

TRANSLATION MEDICINE, BIOMEDICINE AND MEDICAL BIOTECHNOLOGY: THE TRANSITION TO PERSONALIZED MEDICINE

O. V. PEREGINYA, T. M. LUTSENKO

National Technical University of Ukraine “Igor Sikorsky Kyiv Polytechnic Institute”

E-mail: tanywalytsenko@gmail.com

Received 12.02.2020

Revised 15.03.2020

Accepted 30.04.2020

Given that biomedical research in the field of molecular and cellular foundations of pathogenesis has been actively developing in the last two decades, there is a need for active collaboration between scientific and laboratory institutions to create new and improve existing methods of treatment to provide effective professional care for the patient. The transition to personalized therapy, which aims to create methods of treatment adapted to a specific group of patients or individual, became a big step in the field of translational medicine. An important issue is the introduction of translational medicine into modern clinical practice and its development ensuring on the basis of scientific centers and institutes.

The purpose of the article was to analyze and summarize information regarding translational medicine and its implementation in treatment and scientific and practical activity to ensure more effective therapy for patients.

The literature concerning the development of translational medicine, its application in clinical practice and methods of implementation in the scientific field was reviewed and analyzed. The information about personalized medicine was generalized.

Translational medicine contributes to the practical application of scientific advances to the development and implementation of new methods of prevention, diagnostics, treatment and rehabilitation. An important characteristic of translational medicine is its double-sided concept, which consists in the collaboration of laboratory and clinical institutions in order to regularly information exchange. The introduction of personalized medicine allows, based on the individual characteristics of the patient, to find an effective approach to treatment.

Translational medicine is a promising area of treatment, the introduction of which in clinical practice would enable to create and improve effective methods of various diseases therapy. The widespread use of personalized medicine will increase the percentage of positive treatment outcomes due to the individual approach to each patient. For the active development and spread of this type of therapy, there is a need to create more institutes of translational medicine, to hold scientific conferences on this subject, and to introduce into the curricula of universities the disciplines for the study of the basics of translational medicine.

Key words: translational research, translational medicine, cancer, personalized medicine.

In the last 20 years there has been an active development of biomedical research in the field of genomics, molecular and cellular bases of various diseases pathogenesis, identification of new targets for medicines and creation of new drugs with high efficiency. The growing distance between practical healthcare and theoretical information in the

field of biomedical research creates the need for professional contact between clinicians and scientists in order to actively transfer (translate) modern fundamental research to effective medical care for a specific patient, i. e. personalized therapy [1].

This approach to treatment was called translational medicine. Its essence is to use the

advances of fundamental research to develop new or improve existing methods of treatment.

The purpose of the article is to review and analyze the literature related to translational medicine.

The history of the concept emergence and its essence

At the beginning of the 21st century, the medical community of the world came to the conclusion that, although significant advances had been made in theoretical biomedical disciplines, the degree of existing developments implementation in practical healthcare remained rather low. Despite the fact that enormous resources have been invested in fundamental research and the associated great advances in understanding the mechanisms of disease development, this has not led to an increase in the number of new methods of treatment and diagnostic systems.

The term “translational research” was introduced in 1986 to denote a medical research that promoted the practical application of scientific advances to the development and implementation of new methods of prevention, diagnostics, treatment and rehabilitation. In the medical literature of the 1990s, there were relatively few references to this term and most of them concerned cancer research [1, 2].

The pharmaceutical company Pfizer was one of the first which determined translational medicine as a recognized discipline in the field of medicines production. Pfizer defined translational medicine as the integrated use of innovative pharmacological tools, biomarkers, clinical methods and technologies to increase confidence in medicines, to improve the economic solution, sustainable production of new products [3, 4].

The impetus for conducting translational research is usually a clinically relevant problem [5]. The possibility of solving the existing problem stimulates to carry out fundamental medical researches aimed at identification of targets for diagnostics and therapy of the disease. Quite often, biomedical research leads to the development of a new medicine or technology that is being tested in clinical settings. After evaluating the results of the introduction of a new treatment method, the translation cycle is closed and the developed approach is refined using the methods of fundamental medicine [6, 7].

There are 3 phases of translational research.

The first phase is a scientific-research process that examines the needs of medicine in potential methods of diagnostics and treatment, conducts tests on the safety and effectiveness of developments. The first phase is the translation of the basic scientific discoveries into the system of public healthcare under controlled conditions, that is, in the course of clinical research. Many pharmaceutical companies organize special structures for the I phase of translational research that facilitate the interaction between researchers and medical practitioners [7, 8].

The second phase of translational research examines the results of clinical developments, assesses the effectiveness and safety of the scientific approaches used in the first phase of translational research. Thus, the possibility of new developments usage in clinical practice through patient-based research is evaluated. The second phase of translational research informs about the needs, acceptability, effectiveness and cost-effectiveness of new developments under real political conditions and facilitates their promotion in the healthcare system.

The third phase of translational research contributes to the implementation of prospective clinical trials into the healthcare system [9].

Currently, translational medicine is a comprehensive system of scientific research, practical and social activities that are closely linked. Organizational aspects of this area development include further scaling up of scientific research in this field, attracting broad financial support from the state and private investors, reviewing and developing of legal and ethical standards in the light of new advances in translational medicine. In scientific research and applied fields, the priority of translational medicine is the creation of new medical technologies.

Double-sided concept of translational medicine

The double-sided concept is the collaboration of the laboratories where the experiments are conducted and the clinical institutions. It must be ensured that the flow of information flows in both directions, from laboratory to hospital and from hospital to laboratory.

This concept was developed in 1999, when the total volume of biomedical research started to be more and more dependent on multidisciplinary biomedical, clinical,

fundamental scientists and engineers, and new technologies. Subsequently, in 2001, adequate funds were earmarked for the study of human diseases [10].

The double-sided concept of translational medicine can be reflected by defining the following interactions between research and medical institutions (Figure):

Benchside to Bedside;

Bedside to Benchside.

Benchside to Bedside — from lab to patient. This interaction aims to increase the effectiveness of clinical trials of new therapeutic strategies developed in the course of research.

Bedside to Benchside — from patient to lab. The purpose of this interaction is to provide feedback on the use of new methods of treatment and opportunities for their improvement [6, 9].

The purpose of this concept is to identify and avoid common obstacles, barriers and problems in the way of scientific breakthroughs in the clinic. It envisages the return of clinical research to laboratory research in order to refine or create new hypotheses that can lead to innovative discoveries [7].

Transition to personalized medicine, biomedicine and medical biotechnology

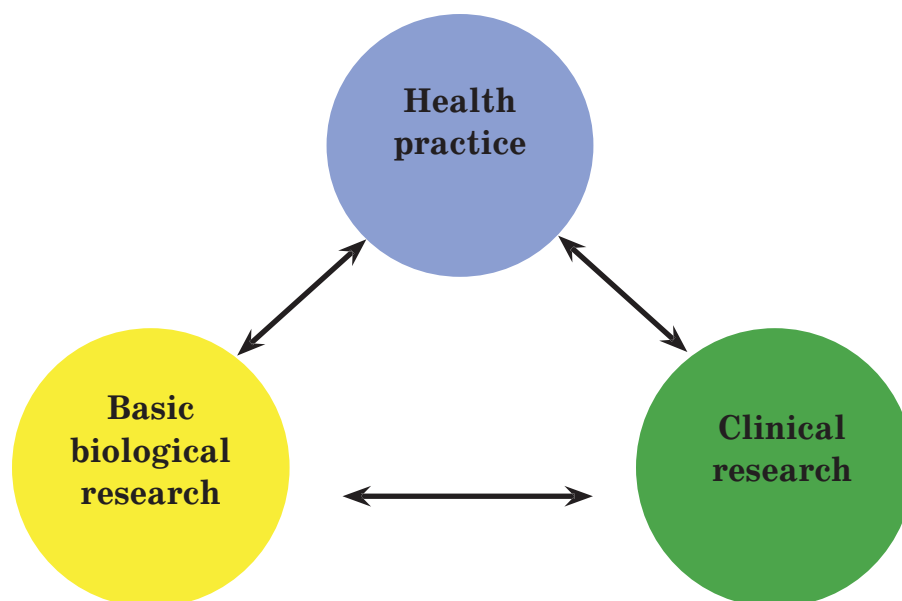
Until recently, it was assumed that patients with the same disease have the same causes of the disease. The same treatment was prescribed them. However, clinical experience shows that the organism of different patients may respond differently to treatment.

In most patients with the same disease, its causes may differ. Therefore, the development of medicines and treatment methods that are adapted to specific groups of patients or individuals has been started. This type of treatment is called personalized medicine. The term “personalized medicine” was first introduced in 1998.

Personalized medicine is a highly specialized focused approach to the prevention, diagnosis and treatment of a disease, based on the individual characteristics of the patient.

Over the past six decades, there has been a great deal of evidence that a significant proportion of variability in response to medicines is genetically determined by age, nutrition, health, environmental effects, and epigenetic factors. To achieve individual drug therapy, it is necessary to take into account the different patterns of medicines response among geographical and ethnic populations. Pharmacogenomics is a science that helps to identify genes that affect a patient’s response to medication and, thus, to identify genes that are potential targets for certain drugs [11].

One of the directions of translational medicine is the identification of specific biomarkers and bioprocesses that allow clinicians to choose the optimal treatment for a specific patient. Analysis of personal biomarkers of a definite disease is based on databases. Thanks to such databases, it is possible to develop treatment regimens for different diseases, that is, to identify drugs that act on several mechanisms of the investigated pathology. The



Bilateral concept of translational medicine

results obtained can be used to develop the most effective individualized treatment approach that will be based on the analysis of experimental data related to a particular pathology. Such databases can help to find certain combinations of drugs that will provide the most effective impact on molecular targets of the disease and to analyze the possible side effects of the medicines. Development of databases with information about possible biomarkers of known pathological conditions will allow to correct the diagnostics and create the most effective therapy for each individual patient [12].

Through the adaptation to each patient, opportunities to obtain early diagnoses, risk assessments and optimal treatment methods, personalized medicine aims to improve healthcare and reduce treatment costs [13].

Personalized medicine can be considered a continuation of traditional approaches to understanding and treating diseases, but with greater accuracy. The variation profile of the patient's gene may be guided by the choice of medicines or treatment protocols that minimize adverse side effects or provide more successful outcomes. Personalized medicine can also indicate a person's predisposition to certain diseases before they occur, allowing doctors and patients to develop a monitoring and prevention plan [11].

Implementation of translational medicine in the diagnostics and treatment of human diseases: the role of medical biotechnologies

Translational medicine plays an important role exactly in the field of oncology. Decoding of the human genome and the development of genomics made it possible to obtain information about the association of individual proteomic disorders with the probability of certain diseases occurrence.

Futreal conducted research on human genes involved in oncogenesis in 2004. He found 291 known at that time genes, which was 1% of the complete human genome. It has been found that the most of these genes are associated with leukemia and lymphoma, although the prevalence of these cancers accounts for only 10% of all cancer cases. As a consequence, the Catalog of Somatic Carcinogenic Mutations (COSMIC) (Catalog of Somatic Mutations in Cancer) was created on the basis of these data. It has been expanded due to the results of a genomic cancer project in the UK (Wellcome Trust Sanger Institute, UK). By 2008, this cell catalog included 4800 genes. The catalog is

updated every two months [14].

Over the past three decades, more than 200 potential biomarkers of ovarian cancer have been identified. During the 1990s, studies focused more on diagnostic markers, but in the last 20 years, attention has gradually shifted towards prognostic markers that help to evaluate the effectiveness of treatment [16]. For example, a series of studies conducted at a cancer institute in the United States found that high immunohistochemical expression of cyclin E is associated with unfavorable prognosis of the disease. And the low expression of BRCA1, a malignant suppressor gene, is associated with a reduced risk of disease progression and mortality. The postgenomic era provides new opportunities for individual (personalized) cancer therapy, which will not only predict the prognosis of the disease but also reveal the individual response to medicines [16, 17].

Simultaneously with the search for biomarkers in oncology, translational medicine pays great attention to the development of medicines whose action is aimed at specific molecular targets, which are key receptors, enzymes, or specific centers for ligands to their receptors binding [1].

Another problem in oncology that translational research can solve is to increase the effectiveness of analgesic therapy for metastases based on the study of the mechanisms of pain syndrome in bone tissue and the subsequent introduction of developed medicines into clinical practice.

Long-term therapy with anticancer drugs may be accompanied by the development of heart failure. Therefore, translational studies of signaling mechanisms associated with abnormalities in myocardial cells in cardiovascular disease need to be correlated with the processes that accompany anticancer therapy. An interdisciplinary seminar was organized in Brussels in 2009 by the European Cardiology Community in order to monitor the researches in this area. Specialists in the field of cardiology and oncology, translational and pharmaceutical science participated in the seminar [18].

Much attention is paid to the search for protein markers in the proteome and low molecular weight metabolites in the blood serum. In patients with heart failure, changes in the expression of protein genes have been identified, which are involved in the processes of inflammation, growth, differentiation, intracellular signaling, organization of channels and receptors, myocardial remodeling. The metabolites 2-oxoglutarate

and pseudouridine were identified as markers of heart failure. Such studies of heart diseases can identify indicators that are associated with arrhythmia and should help in the choice of therapy and reduce the risk of unexpected death caused by this syndrome [1].

Translational medicine is also used in the treatment of bone diseases. In the US, about 10 million people (8 million women and 2 million men) suffer from osteoporosis, while about 34 million people have osteopenia and are prone to osteoporosis.

New therapeutic methods are aimed at either osteoclasts (cells that destroy bone) or osteoblasts (cells that form bone). Therefore, osteoporosis treatment methods can be divided into two categories: antiresorptive medicines (osteoclastic agents) and anabolic drugs (osteoblastic agents). The main current types of osteoporosis therapy use estrogens, selective estrogen receptor modulators, parathyroid hormone (PTH), calcitonin, vitamin D derivatives and, in some countries, strontium. These medicines, with the exception of strontium and PTH, slow the destruction of bone tissue [3].

Scientific and practical implementation of translational medicine concept

The development of translational medicine aims at creating research centers with a defined infrastructure that facilitates the effective use of science achievements and their successful implementation in practice. To achieve these goals, it is necessary to manage the flow of knowledge and technologies and to coordinate the efforts of universities, scientific and research institutes, medical institutions, business and pharmaceutical companies.

Important place in the development of translational medicine centers is occupied by structures that provide the expansion of knowledge-intensive technologies, such as the Center for Experimental and Transgenic Animals, the Center for Transfer and Medical Technology, and the biobanks [12].

The first Institute in the field of Translational Medicine in the United States was the Institute of Translational Medicine and Therapy (ITMaT), organized in the beginning of the year 2005. Its main activity is focused on clinical and translational research. Today, it is a large organization that includes various medical institutions, the number of which is constantly increasing. Since its inception, ITMaT has expanded and, as of today, includes over 800 members and has more than 100,000 National Institutes of Health (NIH) funded

programs in the field of scientific, pre-clinical and clinical research.

In 2011, the National Center for Advancing Translational Sciences (NCATS) was created under the auspices of the NIH. It helps pharmaceutical companies and non-core organizations find a collaborative solution that enables prospective developments to complete successfully the first phase of research.

Almost every major US institute has an institute of translational medicine. In California, 1.5 billion dollars has been earmarked for research in translational medicine. Similar institutions are being created in Europe. In 2010, a grant program called "TRANSMED" was launched at the University of Helsinki, which funded research in the field of translational medicine. The main focus of the program was on the research of genomic technologies, molecular medicine, molecular biology of tumors and others [12].

In Ukraine, translational medicine is being developed at the Kavetsky Institute of Experimental Pathology, Oncology and Radiology of the NAS of Ukraine. Through the efforts of the staff of this institute, the database "Diagnostics, therapy, oncogenome and oncoproteome" was created, which contains information about molecular processes, regulatory factors, signaling cascade systems, functional state of the genome, epigenetics from individual tumor locations.

This program is designed as an easy-to-use tool, the use of which in clinical practice of the doctor will allow providing a high level of diagnostics and search of the optimum schemes of healthcare delivery in personalized treatment [19].

The work was written as a part of the following research work: "Scientific and methodological justification of the principles of biopharmaceutical products and the organization of its production" (2017–2118, state registration ТН 0116U007718).

Conclusion

This article summarizes information from literary sources regarding translational medicine and its implementation in clinical practice. Translational medicine, combining the successes of scientific research with the informativeness of diagnostic approaches, designed to promote enhancement the efficiency and effectiveness of treatment and, as a consequence, improve the quality of life. It can be regarded as a process that involves

the transfer of discoveries made through fundamental biomedical research into medical practice to improve diagnostics and treatment.

Recently, personalized therapy based on an individual approach to analyzing the occurrence and course of the disease of each patient is spreading.

The development of translational medicine

is a major step forward in treatment and, by combining the results of scientific research, diagnostic approaches and clinical research data, helps to improve the effectiveness and efficiency of therapy and, consequently, improve the quality of life.

REFERENCES

1. Ipatova O. M., Medvedeva N. V., Archakov A. I., Grigor'ev A. I. Translational medicine as a way from fundamental biomedical science to public health services. *J. RAMS*. 2012, V. 6, P. 57–65.
2. Rubio D. McGartland, Schoenbaum E. E., Lee L. S., Schteingart D. E., Marantz P. R., Anderson K. E., Platt L. D., Baez A., Esposito K. Defining Translational Research: Implications for Training. *Acad. Med.* 2010, 85 (3), 470–475.
3. Littman B. H., Krishna R. Translational Medicine and Drug Discovery. *Cambridge University Press*. 2011, 361 p.
4. Tatonetti N. P. Translational medicine in the Age of Big Data. *Briefings in Bioinformatics*. 2019, 20 (2), 457–462.
5. Jorge Otávio Maia Barreto, Everton Nunes da Silva, Rodrigo Gurgel-Gonçalves, Suêlia de Siqueira Rodrigues Fleury Rosa, Maria Sueli Soares Felipe, Leonor Maria Pacheco Santos. Translational research in public health: challenges of an evolving field. *Saude Debate*. 2019, 43 (2), 4–9.
6. Zerhouni E. A. Translational and clinical science-time for a new vision. *N. Engl. J. Med.* 2005, 353 (15), 1621–1623.
7. Marincola F. M. Translational medicine: A two-way road. *J. Transl. Med.* 2003, 1 (1), 32–33.
8. Littman B. H., Di Mario L., Plebani M., Marincola F. M. What's next in translational medicine? *Clin. Sci. (Lond)*. 2007, 112 (4), 217–227.
9. Abernethy A. P., Wheeler J. L. True translational research: bridging the three phases of translation through data and behavior. *Transl. Behav. Med.* 2011, 1 (1), 26–30.
10. Cohrs R. J., Martin T., Ghahramani P., Bidaut L., Higgins P. J., Shahzad A. Translational Medicine definition by the European Society for Translational Medicine. *New Horizons in Translational Medicine*. 2015, V. 2, P. 86–88.
11. Vogenberg F. R., Barash C. I., Pursel M. Personalized Medicine. Part 1: Evolution and Development into Theranostics. *Pharmacy and Therapeutics*. 2010, 35 (10), 60–67.
12. Paltsev M. A., Belushkina N. N. Translational medicine — a new stage of molecular medicine development. *Mol. Med.* 2012, V. 4, P. 3–6.
13. Hendriks B., Simons A., Reinhart M. What are clinician scientists expected to do? The undefined space for professionalizable work in translational biomedicine. *Minerva*. 2019, 57 (2), 219–237.
14. Futreal P. A., Coin L., Marshall M. Down T., Hubbard T., Wooster R., Rahman N., Stratton M. R. A census of human cancer genes. *Nat. Rev. Cancer*. 2004, 4 (3), 177–183. <https://doi.org/10.1038/nrc1299>
15. Grigorenko V. R. Modern methods of morphological diagnosis and prognosis of serous ovarian tumors. *Bull. Probl. Boil. Med.* 2018, 2 (144), 17–22.
16. Suh K. S., Park S. W., Castro A., Patel H., Blake P., Liang M., Goy A. Ovarian cancer biomarkers for molecular biosensors and translational medicine. *Expert. Rev. Mol. Diagn.* 2010, 10 (8), 1069–1083. <https://doi.org/10.1586/erm.10.87>
17. Darcy K. M., Birrer M. J. Translational research in the Gynecologic Oncology Group: evaluation of ovarian cancer markers, profiles, and novel therapies. *Gynecol. Oncol.* 2010, 117 (3), 429–439.
18. Eschenhagen T., Force T., Ewer M. S., de Keulenaer G. W., Suter T. M., Anker S. D., Avkiran M., de Azambuja E., Balligand J.-L., Brutsaert D. L., Condorelli G., Hansen A., Heymans S., Hill J. A., Hirsch E., Hilfiker-Kleiner D., Janssens S., de Jong S., Neubauer G., Pieske B., Ponikowski P., Pirmohamed M., Rauchhaus M., Sawyer D., Sugden P. H., Wojta J., Zannad F., Shah A. M. Cardiovascular side effects of cancer therapies: a position statement from the Heart Failure Association of the European Society of Cardiology. *Eur. J. Heart Fail.* 2011, 13 (1), 1–10. <https://doi.org/10.1093/eurjhf/hfq213>
19. Chekhun V. F. From system biology of cancer to methodology of personalized treatment. *Oncology*. 2012, 14 (2), 84–88.

ТРАНСЛЯЦІЙНА МЕДИЦИНА, БІОМЕДИЦИНА ТА МЕДИЧНА БІОТЕХНОЛОГІЯ: ПЕРЕХІД ДО ПЕРСОНАЛІЗОВАНОЇ МЕДИЦИНИ

Перегиня О. В.
Луценко Т. М.

Національний технічний університет України
«Київський політехнічний інститут
імені Ігоря Сікорського»

E-mail: tanywalytsenko@gmail.com

Метою роботи був аналіз та узагальнення інформації стосовно трансляційної медицини та її реалізації у лікуванні та науково-практичній діяльності для забезпечення ефективнішої терапії пацієнтів.

Розглянуто та проаналізовано літературу, що стосується розвитку трансляційної медицини, застосування її в клінічній практиці та методів реалізації в науковій сфері. Узагальнено інформацію щодо персоналізованої медицини.

Трансляційна медицина сприяє практичному застосуванню наукових досягнень для розроблення та впровадження нових способів профілактики, діагностики, лікування та реабілітації. Важливою характеристикою трансляційної медицини є її двостороння концепція, яка полягає у співпраці лабораторних та клінічних установ з метою регулярного обміну інформаційними даними. Впровадження персоналізованої медицини дає змогу на основі індивідуальних характеристик пацієнта знаходити ефективний підхід до лікування.

Трансляційна медицина є перспективним напрямом у лікуванні, впровадження якого у клінічну практику уможливить створення та вдосконалення ефективних методів терапії різних захворювань. Широке застосування персоналізованої медицини дасть можливість збільшити відсоток позитивних результатів лікування завдяки індивідуальному підходу до кожного пацієнта. Для активного розвитку та поширення цього виду терапії існує потреба створення більшої кількості інститутів трансляційної медицини, проведення наукових конференцій та впровадження у навчальні програми університетів дисциплін з вивчення основ трансляційної медицини.

Ключові слова: трансляційні дослідження, трансляційна медицина, онкологічні захворювання, персоналізована медицина.

ТРАНСЛЯЦИОННАЯ МЕДИЦИНА, БИОМЕДИЦИНА И МЕДИЦИНСКАЯ БИОТЕХНОЛОГИЯ: ПЕРЕХОД К ПЕРСОНАЛИЗИРОВАННОЙ МЕДИЦИНЕ

Перегиня О. В.
Луценко Т. М.

Национальный технический университет
Украины «Киевский политехнический
институт имени Игоря Сикорского»

E-mail: tanywalytsenko@gmail.com

Целью работы был анализ и обобщение информации о трансляционной медицине и ее реализации в лечении и научно-практической деятельности для обеспечения эффективной терапии пациентов.

Рассмотрена и проанализирована литература, касающаяся развития трансляционной медицины, применения ее в клинической практике и методов реализации в научной сфере. Обобщена информация по персонализированной медицине.

Трансляционная медицина способствует практическому применению научных достижений для разработки и внедрения новых способов профилактики, диагностики, лечения и реабилитации. Важной характеристикой трансляционной медицины является ее двусторонняя концепция, которая заключается в сотрудничестве лабораторных и клинических учреждений с целью регулярного обмена информационными данными. Внедрение персонализированной медицины позволяет на основе индивидуальных характеристик пациента находить эффективный подход к лечению.

Трансляционная медицина является перспективным направлением в лечении, внедрение которого в клиническую практику даст возможность создавать и совершенствовать методы терапии различных заболеваний. Широкое применение персонализированной медицины позволит увеличить процент положительных результатов лечения благодаря индивидуальному подходу к каждому пациенту. Для активного развития и распространения этого вида терапии существует необходимость создания большего количества институтов трансляционной медицины, проведение научных конференций и внедрение в учебные программы университетов дисциплин по изучению основ трансляционной медицины.

Ключевые слова: трансляционные исследования, трансляционная медицина, онкологические заболевания, персонализированная медицина.