

TRANSLATIONAL MEDICINE: UNTRANSLATED REGIONS AND THE STOP CODONS

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4P medicine is impossible without an efficient transfer of advanced laboratory techniques (such as regenerative cell technology, high-throughput sequencing, genome editing, etc.) into clinical practice. Translational Medicine - a new scientific field, designed to reduce the time of transfer of long-term achievements of fundamental scientific research in the development of innovative product applications. However, on the path of innovation in medicine, there are a number of natural barriers that do not allow to go to practice unsafe and ineffective products. The system of these barriers must be dynamic and up-to-date. As well as the education system for work at the "science–medicine" junction.

Keywords: translational medicine, innovations, preclinical trials, clinical trials

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ТРАНСЛЯЦИОННАЯ МЕДИЦИНА: НЕТРАНСЛИРУЕМЫЕ ОБЛАСТИ И СТОП-КОДОНЫ

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Медицина 4П невозможна без эффективного перевода на медицинские рельсы новейших лабораторных технологий, таких как регенеративные клеточные технологии, высокопроизводительное секвенирование, редактирование генома и др. Трансляционная медицина — новое научное направление, призванное сократить сроки перевода достижений длительных фундаментальных научных исследований в прикладные разработки инновационного продукта. Однако на пути внедрения инноваций в медицину есть ряд естественных барьеров, не позволяющих пройти в практику небезопасным и неэффективным разработкам. Система этих барьеров должна быть динамичной и отвечающей требованиям времени. Так же, как и система подготовки кадров для работы на стыке «наука–медицина».

Ключевые слова: трансляционная медицина, инновации, доклинические исследования, клинические исследования

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Now, *here*, you see, it takes all the running *you* can do, to keep in the same place. If you want to get somewhere else, you must run at least twice as fast as that!

The Red Queen from *Alice Through the Looking Glass* by
Lewis Carroll

Let's take a closer look at the list of Nobel Prizes in chemistry and physiology awarded over the past 30 years: a tremendous number of awards celebrate advancements in molecular and cellular biology with respect to their application in medicine (there is no Nobel Prize in biology). More than half of the articles published in *Nature* and *Science* focus on molecular and cellular biology.

After humanity got some insight into the structure of atoms and molecules, it decided to turn to what naturally builds around them, i.e. a living system. We are witnessing a revolutionary shift in the understanding of how living systems are organized, and are coming to realize the connections

between the basic structural units of living things, which opens up new opportunities for improving public health and longevity.

Modern medicine is based on P4 principles: prediction, prevention, personalization and patient's participation.

One of the essential components of P4 medicine is breakthrough discoveries and advances in genetics, genomics, transcriptomics, proteomics, molecular biology, and genetic and protein engineering seen in the last few decades. The evolution of medical technologies used in genetics and genomics has made it possible to achieve high accuracy in the prediction of inherited monogenic diseases and multifactorial disorders with an inherited component. Cheaper diagnostic

tests can expedite the launch of population screening programs aimed to reduce the proportion of deleterious mutations in the human population. But transition to P4 medicine is impossible without incorporating such state-of-art lab technologies as regenerative cell technologies, high throughput sequencing, genome editing, etc. into clinical routine.

Translation of a discovery from a scientific lab to the clinical setting requires a comprehensive assessment of the effectiveness and safety of the innovation.

The history of medicine has seen some monstrous outcomes of hasty introduction of new technologies or pharmaceutical agents into clinical practice (remember a thalidomide tragedy [1], Fig. 1). Given that science is evolving rapidly, a thoroughly elaborated and dynamic approach to the adoption of innovations in public healthcare is required, giving birth to translational medicine.

What is translational medicine?

Translational medicine is a new scientific field which aims to narrow or completely eliminate the existing gap between research and clinical practice [2]. According to the basic principles of translational medicine, there are three stages of translational research (Fig. 2) [3]. The first stage is preclinical research that involves monitored translation of scientific discoveries into clinical practice, identifies the need for the diagnostic and treatment methods in question, and also focuses on the effectiveness and safety assessment of innovations. In the second stage, experts determine if innovations can be used in the clinical setting on real patients. In the third stage, clinical research findings make their way into the public health system.

Smooth adoption of an innovation into clinical practice is largely determined by a number of factors: how well research has been scaled up; whether high-tech methods have been applied; whether financial support can be provided by either

the state or private investors; whether legislation and ethical standards have been adjusted considering the achievements of translational medicine.

State institutions for translational medicine development started to emerge in the 2000s, and are currently found in the USA, some European countries, China and Russia [4]. The number of research works on translational medicine has been expectedly increasing: the analysis of data stored in the Web of Science database revealed that there were only 5 publications on translational medicine in 1993, while by 2011 their number had reached 1 500 [4].

Lost in translation

As an innovative product is making its way from bench to bedside, it usually bumps into different barriers. Here, we face the need for new technologies that would allow us to make accurate predictions about the effectiveness and safety of novel compounds and medications and to improve the quality of preclinical and clinical trials. Of particular importance are services and projects aimed to ensure broad cooperation between state, commercial and non-profit organizations and to provide better access to and transparency of the new data to all researchers who work in translational medicine.

Over 80 % of substances (depending on the area of research) fail in a preclinical trial; only one of 20 drugs manages to successfully pass through all stages of a clinical trial [5]. Modern safety concepts improve the effectiveness of toxicity tests that new pharmaceutical agents have to undergo and expedite transition from animal testing to *in vitro* experiments. A key to the evolution of preclinical research is development of robotic cell based assay systems for quantitative high throughput screening. Biomodeling *in silico* allows researchers to test dose-response associations and build pharmacokinetic models under simulated conditions. Compared to traditional



Fig. 1. Thalidomide was a sedative prescribed to pregnant women in the late 1950s and 1960s. Among its adverse effects were congenital deformities. The photo shows a child born in 1963 (photo courtesy of *The Age*)

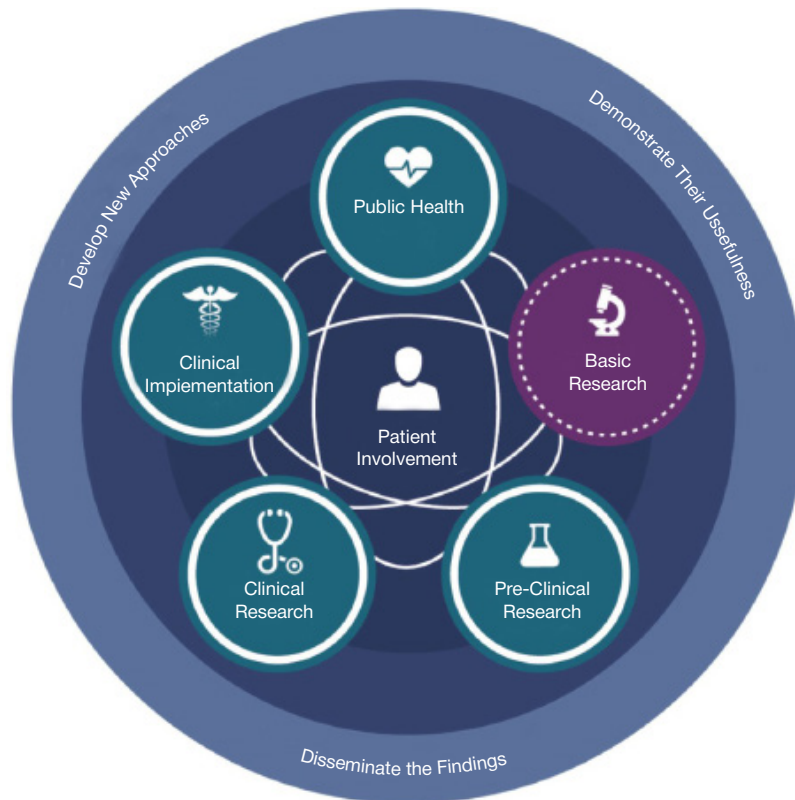


Fig. 2. Translational science spectrum as suggested by the US National Center for Advancing Translational Sciences [3]

toxicological strategies, such computer systems increase predictive capacity of research outcomes as the product moves on to the clinical stage [5, 6].

State-funded research centers and private pharmaceutical companies have always tended to collaborate, because scientists have always been concerned about finding a sponsor for their research and manufacturers have always been interested in developing effective medications in a short time and at little expense. However, recently the nature of this collaboration has changed due to the “customized” approach to research and development and better access to a tremendous volume of digital patient data available to researchers (primarily, in the US) [7]. Digital databases that store large volumes of information on many patients across the world hold promise to improve quality of preclinical and clinical research (Fig. 3); at the same time, there is a need to make this information even more accessible for researchers worldwide to improve its accuracy and quality.

Some barriers that innovations face on their way to practical medicine are quite natural as they prevent dangerous or ineffective products from entering clinical practice. But at the same time, these barriers are a major obstacle [8, 9]. Translational medicine aims to optimize algorithms that serve to incorporate innovations into real life and to make timely amendments to the legislation. Barriers should not be set higher than necessary.

Innovations travel the world at almost light speed, the underlying reason here being globalization. A promising medical technology, no matter where it was created, is bound to evolve and be successfully used in those countries where regulations are more flexible or liberal. Early implementation of innovative approaches gives those countries a head start over others, even if their risks are high. Tough regulations that block scientific achievements from entering medical practice may result in the loss of market.

An example of such competition is a situation in the USA and UK observed some years ago. Regulatory agencies kept banning CRISPR/Cas9 research on human embryos. However, after Chinese researchers published their work on human embryo genome editing that they had carried out using the above mentioned technique, British scientists got permission to use CRISPR/Cas9 and similar designer nucleases in February, 2016 [10]. As technologies find their way into practical application, public opinion starts to change and pushes the local legislation to introduce necessary adjustments.

Ethical factors related to the application of innovations, especially those of human genome editing, are a separate element of the system of translational medicine [11]. If these factors affect clinical implementation of novel technologies, they must be recorded and clarified by ethics committees and authorized agencies.

Structural gap

In Russia, translational technologies do not enjoy much support. Thus, after the Federal Law No. 323 *On fundamental healthcare principles in the Russian Federation* dated November 21, 2011 and the Federal Law No. 532 *On the amendments to individual legislative acts of the Russian Federation on the countermeasures against circulation of faked, counterfeit, improper and unregistered medicines, medical items and faked dietary supplements* dated December 31, 2014 were passed, the majority of innovative medical techniques and equipment created under federal grants or projects were blocked from entering clinical practice (or the procedure was delayed for 3–5 years).

A legislative trap has closed on 1) tests for rare diseases (mass production of medical products used to treat the latter is not profitable and their registration is unreasonable)

and 2) innovative technologies whose effectiveness, safety and clinical significance have been proved, but mass production and registration are still pending (usually the whole procedure takes about 5 years). But sometimes such innovations do not appear on the market because manufacturers do not have any financial reason to register them as medical products.

At the same time in most countries, such as the US, EU member countries and Australia, mass production of commercial medical products and medical laboratory practices are regulated by different laws. The use of unregistered materials or equipment in medical research is permitted if an institution strictly adheres to regulations and requirements established by law.

In these countries, laboratories that meet the established requirements and are closely monitored by authorized agencies are permitted to use in-house tests (or home brew tests, as they are referred to in Europe and Australia; in the USA they are called laboratory developed tests) or equipment/ materials adapted for clinical use (IVD products labeled RUO). Unfortunately, the Russian market may still be unable to offer foreign analogues of medical devices/agents because of their high cost, policies of foreign manufacturers and federal sanctions.

Translational offshore companies

Translation of a discovery from research to medical practice can be more or less difficult depending on a country's legislation; at the same time, administrative regulations within the same jurisdiction can be rather controversial. For example, the Federal Law No. 160 *On the International Medical Cluster and Amending Individual Legislative Acts of the Russian Federation* dated June 29, 2015 created a paradox: neither of Russian federal and national public health institutions now have a right to use unregistered innovative technologies and equipment in

their work, while international joint ventures are permitted to do it on the territory of the Russian Federation.

Perhaps, such offshore companies (like Skolkovo) will pioneer translation of research into medical practice in Russia and encourage other public health institutions to adopt those tested and approved technologies. But if some players have everything while others have nothing, there remains a risk that a system cannot keep its balance and we will lose a chance to create a really effective translational space.

Medical education

If we want to expedite the process, we have to update the concept of medical education. A good example is the International School of Personalized and Translational Medicine, a part of Sechenov First Moscow State Medical University, established to develop solutions to the problem of basic research translation into a practical task of creating effective and safe methods of prevention, diagnosis and treatment based on the personalized approach tailored to individual characteristics of every patient. One of the areas the School focuses on is implementation of a new model of medical and pharmaceutical education. As the whole healthcare system is undergoing a unique transformation and the old model is being replaced by personalized and translational medicine, pharmaceutical industry is starting to play a very special role in expediting a pharmaceutical drug lifecycle from its inception to application and promotion. That is why in 2016 the Institute of Pharmacy and Translational Medicine was founded as part of the School structure. The goal of the Institute is to create effective research and learning environment that stimulates the development of innovative biomedical products and ensures excellent research work in all stages of their life cycle with further integration of scientific achievements into the educational

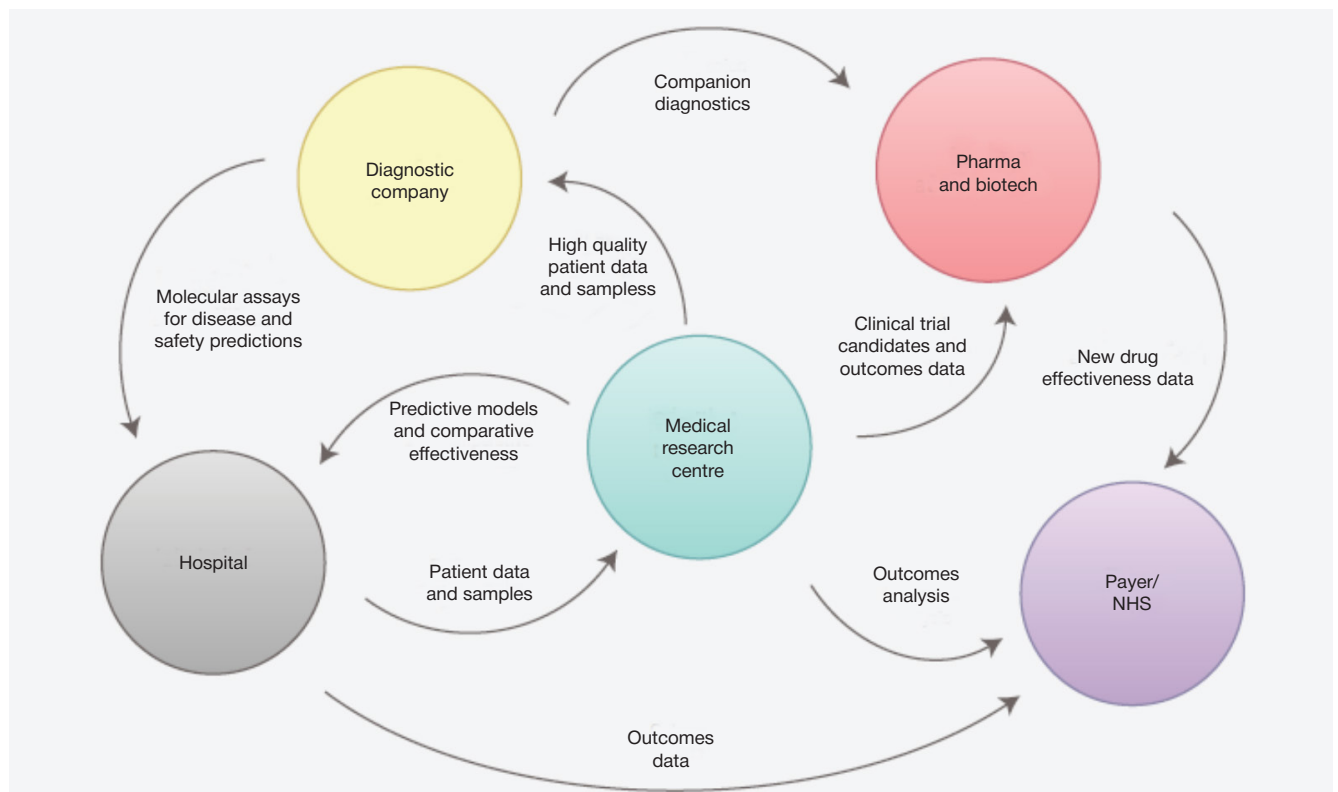


Fig. 3. Digital data on a large number of patients help to expand collaboration of state-funded research centers and private pharmaceutical companies [7]

process. The latter aims to prepare highly qualified specialists and top-class researchers for pharmaceutical industry. The Institute implements the principle of a full product cycle for biomedical products, from a basic idea, through applied and translational research to introduction into clinical practice and postmarketing studies. The Institute develops scientific and methodological principles that can underpin the creation of safe and effective biomedical products.

The Institute provides professional training in the field of translational research of any level. The Institute of Pharmacy and Translational Medicine in cooperation with its key partners was the first educational establishment in Russia to launch an innovative educational project ("Pharmacy") aimed to provide specialized training for the next generation of researchers who will work in various fields of biopharmaceutical industry. The students of the Institute get profound knowledge of molecular and cellular biology, medical genetics, bioinformatics, development of pharmaceutical agents, learn to apply the principles of good practice (laboratory, manufacturing, clinical, etc), study legal aspects of developing and promotion of biomedical products. Students obtain theoretical knowledge and practical skills from top scientists and experts of the pharmaceutical industry. A compulsory component of the educational curriculum is participation in international conferences and symposiums, internship in the world leading universities and international and Russian pharmaceutical companies; grant contests are also a part of the project. All students are required to write a thesis based on the research that they carry out using the facilities of the Institute or partner organizations. Over the course of their research, students must apply knowledge and skills they have obtained into real practice and acquire additional competencies in the specialty they have chosen. The Institute cooperates with private and state organizations and participates in joint projects. It contributes to the development of a system for commercializing innovative products, supports original projects and services that meet the challenges of modern science developed in cooperation with Russian and foreign pharmaceutical companies and other high-tech and research organizations. The Institute

collaborates with Chumakov Federal Scientific Center for Research and Development of Immune and Biological Products of the Russian Academy of Sciences, Genium International Biotechnology Center, the Institute of Problems of Chemical Physics of the Russian Academy of Sciences, Federal State Unitary Enterprise "Moscow Endocrine Plant", JSC Rafarma, LLC Rigla, JSC R-Pharm, ITMO University and others.

Another example of integration of medical innovations into the educational system is the Research Institute of Translational Medicine founded in 2014 as part of Pirogov Russian National Medical Research University. Its innovative initiatives gave impetus to the foundation of "Southern" Moscow Medical Technology Cluster in 2015. The Cluster consists of "Slava" Technology Park, 2 higher education institutions, 8 research institutions, 4 clinical and 30 innovative biotech companies. Currently the Cluster supervises over 20 projects on medical product development, hosts a prototyping center, and collaborates with the Foundation for Assistance to Small Innovative Enterprises in Science and Technology. "Southern" MedTech cluster has prepared the environment to implement the full life cycle of innovative products, from a student's idea, through Umnik competition and the prototyping center to mass production at the facilities of small and medium-sized enterprises of "Slava" technology park and Cluster's partners.

CONCLUSION

With regard to the above and in order to deliver the advanced medical care based on the most recent achievements of science and technology to Russian citizens and to bridge a possible gap in medical innovation, we believe it necessary to introduce amendments to the current legislation, specifically, to Art. 38 of the Federal Law No. 323 of November 21, 2011 that would eliminate restrictions on the use of unregistered medical products by medical institutions and establish special requirements to in-house monitoring (similar to the international regulations applied to LDT and IVD-RUO) that may be performed by a local Ethics Committee or Academic Board.

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