Preclinical Pharmacology and Toxicology: an Important Aspect in Drug Discovery

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Abstract

It is imperative to have safety and efficacy evaluation completed for a test compound before proceeding to translate for clinical trials. Preclinical pharmacology and toxicological studies play an essential role for providing particulars to design clinical studies to determine whether the test compound is as efficacious and safe in humans as it was observed in animal studies. Study performed in preclinical setting includes determination of safety, efficacy, tolerability and toxicity for the test compound. These studies help to propose a safe and efficacious startup dose for human studies. Furthermore, it won't be wrong to state that without these preclinical pharmacological and toxicological studies it is not possible to strategize and design clinical trial in humans.

Keywords: Pharmacology; Toxicology; Preclinical; Drug discovery; Translational studies; Hits; Lead

Abbreviations: ADME: Absorption Distribution Metabolism Excretion; GLP: Good Laboratory Practice; PK: Pharmacokinetic; TK: Toxicokinetic; PD: Pharmacodynamic; AUC: Area Under Curve; IND: Investigational New Drug; NDA: New Drug Application

Introduction

Drug discovery is a long term process broadly divided into four stages- it initiates with drug candidate screening and lead identification; this is followed by safety and toxicity evaluation in preclinical setting which eventually helps to design clinical trials and finally regulatory body approval of the drug before it can be launched. This entire procedure could take around 15 years before a final FDA approved drug could reach market [1-5] (Figure 1). Drug development process starts with screening for thousands of molecules which might end up with few or just one FDA approved drug that will be available commercially. Most of the time, many potent drug candidates cannot clear clinical trials in different phases due to efficacy or toxicity issues during the study [6]. It is extremely important to have the drug candidate appropriately tested for its

efficacy and toxicity in a relevant test system during preclinical evaluations which eventually help to design accurate dose, regimen and test condition for human studies.

Figure 1: Drug discovery process at a glance.
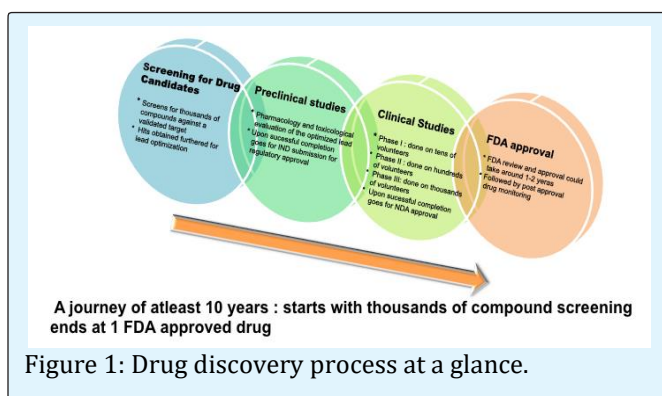
Discussion

As depicted below in (Figure 1), drug discovery is an interdisciplinary research work involves studies from chemical characterization, drug candidate screening to

evaluation of biological potency first in animals followed by human studies. Even after so many years of research work and huge investment, there is no assurance that the drug will clear clinical trials successfully or will get FDA approval.

Screening for drug candidates

This starts with screening for "hit" molecules against a particular target. Usually these molecules are some sort of inhibitors against the biological target in question. Before starting with screening, target validation is extremely important to confirm the significance of the protein for the given disease condition [7,8]. Not only understanding the role of target in a given disease condition is essential but it is also important to have a relevant drug screening system before proceeding with drug molecule selection. This drug screening could be an *in vitro*, *in vivo* or in silica test system. The therapeutic target chosen for screening purpose should have shown or reported to have biological relevance in the human disease. High throughput screening is a technology that allows assaying for large repertoire of biological modulators against a specific target [9].

Lead optimization

Following the primary screening for "hits", the candidate drug needs to be further confirmed by lead optimization steps. Lead optimization is a very crucial step to confirm the efficacy of the drug candidate against the biological target in question by primary and secondary screening assays. These would include preliminary *in vitro*, *in vivo* efficacy and toxicity, mutagenicity studies along with ADME (Absorption Distribution Metabolism Excretion) profiling and lead characterization. Lead characterization would include analysis of formulation stability, impurity and active ingredients [10-14]. Lead optimization is followed by preclinical studies for detailed non GLP and GLP pharmacology, toxicity, mutagenicity profiling along with pharmacokinetic (PK) and toxicokinetic studies (TK).

Preclinical studies

Pharmacological studies gauge biological effect, efficacious dose range and overall potency of the optimized lead. It is very important to perform all pharmacological studies in relevant in vitro and in vivo test system, which has closest resemblance to human disease condition. These studies give a further understanding into the mechanism of action of the lead and an in depth understanding of the drug action by pharmacodynamic (PD) studies. Whereas a PK study gives

a detailed insight on drug distribution in different organs of study animals post drug treatment; toxicity studies support toxicity profiling and safety evaluation for the drug candidate which includes a battery of in vivo and in vitro mutagenicity studies; animal toxicity studies in two species [15-17]. Single dose acute studies could help determine the drug wash out period and its correlation with signs of toxicity, if any. Whereas repeated dose TK studies helps determining drug tolerability dose range from area under curve (AUC) of drug plasma level [18]. These results eventually help to determine no-adverse-effect-level (NOAEL) and maximum tolerated dose (MTD) for the drug which ultimately helps in calculation for a safer and potentially effective start up dose regimen for human studies [19].

Depending on indication, drug target population, duration and frequency of the drug consumption, toxicity evaluation can be further extended to other repeated dose studies like chronic or sub- chronic repeated dose studies. If drug usage covers people of reproductive age group then animal reproductive segment studies needs to be conducted [20]. Based on results obtained from preclinical assessments viz. pharmacological safety, efficacy, ADME and toxicological profile of the drug, clinical phase studies are designed and IND (Investigational New Drug) filing is done which needs approval from regulatory bodies like FDA before the drug gets permission for clinical trials.

Conclusion

Drug discovery is a very long process which starts from biological target identification relevant to human disease condition till IND filing followed by clinical trials, before it gets approved for ultimate market launch. Preclinical studies play an inevitable role in deciding and designing clinical studies which only gets approval based on preclinical assessments on pharmacology and toxicology profile of the drug. This needs interdisciplinary collaborative research work which eventually helps to design a safe and efficacious start up dose for human studies.

References

1) Steinmetz KL, Spack EG (2009) The basics of preclinical drug development for neurodegenerative disease indications. BMC Neurol 9(S1): S1-S2.

2) Dahlin JL, Inglese J, Walters MA (2015) Mitigating risk in academic preclinical drug discovery. Nat Rev Drug Discov 14(4): 279-294.

3) Whiteside GT, Pomonis JD, Kennedy JD (2016) Preclinical Pharmacological Approaches in Drug Discovery for Chronic Pain. Adv Pharmacol 75: 303-23.

4) Chung TD (2014) Collaborative pre-competitive preclinical drug discovery with academics and pharma/biotech partners at Sanford| Burnham: infrastructure, capabilities & operational models. Comb Chem High Throughput Screen 17(3): 272-289.

5) Jenks S (2012) New NIH center broadens scope of translational research. J Natl Cancer Inst 104(10): 728-731.

6) http://www.ncbi.nlm.nih.gov/pubmed/?term=Roger s%20Z[Author]&cauthor=true&cauthor_uid=271966 29.

7) Rupa G (2015) Emerging Trends in Phytopharmaceuticals. Antiviral Phytopharmaceutical Screening by In Vitro Assays 77-84.

8) Caitlin Smith (2003) Drug target validation: Hitting the target. Nature 422, 341-347.

9) Szymanski P, Markowicz M, Mikiciuk-Olasik E (2012) Adaptation of high-throughput screening in drug discovery-toxicological screening tests. Int J Mol Sci. 13(1): 427-452.

10) Honndorf VS, Wiehr S, Rolle AM, Schmitt J, Kreft L, et al. (2016) Preclinical evaluation of the anti-tumor effects of the natural isoflavonegenistein in two xenograft mouse models monitored by [18F] FDG, [18F]FLT, [64Cu]NODAGA-cetuximab small animal PET. Oncotarget.

11) Farsi E, Esmailli K, Shafaei A, MoradiKhaniabadi P, Al Hindi B, et al. (2016) Mutagenicity and preclinical safety assessment of the aqueous extract of Clinacanthus nutans leaves. Drug ChemToxicol 1: 1-13.

12) http://www.tetraq.com.au/

13) Simon L, Srinivasan KK, Kumar N, Reddy ND, Biswas S, et al. (2016)Selected novel 5'-amino-2'-hydroxy-1, 3-diaryl-2-propen-1-ones arrest cell cycle of HCT-116 in G0/G1 phase. EXCLI J 13(15): 21-32.

14) Selby TP, Lahm GP, Stevenson TM (2016) A Retrospective Look at AnthranilicDiamide Insecticides: Discovery and Lead Optimization to Chlorantraniliprole and Cyantraniliprole. Pest Manag Sci.

15) Nose T, Kondo M, Shimizu M, Hamura H, Yamaguchi Y, et al. (2016) Pharmacological Profile of GPD-1116, an Inhibitor of Phosphodiesterase 4. Biol Pharm Bull 39(5): 689-698.

16) Orallo F, Garcia-Ferreiro T, Enguix MJ, Tristan H, Masaguer C, et al. (2003) In vivo and in vitro pharmacological studies of a new hypotensive compound (QF0301B) in rat: comparison with prazosin, a known alpha1-adrenoceptor antagonist. VasculPharmacol. Feb 40(2): 97-108.

17) Warheit DB, Brown SC, Donner EM (2015) Acute and subchronic oral toxicity studies in rats with nanoscale and pigment grade titanium dioxide particles. Food ChemToxicol 84: 208-224.

18) Koszalka GW, Johnson NW, Good SS, Boyd L, Chamberlain SC, et al. (2002) Preclinical and Toxicology Studies of 1263W94, a Potent and Selective Inhibitor of Human Cytomegalovirus Replication. Antimicrobial Agents and Chemotherapy 46(8): 2373–2380.

19) Chen CC, Chen JJ (2014) Benchmark dose calculation for ordered categorical responses. Risk Anal 34(8): 1435-1447.

20) Chen D, Kannan K, Tan H, Zheng ZG, Feng YL, et al. (2016) Bisphenol Analogues Other Than BPA: Environmental Occurrence, Human Exposure, and Toxicity - A Review. Environ Sci Technol.

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