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Contents

Drug repurposing

- Drug repurposing (also known as drug repositioning) is a process of identifying new therapeutic use(s) for old/ existing/ available drugs.
- It involves establishing new therapeutic uses for already known drugs, including approved, discontinued, abandoned and experimental drugs establishing new therapeutic uses for already known drugs.
- Discovering new uses of approved drugs can provide the quickest possible transition from bench to bedside.[1]

Examples of the drug repurposing[2]

Name of Drug	Original Indication	New Indication
Amphotericin B	Fungal infection	Leishmaniasis
Amantadine	Influenza	Parkinson's disease
Allopurinol	Cancer	Gout
Atomoxetine	Depression	Attention deficit hyperactivity disorder
Bromocriptine	Parkinson's disease	Diabetes mellitus
Bupropion	Depression	Smoking cessation
Cycloserine	Urinary tract infection	Tuberculosis
Finasteride	Benign prostatic hyperplasia	Male pattern blindness (MPB)
Gemcitabine	Viral infection	Bladder cancer, breast cancer
Interferon- α	Hepatitis B and C	As immunotherapy in pancreatic and bladder cancers
Minoxidil	Hypertension	Hair loss
Raloxifene	Osteoporosis	Postmenopausal breast cancer
Retinoic acid	Acne	Promyelocytic Leukemia
Thalidomide	Morning sickness	Multiple myeloma / leprosy
Tranexamic acid	Hemorrhage	Melasma

Methods of drug repurposing[3]

1

Drug Oriented

The structural characteristics of drug molecules, biological activities, adverse effects and toxicities are evaluated

Through **serendipity or clinical observation**, if follows traditional pharmacology and drug discovery principles. E.g. **Minoxidil** used for hypertension – repurposed for hair growth

2

Target Oriented

*"**In silico**"* screening or "virtual high-throughput screening (**vHTS**)" of drugs or compounds from drug libraries/compounddatabases

Most biological targets directly represent the disease pathways/ mechanisms method -**Significant success rate** as compare to drug-oriented discovery e.g. **anticancer drugs**

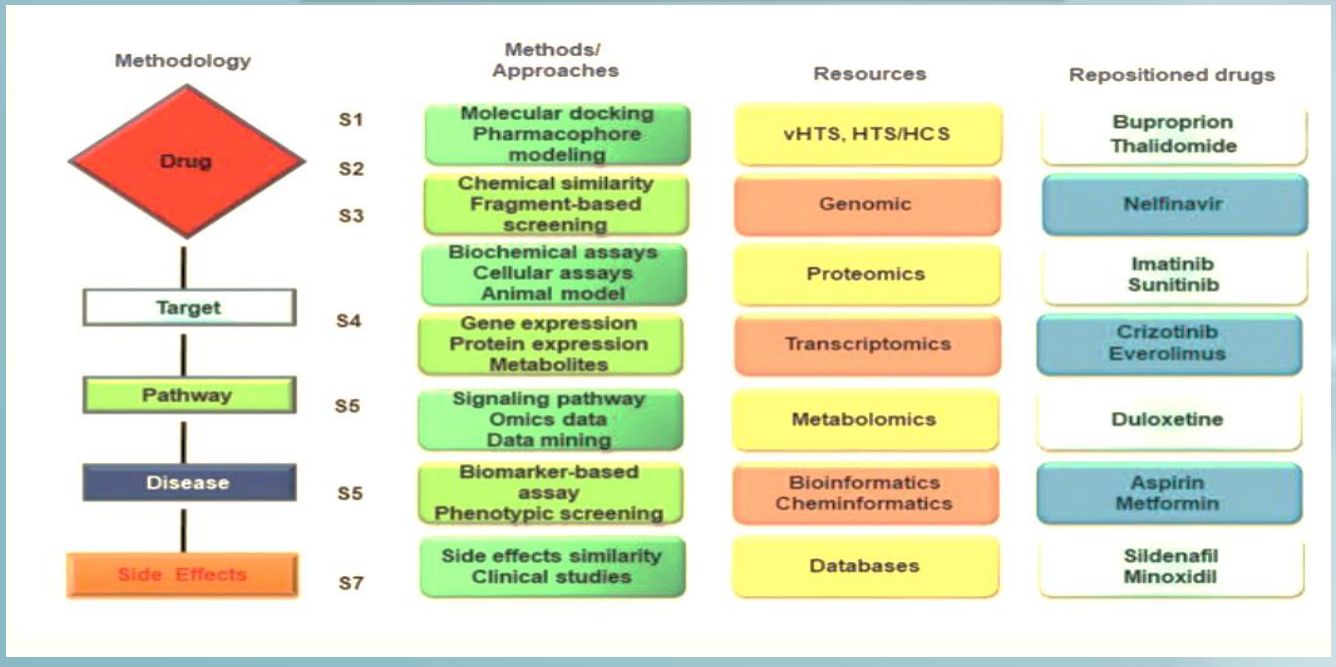
3

Disease/therapy-oriented

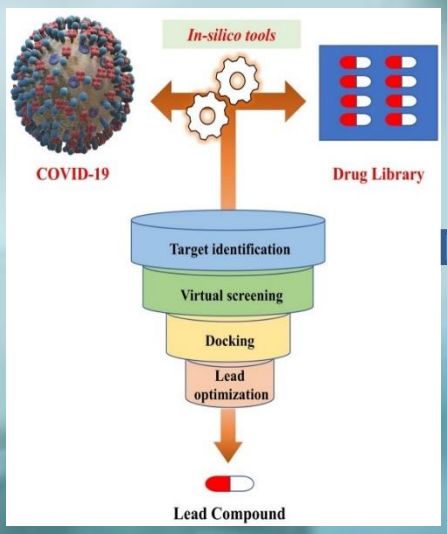
Based upon availability of information given by proteomics, genomics, metabolomics (disease specific metabolic pathways/profile) and phenotypic data (off-target mechanism, pharmacological targets, disease pathways, pathological conditions, adverse and side effects)

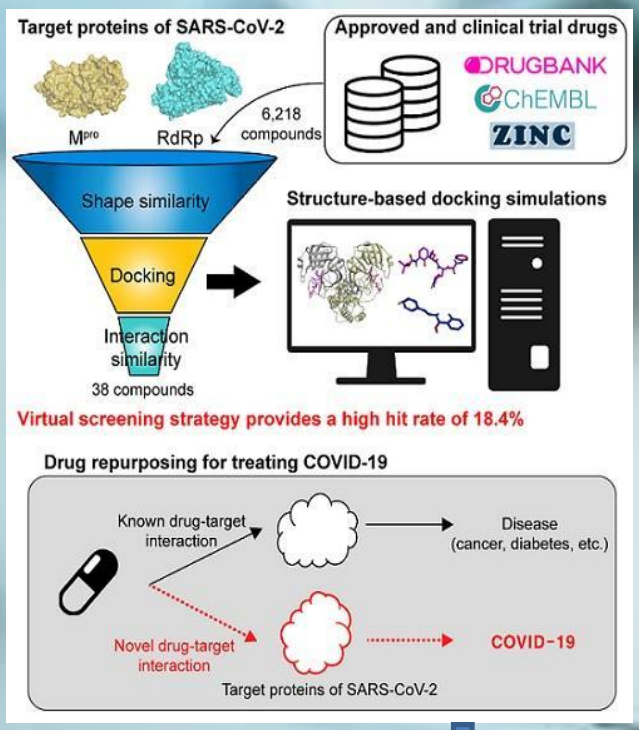
Requires **construction of specific disease networks**, recognizing genetic expression, key targets, protein molecules for metabolic pathways of interest in the disease model. e.g. **Drugs used in Alzheimer disease**

Examples of drug repurposing methodology



Drug repurposing for Covid 19 [4,5]





Repurposed drug in COVID-19 treatment[6]

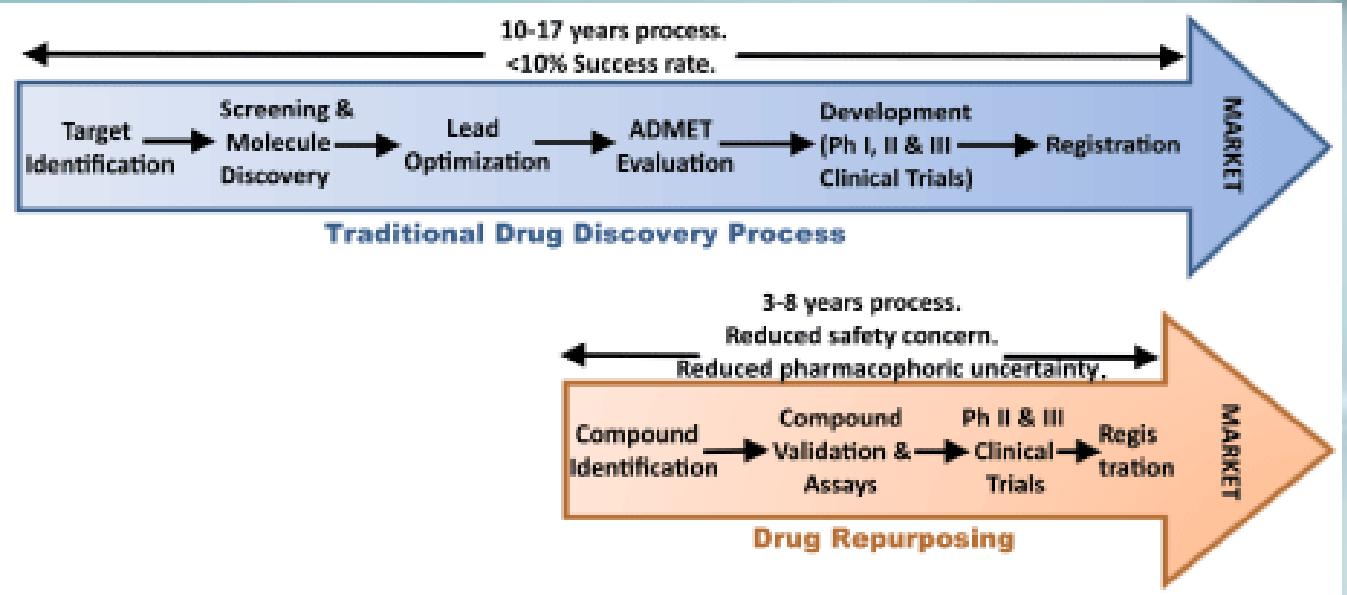
Repurposed Drug/Molecule	Original Approved Therapeutic Use	Probable Mechanism of Action against COVID-19
Baricitinib	Rheumatoid arthritis	Modulates cytokine production.
Chloroquine and Hydroxychloroquine	Malaria, chronic inflammatory diseases.	Prevents virus entry and decapsidation. Modulates the host immune system.
Dexamethasone	Inflammatory conditions (e.g., bronchial asthma, endocrine and rheumatic disorders).	Binds to the cellular glucocorticoid receptor, modulates production of pro-inflammatory and anti-inflammatory signals.
Favipiravir	Influenza virus	Inhibits virus RNA synthesis.
Ivermectin	Anti-parasitic. Intestinal strongyloidiasis and onchocerciasis, pediculosis and rosacea.	Inhibits the cellular importin α/β-mediated nuclear transport of proteins.
Lopinavir-Ritonavir	HIV/AIDS	Inhibits the virus 3CL protease.
Masitinib	Cancer, asthma, Alzheimer's disease, multiple sclerosis, amyotrophic lateral sclerosis.	Inhibits the virus 3CL protease.
Molnupiravir	Influenza viruses and encephalitic alphaviruses.	Inhibits virus RNA synthesis.
Remdesivir	Ebola virus	Inhibits virus RNA synthesis.
Tocilizumab	Rheumatoid arthritis, other autoimmune rheumatic diseases.	Inhibits IL-6 activity.
Umifenovir	Influenza and other respiratory viruses.	Blocks virus attachment and entry. Modulates immune response and interferon production.

Drug repurposing evidence level [7]

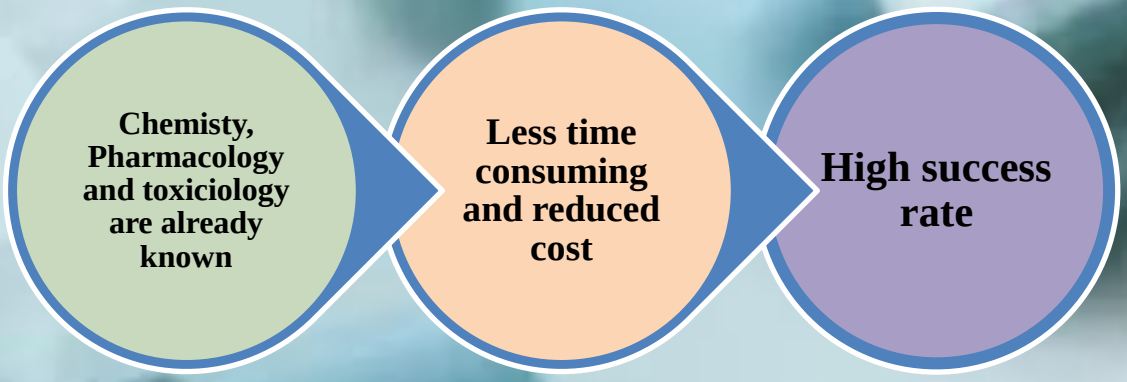
Drug repurposing evidence level	Quality of scientific level
0	No evidence; includes in silico prediction without confirmation
1	In vitro studies with limited value for predicting in vivo/ human situation
2	Animal studies with hypothetical relevance in man
3	Incomplete studies in man at the appropriate dose e.g. proof of concept; very few cases or inference for the medical records; some clinical effects observed
4	Well documented clinical end points observed for the repurposed drug at doses within safety limits.

Traditional drug discovery verses drug repurposing[8]

- The traditional drug discovery involves de novo identification to FDA approval & marketing and takes **10-17 years (with 10% success rate**).
- Drug repurposing takes **3-8 years** from compound identification to FDA approval as pharmacogical data already known.



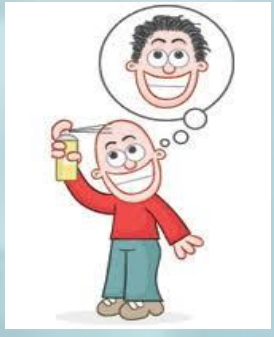
Advantages of drug repurposing[3]



Regulatory pathway for drug repurposing[7]

Pre-Entry	Scientific Advice through FDA or EMA or National Authority	Dossier Development /Clinical Phase	Regulatory Submission/Licensing Route	Post Approval Phase
• New Indication Interest • Using Identified resources and data submit the proposal to enter the pathway to regulatory authority	• Suitability will be reviewed by HA , conduct meetings, Provide recommendations , added clinical benefits could be debated	• Company follows advice from HA and develop Quality and additional Clinical Evidence	• Safety , Efficacy , Quality data demonstrated and submit to authority for approval; Abridged application process in most cases. (No hurdle of full dossier review)	• Life Cycle • Post Authorisation Studies/monitoring

Puzzle Time



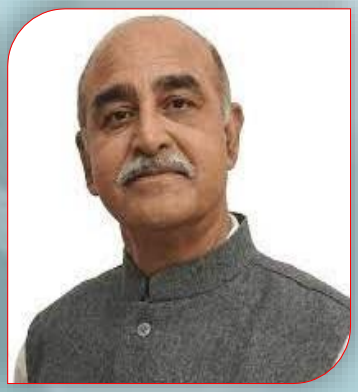
Identify the repurposed drug?

Identify the repurposed drug?

References:

1. Sahoo, Biswa, et al. "Drug Repurposing Strategy (DRS): Emerging Approach to Identify Potential Therapeutics for Treatment of Novel Coronavirus Infection." Frontiers in Molecular Biosciences.2021; 8.Availaable on https://doi.org/10.3389/fmolb.2021.628144. Accessed on 27th Apr. 2023.
2. Khadkaun et al. Repurposing Drugs for COVID-19: An Approach for Treatment in the Pandemic approved use. Alternative Therapies in Health and Medicine.August 2020.
3. Rudrapal M, Khairnar SJ, Jadhav AG. Drug Repurposing (DR):An Emerging Approach in Drug Discovery. Drug Repurposing - Hypothesis, Molecular Aspects and Therapeutic Applications. Available on https://www.intechopen.com/chapters/72744
4. Lochab, Amit, Thareja, Rakhi, Gadre, Sangeeta D.; Saxena, Reena.Potential Protein and Enzyme Targets for In-silico Development and Repurposing of Drug Against Coronaviruses. ChemistrySelect ;2021; 6(46):13363-1338.
5. News Release 202. The Korea Advanced Institute of Science and Technology(KAIST)Repurposed drugs present new strategy for treating COVID-19.) Available on https://www.eurekalert.org/news-releases/734890. (Assessed on 25th Apr. 2023)
6. Rodrigues, L., Cunha, R. B., Vassilevskaia, T., Viveiros, M., & Cunha, C. (2022). Drug Repurposing for COVID-19: A Review and a Novel Strategy to Identify New Targets and Potential Drug Candidates. Molecules, 27(9). https://doi.org/10.3390/molecules27092723
7. Repurposing Off-Patent Drugs: Research & Regulatory Challenges. FDA, NCATS and Reagan Udall Foundation for FDA. Available on https://videocast.nih.gov/watch=35412. (Assessed on 25th Apr. 2023)
8. Chakraborty A and Trivedi V. Streamlining the Drug Discovery Process through Repurposing of Clinically Approved Drugs. Austin J Biotechnol Bioeng. 2015;2(3): 1047.

Answers: 1. Minoxidil, 2. Bromocriptine



Message from Executive Director.....

"I heartily congratulate the department of pharmacology for bringing this informative newsletter on clinical pharmacology and therapeutics- repurposing of drugs. My best wishes to the entire team.....

Dr. (Col) CDS Katoch, Executive Director, AIIMS, Rajkot.

Team Pharmacology

This is an effort to bring forward important information on Clinical Pharmacology and Therapeutic advances related to repurposing of drugs. This initiative will be useful for medical practitioners and all readers for rational use of medicines. We hope you enjoy reading this e-bulletin!

- Dr. Rima Shah
(Associate professor, Department of Pharmacology)

Dr. Shubha Singhal
Assistant Professor
Dept of Pharmacology
AIIMS, Rajkot

Dr. Kiran Piparva
Assistant Professor
Dept of Pharmacology
AIIMS, Rajkot

Dr. Siddhartha Dutta
Assistant Professor
Dept of Pharmacology
AIIMS, Rajkot

Dr. Aditya Kadeval
Junior resident
Dept of Pharmacology
AIIMS, Rajkot