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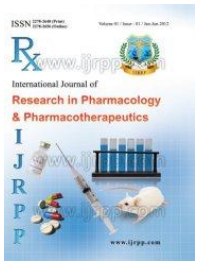

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Translational Pharmacology: New approach of drug discovery

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ABSTRACT

Increasingly, the field is recognizing the need to enable a closer collaboration of industry and academia to create a more efficient system for developing new drugs. In parallel with this, the world of drug discovery has seen the emergence of translational research as an alternative approach to the creation of new drugs, and there is growing support for the claim that this strategy may provide solutions to some of the woes of the pharmaceutical industry. Translational medicine and translational pharmacology have become terms increasingly used to describe the focus of applied pharmacological research to ultimately help patients. Yet, the number of effective medicines reaching the approval stage continues to decline. Drug discovery represents the first step in the creation of new drugs, and takes place in academic institutions, biotech companies, and large pharmaceutical corporations. With the rise of translational research these relationships are shifting and new hubs are emerging, as key players seek to pool the expertise necessary to generate new therapies by linking laboratory discoveries directly to unmet clinical needs.

Keywords: Translational Pharmacology, Drug Discovery, Applied Research.

INTRODUCTION

An untold number of scientists, doctors, researchers and public practitioners go to the work every day hoping to make difference in people's health. They spend lifetime trying to find the best way to prevent heart disease, cancer, motor vehicle crashes, HIV infections, obesity, and hundreds of other public health problem. What would you say if you know that many of the effective strategies to prevent these problems never got used? Sadly this is what happens in public health. The best scientific discoveries often do not make it into practice setting and those that do take more than a decade to get there.

Failure to address the chasm between research and prevention practice not only means we have poorly invested in programs or strategies that are underutilized or not utilized at all, it also means we are failing to harness the best existing science to prevent illness ,injuries, disabilities and death.

Internationally pharma sector spend billions of money each year in both the public and private

sectors on biomedical, clinical, and health services, undergraduate healthcare professional training and continuing professional development, quality improvement, patient safety, and risk management. Even though our pharma sector and healthcare systems fail to ensure that effective and cost-effective programs, services, and drugs get to all of those who need them; and healthcare professionals fail to provide the level of care to which they aspire. One of the most consistent findings from clinical and health services research is the failure to translate research into practice and policy.

Translational medicine and translational pharmacology are the terms increasingly used to describe the focus of applied pharmacological research to ultimately help patients. Yet, the number of effective medicines reaching the approval stage continues to decline. Current investment efforts in pharmaceutical R&D have not warranted serendipity, nor provided a solid basis for the selection of candidate molecules that yield the expected performance in humans. Such a translational gap in drug research has many historical causes, many of which remain entrenched into the scientific rationale currently used for the generation of empirical evidence (1). First, it should be noted that improvement in the translation between pre-clinical (basic) and clinical stages in the R&D process requires a shift away from the industrial setting used in drug discovery and development. Second, some tenets of science cannot be ignored in translational research. The sharply contrasting trends of investment and productivity have gained significant attention and have led the key sectors involved to re-examine their practices and their relationships with one another (2, 3). A changing paradigm for the development of new drugs is emerging, captured by the current buzzword 'translational research'. This new approach is based on directly matching ideas for new therapies with the needs of patients as observed in the clinic, and represents a more focused strategy for creating new drugs than the traditional model. In this review I will discuss how these different institutions are embracing translational research and are re-organizing their relationships with one another to increase the efficiency of bringing new drugs to market.

Non-clinical pharmacological studies, including primary pharmacology, secondary pharmacology and safety pharmacology (SP), are an essential element of the drug discovery and development process. Unlike primary and secondary pharmacology studies that explore the mode of action of the candidate drug and its effects related or unrelated to the therapeutic target, respectively, Safety pharmacology identifies the "potential undesirable pharmacodynamic effects of a substance on physiological functions in relation to exposure in the therapeutic range and above" (4) which are not identified by standard non-clinical toxicological studies.

DEFINING TRANSLATIONAL RESEARCH

Increasingly, the field is recognizing the need to enable a closer collaboration of industry and academia to create a more efficient system for developing new drugs (5,6). In parallel with this, the world of drug discovery has seen the emergence of translational research as an alternative approach to the creation of new drugs, and there is growing support for the claim that this strategy may provide solutions to some of the woes of the pharmaceutical industry (7,8).

The relationship between dose, systemic exposure, and both safety and efficacy are the most important elements in biopharmaceutical/ drug development. In order to proceed successfully through clinical development, it is necessary to accurately assess and demonstrate a favorable risk/benefit relationship at each milestone. Results of the preclinical pharmacology-toxicology program are submitted to the FDA as part of an Investigational New Drug (IND) Application to support the proposed first-in-human clinical trial. The focus of the FDA's clinical reviewers when assessing a Phase I IND application is whether the first-in-human clinical study is designed to demonstrate safety in a small number of subjects without putting these subjects at unnecessary risk.

Although safety is the main focus in the preclinical studies and early clinical trials, the sponsor should also be thinking in terms of defining the relationship between dose, exposure and efficacy. Contemporary Phase 2 clinical trials most often fail because

insufficient attention was paid to accurately translating preclinical efficacy findings to clinical doses that are not just safe, but have a high chance of demonstrating efficacy (9, 10), In fact, the incidence of failure due to efficacy in Phase 2 clinical trials is actually increasing based on an analysis of 2008-2010 data. Analysis of Phase 3 trial failures between 2003-2007 indicate that ~45% are unsuccessful because of failure to demonstrate efficacy compared to placebo (11). These data for Phase 2 & 3 failures are very sobering to CEOs and investors when considering the prospects for success and return on investment.

Translational research, translational medicine, and translational science are often used synonymously, and the term 'translational' has been used to generate a variety of other disciplines such as translational genomics (12), translational psychiatry (13), translational bioinformatics (14), and translational neuroscience (15). The common element among these is the notion of translating discoveries in the laboratory into new clinical therapies. Often described as research 'from bench to bedside and back again' (16), translational research is based on the concept that the creation of new drugs should relate directly to patient needs and should couple laboratory research with observations made in the clinic.

The hallmark of the translational approach to drug development is that it incorporates the target of a specific unmet clinical need from the outset. Unlike traditional research-based discovery, which seeks to understand basic cellular mechanisms and apply these learning's to design new therapies, translational research targets mechanisms underlying clinically relevant problems and designs drugs to address those issues directly. At its broadest, translational research encompasses three principal components: laboratory research, clinical practice, and population effects in the community. These are often described in a two-stage process, termed T1 and T2, which refer to laboratory-to-clinic and clinico- community stages, respectively (17).

By focusing drug design and testing stages on the defined goal, translational research represents a streamlined approach with the potential to yield new drugs faster than the traditional drug development, and with a greater probability of success in the defined patient population.

THE FUTURE OPPORTUNITY

We view preclinical and clinical PK/PD studies as a continuum that permits optimal translation of dose from animal studies to clinical trials and finally to clinical practice. PK/PD analysis should not be performed as an afterthought or simply to meet regulatory requirements, but rather must be carried out with careful planning from early development through product approval. The fundamental principle of translational pharmacology is to design pharmacokinetic and toxico-kinetic studies in the preclinical setting and early Phase 1 clinical trials with the purpose of accurately and effectively modeling the dosing so that critical clinical trials maximize their chance of success with respect to both safety and efficacy. Therefore, the goal of translational pharmacology is not simply to design preclinical studies to demonstrate safety for first-in-human clinical administration, but to design studies that, together with Phase 1 clinical data, will be used to maximize the chances of success in the Phase 2 and Phase 3 clinical trials. It is worth noting that preclinical, first-in-human and other Phase 1 studies can be particularly well suited to PK/PD analyses since a wide range of dose levels are often assessed and blood sampling tends to be intensive (data rich). Furthermore, depending on the therapeutic area, biomarker data can be incorporated into such studies relatively easily and biomarkers can play a role in bridging animal and human pharmacology, toxicity/safety evaluation, dose selection, patient selection. The use of biomarkers can be an integral part of reducing the risk of Phase 2 trial failure (18).

Later in clinical development, we utilize data gathered across clinical trials to characterize the relationships between dose, safety, efficacy, biomarkers and key population covariates. These data are used to help define dosing guidelines for use in clinical practice following approval.

Many of the departments, centers, and institutes identified as having translational departments are involved in collaborations between different organizations, frequently including academic institutions and hospitals. These relationships represent the core of translational research in

facilitating access between clinicians treating patients and bench scientists exploring mechanisms of drug action. The diverse use of 'translational' in these departments' names or projects reflects a range of different objectives, which broadly can be categorized into T1 and T2 research. T1 departments reside primarily in universities or other institutes of higher learning, and focus on the laboratory discoveries that relate to specific clinical endpoints. Idea generation for new drugs and the earliest stages of drug discovery occur in these T1-oriented departments, which enable laboratory scientists to team together with practicing physicians who provide input into clinical practices for different diseases, and who can perform early stage clinical trials on new drugs. Similarly, as the clinicians discover significant unmet needs among their patients, these centers allow them to brainstorm directly with laboratory researchers, and to devise potential solutions or plan projects that determine the underlying molecular mechanisms.

T2 departments integrate community outreach programs with clinical practices, with the aim of providing a means for understanding how well treatment strategies are working at a population level. Fewer departments appear dedicated solely to T2 rather than T1 research, although this may reflect a lower tendency to publish in the scientific literature, issues related to patient confidentiality or ability to obtain NIH-funded grants. T2-focused centers can relay medical issues in the community to physicians, leading to the adoption of improved treatment paradigms.

HOW TO ACHIEVE THIS FROM HERE

The importance of preclinical and clinical pharmacokinetics to designing a successful clinical trial design cannot be overemphasized. The expense associated with PK/PD analysis and modeling is trivial compared to the cost of failed clinical trials and the potentially devastating consequences for small companies. Therefore, the careful planning of a translational pharmacology program that spans preclinical through clinical studies and provides information that maximizes the chances of success in the clinic is a service that adds great value to a clinical development program for a biopharmaceutical or drug.

Accordingly, our approach is to establish a program that utilizes state-of-the-art PK/PD analysis and modeling that will target and optimize the likelihood of demonstrating efficacy as early as possible in clinical testing. Application of pharmaco-metrics across the entire development life cycle is critical to:

1) The design and execution of a preclinical pharmacology-toxicology program;
2) The design and execution of successful clinical trials;
3) Achieving a positive benefit/risk balance supporting licensure;
4) Establishing an effective post-marketing and pharmaco-vigilance program.

Thus, PK/PD models are becoming increasingly critical knowledge-building tools, not only for late phase clinical trials, but throughout the entire drug development process.

Biologics Consulting Group consultants welcome the opportunity to bring their unparalleled depth and breadth of experience to navigate the major challenges inherent in the development pathway to new therapeutic drug/biopharmaceutical licensure.

PRE-CLINICAL AND CLINICAL PHARMACOKINETICS/PHARMACODYNAMICS STUDIES

Pre-clinical and clinical PK/PD studies permit optimal translation of dose from animal studies to clinical trials and finally to clinical practice. PK/PD analysis shouldn't be performed as an afterthought or simply to meet regulatory requirements, but rather carried out with careful planning from early development through product approval.

The fundamental principle of translational pharmacology is to design PK and toxico-kinetic studies in the pre-clinical setting and early phase I clinical trials with the purpose of accurately and effectively modeling the dosing so that critical clinical trials maximize their chance of success with respect to both safety and efficacy. The goal of translational pharmacology is not simply to design pre-clinical studies to demonstrate safety for first-in-human clinical administration, but to design studies that, together with phase I clinical data will be used to maximize the chances of success in the phase II and phase III clinical trials.

Pre-clinical, first-in-human and other phase I studies can be particularly suitable to PK/PD analyses since a range of dose levels are often assessed and blood sampling tends to be intensive (data rich). Depending on the therapeutic area, biomarker data can be incorporated into such studies easily and biomarkers can help bridge animal and human pharmacology, toxicity/safety evaluation, dose selection, patient selection. The use of biomarkers can be an integral part of reducing the risk of phase II trial failure. Later in clinical development, data gathered across clinical trials can characterize the relationships between dose, safety, efficacy, biomarkers and population covariates.

This data helps define dosing guidelines for use in clinical practice following approval. Biomarkers play a key role in accelerated approval. There is a need and a critical role that PK/PD assessments and modeling can play in increasing the chances for success in the development process. Particularly for an oncology drug, it's a therapeutic area that has one of the highest failure rates (estimated at 90 per cent).

CONCLUSION

Academia, biotech companies and pharmaceutical corporations are embracing translational research for its potential to increase the number of drugs successfully brought to market. Acknowledging the need for greater collaboration between these different sectors, substantial investments have been made by the National Institutes of Health (NIH) and the pharmaceutical industry, Nonetheless, translational research clearly represents a dominant new strategy across the field of drug discovery, and the next decade will most probably see significant changes in the relationships between academics, biotech companies, and pharmaceutical corporations.

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