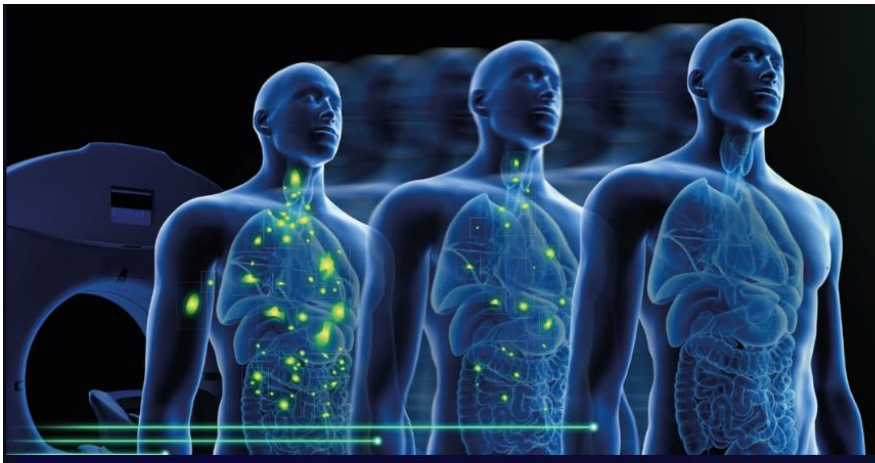

RADIOMOLECULAR
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ICPO Whitepaper

Highlights of the ICPO Theranostics Virtual Summit 2024

November 14 and 15, 2024

Radiotheranostics: New Era for Alpha Emitters and Radiopharmaceuticals

with 35 world-class experts

www.icpovirtualsummit.com

Scientific Program, Day 1, Nov 14, 2025

KEYNOTE: History of Alpha Therapy - S. Larson (USA)

SESSION I: Alpha Emitters Fundamentals

- Radiobiology need to know about Alphas - J-P. Pouget (France)
- Alpha emitters in development for theranostics – W. Digby (USA)
- Dosimetry techniques for alpha radioligand therapy: where are we now? - P. Fragoso Costa (Germany)
- Radiochemistry Alpha specificities and latest advances - M. Nader (Germany)

SESSION II: Alpha Emitters from Bench to Bed Side

- Ac225 Clinical Insights from WARMTH Act LANCET Oncology Study - M.Sathekge (South Africa)
- At211 from preclinical to the clinic - T. Watabe (Japan)
- Pb212 Preclinical Experience and Clinical Potential - N. Pullen (Switzerland)
- Pb-212-PSMA clinical experience in prostate cancer and the promise of Pb-212 based radiopharmaceuticals with novel targets and indications - A. Karmann (USA)

SESSION III: Alpha Emitters beyond PSMA

- Update and Innovation in Ac225 Supply - C.S. Cutler (USA)
- Next-generation SSTR2 targeting in Small Cell Lung Cancer with Ac-225 - G. Gericke (Germany)
- Innovative approaches to Targeted Alpha Therapy with 212-Pb - V. Wagner (France)
- Pb212 Dotamate in NET - E. Delpassand (USA)

SESSION IV: Challenges of Alpha therapies versus conventional emitters

- Global supply status and challenges of Ac225 and other alphas - N.Quigley (Germany)
- At211 the European Network - J-F Gestin (France)
- Pb212 Generators: Different Concepts & Logistics - M. Schultz (USA)
- Development of Alpha therapies versus conventional emitters - D. Chetty (USA)
- Ethics in Clinical trials of Alpha Therapies - J. Mailman (USA)

PANEL: Global perspective on patient access today and in 5 years

Moderators: R. P. Baum and F. Giesel (Germany)

Wrap up and Closing of Day 1

Scientific Program, Day 2, Nov 15, 2024

KEYNOTE: History of FAP till today - A. Scott (Australia)

SESSION V: FAP Diagnostics in Oncology and non-Oncology

- FAP Dx into clinical practice today – malignant and non-malignant - F. Giesel (Germany)
- "Myocardial and organ fibrosis" in the FAP Diagnostics - M. Dweck (UK)
- FAP Dx Some On-going Clinical Trials - S. Mosessian (USA)

SESSION VI: FAP Therapy

- FAP Peptide Targeted Tx - R.P. Baum (Germany)
- Innovative ^{177}Lu-FAPi Therapy: Medullary Thyroid Cancer & Sarcomas - S. Ballal (India)
- Optimisation of FAP ligands for therapy through multimerization and medicinal chemistry approaches - Jacqueline Mock (Switzerland)

PANEL 2: FAP as Imaging Biomarker

Moderator: E. Zan (USA)

SESSION VII: CA9 and G250

- CA9 Theranostics with Small Molecules - M. Hofman (Australia)
- CA9 Some On-going Clinical Trials - D. Cade (Australia)
- G250 Antibody Renal Cell Cancer - S.T. Lee (Australia)

SESSION VIII: CXCR4, GPC3 and GPC1

- CXCR4 Hematological Indications - R. Werner (Germany)
- CXCR4 some On-going Clinical Trials - H. Bouterfa (Germany)
- GPC3 Promise for Oncology - W. Weber (Germany)
- GPC1 Promise for Oncology - S. Serada (Japan)

PANEL 3: Antibody Drug Conjugates contra Radiopharmaceutical Therapies?

Moderator: K. Herrmann (Germany)

FINAL ROUND TABLE: A new theranostics era for patients, fueled by innovation & regulatory advances

Wrap up and Closing of Summit 2024

ICPO Whitepaper

Highlights of the ICPO Theranostics Virtual Summit 2024 held on November 14 and 15, 2024

Day 1- November 14, 2024

The ICPO Summit began with a keynote by **Prof. Steven M. Larson of Memorial Sloan Kettering Cancer Center, New York, USA**, who provided an insightful historical perspective on alpha emitters, tracing their origins from Marie Curie's pioneering work with Polonium and Radium to modern therapies using Bismuth and Actinium. He highlighted the proven tumoricidal properties of alpha emitters across a range of radionuclides used in RPT. Dr. Larson also discussed the critical challenges posed by long-circulating vectors, which produce radioactive daughters that limit tumor doses and impact normal tissue toxicity. He underscored the potential of targeted peptide therapies and pre-targeting solutions, such as DOTA-PRIT and click chemistry, which offer high therapeutic indices and rapid clearance of non-tumor-binding radioligands. Dr. Larson called for greater investment in theranostic approaches tailored for alpha emitters, emphasizing the need for robust support from both government and private sectors.

Jean-Pierre Pouget from Inserm, France, then focused on the radiobiological advantages of alpha particles, emphasizing their ability to induce precise double-strand DNA breaks in tumors, which makes them highly effective in cancer therapy.

Ward Digby from Siemens Healthineers, USA, highlighted the technical challenges in imaging alpha emitters like Ac-225 and Pb-212, stressing the urgent need for innovative agents to improve dosimetry and treatment planning**.**

Pedro Fragoso Costa from UK Essen, Germany elaborated on the difficulties of imaging alpha-emitter biodistribution due to the lack of sufficient gamma emissions and highlighted the necessity of accounting for daughter radionuclide biodistribution to ensure accurate dosimetry. He also stressed the importance of microdosimetry to assess heterogeneous activity distributions and develop precise dose profiles in alpha RLT.

Michael Nader also from UK Essen, **Germany**, reviewed recent advances in alpha radiochemistry. He outlined key challenges to be overcome in order to advance clinical applications, including vector chemistry, complex stability, recoil effect, as well as the worldwide production limitations of alpha-emitting isotopes.

Mike Sathekge from NuMeRI, South Africa, presented compelling clinical data on the success of Ac-225 PSMA therapies in prostate cancer, citing the WARMTH Act LANCET Oncology Study, which underscores the significant potential of these therapies in oncology. He also addressed challenges related to stabilizing Astatine-211, underscoring its emerging role in radioligand theranostics. Dr. Sathekge stressed the critical need for expanding radionuclide production facilities, fostering interdisciplinary collaborations to establish theranostic centers, investing in workforce training, streamlining reimbursement protocols, and ensuring global availability of radioisotopes.

Tadashi Watabe from Osaka University, Japan, highlighted the promise of Astatine-211 in treating thyroid and prostate cancers, supported by ongoing global preclinical work and clinical trials. He also gave the historically unique perspective of Japan when it comes to isotope production.

Nick Pullen from ARTBIO, USA, showcased Pb-212-based therapies in preclinical development, emphasizing their potential for targeted alpha therapy and the challenges in scaling from laboratory research to clinical application. Building on this,

Anna Karmann from AdvanCell, USA, shared early clinical data on Pb-212-PSMA for metastatic prostate cancer, revealing its strong efficacy and safety profile. Dr. Karmann further stressed the importance of dose optimization in the development of radiopharmaceuticals, emphasizing that pre-market optimization is essential to successful clinical programs. She noted that guidance on dose selection for first-in-human trials and dosage refinement for radiopharmaceuticals remains a critical area for future research and regulatory alignment.

Cathy S. Cutler from Brookhaven National Laboratory, USA and President of SNMMI, highlighted the global supply limitations of Ac-225 and the ongoing efforts to scale up its production to meet the increasing clinical demand. She discussed various strategies being pursued, including reactor-based, accelerator-based, and alternative methods, to address the challenges associated with producing this critical isotope. Cutler emphasized the importance of innovative solutions and sustainable supply chains to ensure a steady and reliable supply for targeted alpha therapies. She estimated that the first alpha-emitting radiopharmaceutical utilizing Ac-225 could reach the market by 2028, marking a transformative milestone in oncology. She also underscored the significant logistical and infrastructural challenges that need to be overcome to support the growing need for Ac-225, highlighting its pivotal role in advancing cancer treatment.

Thereafter**, Germo Gericke from Ariceum Therapeutics, Germany,** showcased the potential of Ac-225 in treating small cell lung cancer, and particularly neuroendocrine tumors, marking a pivotal development in cancer treatment.

Volker Wagner from Orano Med, France, highlighted advancements in targeted alpha therapy with Pb-212, celebrating their FDA Breakthrough Therapy Designation for AlphaMedix™ as a milestone toward clinical implementation.

Ebrahim Delpassand from Radiomedix, USA shared compelling data on the unprecedented efficacy of Pb-212 DOTAMATE against neuroendocrine tumors, demonstrated thanks to Ga-68 DOTATATE PET/CT scans.

Neil Quigley from ITM Isotope Technologies Munich, Germany, discussed the global supply status and challenges of actinium-225 and other alpha emitters. He emphasized the key difference between alpha and beta emitters, particularly the highly energetic alpha decay, which can impact chromatography systems during scaling up activity. Neil explained that gaseous alpha emitters present significant hazards, but these can be managed with the appropriate facilities.

Jean-François Gestin from Inserm, France, and **Michael Schultz from Viewpoint Molecular Targeting, USA,** developed the critical role of international collaborations to secure and expand the global supply of Astatine-211 and Pb-212.

Dushen Chetty from Novartis, USA, talked over the development differences between alpha therapies and therapies involving conventional emitters. He also reinforced the broad therapeutic applications of radiotheranostics across various cancer types.

Closing the session, international patient advocate **Josh Mailman from USA,** delivered a poignant address on the ethical considerations in theranostics clinical trials, underscoring the importance of safeguarding patient safety and autonomy as the field advances.

A panel discussion, led by **Richard P. Baum, President of the ICPO Academy for Theranostics** and **Frederik L. Giesel, Director, University Clinic Düsseldorf, Germany**, offered strategic perspectives on managing isotope availability while meeting the growing demand for personalized care in theranostics today and in 5 years. This panel was composed of Cathy S. Cutler, Michael Sathekge, Michael Schultz, Germo Gericke and Josh Mailman.

Day 2 - November 15, 2024

Andrew M. Scott, Director at the Olivia Newton-John Cancer Research Institute, Australia, presented groundbreaking insights into FAP-targeted theranostics for oncology and fibrosis-related conditions. He detailed the immunosuppressive role of FAP cancer-associated fibroblasts (CAFs) within the tumor microenvironment, explaining their involvement in extracellular matrix formation, immune modulation, and T-cell infiltration reduction. Dr. Scott highlighted that FAP+ CAFs secrete CCL2, recruit myeloid cells, and promote CD4+CD25+ T-cell differentiation. Depleting FAP+ CAFs were shown to induce tumor regression in immunogenic models and increase responsiveness to PD-L1 therapy, demonstrating significant potential for enhancing immunotherapy outcomes.

Frederik L. Giesel, Director of the Department of Nuclear Medicine at the University Clinic Düsseldorf, Germany, explored the clinical significance of FAP diagnostics, focusing on its superiority in oncology, where FAP PET imaging outperforms FDG PET for detecting metastases in lung adenocarcinoma. He also examined its potential applications in non-malignant diseases, including fibrosis and chronic inflammation, positioning FAP PET as a key player in theranostics and personalized medicine. Ongoing trials continue to broaden FAP applications. Dr. Giesel concluded both the already established clinical use as well as additional future potential of FAP diagnostics.

Sherly Mosessian from Sofie Bioscience, USA, presented the latest developments in clinical trials for FAP diagnostics, highlighting its rapid adoption in academic research and its overall growth. Over 10,000 oncology patients have been studied, showcasing FAP's potential alongside FDG, particularly in areas like gastrointestinal cancers, esophageal cancer, and sarcomas, where FDG underperforms. Shirley emphasized the need for more disease-specific studies, robust supply chains, and infrastructure to support both diagnostics and companion diagnostics for therapies.

Marc Dweck, Director Clinical Cardiology, University of Edinburgh, UK discussed FAPI's role in cardiovascular diseases, especially myocardial fibrosis. FAPI, once seen as a marker of fibrosis, now indicates fibroblast activation, which drives cardiac remodeling and heart failure. Unlike cardiac MRI, which measures established fibrosis, FAPI-PET tracks fibroblast activity. The study showed fibroblasts activate early after myocardial infarction (MI) and persist very long-term. FAPI PET showed higher uptake than MRI, even in the right ventricle, and correlates with future heart failure risk. FAPI has potential in diagnosing and monitoring conditions like ARVC, congenital heart disease, and atrial fibrillation, where traditional imaging techniques struggle, offering new diagnostic insights.

Richard P. Baum, President of the ICPO Academy for Theranostics, Germany, presented on FAP-directed Radiopharmaceutical Therapy (FRP) using Lu-177 labeled peptides (FAP-2286 and 3BP-3940) and TANDEM-FRP using Y-90 and Ac-225 for peptide labeling. He detailed the therapies promising survival benefits for patients with advanced pancreatic ductal adenocarcinoma (PDAC), reporting a mean survival exceeding seven months. FRP using 3BP-3940 has been applied to over 100 patients since 2020 across more than 20 different malignancies, including sarcomas. Prof. Baum emphasized the need for further trials with larger cohorts and COMBOS (combining FRP with antibodies, chemotherapy and targeted small molecules to confirm and advance these encouraging results.

Sanjana Ballal from All India Institute of Medical Sciences, India, discussed Lu-177 FAPi dimer therapy for rare and aggressive cancers, including medullary thyroid cancer (MTC) and sarcomas. The therapy demonstrated improved survival and disease management. Dr. Ballal also noted the potential for even greater efficacy when combined with an Ac-225 analog. The therapy shows promise in treating other cancers, such as breast cancer, and she concluded that FAPI theranostics represent a promising avenue for progressive MTC and sarcomas, warranting validation through larger prospective trials.

Jaqueline Mock from Philochem, Switzerland, presented preclinical data on Philochem's OncoFAP-23, which demonstrated optimal tumor residence time and favorable tumor-to-organ ratios for delivering therapeutic

radionuclides. Additionally, the therapeutic efficacy of Lu-177 OncoFAP-23 was enhanced when combined with the antibody-cytokine fusion L19-IL2 in mouse cancer models. A Phase I clinical trial to evaluate the safety and optimal dosing of Lu-177 OncoFAP-23, both as a monotherapy and in combination with L19-IL2, is set to commence.

Elcin Zan from Division of Nuclear Medicine, Cleveland Clinic, USA, moderated a panel discussion on FAP as Imaging Biomarker. The panelists covered also the role of FAP-directed PET imaging in understanding fibrogenesis and post-myocardial infarction (MI) recovery. This panel was composed of Richard P. Baum, Frederik L. Giesel, Andrew Scott, Sherly Mosessian and Marc Dweck.

Michael Hofman from Peter MacCallum Cancer Centre, Melbourne, Australia, contributed valuable insights into advancements in the use of Carbonic Anhydrase 9 (CA-9), particularly with the I-131 G250 markers for renal and other cancers, and its applications beyond oncology. He highlighted the role of CA-9 in clear cell renal cancer (ccRCC), where over 90% of cases contribute to tumor genesis. Dr. Hofman discussed the theranostic potential of the Ga-68 labeled CA-9-binding peptide DPI-4452. The peptide showed exceptional tumor uptake, with an average SUVmax of 64.6 across 36 lesions. It also identified 17 lesions that were missed by conventional imaging, and no clinically significant toxicity was observed. These findings support the potential of DPI-4452-Lu-177 in future therapeutic applications.

David Cade, from Telix Pharmaceuticals, Australia, discussed ongoing studies reinforcing the potential of CA-9 as a therapeutic target. He presented data from the STARBURST imaging study, which explores the theranostics utility of TLX250-CDx PET/CT imaging in patients with various solid tumors. Dr. Cade also shared insights from the STARLITE-1 and STARLITE-2 studies, which focus on combination immuno-oncology therapies using TLX250, cabozantinib, and nivolumab in advanced ccRCC patients. Additionally, the STARSTRUCK study examines the combination of TLX250 with a DNA damage response inhibitor (DDRi), peposertib, in patients with CA-9-expressing solid tumors, further expanding the therapeutic possibilities of CA-9 targeting.

Sze Ting Lee from Austin Health, Australia could unfortunately not join; however, her presentation on G250 antibody in renal cell cancer, highlighting the ZIRCON study where Austin Hospital was a top recruiter, is made available. Her conclusion is that molecular imaging with PET/CT can detect small metastatic deposits, improving staging sensitivity. Conventional FDG-PET has limited application due to renal excretion, but Immuno-PET is advancing, enhancing imaging capabilities with various tumor-targeted monoclonal antibodies.

Rudolf Werner, from University Clinic Frankfurt/Main, Germany discussed CXCR4, GPC3, and GPC1 in relation to hematological indications, the current outcomes as well as future promises. He reviewed on-going trials from an academic multidisciplinary perspective much needed in the field.

Hakim Bouterfa from PentixaPharm, Germany talked about Y-90-CXCR4 showed promising data in broad variety of lymphomas and its indications of CXCR4 beyond oncology. One is the Lymphor trial, which evaluates the diagnostic capability and safety of Ga-68 PentixaFor in comparison to F-18 FDG PET/CT for staging patients with confirmed marginal zone lymphoma (MZL). Another one was a study for primary aldosteronism, one major course of hypertension. This study will bring PET diagnostic to the endocrinology field, potentially guiding patients to a curable treatment.

Wolfgang Weber from TU Munich, Germany discussed the potential of Glypican-3 (GPC3) as a promising target for both imaging and therapy of hepatocellular carcinoma (HCC). He reviewed preclinical and initial clinical imaging studies of GPC3, highlighting its restricted expression in normal and cirrhotic liver tissue. Prof. Weber noted that successful human imaging studies have been conducted with radiolabeled antibodies and more recently with macrocyclic peptides. However, while animal studies suggest that therapeutic targeting of GPC3 is feasible, no clinical data have been published yet.

Serada Satoshi from Iwate Medical University in Japan presented on Glypican-1 (GPC1), a cancer-associated antigen in pancreatic ductal adenocarcinoma (PDAC). His research focused on developing novel therapies targeting

GPC1, not only in cancer cells but also in stromal fibroblasts. This includes an antibody-drug conjugate and GPC1 theranostics using an anti-GPC1 antibody labeled with 89Zr or 211At, offering potential for more effective and targeted treatment of PDAC.

The next panel discussion, moderated by **Ken Herrmann, Director, Nuclear Medicine, University of Essen, Germany,** debated the topic of antibody-drug conjugates (ADCs) contra radiopharmaceutical therapies. Ken and his panelists highlighted the versatility of radiotherapies, noting concerns about the systemic toxicity of ADCs, which circulate for extended periods**. Elcin Zan, from Cleveland Clinic, USA** focused on receptor targeting, emphasizing that while more receptors generally lead to better activity, the exact thresholds for effectiveness remain unclear. **Sherly Mosessian from Sofie Biosciences, USA,** pointed out the challenges of accurately quantifying receptor numbers in clinical settings and stressed the importance of vascular permeability in tumor targeting**. Chris Bremer from Navigo Proteins, Germany,** proposed that ADCs and radiopharmaceuticals could work together, but cautioned against targeting the same receptor, suggesting that different targets might prevent resistance and improve outcomes**. Germo Gericke, Ariceum Therapeutics, Germany,** discussed the safety profile of radioligands, contrasting their predictable schedules and fewer side effects with the more chemotherapy-like toxicities of ADCs. The panelists agreed that combination therapies hold significant promise, with a focus on improving personalized medicine through more precise imaging and diagnostic techniques. They concluded that despite challenges, the evolving landscape of combination therapies could offer more effective treatments for patients with fewer side effects. Panelists included Wolfgang Weber, Elcin Zan, Germo Gericke, Chris Bremer and Sherly Mosessian.

In conclusion of the 2 event days, fully supporting the mission of the ICPO Foundation, the ICPO summit underscored cutting-edge advancements in theranostics and radiopharmaceutical therapies, particularly the use of alpha emitters such as Ac-225, At-211 and Pb-212 as well as of new radiopharmaceuticals such as mainly FAP, CA9, CXCR4 and GPC3. These innovations are showing transformative potential in treating cancers resistant to traditional therapies, offering hope for more effective and targeted treatment options for cancer patients worldwide regardless of their geographic and social origins.