Lead identification in drug discovery research

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Drug discovery research for novel drug targets is increasingly of great importance in developing innovative drugs, attendant upon the development of post-genome research. The exploratory stage in drug discovery research has a big impact in furthering the drug discovery process. The exploratory stage roughly consists of two stages. The first is identification of a drug target that participates in the pathogenic cause; the second is identification of a low molecular weight (LMW) compound as a lead, which interacts with the drug target. The project in which the drug target and lead compound are discovered at these two stages is then advanced to the lead optimization stage as a novel research project in order to select the preclinical candidate. In the first stage of the exploratory research, drug targets are identified by pharmaceutical companies independently using their own technology derived from genome, post-genome and proteomics research. It is extremely critical to validate whether the novel drug target is involved in disease pathogenesis and is effective in patient treatment. Therefore, target validation using the LMW compound, which has been found by evaluation of drug efficacy on the basis of a working hypothesis, is the most reliable and effective method contributing directly to drug discovery research. The target is forwarded to the second stage in which the lead compound is identified. Presently, lead identification is performed in two ways. One is the case in which the structure of the target protein, for instance membrane proteins such as GPCR and ion channel, is unknown. In this case the conventional technique such as random screening of natural products and a chemical library is applied and thusly many drugs have been developed and placed on the market. A variety of hit compounds have been identified from high-throughput screening (HTS) of chemical libraries developed with consideration of molecular diversity and drug-likeness using the technique of combinatorial chemistry for the last several decades. The hit compounds are validated using the technique of biochemistry and pharmacology and are optimized using the technique of medicinal chemistry from analysis of structure-activity relationships. On the other hand, when the three-dimensional structure of the target protein has been determined, it is possible to design a lead compound rationally using the technique of computational chemistry based on the structure. When the LMW compound is obtained from HTS, structural information of the complex of the target protein with the compound determined by X-ray crystallography serves to design the compound effectively in the hit-to-lead process. In addition, the lead compound is identified by *in silico* screening of in-house, commercially available and/or virtual chemical libraries, instead of performing random screening. In the future, accuracy of rational drug design will be dramatically improved by knowledge accumulated from information of structural biology in terms of the structure-function relationship of the important target protein. Furthermore, lead identification in drug discovery will be significantly improved by prediction of not only the inhibitory activity and selectivity for the target protein but also toxicity and metabolism based on mechanisms. The next-generation drug discovery research should be established in order to develop a novel drug rapidly, adapting an innovative approach.