Revista da SOCESP
Sociedade de Cardiologia do Estado de São Paulo

THE NEW FRONTIER TRANSLATIONAL MEDICINE

MEDICINA TRANSLACIONAL - NOVA FRONTEIRA

Protásio Lemos da Luz[1]

Heart Institute of the University of São Paulo INCOR-HCFMUSP, São Paulo, SP, Brazil

Correspondence:
Av. Dr. Enéas de Carvalho Aguiar, no. 44 - 5º andar - Bloco II - Sala 08, Cerqueira César - São Paulo, SP, Brazil. CEP: 05403-000
protasio.luz@incor.ups.br

Received on 11/24/2017,
Accepted on 03/06/2018

ABSTRACT

The concept of Translational Medicine covers three aspects: a) acceleration of the transmission of basic research knowledge to clinical application; b) in-depth investigation of clinical observations in search of a better pathophysiological understanding, through interaction with basic science; and c) application of basic knowledge and concepts from clinical research, to the general population. Thus, essentially, translational medicine seeks to speed up the transmission of knowledge generated by research, transforming it into practical tools for diagnosis and/or treatment. For this purpose, appropriate technical and administrative structures are needed, including researchers, institutions, funds, and a culture of integration between the different research teams. Given the complexity of such structures, only institutions of excellence can successfully undertake programs of this type. Brazil already has several medical service and research institutions that meet these requirements. It is critical to the development of translational programs that universities adhere to the principle of meritocracy. In this aspect, radical change is needed in brazilian universities. Finally, translational medicine, by striving for scientific advancement and improvement in the population health, also plays a part in reducing social inequalities, and among these the health of the population is paramount.

Keywords: Universities; Translational research; Public health.

RESUMO

O conceito de Medicina Translacional abrange três aspectos: a) a aceleração de transmissão de conhecimentos de pesquisa básica à aplicação clínica; b) aprofundamento de observações clínicas, em busca de melhor entendimento fisiopatológico pela interação com ciência básica; c) aplicação à população geral de conhecimentos básicos e conceitos oriundos de pesquisas clínicas. Assim, no geral, a medicina translacional procura acelerar a transmissão de conhecimento gerado em pesquisa, transformando tais conhecimentos em instrumentos práticos de investigação diagnóstica e/ou tratamentos. Para tanto, necessitam-se estruturas técnicas/administrativas que incluem: pesquisadores, instituições, orçamento e cultura de integração entre as diferentes equipes de trabalho. Pela complexidade desse conjunto, apenas instituições de excelência podem se engajar com sucesso em tais programas. O Brasil já conta com algumas instituições de prestação de serviços médicos e pesquisa que atendem esses requisitos. Crucial ao desenvolvimento de programas translacionais, as universidades devem atender dentro do princípio de meritocracia. Neste ponto, universidades brasileiras precisam de transformações profundas. Por fim, a medicina translacional, ao visar o progresso científico e a melhoria da saúde populacional, também contribui para diminuir as desigualdades sociais, entre essas, a saúde da população esta em destaque.

Descritores: *Universidades; Pesquisa translacional; Saúde pública.*

INTRODUCTION

Important scientific findings are often restricted to academia for a long time. Practical application of this knowledge may depend on new techniques, factors associated with clinical circumstances, or even adequate publication. One example is the case of acute myocardial infarction. In the 1950s, infarction treatment was restricted to bed rest and palliative measures. In the late 1950s, preliminary studies suggested, without consistency, that hyaluronidase and corticosteroids could reduce electrocardiographic signs of ischemic injury caused by acute infarction in dogs and few human cases.[1,2] In 1971, Maroko et al.[3] showed ST-segment elevations after a 15-minute coronary occlusion in the ischemic region, whereas such phenomenon did not occur in non-ischemic areas. With this model, they suggested that infarct size could be modified through therapeutic interventions. By this time, Reimer et al.[4] published the work entitled, "Wavefront phenomenon," in which they described the progression of

necrosis in a dog's papillary muscle after occlusion of the circumflex artery. They showed that necrosis progressed linearly in the first 3 hours after occlusion and that afterward, the time-necrosis relationship displayed a "plateau", indicating that the necrotic process was completed. At the same time, the concept of "stunned" myocardium emerged,[5] in which, after acute short-term coronary occlusion, return of myocardial contraction to normal conditions could take up to 24 hours, even after blood flow restoration. Myocardial reperfusion was also shown to restore mechanical function in situations of chronic ischemia; this phenomenon was named "hibernated" myocardium.[6] Such hibernated myocardium was observed in both experimental and clinical models. Thus, in patients with ischemic cardiomyopathy, an improvement in left ventricular function documented in ventriculography was observed after implantation of the mammary artery or saphenous vein graft. From these observations, the concept of myocardial viability emerged for situations in which the non-contractile cardiac muscle was not really "dead" and could resume the contractile capacity once the coronary blood flow was restored. Thus, muscle with myocardial viability could be differentiated from fibrosis in which myocardial immobility indeed corresponds to necrosis/fibrosis.

However, the clinical application of these concepts would take some time. In 1972, in the Hospital das Clínicas of the University of São Paulo, Galiano et al.[7] observed that in two patients with cardiogenic shock due to acute infarction, coronary occlusion was caused by acute thrombosis; the patients were submitted to mechanical recanalization of the thrombosed artery with the same catheter used for catheterization. One of them was operated by Dr. Sérgio Almeida de Oliveira and received a saphenous vein graft in the right coronary; the other one was treated with medication alone. Both recovered well.

In Russia, Chazov[8], in 1976, also showed that opening a coronary artery acutely occluded by thrombus is possible. In 1977, Gruentzig demonstrated that coronary angioplasty allowed oppening chronically occluded arteries.[9] In 1980, a serminal work was published by Dewood.[10] He showed in 322 patients with acute myocardial infarction that a thrombus was responsible for coronary occlusion. This changed the physiopathological concept of infarction, as no reports until then showed acute thrombus obstructing the artery. As a result, this raised the hypothesis that thrombolysis could be used to treat acute myocardial infarction. In 1981, Ganz[11] and Rentrop[12] reported the use of intracoronary thrombolysis with streptokinase in human acute myocardial infarction (AMI). Later, in 1984, Ganz[13] reported the use of systemic intravenous streptokinase in 81 patients with acute myocardial infarction, with 96% culprit artery reperfusion according to clinical criteria. However, it was Geoffrey[14] who presented the first 16 cases of acute myocardial infarction treated with angioplasty at the annual meeting of the American College of Cardiology on April 29, 1982. From then on, the method was consecrated and became routine until today. Among the methods of myocardial protection in human infarction reperfusion with angioplasty, thrombolysis or surgery has gained worldwide acceptance and is now the main approach for the treatment of human AMI. However, it took more than 10 years until the first systematic studies on perfusion in man were published.

Another example of delayed application of basic knowledge is atherosclerosis. Although atherosclerotic disease has been documented in mummies of 4,000 years BC[15], the causes and pathophysiology of the disease remained unknown for centuries. In 1908, the Russian group led by Anichkov fed rabbits with a mixture of eggs and milk and documented the occurrence of atherosclerosis.[16] Initially, they attributed this to milk proteins. Two years later, Stuckey et al.[16] observed that egg yolk, but not egg white, promoted atherosclerosis. In 1913, Anichkov and Chalatov[16] compared pathological anatomy data and noticed that the crystals in the atherosclerotic lesions in human arteries were identical to the crystals in the arteries of rabbits and were formed by cholesterol. They then fed rabbits with a supplement of pure cholesterol, and the animals developed atherosclerosis. Hence, they concluded that egg yolk cholesterol caused atherosclerosis. This was one of the first evidences suggesting the role of dyslipidemias in the genesis of atherosclerosis. However, the work that really established the role of cholesterol in human atherosclerosis was only published in 1961, the Framingham. Kannel et al.[17] observed in many individuals that hypercholesterolemia was associated with a higher mortality rate due to cardiovascular diseases and that association with arterial hypertension accentuated such association. The discovery of the various chemical stages of cholesterol formation justified the Nobel Prize in Medicine awarded to Konrad Bloch and Feodor Lynen in 1964.[18] In 1975, Brown and Goldstein[19] described the LDL receptor in cells and thus unraveled the mechanism by which LDL particles are internalized, leading to the formation of foam cells and, subsequently, to the formation of plaques. This crucial finding also justified the Nobel Prize in Medicine awarded 10 years later to Brown and Goldstein. However, 48 years have passed between experimental observations and clinical evidence. Subsequently, Endo et al.,[20] in Japan, found a potent inhibitor of HMGCoA (hydroxy-methyl-glutaryl coenzyme A reductase) in the liver, which led to the development of statins; but the first multicenter studies with these molecules, proving its effectiveness in the man, only begin in the 1980s. These achievements revolutionized tremendously the treatment of cardiovascular diseases with a reduction in overall cardiac morbidity and mortality and a decrease in hospitalization rate.[21] The third example is aortic valve replacement using a catheter. According to Alain Cribier, from the initial idea to the first experiments and first clinical application, 26 years have passed. What was initially indicated only for high-risk individuals is now being used successfully for intermediate-risk patients[22,23] and continues to evolve. Perhaps with technical improvement, it will be the preferred method in the future for the treatment of aortic lesions.

THE LESSON

Both studies by Ebaid[2] and Galiano[7] illustrate the importance of the research system in scientific development. Although these observations were pioneer, they did not have repercussions and did not have adequate dissemination, since systematic research with adequate numbers of cases, following basic scientific criteria, was never performed. It is

not enough to make an interesting clinical observation. It must be transformed into a scientific fact. It is necessary to demonstrate that the phenomenon occurs consistently in patients. Finally, if the results are not published in widely assessed scientific channels, the international community does not know. This is what happened with the first studies on cholesterol and atherosclerosis published in russian language. This was also the case with mechanical reperfusion studies in acute infarction performed in Brazil and published in portuguese. The lesson is to create: a scientific fact that changes clinical practice, an isolated observation is not enough. You must convince the world. This can only be achieved by following the classical criteria of scientific research. For basic findings, its clinical relevance should be shown. For clinical observations, it is necessary to prove that the phenomenon is consistent and is not an isolated fortuitous event.

THE ROLE OF TRANSLATIONAL MEDICINE

In this context, the idea of translational medicine emerged initially in the United States, and can be conceptualized as transferring knowledge from basic sciences to the clinic, identifying physiological structures and functions, aiming at understanding the mechanisms or development of diagnostic or therapeutic tools for clinical use. In fact, in addtion there are two other aspects as follows: starting from clinical observations, experimental research emerges with a focus on mechanistic understandings, and the other is the transference of clinical research for application in the community. As illustrated in Figure 1, translational medicine is based on four pillars, namely *the researcher*, *the institution*, *the budget*, *and the culture of integration.*

As for *researchers*, currently, in Brazil, we already have considerable critical mass in practically all areas of medicine. Postgraduate training is programs are a major source of training for researchers. Currently, approximately 20,000 doctors graduate every year in Brazil, of whom 10–15% are medical doctors. Approximately 60,000 papers are published every year, representing 2.7% of world production (TR Incites 2012). Universities and research institutes are the places where researchers are formed and work. Naturally, for the researcher to be able to accomplish, a career plan in which he has adequate salary and guaranteed academic progression. This progression must be based in meritocracy; otherwise, the researcher will feel helpless, discouraged, and eventually quits. Another essential aspect is that the researcher needs freedom to create and express his imagination. The researcher only performs effectively when guided by his scientific interests, not following orders.

For the institution, to develop a translational medicine program, it must meet certain requirements. First is to have excellence in work performance, that is, high-quality standards. Even routine procedures such as catheterizations, surgeries, preoperative and postoperative care, nursing, physiotherapy, and medical consultations must comply with high-quality standards. Otherwise, clinical data that could be used in translational studies will have no value. Second, it requires experimental and clinical research laboratories equipped with modern instruments and technologies. Without, going into details it suffices to say that a modern institution needs modern laboratory techniques for chemical analysis, imaging, ultrasonography, tomography, magnetic resonance,

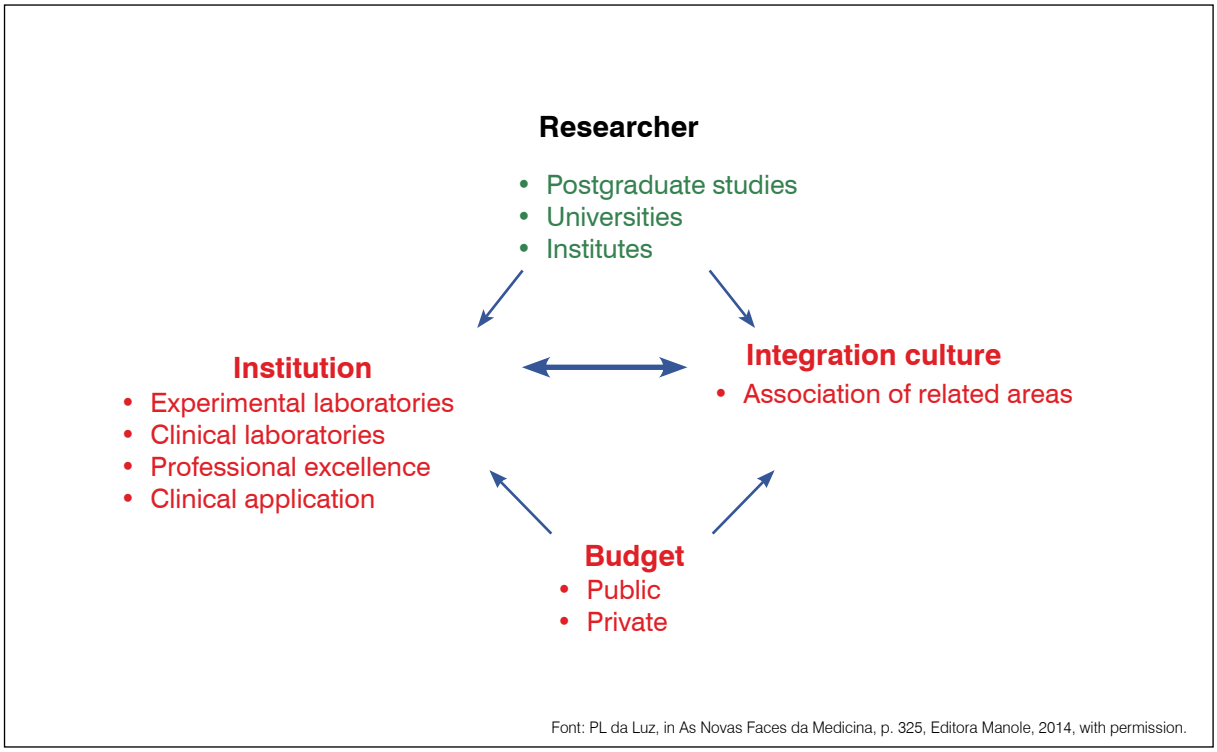

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Figure 1. Pillars of Translational Medicine.

and training for diagnostic and therapeutic procedures, whether invasive or noninvasive. When we refer to technical training, it is necessary to remember the great recent developments on intracellular research methods; thus, specific markers are used to study functions of proteins, enzymes, ions, and intracellular markers. Knowledge on genetics and epigenetics has been rapidly accumulating and improving our understanding of the causes and mechanisms of diseases. Studies on the "omics" science, especially metabolomics, using sophisticated statistical methods and techniques such as magnetic resonance spectroscopy and mass spectroscopy are rapidly promoting the knowledge of disease mechanisms and identifying biomarkers. MicroRNAs, which are small portions of the non-coding genome, are the basis of major studies. Recent developments regarding monoclonal antibodies such as evolocumab and canakinumab have had their clinical usefulness documented.[24,25] This also means having technical personnel capable of performing the procedures, whether clinical or experimental, and not necessarily researchers.

We currently have several centers of excellence in the country that fulfill these conditions, including Instituto do Coração de São Paulo, Instituto Oswaldo Cruz, Instituto Butantã, ICESP (Institute of Cancer of the State of São Paulo), Instituto AC Camargo, Hospital das Clínicas of Porto Alegre, and National Cancer Institute of Rio de Janeiro. InCor-SP was created as a translational institution; from the beginning, it had three basic units, namely the clinical, surgical, and experimental divisions, which have similar administrative structures, physical spaces, medical and technical personnel, and laboratory infrastructures. The idea was always that these divisions worked in close contact, which in fact, has been occurring, although not in a perfect manner. However, the various clinical and surgical teams have always had access to basic areas, and today, all have their own research programs, both experimental and clinical. It is due to this political/administrative organization, which treats basic and clinical areas with equal respect for their priorities, that InCor is the largest research institution in cardiology of Latin America. Add to this the policy of renewing the institution's research staff, which is being done regularly through numerous agreements with American and European universities. Another crucial factor is the full-time researcher career and exclusive dedication that InCor maintains owing to the work of the Zerbini Foundation, which provides financial support to those investigators. Regarding this, university hospitals play a prominent role as teaching hospitals and are the most qualified to run such programs. As an example, the REHOT study on resistant hypertension was conducted in 24 university hospitals and coordinated by InCor.[26]

Recognizing the importance of academic institutions to disseminate knowledge to the population, several countries such as the United States, England, Singapore, Canada, and the Netherlands have created Academic Health Centers (AHCs) to improve local health. As Dzau expressed:[27] "To create infrastructure in which innovations are moved quickly along the discovery-care continuum, AHSSs should create horizontal, functionally integrated organizations that transcend academic departamental structures and promote interdisciplinary collaboration and efficient use of common resources".

The general idea is that these flexible systems bypass the bottlenecks of technological knowledge transfer and promote the dissemination of various types of knowledge in the *continuum* of discovery/medical care. This means that such systems are above, superimposed on the organ/system-oriented model (cardiology, hematology, and biochemistry), and incorporate several areas of knowledge, including biochemistry, psychiatry, surgery, genetics and epigenetics, epidemiology, clinical medicine, and pathophysiology. An example of this organization is The Duke Translational Medicine Institute, which has four organizations as follows:[27] a) Translational Research, an institute focused on the translation of initial findings into clinical applications; b) Clinical Research Unit, in charge of biological proof-of-concept studies with advanced genomics and imaging techniques; c) Clinical Research Institute, performs many clinical studies and registries, health policies, and educational programs in research methods; and d) Center for Community Research, develops best practices for community research and the development and testing of new assistance models. Furthermore, the Duke Translational Medicine Institute offers to each unit computers, information technology, biostatistics, ethics, nursing, and staff support for specific types of research.

Another notable example is the Imperial College London, which created the first university-owned technology transfer company to be placed on the UK stock exchange. In 2007, *Imperial Innovatiors* created 11 companies and published 354 new inventions.[27] The University of Toronto and Duke University have also created spaces for companies to promote innovation by uniting different worlds of science and technology with industry and capital. In Brazil, the University of São Paulo and the Federal University of the State of São Paulo have created community assistance programs implemented and/or supervised by university doctors. These initial programs have shown encouraging results in improving service and reducing costs.

Implementing such organizations requires several support mechanisms. Investments in information technology are crucial; this facilitates the processing of substantial amounts of data, can increase system efficiency and reduce costs. Changes in the philosophy of universities is also essential. Today, in addition to diseases, universities must study political, environmental, and social factors that contribute to global health inequalities. In fact, by 2012, 60 American universities with interdisciplinary centers dedicated to global health have been established. The key point is that global health is a paramount factor in the equilibrium of relationships between countries and maintenance of world peace. This requires a broad process that encourages relevant discoveries and their availability to the population so that global health can be improved.

However, it must be recognized that many brazilian institutions are still in a learning curve regarding experimental clinical research. These institutions have been engaged in advanced research programs only in the last 10 years. One thing is to

perform medical procedures with proficiency, another is to run investigation protocols. Thus, we have in the country a situation of some immaturity regarding the training for clinical research. However, to reiterate, institutions of excellence have been established.

The third pillar is what I call a culture of integration. So far, what has predominated is the relatively restrictive activities within the basic and clinical areas. Each looking to provide the best, but in its area. For translational medicine programs, a real and constant integration is required. Basic and clinical researchers should work closely together, in a practically daily coexistence. The studies must have input of the two sectors; this common questions are followed by joint strategies to find the solution. This is especially relevant when issues of causes and mechanisms are at stake. In general, the clinical areas do not have the techniques for intracellular studies, but the basic areas have them. On the other hand, the relevance of pathophysiological concepts depends on clinical evidence.

In Brazil, to achieve this integration, a real cultural change is required. For example, related medical areas should work in association. If genetics is considered as a paradigm, it would be common to almost all specialties. The techniques to identify genes are the same, even if the questions are from surgery, clinics, or oncology. Therefore, the interaction between related areas is a necessity. Possibly, such integration involves modifications in the academic structures such as the departments of our colleges. This need for integration was one of the reasons for the creation of the Institutes of Translational Medicine in the United States and Europe.

Finally, there is the budget issue. Translational medicine by its nature, by including basic science and encompassing hypothesis testing, which will not always be proven, is not a business meant to make a profit and is not self-sustainable. Therefore, the government should finance such programs through funding agencies. This is a strategic issue for the development of the country. In fact, this is how it is being done in Europe and the United States. In the United States, specifically the NIH (National Institute of Health) has created special funds for such programs, in the order of billions of dollars for NCASTS (National Center for Advancing Translational Sciences). The practical reason is to accelerate the transformation of knowledge in public health instruments, which will lower costs. On the other hand, funding should focus on centers of excellence so that resources are not pulverized. This is a critical aspect of the issue. Unfortunately, at the moment, Brazil is experiencing the worst crisis in its history in the research area. Budgets from the Ministry of Science and Technology have been drastically reduced, laboratories are inoperative owing to maintenance deficiency, and young researchers are leaving the country. All these occur because of a distorted view of how countries progress. The populist government view of recent years has ignored academic meritocracy, drained research programs, and compromised for years the scientific progress that had begun. Public authorities should have a more modern view on the importance of science for progress, as explained by Chaimovich and Cruz[28] in a recent article.

As well expressed by Professor Elcio Abdalla,[29] "public universities thrive on the idea that universities are an image of democracy, and that all, from students to professors and employees, should have the same weight in major decisions. There is no deeper and deleterious mistake than this kind of university populism."

CURRENT CHALLENGES

Some areas of medical knowledge are of obvious interest in translational medicine, including the following:

1) In genetics, search for high-risk genetic markers, gene therapy, and pharmacogenetics is essential. Despite great expectations and countless studies, incorporation of genetics *sensu latu* to the clinic is still at its early stage. 2) In regenerative medicine, stem or pluripotent cells, and cellular reprogramming in tissue regeneration are important aspects. Conceptually, regeneration of damaged tissues makes perfect sense. Clearly, we are still at the initial stages in that area. We need a deeper understanding of the pathophysiological mechanisms. 3) In pharmacogenetics, the main objective is personalized therapy, aiming at identifying specific responders to the various drugs, based on genetic and population characteristics. 4) In aging, an area of great interest is cognitive function, which degenerates with age and whose mechanisms are not known. Perhaps, this is the area that lacks more knowledge in medicine. 5) In oncology, cancers are the second cause of death among chronic noncommunicable diseases; susceptibility to disease development, progression, and therapeutic responses certainly deserve further research, both basic and clinical. Monoclonal antibodies currently represent a major evolution. 6) In atherosclerosis, molecular mechanisms that influence its pathophysiology should be further investigated. Treatments with anti-lipid and anti-inflammatory monoclonal antibodies are starting to be tested, but their clinical usefulness still requires the test of time. Despite recent advances in treatment, the residual risk problem remains, even when risk factors are treated efficiently. 7) Planning clinical studies could be improved by a more precise knowledge of people at risk, which theoretically could be attained by genetic susceptibility tests.

In conclusion, translational medicine is a new frontier to be conquered for the advancement of science and rapid improvement of the medical care offered to the population. The aim is to accelerate the transmission of basic knowledge to its clinical application and enable clinical problems to have greater etiological and pathophysiological clarification. This is achieved by the intimate and constant integration of basic area researchers and clinical researchers.

Change of culture within the universities is also fundamental for integration and to ensure multidisciplinarity. In Brazil, centers of medical excellence have the conditions and obligation to engage in translational programs.

CONFLICTS OF INTEREST

The author declares that he has no conflicts of interest in this work.

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