EXTENDED ABSTRACT

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Drug repositioning what, why and how

R. K. Dixit

King George's Medical University Lucknow, India

Abstract:

Bringing a new drug to market is expensive, time taking and risky business. Only one out of 8000 compounds tested in animals reaches human testing, and only one of five compounds reaching clinical trials is eventually approved. When new compound is evaluated for its potential therapeutic place the journey starts from the preclinical safety, toxicity and acceptability studies followed by the various phases of clinical trials devoted to the acceptability pharmacokinetics dose assessment and therapeutic uses. A huge amount of time and money is required for doing the preclinical studies and getting approval for the first administration to human. Therefore, it becomes rational to explore better and new in the existing compound rather than screening and doing the preliminary studies in the newer one. Drug repurposing (repositioning) is done for those compounds which have already been assessed preclinically and the data of safety and preliminary pharmacokinetics can suggest to proceed further or not. Therefore, the repurposing can save lots of money and time involved in the new drug development. Drug repurposing is an important component of therapeutic developments in the era of medicine paradigm. These studies become more important in finding the therapeutic solutions for complex diseases including cancers and orphan diseases. Sophisticated analysis including molecular profiling and critical evaluation of clinical data are the needs and opportunities to reposition approved drugs for alternative indications. It requires computational and experimental data, molecular and clinical data, bioinformatics, statistical tools and experimental techniques to find out new place of old drug. Important examples of using approved drugs for new indications are anti-malarial drugs in systemic lupus erythematosus, rheumatoid arthritis, and connective tissue diseases, thalidomide as an anticancer agent and the use of duloxetine for urinary tract infection. Biggest additions are genomics technologies and computational approaches to enhance the novel approaches for drug repurposing. Use of these has found the positive indications for the usefulness of old drugs in treatment of different types of cancers. Different methods used for drug repurposing are target-based repositioning, disease-based drug repositioning, expression datasets or signature-based drug repositioning etc. Semi /high throughput approaches, target-based screens, molecular profiling screens, gene expression profiling are used for systematic drug repurposing. Drug repurposing study is three-step process. Primary analyses use data from expression signatures, target biology, protein-protein or protein-small molecule network datasets (co-expression or Bayesian) and generates a list of ranked compounds for further evaluation. Secondary analyses approach to filter compounds for validation. Tertiary analyses aim to validate the compounds using experimental, pre-clinical models and assess outcomes. Some of the data bases used for the drug repurposing are Cancer Cell Line Encyclopedia (CCLE), ChEBI, Chemistry Development Kit (CDK), ChemMine Tools, ChemProt etc. Drug repurposing can bring new therapies in approximately half the budget and time due to availability of pre-existing data on efficacy, toxicity, dosing and biological knowledge of the compounds. Molecules that have failed clinical trials due to lack of efficacy or minor adverse profiles can also be used as candidates for drug repurposing for the new indications. Drug repurposing may solve by providing therapeutic compounds for complex, chronic or orphan diseases using already existing molecular information. The future outlook of drug repositioning is promising for translational researchers. Drug repurposing offers a cost-effective, accelerated and effective strategy for therapeutic options. Therefore, following are the answers related to quires of drug repurposing,

What is drug repurposing? Ans is Drug repurposing (also known as drug repositioning or drug reprofiling) is the process of redeveloping a compound for use in a different disease. The compounds have already been tested in preclinical and clinical testing and detailed information is available on their pharmacology, formulation, dose, and potential toxicity.

Why we need drug repurposing? Ans is to reduce time, money and risk in drug development. Also, it is well-known fact that common molecular pathways contribute to many different diseases therefore the compound useful in one disease may be of use in some other ailments.

How drug repurposing is done? Ans is by either of the two 'activity-based drug repositioning' or 'in silico drug repositioning'. In former application of actual drugs for screening while in later public databases and bioinformatics tools to systematically identify interaction networks between drugs and protein targets are utilized. Both strategies have certain advantages and drawbacks. In general, in silico drug repositioning is fast, less expensive but need very high-resolution structural targets, disease phenotypic information and gene expression profile of drug.

A few examples of overcoming adversity of medication repositioning carried worldwide consideration regarding the current medication space for potential off-target impacts that might be useful to specific maladies, for example, malignant growth. Since existing medications have just been utilized in people, they have entrenched portion routine with ideal pharmacokinetics (PK) and pharmacodynamics (PD) properties just as middle of the road reactions, making old medications helpful wellsprings of new anticancer medication revelation. In mid 2000s, we propelled another activity to amass a library of existing medications, named the Johns Hopkins Medication Library (JHDL) . JHDL has around 2,200 medications that have been affirmed by US-FDA or by its remote partners and around 800 non-endorsed tranquilize applicants that have entered different periods of human clinical preliminaries. We note that NIH Compound Genomics Community (NCGC) as of late fabricated an assortment of existing medications called NCGC Pharmaceutical Assortment (NPC) which contains 2,400 little sub-atomic elements that have been endorsed for clinical use in US (FDA), EU (EMA), Japan (NHI), and Canada (HC) . Notwithstanding these, a large number of clinical medication assortments are as of now financially accessible. These clinical medication assortments have demonstrated to be valuable sources to discover new signs of existing medications.