CLINSILICO: AN IN-SILICO CLINICAL TRIAL SUPPORT SYSTEM FOR ACCELERATED BIOMEDICAL DISCOVERY.

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Abstract: Cancer is one of the leading causes of death in United States and worldwide. Discovery and development for cancer therapeutics takes several years before a patient is benefited from a new drug. The drug has to be first proven safe and effective before proceeding to treat diseases. On average, it takes 8 to 12 years and several million dollars to bring a new drug to market, with clinical trials accounting for approximately one-half of the time and one-third of the cost required. Additionally, a new drug undergoes an average of 64 trials before submitting for review by the U.S. Food and Drug Administration (FDA), yet a huge amount of these trials fail to provide conclusive or useful results. This lengthy process consists of several phases: Preclinical testing, Phase I, Phase II, Phase III and finally marketing approval. While there is no substitute for actual biological data in assessing drug candidates, insights into various aspects of the pharmacokinetic profile (absorption, metabolism, protein binding) can be predicted via various in silico techniques. Over the years biologists working in tandem with computational chemists have come up with several prediction algorithms to predict ADMETox (Adsorption, distribution, metabolism, excretion and toxicity) properties (1-3). Lipinski’s “Rule of Five”, classifies compounds that are likely to have good intestinal absorption (membrane absorption or permeability). In addition to the Lipinski's rules properties such as the number of rotatable bonds, number of aromatic rings, branching behavior and polar surface area are commonly used. In-silico methods have by far the highest throughput, followed by the in vitro and in vivo approaches. However, there is no integrated prediction tool or in silico techniques for accurately predict the fate of the drug in human body especially drugs that hit alternative targets and drug resistance. Here we present an in-silico clinical trial support system called “ClinSilico”, which combines biomedical research with informatics, to address the high cost of drug development, threat of competition and the high attrition rate of drug candidates during clinical trials for poor pharmacokinetic and ADMETox properties. 1) Cancer Informatics database (CID) of drugs and the major targets that are in clinical trials in Cancer target database (CTD) along with information about major outcomes of the study under concern were developed. 2) structural and functional fragments of the successful and failed drug candidates that are prone to ADMETox, Phase I enzymatic reactions and Phase II bio-transformations were identified and generated a database of Phase I and II enzymes (DOPE). 3) Performed thorough computational studies for each drug from CID using state-of-the-art docking and computational tools with targets from CTD and DOPE. 4) Integrated information from CID, CTD and DOPE and developd “ClinSilico”, an in silico clinical trial support system. 4) Performed virtual clinical trials using ClinSilico of potential drug candidates from an in house DB of ~25 million compounds (including major small molecule databases from ZINC, NCI, May Bridge and ACD laboratories). In-silico discovery of potential anti-cancer drugs would minimize the risk of trial failure before embarking on the clinical trials process. The potential therapeutics will accelerate biomedical discovery and complement ex-silico clinical trials.

Keywords: ClinSilico, cancer, cancer target database, cancer informatics database.

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