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Mini Review

DRUG RESEARCH TECHNOLOGIES TO UNDERSTAND DRUG TOXICITY MECHANISMS

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ABSTRACT

Drug development and medical care both depend heavily on rug safety. Drug safety is primarily concerned with preventing adverse medication events, which are harms brought on by any drug-related action. Annually, adverse medication events in the USA result in about 3.5 million outpatient doctor visits and 2 million inpatient hospital admissions. Some adverse drug events, such as dosage errors, overdoses, and allergic responses, can be avoided, whilst others are expressly referred to be adverse drug reactions or drug side effects because they are brought on by underlying drug-induced mechanisms. It is crucial to avoid these side effects in healthcare in order to improve both clinical and financial outcomes.

Along with structure- and ligand-based approaches, there are other in silico techniques for virtual compound screening that enable better profile analysis, quicker non-target compound elimination, and more cost-effective selection of therapeutic molecules. The physical, chemical, and toxicological properties are taken into account by drug design algorithms like coulomb matrices and molecular fingerprint identification to choose a lead compound.

Keywords: Toxicogenomics; Drug side effects; Drug safety

INTRODUCTION

Assigning the right target during drug molecule development is crucial for effective treatment. The development of the disease involves many proteins, some of which are overexpressed. Therefore, it is essential to predict the structure of the target protein while designing the therapeutic molecule in order to selectively target disease. Because the design is in accordance with the chemical environment of the target protein site, AI can help in structure-based drug discovery by anticipating the 3D protein structure. This aids in anticipating the effect of a compound on the target as well as safety considerations before their synthesis or production [1,2].

Many medication combinations are authorised and marketed to treat complex illnesses like TB and cancer because they can hasten recovery times by working in synergy. For example, cancer therapy requires six to seven drugs as a combination therapy, which makes the process laborious. The selection of precise and potential drugs for combination requires high-throughput screening of a

sizable number of drugs. Drug combinations can be screened using ANNs, logistic regression, and network-based modelling, which can also enhance the overall dosing regimen.

To assess the feasibility and safety of possible drug candidates, toxicology studies are conducted. The information from these studies is used to support regulatory filings. Researchers are seeking for techniques to carry out toxicological studies as effectively as possible because it is well recognised that toxicity contributes to drug candidate attrition and because there is a growing need for speedier and less expensive medication development [3].

MATERIALS AND METHODS

When creating a new therapeutic, the new therapeutic must meet two straightforward requirements. The therapy must, first and foremost, be effective in curing the illness or improving the patient's quality of life. Second, the therapy must be risk-free and refrain from harming the patient in an unacceptable or additional way. Before a new drug is given to patients or volunteers taking part in clinical trials, toxicology studies are created and carried out to identify and describe any potential adverse effects or toxicities. Several nonclinical toxicological investigations are carried out in non-human in-vivo and in-vitro models to achieve this goal. Additionally, these investigations assist "first-in-human" clinical trials and the clinical trials necessary to introduce the medicine to the market, which are required for regulatory submissions around the world.

History has proven that testing using these complete animal toxicology models has and continues to safeguard humans/patients from hazardous medications, even though the predictiveness of animal toxicology models may not be as predictive of human results as researchers would want. Additionally, the predictive power of our models will increase as more is understood about cellular and molecular pathways as well as how organ systems function and interact. The reproducibility of results will also increase as researchers continue to learn more about how to take better care of and manage study animals [4].

DISCUSSION

Without changing the DNA sequences that can affect gene expression, epigenetic alterations suggest a heritable phenotype. 12 The majority of pharmacological research concentrates on DNA methylation processes, in which methyl groups are added to or deleted from cytosines in DNA, among other epigenetic modifications, including modifications of histone and other Tudor domain proteins (i.e., 5-methylcytosine; 5mC). By monitoring gene expression or alternative splicing, changing 5mC levels can affect the functional state of specific genomic regions; this can be brought on by medications and can continue even after therapy. For instance, the well-known antibiotic rifampicin has the ability to change DNA methylation regions linked to liver damage. 14 A doxorubicin study in rats demonstrated the relationship between long-lasting cardiac mitochondrial functioning and epigenetic dynamics [5,6].

CONCLUSION

With a wide range and high sensitivity, RNA sequencing (RNA-Seq) uses NGS to detect and quantify RNA in biological materials, from whole transcriptome to focused sequencing. While mRNA sequencing uses poly(A) selection to analyse protein-coding gene expression, total RNA or whole-transcriptome sequencing can study coding and non-coding RNAs simultaneously. Small RNA-Seq has been created to specifically quantify miRNAs in response to concerns regarding

transcript length. All of this RNA-Seq methods use hypothesis-free experimental designs to cover the entire transcriptome in a biological sample, whereas focused RNA-Seq concentrates on particular genes at a lesser cost. 30 Popular NGS approaches have a limited ability to detect transcript isoforms but can produce high-throughput and reliable data since they are based on the short-read sequencing paradigm.

The metabolome, or the complete collection of small-molecule metabolites inside the cell, has attracted the attention of toxicologists in recent years. Metabolites are the products of all these biological processes, but drug-induced changes in DNA methylation, transcriptome, and proteome can merely indicate prospective outcomes. Thus, a direct connection between pharmacological impacts and cellular responses can be found by analysing the metabolome. Cohort studies have highlighted previously undiscovered toxicity mechanisms of these medications by describing the changes in endogenous metabolites in response to pulmonary TB therapies, such as isoniazid and rifampicin. The metabolome has also been utilised by researchers to forecast the method of action of novel antibacterial substances. Researchers can therefore find prospective drug side effects, locate toxicity-related biomarkers, and identify potential drug adverse effects by observing changes in the metabolome in response to drug exposure.

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