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Exploring Molecular Targets for Repositioning of Hypertensive Drugs

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ABSTRACT

Drug repositioning or drug repurposing or drug profiling is the discovery of new applications for approved or failed drug.. Drug repositioning is the development of new approved drug applications. The cost of bringing a medicine to the market is around one million which include clinical and preclinical trials. Repositioning of drugs help in cutting down costs as well as time involve in intial validation and authorization. The procedure involved in Drug repositioning is generally performed during the drug development phase to modify or extend an active molecule's distribution line. On a fundamental level, repositioning opportunities exist because drugs perturb multiple biological entities and engage themselves in multiple biological processes. Therefore, a drug can play multiple roles or perform a various mode of actions that are responsible for its pharmacology. Hypertension, is a condition that causes increase in the risk of cardiovascular diseases. In this study an attempt has been made to reposition hypertensive drugs for different diseases by exploring molecular targets of hypertensive drugs. Consider that they often need to be administered for long periods of time, often over whole life time Side effects although present, have been found safe enough to be used for such long durations, hence repurposing these drugs for other diseases may be beneficial with limited side effects.

KEYWORDS: *HCQ, hypertension, cancer*

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INTRODUCTION

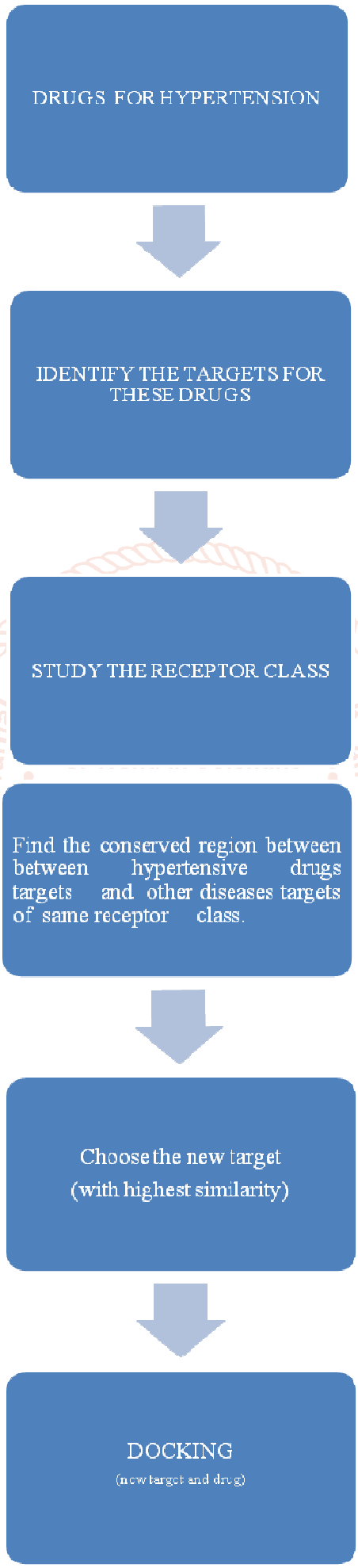
The standard method of drug production requires vast quantities of time and energy before a compound is labored into the market. Despite huge investments a lead molecule often has have minimal chances of entering the open market. The research molecule's itinerary remains unpredictable in its entire lifecycle. This situation causes pharmaceutical companies to discover new drugs on dreams. Drug g repositioning is one of the feasible choices for beginners in the area of new drug science [1]. Drug discovery is the process of identification of biologically active small molecules against different disease conditions.

Classical drug discovery starts from the identification of disease target, lead compound identification and optimization, ADMET studies and finally to market. [2]. Developing a Single molecule may take 10−17 years and the success rate can be as low as 0.01%.. The global annual budgets of R&D became $ 130 billion with fewer new drugs. The numbers of new drugs or New Molecular Entities (NME) released in the market are decreased and there is acute pressure on the R&D circle to increase the number of candidate drugs in the late stage pipeline [3].

These NMEs have to go through a number of pharmacokinetic and toxicity studies for their release into market. Molecules with potential drug like activities are evaluated simultaneously for their toxicity effects in cell and animal models.

After a strenuous and systematic evaluation of drug activity and other properties, several drug like molecules may have to be dropped because of undesired bio-distribution and toxicity. A new concept called "drug repositioning" is being emerged in the pharmaceutical R&D circle. Drug repositioning is the process of finding new uses outside the scope of the original medical indication for which the drug is prescribed[4] A repositioned drug can go directly to preclinical testing and clinical trials and save the initial 6−9 years essentially needed for the development of a new drug, with reduced risk and costs[5]. Drug repositioning is achieved by understanding of molecular mechanisms of drug action and by identification of the interacting proteins of the drug.

METHODOLOGY



RESULTS AND DISCUSSION

Drug discovery is an expensive and time consuming process. This process preceeds through three stages, first discovery where new compounds are screened and identified then preclinical stages where compounds are tested invitro and animal models and clinical development drugs tested in human beings. Using already existing drugs for different diseases reduced development cost and time due to availability of previously collected pharmokinetics, toxicology and safety data.

Nowdays, due to hectic and busy life hypertension or high blood pressure become very common problem mainly in youngster. Hypertension is associated with increased cardiovascular risks which include heart attack and stroke. Hypertension is a major cause of premature mortality. consider that they often need to be administered for long periods of time, often over whole life time Side effects although present, have been found safe enough to be used for such long durations, hence repurposing these drugs for other diseases may be beneficial with limited side effects.

No new antihypertensive medication has been introduced to clinical practice sine 2007therefore drug repurposing of already existing drugs for hypertension become very important.

DRUGS FOR HYPERTENSION

Table 1 shows repositioned drugs for hypertension. These are different drugs that worked for different diseases here, we repositioned these drugs as antihypertensive agents.

ACCESSION NO	DRUG	DISEASES	TARGETS
DB00555	Lamotrigine	Bipolar disorder	Calcium channel
DB12093	Tetrahydropalmatine	Schizophrenia	Calcium channel
DB00492	Fosinopril	Diabetes	Angiotensin Converting enzyme
DB00726	Trimipramine	Depresion	Beta adrenergic receptor
DB00715	Paroxetine	Depresion	Beta adrenergic receptor

TABLE1: REPOSITIONED DRUGS

TARGETS AND THEIR RECEPTOR CLASS

Now, we repositioned hypertensive drugs by identifying new targets for these repositioned drugs. We can identify new targets for hypertensive drugs by comparing the similarity percentage of repositioned drug targets with other targets of the same receptor class.

TARGETS	RECEPTOR CLASS
Calcium channel	ION CHANNEL RECEPTOR
Calcium channel	ION CHANNEL RECEPTOR
Angiotensin Converting enzyme	ENZYME LINKED RECEPTOR
Beta adrenergic receptor	GPCR
Beta adrenergic receptor	GPCR

TABLE2: SHOWING TARGETS AND THEIR RECEPTOR CLASS

Calcium channel percentage indicates that the calcium channel receptor shows the highest similarity with the serotonin receptor. receptors belong to the ion channel receptor class. The below table shows the similarity percentage of calcium channel receptors with other targets.

TARGET	SIMILARITY PERCENTAGE
Nicotini acetylcholine	48%
Zinc activated ion channel	43%
GABA	28.85%
Glutamate receptor	31.25%
Serotonin	54.55%

TABLE3: SHOWING SIMILARITY PERCENTAGE OF CALCIUM CHANNEL WITH OTHER TARGETS

Angiotensin converting enzyme belong to the enzyme linked receptor class. The below table shows the similarity percentage of angiotensin converting enzyme with other targets. The similarity percentage indicates that the angiotensin converting enzyme shows the highest similarity with sumo converting enzymes.

TARGET	SIMILARITY PERCENTAGE
Epidermal growth factor receptor	23.64%
Glial cell derived neutrophic factor	20 %
Trk neutrophin receptor	19%
Toll like	30%
Sumo converting enzyme	58.33%
Androgen reeptor	27.59%
Endothelian converting enzyme	31.25%

TABLE4: SHOWING SIMILARITY PERCENTAGE OF ANGIOTENSIN CONVERTING ENZYME WITH OTHER TARGETS

Beta adrenergic receptor belong to the GPCR class. The below table shows the similarity percentage of beta adrenergic receptor with other targets. The similarity percentage indicates that the beta adrenergic receptor shows the highest similarity with opoid receptor.

TARGET	SIMILARITY PERCENTAGE
Chemokine receptor	24.02%
Angionestin receptor	24%
Bradykinin	23.68%
Opoid receptor	53.85%
Somatostatin receptor	25.46%
Galamin receptor	20.33%
Relaxin receptor	18%
Melatonin receptor	34%
Eicosanoid receptor	36.76%
Alpha adrenergic receptor	34.31%
Dopamine receptor	36.76%
Histamine receptor	29.74%

TABLE5: SHOWING SIMILARITY PERCENTAGE OF BETA ADRENERGIC RECEPTOR WITH OTHER TARGETS

DRUGS WITH NEW TARGETS

Based on the similarity percentage of repositioned drugs targets with other targets, table 6 shows repositioned drugs with new targets that worked on different diseases.

DRUGS	NEW TARGET	DISEASES
Lamotrigine	Serotonin receptor	Depresion
Tetrahydropalmatine	Serotonin receptor	Depression
Fosinopril	Sumo converting enzyme	Alzheimer diseases
Trimipramine	Opoid receptor	Cancer
Paroxetine	Opoid receptor	Cancer

Table 6: SHOWING DRUGS WITH NEW TARGETS

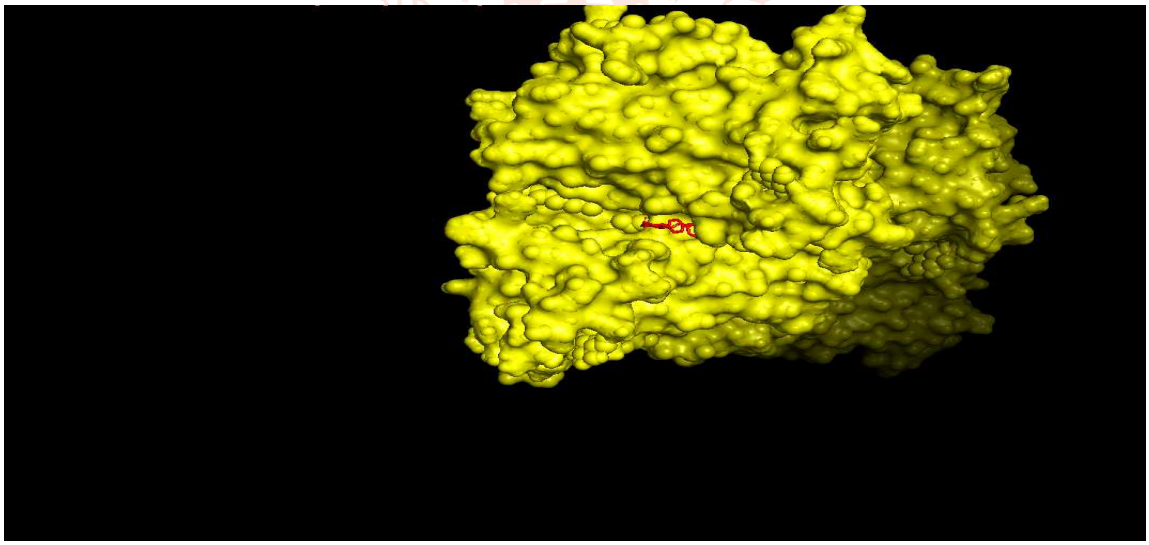
DOCKING OF DRUGS WITH NEW TARGET

Now, to identify new therapeutic uses of repositioned hypertensive drugs we perform docking of repositioned drugs with new targets.

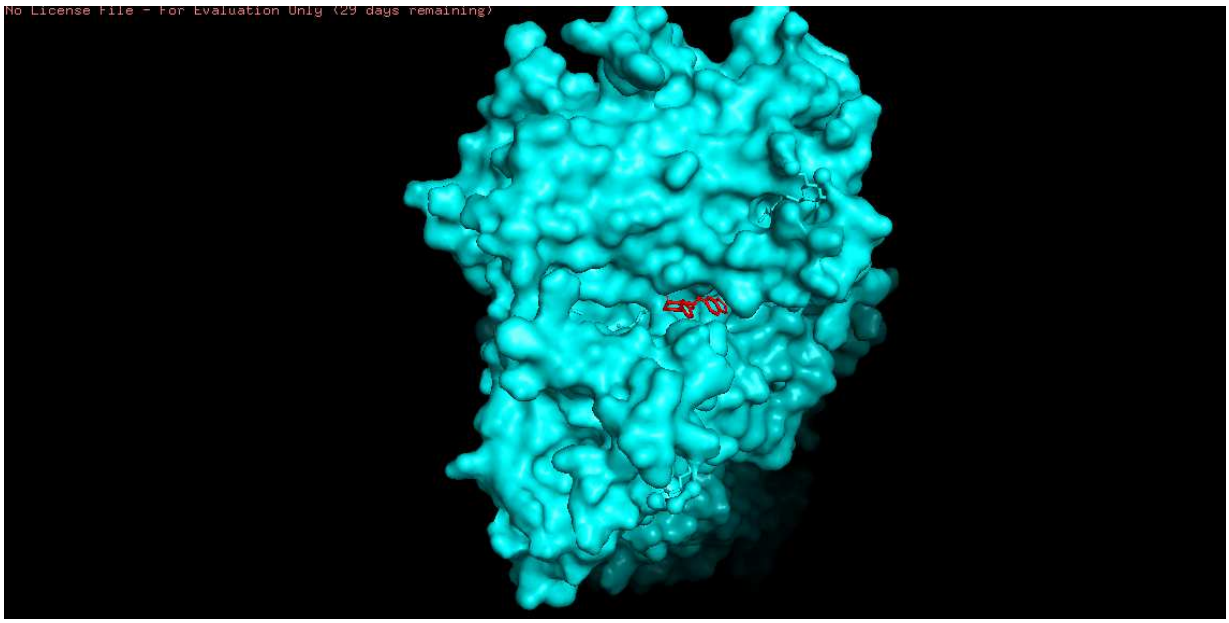
DRUGS	NEW TARGET	DOCKING SCORE
Lamotrigine	Serotonin receptor	-7.07
Tetrahydropalmatine	Serotonin receptor	-6.95
Fosinopril	Sumo converting enzyme	-6.25
Trimipramine	Opoid receptor	-7.24
Paroxetine	Opoid receptor	-8.58

TABLE7: SHOWING DOCKING SCORE

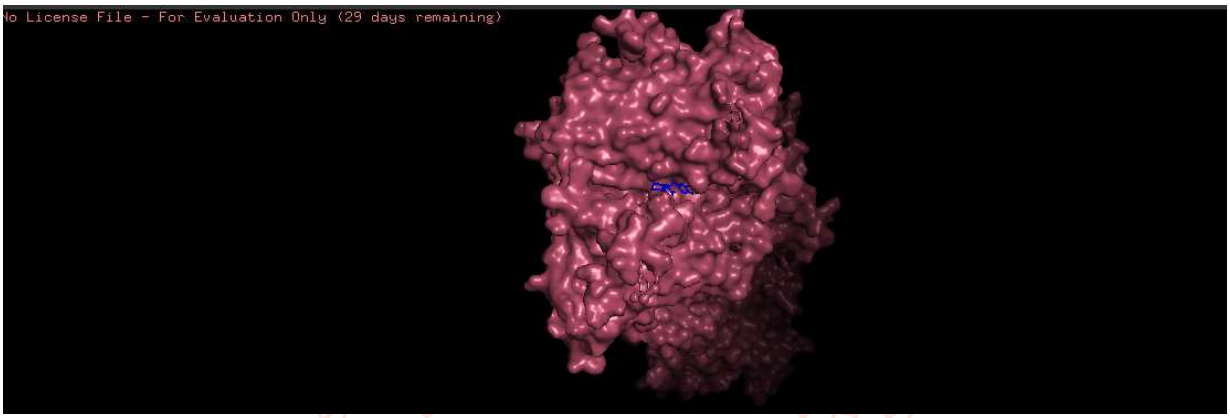
Based on docking score, Paroxentine shows minimum binding energy. So, we can repositioned paroxetine for the treatment of cancer.



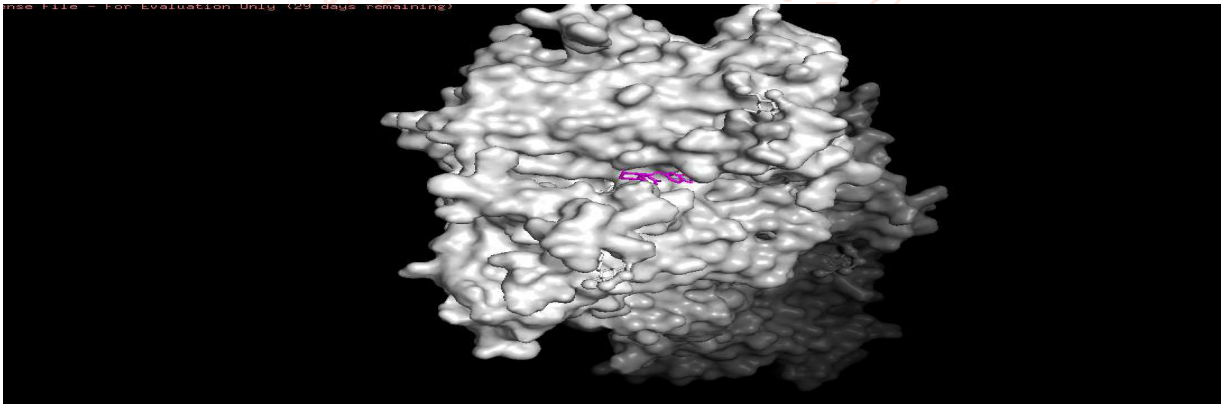
Lamotrigine docked to serotonin receptor



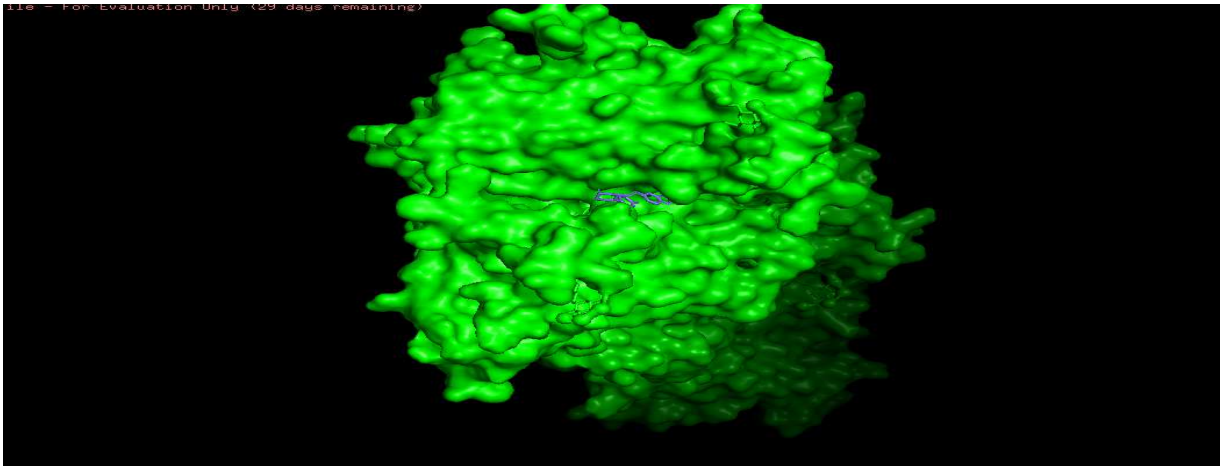
Tetrahydropalmatine docked to serotonin receptor



Fosinopril docked toSUMO converting enzyme



Trimipramine docked to opoid receptor



Paroxetine docked to beta opoid receptor

CONCLUSION

Drug discovery and development is time consuming, costly and extremely risky business. To speed up the process of drug development with a reduced risk of failure and lower costs, pharmaceutical companies have adopted drug repositioning as an alternative. We discovered new drugs for hypertension i.e lamotrigine, tetrahydropalmatine, fosinopril, trimipramine, paroxetine from already existing drugs by using docking. Consider that these hypertensive drugs often need to be administered for long periods of time, often over whole life time. Side effects although present, have been found safe enough to be used for such long durations, hence repurposing these drugs for other diseases may be beneficial with limited side effects.

In this study an attempt has been made to repositioned these hypertensive drugs for different diseases by exploring their molecular targets (Beta adrenergic receptor, calcium channel, aldosterone receptor, angiotensin converting enzyme). Firstly, facilitate the information about therapeutics targets and their receptor class, then find the conserved region between hypertensive drugs targets and other diseases targets of same receptor class. and select the new targets having highest similarity with hypertensive drug targets. New targets are opoid receptor, serotoin receptor, sumo converting enzyme. By using docking calculate the binding affinity of hypertensive drugs with new targets for different diseases and choose the drugs with highest affinity for new targets for drug repositioning. Based on docking score, Paroxentine shows minimum binding energy. So, we can repositioned paroxetine for the treatment of cancer.

REFERENCES

[1] Sardana D, Zhu C, Zhang M, Gudivada RC, Yang L, Jegga AG (2011). Drug repositioning for orphan diseases. Brief Bioinform6 (22): 484-488.

[2] Meier CR, Derby LE, Jick SS (2000) Angiotensin-converting enzyme inhibitors, calcium channel blockers, and breast cancer. Arch Intern Med. 145 (2): 3477-3486.

[3] Deotarse P. P. 1, Jain A. S. 1, Baile. M. B, et al (2005). Drug repositioning: a review40 (3): 10-15

[4] Deotarse P. P. 1, Jain A. S. 1, Baile. M. B, et al (2015). Drug repositioning: a review. Int J Pharma Res Rev22 (5): 1239-1249

[5] Ashburn TT, Thor KB (2010). Drug repositioning: identifying and developing new uses for existing drugs. Nat Rev Drug Discov 437 (7058): 491-493.

[6] Keiser MJ, Setola V, Irwin JJ, Laggner C, Abbas AI, et al (2009). Predicting new molecular targets for known drugs42 (22): 1118-1125.

[7] Sleigh SH, Barton CL (2010). Repurposing strategies for therapeutics. Pharm Med483 (7931): 570-575.

[8] Cain AE, Khalil RA (2002). Pathophysiology of essential hypertension: role of the pump, the vessel, kidney40 (3): 1110-11107.

[9] Franklin SS, Khan SA, Wong ND, Larson MG, Levy D (2019). Is pulse pressure useful in predicting risk for coronary heart disease59 (6): 222-225.

[10] Haynes WG, Webb DJ (2018). Endothelin as a regulator of cardiovascular function in health and disease5 (8): 35-55.

[11] Y. Li and S. Jones, "Drug repositioning for personalized medicine", *Genome Medicine*, vol. 4, no. 3, 2012. Available: 10. 1186/gm326.

[12] Ashburn, T. T. and Thor, K. B. (2004). Drug repositioning: identifying and developing new uses for existing drugs. Nature reviews Drug discovery, 3 (8): 673–683.

[13] M. Ashburner et al., "Gene Ontology: tool for the unification of biology", *Nature Genetics*, vol. 25, no. 1, pp. 25-29, 2000. Available: 10. 1038/75556.

[14] R. Insa, "Drug Repositioning: Bringing New Life to Shelved Assets and Existing Drugs. Edited by Michael J. Barratt and Donald E. Frail", *ChemMedChem*, vol. 8, no. 2, pp. 336-337, 2012. Available: 10. 1002/cmdc. 201200552.

[15] A. Chiang and A. Butte, "Systematic Evaluation of Drug–Disease Relationships to Identify Leads for Novel Drug Uses", *Clinical Pharmacology & Therapeutics*, vol. 86, no. 5, pp. 507-510, 2009. Available: 10. 1038/clpt. 2009. 103.

[16] DiMasi, J. A. (2001). New drug development in the united states from 1963 to 1999. Clinical pharmacology and therapeutics, 69 (5): 286.

[17] Duran-Frigola, M., Aloy, P., et al. (2012). Recycling side-effects into clinical markers for drug repositioning. Genome Med, 4 (3).

[18] Swinney, D. C. and Anthony, J. (2011). How were new medicines discovered? Nature reviews Drug discovery, 10 (7): 507–519.

[19] Teo, S. K., Stirling, D. I., and Zeldis, J. B. (2005). Thalidomide as a novel therapeutic agent: new uses for an old product. Drug discovery today, 10 (2): 107–114.

[20] Liu R, Singh N, Tawa GJ, Wallqvist A, Reifman J. Exploiting large-scale drug-protein interaction information for computational drug repurposing. BMC bioinformatics. 2014; 15: 210. doi: 10. 1186/14712105-15-210 PMID: 24950817