Asian Journal of Pharmaceutical Technology and Innovation

Editorial

Analytical Structures in Pharmacogenomics

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Genomic studies are producing large databases of molecular information on cancers and other cell and tissue types. Hence, we have the opportunity to link these accumulating data to the drug discovery processes. Our previous efforts at 'information-intensive' molecular pharmacology have focused on the relationship between patterns of gene expression and patterns of drug activity. In the present study, we take the process a step further-relating gene expression patterns, not just to the drugs as entities, but to approximately 27,000 substructures and other chemical features within the drugs.

This coupling of genomic information with structure-based data mining can be used to identify classes of compounds for which detailed experimental structure-activity studies may be fruitful. Using a systematic substructure analysis coupled with statistical correlations of compound activity with differential gene expression, we have identified two subclasses of quinones whose patterns of activity in the National Cancer Institute's 60-cell line screening panel (NCI-60) correlate strongly with the expression patterns of particular genes:

(i) The growth inhibitory patterns of an electron-withdrawing sub-class of benzodithiophenedione-containing compounds over the NCI-60 are highly correlated with the expression patterns of Rab7 and other melanoma-specific genes;

(ii) The inhibitory patterns of indolonaphthoquinone-containing compounds are highly correlated with the expression patterns of the hematopoietic lineage-specific gene HS1 and other leukemia genes.

As illustrated by these proof-of-principle examples, we introduce here a set of conceptual tools and fluent computational methods for projecting directly from gene expression patterns to drug substructures and vice versa. Large-scale comparative analysis of drug-target polymorphism structures enables the rational design of next generation 'super drugs'--drugs that are less prone to development of drug resistance or that work for the largest possible fraction of the patient population.

The economic impact of incorporating pharmacogenomics insights early on in the drug discovery process will be substantial and will afford significant competitive advantages to companies that successfully incorporate this technology. The term pharmacogenomics is often used interchangeably with pharmacogenetics. Although both terms relate to drug response based on genetic influences, pharmacogenetics focuses on single drug-gene interactions, while pharmacogenomics encompasses a more genome-wide association approach, incorporating genomics and epigenetics while dealing with the effects of multiple genes on drug response.

Pharmacogenomics also attempts to eliminate the trial-and-error method of prescribing, allowing physicians to take into consideration their patient's genes, the functionality of these genes, and how this may affect the efficacy of the patient's current or future treatments. Pharmacogenomics was first recognized by Pythagoras around 510 BC when he made a connection between the dangers of fava bean ingestion with hemolytic anemia and oxidative stress.

Basics of Pharmacogenomics

In pharmacogenomics, genomic information is used to study individual responses to drugs. When a gene variant is associated with a particular drug response in a patient, there is the potential for making clinical decisions based on genetics by adjusting the dosage or choosing a different drug, for example. Scientists assess gene variants affecting an individual's drug response the same way they assess gene variants associated with diseases: by identifying genetic loci associated with known drug responses, and then testing individuals whose response is unknown. Modern approaches include multigene analysis or whole-genome single nucleotide polymorphism (SNP) profiles, and these approaches are just coming into clinical use for drug discovery and development.

Citation: Kiran Kumar Vangara; Analytical Structures in Pharmacogenomics, 9(34).