QUO VADIS DRUG DISCOVERY?

Donatella Verbanac**,** Dubravko Jelić, Sanja Koštrun, Višnja Stepanić, Dinko Žiher

PLIVA - RESEARCH INSTITUTE Ltd., Prilaz baruna Filipovića 25, 10 000 Zagreb, Croatia

New century started with the characteristics of being landmark period for the science, medicine and drug discovery, as well. The drugs developed over the last four decades are targeted at about 500 different biological targets. With the sequencing of the human genome, over 100,000 new biological targets will be recognized. It has been estimated that at least 10 % of them could be used as targets for drugs. This will bring additional problems to be solved for an already "over- spread out" drug industry. There are a variety of factors exerting increasing pressure on the discovery and development of novel drug candidates, not the least of these being the cost and time needed to pass through the various phases of the process. Over the past decade, a variety of scientific advances and economic pressures have driven the need for improved drug discovery screening technology.

High throughput screening (HTS) is system for analyzing compound libraries and natural products in order to identify new therapeutic hits and leads on potential targets. In combination with combinatorial chemistry it resulted in a paradigm shift from knowledge-based sequential synthesis and testing to parallel processing of multiple compounds. With the objective to improve success rates and cycle times for discovering new hits, HTS is set to become one of the cornerstones of drug discovery.

In PLIVA - RESEARCH INSTITUTE Ltd. we introduced dedicated Screening Unit in mid 2000. with screenings of selected targets in anti-infective and anti-inflammatory area. The compounds we screened are produced in house and are acquired from different providers. In response to the rapidly changing discovery paradigm, it is important to consider preclinical properties at the earliest stages to assist in compound prioritization and to avoid downstream failure as related to drug delivery, pharmacokinetic or toxicological performance. Implementing screens for physicochemical properties (e.g. ID/purity, stability, solubility, permeability) and *in vitro* metabolism can provide data to prioritize hits and leads in favor of those most likely to possess acceptable preclinical properties. The design of these assays must appropriately balance throughput, accuracy and cost depending upon the intended objective and at what phase of this discovery process the data are needed.

In parallel, *in silico* data mining approaches such as high-throughput ADME/tox predictions and virtual screening including 2D and 3D methods are growing rapidly and are ongoing in PLIVA - RESEARCH INSTITUTE Ltd.

An overview in developing an integrated approach in providing these data, challenges for selected assays, and application to hit-set deconvolution will be presented.