

## >>>Rapid Drug Discovery – the fast way in drug discovery

### >>> market opportunity

Increasing the probability of success while decreasing the time and cost to market are major goals for the drug discovery process. The WABRI Rapid Drug Discovery Program (RDDP) utilises advanced Computer Aided Drug Design (CADD) to accelerate the discovery process while building in range of important fitness functions to assist in the selection of compounds. The Program relies on insightful observations of common drug features and where these bind to protein structures (at the “biophore” site) to assist in the prediction of developable drug molecules.

### >>> competition

With current advances of computing power and skill, numerous companies and organisations are engaged in this endeavour. Specifically companies like Tripos and Accelerlys are able to offer software suites to aid in the drug discovery process. The approach of the RDDP in searching for binding sites of common drug chemical substructures gives a unique advantage and aids the rapid delivery of compounds for testing.

### >>> technology

A key strategy to improve the chances of success in drug discovery is to rationally select compounds against important “developability criteria”.

WABRI RDDP strategy is as follows:

- Identify chemical structures that are common in existing drug molecules (“privileged substructures”)
- Determine if a common binding sites exist for these “privileged substructures” in protein drug targets
- Select protein targets that have binding sites for privileged scaffolds, adjacent to (and / or including) critical protein function sites
- Using computer-aided drug design software, screen a compound library for compounds that bind to the drug

- target protein at the proposed drug site
- Analyse library “hits” for developability criteria, including, Lipinski’s Rule of Five and other chemical features, ADME and Toxicity characteristics, Ease-of-Synthesis etc
- Prioritise compounds on calculated docking affinity and structure-based drug design
- Procure compounds from third-party suppliers and test in biological assays, including animal models
- Conduct further analysis as required for “Product Candidate” and “First Time In Man” studies.

This approach uses advanced computer algorithms in a unique configuration to accelerate the discovery process and lower the attrition rate of compounds during the development stage.

### >>> privileged compound database

A chemical database of over 4,000 heterocycle based compounds has been curated to provide drug-like molecules, the majority of which can be procured from third-party providers for immediate biological “proof-of-principle” testing.

The database has been carefully constructed, removing redundancies and incorporating ionization states. These are stored in 3D making the database immediately available for *in silico* screening.

Compounds populating the Privileged Compound Database have been selected to be available as “off-the-shelf” in small amounts for screening. The sources include:

- Tripos, Inc - Lead-Quest
- Maybridge – Building Blocks & Screening Compounds
- NCI -Database incorporating ChemIDPlus, NCI-3D etc
- Merck Index (Drugs from different pharmaceutical companies)
- CambridgeSoft, Inc - Chem-ACX

Compounds are reportedly available at purity levels of more than 80% pure with most being more than 90% pure.

## >>> primary and secondary filters

The Privileged Compound Database has been characterised to show that 88% of compounds comply with the primary filter of Lipinski's "Rule of Five", namely, Mol. Wt. (< 500), cLogP (< 5), nHBDon (< 5), nHBAcc (< 10), a pair wise combination of any of these.

Secondary filters utilised to inform on ADME and Toxicity include the Flexibility of the molecule (Number of rotatable bonds), the Topological Polar Surface Area (TPSA) and an Initial Oral Acute Toxicity screen developed from information in mammals for:

- Carcinogenicity
- Teratogenicity
- Mutagenicity
- Herg channel Inhibition (cardiotoxicity indicator)
- Membrane irritation
- Skin sensitization
- Immunotoxicity
- Neurotoxicity

A ranking of synthetic ease is possible using Sybyl™ software; however, this is often not as reliable as medicinal chemistry expertise for key decision-making.

## >>> intellectual property

The technology is very competitive and difficult to enforce. Application patents will be applied for following demonstration of biological activity.

## >>> expected outputs of the project

A rapid description of compounds that map to specific sites on target proteins known to be important for protein function. Estimated 12 week delivery of sample compounds for testing together with descriptions of compounds fit.

## >>> further information

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