TARGET SELECTION IN DRUG DISCOVERY

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1 INTRODUCTION

The annual output of the pharmaceutical industry has been relatively constant from 1993 to 2003 with an average of 30 new molecular enties (NME) per year [1, 2]. Only about 10% of these NMEs were directed at novel targets as identified by the Food and Drug Administration (FDA) [1]. This relatively constant output and low innovation has occurred despite a twofold increase in investment by both the National Institutes of Health (NIH) and the pharmaceutical industry [2] as well as dramatic advancements in technology, such as sequencing the human genome, transcriptomics, and expanded small-molecule collections. The combination of the constant output plus increased investment has driven the cost per successful NME from $1.1 billion for the period 1995–2000 to $1.7 billion for the period 2000–2002 [2]. These trends clearly threaten the long-term health of the pharmaceutical industry.

The reasons for attrition of therapeutic compounds have been studied to help understand how to increase the number of NMEs and innovative therapies. Based on an analysis of investigational new drugs (IND) that were abandoned in the period 1981–1992, one study found that compound attrition was due to a lack of efficacy (35%), economics (32%), safety (20%), and other reasons (13%) [3]. In a separate study, data gathered directly from 10 large pharmaceutical companies for the period 1991–2000 showed that attrition was primarily due to lack of efficacy (about 30%) and safety (about 30%) [4]. Taken together, these studies indicate that efficacy, safety, and economics are the major reasons for attrition. Clearly, identifying targets that are well linked to the disease, likely to have an acceptable therapeutic index with respect to mechanism-based toxicity, and appear economically attractive will decrease attrition. This review will focus on these criteria and an additional criterion, chemical tractability, that assesses the likelihood of identifying a compound with the desired pharmacology and pharmacokinetics. While every target in drug discovery brings unexpected challenges, an accurate assessment of targets with respect to these four criteria will help increase the likelihood of developing successful therapeutics. Other reviews with additional perspectives on target selection for drug discovery are available [5–7].

2 CRITERION 1: TARGET LINKAGE TO DISEASE

Connecting a target to the disease is the most important criterion for selecting a target for drug discovery. There are several ways to make this connection, including

1. Human clinical results
2. Human genetics
3. Pathway linked to the disease by human clinical results or human genetics
4. Preclinical studies in model systems
5. Target expression perturbion in the disease

In practice, good targets are supported by several of these connections.

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