Editorial

Paweł Moskal* and Ewa Ł. Stępień*

New trends in theranostics

https://doi.org/10.1515/bams-2021-0204

We are pleased to present you the timely and insightful special issue of *Bio-Algorithms and Med-Systems* dedicated to *New trends in theranostics*. This short and intriguing title of the special issue contains a word *theranostics* that has acquired a special meaning and importance in recent years. *Theranostics* is a portmanteau word derived from terms *therapeutic* (Greek *therapeia*) and *diagnostics* (Greek *diagnõsis*). However, some authors have proposed the other term *theragnostics* which refers more to a pretreatment strategy as diagnostics tests that identify patients most likely to be cured with a new medication or a targeted therapy based on the test results. This extended notion of theranostics is beautifully revealed by our contributors Leszek Królicki and Jolanta Kunikowska in the article entitled **"Theranostics – present and future"** [1]. In their article, Królicki and Kunikowska pay attention to the two important aspects of theragnostic nuclear medicine: targeting and dosing of a radionuclide based on receptors density or metabolic pathway activity, and development of new detecting systems allowing to conduct dynamic imaging. Dosimetry and safety are the ultimate goals of current and future routes in nuclear medicine, especially for targeted therapy with α-emitters and boron neutron capture therapy (BNCT). The other hallmarks of theranogostics are the development of specific ligands and carriers for radionuclides. The authors provided many examples of new radiopharmaceuticals being developed in the preclinical phase or established clinical trials in the early phase [1].

This special issue is also a historical journey for us, taking us back to the time when Roentgen's discovery (1895) of X-rays ran a major change in the day-to-day practice of medicine to help the medical community in imaging of "invisible" structures in a human body and find a power of radiotherapy.

A brief outline on the history of radiotherapy in Poland from its beginnings until first decades of the second half of 20th century is described in the article by Ryszard W. Gryglewski [2]. A beneficial effect of X-rays was applied soon (1896) after Roentgen's discovery, by American (E.H. Grubbe), French (V. Despeignes) Austrian (L. Freund), and then in 1898, by English (C.T. Holland) practitioners. First steps in Poland were proceeded soon in 1899–1900 (W. Łapiński, S. Boczar), and then a after the monography by M. Nartowski (1900) X-ray therapy was implemented to treat different diseases [2]. However, the origin of theranostics can be traced back to the mid-1950s, when the first theragnostic procedure was used with radioiodine in treatment of thyroid diseases [1].

Imaging of "invisible" would be not possible without the introduction of the instrument called "scintillation camera" which significantly impacted the role of radionuclide-based imaging techniques and allowed visualize large segments of the body with one data acquisition (tomography). The concept of molecular imaging based on pure positron-emitting radionuclides was introduced by investigators at PENN in the early 70s. The story of **"Unparalleled and revolutionary Impact of PET imaging on research and day-to-day practice of medicine"** is said in this issue by the pioneer of 18F-Fluorodeouxyglucose (FDG) administration to human beings Abass Alavi [3]. The introduction of FDG and significant improvements in instrumentation enhanced the prospects for PET imaging for research purposes and clinics, demonstrating PET imaging as the most quantitative modality for assessing disease activity in medicine.

Since its invention six decades ago the development of PET technology and its applications in clinics is still accelerating. Recently the first total-body PET scanners were taken into operation [4–8] changing the imaging paradigm by enabling simultaneous whole-body dynamic and parametric imaging of all tissues in the body simultaneously [3]. Total-body PET may cause a revolutionary change for the theranostic approach in nuclear medicine. Abass Alavi et al. [3] mention the many advantages of total-body PET systems as e.g. possibility of imaging the entire body within a few minutes, administering significantly low

***Corresponding authors: Paweł Moskal and Ewa Ł. Stępień**, Faculty of Physics, Astronomy and Applied Computer Science, M. Smoluchowski Institute of Physics, Jagiellonian University, Krakow, Poland; Total-Body Jagiellonian-PET Laboratory, Jagiellonian University, Kraków, Poland; and Theranostics Center, Jagiellonian University, Kraków, Poland, E-mail: p.moskal@uj.edu.pl (P. Moskal), e.stepien@uj.edu.pl (E.Ł. Stępień). https://orcid.org/0000-0002-4229-3548 (P. Moskal), https://orcid.org/0000-0003-3589-1715 (E.Ł. Stępień)

doses of FDG and other radiotracers for generating optimal results as well as screening the entire body for diagnosis of systemic diseases. However, despite such unquestionable diagnostic advantages, due to the extremely high costs, the total-body PET is now available only in a few centers in the world. Stefaan Vandenerghe in the contribution entitled **"Progress and perspectives in total body PET systems instrumentation"** [5] describes the further prospects of the development of total-body PET scanners in order to make them more cost-effective. The author discusses possibilities such as decreasing the crystal thickness, reducing the number of readout channels, reducing the amount of detector by introducing sparse geometries, or using other detector materials and configurations as PET with the axial arrangement of plastic scintillators developed by the J-PET group [6, 7]. Furthermore in the comprehensive review article entitled **"Perspectives of brain imaging with PET systems"**, Stan Majewski presents his expert vision of what may be the future of dedicated brain PET scanners [8]. The article presents the state of the art of brain scanners and includes a comprehensive description of PET brain imager of the next generation including mobile, wearable PET and also multi-photon brain-PET [9]. Stan Majewski argues that the best strategy for PET could be to develop the very high-performance dedicated brain imagers coupled to the economical long axial length PET scanners.

In Poland, it was not without difficulties in implementing PET in routine imaging diagnostics resulting from the provision of radiopharmaceuticals and obscure financing. Intriguing facts and dates, how positron emission tomography infrastructure has developed within the last 20 years, are given by Paulina Cegła and Tomasz Piotrowski in their article **"History of PET in Poland"** [10]. Polish medicine entered the path of theranostics and raise funds for the installation of the first medical PET scanners thanks to the extraordinary effort of a handful of enthusiasts and scientists, such as Prof. W. Graban and Dr. Z. Pawłowicz. Currently, in Poland, there are 31 centers with PET/CT scanners and nine cyclotrons in use for PET-radiopharmaceutical production, mainly FDG, 18FLT, 18FET and 11C-acetate, showing a rapid increase in the PET infrastructure in Poland [11]. We learn also from Abass Alavi et al. [3] that the basis for synthesizing FDG labeled with radioactive Fluorine was laid down in 1934 by the discovery of radioactive Fluorine by Polish students M. Danysz and M. Żyw [12] who were trainees under the supervision of Professor L. Wertenstein in the Radiological Laboratory of the Warsaw Learned Society. The first production of radioactive Fluorine was accomplished in 1934, concurrently with the discovery of artificial radioactivity by F. Joliot and I. Curie [13]. Both discoveries were published in the same issue of Nature [14, 15] and constitute the very foundation for imaging with radiolabeled tracers.

The theranostic approach assumes to use of radionuclides emitting positrons or gamma-radiation for imaging and low energy corpuscular radiation (β-, α, and Auger electrons) for therapy. In the review by Jarosław Choiński and Monika Łyczko entitled **"Prospects for the production of radioisotopes and radiobioconjugates for theranostics"** the examples of theranostic isotope pairs including $^{123,124}I/^{131}I$, $^{99m}Tc/^{186}Re$, $^{43,44}Sc/^{46,47}Sc$, $^{60,61,64}Cu/^{67}Cu$, $^{68}Ga/^{67}Ga$, $^{68}Ga/^{177}Lu$, $^{72}As/^{77}As$, $^{86}Y/^{90}Y$, $^{111}In/^{90}Y$ or less common $^{203}Pb/^{212}Pb$ and $^{197}Au/^{198}Au$ are discussed [16]. Shortcomings related to the production of such pairs and decay properties of each pair are given to present utility for radiobioconjugate synthesis. In the review by Tomasz Matulewicz entitled **"Radioactive nuclei for β+γ PET and theranostics: selected candidates"** [11], the author identifies the best candidates for theranostics PET by introducing the figure of merit (FOM) as the product of β+ branching ratio and the fraction of deexcitation γ emission in the decay of the daughter nucleus. The largest values (over 90%) of such defined FOM are obtained for ^{44}Sc and ^{52m}Mn isotopes among which scandium has a much longer lifetime, more appropriate for clinical applications. ^{44}Sc radionuclide was already proposed [14] as one of the most promising β+γ theranostic isotopes for multi-photon and positronium imaging due to (i) its convenient half-lifetime (3.9 h), (ii) emission of only single prompt 1,157 keV gamma with high probability (99%), (iii) short average time of prompt gamma deexcitation (1.6 ps), and (iv) chemical affinity enabling labeling of e.g. DTPA and DOTA-peptides which may be attached e.g. to trastuzumab-herceptin or PSMA tracers, respectively. Notably, radioactive scandium was discovered already in 1934 in the Radiological Laboratory in Warsaw by above mentioned M. Żyw who bombarded potassium with α particles [15]. Currently, scandium appears to be the most promising radionuclide for labeling various compounds for theranostics including also recently demonstrated three-photon [17] and the positronium imaging [18, 19]. Effective registration of three-photon images becomes realistic with the advent of total-body PET scanners with a multi-fold increase in sensitivity with respect to the standard 20 cm long PET systems. Also, positronium imaging requiring direct imaging with excellent time resolution may become soon practical, as we presently experience rapid development in improving the PET systems time resolution [20–23]. Paweł Moskal and Ewa Stępień in the review entitled **"Positronium as a biomarker of hypoxia"** [21], based on the recent observation that positronium lifetime is changing inversely proportional with the

concentration of oxygen in organic liquids [22, 23], present arguments demonstrating that the high sensitivity total-body PET systems and the invention of the method of positronium imaging [19, 22], open realistic perspectives for the application of positronium as a biomarker for *in-vivo* assessment of the degree of hypoxia.

In clinics, the example of peptide receptor radionuclide therapy (PRRT) in severe hypoglycemia in course of inoperable insulinoma as an effective first or second-line treatment is presented. In their article, Marta Opalińska et al. discuss cases of three patients treated with 90Y (/177-Lu)-DOTA-TATE showing significant improvement in quality of life and extended progression-free survival in these patients [24].

The theranostic approach in nuclear medicine requires an effective way of the delivery of radionuclide to the targeted tissue. Ewa Stępień, Carina Rząca and Paweł Moskal in the contribution entitled **"Novel biomarker and drug delivery systems for theranostics – extracellular vesicles"** [25] makes a proposal of the application of radiolabelled extracellular vesicles (EVs) in diagnostic and interventional medicine as a potential drug delivery system (DDS) in Theranostics. EVs are nano- and micro-sized double-layered membrane entities derived from most cell types and released into biological fluids [26] and deliver characteristics molecular signature of alterations in cellular processes [27, 28]. Combination of techniques for EV generation and tracking is an important issue for EV-based DDS [29]. The article discusses challenges in scaling of EV production for theranostic purpose, efficiency in EV isolations, methods of EV- radiolabelling, and perspectives for spatial and temporal *in-vivo* tracking of radiolabelled EVs in the whole human body by means of the total-body PET scanners enabling simultaneous dynamical imaging of radiotracers' distribution in all tissues of the human body.

Boron neutron capture therapy (BNCT) is an excellent example of targeted oncological treatment by α particles, nevertheless, the assessment of boron distribution in tissue exposed to neutron therapeutic beam is a serious drawback of this therapy. In their short review, Michał Silarski, Katarzyna Dziedzic-Kocurek, and Monika Szczepanek discussed **"Combined BNCT and PET for theranostics"** to determine boron uptake by cancer and healthy tissue before the treatment [30]. The use of ^{18}F labeled of ^{10}B isotope carriers is presented and state-of-the-art of total-body PET scanners to improve the boron imaging is discussed. Synergistic development of neutron generators technology and new boron carriers based on metallacarboranes and their nucleoside conjugates [31] will bring new perspectives in BNCT for Theranostics.

This special issue on new trends in theranostics gives an account of the new imaging and therapeutic technologies and new biomarkers (as positronium and extracellular vesicles) which possess a great potential for the development of theranostics approach in modern personalized nuclear medicine.

References

1. Królicki L, Kunikowska J. Theranostics – present and future. Bio Algorithm Med Syst 2021;17:199–202.
2. Gryglewski RW. History of radiotherapy in Poland. A brief outline of the problem. Bio Algorithm Med Syst 2021;17:227–33.
3. Alavi A, Werner TJ, Moskal P, Stępień EŁ. Unparalleled and revolutionary impact of PET imaging on research and day-to-day practice of medicine. Bio Algorithm Med Syst 2021;17:203–12.
4. Badawi RD, Shi H, Hu P, Chen S, Xu T, Price PM, et al. First human imaging studies with the EXPLORER total-body PET scanner. J Nucl Med 2019;60:299.
5. Vandenberghe S. Progress and perspectives in total body PET systems instrumentation. Bio Algorithm Med Syst 2021; 17:265–7.
6. Moskal P, Kowalski P, Shopa RY, Raczyński L, Baran J, Chug N, et al. Simulating NEMA characteristics of the modular total-body J-PET scanner – an economic total-body PET from plastic scintillators. Phys Med Biol 2021;66:175015.
7. Niedźwiecki S, Białas P, Curceanu C, Czerwiński E, Dulski K, Gajos A, et al. J-PET: a new technology for the whole-body PET imaging. Acta Phys Pol B 2017;48:1567–76.
8. Majewski S. Perspectives of brain imaging with PET systems. Bio Algorithm Med Syst 2021;17:269–91.
9. Yoshida E, Tashima H, Nagatsu K, Tsuji AB, Kamada K, Parodi K, et al. Whole gamma imaging: a new concept of PET combined with Compton imaging. Phys Med Biol 2020;65: 125013.
10. Cegła P, Piotrowski T. History of PET in Poland. Bio Algorithm Med Syst 2021;17:259–64.
11. Matulewicz T. Radioactive nuclei for β+γ PET and theranostics: selected candidates. Bio Algorithm Med Syst 2021;17:235–9.
12. Wertenstein L. An artificial radioelement from nitrogen. Nature 1934;133:564–5.
13. Joliot F, Curie I. Artificial production of a new kind of radioelement. Nature 1934;133:201–2.
14. Moskal P, Stępień E. Prospects and clinical perspectives of total body PET imaging using plastic scintillators. Pet Clin 2020;15: 439–52.
15. Żyw M. Induced radioactivity of potassium. Nature 1934;134:64–5.
16. Choiński J, Łyczko M. Prospects for the production of radioisotopes and radiobioconjugates for theranostics. Bio Algorithm Med Syst 2021;17:241–57.
17. Moskal P, Gajos A, Mohammed M, Chhokar J, Chug N, Curceanu C, et al. Testing CPT symmetry in ortho-positronium decays with positronium annihilation tomography. Nat Commun 2021;12: 5658.
18. Moskal P, Dulski K, Chug N, Curceanu C, Czerwiński E, Dadgar M, et al. Positronium imaging with the novel multiphoton PET scanner. Sci Adv 2021;7:eabh4394.

19. Moskal P, Jasińska B, Stępień EŁ, Bass SD. Positronium in medicine and biology. Nat Rev Phys 2019;1:527–9.
20. Lecoq P, Christian Morel C, Prior JO, Visvikis D, Gundacker S, Auffray E, et al. Roadmap toward the 10 ps time-of-flight PET challenge. Phys Med Biol 2020;65:21RM01.
21. Moskal P, Stępień EŁ. Positronium as a biomarker of hypoxia. Bio Algorithm Med Syst 2021;17:311–9.
22. Shibuya K, Saito H, Nishikido F, Takahashi M, Yamaya T. Oxygen sensing ability of positronium atom for tumor hypoxia imaging. Commun Phys 2020;3:1–8.
23. Stepanov P, Selim F, Stepanov S, Bokov A, Ilyukhina O, Duplâtre G, et al. Interaction of positronium with dissolved oxygen in liquids. Phys Chem Chem Phys 2020;22:5123–31.
24. Opalińska M, Sowa-Staszczak A, Al Maraih I, Gilis-Januszewska A, Hubalewska-Dydejczyk A. Peptide receptor radionuclide therapy as a tool for treatment of severe hypoglycemia in patients with primary inoperable insulinoma. Bio Algorithm Med Syst 2021;17:221–6.
25. Stępień EŁ, Rząca C, Moskal P. Novel biomarker and drug delivery systems for theranostics – extracellular vesicles. Bio Algorithm Med Syst 2021;17:301–9.
26. Stępień EŁ, Durak-Kozica M, Kamińska A, Targosz-Korecka M, Libera M, Tylko G, et al. Circulating ectosomes: determination of angiogenic microRNAs in type 2 diabetes. Theranostics 2018;8: 3874.
27. Roman M, Kamińska A, Drożdż A, Platt M, Kuźniewski M, Małecki MT, et al. Raman spectral signatures of urinary extracellular vesicles from diabetic patients and hyperglycemic endothelial cells as potential biomarkers in diabetes. Nanomedicine 2019;17:137–49.
28. Kamińska A, Roman M, Wróbel A, Gala-Błądzińska A, Małecki MT, Paluszkiewicz C, et al. Raman spectroscopy of urinary extracellular vesicles to stratify patients with chronic kidney disease in type 2 diabetes. Nanomedicine 2022;39:102468.
29. Yuana Y, Balachandran B, van der Wurff-Jacobs KMG, Schiffelers RM, Moonen CT. Potential use of extracellular vesicles generated by microbubble-assisted ultrasound as drug nanocarriers for cancer treatment. Int J Mol Sci 2020;21:3024.
30. Silarski M, Dziedzic-Kocurek K, Szczepanek M. Combined BNCT and PET for theranostics. Bio Algorithm Med Syst 2021;17:293–300.
31. Leśnikowski ZJ, Paradowska E, Olejniczak AB, Studzińska M, Seekamp P, Schüssler U, et al. Towards new boron carriers for boron neutron capture therapy: metallacarboranes and their nucleoside conjugates. Bioorg Med Chem 2005;13: 4168–75.