Chapter 3
Lead Optimization in the Drug Discovery Process

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ABSTRACT

Discovering a new drug molecule against disease is the main objective of drug discovery. Lead optimization is one of the important steps and acts as a starting point. Over the years, it has significantly changed the drug discovery process. Its main focus is the development of preclinical candidates from "Hit" or "Lead." Lead optimization comprises lead selection and optimization, drug candidate confirmation, and preclinical drug characterization. Lead optimization process can improve the effectiveness towards its target potency, selectivity, protein binding, pharmacokinetic parameters, and to develop a good preclinical candidate. Lead optimization from high-throughput screening to identification of clinical drug candidate is a seamless process that draws new techniques for accelerated synthesis, purification, screening from iterative compound libraries, validation, and to deliver clinical drug candidate with limited human resources. In conclusion, lead optimization phase is done under the suggestion that the optimized lead molecule will have activity against a particular disease.

INTRODUCTION

To develop a new drug molecule about a decade to reach the market with an average cost of around $1 billion. Today pharmaceutical industry faced steady turn down in R&D efficiency and approval of fewer drugs to the market regardless of the increased investments (Adams & Brantner, 2006; DiMasi *et al.,* 2003). Withdrawn of the drugs from the market due to its adverse drug reactions and failures in clinical phase III are the other problems faced by the Pharmaceutical industries (Congressional Budget Office (CBO) study, Research and Development in the Pharmaceutical Industry, 2016). Major reasons for the failure of the drug candidate in the final stage are due to its safety issues or side effects which are undiscovered in the initial stage of drug discovery process.

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Failures of the new drug molecule in the drug discovery and development process are

1. Inability to configure a reliable assay
2. Unable to get a developable hits through HTS
3. Drug molecule may not have a desired assay or activity
4. Drug molecule might to toxic *in vitro* or *in vivo*
5. Undesirable side effects
6. Unable to get good PK or PD profile
7. Unable to get good permeation to the desired target site (Hughes *et al.,* 2011).

Today developing a new drug molecule for many health issues through drug discovery process is a challenging and complex because it includes different phases such as analysis, modelling and experimentation on the data. An ideal new drug molecule must have therapeutic effect in a defined pathway towards its biological target with minimal effects on other pathways and to have fewer side effects. Success towards the drug discovery for a particular disease is depends on the selection of the target interest and its validation. Two key issues in the drug discovery and development of new drug molecules are

1. Selection of biological target
2. Appropriate therapeutic agent towards the activity of the target (Hajduk & Greer, 2007)

BIOLOGICAL TARGET IDENTIFICATION

Biological target is a collective term for a macromolecule includes protein, genes, RNA and DNA. Generation of protein function modulators are the key process in the biological target identification. A good target must be safe, meet the clinical needs and it should be druggable one. Druggable target is an accessible by drug molecule upon binding and produces its biological activity, which can be determined by *in vitro* and *in vivo* methods (Keseru & Makara 2006; Yang *et al.,* 2009).

Approaches in Target Identification

If the target is identified, examine the certain protein role in disease onset and its biological consequences. Approaches in the target identification are

1. Screening of genome wide forward and reverse genetics
2. small-interfering RNAs (siRNAs)
3. Gene expression profiling
4. Examination of mRNA/protein levels
5. Genetic associations
6. Phenotypic screening (Hajduk & Greer, 2007; Butcher 2005; Van der Greef & McBurney 2005; Hardy & Peet 2004; Betz *et al.,* 2005)