

TRANSLATIONAL MEDICAL EDUCATION AND RESEARCH : SRI RAMACHANDRA UNIVERSITY INITIATIVES.

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ABSTRACT:

Translational medicine is a branch of medical research that attempts to more directly connect basic research to patient care. Translational medicine is growing in importance in the healthcare industry. In the case of drug discovery and development, translational medicine typically refers to the "translation" of basic research into real therapies for real patients. The emphasis is on the linkage between the laboratory and the patient's bedside, without a real disconnect. This is often called the "bench to bedside" definition. Translational medicine can also have a much broader definition, referring to the development and application of new technologies including therapeutics in a patient driven environment - where the emphasis is on early patient testing, evaluation and management.

Translational Medicine encompasses (a) Basic science studies which define the biological effects of therapeutics in humans (b) Investigations in humans which define the biology of disease and provide the scientific foundation for development of new or improved therapies for human disease (c) Non-human or non-clinical studies conducted with the intent to advance therapies to the clinic or to develop principles for application of therapeutics to human disease (d) Any clinical trial of a therapy that was initiated based on (a) to (c) with any endpoint including toxicity and/or efficacy. (e) Appropriate product development for clinical use in various stages of investigational clinical trial before

initiating Phase III trials as required by the regulators and (f) The adoption of best practices that lead to greater understanding of the link between medical learning (how one acquires and applies relevant attitudes, knowledge and skills in medicine) and patient outcomes via real-world clinical decision-making and other physician actions.

The requirements of Translational education & research are (i) Academic setup with components of Clinical and translational Science (ii) Institutional culture and commitment for Clinical and Translational science (iii) Education, training and Career development opportunities (iv) Clinical research Informatics (v) Intra and Inter Institutional Collaboration and (vi) appropriate manpower with the capacity to envisage the whole process from "bench to bedside" to be generated by due educational program.

Sri Ramachandra University has conceived a M.Sc in Translational Medicine and a Post graduate Fellowship in Translational Health sciences for consideration of support by the Department of Biotechnology, Government of India. To promote Translational research, a Central Research Facility has been created for intra institutional collaboration and multi-investigator cum interdepartmental research projects. Institute- Industry collaboration has also been strengthened for drug discovery program and/or clinical trials.

Key words : Research, Education

INTRODUCTION:

Until recently, basic science advances have made oversimplified assumptions that have not matched the true etiological complexity of most common diseases; while clinical science has suffered from poor research practices, overt biases and conflict of interest. The advent of molecular medicine and the recasting of clinical science along the principles of evidence-based medicine provide a better environment where translational research may now materialize its goals.

The status of translational research has drawn increasing attention recently in top biomedical journals [1-5] and in the policy making of the NIH, as reflected also in the NIH Roadmap [6]. Translational medicine encompasses all the disciplines that intervene in moving scientific progress from

the bench to the bedside and in conveying stimulating information from the bedside back to the bench [5]. While basic sciences are conceived as having made amazing leaps forward, this progress has not resulted in many major cures [7]. At the other end, clinicians are considered too unfamiliar with the capacities of modern science to bring fruitful questions to the attention of basic scientists [5]. Nevertheless, recent evolutions in basic and clinical science have created a new window of opportunity for the growth of translational medicine.

What is Translational Medicine?

Translational medicine is a rapidly emerging discipline focused on bridging technologies and discoveries in the laboratory with clinical research and practice. The same principles apply in academic, biotechnology and pharmaceutical environments. Numerous definitions of translational medicine exist. The National Institute of Health (NIH) at USA has stated that " To improve human health, scientific discoveries must be translated into practical applications. Such discoveries typically begin 'at the bench' with basic research- in which scientists study disease at a molecular or cellular level- then progress to the clinical

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level, or the patient's 'bedside', thus terming translational medicine as 'bench to bedside research'[6]. The Medical Research Council(MRC), UK has summed up the concept succinctly as, "The process of the bidirectional transfer of knowledge between basic work (in the laboratory or elsewhere) with that of the person, in health or disease"[36].

Historical Background:

In embarking on its Roadmap for Medical Research, the National Institutes of Health (NIH) has pledged to accelerate the application of "scientific advances to real-world [medical] practice" through translational research.[6,8] As a cornerstone of its Roadmap Initiative, the NIH introduced Clinical and Translational Science Awards (CTSAs) in the year 2002 designed to overcome the "bench-to-bedside" barriers of translational research by promoting interdisciplinary and cross-institutional collaboration, with the goal of "enhancing the adoption of best practices in the community." [9] Historically, "bench to bedside" translational research has been equated with the conversion of scientific discoveries into promising diagnostic and therapeutic modalities.

Over the past decade, a multitude of editorial commentaries, journal articles, and blue ribbon reports have called for a concerted effort to advance translational medical educational research[10-20]. Yet progress has been slow. Major obstacles to progress include lack of funding[21], scarcity of experienced medical education researchers[22] and the absence of a "national research infrastructure to build and sustain a medical education research enterprise." [22] Other obstacles are related to the inherent structural and methodological difficulties of designing and conducting educational research, particularly controlled interventional studies, on medical students, residents and practicing physicians. Recruitment of subjects, long-term follow-up, the lag between the educational intervention and end-point/measurement timing, cross-contamination between control and experimental groups,, and the inability to control for an ever-changing learning environment make it challenging to produce high quality studies that demonstrate a clear link between the educational intervention and outcomes that matter, including health outcomes of patients[17,23]. Finally, there is currently no widely accepted "theory of medical education and its influence on outcomes" to use as a foundation for designing and implementing research studies[19]. Limited by these obstacles, translational medical education research has generally lacked the methodological depth, breadth and rigor necessary to inform with conviction the development and adoption of best educational technologies and practices in physician lifelong learning and professional development. Country specific initiatives are now being taken to operationalise translational education and medical research in view of basic sciences maturing in complexity and Clinical science maturing in its evidence base.

Basic sciences: Maturing in complexity

Basic science advances in the last few years have indicated that most common diseases entail extremely complex patterns of pathogenesis, involving the regulation of dozens and hundreds of genes and their protein products. In the light of advances in genomics, proteomics, and bioinformatics, basic science of the 1980s and 1990s where single or few pathways were investigated would currently seem naïve at best. We don't know yet whether the molecular medicine of the early 21st century may seem equally oversimplified even within a decade or two. The complex new patterns of disease etiology and regulation still pose considerable problems of validation and testing of generalizability [24,25]. The role of environmental parameters and their interactions at the molecular level with intrinsic factors is yet largely unknown. These interactions may prove to be even more formidable. The intractability of several chronic diseases, the unpredictable emergence of new diseases such as AIDS, SARS, and mad cow disease and the equally unpredictable re-emergence of old diseases such as tuberculosis makes such a target an utopia. Nevertheless, provided that we approximate the depth of the complexity of the molecular issues involved, translational medicine may have indeed a more solid starting point now in its efforts.

Clinical sciences: Maturing in evidence base

Clinical research has been even more revolutionized in the last decade, in particular with the advent of evidence-based medicine. It is now acknowledged that a large corpus of clinical information that has haunted the top medical textbooks and experts' opinions was wrong, outdated, and/or dangerous for human health [26]. Evidence-based medicine has placed emphasis on robust scientific principles, the dissection of strengths and limitations of various clinical research designs, and the identification of bias in medical research [27]. We are now aware that serious errors may underpin much of clinical research, and even randomized trials may succumb to biases [28]. Moreover, clinical scientists have now tried to systematize their knowledge base. Efforts such as the Cochrane Collaboration [29,30], an international coalition that aims to generate systematic reviews on all aspects of health care, has been hailed as equivalent in scope to the Human Genome Project [31]. Such systematic efforts can tell us reliably for each disease and condition whether we have enough evidence for its effective management, and whether this evidence is biased or not. Furthermore, rigorous approaches have been recently developed to quantify the burden of disease for various conditions [32]. It is thus becoming evident that for several trivial issues, there is often a waste variety of expensive treatments, while for many serious conditions there is no effective intervention at all and little research is targeted at them [33,34].

Priorities and cross-links between diseases

With genuine progress in the basic and clinical sciences, translational efforts have a better chance of being successful. Even under these circumstances though, the question remains on who will do this research and where it will be done. A very large portion of all current research is done in the USA. Scientific papers with US authorship attract approximately half of all citations in the Web of Science (over 30 million citations in the last decade alone, followed by England with less than 6 million) [35]. A handful of developed countries make up another 40–45% of the total citations. NIH is by far the greatest governmental funding body for biomedical research globally and hence has laid out a road map as mentioned earlier for translational education and research.

NIH Roadmap for Re-engineering the Clinical Research enterprise-Translational research :

Starting in 2002, the NIH in the USA began a process of charting a “roadmap” for medical research in the 21st century [6,8], identifying gaps and opportunities in biomedical research that crossed the boundaries of then extant research institutions. A key initiative that came out of this review is a move to strengthen *Translational Research*, defined as the movement of discoveries in basic research (the *Bench*) to application at the clinical level (the *Bedside*)

This NIH roadmap framed guidelines for the above mandate under the following five areas:

- i) **Components of a Clinical and Translational Sciences, Academic Home**, describing the methodology to identify the desirable components which would work. Together and how to prioritize these components, and govern them;
- ii) **Institutional Culture and Commitment for Clinical and Translational Science:** To get the institutions to change and to sustain the change with a mission mode approach including the space allocation, finances, service benefits of the personnel and the educational pathways;
- iii) **Education, training and career development:** To evolve a more efficient and effective education, training and career development pathway for the clinical and translational sciences and to design the pathway not only for principal investigators, but also for all members of multidisciplinary teams;
- iv) **Clinical research Informatics:** To identify areas where informatics would be most helpful, and to consider what type of institutional leadership would be needed to take full advantage of informatics in the clinical and translational sciences.
- v) **Intra and Inter-Institutional Collaboration:** To consider how the project sites might work together to develop the tools and training programs needed for clinical and

translational sciences and then to share and distribute their findings to a wider community. Also to design modalities to enhance discipline of Clinical and translational sciences by collaboration at institutional, regional and national levels.

MRC Guidelines for Translational Medical Research:

More recently, the Medical Research Council (MRC), UK in the year 2007 came out with Guidelines for accelerating the translation of Medical Research [36]. Approximately 50 members of MRC’s community including industry and representatives from the Health Departments came together in February 2007 to discuss these issues. Delegates discussed the translational research process, MRC’s role and what more MRC could do. The main issues to emerge were the need for:

- i) Cultural change within the research community and recognition that translating research findings and communicating findings to research users was part of a researcher’s role. Structures and funding mechanisms needed to be put in place to encourage and reward researchers to move into and become active in these areas.
- ii) Guidance on the process of translation and an accompanying vocabulary to describe more precisely translational activities. Process maps could be used to educate and assist researchers in identifying the next steps in progressing research findings and also provide metrics against which MRC could evaluate its process.
- iii) A separate funding stream to build capacity and provide project support for early translational research (e.g. experimental medicine; biomarkers; proof-of-concept studies). Where possible, these new initiatives should be undertaken through partnerships with industry.
- iv) MRC’s should continue to build on its high quality basic research portfolio but a much greater focus must be placed on the management of the findings from MRC funded research. Resources needed to be provided for the proactive brokering of partnerships between researchers and research users and for catalysing bottlenecks in the process in order to facilitate translation.

Translational research and the information ecosystem

Much of the ability of biomedical researchers and health care practitioners to work together – exchanging ideas, information, and knowledge across organizational, governance, socio-cultural, political, and national boundaries – is mediated by the Internet and its ever-increasing digital resources. These resources include scientific literature, experimental data, summaries of knowledge of gene products, diseases, and compounds, and informal scientific discourse and commentary in a variety of forums. Together this information comprises the scientific

“information ecosystem” [6]. Despite the revolution of the Web, the structure of this information, as evidenced by a large number of heterogeneous data formats, continues to reflect a high degree of idiosyncratic domain specialization, lack of schematization, and schema mismatch.

The lack of uniformly structured data affects many areas of biomedical research, including drug discovery, systems biology, and individualized medicine, all of which rely heavily on integrating and interpreting data sets produced by different experimental methods at different levels of granularity. Complicating matters is that advances in instrumentation and data acquisition technologies, such as high-throughput genotyping, DNA microarrays, protein arrays, mass spectrometry, and high-volume anonymized clinical research and patient data are resulting in an exponential growth of healthcare as well as life science data. This data has been provided in numerous disconnected databases – sometimes referred to as data silos. It has become increasingly difficult to even discover these databases, let alone characterize them. Together, these aspects of the current information ecosystem work against the interdisciplinary knowledge transfer needed to improve the bench-to bedside process.

Curing and preventing disease requires a synthesis of understanding across disciplines:

In applying research to cure and prevent diseases, an integrated understanding across subspecialties becomes essential. Consider the study of neurodegenerative diseases such as Parkinson’s Disease (PD), Alzheimer’s Disease (AD), Huntington’s Disease (HD), Amyotrophic Lateral Sclerosis (ALS), and others. Research on these diseases spans the disciplines of psychiatry, neurology, microscopic anatomy, neuronal physiology, biochemistry, genetics, molecular biology, and bioinformatics. Hence both Translational Education and Medical Research requires interdisciplinary information system [37].

Major Components and role of Translational Medicine:

Translational Medicine encompasses:

- a) Basic science studies which define the biological effects of therapeutics in humans
- b) Investigations in humans which define the biology of disease and provide the scientific foundation for development of new or improved therapies for human disease
- c) Non-human or non-clinical studies conducted with the intent to advance therapies to the clinic or to develop principles for application of therapeutics to human disease
- d) Any clinical trial of a therapy that was initiated based on #1–3 with any endpoint including toxicity and/or efficacy.
- e) Translational research may play a role as appropriate product development for clinical use in various stages

of investigational clinical trial. For example, identity, purity and potency of a drug product must be studied during the early stages of the clinical trial. However, these tests must be in place before implementing phase 3 trials as required by the regulators.

- f) The critical role that translational medical education and research can play in ensuring the adoption of best practices that lead to greater understanding of the link between medical learning (how one acquires and applies relevant attitudes, knowledge and skills in medicine) and patient outcomes via real-world clinical decision-making and other physician actions is necessary if we are to fully realize the NIH’s “bench to bedside” mission

Industries and Translational Medicine:

Traditionally, basic research has been separated from the clinical practice of medicine by a series of hurdles or fences. New drugs were developed independently of the clinic, and often “thrown over the fence” for safety testing and clinical trials. The move toward translational medicine is focused on removing these fences, and stimulating “bench to bedside” research. A large number of developments show the growing influence of translational medicine across academia and industry. A couple of these over the past year include a 50 million pound sterling investment by Wyeth and Scottish Enterprise in the Translational Medicine research. Many pharmaceutical companies are building translational medicine groups to facilitate the interaction between basic research and clinical medicine, particularly in clinical trials.

International Funding support for Translational Medicine Research:

The National Institutes of Health has awarded UW-Madison’s new Institute for Clinical and Translational Research (ICTR), one of the largest grants in the history of the School of Medicine and Public Health and has identified UW-Madison as a key player in an ambitious NIH plan designed to transform the country’s clinical and translational research enterprise. With \$ 41 million over five years, ICTR will aggressively address clinical and translational research in Wisconsin by first building a network of key partners from across campus and around the state including even international partners.

In the UK, Collaboration across a consortium of research universities and launch of six major MRC translational medicine centres has evidenced that government also is tuning into the potential for translational medicine to overhaul medical research.

Government of India Initiative for Translational Education and research:

Department of Biotechnology, Government of India has announced awards for institutions desiring to create

centres or new expanded or remodeled departments for translational research. These centres will have to focus on translational biology and clinical research in an interlinked way. The purpose is to enable and accelerate the translation of basic scientific and engineering knowledge from lab to patients. To facilitate more translational research, the centre will facilitate PhD's to engage in strategic basic sciences based on patients, and animal models of disease.

The support where appropriate can cover physical infrastructure, renovation, PhD fellowships, post doctoral fellowships, strengthening platform technologies and short term training for skill acquisition and R&D costs on five years basis extendable thereafter based on performance and institutional commitment. The participating scientists could belong to a nodal department and to other collaborating departments. DBT will consider support for 5-10 years to any new faculty recruited to strengthen research and working at least 60% of their time on the centre's programmes. A clear defined R&D strategy is important for a successful award; disconnected, multiple proposals even of good quality will fall short of our prescribed benchmark.

The Indian Council of Medical Research, which has now become part of the Department of Health Research, Govt. of India has announced its policy decision to launch Translational Medicine program. It has jointly announced with DBT to set up an Institute of Translational Research recently.

Sri Ramachandra University Initiatives in Translational Education and Research:

(a) Translational education:

In 2006, Sri Ramachandra University responded to the call of the Department of Biotechnology, Government of India by developing the curricula, syllabi and the academic structure for conducting (i) M.Sc (Translational Science) and (ii) Post Graduate Fellowship in Translational Health Sciences. It was also planned to bring in place (a) Division of Translational research, (b) Division of Clinical Trials and (c) Division of Outcomes, Clinical Epidemiology and Health outcomes as umbrella structures for the Basic and Clinical Sciences departments to undertake these programs.

(b) Translational Medical research:

A Central research Facility along with a Central Animal House have been established and being strengthened since May, 2007 to facilitate intra-institutional collaboration and multi-investigator cum interdepartmental research projects to realise the requirements of Translational Medical Research. Some of the success stories in implementing Research projects as per the concept of Translational Medicine are (i) The Department of Science & Technology supported Population Based Risk factor analysis & Prevention

(PURSE-HIS) study for Cardio Vascular Diseases under Dr.S.Thanikachalam of Cadiac Care Centre in collaboration with the departments of Periodontal diseases, Genetics, Nutrition, Biochemistry and Biotechnolgy (ii) The Department of Biotechnology and Department Atomic Energy supported Cardiomyocyte tissue-engineering and Artificial Heart project under Dr.K.R.Balakrishnan of Cardiothoracic Surgery with Department of Patholgy, SRU and Central Leather Research Institute; (iii) The Department of Biotechnology supported Chondrocyte tissue-engineering project under Dr.S.Arumugham of Department of Sports Medicine & Orthopedics with the Department of Pathology and Central Leather Research Institute and (iv) The Herbal Research Laboratory under Dr.Hanna R.Vasanthi with Herbal/Indigenous drug development/ validation projects supported by Department of Scientific & Industrial Research, AYUSH etc., in collaboration with Departments of Cardiology, College of Pharmacy and Central Leather Research Institute. Many more projects/programmes are in the pipeline to be supported by Indian Council of Medical Research/Department of Biotechnology in collaboration with National Centre for Biological Sciences, Bangalore, National Institute of Immunology, Delhi besides interdepartmental participation.

CONCLUSION:

As basic and clinical sciences mature, translational research has a chance of making an important difference for human health. However, priorities need to be selected with broad horizons in mind. A global perspective including that of the developing world should be assumed not only in priority setting, but also on the conduct of research. Universal guidelines that are consistent with the realities of the 21st century biotechnology industry and academic science should be adopted. The rules should be clear and they should reward creativity, maximize transparency, and exploit local strengths, not to stifle progress with irrelevant administrative burdens. The ability to create a truly international scientific society with high standards, transparent processes and academic independence may create a healthier world for all humans across the globe.

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