Researchers seek to beat 'molecular obesity'

January 26 2012

(PhysOrg.com) -- Researchers from the University of Dundee have come up with a new innovative approach in the quest to reduce failure rates in the drug discovery process and fight 'molecular obesity'.

Professor Andrew Hopkins and his team from the University's College of Life Sciences have developed a mathematical formula that they believe has the potential to more effectively identify compounds that have the best chance of being successfully developed into drugs to treat and protect against disease.

In order to succeed as a drug, a compound has to have the right balance of properties. Those compounds that are too large or too greasy - said to be molecularly obese - tend not to be well absorbed by the body when taken orally as pills and have been blamed for increasing rates of failure and rising costs in the drug development process.

This is why the most commonly used and effective orally dosed drugs that are available on the market tend to be relatively small and lean. Compounds sharing these properties are said to be "drug-like" and assessment of "drug-likeness" is a key consideration when selecting compounds for further development.

Until now this assessment has been made according to a widely used set of rules that determine whether or not compounds are suitable for further development as orally absorbed pills.

However, the evaluation of drug-likeness in black and white terms does

not adequately reflect the whole spectrum of compound quality as many successful drugs apparently 'break the rules' so the Dundee team set about developing an alternative model.

They have pioneered a measure of drug-likeness based on the concept of desirability called Quantitative Estimate of Druglikeness (QED) which rates a compound between 0-1 based on its molecular properties, with 1 indicating an ideal candidate.

Once the scores have been calculated any set of compounds can be easily ranked by their relative merit. Importantly, the formula is derived entirely from historical data on the observed properties of successful drugs. This approach is more flexible than simply attributing a pass or fail to a compound, and offers several advantages to researchers looking to develop new drugs, according to Professor Hopkins.

"We think this may be a better way of appraising compounds in drug discovery," he said. "What we are trying to overcome is a problem of judging which compounds have the lowest risk of failure before synthesizing or buying them. This is important because the cost of drugs is in part driven by the high failure rate in developing new therapies.

"Compounds that don't have the correct properties or features make them particularly unsuitable, but this doesn't tell the whole story. Scientists judge them according to the rules, which might suggest a particular compound will work, but not that they will only work to a certain extent and that there are more effective alternatives available.

"Over the past two decades the compounds made by the pharmaceutical industry have tended to get larger and greasier. This trend has been called molecular obesity, and while these "obese" compounds may pass the rules they are far from the ideal.

"Some experts in the industry argue that the increasing failure rate and increasing cost in developing new drugs may be due to the rise in molecular obesity of new compounds. QED gives us a new tool to guide drug design toward leaner, fitter, more attractive compounds, with hopefully a greater overall chance of success.

"The rules which chemists use are useful, but only as far as telling us that it does or doesn't work. We are trying to get away from the concept of using hard and fast rules and looking instead at the shades of grey, which reflect the reality of the situation. What we are trying to do is increase the odds of identifying a successful compound."

The Dundee team's work is published in the most recent edition of the *Nature Chemistry* journal. The paper, entitled 'Quantifying the chemical beauty of drugs', is co-authored by colleagues in England and Sweden.

After attributing values to several thousand compounds, the researchers asked around 80 chemists to evaluate them based on their own knowledge and scientific methods. This showed that the Dundee method was an effective way of identifying attractive candidates which agreed very well with the chemists' intuition.

Professor Hopkins continued, "Chemists often refer to compounds as looking "good, bad or ugly" according to their suitability, and we asked the chemists who took part in this survey whether a drug was attractive or not, and found their tacit knowledge fitted well with our calculation.

"The whole idea is to use statistics, data, and underlying probability distributions which has been gathered on drugs over the years to help us more quickly and effectively identify attractive compounds in the future.

"The formula encodes the properties that seem to determine a compound's attractiveness, and reflects the knowledge required in drug

discovery. What we found exciting is the idea of a mathematical formula that reflects the chemists experience and intuition of what they consider an "attractive" compound to synthesise.

"From here we can develop a more nuanced approach to identifying lower risk compounds for drug discovery."

Provided by University of Dundee