Review Article

Translational pharmacology: role and its impact

Sumit Kumar*, Bhagya M. Sattigeri

Department of Pharmacology, SBKS MI and RC, Vadodara, Gujarat, India

*Correspondence:
Dr. Sumit Kumar,
E-mail: drsumit.kumar@yahoo.com

ABSTRACT

Translational Pharmacology is a newly evolved branch as an extension of clinical pharmacology. Translational Pharmacology aims to move the results of the molecular pharmacological research to the patient level, which is focussed on developing the new drug that correlates with the patient needs. The basic objective is to study the changing trends from experimental to clinical pharmacology. It also helps to gather data from the preclinical studies, so as to have accurate and effective dosing in the critical clinical trials. Thus, we can conclude that Translational Pharmacology tries to bridge the gap between the basic molecular research studies in pharmacology to the clinical trials. This also reduces the time and economic burden on research. Thus, it helps in translating the knowledge from the basic animal studies to the bedside patient studies.

Keywords: Clinical trial, Translational, Molecular pharmacology

INTRODUCTION

In the present days with advancement in field of science and technology research has greatly progressed. Despite of the progress, there has been delay in introduction of a new drug into the market and difficulty in successful implementation of it in the clinical use. Hence, an integration in the field of basic science, its use in clinical practice and its application in the community at large scale. This is possible with the evolution of translational pharmacology as an extension of clinical pharmacology.

Clinical pharmacology: translational pharmacology

Clinical pharmacology was found by Harry Gold in 1950s which involved scientific study of drugs in man, their rational use, safety, efficacy, cost and benefit availability and personalized medicines. It contributes to the development of new drugs, clinical research, and clinical trials for new drug regimes rational use of medicines, pharmacogenetics, pharmacoeconomics and pharmacovigilance. Academic institutions, the pharmaceutical companies and the institutions such as Council for Scientific and Industrial Research (CISR), the World Health Organization (WHO) and Indian council of Medical Research (ICMR) all contributes to the various branches of clinical pharmacology.[1]

The basic biological research work undertaken at various institutions, government organizations such as National Institute of Virology, National Institute of Immunology etc. may be found to be inadequate in product development. With all efforts taken by the government there exists a gap between the need, development and the availability of the medicines. As suggested by the pioneer of clinical pharmacology from UK, Dr CT Dollery, the development of experimental and translational medicine contributing to personalized medicine serve as a support to pharmacotherapy education of the medical students and the practioners.[2] It would further contribute in the

growth of clinical pharmacology and such growth in clinical pharmacology would enable to develop expertise training in developing safe and effective economic products for healthcare management in the country particularly in the rural and developing areas.

Advanced information technology and nano technology are the fields that are currently considered as newer technologies in focused research and targeted therapy as a solution for many areas of healthcare management. Thus, clinical research and translational medicine units should be essentially set up to carry out the proof of concept studies which will be further confirmed through translational studies in the form of medical college networks, hospital studies, specialized database studies and disease based studies.

Translational pharmacology: pharmacoeconomics

Globally the estimates on the drug development have shown an unsustainable economic status pandemic. The exponential inflation on the expenses incurred is exemplified on pharmacotherapy which is expressed as cost effective component in treating a disease. The treatment that costs few hundred dollars two decades ago is replaced with the new drugs which cost in excess hundreds of thousands of dollars adding to the economic burden in treating the same disease conditions.[3,4]

Far beyond the established pharmacotherapy of various medical conditions many diagnostic and therapeutic products of uncertain impact are offered to the patients that are known to concourse with several factors such as the ageing process, unestablished clinico-pathological correlation etc. In such instances translational medicine would be dynamic to meet the optimum healthcare requirements that range from diagnosis, therapeutic strategies, discovery and development of drug.

However, there is a potential for translational medicine to add economic stress in clinical management of the condition with the existing over burdened health care system which makes it difficult to understand whether there is an adequate evidence to adapt all the changes into the clinical practice.

It integrates the disease pathophysiology with the disease management based on targeted diagnostics and therapeutics. Thus, it is pivotal in linking between the laboratory to the patient and the population.[5] On integration it has been possible to apply the translational molecular insights and biological innovations into the clinical practice and the case management. Further, it has provided tools to define the underlying disease initiation, its progression, diagnosis and therapeutic management. Thus, translational medicine is pivotal in quantifying molecular diagnostic aspects, their clinical outcomes, therapeutic response and idiosyncratic behaviour.

Translational pharmacology: transformation of health care

The integrated personalized therapy is tailored based on the genetic profiles, diagnosis and therapeutic specificities thus benefitting the community to the maximum with minimum adverse effects. Personalization has thus become a part of daily practice.[6-9] With the application of the translational medicine, it has been possible to bridge the disease management from palliation to cure. Such transformation with integration from the basic science along with research and pharmacotherapy of the clinical condition has reached beyond the individual patient to the global population.[6,7]

It anchors the principle with evidence-based case management and adds value to the treatment of individual patient, population society and the health care system. The genotyping and phenotyping would enable to identify the individual at greater risk for the adverse drug reactions, which would enable to focus on the safety measures in the therapy of the given clinical condition. Whereas, for academia this transformation encourages the individuals in the field of research, to test their novel ideas, that are generated from basic investigation hoping for their clinical applications. While for physicians or the clinical practioners it facilitates to capture the research benefits and to understand what is known and what is practiced. While, as for the commercial pharmaceutical industry it measures assessment of the new entities at earlier phases, to identify the problems early, so as to solve them at an early stage to reduce the cost of product development.

With the evolution of science and technology, translational pharmacology has evolved as a new branch to meet today's healthcare need and is considered as an extension of clinical pharmacology.[10] Translational Pharmacology, translational research and translational medicine are the interchangeable terminologies where the word translational focuses on development of a new drug which deals with the patient needs and targets to deal the specific issues.[11] It has varied roles and applications in the present era in aspects to the drug development, which tries to bridge the gap between the basic science i.e. molecular pharmacology and extends to reach the patient requirement to heal the relevant clinical problems. It covers the areas of molecular research, animal experimentation and their application with reasoning in patients to treat the clinical condition. It is a rapidly growing discipline that aims to expedite newer diagnostic and therapeutic measures being highly collaborative ranging with research work from laboratory to patients.

Such translation would focus on ensuring with evidence based proven strategies in management and prevention of the clinical conditions which can actually be implemented within the community. Hence, translational pharmacology is a bridge between the bench to the

bedside, which caters to the need of patients and specific therapeutic areas as indicated in Figure 1.[12,13]
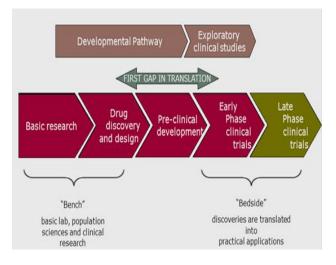

Figure 1: Bridging of basic science to clinical practice.

As defined by the European society for translational medicine the term translational research is an inter-disciplinary branch of a biomedical field that are greatly supported by three main pillars bench side (laboratory research), bed side (clinical practice) and the community (population needs).[14] Such kind of integration and inter-disciplinary research is useful to qualify the efficacy of drug molecule introduced along with which one gets to know the limitation in the use of introduced molecule.

Translational Pharmacology encompasses three principal components such as the laboratory research, clinical practice and the population needs in the community which are often described as two stage process that refers to laboratory to clinic and clinic to community with the main objectives to identify the relevant problems and design the drugs to address the specific therapeutic issues directly. Hence, translational pharmacology can be appropriately used to describe successful integration of the scientific discoveries with their clinical application in treating various diseases of the human beings.[15]

The objectives of translational pharmacology are to discover the origin, pathway and mechanism of the diseases including the responsible biomarkers, to discover and develop new diagnostic and therapeutic measures and to discover the newer drugs in short duration of time. The translational pharmacology includes the pharmacokinetic and pharmacodynamic modelling in translational research that provides better understanding as per the drug efficacy and safety. The mechanism based pharmacokinetic and pharmacodynamic models would describe the drug specific properties and system specific property which include the routes of drug administration, drug exposure, plasma protein binding, unbound concentration species dependent variation metabolism of the drug, active metabolites of the drug, dosing schedule and difference

between the concentration of the drug used and its response. The drawback with the basic science research with experimental pharmacology lies in reproducibility of the findings. The success rate of which is being reported as low.[16] This problem could be attributed to poor specified methods variation in the behavioural methods poor post hoc analysis or the significant statistical finding. Thus, quantitative pharmacology studies will help to analyze the concentration response and the response time relationship with special impact of the drugs on the target disease. The translational pharmacology thus involves 5 major steps such as[17]

- Basic research with the drug discovery and designing the molecule and study the physiochemical properties of the designed molecule in relation to the biology,
- The preclinical development includes the study on its pharmacodynamics, pharmacokinetics, toxicology and the safety concern, all these are performed on the experimental animals.
- Establishing the relation between the observations made at the pre clinical studies with the early clinical trials which would involve the healthy volunteers.
- Evaluation of the gathered data from the early clinical trial in terms of dose, safety, efficacy so as to formulate the guidelines for their use in clinical practice.
- Lastly, to bring the result of basic research by minimizing their adverse effects and benefitting to treat the focussed cause.

In translational research, the bench side study includes; in-silico studies, *in-vitro* studies and *in-vivo* studies. In-silico studies have the potential to speed the rate of discovery of a new molecule which reduces the need for expensive laboratory work and clinical trials for e.g. in 2010 using protein docking algorithm EADock, potential inhibitors to an enzyme associated cancer activity were found by in-silico studies, 50% of which were shown to be active inhibitors through the in-vitro studies.[18] Similarly, in 2007, an in-silico model of tuberculosis that aided faster drug discovery to benefit than its real time (in minutes to rather than month), which was achieved by computer model of cellular behaviour.[19] Thus, the virtual screening cell models, digital genetic sequence all may be used for in-silico studies. The in-silico models include developing and validating complex mathematical models that are capable of reflecting the human diseases and response to the therapeutic intervention. The results obtained then can be refactored into integrated mathematical models which may enhance their translational potential.

Hence, the translational research would be helpful to prepare a model based on the pharmacokinetic and pharmacodynamic studies so that the safety and efficacy of newly introduced drug can be assessed prior to its use in the clinical trials.[20,21] This can be achieved with the

help of the mathematical tool called pharmacometrics, which is a branch of science that involves mathematical models of biology, pharmacology and disease. It also helps to describe the interaction between the xenobiotics and the patients which may include beneficial and harmful effects.[22,23]

Considering the safety and efficacy of any newly introduced molecule the translational pharmacology also further considers the relationship between the doses, systemic exposure its effects with the maximum benefit and minimum adverse effects.[21] Therefore, a careful study and a proper bridging from preclinical to clinical helps a proper translation of the research from the bench to the bedside, so as to get focussed benefit from the targeted clinical condition. Thus, eventually the translational pharmacology will be helpful in maximizing the chances of success of a new drug development. Thus, successfully helping evaluation of the newly developed drug balancing the positive benefit and the risk involved in the developed drug. It also helps in achieving effective post marketing surveillance.

However, the scientific problems, the ethical issues regulatory concerns inadequate financial support, shortage of investigators, inadequate samples, conflict of interest, right to privacy, fragmented poor infrastructure, incompatible databases and public support would be the major limitations in translational pharmacology. Lack of incentives on translational research in academia differentiates with the group of researchers in industry with large financial incentives in translational research. Therefore, indicating excessive expenditures by the industries in translational research as compared to academia.

CONCLUSION

Development of a new drug has been expensive and a long process yet unclear about the fate of the developed molecule. Translational pharmacology benefits with the translational medicine by focussed research and a plan for a new drug project. Use of database translates to reduce the cost involved and reduce the time for the drug development.

Thus, it helps to combine firmly the principles of basic and clinical pharmacology with the modern research technologies, so as to provide a proper bridge with the basic molecular pharmacological research in the research field and provide opportunities to the academic centres to commercialize their discoveries.

ACKNOWLEDGEMENTS

REFERENCES

1. Kshirsagar NA. History of clinical pharmacology in India: A brief account. In: Patil PN, Gulati OD, Balaraman R, editors. Chapter in the book on 'Topics in the History of Pharmacology'. Ahmadabad, India: Publisher RK Goyal;2005:148-69.
2. Dollery CT. Clinical pharmacology-The first 75 years and a view of the future. Br J Clin Pharmacol. 2006;61:650-65.
3. Hay JW. Using pharmacoeconomics to value pharmacotherapy. Clinical Pharmacology and Therapeutics. 2008;84(2):197-200.
4. Pizzi LT, Singh VP. Pharmacoeconomics is coming of age. Clinical Pharmacology Therapeutics. 2008;84(2):188-90.
5. Lesko LJ. Paving the critical path: how can clinical pharmacology help achieve the vision? Clinical Pharmacology and Therapeutics. 2007;81(2):170-7.
6. Woodcock J. The prospects for "personalized medicine" in drug development and drug therapy. Clinical Pharmacol Therapeutics. 2007;81(2):164-9.
7. Cortese DA. A vision of individualized medicine in the context of global health. Clinical Pharmacol Therapeutics. 2007;82(5):491-3.
8. Wagner JA, Williams SA, Webster CJ. Biomarkers and surrogate end points for fit-for-purpose development and regulatory evaluation of new drugs. Clinical Pharmacol Therapeutics. 2007;81(1):104-7.
9. Waldman SA, Terzic A. Pharmacoeconomics in the era of individualized medicine. Clinical Pharmacol Therapeutics. 2008;84(2):179-82.
10. Anger GJ, Piquette-Miller M. Translational pharmacology: harnessing increased specialization of research within the basic biological sciences. Clin Pharmacol Ther. 2008;83(6):797-801.
11. Khoury MJ, Gwinn M, Yoon PW, Dowling N, Moore CA, Bradley L. The continuum of translation research in genomic medicine: how can we accelerate the appropriate integration of human genome discoveries into health care and disease prevention? Genetics in Medicine. 2007;9(10):665-74.
12. Ledford H. Translational research: the full cycle. Nature News. 2008;453(7197):843-5.
13. Disis ML, Slattery JT. The road we must take: multidisciplinary team science. Science translational medicine. 2010;2(22):22cm9.
14. Cohrs RJ, Martin T, Ghahramani P, Bidaut L, Higgins PJ, Shahzad A. Translational medicine definition by the European Society for Translational Medicine. 2015:86-8.
15. Woolf SH. The meaning of translational research and why it matters. JAMA. 2008;299(2):211-3.

16. Begley CG, Ellis LM. Drug development: Raise standards for preclinical cancer research. Nature. 2012;483(7391):531.

17. Curry S, McCarthy D, DeCory H, Marler M, Gabrielsson J. Phase I: the first opportunity for extrapolation from animal data to human exposure. Principles and practice of pharmaceutical medicine. 2nd ed. West Sussex: Wiley. 2007:79-100.

18. Ludwig Institute for Cancer Research. New computational tool for cancer treatment. Science Daily. 2010.

19. University of Surrey. In Silico cell for TB Drug Discovery. ScienceDaily. 2017. Retrieved on February 12, 2010.

20. Hurko O. The uses of biomarkers in drug development. Annals of the New York Academy of Sciences. 2009;1180(1):1-0.

21. US food and drug administration. FDA guidance for industry: estimating the maximum safe starting dose in initial clinical trials for therapeutics in adult healthy volunteers. 2005.

22. Barrett JS, Fossler MJ, Cadieu KD, Gastonguay MR. Pharmacometrics: a multidisciplinary field to facilitate critical thinking in drug development and translational research settings. J Clinical Pharmacol. 2008;48(5):632-49.

23. Rosenblum D, Alving B. The role of the clinical and translational science awards program in improving the quality and efficiency of clinical research. CHEST J. 2011;140(3):764-7.