Translational and Reverse Pharmacology

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Abialbon Paul

Abstract

Translational pharmacology is the branch of pharmacology that deals with the application of results from molecular and preclinical research into clinical practice. Translational pharmacology aims to reduce the high failure rate of drug development process, thereby reducing the cost and time required for bringing a new drug to the market. It does this by elucidating the target properly, improving the predictive value of early preclinical trials and optimizing dose selection. Reverse pharmacology is the field of drug discovery where the drug targets which might act as critical intervention points in the pathogenic process of diseases are first identified and characterized. Reverse pharmacology aims to characterize the target first and fish for an appropriate ligand.

Keywords

Translational pharmacology · Reverse pharmacology · Drug discovery

22.1 What Is Translational Pharmacology?

Translational pharmacology is the branch of pharmacology that deals with the application of results from molecular and preclinical research into clinical practice. In essence, translational pharmacology helps translate the results obtained in the laboratory into clinically meaningful practices. This helps in increasing the number of drug candidates that will succeed as marketable drugs and decrease the number of drug candidates that will fail later in the drug development process, hence, speeding up the drug development process.

A. Paul (✉)
Department of Pharmacology & Clinical Skills, Medical University of Americas, Charlestown, Nevis, Saint Kitts & Nevis, West Indies

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22.2 Why Translational Pharmacology?

- Increased cost of the drug development process.
- High failure rate of the traditional drug development process.
- Poor reproducibility of results from molecular research and other preclinical animal studies.
- Failure to pick up important toxicities observed during the post-marketing surveillance in the preclinical phases.
- The major reason for a drug to fail during the later stages of drug development process is lack of efficacy.

22.2.1 Reasons for Poorly Reproducible Results from Preclinical Testing

- Poorly written methods.
- Not quantifying the context where the tools work.
- Statistically underpowered studies.
- Less rigorous experimental designs.
- Non-suitability of the models being tested.
- No consideration for the presence of comorbidities in the disease process.
- Inadequate modelling from animal to human pathophysiology.
- *P* hacking refers to the process of analyzing data to show statistically significant results, while no such effect exists in reality.

22.3 Main Objectives of Translational Pharmacology

- Improve the predictive value of the tools that assess the success or suitability of drug candidates during preclinical research.
- Bring down the costs of the drug development process.
- Shorten the time frame for bringing a new drug into the market.
- Decrease attrition of the drug candidates late in the drug development process.
- Predict the response of the drug in the diseased population including adverse drug reactions, mode of resistance and long term toxicity.

22.4 Processes of Translational Pharmacology

22.4.1 Better Target Elucidation

- The molecular target is better elucidated with the help of genomic databases and high-throughput assays. The role of the receptor in the pathogenesis of the disease has to be fully understood to create drugs with higher efficacy and lesser side effects.

- Availability of genetic libraries helps in the computational discovery of receptors and receptor structures to be tested as molecular targets in specific pathogenic processes.

22.4.2 Improving Predictive Value of Early Preclinical Trials

The predictive value of early preclinical trials can be improved by:

- Chip-based genetic assays that can improve the accuracy and speed of detection
- Human cell lines instead of small animals
- Better mathematical modelling of pharmacokinetic data from smaller animals to humans
- Improving the disease model to emulate all characteristics observed in the clinics
- In silico studies to better characterize the drug receptor binding and potential off-target side effects

22.4.3 Dose Selection

- Use of in silico assays and mathematical modelling helps in the selection of appropriate dose ranges to be tested in human volunteers thereby helping to increase the efficacy of the drug tested while reducing the number of adverse drug reactions.

22.5 Hurdles to Translational Pharmacology

Some of the hurdles in the deployment of translational pharmacology processes are as follows:

- Lack of cooperation among researchers
- Inadequate financial support
- Difficulties with the use of some genetic databases

22.6 Reverse Pharmacology

Reverse pharmacology is the field of drug discovery where the drug targets which might act as critical intervention points in the pathogenic process of diseases are first identified and characterized. It is followed by high-throughput screening of large chemical libraries to identify suitable chemical ligands with high affinity and specificity for the chosen drug target. Reverse pharmacology is also called as *target-based drug discovery (TDD)*.

22.6.1 Basic Steps in Reverse Pharmacology

- **Target Mining**
  - A suitable receptor target that could play a role in altering the course of the disease in question is identified.
  - Bioinformatics and data from the human genome project are used to computationally compare DNA sequences and three-dimensional protein structures to find novel targets.
  - Targets can also be identified by clinical observation of the effects of various drugs used in alternative medicine like in Ayurveda.
- **Ligand fishing**
  - Ligand-binding studies are carried out with large chemical libraries to find suitable candidates that will bind to the target with higher affinity and specificity.
  - Promising candidates are then subjected to chemical modification, and their biological action is assessed through cellular assays.
  - The final drug candidate is then tested in animals, and extensive clinical trials are done.

22.6.2 Differences from Classical or Forward Pharmacology

- The initial step in classical pharmacology is the identification of functional activity of a compound.
- The mechanism of action of the drugs is elucidated, and proof of concept studies are done to confirm its beneficial activity.
- The molecular target is identified, and further drug candidates may be screened for better affinity and specificity to the target.
- The compound is then modified for better selectivity and pharmacokinetics.
- Preclinical and clinical testing is done before the drug is released in the market.

22.6.3 Advantages of Reverse Pharmacology over the Conventional Approach

- Increased speed of drug delivery
- Better chances of success in clinical trials as the affinity and specificity of the drug to the target are better established
- Decreases drug discovery costs
- An efficient process of drug discovery compared to the traditional method of drug discovery

22.6.4 Reverse Pharmacology and Ayurveda

- Drug discovery from natural products greatly utilizes the process of reverse pharmacology to discover new drugs for clinical use and large-scale manufacturing and marketing.
- Since these preparations already have a known clinical application, the extracts are tested for potential molecular targets they modulate to produce beneficial clinical action.
- Once the receptor is identified, the active principle responsible for eliciting a response from the receptor is identified and modified to make a better drug candidate that can be tested for marketing.
- Examples of application of reverse pharmacology in Ayurveda:
  - *Mucuna pruriens* for Parkinson's disease
  - *Zingiber officinale* for nausea and vomiting
  - *Picrorhiza kurroa* for hepatitis
  - *Curcuma longa* for oral cancer
  - Panchvalkala for burns and wounds
  - *Azadirachta indica* for malaria

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