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Computer Abetted Drug Design: New Therapeutic Approach ForDevelopment Of Target Database

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Abstract:

In modern drug discovery practices, drug leads are designed against a pre-selected drug target. Rapid discovery of new therapeutic targets is also very important as it may not only introduce more efficient therapeutic targets for certain diseases, but also increase the flexibility in designing of novel therapeutic intervention strategies by exploiting the synergies between known and newly discovered targets. This work begins with the development of the Therapeutic Target Database (TTD), which provides a comprehensive information source of known therapeutic targets. A relational data model was designed specifically for this database which aims to maximize the ability to accommodate future extensions and facilitate the integration of information.

Keywords : *TTD, Relational Data, Novel Therapeutic Intervention.*

1. Introduction To Drug Discovery

The search for new, effective and safe drugs has become increasingly sophisticated. Two pronounced characteristics marked the modern age of the pharmaceutical industry: "competitiveness" and "high cost". Driven by the high exclusive marketing profit, competition between pharmaceutical companies is much more intensive than before. Moreover, it is a competition by innovation [1], as highlighted by the title of an article in a research management journal: "'Innovate or die' is the first rule of international industrial competition" [2]. Besides the profit, the cost of discovering a new drug is also very high. More and more computer approaches are now being developed to reduce the cost and cycle time for discovering a new drug. In order to appreciate the drug target directed *in silico* approaches in drug discovery and development, the background of drug discovery is necessary to be introduced first.

1.1.Modern Drug Discovery

After more then 150 years of development, the discovery and development of a new drug is still a long and expensive process while it has become much more competitive. At present, new agents discovered not only need to show the desired therapeutic effects, but also need to be demonstrably better than existing drugs in terms of less side effects and higher efficacy. The development and improvement of drug discovery technologies is indispensable in order to win the competition of innovation [1] in the modern pharmaceutical industry. As illustrated in Fig 1.1, a typical new drug discovery process starts from target identification, which is followed by the search for drug leads and then clinical trials. The increasingly better understanding of the drug-target interaction mechanism and rapid advances in biochemistry and organic chemistry lead to the advent of computer aided drug design (CADD) [3-9], which aims to help the rapid and efficient discovery of drug leads.

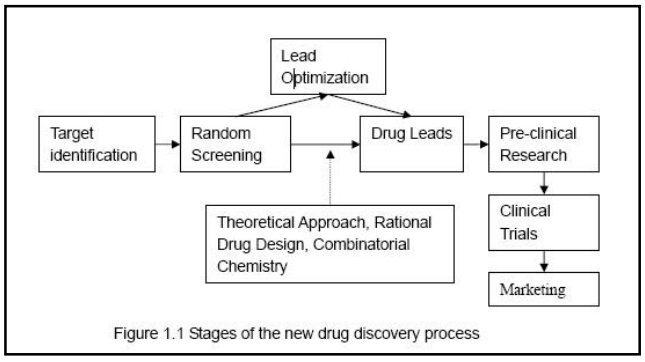

Figure 1.1 Stages of the new drug discovery process

2. Therapeutics Target And Drug Discovery

2.1. Information Resources Of Therapeutic Targets

A comprehensive knowledge database on therapeutic targets summarizing known drug target information will undoubtedly help the selection of therapeutic targets and the design of therapeutic intervention strategies that explore the synergies between known targets [10]. However, the information about known drug targets is still scattered among the millions of available references. Work needs to be done in order to collect and sort the drug target information. We therefore directed our effort in developing a database of known therapeutic targets with the aim to facilitate convenient access of the relevant information and knowledge discovery [11].

All the information in the Therapeutic Target Database (TTD) was manually collected from available literature data with the help of a few simple automated text retrieval programs. A relational data model [12] was designed specifically for this database with deliberate effort to maximize the ability to accommodate future extensions and facilitate the integration of information. The database was finally implemented on an Oracle 9i DBMS (DataBase Management System) [13] and a public accessible web interface was built using the Active Server Page (ASP) technology [8,6]. The database schema and web interface of TTD has been extended to develop two other databases -- Drug Adverse Reaction Target (DART) database and drug Absorption, Distribution, Metabolism, Excretion Associated Protein (ADME-AP) database.

3.Therapeutic Target Database Development

Developing a publicly accessible drug target database, Therapeutic Target Database (TTD), which provides information about the known protein and nucleic acid therapeutic targets together with the targeted diseases / conditions, their pathway information and those corresponding drugs / ligands directed at each of these targets. An ontology-like database structure is devised to manage the drug target information as well as maintaining the maximum flexibility to accommodate new interests in drug mechanisms. Web interfaces built on this database structure inherits this flexibility. The work of TTD has been extended to the construction of two other drug mechanism information databases, namely Drug Adverse Reaction Database (DART) and drug Absorption Distribution Metabolism and Excretion Associated Protein database (ADME-AP).

3.1. Requirement Analysis

The database system is expected to store and manage the information about known therapeutic targets. In consideration of the fast enriching data about known drugtargets or potential drug targets, a convenient updating mechanism is needed for this database. Also, a good system should not be designed to satisfy only the current needs; it should also take full consideration of the possible change and extension in future. Rational drug design is pacing fast nowadays. Different designing approaches take interests in different facets of drug targets. In the foreseeable future, more types of information will be needed by new or improved rational drug design approaches and therefore needed to be added into this database. Small changes or a complete overhaul of the database structure may be needed with this regard. No database or other software can be suitable for use forever; however, a flexible database structure that can be extended to incorporate these new interests with minimum necessary changes is desired. Moreover, the data collection work of two other drug mechanism information databases was in progress parallel to the development of TTD. As an augmented goal, it would be better that the design and implementation codes of TTD can be re-used in the development of these two databases. Before the actual database development, it is also to be determined which technology platform and software tool are to be used to establish this database.

3.2.Databases Development Approaches

There are several approaches to establish a database in past bioinformatics practices. The common ones include the flat-file approach, the relational approach, and the manual approach. In the flat-file approach, data is organized in text files where individual records of data are represented by a set of lines in strict order with symbols that allow the computer to find and retrieve specific pieces of information [23,24]. SWISS-PROT, EMBL, Gene Bank and OMIM are examples of the databases using this approach. In the manual approach, the information is manually coded into static web pages. Data are organized hierarchically and can be navigated following the hyper-links from the portal page. Usually no software helping the search and management of the data is used and limited search facility is provided. Manual approach is the easiest way to create an information repository without the requirements of any specific software. However, its limitations in search facility and data maintenance are severe drawbacks for middle and large scale databases. The scale of TTD rules out the manual approach as a good choice.

4.ERD derived database structure

The algorithm for translating a sound conceptual design into a relational data structure is given in [25,26] as the following four steps:

- First, construct a table for each entity type, containing all the attributes of the entity type and having a primary key or a unique identifier filed.
- Second, construct a table for each many-many relationship type containing the unique identifier for each side of the relationship along with the attributes of the relationship.
- Third, for each one-many relationship type, add the unique identifier from the "one" side to the table corresponding to the entity on the "many" side, along with all the attributes of the relationship.
- Finally, for each one-one relationship type, add the unique identifier from either side to the table for the other side, along with the attributes of the relationship.

Table Name	Columns	Table Relationships
TTDTG: Drug targets	TID: Target unique identifier NM: Recommended target name	
TTDDG: Drugs	DID: Drug unique identifier NM: Recommended drug name MW: Molecular weight MF: Molecular formula	
TTDLG: Natural Ligands	LID: Natural Ligand unique identifier NM: Recommended ligand name MW: Molecular weight MF: Molecular formula	
TTDLG: Natural Ligands	LID: Natural Ligand unique identifier NM: Recommended ligand name MW: Molecular weight MF: Molecular formula	
TTDRF: References	RFID: Reference unique identifier RF: Reference citation	

Table Name	Columns	Table Relationships
TTDTP: Target involved pathways	TID: Target unique identifier PW: Pathway name RF: Reference unique identifier	TID ∈ TTDTG.TID RF ∈ TTDRF
TTDTD: Target related diseases	TID: Target unique identifier DN: Disease name RF: Reference unique identifier	TID ∈ TTDTG.TID RF ∈ TTDRF.RFID
TTDTD: Target related diseases	TID: Target unique identifier DN: Disease name RF: Reference unique identifier	TID ∈ TTDTG.TID RF ∈ TTDRF.RFID
TTDTF: Target functions	TID: Target unique identifier FN: Target function RF: Reference unique identifier	TID ∈ TTDTG.TID RF ∈ TTDRF.RFID
TTDTDG: Drugs that bind targets	TID: Target unique identifier DG: Drug ID TP: Drug category RF: Reference unique identifier	TID ∈ TTDTG.TID RF ∈ TTDRF.RFID DG ∈ TTDDG.DID
TTDTLG: Natural ligands that bind targets	TID: Target unique identifier LG: Natural ligand ID RF: Reference unique identifier	TID ∈ TTDTG.TID RF ∈ TTDRF.RFID LG ∈ TTDLG.LID
TTDDS: Drug synonyms	DID: Drug unique identifier SN: Drug synonym	DID ∈ TTDDG.DID
TTDDR: Drug CAS RN	DID: Drug unique identifier CAS: CAS Registration Number	DID ∈ TTDDG.DID
TTDDC: Drug chemical Classification	DID: Drug unique identifier DC: Drug classification	DID ∈ TTDDG.DID

Table Name	Columns	Table Relationships
TTDLR: Ligand CAS RN	LID: Natural ligand unique identifier CAS: CAS Registration Number	LID ∈ TTDLG.LID
TTDLC: Ligand chemical classification	LID: Natural ligand unique identifier LC: Natural ligand classification	LID ∈ TTDLG.LID

Table 1: The data tables created in the first design of TTD.

After the tables and their relationship (constraints) were created, a web interface of the database was sketchily implemented and the system was analyzed on a small set of testing data.

5. Conclusion:

Therapeutic target database is developed from information in available literature, which is a result of collective and persistent effort over the years. It integrates the general information of therapeutic targets such as physiological functions and their therapeutic related aspects. With the rapid development of proteomics [16,17] and pathway analysis [28], the relevant information can be incorporated or the corresponding databases can be cross-linked to TTD to provide more comprehensive information about the drug targets and their relationship to other biomolecules and cellular processes. The completion of TTD not only provides a convenient way of looking up therapeutic target information, but also brings new research opportunities, such as the study of novel approaches in discovery of new therapeutic targets and new therapeutic intervention strategies.

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