MEDICAL UNIVERSITY OF LODZ

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Łódź, 18.08.2025

REVIEW

Nasrin Abbasi Gharibkandi doctoral dissertation

" Nanoparticle radioconjugates of $^{103}Pd/^{103m}Rh$ and $^{109}Pd/^{109m}Ag$ *in vivo* generators for Auger electron Therapy."

The peer-reviewed doctoral thesis of Nasrin Abbasi Gharibkandi was made in Laboratory of Radiopharmaceutical Chemistry, Centre of Radiochemistry and Nuclear Chemistry of Institute of Nuclear Chemistry and Technology in Warsaw. Thesis supervisior is prof Aleksander Bilewicz PhD-DSc and auxiliary supervisor Agnieszka Majkowska-Philip PhD-DSc.

In recent years, there has been more research into the potential application of nanotechnology in nuclear medicine. The basis of both diagnosis and therapy in nuclear medicine are radiopharmaceuticals, which, using their ability to accumulate selectively in specific organs and tissues. They are administered to patients mainly in the form of injections. It is anticipated that the use of nanosystems may further increase the selectivity of radiopharmaceuticals by exploiting their distinct pharmacokinetic properties. Of course, several nanoforms such as 99mTc colloids have been used in diagnostics for decades. However, only a few new radiopharmaceuticals have been registered, despite intensive research. On the other hand, due to the problems of nanoparticles with metabolism and excretion, further research is needed to verify the safety and efficacy of their use. When designing new radiopharmaceuticals, the aim is to find substances that, when combined in various ways with nanoparticles, will be able to transport substances to specific sites in the patient's body. In addition, they will be safer and more selective in relation to the selected target sites. Therefore, "nanoradiopharmaceuticals" seem to be the future of nuclear medicine and the goal towards which the largest laboratories involved in the design of new radiopharmaceuticals are striving.

The reviewed doctoral thesis is a series of scientific publications accompanied by a summary of the work. The publications are thematically consistent and contain all co-authors' statements. The statements presented clearly indicate the doctoral student's significant contribution to the preparation of the manuscripts. It should be emphasized that in each of these publications, the doctoral student is the first author. The results contained in the dissertation are published in four publications of international scope with a total impact factor (IF) of 17.1. Doctoral student in all publications is the first author which clearly indicates the significant contribution of the Doctoral student in the preparation of the manuscripts. The publications are placed at the end of the monograph. Declarations of participation in the publications of co-authors attached at the end of the dissertation. To sum up her entire scientific achievements, she is a co-author of a total of 11 publications in which she presented the results of her research with a total impact factor (IF) of 42.5. The entire work submitted for evaluation was prepared in English Additionally, it should be noted that the research during the doctoral thesis was financed from two grants from The National Science Centre of Poland: Opus Grant no 2022/45/B/ST5/01861 and Opus Grant no. 2019/35/B/ST4/01433.

The part of the doctoral dissertation that constitutes the self-report author's summary comprises 60 pages of the dissertation. The remaining part consists of four publications together with statements from co-authors and scientific achievements. Within this section, we can distinguish a theoretical part described on 21 pages of the typescript. It contains the latest information on Auger emitters, which provides an excellent introduction to the subject of the work. The doctoral student described various forms of radiobioconjugates and labeling. She also characterized the individual types of substances that were combined with Auger. The content leaves something to be desired because, due to the interesting subject matter, a more detailed description of individual examples of radiopharmaceuticals and development work in this area would be desirable. However, given the form of the dissertation, I understand the necessity of this form of description. At this stage, I would like to emphasize the doctoral student's remarkable ability to write in a clear and concise manner and to present a large amount of information in a synthetic and concise way. This is an advantage that only the best scientists possess.

The aim of the doctoral thesis itself was presented on two pages of the manuscript and the main objective of the doctoral thesis is to experimentally verify the effectiveness of radioconjugates of $^{109}Pd/^{109m}Au$ in an *in vivo* generator for combined beta- and Auger electron

therapy. The final goal of this doctoral thesis was verify whether ^{109m} Auger can diffuse from the nanoparticles surface after the decay of ^{109}Pd. Additionally, the plan was to investigate the cytotoxic effects of the obtained substances on healthy cells. This description and subsequent execution of the research demonstrate that the PhD student's activities were thoroughly considered and carefully planned. This approach to research makes one admire the PhD student's scientific maturity.

The main body of the thesis consists of four publications in peer-reviewed journals. The first is a review publication that provides an introduction to the entire research topic undertaken by the doctoral student. There, the doctoral student describes the concept of nanoparticle-mediated radionuclide delivery in the cancer treatment. Furthermore, the development of nanostructures for cancer therapy using Auger electron radionuclides is presented. The publication also describes various types of nanostructures that can be used as carriers for Auger electron emitters, design principles, nanoparticle materials, and targeting vectors that have overcome major challenges. This is valuable research material and demonstrates the doctoral student's thorough understanding of the topic. It also contributes to the discussion regarding the necessary changes that could lead to nanoparticle-based Auger electron radionuclide therapy being implemented in clinical applications. In the next publication, the PhD student presented the results of her research. She obtained a ^{109}Pd radiobioconjugate deposited on 15-nm gold nanoparticles, exceeding a efficiency rate 95%. She attached polyethylene glycol chains and the monoclonal antibody trastuzumab to the Au@Pd nanoparticles. The synthesized bioconjugate contained an average of 9.5 trastuzumab molecules per nanoparticle. In vitro cellular studies performed by the PhD student demonstrated specific binding of the radioconjugate to the HER2 receptor on SKOV-3 cells, resulting in 90% internalization. The PhD student observed a significant cytotoxic effect, significantly greater than that observed with pure β- and pure Auger electron emitters. Based on this, she hypothesized that in the studied system, the cytotoxic effect of Auger electrons could also occur through damage to the cell's nuclear membrane emitted from nanoparticles accumulated in the perinuclear region. This is undoubtedly a significant scientific achievement and indicates a new direction in the area of cytotoxic mechanisms using selected radiopharmaceuticals. In the next study, PhD student used ^{109}Pd (T1/2 = 13.7 h) in the form of a ^{109}Pd/^{109m}Ag in vivo generator as a source of β− particles and Auger electrons in targeted radionuclide therapy for TNBC. ^{109}Pd, obtained through neutron irradiation of the ^{108}Pd

target, was deposited similarly to the previous publication onto 15 nm gold nanoparticles to form Au@^{109}Pd core–shell nanoparticles, which were then conjugated to the panitumumab antibody. In the conducted research with the cell line, the PhD student demonstrated the Au@^{109}Pd-panitumumab radioconjugate significantly reduced the metabolic activity of MDA-MB-231 cells in a dose-dependent manner. She also showed that Au@^{109}Pd-PEG-panitumumab nanoparticles show potential as a therapeutic agent for combined β−–Auger electron targeted radionuclide therapy of TNBC. In the last publication PhD student palladium nanoparticles with a size of 5 nm were synthesized using ^{109}Pd produced through neutron irradiation of natural palladium or enriched ^{108}Pd. Next, she performed tests on a cell line and revealed that the nanoparticles accumulated inside cells, reaching around 50% total uptake. The ^{109}Pd-PEG nanoparticles exhibited high cytotoxicity, even at low levels of radioactivity (6.25 MBq/mL), resulting in almost complete cell death at 25 MBq/mL. This proves that the doctoral student will achieve a positive result in this case as well. In this way, she showed that her achievements are significant and can serve as guidelines for further work in this field.

In conclusion, the research carried out within the dissertation submitted for evaluation is an example of excellent research work highlighting the multidisciplinary nature of radiopharmacy. The doctoral student has thus confirmed that she has skills with a very broad scope. Which is very rare. In the work, we can find practically all fields of pharmaceutics starting from the search for new drug, synthesis, checking the safety of the new compounds and radiolabelling. The latter elements in particular demonstrate the extensive skills of the PhD student. The research conducted indicates that Nasrin Abbasi Gharibkandi is skilled not only in synthesis, but also in the selection and use of highly specialised in nanotechnology and radioactive isotope labeling. This bodes well for her future scientific career. With regard to the planning of the research and the interpretation of the results, it can be clearly stated that the doctoral student demonstrates a high degree of scientific maturity. The research plan was well thought out, the experiments were carried out correctly and the conclusions were drawn correctly, as evidenced by the publications in very good scientific journals. Therefore it can be concluded that the research is definitely of significant value, not only cognitively, but also in extending the knowledge of applications of nanotechnology in radiopharmacy and indication of directions for the development of Auger emitters.

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From the reviewer's point of view, I can only say that the doctoral thesis are very well prepared, the research techniques are correctly selected, and the conclusions are precise. It also does not contain any serious editorial errors that significantly affect its aesthetics, and while participating in the discussion, I would ask the doctoral student to present their plans for further research in the field of radiopharmacy and the use of nanotechnology in nuclear medicine. Please also present the possibilities for the practical application of the obtained radiopharmaceuticals, especially in terms of regulations related to the use of nanoparticles.

In conclusion, the doctoral dissertation meets the conditions specified in Article 187 of the Law of July 20, 2018. Law on Higher Education and Science (i.e., Journal of Laws 2023, item 1742 as subsequently amended) in Poland and therefore I request the Scientific Council of the Institute to admit Nasrin Abbasi Gharibkandi, to further stages of her doctoral dissertation. In view of the scientific achievement and the publication of the results in journals of high scientific standing, I recommend awarding distinction to Nasrin Abbasi Gharibkandi doctoral thesis .

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Niniejszym wnioskuję do Rady Naukowej Instytutu Chemii i Techniki Jądrowej w Warszawie o wyróżnienie pracy doktorskiej Pani Nasrin Abbasi Gharibkandi.

Wniosek uzasadniam dużą wartością poznawczą pracy, multidyscyplinarnością oraz innowacyjnością w porównaniu do powszechnie istniejącej wiedzy w zakresie radiofarmacji i zastosowania w niej nanocząsteczek. Ponadto istnieje realna szansa, że dokonania naukowe przedstawione w dysertacji wpłyną na rozwój opracowanych rozwiązań i możliwość wprowadzenia ich do powszechnego stosowania co byłoby spójne z trendami prezentowanymi przez towarzystwa naukowe związane z medycyną nuklearną w zakresie diagnostyki, terapii i teranostyki chorób cywilizacyjnych.

Ponadto bardzo wysoko oceniam dorobek naukowy Doktorantki. Nasrin Abbasi Gharibkandi opublikowała wyniki badań stanowiących podstawę rozprawy doktorskiej w 4 publikacjach o łącznym współczynniku oddziaływania IF **17,1** punktów. W każdej z publikacji Doktorantka jest pierwszym autorem. Ponadto całkowity dorobek naukowy stanowi 11 publikacji o łącznym współczynniku oddziaływania IF **42,5** punktów.

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