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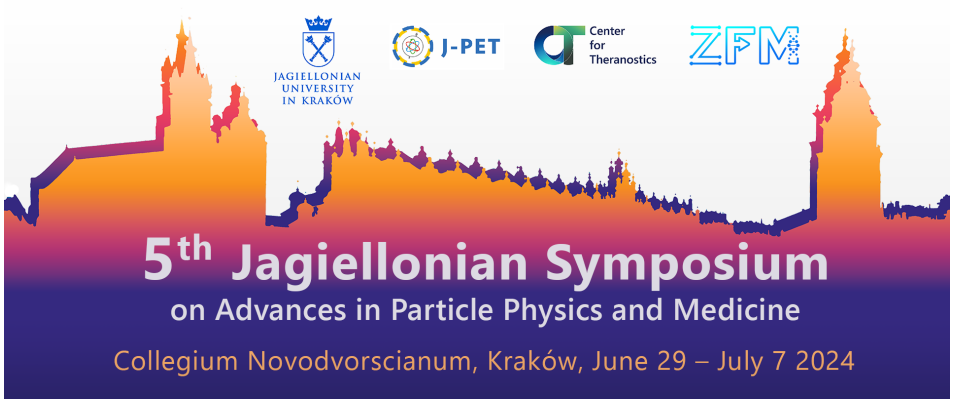

Book of Abstracts

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Beginnings and Prospects of PET

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The past 5 decades have witnessed a great revolution in applications of medical imaging to the day-to-day practice as well as research settings. The introduction of X-ray by Roentgen in 1895 was revolutionary in nature and allowed planar imaging of various organs and structures with significant limitations. Tomography was introduced by Dr. David E Kuhl at the University of Pennsylvania (Penn) in the 1960s by using single gamma emitting radiotracers with great success. By the early 1970s, this approach was tested mostly in assessment of central nervous system disorders. However, the introduction of Computed Tomography (CT) by Hounsfield very close in time clearly demonstrated the importance of tomographic imaging to detect structural abnormalities in various organs in the body. However, both CT and SPECT imaging were primarily used to detect blood brain barrier abnormalities with significant limitations in their capabilities to assess brain function in disease states. Investigators at Penn became very excited about using PET imaging for assessment of brain function and other organs in the early 1970s and this led to the synthesis of 18F-Fluorodeoxyglucose (FDG) which was administered to the first human being in August 1976. The introduction of Magnetic Resonance Imaging (MRI) by Peter Mansfield and Paul Lauterbur was also of great importance because of its ability to detect soft tissue abnormalities, particularly in the brain. While the original instruments for any of these three imaging modalities were confined to assessing brain abnormalities, by the 1980s, total body imaging became a reality for examining the rest of the body.

During the past 4 decades, it has become quite clear that disease processes start at the molecular level as the beginning of pathologic states, which may lead to functional abnormalities such as blood flow to the disease sites, and then eventually manifests as structural abnormalities. Some diseases may never lead to structural changes and therefore remain undetected. As such, molecular imaging with either PET or SPECT have become very powerful imaging modalities for early detection of the disease and assessing response to treatment. The sensitivity of either CT or MR imaging for detecting molecular level disease process is unachievable and therefore the claims made about extraordinary power of MR imaging with novel contrast agents never materialized. Therefore, this modality is primarily employed for detecting structural changes at later stages of the disease.

The introduction of FDG has clearly demonstrated the power of molecular imaging with PET and has truly revolutionized the impact of modern imaging techniques in the day-to-day practice of medicine. FDG, alone, is of great importance in the diagnosis and management of 8 major, common diseases and disorders of mankind. Furthermore, essential applications of FDG in the practice of medicine have allowed purchasing PET machines in most clinical centers around the world, demonstrating its necessity for patient care in medicine.

The success of FDG-PET has led to introduction of numerous PET tracers by adopting a variety of radionuclides for research as well as the daily practice of medicine.

The introduction of PET/CT in 2000 was also a major step towards popularizing this modality and enhancing its impact in modern medicine. This combination has been of great importance for surgical interventions as well as radiation therapy of patients with a variety of malignancies.

During the past decade, PET/MRI has been introduced as a combined imaging technique for domains best suited for MR applications. However, this combined modality has been confined to major research institutions around the world. As such, its routine use is uncertain at this time. The introduction of Total Body PET instruments over the past several years has shown the enormous potential of this imaging modality for examining new domains that were somewhat limited by conventional PET/CT instruments. This modality has great potential in diseases that are systemic in nature such as atherosclerosis, inflammatory diseases and musculoskeletal abnormalities.

Finally, the rapid development of theranostic approaches is truly revolutionizing the critical role of PET imaging and therefore enhancing its critical role in patient management and outcome.

Based on what we have witnessed over the past 5 decades, medical imaging has completely transformed the practice of medicine as well as impactful research to a level unimaginable when this revolution was initiated. But among these imaging modalities, PET remains the most powerful because of its potential for revealing biological bases of various diseases and disorders, its ability for detecting the efficacy of various interventions, and finally its contributions to developing better drugs for treatment of multiple serious diseases of mankind in the future.

QUANTUM ENTANGLEMENT IN PET / 576

Key talk: Quantum Entanglement and Multimodality Techniques

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Quantum Entanglement and Multimodality Techniques

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This presentation delves into the innovative application of quantum entanglement in Positron Emission Tomography (QE-PET), emphasizing its potential to surpass the resolution and sensitivity of conventional PET imaging. By leveraging the distinctive Compton scattering kinematics of entangled annihilation gamma rays, QE-PET introduces a novel measurable parameter for discerning true coincidence pairs from random events, including false annihilation-prompt gamma pairs. This breakthrough addresses the challenges posed by imaging tracers with dual emission profiles, facilitating simultaneous PET and Compton imaging.
The dual imaging modality, which integrates prompt gamma and Compton imaging with PET, effectively mitigates the positron range effects that are intrinsic to PET, thereby enhancing sensitivity. We demonstrate that incorporating entanglement effects, evident as a unique azimuthal scattering distribution, along with the high-energy prompt gamma attenuation distribution, provides a multidimensional, physics-based method for random event rejection.
This presentation also highlights the potential of cross-strip cadmium zinc telluride (CZT) detectors, whose unique characteristics and sensitivity to Compton events make them ideal for more precise gamma/positron imaging. Our findings suggest that QE-PET, through its first-principle approach, offers a significant advancement in PET imaging technology, promising improvements in both resolution and sensitivity.

POSITRONIUM IN FUNDAMENTAL AND MATERIAL PHYSICS / 621

Ortho-Positronium Detection with a High-Resolution PET Scanner

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Ortho-Positronium Detection with a High-Resolution PET Scanner

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We have designed and fabricated a research time-of-flight PET scanner for in-vivo range verification for proton therapy. Featuring state-of-the-art spatial, timing, and energy resolutions, this scanner can also serve as a precision tool for positronium imaging. We present preliminary results from using our scanner to search for ortho-positronium (o-Ps) three-photon self-annihilation events within the plastic casing of a Na-22 button source. By processing experimental data into triple coincidences and filtering out false events, such as those produced by the Compton scattering of back-to-back gammas, we have successfully observed the signature of true o-Ps formation. This was achieved through three distinct filtering techniques, inspired in part by the pioneering work of the J-PET Collaboration, based on energy, decay plane position, and momentum. The experimental results are further validated by GEANT4-based simulations. Additionally, we will discuss future analysis directions, new experimental configurations to optimize o-Ps formation, and further development of simulations to provide robust truth information.

CLOSING SESSION / 609

Closing talk: Beginnings and Prospects of PET

MEDICAL IMAGING INNOVATIONS / 598

Invited talk: Recent Advances in Hyperpolarized Xenon-129 Molecular Imaging: Are We Close for a Practical Application?

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Recent Advances in Hyperpolarized Xenon-129 Molecular Imaging: Are We Close for a Practical Application?

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Molecular imaging is a rapidly developing field of visualization, characterization, and measurement of biological processes at the molecular and cellular levels [1], which became a stepping stone for active implementation and further development of personalized medicine paradigms [2]. Conventional magnetic resonance imaging (MRI) does not perform well in molecular imaging settings due to the overall high background signal and general lack of sensitivity. To overcome these challenges, a hyperpolarized chemical exchange saturation transfer (HyperCEST) imaging approach has been developed [3]. It relies on the utilization of hyperpolarized (HP) xenon-129 (129Xe) MRI, which provides up to five orders of magnitude signal boost due to metastable HP nuclear state, in conjunction with supramolecular macrocycles capable of reversible encapsulation of HP 129Xe. By irradiating the encapsulated 129Xe with an external radiofrequency (RF) pulse(s), it is possible to destroy the HP state which in conjunction with a constant chemical exchange with a much larger dissolved HP 129Xe pool will result in an overall signal reduction on MRI image.

HyperCEST contrast mechanism allows for up to eight orders of magnitude MRI sensitivity enhancement making this a suitable approach for molecular imaging. While the practical application of this technique has proven its feasibility for molecular imaging in living organisms, there are two major limitations that restrain HyperCEST molecular MRI imaging from rapid growth and implementations for disease detection. Firstly, there are no fully designed HyperCEST active molecular imaging biosensors due to the challenges of functionalization of various supramolecular cages. Secondly, for more than a decade, there was no MRI pulse sequence optimization performed to maximize the sensitivity of the developed HyperCEST molecular agents. Overcoming these two limitations became a focus of our work.

In our group, we performed the first HyperCEST molecular imaging pulse sequence optimization resulting in up to 4 times sensitivity increase for the imaging of cucurbit[6]uril [4] – the only HyperCEST agent previously used for in vivo imaging. This increased sensitivity allowed us, for the first time, to observe HyperCEST contrast not just from blood plasma, but also from red blood cells. The same pulse sequence was utilized next to detect, for the first time, a HyperCEST effect from novel resorcinarene trimer (R3) methanesulfonate (R3- Noria-MeSO3H) [5]. This novel supramolecular cage demonstrated a strong HyperCEST contrast, extreme solubility in aqueous solutions, and additional strong negative effective spin-spin relaxation contrast. This novel R3- Noria-MeSO3H macrocycle is also easy to functionalize due to the presence of the 12 sulfonic acid groups. Overall, the implementation of the novel R3- Noria-MeSO3H with optimized HyperCEST MRI pulse sequence has the potential to bring us much closer to clinical applications of HyperCEST molecular imaging.

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Quantitative modeling of human physiology using PET

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Long axial field of view (LAFOV) positron emission tomography (PET) scanners enables measurements of human physiology with high time resolution due to its high sensitivity. The high time-resolution of dynamic PET data can be used for novel applications and quantitative metrics previously unattainable for previous generation short axial field of view scanners. In the current talk we will discuss quantitative metrics directly from time-resolved PET images ranging from blood concentration input functions to modelling of physiology with high time resolution
An automated extraction of the blood concentration function validated against arterial input functions will be presented based on an initial segmentation of the aorta. The input function is robust and quantitative as both demonstrated by phantom measurements and validation against the, in the field generally accepted as gold standard, arterial input function. The high-time resolved quantitative input function will be used for model-free deconvolution of the tissue response function from where a number of quantitative measures can be extracted such as mean transmit time, extraction fraction, perfusion etc. We additionally show the application of this type of modelling across a range of tracers and organs illustrating the general applicability of the method.

TOTAL-BODY PET / 545

Invited talk: Quantitative modeling of human physiology using PET

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ARTIFICIAL INTELIGENCE FOR MEDICINE / 635

Unravelling Extracellular Vesicle Morphology: Machine Learning approach for Biomarker Identification

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Unravelling Extracellular Vesicle Morphology: Machine Learning approach for Biomarker Identification

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Extracellular vesicles (EVs), or exosomes, represent a diverse class of small, nano-, and micro-sized double-layered membranes ubiquitously produced by all cell types and readily found in biological fluids. These vesicles play a pivotal role in intercellular communication, orchestrating the transfer of genetic and proteomic information between cells. Moreover, EVs have emerged as promising biomarkers for various metastatic malignancies and tumours, which has successfully increased their abilities to achieve an advanced EV-based drug delivery system. This system offers superior biocompatibility, exploits homing effects, and enables facile surface modifications for targeted delivery. The most challenging part is characterising EVs due to their heterogeneous nature and distribution. This research aims to develop and evaluate a machine learning U-Net segmentation model for accurately identifying and quantifying exosome morphology attributes such as size, shape, area, and aggregation. The model will undergo training and evaluation using a curated dataset comprising transmission electron microscopy (TEM) and cryo-EM images, demonstrating its adeptness in delineating individual extracellular vesicles (EVs). Furthermore, future subsequent iterations will focus on refining and optimizing the model for enhanced performance and broader applicability within the field of EVs analysis. This iterative approach underscores our commitment to advancing scientific methodologies and computational tools for comprehensive EVs characterization and understanding of intercellular communication dynamics. Through comprehensive data analysis and biomarker identification efforts, this research endeavors to pave the way for the development of targeted therapeutic strategies and an improved drug delivery system (DDS) in
the context of metastatic malignancies and other diseases.

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Total-Body PET: In Search of the ”Killer App”

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Since the first Total-Body Positron Emission Tomography (TB-PET) scan was performed on a human subject in the summer of 2018, the world has entered a new age of high-performance PET. TB-PET offered a sensitivity increase of more than an order of magnitude over the conventional PET scanners of the time, creating great opportunities to improve the way that clinical PET is performed – allowing better and faster imaging with lower dose, or later after injection. However, since 2018 there have also been very significant advances in the performance of conventional PET scanners that have reduced the advantage of TB-PET to less than an order of magnitude. This weakens the case for such scanners if all that is to be done is to use them in the way that PET has always been used since its introduction into the clinic in the 1990's.
However, there is one feature of TB-PET that can never be realized with conventional PET, and that is using the total-body coverage for high frame-rate total-body dynamic imaging. This talk will explore some of the possible ways that this capability might be used for positive impact in clinical care.

TOTAL-BODY PET / 528

Key talk: Total-Body PET: In Search of the "Killer App"

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An analytic, moment-based method to estimate orthopositronium lifetimes in positronium lifetime imaging

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Recently, positron-electron annihilation events have been identified as a possible biological indicator of tissue oxygen concentration [1]. In normal positron emission tomography (PET) scans, positron-electron annihilation events from radioisotopes produce coincidence gamma-ray pairs which are detected, and their annihilation positions are reconstructed to create an activity image. In approximately 40% of annihilations, the positron-electron bound state positronium (Ps) is formed. By choosing a prompt gamma-ray emitting isotope, the Ps lifetime may be calculated. The lifetime is defined as the time-difference between the coincidence and prompt photons, and the histogram of these times can be modeled by a sum of exponentially modified Gaussian distributions (EMG) [2]. Specifically, one of the distributions in the sum models the orthopositronium (o-Ps) component, which is of interest as it is sufficiently long-lived to interact with the surrounding environment. o-Ps lifetimes have been shown to correlate with local oxygenation [3].
To extract the o-Ps lifetime, one method is to fit an exponential curve to the exponential decay region of the EMG [3]. A full EMG fit can also be used [2]. Thus far these methods have produced precise results, however they require the image to first be reconstructed, and for a time-difference histogram to be generated for each individual voxel. Presented here is a novel method for estimating

o-Ps lifetimes. This method is analytical, does not require a prior reconstruction, and can be applied to whole datasets. A derivation is not done here for brevity, however in short, it can be shown that the ratio of the n^{th}+1 and n^{th} moments of the time-difference histogram is related to the o-Ps lifetime, if the o-Ps lifetime is assumed to be sufficiently large compared to other Ps components. Figure 1 presents preliminary results of this technique on simulated 2-dimensional PET data. The method is in-general faster than curve-fitting methods at the expense of contrast resolution. The reduction of noise and the possible direct use of the moment images will be explored in the future.

FIG. 1: a) Reconstructed image using the 5^{th} moment of the data. b) Reconstructed image using the 6^{th} moment of the data. c) Reconstructed o-Ps lifetime image using the ratio of images (b) and (a). d) Ground-truth o-Ps decay rate image. All image pixels contained $1x10^6$ counts, and the PET images were reconstructed with five ordered subset expectation maximization (OSEM) iterations, with a time-of-flight of 300 ps. The color bars are in units of inverse nanoseconds (ns^{-1}) and display the o-Ps lifetime.

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POSITRONIUM IN MEDICINE / 557

An analytic, moment-based method to estimate orthopositronium lifetimes in positronium lifetime imaging

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Session 2 / 575

Developing of dual-tracer imaging with modular J-PET

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PARTICLE DETECTION TECHNOLOGIES / 612

Invited talk: Modeling the effect of neutron damage on LGAD sensors

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Modeling the effect of neutron damage on LGAD sensors

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Low-Gain Avalanche Detectors (LGADs) are pivotal for the advancement of future nuclear, particle, and astroparticle experiments due to their exceptional fast timing capabilities and radiation hardness. Studying the performance of these detectors under adverse radiation environment is of significant importance, both from the fabrication and modeling aspects. This research aims to develop a reliable neutron-induced radiation damage model specifically for LGAD detectors using the TCAD simulator, Silvaco. The capabilities of the neutron damage model in Silvaco, originally developed by our group for pad detectors, is enhanced further by incorporating the acceptor removal mechanism, and thus making it applicable to both thin and thick LGADs. Validating this model is essential to ensure the reliability and performance of LGADs in high-radiation environments, thereby supporting their integration into next-generation collider experiments.

NOVEL PHARMACEUTICALS FOR THERANOSTICS / 591

Invited talk: Improvement of cancer contrast in MRI using nanoparticles in the animal model

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QUANTUM ENTANGLEMENT IN PET / 578

Invited talk: A first detailed study of the quantum decoherence of entangled gamma photons

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A first detailed study of the quantum decoherence of entangled gamma photons

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The impacts of the quantum entanglement of annihilation gamma on PET imaging is an active area of research [1-3]. However, the decoherence of the entangled state by a Compton scattering (e.g. in the patient) and its effect on the scattering correlation remain unclear. To understand this phenomenon, we measured the enhancement ratio (R) reflecting the amplitude of the azimuthal correlation, $\Delta\phi$, between the Compton scattering planes of the two annihilation gammas after one of them underwent an intermediate Compton scattering (ICS) and compared to simulations using a variety of decoherence models [4].

We used two detectors, each consisting of 256 3 x 3 x 20 mm3 LYSO crystals to measure $\Delta\phi$ from the crystal hit positions after one of the annihilation gamma Compton scattered off a 3 x 3 x 5 mm3 LYSO detector giving access to θICS from the energy. R was measured by fitting the $\Delta\phi$ distribution for θICS in the range 0° to 70°.

The results demonstrated the robustness of the quantum entanglement following the Compton scattering process. The measured R, deconvolved from multiple scattering backgrounds, remains constant (R~2.1) for θICS up to 60°, with some evidence for a reduction at larger angles. It exceeded the classical limit (R~1.4) as provided by a simulation where an ICS collapsed the entangled state. The data are consistent with predictions from simulation based on a quantum theory of entangled triple Compton scattering developed in our group [5], as well as a simple model assuming that the entanglement is fully maintained after an ICS.

These findings advance our understanding of the quantum entanglement decoherence at the MeV scale, which is crucial for developing societal applications, such as quantum entangled PET imaging.

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Clinical practice and clinical research on Total Body PET

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Recently long axial field-of-view (LAFOV) positron emission tomography (PET) scanners have been introduced into the clinic. Compared with conventional short axial field-of-view systems, these new scanners have a larger axial coverage of the body and, thereby, a substantially higher system sensitivity. This provides new opportunities for applying PET in clinical practice. Some examples are reduction of scan time duration for example in intensive care unit patients; reduction of the amount of radiotracer administered to the patient, which is very important when imaging younger patients or pregnant women; longitudinal or delayed imaging for using short- and long-lived radiotracers; and applications of whole body dynamic or parametric imaging. In addition to this, new emerging techniques, such as artificial intelligence and imaging with multiple radiotracers could aid in a more general clinical application of LAFOV PET. The main objective of this presentation is to highlight these opportunities and to indicate future directions with LAFOV PET from a clinical perspective at the University Medical Center Groningen (UMCG).

TOTAL-BODY PET / 543

Invited talk: Clinical practice and clinical research on the Total Body PET

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New bunched positron beam at the AntiMatter Laboratory in Trento: planned quantum experiments with positronium

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New bunched positron beam at the AntiMatter Laboratory in Trento: planned quantum experiments with positronium

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The AntiMatter Laboraty (AML) of Trento is equipped since many years with an electrostatically transported continuous positron beam. This beam allows solid state and fundamental studies of positrons and positronium (Ps) interaction with matter [1, 2].
A new set-up to produce intense bunches of positrons (~10^5) with a time duration of 2.5 ns and energy tunable up to 20 keV is in advanced construction [3]. with the purpose to produce intense clouds of Ps into vacuum
The new apparatus is composed by three sections. The first one produces a continuous positron beam moderating positrons with a solid rare gas moderator. This beam can be switched to provide positrons to two different lines. The first line will be devoted to fundamental studies with Ps while the second line to solid state studies. In the first line we have the other two sections: A Surko trap and a buncher. A novel non adiabatic extraction from the 700 Gauss magnetic field of the Surko trap is realized with a prebunching. The following buncher and the last electrostatic lenses are designed to focus the positron bunches in a magnetic and electrostatic field free region.
In this talk, I will: 1) describe the novel design of the positron bunched beam 2) show the advance in the construction of the set-up, presenting a systematic characterization (energy spread, positron yield, spin polarization) of the continuous positron beam [4] 3) illustrate the planned experiments : measure of the entanglement of the three annihilation gammas of ortho-positronium prepared into vacuum in selected quantum states, inertial sensing measurement on Ps in 23S state [5] and possible high resolution spectroscopies with cooled Ps [6].

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POSITRONIUM IN FUNDAMENTAL AND MATERIAL PHYSICS / 546

Invited talk: New bunched positron beam at the AntiMatter Laboratory in Trento: planned quantum experiments with positronium

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Improvement of cancer contrast in MRI using nanoparticles in the animal model

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After lung cancer, prostate cancer (PC) is the most common and the second leading cause of cancer death (1). Currently, the gold standard for PC diagnosis is prostate-specific antigen (PSA) testing and digital rectal examination (2). Computed Tomography, Positron Emission Tomography (3) etc are used for PC diagnosis and staging, yet they are of limited value. Molecular MRM using targeted contrast agents may rectify limitations of these methods.
To improve the tumor contrast we have developed new core/shell NaDyF4/NaGdF4 nanoparticles changing both T1 and T2 relaxation times of surrounding water molecules and conjugated them with tumor specific antibodies and proteins. We also investigated toxicity, biodistribution and clearance of the new contrast agent. The relaxation times (T1 and T2) of the nanoparticles with various core/shell sizes and concentrations were measured at 9.4T. We performed in vivo imaging using mouse model of cancer and used 9.4T MRI system. We imaged nude mouse with the tumor before and after the injection of targeted and non-targeted contrast agents.
Our results show that the new contrast agents may allow earlier detection of cancerous tissues than standard T1- or T2-only contrast.

Acknowledgments:
This work was funded by the National Science Center, Poland Grant numbers: Harmonia: 2018/30/M/NZ5/00844.

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QUANTUM ENTANGLEMENT IN PET / 579

Invited talk: Theoretical Framework for Multiple Compton Scattering of PET Annihilation Photons

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Theoretical Framework for Multiple Compton Scattering of PET Annihilation Photons

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The influence of entanglement on the scattering probabilities of entangled photons involved in multiple Compton scattering events remains a topic of ongoing investigation, particularly within the realm of Positron Emission Tomography (PET). A methodology is presented that takes into account the impact of entanglement correlations on scattering distributions when entangled photons undergo successive scattering phenomena. We apply this framework to analyse Compton scattering involving annihilation photons. Specifically, our focus lies on the examination of the cross section related to 3-Compton scattering scenarios. These scenarios, frequently encountered in PET scans, involve one photon undergoing intermediate Compton scattering, followed by the simultaneous detection of both photons using Compton polarimeters operating in coincidence mode. Additionally, we discuss the quantification of the degree of entanglement between the resulting photons following a Compton interaction. This study could have implications for PET imaging or related fields where understanding the behaviour of annihilation photons is crucial.

PARTICLE THERAPY MONITORING / 624

First PET Studies of a FLASH Proton Beam

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PET Image-Guidance in Conventional and FLASH Proton Therapy

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Proton therapy has long been valued as a highly effective and promising technique in radiation oncology, particularly due to its ability to limit radiation dose to healthy tissue surrounding tumors. Over time, this form of therapy has seen numerous advancements in medical accelerators, beam delivery technology, beam energy modeling, and the overall treatment planning process. However, a lacking and highly desired feature is the ability to monitor and assess, in-vivo, the dose and end-point location of each irradiation. Known as proton range verification, this capability can be employed by incorporating a positron emission tomography (PET) system in both conventional and emerging proton therapy treatment modalities, such as FLASH proton therapy, to greatly improve patient outcomes.

Furthermore, FLASH proton therapy, with its ultra-high dose and dose rates, has the potential to revolutionize radiation oncology with its purported ability to better spare healthy tissue while still eradicating cancerous tumor cells. One of the primary reasons that this modality hasn't yet been exploited clinically is that the underlying mechanisms for the so-called "FLASH effect" haven't yet been understood. In this endeavor, an in-beam PET (and possibly a hybrid PET/PGI/SPECT) system would be an invaluable tool to compare conventional and FLASH proton beam irradiations to understand the mystery of the FLASH effect.

We summarize here our work in developing PET scanner technology focused on establishing in-beam PET modalities and elucidating the mystery of the FLASH effect. We discuss the Time-of-Flight PET for Proton Therapy (TPPT) project as well as early results from experiments producing quantitative PET imaging data from FLASH beam irradiations.

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SRG Induced Three-body Forces.

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Understanding the intricate dynamics of three-body interactions in nuclear systems is paramount for unraveling the mysteries of atomic nuclei. In this study, we delve into the realm of three-body forces induced by the Similarity Renormalization Group (SRG) method, a powerful tool in modern nuclear physics. SRG is based on continuous unitary transformations that suppress off-diagonal matrix elements, forcing the Hamiltonian towards a band-diagonal form. The SRG produces unitary transformations capable of softening potentials while consistently addressing many-body forces.
At first, the SRG is applied to the 2-body observables, due to the unitarity the observables transformed have the same eigenvalue. But due to this, a three-body force is induced, which can affect the observables cross-section, analyzing powers, etc. After that, The Hamiltonian with three-body interaction is involved using SRG an results are analyzed.
Furthermore, we discuss the implications of our findings for theoretical frameworks and experimental observations, highlighting the significance of SRG-induced three-body forces in advancing our understanding of nuclear structure and dynamics.
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Possibilities of producing scandium isotopes in Poland

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In the first decade of the 21st century, the first centers equipped with the so-called medical cyclotrons have been established for the production of 18F-fluorodeoxyglucose (FDG) for PET scanners in Poland. One such center, the Radiopharmaceutical Production and Research Center (RPRC) has been built at the Heavy Ion Laboratory, University of Warsaw. Regular production of FDG under the GIF permission RPRC began in 2014. The PETtrace cyclotron installed in the RPRC has 6 exit ports. At one of these ports, the installation of a beamline with a station for irradiation of metallic or powder targets was planned from the beginning. The remaining ports were occupied by targets for the production of 18F, 15O and 11C.
A grant obtained by the consortium of the POLATOM – National Centre for Nuclear Research, the Institute of Nuclear Chemistry and Technology and the University of Warsaw (HIL) - " Alternative Methods for the 99mTc Production, Agreement No PBS1/A9/2/2012 funded by the National Centre for Research and Development gave us the opportunity to build the first version of the ion guide with a target station.
Shortly afterwards, the consortium of the Institute of Nuclear Chemistry and Technology, the POLATOM – National Centre for Nuclear Research and the University of Warsaw obtained a grant "The development of methods for production of new radiopharmaceuticals based on Sc radionuclides used in positron tomography (PET)" [PET-SKAND], Agreement No PBS3/A9/28/2015 funded by the National Centre for Research and Development. The aim of the grant was the production and use of scandium isotopes, i.e. 43Sc, 44mSc and 44gSc in PET diagnostics. The funds received made it possible to expand the beamline and the target station to its current form. At the mentioned station,

scandium isotopes were produced in a nuclear reaction (p,n) on a target with natural calcium. During the grant, reactions: for 43Sc - 40Ca(α,n) 43Sc and 42Ca(d,n) 43Sc; for 44Sc - 42Ca(α,2n) 44Sc and 44Ca(p,n) 44Sc; for 47Sc - 48Ca(p,2n)47Sc were tested. The team from the Institute of Nuclear Chemistry and Technology has developed easy and quick methods to isolate 43Sc, 44Sc and 47Sc from the calcium target. The production of scandium isotopes in reactions requiring proton energy below 20 MeV or deuterons below 10 MeV was performed at RPRC. In the case of nuclear reactions requiring alpha beams below 34 MeV, the U-200P cyclotron at Heavy Ion Laboratory was used. Irradiation of targets with proton beams above 20 MeV was carried out in foreign centers and the National Centre for Nuclear Research. As a result of execution of the PET-SKAND grant, a target station for the production of scandium isotopes was built. Effective methods of isolating scandium from irradiated targets as well as methods of synthesizing scandium with selected carriers have been developed. The presentation will list existing and currently under construction cyclotron centers in Poland and their possible possibilities of producing scandium isotopes and synthesising scandium-containing chemical carriers for PET diagnostics.
In particular, further research work at the Heavy Ion Laboratory, University of Warsaw on the production and use of scandium isotopes is financed by the National Center for Research and Development, OPUS-22, 2021/43/B/ST2/02150 “Development of three-photon radiotracers for positron imaging”. The above-mentioned grant was awarded to the consortium of the Jagiellonian University, the University of Warsaw, the Institute of Nuclear Chemistry and Technology.

SCANDIUM FOR PET / 553

Invited talk: Possibilities of producing scandium isotopes in Poland

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Application of Deep Learning-Based Methods in medical imaging

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Background: Development and application of modern medical imaging techniques allows for non-invasive quantitative assessment of various biophysical parameters in human tissue. Despite its potential, modern medical imaging techniques such as Magnetic Resonans Elastography (MRE) or Positron Emission Tomography/Magnetic Resonans Imaging (PET/MRI), in comparison to conventional imaging methods like ultrasound or magnetic resonance imaging, faces several challenges, including manual evaluation through the drawing of regions of interest. Manual assessment of data is susceptible to low intra- and inter-rater reliability and is time-consuming. Moreover, exams can be affected by patient motion due to breathing or shifting. In this study, we explore the utility of deep learning-based methods for data analysis and enhancement.
Methods: Deep learning methods have gained significant attention in recent years for biomedical image analysis. We conducted an extensive literature review to identify prior work on the application of deep learning. We tested similar approaches on data collected in our laboratory, utilizing

deep learning for tasks such as image enhancement and exam interpretation.
Results: Aldoj et al. employed deep learning to automate the quantification of biomechanical tissue parameters in prostate MRE, achieving performance comparable to human readers and enabling automated quantification of tissue viscoelasticity [1]. Pollack et al. developed a deep learning-based model capable of predicting liver stiffness using conventional MRI images, which may enhance result reliability assurance [2]. Shan et al. explored the feasibility of accelerating MRE using deep learning and demonstrated its potential for rapid MRE acquisition [3]. Our team also developed and tested deep learning-based algorithms for automated image segmentation and patient motion reduction. Our algorithms automatically delineate the region of interest (with a dice score of approximately 0.7) and generate motion-free images with an approximately 30% relative error compared to ground truth images.
Conclusions: Deep learning proves to be a robust tool for biomedical image analysis, encompassing tasks like region of interest segmentation, image assessment, and quality enhancement. However, although deep learning shows promise in various aspects, further development is necessary for its full integration into clinical practice.

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ARTIFICIAL INTELIGENCE FOR MEDICINE / 634

Application of Deep Learning-Based Methods in medical imaging

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POSITRONIUM IN FUNDAMENTAL AND MATERIAL PHYSICS / 620

Advancements in sensitivity of CPT symmetry test for ortho- positronium decays in J-PET

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Advancements in sensitivity of CPT symmetry test for ortho-positronium decay with J-PET

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The deviations from combined Charge, Parity and Time (CPT) symmetry could indicate the presence of New Physics beyond the current theoretical framework. Positronium (Ps), the lightest bound state of an electron-positron pair, offers a unique probe for such investigations due to an eigenstate of charge conjugation (C) and parity (P). This work explores the potential of the Jagiellonian Positron Emission Tomography (J-PET) detector for sensitive tests of CPT symmetry in the three-photon decay of ortho-Ps (o-Ps) atom [1]. The CPT symmetry invariance in o-Ps decays has been previously tested using the J-PET detector, measuring the CPT-violating angular correlation between o-Ps spin and its annihilation photon momenta, achieving a precision of 10^{-4} level [2]. However, there is still a range of five orders of magnitude unexplored to test its exactness [3]. This work investigates new limits of CPT invariance using J-PET by utilizing a low-activity source, combined with a symmetric positronium production geometry, and an extended measurement duration exceeding one year. These advancements led to the improvement in the CPT invariance limit obtained with J-PET compared to previous results [2]. We will also discuss the further prospects in enhancing the sensitivity of the CPT symmetry test to 10^{-5} with a new detector prototype.

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Study of the mechanism of positronium formation on solid surfaces

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There are several ways in which positronium (Ps) can be formed on a solid surface: (i) *emitted Ps*, where a thermalized positron diffusing back to the surface picks an electron at the surface forming Ps, which is then emitted from the surface into the vacuum; (ii) *thermally desorbed Ps*, where a positron trapped in a surface state, i.e. in an image surface potential well, can escape by coupling with an electron from the surface to form Ps; (iii) *glancing-angle scattering*, where low energy positrons arriving at the surface at low angles of incidence are quasi-elastically scattered while picking up an electron from the conduction band to form Ps. In this work we used magnetically guided variable energy slow positron beam to investigate Ps formation on metal surfaces by measuring 3 gamma / 2 gamma annihilation ratio. It was found that Ps is formed only when the energy of incident positrons does not exceed 1 keV. No correlation was observed with the Ps yield and the positron diffusion length in the material. It means that the fraction of Ps formed via the mechanism (i) is negligible. In-situ measurements of Au sample at different temperatures showed that the yield of Ps strongly increases with temperature above ~ 400 K indicating thermally desorbed Ps is formed. At ambient temperature, however, positrons are trapped at the image potential on the surface and the formation of thermally desorbed Ps is suppressed. The dominating process of Ps formation at low temperatures (< 300 K) is thus the glancing angle scattering of low energy positrons. It explains why the Ps yield does not correlate with the positron diffusion length in the material.

POSITRONIUM IN FUNDAMENTAL AND MATERIAL PHYSICS / 547

Invited talk: Study of the mechanism of positronium formation on solid surfaces

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PET IMMAGING INNOVATIONS / 629

Walk-Through PET scanner: A high throughput, high resolution scanner

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Walk-Through PET scanner: A high throughput, high resolution scanner

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The WT-PET scanner represents a significant advancement in the field of molecular imaging, offering a cost-effective alternative to traditional high-cost Total-Body PET systems. Developed at Ghent University, this innovative scanner features two flat panels that allow for high-resolution imaging while standing, drastically reducing scan times to just 30 seconds and throughput to a couple of minutes[1]. Utilizing monolithic detectors coupled with SiPM arrays, the WT-PET achieves exceptional spatial resolution and offers depth-of-interaction decoding capabilities. The study highlights the WT-PET's capability to detect small lesions accurately, which is crucial for early diagnosis, precise cancer grading, and effective treatment planning.

The WT-PET system's design optimizes detector placement close to the patient, significantly reducing the number of required detectors and overall costs compared to conventional systems like the Siemens Biography Quadra PET/CT. With an impressive inartistic resolution of 1.3 mm FWHM and a coincidence time resolution of 327 ps FWHM, the WT-PET system ensures high-quality imaging across the entire imaging volume without the need for acceptance angle cuts. This design maximizes sensitivity, achieving 154.0 cps/kBq, which is notably higher than that of comparable systems. The upright patient positioning further reduces scatter fraction, enhancing image quality and improving contrast recovery for small lesions [2].

The study's findings demonstrate the WT-PET scanner's potential to detect small lesions which can lead to earlier cancer detection and more accurate patient monitoring by providing high sensitivity and spatial resolution at a lower cost. The WT-PET scanner's performance in detecting sub- centimeter tumors underscores its clinical value, promising to enhance diagnostic accuracy and patient outcomes [3]. The ongoing research and interdisciplinary collaboration at Ghent University continue to push the boundaries of affordable and effective cancer imaging technologies.

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Preliminary Studies of Positronium Lifetime Estimation in Human Livers ~In Vivo

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Abstract

Positronium, an exotic atom formed by an electron and a positron, shows decay properties sensitive to tissue nanostructure and metabolism, forming in approximately 40% of PET examination annihilations [1]. Initial imaging reveals significant lifetime differences between healthy and cancerous tissues, indicating its potential as a novel in-vivo cancer biomarker [2,3,4].

This study examines mean positronium lifetimes in the livers of patients with neuroendocrine tumors (NETs) using [68Ga]-Ga-DOTA-TATE for positronium imaging due to its prompt gamma emission. Following standard PET/CT scans, patients were assessed with the modular J-PET system, a new multi-photon PET system capable of simultaneous PET and positronium imaging. The mean lifetime of positronium in the liver was estimated using the methodology outlined in the article on the first positronium imaging of the human brain [4]. Preliminary findings of positronium mean lifetimes in NET-affected livers will be presented and discussed at the conference.

Acknowledgement

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POSITRONIUM IN MEDICINE / 560

Preliminary studies of positronium lifetime estimation in human livers

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PET IMAGING INNOVATIONS / 601

Invited talk: Exploring PET imaging with scattered photons and polarization characteristics

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Exploring PET imaging with scattered photons and polarization characteristics

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PET research strives to find ways to improve the image quality, but the scattering of photons remains a significant obstacle. Conventionally, the scattering - that happens in a large amount within the phantom - is treated as noise and rejected. With the advent of list-mode data and powerful computing technology, it has been possible to incorporate single scattered events [1, 2] for imaging. Recently, we proposed [3] a technique using solely the single-scattered (inside phantom) data in triple-gamma Compton-PET imaging. We determined the source activity distribution directly using the intersection points of the tissue-scattered surface and Compton cone of the extra gamma-ray (1157 keV) from a non-pure beta-emitter (44Sc). In another study [4], we generated images using the single-scattered events in TOF-PET with the Lucy-Richardson deconvolution technique. Using these images as an initial estimate in non-TOF-MLEM image reconstruction, we compared the CNR values with other initial estimates and obtained better results. Moreover, we could stop at an early iteration number with our initial estimate.

Presently, we are studying image reconstruction with single-scattered photons detected in PET systems like J-PET with solely the time of flight (TOF) information. This proof-of-concept study involves developing a mathematical model and suitable algorithms for image reconstruction. Without knowing the energy of the scattered photon, determining the locus of the scattering point becomes challenging. However, with TOF information, we could trace the annihilation point lying on a circular arc in a 2D model. We have successfully determined a region encompassing the annihilation point by utilizing many single-scattered events generated through GATE simulation. Interestingly, the geometrical picture is general enough for unscattered (true) events as well, as if they arise with scattering angle zero. The challenge now lies in generalizing the model to 3D and applying suitable filters to sharpen the image.

Another aspect of PET - the orthogonal polarization of two annihilation photons - has also been our research focus. Indeed, energy plus polarization-based binning provides a better selection of events when compared to only energy-based binning at a high counting rate when the random coincidences are significant [5]. We have utilized GEANT4 to generate list-mode data with polarization information and reconstructed images using the software STIR for standard NEMA phantoms. Our results are preliminary, but there seems to be an improvement in the image quality by incorporating polarization filtering, particularly for small activity distribution.

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PARTICLE DETECTION TECHNOLOGIES / 613

Organic high-Z scintillators for a flexible and fast total body nuclear imaging

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Organic high-Z scintillators for a flexible and fast total body nuclear imaging

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In this contribution, we present the results achieved in the development of innovative organic scintillators enriched with high-Z elements. Specifically, we have investigated organic scintillators to take advantage of their extremely fast scintillation process which is facilitated by extremely fast fluorophores [1,2]. Additionally, with the enhancement of Z, we aim to reduce the attenuation length of gamma rays and increase the probability of photon interaction via the photoelectric effect.

Enriched scintillators have been produced with a Bismuth concentration ranging from 2% to 10%. The results show promise in terms of light output and time resolution, with respect to the commercial samples of EJ Technology at 1.5 and 5% of lead that have been used as a reference.

One application of these high-Z organic scintillators is the realization of a total body SPECT detector - reSPECT – which utilizes a tungsten metal frame serving both as a collimator and a container for the scintillator segments. These segments are organized in a grid geometry with holes of a few millimeters in diameter. Additionally, the scintillators are being characterized for potential dosimetric applications in bone scans (Lu177).

Images from patients at Policlinico Umberto I Hospital have been used as a starting point for a Monte Carlo-based reconstruction study, aimed at optimizing the detector geometry and evaluating achievable performance.
In this contribution, we will present the characterization of the high-Z organic scintillator samples, the expected performance of a total body system, and considerations on the possible future applications of those new materials.

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ARTIFICIAL INTELIGENCE FOR MEDICINE / 569

Key talk: Artificial intelligence in medical imaging: influencing precision care

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Artificial inteligence in medical imaging: influencing precision care

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Artificial intelligence applications are now being applied in all aspects of medical imaging — in image acquisition,reconstruction and denoising, segmentation and quantitative analysis, diagnosis and decision assistance. Importantly, it is also used to integrate holistic diagnostic and prognostic risk from clinical data and images. Incorporation of artificial intelligence in medical imaging holds great promise to further medical imaging in precision medicine. We expect that such personalized medicine would help physicians find the right answers for their patients, and further, to help reduce their disease burden.

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Ortho-Positronium Lifetime Spectroscopy for 2-D Liver Tissue Imaging

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This work showcases the ortho-positronium lifetime as a probe for soft-tissue characterization and imaging without prompt gamma-ray detection.
We used positron annihilation lifetime spectroscopy (PALS) to measure the three components of the positron annihilation lifetime, namely para-positronium (p-Ps), ortho-positronium (o-Ps), and positron, for three types of non-fixed soft tissues obtained from pigs: adipose, hepatic, and muscle. The o-Ps lifetime for adipose tissues (3.4 ± 0.01 ns) was approximately 25% longer than that of hepatic (2.71 ± 0.01 ns) and muscle (2.72 ± 0.1 ns) tissues. It is noteworthy that o-Ps lifetime measurements provide better differentiation between adipose tissue and other tissues than X-ray phase-contrast imaging, which is currently the state-of-the-art technique for soft-tissue analysis.
Building upon these promising results, a new physics-based model was developed to simulate positron annihilation and positronium decay, using GEANT4. The model was tested using reference materials, namely polycarbonate and quartz. The simulated o-Ps lifetime closely matched the actual measurements, with relative errors of less than 0.00% in polycarbonate and 11.81% in quartz. We extended our model to generate a 2D o-Ps lifetime image of different types of soft tissue by simulating an Inveon small-animal PET scanner. This image was obtained from the local ratio of the three-gamma coincidences, due to o-Ps decay only, and the total number of annihilation events, without the need for a prompt-gamma emitter to measure the o-Ps lifetime. The resulting image from a 1-mCi equivalent source notably revealed a higher o-Ps lifetime in adipose tissue than hepatic, consistent with theoretical expectations and measured results. The contrast o-Ps lifetime image facilitated good discrimination between hepatic and adipose tissue, holding significant promise for advancements in early liver disease diagnosis.

POSITRONIUM IN MEDICINE / 558

Invited talk: Ortho-Positronium Lifetime Spectroscopy for 2-D Liver Tissue Imaging

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NOVEL PHARMACEUTICALS FOR THERANOSTICS / 592

Targeted Cellular Tracking of Pancreatic Tumor Cells via Magnetic Particle Spectroscopy/ Imaging (MPS/MPI)

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Targeted Cellular Tracking of Pancreatic Tumor Cells via Magnetic Particle Spectroscopy/ Imaging (MPS/MPI)

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Statistic studies showed that, pancreatic cancer is the fourth cause of cancer death. Pancreatic ductal adenocarcinoma (PDAC) is
the most prevalent type (over 95%). The standard methods of detection are blood-based tests and imaging modalities. Biomarkers
are crucial indicators related to blood-based tests. Mesothelin, a cell-surface glycoprotein, and vimentin, intermediate filament
protein, are promising biomarkers. Both have potentials in detection of circulating tumor cells (CTCs). The CTCs have ability to
dissociate from the primary tumor and reside in the bloodstream. During dissemination, CTCs undergone a phenomenon known as
epithelial-to-mesenchymal transition (EMT), and act as the cancer stem cells (CSCs). The above mentioned biomarkers could be
used for detection of various phenotypes of CTCs. Tracking the pancreatic tumor cells by combination of biomarkers-conjugated
magnetic nanoparticles (MNPs), magnetic particle spectroscopy (MPS) and magnetic particle imaging (MPI) is the main strategy
of this study. In fact, ability to tracking the tumor cell populations is a powerful diagnosis method. Quantification of labelled cells
through modalities of MPS and MPI is a new approach with superior sensitivity in detection of MNPs than other modalities.
In this research, the following steps were taken to track pancreatic cancer cells. The candidate biomarkers (anti-mesothelin and
anti-vimentin) were conjugated to the fluorescent MNPs. Their characteristics were evaluated through FT-IR, DLS, and ICP
instruments respectively. In vitro experiments was conducted on the pancreatic cell lines (capan-1 and AsPC-1) and mesenchymal
stem cells (MSC) (adipose-derived=AD, bone marrow= BD) respectively. The cells were treated with MNPs, harvested, and
measured by MPS and confocal microscopy. The recorded signals demonstrated that, delivery of conjugated NPs to desired cells
was remarkably higher than plain NPs. It is important to mention the detection limit of homemade MPS device was 5 ng of NPs.
The uptake of mesothelin conjugated NPs was higher in pancreatic cell lines, while the vimentin conjugated NPs have the same
pattern of uptake in MSC. To conform the possibility of cell tracking on level of in vivo, the pancreatic mouse model was used.
The MNPs was injected to mice body via subcutaneous way and in the following, MPI images and In vivo imaging system (IVIS)
were conducted by time intervals. The obtained results illustrated the accuracy of this study hypothesis, and the desired cells could
successfully track in both level of in vitro and in vivo subsequently. The novel approach for thisstudy for pancreatic cancer detection
suggest that the modalities of MPS and MPI have capability in quantification imaging strategy

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Remarks on Positronum in molecular matter and other

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Positronium (Ps) is a metastable bound state of a positron and an electron. This state is formed in a vacuum but also in matter only where the energetic conditions are suitable. The decay of Ps thought emission of annihilation photons is sensitive to the environment where this state is formed and lived. This means that observation of decay can be useful for studies of the matter at atomic or molecular level. Several examples will be presented to link the decay of Ps and polymer material's properties. Ps is also widely to detect the porus size. The computer code-named Psc for such calculations will be also demonstrated.

POSITRONIUM IN FUNDAMENTAL AND MATERIAL PHYSICS / 563

Invited talk: Remarks on Positronum in molecular matter and other

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Observations of electron emissions from the DD reaction: its implications in fundamental and applied research

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\usepackage{graphicx}
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He nuclei produced via dd, dp, and fusion reactions are of interest for understanding the nucleosynthesis process in stellar environments \cite{Raiola2002} and for designing future clean energy sources. While studies of these reactions have been conducted by various groups, there are still intriguing problems that need to be addressed. For example, He^4 nuclei originating from bombarding a deuterium beam on a deuterated Zr target at very low energies support the idea of a strong contribution of a 0^+ resonance placed close to the DD reaction threshold \cite{Czerski2022}.

Since observing the first indication of electron emission from DD in a ZrD_2 environment \cite{Czerski2024}, over the past two years, we have conducted an experimental campaign to understand the DD threshold resonance. To study these new events more carefully, we have performed a series of experiments with different charged particle detector setups, including Si detectors of varying thicknesses (1-3 mm), various Al absorption foils (1-125 μm), and a dE-E telescope, with reactions occurring at 2-20 keV deuteron energy. We have compared the experimental results with Geant4 Monte Carlo calculations of the reaction branching ratio \cite{Gokul2024, DubeyAPB_2024, Dubey_2024}. Observations of electron emissions in the DD reaction at very low energy, even theoretically predicted to be the most dominant decay channel at room temperature, might be the first step towards the development of a portable fusion fuel cell at thermal energies.

This study is part of the CleanHME project, which has received funding from the European Union's Horizon 2020 research and innovation program under grant agreement No. 951974.

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EXOTIC ATOMS AND NUCLEI, NUCLEAR PHYSICS / 550

Invited talk: Observations of electron emissions from the DD reaction: its implications in fundamental and applied research

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PARTICLE THERAPY MONITORING / 597

Short-term response of melanoma spheroids and melanocytes to FLASH proton therapy - the use of colorimetric microscopy and infrared microscopy

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Short-term response of melanoma spheroids and melanocytes to FLASH proton therapy - the use of colorimetric microscopy and infrared microscopy.

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Short-term response of melanoma spheroids and melanocytes to FLASH proton therapy - the use of colorimetric microscopy and infrared microscopy.

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Indroduction: Melanoma is an aggressive cancer that accounts for approximately 5% of all malignancies, which grown from uncontrolled proliferation of melanocytes [i,ii]. Given that it usually shows well-expressed lymphatic infiltration, it is considered an extremely immunogenic tumor [iii] The ultimate goal of radiotherapy, which is required by 60–70% of cancer patients during their treatment, is to eliminate cancer cells without toxicity to non malignant tissue [iv,v]. Ultra-high dose rate (FLASH) radiotherapy is recognized as one of the most promising breakthroughs in the treatmeant of cancer. It is the delivery of ultra-high dose rate radiation (>40 Gy/s) several orders of magnitude higher than what is currently used in conventional clinical radiotherapy (0.5–5 Gy/min) [vi,vii].

Methods: The aim of our study was to investigate the short-term response of melanoma cells (Wm-266-4) and normal skin cells (melanocytes- HEMA-Lp) to FLASH proton radiotherapy (60 Gy/s) with a final dose of 3, 20 and 40 Gy. For comparison, we also used a conventional method with a dose rate of 0.15 Gy/s with a final dose of 3 Gy. Tumorospheres produced in the ClinoStar incubator were cultured for 8 days after irradiation. After this period, they were fixed with 2.5% paraformaldehyde.

Results/Discussion:

The experiment we designed is based on the use of modern colorimetric microscopy (C-Microscopy) technology [viii], which uses color calibrated images (D65 illuminant) quantitatively to track color changes at microscale, resulting from light-matter interaction, of the whole spheroid surface as a consequence of radiation. Statistical colorimetric analysis of the whole spheroids surface shows existence of the colorimetric marker related to the color distribution on the spheroid surface which differentiates between different proton irradiation conditions. The observation of changes in the color distribution of the tumorosphere of the whole spheroids, are related to difference of light-matter interaction and indicate changes occurring within the spheroid. This may be related to changes in the biochemical composition of the spheroid. For this purpose, we performed as a next step Infrared microscopy analyzes on 8 um sections of the spheroids.

IR analysis showed changes in the fingerprints region and lipids depending on the dose of radiotherapy used. The 40 Grey dose on tumor cells shows similar changes in both regions compared to the 3 Grey dose delivered conventionally. Doses 3 and 20 Grey delivered by the FLASH method show spectra in both bands similar to those of the control spheroids. The dose of 20 and 40 Grey turned out to be a terminal dose for normal cells.

Conclusions: Our results show differences between irradiated and control samples,
which suggests the potential use of colorimetric microscopy and infrared spectroscopy for short-term evaluation of radiotherapy in tumorspheres.
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PET IMMAGING INNOVATIONS / **627**

Invited talk: Resistive Plate Chambers for brain PET imaging and particle tracking and timing

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Resistive Plate Chambers for brain PET imaging and particle tracking and timing

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In this communication we will describe the application of position-sensitive Resistive Plate Chambers to the specialized PET imaging of the human brain, yielding a sub-millimetric image resolution (beyond the state-of-the-art), as well as for the tracking and timing of charged particles with time resolution of 61 ps and position resolution below 150 micrometers.

PARTICLE THERAPY MONITORING / 625

Experimental characterization of LET spectra in proton therapy

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Tests of T, CP and CPT discrete symmetries via kaons' transitions at KLOE-2

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The transitions of neutral Kaons between the eigenbases of CP symmetry and flavor led to the measurement of T, CP, and CPT symmetries. Using the decays $K_S K_L \rightarrow (\pi^{\pm} e^{\mp} \nu)(3\pi^0)$ and $K_S K_L \rightarrow (\pi^+ \pi^-)(\pi^{\pm} e^{\mp} \nu)$ a first direct, model-free measurement of T and CPT symmetries with the total errors up to 3.5% was performed with $1.7 fb^{-1}$ of data collected with the KLOE detector in 2004-2005 at the DAΦNE Frascati Phi-factory. The analysis will be presented together with the status of the kaon-related analyses of the data collected by the KLOE-2 experiment.

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Production of 64Cu radioisotope by proton irradiation in a medical cyclotron for theranostic applications

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Copper-64 is one of many copper radioisotopes, exhibiting properties, allowing for theranostic application. Copper-64 half-life is 12.7 hours and it decays in 3 ways - electron capture (44%), electron (β-) (39%) and positron (β+) emission (17%) [1], [2] and it can be used both in positron emission tomography (PET) and in targeted cancer radiotherapy. Recently there are numerous reports in the literature on clinical applications: diagnostics of treatment progress using monoclonal antibodies [3], diagnostics of neuroendocrine tumors [4], diagnostics of the oprostate cancer and its metastases [5] and finally in the investigation of biological processes by tracking copper ion metabolism in conditions such as Wilson's disease or Alzheimer's [6], [7].
In this work we present the results of three runs of the copper-64 isotope production in the form of copper chloride: [64Cu]CuCl2 with use of the solid target method in small medical cyclotron at VOXEL Radiopharmaceutical Production Center in Krakow via nuclear reaction 64Ni(p,n)64Cu. Used method allows for the production in approximately 7-8 hours, including irradiation, purification, and formulation time. The obtained isotope was produced with the activity about 10 GBq at EOP, which allows the distribution and more widespread use of this isotope in nuclear medicine. Also the isotope was characterized by excellent radionuclide purity which in the future could allow for the development of new radiopharmaceuticals for theranostic applications.

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Design study of a breast-dedicated PET/SPECT detector built from inorganic scintillators and WLS fibers.

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Positron emission mammography shows promise as a breast screening technique for the detection and diagnosis of breast cancer in its early stages. In this report, we present an application of the Geant4 toolbox for simulating optical photon transport in inorganic scintillators combined with wavelength-shifting (WLS) fiber readout. An advantage of the WLS fiber readout technique over direct readout with a position-sensitive photo-sensors is the reduced number of photodetectors required compared to direct readout of scintillation photons emitted by the scintillator. This allows for the reduction of required data acquisition channels while maintaining a spatial resolution on the order of 2 mm. We simulated detectors of different geometries and have found that for configuration consisting of four 50 mm x 50 mm x 15 mm optically coupled LYSO scintillators readout with 4 mm square shape WLS fibers connected to 4 mm x 4 mm silicon photomultipliers (SiPMs) for the simulated 511 keV photons the reconstructed spatial resolution is 2 mm FWHM. Another configuration consists of a monolithic CsI(Na) scintillator 100 mm x 100 mm x 15 mm read out with the same size WLS fibers and SiPMs spatial resolution is 2.5 mm FWHM. Also we modeled 140 keV photons for Tc-99m for both detector configurations to evaluate their performance as a gamma camera. It was found that spatial resolution is 1 mm FWHM in both cases. The better resolution obtained for 140 keV gamma rays is the result of high probability of photoabsorption, which results in the deposition of all the gamma ray's energy at a single point within the crystal, leading to a more localized light spread function.

PET IMMAGING INNOVATIONS / 630

Design study of a breast-dedicated PET/SPECT detector built from inorganic scintillators and WLS fibers

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THE EFFECT OF HEME OXYGENASE-1 ON THE p53 PATHWAY DEPENDS ON HEME AVAILABILITY

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Heme oxygenase-1 (HO-1) degrades heme, protecting cells from heme-induced oxidative damage. The role of HO-1 is not limited to its enzymatic activity, as it can interact with poly(ADP-ribose) polymerase1 (PARP1), a protein involved in the regulation of DNA repair and viral-host interaction. Among PARP1 targets is p53, which participates in the response to viral infection and promotes the type I IFN response. We recently demonstrated that HO-1 deficiency leads to replication stress and decreases the activity of p53. Here, we aimed to identify the pathway underlying this relationship.

Experiments were performed in HEK293T cells with either control or turned-off HO-1 expression as well as in murine iPS cells devoid of HO-1 and HO-2, or with a nuclear form of HO-1. In such cells, HO-1 reduced the accumulation of G-quadruplexes and the resulting replication stress. Induction of heme synthesis by δ-aminolevulinic acid (ALA) increased the proportion of stalled forks in wild-type cells and further enhanced replication stress in HO-1 deficient cells, whereas the opposite effect was observed in response to a heme synthesis inhibitor. Interestingly, in HO-1 deficient cells, despite a higher percentage of stalled forks, the speed of ongoing fork progression was higher. This indicates a dysregulation of the PARP1-p53-p21 pathway. Using a proximity ligation assay, we demonstrated

that HO-1 colocalizes with PARP1. Furthermore, in the absence of HO-1, PARP1 intranuclear motility was higher, and the intracellular dynamics of laser micro-irradiation-induced PARylation were increased. We did not observe, however, any effect of HO-1 on the autoPARylation of isolated PARP1 protein. Then we transfected cells with a plasmid encoding a p53-GFP fusion protein to test nuclear translocation of p53. Time-lapse analysis during the first 3 hours after stimulation with etoposide showed complete inhibition of nuclear import of p53 in the absence of HO-1. This was accompanied by a decrease in the expression of a direct transcriptional p53 target, Cdkn1A (p21).
Importantly the effect of HO-1 deficiency disappeared if experiments were conducted under heme-deprived conditions. In contrast, the effect of HO-1 status was still evident in cells treated with olaparib, an inhibitor of PARP1 and PARP2. Thus, the effects of HO-1 on the p53 pathway are associated mainly with the regulation of free heme and not with PARP1-mediated regulation. If heme levels are low, the presence of HO-1 is irrelevant to p53 transcriptional activity.

To sum up, HO-1 deficiency impairs the PARP1-p53-p21 axis, decreasing p53 nuclear import and accumulation in a heme-dependent manner

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Yes

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Late-time decay for electromagnetic bound states

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We discuss the decay of electromagnetic bound states, such as excited atoms or positronium states, at late times. In particular, we are interested in the appearance of a power-law behavior and to the presence of more than a single decay channel. Typically, for such systems the deviations for the standard exponential decay law are pretty small, but the case of multiple channel may enhance this effect.

POSITRONIUM IN FUNDAMENTAL AND MATERIAL PHYSICS / 566

Invited talk: Late-time decay for electromagnetic bound states

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DOPPLER COOLING OF POSITRONIUM WITH A BROADBAND LASER PULSE

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Experimental studies with positronium, the metastable bound state of an electron and a positron, have been limited by the significant velocity distribution and corresponding Doppler broadening of transition lines of available positronium sources. The concept of Doppler cooling to mitigate this issue was initially proposed about 30 years ago by Liang and Dermer [1], who outlined the necessary key techniques.

Here, we report on the successful demonstration of Doppler cooling of positronium along the 13S–23P transition using a broadband laser pulse [2]. Leveraging a customized Q-switched alexandrite laser system tailored to this purpose, we observe two effects induced by strongly saturating the 13S–23P transition: an increase in the number of ground state atoms after decay from the long-lived 23P states and one-dimensional Doppler cooling, resulting in a reduction of the cloud temperature from 380(20) K to 170(20) K.

The ability to cool positronium opens avenues for precise measurements with a matter-antimatter system and for tests of Quantum Electrodynamics and the Equivalence Principle. Further development of the methodology carries the prospect of forming a Bose-Einstein condensate of a matter-antimatter system. A positronium Bose-Einstein condensate is considered the basis for the potential realization of a source of coherent light in the gamma-ray regime, presenting intriguing prospects for future research.

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POSITRONIUM IN FUNDAMENTAL AND MATERIAL PHYSICS / 548

Invited talk: Doppler cooling of positronium with a broadband laser pulse

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IMAS: a total body PET with TOF and DOI capabilities

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Total-Body Positron Emission Tomography (TB-PET) technology and designs have become very popular in recent years. These systems are very attractive because of their high sensitivity, achieved through their extended axial Field of View (FOV) and, potentially, Time of Flight (TOF) capabilities,

allowing for the simultaneous study of the kinetics of multiple organs. Most of TB-PET designs and implementations are based on LYSO crystal pixels without DOI. In this work we present a TB-PET system based on semi-monolithic crystals and, therefore, simultaneously enabling TOF and depth of interaction capabilities. Our design, named IMAS, makes furthermore use of a reduction of signals without compromising performance. We first carried out exhaustive simulation studies of the system geometry, based on 5 rings of 10 cm in the axial direction each, and gaps of about 5 cm, with a total axial length of 71.4 cm. These studies confirm the good performance of the system in terms of spatial resolution, sensitivity and other relevant parameters. The system has been constructed and installed (June 2023) at the largest hospital in our region named La Fe. Very preliminary experimental tests, already predict an almost homogeneous spatial resolution below 4 mm in the whole FOV (as far as at 30 cm off-radial), outperforming any other scanner with a long axial FOV. The system sensitivity is 7.6% with a source at the Center of Field of View (CFOV). The detectors reached a TOF of about 350 ps. We aim to report a full characterization of the scanner during the workshop.

POSITRONIUM IN FUNDAMENTAL AND MATERIAL PHYSICS / 565

Invited talk: Many-body theory of positron and positronium interactions with atoms and molecules

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Many-body theory of positron and positronium interactions with atoms and molecules

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Low-energy positron interactions with atoms and molecules are characterised by strong correlations, including positron-induced polarization of the electron cloud, screening of the electron-positron Coulomb interaction, and the unique process of virtual-positronium formation (where an electron temporarily tunnels to the positron). These correlations significantly modify the scattering dynamics, modify the shape of the annihilation gamma spectra, and enhance annihilation rates by orders of magnitude. They make the theoretical description of the positron-atom/molecule system a challenging many-body problem. Positronium interactions with atoms and molecules are more complicated still, owing to the need to allow for distortion of the projectile as well as the target.

I will review our many-body theory of positron [1] and positronium [2] interactions with atoms and molecules and share the fundamental insights it has provided. For positrons, I will focus on positron binding, for which our approach has given the first ab initio calculations in agreement with decades of measurements [1,3-6], and the extension to positron scattering [4] and annihilation gamma spectra in our Gaussian-basis code EXCITON+ [1]. For positronium, I will present theory and calculations for scattering and pick-off annihilation (where a positron from Ps annihilates with an atomic electron) [2].

Beyond providing fundamental understanding required to support ongoing experiments and advance antimatter technologies (traps, accumulators, beams and PET), our results provide bench-

marks for other methods tackling the computational many-body problem.

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EXTRACELLULAR VESCICLES FOR THERANOSTICS / 532

Invited talk: Insight into proteome of follicular fluid-derived extracellular vesicles following vitamin D3 and insulin treatment – an in vitro study on a pig model

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Insight into proteome of follicular fluid-derived extracellular vesicles following vitamin D3 and insulin treatment – an in vitro study on a pig model

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The ovarian follicle is a functional unit supporting the growth and maturation of the oocyte that requires extensive cell-to-cell communication between follicular cells. The signaling between somatic cells and the oocyte is coordinated through various hormones, growth factors and molecules present in the follicular fluid, including extracellular vesicles (EVs). EVs represent a heterogeneous population of membrane-bound nanoparticles, which are involved in the regulation of follicle growth and oocyte competence via their miRNA or protein cargo. Recent evidence highlights the crucial role of vitamin D3 (VD) in the regulation of ovarian functions under physiological and pathological conditions such as polycystic ovary syndrome (PCOS). However, there is a lack of data whether VD could exert its effect by influencing follicular fluid-derived EVs, especially their protein cargo. Given that PCOS is often characterized by VD deficiency and hyperinsulinemia, the study aimed to examine the influence of VD and insulin (I) on the proteome of EVs isolated from porcine follicular fluid, providing thereby a novel molecular mechanism of VD and I interaction at the ovary level. Whole porcine antral follicles (n=12/each group, 3 replicates) were incubated in vitro for 12 hours with compounds: VD, I, VD+I or without any treatment (C; control). After incubation, follicular fluid was collected for EVs isolation using size-exclusion chromatography (SEC). Then, EVs characterization was performed by nanoparticle tracking analysis (NTA), transmission electron microscopy (TEM) and flow cytometry (FC), as well as the global analysis of EVs proteome cargo was conducted

by liquid chromatography-tandem mass spectrometry (LC-MS/MS) coupled with the TMT-isobaric mass tag labeling. A typical cup-shaped vesicular morphology in the enriched EV samples were identified using TEM. Particle sizes were measured with NTA and the size range of EVs was between 50 to 350 nm. In the I and VD+I groups, the average particle size decreased in comparison to the VD group. The LC-MS/MS analysis identified typical EV-related proteins and the abundance of CD63 and CD81 was confirmed by FC analysis. Global proteomic analysis showed 3977 proteins in the EV samples. A comparative proteomic analysis (the cutoff value of 1.5-fold change and $q<0.05$; R package v4.2.3) revealed 19, 16, 8, 8 and 10 differentially abundant proteins (DAPs) between comparisons: C vs VD, C vs I, C vs VD+I, VD vs VD+I and I vs VD+I, respectively. DAPs were functionally analyzed using gProfiler and STRING database (B-H FDR $p<0.05$). Interestingly, most of DAPs identified in the analyzed groups were assessed to proteins metabolism and ribosomes, indicating the potential involvement of EVs in the basal cellular processes, such as protein synthesis.

This work was supported by the National Science Centre (NCN, Poland, grant no. 2019/35/O/NZ9/02678).

EDUCATION AND BIO-ALGORITHMS AND MED-SYSTEMS / 615

Invited talk: Nurturing the Future Stars of Physics: The International Physics Olympiad

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Nurturing the Future Stars of Physics: The International Physics Olympiad

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The International Physics Olympiad (IPhO) is a prestigious annual competition in which high school students from around the world compete for medals in theoretical and experimental physics problems. While it may seem out of place to discuss the IPhO at the 5th Jagiellonian Symposium on Advances in Particle Physics and Medicine, there is a historical connection - the first IPhO was held in Poland in 1967, initially involving countries from the Eastern Bloc, but later expanding globally.

In 2023, the 53rd IPhO was held in Tokyo, Japan, where I chaired the Academic Committee. Despite the challenges posed by COVID-19 and international conflicts in recent years, IPhO2023 was successfully conducted in person, attracting nearly 400 participants from 80 countries and regions, making it one of the largest IPhO to date.

Participants faced a grueling exam process, with two experimental problems to be solved in 5 hours on one day, followed by three theoretical problems to be solved in another 5 hours two days later. This rigorous assessment tests students' deep understanding of physics concepts and their ability to apply them to complex, real-world scenarios. In addition to the intense competition, participants also engaed in cultural exchange programs organized by the host country.

The IPhO is an excellent platform for introducing young minds to the wonders of physics and attracting talented individuals to pursue careers in the field. Recent editions have also emphasized diversity, with the IPhO2023 awarding Diversity Commendations to countries with a notable gender balance among their participants.

In this talk, I plan to discuss the history of IPhO, provide insights into the theoretical and experimental problems, share experiences of international cultural exchange, and outline future challenges. I hope that this talk will inspire more people to draw the attention of younger generations to the fascinating world of physics.

Publication agreement (CC BY 4.0):

Yes

Session 2 / **573**

Invited talk: Multiplexed PET based on triple coincidences

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Multiplexed PET based on triple coincidences

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In conventional positron emission tomography (PET), only one radiotracer can be imaged at a time because all PET isotopes generate two 511 keV annihilation photons. We have recently presented multiplexed PET (mPET), a method for simultaneous quantitative in vivo imaging of two PET radiotracers, where one of them is labeled with a positron-gamma emitter such as 124-I, 82-Rb, or 44-Sc. This method is based on the adequate processing of triple coincidences between annihilation photons and prompt γ-ray emissions. As it is not based on the energy information of the detected events, it works with regular preclinical and clinical PET scanners without any hardware or firmware modifications. We will present results obtained with mPET from phantom, animal, and human acquisitions in a variety of scanners, and discuss the challenges and potential applications of this method.

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Yes

EXOTIC ATOMS AND NUCLEI, NUCLEAR PHYSICS / **589**

Invited talk: Structure of \Xi hypernuclei

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structure of \Xi hypernuclei

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It is important to study Ξ hypernuclei to obtain ΞN interaction. For this purpose, I have been studying s-shell to p-shell Ξ hypernuclei using HAL potential, which is based on Lattice QCD potential. In this symposium, I report what kind of ΞN potential could be obtained from these structure study.

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Enhanced Two-Component Positronium Lifetime Imaging in Time-of-Flight PET

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Positron Emission Tomography (PET), crucial for diagnosing diseases like cancer and Alzheimer's, benefits significantly from Positronium Lifetime Imaging (PLI) using Time-of-Flight (TOF) technology. This study introduces a two-component reconstruction model for PLI, integrating both slow-decay and fast-decay components to refine the assessment of the tissue micro-environment. We conducted simulation studies to validate our model's performance, comparing it with conventional single-component approaches. Our findings demonstrate that the two-component model more accurately captures tissue intricacies, enhancing the diagnostic capabilities of PLI in TOF PET systems and providing a more nuanced understanding of disease mechanisms.

POSITRONIUM IN MEDICINE / 555

Invited talk: Enhanced Two-Component Positronium Lifetime Imaging in Time-of-Flight PET

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Radioisotope labelled somatostatin receptor antagonists as a promising tool to improve the diagnosis and treatment of patients with neuroendocrine tumors.

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Neuroendocrine tumors (NETs) are characterized by a slow rate of tumor growth and often a lack of specific complaints and symptoms, which is the reason for late diagnosis in the disseminated stage of the disease. Moreover, all tumors may potentially be aggressive, irrespective of the initial diagnosis and regardless of the initial stage of the disease due to their significant cellular heterogeneity. What we can say, however, is that early location and accurate staging can improve the patients' outcomes. Approximately 90% of these tumors show SSTR expression and adequate assessment of SSTR status of the primary lesion and metastases have a critical impact on the management of NEN patients. The introduction of radiolabeled SSTR agonist was a breakthrough in the care of patients with NEN, optimizing the imaging diagnostics and enabling targeted therapy in a theranostics approach. However, today we already know that in some clinical situations we need an even more sensitive diagnostic tool and perhaps a better targeted therapy. Radiolabeled SSTR analogues were constructed aiming at their agonistic behavior, based on their internalization after SSTR activation and consequent retention within the tumor cell. Recently, it has been shown that novel molecular probes, SSTR antagonists, recognize more binding sites and hence improve diagnostic efficacy, especially when the density of SSTR is low. High-affinity SSTR antagonists can provide better SSTR visualization (higher tumor uptake, higher tumor/background ratio) than agonists and are potentially superior also as therapeutic agents. There are already data in the literature showing successful treatment with the [177Lu]-labelled SSTR antagonist in patients with neuroendocrine tumors. In these patients, successful treatment effects with disease remission were also achieved in the case of a negative pre-treatment PET/CT scan with the 68Ga-labelled SSTR agonist but positive with the 68Ga-labelled antagonist.
Despite previous concerns that somatostatin receptor agonists seem to be more suitable as a tool for SSTR imaging because they are internalized, somatostatin receptor antagonists appear to be of great clinical importance and may be a step towards a more reliable assessment of SSTR status. The [177Lu]-labelled antagonist in PRRT can be used instead of [177Lu]-labelled agonists leading to improved outcomes for patients with NENs.

NOVEL BIOMARKERS FOR THERANOSTICS / 539

Key talk: Radioisotope labelled somatostatin receptor antagonists as a promising tool to improve the diagnosis and treatment of patients with neuroendocrine tumours

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Theranostic Scandium-44 : a review from the production to preclinical studies, needs and prospective

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In the frame of "precision medicine", the scandium radionuclides have recently received considerable interest, providing personalised adjustment of radiation characteristics to optimize the efficiency of medical care or therapeutic benefit for particular groups of patients. Radionuclides of scandium, namely scandium-43 and scandium-44 (43/44Sc) as positron emitters and scandium-47 (47Sc), beta-radiation emitter, seem to fit ideally into the concept of theranostic pair. Additionally, using the same targeting vectors and the combination of positron emitter scandium-43 or 44 for diagnostic imaging and matching therapeutic counterpart beta-emitting radionuclides such as lutetium-177 (177Lu) or terbium-161 (161Tb). This paper aims to review the work on scandium isotopes production, especially on the production done at Arronax facility. This presentation will also present work on coordination chemistry, radiolabeling and preclinical studies. A discussion will be done on the needs and future of Scandium isotopes in the panel of radionuclides available for Nuclear Medicine.

EXOTIC ATOMS AND NUCLEI, NUCLEAR PHYSICS / 590

Invited talk: The eta-deuteron interaction studied in coherent neutral-pion and eta-meson photoproduction on the deuteron

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The eta-deuteron interaction studied in coherent neutral-pion and eta-meson photoproduction on the deuteron

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The interaction between an eta meson and a nucleus provides the in-medium modification of the eta meson and/or a chiral partner candidate of the nucleon N(1535)1/2-, to which the eta meson and nucleon couples. We have studied such an interaction for the lightest nucleus, deuteron, from the measurement of cross sections for coherent neutral-pion and eta-meson photoproduction on the deuteron. We have found a narrow resonance-like bump in the eta-deuteron subsystem at the vicinity of the threshold, suggesting strong eta-deuteron attraction. The sharp backward-peaking angular dependence of deuteron emission, predicted by the existing theoretical calculations, does not appear. We discuss the deduced scattering length between the eta meson and deuteron, and that between the eta meson and nucleon.

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460

Chiral symmetry restoration in nucleus observed in pionic atoms

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We discuss deduction of the chiral condensate, an order parameter of the chiral symmetry, reduced in the nuclear matter for the partial restoration. We have conducted a high-precision spectroscopy of pionic atoms to determine the pion-nucleus interaction with unprecedented precision. The determined interaction presented enhancement of the isovector interaction due to the nuclear medium effects. The enhancement is interpreted in terms of the wavefunction renormalization to quantitatively deduce the reduction of the chiral condensate for the partial restoration of the chiral symmetry. We also discuss our new experiments to deduce the density dependence of the chiral condensate.

EXOTIC ATOMS AND NUCLEI, NUCLEAR PHYSICS / 551

Invited talk: Chiral symmetry restoration in nucleus observed in pionic atoms

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Exploring Novel Techniques for Optical Vortex Beam Generation and Detection Using Mach-Zehnder Interferometer and Spiral Zone Plate

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In this research, optical vortex beams were produced through the use of a Mach-Zehnder interferometer. This involved incorporating two binary spiral zone plates into each arm to generate the desired optical vortices for interference. Interference of these distinct optical vortices, enable us to generate a new optical vortex with integer or fractional topological charges. We demonstrated that the resulting vortex charge is determined by the initial topological charges of the two input vortices. Additionally, a range of beam shapes and light patterns such as petals, doughnuts, ring lattices, fractional vortex beams, and multi-spot beams were created. Furthermore, this method can be utilized to identify the charge of an unknown optical vortex by analyzing the charge of the generated vortex. The Mach-Zehnder interferometer is a double-arm coaxial interferometer makes it particularly useful for meteorological applications. One key advantage of this technique is the ability to adjust the sample positions to produce a variety of optical vortex beams at different distances. The method

was analyzed theoretically and mathematically, and simulation results were confirmed through experimental testing.

EXOTIC ATOMS AND NUCLEI, NUCLEAR PHYSICS / 587

Invited talk: Formation of long lived nuclear molecules in (p, 2He) nuclear reactions on 181Ta and 159Tb

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Formation of long lived nuclear molecules in $(p,^2 He)$ nuclear reactions on ^{181}Ta and ^{159}Tb

Authors: Ihor Kadenko[1]; Borys Bondar [2]; Nadiia Sakhno[1]; Barna Biró[3]; András Fenyvesi[3]

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In nuclear experiments, there are known phenomena when two different nuclei can co-exist during a very short, but certain time. These observations include forced and spontaneous fission of heavy nuclei, fusion of light and/or heavy nuclei, alpha, proton and two-proton decay, nuclear reactions with emission of charged particles like the deuteron, helion etc. Detailed consideration of this unique configuration have led scientists to introduce so called molecule-like nuclear systems, referred as dinuclear systems (DNS), or nuclear molecules, with a corresponding mean lifetime ~ 10^{-20} s.
Our previous research shed light on the possible existence of a bound diproton as an exotic nucleus. As we assumed and then observed in experiments, this nucleus may have lifetime up to several thousand seconds and decay via positron emission, forming a broadened 511 keV peak in the instrumental gamma-spectrum. We designed and carried out experiments for irradiation of ^{159}Tb and ^{181}Ta with protons of about 6 MeV energies to detect annihilation gamma-rays. Notwithstanding, the consideration of 511 keV in instrumental spectra gamma-peak to confirm an existence of a bound diproton is necessary but insufficient because there might be several other positron contributors to form 511 keV annihilation gamma peak after irradiation of metal samples with protons. Therefore, besides 511 keV gamma peak in the instrumental gamma-spectra, the subject of our interest in this research is the characteristic radiation to prove coexistence of ^2He and another heavy nuclei with a mean lifetime, much greater than typical values for DNS.
After irradiation of Ta foil sample at the MGC-20E cyclotron with 5.8 MeV protons at Atomki, Debrecen, Hungary, we have analyzed the dependences of 511 keV gamma-peak intensities vs time as well as K-alpha and K-beta analogical dependences due to EC decay of ^{181}W as the $^{181}Ta(p,n)$ nuclear reaction product. For all these time series, we derived the half-life to be equal 0.47+/-0.02 h. This value is very much different from expected value 121.2 d as the half-life of ^{181}W. Then based on our previous and the current experiments we assumed that the 2He nucleus, being formed in $^{181}Ta(p,^2 He)^{180}Hf$ nuclear reaction, might also decay via EC mode, forming corresponding K-alpha and K-beta series.
These experimental results can be interpreted in favor of the formation of the nuclear molecule, consisting of the stable nucleus ^{180g}Hf and beta-plus and EC decaying ^2He, coexisting at several fm distance. Such coexistence results in the equivalent of 182W nucleus, i.e. formally stable isotope of

tungsten, but the presence of K-alpha and K-beta series confirms radioactive instability of such DNS with the corresponding half-life.
Summing up: in our experiment, we created an atom of W, which might be stable, but it is not because of the presence of two nuclei, one of which is EC and beta+ radioactive. We modeled the experimental conditions to detect the beta+ spectrum of ^{2}He due to the $(p,^{2}He)$ nuclear reaction on ^{181}Ta and ^{159}Tb and concluded the latter isotope is even more preferable for the observation of such a unique DNS configuration.
This research opens up the way to construct DNS of special configuration that might be useful both for fundamental and practical applications, incl. medical purposes.

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Two axes sliding gantry for total-body J-PET / CT scanner

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Abstract

Conventional Positron Emission Tomography (PET) / Computed Tomography (CT) devices use a moving patient table along the scanning axis, where both scanners are positioned sequentially under a single or two envelopes. It's possible to make "whole-body" imaging with conventional devices however, due to repeating discrete examination steps, possibility of artefacts caused by motion is higher than "total-body" imaging approximation which fully covers patients during examination and acquires metabolic data simultaneously. Total-body imaging has also a big advantage to examine the same volume with lower radiopharmaceutical dosage[1,2] compared to whole-body imaging. In the other hand, in total-body PET/CT systems, the axial size of the detector geometry defines the device size relative to covered volume and also a separately moving long table is required to move patients through the gantry bore when same method for conventional PET/CT scanners used in total-body imaging. In contrast to conventional sequential and same axis imaging approximation, Jagiellonian-PET (J-PET) group is developing a total-body scanner[3,4] to utilise PET and CT scanning from different axes but on the same fixed patient table. Due to fixed position patient table, involuntary patient motion caused artifact is less probable and all parts of the scanner can be kept in a compact form in a small examination room. However, construction of such a system is not a straightforward process due to mechanical limitations. The system requires carrying devices heavier than 1000 kg with sub millimetre resolution on crossed axis on the same surface, which is currently not possible via classical linear motion rules. In this work, the status of the current design and construction process for the two axes sliding gantry system[5] is presented. The system contains specially positioned discrete rails and screw miles to make possible two axes scanning on the same surface for PET/CT scanning. Designed system will be constructed at Theranostics Center located in Krakow.

Acknowledgements

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Research University at Jagiellonian University

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PET IMAGING INNOVATIONS / 605

Optical quality control of plastic scintillators for the total-body J-PET scanner

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Optical quality control of plastic scintillators for the total-body J-PET scanner

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Total-body Jagiellonian positron emission tomography (TB-J-PET) is based on long plastic scintillators [1] which decrease cost of the scanner [2]. Total-body PET scanners enable positronium imaging [3], measurements of polarization of photons [4] and beam therapy monitoring [5]. Development of TB-J-PET requires application of transparent plastic scintillators with low light attenuation [6] to build long modules with silicon photomultipliers attached at both ends of the scintillators. For modular TB-J-PET construction we choose BC-408, one of the most transparent plastic scintillator from our previous measurements [7].

Purpose of this research is to verify quality of received plastic scintillators with dimensions 6 mm × 30 mm × 330 mm. The scintillators were inspected for optical and mechanical defects and all dimensions were measured. Scratches, mechanically damaged corners and edges, encapsulated dust and fibers in the volume of scintillators were found under light from a ceiling lamp. Line defects on the as-cast surfaces were easy visible in plane polariscope setup consisted of crossed horizontal and vertical polarizer foils.

Transmittance at the wavelength of maximum emission through 6 mm thick scintillator and technical attenuation length along 330 mm long scintillator were measured on linear CCD array spectrometer for random selected scintillators from each delivered batch. Additionally, scintillators optical homogeneity was measured on light transfer setup consisting of exciting LED and photodiode matrix. Majority of obtained plastic scintillators meet the transparency criteria and are within dimensional tolerances.

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PET IMAGING INNOVATIONS / 535

Invited talk: Total-body multi-parametric PET imaging: recent advancements and future perspective for its clinical adoption

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Total-body multi-parametric PET imaging: recent advancements and future perspective for its clinical adoption

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Dynamic whole-body multi-parametric PET imaging has recently garnered increased interest in nuclear medicine as a potential extension of the standard-of-care static whole-body PET clinical exams to benefit from the absolute quantification of the tracers spatiotemporal multi-parametric uptake features beyond the semi-quantitative standardized uptake value (SUV) images attained with routine static PET exams. The recent trend for multi-parametric PET has mainly been driven by technological advancements permitting the application of streamlined dynamic PET imaging protocols across the total human body extent which could enable the widespread adoption of dynamic PET scans and multi-parametric PET in oncology. More specifically (i) the commercial adoption of whole-body dynamic PET acquisition protocols coupled with direct 4D parametric image reconstruction algorithms, (ii) the advent of commercial total-body human PET scanners, and (iii) the continuous advancements in Time-of-Flight measurements precision in the last decade have collectively paved the way for the streamlined application of multi-parametric PET imaging beyond the limitations of conventional static SUV PET to complement diagnostic, thera(g)nostic and treatment response assessments. Of those developments, the recent emergence of commercial total-body human PET systems combining all aforementioned technologies has undoubtedly been the major driving force to explore the potential of multi-parametric PET translation to the routine clinical workflow as the new standard-of-care PET exam.
However, the actual clinical value of the additional quantitative imaging biomarkers enabled by total-body dynamic and multi-parametric PET imaging protocols has not yet been systematically assessed in the clinical environment for specific oncology, cardiology, neurology and systemic multi-organ interaction studies. In this abstract, we review the latest technological advancements of whole-body multi-parametric PET imaging, the crucial role of total-body PET scan technology for its transformation into a clinically adoptable nuclear medicine exam, the open challenges for its systematic clinical

validation and the future perspectives for its potential clinical translation as the new standard-of-care clinical PET exam.

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Application of spin-polarized positron annihilation spectroscopy to spintronics materials

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Towards the innovation of electronic device technology achieving further energy-saving and new functionality, recently, the spintronics research and development is rapidly advancing. To understand new phenomena related to electron spins associated with materials, unprecedented experimental tools should also be established. Spin-polarized positron annihilation spectroscopy is thought to be a unique tool meeting this requirement.
As a matter of fact, the spin-polarized positron annihilation spectroscopy started to be used for studying ferromagnetic band structures already in 1950's upon the discovery of the parity violation in the weak interaction, i.e., the spontaneous spin-polarization of positrons (electrons) emitted through the beta decay. However, since then, this method has not much been used for long time. One breakthrough was demonstrated as the spin-polarized surface positronium spectroscopy by the Michigan group in 1982 [1]. A decade ago, we have been attempting to revive this old and new technology concerning the vital spintronics field. In this talk, focusing on its application to materials science, I would like to introduce the current status of spin-polarized positron annihilation spectroscopy and the future prospects.
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POSITRONIUM IN FUNDAMENTAL AND MATERIAL PHYSICS / 562

Invited talk: Application of spin-polarized positron annihilation spectroscopy to spintronics materials

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Spectroscopic methods in the study of the effect of the ketogenic diet on glial scar development in terms of time and gender

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The processes occurring in nervous tissue after brain damage are characterized by very high dynamics. Identification of therapies, which applied early or at the appropriate moment can minimize the side effects of brain injury, is of crucial importance. Therefore, in this study we tried to verify the benefits of the use of ketogenic diet (KD) in case of traumatic brain injury (TBI) in rats. During KD 90% of energy is derived from fat metabolism and the diet has clinical applications as an aid in mitigating seizures in drug-resistant epilepsy.
As therapeutic window plays an important role in TBI, four time points (2, 8, 16 and 30 days after the injury) were taken into account during investigation. The spectroscopic techniques allowing quantitative or semi-quantitative as well as topographic biomolecular analysis of tissues were used for the study. These were FTIR, Raman and XRF microscopy. The first two methods were applied to follow the changes in the distribution and accumulation of biomolecules in brain tissue during the glial scar formation. In turn, the last one was utilized for the topographic and quantitative elemental analysis of the area of primary injury.
The obtained results showed decreased content of examined organic compounds within the injury site. This decrease was observed for male and female rats on both diets and different times passing from the primary injury. For the same area the increased content of proteins with beta-sheet secondary structure was found. Raman spectroscopy proved to be highly useful in analysing the changes in lipid structure. It allowed to show the alterations in unsaturation and branching degree of lipids as well as the decreased cytochrome C/DNA and the intensity of amid III band within the injury site. The preliminary topographic elemental analysis carried out for the area of the mechanical damage confirmed the involvement of many tested elements in the process of glial scar formation. The damage area was characterized, among others, by the reduced P and increased Ca and Fe levels. However, the progress over time of changes in the accumulation of these elements varied significantly. The P level in the injury site remained similarly low during the whole time of glial scar formation. The Ca level, very high on the second day after the injury, decreased with time passing from the primary brain damage. In turn, Fe accumulation increased in the first period after the damage and remained at a high level even in the fully formed glial scar.

ARTIFICIAL INTELIGENCE FOR MEDICINE / 571

Deep learning in online adaptive MRI guided radiotherapy at the MRIdian MR-Linac

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Deep learning in online adaptive MRI guided radiotherapy at the MRIdian MR-Linac

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The introduction of combined magnetic resonance (MR) linear accelerators (Linacs) into clinical practice has changed the way fractionated radiation therapy is administered [1]. MR-Linacs enable daily MR imaging (MRI) and online dose optimization to accurately position patients and create treatment plans tailored to the most recent anatomy. Additionally, real-time cine MRI acquisition during irradiation captures breathing, gastrointestinal motions, and patient movements, which allows for pausing the treatment when the beam misses the target (called gating) [2]. Combining gating and daily plan adaptation gives confidence to reduce safety margins. This results in less normal tissue being irradiated, leading to lower toxicity and fewer side effects. Simultaneously, higher daily doses can be delivered to the tumor in fewer fractions, which shortens the total treatment time. However, the benefits of MRgRT at MR-Linacs come at the cost of longer radiotherapy workflows. There are several steps in which artificial intelligence (AI) or, more specifically, deep learning (DL) could bring improvements. With this contribution, we aim to show three research areas we investigate in our group to improve the MRIdian radiotherapy workflow. The main focus is on personalized auto-segmentation.

First, a planning computed tomography (CT) image is acquired for each patient to provide electron density for treatment planning. The electron densities from the planning CT are mapped to the current anatomy for dose calculation at each irradiation fraction. Replacing the actual CT with a DL-generated synthetic CT (sCT) would bypass the need for an additional scan, avoiding the imaging dose, and eliminating the registration error between the CT and MRI [3].

Second, each optimization and re-optimization of a treatment plan requires delineating target volumes and organs at risk (OARs). This is a repetitive and time-consuming task, which could benefit from automation. The most promising techniques developed recently are based on DL. The underlying assumption in DL is that neural networks must perform well on new and diverse examples. However, this assumption can be relaxed for auto-segmentation at MR-Linacs. Fraction images from the same patient are strongly correlated, and we can exploit the segmented planning MRI of each patient. Therefore, teaching each personalized model characteristics that are specific to a given patient but not necessarily shared among the general population can improve auto-segmentation for fractionated treatment.

Third, during gated treatment, the tumor's position is monitored on a 2D cine MRI acquired with a frequency of up to 8Hz. The irradiation is paused when the tumor moves outside a pre-defined position, resulting in duty cycle efficiencies of 20% to 50%. Using long-short-term memory (LSTM) models for tumor motion prediction and transformer-based deformation models for tumor detection could eventually enable multi-leaf collimator (MLC) tracking of the tumor and provide continuous patient irradiation.

Our research showed that personalized auto-segmentation methods outperform conventional population models. In most cases, DL contours could be used for treatment adaptation with no or only minor corrections, suggesting time-saving with respect to the current workflow [4]. LSTMs showed great potential as respiratory motion predictors in MRgRT and were experimentally shown to improve the MLC-tracking performance compared to a baseline no-predictor significantly [2, 5]. A transformer-based deformable image registration model achieved accurate performance for real-time target tracking during MRgRT for a wide range of tumor sites when using a personalized training approach.

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Search for New Particle in Positronium Decay

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Positronium is a bound state consisting of an electron and positron that annihilate each other and form either ortho-positronium or para-positronium. They produce two or more gamma rays by annihilation or radioactive decay through the Quantum Electrodynamics (QED) process. Positronium decay can confirm the QED process and new particle search through invisible decay modes such as milli-charged particles, mirror world, new light X-boson, Dark photon, Axion, and extra dimensions. KAPAE (KNU Advanced Positronium Annihilation Experiment) is a table-top experiment using Na-22 positronium source and has developed with two phases of KAPAE-I and KAPAE-II. They are all hermetic detectors using BGO crystal scintillators and SiPM. The KAPAE-I has a fine segmentation with 200 BGO crystals searching for violation of QED. The KAPAE-II has thick BGO crystals that aim to detect every gamma-rays emitted during the annihilation of positronium and identify missing energy for invisible new particle search. It consists of a 5 × 5 array of BGO scintillation crystals, each measuring 3 × 3 × 15 cm3, along with a SiPM array. After calibration of KAPAE-II, it will be installed in Yemi deep underground laboratory with Pb shielding to remove environmental and cosmic-ray induced background.

POSITRONIUM IN FUNDAMENTAL AND MATERIAL PHYSICS / 561

Key talk: Search for New Particle in Positronium Decay

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Verification of Proton beam Range using photopolymerized PMMA base plastics scintillator

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Compared to photon radiation therapy, charged particle radiation therapy, including protons, has the advantage of excellent biological effects due to high LET (linear energy transfer) and good spatial dose distribution that can focus on cancer cells caused by Bragg's peak [1]. Due to these advantages, there is much interest in treating cancer patients, and in Korea, proton beam treatment is performed in 2 hospitals. Due to the Bragg peak, proton beams always have a lower integral dose in normal tissue than photon rays for patients during radiation treatments. However, uncertainties about the radiation may occur depending on the energy of the human tissue and the proton beam, treatment accessories, etc. Much research is being done to control the quality with Monte Carlo simulation [2], in-vivo [3], 3D QC system, etc. [4]. In this study, we developed optical dosimetry with an MMA-based tissue equivalent plastic scintillator. We confirmed the possibility of being a photometric dosimeter for the 100 MeV proton beams in KOMAC (Korea Multi-purpose Accelerator Complex).

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PET IMAGING INNOVATIONS / 607

Using 3D CNNs for distortion corrections in PET imaging

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Using 3D CNNs for distortion corrections in PET imaging

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In Positron Emission Tomography the problem of image distortion due to scattered photons or accidental coincidences becomes more pronounced for large field-of-view scanners capable of measuring the whole patient in one scan. We propose a novel method of encoding coincidence event information to enhance the efficiency of noise filtration classification. The proposed encoding enables the usage of Convolutional Neural Networks as feature extractors in the classification task. We take advantage of the voxel nature of underlying data and evaluate the performance of the 3-D CNN network to classify true, scattered and accidental coincidences for imaging quality improvement with large field-of-view PET scanners.

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Integrative Biophysical and Computational Approaches for Melanoma Drug Combination Selection via Glycosylation-Based Biomarkers

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Melanoma, a malignancy originating from melanocytes, poses significant challenges in treatment selection due to its heterogeneity and potential for metastasis. Traditional methods of stratifying treatment options often rely on histopathological characteristics, which may not fully capture the underlying molecular diversity of the disease. Moreover, even with an initial response to treatment, melanoma cells can easily develop drug resistance through the emerging activation of compensatory or bypass pathways. To achieve effective and sustainable clinical responses in cancer patients, who become resistant to standard treatment, new and multi-targeted drug combinations are urgently needed. The exponentially increasing number of possible drug combinations makes an experimental approach unfeasible, even with automated drug screening tools. Currently, the scope of collected data together with the methods of their processing and analysis turn out to be crucial for the possibility of further development of oncology.

Recent advancements in biophysical and computational techniques have opened new avenues for personalized medicine, particularly in the realm of glycosylation-based biomarkers. The biophysical properties of melanoma cells and exosomes isolated from melanoma cells, focusing on alterations in glycosylation patterns that contribute to tumor progression will be discussed. Additionally, computational models will be demonstrated for integrating multi-omics data to identify glycosylation signatures associated with treatment response and patient outcomes.

Correlation of experimental data with the results of bioinformatic analysis will allow for the selection of the best drug combinations. New standards for the exchange and archiving of biophysical data will be developed. This will ensure the interoperability of information with other bioinformatics research infrastructures processing biological data. Standardization would facilitate the inclusion of biophysical data in existing and emerging biological and molecular databases.

NOVEL BIOMARKERS FOR THERANOSTICS / 540

Invited talk: Integrative Biophysical and Computational Approaches for Melanoma Drug Combination Selection via Glycosylation-Based Biomarkers

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EDUCATION AND BIO-ALGORITHMS AND MED-SYSTEMS / 616

Invited talk: How do digital technologies fit into clinical reasoning education?

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How do digital technologies fit into clinical reasoning education?

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Clinical reasoning is a complex set of skills that health professionals develop from the early years of their medical education. It involves thinking and acting during patient assessments, diagnostics, and management in clinical settings, while considering the patient's specific circumstances and preferences. Many medical errors have their roots in faults in clinical reasoning. Therefore, it is crucial for medical schools to have capabilities to teach this skill effectively. Digital technologies hold the potential to greatly enhance clinical reasoning education in several ways: by providing instant access to evidence-based information resources, creating interactive virtual learning environments for simulating clinical scenarios, and offering advanced feedback and assessment systems. Digital health tools are increasingly incorporated into the clinical reasoning process as a means to augment health professionals' skills, a development that also necessitates a thoughtful teaching strategy. The aim of this presentation is to take the audience on a journey from the early applications of e-learning and decision support systems, through the use of versatile virtual patient systems, to advanced simulations and artificial intelligence tools, highlighting both the opportunities and limitations of technology-aided clinical reasoning education. By adopting an interdisciplinary approach, the high technology-oriented community can assist medical educators in their task to deliver digital tools and innovative learning opportunities to enhance and modernize clinical reasoning education.

EXTRACELLULAR VESCICLES FOR THERANOSTICS / 606

Possibilities of using extracellular vesicles (EVs) of microbial origin as natural carriers of drugs used in anticancer therapies – EVs-

DDS (EVs-based Drug Delivery System)

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Possibilities of using extracellular vesicles (EVs) of microbial origin as natural carriers of drugs used in anticancer therapies – EVs-DDS (EVs-based Drug Delivery System)

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At present, many drug delivery systems are based on chemically obtained nanoparticles. However, the world strives to develop technologies that will burden the environment as little as possible. A very promising alternative to the nanocarriers mentioned above are extracellular vesicles (EVs). These nanosized structures are produced by most of the living cells, e.g., probiotic yeasts or nonpathogenic bacteria. EVs are naturally filled with different bioactive cargo, e.g., proteins, lipids, RNAs, and pigments. Cells use these compounds to communicate with each other. Present studies mainly focus on pathogenic microorganisms that infect the human body and secrete EVs for successful and long-term host colonization.

Our work focuses on nonpathogenic microbes and the EVs they produce because the knowledge about them is very limited. As main EVs' producers, we have chosen *Saccharomyces boulardii* CNCM 1-745 (Enterol®, BIOCODEX) and *Janthinobacterium lividum*. First, we concentrated on getting to know these nanoparticles well by choosing isolation and purification methods, NTA analysis (measuring the size and concentration of EVs), and looking closer at their protein cargo via MS analysis. Next, we confirmed their *in vitro* safeness on the human intestinal cells' metabolism through various tests – MTT / ROS / CV assays and FDA/Pi staining. One of the most crucial tests was confirmation that EVs can transfer their cargo into human cells. To do so, we loaded EVs with NileRed (lipophilic fluorescence dye) or doxorubicin hydrochloride (hydrophilic fluorescence cytostatic drug) and incubated them with cells. We confirmed that both loaded compounds were transferred into the cells, and the doxorubicin stayed active.

The second aim of our work is to look closer at violacein (VIO) – a multifunctional compound produced by bacteria of the genus *Janthinobacterium lividum*. This is not only an intense purple pigment but also an anticancer and antimicrobial agent (for *Staphylococcus aureus* and other G+ bacteria). Literature gives us many more functions as an antioxidant and inhibits inflammation. One of the biggest problems with violacein is that this compound is totally water-insoluble. Bacteria handle this by packing VIO into EVs. The water sample of EVs-VIO is much more stable than the methanol extract from bacteria containing VIO. Thanks to this, we can isolate quite a large amount of this compound and transfer it to the cells with no worries about alcohol's influence on cells.

Our results opened a new research gap for further testing with EVs as new drug carriers and obtaining a promising EVs-based Drug Delivery System (EVs-DDS).

Keywords: *Saccharomyces boulardii*, *Janthinobacterium lividum*, extracellular vesicles, EVs, intestinal cells, Doxorubicin, Nile Red, Violacein, EVs-based Drug Delivery System, EVs-DDS

QUANTUM ENTANGLEMENT IN PET / 581

Positron emission tomography imaging using polarization- correlated annihilation quanta – experimental study

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Positron emission tomography imaging using polarization-correlated annihilation quanta – experimental study

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Positron emission tomography (PET) is a medical imaging modality that utilizes positron annihilation in matter into two gamma photons, subsequently detected in coincidence. These photons are emitted back-to-back with 511 keV energies, and their polarizations are orthogonal. The orthogonality is a property not yet utilized in commercial PET systems, that could help distinguish true coincidences from random ones and therefore reduce background noise that has no such correlation. Measurement of the polarization-correlated gamma photons through their respective Compton scatterings in polarimeters enables exploration of this property, which is reflected in the distribution of the difference of their azimuthal scattering angles, that reflects the initial orthogonality of the polarizations. We use single layer polarimeters built with GAGG(Ce) scintillating crystals, 3 mm x 3 mm x 20 mm each, set in a 16x16 matrix with 3.2 mm pitch, coupled to silicon photomultipliers. Two such matrices are mounted on a circular gantry of the PET demonstrator, opposite of one another with the possibility of setting different diameters and precisely rotating around the source placed in the scanner's field of view. The set-up was tested at the University Hospital Centre Zagreb with sources having clinically relevant activities, such as Ge-68 line sources and the small animal NEMA phantom filled with Ga-68 solution. Preliminary results show that a source image can be reconstructed using solely correlated Compton scattering events. We will present the study of the scanner's properties and discuss the possibility of signal-to-background enhancement through measurements of the correlated quanta at different activities.

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Design, Synthesis, and Evaluation of Novel Gold Nanorod-Based Theranostic Agents for Anticancer Therapy

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Introduction

Pancreatic ductal adenocarcinoma (PDAC) is recognized as one of the most hypoxic and treatment-resistant tumor types. To address this challenge, we have designed AuNRs-GEM, a novel theranostic agent targeting PDAC. This agent combines the chemotherapeutic efficacy of gemcitabine with thermal therapy induced by near-infrared (NIR) light absorption.

The dual therapeutic approach leverages the benefits of both chemotherapy and localized hyperthermia. Gemcitabine, a standard chemotherapeutic agent, is known for its effectiveness against PDAC, while hyperthermia, induced by NIR absorption by gold nanorods (AuNRs), enhances drug delivery by increasing vessel dilation and altering tumor oxygen partial pressure (pO2). This multimodal treatment strategy aims to overcome the inherent resistance of hypoxic tumors to conventional therapies.

Additionally, AuNRs-GEM enables high-resolution imaging through photoacoustic imaging and computed tomography (CT), providing valuable insights into tumor morphology and treatment efficacy. By integrating these diagnostic and therapeutic modalities, we aim to improve the overall treatment outcomes for patients with PDAC.

Methods

The AuNRs-GEM nanohybrid was synthesized via amide bond formation between carboxylated gold nanorods and gemcitabine using the water-soluble carbodiimide method (EDCI-NHS). This nanohybrid was characterized using UV-VIS, FT-IR, and XPS spectroscopies. The concentration of AuNRs-GEM was established using RP-HPLC and TXRF techniques. The morphology and structure of the gold nanomaterial were determined by TEM and SEM, followed by DLS measurements and zeta potential examination.
The gold theranostic agent was tested in vitro against mouse and human PDAC cell lines (Panc1, Pan_O2, AsPc1). Metabolic activity and cell number were assessed after exposure to AuNRs-GEM and light in both hypoxic and normoxic conditions. A C57BL/6J mouse PDAC model was established utilizing the Pan_O2 cell line. Tumor oxygenation was measured using electron paramagnetic resonance (EPR) spectroscopy, employing Jiva-25 or Bruker E540L instruments, with trityl OX071 or Oxychip as the spin probe. Tumor anatomy and vascular structure were evaluated using ultrasound, including B-mode and Power Doppler with Vevo F2 from FujiFilm VisualSonics.
The therapeutic approach involved administering AuNRs-GEM (gold nanorods loaded with gemcitabine) combined with hyperthermia using near-infrared light (~808 nm). The treatment regimen included six doses of AuNRs (approximately 1 μg/ml) along with GEM (approximately 45 mg/kg BW) and near-infrared heating (approximately 3 x 1.5 min during 12 min) administered every 72 hours. All experiments obtained approval from the Local Ethics Committee (no. 151/2022 and no. 250/2020).

Impact

The developed compound holds the potential to enhance the efficacy of unresectable PDAC in the future. pO2 can be predictive of therapy results.

Acknowledgment

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NOVEL BIOMARKERS FOR THERANOSTICS / 541

Invited talk: Design, Synthesis, and Evaluation of Novel Gold Nanorod-Based Theranostic Agents for Anticancer Therapy

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Calibration of PALS system with CRM materials for bio-medical studies.

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Positron annihilation lifetime spectroscopy (PALS) is a powerful technique in materials science that allows the investigation of the properties and behavior of positrons in various materials [1]. This technique involves the detection, measurement, and interpretation of the lifetimes of the positrons, which provides valuable information on the electronic structure and dynamics of materials. By analyzing the positron lifetimes, researchers can gain insight into defects, vacancies, and other imperfections in materials, as well as investigate the diffusion and trapping processes of positrons. In addition to using PALS in the investigation of solid structures, it can also be used to investigate biological samples[1 - 6].
Combining PALS technique with PET imaging [6 - 8] makes it possible to study the human cells and tissues in nanometer scale and enable to use positronium properties as additional diagnostic parameter. The first positronium images have recently been taken ex vivo [2] and in vivo [8]. Positronium imaging as well as PALS setup need to be correctly calibrated for positronium lifetime studies in the range relevant for biological materials. This can be obtained by characterizing it with CRM materials [9], [10].
Here we present results from calibration te PALS system with CRM materials. Positronium Lifetime Spectroscopy were used to obtain positron lifetime of Sodium-22 source with activity around 1.34 MBq only covered by kapton film and later parafilm in Aluminium chamber. Source was placed between plates made from certified materials No_30 (Polycarbonate) and No_40 (Fused silica) made by National Institute of Advanced Industrial Science and Technology (AIST) in Tokio, Japan to ascertain if parameters where correctly identified. All measurements were made at a temperature of 22 ℃.
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QUANTUM ENTANGLEMENT IN PET / 580

Studies of the quantum entanglement of photons from electron-positron annihilation in the porous material using J-PET scanner

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Studies of the quantum entanglement of photons from electron-positron annihilation in the porous material using J-PET scanner

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Quantum entanglement, a fundamental phenomenon in quantum mechanics, remains elusive in the high-energy regime of photons. According to quantum electrodynamics, annihilation photons from the singlet state of positronium decay exhibit entangled polarization [1]. However, the high energy of these photons (511 keV) makes it impossible to use traditional polarizers. We address this issue by utilizing Compton scattering as a polarization analyser, exploiting the strong dependence of the scattered photon direction on the incident photon polarization [2, 3]. By measuring the angle between the scattering planes of the two annihilation photons, we investigate entanglement at these high energies [4, 5].

The J-PET detector, made from plastic scintillators, is particularly well-suited for this research due to its proficiency in registering Compton scattering events [6, 7]. Our preliminary results indicate a clear signature of non-maximal entanglement between the annihilation photons in the porous medium. In this presentation, we will highlight the advanced features of the J-PET detector and present our findings on the polarization correlation of annihilation photons.

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MEDICAL IMAGING INNOVATIONS / 595

Invited talk: Superparamagnetic nanoparticles – a versatile platform for imaging and theranostic innovations

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Superparamagnetic nanoparticles – a versatile platform for imaging and theranostic innovations

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Super-Paramagnetic Iron Oxide Nanoparticles (SPIONs) offer the potential for enhancing contrast in Magnetic Resonance Imaging (MRI) and also, when suitably radiolabelled, for diagnostic imaging with PET, PET-MRI and SPECT. In this talk, I will present an overview of our research on imaging with SPIONs, including imaging brain tumours and imaging with ultra-low field MRI. I will also briefly discuss how SPIONs may provide a therapeutic enhancement for theranostics, both for MRI-guided radiotherapy and in nuclear medicine, where novel targeted radiotherapeutic approaches are being developed.

Yes

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Long-term Covid-!9 effect on reproductive health - diseases versus vaccination

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Long-term Covid-19 effect on reproductive health – disease versus vaccination

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There has been noted a transient decreae in quality of reproductive health possibly linked with activation of innate immunity and the outburst of cytokines – both locally (in male and female reproductive tracts) and systemically – due to Covid-19 or post-vaccination adverse reaction. Elevated level of IL-8 in peripheral blood/semen appeared to demonstrate a pro-dromal meaning. Elevated ROS secretion connected with IL-8 presence (which recruits leukocytes to semen or other organs) may increase a risk of reproductive failure both at natural or assisted pro-creation or provoke substantial sperm DNA damage (fragmentation). Interdependence between elevated cytokines and stimulation of pro-oxidants has been well known both locally and systemically (also due to SARS-Cov-2 vaccination scheme) and can be suspected when boosting patients with vaccine next doses. In our earlier findings we have reported statistically significant elevation of blood cytokines in males with idiopathic infertility. Similar scheme has been visible when several vaccine boosting doses were applied against SARS-Cov-2. Both males and females present a risk for elevated cytokines due to past Covid-19 disease and repeated vaccinations. Therefore, we have been treating patients with different anti-TNF alfa preparations (Enbrel. Idacio) but with different effects. Often, Enbrel as competing chimeric protein did augment further cytokines release. In such cases steroid intervention together with standard immunosuppressants was desired, however, this was also non effective in all the cases. There is known an adverse effect of TNFalpha at the stage of implantation when destroying early embryo or inducing abortion. In turn, in males, an Aitken hypothesis stated a substantial danger for 1) gene mutation responsible for spermatogonial stem cell renewal, 2) sperm DNA damage with consequences for pro-creation, 3) subsequent mutations in DNA hot spots with direct effect on neuro-developmental diseases

Opening / **527**

Opening talk: Long-term Covid 19 effect on reproductive health-vaccination versus disease !

PET IMAGING INNOVATIONS / **537**

Invited talk: Ultrafast Timing Reconstruction-free Direct Positron Emission Imaging (dPEI)

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Ultrafast Timing Reconstruction-free Direct Positron Emission Imaging (dPEI)

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Three-dimensional biomedical imaging techniques, including X-ray computed tomography (CT), single-photon emission computed tomography (SPECT), and positron emission tomography (PET), measure one- or two-dimensional projections from the object of interest. These projections are subsequently reconstructed into cross-sectional images or three-dimensional image volumes using analytic computed tomography algorithms. In all these imaging modalities, a measured data point does not have a 1:1 correspondence with a point in image space, and the spatial distribution of the signal must be inferred by a reconstruction step. Additionally, accurate tomographic image reconstruction depends on adequate angular sampling of the data. Uniquely, positron-emitting radiotracers used in PET emit a pair of annihilation gamma photons per radioactive decay in back-to-back directions. Therefore, ultimately, cross-sectional images or three-dimensional images of the radiotracer distributions can be directly obtained by simply measuring the difference in arrival time of the two photons without any reconstruction step. The first demonstration of this reconstruction-free positron emission imaging was achieved using two ultrahigh timing-resolution gamma-ray detectors and convolutional neural networks, a technique referred to as direct positron emission imaging (dPEI). By removing the typical constraints associated with the sampling necessary for tomographic reconstruction, dPEI opens up many new possibilities for designing novel imaging systems. This presentation will focus on 1) the principle of dPEI, 2) the current progress and technology roadmap toward dPEI scanner systems, and 3) the new opportunities for the application of dPEI in biomedical research.

PARTICLE THERAPY MONITORING / 583

Key talk: Image-guided FLASH proton therapy

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Image-guided FLASH Proton Therapy

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Image-guidance and dosimetry of the in-vivo proton range verification is one of the most underinvested aspects of radiation cancer treatment. The scarcity of sensitive instruments and treatment protocols for precision monitoring of effects of beam radiation leaves much room for improvement. This is despite that such measurements may dramatically enhance the treatment accuracy and lower the post-exposure toxicity, improving the entire outcome of cancer therapy.
In this talk, we will discuss designing and building of an in-beam time-of-flight positron-emission-tomography (PET) scanner to be tested in pre-clinical studies at Proton Therapy Center of MD Anderson Cancer Center in Houston. We will also discuss selected results of recent experiments with FLASH proton beam irradiations of phantoms and other related ideas towards improving and expanding the use of PET detectors, including the total body imaging. This endeavor has been made possible by the support of the U. of Texas – Portugal program at the University of Texas at Austin.

PET IMAGING INNOVATIONS / 603

Invited talk: New tricks with old PETs

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New tricks with old PETs

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Adaption and redeployment of ex-clinical PET systems enables novel solutions to problems in physics and engineering. Positron emission particle tracking (PEPT) uses modified positron cameras to measure the trajectory of a freely moving tracer particle in investigating the dynamics of particulate and multiphase flows. From the time series trajectory data kinematic quantities including velocities and accelerations are derived. Residence time distributions are determined without correction for attenuation or scattering and resolved at spatial resolution surpassing that of the point spread function.

Developments have been made in all aspects of positron imaging: radioisotope production and radiochemistry meet the needs of single tracer particles and industrial settings, and bespoke data acquisition systems acquire singles and coincidence information at high time resolution with flexibility in processing. Modular detector geometries are constructed arbitrarily, without constraint of field-of-view uniformity or production of image artifacts, underpinned by advanced computation and Monte Carlo modelling.

Deployed as general-purpose large scale pixellated detector arrays, new approaches are being explored. Digital data acquisition enhances the scintillator block detector readout, improving spatial uniformity and signal to noise ratio. Measurement of the angular distribution of gamma emission cascades and positronium decay independently provide information about the local chemical environment to the tracer. System modifications open possibilities for multimodal measurements including single photon and X-ray tomography. New tricks are being realised with these technologies, paving the way for enhanced measurement applications in particle and flow dynamics.

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Biological Multiplexing with PET: Technologies that enable the ability to interrogate multiple disease biomarkers in a single PET imaging session

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In this paper we describe methods that facilitate what we believe will be an important new direction for PET: The ability to image more than one positron-emitting tracer in a single PET imaging session. Molecular-based characterization of the hallmarks of cancer, neurological disorders, and cardiovascular disease relies on the ability to study multiple disease biomarkers. However, to date, all commercially available PET scanners do not have the ability to visualize and quantify more than one biomarker per study, owing to the indistinguishability of positron annihilation photons emitted by the associated radiotracer contrast agents administered into the patient. Performing separate PET scans with different tracers on different days is logistically very challenging and thus never done in practice, and the status of different biomarkers would likely change between scans performed weeks or months apart. However, if a tracer is labeled with a positron emitter that also emits a prompt gamma ray that has a much higher energy than 511 keV, it is possible to distinguish that tracer from one labeled with a pure positron emitter, as the former yields a triple photon coincidence, comprising two 511 keV photon + one higher energy interaction. In this abstract we discuss PET system, signal processing algorithms, and tracer requirements to enable clean unmixing of up to three tracer signals that, if successful, will allow us to interrogate up to three disease biomarkers in a single PET imaging session. We hypothesize that this capability would give us a more complete "molecular" picture of the patient's disease, leading to more effective treatments.

PARTICLE THERAPY MONITORING / 594

Invited talk: Compton cameras for cancer treatment assessment

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Compton cameras for cancer treatment assessment

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Compton cameras are showing promising results in different medical imaging areas. The IRIS group has wide expertise in the development of Compton cameras for medical applications, including protontherapy treatment monitoring and assessment of radionuclide therapy.
Starting from a basic prototype, the group has improved its capabilities and modified the system towards the requirements of those two applications. The system is based on LaBr3 crystals coupled to SiPM arrays. The initial prototype, which has now reached the third version (MACACO III) employs the ASIC VATA64HDR16, driven by the AliVATA readout board. In the latest version (MACACO III+), employed for radionuclide therapy assessment, the device features two planes, the first one composed of one detector and the second one with four detectors. The system has shown very promising results in this application in the visualization of different radionuclides.
An alternative version (MACACOp) has been developed employing the ASIC TOFPET2 from PETSYS, in order to improve the timing resolution and readout speed for proton therapy treatment monitoring. This ASIC has also enlarged the detector dynamic range. After the successful tests carried out with the two systems at the Krakow protontherapy centre, where 2 mm proton range variations could be visualized, the device has been tested at the Quironsalud protontherapy centre in Madrid. The last version, known as FALCON, also features four detectors in the second plane and it has been able to reconstruct the prompt gamma distribution in the challenging conditions imposed by the accelerator.

QUANTUM ENTANGLEMENT IN PET / 577

Invited talk: Probing polarization correlations of annihilation quanta in Compton scattering experiment and their implementation in Positron emission tomography

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Probing polarization correlations of annihilation quanta in Compton scattering experiment and their implementation in Positron emission tomography

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Annihilation quanta emerging after positron annihilation have orthogonal polarizations and are predicted to be entangled. While the polarization correlations of back-to-back quanta have been widely studied, the behavior and the underlying nature of the polarization correlations of quanta following a Compton scattering have not been fully explored yet. Furthermore the implications and possible benefits of using polarization correlations in Positron emission tomography are also yet to be systematically evaluated. We designed, assembled and put into operation a modular gamma-ray polarimetry system - the Single Layer Gamma-ray Polarimeter (SiLGaP). It is based on single-layer detectors where the Compton scattering is reconstructed in a single scintillator matrix and the gamma ray polarization can be measured, based on the azimuthal scattering angle. The system was used to measure the polarization correlations of annihilation quanta following a Compton scattering of one

of them and as a strong correlation persisting at low Compton scattering angles (<50°) was reported. I will present the measurements of the correlations at large scattering angles (=>50°) where they seem to show a significant change in behavior. I will also report on the status and the outlook of the experimental evaluation of polarization correlations in Positron emission tomography undertaken with the SiLGaP system.

EXTRACELLULAR VESCICLES FOR THERANOSTICS / 604

Invited talk: Probing red blood cell - derived microparticles (RMPs): Insights from Raman spectroscopy and complementary techniques

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Probing red blood cell - derived microparticles (RMPs): Insights from Raman spectroscopy and complementary techniques

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Red blood cell (RBC) microvesicles, intricately linked to cellular, serve as crucial indicators of cellular health and functionality. Lecture sums up the dynamic alterations in RBC membranes and RBC-derived microparticles (RMPs) due to different pathologies 1-4, employing a multi-faceted approach integrating atomic force microscopy (AFM), biochemical assays, and advanced spectroscopic techniques such as surface-enhanced Raman spectroscopy (SERS) and tip-enhanced Raman spectroscopy (TERS)5.

Our findings unveil a progressive evolution in RBC membrane characteristics, manifesting in changes in membrane height, diameter, and the emergence of RBC-derived microparticles (RMPs) due to RBCs storage2,3 as well as RBCs obatined from mice model of atherosclerosis4. Utilizing AFM, we discerned the early onset of vesiculation, emphasizing its utility in visualizing RMPs even at nascent stages. Importantly, we establish a correlation between membrane lipid leakage and RMP formation, indicative of a sex-specific response to storage conditions. Notably, male RBCs exhibit heightened susceptibility to storage-induced alterations, characterized by accelerated membrane lipid leakage and reduced deformability, contrasting with the resilience of female counterparts. Moreover, employing surface-enhanced Raman spectroscopy (SERS) and tip-enhanced Raman spectroscopy (TERS), we delve into the nanoscale characterization of extracellular microvesicles (EVs) and their membranes5. Our study underscores the potential of SERS and TERS in delineating the biochemical composition of EVs, discerning individual amino acids, protein, and lipid compartments.

These findings underscore the imperative for refined strategies in blood product management, advocating for tailored approaches considering sex-related disparities in RBC response to storage conditions. Furthermore, our study sets the stage for future investigations leveraging spectroscopic techniques for disease diagnosis and therapeutic interventions, propelled by a nuanced understanding of EV dynamics and functionality.

Keywords: Red blood cells, Microvesicles, Raman spectroscopy, Atomic force microscopy, Surface-enhanced Raman spectroscopy, Tip-enhanced Raman spectroscopy, Biomedical applications.

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Differential Cross Sections Measurement of 12C fragmentation on C, O and H in the Energy Range of interest for Carbon Ion Therapy Applications.

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In Particle Therapy treatments with carbon ions, the carbon ion fragmentation might occur in the interaction with tissue nuclei, changing the planned dose release inside the patient body. The study of the nuclear fragmentation at the PT beam energies is important for the development of even more specific treatment plans and, moreover, for the development of range monitoring techniques based on charged secondary particles. In this contribution, the preliminary results of a data taking performed at the CNAO particle therapy center (Pavia, Italy) by the FOOT collaboration will be presented. The production of protons, deuterons and tritons fragments, detected at 32, 60 and 90 degrees, generated by carbon ion beams of 115-351 MeV/u kinetic energy impinging on thin targets of graphite (C), PMMA (C2O5H8) and polyvinyl-toluene (plastic scintillator, CbHa) has been measured. The differential production cross sections of 12C beam on C, O and H have been obtained exploiting the target subtraction strategy. The experimental results have been compared to the Monte Carlo simulation by means of the FLUKA code. Thin plastic scintillator detectors have been exploited for the fragments time-of-flight measurement. The deposited energy in LYSO crystals has been used to perform the fragment charge identification. An unfolding technique has been applied to express the preliminary results of the differential cross sections as a function of the kinetic energy of the fragments at production.

PARTICLE THERAPY MONITORING / 626

Differential Cross Sections Measurement of 12C fragmentation on C, O and H in the Energy Range of interest for Carbon Ion Therapy Applications

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Study of defects in TiO2 polymorphs using positron annihilation

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Titanium dioxide (TiO2) is an important photocatalytic material that facilitates environmentally important chemical reactions such as the splitting of water to produce hydrogen or photocatalytic reduction of CO2. In addition, TiO2 as an inert and non-reactive substance that does not infers with active ingredients is widely used in pharmaceuticals as an essential component of drug coatings. Functional properties, e.g. catalytic activity of TiO2, are strongly influenced by point defects. One of the most interesting phenomena is the room temperature ferromagnetism observed in TiO2 thin films and some nanopowders. The origin of this phenomenon is attributed to vacancies in the subs-surface region of TiO2, although the corresponding physical mechanism is still not fully elucidated. For these reasons it is important to characterize point defects in TiO2. Positron annihilation spectroscopy (PAS) using positron or positronium as a probe of open volume defects is a powerful tool for defect studies. This work presents the results of PAS investigations on three most important TiO2 polymorphs: anatase, rutile and brookite. The TiO2 polymorphs have been investigated in the form of polycrystalline powders and nanopowders, pellets compacted from the powders and sintered ceramics. Experimental results were compared with ab-inito calculations of positron lifetimes in various polymorphs. Anatase was found to have the most open structure and exhibit the longest positron lifetimes. In contrast, the shortest positron lifetimes were observed for rutile. Polycrystalline and nanocrystalline powders contain vacancies, vacancy clusters and nanoscale porosity where positronium forms. Sintering process results in disappearance of the nanoscale porosity while vacancy clusters remain also in sintered ceramics.

EXTRACELLULAR VESCICLES FOR THERANOSTICS / 533

Invited talk: The role of extracellular vesicles secreted by senescent vascular smooth muscle cells in modulation of immune cell function

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The role of extracellular vesicles secreted by senescent vascular smooth muscle cells in modulation of immune cell function.

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Aging is a complicated biological process leading to progressive deterioration of physiological function and increased vulnerability to death and diseases. Recently it was demonstrated that aging at the cellular level – cellular senescence, contributes to aging of the organism but also promotes development of age-related diseases. One of the most important features of senescent cells, named Senescence Associated Secretory Phenotype (SASP), is increased secretion of many bioactive factors like cytokines, growth factors, chemokines and matrix modifying enzymes. Apart from a myriad of soluble proteins, extracellular vesicles (EVs) were shown to participate in SASP. Factors secreted by senescent cells influence microenvironment and promote low grade inflammation associated with aging. Atherosclerosis is a commonly recognized inflammatory disease that affects elderly people. Importantly it was demonstrated that senescent cells accumulate in atherosclerotic plaque. However little is known about the influence of SASP on immune cells that contribute to plaque development. Thus our study aimed at revealing the role of extracellular vesicles secreted by senescent human vascular smooth muscle cells (hVSMCs) in the modulation of T cell functioning. We performed unbiased proteomic analysis of EVs, which revealed marked differences in the EVs composition derived from senescent cells (senEVs) compared to young hVSMCs. Moreover we found that senEVs carry proteins involved in the regulation of immune response. Accordingly, we demonstrated that EVs secreted by senescent cells influence production of cytokine by T cells and monocytes. Altogether our results suggest that EVs secreted by senescent VSMCs may facilitate inflammation having deleterious impact on atherosclerosis development.
This work was supported by National Science Center grants UMO-2014/15/B/NZ3/01150, UMO-2018/31/B/NZ3/02931

POSITRONIUM IN MEDICINE / 530

First positronium imaging of humans

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A vision to increase the availability of PET diagnosis by combining a low-cost modular J-PET tomograph with the 44Ti/44Sc generator

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The poster will present the prospects for increasing the availability of PET diagnostic by combining cost-effective, lightweight and easily portable modular J-PET with the ^{44}Ti/^{44}Sc generator. J-PET is constructed based on the low-cost axially arranged plastic scintillators [1, 2] that may enable construction of PET scanners 5 to 10 times less expensive compared to current PET systems which are based on crystal detectors [1]. Development of the radionuclide ^{44}Ti/^{44}Sc generator with the 60 years half-lifetime [3-10] would facilitates long-term onsite production of ^{44}Sc labelled radiopharmaceuticals, eliminating the need for extensive and costly infrastructure typically associated with nuclear medicine. Presently applied ^{68}Ge/^{68}Ga generators with the 270 days half-lifetime [11] require renewal every year. ^{44}Ti/^{44}Sc generator could in principle be purchased once for half a century. This feature, combined with the scanner's low weight and high portability, allows for deployment in remote and underserved regions, thus democratising access to advanced medical imaging technologies. We explore the prospects of the modular J-PET and discuss its broad medical applications, emphasising its potential to revolutionise the field of nuclear medicine by providing high-quality imaging solutions anywhere in the world.

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Mirror Matter in Ortho-Positronium Decay Searches using the J-PET Detector

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Positronium (Ps), governed by Quantum Electrodynamics (QED), offers a fascinating realm for exploring fundamental physics. Monte Carlo simulations of its decay shed light on diverse particle physics aspects. The development of the J-PET setup [1], a novel tomography system at Jagiellonian University utilizing scintillator detectors with high angular and timing resolutions, not only facilitates multi-disciplinary studies encompassing fundamental physics tests, medical research, and quantum entanglement measurements [2, 3], but also enhances our capacity to investigate positronium decays in pursuit of potential dark matter (DM) candidates, a lingering enigma within the current SM framework.

In our research, we are utilizing the J-PET detector to investigate ortho-positronium (o-Ps) decays as part of our ongoing quest for dark matter. The primary objective is to explore mirror matter, a proposed form of matter aimed at reinstating parity invariance and considered a potential candidate for the Universe's DM component. Our study aims to stretch the current boundaries of precision measurement regarding the decay width of o-Ps decay to three gamma quanta, to compare these findings to the precise description in our pursuit of understanding the elusive nature of dark matter [4].

We acknowledge support from the National Science Centre of Poland through Grants No. 2019/35/B/ST2/03562, 2020/38/E/ST2/00112, the Ministry of Education and Science through grant no. SPUB/SP/490528/2021, and the SciMat and qLife Priority Research Area budget under the auspices of the program Excellence Initiative-Research University at Jagiellonian University.

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POSITRONIUM IN FUNDAMENTAL AND MATERIAL PHYSICS / 584

Key talk: Experimental studies on the positronium negative ion, a three-body bound state composed of a positron and two electrons

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Experimental studies on the positronium negative ion, a three-body bound state composed of a positron and two electrons

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The positron, an antiparticle of the electron, is bound to an electron to form positronium (Ps). Ps is a system composed only of leptons and is used to verify quantum electrodynamics and to measure void size distributions in materials. As an example of the lightest neutral atom, it is also valuable in atomic physics.
Ps can further combine with another electron to form a positronium negative ion (Ps^-). This ion is a system of three particles of equal mass and has been the subject of numerous theoretical studies since Wheeler predicted the existence of Ps^- in 1946 [1]. The first actual production of Ps^- was performed by Mills in 1981 [2] when he passed a slow positron beam through a thin carbon film and observed Ps^- emission from the downstream. Since the discovery in 2008 that Ps^- can be produced with high efficiency using alkali metal coated surfaces, several new experimental studies on Ps^- have been conducted [3]. For example, there have been studies on photodetachment of an electron in Ps^- by irradiation with laser light [4], observation of a resonance state of Ps^- using the photodetachment techniques [5] and measurement of the binding energy of Ps^- by examining the threshold of photodetachment [6]. Recently, the dependence of photodetachment on laser light polarization angle has also been studied [7].
Ps^- can be easily accelerated by an electric field, and photodetachment in this state can generate an energy tunable Ps beam [8]. Ps beams generated in this way have been used for experiments of motion-induced resonance of Ps [9], observation of Ps transmission through graphene films [10] and quantum interference of Ps wave functions.

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Kaonic Atoms with the SIDDHARTA-2 experiment

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Kaonic atoms are a unique tool to explore quantum chromodynamics in the strangeness sector at low energy, with implications reaching neutron stars and dark matter. Precision x-ray spectroscopy can fully unlock the at-threshold isospin dependent antikaon-nucleon scattering lengths, via the atomic transitions to the fundamental level. While the SIDDHARTA experiment at the INFN-LNF DAΦNE collider successfully measured kaonic hydrogen, its successor SIDDHARTA-2 is finalizing its data taking campaign aiming to finally fully disentangle the isoscalar and isovector scattering lengths via the measurement of kaonic deuterium. An overview of the first experimental results

from a preparatory run for the SIDDAHARTA-2 experiment, as well as the future plans, will be presented.

Publication agreement (CC BY 4.0):

Yes

EXOTIC ATOMS AND NUCLEI, NUCLEAR PHYSICS / 552

Invited talk: Kaonic Atoms with the SIDDHARTA-2 experiment

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Toward More Affordable Multi-dimensional PET Imaging

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Simultaneous imaging of the different hallmarks of a disease and of the contributing organs can provide more detailed understanding of its microenvironment and onset. This is usually done with imaging of tracers targeting different molecular pathways and/or organs on different days due to PET inherent limitation.
PET imaging is a powerful tool for studying metabolic and biochemical functions, pharmacology, and pathology in the human body. Combined information from different disease hallmarks and contributing organs can synergistically allow a more detailed understanding of their interactions and of the underlying microenvironment, and hence can deepen our comprehension of the crucial biological factors influencing the onset of the disease, and, its progression and response to therapy. Due to PET inherent limitation and relatively short axial field-of-view (AFOV), this is achieved through multiple imaging sessions, usually performed on different days, thus reducing the overall quantitative accuracy and clinical feasibility. These limitations can be overcome using non-exotic imaging approaches and analyses combined with long AFOV scanners, a technology whose wide dissemination continues to be limited due to the associated high costs.

In this presentation, the aforementioned PET limitations will be discussed. Specifically, results from ongoing clinical trials on dual-tracer PET imaging using dual-compartmental kinetic modeling in neuro-oncology and neurology will be presented, as well as preliminary findings on PET imaging of brain-heart axis. Furthermore, potential solutions for cost-effective PET scanners with long AFOVs, specifically with sparse detector configuration, will be presented together with the corresponding physical performance evaluation.

Publication agreement (CC BY 4.0):

Yes

TOTAL-BODY PET / 529

Key talk: Toward More Affordable Multi-Dimensional PET Imaging

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EXTRACELLULAR VESCICLES FOR THERANOSTICS / 600

Key talk: Developing a strategy to measure concentrations of extracellular vesicles in human plasma for biomarker exploration

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Detectors for the Study of Nuclear Structure and Related Developments

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Large arrays of gamma-ray detectors continue to provide new information about the atomic nuclei at extremes of angular momentum and isospin. Highlights of our involvement in developing different types of gamma-ray detectors for nuclear structure studies will be presented [1,2,3,4,5]. The use of these detectors for fundamental nuclear physics research and applications will be discussed.

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PARTICLE THERAPY MONITORING / 622

Key talk: A high-resolution, spherical in-beam PET scanner for range monitoring and biological guidance of ion beam therapy

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A high-resolution, spherical in-beam PET scanner for range monitoring and biological guidance of ion beam therapy

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Precision radiation research in small animals is a young, emerging field that aims to provide new experimental insights into the response of tumours and normal tissue to ionizing radiation in order to advance the understanding of the underlying complex mechanisms of radiation effects and provide the basis for new therapeutic strategies. Despite the recent development and commercialization of modern small animal radiotherapy research platforms for X-ray irradiation, no commercial systems exist yet for ion beam therapy. To fill this gap, in the ERC (European Research Council)-funded project SIRMIO (Small animal proton irradiator for research in molecular image-guided radiation-oncology, www.lmu.de/sirmio) we developed an innovative platform to enable precision image-guided small animal irradiation at clinical proton therapy facilities. In this context, we designed and realized a novel high-resolution, spherical in-beam PET scanner which can serve for in-vivo monitoring of the beam stopping position through the detection of the irradiation induced ß+-activity, and possibly also provide biological guidance via detection of injected radiotracers. This presentation will highlight the first in-beam deployment of our portable in-beam PET scanner in irradiation campaigns with different ion beams at different facilities, as well as the first studies investigating its suitability for tracer imaging, which would extend its applicability also in the context of biological guidance in small animal radiation research for irradiation with ion beams as well as X-rays.

Acknowledgement: This work has been supported by the European Research Council grant agreements 725539 (SIRMIO) and 883425 (BARB), along with the EU project 730983 (INSPIRE). We thank the broad network of collaborators, particularly H.G. Kang and T. Yamaya from NIRS-QST, M.K. Sitarz, P. Poulsen, N. Bassler and colleagues of the Danish Center for Particle Therapy, A. Zoglauer from University of California, M. Durante and the BARB collaboration at GSI.

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Study of 3γ/2γ positronium decay ratio in materials using the J-PET scanner

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Traditional PET imaging requires administration of a radiopharmaceutical containing radioisotope. Following its β^+ decay, formation of metastable positronium (Ps) may occur, further annihilating into 2 (para-positronium, p-Ps) or 3 (ortho-positronium, o-Ps) photons [1,2]. The formation probability of p-Ps and o-Ps, as well as survivability of the latter due to pickoff and conversion processes

depends on the creation environment [3,4]. Hence, registration of the 3γ/2γ decay ratio may infer characteristics of the medium and yield new complementary diagnostic information [5].

In this work we inspected the feasibility of this imaging approach in both simulation (GATE software [6]) and experiment. In both cases the J-PET tomograph, which practicability was already proven for positronium imaging [1,7,8], was utilized for imaging. During the experiment we examined three different types of materials:
- various samples of recycled glass granulate containing small pores
filled with air,
- fat, muscle and skin tissue,
- water.
Each sample was prepared in a cylindrical container (1 cm radius and 2 cm height), with a ~1MBq drop of [^{18}F]Fluorodeoxyglucose (FDG) at its center (apart from water sample, where FDG was mixed) and situated at the center of the J-PET scanner. In case of simulation, point sources of defined 3γ/2γ decay ratios were investigated.

Based on the simulated tomograph's response, types and efficiencies of analysis cuts were determined. Moreover, sensitivity maps for 3γ and 2γ positronium decays were prepared. Further, the experimentally gathered data was analyzed, exploring the differentiation prospect of investigated materials based on the 3γ/2γ positronium decay ratios.

Acknowledgements
The abovementioned work is presented on behalf of the J-PET Collaboration. This work was supported by Foundation for Polish Science through TEAM POIR. 04.04.00-00-4204/17, the National Science Centre, Poland (NCN) through grants no. 2021/42/A/ST2/00423 and 2021/43/B/ST2/02150, and SciMat and qLife Priority Research Area budget under the program Excellence Initiative - Research University at Jagiellonian University.

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POSITRONIUM IN FUNDAMENTAL AND MATERIAL PHYSICS / 619

Dark Matter in Positronium and J-PET prospects

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Dark Matter in Positronium and J-PET prospects

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The “observable” Universe, thus is, the baryonic matter that conforms to it and we can detect and see with our experiments and measurement devices, amounts to a tiny fraction of the whole. This leaves us with a large unknown which we have come to call Dark Matter and Dark Energy.
The J-PET apparatus [1], at the Jagiellonian University, is a novel multi-disciplinary tomography system based on plastic scintillators. It allows for tests of fundamental physics, medical research, and quantum entanglement measurements, among others [2, 3].
This talk will explore some of the proposed models of Dark Matter candidates that can be produced in Positronium decays. The J-PET setup capabilities and prospects will be discussed, particularly Mirror Matter searches in ortho-positronium decays [4].
We acknowledge support from the National Science Centre of Poland through Grants No. 2019/35/B/ST2/03562, 2020/38/E/ST2/00112, the Ministry of Education and Science through grant no. SPUB/SP/490528/2021, and the SciMat and qLife Priority Research Area budget under the auspices of the program Excellence Initiative-Research University at Jagiellonian University.
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A limited-angle PET imager with ultrafast flat-panel detectors

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This contribution presents the development of a limited-angle Positron Emission Tomography (PET) imager utilizing ultrafast flat-panel detectors. It aims to revolutionize the accessibility and efficiency of Time-of-Flight PET devices by targeting a coincidence timing resolution below 100 ps. This innovation addresses the challenge of incomplete sampling due to partial acceptance. Key advancements include Creating an integrated photon detector module featuring an optimized Silicon Photomultiplier (SiPM) sensing layer and a novel Application-Specific Integrated Circuit (ASIC) based on the FastIC chip; 2.5D integration of the SiPM and photon detector, enhancing performance and reducing system complexity, and the design of a PET imager with incomplete sampling without compromising image quality. Preliminary simulation results indicate that a large-area field-of-view (LAFOV) device with this technology can achieve performance levels comparable to existing LAFOV devices but at a significantly lower cost. This research promises to make advanced PET imaging more accessible and cost-effective, benefiting both clinical and research applications.

PARTICLE DETECTION TECHNOLOGIES / 611

Invited talk: A limited-angle PET imager with ultrafast flat-panel detectors

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QFT approach to positronium decays

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We study the two-photon decay of the ground-state positronium using quantum field theoretical techniques. This amounts to the evaluation of a triangle-shaped diagram with virtual electrons circulating in it. An important role is played by the positronium electron-positron vertex, which is linked to the wave function of the positronium. We show how possible choices for the vertex affect the $\gamma\gamma$ decay rates. Outlooks to other decay channels, e.g. four γ, and to other positronia (scalar, vector,...), are presented.

POSITRONIUM IN FUNDAMENTAL AND MATERIAL PHYSICS / 568

QFT approach to positronium decays

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EXTRACELLULAR VESCICLES FOR THERANOSTICS / 534

Invited talk: Leukemic extracellular vesicles as drivers of T cell-mediated immunosuppression

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Leukemic extracellular vesicles as drivers of T cell-mediated immunosuppression

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The full landscape of interactions between leukemic and immune cells and their role in disease development and resistance is still not clear. This includes immunosuppression which in myeloid leukemias remain largely unexplored and immune checkpoint therapies are still not successful. Extracellular vesicles have been implicated as effective drivers of cross-talk between distant cells, as well as potent diagnostics particles. Here, we aimed at characteristics and function of CML and AML-derived EVs in remodeling of immunosuppressive effector regulatory T cells (Tregs) and exhausted T cells as well as assessing relevance for leukemia progression.

Leukemic EVs were characterized by bioimaging techniques, Nanosight size/tracking analysis and specific protein marker distribution. Also, recently implemented EVs analysis by spectral cytometry will be discussed. EVs transfer was assessed by fluorescent tracking by flow cytometry. We found that leukemic EVs induced Foxp3+ Tregs and amplified suppressive activity of mature Tregs by remodelling of STAT5 and mTOR-S6 signaling,expression of Treg-regulatory genes and changed secretion of effector cytokines. Using 23-color spectral flow cytometry followed by unsupervised clustering we identified two distinct, effector Treg subsets upregulated by leukemic EVs. Mass spectrometric profiling of EVs proteome identified specific costimulatory protein 4-1BBL, which elevated suppressive activity of Tregs. Additionally, we revealed that leukemic (AML/CML) EVs promoted another immunosuppressive mechanism mediated by exhausted non-regulatory T cells expressing CD39+ molecule, which generates metabolic immunosuppressive environment via remodeling of adenosinergic axis. Vesicle-driven dysfunctional CD39+ T cells (distinct from PD-1+ exhausted cells) were present in the peripheral blood of leukemic patients, showed decreased secretion of IL-6, TNFa, and IFNg and correlated with disease burden. Finally, in vivo model of CML-like disease revealed that leukemic EVs contributed to elevated Treg numbers, increased expression of immunosuppressive markers including CD39 and stronger engraftment of leukemic cells, pinpointing relevance of EVs in immunosuppression and leukemia progression.

Altogether we characterized leukemic EVs and found that they constitute a novel factor that drives immunosuppressive microenvironment by T cells remodeling, associated with progression of myeloid leukemias. This includes EVs-driven higher abundance of specific immunosuppressive subsets of Tregs and promotion of subsets of CD39+ exhausted/dysfunctional T cells. This could be implemented into diagnostic immune monitoring of the immunosuppressive state and could facilitate development of novel therapeutic strategies both in AML and CML.

National Science Centre: 2019/35/O/NZ3/01936 (KP), 2018/29/N/NZ3/01754 (JS), Foundation for Polish Science POIR.04.04.00-00-23C2/17-00 (KP)

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An Overview of Design and Development of Electronics for a Preclinical Prototype TOF-PET System with 100 ps Time Resolution and < 2 mm 3D Position Sensitivity

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It is known that in order to achieve 100 ps CTR one must reduce the temporal variance of various elements of the 511 keV annihilation photon detection chain. Some of the most important elements can be named as high light-yield scintillators with short scintillation decay time, high-speed compact silicon photomultipliers (SiPMs) with high photo-detection efficiency (PDE>50%), and side-readout configurations to enables near complete (>90%) scintillation light collection efficiency (LCE) with reduced transit time jitter of scintillation light photons. However, a high-performance stable electronics chain is still necessary to precisely record the arrival time of each annihilation photon, and precisely measure its deposited energy. In this talk we outline the development of our highly compact custom-designed electronics chain with 24:1 multiplexed detector layers, employed to engineer large area PET detector modules capable of 100 ps FWHM CTR with 20 mm effective length scintillation crystals. Moreover, to significantly enhance the quality and uniformity of the reconstructed PET images, our multiplexed detector layers are also capable of offering accurate 3D positioning of photoelectric or scattered events with < 2 mm continuous depth-of-interaction (DOI) positioning in 2×4 arrays of 3×3×10 mm3 side-coupled crystals while saving ~30-40% power dissipation compared to common high performance PET detector designs.

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An Overview of Design and Development of Electronics for a 100 ps TOF-PET System with < 2 mm 3D Position Sensitivity

Authors: Shirin Pourashraf[1]; Joshua W. Cates[2]; Derek Innes[3]; Muhammad Nasir Ullah[3]; Craig S. Levin[4]

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It is known that in order to achieve 100 ps CTR one must reduce the temporal variance of various elements of the 511 keV annihilation photon detection chain. Some of the most important elements can be named as high light-yield scintillators with short scintillation decay time, high-speed compact silicon photomultipliers (SiPMs) with high photo-detection efficiency (PDE>50%), and side-readout configurations to enables near complete (>90%) scintillation light collection efficiency (LCE) with reduced transit time jitter of scintillation light photons. However, a high-performance stable electronics chain is still necessary to precisely record the arrival time of each annihilation photon, and precisely measure its deposited energy. In this talk we outline the development of our highly compact custom-designed electronics chain with 24:1 multiplexed detector layers, employed to engineer large area PET detector modules capable of 100 ps FWHM CTR with 20 mm effective length scintillation crystals. Moreover, to significantly enhance the quality and uniformity of the reconstructed PET images, our multiplexed detector layers are also capable of offering accurate 3D positioning of photoelectric or scattered events with < 2 mm continuous depth-of-interaction (DOI) positioning in 2×4 arrays of 3×3×10 mm3 side-coupled crystals while saving ~30-40% power dissipation compared to common high performance PET detector designs.

Yes

EXTRACELLULAR VESCICLES FOR THERANOSTICS / 602

Invited talk: The glycosylation status of melanoma cells directly affects the proteome composition of extracellular vesicles they release

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The glycosylation status of melanoma cells directly affects the proteome composition of extracellular vesicles they release

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Melanoma is one of the most aggressive and treatment-resistant cancers in humans. Therefore, there is an urgent need for early diagnosis and effective treatment of melanoma, given the increased mortality rates associated with high metastatic properties. The hallmarks of cancer driving its progression are enhanced through communication between cancer cells and tumor microenvironment via extracellular vesicles (EVs). It is known that the effect exerted by EVs on target cells depends on the composition of their cargo. The precise mechanisms of sorting bioactive molecules into EVs and factors influencing the efficiency of the sorting process and EV incorporation into the recipient cells are still not well established. However, there is evidence that glycosylation is also involved.

Numerous studies have shown that changes in glycan biosynthesis are frequently observed at an early stage of neoplastic transformation and are intensified further during the progression to advanced stages. This leads to the appearance of so-called tumor associated carbohydrate antigens (TACAs) on the cell surface. Changes in protein glycosylation are observed not only at the cellular level, but also in isolated populations of EVs. Additionally, the presence of several cancer glycobiomarkers that are currently in clinical use has been confirmed in various EV populations.

The lecture will present the results of LC-MS/MS study aimed at monitoring changes in the proteome composition of two subpopulations of EVs (microvesicles and exosomes) released by melanoma cells at different stages of malignancy. Changes in the glycosylation profile of melanoma cells resulting from disruption of the N-glycosylation process were induced by their culture in the presence of two N-glycosylation inhibitors (tunicamycin and 1-deoxymannojirimycin) as well as by induced overexpression of N-acetylglucosaminyltransferase III and N-acetylglucosaminyltransferase V. Qualitative and quantitative changes in the EV proteome, results of Gene ontology (GO) analysis, the impact on melanoma cell proliferation and migration, and the functional implications of these changes for tumor progression will be presented.

Funding
The research was funded by the BioS Priority Research Area under the program 'Excellence Initiative - Research University' at the Jagiellonian University in Krakow (U1U/P03/NO/03.22 to MP).

ARTIFICIAL INTELIGENCE FOR MEDICINE / 633

Invited talk: Experimental data-driven predictive modeling of DNA damage induced by low-temperature plasma radiation

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Experimental data-driven predictive modeling of DNA damage induced by low-temperature plasma radiation

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Recent advances in plasma technology have developed a non-traditional type of radiation formed due to electric discharges under ambient conditions, called low-temperature plasmas (LTPs), and unlocked a wide breadth of potential applications in the medical areas. Yet, its clinical application cannot be realized without rigorous protocols for assessing radiation dose rate. I will present an alternative approach to the standard dosimetry techniques, developed by my research team. We revealed the plasma dose rate based on the correlation between the experimental outcomes observed in DNA exposed to LTP and other types of radiation that we incorporated into predictive modeling of plasma-induced DNA damage [1]. In addition, our recent research explored the possibility of implementing DNA and its damage as a probe for specific plasma diagnostics such as reactive plasma species formation and transient local heating. My team implemented a physics-guided neural network model to predict the formation of strand breaks in DNA and its denaturation, and their yields for a given LTP conditions [2]. Beyond this fundamental research, the outcome of our approach to diagnose LTP through the experimental data-driven predictive modeling of plasma-induced DNA damage has potential for further breakthroughs in plasma medical applications.
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POSITRONIUM IN MEDICINE / 531

Invited talk: From SPLIT to SIMPLE: High-Resolution Statistical Image Reconstruction Methods for Positronium Lifetime Imaging

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From SPLIT to SIMPLE: High-Resolution Statistical Image Reconstruction Methods for Positronium Lifetime Imaging

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Positronium lifetime imaging has garnered growing interest due to the potential of utilizing ortho-positronium (o-Ps) lifetime as a biomarker to study the tissue microenvironment in vivo. Traditional methods for positronium lifetime image reconstruction rely on time-of-flight information for spatial localization, often resulting in poor spatial resolution. In this talk, we will explore several high-resolution statistical image reconstruction methods that we have recently developed, specifically tailored for in vivo positronium lifetime imaging. The discussion will begin with an overview of the statistical model of lifetime events. We will then trace the development from SPLIT (Statistical Positronium Lifetime Image Reconstruction via time Thresholding) to SIMPLE (Statistical IMage reconstruction of Positron Lifetime via time-wEighting), detailing their foundational principles and algorithmic structures, and providing a comparative analysis of both methods. Applications of these methods to simulation and real data will be presented to demonstrate their potential impact in advancing positronium lifetime imaging.

Session 2 / **574**

Extension of MLEM algorithm for simultaneous dual-tracer PET image reconstruction

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Extension of MLEM algorithm for simultaneous dual-tracer PET image reconstruction

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Positron Emission Tomography (PET) is widely used nuclear technique for functional imaging of the human body. Currently, dual-isotope PET (DIPET) imaging has become a perspective branch of PET. In DIPET studies, two radiotracers are injected simultaneously, and thereby the independent quantification of two molecular images is provided. In such an experiment, apart from the events

originated from two back-to-back annihilation photons, a second class of coincidence events comprised with additional prompt photon is registered. However, current techniques ignores the configuration of triple-coincidence during the reconstruction of distribution of radioisotope that emits additional prompt photon and considers only the annihilation photon pairs in calculations of system matrix elements. In this paper we introduce a novel iterative method for simultaneous DIPET image reconstruction. We incorporate the optimization transfer principle and derive the closed-form update equation for the dual-tracer radioactivity distribution. The proposed method extends the standard Maximum Likelihood Expectation Maximization (MLEM) reconstruction by taking into account both two- and three-photons coincidence events at the same time. It will be shown that the modified MLEM method has very similar properties as the original algorithm.

ARTIFICIAL INTELIGENCE FOR MEDICINE / 572

Advancing cardiac detection in chest X-ray images using Machine Learning: A practical application of AI in medical imaging

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Advancing Cardiac Detection in Chest X-ray Images Using Machine Learning: A Practical Application of AI in Medical Imaging

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Abstract

The primary objective of this study is to develop a machine learning model capable of precisely localizing and delineating the cardiac region within chest X-ray images using bounding boxes [1, 2]. This research is motivated by the critical clinical need to identify cardiac abnormalities, including cardiomyopathy affecting myocardial tissue and positional changes of the heart associated with pneumothorax or atelectasis. Early detection of these abnormalities is paramount for prompt medical intervention and improving patient prognoses.

To accomplish this goal, a dataset comprising 469 annotated chest X-ray images [3, 4] is employed to train a machine learning model based on a modified ResNet architecture [5]. This model is specifically designed for regression tasks, enabling it to predict the coordinates of bounding boxes encapsulating the cardiac regions in the X-ray images.

This work exemplifies a practical application of artificial intelligence in medical image analysis, with a distinct focus on cardiac detection. By successfully training a model to autonomously identify and localize the heart within X-ray images, this research aims to advance clinical diagnostic and therapeutic strategies. The development and evaluation of this model offer valuable insights into harnessing machine learning to improve healthcare outcomes, particularly in the realm of cardiac imaging and disease detection.

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TOTAL-BODY PET / 542

Key talk: Total-Body PET: where are we today?

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Total-Body PET: where are we today?

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Recently, long axial field-of-view (LAFOV) scanners (>1m) with SiPM detection systems have been developed and are now commercially available. The sensitivities and axial body coverage of such a LAFOV system open up new horizons both in the scientific context and in clinical routine.
It allows for reductions in acquisition times while maintaining diagnostic quality or on the other hand reductions in the administered radioactivity without significant impact on image noise.
Delayed imaging might result in higher detectability of tumor lesions. Low count statistics PET such as Y-90 PET is possible within time slot lengths comparable to clinical routine of diagnostic tracers.
Last but not least dynamic imaging protocols covering all major organs simultaneously are another major advantage compared to previous scanner generations. This allows for kinetic modeling and generation of multiparametric images, adding potentially relevant data information.
Therefore both opportunities and also challenges coming along with such a system will be presented, in light of clinical and research aspects.

PARTICLE THERAPY MONITORING / 596

Range monitoring capabilities with the SiFi-CC Compton camera: spectral-spatial imaging with Monte Carlo-simulated data

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Range monitoring capabilities with the SiFi-CC Compton camera: spectral-spatial imaging with Monte Carlo-simulated data

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The SiFi-CC project is developing a scintillating-fiber based Compton camera for high-efficiency gamma-ray imaging, specifically tailored for online range verification in particle therapy. After thorough optimization studies, including the development of neural-network approaches for event selection, the capability of the prototype for detecting range deviations is being studied by using accurate Monte Carlo simulations. We have implemented a spectral-spatial reconstruction based on the LM-MLEM algorithm and spectral analytical models for the system matrix and the sensitivity (Muñoz, 2020). In this work, we show the reconstructed images obtained from the irradiation of PMMA phantoms with $4 \cdot 10^9$ protons at therapeutic energies. The results show the capability of SiFi-CC to recover the 4.44 MeV prompt-gamma line and the detection of 5-mm Bragg peak shifts.

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INTERDISCIPLINARY ACTIVITY : PHYSICS + MEDICINE

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More than 20 years ago the interdisciplinary activity was very difficult. The application of computer simulations in many disciplines appears to play a significant role. Medicine is of highest activity. There is no medical doctors position not equipped with computer tools. It covers the whole spectrum : from basic disciplines through drug design to practical medicine.
To face these problems and to open the possibility for interdisciplinary activity the journal covering the large spectrum of disciplines with computer techniques in a background the journal Bio-Algorithms and Med-Systems was erected starting 2005.
The name of journal was constructed to cover the whole spectrum from : theoretical and basic disciplines „Bio-Algorithms" to all practical disciplines expressed by „Med-Systems".
The journal survived almost the 20 years of activity with better and less periods being currently in

the best hand of specialists in physics collaborating with biologists. The optimistic future is open for the journal Bio-Algorithms and Med-Systems.

EDUCATION AND BIO-ALGORITHMS AND MED-SYSTEMS / 617

Invited talk: Story of the Bio-Algorithms and Med-Systems

PARTICLE THERAPY MONITORING / 623

Invited talk: Proton therapy range monitoring using the J-PET scanner

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Range monitoring in proton therapy using the J-PET scanner

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Jagiellonian positron emission tomography (J-PET) technology [1,2], based on plastic scintillator strips, has been proposed as a cost-effective tool for in-vivo range monitoring during proton therapy. Our extensive simulation studies tested various J-PET geometries in phantoms and clinical imaging protocols with patient data. Eventually, a triple-layer dual-head J-PET setup was selected for the first experimental tests in uniform phantoms with therapeutic proton beams.

Simulation works covered the development of a dedicated Monte Carlo (MC) framework, ProTheRaMon, that enables multi-stage simulation of β+ activity generated in a patient or phantom, its decay, propagation towards the detector, and generation of coincidence events in the PET scanner. ProTheRaMon explores GATE for MC simulations and CASTOR for PET image reconstruction 3. Preliminary simulations of the J-PET scanners provided information that double-layer full-ring and triple-layer dual-head geometries are the most cost-effective in terms of scanner efficiency 4. Further, detailed simulations of treatment plans for a large cohort of proton patients focused on selected J-PET geometries. 90 patients who underwent intensity modulated proton therapy (IMPT) at Cyclotron Centre Bronowice (CCB) in Krakow (Poland) were studied, with errors in patient positioning and HU-proton stopping power calibration artificially introduced. From the patient simulations, a correlation was observed between the standard deviation of proton range shift maps and those of shifts in activity as reconstructed with J-PET data 5. The first-ever experimental tests of the J-PET detector in a triple-layer dual head configuration selected from the efficiency simulations were conducted using seven proton Spread Out Bragg Peaks (SOBP) of range varying from 1 to 19 mm. For each SOBP, PET images were reconstructed and analyzed to demonstrate the feasibility of the J-PET in monitoring the proton beam range difference. The experiments showed the precision of the

PET-based range monitoring with the J-PET detector for a given treatment dose down to 2 Gy and post-irradiation PET data acquisition time down to 5 minutes, which is in the range of 1-2 mm [6]. Future plans for pre-clinical studies with J-PET and proton beams include evaluating the detector's ability to acquire β+ activity during proton treatment and conducting the first clinical tests with patients at the CCB Krakow proton beam therapy center.

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PET IMMAGING INNOVATIONS / 628

Simulation studies of a brain PET insert for the total body J-PET tomograph

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Simulation studies of a brain PET insert for the total body J-PET tomograph

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Over the past few years, the J-PET (Jagiellonian-positron emission tomography) collaboration has constructed the first J-PET prototype [1, 2, 3] as well as the modular J-PET [4, 5] and conducted various experiments ranging from fundamental physics tests to medical applications. The key distinguishing aspect of these devices used for the detection of the 511 keV annihilation photons is the utilization of plastic scintillators over inorganic scintillation crystals (such as BGO or LSO) usually employed in conventional PET scanners. Their superior cost-effectiveness motivates the construction of larger scanners with higher sensitivity, i.e. the total body J-PET (TB-J-PET) [6, 7], which is currently under development. The molecular information that can be provided by specific radiotracers has also driven forward the advancement of dedicated brain PET scanners. Maps of serotonin [8] or kappa receptors [9], kinetic modeling to e.g. quantify blood flow [10] and the diagnosis of neurological diseases, such as dementia or cancer, are some of the applications for brain PET scanners [11]. Both standard cylindrical geometries, such as the Siemens HRRT [12] or the NeuroEXPLORER [13] as well as dedicated geometries (e.g. helmet PET [14, 15])
have been built for this purpose.

In this work, we conduct Monte Carlo simulations to study the impact of an additional scanner to be added to the TB-J-PET for brain imaging. We consider both a frontal detector (end cap) as well as a cylindrical insert. The latter constitutes a unique aspect of working with plastic scintillators. The

relatively low interaction probability (usually considered a disadvantage) allows a nesting of such detectors. Since high sensitivity and high spatial resolution are the two major requirements for brain imaging, the geometries under consideration are studied with respect to those criteria. The simulations are carried out with the GATE software package. Since the latest release v9.3 [16], capabilities for simulating multi-detector geometries are available. We revised the source code for an accurate count of Compton scattering (main interaction of plastic scintillators) and proper data filtering between detectors. The new geometries were implemented and the data were reconstructed with CASToR [17] using the MLEM algorithm. We present comparisons of different detector parameters, such as crystal thickness or different types of SiPMs.

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Novel approaches to light hypernuclei with heavy ion beams, image analyses and machine learning

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Studies of hypernuclei, sub-atomic nuclei with strange qurks, have been contributing for understanding the fundamental baryonic interactions as well as the nature of dense nuclear matters. They have already been studied for almost seven decades in reactions involving cosmic rays and with meson- and electron-beams. In recent years, experimental hypernuclear physics enters a new era. Hypernuclei can also be studied by using energetic heavy ion beams, and some of these experiments have revealed unexpected results on the lightest hypernucleus, the hypertriton, on its short lifetime and large binding energy. One of the experiments has also shown a signature of the unprecedented bound state with a Lambda hyperon with two neutrons. We are studying those light hypernuclear states by employing different approaches from the other experiments. We employ heavy ion beams on fixed nuclear targets with the WASA detector and the Fragment separator FRS at GSI (the WASA-FRS project) in Germany for measuring their lifetime precisely. The experiment was already performed in 2022. We also analyze the nuclear emulsions with machine learning, that were irradiated by kaon beams in the J-PARC E07 experiment. We have already uniquely identified

events associated with the production and decays of the hypertriton, and the binding energy of the hypertriton is to be determined. We also search events of other single-strangeness hypernuclei and double-strangeness hypernuclei in the E07 emulsion to understand the nature of Lambda-nucleon, Lambda-Lambda and Xi-nucleon interactions. We are using Machine Learning techniques for all our projects with heavy ion beams and nuclear emulsions. We'll discuss on these project and the current status of data analyses, we'll also present future plans of these projects.

EXOTIC ATOMS AND NUCLEI, NUCLEAR PHYSICS / 549

Invited talk: Novel approaches to light hypernuclei with heavy ion beams, image analyses and machine learning

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Cross sections of (p, x) reactions on ^{12}C, ^{14}N and ^{16}O for $^{10,11}C$ production

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One of the most promising method for in vivo radiation dose delivery validation in proton beam therapy is positron emission tomography (PET) 1. Though, contrary to the common practice of PET procedures, the positron emitters are being produced in the patient body during the time of proton beam passing some distance through the light elements. Then validation of dose delivery must be done with application of the corresponding experimental techniques. However, before designing such experimental techniques, thorough calculations must be performed in order to have beam-on PET imagine results as expected. In the frames of such an approach for a proton beam of 150 MeV energy, many nuclear reaction channels will be open and contribute towards production of short-lived nuclides. These nuclides will facilitate the creation of images by producing a big amount of counts. Therefore, it would be worthwhile to separate those counts in time making the picture of proton passing more precise. To do so, radionuclides produced with quite different half-lives would be of great value to make images more sharp and consistent 2. In this study, the subject of our interest includes two isotopes of carbon: ^{10}C and ^{11}C, being the reaction products due to proton initiated nuclear reactions in human bodies.
Carbon isotopes ^{10}C (the half-life 19.309 s) and ^{11}C (the half-life 20.364 m) can be produced in (p, x) reactions on ^{12}C, ^{14}N and ^{16}O for acquiring good statistics. To this end, we need cross section vs proton energy dependences to be calculated with a reliable nuclear code to be further compared with experimental and/or evaluated nuclear data from available nuclear data libraries. Therefore, with Talys-2.0 3 code we calculated cross sections of proton-induced nuclear reactions on ^{12}C, ^{14}N

and ^{16}O, leading to the formation of $^{10,11}C$ with equilibrium and pre-equilibrium models. We also compare the results of cross section calculations with experimental and evaluated data available in order to further use these comparison data for verification of dose delivery to the patient, in particular, of the absorbed dose and tracking a beam positioning up to its final destination.
This work was supported by the Foundation for Polish Science through the TEAM POIR.04.04.00-00-4204/17 program.

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PARTICLE DETECTION TECHNOLOGIES / 608

nvited talk: Development of fast scintillation detectors for photon-counting CT

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Development of fast scintillation detectors for photon-counting CT

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Photon-counting computed tomography (PCCT) is a rapidly emerging medical imaging technology. Several PCCT scanners were recently developed based on finely pixelated room-temperature semiconductor detectors (RTSD). Although scintillation detectors were traditionally considered too slow to handle the count rates higher than 100 Mcps per square millimeter per second encountered in PCCT, the fast signals provided by modern scintillators and silicon photomultipliers (SiPMs) allow us to reconsider this paradigm. SiPM-based scintillation detectors are already common in clinical positron emission tomography (PET) scanners. Recent research indicates that SiPMs combined with ultrafast scintillators can also provide a robust, scalable, and affordable detector technology for X-ray photon-counting applications. This presentation offers an overview of recent theoretical and experimental work, demonstrating the potential of SiPM-based scintillation detectors as an alternative for direct-conversion detectors. It will be illustrated how the choice of scintillator and other factors affect detector performance parameters such as count-rate capability and spectroscopic performance. Moreover, research opportunities in the areas of scintillator development, SiPM design, and X-ray photon counting medical imaging devices will be outlined.

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Conferences are place to share knowledge

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POSITRONIUM IN FUNDAMENTAL AND MATERIAL PHYSICS / 567

Invited talk: Studies of ortho-positronium mean lifetime with the J-PET tomograph

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ARTIFICIAL INTELIGENCE FOR MEDICINE / 570

Key talk: Knowledge-guided Artificial Intelligence for Personalized Nuclear Medicine Theranostics

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Knowledge-guided Artificial Intelligence for Personalized Nuclear Medicine Theranostics

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Despite the success of radiopharmaceutical therapy (RPT), there is a belief that personalized treatment can further enhance treatment outcomes while maintaining low side effects. Developing personalized RPT poses greater challenges compared to external beam radiotherapy (EBRT) due to the complex dynamics of radiation dose delivery after intravenous injection of radiopharmaceuticals. Furthermore, conventional radiobiological modeling used in EBRT is not applicable to RPT due to increased dose complexity and tumor heterogeneity. While artificial intelligence (AI) has the potential to support personalization efforts, purely data-driven approaches have limitations in handling the multi-level heterogeneity present in RPT.
In this presentation, we'll delve into how AI can benefit from the integration of domain knowledge, such as physics, pharmacokinetic modeling, and computational biology, to advance personalized

nuclear medicine theranostics. Specifically, we'll discuss the integration of spatial transcriptomics-based modeling into AI-driven drug development. These physiological models can offer valuable prior knowledge for refining and enhancing AI methodologies. The refined AI has the potential to revolutionize single-time-point dosimetry practices. Moreover, physiology-integrated deep learning holds promise for enhancing pre-therapy prediction of RPT dosimetry. Additionally, we'll explore how knowledge-guided AI can augment imaging applications in theranostics.

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Challenges and prospects of the positronium imaging reconstruction in J-PET

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We summarise the recent achievements in the development of reconstruction methods for positronium imaging (PI), conducted by the Jagiellonian PET (J-PET) collaboration [1–3]. PI is a new technique complementary to positron emission tomography (PET), where specific isotopes are utilised which emit a de-excitation photon during their decay. That allows one to assess the lifetime of the positronium (Ps) – a metastable compound of an electron (e^-) and a positron (e^+), responsible for about 40% of all e^+e^- annihilation events. PI primarily targets the mean lifetime of the Ps triplet states called ortho-positronium (o-Ps), which are forced to decay earlier than in vacuum (142 ns) via pick-off or conversion processes, depending on the neighbouring matter and producing pairs of 511-keV annihilation photons.

The studies of PI in J-PET included Monte Carlo simulations and experimental measurements of point-like sources, as well as the first clinical scans [2–3]. The methods of estimating the o-Ps mean lifetimes have evolved from the generic arithmetic mean to realistic modelling of the Ps decay, applying the exponentially modified Gaussian functions to fit time delay histograms for specific voxels [1–4]. Due to lower sensitivity and more complex selection criteria for the three-photon events, it proved to be difficult to collect enough counts per voxel, in particular during clinical scans. To resolve that, the algorithms based on maximum likelihood expectation maximisation (MLEM) were employed – either for refining histograms 3, but also for the full PI reconstruction 5. Another problem arises from the need for additive factors, in particular scatter and random corrections, which require novel approaches, such as based on time windows 5.

Further prospects include the adaption of reconstruction methods to whole-body scanner geometries crucial for large objects, as well as accounting for the positron range, which is significant for many isotopes used in PI.

We acknowledge support from the National Science Centre of Poland through grant 2021/42/A/ST2/00423

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POSITRONIUM IN MEDICINE / 556

Invited talk: Challenges and prospects of the positronium imaging reconstruction in J-PET

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TOF-SIMS DEEPER EXAMINATION OF LIPID ALTERATIONS IN EXTRACELLULAR VESICLES IN THE URINE OF TYPE 1 DIABETES PATIENTS

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Introduction
Kidney damage is a significant problem in both type 1 (T1DM) and type 2 diabetes. When diagnosing kidney damage, doctors assess glomerular filtration rate (eGFR) and albumin excretion to look for evidence of diabetic kidney disease (CKD). However, it would be beneficial to have an early marker of kidney damage and urine extracellular vesicles (uEVs) have been proposed as one such indicator. These vesicles undergo molecular changes, such as alterations in amino acid and lipid profiles and transported cargo, which can provide valuable information about the onset or presence of a disease in the biological system, such as CKD 1. Our study used time-of-flight secondary ion mass spectrometry (ToF-SIMS) to examine changes in lipid content for six different lipid groups.

Methods
Urinary EVs (uEVs) were collected from 33 patients with T1DM who had good metabolic control, in whom CKD was excluded (15 years duration, using personal insulin pumps and HbA1C ~7%) and 13 healthy individuals. The patients were recruited from the Clinical Department of Metabolic Diseases and Diabetology of the University Hospital. The uEVs were concentrated and purified using low-pressure filtration, pelleted by ultracentrifugation, and suspended in PBS. ToF-SIMS measurements were conducted after the uEVs were placed on cleaned silicon surfaces and analyzed using a Bi3+ gun. The ToF-SIMS technique enables the comparative analysis of lipids without requiring extraction or specific determination 2. The study involved two biological replications and examined three areas on sample surfaces.

Results
This study presents a comparative analysis using ToF-SIMS on uEVs (urinary extracellular vesicles). The main focus of the analysis was to observe changes in the percentage of amino acids and six lipid groups. The clinical data analysis revealed a significant difference in HbA1c concentration between the patient and control groups. The concentration of HbA1c was 5.1 ± 0.3 in the control group and

6.25 ± 1.15 in the patient group ($p<0.0001$). However, no significant differences were observed in age, serum creatinine, estimated glomerular filtration rate (eGFR), urine albumin, LDL, HDL, total cholesterol, and triglycerides level between the two groups. The results of the comparative ToF-SIMS analysis demonstrate statistically significant changes in the content of lipids from the group of sterols (cholesterol fragments), glycerolipids (DAG and TAG), and fatty acids (myristic, palmitic, oleic, and stearic acids), which differentiate the patient group from healthy individuals. Furthermore, the content of all lipid groups was summarized, indicating that the lipid profile of the patient group differs from that of the healthy group.

Conclusion
uEVs play an informative role and show promise as markers for kidney function. By observing changes in the ToF-SIMS mass spectra of uEVs, the development of diagnostics can aid in the early detection of metabolic changes. This research identifies a group of biomolecules that change in uEVs in the development of kidney disease resulting from diabetes.

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Acknowledgements

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Public lecture: Artificial Intelligence and Medicine: Crossing the Rubicon

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EXOTIC ATOMS AND NUCLEI, NUCLEAR PHYSICS / 588

Invited talk: Spectroscopy of antiprotonic atoms

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Spectroscopy of antiprotonic atoms

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Several high-precision experiments at the Antiproton Decelerator complex at CERN aim to look for any significant differences between matter and antimatter. One of these experiments is AEgIS, whose primary goal is to test the weak equivalence principle for antimatter by measuring (with atomic accuracy) the free fall of a neutral antihydrogen atom in the Earth's gravitational field. It turns out that the experimental setup and techniques developed at AEgIS, when expanded appropriately, can be used to produce on-demand complex bound states of matter and antimatter, and then to study their spectroscopic properties. One such natural direction is the possibility of producing neutral antiprotonic atoms, i.e., atoms in which one of the electrons is substituted by almost 2,000 times heavier antiproton. During my talk, I will present how this research can contribute to a better understanding of the bound states of matter and antimatter, as well as the internal structure of atomic nuclei, and how it could potentially become yet another opportunity for precise testing of fundamental theories.

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Experimental characterization of LET spectra in proton therapy

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Proton therapy is recognized as an effective treatment method for tumors, allowing significant sparing of normal tissues and minimizing side effects. Clinical proton beams produce mixed radiation fields consisting of particles ranging from low- to high-linear energy transfer (LET), while the high-LET protons are responsible for increased relative biological effectiveness. Here, we present the development and application of experimental and fast computational methods for the single-proton LET spectra characterization in mixed radiation fields for the purpose of advancing proton therapy treatment planning.

The single particle tracking with the semiconductor pixel detector Timepix (see Figures 1a and 1b) and the developed convolutional neural network [1, 2] allow the experimental characterization of

LET for each proton in the mixed radiation field produced by therapeutic proton beams in phantoms. We performed proof-of-concept measurements with single pencil beams in water [1, 2], as well as measurements for a heterogenous layer irradiated with a 120.8 MeV scanning pencil beam behind a solid RW3 phantom (see Figure 1a and 1c). The LET spectra scorers implemented in the fast, GPU-accelerated Monte Carlo (MC) code FRED 3 were applied for the computation of the LET spectra for intensity-modulated proton therapy treatment plans [4, 5].

An accuracy of over 95% was achieved for proton recognition with the CNN model, and a wide spectrum of LET values was observed for recognized protons, ranging from a fraction of keV/µm to about ten keV/µm [1, 2]. A good agreement was obtained between LET spectra derived based on measurements and simulations for a heterogeneous layer (see Figure 1d).

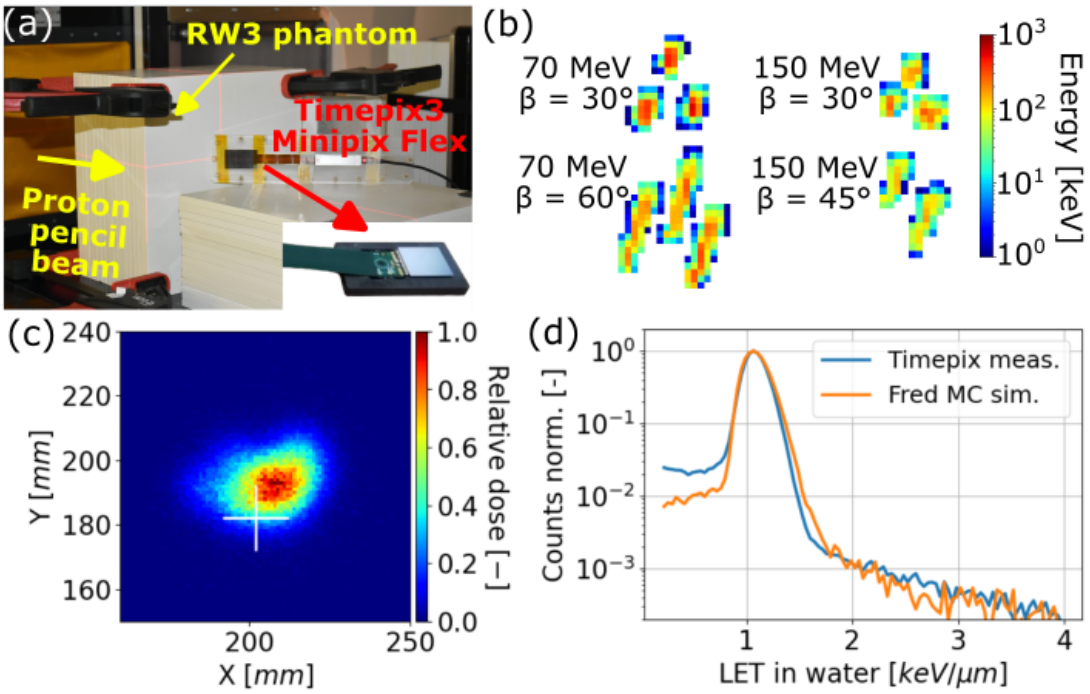

Figure 1:

Figure 1. An experimental setup consisting of RW3 phantom and Minipix Timepix3 detector in Flex configuration with 300 µm thick pixelated silicon sensor (a). Example proton tracks registered with Timepix at various incident angles β 1 (b). Relative dose distribution for a heterogenous field irradiated with a 120.8 MeV scanning proton beam (c). LET spectrum obtained based on measurements and simulations in the sensor position indicated in the dose distribution (d).

The methodology for LET spectra characterization in the clinical environment of proton therapy is essential for verifying treatment plans optimized with both dose and LET. The presented measurement approach can be applied for the commissioning and quality assurance of LET in treatment planning systems that include LET-based optimization. Potentially, low- and high-LET components could be considered separately in treatment plan optimization to model the increased biological effectiveness of high-LET protons more accurately. The presented project provides computational and experimental solutions for LET characterization to support treatment planning and quality assurance in the clinical routine of proton therapy.

Acknowledgments

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Radiovesicolomics

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Extracellular vesicles (EVs) are lipid bilayer-enclosed nanoparticles released by cells, ranging from 30 nm to several micrometers in diameter. EVs transport biological cargos such as proteins, lipids, RNAs, DNAs and glycans facilitating local and distant cell interactions. Recent advances have highlighted the potential of EVs in regenerative medicine and disease diagnostics. In this context, the innovative strategies for EV imaging have been developed. These methods allow visualization and study of EV spatiotemporal properties. Notably, EVs offer advantages over donor cells themselves, including safety and ease of clinical application. One emerging approach is radiovesicolomics, which combines molecular data on EVs with imaging techniques like positron emission tomography (PET) and single photon emission computed tomography (SPECT). By integrating these modalities, the new strategy for identifying novel biomarkers can be developed.
Acknowledgements
The study was supported from NCN grant 2022/45/B/NZ7/01430 to E. Stępień and the Jagiellonian University via projects CRP/0641.221.2020, SciMat and qLife Priority Research Areas budget under the program Excellence Initiative - Research University (Center for Theranostics).

EDUCATION AND BIO-ALGORITHMS AND MED-SYSTEMS / 618

Introduction into the ESMI

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Development of HPGe Detectors for Ultra High Rate Spectroscopy and Imaging

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While High Purity Germanium (HPGe) detectors are the gold standard for high-resolution gamma-ray spectroscopy, conventional, coaxial HPGe detectors show significant performance degradation at high rates (tens of thousands of counts per second (cps)). A new HPGe detector prototype has been designed at Lawrence Berkeley National Laboratory (LBNL). It is intended to maintain resolution and throughput performance at ultra-high rates (5 Mcps) and feature 3D position sensitivity.

The detector geometry, a double-sided strip detector with fine strip pitch, was selected by performing analytic and numerical calculations to evaluate the expected efficiency, throughput, timing, energy, and position resolution for various geometries and electrode configurations. The design of this prototype and characterization of an initial device will be presented.

PARTICLE DETECTION TECHNOLOGIES / 614

Development of HPGe Detectors for Ultra High Rate Spectroscopy and Imaging

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Positronium lifetime measurement using a clinical PET system for biomedical applications

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Positronium (Ps) imaging has been recently spotlighted for its potential biomedical applications. We and some groups reported that the Ps lifetime is related to the oxygen partial pressure (pO₂) in water, indicating that the Ps lifetime can be a sensor for tumor hypoxia [1, 2]. We also reported the possibility of quantifying radicals in vivo by the Ps lifetime 3.
In this study, we carried out the Ps lifetime measurements using the world's first hemispherical brain PET system, VRAIN 4. The first measurement target was two ²²Na aqueous solutions with different pO₂ values. Those solutions were adjusted to pO₂ values corresponding to a hypoxic tumor (10 mmHg) and a normal healthy cell (40 mmHg), and measured individually. The measured Ps lifetime values of 10 mmHg and 40 mmHg were 1.9360 ± 0.0026 ns and 1.9291 ± 0.0024 ns at statistics of 600 million counts, and the difference could be distinguished with an error value of more than ± 1σ. The second measurement target was a ²²Na radioactive source in contact with three aqueous solutions having different radical concentrations. Those solutions were adjusted to 0 mM, 1 mM, and 2 mM radical concentrations and measured individually. The measured Ps lifetime values of 0 mM, 1 mM, and 2 mM were 1.9373 ± 0.0065 ns, 1.9246 ± 0.0065 ns, and 1.9110 ± 0.0065 ns, respectively, at statistics of 170 million counts, and the difference could

be distinguished with an error value of around ± 1σ. The details of those measurement results and the relationship between the number of counts and the accuracy will be reported at the conference presentation.

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POSITRONIUM IN MEDICINE / 559

Invited talk: Positronium lifetime measurement using a clinical PET system for biomedical applications

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Multi-Photon decays of ortho-Positronium with J-PET

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Based on plastic-scintillators, Jagiellonian PET (J-PET) is a multi-discipilinary PET scanner [1, 2, 3] having a wide range of applications. With the potential of J-PET to register multiphotons, we aim to explore the rare and forbidden decay channel of the Ps triplet state, the ortho-Positronium (o-Ps) 4. The o-Ps decaying into higher number of photons than the predominant mode (o–P s $\longrightarrow 3\gamma$) is six orders of magnitude smaller as expected from the Quantum Electrodynamics (QED) calculations [3, 5, 6].
In this presentation we intend to present the status of the preliminary studies of the multi-photon decays of ortho-Positronium. We will present toy Monte Carlo simulations involving 4- and 5-gamma decays of the o-Ps, together with a preliminary estimation of a J-PET like detector efficiencies for these channels. Preliminary results with J-PET official Monte Carlo and data will be shown.
Acknowledgement
We acknowledge support from the National Science Centre of Poland through Grants No. 2019/35/B/ST2/03562, 2020/38/E/ST2/00112, the Ministry of Education and Science through grant no. SPUB/SP/490528/2021, and the SciMat

and qLife Priority Research Area budget under the auspices of the program Excellence Initiative-Research University at Jagiellonian University.

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Multi-organ kinetic modelling and connectome analysis for Total-Body PET

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The recent development of total-body Positron Emission Tomography (PET) scanners has propelled the field forward by significantly widen the horizons of systems biology research in the context of human physiology and pathobiology. It has also expanded the role of PET imaging in the clinical setting by reducing radiation doses with benefits for some clinical populations (e.g. paediatrics) while enabling the use of PET not only for diagnosis, prognosis and therapy monitoring, but also for preventive medicine. Despite the transformative potential of total-body PET, there are challenges ahead with regards to harnessing multi-organ kinetic modelling and connectome analysis successfully. This talk will describe some of these challenges and propose solutions to overcome them, so we can deliver on the great promise that is total-body PET technology.

PET IMAGING INNOVATIONS / 536

Invited talk: Multi-organ kinetic modelling and connectome analysis for Total-Body PET

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PET IMMAGING INNOVATIONS / 631

Evaluation of lesion contrast and performance characteristics in Modular J-PET scanner

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Evaluation of lesion contrast and performance characteristics in Modular J-PET scanner.

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Evaluation of lesion contrast and performance characteristics in Modular J-PET scanner.

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Abstract
This study presents the performance characteristics of the Modular J-PET scanner 1, adhering to the National Electrical Manufacturers Association (NEMA) NU 2-2018 standard 2, at both simulation and experimental levels. Additionally, it evaluates lesion detection capabilities using the Modular J-PET scanner in simulations level. The Modular J-PET consists of 24 modules arranged in a 24-sided polygon, each module containing 13 scintillator strips with dimensions of 50 cm in length and a cross-section of 6 mm × 24 mm. Scintillation light is read out by analog Silicon Photomultipliers (SiPMs) at both ends of each strip 3. Experimental data analysis was conducted using the in-house J-PET Framework software 4, and validated through Monte Carlo GATE simulations 5. Furthermore, Monte Carlo GATE simulations, combined with XCAT anthropomorphic phantoms, were employed to evaluate lesion contrast in the lung, liver, and breast for various lesion diameters and activity concentration ratios. Images were reconstructed iteratively using list-mode maximum likelihood expectation maximization, and contrast recovery coefficients (CRCs) were obtained for the reconstructed lesions. The results demonstrate the scanner's capability in detecting lesions, and overall imaging performance.

Acknowledgement
The authors acknowledge also the support provided by the Foundation for Polish Science through the TEAM POIR.04.04.00-00-4204/17 program; the National Science Centre of Poland through grants MAESTRO no. 2021/42/A/ST2/00423 and OPUS no. 2021/43/B/ST2/02150; the Ministry of Education and Science through grant no. SPUB/SP/490528/2021; the SciMat and qLife Priority Research Areas budget under the program Excellence Initiative - Research University at the Jagiellonian University, and Jagiellonian University project no. CRP/0641.221.2020.

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Optimizing the length of a single ring of the Total body J-PET

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Abstract:
Total-body PET has begun to be used in clinics, and to expand its applications in hospitals, reducing construction costs is imperative 1, 2. We are developing a cost-effective total-body PET system utilizing plastic scintillators 2, 3. The Total Body J-PET scanner comprises several rings, each consisting of 24 modules. A single module contains 32 plastic scintillators divided into two layers, which are read out on both ends by silicon photomultipliers (SiPMs). An additional wavelength shifter (WLS) layer is sandwiched between two plastic layers, which are read with SiPMs on one side.
One crucial aspect of having a cost-effective total-body PET system is optimizing the length of detector for total-body J-PET. We conducted tests on single detector units equipped with SiPMs connected to plastic scintillator strips at the axial ends. By utilizing a collimated beam of 511 keV photons from the Na-22 isotope, we characterized the detector performance, including amplitude, charge, rise time, fall time, and time resolution for various scintillator lengths. The comparison results of various scintillator lengths for optimizing the length of a single ring of the total-body J-PET will be presented and discussed.

Acknowledgment:
We appreciate the support from the National Science Centre of Poland through grant no. 2021/42/A/ST2/00423, 2021/43/B/ST2/02150, and OPUS no. 2019/35/B/ST2/03562

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Theoretical estimation of the weights of C, P and CP symmetry-violating terms in positronium wave function

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A new theoretical method is developed for the solution of the two-body bound-state Dirac equation for positronium. Only Coulomb potential was included in the Dirac Hamiltonian. It is shown that the two-body Dirac Hamiltonian can be written in the Hermitian matrix form of the 4×4 size and contains terms, responsible for the violation of the P, C, and CP symmetries. Numerical results for the energy spectrum of the para- and ortho-positronium ground states performed within the variational method using the harmonic oscillator basis functions are in good agreement with a high-precision nite-element method of T.C. Scott et al. The weights of the P and CP symmetry-violating components in the para-positronium ground state are identical to the weight of the P symmetry-violating component of the ortho-Ps and are estimated to be 6.6E-6. The weights of the C and CP symmetry-violating components of the ortho-Ps are equal to the 2/3 and 1/3 parts
of this value, respectively. These numbers are less by two orders of magnitude than the accuracy limit of current experimental facilities.

MEDICAL IMAGING INNOVATIONS / 593

Key talk: Uncovering Novel Treatment Strategies to Combat Life-Threatening Infections with Multimodal Imaging

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Uncovering Novel Treatment Strategies to Combat Life-Threatening Infections with Multimodal Imaging

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Fungal infections, especially in individuals with pre-existing immunodeficiencies or viral lung diseases, often lead to life-threatening complications. However, our understanding of the interplay between pathogen and host factors remains incomplete, with significant therapeutic, methodological, and fundamental knowledge gaps. Resistance to current antifungal therapies necessitates the development of alternative strategies. Host factors can either inhibit or facilitate infection dissemination, yet the paradoxical roles of immune cells in this process are not well understood.
To address these challenges, researchers typically rely on end-stage analyses of experimental models. While useful, these models are limited to providing a static snapshot of dynamic pathogen- and host-related processes. Repeated follow-up is essential to fully understand these dynamic interactions. Our goal is to bridge these gaps by developing novel longitudinal imaging-derived biomarkers to assess lung disease burden, infection status, and host response. These biomarkers will be applied

to new treatment strategies for life-threatening fungal (super)infections, including cryptococcosis, azole-resistant aspergillosis, viral-associated pulmonary aspergillosis, and mucormycosis.
Our treatment strategies may target the pathogen directly or aim to restore a balanced and effective antifungal host response by unraveling the complex host-pathogen relationship. To achieve this, we continuously innovate dual-channel imaging techniques to monitor both the pathogen and its interaction with host cells in vivo. This approach will help elucidate the hypothesized dual role of macrophages in providing defense and acting as a vehicle for fungal dissemination in cryptococcosis.
Ultimately, we aim to deliver a versatile imaging platform applicable to various infectious diseases, providing dynamic, translational insights into the host-pathogen relationship.

POSITRONIUM IN FUNDAMENTAL AND MATERIAL PHYSICS / 564

Invited talk: S-QM/MM approach to positronium in liquids

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S-QM/MM approach to positronium in liquids

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Positrons and positronium (Ps) atoms are used as probes in materials sciences. In particular, positron annihilation lifetime spectroscopy (PALS) is widely applied, e.g., to investigate conformational, structural, and microenvironmental properties of biomimetic systems 1, as well as phase transitions of lipid bilayers 2 and pharmaceutically relevant compounds 3. The Ps signal contribution to positron emission tomography (PET) could also allow for improved accuracy 4 and diagnosis 5.

In view those applications, we have combined computational techniques to model Ps atoms in liquids. Specifically, we employ the Sequential Quantum Mechanics/Molecular Mechanics (S-QM/MM) method 6 with the Any-Particle Molecular Orbital (APMO) method [7]. Since the initial MM step consists of classical Monte Carlo simulations for the liquid system, an essential aspect is to develop Ps-atom force fields, i.e., model interactions to be used in the Monte Carlo calculations. Once statistically uncorrelated Ps-solvent configurations are obtained, quantum properties can be obtained from Hartree-Fock (HF) and post-HF APMO calculations, properly averaged over the statistical ensemble.

We discuss recently obtained results for Ps in water [8] and other polar solvents, namely methanol, ethanol and acetonitrile. Our ultimate goal is obtaining reliable force fields to describe Ps interactions with several elements, such that complex chemical environments can be studied. We believe our present results are encouraging.

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FEASIBILITY STUDY OF PET IMAGE RECONSTRUCTION USING SINGLE-SCATTERED EVENTS WITH TOF

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A substantial amount of scattered data is rejected in a conventional PET. We propose a novel algorithm for PET image reconstruction from single scattered (inside tissue) events with known time of flight (TOF) and without energy information, particularly useful for plastic scintillators like J-PET 1. Previous reconstruction algorithms, as described by Hemmati et al. 2, utilized both energy and time information. In their approach, the locus of a single scattering point forms a circular arc for 2D and a prolate spheroid for 3D geometry. Our method focuses solely on utilizing TOF information to estimate the annihilation point. The feasibility of the algorithm is demonstrated through analytical modelling and GATE simulations.

Loci of annihilation points are generated for each possible scattering angle permissible by the phantom size due to an unknown direction of the scattered photon. The locus of scattering points is formed by creating circles with a consistent radius from both detection points, intersecting at two points when the radius exceeds half the LOR distance. Circles of equal radius from these intersection points ensures that they passed through both detection points. This method ensures that the scattering points established on the arc are absolute and free from any tolerance errors.

Simulated Data were generated with a generic Cylindrical PET system with LSO and BGO crystals attached with 8 radial sectors with 16 modules arranged in a 4x4 grid in each sector. Each module is subdivided into 25 submodules and further into 25 crystal blocks, each with dimensions of 3 mm by 3.8 mm. A cylindrical phantom of radius 10 cm and height 70 cm of uniform attenuation filled with water is kept at the center of the geometry.

The images were reconstructed using the TOF information available in the list mode PET data. Events are classified based on axial difference of less than 1 mm to assume it a 2-D geometry. A ^{18}F line source of length 70 cm and thickness of 0.5 mm for 10^7 events is kept at different locations in the phantom. For our simulation roughly 0.01% to 0.02% of the detected events are single scattered and assumed planar for reconstruction. The reconstructed events are passed through a ramp filter.

The resolution of the line profiles is 10.73 ± 0.12 cm for the back-projected image. The resolution is improved to the order of 6.503 ± 0.08 cm after the application of ramp filter. We are currently working on a 3-D approach which will lead to a better statistics and that can help improve the spatial resolution and sensitivity for PET scanners with plastic scintillators like J-PET 1.

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Origin of the signal in Positron/Positronium Annihilation Spectroscopy studied intravitally in multi-layered cell sheets

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Positron and positronium annihilation spectroscopy (PPAS) has been extensively used for the characterization of materials at the nanoscale level, for example in the identification of defects inside condensed matter. In recent years, the possibility to use PPAS to analyze tissues and organs received increasing attention, because it is non-destructive, which means that the structural characteristics of living samples are preserved 1, underlining the potential of the technique for tissue inspection and diagnostic. Currently, PPAS in biological samples focuses mainly on 3D samples, thick portions of tissues or even organs 2.This allowed the identification of positron lifetime differences between healthy and diseased/tumoral tissues, with the recognition of oxygen concentration as one of the factors involved in the variation in ortho-positronium (o-Ps) formation 3. This is an important result considering that in the solid tumor microenvironment the oxygen concentrations are lower (hypoxic condition) 4. However, recognizing and understanding the mechanisms and the peculiarities of biological tissues responsible for differences in the lifetime of positrons and positronium is currently a difficult task, and oxygen is not the only factor that produces a change in o-Ps formation and annihilation lifetime. In fact, biological systems are composed of several components and substances, interacting with each other in a dynamic way. Furthermore, each different tissue has a specific function other than physical, structural, and morphological peculiarities, which complicate the ability to focus on a specific phenomenon to study.

To isolate the effect of a single cell type and highlighting the morphological and structural impact of the microenvironment to positron annihilation, here, I propose a different approach for the PPAS intravital study of living 3D biological samples, by creating layer-by-layer tissue phantoms. I produce these layers by means of the cell-sheet technology 5 based on the thermo-responsive approach. I employed several cell types such as endothelial, epithelial and fibroblasts which were seeded on a methylcellulose substrate for 14 days with 5% pCO2 and a temperature of 37℃. Then, once reached the monolayer confluence I decreased the culture temperature from the incubator conditions to 25℃, causing the detachment of the newly formed layer. Thr PPAS analysis on single cell layers allows the identification of positron and positronium lifetime differences depending on cell type, layer organization, structure, and microenvironment. This employed model will allow to obtain multi-layered 2.5D tissues, instead of conventional 3D biopsies, for the study of how the interaction in a three-dimensional environment of cells influences the positron and positronium annihilation with respect to the 2D condition. Furthermore, the overlapping of layers of different cell types opens the possibility to distinguish cell-specific differences in a 2.5D condition, constituting a bridge from simplified models to complex 3D biological tissues.

Acknowledgements

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ARTIFICIAL INTELIGENCE FOR MEDICINE / 632

Invited talk: Deep learning for data corrections in quantitative NM imaging

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POSITRONIUM IN FUNDAMENTAL AND MATERIAL PHYSICS / 585

Invited talk: Applying positron-emission diagnostic techniques to magnetically confined electron–positron pair plasma

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Applying positron-emission diagnostic techniques to magnetically confined electron–positron pair plasma

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The objective of the APEX (A Positron Electron eXperiment) collaboration is to magnetically confine an electron-positron pair plasma and study its behavior. To diagnose this matter-antimatter plasma, it is necessary to develop techniques based on the distinct emission provided by annihilation and relate them to plasma properties. The pair plasma will generate gamma rays (1) in the bulk plasma from direct annihilation and decay of positronium, (2) in the vacuum and along the surrounding walls from the decay of ortho-positronium, and (3) from locally increased annihilation on an inserted limiter due to plasma transport. The spatial profile of the two-gamma decays from (1) can be tomographically reconstructed from coincident detections. The localized annihilation source (3) can be identified using distance-attenuation fits to single-photon detections.
The effectiveness of these techniques is demonstrated in recent positron confinement experiments in a permanent magnet trap, where 10^5 positrons are confined with a combination of magnetic mirroring and electrostatic reflection in the dipole field of a biased magnet. A 21-BGO-detector array is placed in re-entrant ports 1cm from the confinement volume. FPGA processing timestamps detections to 24ns accuracy and records photon energy with 66keV resolution. Coincident lines of response can differentiate between losses at the magnet (when biased below the positron energy) and losses at the walls due to diffusion via collisions with neutrals. Annihilation lifetime, energy spectroscopy, and the detection fraction of triplets identify positronium formation through charge-exchange as an annihilation mechanism for positrons with kinetic energies above a threshold within the first second of confinement.

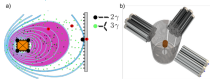

Figure 2: a) Illustration of expected annihilation in a magnetized pair plasma, specifically a cross-section of pair plasma confined in a levitating dipole device. b) Setup of gamma-detector array in recent positron confinement experiments.

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Production of theranostic pair 43/44Sc - 47Sc on calcium targets

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The 43Sc ($t_{½}$ = 3.89 h) and 44Sc ($t_{½}$= 3.92 h) are ideal β+ emitters in PET diagnosis. Both radionuclides can be used as an alternative to 68Ga, because 43/44Sc has a longer half-life and forms theranostic

pair with β- emitter 47Sc. However, in comparison with 44Sc, 43Sc has a half-life and beta plus radiation similar to 44Sc. Nevertheless, its gamma-ray energy emission and intensity are much lower (372 keV, 23%) than in the case of 44Sc (1157 keV, 99%). On the other hand high energy and intensity gamma line makes 44Sc 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 43Sc in 42Ca(d,n)43Sc nuclear reaction, 47Sc by proton irradiation of 48Ca target in 48Ca(p,2n)47Sc and 48Ca(p,d)47Ca→47Sc reactions and also by neutron irradiation reaction 46Ca(n,γ)47Ca→47Sc in the "Maria" Nuclear Reactor.
In our work, we used enriched 42/44/46/48CaCO3 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, CaCO3 targets were dissolved in 1 M HCl, and a microfiltration process after alkalization of the target material solution was used to separate 43/44Sc from calcium target materials and for the production of 47Sc generator. In the case of proton irradiation of 48Ca obtained product contained a mixture of radionuclides 47Sc, 48Sc, and 47Ca which is a 47Sc 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 47Sc by 5,6 days, 44 MBq/μAh of 47Sc can be eluted from the generator with no other contaminating scandium activity. A similar procedure was used for 46CaCO3 targets irradiated in the "Maria" Nuclear Reactor. After separation solution of 43/44/47Sc was loaded on cation exchange Dowex50wX4 resin for purification and change of environment.
The proposed methods allow obtaining high activity of 43Sc, 44Sc, and 47Sc. 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 46CaCO3 and 48CaCO3 make 47Sc not very economically profitable. Instead of 47Sc, a suitable candidate for the theranostic pair with 43/44Sc is 177Lu, 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%.
This project is financed from NCN, OPUS-22, 2021/43/B/ST2/02150 "Development of three-photon emitting radiotracers for positronium imaging".

SCANDIUM FOR PET / 554

Invited talk: Production of theranostic pair (43/44)Sc – (47)Sc on calcium targets

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TOTAL-BODY PET / 544

Invited talk: Molecular transport imaging of radiotracers with total-body dynamic PET

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Molecular transport imaging of radiotracers with total-body dy-

namic PET

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Most radiotracers for PET imaging are utilized to assess their end-product properties (e.g. for assessing glucose metabolism with F18-FDG). The intermediate molecular transport processes of a radiotracer, e.g., the transport rate across endothelial cell barriers, are much less explored. Still, they may provide rich information on health and disease. This talk will present our effort in developing enabling techniques with total-body dynamic PET and tracer kinetic modeling to image the molecular transport properties of a radiotracer for single-tracer multiparametric imaging.

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In vitro characterization of large-scale produced extracellular vesicles with cryo-EM and lensless holographic microscopy – proof of concept

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The development of novel drug delivery systems based on extracellular vesicles (EVs) is one of the most innovative and promising concepts for using nanotechnology in translational research. Designing a carriers based on vesicles naturally produced and secreted by cells require providing large scale EVs production and understanding the natural behavior of these structures under physiological/pathological conditions. Monitoring EVs intercellular transport pathways, determining the type of interactions they have with other cells and exploring the uptake mechanisms should enable their implementation into the preclinical studies for theranostic applications in the near future.

The aim of this study is to use hollow fiber bioreactor for long-term and large-scale EVs production from hTERT-immortalized cells exhibiting endothelial-like morphology (TIME). Obtained EVs will undergo a complex structural characterization with cryo-EM. Three-dimensional visualizations of tomographic (CT) reconstructed images will be used to analyze morphology and internal structure of EVs in their native state, thus being beneficial to traditionally used imaging techniques frequently affecting.

In order to enhance our understanding of EVs biology and intercellular interactions, we will use an innovative lensless holographic microscopy techniques. With advanced computational models used for image reconstruction these label-free methods enable precise tracking of EVs even after they have penetrated into the interior of target cells. Additionally, comparable assessment of refractive index (RI) distribution will provide an important insight into the EVs heterogeneity and size.

Precise label-free in vitro tracking of extracellular vesicles will provide an interesting insights into EVs biology under different physiological and pathological conditions. Discovering and understating of specific transport routes and internalization mechanisms will be an important step forward in EVs-based drug delivery systems approach.

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NOVEL BIOMARKERS FOR THERANOSTICS / 538

Key talk: Proteomic profiles of melanoma-derived and lymphocyte-derived exosomes from plasma of melanoma patients

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Proteomic profiles of melanoma-derived and lymphocyte-derived exosomes from plasma of melanoma patients

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Molecular profiling of exosomes (also known as small extracellular vesicles) isolated from the plasma of cancer patients emerges as a promising strategy for biomarkers discovery. We investigated the proteomic profiles of plasma exosomes derived from melanoma and T cells using immunopurification by anti-CSPG4 and anti-CD3 antibodies, respectively. Proteomes of specific exosome fractions purified from the plasma of melanoma patients were analyzed using high-resolution mass spectrometry. First, melanoma cell-derived (MTEX) and non-malignant cell-derived (NMTEX) vesicles were compared, which revealed 73 cancer-related proteins over-represented in MTEX. Moreover, we also identified the MTEX profile that discriminated between patients with no evidence of melanoma (NED) after therapy and patients with progressive disease (PD); PDCD6IP proteins had the highest discriminating value. Second, we compared proteomic profiles of T cell-derived CD3(+) exosomes from the plasma of melanoma patients (MPs) and healthy donors (HDs). The majority of proteins specific for CD3(+) exosomes were detected in the T lymphocyte proteome, indicating that the protein content of these vesicles mimics that of parent T lymphocytes. The abundance of 66 proteins detected in CD3(+) exosomes (out of 226 T cell-derived proteins) differentiated the MP and HD cohorts. The differentially expressed proteins were associated with the processes linked to cancer-related functions, including signaling pathways dependent on Rho GTPases, cytokines, and MAPK family kinases; in MPs, the hypothetical activity of pathways related to the aberrant BRAF predominated among all upregulated proteins. We were the first to show that proteomes of melanoma-derived exosomes in patients' plasma have a prognostic value. Moreover, we found that proteomic profiles of CD3(+) exosomes were distinct in MPs from those in HDs and recapitulated the proteome of tumor-responding T cells, potentially serving as a "liquid T cell biopsy".

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Efect of N-glycosylation on protein sorting into microvesicles and exosomes released by WM115 melanoma cells

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Introduction: Intercellular transport of proteins via extracellular vesicles (EVs), such as exosomes (EXO) and microvesicles (MVs), plays a significant role in facilitating carcinogenesis. Therefore, studying the proteome of melanoma-derived EVs may improve our understanding of the mechanisms of melanoma progression and help develop alternative biomarkers. However, it has been shown that altered glycosylation can dramatically alter the protein content of EVs. Therefore, this study aimed to analyze how induced changes in glycosylation affect protein sorting into EVs.
Methods: WM115 melanoma cells, cultured in RPMI-1640 GlutaMAXTM medium, were treated with 1-deoxymannojirimycin (DMJ; the selective inhibitor of α-mannosidases) or tunicamycin (TM; the inhibitor of the transfer of N-acetylglucosamine 1-phosphate to dolichol) for 72 hours. After the treatment media were collected and intended for the isolation of EXOs and MVs by differential centrifugation and low-vacuum filtration procedure. To analyze surface glycosylation of cells and their EVs flow cytometry with a panel of 6 lectins was used. To analyze the effectiveness of isolation transmission electron microscopy, nanoparticle tracking analysis, and western blot for vesicular markers have been performed. The shotgun nanoLC-MS/MS approach was applied to analyze the protein content of EXO and MVs derived from WM115 cells cultured with or without inhibitors.
Results: Treatment of WM115 cells with TM significantly decreased cells relative fluorescence intensity (RFI) in all lectin stainings. However, treatment with DMJ did not increased RFI of cells in GNA staining. WM115DMJ MVs had 3-fold higher RFI in GNA staining compared to WM115Control MVs, while WM115DMJ EXO RFI in this staining increased only slightly. In the case of WM115TM MVs and EXO RFI decreased almost in all stainings. LC-MS/MS analyses of MVs allowed for the identification of 1607 individual proteins. In detail, 1278 proteins in WM115Control MVs, 1027 proteins in WM115DMJ MVs, and 1064 proteins in WM115TM MVs. Proteomic analysis of EXO allowed the identification of 1266 individual proteins. In detail, 817 proteins in WM115Control EXO, 621 proteins in WM115DMJ EXO, and 1032 in WM115TM EXO. Quantitative changes have also been found.
Conclusions: The use of N-glycosylation inhibitors significantly altered the glycosylation profile of EVs released by melanoma cells and resulted in significant changes in the proteome of both microvesicles and exosomes. Therefore, a better understanding of the role of glycosylation in the protein sorting mechanisms into EVs may be crucial to understanding the role of EVs in melanoma progression and their potential for diagnostic and therapeutic purposes.
Funding: This study was supported by funds from the BioS (U1U/P03/NO/03.22 (to Małgorzata Przybyło) Priority Research Area under the program “Excellence Initiative - Research University” at the Jagiellonian University in Krakow.

PET IMAGING INNOVATIONS / 599

Key talk: Bench-to-clinical research on novel application-specific PET systems

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Bench-to-clinical research on novel application-specific PET systems

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Bench-to-clinical research on novel application-specific PET systems

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Why are physics researchers developing novel medical systems on their own? The reason is that current equipment is not fully exploiting the potential of nuclear medicine, and patients are waiting for new technology to emerge. Therefore, it goes without saying that inventing something to solve a clinical problem is most important, but it is meaningless unless the results are delivered to patients. Transferring research results to existing medical device companies is the gold standard, but in reality, the more novel the idea, the more cautious the company will be. What can academia do in such cases? Should we just give up? If our idea is real and we believe it will help save patients, we have no choice but to move forward. In this lecture, the importance of "bench-to-clinical" research will be introduced while introducing a recent case study of the development of the world's first hemispheric brain PET system. The initial idea for the hemispherical geometry was invented in 2013 when we were searching for the most ideal PET for brain imaging. Most importantly, prototyping demonstrated the feasibility of the idea. And the idea was eventually commercialized in Japan in 2022 as VRAIN 1. Finally, we arrived just in time for the arrival of an effective drug to treat Alzheimer's disease. The high sensitivity and fast TOF resolution of 229 ps of VRAIN also offer the potential for positronium lifetime imaging 3. High-energy physics has great potential to save more patients. The important message in this lecture is a simple one: identify the essence and do it seriously.

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POSITRONIUM IN FUNDAMENTAL AND MATERIAL PHYSICS / 586

Invited talk: Possibility to Detect Electrolyte Disorder Using PET with Positron Annihilation Lifetime Spectroscopy

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Possibility to Detect Electrolyte Disorder Using PET with Positron Annihilation Lifetime Spectroscopy

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Aqueous solutions of NaCl, KCl and NaCl + KCl with different concentrations were studied using positron annihilation lifetime spectroscopy (PALS). A strong dependence of the o-Ps intensity as a function of solution concentration was demonstrated. On this basis, the average positron lifetime and the sum of counts in a selected time interval were proposed as reliable parameters for detecting ion imbalance in living organisms. The use of these parameters to differentiate healthy and cancerous tissues allows the development of auxiliary diagnostic methods in a new generation of PET scanners equipped with a PALS detection module.

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Session

CLOSING SESSION / 610

CLOSING CEREMONY

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CLASSICAL CONCERT