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Review Article

Integrative approach in the era of failing drug discovery and development

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ABSTRACT

The productivity decline in drug discovery and development is mainly caused by two factors; higher regulatory hurdles and low-hanging fruits being all picked. In addition, the recent target-based approach is thought to be increasing the price of innovation. Although target-based approach had many successes, a postreductionism method, which is systems biology, is on the rise. In this review, we discuss the foundations of two distinct approaches in finding a new drug.

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1. Introduction

The pharmaceutical industry is currently facing unparalleled challenges to develop innovative new drugs. Although the annual number of new drugs approved by the Food and Drug Administration (FDA) has not changed much, research and development (R&D) investment per drug is escalating at a marked rate. The estimated cost of developing a new drug is approximately $1 billion.[1–3] This phenomenon, the increase in R&D investment without the corresponding increase in the number of new drug approval, is known as the "innovation gap."[4] After the Thalidomide and Vioxx incidents, regulatory bodies throughout the world are demanding more safety data, which in turn increases the development costs. Lack of efficacy is another important factor that contributes to the high attrition rate. Nowadays, even me-too drugs must provide more benefit than the conventional therapeutics to be approved. Both safety and efficacy hurdles are responsible for the rising cost in drug discovery and development. To minimize the risk in internal R&D, pharmaceutical companies began to rely more on outside innovation. The effectiveness of big pharmaceutical companies' (big pharmas) R&D externalization strategies are being questioned as more and more assets are put into early-stage pipelines. Many state-of-the-art technologies such as high-throughput screening are speeding experimental procedures that are required by today's drug discovery and development. However, applying new technologies and devices also means increased costs. From 1950 to 2008, the FDA approved 1222 new drugs new molecular entities or new

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biological entities (NMEs or NBEs). Even though the amount of investment per drug has increased exponentially, the annual number of approvals has remained unaffected.[5] There are > 4000 companies undergoing some forms of drug discovery and development. However, only 261 companies have succeeded in registering a new drug since 1950. In the United States alone, > 50,000 doctoral and postdoctoral researchers are conducting basic, translational, and clinical research. These research ventures spend > $90 billion annually. The National Institute of Health alone provides $33 billion into life sciences. Lazonick and Tulum[6] explained that the strength of the U.S. biopharmaceutical industry originated on three factors: large National Institute of Health funding, strong appetite for biotechnology initial public offering, and vibrant venture capital investment. Indisputably, the pharmaceutical industry contributed greatly to improve health conditions and longevity. Nevertheless, the time is ripe to discuss the mounting problems in drug discovery and development approaches to push the pharmaceutical industry into the next level. So, two questions arise. Is target-based approach the reason behind the current fall in productivity? Should the concept of systems biology replace the reductionists' view to succeed in drug discovery and development?

2. Target-based approach and systems biology

The purpose of drug design is to find the optimal structure that possesses high specificity around the target and interferes less with other sites to decrease the likelihood of side effects. Screening is very expensive, thus contributing heavily to drug development cost. In the past few decades, knowledge in science has leaped forward dramatically. With the help of reductionist methodologies, our understanding of the human body and diseases has increased enormously. Reductionism, as preached by Ernest Nagel, considers that all higher-level theories can be reduced to some basal-level theories.[7,8] This is in agreement with Marshall Nirenberg's dictum that science progress best when there are simple assays capable of generating large data sets rapidly.[9] In short, gene to protein to function is the central tenet in modern biology. Because most drug action sites are proteins, targeting protein became the foundation of modern drug discovery and development. Meanwhile, the so-called low-hanging fruit is now picked, which suggests that more effort, whether financial or scientific, is needed to develop a new drug. Therefore, redefining the drug discovery and development is a grand challenge for the pharmaceutical industry. In order to endure the upcoming challenges, for example, blockbuster patent cliff and price containment pressures from the payers, a more integrative approach must be implemented.

Until the 1990s, drug discovery and development was largely based on a phenotypic approach or observation-based approach. However, the accumulation of knowledge in biochemistry and molecular biology led to a shift toward the target-based approach. The appearance of recombinant DNA and low-cost fast protein liquid chromatography facilitated this change.[10] At that time, the phenotypic approach was challenged by many scientists just as target-based approach is being scrutinized at present. Even in Phase 1 of the clinical trial, the phenotypic approach was unable to provide the mechanisms of the action of a drug. Lack of knowledge was particularly risky when tested on human volunteers for various reasons (e.g., toxicity). Therefore, drug-developing chemists and biologists in the 1990s mostly welcomed the transformation into a target-based approach, which was thought to be more predictable and science-driven. Two decades of experience shows that the target-based approach is failing to boost the productivity in drug discovery and development. Selected targets were often not druggable and with poor disease linkage, leading to either high toxicity or poor efficacy. The off-target effect of a drug was much more difficult to predict in comparison to the phenotypic approach. Because the whole industry was using similar compound libraries for druggable targets, the diversity of pharmaceutical companies' portfolio has been damaged. This led to intense competition, where speed of clinical trials and marketing were the main attributes in determining the first-in-class or best-in-class.

The decline in productivity in the past two decades coincided with the introduction of target-based approaches.[11] However, the target-based approach is not the only explanation for this decline in productivity because innovative therapeutics such as monoclonal antibodies, antibody-drug conjugates (ADCs), and Gleevec had appeared. However, once the target-based approach has become a standard in all disease areas, it may lead to a predicament. The debate on physiology-based approach and target-based approach is still ongoing. But both physiology-based and target-based approaches should be taken into account to have a better chance of controlling the so-called difficult diseases. A holistic view or integrative approach is therefore the key to blend the two contradictory, yet complementary, methods (Fig. 1).[12]

Consequently, no one pharmaceutical company can handle the entire spectrum of science, not to mention the vast disease areas. This is why collaborations between the industry and universities are becoming a prerequisite. To keep going in this challenging era, pharmaceutical companies need to innovate constantly with the outside world. Open innovation, which was first coined by Henry Chesbrough,[13] is the most talked-about term when discussing future research and development (R&D). More and more pharmaceutical companies are implementing the concept of open innovation in their business model. Although the limits of target-based approach are well established, it still remains as the gold standard to push the candidate molecule all the way to Phase 3. This is also the case in government grants or when submitting a research paper. Prior to the rise of molecular biology, phenotypic screening was the norm in finding a new candidate molecule. At that time, the mode of action was not fully elucidated. Thus, the majority of drugs entered clinical trials without the understanding right down to a molecular level. A single target drug is very desirable theoretically in terms of both safety and efficacy. It will be straightforward to predict and control the strength of action. Alas, each drug on average acts on at least five different targets, causing mild to severe side effects. In reality, a drug that acts via a single target is very difficult to find. With the advent of information technology, the concept of big data is infused into the early stage screening process. Even with the today's gigantic computing power, it is not feasible to examine

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