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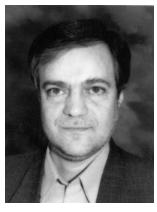
Editorial



Application of Proteomics Technologies in the Drug Development Process

Seyed Hassan Moghaddamnia

Proteins are the main targets in drug discovery. Most large pharmaceutical companies now have a proteomics-oriented biotech or academic partner or have started their own proteomics division. Common applications of proteomics in the drug industry include target identification and validation, identification of efficacy and toxicity biomarkers from readily accessible biological fluids, and investigations into mechanisms of drug action or toxicity. Target identification and validation involves identifying proteins whose expression levels or activities change in disease states. These proteins may serve as potential therapeutic targets or may be used to classify patients for clinical trials. Proteomics technologies may also help identify protein–protein interactions that influence either the disease state or the proposed therapy. Efficacy biomarkers are used to assess whether target modulation has occurred. They are used for the characterization of disease models and to assess the effects and mechanism of action of lead candidates in animal models. Toxicity (safety) biomarkers are used to screen compounds in pre-clinical studies for target organ toxicities, as well as later in development during clinical trials. Complementary approaches such as metabolomics and genomics can be used in conjunction with proteomics throughout the drug development process to create more of a unified, systems biology approach. The traditional approach to drug discovery is based on generation of a hypothesis based on a biochemical and pharmacological approach to a disease. Targets are defined on the basis of this hypothesis and lead discovery is a matter of chance. The classical drug-discovery effort also involves isolating and characterizing natural products with some biological activity. These compounds are then 'refined' by redesigning their molecular structures to yield new entities with higher biological activity and lower toxicity/side effects. The main limitation of such a process is that the discovery of natural products with defined biological activity is essentially a hit-or-miss approach and therefore lacks a rational basis. Advances in drug discovery include introduction of combinatorial chemistry, which involves the use of high-throughput technologies for preparing a large number of compounds for use in screening of a variety of biological targets. Genomics was used as a means to improve our understanding of disease with the hope that a comprehensive knowledge of an organism's genetic makeup would lead to more efficient drug discovery. Although useful, DNA sequence analysis alone does not lead efficiently to new target identification, since one cannot easily infer the functions of gene products (proteins) and protein pathways from DNA sequence. Drug discovery is a lengthy and expensive process with shortage of promising drug leads. Functional genomics and proteomics have provided a huge amount of new drug targets. The challenge now is to increase the efficiency of testing lead efficacy and toxicity. In practice, this is not easy because an infinite number of genes, proteins and other molecules interact with each other in signaling pathways to direct cell function. With advances in proteomic technologies, there is an increasing interest in the application of these to improve the drug-discovery process. Because most of the drugs act on proteins, it is important to focus drug-discovery efforts at this level.

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