

Novel Approaches in Drug Design

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ABSTRACT

Novel approaches in drug designing & development is a research focusing upon drug designing methodologies, new drugs developments in chemical and biological research. Novel approaches in drug design involves multidisciplinary field, ranging from drug designing, drug development, drug discovery and it also involves medicinal chemistry, pharmacology, drug delivery systems, pharmacokinetics and pharmacodynamics, drug absorption and metabolism, pharmaceutical and biomedical analysis, including gene delivery, pharmaceutical biotechnology, drug targeting, pharmaceutical technology, and clinical drug evaluation. My research reflects that various approaches as used in drug design & development process.

Keywords: Array technology, Pharmacogenomics, Combinatorial Chemistry, Proteomics, NCE (New chemical entities)

INTRODUCTION

The drug is most commonly an organic small molecule that activates or inhibits the function of a biomolecule such as a protein, which in turn results in a therapeutic benefit to the patient. In the most basic sense, drug design involves the design of small molecules that are complementary in shape and charge to the biomolecular target with which they interact and therefore will bind to it. Drug design frequently but not necessarily relies on computer modeling techniques. This type of modeling is often referred to as computer-aided drug design. Finally, drug design that relies on the knowledge of the three-dimensional structure of the biomolecular target is known as structure-based drug design. Drug Design molecules that bind to a target (e.g. protein, nucleic acid). It relies on prior knowledge of the structure, function, and mechanism of the target, thereby avoiding random testing of thousands of molecules [1,2].

Selected/Designed molecule should be:

- Organic small molecule
- Complementary in shape to the target
- Oppositely charge to the bio-molecular target

The molecule will:

- interact with target
- bind to the target

- Activates or inhibits the function of a bio-molecule such as a protein

Novel drug approaches like

- CADD (Computer Aided Drug Design)
- Molecular Modelling
- Structure based drug design
- Analog drug design
- Combinatorial chemistry
- Computational chemistry
- Array technology
- Pharmacogenomics
- Combinatorial Chemistry
- Proteomics
- Recombinant DNA technology etc.

METHODS

- Array technology
- Pharmacogenomics
- Combinatorial Chemistry
- Proteomics
- Recombinant DNA technology.

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Array technology

Based on RNA & DNA hybridization reaction:

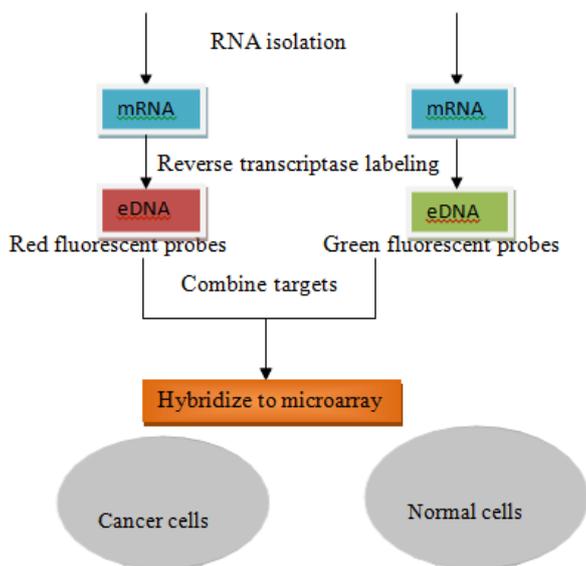
- Simultaneously several of genes can be analyzed.

Advantages:

- Miniaturization,
- Development of fluorescent labelled nucleotides, which is detected by laser screening.
- Decreased use of hazardous & cumbersome radioactive labeled DNA.

Methods used:

- Chips located with synthetic oligonucleotides.
- Chips located with a DNA fragment isolated directly from respective genes.



Types

- DNA microarray
- RNA microarray
- Protein microarray
- Antibody microarray
- Tissue microarray

Application of microarray

Monitor gene expression

- Study regulatory networks
- Drug discovery – mechanism of action
- Diagnostics – tumor diagnosis

Genomic DNA hybridizations

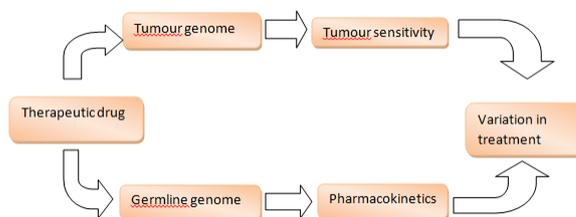
- Explore microbial diversity
- Whole genomic comparisons – genome evolution
- Identify DNA binding sites
- Diagnostics – tumor diagnosis

Pharmacogenomics

Pharmacogenomics is the study of the role of the genome in drug response. Its name reflects its combining of pharmacology and genomics. Pharmacogenomics analyzes how the genetic makeup of an individual affects his/her response to drugs. 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. This identification was later validated and attributed to deficiency of G6PD in the 1950s and called favism [2-4].

There are several known genes which are largely responsible for variances in drug metabolism and response. The focus of this article will remain on the genes that are more widely accepted and utilized clinically for brevity [5,6].

- Cytochrome P450s
- VKORC1
- TPMT



Pharmacogenomics aims to develop rational means to optimize drug therapy, with respect to the patients' genotype, to ensure maximum efficiency with minimal adverse effects. Through the utilization of pharmacogenomics, it is hoped that pharmaceutical drug treatments can deviate from what is dubbed as the "one-dose-fits-all" approach. 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.

Application

The list below provides a few more commonly known applications of pharmacogenomics:

- Improve drug safety, and reduce ADRs(Adverse drug reaction)
- Tailor treatments to meet patients' unique genetic predisposition, identifying optimal dosing
- Improve drug discovery targeted to human disease
- Improve proof of principle for efficacy trials

Pharmacogenomics may be applied to several areas of medicine, including pain management, cardiology, oncology, and psychiatry. A place may also exist in forensic pathology, in which pharmacogenomics can be used to determine the cause of death in drug-related deaths where no findings emerge using autopsy. And, used in cancer treatment, cardiovascular disorders, psychiatry disorders, etc.

Example case studies

- Case A – Antipsychotic adverse reaction
- Case B – Pain Management
- Case C – FDA Warning on Codeine Overdose for Infants

Proteomics

Proteomics is the large-scale study of proteins. Proteins are vital parts of living organisms, with many functions. The proteome is the entire set of proteins that is produced or modified by an organism or system. Proteomics has enabled the identification of ever increasing numbers of protein. This varies with time and distinct requirements, or stresses, that a cell or organism undergoes. Proteomics is an interdisciplinary domain that has benefitted greatly from the genetic information of various genome projects, including the Human Genome Project. It covers the exploration of proteomes from the overall level of protein composition, structure, and activity. It is an important component of functional genomics. Proteomics generally refers to the large-scale experimental analysis of proteins and proteomes, but often is used specifically to refer to protein purification and mass spectrometry.

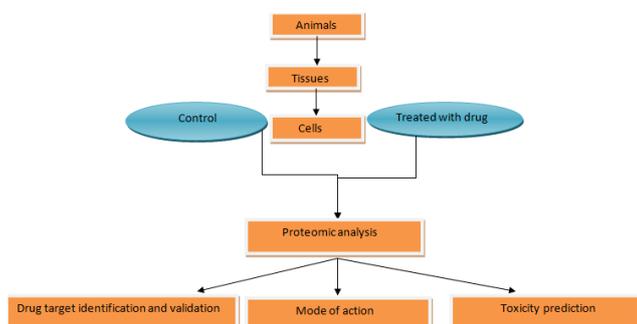
Proteomics is the study of proteomes, which are the collections of proteins expressed in cells. Whereas genomes are essentially invariant in different cells in an organism, proteomes vary from cell to cell, with time and as a function of environmental stimuli and stress.

The first studies of proteins that could be regarded as proteomics began in 1975, after the introduction of the two-dimensional gel and mapping of the proteins from the bacterium *Escherichia coli*.

Methods

Three methods for separation of complex protein or peptide samples are preferred in proteomics:

- Denaturing polyacrylamide gel electrophoresis (PAGE) or sodium dodecyl sulphate polyacrylamide gel electrophoresis (SDS-PAGE)
- Two-dimensional gel electrophoresis
- High-performance liquid chromatography (HPLC)



Application

- New Drug Discovery
- Interaction proteomics and protein networks
- Expression proteomics
- Biomarkers
- Proteogenomics

- Structural proteomics

Trends

A number of emerging concepts have the potential to improve current features of proteomics. Obtaining absolute quantification of proteins and monitoring post-translational modifications are the two tasks that impact the understanding of protein function in healthy and diseased cells. For many cellular events, the protein concentrations do not change; rather, their function is modulated by post-translational modifications (PTM).

- System biology
- Human plasma proteome

RESULTS

The various approaches used in drug design include the following:

- Random screening of synthetic compounds or chemicals and natural products by bioassay procedures.
- Novel compounds preparation based on the known structures of biologically active, natural substances of plant and animal origin, i.e., lead skeleton.
- Preparation of structural analogs of lead with increasing biological activity.
- Application of bio isosteric principle.

The current trend in the drug design is to develop new clinically effective agents through the structural modification of lead nucleus. The lead is a prototype compound that has the desired biological or pharmacological activity but may have many undesirable characteristics, like high toxicity, other biological activity, and insolubility or metabolism problems. Such organic leads once identified, are easy to exploit. This process is rather straightforward. The real test resides with the identification of such lead bioactive positions on the basic skeleton of such leads.

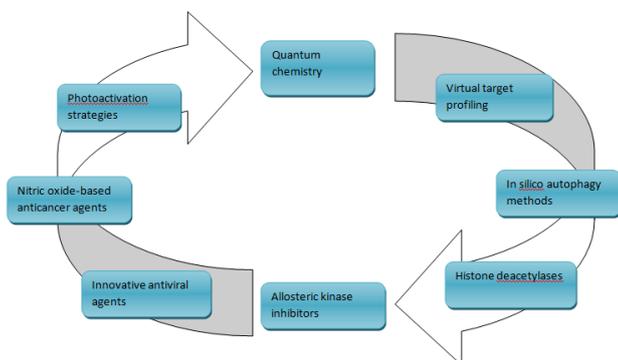
DISCUSSION

The rate of drug design & discovery is dependent on the ability to identify, characterize novel, patentable newer target drug molecules, usually termed as New Chemical Entities (NCE's), which is essentially possess the inherent capability and control of a specific disease/ailment. Besides, being efficacious and safer in character. With the advent of latest technological advancements in the specialized areas related to genomics and combinatorial chemistry an appreciable in the R&D strategies. NCE status, position and recognition is an absolute must not only to ensure marketing exclusively but also to justify the huge investment in the ensuring R & D process there by making more or less core element of the entire drug design & discovery process.

New techniques and strategies in drug design & discovery:

- Quantum chemistry
- Virtual target profiling
- In silico autophagy methods
- Histone deacetylases

- Allosteric kinase inhibitors
- Innovative antiviral agents
- Nitric oxide-based anticancer agents
- Photoactivation strategies



New techniques and strategies in drug discovery

CONCLUSION

Novel approaches in drug design are the creative process of finding new remedies based on the knowledge of a biological target. This review discusses principle of drug design, various approaches of drug design, lead discovery, lead modification & various types of drug discovery. Bio-isosteres is an important lead modification approach that has been shown to be useful to attenuate toxicity or to modify the activity of a lead, and may

have a significant role in the alteration of pharma kinetics of a lead. The process of drug discovery by laboratory experiments is time consuming and very expensive as compared to computational methods and play an vital role in Pharmaceutical Development of new drug for therapeutic efficacy.

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