the use of rituximab versus CHOP chemotherapy (cyclophosphamide, hydroxydaunomycin, vincristine, and prednisone) plus ^{131}I-tositumomab in newly diagnosed follicular NHL (*28*) were reviewed.

The mechanism of action and therapeutic regimen for ^{90}Y-ibritumomab tiuxetan (Zevalin; Spectrum Pharmaceuticals, Inc.), a monoclonal antibody TRT for relapsed or refractory, low-grade follicular or transformed B-cell NHL, was presented. It was mentioned that response rates for ^{90}Y-ibritumomab tiuxetan were better than those for rituximab alone in phase III trials (*29*). Also, it was suggested that recent follow-up to the multicenter first-line trial of ^{90}Y-ibritumomab tiuxetan as consolidation therapy for first remission in advanced-stage follicular NHL indicates high overall and complete response rates (*30*). However, although ^{90}Y-ibritumomab tiuxetan appears to be well tolerated and treatment can be given on an outpatient basis without radiation-related lifestyle restrictions, its toxicity may be dose-limiting and proper patient selection remains an important part of clinical practice. Variability in toxicity, response, and organ dose has been identified but not yet entirely explained. Methods to account for these variabilities and accurately estimate delivered activity are under investigation, including the use of ^{111}In-based organ dosimetry (*31*).

Current challenges in radiolabeled somatostatin analog therapy were then discussed, including the question of whether to administer small empiric doses without prior dosimetry calculations or to use dosimetry calculations to modulate renal dose (*32*). The importance of dose escalation studies in answering these questions was emphasized (*33,34*). Also briefly discussed were the growing use of ^{90}Y-labeled microsphere and particle treatment for liver metastases and primary tumors and FDA-approved therapies for bone metastases, including ^{153}Sm-EDTMP (ethylenediaminetetramethylene phosphoric acid), ^{89}Sr, and, most recently, ^{223}Ra-dichloride.

In summarizing the current outlook for TRT, Dr. Wahl suggested that an overall limitation is the need to ensure accurate delivery of radiopharmaceutical to the target and that despite evidence suggesting TRT is effective as a single agent, combination of TRT with additional anticancer therapy may be essential to curative approaches. Dr. Wahl emphasized that collaborative work is needed to integrate TRT into standard oncologic treatment regimens (*35*), an effort that will require a cadre of knowledgeable health-care professionals. Dr. Wahl also stressed that personalized dosimetry-based therapy is likely to become increasingly important in TRT and that economic concerns, including risks associated with developing new agents and reimbursement issues, will need to be addressed for TRT to become a viable option. Finally, the need for exploration of different targets and delivery methods was emphasized, and an effort to create well-defined TRT funding mechanisms and collaborative trial groups was proposed.

A Medical Oncologist Perspective (Lymphoma)

Dr. Eric Jacobsen discussed the role of radioimmunotherapy in lymphoma with emphasis on follicular lymphoma, diffuse large B-cell lymphoma, and mantle cell lymphoma. A thorough overview of clinical trials in these disease settings was provided (*36–41*).

The effectiveness of the anti-CD20 murine monoclonal antibodies (^{90}Y-ibritumomab tiuxetan and ^{131}I-tositumomab) in relapsed or refractory follicular lymphoma was reviewed. It was noted that both agents are FDA-approved (2002 and 2003, respectively), and their advantages as single-agent, front-line therapy when compared with rituximab were discussed (*26,42,43*). The challenges faced by medical oncologists considering ^{90}Y-ibritumomab tiuxetan or ^{131}I-tositumomab therapy for patients with follicular lymphoma were also mentioned. The fact that medical oncologists frequently report concerns about bone marrow damage and late side effects associated with therapy, as well as a general preference for nonradioactive treatment alternatives, was discussed. Practical concerns were emphasized, including difficulty finding an appropriate site for patient referral, the complexity of the referral process, and the fact that referring patients to another physician for treatment may adversely affect the referring practice's bottom line. Dr. Jacobsen also noted that a compelling barrier to the use of ^{90}Y-ibritumomab tiuxetan or ^{131}I-tositumomab from a medical oncologist perspective is the lack of definitive randomized clinical trial data showing therapy effectiveness and improved outcome. The available studies, he suggested, leave unanswered questions about the role of radioimmunotherapy in first-line or consolidation treatment for follicular lymphoma (*43,44*).

In diffuse large B-cell lymphoma, although radioimmunotherapy has met with success as consolidation therapy after rituximab/CHOP in high-risk, untreated disease (*45,46*), recent trials comparing rituximab/BEAM (carmustine, etoposide, cytarabine, and melphalan) versus ^{131}I-tositumomab/BEAM in relapsed diffuse large B-cell lymphoma after autologous stem cell transplantation found no difference in progression-free or overall survival (*47*). Dr. Jacobsen summarized his review of trials on diffuse large B-cell lymphoma by defining current barriers to implementation of radioimmunotherapy. Indeed, radioimmunotherapy may be contraindicated or less effective in patients with extensive marrow infiltration, cytopenia, or bulky disease. Currently available data on the use of radioimmunotherapy in upfront consolidation are not definitive and in some cases are negative. Further, patients may be unwilling to face intervention before ^{90}Y-ibritumomab tiuxetan or ^{131}I-tositumomab therapy such as the need for a bone marrow biopsy. Also, there remains concern about the effect of radioimmunotherapy on the potential range of future treatments.

Dr. Jacobsen concluded his review with a brief look at current research on the potential for radioimmunotherapy as consolidation therapy or as preconditioning in mantle cell lymphoma (*48,49*).

A Medical Oncologist Perspective (Bone Disease)

Dr. David I. Quinn reviewed past and current TRT in bone disease. In metastatic castration-resistant prostate cancer, treatment options are again proliferating after a hiatus from about 2004 to 2010. The spectrum of therapy available for prostate cancer was reviewed, including the recent development of several novel agents including immunotherapy, cytotoxic chemotherapy, rank-ligand inhibitors, and agents targeting the androgen-receptor pathway. In the midst of this dynamic milieu, level 1 clinical evidence of benefit for TRT has emerged, along with unanswered questions regarding optimal treatment selection and sequence of therapy (*50–59*).

Dr. Quinn reviewed new treatments, with a focus on current and recently completed trials (*57,60,61*). He noted that the use of radionuclides in bone disease is not new. Both strontium and samarium have been in use for more than a decade. For each trial cited, Dr. Quinn reviewed the historical precedents. He gave special attention to data from the Alpharadin in Symptomatic Prostate Cancer Patients (ALSYMPCA) trial, a phase III study of ^{223}Ra-dichloride in men with symptomatic castration-resistant prostate cancer and skeletal metastases sponsored by Bayer HealthCare Pharmaceuticals and Algeta ASA, and opened in 2008 (*62*). The aim of the study was to compare the efficacy of standard of care plus ^{223}Ra-dichloride versus standard of care plus placebo. The primary efficacy endpoint was overall survival, and secondary endpoints included evaluation of total serum alkaline phosphatase and prostate-specific antigen levels. The ALSYMPCA trial's rationale was based on numerous studies suggesting that ^{223}Ra targets areas of new bone formation and metastases, with highly localized cell killing and minimal damage to surrounding normal tissues (*63,64*). Results indicate that in men with castration-resistant prostate cancer and bone metastases, ^{223}Ra-dichloride significantly improved survival (median, 14.9 mo vs. 11.3 mo; hazard ratio, 0.70; 95% confidence interval, 0.58 0.83; $P < 0.001$) and median time to first skeletal related event compared with standard of care (*62*). ^{223}Ra-dichloride was also associated with low myelosuppression rates and fewer adverse events.

Dr. Quinn concluded by suggesting that TRT will soon become a mainstay of prostate cancer treatment, with opportunities for expansion to other cancers, such as breast, lung, and primary bone tumors, as well as in myeloma. Dr. Quinn also suggested the need for treatment algorithms leading to a personalized therapy approach in men with castrate-resistant disease.

A Medical Oncologist Perspective (Neuroendocrine Tumors [NETs])

Dr. Jorge Carrasquillo provided an overview of radionuclide therapy in NETs, a diverse group of diseases with widely varying characteristics requiring different therapeutic approaches. Dr. Carrasquillo provided a comprehensive review of the current status of research in this area. He discussed the role of ^{131}I-metaiodiobenzylguanidine (^{131}I-MIBG), which was first used in the early 1980s to target the noradrenaline receptor (*65*), and he reviewed a variety of NETs that express this receptor and have been targeted for imaging and therapy. The literature of ^{131}I-MIBG therapy in patients with paraganglioma, pheochromocytoma, and neuroblastoma was discussed (*66–85*), and TRT in carcinoid and medullary thyroid cancer was reviewed. Dr. Carrasquillo also reviewed patient preparation, protocols for TRT, and response criteria assessment across the spectrum of disease. Other topics included combination of TRT with chemotherapy or sensitizing agents, intraarterial TRT administration, pretherapy imaging providing quantitation of therapeutic delivery, therapy regimens varying in specific activity and dose, and the potential for astatine-labeled MIBG.

Somatostatin receptors in NETs, particularly in carcinoids and gastroenteropancreatic tumors, were discussed with emphasis on the use of ^{111}In, ^{90}Y, and ^{177}Lu labels and theranostic agents. Somatostatin receptors, including the 5 subtypes (1, 2a and 2b, 3, 4, and 5) have been well described in the literature, and numerous studies have reported on the characteristics and affinities of radiolabeled somatostatin analogs, including ^{111}In-DTPA-octreotide (Octreoscan; Mallinckrodt Pharmaceuticals), ^{90}Y/^{177}Lu DOTATOC, ^{177}Lu/^{90}Y DOTATATE, and ^{90}Y DOTA-lanreotide (*86,87*). Studies have addressed response rates, outcomes, the role of imaging (particularly PET/CT with ^{68}Ga-DOTATOC) in guiding therapeutic management, and the relative effectiveness of different radiolabeled somatostatin receptor agents (*88–107*). Concerns about renal toxicity were discussed, and the use of dose fractionation, amino acid infusions,

radioprotectants, and other mitigating approaches were reviewed as a way to lessen adverse effects.

Dr. Carrasquillo concluded that although both ^{131}I-MIBG and radiolabeled somatostatin analogs have shown benefits in symptomatic management and disease response, the impact of study data on clinical practice has been limited for a variety of reasons, including in part the relatively low incidence of target diseases. The need for future investigation to identify optimal peptides and chelates, develop practical and effective therapy protocols, establish dosimetry models, and determine which diagnostic imaging agents are best suited to specific therapy was touched on. Dr. Carrasquillo noted that each of these concerns should be addressed through well-designed clinical trials.

A Radiation Oncology Perspective

Dr. Bhadrasain Vikram reviewed the complementary role of TRT in radiation oncology. He began by reminding attendees that radiation oncologists attempt to deliver radiation doses as high as possible to malignant targets while avoiding toxicity to nonmalignant tissues. External-beam (teletherapy) and implanted solid radioactive sources (brachytherapy) are the 2 most common delivery approaches. However, the challenge remains that the ability to distinguish malignant from nonmalignant tissues is key and often difficult. Further, distinguishing these tissues may be complicated by the presence of occult metastases. The use of diagnostic and therapeutic radionuclides and radiopharmaceuticals can complement both teletherapy and brachytherapy. For this to be practical, however, improved targeting and labeling methods, optimization of radionuclide agents, and improved dosimetry are urgently needed such that TRT will be accepted as a routine adjunct to clinical radiation oncology practice.

Dr. Vikram discussed next-generation characteristics of teletherapy and the need for accurate identification of subvolumes that would benefit from high radiation doses versus those that would not. He identified the disciplinary tasks that would be required to create and disseminate the next generation of TRT in radiation oncology practice. From a basic sciences perspective, he stressed that these include identification of optimal radionuclides, refinement of microdistribution-based treatment planning, and development and commercialization of new delivery and supporting technologies. Careful attention to radiolabeling techniques for new and evolving tumor-targeting agents is needed, and identification and characterization of new tumor-specific targets, biomarkers, and radiosensitizers is important. Validation using preclinical and translational studies will be essential. To be adopted into clinical practice, clinical trials must be carefully planned and initiated, and tumor TRT will need to be incorporated or compared with current treatment strategies.

CONSENSUS FROM MULTIDISCIPLINARY WORKSHOPS

Four breakout discussion sessions were held as part of the NCI/SNMMI workshop. In these sessions, cross-sections of stakeholders were asked to focus their discussion on one of the following topics: lymphoma, bone therapy, solid tumors, and NETs. Summaries of the discussions and consensus reached by each group were presented with a focus on current TRT state of the art, clinical indications, apparent strengths and weaknesses, the most promising advances in the field, and challenges to overall acceptance and incorporation into routine clinical use. Despite the spectrum of diseases discussed, the groups shared several similar conclusions.

Lymphoma

Dr. Janis O'Malley summarized the results of the breakout group focusing on lymphoma. The group identified, among other long- and short-term objectives, the need for evidence-based clinical trials to generate robust data on radioimmunotherapy and TRT effectiveness, the utility of developing centers of excellence to coordinate and translate advances from basic science to clinical use, and the benefit of increased interaction across the spectrum of stakeholders in targeted therapy.

The group commented on the limited use of radioimmunotherapy in routine clinical practice today, now more than a decade after initial FDA approval of radioimmunotherapy for relapsed or refractory low-grade or follicular NHL and the expansion of approval in 2009 to first-line radioimmunotherapy in previously untreated follicular NHL with partial or complete response to chemotherapy. Although data on ibritumomab and tositumomab in lymphoma suggest radioimmunotherapy is well tolerated and may be superior to rituximab alone, many of the prior clinical trials were single-arm studies or compared radioimmunotherapy with chemotherapeutic agents that are now obsolete. Moreover, the poor cure rate of aggressive, transformed low-grade lymphoma has contributed to skepticism among referring clinicians about the true extent of radioimmunotherapy benefit. Several participants suggested there was a need for additional data from well-designed clinical trials to advance acceptance and widespread use of radioimmunotherapy in lymphoma. Such trials, it was thought, would ideally compare radioimmunotherapy with current chemotherapeutic strategies and provide data on cost effectiveness, quality-of-life benefit, progression-free survival, and overall survival. It was recognized that a major challenge to developing these trials would be the dynamic nature of cancer treatment since therapies are rapidly evolving and may have changed by the time of study completion. Trial design and selection of the targeted patient pool were thought to be critical as well. The careful selection of patient groups most likely to benefit from radioimmunotherapy would likely expedite therapy to those in most need. Identification of underserved patient groups, genomic and individual characteristics, and development of multicenter collaborative initiatives to expedite statistically significant findings would be helpful. Patients most likely to benefit from radioimmunotherapy were thought to include the elderly and those with difficult-to-treat disease (e.g., mantle cell lymphoma and diffuse large B-cell lymphoma with activated B-cell monotype).

One challenge to increasing radioimmunotherapy acceptance and use in lymphoma is that current ^{90}Y- and ^{131}I-labeled CD20-targeting agents are not sufficient for the range of diseases. The group suggested that researchers should consider looking beyond CD20 as a target in NHL to applications in Hodgkin lymphoma and T- and B-cell NHL. Further, the logistics of current radioimmunotherapy use were seen as a barrier to growth. The field has no academic or research home—in various institutions radioimmunotherapy practice may be centered in radiation oncology, nuclear medicine, hematologic oncology, or general oncology, with research distributed among basic scientists and health-care professionals. Personnel trained in radioimmunotherapy are difficult to find, and champions are few, even in many academic centers. Current protocols and referral processes that are often disruptive to routine clinical practice may offer obstacles in terms of stakeholder interest and reimbursement issues.

The group suggested that to increase radioimmunotherapy use, dissemination of knowledge across multiple disciplines, implementation of easily available and useable agents, appropriate reimbursement,

and the support of well-trained and enthusiastic physicians and dedicated personnel are needed. Agents with new cell targets, minimal side effects, and novel carrier molecules would be of benefit. Studies exploring personalized dosimetry remain a critical issue.

The discussion group recommended a collaborative approach, both within and among institutions, in which basic researchers and clinicians would regularly meet and assess strategies to investigate new targets, labels, patient populations, and regimens. The group cited as an example the potential of various radiolabels (e.g., ^{211}As and ^{225}Ac) that have shown promising characteristics for radioimmunotherapy. Sites with the capability of developing, validating, and evaluating these agents both preclinically and clinically could play a central role. It was suggested that the creation of a network of centers of excellence that could pool expertise and findings would be helpful.

One of the overarching needs is to bring patients more actively into the focus of TRT research. Many patients are afraid of radiation or may not be willing to undergo the work-up needed for TRT. Studies providing compelling evidence that TRT improves outcomes—with lower toxicity than chemotherapy—are needed, preferably including validated metrics of patient-reported outcomes and toxicities. To facilitate the range of steps needed to advance understanding and use of TRT, the group made several short- and longer-term recommendations.

In the short term:

- The SNMMI should reach out to various societies such as the American Society of Clinical Oncology and the American Society of Hematology and invite them to scientific meetings and special sessions to promote collaboration.
- A lymphoma summit meeting, modeled on this workshop, including scientists, clinicians, and support personnel, would be helpful in identifying low-hanging fruit in TRT and creating collaborations among researchers across institutions.
- Collaborative trials focused on underserved populations or new targets and agents should be formed. In particular, the group suggested that an interdisciplinary panel might plan a new collaborative national trial on ibritumomab or tositumomab.

In the longer term:

- A working group should be formed either to identify an existing nationwide trial network or to support creation of a new network to coordinate nationwide centers of excellence in TRT to jointly explore advances from basic sciences to clinical implementation. This would include development of multicenter protocols and trials.
- Increased outreach and training should be emphasized. Clinicians and investigators with the expertise, training, and tools to advance radioimmunotherapy are essential to sustain forward motion in the field. It was recommended that work with residency review committees across specialties be done to promote inclusion of TRT in training. Maintenance-of-certification programs could also be used as a tool to engage both those who are already involved in TRT and those who have an interest, and these programs could be offered both within and outside the traditional core of nuclear medicine–oriented professional meetings. Certification examinations could also be amended to include TRT as a requisite part of training.

Bone Disease

Dr. David Quinn presented the results from the breakout group focusing on bone therapy, summarized factors affecting current and future standards of care, and discussed key questions for future clinical trials. The importance of fostering cooperative groups was emphasized.

Dr. Quinn suggested that current treatment of bone metastases is changing, as is our understanding of the science that underlies it. The availability of new oral hormonal agents, for example, may mean that patients will remain longer under a urologist's care and that the urologist will be required to interact with other specialists to obtain immunotherapy or radionuclide treatments for patients. The introduction of new medications also means that the treatment paradigm will change. As urologists treat patients for a longer time with abiraterone and enzalutamide, for example, the patterns of metastases at referral to radiation or medical oncology could be different. Models of care are likely to evolve as well, with the need for multidisciplinary care teams that bridge academic and community interests, perhaps with specific bone metastasis focus groups. The question of who is likely to own radionuclide therapy in the future remains unclear, although it seems certain that institutions will vary in their approaches. Whether radionuclides are administered by nuclear medicine, radiation oncology, or other specialists, it is important that adequate and appropriate credentialing be available and required for all.

The organization of current radionuclide research was discussed, with a focus on efforts to create cooperative studies. It was noted that the field is driven largely by industry, with less current research under way than might be expected from the original promise of TRT. It was stressed that industry alone cannot address the range of scientific questions that should be answered to move the field forward. One challenge cited was the Radiation Therapy Oncology Group reorganization of research interests into organ and body sites, which eliminated the previous radionuclide subgroup active in the 1990s. The discussion group noted that there was no current overlap in research through the SNMMI, Radiation Therapy Oncology Group, or other national groups and recommended that leaders with an interest in radionuclide therapy become involved in key committees of these cooperative groups. SNMMI or NCI might also choose to lead in new non–industry-driven research through a variety of initiatives and mechanisms.

Many questions remain about α-particle therapy in bone metastases, and the discussion group identified several key questions that should be the focus of novel research:

- How can we better assess and use information about differential toxicity between normal and malignant tissues?
- Has the maximum tolerated dose of ^{223}Ra and other α emitters been established? Should researchers look more carefully at myeloablation?
- How can we secure more useful data on the dosimetric, pharmacokinetic, and imaging correlates of α-emitter therapy in bone metastases? Are bone metastases heterogeneous? If we understand this heterogeneity and the differential responses it engenders, metastases can be targeted in a more rational way.
- How can we enhance the quality of information provided by imaging and assessment of the circulating microenvironment, which are clearly preferable to biopsy?

The discussion group looked at various approaches to new trials, including use of α-particle therapy as an adjuvant in high-risk patients with androgen deprivation therapy or in those with suboptimal response to androgen deprivation therapy. Future trials should assess optimal therapeutic protocols for ^{223}Ra in combination or in sequence with novel hormonal agents, combinations of

novel agents with immunotherapy (such as the work currently under way with ^{153}Sm-EDTMP and prostate-specific antigen–TRICOM [Therion Biologics Corp.] vaccine), targeting of the epithelial compartment with nanoparticle delivery of reagents, induction of additive or synergistic DNA damage with cytotoxic chemotherapy or radionuclide targeting, and alternative targeted therapies in prostate cancer, such as blockade of the PI3K/Akt/mTOR (phosphatidylinositol-3′-kinase/protein kinase B/mammalian target of rapamycin) pathway in combination with radiation.

Basic and translational researchers will need to continue to explore modulation of the treatment microenvironment, beginning with the bone environment. Important questions center on whether α particles can kill cancer stem cells (when these can be identified) and, if so, what cell dose dynamics are involved. Animal models of bone metastasis heterogeneity were discussed, as well as the potential for rapidly transitioning data from such studies into clinical trials. More studies on mouse models of heterogeneity of tumor response to radionuclide therapy are needed, as are well-defined and replicable quantitative imaging approaches that can transition from translational models to clinical trials. The creation of interdisciplinary working groups, including not only imaging specialists but also cancer biologists and others, was suggested as one approach to advancing imaging technologies and techniques.

Solid Tumors

Dr. Wolfgang Weber summarized the discussions of the breakout group focusing on solid tumors. After a review of the current status of TRT in solid tumors, the group looked in detail at the immediate challenges, the most promising technologic and radiopharmaceutical advances, and the most likely near-term disease targets.

Although targeted radiotherapy has been used clinically in thyroid cancer since the 1940s (*4*), recent advances in molecular biology have identified a variety of novel targets. Significant progress has been made in the development of ligands binding to these targets, and techniques to calculate and personalize radiation doses.

In current clinical practice, radioiodine therapy is effective as an adjuvant to radioablation in thyroid cancer, treatment for metastatic disease, and modulation of iodine metabolism by protein kinase inhibitors to improve the effectiveness of therapy. Radioiodine therapy may also be enhanced by PET-based radiation dosimetry to predict tumor response (*22*). Results include improvement in progression-free survival, overall survival, and symptom palliation. Current clinical indications for TRT go beyond thyroid cancer to include ^{90}Y microsphere treatment in liver metastases, for which improvement in progression-free survival has been documented. The discussion group cited several promising preclinical and initial clinical studies that suggest future routine use of TRT in intracavitary therapy of tumors in the central nervous system, intraperitoneal therapy of ovarian cancer, targeting of HER2-expressing tumors, and systemic therapy of prostate cancer (*108–110*). Two promising example studies described were imaging and therapy of prostate cancer with gastrin-releasing peptide receptor (bombesin) antagonist ^{177}Lu-RM2 (4-amino-1-carboxymethyl-piperidine-D-Phe-Gln-Trp-Ala-Val-Gly-His-Sta-Leu-NH_2) and case reports of the efficacy of a ^{64}Cu-labeled bombesin antagonist (*111,112*).

The strengths of TRT identified by the discussion group included that, in principle, it can be applied to all malignant tumors; that targets can include tumor cells, tumor stroma, the vasculature, and the physiologic state of the tumor (e.g., pH or hypoxia); and, perhaps most significant, that TRT can be tailored to address the heterogeneity of cancer cells. The most significant weakness of TRT is that specific tumor uptake of currently available radiopharmaceuticals may be suboptimal in some patients.

The issue of heterogeneity was discussed in some detail. Interpatient heterogeneity is well documented, with breast cancers having an average of 60 mutations per tumor compared with 848 mutations per tumor in lung cancer, and 78,775 mutations per tumor in malignant melanoma (*113–115*). This results in heterogeneity between tumors and can be seen as an important factor in how tumors spread, probably explaining the low response rates in unselected patient populations and rapid development of resistance after initial response. An example of intrapatient heterogeneity in renal cell cancer was detailed (*116*).

One consensus arising from the group discussion was that TRT is a viable and promising solution for treating heterogeneous tumors. Pretherapeutic imaging in TRT practice can confirm target expression in individual patients and lesions, determine the magnitude of uptake of the therapeutic radiopharmaceutical, estimate radiation dose, and predict treatment efficacy. Tumors not expressing the therapeutic target can be treated by the crossfire effect, with limited resistance to high doses of ionizing radiation. In principle, TRT can address these issues that arise from the heterogeneity of cancer cells and their genetic instability.

Despite the potential for broad efficacy in solid tumors, TRT faces several challenges. These include but are not limited to the fact that the procedure is perceived as complex; requires interdisciplinary collaboration and team science across diverse disciplines; is costly, with significant reimbursement concerns; and is supported by clinical studies of limited size and quality. The group noted that these concerns will most likely be overcome when targeted radiopharmaceuticals have demonstrated clinical benefit in diseases with limited treatment options.

The most promising advances now under investigation are likely to be seen with α-particle therapies, nanoparticle-based therapies, novel combinations of imaging and therapy (including radioactive and optical imaging probes developed in tandem with therapeutic radiopharmaceuticals), and combinations of external-beam radiotherapy and TRT. The most promising disease targets under current investigation include prostate cancer (many potential targets), ovarian cancer (intraperitoneal therapy), breast cancer (HER2-directed therapy), brain tumors (intrathecal, intracavitary therapy), and head and neck cancers (p16-negative tumors).

To advance TRT in solid tumors, several scientific and organizational steps are needed. More quantitative analyses of target expression in human tissues are needed to quickly and definitively identify promising targets for radiopharmaceutical development. An infrastructure that supports new radiopharmaceutical development and optimization, and robust, clinically feasible dosimetry, should be encouraged. Interdisciplinary collaborations that drive multiinstitutional trials should be formed, and TRT stakeholders should consider formation of a radiopharmaceutical therapy cooperative trials group, either under the umbrella of an existing organization or as a new effort.

NETs

Dr. Ananth Srinivasan reported on the breakout group discussion regarding NET therapies. The group looked at both the strengths and the weaknesses of radionuclide therapy in NETs, including the discrepancy between the wide availability of such treatment in Europe and its lack of coverage in the United States, although the possibility of treating patients with NET using ^{177}Lu-DOTA-Tyr^3-octreotate

(Lutathera; Advanced Accelerator Applications) in the United States through an open trial was mentioned. As in the other breakout sessions, participants called for more basic scientific work to enhance our understanding of the biology of radionuclide therapy.

The group identified the currently most widely used radiopharmaceuticals for therapy in NETs as being ^{90}Y-DOTA-Tyr^3-octreotide (or ^{90}Y-DOTATOC or ^{90}Y-octreotide), ^{177}Lu-DOTA-Tyr^3-octreotate (or ^{177}Lu-DOTATATE or ^{177}Lu-octreotate), ^{111}In-DTPA-octreotide, ^{131}I-MIBG and companion imaging agents for patient selection and following progress (in only a few patients), and ^{68}Ga-DOTA-octreotide (for PET imaging). ^{111}In-DTPA-octreotide is the only FDA-approved imaging agent in use. Other compounds under investigation include ^{90}Y-DOTA-Tyr^3-octreotate and ^{177}Lu-DOTA-Tyr^3-octreotide. Studies performed in Europe over the past 15 y suggest that ^{90}Y- or ^{177}Lu-labeled peptides can deliver consistent radiation doses to lesions and achieve significant tumor responses (*117*).

Current clinical practice with ^{177}Lu-DOTA-Tyr^3-octreotate was reviewed, including details of a decade-long study involving almost 400 patients and representing state-of-the-art practice (*118*). Results showed that, compared with historical controls, patients undergoing TRT had survival benefits of 40–72 mo, with median time to progression of 40 mo and limited toxicities. Phase III trials have been initiated in the United States and Europe, and the radiopharmaceutical has received orphan drug status.

In a state-of-the-art clinical study with ^{90}Y-DOTA-Tyr^3-octreotide, survival was nearly 3 times longer than expected in patients treated with conventional approaches (*117*). Median survival from diagnosis was 94.6 mo, 2.9 times longer than the expected survival in patients with differentiated metastasized neuroendocrine cancer receiving other treatments (*119*). However, 12.8% of patients developed severe transient grade 3–4 hematologic toxicities, with 9.2% experiencing severe permanent renal toxicity.

Combination TRT is also a current state-of the-art approach in NET treatment. The group cited the example of a study comparing ^{90}Y-DOTA-Tyr^3-octreotide with and without ^{177}Lu-DOTA-Tyr^3-octreotide in almost 500 patients (*120*). Patients receiving combination therapy had a significantly longer survival than patients receiving ^{90}Y-DOTA-Tyr^3-octreotide alone, with comparable rates of severe hematologic and renal toxicities.

Several ongoing clinical trials of somatostatin receptor–based therapies were reviewed, as was the most recent consensus report of the NCI Neuroendocrine Tumor Clinical Trials Planning Group on future strategies (*121*). Although key recommendations included creation of randomized phase III studies comparing peptide receptor radiotherapy with standard systemic therapy, the NCI group did not directly address TRT except for the following statement: ". . .many reported studies have had suboptimal methodology, lacked intent-to-treat analyses, and used nonstandard end point definitions. Furthermore, no studies have compared the relative efficacy and toxicity of ^{177}Lu-DOTA-Tyr^3-octreotate and ^{90}Y-DOTA-Tyr^3-octreotide."

Current clinical practice with TRT in NETs is severely limited in the United States, and U.S. patients who are deemed appropriate for TRT (and who can afford the journey) have often gone to specialized European centers, such as those in Rotterdam, The Netherlands; Basel, Switzerland; and Milan, Italy. A small number of patients in the United States are enrolled in other treatment protocols, which in a few centers include ^{131}I-MIBG. There is an urgent need to improve access to TRT for NETs in the United States.

The workshop group identified several strengths for TRT in the treatment of NETs. These include the fact that even though a variety of NETs are treated, they all share expression of somatostatin receptor subtype 2, which can be treated with agents that have already shown efficacy, particularly in median survival and quality of life. Weaknesses include a lack of evidence on complete response rates and well-designed multicenter trials. Additional studies are needed to define the point at which TRT should be initiated, including consideration of TRT as first-line therapy.

Several logistic challenges face widespread adoption of TRT in clinical use. Currently available agents are not approved or reimbursed, with some patents expiring in the short term, making industry less likely to sponsor new research. Cost is an issue for patients and physicians; for example, ^{131}I-MIBG is reimbursed in some cases but not in others, an area in which SNMMI advocacy might play a role. In many institutions, nuclear medicine physicians are willing to treat patients but patients are not referred, a situation that calls for more collaboration and outreach to endocrinologists and gastrointestinal oncologists. Evidence of treatment efficacy could be accelerated by more methodologies identifying potential responders.

Promising potential advances in somatostatin receptor imaging with antagonists have been shown using radioligands. These radioligands have been shown to label a higher number of receptor-binding sites than conventional agonist radioligands (*107*). Peptide antagonists labeled with β emitters may prove to be useful in combined imaging and therapy (*122*).

The group addressed areas requiring additional research to advance the field. These include preclinical therapy studies using ^{90}Y/^{177}Lu antagonists followed by proof-of-concept studies in humans. Human studies with somatostatin receptor antagonists can validate the concept for other indications in which antagonists have been used for imaging. Additional basic studies are needed to better understand radiobiology and develop new dosimetry models. Renal toxicities remain a challenge, and new methods of protecting the kidneys should be explored. Preclinical studies with uptake enhancers to increase receptor expression are also needed.

To accelerate these strategies, the group pointed to the creation of new funding mechanisms that might establish centers of excellence in TRT in different geographic regions of the United States. This not only would provide institutional settings for basic, preclinical, and clinical studies but also would make beneficial treatments more easily available to patients.

WORKSHOP SUMMARY

Dr. Hossein Jadvar provided an overview and highlights of the workshop, emphasizing areas of consensus, including the regulatory and economic environment, basic biology, and radiochemistry. He provided a list of current and future issues for consideration, based on presentations at the workshop. Specifically, research is under way, he mentioned, to determine optimal biologic targets and create in vitro and in vivo models to validate new agents and propel them into human trials. High-quality, reproducible data are needed, with basic and preclinical studies performed under good laboratory practices. First-in-human data, including data on absorption, distribution, metabolism, and excretion, will follow, providing information on biologic efficacy, toxicities, and side effects. Among considerations for development and production are ease of radiochemical incorporation (particularly in the generation of theranostic pairs); evaluation of data on specific activity, synthesis yields, chemical and biologic stability, personalized dosimetry, radiobiologic modeling,

and radiolysis; assessment of the availability of similar or less costly agents with the same action; and easily accessible protocols. Also of importance are the costs of raw materials and the development of reliable distribution networks. Responding to these considerations is not a trivial endeavor.

Few molecular imaging and contrast agents in development make the transition to marketing, and even fewer TRT agents have passed these hurdles in the United States or worldwide. This is in part the result of the economic and regulatory landscape in which these agents are developed, approved, and marketed. Market size, market share, price resistance, and likelihood of reimbursement affect industry decisions on whether and how to develop a new agent, even when that agent is clearly beneficial. Challenges include the cost of supporting clinical trials needed for approval, issues of exclusivity in terms of patent protection, market competition from same-disease-targeted agents, and a regulatory environment that places constraints on dosimetry, administration, transport, and waste disposal.

A major challenge for TRT is ready availability of radioisotopes for research and clinical use. Some radioisotopes are not available in the United States; others are unavailable for clinical use because of lack of reimbursement and approval; some are available but underused in the clinic. Integration and determination of optimal sequencing of TRT with existing standards of care might advance clinical use, as would better data on side effects, toxicity, and complications compared with conventional therapies. More attention to patient-reported outcomes assessing quality-of-life benefits with TRT is also needed.

Although data on TRT efficacy are available from other countries, non-U.S. data are rarely sufficient for approval and reimbursement in the United States. The result is that for U.S. approval, scientists are often forced to reinvent the wheel, duplicating studies that have already been published in respected peer-reviewed literature. One challenge that should be considered by stakeholders is to identity ways to propel existing data on TRT forward more quickly in support of U.S. approvals. Another challenge is to directly address the various logistic problems cited in the workshop: limited access to TRT for patients and providers, perceived high cost, turf issues, patient perceptions and fears, and the need for multidisciplinary teams supported by strong TRT education efforts (*123–132*).

During his tenure as director of the National Institutes of Health, Dr. Elias Zerhouni introduced the 4 Ps of medicine: personalized, predictive, preemptive, and participatory. These apply to TRT, with the additional need for partnership. Education and collaboration are key to ensuring a multidisciplinary approach. Stakeholders involved in such collaborations are numerous and include federal agencies, academia, pharmaceutical companies, patients and patient advocacy groups, providers (preferably in multispecialty teams), payers, professional societies, and philanthropists and venture capitalists. The ultimate goal, as in all of medicine, is to ensure that patients receive timely, appropriate therapy in a cost-effective manner. Balancing these forces through multidisciplinary collaboration, bench-to-bedside discovery, innovation, documentation, and validation of enhanced outcomes is a challenge that will require new cooperative mechanisms and the involvement of the broadest range of stakeholders interested in advancing TRT.

CONCLUSION

TRT has great potential for cancer therapy across a spectrum of tumor types including breast, lung, bone, lymphoma, and NETs, among others, and may be particularly helpful to treat heterogeneous tumors. TRT could be applied as a primary therapy or in conjunction with other approaches, including external-beam radiation or brachytherapy. However, TRT requires a multidisciplinary approach, and for this potential to be realized, cooperative structures must be developed across institutions to gather the necessary basic science and clinical trial data. This research most likely will need to go far beyond that which is typically industry-sponsored. Therefore, a multiinstitutional infrastructure would likely be helpful to facilitate the collection of such data.

As new potential agents are developed, knowledge of the microenvironment and metabolism both in the tumor and in normal tissue must be sought, leading to patient-specific radiobiology-based dosimetric models and allowing for effective treatment planning. Effort should also be made to establish routine production at high activity levels. New, effective models and production methods will also be desirable for agents in current use. Since no single institution will likely have expertise in all areas, a multiinstitutional research network may be effective in enhancing the advancement of this research.

Once an agent is ready for in-human investigations, large-scale randomized, evidence-based clinical trials that establish its effectiveness with respect to cost, quality of life, and patient outcome will be needed. Study design and patient selection are critical for implementation, and time will be of the essence so as to allow comparison to current alternative therapies. This will most likely require a multiinstitutional cooperative infrastructure beyond that provided through industry-based trials.

The clinical implementation of TRT will require a multidisciplinary approach and education of all involved, including basic scientists, physicians, and support personnel. Further careful treatment planning and patient selection will be needed to ensure treatment benefit.

This workshop was unique in that it included a wide range of stakeholders invested in the success of TRT, including a variety of clinicians (nuclear medicine physicians, radiation oncologists, and medical oncologists) and basic scientists (radiochemists, physicists, and radiobiologists). In order for the promise of TRT to be realized, more such gatherings would be helpful since the most successful implementation will be multidisciplinary. Although focus on a particular disease such as lymphoma or bone disease may be helpful, interdisciplinary cooperation will clearly be critical, both across and within institutions.

ACKNOWLEDGMENTS

The Organizing Committee is made up of the following individuals: Frederic Fahey, DSc (Boston Children's Hospital, Boston, Massachusetts, and Harvard Medical School, Boston, Massachusetts); Katherine Zukotynski, MD, FRCPC (Sunnybrook Health Sciences Centre, University of Toronto, Ontario, Canada, and Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts); Jacek Capala, PhD (National Cancer Institute/NIH, Bethesda, Maryland); Hossein Jadvar, MD, PhD, MPH, MBA, FACNM (University of Southern California, Los Angeles, California); Gary Dillehay, MD, FACNM, FACR (Northwestern University Medical School, Chicago, Illinois); Peter Herscovitch, MD (National Institutes of Health Clinical Center, Bethesda, Maryland); Nancy Knight, PhD (University of Maryland School of Medicine, Baltimore, Maryland); and Virginia Pappas, CAE (SNMMI, Reston, Virginia).

The contributors include George Sgouros, PhD (Johns Hopkins University School of Medicine, Baltimore, Maryland); Michael R.

Zalutsky, PhD (Duke University Medical Center, Durham, North Carolina); Richard L. Wahl, MD (Johns Hopkins University School of Medicine, Baltimore, Maryland); Eric Jacobsen, MD (Dana–Farber Cancer Institute, Boston, Massachusetts, and Harvard Medical School, Boston, Massachusetts); David I. Quinn, MBBS, PhD, FRACP (USC Norris Comprehensive Cancer Center, Keck School of Medicine, University of Southern California, Los Angeles, California); Jorge A. Carrasquillo, MD (Memorial Sloan–Kettering Cancer Center, New York, New York); Bhadrasain Vikram, MD (National Cancer Institute/NIH, Radiation Research Program, Bethesda, Maryland); Steven Larson, MD, FACNM (Memorial Sloan-Kettering Cancer Center, New York, New York); Janis P. O'Malley, MD (University of Alabama at Birmingham, Birmingham, Alabama); Wolfgang Weber, MD (Memorial Sloan–Kettering Cancer Center, New York, New York); and Ananth Srinivasan, PhD (Stanford University, Palo Alto, California).

The participants include Robert R. Bahnson, MD, FACS (Ohio State Wexner Medical Center, Columbus, Ohio); Martin W. Brechbiel, PhD (National Cancer Institute, Bethesda, Maryland); David Y.T. Chen, MD, FACS (Fox Chase Cancer Center, Rockledge, Pennsylvania); Xiaoyuan Shawn Chen, PhD (National Institute of Biomedical Imaging and Bioengineering, Bethesda, Maryland); Norman Coleman, MD (National Cancer Institute, Rockville, Maryland); Adam P. Dicker, MD, PhD (Jefferson Medical College of Thomas Jefferson University, Philadelphia, Pennsylvania); David M. Goldenberg, ScD, MD (Immunomedics, Inc., Morris Plains, New Jersey); Roger W. Howell, PhD (Rutgers New Jersey Medical School, Newark, New Jersey); Edvardas Kaminskas, MD (Office of Hematology and Oncology Products, Food and Drug Administration, Silver Spring, Maryland); Adam Opanowski, CNMT, PET, NCT, RT(N) (ACR Clinical Research Center Core Laboratory, Philadelphia, Pennsylvania); Karel Pacak, MD (National Institute of Child Health and Human Development, Bethesda, Maryland); Daniel Pryma, MD (University of Pennsylvania, Philadelphia, Pennsylvania); Tod W. Speer, MD (University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin); Suresh C. Srivastava, PhD (Brookhaven National Laboratory, Upton, New York); Cindy Tomlinson (American Society for Radiation, Fairfax, Virginia); John F. Valliant, PhD (McMaster University, Hamilton, Ontario, Canada); Barry W. Wessels, PhD (University Hospitals–Case Western Reserve University, Cleveland, Ohio); and D. Scott Wilbur, PhD (University of Washington, Seattle, Washington).

The contributions of Terpse Gentile, Nikki Wenzel-Lamb, and Amelia Ballinger (SNMMI) to this work are gratefully acknowledged.

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CHAIRMAN Resource

From: Bunning Sue <sbunning@snmmi.org>
Sent: Thursday, March 10, 2016 2:43 PM
To: CHAIRMAN Resource; CMRSVINICKI Resource; CMROSTENDORFF Resource; CMRBARAN Resource
Subject: [External_Sender] Training and Experience Requirements for Authorized Users of Alpha and Beta Emitters
Attachments: NRC_alpha_beta_emitter_Letter_FINAL.docx; JNM-2015_attachment2.pdf; TRT-JNM_attachment1.pdf

Dear NRC Commissioners:

Please find attached a letter from SNMMI President Hossein Jadvar. We appreciate the opportunity to meet with you regarding the ACMUI Subcommittee Report on training and experience requirements for authorized users of alpha and beta emitters.

Thank you.

Sue Bunning

Sue Bunning
SNMMI SOCIETY OF NUCLEAR MEDICINE AND MOLECULAR IMAGING
Director, Health Policy and Regulatory Affairs
phone: 703.326-1182 | cell: 703.340-4100
email: sbunning@snmmi.org
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