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Teaser Drug discovery and development suffers from high cost and attrition owing to toxicity. The application of unique toxicogenomic platforms has the potential to produce safer drugs and decrease research and development costs.

Current status and future prospects of toxicogenomics in drug discovery

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In drug discovery and development (DDD), the efficacy, safety and cost of new chemical entities are the main concerns of the pharmaceutical industry. Continuously updated and stricter recommendations imposed by regulatory authorities result in greater challenges being faced by the industry. Reliable high-throughput techniques integrated with well-designed analytical tools at all stages of DDD (termed 'next-generation DDD') could be a possible approach to obtaining new drug approval by cutting costs as well as ensuring the highest level of patient safety. In this review, we describe the various components of holistic toxicogenomics with examples of applications, and discuss the various analytical tools and platforms to illustrate the current status and prospects of next-generation DDD.

DDD, currently one of the most challenging and costly businesses, begins with the identification of new drug candidates either by systematic screening or serendipity, and generally ends after the compound has successfully passed clinical trials. Typically, 90% or more of the budget is spent on clinical trials, mainly in Phase III (http://www.manhattan-institute.org/html/fda_05.htm). One of the most common causes of Phase III failure is drug-induced toxicity. Additionally, drug withdrawals from the market also contribute to the escalation of costs of DDD, with subsequent drops in new lead discoveries. In a study of 548 new lead compounds approved between 1975 and 1999, 56 acquired a black box warning (the strongest warning by the FDA for a scientifically proved significant risk of serious or even life threatening adverse effects) and 16 were withdrawn [1]. A report by the North Carolina General Assembly (NCGA) (29 March, 2012 meeting; subcommittee on pharmaceuticals liability) described how the US Food and Drug Administration (FDA) had approved approximately 300 new drug applications over the past decade, of which at least 15 have since been withdrawn from the US market (http://www.ncleg.net). Surveys indicate that, in the USA, a new lead compound takes 10–15 years on average to reach the market, with an associated cost of approximately US$1.8 billion and an average success rate of only 8% [2]. Increasing the success rate of DDD and decreasing drug attrition, although challenging, could

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reduce overall costs. If lead compounds can be selected based on both possible toxicity and desirable efficacy during early stages of DDD, it would provide the opportunity to not only select a few lead compounds for preclinical and clinical studies, but also reduce the chance of lead rejection owing to undesirable toxicity during clinical and post-marketing stages. The outcome would benefit all aspects of DDD and increase patient safety. However, conventional drug toxicity testing is not sufficient to predict all the possible clinical toxicities, although it does provide a vista to understand drug-induced toxicity from a mechanistic perspective. Therefore, a potential alternative (or addition) could be the involvement of toxicogenomic approaches integrated with informatics at every stage of DDD (e.g. lead selection and optimization, and preclinical and clinical studies).

In this review, we present toxicogenomics as a necessary tool to be integrated into the drug toxicity research phase of DDD. This would ideally lead to the next generation of DDD (Fig. 1). Here, toxicology studies applying high-throughput techniques (omics), predictive (i.e. based on chemical structure) and translational informatics tools are collectively termed 'toxicogenomics', which globally encompasses the tools of transcriptomics, epigenomics, global miRNA analysis, proteomics, metabolomics and informatics (bioinformatics and cheminformatics). Together, these approaches could provide valuable information about drug-induced toxicity, its mechanisms and potential toxicological biomarkers for DDD in a predictable and cost-effective manner (Fig. 2) [3,4]. Although the concept of toxicogenomics was originally introduced by Nuwaysir *et al.* in 1999 [5], it has not yet been recommended by regulatory authorities as a mandatory toxicological approach to evaluate the safety profile of new drug compounds in either preclinical or clinical studies [6].

Omics is now widely used in research areas in both academia and industry. However, the use of the integrated form or holistic approach to omics (i.e. the combination of genomics, proteomics, epigenomics, global miRNA analysis, metabolomics, etc.) is more rare. Here, we emphasize the use of holistic toxicogenomics as a means of obtaining comprehensive information, given that there is no automatic established correlation between different omics, and their results can only be integrated manually. For example, a recent estimate of the gene content of the human genome was approximately 25 000 genes, accounting for less than 5% of the total genomic DNA [7]. Genes, the blueprint for functional proteins, can be switched on or off to synthesize different proteins. The exons of pre-mRNAs can be variably retained during splicing

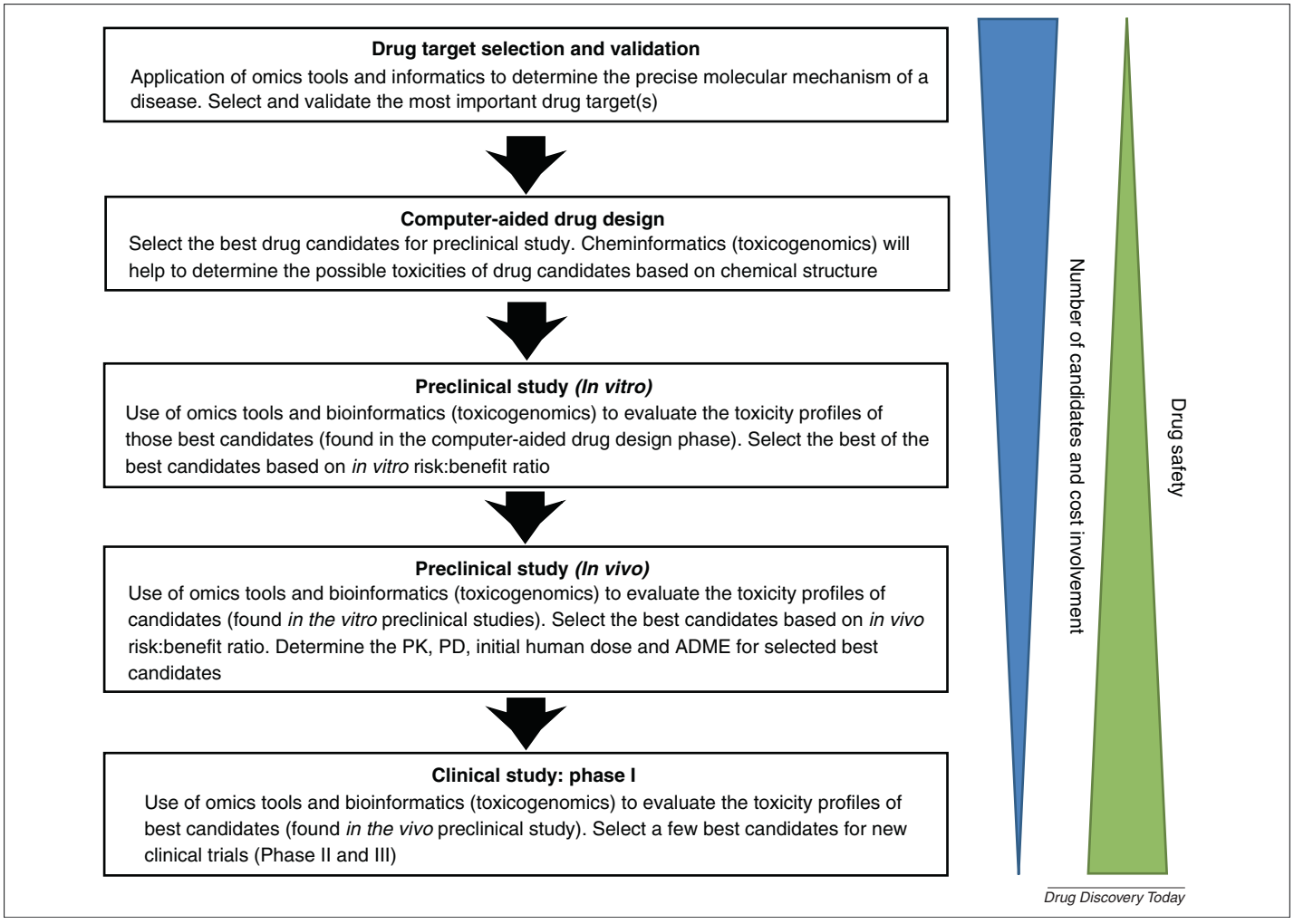

FIGURE 1

Next-generation drug discovery and development project work-flow, illustrating its impact on reducing expenditure as well as ensuring the highest level of patient safety. *Abbreviations*: ADME: absorption, distribution, metabolism, and excretion; PD: pharmacodynamics; PK: pharmacokinetics.