

Review Article**TRANSLATIONAL RESEARCH: LOOKING INTO THE CRYSTAL BALL**

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ABSTRACT

The landscape of research is profoundly different today from that one decade ago. Basic science is moving rapidly and biotechnological revolutions have completely modified the opportunities and concepts for treatment. Still the up gradation in research and developmental science has not been mirrored by the same level of progress in conceptualizing the clinical basis of various diseases and ultimately the development of treatment which are novel and more effective. This gap can be bridged by applying translational research throughout the late-stage discovery and exploratory development stages of drug development.

More specifically, translational research is an emerging field of science, embracing disciplines in medicine and public health to create a full-spectrum research agenda. Often described as science “from bench to bedside and back again,” translational research may be better described as “from bench to behavior.”

By achieving a two way dialogue between researcher and clinicians with more inclination towards the pharmacology and clinical basis for disease, it will help to deliver biomarkers that enable drug development decisions to be made earlier and with increased confidence.

Also with the development in technologies of proteomics, transcriptional profiling, metabolomics translational research has become a key factor in the production of new innovative therapies.

Thus, today translational research has become a buzzword in the life sciences, aimed at moving discoveries from the “bench to the bedside.”

KEYWORDS Translational Research, bench-to bedside, proof-of concept, biomarkers

INTRODUCTION

Drug discovery is cost, time and risk intensive process. It takes more than 500 million dollars and about 10 years to bring drug from concept to clinic.

The majority of compounds do not progress from laboratory to patients, only 20% of the product enters the phase I trials eventually cleared the obstacle of FDA approval. The high attrition rate has led to skyrocketing development cost. The FDA estimates that just a 10% improvement in predicting a product’s failure in clinical trials could save millions of dollars in drug development. Because most drug candidates fails in early drug development, it should have a primary and overarching focus on the plans and options that proceed to this point with minimum investment, based on an active reduction in the uncertainty around – pharmacology, pharmacokinetic–pharmacodynamic (PK–

PD) properties, safety and so on.¹ A need exists to translate more quickly the numerous discoveries into more effective applications relevant to human health and disease.² The US National Institute of Health (NIH) in 2002 began a process of charting a “roadmap” for medical research in 21st Century, identifying gaps and opportunities in biomedical research. A key initiative that came out of this is a move to strengthen Translational Research, defined as the movement of discoveries in basic research (the Bench) to application at clinical level (the Bedside).³ Traditional approach of inquiry and investigation have centered on laboratory-based research and also disease- and patient-oriented research. Translational Research is a different pathway emerged in investigative medicine.⁴

WHAT IS TRANSLATIONAL RESEARCH

Translational Research describes a bi-directional sharing of knowledge and ideas by scientific and clinical disciplines. 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.”²

It fills the gap of scientific and operational approach between *in vivo* research (lead generation) and early –stage clinical studies (proof-of-concept). In simple words it includes activities that bridge between drug discovery in animals and drug development in human patients. It places researchers in new context and ushers in a range of new contacts and relationships.

Translational Research is defined by the NIH 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 concern research aimed at enhancing the adaptation of best practices in the community. Cost-effectiveness of prevention and treatment strategies is also an important part of translational science.

Translational Research will shift the focus from the scientist to the user. In Translational Research model, end user plays a more prominent role. They influence the researcher priorities.⁵

TRANSLATIONAL RESEARCH MODELS

Translational Research has two key elements and can be described as thought process by which information is applied.²

- From research to development it relates signals from animal studies that can predict the efficacy (confidence in

rationale) and safety (confidence in safety) of compounds in early development (animal pharmacology and associated exposures describes PK–PD translation of PK–PD to humans, and animal disease model efficacy describes projected efficacious exposures translation of efficacy to clinical patients). Such correlates can be derived from mechanistic biomarkers. They can have, or turn out to have, poor correlation with disease but they measure the pharmacology of a compound in humans.

- The transition from development to research findings in humans and patients with diseases enables a clear understanding of the biology and pathophysiology, and so can trigger *in vitro* and animal experiments that better mimic the human and patient condition. This is, therefore, likely to enhance confidence in the appropriateness of the target and help in the dose selection for subsequent trials. These are referred to as disease-orientated biomarkers.

Translational Research may be described as having a layered and sequential approach. Different phases are shown as in FIG 1.

The first phase may be considered as the journey from “bench to bedside” and reflects the sojourn between the discovery of mechanistic pathways and molecular and genetic contributors to disease, as well as the development of pharmaceutical products, to trials examining treatment efficacy.

This phase of translation—preceding and proceeding through clinical trials—has been incorporated into radiation and cancer therapy, as well as gastroenterology and gynecology.

Many of these projects reflect the traditional clinical trial and focus on physician–scientist relationships.

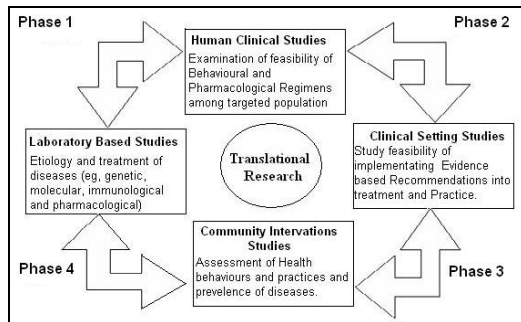


FIG 1 Different Phases of Translational Research

The first, described in phase 1, occurs when laboratory based findings are initially tested with human subjects. The second focuses on the dissemination of the results from phase 1 to overall clinical practice and on either physician patient relationships or scientist-subject relationships. To be truly valuable, the results of large, controlled trials must be replicated in clinical settings with equally positive outcomes.

In some cases, this is referred to as the willingness to incorporate evidence-based recommendations into treatment programs. Practical feasibility considerations, including cost, compliance, ease of administration, subject burden, safety, physician training, physician-patient communication, and clinic organizational factors, are often a large part of these studies. Although phases 3 and 4 have not been coined in the literature, they clearly exist and have existed for quite a long time. Phase 3 may be described as broader, public health applications of clinical trials—moving beyond what works in a controlled “idyllic setting” and to “what will work” on a community level.⁶

STEPS IN TRANSLATIONAL RESEARCH⁷

In vitro Experiments

The development of new treatment or improvement of existing one often depends on the study of cells in culture. An important role for *in vitro* models is as a means of investigating unexpected outcomes or phenomena arising further up

the translational chain, in animal models or the clinic.

Animal Studies

Experiments in animals, by adding the complexity of tissues and whole organisms, are expected to be more relevant to the clinical situation than *in vitro* studies. The underlying assumption is that the mechanisms that operate in one model system with defined genetic, physiologic, and immunologic conditions govern results in other species where the same or similar conditions prevail. In contrast to clinical trials, animal experiments permit the study of a specific intervention in a large number of (almost) identical organisms thereby allowing more stringent control of cofactors and less inter individual variability than with the human situation. An important limitation of animal models is its poor predictiveness.

Mathematical modeling

The natural science is stuffed with examples where hypothesis driven mathematical modeling has led to predictions that were then tested experimentally and “paved the way” for understanding at deeper level. The contribution to Translational Research of such model is mainly conceptual and arises at the stage of hypothesis generation.

Phase I & II studies

Classically, Phase I studies have been used to assess feasibility and safety of a new approach to treatment, and have used increasing doses of the treatment components to define maximally tolerated doses. Phase II studies seek evidence of efficacy and aid in decision making. Their purpose is to determine whether or not there is sufficient evidence of efficacy to warrant the conduct of a larger randomized Phase III study. Nonrandomized studies can and should also be used as part of a sequence of translating laboratory-based research to the clinic.

ADVANCES THAT ASSIST TRANSLATIONAL RESEARCH²

Current advances in technology are important tools that help us to understand these pathways. The pharmaceutical industry's efforts in the Translational Research are increasingly focused to enhance the ability to translate new mechanisms to clinical applications.

Polyomics

Revolutionary progress in basic research, such as human genomics, together with the sequencing of the genome of many of the commonly-used laboratory species, provides an important opportunity to understand the comparative determinants of efficacy, toxicity and adverse reactions.

Polyomics can be defined as the integration and mining of information-rich datasets (obtained through analysis of preclinical and clinical specimens using technologies with the aim of improving discovery) with the development and use of novel therapeutic agents. A recent example is a monoclonal antibody that targets the over expression of HER2 protein in certain breast cancer patients, HerceptinTM (trastuzumab).

It is based on a variety of platform technologies, which have been developed throughout the last decade, offering the opportunity to 'industrialize' the generation of biomedical data. Through the application of such polyomics, which include genomics, transcriptomics, peptidomics, proteomics and metabonomics, drug development will occupy an even more pivotal role, because many more drug candidates will be generated in the years ahead compared with the present.

The impact of polyomics and the potential for pharmaceutical drug development to respond appropriately can be considered at three levels: (i) increased understanding of disease etiology, and target identification and validation; (ii) improved decision-making during the development process and (iii) the identification of diagnostic

tests to improve prescribing precision by identifying subjects likely to have a poor response or an adverse event before starting therapy.

The application of the above technologies generates large quantities of biological data, which will alter as a result of the disease state and severity and pharmacological interventions. There is already evidence that these tools can be used to detect specific changes that predict disease prognosis and drug response. However, each technology examines different components of the biological system under study. As a result, it is widely expected that integration of the information derived from all the technologies will produce a synergistic increase over the sum of their individual value. This integration requires appropriate biomedical, informatics, data management, and statistical and mathematical resource.

Biomarkers

Biomarkers are quantitative measures of biological effects that provide informative links between mechanism of action and clinical effectiveness. For this reason, thoughtful and proactive use of biomarkers can improve the mechanistic information generated in drug development. This would allow a better understanding of sources of variation and the correlation between discovery, preclinical and clinical information. Biomarker use can actively reduce the uncertainty around key risks in the drug development cycle (pharmacology, PK-PD, toxicology and safety, and so on). Through the incorporation of appropriately validated biomarkers, one can expect better clinical study designs, in more suitably defined populations, with endpoints yielding improved labeling and marketing information. Biomarkers move us closer to realizing the goals of personalized medicine. Their ability to deliver improved preclinical screening, diagnosis, disease staging and monitoring of treatment better enables clinicians to determine the most appropriate drug for an

individual patient at a given stage of disease or treatment.

Optimizing selection of Phase II dose and regimen using biomarkers in Phase I clinical trials has several important considerations. Biomarker signals (of both desirable and undesirable pharmacological activity) that are safe and are indicative of efficacy must be established. These can come from preclinical models, from studies of the biomarker in patients with various levels of disease activity and from the comparison of the biomarker signal in patients and normal subjects. Detailed knowledge of biomarker responses associated with efficacy, such as whether intermittent high levels of pharmacological activity or constant levels of pharmacological activity are preferred.

The use of biomarkers in Phase I to help compounds through Phase II is an important benefit but selection of a threshold level of pharmacological activity, which is required to initiate Phase II, has the inherent risk of discontinuing development after Phase I if the amount of pharmacological activity at the maximum tolerated dose is less than an agreed threshold. A false-negative decision at this stage is serious because it could lead to the loss of a good compound and possibly the discontinuation of a programme owing to an incorrect conclusion about the efficacy or safety of the mechanism. Setting biomarker criteria for Phase II should therefore be data-driven. This requires an understanding of the relationship between biomarker signal and efficacy in preclinical animal models, the relationship between biomarker signal and disease activity from human data and the relationship between biomarker signal and disease activity from previous Phase II studies with similar compounds.

CHALLENGES IN TRANSLATIONAL RESEARCH

The expanding knowledge in biology might not easily translate into new

substantially better drugs. This statement leads to questions of whether the process of Translational Research is slower than anticipated. Translational Research might suffer from shortcomings.⁸

The preclinical “proof-of-concept” study is a critical element of Translational Research. Using an animal designed to mimic a human disease, the demonstration that a drug or intervention has a salutary effect on a surrogate endpoint provides the necessary support to move the treatment strategy forward into the clinic. Preclinical studies can be largely exploratory, designed to generate hypothesis, so hardly called “proof-of concept”.

The tension between variability and effect size is common to all translational research: to detect the consequences of an intervention, the effect size must overcome the variability in the model.

In the case of Translational Research, proving the feasibility of an original approach to the treatment of a disease provides yet another inducement to achieve positive results, and proof of feasibility may lead to patents and lucrative licensing arrangements. These incentives lead to powerful biases, both conscious and subconscious, with the potential to undermine a study.⁹

Translational Research may require highly sophisticated machines, specific imaging techniques, biochemistry laboratories and imposes other infrastructural prerequisites. The usefulness of data generated along Translational Research projects is highly dependent on the quality of the assays and the availability of sufficient number of samples. Translational Research into a routine research agenda faces a number of challenges which relate to ethics, regulations, logistics, scientific and costs.¹⁰

APPLICATION OF TRANSLATIONAL RESEARCH

Translational Research utilizing developments in biochemical research and medical informatics offers improved prospects for treatment.

Cancer research

Translational research clearly has impact on clinical practice in radiation oncology. Important parts of this research are “reverse translation” and “accumulation of knowledge” serving as a reservoir of background information for researcher and clinicians. Thus, the “translational process” is by no means unidirectional nor does it even require a hierarchical structure to make useful advances in cancer therapy. Rather, the important component is a continuing and fruitful multiway dialog among basic scientists, applied scientists, clinical scientists, and clinical oncologists.⁷

Central Nervous System

The increasingly high failure rate of CNS compounds in human trials has demonstrated that this success in animals is no guarantee. The development of the blood brain barrier and the inaccessibility of brain targets to direct measurements *in vivo*. A useful understanding for Translational research for the development of CNS drugs is the development and execution of estimates of drug-receptor occupancy.

Translational studies using efficacy biomarkers and more highly selected test population could provide a test of efficacy with smaller test groups and shorter observation periods.¹¹

CONCLUSION

Translational research can enhance many aspects of the pharmaceutical business. The efficient use of predictive technology and new techniques could ensure the timely removal of poor compounds and facilitate the identification and acceleration of good compounds that fulfill a medical need, as well as those that are based on a better clinical profile that will deliver the label the clinician and patient needs. In this way, translational research will bring increased confidence in the rationale supporting the mechanistic

approaches at a much earlier point in the research and development process.²

Opportunities in Translational research relevant to the impact of the environment may be enhanced in diseases with changing prevalence. The importance of Translational research is best quoted by Goethe “Knowing is not enough, we must apply. Willing is not enough, we must do.”³

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