NMRO

ACNM
American College of Nuclear Medicine

Scintillator

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President's Message

Joseph Trak, MD, MBiotech

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Hello and welcome to the Fall issue of the Scintillator!

We are excited to share an overview of the trainee research award by Dr. Simin Dadparvar, an interview with ACNM President Dr. Katherine Zukotynski by resident physician and NMRO board member Matteo Novello, a short piece on alpha therapy by resident physician and NMRO board member Ahmed Abdelrahman, and an overview of the ACNM NMRO networking event that took place at the 2023 SNMMI Annual Meeting by resident physician and NMRO board member Thangalakshmi Sivathapandi.

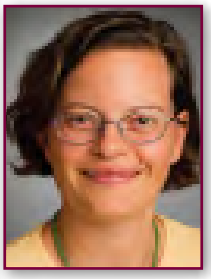
Speaking of the SNMMI Annual Meeting, I hope you were able to make it to Chicago this year! There were many great sessions. I'm most excited about FAPI; I'm curious to see the result of further developments in the diagnostic and therapeutic fronts.

We hope to see you at the **2024 ACNM Annual Meeting**, February 1-3, 2024, in Orlando, Florida. In addition to an amazing educational experience, please join us for the ACNM Banquet where the 2024 ACNM Award recipients will be announced. **Click here** to register today!

As always, for any questions or concerns, please feel free to reach out to us at **acnm@acnmonline.org**.

Interview with Dr. Zukotynski

Matteo Novello, MD



Katherine Zukotynski, MD, PhD, PEng, FSNMMI

1. What is the happiest memory in your nuclear medicine career?

My happiest memory was probably attending the SNMMI Annual Meeting in 2008. I remember it distinctly because this was my first SNMMI Annual Meeting and my first exposure to research and real advances in our field. For example, this was when I first learned about new radiopharmaceuticals for amyloid deposition and thought we might finally be heading toward a breakthrough in dementia. After that, I spent an evening with friends and colleagues watching the Celtics win the championship! Double celebration.

2. What is the next big thing you are looking forward to in nuclear medicine?

I'm looking forward to more novel radiopharmaceuticals for both imaging and therapy. One of the main areas of medicine I have found challenging is finding the best tools to make a reliable diagnosis and then treat the medical issue while minimizing toxicity. I was fortunate enough to witness new prostate cancer tracers moving from bench to bedside and the evolution in imaging and therapy that happened hand in hand with this. Similarly, I have seen new tracers go from bench to bedside in dementia imaging and new therapies that can treat the disease we see. I look forward to phenomenal changes in patient care, and I believe our future is scintillating.

3. Which ideal vision of nuclear medicine do you have in 20 years?

My vision is for nuclear medicine to play a key role in patient care, with both our colleagues and patients recognizing its importance. We just may have it all, acting both as the consultant's consultant and as the front-facing physician who discusses imaging and treatment with our patients.

4. What are the common pitfalls to avoid when starting an academic career?

My best advice for early career professionals is to listen. Pay attention to what the healthcare team and the patients

Continued on page 3. Interview with Dr. Zukotynski.

ACNM NMRO Networking Event

A networking event organized by the NMRO took place on Sunday, June 26, as part of the 2023 SNMMI Annual Meeting. Dr. Bital Savir delivered the introductory speech to the gathered residents and members. ACNM recognized Dr. Bora Cengiz as the recipient of the 2023 ACNM Resident/Fellow Research Award. The event featured an excellent presentation titled "Laying the Foundation Today for a Better Tomorrow" by David Thyen, a financial planner from the Larson Company. Various investment plans available for residents were discussed in detail. Residents had a productive networking opportunity while enjoying evening snacks.

NMRO Session at the 2024 ACNM Annual Meeting

The global market for nuclear medicine is constantly growing. Reports suggest that the market size was around 7.5 billion USD in 2022 and is expected to reach 30 billion USD by 2030. This means that there is a need to train more nuclear medicine professionals, including physicians, technologists, radio pharmacists, and support staff, to meet the increasing demand. Organizations such as ACNM and SNMMI are playing a crucial role in meeting this demand worldwide. The upcoming ACNM annual/SNMMI mid-winter meeting in Orlando, FL, in February 2024, will showcase the efforts being made by these organizations.

One of the sessions at the upcoming ACNM mid-winter meeting, sponsored by the Nuclear Medicine Resident Organization (NMRO), will take place on Saturday, February 3rd, from 4-6 PM. The session will feature talks from leaders in nuclear medicine on theranostics during residency training and grant writing.

Dr. Munir Ghesani, the section chief of nuclear medicine at Mount Sinai Health in New York, will discuss the current state of theranostics and its integration into the nuclear medicine residency curriculum. As an experienced nuclear medicine educator and theranostics expert, Dr. Ghesani will highlight the importance of a multidisciplinary approach to theranostics, the requirements to become an authorized user, and the skills needed to become an effective nuclear medicine physician.

Dr. Babak Saboury, chief clinical data science officer at the National Institute of Health, will provide valuable insights into effective research involvement, identifying the right opportunities, and writing successful grants. He will also emphasize the importance of publishing in peer-reviewed journals, presenting at conferences, and writing book chapters.

This NMRO-sponsored session will showcase the importance of such events and their potential to greatly impact the field of nuclear medicine.

Interview with Dr. Zukotynski continued from page 1.

are requesting. What are their questions? What can we offer them? Working as a team and presenting a unified front often leads to the best care. When you graduate, you may feel a mix of insecurity and overconfidence; remember that you are not alone. You can help by listening to what others have to say and asking questions. Use feedback as an opportunity to move things forward, and understand that most people want to help.

5. What are the strengths and weaknesses of academia versus private practice versus industry-oriented careers?

In an academic career, you have trainees. This is a great opportunity to discuss interesting cases and get other points of view, and that leads you to constantly think about what we do and why. You also may have support for academic activities, including administrative roles and research, so your career can include a spectrum of clinical work, teaching, and research.

In private practice you are less likely to have trainees. Case volume tends to be higher, and the work is more often solo. You may not have the opportunity or time to discuss and share the interesting things that you see and do. The benefits tend to be better compensation and more autonomy. Also, you likely will not have to worry about publishing papers, giving lectures, or academic commitments/promotion.

In industry you are often at the cutting edge of developments in our field. The pace in research can be fast, and the potential rewards, both in terms of patient care and compensation, can be enormous. Then again, the risks can also be high, and early developments can sometimes be abandoned, heartbreaking though this may be. You may also be unable to speak freely about exciting advances due to conflicts of interest.

6. What is a common task for nuclear medicine physicians who are working in industry-oriented careers?

The nuclear medicine physician involved in industry plays a critical role in designing clinical trials, analyzing results, and evaluating how these impact patients. Typically medical questions in the clinical trial are evaluated by/discussed with physicians.

7. What was your main priority after being elected as president of ACNM?

My main priority was education and building bridges with other societies and professionals. As president of the ACNM, my goal was to be transparent/inclusive, improve benefits for our community, increase our membership, and raise the profile of ACNM within our field and abroad.

8. What is the most valuable piece of advice you would like to offer to nuclear medicine trainees?

You always have to be able to stand on your own two feet, and you must know, in your soul, that nuclear medicine is the future. Listen to others, try to understand where they are coming from and why—but ultimately, believe in yourself. Life is a cross-country run, and it is a long road, not a sprint.

We live in interesting times, and giving up is not an option. Just as RAI helped humanity in the 1940s, so today does our field evolve and grow. The sky is the limit.

American College of Nuclear Medicine Resident/Fellow Researcher Award in North America

Simin Dadparvar, MD, NMRO Founder

Turgut Bora Cengiz, MD

The American College of Nuclear Medicine is pleased to announce the establishment of the North American Nuclear Medicine Resident/Fellow Researcher Award. The award is given to the top two nuclear medicine resident/fellow researchers from North America and is presented at the SNMMI Annual Meeting during the Nuclear Medicine Resident Organization session. It is funded by a donation from the Education and Research Foundation for Nuclear Medicine and Molecular Imaging.

This year, the inaugural recipient of the award was Dr. Turgut Bora Cengiz, MD, of the Department of Diagnostic, Molecular and Interventional Radiology at Mount Sinai Hospital, New York, NY. He received a recognition plaque, presented by Dr. Bital Savir Baruch, MD, NMRO mentor, at the SNMMI Annual Meeting in Chicago, Illinois.

We congratulate Dr. Turgut Bora Cengiz for his outstanding achievements and wish him success in the field of nuclear medicine.

When ^{177}Lu-PSMA Falls Short: Future Directions in Theranostics Beyond the VISION Trial

Ahmed Abdelrahman, MD and Bital Savir-Baruch, MD, FACNM

Radioligand therapy (RLT) has gained significant momentum in the past few years due to advances in precision medicine. PSMA theranostics has significantly changed the management of metastatic prostate cancer. Currently, ^{177}Lu-PSMA-617 is the only FDA-approved PSMA-based radioligand for treatment of patients with metastatic castration-resistant prostate cancer (mCRPC), based on the success of the VISION trial.[1] The approved therapy includes six cycles of 200 mCi (7.4 GBq) of ^{177}Lu-PSMA-617 every six weeks. Despite the success of the VISION trial, the durability of treatment response is short-lived, and 30% of patients developed resistance to RLT.[2]

Moreover, several important questions remain unanswered. For instance, is a one-size-fits-all dosing strategy appropriate? Who is more likely to respond favorably? Should treatment be limited to just six cycles? Is it necessary to administer the full six doses if PSA levels become undetectable? What are the predictive markers for a response to therapy?[3]

Several factors have been hypothesized to explain the resistance to ^{177}Lu-PSMA, including insufficient dose delivery, heterogeneity in tumor PSMA expression, distribution of disease affecting radiosensitivity, and tumor mutational factors.[2] This article briefly highlights some of the recent trials exploring the use of PSMA beyond VISION.

Extended Dosage

The literature and experience regarding extended PSMA RLT therapy for selective populations beyond the six standard doses are limited. Derlin et al. retrospectively evaluated the extended use of ^{177}Lu-PSMA RLT in 26 patients who completed a standard six cycles of ^{177}Lu-PSMA without any evidence of progression and with no grade 3 (or higher) toxicity. The additional cycles ranged from 7 to 13 and resulted in PSA response in 52% of patients.[3] This study concluded that extending therapy beyond six cycles is feasible.

Another study by Mader et al. explored the use of extended therapy in patients who had no alternative therapy available and who presented with persistently high disease volume. Overall, 26 patients received 7 to 16 cycles, and 81% of those showed further decline in PSA. The study concluded that extending PSMA RLT beyond six therapies for selected patients with high-volume disease may offer survival benefits.[4]

Combination Therapy

^{177}Lu-PSMA RLT is currently given as a stand-alone therapy. Yet, some consider incorporating other "standard of care" therapy regimens similar to the VISION trial. It remains unclear whether ^{166}Lu-PSMA can be given as part of a combination therapy.

Several ongoing trials are investigating the use of combination therapy with FDA-approved agents to increase the efficacy of ^{177}Lu-PSMA. These agents include androgen receptor pathway inhibitors (ARPIs), PARP inhibitors, immune checkpoint inhibitors, and chemotherapy. ENZA-p (NCT04419402) is a phase 2 trial enrolling 160 patients with mCRPC to investigate the use of ^{177}Lu-PSMA-617 in combination with enzalutamide versus enzalutamide alone in 1:1 ratio. LuPARP (NCT03874884) is a phase 1 dose-escalation and dose-expansion study that enrolled 52 patients with mCRPC to evaluate the safety and tolerability of olaparib in combination with ^{177}Lu-PSMA.

Moving Up in the Treatment Chain

Several clinical trials are investigating the use of ^{177}Lu-PSMA-617 at an earlier stage, including both mCRPC and metastatic hormone-sensitive disease (mHSPC). For mCRPC, the PSMAfore (NCT04689828) trial is a phase III, open-label, multicenter randomized study aiming to enroll 450 patients with taxane-naïve mCRPC who have progressed (only once) on prior second-generation androgen receptor directed therapy (ARDT) such as abiraterone, enzalutamide, darolutamide, or apalutamide. Patients were randomized (1:1) for ^{177}Lu-PSMA-617 with best supportive care, including ADT, versus a change in ARDT to either abiraterone or enzalutamide with best supportive care, including ADT.[5] In December 2022, Novartis announced that the trial had reached its primary endpoint by achieving statistically significant and clinically meaningful improvement in radiographic progression-free survival (rPFS).

For the mHSPC population, the PSMAddition trial (NCT04720157) is an open-label, randomized (1:1), phase 3 study investigating the use of ^{177}Lu-PSMA-617 with the standard of care (SoC) including ARDT and ADT, versus SoC alone (ARDT +ADT) in patients with mHSPC.[6] The study aims to enroll 1126 patients, with primary endpoint being rPFS. Some of the secondary endpoints include overall survival, progression-free survival, and the proportion of patients with a prostate-specific antigen (PSA) decline of ≥ 90% from baseline and time interval to development of mCRPC.

Alpha Particles

The most commonly used radiotracers in theranostics are beta emitters. Alpha particles are significantly larger

Continued on page 5. When ^{177}Lu-PSMA Falls Short.

When ^{177}Lu-PSMA Falls Short continued from page 4.

than beta- particles (5–9 MeV vs 0.13 -2.2 MeV) and possess a larger linear energy transfer (80 keV/mm vs 0.2 keV/mm), enabling them to cause double-stranded breaks in DNA. They also have a shorter range (0.04-0.1 mm vs 0.05- 12 mm), which may result in less bone marrow exposure and toxicity. Currently, the only FDA-approved alpha particle used in theranostics is ^{223}Ra. Following the success of the ALSYMPCA trial, which demonstrated overall survival benefit, ^{223}Ra is FDA-approved for patients with mCRPC and symptomatic bone metastases with no known visceral metastatic disease.[7]

The use of alpha-based PSMA-RLT is being studied extensively around the world. One of the most studied alpha radioligands is ^{225}Ac-PSMA-617 (phase 1 trial by Novartis NCT04597411). A systematic review and meta-analysis of 3 trials evaluating the use of ^{225}Ac-PSMA in 141 patients reported that 83% of patients experienced some degree of PSA decline, and 59% had at least 50% PSA decline.[8] An additional promising alpha emitter radionuclide is ^{212}Pb. TheraPb (NCT05720130) is a phase 1/2 non-randomized dose escalation and toxicity study that will enroll up to 18 patients with mCRPC to receive ^{212}Pb-ADVC001, a compound with close proximity to PSMAI&T.

Conclusion

RLT such as ^{177}Lu-PSMA has established itself as a third-line treatment for patients with mCRPC. Now multiple ongoing trials are investigating its efficacy early in the disease process and in combination with other agents to combat the development of resistance. An increasing number of targeted alpha-emitting isotopes is currently being tested in clinical trials and has shown promising results.

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