Chapter 10
Hunting Drugs for Potent Antigens in the Silicon Valley

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ABSTRACT

Diseases are persistently getting diversified, evolved and thus require rapid vaccine development methodologies. Complex archaic methods require painstaking efforts over a larger time span. In silico methods are utilized these days to screen potent antigens. This approach paves a future way to reduce the number of wet-lab experiments. Its importance is also highlighted by the rapid scattering of diseases and evolution of their variants. This cited work explains immunological aspects and algorithms applied for epitope selection, with their practical problems. Current techniques used to model the native state conformation of epitopes are then described with their fundamental problems. So, the algorithms to validate such models are discussed. Techniques to screen effective potent drugs against the target epitopes are then considered. Lastly, scope for further research in developing better methodologies is highlighted.

INTRODUCTION

The significant progress in Genomics Research and Systems Biology has offered an overflow of novel potential targets for Drug discovery (Logging & Harland, 2007). Enhanced technological advances have governed a significant pace in the drug discovery process.

High-throughput gene sequencing has also reformed the process employed in identifying novel drug targets. Till date, large number of novel gene sequences and their specific signature patterns have been studied but only a limited number have been successfully employed for targeting diseases. The increased figure of prospective targets and lack of their molecular mechanism information has been a bottleneck in the target validation process, since a long time. (Ofran, Punta, Schneider & Rost, 2005; Zheng, Lianyi & Chen, 2006) used multiple superior methods including integrated and systems-based approaches, studied by (Lindsay, 2005; Sams-Dodd, 2005) and (Hardy & Peet, 2004). Current computa-

DOI: 10.4018/978-1-61520-977-4.ch010

tional algorithms are mainly based on the detection of conserved functional domains which have similarity to known targets, as studied initially by (Hopkins & Groom, 2002), later by two groups (Wang, Sim, Kim, & Chang, 2004; Kramer, & Cohen, 2004); and the conformational analysis of statistical, energetic features of predicted models (Hajduk, Huth, & Fesik, 2005; Hazduk, Huth, & Tse, 2005). Such algorithms have been ineffective in finding the best targets as they exhibit negligible sequence similarity to known templates with available three-dimensional (3D) structure of proteins in the PDB (Protein Data Bank). Heterologous and structurally mysterious proteins constitute a substantial percentage, almost from 20% -100%, of the Open Reading Frames (ORFs) in many of the completed genomes and therefore, they are still an untapped source of novel drug targets (Han, Cai, Cao, & Chen, 2004). Hence, algorithms which are not dependent upon sequence similarity to known structural protein templates are highly desirable.

Thus still, the drug discovery process is incapable to meet the requirements because of the evolution of variants, which broaden the complexity of diseases and thereby makes the available drugs ineffective for them. Conceivably, the utmost source of inefficiency in traditional drug discovery process arises from the high percentage of evaluated drugs that have a low propensity of being successful. To aim leading optimized preliminary preclinical trials, compound libraries have been dedicated in a virtual pool (Good, Krystek, & Mason, 2000; Schnecke, & Bostro, 2006). The sorted compounds are synthesized and experimentally screened for clinical trials. Each such compound is selected based on conformational and geometric properties that augment the chance ratio of stably targeting the specific targets in the course of preclinical development.

This chapter is solely devoted to learn current algorithms to trace potent antigenic epitopes in the considered sequence, predict, assess and validate their predicted structures. Lastly, it focuses on docking methodology and simulation studies to screen the best drug against target protein, with the final step as *in-vivo* and *in-vitro* experimental trials.

BACKGROUND

Quantitative Structure Activity Relationship (QSAR) model(s) and/or docking stimulations are often used in screening such dedicated compound libraries (Anderson, & Wright, 2005). *De novo* drug designing employs computational algorithms to harmonize target protein binding site structurally & energetically for the selected drug molecule (Mauser, & Guba, 2008). Successful *de novo* design aims at effective drug structures that have high binding affinity against their target protein's docking sites. Such an approach is extremely successful when genetic and investigational data of drugs and target proteins are available. Two major approaches behind development of such tools are the following.

a. **Molecular Fragment Approaches (Jhoti, 2007):** This approach docks molecular fragment of drug to resolve energetically approving loci on the active site, before being "linked". This method first searches key locations in the binding pocket of the target protein structure and then assembles the drug fragments. Once the functional groups are integrated, the next step is to connect them with scaffolds. Optimization steps were mandatory in earlier methodologies, where bonds can be wrecked and resealed back. Monte Carlo (MC) Simulation and evolutionary algorithms have also attempted this optimization. For e.g. Pro-Drug (Westhead, Clark, Frenkel, Murray, Robson, & Waszkowycz, 1995).
b. **Sequential Growth Approaches (Honma, 2003):** Here, molecules are "developed" into an active site starting from a seed moiety already bound to the active site. The drug matures atom by atom to complement the