

Review
for the thesis of Gurin A.N.
on the topic "Development of a radiopharmaceutical based on Lu-177 labelled
elagolix for therapy and diagnosis", submitted for the degree of Doctor of
Philosophy (PhD) in the specialty "6D060600-Chemistry"

1. Relevance of the research topic

Breast cancer is the most common cancer disease among women. It is the second most common disease after lung cancer in the human population. Development of pharmaceuticals for treatment and diagnosis of the above indicated disease is one of the urgent tasks of modern medicine.

According to assessment of the experts from the World Health Organization, from 800 thousand to 1 million new cases of breast cancer are registered in the world every year. In terms of the number of deaths from cancer in women, this type of disease is the second in the world. Various methods of treatment are used to treat breast cancer: surgery, drug treatment and radiation therapy or a combination of both. One of the promising areas of modern science and health care is production of radiopharmaceuticals for cancer treatment, able to diagnose and treat this disease at early stage.

The number of radiopharmaceuticals in clinical use is rapidly growing, which allows medical professionals to gain access to detailed information about the characteristics of various types of tumors. The candidate for the thesis carried out the works on creation of a Lu-177 containing radio-metallic chelate for treatment and diagnosis of the mammary gland based on elagolix, which has recently been widely used to treat gynecological diseases.

The thesis was carried out within the framework of grant funding of the Science Committee of the Ministry of Education and Science of the Republic of Kazakhstan for the period 2018-2020 on the topic "Determination of the optimal technological parameters for preparation of a new radiopharmaceutical for diagnosis and therapy of thrice-negative breast cancer (TNBC) with an elagolix-¹⁷⁷Lu of the antagonistic mechanism of action", which in turn complements the relevance of this topic on a national scale.

2. Scientific results within the framework of the requirements for dissertations

As a result of the conducted systematic studies, the following theoretically and practically important results were obtained:

- Lu-177 with the desired activity and purity for Elagolix labeling was obtained by the reaction of neutron activation with thermal neutrons;
- the optimal parameters for synthesis of Lu-177 labeled DOTAELA were found at pH-4.5 with radiochemical yield of 50.1%, temperature of 90-100 °C with a radiochemical yield of 95.3%, complexation time of 40 minutes with a radiochemical yield of 50.1%;
- preparation of the block diagram of the complex preparation of ¹⁷⁷Lu-DOTAELA showing the target preparation, the synthesis conditions and packaging leading to RCP ≥ 95%, and a draft specification for development of its pilot batches.

3. The degree of validity and reliability of the results and conclusions provided in the thesis

The degree of validity and reliability of each thesis result is high: the results were obtained through numerous experiments to determine the optimal parameters of DOTAELA radioactive labeling, study of purification and stability of the resulting complex, the composition of reagents was developed, the dosage form of the radiopharmaceutical was prepared, etc. the obtained experimental data were analyzed using gamma-spectrometry, pH-metry, GC, ICP-AES, HPLC and paper chromatography.

4. The degree of novelty of each scientific result and conclusions of the applicant provided in the thesis

The results of the thesis are new since they were carried out for the first time:

- selection of a paper chromatography system for evaluating the yield of ^{177}Lu -DOTAELA;

- determination of the optimal technological parameters for synthesis of ^{177}Lu -DOTAELA;

- development of the composition of the reaction mixture and the technological scheme for preparation of the DOTAELA-based radiopharmaceutical;

- development of the methods of analytical quality control of the “ ^{177}Lu -DOTAELA” radiopharmaceutical, approbation of the methods of qualitative and quantitative determination of the main components in the composition and preparation of the draft Specification for a new radiopharmaceutical.

The novelty of the thesis is confirmed by the author's publications in the leading journals of the near and far abroad, wide presentation at the national and international conferences.

5. Assessment of the internal unity of the obtained results

The internal consistency of the obtained results is high since the thesis is devoted to DOTAELA radiolabeling with Lu-177, followed by development of a potential radiopharmaceutical for diagnosis and treatment of triple-negative hormone-sensitive breast cancer.

6. The focus of the obtained results on solution of the relevant urgent problem

The results of the thesis are focused on solving the urgent theoretical and applied problems of health care, early diagnosis and treatment of triple-negative breast cancer. The results of the performed works will promote development of highly informative and minimally invasive methods of nuclear medicine and contribute to creation of new local radiopharmaceuticals for diagnosis and therapy of breast cancer. In the course of the thesis preparation, the technology for preparation of a dosage form of the ^{177}Lu -DOTAELA radiopharmaceutical, the methods for quality control of the main components were developed, and a draft specification was proposed for production of the pilot batches of radiopharmaceutical for its subsequent pre-clinical studies.

7. Confirmation of publication of the main provisions, results and conclusions of the thesis

The main results are sufficiently described in 10 scientific papers, including the publications in the peer-reviewed scientific journals indexed in Web of Science and Scopus, as well as in journals recommended by the Committee of Control in Science and Education of the Ministry of Education and Science of the Republic of Kazakhstan.

8. Deficiencies in the content and design of the thesis

There are no fundamental comments for the thesis of Gurin A.N., however, the proper attention shall be paid to the following disadvantages:

1) NMR, IR spectrometry and X-ray structural analysis of the obtained complexes should have been carried out in addition to the performed analysis to obtain the detailed structure determination.

2) The thesis is finalized with preparation of the Specification for production of the experimental batches of the drug. Typically, such document is an integral part of the production regulation for production of the drug for pre-clinical and clinical trials and subsequent industrial production. The non-radioactive ingredients of the drug are produced in the form of a lyophilisate or a set of reagents to prepare any radiopharmaceutical in the medical organization. Therefore, it seems appropriate to address the issue on possibility of future works on creation of a standard set of reagents (lyophilisate) for preparation of the drug in the clinical organization. What has been done or is being done in this area?

3) There are mistakes of stylistic, spelling and editorial nature.

These remarks do not affect the overall high level of experiment performance and do not diminish the scientific and practical value of the peer-reviewed paper.

9. Compliance of the thesis with the requirements of the Committee

The thesis of Gurin A.N. on the topic "Development of a radiopharmaceutical based on Lu-177 labelled elagolix for therapy and diagnosis" submitted for the degree of Doctor of Philosophy (PhD) is a completed, independent scientific and qualification work, containing the solution of the urgent problem of cancer diagnostics and treatment and fully complies with the requirements for dissertations and can be recommended for further defense.

**Reviewer,
Deputy Chairman of the Board of the
I. Zhakhaev Kazakh Research Institute
of Rice growing, Candidate of Chemical
Sciences, Professor**



Appazov N.O.