NOMRAD

NOMATEN International Radiopharmaceutical Conference

25-27.06.2024
WARSAW, POLAND

NOMATEN
Centre of Excellence in Multifunctional Materials for Industrial and Medical Applications

NATIONAL CENTRE FOR NUCLEAR RESEARCH ŚWIERK

NAWA POLISH NATIONAL AGENCY FOR ACADEMIC EXCHANGE

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ISBN 978-83-965280-3-2

 

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General information

1. **Venue**

The conference will be held in the NOVOTEL Warszawa Centrum conference room **IRYS** located on the ground floor.
NOVOTEL Warszawa Centrum
Marszałkowska 94/98, Warsaw
Google maps: https://maps.app.goo.gl/sx53DbX2xz5PUMDC8

2. **Welcome Reception**

Welcome Reception will take place in the NOVOTEL Warszawa Centrum at the **PROMENADA** conference room.

3. **Gala Dinner**

Gala Dinner will take place in the NOVOTEL Warszawa Centrum at the **PROMENADA** conference room.

4. **Internet access**

To connect to the free Wi-Fi network, select the network name NOVOTEL. Once you have selected the network, you will see the NOVOTEL network login notification, which will send you to the Accor.com website. On the page, enter your email address (no email verification is required) and the network login is complete.

5. **Visit to NCBJ on Thursday 27.06.2024**

The bus to NCBJ will depart at 7:30 a.m. and will be based at the back of the NOVOTEL Warszawa Centrum hotel. Once the bus has left, there will be no other way to get to NCBJ, so we encourage everyone to come to the meeting point **5 - 10 minutes earlier**.

- The bus will be marked with the symbol **'ŚWIERK'**
- Those going on to the NCBJ excursion will need to **bring the ID or passport** they registered earlier in the registration form
- Only computer equipment declared in advance on the registration form will be allowed to be brought onto NCBJ premises
- NCBJ has luggage storage facilities (if you will be going straight to the airport and need to take your luggage with you)

6. **Young Scientists Awards**

NOMRad will give three young researchers (master's student, PhD student or junior scientist (post-doc included)) the opportunity to participate in another international scientific congress of his/her choice, by receiving an award of 500 €. Three prices will be attributed in the following categories:

- Best MT180 (My thesis in 180 second; for PhD students only)
- Best poster presentation
- Best oral presentation

National Centre for Nuclear Research (NCBJ)

National Centre for Nuclear Research (NCBJ) is one of the largest scientific institutes in Central Europe and is also a unique research unit in the country. Institute has a very rich history and, above all, a huge scientific output, mainly in fields such as physics, nuclear and plasma technologies, astrophysics. We conduct basic and applied research related to nuclear energy and various areas of subatomic physics.

Interdisciplinary research performed in NCBJ covers the following scientific fields: physics, materials engineering, automation, electronics and space technologies, environmental engineering, mining and energy, and pharmaceutical sciences.

At the Nuclear Research Institute, since its inception, work has been carried out in high and low energy nuclear physics, nuclear chemistry, reactor physics and technology. Cooperation has been established with the most important scientific centres in the world, including the United Institute for Nuclear Research - ZIBJ (Russian: Объединённый институт ядерных исследований, ОИЯИ) in Dubna near Moscow and the European Organisation for Nuclear Research CERN (French: Organisation Européenne pour la Recherche Nucléaire).

A wide-ranging programme of basic research was launched, continuing to this day at the National Centre for Nuclear Research. The greatest achievement was the groundbreaking work on hyperfragments - a new type of atomic nucleus containing a strange particle (lambda hyperon) instead of one of the nucleons. The discoverers of hypernuclei, Institute staff Professors Marian Danysz and Jerzy Pniewski, were nominated for the Nobel Prize for this discovery.

NOMATEN Centre of Excellence

The NOMATEN Centre of Excellence was created as an answer to Europe's demand to close the gap between nuclear and non-nuclear applications and to maintain Europe's long-term competitiveness in nuclear technologies and, importantly, to transfer cutting-edge knowledge from the nuclear sector to provide results important for general industry and healthcare. Inspired by this motivation, two internationally leading institutions with established reputations and outstanding scientific and innovation expertise, CEA and VTT, decided to sign a trilateral Framework Agreement with NCBJ that demonstrates the clear and strong intention of all partners to operate the NOMATEN CoE and provide their research capacity and infrastructure for the purposes of the CoE.

The NOMATEN Centre of Excellence uses a unique infrastructure of research and measurement facilities, including nuclear facilities. The scientific work at NOMATEN CoE is carried out in five research groups to develop novel scientific innovations and also to support the industrial needs. *Complexity in Materials Research Group* focuses mainly on modelling and studying materials for extreme service conditions. Research group of *Functional Properties* specializes in multiscale methods of measuring mechanical properties and finding their relationship to their microstructure. The studied materials are largely intended for use in new-generation nuclear power plants. *Materials Characterization* research group conducts advanced characterization of new multifunctional materials at the atomic level using state-of-the-art scanning and transmission electron microscopes and its researchers focus mostly on observing and analysing the effects of high temperature, oxidizing atmospheres, and radiation on the structural and microstructural properties of materials. The *Materials, Structure and Function Informatics* research group is pursuing research tracks on modelling nanoindentation, simulating materials using advanced machine learning strategies, developing interatomic machine learning potentials (MLIP) for multiscale modelling applications, designing materials using machine learning methods (especially for alloy applications), and developing web-based applications and software for materials informatics, targeting researchers and scientists in materials engineering, surface engineering and solid-state physiochemistry. The research group *Novel Radiopharmaceuticals for Medical Purposes* is focused on the design and synthesis of theranostic molecular radiopharmaceuticals for targeted, personalized medicine *via* looking for new production routes of commercial and also potentially applicable new radionuclides in research reactor (MARIA) and recently installed at NCBJ (CERAD centre) IBA Cyclone XP 30 cyclotron; material preparation and its irradiation in reactor or cyclotron, radiochemical separation of interested radionuclide and target material recovery; labelling of biomolecules (monoclonal antibodies and their fragments, peptides etc.) with radionuclides *via* chelators or prosthetic groups; development of multimodal nanomaterials for diagnostic and therapeutic applications in medicine; preclinical *in vitro* and *in vivo* evaluation of developed compounds and materials.

National Centre for Nuclear Research – NCBJ

NCBJ fundamental/applied research profile combines nuclear power-related studies with various fields of sub-atomic physics (elementary particle physics, nuclear physics, hot plasma physics etc.). The Centre is intensely involved in developing nuclear technologies and promoting practical applications of nuclear physics methods. Major market products manufactured in the NCBJ include radiopharmaceuticals (Radioisotope Centre POLATOM Department) and a range of particle accelerators for science, various industry sectors and medicine (Nuclear Equipment HITEC

Department). The NCBJ Centre is an IT and R&D background infrastructure in dispensable to provide expert support for decision-makers in the project to develop the nuclear power industry in Poland in the coming years. The National Centre for Nuclear Research is the largest research Institute in Poland. We are the only Polish research institution operating a research nuclear reactor (MARIA Reactor). Currently, hiring over 1000 employees. Our research and scientific staff includes about 70 Professors and habilitation degree holders, as well as over 200 PhDs and Doctoral Students.

The Atomic Energy and Alternative Energy Commission – CEA

Commissariat à l'Énergie Atomique et aux Énergies Alternatives is a public establishment devoted to scientific, technical and industrial research and development under the authority of the Ministries of Energy, Research, Industry and Defence. Today, the CEA is a major player in research, development and innovation in defence and security, low-carbon energies (nuclear and renewable), technological research for industry and fundamental research (sciences matter and life sciences). The CEA conducts a part of its research in the French nuclear deterrent programme framework. It also provides technology to strengthen security in the face of new hazards such as terrorism and cyber-attacks and to upgrade response to earthquakes and tsunamis. As a key player in energy research, the CEA mobilizes its expertise and multidisciplinary competencies to propose innovative technological solutions to address major societal challenges, such as energy transition, nuclear and renewable energy, and understanding the mechanisms of climate change. Besides energy and climate change challenges, the CEA also mobilizes its expertise and multidisciplinary competencies to biotechnologies and biomedical innovations. Challenges linked to personalized medicine and technologies for the medicine of the future are priorities, and dedicated research are conducted in the field of *in vivo* molecular imaging probes, diagnostic tools and molecules for therapeutic or theranostic uses. Methodologies devoted to isotopic labelling remain a CEA specificity, both serving drug development and radiopharmaceutical development.

VTT Technical Research Centre of Finland – VTT

VTT is the leading research and technology company in the Nordic countries. VTT use research and knowledge to provide expert services for our domestic and international customers and partners both from the private and public sectors. We use 4,000,000 hours of brainpower a year to develop new technological solutions. VTT Group's turnover is approximately 270 million EUR yearly. VTT's mission is to help customers and society to grow and renew through applied research. We have 75 years of experience supporting our clients' growth with top-level research and science-based results. VTT develops new smart technologies, profitable solutions and innovation services, and cooperate with its customers to produce technology for business and build success and well-being for the benefit of society. A brighter future is created through science-based innovations. With over 2200 employees, VTT advances the utilisation and commercialisation of research and technology in commerce and society and provides expert services for domestic and international customers and partners, both private and public sectors. Through scientific and technological means, VTT turns large global challenges into sustainable growth for businesses and society, bringing together people, business, science and technology to solve the biggest challenges of our time. VTT represents a multidisciplinary technological know-how and has strong expertise in materials research and nuclear energy research to support the energy transition and pathway towards a sustainable economy.

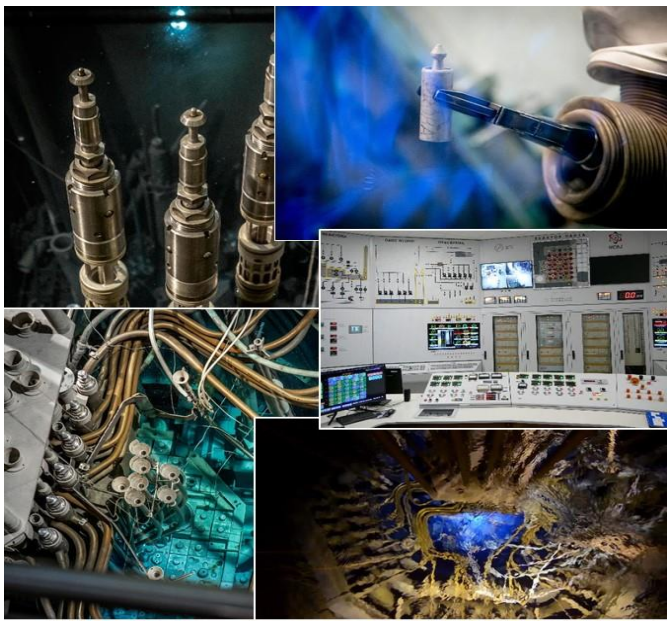
MARIA Research Reactor

The MARIA research nuclear reactor is currently the only operating nuclear reactor in Poland and the fourth largest research reactor in Europe in terms of power. The MARIA reactor has been in operation since December 1974 at the Institute for Nuclear Research in Świerk and is the largest research device in the country and the only source of intense fast and thermal neutron beams in Poland, which are used, among others, for:

- irradiation of materials for medical and industrial purposes;
- material and technological research;
- neutron spectrometry;
- training purposes in the field of reactor physics and technology.

The neutrons produced in the reactor core are used to irradiate target materials in order to obtain radionuclides used in medicine (radiopharmaceuticals) and industry, as well as in research laboratories. The MARIA reactor is among the world's leading producers of isotopes for the production of radiopharmaceuticals. This applies in particular to radiopharmaceuticals based on isotopes of Iodine, Molybdenum (precursor of medical Technetium-99m), Lutetium or Scandium. The importance of two radiopharmaceuticals obtained using the MARIA reactor should be emphasized: Iodine-131 and Molybdenum-99. The MARIA reactor currently accounts for 30% of the global demand for Iodine-131 and covers approximately 10% of the global demand for Molybdenum-99.

Research at the MARIA nuclear reactor can be divided into two groups: research using horizontal channels and irradiation in the reactor core in the vertical channels, including the so-called hydraulic rabbit. Experiments conducted in the reactor core are primarily research on nuclear techniques, conversion of target materials for medical and industrial purposes and material research. The MARIA reactor, as the only nuclear facility of its kind in the country, is used to conduct research and development work, which includes research on materials in the field of radiation damage (DPA). The construction of special probes at NCBJ also enabled



irradiation experiments for testing materials that are to operate in extreme temperature conditions (up to 1000° C). The construction of the MNL (Maria Neutron Laboratory) is underway, which will include 5 diffractometers and a spectrometer with equipment, located at the horizontal channels of neutron beams in the MARIA reactor. The installation of the discussed instruments at the MARIA reactor will lead to the creation of a European-class laboratory in Poland for testing the microscopic structure of materials using thermal neutrons. The MARIA reactor also plays an important role in educating engineers in the field of engineering and nuclear medicine.

CERAD – Centre for Design and Synthesis of Molecularly Targeted Radiopharmaceuticals

To meet the high demand for radiometals with potential for medical applications, with a particular focus on their theranostic value, the new research facility is being built at NCBJ/POLATOM, with the name "*Centre for Design and Synthesis of Molecularly Targeted Radiopharmaceuticals, CERAD*". Its main component is the 30 MeV cyclotron which will accelerate protons and alpha particles to 30 MeV and deuterons to 15 MeV. It will be a powerful tool for the production of novel radioisotopes for medical use, which are not available in Poland today. Among them the radioisotopes such as ^{18}F, $^{44/43}$Sc, ^{64}Cu, ^{67}Cu, Ge^{68}, ^{89}Zr, ^{123}I and ^{211}At will be produced. Installation of a new high-current cyclotron at NCBJ, with equipment and infrastructure, combined with an already existing scientific base, creates unique and pro-development research capabilities.

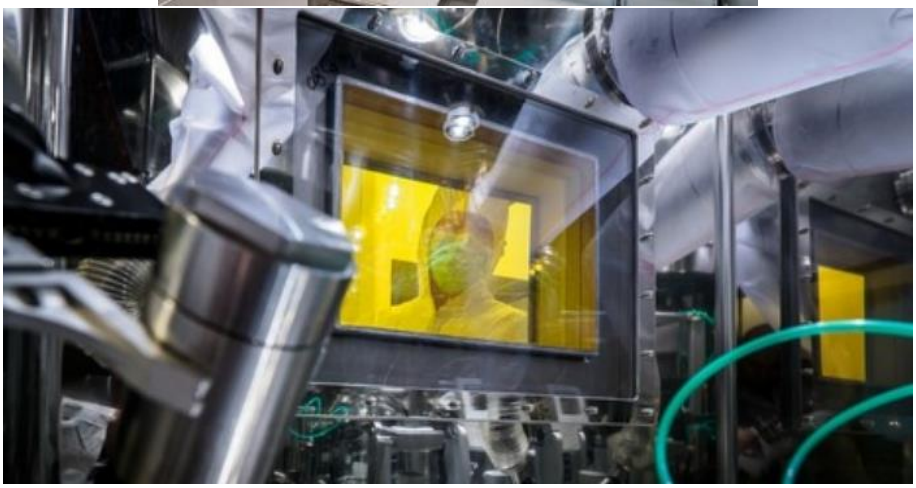
The cyclotron of CERAD, Cyclone 30XP, was built by the Belgian company Ion Beam Applications. Next to protons and deuterons, it also accelerates alpha particles. For that, it is equipped with an alpha ion source, and the alpha particles will be accelerated to up to 30 MeV. The cyclotron is installed in the new building which not only hosts the cyclotron but also several dedicated labs with hot-cells for radioisotope processing, with the QC and research laboratories. The entire facility offers a space of 2500 m^2. The upcoming infrastructure will be open to external users' projects.

CERAD project is co-financed under Smart Growth Operational Programme 2014-2020, Priority IV: INCREASING THE RESEARCH POTENTIAL, Measure 4.2. Development of modern research infrastructure of the science sector.

Radioisotope Centre POLATOM

Within NCBJ the infrastructure of Radioisotope Centre POLATOM is focused on research programs related to the processing of radioisotopes and to the design of radiopharmaceuticals. Developed technologies can be then implemented into routine production technologies.

NCBJ's Radioisotope Centre POLATOM is GMP-certified for radiopharmaceutical manufacture and provides radiopharmaceuticals for both diagnostic and therapy. The research activities of POLATOM include new technologies for the production of radioisotopes *via* reactor and accelerator routes, design of novel radiopharmaceuticals and methods for assessing their quality, with the full range of pre-clinical studies as well as pharmaceutical formulations for clinical studies. POLATOM is also GMP-certified for the preparation of radiopharmaceuticals for clinical trials.



Radiopharmaceutical laboratories at NCBJ/Polatom

Committees

SCIENTIFIC COMMITTEE

- Marek Pruszyński, DSc
- prof. Renata Mikołajczak, PhD
- Frédéric Dollé, DSc
- Kristiina Iljin, DSc

ORGANIZING COMMITTEE

- Marek Pruszyński, DSc
- Anna Krzyczmonik, PhD
- Monika Madigan, BA
- Karolina Zajdel, PhD
- Gopi Elumalai, PhD
- Marcin Zieliński, PhD

Marek Pruszyński, PhD, DSc

Marek Pruszyński studied chemistry (MSc specialization in analytical chemistry) at the Faculty of Biology and Chemistry at the University of Białystok in Poland. Since 2002 he works at the Institute of Nuclear Chemistry and Technology in Warsaw, where in 2008 he obtained PhD degree (specialization radiochemistry), and in 2019 doctor habilitus (DSc) and became Head of the Laboratory of Radiopharmaceuticals and Cellular Research. Since May 2021, he is an Associate Professor at the National Centre for Nuclear Research (NCBJ) in Świerk-Otwock and Research Group Leader of the Novel Radiopharmaceuticals for Medical Application group at NOMATEN Centre of Excellence at NCBJ. His research interest focuses on design and synthesis of theranostic molecular radiopharmaceuticals for targeted personalized medicine *via*: i) exploring new production routes of commercial and also potentially applicable emerging radionuclides; ii) target's material preparation and its irradiation in reactor or cyclotron, radiochemical separation of interested radionuclide and target material recovery; iii) labelling of biomolecules (monoclonal antibodies and their fragments, peptides etc.) with radionuclides *via* chelators or prosthetic groups; iv) development of multimodal nanomaterials for diagnostic and therapeutic applications in medicine; v) preclinical *in vitro* and *in vivo* evaluation of developed compounds and materials. He co-authored over 30 full length journal papers cited over 1100 times. He has been also Principal Investigator of several projects funded by Polish agencies (NCN, NCBiR, NAWA), bilateral with Belgium and Czech Republic, as well as IAEA and EU COST. He received prestigious scholarships and awards from the Fulbright Commission, IAEA, Grzegorz Białkowski Award and Alavi-Mandell Award from the Society of Nuclear Medicine and Molecular Imaging for the article published in Journal of Nuclear Medicine (2014).

Prof. Renata Mikołajczak, PhD

Renata Mikołajczak from National Centre for Nuclear Research, Radioisotope Centre POLATOM has over 30 years in radioisotope and radiopharmaceutical development. Renata Mikołajczak is currently coordinating the research activity of the Radioisotope Centre POLATOM, National Centre for Nuclear Research in Poland. She is a professor of Medical Sciences and holds a Ph.D. in Physics and a DSc in Medical Biology. Since 2020 has served as a chair of the expert group, PRP Working Party - Precursors for Radiopharmaceutical Preparations, European Pharmacopoeia of EDQM. Organizer of multi-centre research teams, and collaborations both in Poland and internationally. IAEA expert and lecturer in Radiopharmacy and 2019-2021 a member of the IAEA's Standing Advisory Group on Nuclear Applications (SAGNA). Contributor to over 20 research grants on radionuclides and radiopharmaceuticals, including PRISMAP (https://www.prismap.eu/) and TOURR (https://www.tourr.eu/) and the coordinator of the CERAD project with its 30 MeV cyclotron. Since October 1, 2022, she has been coordinating the SECURE project (https://cordis.europa.eu/project/id/101061230).

Frédéric Dollé, DSc

Frédéric Dollé completed his PhD (organic chemistry) in 1991 from Strasbourg University (France). He then moved to Research Triangle Park, North Carolina, USA, to work for a pharmaceutical company (Rhône-Poulenc-Rorer, today SANOFI) for two years, before joining in 1993 the CEA and the Service Hospitalier Frédéric Joliot (Orsay, France). In 2000, he completed his HDR degree (habilitation à diriger des recherches, Paris-South University), and from 2000 to mid-2014, he was at Orsay in charge of the Chemistry / Radiochemistry section, a unit which supported all PET molecular imaging programs within the institute, before coordinating for another year, the newly created "Molecular Probes" team (as part of IMIV - Imagerie Moléculaire In Vivo - UMR1023), now also dealing with metabolism-related activities. For over 20 years, his research interests have focused on the development of radiotracers for *in vivo* molecular imaging using PET, as well as the development and application of novel methods for the synthesis of $^{11}C/^{18}F$-labelled probes (225 scientific publications, 12 book chapters, 7 patents – 1 licensed). In 2015, he joined the governing board level of his institute (at this time, Institut d'imagerie biomédicale (I2BM)) as scientific assistant to the director, also in charge of the relations with the newly created Paris-Saclay University. In February 2017, I2BM and IBITEC-S - another CEA institute - merged into a novel structure - Institut des sciences du vivant Frédéric Joliot - in which he is also today in charge of the doctoral (PhD) program and the CEA expertise hub / career development program. Appointed Director of Research at CEA (2021), he is still involved in EU projects, notably the CSA action (teaming) NOMATEN (2019-2026, #763604), in which he coordinates WP6 actions when Radiopharmaceutical Sciences are concerned.

Kristiina Iljin, DSc

Kristiina Iljin has a MSc in Biology (Genetics, 1997) from University of Turku, Finland, and a PhD in Molecular Biology (2003) from University of Helsinki, Finland. She did her post-doctoral research at University of Zürich, Switzerland, focusing on childhood malignancies. She joined VTT Technical Research Centre of Finland in 2005 and worked as a Team Leader of Cancer Systems Biology Team from 2009 to 2012. She spent a year as a Research Assistant Professor at Oregon Health and Science University, USA, where she learned about microscopy and drug resistance mechanisms. During the past ten years, she has been working on various antibody isolation and characterization projects at VTT Technical Research Centre of Finland Ltd. She currently leads the Immunotechnology team at VTT working on antibody discovery, immunoassay development, protein engineering and biosensor development. She has collaborated with several national and international teams and participated in multiple European projects, such as the EU-NOMATEN project on advanced materials for medical technology. She has 59 peer-reviewed publications (citations 3253, H-index 29) and 1 patent application.

Programme Overview

Monday (24.06)	Tuesday (25.06)	Wednesday (26.06)	Thursday (27.06)
	08:00-08:30 Registration & morning coffee	**08:00-08:30** Registration & morning coffee	**07:30-08:30** Transport to NCBJ
	08:30-09:00 Opening of NOMATEN International Radiopharmaceutical Conference - NOMRad	**Session 5** Radiolabeling & Biomolecules	**08:30-09:00** Morning coffee & snacks
	Session 1 Radionuclides Production and Separation	**08:30-09:15** Invited speaker **Alfred Morgenstern**	
	09:00-09:45 Invited speaker **Valery Radchenko**	**09:15-10:30** **Sub-session 5.1 -** Metallic Radioisotopes Scientific presentations	**09:00-12:00** Visits to Maria Reactor, CERAD Centre, POLATOM, LBM and CoE NOMATEN
	9:45-11:00 Scientific presentations	**10:30-11:00** Coffee break & snacks	
	11:00-11:30 Coffee break & snacks	**11:00-12:15** **Sub-session 5.2 -** Non Metallic Radioisotopes Scientific presentations	
	11:30-12:00 Scientific presentations		
	Session 2 Presentations of Industry		**12:00-13:00** Lunch
	12:00-12:50 Industrial presentations	**12:15-13:00** **Sub-session 5.3 -** Isotopic Radiolabelling Scientific presentations	
	12:50-13:00 **Conference Photo**		
	13:00-14:00 Lunch	**13:00-14:00** Lunch	**13:00-14:00** Free B2B Discussion + Coffee
	14:00-15:00 Invited speaker **Michael R. Zalutsky**	**Session 6** Clinical Research	
	Session 3 Presentations of PhD Students (MT 180')	**14:00-14:45** Invited speaker **Jolanta Kunikowska**	**14:00** Transfer back to Warsaw or directly to the airport
	15:00-16:00 Presentations of PhD Students (MT 180')	**14:45-15:45** Scientific presentations	
	16:00-16:30 Coffee break & snacks	**Poster Session**	
	Session 4 Radiopharmaceuticals and Beyond	**15:45-17:00** Poster presentations Coffee & Snacks	
	16:30-18:00 Scientific presentations	**17:00-17:15** Awards for young scientists	
		17:15-17:30 Closing of NOMATEN International Radiopharmaceutical Conference - NOMRad	
	Free Time		
19:00-22:00 Welcome Reception	**20:00-23:00** Gala dinner		

Detailed Programme

24.06.2024 - MONDAY		
19:00-22:00	**Networking Welcome Reception** - Hotel Novotel Warszawa Centrum, Marszałkowska 94/98, 00-510 Warsaw	
08:00-08:30	**Registration, Morning Coffee** - Hotel Novotel Warszawa Centrum, Marszałkowska 94/98, 00-510 Warsaw	
08:30-09:00	**Opening of NOMATEN International Radiopharmaceutical Conference - NOMRad**	
	Information about NOMRad Conference - Marek Pruszyński Welcome message from directors of NCBJ, NOMATEN CoE and from National Agency for Scientific Exchange Poland	
09:00-12:00	**Session 1 - Radionuclides Production and Separation**	
09:00-09:45	**Invited Talk**	**Modern Alchemy (Radiochemistry) for the Diagnostic and Therapy of Cancer: TRIUMF Experience** *Valery Radchenko, Life Sciences Division, TRIUMF; and Chemistry Department, University of British Columbia, Vancouver, Canada*
09:45-10:00	**KeyNote Talk**	**Isotope Irradiation in the Maria Reactor and Their Further Development** *Paweł Nowakowski, Nuclear Facilities Operations Department, National Centre for Nuclear Research, Otwock, Poland*
10:00-10:15		**Molybdenum Nanoparticles for the Production of High Specific Activity ^{99}Mo by the Recoil Effect** *Pablo Serra Crespo, European Commission, Joint Research Centre, Petten, The Netherlands*
10:15-10:30		**Inhouse Production of ^{161}Tb** *Ján Kozempel, Department of Nuclear Chemistry, Czech Technical University, Prague, Czech Republic*
10:30-10:45		**Terbium-161 Production in Maria Reactor and Gd-160 Recovery - Preliminary Data** *Małgorzata Żółtowska, Radioisotope Centre POLATOM, National Centre for Nuclear Research, Otwock, Poland*
10:45-11:00		**On the Development of a Method for the Separation of Terbium from Elevated Amounts of Gadolinium Using TK221 and TK211/2 Resins** *Steffen Happel, TrisKem International, Bruz, France*
11:00-11:30	**Coffee Break + Snacks**	
11:30-11:45	**KeyNote Talk**	**CERAD – a 30 MeV Cyclotron and New Opportunities for Medical Isotope Production in Poland** *Renata Mikołajczak, Radioisotope Centre POLATOM, National Centre for Nuclear Research, Otwock, Poland*
11:45-12:00		**Production of Theranostic Pair $^{43/44}$Sc - ^{47}Sc on Calcium Targets** *Rafał Walczak, Institute of Nuclear Chemistry and Technology, Warsaw, Poland*
12:00-13:00	**Session 2 - Presentations of Industry**	
12:00-12:10		**Voxel S.A., Poland** - *Marek Pilch-Kowalczyk*
12:10-12:20		**PioLigOn Sp. z o.o., Poland** - *Piotr Liguziński*
12:20-12:30		**MEDISO, Poland** - *Magdalena Białek-Pietras*
12:30-12:40		**Curium Pharma, France** - *Vincent Bodenant*
12:40-12:50		**TrisKem, France** - *Steffen Happfel*
12:50-13:00	**Conference Photo**	
13:00-14:00	**Lunch**	
14:00-15:00	**Invited Talk**	**Astatine-211 - the Kinder, Gentler α-emitter Coming Soon to a Cyclotron Near You** *Michael R. Zalutsky, Department of Radiology, Duke University Medical Center, Durham, NC USA*
15:00-16:00	**Session 3 - Presentations of PhD Students (MT 180')**	
16:00-16:30	**Coffee Break + Snacks**	
16:30-18:00	**Session 4 - Radiopharmaceuticals and Beyond**	

16:30-17:00		**The Japan Astatine Community: a Hub for Skills and Knowledge of ^{211}At and the Gateway to the World Astatine Community** *Kohshin Washiyama, Advanced Clinical Research Center, Fukushima Medical University, Fukushima, Japan*
17:00-17:30		**IAEA Contribution to the Production and Quality Control of Medical Radioisotopes and Radiopharmaceuticals** *Amirreza Jalilian, Department of Nuclear Sciences and Applications, International Atomic Energy Agency, Vienna, Austria*
17:30-18:00		**VTT´s Recombinant Antibody Technology** *Kristiina Iljin, Sensing Solutions, Immunotechnology, VTT Technical Research Centre of Finland, Espoo, Finland*
18:00-20:00	***free time***	
20:00-23:00	**Gala Dinner** - Hotel Novotel Warszawa Centrum, Marszałkowska 94/98, 00-510 Warsaw	

26.06.2024 - WEDNESDAY		
08:00-08:30	**Late Registration, Morning Coffee** - Hotel Novotel Warszawa Centrum, Marszałkowska 94/98, 00-510 Warsaw	
08:30-13:00	**Session 5 - Radiolabeling & Biomolecules**	
08:30-09:15	**Invited Talk**	**Targeted Alpha Therapy with Actinium-225** *Alfred Morgenstern, European Commission, Joint Research Centre, Directorate for Nuclear Safety and Security, Karlsruhe, Germany*
	Sub-session 5.1 - Radiochemistry and Preclinical Research (Metallic Radioisotopes)	
09:15-09:30	**KeyNote Talk**	**ImmunoPET Imaging of Glioblastoma Biomarkers to Follow and Predict Tumor Evolution** *Hélène Quelquejay, SHFJ-BioMaps (Université Paris-Saclay, Inserm, CNRS, CEA), Orsay, France*
09:30-09:45		**Terbium-161 labelling of glycoproteins PSMA and monoclonal antibodies** *Martin Vlk, Department of Nuclear Chemistry, Czech Technical University, Prague, Czech Republic*
09:45-10:00		**Polymer-Based Radiopharmaceuticals** *Martin Hrubý, SUPRAMOL Centre, Institute of Macromolecular Chemistry CAS, Prague, Czech Republic*
10:00-10:15		**Mercury Radionuclides for Nanobrachytherapy of Triple-Negative Breast Cancer and Glioblastoma Multiforme** *Emilia Majka, Institute of Nuclear Chemistry and Technology, Warsaw, Poland*
10:15-10:30		**^{109}Pd/^{109m}Ag *in vivo* Generator in the Form of Nanoparticles for Combined β$^-$- Auger Electron Therapy of Hepatocellular Carcinoma** *Nasrin Abbasi Gharibkandi, Institute of Nuclear Chemistry and Technology, Warsaw, Poland*
10:30-11:00	**Coffee Break + Snacks**	
	Sub-session 5.2 - Radiochemistry and Preclinical Research (Non Metallic Radioisotopes)	
11:00-11:15	**KeyNote Talk**	**Labeling of Proteins with Fluorine-18, Two Unlikely Partners for PET Imaging** *Simon Specklin, SHFJ-BioMaps (Université Paris-Saclay, Inserm, CNRS, CEA), Orsay, France*
11:15-11:30		**Development of New O^6-Benzylguanine Derivatives Radiolabelled with (Fluorine-18 and Zirconium-89) for Protein Labeling *via* SNAP-tag Approach** *Julen Ariztia, SHFJ-BioMaps (Université Paris-Saclay, Inserm, CNRS, CEA), Orsay, France*
11:30-11:45		**Radioiodination of Octreotide *via* Disulphide Rebridging** *Anna Krzyczmonik, NOMATEN Centre of Excellence, National Centre for Nuclear Research, Otwock, Poland*
11:45-12:00		**Design of New Radiotracers to Target Astrocytes as Biomarker of Neuroinflammation** *Eugénie Pincemail, SHFJ-BioMaps (Université Paris-Saclay, Inserm, CNRS, CEA), Orsay, France*
12:00-12:15		**Development of Radiofluorination of Metal Porphyrin Platforms for PET Imaging and Photodynamic Therapy** *Romain Fontaine-Tuffery, Service de Médecine Nucléaire, Centre Georges-François Leclerc (CGFL); and Institut de Chimie Moléculaire de l'Université de Bourgogne (ICMUB), Dijon, France*

	Sub-session 5.3 - Radiochemistry and Preclinical Research (Isotopic Radiolabelling)	
12:15-12:30		**Electrophilic Cyanation for the Carbon-11 Isotopic Radiolabeling of the Nitrile Function** *Alexandre Hauwelle, SHFJ-BioMaps (Université Paris-Saclay, Inserm, CNRS, CEA), Orsay, France*
12:30-12:45		**Radiosynthesis and Use of [^{11}C]phosgene** *Thomas Keller, Radiopharmaceutical Chemistry Laboratory, Turku PET Centre, University of Turku, Turku, Finland*
12:45-13:00		**Isotopic Radiolabelling of Emtricitabine with Fluorine-18 for PET Imaging of HIV-1 Reservoirs** *Steve Huvelle, SHFJ-BioMaps (Université Paris-Saclay, Inserm, CNRS, CEA), Orsay, France*
13:00-14:00	**Lunch**	
14:00-15:45	**Session 6 - Clinical Research**	
14:00-14:45	**Invited Talk**	**Targeted Treatment of Glioma with Radiolabelled Substance-P and PSMA** *Jolanta Kunikowska, Department of Nuclear Medicine, Warsaw Medical University, Poland*
14:45-15:00		**Difference Between Lu-PSMA 617 and Lu-PSMA I&T: a Single-French-Center Experience after Two Years** *David Tonnelet, Centre Henri Becquerel, France*
15:00-15:15		**A Comparative Study of [^{18}F]DCFPyL PET/CT *versus* [^{18}F]Fluoromethylcholine in Biochemical Recurrence of Prostate Cancer** *Vincent Bodenant, Curium Pharma, Saclay, France*
15:15-15:45	**Closing Conf. Talk**	**Prospects of Positronium Imaging Using Scandium-Labeled Pharmaceuticals** *Paweł Moskal, Institute of Physics; and Center for Theranostics, Jagiellonian University, Cracow, Poland*
15:45-17:00	**Session 7 - Poster Session + Coffee & Snacks**	
17:00-17:15		Announcements of 3 Awards to Young Scientists in categories: MT 180', poster and talk
17:15-17:30	**Closing of NOMATEN International Radiopharmaceutical Conference - NOMRad**	

27.06.2024 - THURSDAY	
07:30-08:30	**Transfer to NCBJ**
08:30-09:00	**Morning Coffee + Snacks**
09:00-12:00	Visits of NCBJ facilities:
	Maria Reactor CERAD Centre - cyclotron POLATOM LBM - Laboratory of Materials Science CoE NOMATEN - Laboratory of Materials Characterization
12:00-13:00	**Lunch**
13:00-14:00	Free B2B Discussion + Coffee
14:00	Transfer Back to Warsaw or Directly to Airport

Invited Speakers

Valery Radchenko, PhD

Valery Radchenko is Research Scientist at TRIUMF and an adjunct professor at the University of British Columbia, Chemistry Department with the main research focus on the production and application of therapeutic radionuclides for Targeted Radionuclide Therapy (TRT). Radiochemist by training graduated from Saint-Petersburg State Technical University (Russian Federation) in collaboration with the Joint Institute for Nuclear Research (JINR) in Dubna (Russian Federation). He received his Ph.D. from Johannes-Gutenberg University Mainz (Germany) in 2013 with a thesis focused on the design of production of a promising radionuclide for *immuno*-PET: ^{90}Nb. Further, realizing the potential of targeted radionuclides therapy he pursued a postdoctoral position at Los Alamos National Laboratory, NM, USA, where he worked as a part of the tri-lab effort on the production of ^{225}Ac from spallation of thorium with high-energy protons. Besides, ^{225}Ac production effort, he also worked on other efforts including extraction of valuable medical radionuclides from irradiated thorium targets (e.g. $^{223/224/225}$Ra, ^{230}Pa, ^{103}Ru/^{103m}Rh, ^{111}Ag), design of production alternative for low energy slot at Isotope Production Facility at LANL and others. He published over 90 scientific papers in peer-reviewed journals and served as a guest editor on special issues on alpha and Auger emitters for Targeted Therapy.

Prof. Michael R. Zalutsky, PhD

Michael R. Zalutsky, is the Jonathan Spicehandler, M.D., Professor of Neuro-Oncology Research and a Professor in the Departments of Radiology, Radiation Oncology, and Pathology at the Duke University School of Medicine. In addition, he is Professor of Biomedical Engineering at Duke University and Director of the Radiopharmaceutical Chemistry Laboratory. Prior to joining the faculty at Duke, Michael held positions at Argonne National Laboratory, University of Chicago, and Harvard Medical School. The author of more than 400 scientific publications and patents, his primary research interest is radiochemistry applied to targeted radionuclide therapy and molecular imaging. A major focus of his research has been the development of targeted radiotherapeutics labelled with the alpha-particle emitter ^{211}At, including its production, labelling chemistry, radiation dosimetry and first clinical translation. In addition, his laboratory has been responsible for the development and validation of many of the most widely used methodologies for labelling antibodies and single domain antibody fragments (a.k.a. nanobodies) with radiohalogens including ^{18}F, ^{131}I and ^{211}At. Dr. Zalutsky's honors and awards include the Berson-Yalow Award and the Aebersold Award from the Society of Nuclear Medicine for outstanding achievement in basic nuclear medicine science, and a MERIT Award from the National Cancer Institute for his research in targeted alpha-particle radiotherapy. Publications based on his research received the Paper of the Year Award in 2018 and 2021 from Nuclear Medicine and Biology and Best Basic Science Article for 2022 from the Journal of Nuclear Medicine and Molecular Imaging in 2023.

Prof. Alfred Morgenstern, PhD

Alfred Morgenstern is a Head of Sector "Radioisotopes in Medicine and Technology", JRC Karlsruhe, Germany. Alfred Morgenstern (PhD in radiochemistry from Technical University Munich in 1997) joined the Joint Research Centre of the European Commission in Karlsruhe since 2000 where he is leading the research activities on targeted alpha therapy of cancer, focusing on the development, preclinical and clinical testing of radiopharmaceuticals labelled with alpha emitting radionuclides. In 2013 his group first developed ^{225}Ac-PSMA-617, a novel compound that exhibits remarkable efficacy for the treatment of prostate cancer and that is currently under clinical evaluation in collaboration of JRC Karlsruhe with pharmaceutical industry and numerous hospitals worldwide. Since 2018 he holds an extraordinary professorship at the Faculty of Human Health at the University of Pretoria. To date he has published more than 220 papers in peer-reviewed journals.

Prof. Jolanta Kunikowska, MD, PhD

Jolanta Kunikowska is a nuclear medicine as well as internal medicine physician specialist. She is currently a professor and chief of the Nuclear Medicine Department, Medical University, Warsaw, Poland. Prof. Kunikowska's main research interests are positron emission tomography (PET), molecular imaging applications in oncology and theragnostics (radionuclide therapy). She has a particular interest in novel PET radiotracer and theragnostic applications including prostate, neuroendocrine tumours and glioblastoma. She has authored over 250 peer-reviewed articles and several book chapters. Prof. Kunikowska is a member of several Editorial Boards, including the European Journal of Nuclear Medicine and Molecular Imaging and the Nuclear Medicine Review. She received several prestigious awards provided by various scientific communities, including the Gold Prize for Hisada award in 2018 and the Marie Curie Award for outstanding scientific work presented at the 29th Annual Congress of the European Association of Nuclear Medicine (EANM) in Barcelona in 2016. Prof. Kunikowska has been and remains actively involved in the European Association of Nuclear Medicine: National Delegate (2008-2015), member of Oncology Committee (2010-2014), Secretary and Treasurer (2015-2018), President Elect (2019-2020) and EANM President (2021-2022).

Modern alchemy (radiochemistry) for the diagnostic and therapy of cancer: TRIUMF experience

Valery Radchenko*[1]

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Chemistry Department, University of British Columbia, Vancouver, Canada
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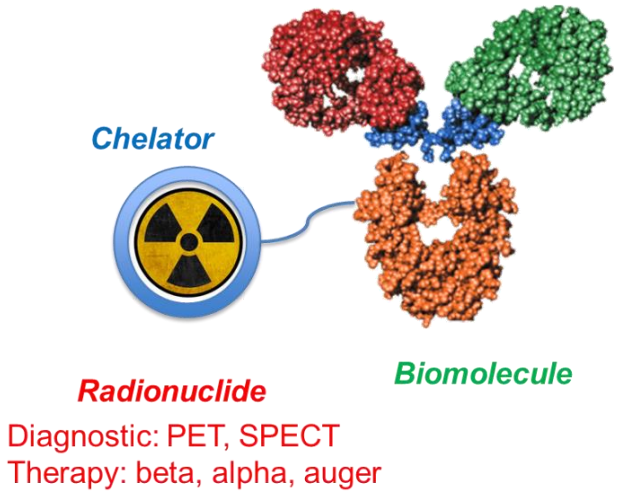
The use of radionuclides has become more and more common in the diagnosis and therapy of cancer. Targeted radionuclide diagnostics and therapy based on the combination of appropriate radionuclides with selective delivery systems (e.g. antibodies, peptides, etc.) maximizes the precision of the imaging as well as minimizes the damage of healthy tissues during therapy. Furthermore, based on imaging results, appropriate therapeutic radionuclides emitting alpha, beta-particles or auger electrons can be utilized. Appropriate bifunctional chelator systems should be in place to effectively attach some of the radionuclides (e.g. radiometals) to biomolecules.



Two main sources are utilized for the production of medical radionuclides including production using charged particles (e.g. protons, deuterons, electrons, and alphas) and neutrons (reactors). Alternatively, radionuclide generator systems can be utilized as effective cyclotron/reactor-independent sources of medical radionuclides, where the parent radionuclide is produced by a cyclotron or reactor and then serves as a source of a shorter-lived daughter radionuclide which can be utilized for nuclear medicine purposes. After production, in most cases, medical radionuclides need to be isolated from the target material and preconditioned for further radiopharmaceutical application[1].

In the present abstract, those principles outlined above will be demonstrated in the example of work performed at TRIUMF in the production of imaging and therapeutic radionuclides using (13 MeV) TR-13 cyclotron, Isotope Separator and Accelerator (ISAC) facility and main cyclotron (520 MeV). Several specific examples to stimulate possible collaboration and complementing research programs of TRIUMF and NOMATEN Centre of Excellence will be presented.

References

[1]Radchenko, V., et al., *Solvent Extraction and Ion Exchange*, **2021**, 39, 714.

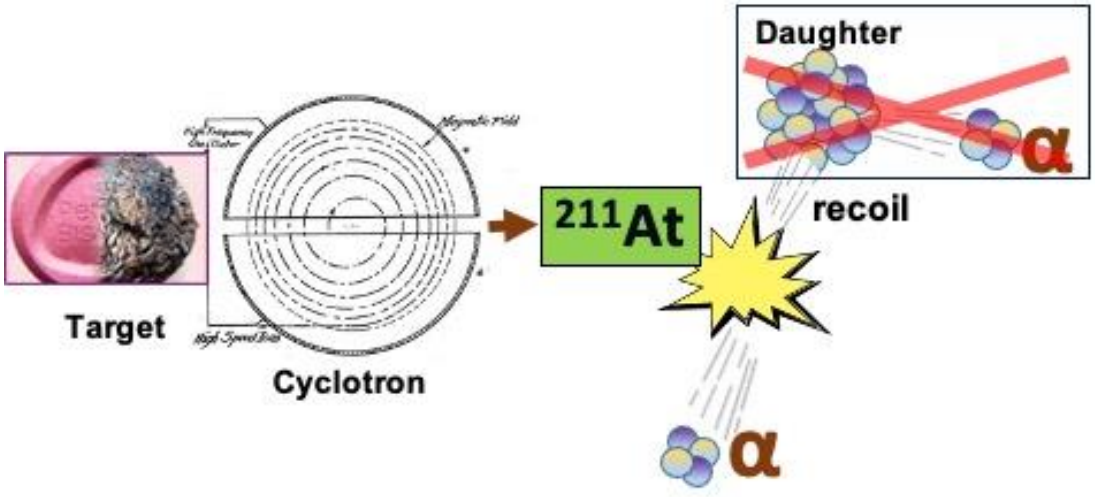
Astatine-211 – the kinder, gentler α-emitter coming soon to a cyclotron near you

Michael R. Zalutsky*[1], Yutian Feng[1], Thao Truc Huynh[1], Yongxiang Zheng[1]

[1]Department of Radiology, Duke University Medical Center, Durham, NC USA
*zalut001@mc.duke.edu

At Duke University, having a 30 MeV cyclotron in house has allowed us to focus our research and translational efforts on exploiting the attractive features of the 7.2-h half-life radio-halogen ^{211}At for targeted α-particle therapy (TAT). These properties include the emission of only 1 α-particle per decay, and no nuclear-recoil-afflicted α-emitting daughters, which can lead to unintended irradiation of normal tissues. For this reason, we consider ^{211}At to be the "kinder, gentler" α-emitter. In addition, by virtue of the emission of polonium K x-rays during its decay, ^{211}At can be imaged allowing real time monitoring of therapy doses thereby facilitating dose optimization and dosimetry determination.

Currently, we produce ^{211}At 1-2 times a week by irradiating natural bismuth targets with 28 MeV α-particles using an internal target and isolate the ^{211}At by dry distillation into the solvent/oxidation state needed for subsequent labeling chemistry. Ongoing work with ^{211}At will be discussed that is exemplified by studies in three areas - organic molecule-based TAT agents, small proteins, and improvements in ^{211}At labeling chemistry.



Regarding small-molecule based strategies, PSMA inhibitors remain at the forefront. We hypothesize that a ^{211}At-labeled PSMA inhibitor could provide greater therapeutic benefit than Pluvicto™ without the confounding toxicities of its ^{225}Ac-PSMA-617 analogue. An update of progress towards clinical translation of our third-generation PSMA inhibitor [^{211}At]YF2 will be provided. We shall also provide and update of our work with a small protein scaffold – single domain antibody fragment (sdAb) – where we observed complete tumor regretion on >70% of animals treated with a single dose of ^{211}At-labeled HER2-targeted sdAb. Finally, we shall describe an improved method for site-specific labeling of sdAbs and other proteins with ^{211}At using a phenyloxadizolyl methylsulfone moiety.

Targeted Alpha Therapy with Actinium-225

Alfred Morgenstern*[1]

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Directorate for Nuclear Safety and Security, Karlsruhe, Germany
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Targeted Alpha Therapy (TAT) is a rapidly evolving field in cancer treatment. Among the various alpha emitting isotopes used in TAT, Actinium-225 (^{225}Ac) is experiencing particularly high interest. Since the concept of using ^{225}Ac in TAT was first conceived in the 1990's at JRC Karlsruhe, a number of pioneering studies were conducted, investigating ^{225}Ac-labeled antibodies and small molecules for therapy of leukemia, Non-Hodgkin's Lymphoma, brain tumors, malignant melanoma, neuroendocrine tumors and bladder cancer. The development of ^{225}Ac-PSMA617 for therapy of prostate cancer by JRC and University Hospital Heidelberg in 2013 marked a breakthrough in this regard and demonstrated strikingly the high potential of TAT. Following the first reports on the remarkable therapeutic efficacy of ^{225}Ac-PSMA617 for treatment of metastatic prostate cancer, worldwide interest in production of ^{225}Ac and development of ^{225}Ac-radiopharmaceuticals surged. Currently numerous clinical studies are investigating ^{225}Ac-radiopharmaceuticals for a variety of cancer types. This presentation will focus on the successful development and the current status of ^{225}Ac-radiopharmaceuticals for therapy of prostate cancer and neuroendocrine tumors.

Targeted treatment of glioma with radiolabelled Substance-P and PSMA

Jolanta Kunikowska*[1]

[1]Department of Nuclear Medicine, Warsaw Medical University, Warsaw, Poland
*jolanta.kunikowska@wum.edu.pl

Glioblastoma multiforme (GBM), is the most common primary malignant brain tumor with a poor prognosis. Due to the aggressive nature of the tumor and the risk of recurrence after standard treatment reaching 95%, the introduction of new treatment options is extremely important. Unfortunately, diagnosed patients mostly relapse and die within 1.5-2 years of treatment. The prognosis for patients with recurrent glioma is even worse, with a median overall survival of less than 6 months in this group.

Regardless of the histological grading, glioma cells are characterized by a high expression of NK-1 receptors which bind the natural ligand Substance-P (SP). SP, initially labelled with beta-emitters and then followed with alpha emitters have been used for locoregional application into the tumour.

[^{213}Bi]Bi-DOTA-SP with activity up to 11.2 GBq was used for local treatment achieving good treatment tolerance, with no clinically significant side effects. The progression free survival (PFS) was 2.7 months, the median overall survival (OS) after disease recurrence 10.9 months. From the diagnosis of the disease, the median overall survival was 23.6 months. In contrast, from the start of treatment with [^{213}Bi]Bi-DOTA-SP, the median survival was 7.5 months.

Given the difficulties in labeling and quality control with the short T½ for ^{213}Bi (46 min), treatment with another alpha emitter ^{225}Ac was introduced as the next step.

An evaluation study was conducted to determine the best tolerated dose of [^{225}Ac]Ac-DOTA-SP, administering activities of 10 MBq, 20 MBq and 30 MBq. Median OS from diagnosis was 35 months and from relapse was 13.2 months. PFS from the start of [^{225}Ac]Ac-DOTA-SP treatment was 2.4 months.

Prostate-specific membrane antigen (PSMA) expression was demonstrated in microvascular endothelium of different glioma tumours and *in vivo* confirmed by [^{68}Ga]Ga-PSMA-11 PET/CT in primary as well in recurrence tumor. This knowledge opens a new way for targeted, PSMA-based treatment.

My thesis in 180 s (MT 180') Competition

MT180 is a **competition open to doctoral students.** The challenge is for students to present their research topics in simple terms. Each participant must make a clear, concise and convincing presentation of his or her research project in **three minutes with a single slide**.

More than just a competition, it is also an opportunity for the junior researchers to **learn how to communicate and popularise** their passion for research.

The competition is inspired by the concept of the *Three minute thesis (3MT),* which originated at the University of Queensland in Australia.

Competition will be held on Tuesday 25.06 at 15:00-16:00. The best presenter will receive Young Scientist award in MT180 category.

Participants:

1. **Electrophilic Cyanation for the Carbon-11 Isotopic Radiolabeling of the Nitrile Function**

   Alexandre Hauwelle, Université Paris-Saclay, CEA, CNRS, Inserm, BioMaps, Orsay, France

2. **Investigation of Theranostic Potentials of Lu-177 Labeled Magnetic Iron Oxide Nanoparticles and their Derivatives**

   Elif Tutun, Department of Nuclear Applications, Institute of Nuclear Sciences, Ege University, Izmir, Turkey

3. **Mercury Radionuclides for Nanobrachytherapy of Triple-Negative Breast Cancer and Glioblastoma Multiforme**

   Emilia Majka, Institute of Nuclear Chemistry and Technology, Warsaw, Poland

4. **Synthesis, Radiolabeling and *In Vitro* and *In Vivo* Characterization of Novel $P2Y_{12}$ Purinergic Receptor Radiotracers**

   Eugénie Pincemail, Université Paris-Saclay, CEA, CNRS, Inserm, BioMaps, Orsay, France

5. **Copper-Catalyzed Nucleophilic rRdioiodination of New Prosthetic Groups**

   Ihab Shokair, NOMATEN Centre of Excellence, National Centre for Nuclear Research, Otwock, Poland

6. **^{109,103}Pd/^{109m}Ag,^{103}Rh *In-Vivo* Generator for Auger Electron Targeted Therapy**

   Nasrin Abbasi Gharibkandi, Institute of Nuclear Chemistry and Technology, Warsaw, Poland

7. **^{55}Co/^{58m}Co-Labeled Anti-Her2 Nanobody as a Theranostic Pair for 3-Gamma PET and Auger Electron Therapy**

   Noman Razzaq, Institute of Nuclear Chemistry and Technology Warsaw, Poland

8. **Synthesis of Fluorinated Metal Porphyrin Platforms for PET Imaging and Photodynamic Therapy**

   Romain Fontaine-Tuffery, Service de Médecine Nucléaire, Centre Georges-François Leclerc (CGFL); and Institut de Chimie Moléculaire de l'Université de Bourgogne (ICMUB), Dijon, France

9. **Radioiodinated Anti-HER2 Monoclonal Antibodies as Potential Therapeutic Radiopharmaceuticals**

   Sahar Nosrati Shanjani, Institute of Nuclear Chemistry and Technology, Warsaw, Poland

10. Development of a GMP-Compliant Synthesis of [^{18}F]AlF-NOTA-Folate on Trasis AllInOne

Simo Salo, Turku PET Centre, University of Turku, Turku, Finland

11. PSMA-Targeted Radionuclide Therapy Enhanced by Ultrasound-Mediated Microbubbles in a Preclinical Mouse Model of Human Prostate Cancer

Sophie Tran, BioMaps, Laboratoire d’imagerie biomédicale multimodale, Université Paris-Saclay, CEA, France

12. Terbium-161 Production and Quality Control

Tereza Janská, Department of Nuclear Chemistry, Czech Technical University, Prague, Czech Republic

13. A Criterion for BCC Phase Stability in Cobalt-Free Refractory High Entropy Alloys for Radiation Environment

Yulin Li, NOMATEN Centre of Excellence, National Centre for Nuclear Research, Otwock, Poland

14. New Phase Transfer Agents for Fluorine-18 Radiolabeling

Zélie Faudemer, Université Paris-Saclay, Inserm, CNRS, CEA, Laboratoire d'Imagerie Biomédicale Multimodale Paris-Saclay (BioMaps), Orsay, France

ORAL PRESENTATIONS

OP1 – KeyNote Talk - **Isotope Irradiation in the Maria Reactor and Their Further Development**

Paweł Nowakowski, Nuclear Facilities Operations Department, National Centre for Nuclear Research, Otwock, Poland

OP2 – **Molybdenum Nanoparticles for the Production of High Specific Activity ^{99}Mo by the Recoil Effect**

Pablo Serra Crespo, European Commission, Joint Research Centre, Petten, The Netherlands

OP3 – **Inhouse Production of ^{161}Tb**

Ján Kozempel, Department of Nuclear Chemistry, Czech Technical University, Prague, Czech Republic

OP4 – **Terbium-161 Production in Maria Reactor and Gd-160 Recovery - Preliminary Data**

Małgorzata Żółtowska, Radioisotope Centre POLATOM, National Centre for Nuclear Research, Otwock, Poland

OP5 – **On the Development of a Method for the Separation of Terbium from Elevated Amounts of Gadolinium Using TK221 and TK211/2 Resins**

Steffen Happel, TrisKem International, Bruz, France

OP6 – KeyNote Talk - **CERAD – a 30 MeV Cyclotron and New Opportunities for Medical Isotope Production in Poland**

Renata Mikołajczak, Radioisotope Centre POLATOM, National Centre for Nuclear Research, Otwock, Poland

OP7 – **Production of Theranostic Pair $^{43/44}$Sc -^{47}Sc on Calcium Targets**

Rafał Walczak, Institute of Nuclear Chemistry and Technology, Warsaw, Poland

OP8 – **The Japan Astatine Community: a Hub for Skills and Knowledge of ^{211}At and the Gateway to the World Astatine Community**

Kohshin Washiyama, Advanced Clinical Research Center, Fukushima Medical University, Fukushima, Japan

OP9 – **IAEA Contribution to the Production and Quality Control of Medical Radioisotopes and Radiopharmaceuticals**

Amirreza Jalilian, Department of Nuclear Sciences and Applications, International Atomic Energy Agency, Vienna, Austria

OP10 – **VTT´s Recombinant Antibody Technology**

Kristiina Iljin, Sensing Solutions, Immunotechnology, VTT Technical Research Centre of Finland, Espoo, Finland

OP11 – KeyNote Talk - **ImmunoPET Imaging of Glioblastoma Biomarkers to Follow and Predict Tumor Evolution**

Hélène Quelquejay, SHFJ-BioMaps (Université Paris-Saclay, Inserm, CNRS, CEA), Orsay, France

OP12 – **Terbium-161 Labelling of Glycoproteins PSMA and Monoclonal Antibodies**

Martin Vlk, Department of Nuclear Chemistry, Czech Technical University, Prague, Czech Republic

OP13 – **Polymer-Based Radiopharmaceuticals**

Martin Hrubý, SUPRAMOL Centre, Institute of Macromolecular Chemistry CAS, Prague, Czech Republic

OP14 – **Mercury Radionuclides for Nanobrachytherapy of Triple-Negative Breast Cancer and Glioblastoma Multiforme**

Emilia Majka, Institute of Nuclear Chemistry and Technology, Warsaw, Poland

OP15 – **^{109}Pd/^{109m}Ag *In Vivo* Generator in the Form of Nanoparticles for Combined β^-- Auger Electron Therapy of Hepatocellular Carcinoma**

Nasrin Abbasi Gharibkandi, Institute of Nuclear Chemistry and Technology, Warsaw, Poland

OP16 – KeyNote Talk - **Labeling of Proteins with Fluorine-18, Two Unlikely Partners for PET Imaging**

Simon Specklin, SHFJ-BioMaps (Université Paris-Saclay, Inserm, CNRS, CEA), Orsay, France

OP17 – **Development of New O^6-Benzylguanine Derivatives Radiolabelled with (Fluorine-18 and Zirconium-89) for Protein Labeling *via* SNAP-tag Approach**

Julen Ariztia, SHFJ-BioMaps (Université Paris-Saclay, Inserm, CNRS, CEA), Orsay, France

OP18 – **Radioiodination of Octreotide *via* Disulphide Rebridging**

Anna Krzyczmonik, NOMATEN Centre of Excellence, National Centre for Nuclear Research, Otwock, Poland

OP19 – **Design of New Radiotracers to Target Astrocytes as Biomarker of Neuroinflammation**

Eugénie Pincemail, SHFJ-BioMaps (Université Paris-Saclay, Inserm, CNRS, CEA), Orsay, France

OP20 – **Development of Radiofluorination of Metal Porphyrin Platforms for PET Imaging and Photodynamic Therapy**

Romain Fontaine-Tuffery, Service de Médecine Nucléaire, Centre Georges-François Leclerc (CGFL); and Institut de Chimie Moléculaire de l'Université de Bourgogne (ICMUB), Dijon, France

OP21 – **Electrophilic Cyanation for the Carbon-11 Isotopic Radiolabeling of the Nitrile Function**

Alexandre Hauwelle, SHFJ-BioMaps (Université Paris-Saclay, Inserm, CNRS, CEA), Orsay, France

OP22 – **Radiosynthesis and Use of [^{11}C]phosgene**

Thomas Keller, Radiopharmaceutical Chemistry Laboratory, Turku PET Centre, University of Turku, Turku, Finland

OP23 – **Isotopic Radiolabelling of Emtricitabine with Fluorine-18 for PET Imaging of HIV-1 Reservoirs**

Steve Huvelle, SHFJ-BioMaps (Université Paris-Saclay, Inserm, CNRS, CEA), Orsay, France

OP24 – **Difference Between Lu-PSMA 617 and Lu-PSMA I&T: a Single-French-Center Experience after Two Years**

David Tonnelet, Centre Henri Becquerel, France

OP25 – **A Comparative Study of [^{18}F]DCFPyL PET/CT *versus* [^{18}F]Fluoromethylcholine in Biochemical Recurrence of Prostate Cancer**

Vincent Bodenant, Curium Pharma, Saclay, France

OP26 – Closing Conf. Talk - **Prospects of Positronium Imaging Using Scandium-Labeled Pharmaceuticals**

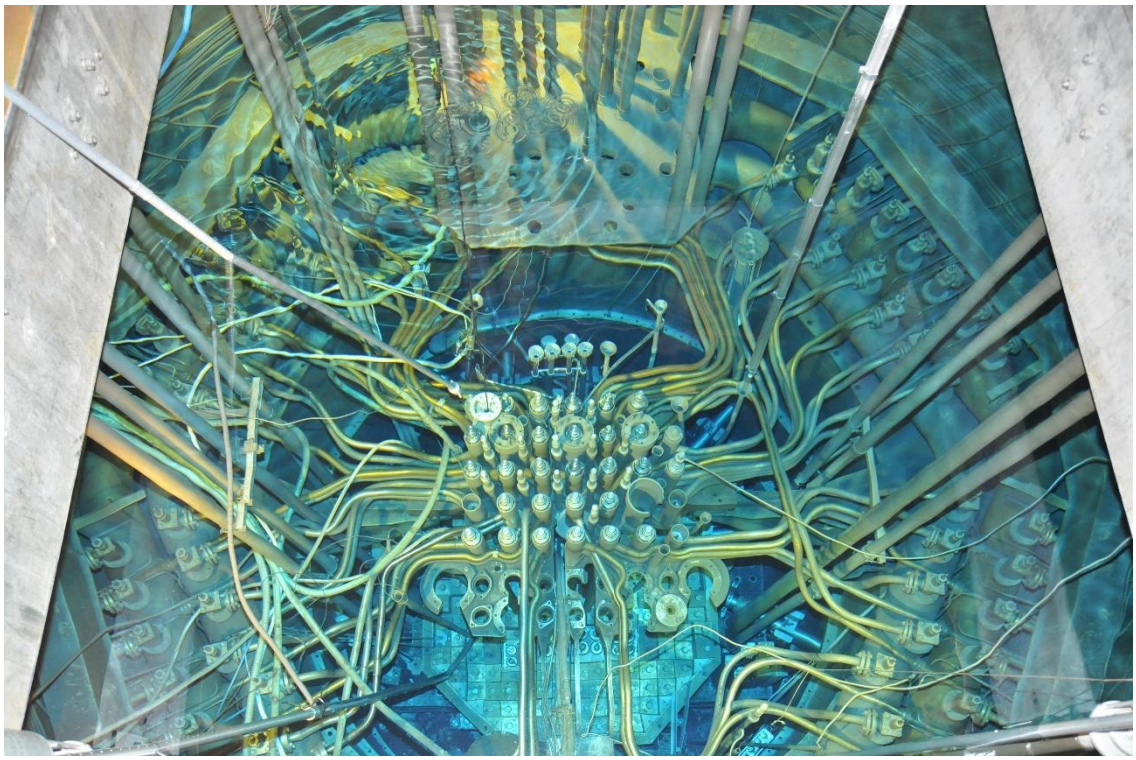
Paweł Moskal, Institute of Physics; and Center for Theranostics, Jagiellonian University, Cracow, Poland

Isotope Irradiation in the Maria Reactor and Their Further Development

Paweł Nowakowski*[1]

[1]Nuclear Facilities Operations Department, National Centre for Nuclear Research, Otwock, Poland
*pawel.nowakowski@cnbj.gov.pl

The presentation introduces the MARIA research reactor. It shows what research is being conducted using the reactor and presents the irradiation capabilities of materials. It also shows research on new materials and the main directions of further development.



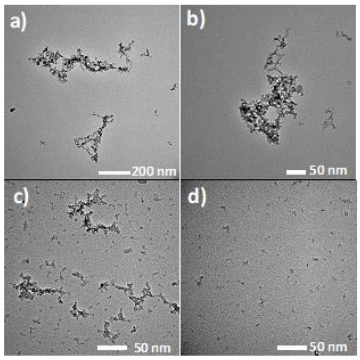
Molybdenum nanoparticles for the production of high specific activity ^{99}Mo by the recoil effect

Pablo Serra Crespo*[1], Andrea Tsinganis[2], Francesco Fumagalli[3], Otmar Geiss[3], Stephan Oberstedt[2], Arjan Plompen[2], Ana Ruiz Moreno[3]

[1]European Commission, Joint Research Centre, Westerduinweg, Netherlands
[2]European Commission, Joint Research Centre, Retieseweg, Belgium
[3]European Commission, Joint Research Centre, Via E. Fermi, Ispra (VA), Italy
*pablo.SERRA-CRESPO@ec.europa.eu

We propose a novel method for producing molybdenum-99 with high specific activity, involving the synthesis of nanoparticle agglomerates of molybdenum oxide through spark ablation. This method comprises the steps of producing these nanoparticles, irradiating them to produce molybdenum-99, and developing a separation technique to separate molybdenum-99 from the agglomerates.

Spark ablation presents a straightforward approach for synthesizing nanoparticles. This method relies on a physical mechanism where sparks erode molybdenum electrodes, leading to the formation of nanoparticles through nucleation and growth in a stream of inert gas. Our findings show that the size of these agglomerates is primarily influenced by the rate of inert gas flow. For instance, as depicted in Figure 1, a flow rate of 1 L/min results in large agglomerates exceeding 200 nm, whereas at 2 L/min, the size approximately halves. At a flow of 5 L/min, smaller agglomerates coexist with tiny particles. Remarkably, at 10 L/min, the process yields only discrete nanoparticles, with agglomerates absent. Given their ease of separation by centrifugation, agglomerates were selected for subsequent experimentation.



- Figure 1. Molybdenum oxide nanoparticles produced by spark ablation. Argon flow of a) 1 L/min, b) 2 L/min, c) 5 L/min and d) 10 L/min.

The MONNET light-ion accelerator at JRC Geel was used to irradiate various samples with fast neutrons. Upon absorption of an incident neutron by naturally present molybdenum-100, the nucleus recoils, with the recoil energy further modified by the emission of two fast neutrons. If the nanoparticle is small enough compared to the range of the recoiling molybdenum-99, then the latter may exit the nanoparticle facilitating extraction.

Post-irradiation, we dispersed the samples in various extraction solutions, incorporating standard metallurgical extracting agents. The choice of solvent for the solid-liquid extraction phase was critical to avoid dissolving the nanoparticle agglomerates, which would reduce the ultimate specific activity of the molybdenum-99. Under certain extraction conditions, we achieved a selective isolation of molybdenum-99, thereby enhancing its specific activity.

Inhouse production of ^{161}Tb

Jan Kozempel*[1], Tereza Janská[1], Matěj Štíbr[1], Marie Skálová[1] and Martin Vlk[1]

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Terbium-161 is a promising theragnostic nuclide that offers low energy and Auger-Meitner electron emissions with low energy gamma rays for SPECT imaging. It could fill the gap between the powerful and more toxic ^{225}Ac, and currently used beta emitter, the ^{177}Lu.
Due to scarsity of the enriched ^{160}Gd tagert material its availability is limited. We report here the inhouse production of ^{161}Tb using the ^{160}Gd(n,γ)^{161}Gd → ^{161}Tb reactions sequence leading to a product suitable for preclinical and potentially clinical trials. Production and possible further developments will be discussed in the presentation, including enriched ^{160}Gd target preparation, its irradiation in a nuclear reactor, Gd/Tb separation, Tb product purification and formulation, enriched Gd recycling and labelling tests with the prepared ^{161}Tb.

Up today, some 20 production runs were performed in our laboratory resulting in an overal ^{161}Tb activity sum of A_{EOB} = 150 GBq. Final product activities ranged up to A_{EOB} = 22 GBq per batch, resulting in high-purity ^{161}Tb of radionuclidic purity over 99,999 % and a mass specific activity in the range of a_m(Tb) = 1,9 – 4 GBq/µg. An outlook to possible regular ^{161}Tb production in the Czech Republic is given with a discussion on future ^{161}Tb developments.

Acknowledgements: This work was supported by the project “Efficient Low-Energy Electron Cancer Therapy with Terbium-161” (ELLECTRA) granted by the Norway and Technology Agency of the Czech Republic within the KAPPA Programme (grant No.: TO01000074).

Terbium-161 production in Maria reactor and Gd-160 recovery – preliminary data

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^{161}Tb ($t_{1/2}$ = 6.9 d; $E_{\beta-av}$ = 0.15 MeV) is an β^- emitter and due to its half-life, beta energy and chemical properties similar to ^{177}Lu, it is used in targeted radionuclide therapy. Terb-161 emits conversion and Auger electrons, making it possible to improve the therapeutic effect compared to lutetium-177. Thanks to the emission of photons with an energy of 167 keV, terbium-161 can be used for SPECT imaging[1,2]. Tb-161 is produced in nuclear reactors from enriched gadolinium-160 in the reaction: ^{160}Gd(n, γ)^{161}Gd →^{161}Tb. The Radioisotope Centre POLATOM is conducting research work on the production of terbium-161 in the Maria reactor and the recovery of Gd-160 target material.

Gadolinium oxide enriched in the isotope ^{160}Gd (97.5%) was activated in the Maria reactor. Irradiation was carried out in a thermal neutron flux of $1*10^{14}$ $n*s^{-1}*cm^{-2}$. Extraction chromatography was used for the two-step process separation of ^{160}Gd/^{161}Tb. In the first step, terbium-161 was separated from gadolinium-160 using LN2 resin (Triskem). Samples were applied to the column after dissolving the target, and terbium-161 was eluted with nitric acid in a gradient system. In the second step, terbium-161 nitrate solution was concentrated and eluted in the form of chlorides from a column with DGA resin (Triskem). Radionuclide purity was measured by gamma spectrometry with an HPGe detector. Radiochemical and chemical purity was verified by terbium-161 radiolabeling of the PSMA-D4 peptide and ICP-OES measurements.

The possibility of recovering the target material by precipitation was investigated. Experiments were conducted to obtain gadolinium oxalate precipitates. The effect of the molar ratio of oxalic acid to gadolinium on the efficiency of precipitation was compared. The gadolinium oxalate was thermally decomposed to gadolinium oxide by heating at 800°C.

High separation efficiency of terbium-161 from gadolinium (95% - 97%) was achieved. The terbium fraction contained only ^{160}Tb as an radionuclide impurity. The efficiency of radiolabeling PSMA-D4 was over 90%. For gadolinium recovery, a gadolinium oxalate precipitation efficiency of 99.98% was achieved using a Gd:$C_2H_2O_4$ molar ratio of about 1.9. After termal decomposition the oxalate at 800°C, gadolinium oxide was obtained with an efficiency of about 95% for Gd, relative to the initial amount of gadolinium in solution.

Acknowledgments: The publication was partially created within the project PRISMAP funded by the European Union under grant agreement No 101008571.
The publication was partially created within the project SECURE funded by the European Union under grant agreement No. 101061230.

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On the development of a method for the separation of Terbium from elevated amounts of Gadolinium using TK221 and TK211/2 Resins

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Terbium radioisotopes have gained strong interest over these last years. This is mainly due to the fact that four Terbium isotopes can be used in nuclear medicine: ^{149}Tb (α-therapy), ^{155}Tb (SPECT), ^{152}Tb (PET) and ^{161}Tb (β^-/Auger-Meitner electron therapy)[1]. Especially ^{161}Tb is, due to its similarity to ^{177}Lu in terms of production, chemistry and half-life, while additionally emitting a significant amount of Auger-Meitner electrons, increasingly finding use. This increased interest in ^{161}Tb requires the development of purification methods for its separation from ^{160}Gd targets of elevated size.

TK211/2/3 Resins[2] were originally developed for the separation of ^{177}Lu from high amounts of ^{176}Yb at very high activity levels. It could be shown though, that they can also be used for the separation of Tb from Gd (and Dy). While initial work[3,4] was limited to 500mg Gd or less, currently ongoing work focusses on larger Gd target sizes (currently up to 3g).

The suggested method is based on an initial TK221 Resin column for the conversion of the dissolved Gd targets to a form more suitable for the separation process (0.05M HCl). The Tb purification is performed on a sequential TK212/TK211 chromatographic separation step. The initial Gd/Tb/Dy separation is performed on a TK212 Resin column. The obtained Tb fraction is directly loaded onto a TK211 column to further increase the Tb purity (polishing step). Finally, a 2 mL TK221 cartridge is used to concentrate and convert the Tb purified via TK212/1 columns to 0.05M HCl. Examples of Tb separation from increasing amounts of Gd (0.5g – 3g) will be shown. Further the decontamination of radioactively contaminated effluents using TK225 Resin[5] will be discussed, as well as on-going work on the 'post-shipment' purification of ^{161}Tb from its Dy daughter.

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CERAD – a 30 MeV cyclotron and new opportunities for medical isotope production in Poland

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To meet the high demand for radioisotopes with potential for medical applications, with a particular focus on their theranostic value, the new research facility is being launched at NCBJ/POLATOM, namely "Center of Design and Synthesis of Radiopharmaceuticals for Molecular Targeting, CERAD". The 30 MeV cyclotron which will accelerate protons and alpha particles to 30 MeV and deuterons to 15 MeV is a key device of CERAD. It constitutes a powerful tool for producing novel radioisotopes for medical use, which were not available in Poland until today. Among them, the radioisotopes such as $^{43/44}$Sc, $^{64/67}$Cu, ^{68}Ge-^{68}Ga, ^{89}Zr, ^{123}I and ^{211}At will be produced. Installation of a new high-current cyclotron at NCBJ, with equipment and infrastructure, combined with an already existing scientific base, creates unique and pro-development research capabilities.

The cyclotron, Cyclone 30XP, was built by the Belgian company Ion Beam Applications. It is installed in the new building which also hosts several dedicated labs with hot cells for radioisotope processing, as well as the QC and research laboratories. The entire facility offers a space of 2500 m^2.

The infrastructure of CERAD can be used for both research and commercial activities, it creates the platform for comprehensive studies oriented on research and design of new medicinal products, in particular radiopharmaceuticals, and for implementing diagnostic and therapeutic procedures for diseases, which are currently treated ineffectively. The upcoming infrastructure will be open to the international community. The CERAD project will offer new radioisotopes but also the possibility to design innovative radiopharmaceuticals. The research potential of NCBJ as a consortium leader is supported by partner institutions: University of Warsaw, Warsaw Medical University, Institute of Nuclear Chemistry and Technology, Jagiellonian University Medical College, and the Medical University of Białystok.

CERAD project is co-financed under the Smart Growth Operational Programme 2014-2020, Priority IV: INCREASING THE RESEARCH POTENTIAL, Measure 4.2. Development of modern research infrastructure of the science sector.

Production of theranostic pair $^{43/44}$Sc - ^{47}Sc on calcium targets

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The ^{43}Sc ($t_{½}$ = 3.89 h) and ^{44}Sc ($t_{½}$= 3.92 h) are ideal β^+ emitters in PET diagnosis. Both radionuclides can be used as an alternative to ^{68}Ga, because $^{43/44}$Sc has a longer half-life and forms theranostic pair with β^- emitter ^{47}Sc. However, in comparison with ^{44}Sc, ^{43}Sc has a half-life and beta plus radiation similar to ^{44}Sc. Nevertheless, its gamma-ray energy emission and intensity are much lower (372 keV, 23%) than in the case of ^{44}Sc (1157 keV, 99%). On the other hand high energy and intensity gamma line makes ^{44}Sc the perfect candidate for the β^+ - γ coincidence PET technique. Thanks to this correlation it is also possible to determine life time of positronium which is a bound state of positron and electron. This allows for imaging the hypoxia state of tumor tissues.
In our work, we propose a new way for cyclotron production of ^{43}Sc in ^{42}Ca(d,n)^{43}Sc nuclear reaction, ^{47}Sc by proton irradiation of ^{48}Ca target in ^{48}Ca(p,2n)^{47}Sc and ^{48}Ca(p,d)^{47}Ca→^{47}Sc reactions and also by neutron irradiation reaction ^{46}Ca(n,γ)^{47}Ca→^{47}Sc in the “Maria” Nuclear Reactor.

In our work, we used enriched $^{42/44/46/48}CaCO_3$ targets pressed in graphite support for irradiation with a beam of the proton or deuteron or in the form of the powder closed in a quartz ampoule for irradiation in the “Maria” Nuclear Reactor. After irradiation, $CaCO_3$ targets were dissolved in 1 M HCl, and a microfiltration process after alkalization of the target material solution was used to separate $^{43/44}$Sc from calcium target materials and for the production of ^{47}Sc generator. In the case of proton irradiation of ^{48}Ca obtained product contained a mixture of radionuclides ^{47}Sc, ^{48}Sc, and ^{47}Ca which is a ^{47}Sc mother radionuclide. After irradiation with a 60 MeV proton beam followed by chemical separation of the Ca isotopes and waiting for the maximum growth of ^{47}Sc by 5,6 days, 44 MBq/μAh of ^{47}Sc can be eluted from the generator with no other contaminating scandium activity. A similar procedure was used for $^{46}CaCO_3$ targets irradiated in the “Maria” Nuclear Reactor. After separation solution of $^{43/44/47}$Sc was loaded on cation exchange Dowex50wX4 resin for purification and change of environment.

The proposed methods allow obtaining high activity of ^{43}Sc, ^{44}Sc, and ^{47}Sc. Scandium isotopes were separated from the targets with an efficiency of more than 90% and eluted in the volume of 0.5 ml. However low availability and high costs of $^{46}CaCO_3$ and $^{48}CaCO_3$ make ^{47}Sc not very economically profitable. Instead of ^{47}Sc, a suitable candidate for the theranostic pair with $^{43/44}$Sc is ^{177}Lu, which exhibits scandium-like chemical properties.

Scandium radionuclides, separated by our method, have sufficient quality for labeling the biologically active bioconjugates for example DOTA-TATE with an efficiency about 99%.

Acknowledgments: This project is financed from NCN, OPUS-22, 2021/43/B/ST2/02150 “Development of three-photon emitting radiotracers for positronium imaging”.

The Japan Astatine Community: a hub for skills and knowledge of ^{211}At and the gateway to the World Astatine Community

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Among radiotherapy treatments, targeted radionuclide therapy (TRT) is categorized as one of the cancer treatments in which radionuclides are labeled on drugs. In recent years, the high therapeutic efficacy of alpha-particle emitting radionuclides has been attracting attention, and the alpha-emitter drug [^{223}Ra] $RaCl_2$ has been approved and prescribed to patients worldwide for the treatment of castration-resistant prostate cancer. In addition, the peptide [^{225}Ac] Ac-PSMA-617, labeled with ^{225}Ac, has achieved remission of systemic metastases of prostate cancer in several patients. However, many of these nuclides are very difficult to manufacture in Japan from the viewpoint of securing materials, hindering research and development progress. Therefore, we focused on astatine-211 (^{211}At), which can be produced by accelerators in Japan, as another promising alpha nuclide, and we established the Japan Astatine Community (JAC) as an organization to promote the use and R&D of this nuclide and to support its subsequent clinical use.

The JAC is working to become a hub for the systematic collaboration of stakeholders in industry, academia, and government for the social implementation of targeted radionuclide therapy using ^{211}At by sharing actions necessary for the early realization of this goal. The JAC also operates the Worldwide Astatine Community (WAC) with 1) the Network for Optimized Astatine labeled Radiopharmaceuticals (NOAR) in Europe and 2) the Astatine User's Community developed by the Department of Energy's Isotope Program in the United States, which share the same goals. The WAC is a global Astatine Users Community that brings together various stakeholders (from manufacturing and labeling synthesis to clinical applications and social implementation) at the global level to explore the full potential of the ^{211}At in targeted radionuclide therapy.

Our activities are ultimately to obtain the following five outcomes:

1. Establish and strengthen the astatine supply network.
2. Provision of up-to-date technical and professional information on astatine to nuclear medicine professionals.
3. Study towards international standardization of astatine-labeled drug production.
4. Access to an international network centered on the WAC.
5. Promotion of rapid transfer of innovations from scientific societies to industry.

IAEA contribution to the production and quality control of medical radioisotopes and radiopharmaceuticals

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Medical radioisotopes and radiopharmaceuticals are major content of nuclear medicine procedures. The production of radioisotopes is routinely performed via nuclear reactors and accelerators by many facilitated in Member States. The International Atomic Energy Agency (IAEA) is supporting Member States in the production and application crucial radioisotopes (such Mo-99, I-131, Lu-177, F-18, Ga-68, etc.) for radiopharmaceutical production ultimately to be used in nuclear medicine centres.

A large list of theranostic radioisotopes including but not limited to Ga-68, Zr-89, Ac-225 and Copper and Terbium radiosiotopes etc. can offer new candidates for clinicians in the future and the IAEA is taking steps to ensure their safe and appropriate application in radiopharmacy. The Agency also supports and promotes other radioisotope production routes, such as power reactors, linear accelerators, etc. *via* activities such as Coordinated Research Projects (CRPs), Technical Meetings (TMs), national/regional training courses and conferences. Initiation and communication with professional networks, development of databases and freely available publications for all Member States are other useful means to support Member States in radiopharmaceutical sciences.

VTT´s recombinant antibody technology

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Antibodies are essential part of the immune system protecting against diseases and harmful pathogens. In addition, antibodies are invaluable reagents in basic research, diagnostics and therapy. Radiopharmaceuticals having both diagnostic and therapeutic capabilities, are gaining more attention and the nuclear medicine market is expected to grow during the coming years.

The current technologies available for recombinant antibody development at VTT are presented. Novel antibodies can be isolated from existing antibody phage display libraries or novel antibody libraries can be constructed upon the need. Selection and screening procedures are designed based on the research question. Recombinant antibodies can be produced in bacterial cells at different scales and in different formats, from small scale (usually 1.8 L) up to 9 L culture. In optimized bioreactor cultivations, production yields normally 100-200 mg/L of soluble active Fab or scFv protein. Recombinant antibodies can be converted into different antibody formats (such as IgG, Fab and scFv). In addition, existing monoclonal antibodies can be converted into recombinant proteins. Antibody engineering can be used for instance for modification of binding properties and addition of purification or conjugation tags. Enzyme-Linked ImmunoSorbent Assays (ELISA), fluorescence activated cell sorting (FACS) and Biacore T200 are typically used in analysis of the binding properties. We can also intergrate the developed antibodies to sensors and µ-systems, which could be of interest e.g. in development of point-of care diagnostics. Some of the recombinant proteins isolated and produced at VTT are used in diagnostic tests and in pre-clinical studies. In the development of novel radioimmunotherapy approaches, the recombinant antibody fragments produced at VTT could be used as carriers to target radiation to the specific cells and tissues in pre-clinical studies.

ImmunoPET imaging of glioblastoma biomarkers to follow and predict tumor evolution

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The standard of care for glioblastoma (GBM), including surgery, radiotherapy, and chemotherapy, is challenged by the tumor's infiltrative nature, leading to residual sites and recurrent tumors within six months. Promising therapies such as antibody drug conjugates, immunotherapy, and fluorescence-guided surgery offer hope for patients with such malignancies, with numerous preclinical and clinical efforts underwa[1]. To tailor treatment effectively to disease progression, it is crucial to employ a theranostic approach, diagnosing predictive biomarkers to guide associated therapies. These biomarkers must exhibit high specificity for GBM tumors, particularly the infiltrative subtype.
Our research group at the BioMaps laboratory in France is developing diverse theranostic strategies, leveraging immunoPET imaging to target the immune system through immune checkpoint blockade, such as anti-PD-L1, and to identify new therapeutic targets, including highly specific tumor biomarkers like endothelin receptors. Given the challenges posed by the blood-brain barrier (BBB), which restricts the passage of therapeutic agents, our focus lies in understanding antibody BBB penetration and devising strategies to overcome this barrier, such as ultrasound therapy[2].

Both strategies, namely, imaging the interaction of the immune system and identifying new GBM biomarkers, will be presented and correlated with their therapeutic implications[3,4]. Our approach involves radiolabeling specific antibody structures to visualize these biomarkers of interest.

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Terbium-161 labelling of glycoproteins PSMA and monoclonal antibodies

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Terbium-161, as a perspective radionuclide, produced in our institute, was used for labelling of prostate-specific membrane antigen (PSMA) beside the investigation of labelling conditions of selected monoclonal antibodies (MABs) rituximab and bevacizumab. The objective of the first part research task was to prepare radiopharmaceuticals ^{161}Tb-PSMA-617 and ^{161}Tb-PSMA I&T in high abundance and specific activity, to study their stability in biological matrices and in a mouse model. Both radioligands were prepared with yields over 99% and demonstrate sufficient stability in 48 hours post reaction. It was demonstrated high uptake in tumors of both PSMA ligands on LNCaP cell lines *in vivo*, while ^{161}Tb-PSMA I&T exibit slower clearence and higher retention in lungs and heart.
Labelling of MABs was studied on an antibody targeting the vascular endothelial factor (VEGF) angiogenesis-stimulating bevacizumab and the anti-CD20-rituximab targeting conjugate. Both conjugates were prepared by conjugating antibodies with DOTA-NHS. Yields were approximately 20% in both cases. The labeled bevacizumab conjugate was separated from free Tb-161 and applied to a mouse model of the SKOV3 tumor line. After 7 days from the application, most of the antibody was taken up in the tumor tissue. On both models we proved, that Tb-161 produced on LVR-15 meet the criteria for labelling and radioconjugates reveals stability and significant tumor uptake *in vivo*.

Acknowledgements: This work was supported partially by the project “Efficient Low-Energy Electron Cancer Therapy with Terbium-161” granted by the Norway and Technology Agency of the Czech Republic within the KAPPA Programme (grant No.: TO01000074).

Polymer-based radiopharmaceuticals

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Self-assembly of molecules into complex supramolecular units with qualitatively new properties is in the chemical foundations of life and is the essence of the ability of living organisms to react to the external environment. A specific case occurs when the hydrophobic part of the molecule, or the part of the molecule responsible for self-assembly significantly changes its physico-chemical properties, such as solubility in water, by the action of an external stimulus (changing temperature, pH, etc.). Then the self-assembly of the system is controlled by such external stimulus. Several such systems designed for radiopharmaceutical applications will be presented in the lecture. These will include ^{90}Y and ^{161}Tb-radiolabeled injectable thermoresponsive polymer depots for cancer immunoradiotherapy where the initial radiotherapy produces immunogenic dead cancer cell debris, against which later the immunoactivating component beta glucan raises immune response affecting also distant metastases. We will also present biocompatible polymer-coated enhanced permeability and retention (EPR) effect tumor-pretargeted hydroxyapatite nanoparticles. These nanoparticles were prepared using hydroxybishosphonate polymer anchoring strategy and were subsequently in vivo targeted with bone-seeking ^{99m}Tc radiopharmaceuticals. Lastly, we will demonstrate an evaluation of the performance of copper scavengers in the gastrointestinal tract as potential Wilson's disease therapeutics with ^{64}Cu and cancer diagnostics targeting fibroblast activation protein (FAP).

Acknowledgments: Financial support from the Ministry of Education, Youth and Sports of the Czech Republic (grant No. LUAUS24272), Ministry of Health of the Czech Republic (grant No. NU22-03-00318) and project New Technologies for Translational Research in Pharmaceutical Sciences /NETPHARM, project ID CZ.02.01.01/00/22_008/0004607, co-funded by the European Union, is gratefully acknowledged.

Mercury radionuclides for nanobrachytherapy of triple-negative breast cancer and glioblastoma multiforme

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Cancers that lack specific receptors' overexpression are currently a significant concern for novel radiopharmaceutical approaches. Triple-negative breast cancer (TNBC) and glioblastoma multiforme (GBM) are highly aggressive cancers with inferior prognoses. TNBC occurs in 10—15% of all breast cancer instances; the survival rate of a metastasized form of TNBC is 12%.[1] GBM is the most common type of brain cancer, being 50.1 % of all malignant brain tumors, with a mortality of 93.1%.[2]
The use of Auger-emitting radionuclides in the therapy of these cancers presents many benefits. They possess exceptional cytotoxicity and localized biological effectiveness over short ranges. Auger electrons have the smallest range in tissue, up to 10 µm, and deposit their energy at short distances with a high LET (4 to 26 keV/µm). This high LET reduces the cancer cell's ability to repair DNA damage by causing double-strand breaks. Mercury radionuclides ^{197}Hg and ^{197m}Hg exhibit exceptional efficacy with 42.6 Auger electron emissions per decay and are highly suitable for Auger electron therapy.[3]

In this project, we present a very efficient Auger-electron emitting radionuclide - $^{197/197m}$Hg amalgamated on the surface of gold nanoparticles (AuNPs) for nanobrachytherapy of TNBC and GBM.

The Au($^{197/197m}$Hg)NPs-PEG radioconjugate was evaluated *in vitro* for its therapeutic potential on MDA-MB-231 and T98G cancer cell lines. Cell cultures were subjected to internalization, subcellular fractionation, MTS assay, and spheroid studies. In addition, flow cytometry analysis assessed apoptosis and cell cycle of treated cells. Moreover, the γ-H2AX phosphorylation technique was applied to determine the number of DNA double-strand breaks caused by the radioconjugate, showing a high level of DNA DSB (Figure 1).

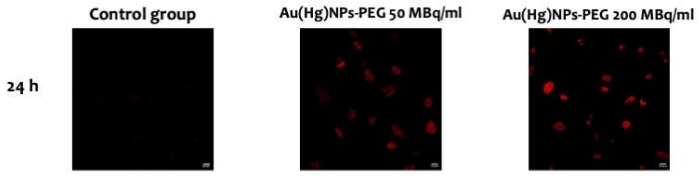

Figure 1. DNA DSB visualized on MDA-MB-231 after 24 h incubation with Au($^{197/197m}$Hg)NPs-PEG.

Moreover, *in vivo* biodistribution and therapeutic efficacy studies were performed on mice in Radiochemical Studies Laboratory, INRASTES, NCSR Democritos in Athens, Greece.

Acknowledgments: This research is financed by the PRELUDIUM 20 grant 2021/41/N/ST5/00322 from the National Centre of Science.

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^{109}Pd/^{109m}Ag *in-vivo* generator in the form of nanoparticles for combined β$^-$ - Auger electron therapy of hepatocellular carcinoma

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Hepatocellular carcinoma (HCC) rates as the fifth most common cancer globally. Despite considerable progress in cancer therapy, liver transplantation is still the most effective. Several strategies such as chemotherapy, broad-spectrum tyrosine kinase inhibitors, and combination of immunotherapy with angiogenesis inhibition can offer a nominal extension of the survival curve which can only be measured in months. Therefore, there is an immense demand for better therapeutic alternatives for liver cancer patients who cannot undergo surgery. The application of nanostructures, particularly inorganic ones, in the treatment of liver cancer offers remarkable advantages, including a reduction in therapy-related toxicity and an improvement in specific drug delivery.

In this study, we propose using ^{109}Pd/^{109m}Ag *in vivo* generator as an alternative to ^{161}Tb due to the larger number of Auger/conversion electrons (18 vs.12.1) and greater energy of β$^-$ particles. To prevent the diffusion of ^{109m}Ag from the target site, we propose a solution involving the use of a ^{109}Pd/^{109m}Ag *in-vivo* generator in the form of 5 nm ^{109}Pd nanoparticles. In contrast to chelator-based *in-vivo* generators, we found complete retention of ^{109m}Ag on Pd nanoparticles. The metallic phase contains delocalized electrons, preventing release of ^{109m}Ag and maximizing therapeutic effectiveness. Auger electron therapy requires radionuclides to be delivered to the cell nucleus, preferably near DNA. The study found that after 24 hours, 28% of the internalized radioactive ^{109}Pd-PEG nanoparticles in cytosol was transferred to the nucleus. This process increased to 50% after 48 hours. The studies also investigated the cytotoxicity of radioactive ^{109}Pd-PEG nanoparticles in radioactivity ranging from 11.25 MBq/mL to 100 MBq/mL Compared to nanoparticles labeled with ^{125}I (an Auger emitter) and ^{131}I (β$^-$ particles emitter), ^{109}Pd-labeled nanoparticles were significantly more toxic and effective in therapy due to the emission of both β$^-$ particles and Auger electrons. Cytotoxicity studies on $HepG_2$ spheroids incubated with ^{109}Pd-PEG nanoparticles demonstrated surface changes and tumor growth inhibition, confirming the previous results.

Inorganic nanoparticles are a special kind of material that, depending on their properties, tend to accumulate in the liver when introduced in vivo. This is usually a disadvantage that makes it difficult to use nanoparticles for therapeutic purposes in medicine. However, in the case of HCC tumors, this property could be an advantage. We believe that subsequently, due to the EPR effect, ^{109}Pd-PEG nanoparticles will accumulate in cancerous liver cells. In our further research, we plan to incorporate targeting vectors such as glycyrrhetinic acid, transferrin, folate, or P-glycoprotein 1 (CD44) ligands to specifically target $HepG_2$ cells while avoiding normal liver cells.

Acknowledgments: This project was funded by National Science Center Poland, grant no 2022/45/B/ST5/01861 and grant no UMO-2019/35/B/ST4/01433.

Labeling of proteins with fluorine-18, two unlikely partners for PET imaging

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The unique targeting properties offered by proteins represent a strong opportunity in PET imaging to develop efficient clinical diagnostic tools. This is particularly exemplified with the rise of immunoPET, using antibodies as targeting vectors will undoubtedly emerge in the coming years as a major paradigm shift in cancer diagnosis. Indeed, the increasing use of immunotherapies and targeted therapies in oncology, coupled with the rise of biotherapies, necessitates innovative diagnostic tools in medicinal imaging. These agents are characterized by a slow pharmacokinetic, IgG antibodies usually need several days to reach a maximum concentration at their target and therefore have to be labeled with a PET radioisotope with a matching half-life, such as zirconium-89 or copper-64. However, many efforts are directed toward the development of smaller antibody formats (Fab, nanobodies, scFv, etc.) displaying shorter pharmacokinetics, favoring a much wider clinical translation.

These vectors then become available for the labeling with fluorine-18, known as the most common isotope in PET imaging. With opposite chemical properties, bonding fluorine-18 with proteins is a major challenge that has driven radiochemists for decades and now takes on greater significance than ever with the rise of immunoPET. In the presentation, we will discuss some recent addition to this field as well as approaches developed by our group focused on enzyme-mediated labeling and the introduction of fluorine-18 by disulfide bond rebridging.

Development of new O^6-benzylguanine derivatives radiolabelled (fluorine-18 and zirconium-89) for protein labeling *via* SNAP-tag approach

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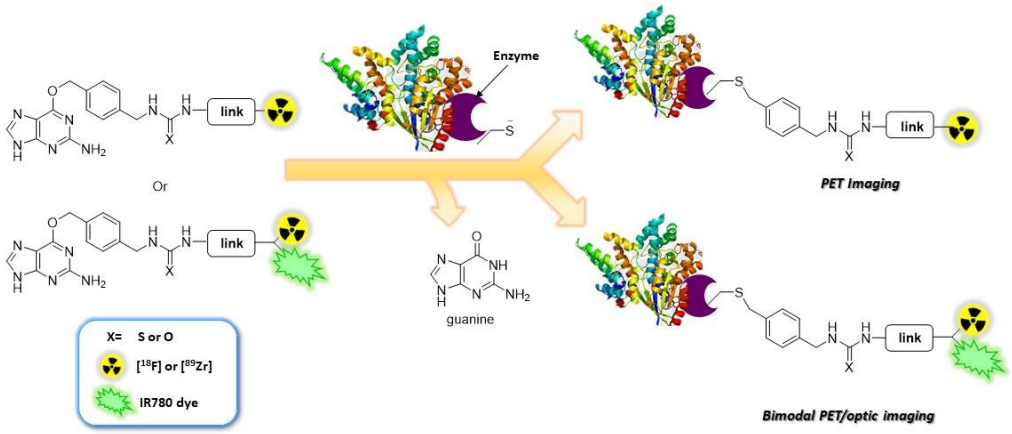
Fluorine-18-labelled biomolecules are widely employed tracers for specific and precise diagnosis imaging. However, given their fragility in classic ^{18}F-C radiofluorination conditions (high temperatures and basic conditions) they are often labelled by a prosthetic approach: radiolabelling of a small molecule followed by the coupling to the biomolecule. The coupling reaction must be relatively rapid due to the fluorine half-life (109.8 min) and with low by-product formation. However, site-selectivity of classic coupling reactions (amidation, thiol etc.) is limited when the biomolecule is a protein.

On this context, Snap-Tag enzymatic labelling approach it is an interesting option for protein labelling due to its full regioselectivity, rapidity and in vivo compatibility. Snap-Tag is based on the use of proteins modified with an enzyme (fusion proteins) who specifically recognizes O^6-benzylguanine derivatives.[1,2] This enzyme catalyses the transfer of the benzyl moiety present on the O^6 position of the guanine (bearing the label) to a reactive cysteine of its active site. Thanks to this enzymatic reaction, a covalent bond is formed between the enzyme and the labelled benzyl moiety with a natural guanine as the only by-product.

In our case, to leverage the best profit of SNAP-Tag, three different O^6-benzylguanine derivatives have been synthetized: one radiolabelled with fluorine-18 ([^{18}F]FPyGu), the second one with double labeling fluorine-18/cyanine ([^{18}F]-FCyGu) for potential bimodal PET/optical imaging applications and the last one labelled with zirconium-89 ([^{89}Zr]-GuPDFO). The [^{18}F]FPyGu, (19 ± 1% yield, 277 ± 91 GBq/µmol molar activity after 60 min EOB) has been tested on fusion proteins (muscarinic receptors / Snap-Tag) expressing cells to verify the specific tracer accumulation. The biodistribution has also been studied *in vivo* on healthy mice.



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Radioiodination of octreotide *via* disulphide rebridging

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Disulphide rebridging allows for the site-selective labelling with minimal modification of the tertiary structure of biomolecule. It was successfully used for the labelling with ^{18}F, ^{64}Cu and ^{89}Zr for diagnostic purposes[1,2]. In this work, we designed and successfully radiolabelled new prosthetic groups for radioiodination *via* disulphide rebridging, which could potentially be used in both diagnostic and therapeutic applications given the theranostic nature of iodine.

Prosthetic groups were labelled with iodine-131 *via* either electrophilic or nucleophilic copper-mediated radioiodination. For the electrophilic labelling [^{131}I]NaI was added to a solution of NCS and stannylated precursor in MeCN and reaction was carried out for 20 min at RT. For the copper-mediated radioiodination [^{131}I]NaI was added to a solution of boronic ester precursor and $Cu(py)_4(OTf)_2$ in MeOH/MeCN, and reaction was carried out for 20 min at RT. Rebridging of octreotide with ^{131}I-labelled prosthetic group was performed in a presence of TCEP and reaction was carried out for 30 min at RT.

Electrophilic labelling of prosthetic groups resulted in formation of the product with radiochemical yield of 80 ± 6 % for compound A and 85 ± 11 % for compound B. Copper-mediated approach resulted in higher radiochemical yield of 95 ± 5 % in both cases. The rebridging reaction was monitored with radioHPLC and showed high radiochemical conversion of 89 %.

We successfully labelled two new prosthetic groups for the radioiodination of biomolecules *via* disulphide rebridging and in our proof-of-concept experiment, we demonstrated their effectiveness by labelling of octreotide peptide.

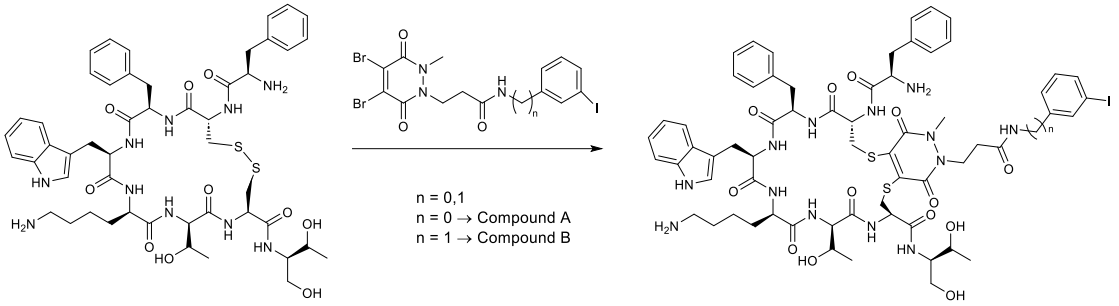

Figure 1. Radioiodination of octreotide *via* disulphide rebridging.

Acknowledgments: Research was funded through the European Union Horizon 2020 research and innovation program under Grant Agreement No. 857470 and from the European Regional Development Fund under the program of the Foundation for Polish Science International Research Agenda PLUS, grant No. MAB PLUS/2018/8, and the initiative of the Ministry of Science and Higher Education 'Support for the activities of Centers of Excellence established in Poland under the Horizon 2020 program' under agreement No. MEiN/2023/DIR/3795.

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Design of new radiotracers to target astrocytes as biomarker of neuroinflammation

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Neuroinflammation (NI) is a common phenomenon to all neurodegenerative diseases affecting the central nervous system (CNS). To this day, little is known about NI and new tools are needed to explore the biological mechanisms behind it. In this context, adenosine has been highlighted for its crucial role in cell signaling during inflammation[1]. Indeed, under stress induced by NI, the modulation of its extracellular concentration leads to a cytoprotective effect. Astrocytes are glial cells of the CNS expressing several adenosine receptors (A_1, A_{2A}, A_{2B} and A_3) and the adenosine kinase enzyme (ADK) which regulates the cellular concentration of adenosine[2]. Adenosine receptors or ADK could thus be used as biomarkers to help elucidate their role in NI *in vivo* with positron emission tomography (PET) imaging.

ABT-702 (Figure 1) is a potent non-nucleoside adenosine kinase ligand with an IC_{50} of 1.7 nM and the ability to go through the BBB[3]. While isotopic labeling is not possible, various positions for introducing fluorine-18 or carbon-11 have been considered (Figure 1). Three cold references as well as two labeling precursors, one for carbon-11 labelling and one for fluorine-18 labelling, have been synthesized. The determination of affinity of the methylated and fluorinated analogues of ABT-702 for ADK are ongoing at the University of Bonn (Pr. Christa Muller lab). In parallel, labelling of [^{11}C]-1 has been implemented on a radiosynthesis automate and biological evaluations of this first radioligand are currently underway.

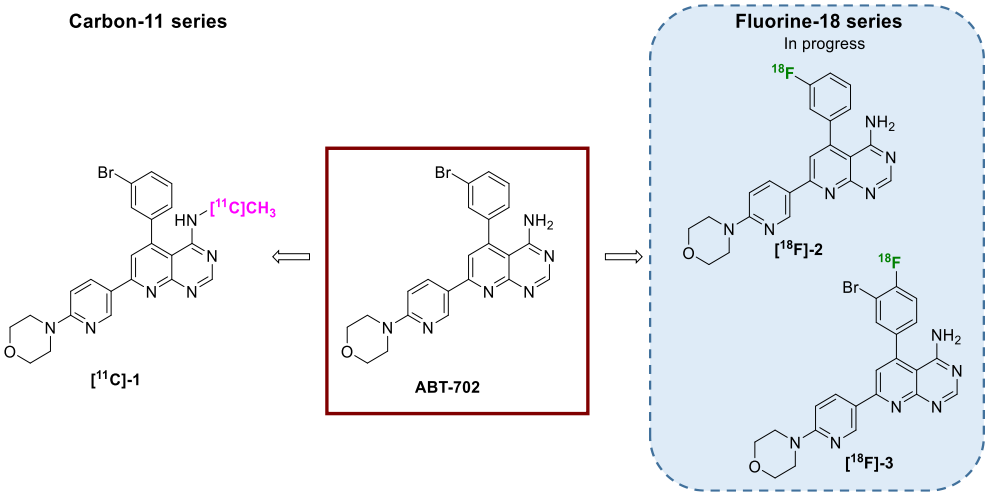

Figure 1. ABT-702 and design of radiotracers labelled with carbon-11 and fluorine-18.

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Development of radiofluorination of metal porphyrin platforms for PET imaging and photodynamic therapy

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Due to its physico-chemical properties, fluorine-18 is the radionuclide of choice to design radiopharmaceuticals for positron emission tomography (PET). As a consequence, many major radiopharmaceuticals are radiolabeled with fluorine-18 (*e.g.* [^{18}F]FDG, [^{18}F]Fluorocholine). In this context, molecular platforms such as porphyrins may be interesting to radiolabel with fluorine-18 for a theranostic approach combining PET and photodynamic therapy (PDT). We first synthesized porphyrins efficiently through the Rothemund reaction (chemical yield = 10% for the tetraphenylporphyrin (TPP(H2)). Then, an aluminium-based metalation of the porphyrins was performed to synthesize the tetraphenylporphyrin aluminium chloride (TPP(AlCl)), with a good chemical yield (*e.g.* 85%), to subsequently generate a strong fluoride-aluminium bond with a view to radiolabeling with fluorine-18. Initially, the labeling was carried out using K[^{19}F]F/K_{222} to fully characterize (NMR, HRMS, HPLC, UV) the "cold" version of our future radiolabeled compound, the tetraphenylporphyrin aluminium fluoride (TPP(Al[^{19}F]F)), with a chemical yield of 27% with 1 equivalent of K[^{19}F]F. Then, the porphyrins were radiofluorinated by transhalogenation on their metal center. ITLCs showed a good radiochemical yield (RCY = 92%) depending on the reaction solvent (DMSO, 10 min), under stirring. Finally, semi-preparative HPLC made it possible to isolate the radiofluorinated porphyrins (TPP(Al[^{18}F]F)). These results open up the possibility of using radiofluorinated porphyrin compounds to exploit their intrinsic therapeutic properties (PDT) to design new theranostic building blocks for PET that can be conjugated to *ad hoc* vectors (*e.g.* peptides, nanoparticles).

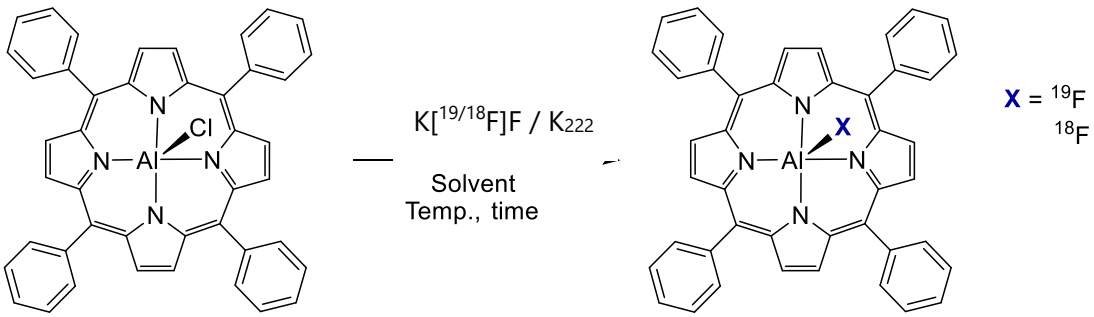

Figure 1. Synthesis of TPP(Al[$^{18/19}$F]F).

Electrophilic cyanation for the carbon-11 isotopic radiolabeling of the nitrile function

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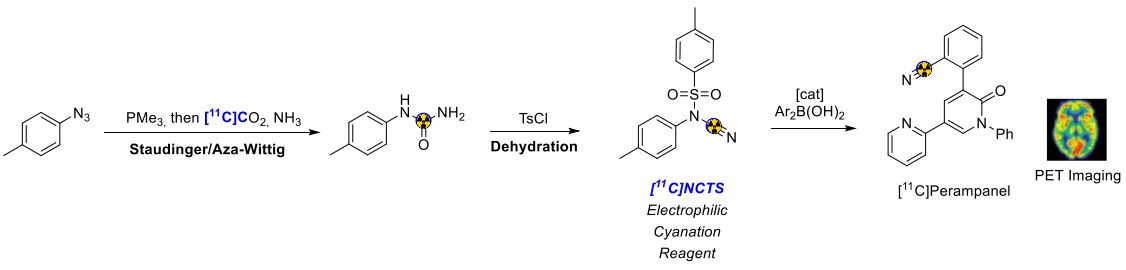
In the field of Positron Emission Tomography molecular imaging, the production of radiotracers represents both a significant challenge in terms of innovation, scientific and technological obstacle to overcome. Isotopic labeling using carbon-11 plays a key role, as it allows for the transformation of a drug or pharmaceutical molecule into radiotracers, effectively leveraging their pharmacokinetic properties while minimizing the risks associated with their development.[1]

However, it is important to note that carbon-11 labeling methods remain currently very limited.[2] The nitrile function, present in a large majority of molecules of interest, provides a striking example of the gaps and challenges we face.[3] Currently, over 95% of existing methods use methylation reactions for carbon-11 labeling. Examples of cyanation using K[^{11}C]CN, the main reactant to introduce a nitrile function, are rare in the literature mainly due to their complexity and intrinsically difficult automatable process.[4]

Given the highlighted concerns, the need to develop more easily implementable methodologies appears essential. In this study, we report a synthesis of ^{11}C-Ureas making use of a Staudinger/Aza-Wittig (SAW) sequence that enable the addition of cyclotron-produced [^{11}C]CO_2 to form a radiolabeled urea with excellent conversions after 30 seconds. Its dehydration allowed us to obtain for the first time [^{11}C]NCTS, an electrophilic source of cyanide. Ongoing experiments are being conducted in order to study the very last step of the reaction: ^{11}C-Cyanation of boronic acids and its feasibility for pharmaceutically relevant compounds.



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Radiosynthesis and use of [^{11}C]phosgene

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Despite the effectiveness of [^{11}C]phosgene ([^{11}C]$COCl_2$) as a ^{11}C-labelling synthon for connecting two heteroatoms using a carbonyl moiety, its broader use has been hindered by poor reproducibility of current synthesis methods. A simpler method of preparing [^{11}C]phosgene for ^{11}C-radiolabelling with good reproducibility has been developed.

Reduction of cyclotron-produced [^{11}C]CO_2 was achieved using a fluoride-activated disilane species (1,2-diphenyltetramethyldisilane and TBAF in THF) as previously reported.[1] The resulting gas mixture was passed through an Ascarite(II) trap to remove any unreacted [^{11}C]CO_2 and purified by gas chromatography. [^{11}C]CO was trapped in a silica-filled stainless steel loop cooled in liquid nitrogen, warming the trap to room temperature released the [^{11}C]CO which was transferred to the illumination chamber using 10% Cl_2 gas in Ne (3.5 bar). The gas mixture was illuminated with 254nm light to promote the reaction between [^{11}C]CO and Cl_2 (Figure 1).

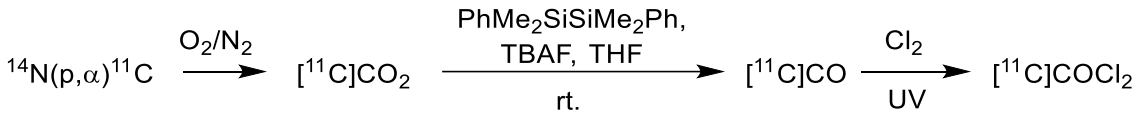

Figure 1. Synthesis of [^{11}C]phosgene.

Due to the high reactivity of [^{11}C]$COCl_2$, [^{11}C]diphenylurea was labelled as a model molecule to allow analysis of the reaction products. For this, the gas mixture containing [^{11}C]$COCl_2$ was passed through an Sb-trap (to remove unreacted Cl_2) and bubbled into a mixture of aniline in DME to produce [^{11}C]diphenylurea. A similar reaction procedure using the appropriate precursor was employed in the synthesis of [^{11}C]thymine.

[^{11}C]$COCl_2$ has been successfully produced and used to synthesise [^{11}C]diphenylurea and [^{11}C]thymine with radiochemical conversions of 89±6% and 18±3% respectively.

This novel method for the production of [^{11}C]$COCl_2$ is fast and reproducible. The use of [^{11}C]$COCl_2$ in labelling of other biologically interesting compounds is currently being studied.

Acknowledgements: Funding was received from the Academy of Finland, grant number 332128.

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Isotopic radiolabelling of Emtricitabine with fluorine-18 for PET imaging of HIV-1 reservoirs

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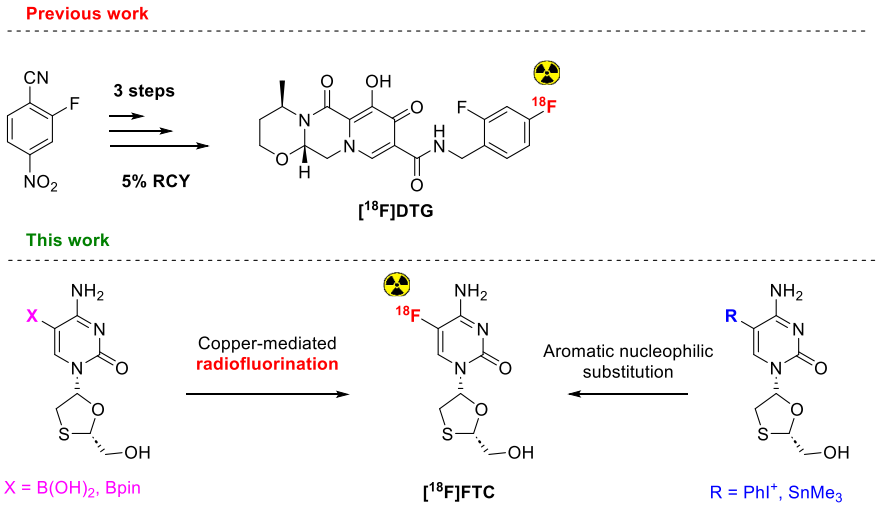
Increasing evidences are making remission an achievable goal for new anti-HIV therapies. Safer and more potent antiretroviral drug (ARD) combinations can significantly improve control of viremia and open the way for new strategies aiming at minimizing the viral reservoirs. Early control of these reservoirs together with the limitation of pharmacological sanctuaries where the exposure to ARD is suboptimal are among the key scientific challenges to address. New in vivo imaging technologies may be of considerable help to tackle with anti-HIV therapy challenges. Positron emission tomography (PET) is the state-of-the-art molecular imaging technique to quantitatively assess kinetics of drugs diffusion and physiological changes at the whole-body scale in real time. As a result, PET imaging using isotopically labeled ARD with positron emitters is a powerful tool to decipher the drug/virus/host interactions at viral rreservoirs. The ARD combinaison is composed of tenofovir (TFV), emtricitabine (FTC) and dolutegravir (DTG). If we previously reported the radiofluorination of DTG with fluorine-18[1], we are currently investigating the radiofluorination ofFTC[2], a nucleosidic reverse transcriptase inhibitor (NRTI) which is composed of an oxathiolane cycle miming the ribose moiety linked to a fluorocytosine core. Considering the presence of a fluorine atom on the heterocycle, we envisaged an isotopic labeling approach to obtain the [^{18}F]FTC. For that matter, we have imagined two different strategies relying either on a copper-mediated radiofluorination from a boronic ester or a trialkyltin precursor or an aromatic nucleophilic substitution from a nitro derivative. Precursors syntheses and radiofluorination optimization are ongoing.



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Difference between Lu-PSMA 617 and Lu-PSMA I&T: a single-french-center experience after two years

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In France, ^{177}Lu-PSMA-617 has been available since December 2021 under the French Early Access Program in patients with metastatic Castration Resistant Prostate Cancer (mCRPC) previously treated with at least one androgen-receptor-pathway inhibitor (ARPI) and one or two taxane regimens and who have PSMA-positive PET/CT.

^{177}Lu-PSMA I&T is also available in France but under an Experimental Drug File Access Program. It is also available for patients with mCRPC previously treated with at least one ARPI. However, on contrary to ^{177}Lu-PSMA-617, ^{177}Lu-PSMA I&T is available in chemotherapy-naïve patients. We present our two year experience in treating patients with mCRPC using ^{177}Lu-PSMA-617 or ^{177}Lu-PSMA I&T.

Between December 2021 and June 2024, 136 patients were referred to our unit for ^{177}Lu-PSMA-617 screening of which 78 received at least one ^{177}Lu-PSMA-617 infusion. All patients had PSMA PET positive lesions.

The Experimental Drug File for ^{177}Lu-PSMA I&T was written between March and May 2023. It was submitted to the authorities on the 13th of May 2023, additional information were asked for in June and July 2024 and accepted on the 7th of July 2023. Since July 2023, 5 patients were referred to our unit for ^{177}Lu-PSMA I&T of which 2 received at least one ^{177}Lu-PSMA I&T infusion. All patients referred for ^{177}Lu-PSMA I&T were contraindicated for chemotherapy because of pre-existing peripheral neuropathy due to amylosis (n=1) or multiple comorbidities (n=4). Reasons for not treating with ^{177}Lu-PSMA I&T were: major FDG positive/PSMA negative discordance (n=1), urinary and fecal incontinence (n=1) and absence of clear progressive disease (n=1). No toxicity was observed.

^{177}Lu-PSMA I&T is an alternative treatment in patients with mCRPC who present a contraindication to chemotherapy. It is also cost effective compared to ^{177}Lu-PSMA-617, and allows continuity of care in case of ^{177}Lu-PSMA-617 shortage.

A comparative study of [^{18}F]-DCFPyL PET/CT versus [^{18}F]fluoromethylcholine in Biochemical Recurrence of Prostate Cancer

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Primary objective of the study is to compare, in patients with first prostate cancer (PCa) biochemical recurrence (BCR), the per-patient detection rates (DR) of [^{18}F]DCFPyL versus [^{18}F]fluoromethylcholine.

A comparative study with randomized treatment administration of [^{18}F]DCFPyL (investigational medicinal product) or [^{18}F]fluoromethylcholine (comparator). Patient enrolled were men with rising prostate-specific antigen (PSA) after initial curative therapy.

A maximum time interval of 12 days has been observed between injection of the two radiopharmaceuticals. DR was defined as the percentage of positive PET/CT scans identified by 3 central imaging readers.

A total of 205 patients with first BCR after radical prostatectomy (73%; median PSA = 0.46 ng/ml [CI 0.16;27.0]) or radiation therapy (27%; median PSA = 4.23 ng/ml [CI 1.4;98.6]) underwent [^{18}F]DCFPyL- and/or [^{18}F]fluoromethylcholine-PET/CTs, between July and December 2020, at 22 European sites. 201 patients completed the study. The per-patient DR was significantly higher for [^{18}F]DCFPyL- compared to [^{18}F]fluoromethylcholine -PET/CTs (58% (117/201 patients) vs. 40% (81/201 patients), $p < 0.0001$). DR increased with higher PSA values for both tracers (PSA ≤ 0.5 ng/ml: 26/74 (35%) vs. 22/74 (30%); PSA 0.5 to ≤ 1.0 ng/ml: 17/31 (55%) vs. 10/31 (32%); PSA 1.01 to < 2.0 ng/ml: 13/19 (68%) vs. 6/19 (32%);PSA > 2.0: 50/57 (88%) vs. 39/57 (68%) for [^{18}F]DCFPyL- and [^{18}F]fluoromethylcholine -PET/CT, respectively). [^{18}F]DCFPyL PET/CT had an impact on PM in 44% (90/204) of patients versus 29% (58/202) for [^{18}F]fluoromethylcholine. Overall, no drug related, nor serious adverse events were observed.

The primary endpoint confirm higher detection rate for [^{18}F]DCFPyL compared to [^{18}F]fluoromethylcholine across a wide PSA range. [^{18}F]DCFPyL was safe and well tolerated.

Prospects of positronium imaging using scandium-labeled pharmaceuticals

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Positronium imaging is a newly invented method of imaging the properties of positronium in living organisms[1]. During positron emission tomography about 40% of positron annihilations occur through the creation of positronium[2]. Positronium, which may be formed in human tissues in the intramolecular spaces, is an exotic atom composed of an electron from tissue and the positron emitted by the radionuclide. Positronium decay in the patient's body is sensitive to the nanostructure and metabolism of human tissues[2]. This phenomenon is not used in present PET diagnostics, yet it is in principle possible to exploit such environment-modified properties of positronium as diagnostic biomarkers for cancer assessment.

In the talk the method of positronium imaging and the first-ever *ex-vivo*[1] and *in-vivo*[3] positronium images of patients obtained with the J-PET tomograph (the first portable PET system based on plastic scintillators capable of multi-photon imaging[4,5]) will be presented and explained. The first in-vivo positronium images were demonstrated using ^{68}Ga labeled pharmaceuticals[3]. The ^{68}Ga radionuclide was applied for positronium imaging because it can emit an additional prompt gamma. The prompt gamma enables the determination of the time of positronium formation, while the photons from positronium annihilation were used to reconstruct the place and time of its decay. However, ^{68}Ga isotope emits prompt gamma in only about one per cent of cases, and therefore much more suitable radionuclide for the positronium imaging would be ^{44}Sc which emits prompt gamma in 100% of cases. We will present perspectives of translating positronium imaging into clinics which may become possible with the application of ^{44}Sc labeled pharmaceuticals and the advent of high-sensitivity total-body PET systems[6,7].

Acknowledgments: We acknowledge support by NCN through grants 2021/42/A/ST2/00423, 2021/43/B/ST2/02150, 2022/47/I/NZ7/03112, the Ministry of Science and Higher Education through grants SPUB/SP/490528/2021, IAL/SP/596235/2023, and the SciMat and qLife Priority Research Areas budget under the program Excellence Initiative - Research University at the Jagiellonian University.

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POSTER PRESENTATIONS

P1 – **Lung Cancer and Hypoxia detection using Radiopharmaceuticals and Positron Emission Tomography: A systematic literature review**

Ahmad Alenezi, Department of Radiologic Sciences, Health Sciences Center of Kuwait University, Jabriya, Kuwait

P2 – **Advanced Separation Methods of Rare Earths and Cellular Microdosimetry of ^{161}Tb**

Alexander Krivokapic, Tracer Technology Department, Institute for Energy Technology (IFE), Kjeller, Norway

P3 – ***In vivo* SPECT imaging of Fibroblast Activation Protein as a non-invasive biomarker of anti-fibrotic efficacy of Gp96 inhibition in idiopathic pulmonary fibrosis**

Bertrand Collin, Centre George-François Leclerc, Service de Médecine Nucléaire, Plateforme IMATHERA (BIOSAND UMS INSERM 58), Dijon, France

P4 – **Investigation of theranostic potentials of Lu-177 labeled magnetic iron oxide nanoparticles and their derivatives**

Elif Tutun, Department of Nuclear Applications, Institute of Nuclear Sciences, Ege University, Izmir, Turkey

P5 – **Copper-catalyzed nucleophilic radioiodination of new prosthetic groups**

Ihab Shokair, NOMATEN Centre of Excellence, National Center for Nuclear Research, Otwock, Poland

P6 – **Nickel electrodeposition for Cu-64 production in a cyclotron**

Izabela Cieszykowska, Radioisotope Centre POLATOM, National Centre for Nuclear Research, Otwock, Poland

P7 – **^{18}F radiolabelled lipid-shell microbubbles for bimodal PET/US imaging: radiolabeling strategies and *in vivo* evaluation**

Julen Ariztia, Université Paris-Saclay, CEA, CNRS, Inserm, BioMaps, Orsay, France

P8 – **Advantages of using AI in combination with radiomics and genomics for breast cancer diagnosis**

Justyna Sykuła, Faculty of Chemistry, University of Warsaw, Warsaw, Poland

P9 – **Overcoming the *in vitro-in vivo* gap in preclinical radiopharmaceuticals evaluation with advanced *in vitro* models**

Kamil Wawrowicz, Department of Medical Physics, M. Smoluchowski Institute of Physics, Faculty of Physics, Astronomy and Applied Computer Science, Jagiellonian University, Kraków, Poland

P10 – **BNCT therapy targeting the tumor phenotype**

Karolina E. Wójciuk, Reactor Research Division, National Centre for Nuclear Research, Otwock, Poland

P11 – **Determination of radionuclidic impurities in the production process of ^{18}F labeled radiopharmaceuticals**

Krzysztof Kilian, Heavy ion Laboratory, University of Warsaw, Warszawa, Poland

P12 – **Investigation of Cu(II)-HMPAO complex as a model for the development of a potential ^{64}Cu radiopharmaceutical**

Marija Mirković, Laboratory for radioisotopes, „VINČA" Institute of Nuclear Sciences - National Institute of the Republic of Serbia, University of Belgrade, Belgrade, Serbia

P13 – **Release of ^{225}Ac and its first progeny from ^{225}Ac labeled Fe_3O_4@APTES nanoparticles**

Matěj Štíbr, Department of Nuclear Chemistry, Czech Technical University, Prague, Czech Republic

P14 – **Theranostic Micellar Nanocarrier for Imaging, targeted Radiosensitization and Internal Radioisotope Therapy**

Mathilde Ponchelle, NOMATEN Centre of Excellence, National Centre for Nuclear Research, Otwock, Poland; Université Paris-Saclay, CEA, INRAE, Department of Bioorganic Chemistry and Isotopic Labelling, Gif-sur-Yvette, France

P15 – **[^{68}Ga]Ga-PSMA-11 and [^{68}Ga]Ga-DOTATOC Preparations Obtained with Use of Cyclotron Produced Gallium-68 Isotope**

Marek Pilch-Kowalczyk, Centrum Produkcji Radiofarmaceutyków VOXEL S.A Cracow, Poland.

P16 – **Cyclotron Production of the theranostic pair Co-55 and Co-58m, their separation from the target and applications for β^+ - γ coincidence PET method**

Noman Razzaq, Institute of Nuclear Chemistry and Technology Warsaw, Poland

P17 – **Radioiodinated anti-HER2 monoclonal antibodies as potential therapeutic radiopharmaceuticals**

Sahar Nosrati, Centre of Radiochemistry and Nuclear Chemistry, Institute of Nuclear Chemistry and Technology, Warsaw, Poland

P18 – **The biodistribution and imaging studies: PEGylated superparamagnetic iron oxide nanoparticles labeled with ^{68}Ga as a PET/MRI contrast agent**

Sahar Nosrati, Centre of Radiochemistry and Nuclear Chemistry Institute of Nuclear Chemistry and Technology, Warsaw, Poland

P19 – **Development of a GMP-compliant synthesis of [^{18}F]AlF-NOTA-Folate on Trasis AllInOne**

Simo Salo, Turku PET Centre, University of Turku, Turku, Finland

P20 – **PSMA-Targeted radionuclide therapy enhanced by ultrasound-mediated microbubbles in a preclinical mouse model of human prostate cancer**

Sophie Tran, BioMaps, Laboratoire d'imagerie biomédicale multimodale, Université Paris-Saclay, CEA, CNRS UMR 9011, Inserm UMR 1281

P21 – **On the Development of Separation Methods for the Purification of ^{225}Ac**

Steffen Happel, TrisKem International, Bruz, France

P22 – **Electrochemical synthesis of Ni-based 2D MOFs**

Suvi Lamminmäki, Advanced materials for nuclear energy, VTT Technical Research Centre of Finland, Espoo, Finland

P23 – **Terbium-161 production and quality control**

Tereza Janská, Department of Nuclear Chemistry, Czech Technival University, Prague, Czech Republic

P24 – **Cyclone® 30 XP at CERAD, a variable-energy Cyclotron to produce a wide range of radioisotopes for medical application**

Tomasz Szyszko, Radioisotope Centre POLATOM, National Centre for Nuclear Research, Otwock, Poland

P25 – **POLATOM's perspectives and experiences in development of ^{225}Ac-radiopharmaceuticals**

Wioletta Wojdowska, National Centre for Nuclear Research Radioisotope Centre POLATOM, Otwock, Poland

P26 – **A criterion for BCC phase stability in cobalt-free refractory high entropy alloys for radiation environment**

Yulin Li, NOMATEN Centre of Excellence, National Centre for Nuclear Research, Otwock, Poland

P27 – **New Phase Transfer Agents for Fluorine-18 Radiolabeling**

Zélie Faudemer, Université Paris-Saclay, Inserm, CNRS, CEA, Laboratoire d'Imagerie Biomédicale Multimodale Paris-Saclay (BioMaps), Orsay, France

P28 – **Innovative radioimmunoconjugates for cancer therapy**

Zuzanna Napora, Faculty of Chemistry, University of Warsaw, Warsaw, Poland

P-29 – **Next-Generation Radiotheranostics: The Power of Luminescent Radiolanthanides for Modern Medicine**

Zajdel Karolina, NOMATEN Centre of Excellence, National Centre for Nuclear Research, Otwock, Poland; Institute of Physics, Polish Academy of Sciences, Warsaw, Poland

Lung Cancer and Hypoxia detection using Radiopharmaceuticals and Positron Emission Tomography: A systematic literature review

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Lung cancer (LC) remains a leading cause of cancer-related mortality, constituting nearly 11% of all cancer cases globally. Non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) are the primary histological types, with adenocarcinoma being the most common NSCLC subtype. Advances in molecular imaging, particularly Positron Emission Tomography (PET) and radiopharmaceutical s industry, have significantly enhanced the non-invasive evaluation of tumor pathophysiology, aiding in diagnosis, prognosis, and therapeutic response assessment.

This systematic review focuses on the use of hypoxia molecular imaging and corresponding radiopharmaceuticals with PET in understanding lung malignancies. Hypoxia, characterized by inadequate oxygen supply, leads to treatment resistance and poor prognosis in lung cancer. Various PET radiotracers, such as ^{18}F-FDG, ^{18}F-FMISO, and ^{18}F-FAZA, are utilized to detect hypoxic regions within tumors. These tracers have different mechanisms of uptake and binding, influenced by the hypoxic environment.

We conducted a comprehensive search of the PubMed® database for articles published between 2007 and 2023 using terms related to hypoxia, PET imaging, and lung cancer. From 730 articles identified, 90 were selected for detailed analysis. Additionally, a search for MRI-related articles yielded 58 relevant studies. The review categorizes PET radiotracers based on their targeting of specific cancer hallmarks such as metabolism, hypoxia, and proliferation.

Findings indicate that while ^{18}F-FDG is widely used for its ability to highlight high glucose uptake in cancer cells, its effectiveness in hypoxia imaging is debated. Other tracers like ^{18}F-FAZA and ^{18}F-FETNIM offer improved imaging of hypoxic regions due to better pharmacokinetics and hydrophilicity. The review underscores the need for further research to refine these imaging techniques, improve tracer specificity, and enhance the accuracy of hypoxia detection in lung cancer patients.

Advanced Separation Methods of Rare Earths and Cellular Microdosimetry of ^{161}Tb

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The development of radionuclides for the pharmaceutical industry is of paramount importance to provide combined diagnostics and therapeutics. IFE's Tracer Technology Department has since the 1980s developed tracer technology for various industrial applications. A part of the group's activity is the production of radionuclides and their chemical separation and purification. The European project "ELECTTRA" focuses on the research & development (R&D) of novel radiopharmaceuticals based on terbium-161 and novel vectors for targeted therapy of tumours. The advantage of Tb-161 is in the emission of large numbers of low energy electrons followed by gamma radiation allowing tomographic imaging and therapy follow-up.
A prototype automated system for purifying ^{161}Tb from gadolinium and dysprosium was assembled and a software for controlling was made in LabView. The setup consists of 3 CAVRO syringe pumps with 6 point or 9-point valves on the head, flow switches and ion exchange columns. Pictures of the setup is below.

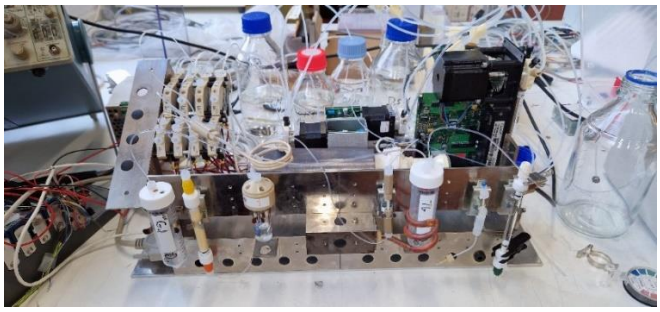

Figure 1. Automated prototype for purification and automated rare earth separation.

The cumulate dose to the cell nucleus has been calculated for single-layer and on 3D structures of tumor cells. The cumulate side dose to the healthy tissues has also been assessed and will be presented.

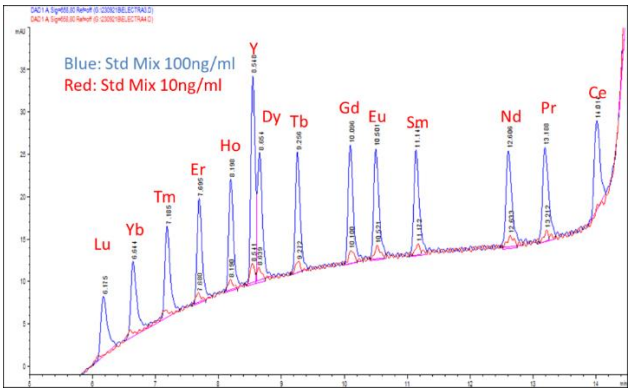

Figure 2. Lanthanide detection and separation at concentrations 100 and 10 ppb.

In vivo SPECT imaging of Fibroblast Activation Protein as a non-invasive biomarker of anti-fibrotic efficacy of Gp96 inhibition in idiopathic pulmonary fibrosis

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Idiopathic pulmonary fibrosis (IPF) is a progressive disease characterized by excessive production and deposition of extracellular matrix (ECM) driven by myofibroblasts expressing Fibroblast Activation Protein (FAP). Inhibition of Gp96, an endoplasmic reticulum chaperone protein overexpressed during fibrosis, may be an appealing target. So, we hypothesize that *in vivo* FAP imaging could enable the monitoring of the efficacy a GP96 inhibitor. C57BL/6 mice (male, 8 weeks old) received a single intratracheal administration of bleomycin (BLM, 1.5 mg/kg, n=14) or NaCl (n=14) as a control, then were treated or not with a Gp96 inhibitor (PU-WS13, 12.5 mg/kg, daily gavage, n=17)) or NaCl (n=16) from D8 to D22. Fibrosis was followed longitudinally by CT imaging at D8, D15 and D22. At D22, lungs and broncho-alveolar lavages (BALs) were recovered for collagen quantification, FAP immunostaining (IHC) and TGF-β1 assay (ELISA). *In vitro*, A549 cells stimulated with TGF-β1 (2 ng/mL, 24h) were treated or not with PU-WS13 (25/50 µM, 24h) to study FAP protein expression (WB) and protein-protein interactions between Gp96 and FAP (PLA). Then, a probe based on anti-FAP antibody fragments was designed for in vivo SPECT imaging ([^{111}In]In-DOTAGA-FAP). The probe was injected intravenously into C57BL/6 mice (100µL, 10MBq, 25µg) and mice underwent SPECT imaging at 1h, 4h and 24h post-injection. *In vitro*, PU-WS13 decreased the interaction between Gp96 and FAP inducing its degradation. *In vivo*, our results demonstrated that PU-WS13 decreased collagen accumulation, fibrous lesions on CT imaging, FAP and TGF-β1 expression induced by BLM. SPECT imaging showed a significant increase in [^{111}In]In-DOTAGA-FAP uptake in the lungs of control fibrotic mice when compared to the PU-WS13 treated group. Gp96 inhibition represents an innovative anti-fibrotic strategy. *In vivo* imaging of myofibroblasts *via* the FAP protein appears capable of monitoring the efficacy of this therapy in our animal model.

Investigation of theranostic potentials of Lu-177 labeled magnetic iron oxide nanoparticles and their derivatives

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Magnetic iron oxide nanoparticles (MNPs) have a great potential for cancer therapy and diagnosis, hyperthermia and magnetic resonance imaging (MRI) applications due to their unique properties such as ease of preparation, facile functionalization, chemical stability, superparamagnetism, and low toxicity[1,2]. This study aims to investigate a multifunctional magnetic nanoparticle radioconjugate which has properties as a magnetic agent for MRI and radiopharmaceutic for cancer treatment. For this purpose, MNPs were synthesized and coated with TEOS (tetraethyl orthosilicate) and PEG (polyethylene glycol). They were then conjugated with non-radioactive fluorodeoxyglucose ([^{19}F]FDG) and Trastuzumab (TmAb) to enhance their intracellular uptake and target specifity by addressing the HER2 receptor and radiolabeled with Lutetium-177 (^{177}Lu; [Eβ(max)= 760.497 MeV, $t_{1/2}$= 6.7 d) to provide a therapeutic potential for cancer treatment. [^{19}F]FDG, which is equivalent to ^{18}F, is actively transported into the cell by a group of related glucose transport proteins. Studies indicate that FDG-MNPs can be used to increase the tumor uptake[2,3,4]. Detailed size distributions, surface morphology and structure of multifunctional magnetic nanoparticles were supported by Transmission Electron Microscopy (TEM) and Scanning Electron Microscopy (SEM), Dynamic Light Scattering (DLS), and Fourier-Transform Infrared Spectroscopy (FTIR) analysis. The synthesized MNPs and FDG-MNPs were a uniform homogeneous cubic crystal structure around 30-40 nm and FDG-MNPs were 180 nm according to TEM images, respectively. The spinel phase of cubic iron oxide nanoparticles were confirmed by X-Ray Diffraction (XRD) analysis.

The labeling efficiency of the radiolabeled nanoconjugate was determined using Instant Thin Layer Chromatography (ITLC). Initially, TmAb was conjugated with p-NCS-Bz-DOTA-GA chelator and then radiolabeled with ^{177}Lu. After this radioconjugation is confirmed, FDG-MNP nanoparticles were conjugated to ^{177}Lu-DOTA-Tras compound. *In vitro* biological behavior of the nanoparticles will be determined with human ovarian adenocarcinoma cells (SKOV-3 cells; HER2 positive) and human breast adenocarcinoma cells (BT-474 cells; HER2 triple positive and MDA-MB231 cells; HER2 negative).

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Copper-catalyzed nucleophilic radioiodination of new prosthetic groups

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Over recent years, an effective copper-mediated radioiodination technique was developed for the convenient labelling of aromatic and heteroaromatic boron reagents with iodine[1-3]. The project aimed to use the copper-mediated iododeboronation technique to label two novel prosthetic groups with iodine-131 (Figure 1). Additionally, it sought to evaluate the effectiveness of various copper catalysts based on established protocols from previous studies[1-3].

Employing $Cu(py)_4(OTf)_2$ as the catalyst resulted in a high radiochemical yield of 87 ± 2% for compound A and 86 ± 9% for compound B, determined from radio-TLC analysis. When $Cu(OCOCF_3)_2$ was used, compounds A and B exhibited a comparable radiochemical yield of 70 ± 11% and 73 ± 12%, respectively. Attempts with Cu_2O as the catalyst were unsuccessful, as no desired products were detected via radio-TLC after the radioiodination.

The $Cu(py)_4(OTf)_2$ proved to be the most effective catalyst for achieving favourable outcomes in radiolabelling the two prosthetic groups. The next step will be the conjugation of the two radioiodinated prosthetic groups with biomolecules *via* disulfide rebridging.

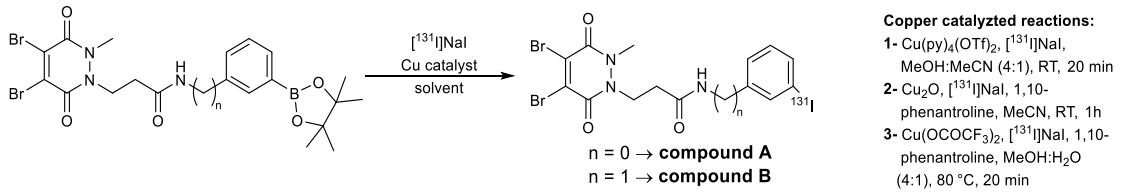

Figure 1. Labelled prosthetic groups

Acknowledgments: Research was funded through the European Union Horizon 2020 research and innovation program under Grant Agreement No. 857470 and from the European Regional Development Fund under the program of the Foundation for the Polish Science International Research Agenda PLUS, grant No. MAB Plus/2018/8, and the initiative of the Ministry of Science and higher Education 'Support for the activities of Centers of Excellence established in Poland under the Horizon 2020 program' under agreement No. MEiN/2023/DIR/3795.

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Nickel electrodeposition for Cu-64 production in a cyclotron

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Copper-64 (^{64}Cu) is a positron emitter utilized in PET diagnostics. In addition, it emits β^- particles, which can be useful for therapy. The ^{64}Ni(p,n)^{64}Cu nuclear reaction is suitable for ^{64}Cu production due to the large cross-section for the energy of protons, which can be easily reached in small biomedical cyclotrons. The target material used for irradiation in a cyclotron needs to be firmly bound on the support, which can be easily mounted in a target station because it is directly exposed to the irradiating particles under vacuum. This study aimed to optimize natural nickel electrodeposition on silver discs as a method of nickel target preparation for cyclotron irradiation.

Natural nickel stock solution with 50 mg ^{nat}Ni/ml concentration was prepared by dissolving nickel foil in concentrated hydrochloric acid and multiple evaporation and dissolution precipitates in water. An appropriate volume of stock solution was alkalized by ammonia to pH =11 to prepare the electrolyte solution. The electrolyte volume was 10 ml. Nickel was electrodeposited on one side of a silver disc (10 mm in diameter). Rotating Pt wire served as an anode. Electrodeposition was performed in galvanostatic mode at a current density of 16 to 110 mA/cm^2. The process was accomplished within 1–7 h. The thickness of the nickel layer was determined by the weight of the nickel deposit on the silver disc.

Depending on current density and electrodeposition time, the thickness of nickel layers fixed on the silver disc was from 44 to 138 µm. The most thick layers, 130 µm and 138 µm, with the highest uniformity, smooth, fine-grained, and indelible were obtained when the initial content of nickel in the electrolyte was 200 mg. This was confirmed by metallographic microscope analysis. For these samples, the current efficiency amounted to 93 - 94 %. Further work aiming to test the strength of electroplated nickel deposits is in progress.

Acknowledgements: This work was performed within the project SECURE funded by the European Union under grant agreement No. 101061230.

^{18}F radiolabelled lipid-shell microbubbles for bimodal PET/US imaging: radiolabeling strategies and *in vivo* evaluation

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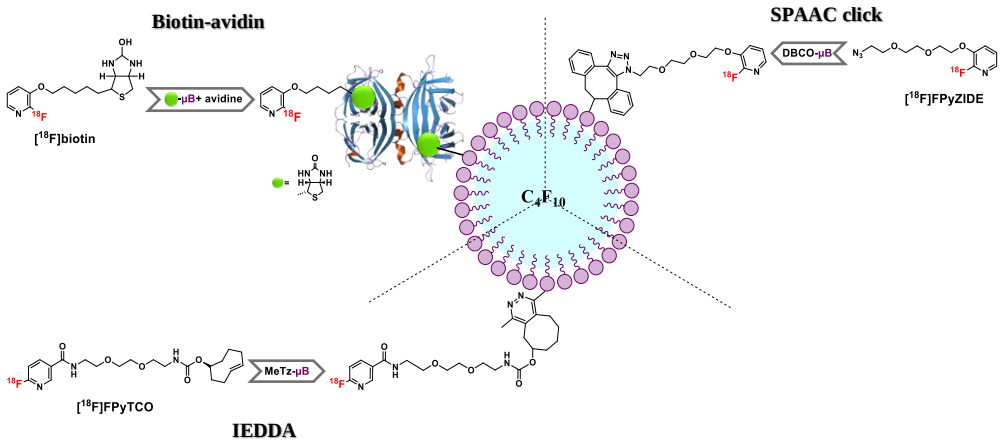
Positron Emission Tomography (PET) is a gold standard method for molecular, metabolic and quantitative imaging of relevant biomarkers.[1] Ultrasound (US) is a real-time imaging modality for anatomical and functional imaging. Their combination will allow studying the microbubble biodistribution and quantification. Additionally, the controlled cavitation of microbubble can be used to enhance radiopharmaceutical delivery in tissues.[2,3] To leverage the best profit of both modalities, lipid-shell microbubbles (µB) have been radiolabeled with fluorine-18.

Three approaches were studied for this propose: avidin-biotin coupling strategy[4] and two different click chemistry strategies (SPAAC and IEDDA).The different radiolabelling precursors and cold references have been synthetized and the fluorine-18 radiolabelling has been fully automated in a Trasis® All In One synthesizer. Lipid-shell-biotinylated microbubbles were successfully radiofluorinated with [^{18}F]biotine using avidin-biotin strategy (96% yield). The SPAAC reaction was optimized using DBCO-liposomes and [^{18}F]FPyZIDE tracer, an azide containing reagent amenable to react with strained cyclocotynes.[5] Then, the optimized conditions allowed us to obtain the ^{18}F-DBCO-µB with good yields (over 97%). For the IEEDA radiolabeling strategy, the [^{18}F]FPyTCO, a tracer containing the trans-cyclooctene moiety needed for the IEDDA reaction with tetrazine (Tz), was successfully obtained and the click reaction with the MeTz-µB was tested. Finally, in order to study the biodistribution of these PET/US dual tools, the simultaneous PET/US imaging was performed on healthy mice using the ^{18}F-avidin-µB.



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Advantages of using AI in combination with radiomics and genomics for breast cancer diagnosis

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Traditional therapies for breast cancer include surgery, chemotherapy, radiotherapy, and hormone therapy. Breast cancer shows great heterogeneity, and it can occur both between patients and for a single tumor. Therefore, each patient needs an individually tailored treatment method. Treatment decisions and prognosis in breast cancer are traditionally based on factors such as tumor size, lymph node involvement, tumor grade, hormone receptor status, and HER2 status. These data are obtained through medical imaging and a biopsy. Unfortunately, the biopsy only provides information based on a single sample and, due to the heterogeneity of the tumor, does not reflect its complete characteristics, which can lead to the selection of the wrong treatment[1].

A new approach and solution to the problem that has been presented is the use of a new method for prognosis: radiogenomics. It is a composite of the two fields of radiomics and genomics. Radiomics is a quantitative approach to medical imaging that aims to enhance existing data available to clinicians through advanced mathematical analysis using artificial intelligence. Genomics refers to the complete set of genes or genetic material present in an organism. Genomic features include risk genes, gene signatures, and biological pathway activities extracted from mRNA expression profiles of breast cancer patients. Radiogenomics explores the relationship between radiological features and genetic traits to construct predictive models of tumor evolution[2]. These models can help clinicians make more informed decisions regarding treatment plans and monitoring strategies for cancer patients. By identifying specific genetic markers associated with certain radiological features, radiogenomics aims to personalize medicine and improve patient outcomes. AI in radiology utilizes computational algorithms to handle large amounts of patient data for tasks like image reconstruction, feature extraction, and cancer analysis. Machine learning, a subset of AI, is used for classification, regression, and clustering based on learning[3]. Deep learning techniques, subsets of machine learning, are being utilized to extract high-order radiomic features from MRI and CT images, enabling more efficient capture of tumor heterogeneity. Extracted images have shown a significant association with the molecular profiles of breast cancer. The integration of genomics and radiomics entail putting genetic information from high-throughput sequencing, clinical epidemiological data, and radiomic features from digital medical images into mathematical models[4].

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Overcoming the *in vitro-in vivo* gap in preclinical radiopharmaceuticals evaluation with advanced *in vitro* models

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Currently available 2D and 3D *in vitro* models differs significantly from *in vivo* cancer tissues regarding the morphology and physiology, especially tumor microenvironment (TME). Mechanism of action of therapeutic radiopharmaceuticals makes them critically sensitive to limitations of biological models adequateness, as cell density at preclinically used systems does not reflect tissue-like conditions. This *in vitro-in vivo* gap corresponds to challenges in reliable evaluation of drug candidates, hindering the progress in the field. Therefore, with this research we aimed to investigate the prospect to obtain advanced *in vitro* cancer model that could more closely assemble real tissues for radiopharmaceuticals assessment.

Primary (FM55p) and metastatic (WM266-4) melanoma tumorspheres were cultured in bioreactor and characterized at various cellular levels revealing meaningful benefits over traditional cell cultures. Month-long growth favoured unique (>2 mm) tumorspheres formation with improved morphology. Significant changes in TME and proteins expression confirmed higher sophistication level of tumorspheres, thus highlighting numerous physiological changes induced within tested approach. Hence, an interesting perspectives for further development of such strategy aimed for advanced biological models implementation for preclinical research were revealed.

Acknowledgments: This work was supported by the National Science Centre of Poland through grant no. 2022/47/I/NZ7/03112 to E.Ł.S., the Jagiellonian University via projects CRP/0641.221.2020, SciMat and qLife Priority Research Areas budget under the program Excellence Initiative - Research University. The study was founded by “Laboratories of the Young” as part of the “Excellence Initiative – Research University” program at the Jagiellonian University in Krakow (U1U/W17/NO/17 (K.W.)).

BNCT therapy targeting the tumor phenotype

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Boron Neutron Capture Therapy is a bimodal therapy - a compound containing the stable 10-B isotope is introduced into cancer cells and then treated with neutron radiation. As a result of the decay reaction, among others, an alpha particle whose task is to damage DNA or the cell membrane. These reactions lead to cell death. However, for this method to apply to cancers, including disseminated or micrometastases, the boron compound must be targeted to the tumor phenotype (the concept of radiopharmaceutical synthesis was used).

The research was looking for a compound with many boron atoms that would undergo a conjugation reaction with a peptide, and this bond would be more stable than its clinically used counterpart. This research aims to characterize a new carrier for clusters of boron-10 with sauvagine analog. Sauvagine binds to the CRF type2a receptor located on pituitary adenomas, pancreatic tumors, central nervous system tumors, prostate, breast and colon cancers.

In this work, there were used several chemical and biological methods to study trimethylammonium 1-mercapto-1-carbadodecarnorate(TMA), triethlammonium decahydrodecaborate(TEA) and BSH(mercaptododecaborate dianion) compounds, including durability in serum, lipophilicity, receptor affinities, toxicity, IC_{50} and apoptotic pathway. Two cell cultures were used: colon cancer cells HCT116 and healthy colon cells CCD841, and the above-mentioned boron compounds. Triplex assay was used to assess viability, cytotoxicity and apoptotic progression.

Both compounds do not differ significantly in biochemical properties and cellular response tests. An initial coupling reaction of TMA with neurotransmitter protein was carried out, but the attempt was unsuccessful.

Acknowledgements: Our research team would like to thank the Institute of Nuclear Chemistry and Technology in Warsaw for the HPLC and ICPMS measurements.
The project is financed by the National Science Center (R. No. 2018/02/X/NZ7/03011).

Determination of radionuclidic impurities in the production process of ^{18}F labeled radiopharmaceuticals

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The main purpose of the work was to identify and quantify the radionuclidic impurities in the production of ^{18}F for the production of [^{18}F]fluorodeoxyglucose (FDG) and [^{18}F]fluorocholine (FCH) and safety assessment of the final product.

The identification of isotopes in the samples was based on gamma spectroscopy. The measurements were carried out using a germanium (HPGe) detector model Canberra BE2825. The detector was connected to the computer through the Ortec 672 amplifier and converter analog-digital. The Tukan8k multi-channel analyzer was used for data acquisition and analysis. For analysis parts of the [^{18}F]FDG and [^{18}F]FCH synthesis kits, as well as recovered water, production waste, and finished products were taken.

Total activity from identified radionuclide contaminants throughout the production process, the ^{18}F was 139 ± 15 kBq at the end of bombardment (EOB). This is about 0.0001% of the activity of ^{18}F EOB. The dominant isotopes were ^{52}Mn and ^{56}Co. The lowest activity of radionuclidic impurities was determined in the final product. The average sum of impurity activities in the samples of the final [^{18}F]FDG product was 35.0 ± 7.9 Bq. More than 99% of the total activity of radionuclide impurities is found in the QMA column and the recovery water and does not go to the next stages of the synthesis of the radiopharmaceutical. The average sum of impurity activities in the samples of the final [^{18}F]FCH product was 18.1±2.8 Bq. This value is 10^{-10} of the activity of the ^{18}F radionuclide at the end of irradiation.

Activity derived from radionuclidic impurities in the final product [^{18}F]FDG and [^{18}F]FCH account for 10^{-7}% of the activity of the ^{18}F EOB radioisotope. This is a significantly lower than the maximum permissible activity of radionuclide impurities (0.1%) specified in the European Pharmacopoeia. Thus, both products meet the legal requirements for radionuclidic purity, and radionuclide impurities found in products do not jeopardize patient safety. Contaminants identified in the recovered water had the highest activity both for the production process of [^{18}F]FDG and for the synthesis of [^{18}F]FCH. Slightly lower was the activity of impurities in the QMA columns. The total activity of impurities in remaining stages of the synthesis of both products was an order of magnitude lower. That is, the purification process on the QMA column is crucial for removing impurities at the initial stage of the synthesis and determining the proper quality of the final product.

Investigation of Cu(II)-HMPAO complex as a model for the development of a potential ^{64}Cu radiopharmaceutical

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Taking into account the biological characteristics of Cu(II) complexes and the properties of hexamethylpropylene amine oxime (HMPAO) ligand used in nuclear medicine, we synthesized a Cu(II) complex featuring the meso-HMPAO ligand. This was done as a model to explore the potential development of a radiopharmaceutical utilizing ^{64}Cu.

The synthesis of the Cu(II)-HMPAO complex follows a procedure, wherein the metal precursor, copper(II) acetate monohydrate, is dissolved in MeOH and reacts with a hot MeOH ligand suspension in a 1:1 molar ratio. The complex's structure was analyzed using FTIR, cyclic voltammetry, and X-ray technique. Additionally, we explored the interactions of the synthesized metal complex with deoxyribonucleic acid (DNA) and human serum albumin (HSA).

Isolated copper complex with meso-HMPAO ligand was air-stable, partially soluble in water and EtOH, soluble in polar (DMSO, MeOH, and CH_3CN) but insoluble in nonpolar solvents (toluene and benzene). From the characterization methods, HMPAO has been shown to act as a tetradentate ligand that coordinates through the nitrogen atoms of the oxime and amine groups. The results of cyclic voltammetry of copper(II) acetate monohydrate, meso-HMPAO, and Cu(II)-HMPAO complex show that the formation of the complex strongly affects the redox behavior of the electroactive groups. The electrochemical analysis confirmed the binding between the complex and DNA molecule. The fluorescence titration experiments revealed a moderate binding affinity of the [Cu-HMPAO]ClO_4 complex to HAS.

Cu(II) complex with meso-HMPAO ligand was successfully synthesized and characterized. The binding affinity of the complexes was confirmed in their interaction with DNA and HAS. The experimental findings provide compelling reasons to explore this complex further, either for its potential as an anticancer agent or for its utility in nuclear medicine as a ^{64}Cu radiopharmaceutical.

Release of ^{225}Ac and its first progeny from ^{225}Ac labeled Fe_3O_4@APTES nanoparticles

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One of the promising radionuclides for alpha therapy is ^{225}Ac. It decays with a half-life of 9.9 days to stable ^{209}Bi, releasing four α particles and two β^- particles. The alpha particles primarily contribute to the therapeutic effect due to their high energy and short range in tissue. Owing to their large surface area and the potential for surface modification, nanoparticles are a promising candidate for the targeted transport of ^{225}Ac.

In this work, volume labeled Fe_3O_4 nanoparticles were prepared *via* coprecipitation of Fe^{3+} and Fe^{2+} solution with added ^{225}Ac stock solution. Subsequently, labeled nanoparticles were treated with (3-aminopropyl)triethoxysilane (APTES) to yield core-shell nanoparticles with amino group surface modification. *In vitro* studies of labeled nanoparticles were conducted in saline, bovine plasma, and bovine serum at 37 °C over the course of 3 days. At specified time intervals, the nanoparticles were separated using a magnet, and an aliquot of the medium was subsequently withdrawn and measured using an HPGe detector.

These experiments were conducted in preparation for future *in vitro* cell experiments with an immunoactive antibody-nanoparticle conjugate. In saline, less than 1 % release of ^{225}Ac and less than 76 % release of its first progeny ^{221}Fr were observed over 3 days. In bovine plasma and bovine serum, less than 15 % release of ^{225}Ac was observed. Similar to the case of saline, less than 76 % release of ^{221}Fr was observed.

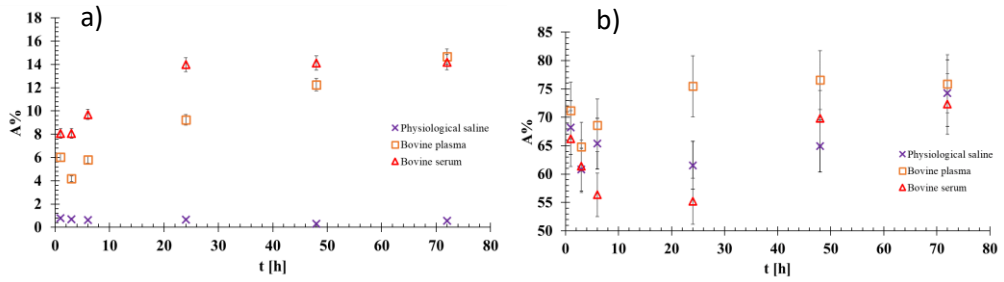

Figure 1. Total released activity of a) ^{225}Ac and b) ^{221}Fr from labeled Fe_3O_4@APTES nanoparticles over 72 hours.

Acknowledgments: This work was supported by the projects “Efficient Low-Energy Electron Cancer Therapy with Terbium-161” granted by the Norway and Technology Agency of the Czech Republic within the KAPPA Programme (grant No.: TO01000074) and “Development of terbium-161-labelled biomolecules as theranostic tools in nuclear medicine” granted by the Agency for Medical Research of the Czech Republic (grant No.: NU23-08-00214).

Theranostic micellar nanocarriers for imaging, targeted radiosensitization, and internal radioisotope therapy

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Internal radioisotope therapy is one of the most widely used methods for treating cancer. However, its success may be limited due to various factors and one of them is hypoxia, i.e. reduced oxygen level in tumour tissue. To counteract this problem, selective tissue re-oxygenation can potentiate the effect of irradiation by increasing the quantity of reactive oxygen species. Another challenge in radiotherapy is to increase the accumulation of the maximum dose in tumour while reducing damage to normal tissue. Therefore, we have designed a micellar nanocarrier combining re-oxygenation properties from a perfluorinated core and dose potentiation from ^{177}Lu, complexed by attached to micelles DOTA-chelator, thanks to encapsulated gold nanoparticles.

Micelles are composed of two amphiphilic units, which are made from the same C_{14} perfluorinated chain. The main amphiphilic unit is composed of a pegylated chain for stabilisation and stealthiness of the nanoparticle. The second amphiphilic unit contains a DOTA group which is able to complex ^{177}Lu after incubation at 80°C, followed by purification *via* size exclusion chromatography. A mixture of those amphiphiles is sonicated in water to produce 10 nm micelles. Gold nanoparticles can be encapsulated in the micelles to produce a nanohybrid system about 15 nm size. Thus, formed nanocarriers, with or without encapsulated Au-NPs, were tested for their toxicity on SK-BR-3 cells by using MTS assay.

The non-radiolabelled alone micelles showed no harmful effects on SK-BR-3 cells, although those with encapsulated Au-NPs slightly decreased cells viability. The preliminary results with ^{177}Lu-radiolabelled micelles seems to show expected toxicity from the ^{177}Lu and a synergistic effect between the radioisotope and the gold nanoparticle.

Preliminary study with both radioactive and non-radioactive micelles seems to confirm the synergistic effect between gold nanoparticle and internal addition of a radioisotope. More detailed *in vitro* toxicity studies will be done followed by planned *in vivo* biodistribution and therapeutic efficacy evaluation.

Acknowledgments: We acknowledge support from the European Union Horizon 2020 research and innovation program under grant agreement no. 857470 and from the European Regional Development Fund *via* the Foundation for Polish Science International Research Agenda PLUS program grant No. MAB PLUS/2018/8, and the initiative of the Ministry of Science and Higher Education 'Support for the activities of Centers of Excellence established in Poland under the Horizon 2020 program' under agreement No. MEiN/2023/DIR/3795. This work is also supported by the "ADI 2022" project funded by the IDEX Paris-Saclay, ANR-11-IDEX-0003-02".

[^{68}Ga]Ga-PSMA-11 and [^{68}Ga]Ga-DOTATOC preparations obtained with use of cyclotron produced gallium-68 isotope

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Currently the ^{68}Ga isotope comes mainly from the ^{68}Ge/^{68}Ga generators for Nuclear Medicine facilities which do not have a cyclotron in place. The demand for this isotope is strongly growing, which caused shortages on generator market. The kits for radiopharmaceutical preparations intended for imaging prostate cancer and neuroendocrine tumors are targeting the prostate-specific membrane antigen (PSMA) and somatostatin receptors (SSTR) respectively. The kits then can be labeled with lutetium-177 and yttrium-90 for theranostic purposes. The main drawbacks of ^{68}Ge/^{68}Ga generators are: high purchase cost, decreasing activity during lifespan, low activity of the obtained isotope, low availability on the market and the need to keep a break between successive elutions. There is intensive work on the gallium 68 isotope of medical cyclotron origin obtained by proton irradiation of zinc-68. The latest registrations of precursors for radiolabelling include: 2021 Galliuc (marketing authorization holder University of Coimbra, Portugal) and 2023 V-Ga68 (marketing authorization holder VOXEL S.A., Poland).

This work presents results of comparative study of [^{68}Ga]Ga-PSMA-11 and [^{68}Ga]Ga-DOTATOC preparations obtained with use of gallium-68 isotope of generator and cyclotron origin. The cyclotron gallium-68 chloride was obtained via a solid target at the VOXEL Radiopharmaceuticals Production Center in Kraków, and its quality is compliant with the Ph. Eur. 3109 monograph and Good Manufacturing Practice (GMP). The method used allows to produce of several vials of gallium-68 chloride from one batch that can be delivered to several end users, and may be an attractive alternative to ^{68}Ge/^{68}Ga generators, thus increasing the availability of the gallium-68 isotope.

The QC results and biodistribution study proved equivalence of gallium-68 isotope of generator and cyclotron origin for currently available radiopharmaceutical kits.

Cyclotron Production of the theranostic pair Co-55 and Co-58m, their separation from the target and applications for β^+ - γ coincidence PET method

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Cobalt-55 ($t_{1/2}$ = 17.53h) as a β^+ emitter (β^+ = 77% E_{max} = 1498KeV) is a promising radionuclide for Positron Emission Tomography (PET). Moreover ^{55}Co emits also high energy and intensity gamma line (477.2 keV) which makes it the perfect candidate β+ γ coincidence PET technique. Thanks for this correlation it is also possible to imaging positronium which is a bound state of positron and electron produced in intra-molecular voids during the Positronium Emission Tomography.
Co-58m on the other hand emits Auger electrons as a result of internal conversion decay ($t_{1/2}$ = 9.10 h, 100% IC) and as such can be used for production of therapeutical radiopharmaceuticals. Therefore, ^{55}Co and ^{58m}Co form a theranostic pair that is one of the most promising pair due to similar half-lives, identical chemical properties, compatibility with biomolecules such as DOTATATE and DOTATOC. Both of these radionuclide can be produced on low energy medical cyclotrons on metallic iron enriched targets.

$$^{54}Fe(d, n)^{55}Co, \ ^{58}Fe(p, n)^{58}Co^{1}$$

In the first stage of the project, the isolation of cobalt radionuclides from iron targets in two step procedure is carried out. After dissolution of irradiated target in 0.3M HCl target material solution is load on AG1x8 anion exchange resin. Cobalt is eluted from the resin with 10 ml of 4 M HCl and iron with 20 ml of 0.1 M HCl. After separation form iron cobalt solution is loaded on N, N, N', N'- tetrakis-2-ethylhexyldiglycolamide (DGA branched extraction resin) for the removal of coproduced radio manganese radionuclide. Numerous applications of Co-55 which include the lung cancer detection, the renal imaging and neuro-imaging especially the brain affected by ischemia stroke.

Acknowledgements: This project is financed from NCN, OPUS-22, 2021/43/B/ST2/02150 “Development of three-photon emitting radiotracers for positronium imaging”.[2]

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Radioiodinated anti-HER2 monoclonal antibodies as potential therapeutic radiopharmaceuticals

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Human epidermal growth factor receptor type 2 (HER2) is overexpressed in various cancers, resulting in aggressive phenotype with poor prognosis. Developed therapeutic monoclonal antibodies (mAbs) targeting HER2-receptor could be useful for Targeted Radionuclide Therapy (TRT). Iodine has several radionuclides suitable for SPECT (^{123}I) or PET (^{124}I) imaging and radiotherapy (^{123}I, ^{125}I, ^{131}I).

This study aimed to optimize radiolabeling conditions of anti-HER2 mAbs (trastuzumab and pertuzumab) with $^{125/131}$I, determine radiochemical purity of final products, binding affinity, specificity, internalization properties, confocal imaging, and cytotoxicity evaluations.

MAbs were radiolabeled with $^{125/131}$I *via* Iodogen and purified on SEC PD-10 columns. Biological properties were evaluated on the HER2-positive SKOV-3 cell line. Various doses of $^{125/131}$I-mAbs were used to determine the EC_{50} values.

Radiolabeling took *ca*. 10 min with a yield of 90-99% and radiochemical purity above 98%. The ^{125}/^{131}I-mAbs retained their high affinity and specificity towards HER2 receptor, as confirmed by significant binding to SKOV-3 cells and negligible binding to non-HER2-expressing cells. Both radiobioconjugates demonstrated internalization properties in specified time intervals. Confocal imaging microscopy confirmed the results of the internalization assay. In the MTS assay the cytotoxic effect was mediated by both the added radioactivity and incubation time. Moreover, in the 3-D cellular model, higher doses of ^{125}I indicated spheroid diameter reduction.

This study concludes that $^{125/131}$I-mAbs are promising radioconjugates for Auger TRT, showing particular effectiveness due to its high internalization and cytotoxic potential.

The biodistribution and imaging studies: PEGylated superparamagnetic iron oxide nanoparticles labeled with ^{68}Ga as a PET/MRI contrast agent

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PET has been designed as an imaging modality based on the emission of positrons from radioactive nuclei. This imaging modality possesses specific properties including high sensitivity, limited depth of penetration, and quantitative capabilities. However, it has some limitations such as a lack of anatomic details at the cellular and molecular levels and inadequate spatial resolution. Therefore, combining PET imaging with modalities like CT can provide characteristics such as non-invasiveness, improved quality for indicating and evaluating biological processes, the capability to produce quantitative images, and higher sensitivity and appropriate spatial resolution.

In this experiment, we designed ^{68}Ga-labeled superparamagnetic iron oxide nanoparticles (SPIONs) that can be used in PET/CT or PET/MRI imaging for the detection of liver and spleen malignancies. This study aimed to determine the potential of ^{68}Ga-PEG-SPION as a contrast agent for the detection of liver and spleen malignancies.

Polyethylene glycol (PEG) coated SPIONs were radiolabeled according to a previous study. Briefly, a $^{68}GaCl_3$ solution was used for the radiolabeling process. The activity was 40-80 MBq in 50 µL (42.5 MBq). 200 µL of SPION was diluted in 800 µL of normal saline. The radiolabeling procedure involved adding the final SPION solution and 42.5 MBq of 68Ga-chloride (in 0.6 M HCl and 0.6 M HEPES). The mixture was left at room temperature (RT) for 30 minutes. After the radiolabeling process, the radiolabeled SPIONs were purified using an LS–MACS column (magnetic-activated cell sorting column) and a strong magnetic field. Quality control (QC), radiolabeling yield, particle characterization, biodistribution of 68Ga–SPIONs in normal mice, and PET imaging studies were performed.

Radiolabeling took approximately 30 minutes with a yield of 66.25% before purification and above 98% after purification. The hydrodynamic size of radiolabeled PEGylated SPIONs was 85 nm. Animal studies demonstrated that radiolabeled SPIONs accumulated in the liver and spleen. PET-CT imaging confirmed the animal study results, showing a predominant accumulation of radiolabeled SPIONs in the liver and spleen.

This study shows that ^{68}Ga–PEG-SPIONs have great potential for application in PET-MRI as a diagnostic agent for the detection of liver and spleen malignancies.

Development of a GMP-compliant synthesis of [^{18}F]AlF-NOTA-Folate on Trasis AllInOne

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[^{18}F]AlF-NOTA-Folate is a promising tracer for imaging inflammation[1] and cancer[2]. Because of the encouraging results in pre-clinical studies, there is demand for a GMP-compliant synthesis method in our centre. Due to the ease of development and our prior expertise with cassette based syntheses, we decided to develop the synthesis for the Trasis AllInOne synthesis device.

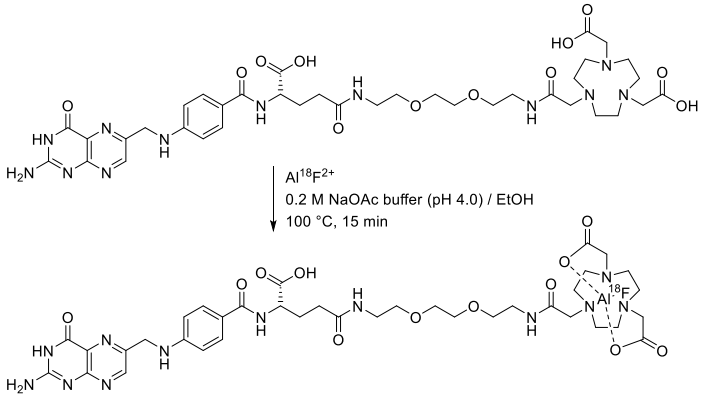

Figure 2. Synthesis of [^{18}F]AlF-NOTA-Folate.

[^{18}F]AlF-NOTA-folate was synthesised according to figure 1. First, aqueous [^{18}F]fluoride was trapped on a QMA cartridge, and eluted to the reaction vial with a solution consisting 300 µL 0.2 M NaOAc buffer (pH 4) and 1000 µL of EtOH. 500 µL of Aluminium lactate solution (0.2 mM in NaOAc buffer and EtOH) was added to form [^{18}F]AlF in 3 minutes at room temperature. After [^{18}F]AlF formation, 250 µg of NOTA-folate in 500 µL of 0.2 M NaOAc buffer was added. Thus, the reaction solution consisted of roughly 1:1 NaOAc buffer and EtOH. The reaction vessel was heated to 100 °C for 15 minutes to form [^{18}F]AlF-NOTA-Folate. The product was purified by semi-preparative HPLC and trapped on a C18 cartidge. The purified product was eluted with ethanol and formulated in PBS.

From starting activities of 4.4–6.5 GBq, the synthesis yielded 240–1100 MBq of product (n=5). The radiochemical purity (RCP) was >99 %. Total synthesis time was 50 minutes.

Developing a GMP-compliant synthesis on the basis of experimental research is not always straight forward. The low volumes used in literature were not practical in a cassette synthesis such as this. The lower concentration resulting from the larger volumes used might affect the yield. Furthermore, It was observed that the precursor was unstable in certain organic solvents to an extent that it decreased the yield. This necessitated careful consideration of the order in which reagents were mixed.

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PSMA-Targeted radionuclide therapy enhanced by ultrasound-mediated microbubbles in a preclinical mouse model of human prostate cancer

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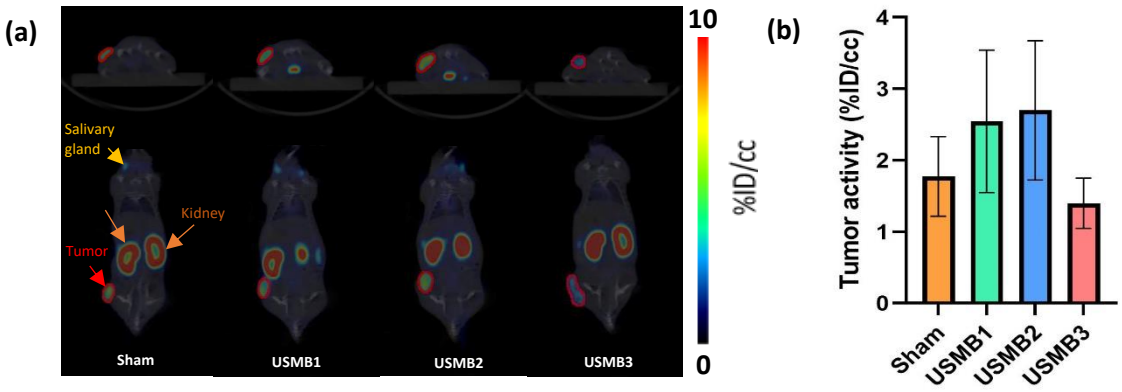
Radioligand therapy targeting the prostate-specific membrane antigen (PSMA) has shown promising clinical results for patients with metastatic Castration-Resistant Prostate Cancer particularly. However, side effects are impacting the well-being of the patient[1].Ultrasound (US) with microbubbles has been shown to transiently permeabilize biological membranes and can be used for efficient and safe drug delivery in tumor tissue, reducing dose-limiting toxicities[2]. This study aims to evaluate the efficacy of this method with a PSMA radiolabelled tracer.

Nude mice with subcutaneous LNCaP tumors were divided into 4 groups, one sham without US and 3 others with different US pressure parameters influencing the endothelial opening (USBM1 to USBM3). Each mouse received an [^{18}F]F-PSMA-1007 i.v. injection of 5.1 ± 1.7 MBq and were imaged by PET/CT 2 h post-injection. An i.v. injection of Rhodamine B Dextran (100µL, 70 kDa, 5mg.mL^{-1}) was performed to quantify by immunofluorescence its extravasation into the tumor correlated with PSMA and CD31 expression. Contrast-enhanced US imaging was carried out to assess tumor perfusion.

PET/CT imaging showed an increased uptake of [^{18}F]F-PSMA-1007 in the tumor for all groups ([2.45 ± 0.78; 2.76 ± 0.79] %ID.cm^{-3}) compared to sham (1.76 ± 0.79 %ID.cm^{-3}) except for one group (USMB3) exposed to short and high pressure pulses (1.31 ± 0.34 % ID.cm^{-3}). Immunoimaging results showed an enhancement of fluorescence intensity of CD31 expression and Dextran level in the tumor for all the groups compared to sham, but only significative ($p < 0.01$) for the group (USMB3). However, evident tissue damage in this group explains the lower uptake of radiolabeled PSMA. These findings suggest heightened blood vessel permeability due to cellular junction disruption for PSMA uptake, emphasizing the need for cautious consideration to prevent tissue damage.



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On the development of separation methods for the purification of ^{225}Ac

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The α emitter ^{225}Ac is receiving high attention as its use in Targeted Alpha Particle Radiotherapy (TAT) has shown great promise. Consequently, the demand for ^{225}Ac is constantly increasing, leading to need for the development and optimisation of new production, and purification, methods. There are several production routes for ^{225}Ac being employed, including i.e. ^{229}Th generators, spallation of ^{232}Th targets with protons of high energy (≥100 MeV), cyclotron irradiation of ^{226}Ra targets with 16 MeV protons (^{226}Ra(p,2n)^{225}Ac, and photon irradiation of ^{226}Ra targets (^{226}Ra(γ,n)^{225}Ra →^{225}Ac)[1].

Depending on the respective production route the impurity profiles of the produced ^{225}Ac may be different (e.g. presence of significant amounts of La, U/Th or Ra and its decay products), which needs to be considered when developing suitable purification methods. To address these challenges two methods have been developed: firstly a two TK221 Resin[2] cartridge method in the case of presence of larger amounts of La, U/Th or Ra; and secondly a simplified method in case these impurities may be assumed to absent, or present in low amounts only.

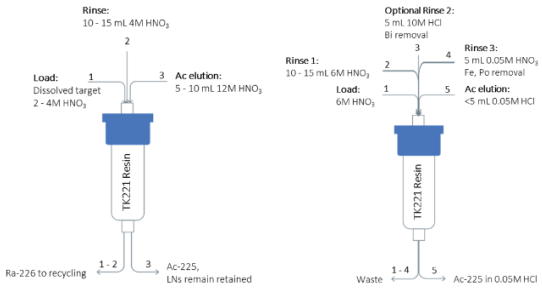

Figure 1. Two TK221 Resin cartridge based ^{225}Ac purification method

The use of a variation of the simplified method for the conversion of ^{225}Ac present in dilute HNO_3 to dilute HCl is discussed. If even further purification e.g. from Ra and its decay products or the removal of ^{225}Ac decay products, e.g. after prolonged storage or shipment, is desired TK101 Resin[3] and/or TK102[4] Resin may be used. The use of the latter resins in Ra purification is briefly discussed.

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Electrochemical synthesis of Ni-based 2D MOFs

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The outstanding electrochemical properties and versatility of electrically conducting 2D metal-organic framework compounds (MOFs) make them suitable for a wide range of applications, paving the way for innovative advancements in energy storage, catalysis, and biosensing technologies. This study investigates the electrochemical synthesis, characterization, and potential applications of these 2D MOFs on nickel surfaces.

Ni-HAB, $Ni_3(HHTP)_2$, and $Ni_3(HITP)_2$ MOFs were synthesized on nickel sheets used as anode a three-electrode cell. Commercially available HAB (Benzene-1,2,3,4,5,6-hexaamine trihydrochloride), HITP (Triphenylene-2,3,6,7,10,11-hexaamine hexahydrochloride) and HHTP (Triphenylene-2,3,6,7,10,11-hexaol) were used in the synthesis. The MOF layers were grown on nickel sheets via electrochemical synthesis method. Nickel sheets surfaces were prepared with mechanical and electropolishing and cleaned by rinsing and plasma cleaning prior to synthesis. Different current densities were tested for optimal MOFs layer formation.

The electrochemical properties of the formed MOFs films were studied through cyclic voltammetry, open circuit potentiometry and electrochemical impedance spectroscopy (EIS). Characterization of the surfaces was also performed using X-ray diffraction and scanning electron microscopy combined energy-dispersive x-ray spectroscopy (SEM-EDS). SEM-EDS and EIS results show that MOFs layers were grown on the surface of the nickel anode.

Due to increased surface area and planar structure, 2D MOFs have more exposed active sites accessible to reactants. They also have fast mass and electron transfer and high electrocatalytic activity. This enhances their responsiveness especially in chemical reactions and sensing applications. High chemical and thermal stability lead to increased performance in different application areas. Future work will focus on creating more sample surfaces with various functional groups to explore additional applications in energy technology and biotechnics.

Terbium-161 production and quality control

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Terbium-161 is a promising radionuclide for medicinal use. Its physical characteristics make it a great candidate for theranostic use. It decays with half-life of 6,89 days while emitting beta minus particles with maximum energy 593 keV and avarege energy 154 keV. Tb-161 also emits 12,4 conversion and Auger electrons per decay which enhances its therapeutic efficiency. In addition, gamma radiation with energy 74 keV is emitted, which can be used for SPECT imaging[1]. No carrier added terbium-161 can be prepared by irradiating Gd in form of oxide or nitrate highly enriched with ^{160}Gd in nuclear reactor.

Terbium-161 was produced by irradiation of highly enriched gadolinium-160 (98,6 %) in the oxide form in the nuclear reactor LVR 15 (CV Řež). Terbium-161 was separated by cation exchange chromatography with the resin Dowex 50W×8 with alpha-hydroxyisobutyric acid (α-HIBA) as eluent. Collected fraction were repurified from α-HIBA on a smaller column using the same cation exchange resin. The purity of prepared Tb-161 was verified by gamma spectrometry on an HPGe detector and by ICP-MS. Quality control of Tb-161 solution was evaluated by radiolabelling DOTA molecule in various molar ratios of Tb: DOTA in various time periods after the end of separation.

One batch typically yields 3,9 – 22 GBq of no carried added 161-Tb with radionuclide purity higher than 99,999 %, which is sufficient as 1 – 3 therapeutical doses.

Acknowledgements: This work was supported by the project “Efficient Low-Energy Electron Cancer Therapy with Terbium-161” granted by the Norway and Technology Agency of the Czech Republic within the KAPPA Programme (grant No.: TO01000074).

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Cyclone® 30 XP at CERAD, a variable-energy Cyclotron to produce a wide range of radioisotopes for medical application

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The heart of the CERAD facility (CERAD, Center of Design and Synthesis of Radiopharmaceuticals for Molecular Targeting) at Radioisotope Centre POLATOM, NCBJ, is the cyclotron - Cyclone 30 XP, installed by IBA (Ion Beam Applications, Belgium). It can serve the production of radioisotopes for medical diagnostics and therapy, such as ^{18}F, ^{64}Cu, ^{89}Zr, ^{68}Ge, ^{123}I, ^{111}In, ^{201}Tl, ^{211}At or ^{225}Ac.

Cyclone 30 XP accelerates protons to energies ranging from 15 to 30 MeV with a maximum intensity of 400 µA, deuterons to energies ranging from 9 to 15 MeV with a maximum intensity of 50 µA and alpha particles to an energy of 30 MeV with a maximum intensity of 50 µAe. These charged particles are accelerated in a variable electric field in a vacuum of around 10-7 mbar. The particles are stimulated by a high-frequency electric field of 33-66 MHz to achieve maximum kinetic energy gain. Ions (charged particles) are injected by an ion source at the central point between the duant magnets.

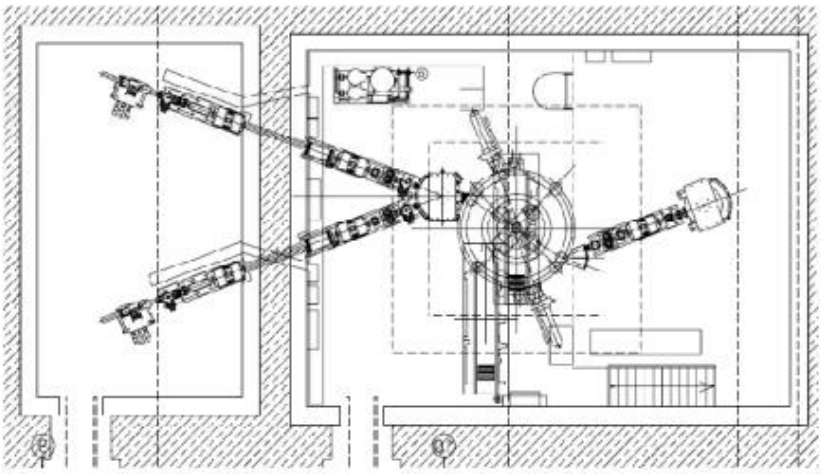

Figure 1. The general layout of Cyclone® 30 XP[1]

Typical layout with two high-power solid targets installed on the left with p,d and alpha beam and a small line with 5 PET targets on the right with p,d beam.

CERAD project is co-financed under Smart Growth Operational Programme 2014-2020, Priority IV: INCREASING THE RESEARCH POTENTIAL, Measure 4.2. Development of modern research infrastructure of the science sector. Financing agreement: POIR 04.02.00-14-A001/16-00.

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POLATOM's perspectives and experiences in development of ^{225}Ac-radiopharmaceuticals

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The development of radiopharmaceuticals containing ^{225}Ac is an active area of commercial research worldwide. The favourable nuclear properties of Ac-225 such as half-life of 9.9 days and a decay chain delivering 4 alpha and 2 beta particles makes ^{225}Ac an attractive candidate for TAT. Despite the interesting properties the ^{225}Ac-radiopharmaceuticals development still faces significant challenges including high cost and limited availability of Ac-225, the challenging chemistry, and the need for stable targeting systems with high radiolabelling yields.

This work focuses on our experiences in development of ^{225}Ac-radiopharmaceuticals.

Ac-225 was obtained from Th-229 generator at Physics and Power Engineering (IPPE, Obninsk, Russia) and supplied as a dried [^{225}Ac]Ac$(NO_3)_3$ salt. The radionuclide purity of the ^{225}Ac solution was determined by gamma spectrometry with HPGe detector. The evaluation of metallic impurities was conducted by ICP-OES method. Two different peptides, DOTA-TATE and PSMA-D4 developed at Radioisotope Centre POLATOM have been tested for ^{225}Ac-radiopharmaceuticals preparation. The different condition of the radiolabelling towards clinical implementation included the evaluation of the addition quenchers like: ascorbic acid, gentisic acid, ethanol for the stabilization were tested. Radiochemical yield and radiochemical purity were verified using TLC and HPLC methods. Additionally, collected 10 s fractions from HPLC analyses were measured in the gamma counter at different time points and different energy windows. Stability of ^{225}Ac-radiopharmaceuticals were investigated in human serum for 72 h using TLC method. For separation of the radiochemical forms variety of mobile phases were evaluated.

The radionuclide purity of the ^{225}Ac solution determined by gamma spectrometry with HPGe detector showed only presence of ^{213}Bi, ^{221}Fr and ^{209}Tl in equilibrium with ^{225}Ac. The amount of metal impurities (Cu, Fe, Zn, Ni, Bi, Pb) assessed via ICP-OES didn't exceed more than 10 µg/mL. A high radiolabelling yield of over 90% was obtained for ^{225}Ac-DOTA-TATE and ^{225}Ac-PSMA-D4 however the stability of the tracers dramatically decreased with time. To maintain high purity of the labelled vector and enhanced shelf-life, radiolysis were reduced by addition of different radical scavengers. These evaluation is ongoing.

A criterion for BCC phase stability in cobalt-free refractory high entropy alloys for radiation environment

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Radiopharmaceuticals are efficient and common medicinal formulations which have been used to treat cancer cells in nuclear medicine. Radiopharmaceuticals must be produced in a radiation environment. Therefore, it is critical to design the structural materials with superb radiation resistance to ensure the quality of medicines and the safety of the equipment. Cobalt-free refractory high-entropy alloys (RHEAs) are strong contenders for structural materials under high intensity radiation because they do not exhibit cobalt activity under irradiation. The RHEAs with solid solution phase have great mechanical properties and thermal stability, which is essentially the body-centered cubic (BCC) phase. The BCC phase formation rules thus became the basic criterion in the compositional design of RHEAs. In this paper, the BCC phase formation rules in cobalt-free RHEAs were determined *via* the calculation of six semiempirical parameters, namely, the entropy of mixing, enthalpy of mixing, atomic size differences, Ω-parameter, d-orbital energy level and valance electron concentration. The mixing enthalpy and atomic size differences are more effective than other semiempirical parameters for predicting BCC phase stability in cobalt-free RHEAs. The presence of aluminum is found to cause a notable alteration in the range of phase stability in cobalt free RHEAs.

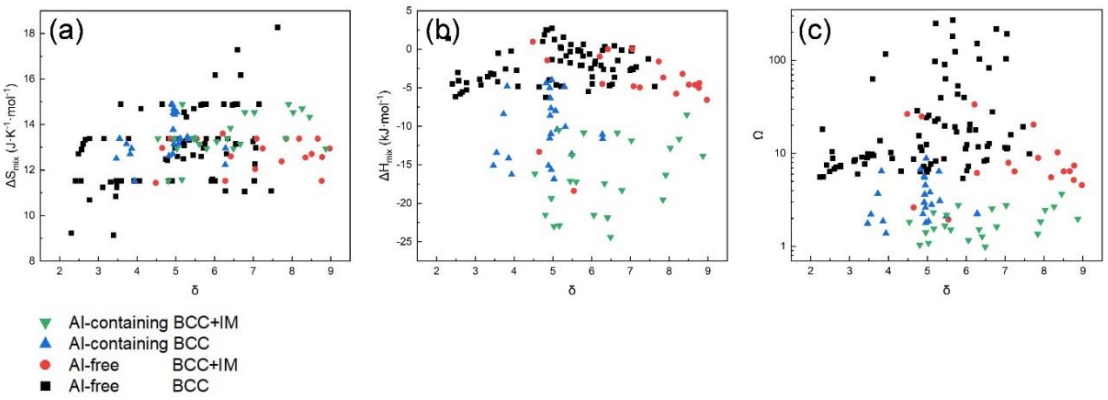

Figure 1. The distribution of δ superimposed on ΔS_{mix}, ΔH_{mix} and Ω in BCC-structured RHEAs.

New Phase Transfer Agents for Fluorine-18 Radiolabeling

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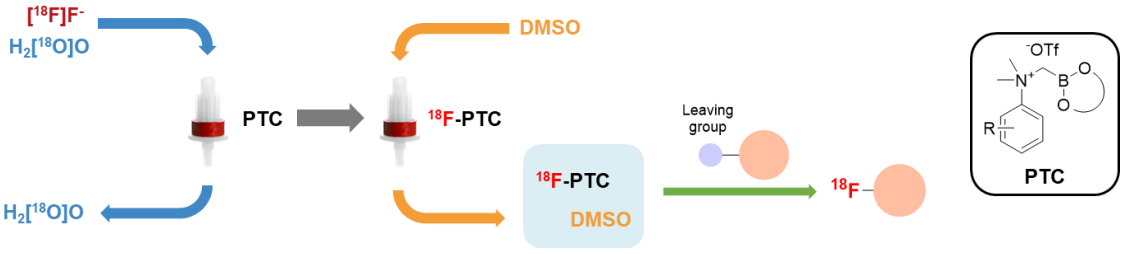
PET imaging has become an indispensable diagnostic method, with fluorine-18 labeled tracers being the most commonly used in clinical settings. The production of these tracers is carried out using fluoride ions, produced by the cyclotron through a nuclear reaction with oxygen-18 enriched water. The activation of the produced [^{18}F]fluoride has been a central issue in fluorine-18 radiolabeling[1]. Fluorine-18 is highly unreactive in water and has to be dehydrated in the presence of a phase transfer agent to restore its reactivity and solubility in an organic medium. The azeotropic drying step, which requires time during which fluorine-18 decays, is systematic in the radiosynthesis process of tracers.

For these reasons, alternative approaches have been proposed[2,3]. The aim of this work is to propose a method to suppress azeotropic drying step by exploiting the boron-fluorine affinity through the development of phase transfer catalyst (PTC). It consists of adsorbing these PTCs on a C18 cartridge, which is eluted with an aqueous solution of [^{18}F]fluoride ions. After trapping the [^{18}F]fluorides, the cartridge is eluted by the organic solvent to directly elute the PTC-[^{18}F] adduct.

After liquid-liquid extraction trials, a first PTC scaffold was selected. The objective of this study was to investigate the impact of various phenyl substituents and boronic ester on the trapping and elution of fluorine-18 on C18, and its influence on the radiolabeling step.

Four PTCs were obtained with good overall yields (71-89%). These compounds showed promising results in the trapping-elution test (trapping > 95% and elution > 45%). Two types of radiofluorination were successfully performed: labeling of activated pyridines (95% RCC) and copper-mediated labeling (74% RCC).



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Innovative radioimmunoconjugates for cancer therapy

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Cancer is second the most common cause of death worldwide. In 2019 it took nearly 27 600 lives each day. Advances in science have provided much valuable knowledge about molecular mechanisms of this complex disease. Despite concerted efforts, we still have not witnessed a significant breakthrough in cancer treatment.

One of the therapeutic pathways that has been consistently developed is radiopharmaceuticals. These are ligands targeted against cancer cells and labeled with a radioactive isotope. Thanks to their high specificity, they offer a chance to save healthy cells and reduce the amount of dose received by the patient in comparison to classical radiotherapy. Of particular note are radionuclides conjugated with antibodies - radioimmunoconjugates.

As of today, the FDA and EMA have approved 1 radioimmunotherapeutic and designated many as orphan drugs. Nevertheless, given the number of ongoing clinical trials and studies, the field continues to grow.

This work is a subjective summary of 3 innovative ligands that were discussed in literature since 2020:

- [^{225}Ac]-FPI-2068 includes a bispecific antibody that targets EGFR as well as cMET. It serves as a targeted alpha therapy for several solid tumors. FPI-2068 provides enhanced tumor specificity when compared to individual monoclonal antibodies against each of these targets[1].

- [^{131}I]-KN046 is a bispecific fusion antibody that targets PD-L1 and CTLA-4 to treat malignant melanoma. Additionally, soft iodine radiation stimulates expression of particular tumor immune receptors enhancing therapeutic effect[2].

- [^{86}Y/^{90}Y]-HOPO-Fab-Sca is a theranostic labeled with a fusion protein system. Siderocalin is fused with Fab and afterwards labeled with [^{86}Y/^{90}Y]-HOPO. It is an affordable, purification-free, cold-kit labeling strategy[3].

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Next-Generation Radiotheranostics: The Power of Luminescent Radiolanthanides for Modern Medicine

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Up-converting nanoparticles (UCNPs) represent a novel class of luminescent nanomaterials consisting of an inorganic host crystal matrix co-doped with trivalent lanthanide ions. These nanoparticles display unique spectroscopic properties, converting near-infrared (NIR) radiation into higher energy ultraviolet (UV) or visible (VIS) wavelengths - a distinctive feature of lanthanide compounds. UCNPs are noted for their excellent photostability, resistance to photobleaching, absence of autofluorescence from organic compounds, and low cytotoxicity. These attributes make them highly effective for multimodal imaging and biomedical applications following target-specific functionalization. A particularly promising clinical application of UCNPs involves their radiolabelling with lanthanide-doped radioactive ions. This multimeric nanosystem, comprising nanoparticles, radionuclides, and targeted biomolecules, is referred to as a nano-radiopharmaceutical. The development of advanced nano-radiopharmaceuticals holds significant potential to enhance diagnostic precision, improve therapeutic outcomes, and reduce off-target effects and damage to healthy tissues in nuclear medicine.

In our research, we synthesized core β-$NaYF_4$:Yb^{3+},Er^{3+} and core@shell β-$NaYF_4$:Yb^{3+},Er^{3+}@$NaYF_4$ UCNPs with diameters of ~25 nm and ~45 nm, respectively. We conducted a comprehensive physicochemical characterization of these nanoparticles and assessed their potential toxic effects and functionality in biological systems at the *in vitro* level. The results indicated that UCNPs are readily internalized by cells, exhibit no cytotoxicity, and demonstrate effective luminescence in *in vitro* models. For further nanoparticles surface functionalization, we employed polysaccharides such as mannan and inulin with hydroxybisphosphonate anchors and evaluated nanoparticles internalization by J777 macrophages. Mannan-coated UCNPs showed higher uptake by cells compared to inulin-coated UCNPs. Notably, inulin coating, while not completely inert, still resulted in significant internalization. Interestingly, non-coated UCNPs were not internalized by the cells. These findings underscore the importance of surface modification in enhancing cellular uptake and potential biomedical applications of UCNPs.

We selected β-$NaYF_4$:20%Yb^{3+},2%Er^{3+} UCNPs for radiolabelling due to their superior luminescent properties, utilizing a $NaYF_4$ matrix. Additionally, yttrium (Y), a key component of these UCNPs, is valuable for applications involving its radionuclides, including therapeutic ^{90}Y and diagnostic ^{86}Y. These radionuclides are critical for developing more personalized treatments in nuclear medicine, an emerging field known as radio-theranostics.

Acknowledgements: Research was funded through the European Union Horizon 2020 research and innovation program under Grant Agreement No. 857470 and from the European Regional Development Fund under the program of the Foundation for Polish Science International Research Agenda PLUS, grant No. MAB PLUS/2018/8, and the initiative of the Ministry of Science and Higher Education 'Support for the activities of Centers of Excellence established in Poland under the Horizon 2020 program' under agreement No. MEiN/2023/DIR/3795

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Funding from the undertaking of the Minister of Science and Higher Education "Support for the activities of Centers of Excellence established under Horizon 2020"

"This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 857470"