

Review article:

Translational research in physiology: Review

¹Dr Motilal C Tayade , ²Dr Vinod , ³Dr Ramchandra G Latti

¹Assistant Professor and PhD Scholar, Department of Physiology, Rural Medical College, Pravara Institute of Medical Sciences, Loni, Tal. Rahata, Dist. Ahmednager, Maharashtra , India

²Assistant Professor, Department of Physiology, M R Medical College, Gulbarga, Karanataka, India

³Professor and HOD, Department of Physiology, Rural Medical College, Pravara Institute of Medical Sciences, Loni, , Tal. Rahata, Dist. Ahmednager, Maharashtra , India

Corresponding author: Dr Motilal C Tayade ; Email: drmctayade@gmail.com

Abstract:

Translational research is dynamic and multidisciplinary research approach applies discoveries from basic science to applied to increase quality of human health. Translational research is seen as an important area of finding clinical practical applications. This has been attempted particularly in medicine. It refers to a process by which the findings of basic research are extended to the clinical research setting (bench to bedside) and then to clinical practice and eventually health policy (bedside to community). The concept of translational physiology applies the translational research model to the physiological sciences. It differs from the traditional areas of integrative and clinical physiology by its broad investigative scope of basic research to community health. Translational physiology offers exciting opportunities, but presently is under-developed. This will allow bidirectional physiological investigation throughout the translational continuum . Basic research observations can be studied up to the population level, and mechanisms can be assessed by 'reverse translation' in clinical research settings and preclinical models based on initial observations made in populations. Translational physiology provides a novel framework for physiology programs and an investigational platform for physiologists to study function from molecular events to public health. It holds promise for enhancing the completeness and societal impact of our work, while further solidifying the critical role of physiology in the biomedical research enterprise. Behind writing this review, our aim is to systematically highlight this under developed and less cited topic.

Keywords: Translational research, Applied Physiology, Human health

Background:

Translational research is dynamic and multidisciplinary research approach applies discoveries from basic science to apply to increase quality of human health.¹ The term 'translational research' was coined 20 years ago and has become a guiding influence in biomedical research. It refers to a process by which the findings of basic research are extended to the clinical research setting and then to clinical practice and eventually health policy. The concept of

translational physiology applies the translational research model to the physiological sciences.^{2,3} It differs from the traditional areas of integrative and clinical physiology by its broad investigative scope of basic research to community health. Translational physiology offers exciting opportunities, but presently is under-developed .^{1,4}

A key challenge be to expand physiological research by extending investigations to communities of patients and healthy (or at risk) individuals. This will

allow bidirectional physiological investigation throughout the translational continuum: basic research observations can be studied up to the population level, and mechanisms can be assessed by 'reverse translation' in clinical research settings and preclinical models based on initial observations made in populations.⁵

Translational physiology provides a novel framework for physiology programs and an investigational platform for physiologists to study function from molecular events to public health. It holds promise for enhancing the completeness and societal impact of our work, while further solidifying the critical role of physiology in the biomedical research enterprise.⁵

Translational research is routinely practiced in fields such as agricultural sciences, environmental sciences, healthcare sector, social sciences etc.² Actually developing approach in application of basic concept towards applied aspects is key for reform. However due to compartmentalization viz preclinical, paraclinical and clinical within health sciences has lead major obstacle in development and research in medical field especially in developing countries. Hence translational research is a key component to finding practical applications. Basic research in terms restrict only towards lab work and explaining concept. It is more speculative. However applied research focuses need of society and turns towards market based research. In developed countries research is always focus towards applied part while in developing countries like in India research focus and linked towards only basic part and promotions. Behind writing this review, our aim is to systematically highlight this under developed and less cited topic.

Translational research phases:⁶

Translational research means research that applies discoveries generated in the laboratory to studies in humans (bench to bedside), or that speeds the adoption of best practices into community settings (bedside to practice). Phases of translational research include:

T1 – First phase of translational research, or “Bench to Bedside,” moves a basic discovery into a clinical application

T2 – “Bedside to Practice” research provides evidence of the value of taking the basic discovery in the clinical setting

T3 – Research that moves the evidence-based guidelines developed in phase 2 into health practice

T4 – Research to evaluate the “real world” health outcomes of the original T1 development.

The first area of translation, from laboratory findings to clinical practice: is often called “bench to bedside and back” or T1 translation.

The second area of translation, to the community and back, is called T2 translation.

In the past, T1 and T2 translation have often been separate activities.

Translational Physiological research verses basic biomedical research:⁷

In current scenario we daily reads about importance of gene therapy and its application in elimination of number of diseases . Such potential new therapies are reported from biomedical research. However the speed of application of these facts is question mark? Second point that such exciting research work never goes beyond laboratory boundaries. What are the causes of this gap between the astonishing advances in basic research and the implementation of this knowledge to understanding and treating human disease? Two important components of translational

research, integrative physiology and clinical physiology, have suffered declining activity in recent years, greatly weakening the translational research chain.⁷

The American Physiological Society (APS) has defined translational research as “the transfer of knowledge gained from basic research to new and improved methods of preventing, diagnosing, or treating disease, as well as the transfer of clinical insights into hypotheses that can be tested and validated in the basic research laboratory.”⁷ This definition clarifies that the process is bidirectional, from the bench to the bedside, as well as from the bedside back to the bench. Observations made in basic sciences can translate into improved patient care, and clinical and population studies can stimulate new ideas and new research approaches in basic science laboratories.

Until the 1980s, basic research and clinical studies were done side by side in most academic medical centers. However, this no longer appears to be the case. Two-track systems, with a research track and a clinical track, are now the rule rather than the exception in academic medical centers. Part of this split can be attributed to the introduction of managed care, which was intended to produce efficient, cost-effective medical practitioners. However, one of the unfortunate consequences of this approach has been the loss of the clinical researcher. This, in turn, has resulted in an almost complete absence of clinical physiology, an important link in the translational research chain. Also contributing to the widening gap between basic research and clinical medicine has been the gradual demise of integrative physiologists working at the whole animal level who can effectively interact with molecular biologists and clinical researchers. Traditionally, the discipline of

physiology has served as the bridge between the basic sciences, such as biochemistry, and clinical research. However, the technological advances in molecular biology and genomics, and the funding pressures that have pushed research in these directions, have led many of us to become very reductionist in our research, to the extent that physiologists are becoming indistinguishable from other basic scientists.

In some ways, this is beneficial to the discipline of physiology. Some of the most interesting physiology takes place at the boundaries of our discipline and results from combining knowledge of various fields, such as biochemistry, genetics, engineering, pharmacology, and bioinformatics. At the same time, however, there are fewer physiologists conducting studies at the whole animal level, an area of research that is critical to the strength of the translational research chain.

Recognizing this growing gap between basic science and clinical research, the American Physiological Society has recently taken several steps to encourage translational research. One of these initiatives was to highlight translational research in APS publications, including the Journal of Neurophysiology and the American Journal of Physiology (AJP). In the June 2001 issues of the APS Journals, the APS issued a special call for manuscripts in the field of translational physiology. APS has encouraged a broad definition of translational physiology in order to facilitate continuing dialog among basic scientists, clinical scientists, and population scientists. Translational physiology papers submitted to the journal may 1) transfer clinical insights into hypotheses that can be tested and validated in the basic research laboratory, 2) transfer knowledge gained from basic research to human physiology,

or3) report improved methods for diagnosing, treating, or preventing disease. The first manuscripts were accepted in July and were published in the November 2001 issue of the AJP.⁸

The gap between basic sciences and clinical medicine obviously cannot be closed simply by offering a forum for publication of translational research. The APS also has developed plans to highlight translational research at its meetings, to encourage physiologists to develop interdisciplinary research teams that bridge molecular physiology and genomics with organ system physiology and clinical research, and to promote translational research as an important career opportunity for physiologists.

In the 1950s through the 1970s, physiologists often received training in medicine as well as basic research. The current training paradigm, however, usually separates clinical medicine and research. Physiology training programs often do not even provide coursework in pathophysiology, and PhD candidates usually do not engage in human research. However, translational research no longer requires that the principal investigator be a clinician. The APS is not alone in its efforts to highlight translational research. The importance of this effort has been recognized by many organizations, including the National Institutes of Health, the American Cancer Society, the Burroughs Wellcome Fund, the Howard Hughes Medical Institute, and others.⁹ It is clear that new approaches are needed not only in the way we conduct our research but also in how we train basic scientists for the postgenomic era. Correcting these problems will require the concerted efforts of many organizations, including the APS, working together with government and industry. Without effective translational research, the exciting molecular discoveries that are currently being made at the

research bench will not benefit the patient. Highlighting and encouraging translational research in APS journals is an important step in the right direction.¹⁰

Why translational research in physiology?

Physiology is major branch in modern medicine on which basis we explain etiopathogenesis. Physiology where action is integrated with research, henceforth newer inventions are possible rather than traditional path. For example, nowadays we are using nerve conduction velocity and electromyography as basic parameters in research as well as in practice. However their real implication in disease management system is just supportive. Unlikely this was initially also happened with ECG. But nowadays ECG is a must initial parameter. There are such number of parameters and happening in physiology. In USA these changes are already noticed and these policymakers made such changes in education, research work and publications etc.¹⁷

Translational research in Physiology and India:¹¹

There is a tendency that Physiology is trying to come out of labs to outside domain. During this period more importance has been given only to 'Clinical Physiology'. This emphasis also extended towards 'Social Responsibility'. Nowadays themes of several conferences, workshops etc are concentrated on multidisciplinary approach which is necessary for translational research. Translational research is actually a not specialized domain, however it is an specified approach. Current few notable conferences from Association of Physiologists and pharmacologists of India like APPICON 2014 conducted in Puri, Odisha moved towards translational physiological research.¹¹ Our country is going through a transition to adopt 'Translational Research'. The major drawback behind growth of

translational research in India is our adopted education pattern. Our pattern has fixed us in compartment system. Teachers from physiology are restricted only in labs and classroom and are labeled as teachers rather than doctors. Our adopted research based system is another major issue. However it is now a ray of hope , that Medical Council of India (MCI) has inspired multidisciplinary pattern and released vision 2015 documents. In that documents major emphasis was given over horizontal and vertical integration in teaching pattern of medical students. MCI has also introduced medical bioethics as part of curriculum from current year.

However concept of translational research is simple and even simpler to practices. It is indeed, like a 'relay race'. The success of which largely depends on competency and skills of individual researcher.

Physiology occupies at the heart of translational research cycle. The cycle may begin with 'Physiology' or end up with 'Physiology'. Therefore, as researchers in Physiology, we need to remain part component of translational research cycle by doing in-depth research and connect it to next mode. The efficiency at component level (in-depth pre-clinical research; robust physiological data, integrating the research to concerned basic field; integrating research to clinical practice; developing guidelines etc.) will result in better scientific delivery to society. The key mantra for achieving success in translational research continuum for physiologists is to attain competency at component levels and to strengthen the links that connect components.¹²

This will not be as one night miracle. We should change our attitude. Our focus should be towards multitask and market based provision of research. We should collaborate with clinical activities, their physiological – pathological consequences etc. We

should update our postgraduate syllabus including biostatistics, software based research applications , translational research models etc . We need to value each component in the cycle and honest integrations.^{11, 12}

Translational research and literature:

On the basis of Medline search the term translational research appeared as early as 1993, there were relatively few references to this term in the medical literature during the 1990s, and most references were to research about cancer.¹³

At the time, the literature on cancer tended to use the term translational research to refer to work spanning different types of research (e.g., immunology studies spanning basic and clinical research) or work spanning disciplines within a particular type of research (e.g., bench research involving molecular genetics and immunology). Today, the literature includes a plethora of attempts in various fields to define the term.¹⁴In a recent announcement about applying for a CTSA, the NIH offered the following definition: Translational research includes two areas of translation. One is the process of applying discoveries generated during research in the laboratory, and in preclinical studies, to the development of trials and studies in humans. The second area of translation concerns research aimed at enhancing the adoption of best practices in the community. Cost-effectiveness of prevention and treatment strategies is also an important part of translational science.¹⁵

In a commentary published in 2008, Steven Woolf pointed out that “translational research means different things to different people”¹⁵ (p211) and argued that the different types of translational research are too narrowly defined. In particular, he argued that if T2 research is going to result in the

knowledge needed to improve health and the quality of life, then T1 research must include sciences related to populations (e.g., epidemiology, psychology, economics, and behavioral sciences).¹⁵

When the Institute of Medicine (IOM) convened the Clinical Research Roundtable, the roundtable group developed a model for translational research that was highly aligned with the NIH definition.¹⁶

Design training implication in translational research:¹⁷

The interaction of several disciplines is required to translate knowledge from one type of research to another. An interdisciplinary research approach has power of emergence of novel concepts and approaches to addressing important health issues. The emergence, development and applications of new ideas are goals of translational research, and there are many possible models of training that can provide the academic path to these goals.

Training in translational research will vary depending on the background of trainees and the areas of research they plan to pursue. Given the diversity of educational backgrounds and research interests, it will be necessary to design a customized curriculum for almost every trainee. To ensure an understanding of complementary disciplines and to enhance communication and collaboration, trainees who have focused on basic laboratory research will need to become immersed in clinical sciences and clinical practice, while trainees with a clinical focus will need to gain exposure to basic science research. Both types of individuals will also benefit from training in population-based sciences, as is encouraged, for example, by the Burroughs Wellcome Fund, which sponsors the Institutional Program Unifying Population and Laboratory Based Sciences.¹⁷

The details of a clinical immersion experience will depend on the area of research interest. For example, trainees interested in neuroscience may wish to accompany clinicians in a psychiatry or neurology clinic, and trainees working on bone tissue regeneration may participate in the activities of a clinical orthopedic surgery program. Trainees seeking laboratory immersion could take courses in techniques of molecular biology or genetics and work at the bench for a concentrated period of 3–4 months. Trainees who have a background in the social sciences or economics and are interested in health services research may need to join a team of investigators working in their area of interest.

All trainees could benefit from fundamental instruction concerning study design, data collection, statistical analysis, ethics and research integrity, protection of human subjects, the search for funding sources, the writing of institutional review board protocols and grant applications, the pursuit of patents and technology transfer, and government requirements for new drugs and devices. Because of the nature of translational research, it is also imperative for training programs to ensure that trainees develop the competencies needed to thrive in a multidisciplinary collaborative team. These competencies include communication and negotiation skills as well as ethical and humanitarian attitudes.

The most effective approach would be to design an individualized curriculum for each trainee, guided by a customized, learner-centered advisory committee that includes mentors with various and complementary backgrounds in clinical practice and basic and clinical research. One of the mentors would assume the role of primary mentor to ensure coordination of efforts and the success of the mentoring process.

Mentoring is a demanding but highly rewarding enterprise whose success depends on the widely varying skills, needs, and attitudes of different individuals.¹⁸ Mentors who are able to monitor the incorporation and understanding of translational research essentials will be crucial to the positive outcomes of training programs. However, trainees will also need to have critical thinking skills and practical knowledge about how to work collaboratively and manage teams. Although most medical schools now realize the importance of teaching their students how to think critically,¹⁹ the truth is, as Jerome Groopman points out, that the older generation of students were not taught to think as clinicians.¹⁸ Although recent emphasis has shifted to training medical students and residents how to follow preset algorithms and decision trees, these approaches are challenging when clinicians need to think outside their domains.¹⁸ Since clinical and translational research in this century necessitates out-of-the-box thinking, training programs must teach young researchers how to excel as critical thinkers.

An effective training program in translational research must use traditional curricular elements in new ways to ensure understanding across disciplines. In addition, it must create and use new curricular elements and approaches to ensure that its trainees are able to do the following: critically examine the research process; think “out of the box” to develop ways to impact health care by transferring knowledge from and to the bench, bedside, and community; engage in multidisciplinary collaboration; understand successful approaches to community engagement; and develop appropriate techniques to manage multidisciplinary research teams in the future. Using multidisciplinary skills, the translational researcher will be able to think and perform in an integrated

interdisciplinary manner and become a new type of investigator.

Meeting these goals is a challenge because research training programs are not traditionally content-based. We need to consider the creation of a community of learners and leaders by fostering the use of problem-based learning^{19,20} as a gateway to collaborative leadership. Adopting these techniques will require a change in culture in medical schools, but the time is right to begin the process of this cultural shift if we wish to take a leap forward in enhancing the practice of moving from bench to bedside to community and back in translational research.

Evaluation approach:

With the necessity of customizing training in translational research, the approach to evaluation must be flexible. One of the most flexible approaches is to design a logic model that offers a graphic display of the relationships between program elements, objectives, and desired outcomes in the short term, intermediate term, and long term. The logic model approach has the advantage of being adaptable as definitions of research and research goals evolve. Specific elements in the model can change, along with indicators and data sources, without completely disrupting the overall logical flow of objectives.

Logic Model for Training in Translational Research^{14,15}

In the logic model for a translational research program, the domains to be evaluated could include (1) whether the tools employed to achieve preestablished objectives, including general and scientific area specific competencies in translational sciences, are adequate; (2) whether the trainees acquire the cognitive and practical skills they need to effectively conduct translational research; (3)

whether the trainees are successful in developing and pursuing a translational research career; and (4) whether the program as a whole promotes and enhances translational research. The outcomes of each of these domains could include (1) evidence that courses, seminars, workshops, and laboratory experiences offered in the program lead to fulfillment of preestablished competency requirements; (2) evidence of improvement over time in the trainees' knowledge and skills regarding translational research topics and endeavors, as assessed via testing and via evaluations provided by scientific advisory committees; (3) evidence of successful career development, as measured by the ability to publish articles in peer-reviewed journals, to obtain research grants and academic appointments, and to gain leadership positions in multidisciplinary teams; and (4) evidence of the increased impact of the program at the institutional level and the national level, as judged by whether more translational research is funded and conducted at these levels.

We believe that translational research moves in a bidirectional manner from one type of research to another—from basic research to patient-oriented research, to population-based research, and back—and involves collaboration among scientists from multiple disciplines. The design of an effective training program in translational research is a challenge because the program must offer each of its trainees the opportunity to master a combination of skills that are not taught together in traditional training programs. The approach to evaluating the success of translational training programs must be flexible enough to accommodate the needs of individual institutions and individual trainees within the institutions, but it must also be rigorous enough to document that the program is meeting its short-,

intermediate-, and long-term objectives and that its trainees are meeting preestablished competency requirements.

Criticism for translational research:^{21,22}

The first problem is that history is not on the side of translational research. Most inventions and practical applications of science and technology which we take for granted have come not from people sitting in a room trying to invent new things but as fortuitous offshoots of curiosity-driven research.

Critics have also demanded that translational research be subjected to the principles of evidence-based policy to establish that it is in fact superior (or more cost-effective) to funding basic research itself.

Examples of failed translational research abound in the pharmaceutical industry and other problems arise from the widespread irreproducibility thought to exist in the translational research literature.^[9]

Translational research requires that information and data flow from hospitals, clinics and study participants in an organized and structured format, to repositories and laboratories. Also, the scale, scope and multi-disciplinary approach that translational research requires means a new level of operations management capabilities within and across studies, repositories and laboratories. Meeting the increased operational requirements of larger studies, with ever increasing specimen counts, larger and more complex systems biology data sets, and government regulations, requires informatics that enables the integration of both operational capabilities and clinical and basic data. Most informatics systems today are inadequate to handle the tasks of complicated operations and contextually in data management and analysis.^{22,23, 24}

Translational research refers to two distinct domains: T1 research, the “bench-to-bedside”

enterprise of translating knowledge from the basic sciences into the development of new treatments; and T2 research, translating the findings from clinical trials into everyday practice.^{23, 24}

Conclusion and scope:

Translational research will allow bidirectional physiological investigation throughout the translational continuum: basic research observations

can be studied up to the population level, and mechanisms can be assessed by 'reverse translation' in clinical research settings and preclinical models based on initial observations made in populations. Translational physiology provides a novel framework for physiology programs and an investigational platform for physiologists to study function from molecular events to public health.

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